Lilly Presents Interim Clinical Data from LOXO-305 Dose Escalation Trial in B-Cell Leukemias and Lymphomas at the American Society Hematology Annual Meeting

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Responses observed at all dose levels in Chronic Lymphocytic Leukemia (CLL) and Mantle Cell Lymphoma (MCL), including patients with BTK Resistance, BTK Intolerance, and BCL2 Resistance

INDIANAPOLIS, Dec. 8, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced interim clinical data from the LOXO-305 global Phase 1/2 BRUIN dose escalation trial. LOXO-305 is an investigational, highly selective, non-covalent Bruton's tyrosine kinase (BTK) inhibitor. These data were presented today at the 2019 American Society of Hematology (ASH) Annual Meeting in Orlando (abstract 501). At all doses studied, LOXO-305 delivered objective responses in patients who had received diverse prior therapies and had exhibited varied molecular mechanisms of acquired resistance.

"We are excited to report that LOXO-305 is active in patients resistant and intolerant to covalent BTK inhibitors, as well as in patients resistant to BCL2 inhibition," said Anthony Mato, M.D., director of the CLL Program at Memorial Sloan Kettering Cancer Center and the presenting author. "We observed compelling response rates in both CLL and MCL. Interestingly, we reported responses regardless of C481 status, a putative mechanism of resistance to the covalent BTK class. We saw objective responses in dose cohort 1 and have not identified a maximum tolerated dose. These data suggest that LOXO-305 has the required selectivity profile and human target coverage to maximize the full potential of this molecular target, combine well with other agents, and perhaps, even move to earlier lines of therapy."

"Put simply, LOXO-305 has exceeded our expectations," said Jacob Van Naarden, chief operating officer of Loxo Oncology at Lilly. "LOXO-305's wide therapeutic index allows us to plan and implement an ambitious comprehensive development program, one that includes combination regimens that exploit the drug's selectivity profile. We look forward to working closely with global regulators to position LOXO-305 in the most appropriate patient populations. It will be exciting to combine Lilly's resources and talent with Loxo's focus and agility for the benefit of this program within Loxo Oncology at Lilly."

Trial Background
The BRUIN Phase 1/2 trial, which began enrolling patients in March 2019, contains a dose escalation phase and a dose expansion phase. The dose escalation phase follows a "3+3" design. LOXO-305 is dosed orally in 28-day cycles. As dose cohorts are cleared, additional patients can enroll in cleared cohorts and intra-patient dose escalation is permitted. The primary endpoint of the trial is the determination of the maximum tolerated dose (MTD) or recommended dose for further study. Secondary endpoints include safety, overall response rate (by disease-specific criteria) and duration of response. The dose expansion phase is designed to further characterize the overall response rate, durability of response, and safety of LOXO-305 in predefined groups of patients with B-cell leukemias and lymphomas.

Key Data Presented at ASH
The data presented at ASH were based on patients treated as of September 27, 2019, with follow-up as of November 5, 2019. Twenty-eight total patients had been enrolled to five dose escalation cohorts: 25 mg QD (n=5), 50 mg QD (n=6), 100 mg QD (n=9), 150 mg QD (n=5), and 200 mg QD (n=3). There were 16 patients with CLL, eight patients with MCL, two patients with Waldenstrom macroglobulinemia, one patient with diffuse large B-cell lymphoma (DLBCL), and one patient with marginal zone lymphoma (MZL). The CLL patients had received a median of four prior systemic therapy regimens and 75% had received at least one prior BTK inhibitor. The MCL patients had received a median of three prior systemic therapy regimens and 88% had received at least one prior BTK inhibitor.

Pharmacokinetic analyses during the dose escalation phase demonstrated dose-dependent and linear increases in LOXO-305 exposure with increasing dose. Starting at the 50 mg QD dose, LOXO-305 delivered >IC90 target coverage for wild-type and C481S-mutated BTK, based on estimates from cell-based potencies.

