Loxo@Lilly Presents Updated Pirtobrutinib Data from the Phase 1/2 BRUIN Clinical Trial at the 2022 American Society of Hematology Annual Meeting

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Pirtobrutinib demonstrates activity across covalent BTK inhibitor pre-treated B-cell malignancies and multiple patient subgroups

INDIANAPOLIS, Dec. 12, 2022 /PRNewswire/ -- Loxo@Lilly, the oncology unit of Eli Lilly and Company (NYSE: LLY), today announced updated clinical data from the pirtobrutinib global Phase 1/2 BRUIN trial in patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Richter transformation (RT), and Waldenström macroglobulinemia (WM). Pirtobrutinib is an investigational, highly selective, reversible (non-covalent) inhibitor of Bruton's tyrosine kinase (BTK). These data are featured in oral and poster presentations at the 2022 American Society of Hematology (ASH) Annual Meeting.

"These data presented at ASH build on previous results with significantly longer follow-up and continue to expand on the body of evidence supporting pirtobrutinib as a potential treatment option for patients previously treated with a covalent BTK inhibitor across a range of B-cell malignancies," said Susan O'Brien, M.D., UCI Health hematology oncologist, Chao Family Comprehensive Cancer Center and professor of hematology/oncology at University of California, Irvine. "For patients with CLL/SLL, MCL, and Waldenström macroglobulinemia who have received the standard of care regimens, including covalent BTK inhibitors, treatment options are extremely limited. For patients with Richter transformation, there are no standard treatment options. These results show that pirtobrutinib may potentially help to address multiple areas of growing unmet need."

"We continue to be very excited by the results of pirtobrutinib across B-cell malignancies," said David Hyman, M.D., chief medical officer, Loxo@Lilly. "These data from the BRUIN Phase 1/2 trial provide further evidence that pirtobrutinib's reversible binding mechanism and pharmacology may allow for extended targeting of the BTK pathway following treatment with a covalent BTK inhibitor. We are appreciative of the investigators and patients involved in the BRUIN study who have contributed to a better understanding of the potential of this medicine."

Key Data at ASH

The BRUIN Phase 1/2 clinical trial is evaluating pirtobrutinib monotherapy in patients previously treated for MCL, CLL/SLL, or other non-Hodgkin lymphomas (NHL). The efficacy data being presented at ASH for MCL and CLL/SLL are based on independent review committee (IRC) assessment while the efficacy data for RT and WM are based on investigator response assessments. The safety cohort consisted of all patients with B-cell malignancies who received at least one dose of pirtobrutinib monotherapy as of the data cutoff date.

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

The BRUIN trial includes one of the largest prospective cohorts of BTK inhibitor pre-treated CLL/SLL patients ever studied. As of the July 29, 2022 data cutoff date, 247 patients with CLL/SLL had received a prior BTK inhibitor and enrolled prior to November 5, 2021, to ensure adequate follow-up. Patients had received a median of three prior therapies (range 1-11). In this dataset, pirtobrutinib demonstrated an overall response rate (ORR) of 82% (95% CI: 76.8-86.7) and median progression-free survival (PFS) of 19.6 months (95% CI: 16.9-22.1). In patients treated with both a prior BTK and BCL2 inhibitor (n=100, median of five prior lines of therapy), the ORR was 79% (95% CI: 69.7-86.5), and median PFS was 16.8 months (95% CI: 13.2-18.7). Response rates were consistent across all subgroups analyzed regardless of mutation status, age, or previous therapies.

Mantle Cell Lymphoma (MCL)

As of the January 31, 2022 data cutoff date, the primary analysis set consisted of the first 90 patients enrolled with MCL who had received a prior BTK inhibitor. Patients had received a median of three prior lines of therapy (range 1-8). In this dataset, pirtobrutinib demonstrated an ORR of 58% (95% CI: 46.9-68.1), a median duration of response (DoR) of 21.6 months (95% CI: 7.5-NE) and a median PFS of 7.4 months (95% CI: 5.3-12.5). Response rates were consistent regardless of number of prior lines of therapy and classes of prior therapy received.

Richter Transformation (RT)

The BRUIN trial also includes one of the largest prospective RT populations ever studied. As of the July 29, 2022 data cutoff date, 75 patients with RT were response evaluable, with 68 patients having received prior treatment for RT. Among these patients, the median number of prior lines of CLL therapy was two (range 0-11) and the median number of prior lines of RT therapy was two (range 1-7). The ORR for the 75 response-evaluable patients was 52% (95% CI: 40.2-63.7), and for the 68 patients previously treated for RT, the ORR was 50% (95% CI: 37.6-62.4). Among all response evaluable patients, median overall survival (OS) was 13.1 months (95% CI: 7.8-NE) and DoR was 5.6 months (95% CI: 2.5-NE), regardless of prior RT therapy.

