# Lilly Presents New Data on Retevmo® (selpercatinib) in Advanced RET Fusion-Positive Gastrointestinal and Other Cancers at 2021 American Association for Cancer Research (AACR) Annual Meeting

April 11, 2021

**Confirmed Objective Response Rate of 47 Percent, with Responses Observed in Nine Unique Cancer Types**
**Median Duration of Response Not Reached at 13 Months Median Follow-Up, with 11 of 15 Responses Ongoing**
**Safety Consistent with Known Profile of Retevmo**
**New Data Expands on Retevmo's Established Data in Lung and Thyroid Cancers**

INDIANAPOLIS, April 11, 2021 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced for the first time data from the Phase 1/2 LIBRETTO-001 trial showing treatment with Retevmo® (selpercatinib) demonstrated encouraging antitumor activity and safety across *RET* fusion-positive advanced solid tumors beyond lung and thyroid cancers, including multiple treatment-refractory gastrointestinal (GI) malignancies. The data were presented at the 2021 American Association for Cancer Research (AACR) Annual Meeting, held virtually April 10-15, 2021.

"We are excited to broaden the body of evidence for Retevmo in *RET* fusion-positive cancers beyond lung and thyroid tumors," said David Hyman, M.D., chief medical officer, oncology at Lilly. "These encouraging outcomes, including in difficult-to-treat GI malignancies, support a growing body of evidence that *RET* fusions are potentially actionable in a wide range of tumor types. These findings further demonstrate the importance of broad tumor profiling in advanced cancers. We look forward to discussing these new data with regulatory authorities this year."

In the Phase 1/2 LIBRETTO-001 trial, 32 adult patients with 12 unique *RET* fusion-positive advanced cancer types were enrolled by the efficacy cutoff date of September 19, 2020 (with follow-up through March 19, 2021). Cancer types treated included pancreatic, colon, breast, salivary, sarcoma, carcinoid, rectal neuroendocrine, small intestine, xanthogranuloma, ovarian, pulmonary carcinosarcoma, and unknown primary cancers. Among the 32 patients, 62.5 percent had gastrointestinal tumors (defined as pancreatic [n=9], colon [n=9], small intestine [n=1], and rectal neuroendocrine [n=1]). Across all 32 patients, the confirmed objective response rate (ORR) was 47 percent (95% CI: 26-65%). Confirmed responses were observed in nine unique *RET* fusion-positive advanced cancer types. The median duration of response (DoR) was not reached, with median follow-up of 13 months. Responses were ongoing in 73 percent (11/15) of responding patients.

| **Retevmo Efficacy** | |
|---|---|
| **Objective Response Rate* % (95% CI)** | **47% (29-65), n=32** |
| Median Duration of Response (range) | Not Reached (2 -33+ months) |
| Responses Ongoing | 73% (11/15) |
| Median Duration of Follow up | 13 months |

** per investigator assessment, + indicates patient ongoing*

Safety among patients in this cohort was consistent with the known safety profile of Retevmo. In this cohort, the most common treatment-emergent adverse events of any grade (≥20%) were increased aspartate aminotransferase (AST)/increased alanine aminotransferase (ALT), dry mouth, hypertension, diarrhea, fatigue, nausea, and abdominal pain. No patients in this cohort discontinued treatment due to treatment-related adverse events.

"While uncommon, *RET* fusions occur in a 'long tail' of solid tumors beyond lung and thyroid cancers, and these patients do not yet have an approved targeted therapy option to address the underlying genomic driver of their cancer," said Vivek Subbiah, MD, associate professor in the Investigational Cancer Therapeutics Department and center clinical medical director of the Clinical Center for Targeted Therapy, of the Cancer Medicine Division, at The University of Texas MD Anderson Cancer Center. "These results demonstrate selpercatinib's potential for this patient population and reiterate the importance of broad-based genomic profiling to identify actionable oncogenic drivers, including *RET* fusions."

In May 2020, Lilly's first-in-class selective RET inhibitor Retevmo received Accelerated Approval from the U.S. Food and Drug Administration (FDA) for the treatment of adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC), in adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy, and in adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). Retevmo was approved based on the Phase 1/2 LIBRETTO-001 trial's endpoints of ORR and DoR. Retevmo (marketed as Retsevmo® outside the U.S.) was approved by the European Commission in February 2021.

**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 Phase 2 portion of the trial had major efficacy outcomes of ORR and DoR, and prespecified secondary endpoints of central nervous system (CNS) ORR and CNS DoR, as determined by an independent review committee according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

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

**About Retevmo® (selpercatinib)**

Retevmo (selpercatinib, formerly known as LOXO-292) (pronounced reh-TEHV-moh) 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.[i] 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 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 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 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.

[i] RETEVMO [package insert]. Indianapolis, IN: Eli Lilly and Company; 2021.

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