Lilly Presents Updated Data on Retevmo® (selpercatinib) in Advanced RET Fusion-Positive Non-Small-Cell Lung Cancer (NSCLC) at the 2022 European Lung Cancer Congress

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INDIANAPOLIS, April 1, 2022 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced updated data from the Phase 1/2 LIBRETTO-001 trial of Retevmo® (selpercatinib 40 mg & 80 mg capsules) in patients with *RET* fusion-positive non-small cell lung cancer (NSCLC). Retevmo (marketed as Retsevmo® outside of the U.S.) is a selective and potent RET kinase inhibitor that is approved in multiple countries including the United States for treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive NSCLC, and the treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy, or advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). These data were presented at the European Lung Cancer (ELCC) 2022 (poster 27p).

"The LIBRETTO trial provides the largest set of clinical data for a RET inhibitor and these results continue to demonstrate evidence of meaningful clinical outcomes for patients with metastatic RET fusion-positive NSCLC treated with Retevmo, including those with difficult-to-treat brain metastases," said David Hyman, M.D. chief medical officer, oncology at Lilly. "We are continuing to build on the robust body of evidence supporting Retevmo, including through an ongoing randomized Phase 3 confirmatory study, with a planned readout in 2023."

The updated analysis utilized a June 15, 2021, data cut-off and included 355 patients who were eligible for efficacy analysis, 247 of which were previously treated with at least one line of platinum chemotherapy and 69 of which were treatment-naïve. Patients who were previously treated with at least one line of platinum chemotherapy received a median of two prior treatment regimens (range: 1-15), with 58% having received anti-PD-1 or anti-PD-L1 therapy. Responses are based on independent review committee (IRC) assessment.

Among 247 patients previously treated with platinum chemotherapy, the confirmed objective response rate (ORR) was 61.1% (95% CI: 54.7-67.2%) and among 69 treatment-naïve patients, the confirmed ORR was 84.1% (95% CI: 73.3-91.8%). Twenty-six patients had measurable central nervous system (CNS) metastases at baseline and treatment with Retevmo resulted in a CNS ORR of 84.6%, with 22 patients having a confirmed best response of complete response or partial response.

At a median follow-up of approximately two years in both the treatment-naïve and platinum-chemotherapy pretreated populations, median duration of response (DoR) is estimated at 20.2 (55.2% censoring rate; 20.3 months median duration of follow-up) and 28.6 (60.9% censoring rate; 21.2 months median duration of follow-up) months, respectively and median progression free survival (PFS) is estimated at 22.0 (53.6% censoring rate; 21.9 months median duration of follow-up) and 24.9 (55.9% censoring rate; 24.7 months median duration of follow-up) months, respectively. Of the 26 patients with measurable CNS disease, Retevmo treatment resulted in a median intracranial PFS of 19.4 months. These median estimates remain immature.

Safety among patients in this cohort was consistent with the known safety profile of Retevmo. In the safety population (all NSCLC patients that received at least one dose of Retevmo, N=356), the most common adverse events (AEs in ≥25% of patients) were dry mouth, diarrhea, hypertension, increased ALT/AST, peripheral edema, constipation, rash, headache, and fatigue. Thirty-four patients discontinued due to an adverse event (10%), eleven (3%) of which were deemed related to Retevmo.

A global, randomized, Phase 3 trial is currently recruiting and will compare treatment with Retevmo to the current standard of care in the first-line treatment of advanced or metastatic RET fusion-positive NSCLC.

Retevmo was the first RET inhibitor to receive Accelerated Approval from the U.S. Food and Drug Administration (FDA) in May 2020 and was the first approved by the European Commission in February 2021. Retevmo was approved under the FDA's Accelerated Approval regulations based on the LIBRETTO-001 Phase 1/2 trial's endpoints of objective response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

About LIBRETTO-001

The Phase 1/2 LIBRETTO-001 trial is the largest clinical trial of patients with *RET*-driven cancers treated with a RET inhibitor. The trial, which spans 16 countries and 89 sites, included a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2). The primary objective was to determine ORR by independent review committee (IRC) and key secondary objectives included DoR, CNS ORR & DOR, safety and PFS.

LIBRETTO-001 continues to enroll patients with *RET*-altered tumors beyond lung cancer.

