Loxo Oncology at Lilly Announces Updated Data from the Phase 1/2 BRUIN Clinical Trial for LOXO-305 in Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma at the American Society of Hematology Annual Meeting

December 7, 2020

62% overall response rate in BTK pre-treated CLL/SLL patients, rising to 84% in patients followed for 10 or more months; consistent response rates regardless of reason for prior BTK discontinuation or BTK mutation status
Similar overall response rates observed in patients previously treated with all classes of available therapy (chemotherapy, anti-CD20 antibodies, BTK inhibitors, BCL2 inhibitors, PI3K-delta inhibitors)
94% of responding patients remain in response and on therapy
Phase 3 program in CLL/SLL to be initiated in 2021, including a superiority head-to-head trial comparing LOXO-305 vs. ibrutinib

INDIANAPOLIS, Dec. 7, 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 chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). 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 542).

"The data presented at ASH reveal an incredibly encouraging and consistent safety and efficacy profile for LOXO-305 in heavily pre-treated CLL and SLL patients, regardless of previous therapies, reasons for discontinuations of those therapies, or presence of resistance mutations", said Anthony Mato, M.D., director of the CLL Program at Memorial Sloan Kettering Cancer Center and the presenting author. "We are increasingly in need of new therapies for patients that have been previously treated with a covalent BTK inhibitor, and LOXO-305 may allow us to continue treating patients in the same biologic class before attempting more complicated therapeutic approaches."

"The LOXO-305 data continue to surpass our expectations, and we are very excited for what these data could mean for patients with CLL and SLL", said David Hyman, M.D., chief medical officer of Loxo Oncology at Lilly. "These emerging data further substantiate our thesis that the drug's reversible binding mode, high selectivity, and robust pharmacology offer a differentiated treatment option across B-cell leukemias and lymphomas. We are eager to initiate a Phase 3 program in 2021."

Key Data Presented at ASH

As of September 27, 2020, 323 patients were enrolled in the study, including 170 with CLL/SLL, 61 with mantle cell lymphoma (MCL), 26 with Waldenström's macroglobulinemia, and 66 with other B-cell lymphomas. The CLL/SLL patients had received a median of three prior lines of therapy with 86% receiving a prior BTK inhibitor, 90% an anti-CD20 antibody, 82% chemotherapy, 34% venetoclax, 21% a PI3K inhibitor, 6% CAR-T therapy and 2% an allogeneic transplant.

Pharmacokinetic analyses during the 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 139 efficacy-evaluable patients with CLL/SLL treated across all dose levels, 88 responded including 69 partial responses (PR), 19 partial responses with ongoing lymphocytosis (PR-L), 45 stable disease (SD), one progressive disease (PD), five discontinued prior to their first response assessment and were considered non-evaluable (NE), resulting in an overall response rate (ORR) of 63% (95% CI: 55-71). The ORR was consistent in various subsets of patients, including:

- In the 121 efficacy-evaluable BTK-pretreated patients, the ORR was 62% (95% CI: 53-71), rising to 84% (21/25) for those followed 10 months or more. This deepening of response over time is consistent with other BTK inhibitors and suggests the overall efficacy profile of LOXO-305 will continue to strengthen with additional follow-up.
- The ORR was similar in patients who previously discontinued a covalent BTK inhibitor for progression (67% [53/79]) versus toxicity or another reason (52% [22/42]).
- The ORR was also similar in those with a BTK C481 mutation (71% [17/24]) and those without (66% [43/65]).
- In patients who previously received prior chemoimmunotherapy, a covalent BTK inhibitor and a BCL-2 inhibitor the ORR was 69% (27/39).

- In patients who previously received all five classes of available CLL/SLL therapy including prior chemoimmunotherapy, a covalent BTK inhibitor, a BCL-2 inhibitor, and a PI3K inhibitor the ORR was 58% (7/12).
- In the 28 patients with a 17p deletion, TP53 mutation, or both, the ORR was 79% (22/28).

As of the data cut-off, 88% of all CLL/SLL patients remain on LOXO-305. Median follow-up for efficacy-evaluable CLL/SLL patients was six months. Of the 88 responding CLL/SLL patients, all except five remain on therapy (four progressed and one achieved a PR and electively discontinued to pursue a transplant). The longest-followed responding patient continues on treatment at 17.8 months.

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

In addition to the previously announced Phase 3 MCL trial, Loxo Oncology at Lilly is preparing to initiate two global, randomized, Phase 3 clinical trials in BTK pre-treated patients with CLL/SLL. The trials will explore LOXO-305, alone and in combination as follows:

- **BRUIN CLL-321**: CLL/SLL patients who progressed or were intolerant to covalent BTK inhibitor treatment will be randomized to receive continuous LOXO-305 therapy or investigator's choice of either Idelalisib plus Rituximab or Bendamustine plus Rituximab. This trial is expected to start in the first quarter of 2021.
- **BRUIN CLL-322**: CLL/SLL patients who progressed or were intolerant to covalent BTK inhibitor treatment will be randomized to receive a time-limited combination of either LOXO-305 plus venetoclax and Rituximab or venetoclax and Rituximab. This trial is expected to start in the second quarter of 2021.

In addition, Loxo Oncology at Lilly is planning to study LOXO-305 in treatment-naïve CLL/SLL, including a global, randomized Phase 3 superiority clinical trial to study LOXO-305 versus ibrutinib, expected to start later in 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

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

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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