Waldenström Macroglobulinemia (WM)

As of the July 29, 2022 data cutoff date, 80 patients with WM were response evaluable, with 63 patients having received prior treatment with a BTK inhibitor. Among the 63 patients, the median number of prior therapies was three (range 1-11). The major response rate (MRR) was 67% (95% CI: 53.7-78.0), including 15 (23.8%) very good partial responses and 27 (42.9%) partial responses. In patients who previously received both chemoimmunotherapy and a covalent BTK inhibitor (n=50), the MRR was 68% (95% CI: 53.3-80.5). Median PFS was 19.4 months (95% CI: 15.1-22.1) in patients who received previous treatment with a covalent BTK inhibitor (n=62).

Safety of Pirtobrutinib from the BRUIN Study

In the safety cohort of all pirtobrutinib-treated patients (n=773), the most frequent treatment-emergent adverse events (TEAE) (≥15%), regardless of

attribution, were fatigue (29%), diarrhea (24%), and contusion (19%). The most frequent Grade ≥3 TEAE was neutropenia (20%). Low rates of Grade ≥3 TEAEs of hypertension (9%), hemorrhage (11%), and atrial fibrillation/flutter (3%) were observed. Overall, discontinuations due to a treatment-related adverse event occurred in 3% (n=20) of all patients. The safety profile was generally consistent across the populations studied.

Safety and Tolerability in Covalent BTK Intolerant Patients

The safety and tolerability of pirtobrutinib monotherapy in patients with relapsed or refractory B-cell malignancies who were intolerant to a prior covalent BTK inhibitor (n=127) was evaluated. Atrial fibrillation was among the most common adverse events (AE) that led to the discontinuation of a prior covalent BTK inhibitor, and in these patients (n=30), this AE recurred with pirtobrutinib treatment in two patients. Most patients did not experience high-grade recurrence of the other common AEs that led to discontinuation of a prior covalent BTK inhibitor, with the exception of neutropenia (in the patients in whom neutropenia recurred, 67% were Grade ≥3). No patient who discontinued a prior BTK inhibitor due to an AE had to discontinue pirtobrutinib for the same AE.

Loxo@Lilly is studying pirtobrutinib in multiple Phase 3 studies. Details on the trials can be found at lillyloxooncologypipeline.com or by visiting clinicaltrials.gov.

About Pirtobrutinib (LOXO-305)
Pirtobrutinib is an investigational, highly selective, reversible (non-covalent) Bruton's tyrosine kinase (BTK) inhibitor. 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 chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenström macroglobulinemia (WM). 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. Pirtobrutinib was found to be highly selective – 300 times more selective in BTK inhibition versus 98% of other kinases tested in preclinical studies. Interested patients and physicians can contact the Loxo@Lilly Physician and Patient BTK Clinical Trial Hotline at 1-855-LOXO-305 or email clinicaltrials@loxooncology.com.

About the BRUIN Phase 1/2 Trial

The BRUIN Phase 1/2 clinical trial is the ongoing first-in-human, global, multi-center evaluation of pirtobrutinib in patients previously treated for mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or other non-Hodgkin lymphomas (NHL).

The trial includes a Phase 1 dose-escalation phase, a Phase 1b combination arm, and a Phase 2 dose-expansion phase. The primary endpoint of the Phase 1 study is maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D). Secondary endpoints include safety, pharmacokinetics (PK), and preliminary efficacy measured by overall response rate (ORR) for monotherapy. The primary endpoint of the Phase 1b study is safety of the drug combinations. The secondary endpoints are PK and preliminary efficacy measured by ORR for the drug combinations. The primary endpoint for the Phase 2 study is ORR as determined by an independent review committee (IRC). Secondary endpoints include ORR as determined by investigator, best overall response (BOR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety, and PK.

About Lilly

Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 47 million 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/newsroom 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 pirtobrutinib as a potential treatment for people with previously treated chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma, Richter transformation, and Waldenström macroglobulinemia and the timeline for future readouts, presentations, and other milestones relating to pirtobrutinib 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 pirtobrutinib will prove to be a safe and effective treatment for relevant indications, that pirtobrutinib will receive regulatory approval, 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.

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