FDA Approves Lilly's Retevmo® (selpercatinib), the First and Only RET Inhibitor for Adults with Advanced or Metastatic Solid Tumors with a RET Gene Fusion, Regardless of Type

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Tumor-agnostic data supporting approval demonstrated an overall response rate (ORR) of 44% across multiple tumor types

FDA simultaneously grants traditional approval in adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a RET gene fusion, as detected by an FDA-approved test

INDIANAPOLIS, Sept. 21, 2022 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced the U.S. Food and Drug Administration (FDA) has granted approval to Retevmo® (selpercatinib, 40 mg & 80 mg capsules) for adult patients with locally advanced or metastatic solid tumors with a rearranged during transfection *(RET)* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. This indication is approved under accelerated approval based on ORR and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

"In the LIBRETTO-001 trial, selpercatinib demonstrated clinically meaningful and durable responses across a variety of tumor types in patients with *RET*-driven cancers, including pancreatic, colon and other cancers in need of new treatment options," said Vivek Subbiah, M.D., associate professor of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center and co-investigator for LIBRETTO-001. "These data and FDA approval of the tumor-agnostic indication underscore the importance of routine, comprehensive genomic testing for patients across a wide variety of tumor types."

In addition to the tumor-agnostic approval, the FDA has granted traditional approval for Retevmo in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *RET* gene fusion, as detected by an FDA-approved test. This FDA action broadens the Retevmo label to include patients with locally advanced disease and converts the May 2020 accelerated approval for NSCLC to a traditional approval.

The labeling for Retevmo contains warnings and precautions for hepatotoxicity (evidence of liver dysfunction), interstitial lung disease (ILD)/pneumonitis, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, tumor lysis syndrome, risk of impaired wound healing, hypothyroidism, and embryo-fetal toxicity.

"Since its initial accelerated approval, Retevmo has shifted the treatment paradigm for patients with *RET*-altered cancers," said David Hyman, M.D., chief medical officer, Loxo@Lilly. "Retevmo is the first and only RET inhibitor to receive both tumor-agnostic accelerated approval and traditional approval in NSCLC, further supporting its ability to deliver meaningful clinical benefit for patients across diverse tumor types."

The two approvals are supported by data from the pivotal LIBRETTO-001 trial, which is the largest clinical trial of patients with *RET*-driven cancers treated with a RET inhibitor. The multicenter, open-label, multi-cohort study enrolled patients with locally advanced or metastatic *RET*-driven solid tumors, including NSCLC. Major efficacy outcomes were ORR and DOR, assessed by a blinded independent review committee (BIRC). Prespecified secondary endpoints included central nervous system (CNS) ORR and CNS DOR.

RET Fusion-Positive Solid Tumors

Among the 41 patients in the tumor-agnostic data set, the most common cancers were pancreatic adenocarcinoma (27%), colorectal (24%), salivary (10%), and unknown primary (7%). Thirty-seven patients (90%) received prior systemic therapy (median 2 [range 0 – 9]; 32% received 3 or more). Efficacy results are summarized below:

	RET Fusion-Positive Solid Tumors
No. of patients	41
Overall Response Rate[1] (95% CI)	44 %(28, 60)
Complete response	4.9 %
Partial response	39 %
Duration of Response	
Median in months (95% CI)	24.5 (9.2, NE)
% with ≥ 6 months[2]	67 %

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

Efficacy results by tumor type are summarized below:

Tumor Type	**Patients (n = 41)**	**ORR**[1,2]		**DOR Range (months)**
		n (%)	**95% CI**	
Pancreatic adenocarcinoma	11	6 (55 %)	(23, 83)	2.5, 38.3+
Colorectal	10	2 (20 %)	(2.5, 56)	5.6, 13.3

Salivary	4	2 (50 %)	(7, 93)	5.7, 28.8+
Unknown primary	3	1 (33 %)	(0.8, 91)	9.2
Breast	2	PR, CR	NA	2.3+, 17.3
Sarcoma (soft tissue)	2	PR, SD	NA	14.9+
Xanthogranuloma	2	NE, NE	NA	NA
Carcinoid (bronchial)	1	PR	NA	24.1+
Carcinoma of the skin	1	NE	NA	NA
Cholangiocarcinoma	1	PR	NA	5.6+
Ovarian	1	PR	NA	14.5+
Pulmonary carcinosarcoma	1	NE	NA	NA
Rectal neuroendocrine	1	NE	NA	NA
Small intestine	1	CR	NA	24.5

+ denotes ongoing response.

