Lilly Receives U.S. FDA Approval for Retevmo™ (selpercatinib), the First Therapy Specifically for Patients with Advanced RET-Driven Lung and Thyroid Cancers

May 9, 2020

- Approved for metastatic RET fusion-positive NSCLC, advanced or metastatic RET-mutant MTC and advanced or metastatic RET fusion-positive thyroid cancer

- Accelerated approval based on data from LIBRETTO-001 Phase 1/2, largest trial ever reported in patients with RET-driven cancers

- Registrational data demonstrated durable objective responses and showed high intracranial response rate in patients with NSCLC that has spread to the brain

INDIANAPOLIS, May 8, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the U.S. Food and Drug Administration (FDA) approved Retevmo™ (selpercatinib, 40 mg & 80 mg capsules), the first therapy specifically indicated for the treatment of adult patients with metastatic rearranged during transfection (*RET*) fusion-positive non-small cell lung cancer (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). 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 (ORR) and duration of response (DoR). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

Retevmo is a selective RET kinase inhibitor. Retevmo may affect both tumor cells and healthy cells, which can result in side effects. Retevmo is an oral prescription medicine, 120 mg or 160 mg based on weight, taken twice daily until disease progression or unacceptable toxicity.[1]

"In the clinical trial, we observed that the majority of metastatic lung cancer patients experienced clinically meaningful responses when treated with selpercatinib, including responses in difficult-to-treat brain metastases," said Alexander Drilon, M.D., acting chief of early drug development at Memorial Sloan Kettering Cancer Center and lead investigator for LIBRETTO-001. "The approval of selpercatinib marks an important milestone in the treatment of NSCLC, making *RET*-driven cancers now specifically targetable in the same manner as cancers with activating EGFR and ALK alterations, across all lines of therapy. I am pleased that patients with these *RET*-driven cancers have this newly approved option."

Retevmo was evaluated in the single-arm, multi-center Phase 1/2 LIBRETTO-001 trial, the largest trial (N=702) of patients with *RET*-driven cancers. The trial enrolled both treatment-naive patients and heavily pretreated patients with a variety of advanced solid tumors including *RET* fusion-positive NSCLC, *RET*-mutant MTC, *RET* fusion-positive thyroid cancer, and certain other solid tumors with *RET* alterations. Major efficacy outcomes were ORR and DoR, assessed by a blinded independent review committee. Prespecified secondary endpoints included central nervous system (CNS) ORR and CNS DoR.

	RET Fusion-Positive NSCLC		*RET*-Mutant MTC		*RET* Fusion-Positive Thyroid Cancers	
	Systemic Treatment Naïve	Treatment Experienced	Cabozantinib /Vandetanib Naïve	Cabozantinib /Vandetanib Experienced	Systemic Treatment Naïve	Treatment Experienced
No. of patients	39	105	88	55	8	19
ORR (95% CI)	85 (70, 94)	64 (54, 73)	73 (62, 82)	69 (55, 81)	100 (63, 100)	79 (54, 94)
Median DoR, months (95% CI)	NR (12, NR)	17.5 (12, NR)	22 (NR, NR)	NR (19.1, NR)	NR (NR, NR)	18.4 (7.6, NR)

NR=Not Reached
Thyroid cancers include: papillary, Hurthle cell, anaplastic, and poorly differentiated

Up to 50 percent of patients with *RET* fusion-positive NSCLCs can have tumors that metastasize to the brain.[2] Among previously treated NSCLC patients with measurable brain metastases, 10 out of 11 patients observed intracranial responses (CNS ORR), with all 10 patients experiencing a CNS DoR of greater than or equal to six months.

The labeling for Retevmo contains warnings and precautions for hepatotoxicity (evidence of liver dysfunction), hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, risk of impaired wound healing, and embryo-fetal toxicity.

In the LIBRETTO-001 trial, there was a five percent discontinuation rate due to adverse reactions (ARs). The most common ARs, including laboratory abnormalities, (≥25 percent) were increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased glucose, decreased leukocytes, decreased albumin, decreased calcium, dry mouth, diarrhea, increased creatinine, increased alkaline phosphatase, hypertension, fatigue, edema (swelling in the arms or legs), decreased platelets, increased total cholesterol, rash, decreased sodium, and constipation. In addition, the most frequent serious AR (≥ 2 percent) was pneumonia.

See Important Safety Information below and full Prescribing Information for additional information, including dosing modifications.

"*RET* alterations account for the majority of medullary thyroid cancers and a meaningful percentage of other thyroid cancers. For patients living with

these cancers, the approval of selpercatinib means they now have a treatment option that selectively and potently inhibits *RET*," said Lori J. Wirth, M.D., medical director of head and neck cancers, Massachusetts General Hospital Cancer Center. "Based on the published data for this new medicine, as well as my personal experience treating patients, this may be a good treatment option."

