Phase 3 results for Lilly's Jaypirca® (pirtobrutinib) in covalent BTK inhibitor pre-treated chronic lymphocytic leukemia or small lymphocytic lymphoma to be presented at the 2024 ASH Annual Meeting

December 9, 2024

Results from BRUIN CLL-321 show Lilly's pirtobrutinib reduced the risk of disease progression or death by 46% compared to idelalisib plus rituximab or bendamustine plus rituximab

Pirtobrutinib prolonged the time to next treatment or death by a median of 23.9 months compared to 10.9 months in the control arm

BRUIN CLL-321 is the first randomized Phase 3 study in CLL ever conducted exclusively in patients previously treated with a BTK inhibitor

INDIANAPOLIS, Dec. 9, 2024 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced results from the Phase 3 BRUIN CLL-321 trial evaluating pirtobrutinib, a non-covalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor in adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) previously treated with a covalent BTK inhibitor. The study's primary endpoint of progression-free survival (PFS) was met at primary analysis[1], demonstrating pirtobrutinib was superior to investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR), based on independent review committee (IRC) assessment. Today's updated results corresponding to the final prespecified analysis, demonstrate consistent improvement in PFS for patients treated with pirtobrutinib, with a reduction in risk of relapse, disease or death by 46% compared to IdelaR or BR. These data will be presented in an oral presentation at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition.

"These results demonstrate the ability of pirtobrutinib to deliver clinically meaningful outcomes in a post-covalent BTK inhibitor setting, which is especially remarkable given the poor prognosis for the patient population enrolled in BRUIN CLL-321," said Jeff Sharman, M.D., Disease Chair, Lymphoma Research Executive Committee, SCRI at Willamette Valley Cancer Institute and Research Center, and one of the principal investigators of the BRUIN CLL-321 trial. "These data also show that pirtobrutinib can significantly prolong the time to next treatment with a median of approximately two years. Coupled with the safety results, the BRUIN CLL-321 data are important as we consider treatment sequencing for this setting."

BRUIN CLL-321 enrolled 238 patients who were randomized to receive pirtobrutinib monotherapy (n=119) or investigator's choice of IdelaR or BR (n=119). Patients across both arms received a median of three prior lines of therapy, with all patients having received at least one prior covalent BTK inhibitor. Approximately half of the patients had also received a venetoclax-containing regimen. Reflective of the poor prognosis of patients enrolled in this study, a high proportion of patients presented with high-risk features indicative of aggressive disease, including TP53 mutation and/or 17p deletion, unmutated IGHV status and complex karyotype.

Efficacy results are based on IRC assessment of the intent-to-treat (ITT) population and utilize an Aug. 29, 2024 data cutoff date. Crossover to the pirtobrutinib arm was allowed after IRC-confirmed disease progression. At median follow-up of approximately 19 months, median PFS was 14.0 months for the pirtobrutinib arm compared to 8.7 months for the control arm (HR=0.54 [95% CI, 0.39-0.75]). PFS results were consistent across key subgroups associated with a poor prognosis, including patients who received prior venetoclax and those with TP53 mutations and/or 17p deletions, unmutated IGHV status and complex karyotype.

Pirtobrutinib also demonstrated clinically meaningful improvements in other secondary endpoints such as investigator-assessed PFS (median PFS: 15.3 vs. 9.2 months; HR=0.48 [95% CI, 0.34-0.67]), event-free survival (EFS) (median EFS: 14.1 vs. 7.6 months; HR=0.39 [95% CI, 0.28-0.53]), and time to next treatment (TTNT) or death (median TTNT: 23.9 vs. 10.9 months; HR=0.37 [95% CI, 0.25-0.52]). Specifically, among patients in the control arm who were eligible for crossover, 76% (n=50/66) crossed over to receive pirtobrutinib. Multiple analyses that adjust for the effect of crossover demonstrate trends in favor of pirtobrutinib (Inverse Probability Censored Weighting methodology: HR= 0.89 [95% CI, 0.52-1.53]; two-stage Accelerated Failure Time methodology: HR=0.77 [95% CI, 0.45-1.26]).

The overall safety profile for patients treated with pirtobrutinib in BRUIN CLL-321 was consistent with safety data from the Phase 1/2 BRUIN study, including adverse events of special interest. In the Phase 3 study, pirtobrutinib treatment was associated with fewer grade 3 or higher treatment-emergent adverse events (TEAEs) and fewer treatment discontinuations due to adverse events compared to IdelaR or BR. When adjusting for exposure, the incidence rate of TEAEs was overall lower in patients receiving pirtobrutinib compared to IdelaR or BR.

