



Loxo Oncology at Lilly Announces Updated Data from the Phase 1/2 BRUIN Clinical Trial for Pirtobrutinib at the American Society of Hematology Annual Meeting

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INDIANAPOLIS, Dec. 12, 2021 /PRNewswire/ -- Loxo Oncology at Lilly, a research and development group of Eli Lilly and Company (NYSE: LLY), today announced updated clinical data from the pirtobrutinib global Phase 1/2 BRUIN clinical trial in patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL) and mantle cell lymphoma (MCL). Pirtobrutinib is an investigational, highly selective, non-covalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor. These data are being presented in oral presentations at the 2021 American Society of Hematology (ASH) Annual Meeting (abstracts 391 and 381).

"BRUIN is now the largest clinical trial conducted to date that has enrolled CLL/SLL patients previously treated with modern standards of care including BTK and BCL2 inhibitors. In this real-world population of relapsed/refractory patients, pirtobrutinib continues to demonstrate robust activity with a safety profile amenable to chronic administration. Now with the longer follow-up that this analysis affords, we are encouraged by evidence of durable disease control in this very heavily pretreated CLL/SLL population," said Anthony Mato, M.D., MSCE, director of the CLL Program at Memorial Sloan Kettering Cancer Center and a presenting author. "As recently detailed by a global panel of experts in *Clinical Cancer Research*, there are currently no evidence-based treatment options for patients following covalent BTK and BCL2 inhibitor therapy. Pirtobrutinib has the potential to offer a meaningful new approach for these CLL/SLL patients, as well as those patients who are less heavily pretreated."

"I'm pleased to share the pirtobrutinib data in MCL patients with the hematology community at ASH", said Michael Wang, M.D., Puddin Clarke Endowed Professor of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center and a presenting author. "Since our last analysis of these data, we have doubled the number of evaluable BTK pretreated patients and observed a nearly-identical response rate. New treatment options following covalent BTK therapy represent an area of urgent unmet need and the durable response rate observed with pirtobrutinib demonstrates its potential to provide a significant clinical advancement for patients with MCL following covalent BTK therapy."

Key Data Presented at ASH

As of July 16, 2021, 618 patients were enrolled in the study, including 296 with CLL/SLL, 134 with MCL, and 188 with other B-cell malignancies. The efficacy data presented at ASH are based on investigator response assessments. Patients were considered efficacy-evaluable if they had at least one post-baseline response assessment or if they discontinued treatment prior to their first post-baseline response assessment.

Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)

Among the 296 CLL/SLL patients enrolled, 261 were previously treated with a BTK inhibitor and are the subject of this analysis. The median number of prior lines of therapy was three with 100% receiving a prior BTK inhibitor, 88% an anti-CD20 antibody, 79% chemotherapy, 41% venetoclax, 20% a PI3K inhibitor, 6% CAR-T therapy and 2% stem cell transplant.

In 252 efficacy-evaluable patients (an additional nine patients ongoing prior to first restaging), 171 responded including two complete responses (CR), 137 partial responses (PR), 32 partial responses with ongoing lymphocytosis (PR-L), and 62 stable disease (SD), resulting in an overall response rate (ORR) of 68% (95% CI: 62-74). Responses continue to deepen over time, with the ORR rising to 73% (88/119) for those followed 12 months or more, and ORR remains consistent regardless of reason for prior BTK discontinuation, type or number of prior therapies or BTK C481 or PCLG2 mutational status.

Pirtobrutinib demonstrated evidence of durable activity with a median progression-free survival (PFS) not reached in patients who had received at least a prior BTK inhibitor (lower limit of 95% confidence interval of 17.0 months, median of three prior lines of therapy). In patients who had received at least a BTK inhibitor and BCL2 inhibitor (median of five lines of prior therapy), the estimated median PFS was 18 months, although these data remain immature and unstable due to the small percentage of patients with progression. As of the data cut-off, 74% (194/261) of BTK pre-treated patients remained on pirtobrutinib. Median follow-up for all BTK pre-treated patients was 9.4 months (range 0.3-27.4 months).

In an exploratory analysis in patients with prior progression on a BTK inhibitor, the PFS with pirtobrutinib was similar in patients with BTK C481-mutated and BTK C481-wildtype CLL and SLL.

Mantle cell lymphoma (MCL)

The 134 patients with MCL received a median of three prior lines of therapy, with 90% receiving a prior BTK inhibitor, 97% an anti-CD20 antibody, 91% chemotherapy, 22% stem cell transplant, 17% immunomodulatory (IMiD) drugs, 15% venetoclax, 13% proteasome inhibitor, 5% CAR-T cell therapy, and 4% PI3K inhibitor.

Of the 100 efficacy-evaluable patients with BTK pre-treated MCL (an additional 23 patients ongoing prior to first restaging, 11 patients had not received a prior BTK inhibitor), 51 responded including 25 CRs and 26 PRs resulting in an ORR of 51% (95% CI: 41-61). Among 11 BTK naïve MCL patients, nine responded including two CRs and seven PRs resulting in an ORR of 82% (95% CI: 48-98). Responses in MCL were observed in patients who received prior stem cell transplant and prior CAR-T therapy.

