New England Journal of Medicine Publishes Phase 1/2 Data for Retevmo™ (selpercatinib) in Advanced RET-Driven Lung and Thyroid Cancers

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- Data demonstrated durable objective responses across both the RET fusion-positive NSCLC and RET-altered thyroid cancer patient cohorts

INDIANAPOLIS, Aug. 27, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the *New England Journal of Medicine* (*NEJM*) published Phase 1/2 study results of the registrational trial for Retevmo™ (selpercatinib), the first and only 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 overall 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. *NEJM* published separate articles focusing on efficacy and safety data in the *RET* fusion-positive NSCLC and *RET*-altered thyroid patient cohorts independently, with data demonstrating durable objective responses across both patient populations.

"After bringing the first FDA-approved RET inhibitor to patients earlier this year, we are pleased to follow up with detailed safety and efficacy findings from the largest clinical trial in patients with *RET*-driven cancers," said Anne White, president of Lilly Oncology. "The meaningful outcomes observed reinforce the value of this precision medicine in treating *RET*-driven NSCLC and thyroid cancer and underscore Lilly's commitment to helping patients with cancer live healthier lives."

The U.S. Food and Drug Administration (FDA) approval of Retevmo in May 2020 was based on results from LIBRETTO-001. The study 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 advanced solid tumors with *RET* alterations. The major efficacy outcomes in LIBRETTO-001 were ORR and DoR.

RET Fusion-Positive NSCLC

The publication highlights the first 105 consecutively enrolled *RET* fusion-positive metastatic NSCLC patients treated with at least prior platinum-based chemotherapy as well as 39 systemic treatment naïve patients. All analyses are presented on an intent-to-treat basis.

	RET Fusion-Positive NSCLC	
	Systemic Treatment Naïve	Prior Platinum-Based Chemotherapy
No. of patients	39	105
ORR (95% CI)[1]	85 (70, 94)	64 (54, 73)
Median DoR, months (95% CI)	NR (12, NR)	17.5 (12, NR)

NR = Not Reached

"Patients living with *RET* fusion-driven NSCLC represent an underserved population in need of tailored therapies that work against this targetable alteration," said Alexander Drilon, M.D.[2], chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center and lead investigator for LIBRETTO-001. "The clinically meaningful responses observed in this study demonstrate that selpercatinib can help fill this need, offering a valuable treatment option to these patients."

Up to 50 percent of patients with *RET* fusion-positive NSCLCs can have tumors that metastasize to the brain.[3] Among previously treated NSCLC patients with measurable brain metastases, 10 out of 11 patients observed intracranial responses (CNS ORR), with all patients experiencing a CNS DoR of greater than or equal to six months.

"Given that patients living with *RET* fusion-positive NSCLC face a high lifetime risk of disease progression to the brain, intracranial effectiveness is a significant consideration in the treatment journey," added Vivek Subbiah, M.D., associate professor of Investigational Cancer Therapeutics and medical director of the Clinical Center for Targeted Therapy at The University of Texas MD Anderson Cancer Center and co-investigator for LIBRETTO-001. "The fact that selpercatinib demonstrated durable intracranial responses in 10 out of 11 patients suggests this is a meaningful therapeutic option for patients with difficult-to-treat brain metastases."

RET-Altered Thyroid Cancers

The publication highlights 162 patients who were treated across the three *RET*-altered thyroid cancer efficacy analysis cohorts (the first 55 consecutively enrolled patients with *RET*-mutant vandetanib and/or cabozantinib-treated MTC, 88 patients with *RET*-mutant vandetanib and cabozantinib-naïve MTC, and 19 patients with *RET* fusion-positive previously systemically treated thyroid cancer). All analyses are presented on an intent-to-treat basis.

	RET-Mutant MTC	*RET* Fusion-Positive Thyroid Cancer

	Cabozantinib and/or Vandetanib Naïve	Cabozantinib and/or Vandetanib Experienced	Systemic Treatment Experienced
No. of patients	88	55	19
ORR (95% CI)	73 (62, 82)	69 (55, 81)	79 (54, 94)
Median DoR, months (95% CI)	22 (NR, NR)*	NR (19.1, NR)*	18.4 (7.6, NR)

NR = Not Reached
Thyroid cancers include: papillary, Hurthle cell, anaplastic, and poorly differentiated
**Unstable median, based on fewer than 10% of total number of events.*

Change in carcinoembryonic antigen (CEA) and calcitonin were prespecified exploratory endpoints and were not error controlled. Biochemical response rate (BRR) is based on the best percent of change in calcitonin and CEA. Among previously treated *RET*-mutant MTC patients, Retevmo therapy resulted in robust BRR for serum tumor markers calcitonin (91% BRR) and carcinoembryonic antigen (64% BRR).

"Based on the published data, selpercatinib demonstrated strong, durable responses in both the first-line and relapsed settings for *RET*-mutant MTC, offering encouraging evidence that this treatment may serve as a new standard of care in both settings," said Lori J. Wirth, M.D., medical director of head and neck cancers, Massachusetts General Hospital Cancer Center.

Safety Data

In the 144 Retevmo-treated patients with *RET* fusion-positive NSCLC, the most common grade ≥3 adverse events were hypertension (14%), increased alanine aminotransferase (13%), increased aspartate aminotransferase (10%), hyponatremia (6%), and lymphopenia (6%). Four patients (3%) discontinued Retevmo due to drug-related adverse events.

Across the 162 Retevmo-treated patients with *RET*-mutant MTC and *RET* fusion-positive thyroid cancers, the most common grade ≥3 adverse events were hypertension (21%), increased alanine aminotransferase (11%), increased aspartate aminotransferase (9%), hyponatremia (8%), and diarrhea (6%). Four patients (3%) discontinued Retevmo due to drug-related adverse events.

In the publications, the adverse event profile of Retevmo in the *RET* fusion-positive NSCLC analyses and in the *RET*-driven thyroid cancer analyses were each broadly similar to the overall safety profile for all 531 patients dosed with Retevmo in LIBRETTO-001. Across all 531 Retevmo-treated patients, 160 (30%) required dose reduction due to treatment-related adverse events, and 12 (2%) patients discontinued Retevmo due to treatment-related adverse events, the most common of which were alanine amino transferase increase (two patients) and drug hypersensitivity (two patients).

Two randomized Phase 3 trials (LIBRETTO-431 and LIBRETTO-531) are currently enrolling patients.

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

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), taken twice daily until disease progression or unacceptable toxicity.[4]

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*.

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.

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%).

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 (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.

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This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Retevmo™ (selpercatinib) and reflects Lilly's current beliefs. 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.

[1] As determined by an independent review committee according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

[2] Dr. Drilon previously provided compensated advisory services to Loxo Oncology (acquired by Lilly in 2019).

[3] 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.

[4] RETEVMO [package insert]. Indianapolis, IN: Eli Lilly and Company; 2020.

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