[1] Confirmed overall response rate assessed by BIRC.

[2] Best overall response for each patient is presented for tumor types with ≤2 patients.

CI = confidence interval, CR = complete response, DOR = duration of response, NA = not applicable, NE = not evaluable, ORR = overall response rate, PR = partial response, SD = stable disease.

"Today's announcement of Retevmo's expanded label reflects an opportunity to bring more targeted treatment options to a broader set of difficult-to-treat solid tumors, such as pancreatic cancer," said Julie Fleshman, president and chief executive officer, the Pancreatic Cancer Action Network (PanCAN). "This news further highlights the importance of broad biomarker testing, which may open the door to new therapy options for more patients."

Retevmo may affect both healthy cells and tumor cells, which can result in side effects, some of which can be serious.

RET Fusion-Positive NSCLC

Efficacy results for patients with both platinum chemotherapy treated and treatment-naïve *RET* fusion-positive NSCLC are summarized below:

	RET Fusion-Positive NSCLC	
	Treatment-Naïve	**Platinum Chemotherapy Treated**
No. of patients	69	247
Overall Response Rate[1] (95% CI)	84% (73%, 92%)	61% (55%, 67%)
Complete response	5.8 %	7.3 %
Partial response	78 %	54 %
Duration of Response		
Median in months (95% CI)	20.2 (13, NE)	28.6 (20, NE)
% with ≥ 12 months[2]	50 %	63 %

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

NE = not estimable

The activity of Retevmo in patients with CNS metastases was also evaluated. Among the 247 patients with previously treated *RET* fusion-positive NSCLC, 16 had measurable CNS metastases at baseline as assessed by BIRC. One patient received radiation therapy (RT) to the brain within two months prior to study entry. Responses in intracranial lesions were observed in 87.5% (14 of 16) of patients; 39% of responders had an intracranial DOR of 12 months or greater. Among the 69 patients with treatment-naïve *RET* fusion-positive NSCLC, five had measurable CNS metastases at baseline as assessed by BIRC. Two patients received RT to the brain within two months prior to study entry. Responses in intracranial lesions were observed in four of these five patients; 38% of responders had an intracranial DOR of 12 months or greater.

"Retevmo's accelerated approval played an important role in providing earlier access for patients who needed new treatment options. We are now pleased to see the conversion from an accelerated approval to a traditional approval," said Andrea Ferris, president and chief executive officer, LUNGevity Foundation. "As a targeted treatment, this traditional approval further reinforces the need for comprehensive biomarker testing for lung cancer patients, with the hope that as many patients as possible can benefit from receiving treatments tailored to their specific tumor mutations."

In the full LIBRETTO-001 safety population (n=796) with advanced solid tumors, the most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased sodium, and decreased calcium. For more information, see "IMPORTANT SAFETY INFORMATION FOR RETEVMO® (selpercatinib)" below.

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 85 sites, included a dose escalation phase (Phase 1) and a dose expansion phase (Phase 2). The primary objective was to determine ORR by blinded independent review committee (BIRC) and other objectives included DOR, CNS ORR & DOR, safety and PFS.

About Retevmo® (selpercatinib, 40 mg & 80 mg capsules)

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 a 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.

IMPORTANT SAFETY INFORMATION FOR RETEVMO® (selpercatinib)

Hepatotoxicity: Serious hepatic adverse reactions occurred in 3% of patients treated with Retevmo. Increased aspartate aminotransferase (AST) occurred in 59% of patients, including Grade 3 or 4 events in 11% and increased alanine aminotransferase (ALT) occurred in 55% of patients, including Grade 3 or 4 events in 12%. 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.

Severe, life-threatening, and fatal **interstitial lung disease (ILD)/pneumonitis** can occur in patients treated with Retevmo. ILD/pneumonitis occurred in 1.8% of patients who received Retevmo, including 0.3% with Grade 3 or 4 events, and 0.3% with fatal reactions. Monitor for pulmonary symptoms indicative of ILD/pneumonitis. Withhold Retevmo and promptly investigate for ILD in any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough, and fever). Withhold, reduce dose, or permanently discontinue Retevmo based on severity of confirmed ILD.