Median duration of response was 18 months (lower limit of 95% confidence interval of 4.6 months). Median follow-up for all responding MCL patients was 8.2 months (range of 1.0-27.9 months) with 60% (36/60) of responses ongoing as of the data cut-off.

Safety data were presented for the entire enrolled BRUIN population. Across all 618 patients enrolled in the study, the most commonly reported adverse events, regardless of attribution, were fatigue (23%), diarrhea (19%), neutropenia (18%) and confusion (17%). In addition, adverse events commonly associated with covalent BTK inhibitors occurred at a low rate, with the majority being Grade 1 or 2. During the Phase 1 dose escalation, no dose limiting toxicities were reported and a maximum tolerated dose (MTD) was not reached. Permanent discontinuations for drug-related adverse

events were observed in 1% (n=6) of patients.

"As the pirtobrutinib data continue to mature we remain extremely excited by its potential to meaningfully improve the treatment landscape for patients with CLL, SLL and MCL", said David Hyman, M.D., chief medical officer, oncology at Lilly. "We have initiated a robust Phase 3 program for pirtobrutinib and look forward to further exploring its potential as monotherapy, in combination, and in earlier lines of therapy."

Real-world evidence studies

A real-world evidence database study on outcomes for patients with CLL previously treated with a covalent BTK inhibitor and a BCL2 inhibitor will be presented in a poster presentation on Monday, December 13 from 6-8 p.m. ET (abstract 3743). Additionally, a study on outcomes for patients with MCL following covalent BTK inhibitor therapy was published as an online-only abstract (abstract 4523).

Loxo Oncology at Lilly is studying pirtobrutinib in multiple Phase 3 studies. Details on the trials can be found in Trials in Progress posters (abstracts 2422, 3732, 3736 and 3742) and on lillyloxooncologypipeline.com.

About Pirtobrutinib (LOXO-305)

Pirtobrutinib is an investigational, highly selective, non-covalent (reversible) 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, mantle cell lymphoma, Waldenström macroglobulinemia, and marginal zone lymphoma. Currently available covalent BTK inhibitors irreversibly inhibit BTK and the long-term efficacy of these therapies can be limited by acquired resistance, most commonly through BTK C481 mutations. In rapidly growing tumors with inherently high rates of BTK turnover, resistance to covalent BTK therapies may be the result of incomplete target inhibition. Pirtobrutinib was designed to reversibly bind BTK, deliver consistently high target coverage regardless of BTK turnover rate, preserve activity in the presence of the C481 acquired resistance mutations, and avoid off-target kinases that have complicated the development of both covalent and investigational non-covalent BTK inhibitors. Interested patients and physicians can contact the Loxo Oncology at 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

This first-in-human, global, multi-center Phase 1/2 trial evaluates pirtobrutinib as a single agent in patients with previously treated chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), or non-Hodgkin's lymphomas (NHL). The trial includes a Phase 1 dose escalation phase and a Phase 2 dose expansion phase. The Phase 1 dose escalation enrolls patients with CLL/SLL or NHL who have received at least two prior lines of therapy and have progressed or are intolerant to standard of care. The dose escalation phase followed a "3+3" design with pirtobrutinib dosed orally in 28-day cycles. As dose cohorts were cleared, additional patients could enroll in cleared cohorts and intra-patient dose escalation was permitted. The primary objective of the Phase 1 portion of the trial is to determine the maximum tolerated dose and recommended Phase 2 dose. Key secondary objectives include measures of safety, pharmacokinetics, and anti-tumor activity (i.e. Overall Response Rate (ORR) and Duration of Response, as determined by appropriate histology-specific response criteria). In the Phase 2 dose expansion, patients are enrolled across various cohorts, depending on disease type and prior therapy. The primary endpoint for Phase 2 is ORR. Secondary endpoints include duration of response (DOR), overall survival (OS), safety, and pharmacokinetics (PK).

About Loxo Oncology at Lilly

Loxo Oncology at Lilly was created in December 2019, combining the Lilly Research Laboratories oncology organization and Loxo Oncology, which was acquired by Lilly in early 2019. Loxo Oncology at Lilly brings together the focus and spirit of a biotech with the scale and resources of large pharma, with the goal of rapidly delivering impactful new medicines for people with cancer. Our approach centers on creating new oncology medicines that unequivocally work early in clinical development and will matter to patients.

About Eli Lilly and Company

Lilly is a global health care leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. P-LLY

Disclosure: Dr. Mato has provided consulting and advisory services to Loxo Oncology at Lilly and Eli Lilly and Company.

Lilly Forward-Looking Statement

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Lilly's pirtobrutinib for the potential treatment of previously treated chronic lymphocytic leukemia, small lymphocytic lymphoma and mantle cell lymphoma 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 studies will be completed as planned, that future study results will be consistent with the results to date, that pirtobrutinib will prove to be a safe and effective treatment for relevant indications, or that pirtobrutinib will receive regulatory approvals or be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's most recent 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.

Refer to: Lauren Cohen; lcohen@loxooncology.com; 617-678-2067 – media
Kevin Hern; hern_kevin_r@lilly.com; 317-277-1838 – investors



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