About Retevmo® (selpercatinib)

Retevmo (selpercatinib, formerly known as LOXO-292) (pronounced ret- tév-mo) is a selective and potent RET kinase inhibitor. Retevmo may affect both tumor cells and healthy cells, which can result in side effects. *RET*-driver alterations are predominantly mutually exclusive from other oncogenic drivers. Retevmo is an U.S. FDA-approved oral prescription medicine, 120 mg or 160 mg dependent on weight (<50 kg or ≥50 kg, respectively), taken twice daily until disease progression or unacceptable toxicity. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION FOR RETEVMO® (selpercatinib)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased alanine aminotransferase (ALT) occurred in 45% of patients, including Grade 3 or 4 events in 9%. The median time to first onset for increased AST was 4.1 weeks (range: 5 days to 2 years) and increased ALT was 4.1 weeks (range: 6 days to 1.5 years). Monitor ALT and AST prior to initiating Retevmo, every 2 weeks during the first 3 months, then monthly thereafter and as clinically indicated. Withhold, reduce dose or permanently discontinue Retevmo based on the severity.

Hypertension occurred in 35% of patients, including Grade 3 hypertension in 17% and Grade 4 in one (0.1%) patient. Overall, 4.6% had their dose interrupted and 1.3% had their dose reduced for hypertension. Treatment-emergent hypertension was most commonly managed with anti-hypertension medications. Do not initiate Retevmo in patients with uncontrolled hypertension. Optimize blood pressure prior to initiating Retevmo. Monitor blood pressure after 1 week, at least monthly thereafter, and as clinically indicated. Initiate or adjust anti-hypertensive therapy as appropriate. Withhold, reduce dose, or permanently discontinue Retevmo based on the severity.

Retevmo can cause concentration-dependent **QT interval prolongation**. An increase in QTcF interval to >500 ms was measured in 6% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 15% of patients. Retevmo has not been studied in patients with clinically significant active cardiovascular disease or recent myocardial infarction. Monitor patients who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, and severe or uncontrolled heart failure. Assess QT interval, electrolytes and TSH at baseline and periodically during treatment, adjusting frequency based upon risk factors including diarrhea. Correct hypokalemia, hypomagnesemia and hypocalcemia prior to initiating Retevmo and during treatment. Monitor the QT interval more frequently when Retevmo is concomitantly administered with strong and moderate CYP3A inhibitors or drugs known to prolong QTc interval. Withhold and dose reduce or permanently discontinue Retevmo based on the severity.

Serious, including fatal, **hemorrhagic events** can occur with Retevmo. Grade ≥3 hemorrhagic events occurred in 2.3% of patients treated with Retevmo including 3 (0.4%) patients with fatal hemorrhagic events, including one case each of cerebral hemorrhage, tracheostomy site hemorrhage, and hemoptysis. Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 4.3% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.6%. The median time to onset was 1.7 weeks (range 6 days to 1.5 years). Signs and symptoms of hypersensitivity included fever, rash and arthralgias or myalgias with concurrent decreased platelets or transaminitis. If hypersensitivity occurs, withhold Retevmo and begin corticosteroids at a dose of 1 mg/kg prednisone (or equivalent). Upon resolution of the event, resume Retevmo at a reduced dose and increase the dose of Retevmo by 1 dose level each week as tolerated until reaching the dose taken prior to onset of hypersensitivity. Continue steroids until patient reaches target dose and then taper. Permanently discontinue Retevmo for recurrent hypersensitivity.

Tumor lysis syndrome (TLS) occurred in 1% of patients with medullary thyroid carcinoma receiving Retevmo. Patients may be at risk of TLS if they have rapidly growing tumors, a high tumor burden, renal dysfunction, or dehydration. Closely monitor patients at risk, consider appropriate prophylaxis including hydration, and treat as clinically indicated.

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway. Therefore, Retevmo has the potential to adversely affect wound healing. Withhold Retevmo for at least 7 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of Retevmo after resolution of wound healing complications has not been established.

Based on data from animal reproduction studies and its mechanism of action, Retevmo can cause **fetal harm** when administered to a pregnant woman. Administration of selpercatinib to pregnant rats during organogenesis at maternal exposures that were approximately equal to those observed at the recommended human dose of 160 mg twice daily resulted in embryolethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with Retevmo and for at least 1 week after the final dose. There are no data on the presence of selpercatinib or its metabolites in human milk or on their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with Retevmo and for 1 week after the final dose.

Severe adverse reactions (Grade 3-4) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were hypertension (18%), prolonged QT interval (4%), diarrhea (3.4%), dyspnea (2.3%), fatigue (2%), abdominal pain (1.9%), hemorrhage (1.9%), headache (1.4%), rash (0.7%), constipation (0.6%), nausea (0.6%), vomiting (0.3%), and edema (0.3%).