"We are extremely proud of how quickly the combined Loxo Oncology and Lilly Oncology teams brought Retevmo to patients, further demonstrating our commitment to delivering life-changing medicines to people living with cancer," said Anne White, president of Lilly Oncology. "Retevmo entered clinical trials in May of 2017 and is now approved less than three years later, representing the most rapid timeline in the development of an oncology medicine with multiple indications. We applaud the FDA for their leadership and collaboration, recognizing the importance of bringing a new therapy to patients with advanced or metastatic *RET*-driven lung and thyroid cancers."

Retevmo should only be used in advanced or metastatic patients whose tumors have a *RET* fusion in NSCLC or thyroid cancer or a *RET* mutation in MTC. This can be determined through biomarker testing. Next-generation sequencing (NGS), either with tumor tissue biopsy or liquid biopsy, can be an appropriate biomarker test to determine actionable genomic alterations, including *RET*. If NGS is not available, *RET* can be detected using other biomarker testing methods. An FDA-approved test for the detection of *RET* fusions and *RET* mutations is not currently available. In LIBRETTO-001, identification of a *RET* gene alteration was prospectively determined in plasma or tumor tissue by local laboratories using NGS, PCR, or FISH. Immunohistochemistry was not used in the clinical trial.

"Increasingly, through the use of comprehensive biomarker testing, patients with metastatic cancer have an opportunity to receive a treatment tailored to the specific genomic nature of their tumor," said Andrea Ferris, president and chief executive officer at LUNGevity. "Retevmo represents an important new advance in this growing field, as the first therapy approved specifically for patients with *RET*-driven tumors. We urge patients to ask their doctors about broad biomarker tests that include *RET* alterations."

Retevmo was granted orphan drug designation by the FDA for the treatment of *RET* fusion-positive NSCLC and for the treatment of *RET* fusion-positive and *RET*-mutant thyroid cancers including poorly differentiated thyroid cancer, undifferentiated or anaplastic thyroid cancer, MTC and locally advanced or metastatic follicular or papillary thyroid cancer. The two confirmatory Phase 3 trials (LIBRETTO-431 and LIBRETTO-531) are currently enrolling patients.

Retevmo is expected to be available from specialty pharmacies within one week.

Click here to view the metastatic *RET* fusion-positive NSCLC fact sheet.

Click here to view the advanced *RET*-driven thyroid cancers fact sheet.

Click here to view the broad panel biomarker testing fact sheet.

Click here to view the Retevmo product fact sheet.

Click here to view the Retevmo product photo.

Click here to view the Retevmo logo.

Visit retevmo.com for more information.

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. Retevmo is an oral prescription medicine, 120 mg or 160 mg dependent on weight (-/+ 50 kg), taken twice daily until disease progression or unacceptable toxicity.[3]

About *RET*-Driven Cancers
Genomic alterations in the *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 NSCLC; and 10-20 percent of papillary, Hurthle cell, anaplastic, and poorly differentiated thyroid cancers. Activating *RET* point mutations account for approximately 60 percent of sporadic MTC and approximately 90 percent of germline MTC. *RET* fusion-positive 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*. *RET*-driver alterations are predominantly mutually exclusive from other oncogenic drivers.

About LIBRETTO-001
The LIBRETTO-001 Phase 1/2 trial was the largest clinical trial of patients with *RET*-driven cancers treated with a *RET* inhibitor. The trial 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 CNS ORR and CNS DoR, as determined by an independent review committee according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Results from the NSCLC population were last presented at the 2019 IASLC World Congress on Lung Cancer (WCLC), while results from the thyroid populations were last presented at the European Society for Medical Oncology (ESMO) 2019 Congress.

Important Safety Information for Retevmo™ (selpercatinib)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 2.6% of patients treated with Retevmo. Increased AST occurred in 51% of patients, including Grade 3 or 4 events in 8% and increased 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. 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.

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%).

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 (33%), 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** decrease 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** increase 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** decrease 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** increase 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.

No dosage modification is recommended for patients with **mild to moderate renal impairment** (creatinine clearance [CLcr] ≥30 mL/Min, estimated by Cockcroft-Gault). A recommended dosage has not been established for patients with severe renal impairment or 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 and Patient Prescribing Information for Retevmo.

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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 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 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 Retevmo will be commercially successful or receive additional regulatory approvals. 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] Retevmo [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.
[2] Drilon A, Lin JJ, Filleron T, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET-rearranged lung cancers. *J Thorac Oncol.* 2018;13(10):1595-1601.
[3] RETEVMO [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.

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