Lilly Announces Positive Registrational Data for Selpercatinib (LOXO-292) in Heavily Pretreated RET-Altered Thyroid Cancers

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- LIBRETTO-001 is the largest trial ever reported in RET-altered cancer patients

- 56 percent objective response rate (ORR) in the registration dataset (n=55) of RET-mutant medullary thyroid cancer (MTC) patients who had previously received cabozantinib and/or vandetanib

- 59 percent ORR in cabozantinib/vandetanib-naïve RET-mutant MTC patients

- 62 percent ORR in heavily pretreated RET fusion-positive thyroid cancer patients

- Sustained durability, measured by both Duration of Response and Progression-Free Survival

- Well-tolerated safety profile; low rate of discontinuation (1.7%) for treatment-related adverse events

- New Drug Application to be submitted by year-end

INDIANAPOLIS, Sept. 29, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today presented data from the LIBRETTO-001 clinical trial intended to support the registration of oral selpercatinib[1] monotherapy, also known as LOXO-292, for the treatment of *RET*-altered thyroid cancers. *RET*-altered thyroid cancers are comprised of two different populations, *RET*-mutant medullary thyroid cancer (MTC) and *RET* fusion-positive thyroid cancers. In the *RET*-mutant MTC registration dataset consisting of the first 55 enrolled patients with prior cabozantinib and/or vandetanib[2], selpercatinib treatment resulted in a 56 percent objective response rate (ORR) (95% CI: 42-70%). This population was heavily pretreated (53 percent previously treated with ≥2 prior multikinase inhibitors), and ORR was similar regardless of prior multikinase inhibitor therapy. As of the data cut-off date of June 17, 2019, median duration of response (DOR) was not reached (95% CI: 11.1-NE) and median progression-free survival (PFS) was not reached (95% CI: 11.3-NE). Selpercatinib therapy also resulted in robust biochemical response rates (BRR) for serum tumor markers calcitonin (91% BRR) and carcinoembryonic antigen (64% BRR). In a safety analysis of all 531 patients enrolled to LIBRETTO-001, selpercatinib was well-tolerated, with only nine patients (1.7%) discontinuing therapy due to treatment-related adverse events. The most commonly observed adverse events, regardless of attribution, were dry mouth, diarrhea, hypertension, increased liver enzymes, fatigue, constipation, and headache. These results were presented today at the European Society for Medical Oncology (ESMO) Congress 2019 in Barcelona, Spain, in session LBA93, Registrational Results of LOXO-292 in Patients with RET-Altered Thyroid Cancers, presented by Lori J. Wirth, M.D., medical director of head and neck cancers, Massachusetts General Hospital Cancer Center in Boston, Mass. Selpercatinib has received breakthrough therapy designation from the U.S. Food and Drug Administration (FDA).

"Current therapeutic options are often challenging for patients with first-line *RET*-altered thyroid cancers and are limited for patients who relapse. The data for selpercatinib show demonstrative efficacy and safety in both the first-line and relapsed settings. Patients with thyroid cancer have long sought targeted therapy tailored to the molecular nature of their disease, and we are hopeful that selpercatinib may be used as the standard of care in the future," said Wirth, who is lead investigator on the trial.

Selpercatinib Data in Cabozantinib/Vandetanib-Naïve *RET*-Mutant MTC patients
Investigators also presented the results of selpercatinib in *RET*-mutant MTC patients who have received neither cabozantinib nor vandetanib. In this analysis of 76 patients, selpercatinib treatment resulted in a 59 percent ORR (95% CI: 47-70%). Median DOR and PFS were not reached in this treatment-naïve population, as the vast majority of patients remain in response or progression-free.

Selpercatinib Data in Heavily Pretreated *RET* Fusion-Positive Thyroid Cancer Patients
Investigators also presented the results of selpercatinib in heavily pretreated *RET* fusion-positive thyroid cancer patients. In this analysis of 26 patients, selpercatinib treatment resulted in a 62 percent ORR (95% CI: 41-80%). Median DOR and PFS were not reached in this population, as the vast majority of patients remain in response or progression-free.

"We're pleased that selpercatinib may offer a meaningful advance for patients with *RET*-altered thyroid cancers," said Anne White, president of Lilly Oncology. "These patients have been a focus of the selpercatinib program from its beginning, as *RET* has been a known oncogene in these diseases for decades. With these data, selpercatinib has delivered on our vision, with unprecedented clinical outcomes in both first-line and relapsed patients, particularly in light of the difficult options for these patients."

Trial Background
The LIBRETTO-001 Phase 1/2 trial is the largest clinical trial of patients with *RET*-altered cancers treated with a RET inhibitor. The trial includes a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2). The Phase 2 portion of the trial had a primary endpoint of objective response rate (ORR) and secondary endpoints of DOR, PFS and safety. The primary analysis set for MTC regulatory submissions, as defined with the FDA, consists of the first 55 enrolled patients with *RET*-mutant medullary thyroid cancer who have experienced prior cabozantinib and/or vandetanib. All data presented at ESMO were as of a data cut-off date of June 17, 2019, and all efficacy measures utilized investigator assessments.

About Selpercatinib (LOXO-292)
Selpercatinib, also known as LOXO-292, is a highly selective and potent, oral investigational new medicine in clinical development for the treatment of patients with cancers that harbor abnormalities in the rearranged during transfection (RET) kinase. *RET* fusions and mutations occur across multiple tumor types with varying frequency. Selpercatinib was designed to inhibit native RET signaling as well as anticipated acquired resistance mechanisms.

Selpercatinib has received breakthrough designation for the treatment of patients with:

- Metastatic *RET*-fusion-positive non-small cell lung cancer who require systemic therapy and have progressed following platinum-based chemotherapy and an anti-PD-1 or anti-PD-L1 therapy;
- *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options; and for
- Advanced *RET*-fusion-positive thyroid cancer who require systemic therapy, have progressed following prior treatment and have no acceptable alternative treatment options.

About *RET*-Altered Cancers
Genomic alterations in RET kinase, which include fusions and activating point mutations, lead to overactive RET signaling and uncontrolled cell growth. *RET* fusions have been identified in approximately 2 percent of non-small cell lung cancer, 10-20 percent of papillary and other thyroid cancers and a subset of other cancers. Activating *RET* point mutations account for approximately 60 percent of MTC. *RET* fusion cancers and *RET*-mutant MTC are primarily dependent on this single activated kinase for their proliferation and survival. This dependency, often referred to as "oncogene addiction," renders such tumors highly susceptible to small molecule inhibitors targeting RET.

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 oral selpercatinib monotherapy (LOXO-292) for the potential treatment of *RET*-altered thyroid cancers 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 selpercatinib 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.

[1] PINN, pending USAN approval

[2] The multikinase inhibitors, cabozantinib and vandetanib, are both FDA-approved for the treatment of progressive and metastatic medullary thyroid cancer regardless of *RET* mutation status.

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