Loxo Oncology at Lilly Announces Updated Data from the Phase 1/2 BRUIN Clinical Trial for LOXO-305 in Mantle Cell Lymphoma and Non-Hodgkin Lymphomas at the American Society of Hematology (ASH) Annual Meeting

December 5, 2020

52% overall response rate in mantle cell lymphoma patients previously treated with a covalent BTK inhibitor
83% of responding mantle cell lymphoma patients remain in response and on therapy
68% overall response rate in patients with Waldenström's macroglobulinemia, 69% of whom were previously treated with a covalent BTK inhibitor; responses also observed across other non-Hodgkin lymphomas
Superiority head-to-head Phase 3 trial of LOXO-305 vs. investigator's choice of covalent BTK inhibitor in relapsed-refractory mantle cell lymphoma to be initiated in Q1 2021

INDIANAPOLIS, Dec. 5, 2020 /PRNewswire/ -- Loxo Oncology at Lilly, a research and development group of Eli Lilly and Company (NYSE: LLY), today announced clinical data from the LOXO-305 global Phase 1/2 BRUIN clinical trial in mantle cell lymphoma (MCL) and other non-Hodgkin lymphomas. LOXO-305 is an investigational, highly selective, non-covalent Bruton's tyrosine kinase (BTK) inhibitor. These data are being presented in an oral presentation at the 2020 American Society of Hematology (ASH) Annual Meeting (abstract 117).

"MCL patients who have been treated with a covalent BTK inhibitor have very few therapeutic options, and outcomes are extremely poor. LOXO-305 has demonstrated a promising efficacy profile in these patients, a setting where we urgently need new therapies," said Michael Wang, M.D., Puddin Clarke Endowed Professor of Lymphoma and Myeloma at The University of Texas MD Anderson Cancer Center and presenting author. "I am also excited about the emerging data for LOXO-305 in other B-cell malignancies including Waldenström's macroglobulinemia."

"We are very excited to share this update on LOXO-305 in MCL with the hematology community and look forward to sharing data on chronic lymphocytic leukemia and small lymphocytic lymphoma patients in the coming days," said David Hyman, M.D., chief medical officer of Loxo Oncology at Lilly. "LOXO-305 was designed to overcome some of the limitations seen with current BTK therapies and we believe the promising efficacy and tolerability data demonstrate its potential to be an important new treatment option for MCL patients. In addition, we look forward to initiating an ambitious Phase 3 study in MCL patients early next year where we aim to demonstrate superiority of LOXO-305 against covalent BTK inhibitors."

Additional data from the BRUIN Phase 1/2 trial in patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) will be presented in an oral presentation at ASH (abstract 542) on Monday, December 7 at 10a.m. ET/7a.m. PT.

Key Data Presented at ASH

As of September 27, 2020, 323 patients were enrolled in the study, including 170 with CLL/SLL, 61 with MCL, 26 with Waldenström's macroglobulinemia (WM), and 66 with other B-cell lymphomas. The 61 patients with MCL received a median of three prior lines of therapy, with 93% receiving a prior BTK inhibitor, 98% an anti-CD20 antibody, 92% chemotherapy, 20% lenalidomide, 25% autologous transplant, 5% CAR-T cell therapy, and 5% allogeneic transplant.

Pharmacokinetic analyses during dose escalation demonstrated consistent dose-proportional exposures with low inter-patient variability across the entire dosing range of 25mg to 300mg daily. Doses of 100mg QD and greater exceeded BTK IC90 target coverage for the entirety of the dosing interval. Responses were observed starting at the first dose level.

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.

- In the 56 efficacy-evaluable patients with MCL, 29 responded to treatment including 14 complete responses (CR) and 15 partial responses (PR) resulting in an overall response rate (ORR) of 52% (95% CI: 38-65). Among the 52 patients who had received a prior covalent BTK inhibitor, the ORR was also 52% (95% CI: 38-66). Responses in MCL were observed in patients who received prior cellular therapy, including 64% (9/14) of patients with prior autologous or allogeneic transplant, and 100% (2/2) with prior CAR-T. Responses were also observed in two of four patients with blastoid variant MCL, an aggressive subtype associated with worse prognosis. Median time to first response was 1.8 months, corresponding with the first response assessment. Median follow-up for the 56 efficacy-evaluable MCL patients was six months. Of the 29 responding MCL patients, all except five remain on therapy (four for progressive disease and one who achieved a CR and electively discontinued treatment to undergo allogeneic stem cell transplant). The longest-followed responding patient continues on treatment at 18.3 months.
- In 19 efficacy-evaluable Waldenström's macroglobulinemia patients, 13 responded including 9 PR and 4 minor responses (MR), resulting in an ORR of 68% (95% CI: 44-87). Among the 13 patients who had received a prior covalent BTK inhibitor, the ORR was 69% (95% CI: 39-91, 5 PR, and 4 MR). Ten of 13 WM responders are ongoing on LOXO-305 treatment at a median follow-up of 4.6 months.
- Among eight efficacy-evaluable patients with follicular lymphoma, responses were observed in four patients.
- Among eight patients with Richter's transformation identified prior to enrollment, responses were observed in six, resulting

in an ORR of 75%.
- Of the remaining 39 efficacy evaluable patients, eight responses were observed (6/25 patients with Diffuse large B-cell lymphoma (DLBCL), 2/9 patients with marginal zone lymphoma (MZL)).

Safety data were presented for the entire enrolled BRUIN population. Across all 323 patients enrolled in the study, the most commonly reported adverse events, regardless of attribution, were fatigue (20%), diarrhea (17%), and contusion (13%). In addition, rates of two adverse events commonly associated with BTK inhibitors, atrial arrythmias and hemorrhage, were low, experienced by two patients and one patient respectively, and considered by investigators as unrelated to LOXO-305. Dose interruptions, reductions and permanent discontinuations for drug-related adverse events were observed in 8%, 2.2%, and 1.5% of patients, respectively. No dose limiting toxicities were reported and a maximum tolerated dose (MTD) was not reached.

LOXO-305 Development Program Update

Loxo Oncology at Lilly is preparing to initiate a global, randomized, superiority Phase 3 clinical trial to study LOXO-305 versus currently available covalent BTK inhibitors in BTK treatment naïve patients with relapsed-refractory MCL. Participants will be randomized to receive either LOXO-305 monotherapy or investigator's choice of ibrutinib, acalabrutinib or zanubrutinib. The trial, BRUIN MCL-321, is expected to begin in the first quarter of 2021.

About LOXO-305
LOXO-305 is an investigational, oral, highly selective, 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, mantle cell lymphoma, Waldenström macroglobulinemia, and marginal zone lymphoma. Currently available 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. LOXO-305 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 Trial
This first-in-human, global, multi-center Phase 1/2 trial evaluates LOXO-305 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 LOXO-305 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, 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

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Lilly's LOXO-305 for the potential treatment of previously treated chronic lymphocytic leukemia, small lymphocytic lymphoma and non-Hodgkin lymphoma and reflects Lilly's current belief. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that studies will complete as planned, that future study results will be consistent with the results to date, or that LOXO-305 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.

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