Serious adverse reactions occurred in 33% of patients who received Retevmo. The most frequently reported serious adverse reaction (in ≥ 2% of patients) was pneumonia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions which occurred in >1 patient included sepsis (n=3), cardiac arrest (n=3) and respiratory failure (n=3).

Common adverse reactions (all grades) occurring in ≥15% of patients who received Retevmo in LIBRETTO-001, were dry mouth (39%), diarrhea (37%), hypertension (35%), fatigue (35%), edema (35%), rash (27%), constipation (25%), nausea (23%), abdominal pain (23%), headache (23%), cough (18%), prolonged QT interval (17%), dyspnea (16%), vomiting (15%), and hemorrhage (15%).

Laboratory abnormalities (all grades; Grade 3-4) ≥20% worsening from baseline in patients who received Retevmo in LIBRETTO-001, were AST increased (51%; 8%), ALT increased (45%; 9%), increased glucose (44%; 2.2%), decreased leukocytes (43%; 1.6%), decreased albumin (42%; 0.7%), decreased calcium (41%; 3.8%), increased creatinine (37%; 1.0%), increased alkaline phosphatase (36%; 2.3%), decreased platelets (33%; 2.7%), increased total cholesterol (31%; 0.1%), decreased sodium (27%; 7%), decreased magnesium (24%; 0.6%), increased potassium (24%; 1.2%), increased bilirubin (23%; 2.0%), and decreased glucose (22%; 0.7%).

Concomitant use of **acid-reducing agents** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid concomitant use of proton-pump inhibitors (PPIs), histamine-2 (H2) receptor antagonists, and locally-acting antacids with Retevmo. If coadministration cannot be avoided, take Retevmo with food (with a PPI) or modify its administration time (with a H2 receptor antagonist or a locally-acting antacid).

Concomitant use of **strong and moderate CYP3A inhibitors** increases selpercatinib plasma concentrations which may increase the risk of Retevmo adverse reactions including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with Retevmo. If concomitant

use of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the Retevmo dosage as recommended and monitor the QT interval with ECGs more frequently.

Concomitant use of **strong and moderate CYP3A inducers** decreases selpercatinib plasma concentrations which may reduce Retevmo anti-tumor activity. Avoid coadministration of Retevmo with strong and moderate CYP3A inducers.

Concomitant use of Retevmo with **CYP2C8 and CYP3A substrates** increases their plasma concentrations which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

The safety and effectiveness of Retevmo have not been established in **pediatric patients less than 12 years of age**. The safety and effectiveness of Retevmo have been established in pediatric patients aged 12 years and older for medullary thyroid cancer (MTC) who require systemic therapy and for advanced *RET* fusion-positive thyroid cancer who require systemic therapy and are radioactive iodine-refractory (if radioactive iodine is appropriate). Use of Retevmo for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. Monitor open growth plates in **adolescent patients**. Consider interrupting or discontinuing Retevmo if abnormalities occur.

No dosage modification is recommended for patients with **mild to severe renal impairment** (estimated Glomerular Filtration Rate [eGFR] ≥15 to 89 mL/min, estimated by Modification of Diet in Renal Disease [MDRD] equation). A recommended dosage has not been established for patients with end-stage renal disease.

Reduce the dose when administering Retevmo to patients with **severe hepatic impairment** (total bilirubin greater than 3 to 10 times upper limit of normal [ULN] and any AST). No dosage modification is recommended for patients with mild or moderate hepatic impairment. Monitor for Retevmo-related adverse reactions in patients with hepatic impairment.

Please see full Prescribing Information for Retevmo.

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About Lilly

Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 47 million people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges, redefining diabetes care, treating obesity and curtailing its most devastating long-term effects, advancing the fight against Alzheimer's disease, providing solutions to some of the most debilitating immune system disorders, and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/newsroom or follow us on Facebook, Instagram, Twitter and LinkedIn. P-LLY

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Lilly Cautionary Statement Regarding Forward-Looking Statements

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Retevmo® (selpercatinib) for the treatment of metastatic *RET* fusion-positive NSCLC, advanced or metastatic *RET* mutation-positive MTC, and advanced or metastatic *RET* fusion-positive thyroid cancer, and as a potential treatment for other indications, and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there is no guarantee that future study results will be consistent with study findings to date or that Retevmo will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties, see Lilly's 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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