The efficacy data presented at ASH are based on investigator response assessments. Responses were observed across all dose levels.

- Of 16 CLL patients enrolled, there were 10 responders (8 partial responses, 2 partial response with ongoing lymphocytosis) among 13 patients eligible for response assessment, resulting in a 77% ORR. All patients with CLL have demonstrated tumor reduction, with evidence of deepening response over time. Responses were observed in patients with acquired resistance to prior BTK therapy (those with and without C481S mutations), in patients who were intolerant to prior BTK therapy, and in patients with acquired resistance to prior BCL2 therapy (including one with a known BCL G101V mutation). As expected, LOXO-305 treatment causes acute lymphocytosis, which resolves over time—a well described pharmacodynamic response associated with effective BTK inhibition. Of the three CLL patients not yet eligible for response assessment (one with the BTK C481S mutation), all three have demonstrated lymphocytosis early in cycle 1. All CLL responding patients remain in response and all CLL patients remain on study.
- Of eight MCL patients enrolled, there were three responses (1 complete response, 2 partial responses) among six patients eligible for response assessment, resulting in a 50% ORR. Two of the responders had progressed on prior BTK therapy (but without a documented C481x mutation). All MCL responding patients remain in response and on study. Three MCL patients discontinued therapy in cycle 1 due to progressive disease.

Most treatment-emergent adverse events were Grade 1 in severity with the most commonly reported events, regardless of attribution, being fatigue

(25% total: 21% Grade 1, 4% Grade 2) and diarrhea (18% total: 14% Grade 1, 4% Grade 2). Two adverse events ≥Grade 3 were attributed to LOXO-305 (Grade 3 leukocytosis and Grade 3 transient neutropenia). No dose limiting toxicities were reported and an MTD had not been reached.

About LOXO-305
LOXO-305 is an investigational, 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, Waldenstrom macroglobulinemia, mantle cell lymphoma and marginal zone lymphoma. Currently available BTK inhibitors irreversibly inhibit BTK and the long-term efficacy of these therapies has been limited by acquired resistance, most commonly through BTK C481 mutations, and intolerance, due to off target inhibition of other cellular targets. LOXO-305 was designed to reversibly bind BTK, 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 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 primary objective of the Phase 1 portion of the trial is to determine the maximum tolerated dose or recommended Phase 2 dose. Key secondary objectives include measures of safety, pharmacokinetics, and anti-tumor activity (i.e. Overall Response Rate and Duration of Response, as determined by appropriate histology-specific response criteria). 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. In the Phase 2 dose expansion phase, six cohorts are planned to allow for the characterization of the preliminary anti-tumor activity of LOXO-305: 1) CLL/SLL failed prior BTK inhibitor with BTK C481 mutation; 2) CLL/SLL failed prior BTK inhibitor without BTK C481 mutation; 3) Waldenstrom macroglobulinemia (WM), mantle cell lymphoma (MCL) or marginal zone lymphoma (MZL) failed prior BTK inhibitor with BTK C481 mutation; 4) WM, MCL or MZL failed prior BTK inhibitor without BTK C481 mutation; 5) CLL/SLL, WM, MCL or MZL intolerant to prior BTK inhibitor; 6) CLL/SLL, WM, MCL or MZL failed prior BTK inhibitor with unknown BTK C481 mutation status and other CLL/SLL, WM, CML, MZL or other NHL patients not meeting the definitions of Cohorts 1 through 5.

About Lilly Oncology
For more than 50 years, Lilly has been dedicated to delivering life-changing medicines and support to people living with cancer and those who care for them. Lilly is determined to build on this heritage and continue making life better for all those affected by cancer around the world. To learn more about Lilly's commitment to people with cancer, please visit www.LillyOncology.com.

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

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 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 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.

Refer to:Lauren Cohen; lcohen@loxooncology.com; (617) 678-2067 – media
Dan Budwick; dan@1abmedia.com; (973) 271-6085 – media
Kevin Hern; hern_kevin_r@lilly.com; (317) 277-1838 – investors

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