Hypertension occurred in 41% of patients, including Grade 3 hypertension in 20% and Grade 4 in one (0.1%) patient. Overall, 6.3% 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 7% of patients and an increase in the QTcF interval of at least 60 ms over baseline was measured in 20% 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 thyroid-stimulating hormone (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 3.1% of patients treated with Retevmo including 4 (0.5%) patients with fatal hemorrhagic events, including cerebral hemorrhage (n=2), tracheostomy site hemorrhage (n=1), and hemoptysis (n=1). Permanently discontinue Retevmo in patients with severe or life-threatening hemorrhage.

Hypersensitivity occurred in 6% of patients receiving Retevmo, including Grade 3 hypersensitivity in 1.9%. The median time to onset was 1.9 weeks (range: 5 days to 2 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 0.6% 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.

Retevmo can cause **hypothyroidism**. Hypothyroidism occurred in 13% of patients treated with Retevmo; all reactions were Grade 1 or 2. Hypothyroidism occurred in 13% of patients (50/373) with thyroid cancer and 13% of patients (53/423) with other solid tumors including NSCLC. Monitor thyroid function before treatment with Retevmo and periodically during treatment. Treat with thyroid hormone replacement as clinically indicated. Withhold Retevmo until clinically stable or permanently discontinue Retevmo based on severity.

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 and females of reproductive potential 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 1 week after the last 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 last dose.

Severe adverse reactions (Grade 3-4) occurring in ≥20% of patients who received Retevmo in LIBRETTO-001, were hypertension (20%), diarrhea (5%), prolonged QT interval (4.8%), dyspnea (3.1%), fatigue (3.1%), hemorrhage (2.6%), abdominal pain (2.5%), vomiting (1.8%), headache (1.4%), nausea (1.1%), constipation (0.8%), edema (0.8%), rash (0.6%), and arthralgia (0.3%).

Serious adverse reactions occurred in 44% of patients who received Retevmo. The most frequently reported serious adverse reactions (in ≥2% of patients) were pneumonia, pleural effusion, abdominal pain, hemorrhage, hypersensitivity, dyspnea, and hyponatremia.

Fatal adverse reactions occurred in 3% of patients; fatal adverse reactions included sepsis (n=6), respiratory failure (n=5), hemorrhage (n=4), pneumonia (n=3), pneumonitis (n=2), cardiac arrest (n=2), sudden death (n=1), and cardiac failure (n=1).

Common adverse reactions (all grades) occurring in ≥20% of patients who received Retevmo in LIBRETTO-001, were edema (49%), diarrhea (47%), fatigue (46%), dry mouth (43%), hypertension (41%), abdominal pain (34%), rash (33%), constipation (33%), nausea (31%), headache (28%),

cough (24%), vomiting (22%), dyspnea (22%), hemorrhage (22%), arthralgia (21%), and prolonged QT interval (21%).

Laboratory abnormalities (all grades ≥20%; Grade 3-4) worsening from baseline in patients who received Retevmo in LIBRETTO-001, were increased AST (59%; 11%), decreased calcium (59%; 5.7%), increased ALT (56%; 12%), decreased albumin (56%; 2.3%), increased glucose (53%; 2.8%), decreased lymphocytes (52%; 20%), increased creatinine (47%; 2.4%), decreased sodium (42%; 11%), increased alkaline phosphatase (40%; 3.4%), decreased platelets (37%; 3.2%), increased total cholesterol (35%; 1.7%), increased potassium (34%; 2.7%), decreased glucose (34%; 1.0%), decreased magnesium (33%; 0.6%), increased bilirubin (30%; 2.8%), decreased hemoglobin (28%; 3.5%), and decreased neutrophils (25%; 3.2%).

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.

Retevmo is a P-glycoprotein (P-gp) inhibitor. Concomitant use of Retevmo with **P-gp substrates** increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of Retevmo with P-gp substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for P-gp substrates provided in their approved product labeling.

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 locally advanced and metastatic *RET* fusion-positive NSCLC and other *RET* fusion-positive solid tumors, 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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