"BRUIN CLL-321 is the only randomized CLL or SLL study ever conducted exclusively in the BTK-inhibitor pre-treated population, where there is significant need for new treatment options, and these data illustrate pirtobrutinib's ability to meaningfully delay disease progression and time to next treatment in this setting," said David Hyman, M.D., chief medical officer, Lilly. "This is the first in our suite of randomized Phase 3 trials for pirtobrutinib to readout and we look forward to continuing to build the body of evidence supporting the role of pirtobrutinib in advancing care for people with B-cell malignancies."

Lilly is committed to the ongoing investigation of pirtobrutinib in people living with hematologic malignancies. The BRUIN clinical trial program consists of six clinical studies, four of which are Phase 3 studies evaluating pirtobrutinib in CLL/SLL. For more information on the BRUIN Phase 3 clinical trial program, please visit clinicaltrials.gov.

Pirtobrutinib is approved as Jaypirca® under the U.S. Food and Drug Administration's (FDA) Accelerated Approval pathway for the treatment of adult patients with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor and adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK 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.

About BRUIN CLL-321
BRUIN CLL-321 is a Phase 3, randomized, open-label study of pirtobrutinib versus investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in BTK inhibitor pre-treated patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL). The trial enrolled 238 patients, who were randomized 1:1 to receive pirtobrutinib (200 mg orally, once daily) or investigator's choice of either IdelaR or BR per labeled doses. This trial's primary endpoint is progression-free survival (PFS) per 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria, as assessed by blinded independent review committee (IRC). Secondary endpoints include PFS, as assessed by investigator; overall response rate (ORR) and duration of response (DoR); event-free survival; overall survival (OS) and time to next treatment (TTNT); safety and tolerability; and patient-reported outcomes (PRO).

About Pirtobrutinib
Pirtobrutinib 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.[2] BTK plays a key role in the B-cell antigen receptor signaling pathway, which is required for the development, activation, and survival of normal white blood cells, known as B-cells, and malignant B-cells. BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas, including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL).[3,4] Pirtobrutinib was developed to reversibly bind BTK, deliver consistently high target coverage regardless of BTK turnover rate, and preserve activity in the presence of the C481 acquired resistance mutations.

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.[5,6] CLL is one of the most common types of leukemia in adults.[5] In the U.S., CLL accounts for about one-quarter of the new cases of leukemia and there will be approximately 20,700 new cases of CLL diagnosed this year.[5,7] SLL is identical to CLL from a pathologic and immunophenotypic standpoint, with the main difference between them being the location of the cancer cells.[5] In CLL, the cancer cells are present in the blood, and in SLL, the cancer cells are found in the lymph nodes.[5]

INDICATIONS FOR JAYPIRCA®
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 ≥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 ≥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 ≥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 (≥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 ≥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 (≥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 ≥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 ≥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.

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

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 adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) previously treated with a covalent 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 studies will be completed as planned, that future study results will be consistent with the results to date, that Jaypirca will prove to be a safe and effective treatment for relevant indications, or that Jaypirca will receive additional regulatory approvals or be commercially successful. 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.

1. Sharman JP, Munir T, Grosicki S, et al. 886 BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib Versus Idelalisib Plus Rituximab (IdelaR) or Bendamustine Plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Abstract presented at: American Society of Hematology Annual Meeting and Exposition; December 9, 2024; San Diego, CA. Session 642.
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. 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
4. 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
5. Mukkamalla SKR, Taneja A, Malipeddi D, et al. Chronic Lymphocytic Leukemia. [Updated 2023 Feb 18]. In: StatPearls [Internet]. *Treasure Island (FL): StatPearls Publishing;* 2023 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470433/
6. The Leukemia and Lymphoma Society. NHL Subtypes. Access here: https://www.lls.org/lymphoma/non-hodgkin-lymphoma/nhl-subtypes. Accessed on October 25, 2023.
7. NIH National Cancer Institute. Cancer Stat Facts: Leukemia – Chronic Lymphocytic Leukemia (CLL). Access here: https://seer.cancer.gov/statfacts/html/clyl.html. Accessed on October 3, 2023.

Refer to: Kyle Owens; owens_kyle@lilly.com; 332-259-3932 (Media)
Michael Czapar; czapar_michael_c@lilly.com; 317-617-0983 (Investors)

View original content to download multimedia:https://www.prnewswire.com/news-releases/phase-3-results-for-lillys-jaypirca-pirtobrutinib-in-covalent-btk-inhibitor-pre-treated-chronic-lymphocytic-leukemia-or-small-lymphocytic-lymphoma-to-be-presented-at-the-2024-ash-annual-meeting-302326603.html

SOURCE Eli Lilly and Company