FDA Approves RET Inhibitor Retevmo for Lung and Thyroid Cancer
Selpercatinib, the first drug in its class, shrank tumors in over two thirds of previously treated patients.

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On May 8, the Food and Drug Administration (FDA) granted accelerated approval of Retevmo (selpercatinib), the first RET inhibitor, for people with non-small-cell lung cancer (NSCLC) and two types of thyroid cancer with specific genetic mutations.

“Innovations in gene-specific therapies continue to advance the practice of medicine at a rapid pace and offer options to patients who previously had few,” Richard Pazdur, MD, director of the FDA’s Oncology Center of Excellence, said in a press release.

Retevmo, from Eli Lilly and company—which obtained the drug, then known as LOXO-292, when it acquired Loxo Oncology last year—is a selective inhibitor of a receptor tyrosine kinase known as RET. This enzyme plays a role in cell proliferation, and mutations or fusions in the RET gene can drive cancer development. RET alterations are rare overall, occurring in less that 1% of all cancers and 2% of NSCLC, but they are more frequent in certain cancer types.

Drugs that work against cancers with a specific genetic alteration anywhere in the body are known as pancancer, or site-agnostic, therapies. Retevmo, however, was approved for specific cancer types. It is indicated for adults with metastatic RET fusion-positive NSCLC and for adults and adolescents (age 12 and up) with advanced or metastatic RET fusion-positive thyroid cancer or advanced or metastatic RET-mutant medullary thyroid cancer. Medullary thyroid cancer, which involves a specific type of cell, is uncommon—accounting for only 4% of all thyroid cancers—but it frequently has RET mutations.

Retevmo can be used regardless of prior treatment history, both by those who have tried prior systemic medications and those starting treatment for the first time.

The accelerated approval was based on promising findings from the Phase I/II LIBRETTO-001 trial. Study results were previously presented at the 2018 American Society of Clinical Oncology annual meeting, the 2019 World Conference on Lung Cancer and the 2019 European Society for Medical Oncology Congress.
LIBRETTO-001 enrolled people with NSCLC, thyroid cancer and a variety of other solid tumors with RET mutations or fusions. Both previously treated patients and those starting systemic treatment for the first time were eligible. Everyone was treated with Retevmo, taken as a pill twice daily; there was no placebo group.

Retevmo led to an overall response rate—meaning complete or partial tumor shrinkage—in 64% of the 105 previously treated people with NSCLC, rising to 85% for the 39 patients new to treatment. The mediation duration of response was 17.5 months for the treatment-experienced group, and was not reached in the newly treated group because a majority were still responding.

When he presented preliminary study findings last year, Alexander Drilon, MD, of Memorial Sloan Kettering Cancer Center in New York City, noted that Retevmo appeared particularly active against cancer that had spread to the brain. Ten of the 11 people with brain metastasis (91%) experienced shrinkage of cancer in the brain, including 18% with complete remission.

“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,” Drilon said in a Lilly press release. “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.”

Looking at the participants with thyroid cancer, the overall response rate was 69% for the 55 treatment-experienced patients and 73% for the 88 previously untreated people with RET-mutant medullary thyroid tumors. Here, the duration of response was 22.0 months for the previously untreated group and not reached for the treatment-experienced group. In the smaller subset of 19 previously treated and eight newly treated people with RET fusion-positive thyroid cancer, the overall response rates were 79% and 100%, respectively. Response duration was 18.4 months in the former group and not reached in the latter group.

“RET alterations account for the majority of medullary thyroid cancers and a meaningful percentage of other thyroid cancers,” said Lori Wirth, MD, of Massachusetts General Hospital Cancer Center. “For patients living with these cancers, the approval of selpercatinib means they now have a treatment option that selectively and potently inhibits RET.”

Treatment with Retevmo was generally safe and well tolerated, with just 5% of participants stopping treatment because of adverse events. The most common adverse reactions include diarrhea, constipation, dry mouth, fatigue, swelling, rash, high blood pressure, elevated ALT and AST liver enzymes, elevated glucose, cholesterol and creatinine, and various other laboratory test abnormalities.

The product label for Retevmo includes warnings about several potential serious side effects: liver toxicity, severe high blood pressure, bleeding, heart rhythm abnormalities, hypersensitivity reactions and slow wound healing. Retevmo can cause fetal harm if used during pregnancy.
A Lilly spokesperson told FiercePharma that Retevmo would be available from specialty pharmacies within a week at a list price of about $20,600 for a 30-day supply.

Drugs that receive accelerated approval based on response rates in early studies are expected to undergo further testing in larger randomized trials to confirm clinical benefits such as improved survival, and the FDA can rescind approval if they don’t measure up. Two Phase III trials, Libretto-431 for NSCLC (ClinicalTrials.gov number NCT04194944) and Libretto-531 for medullary thyroid cancer (ClinicalTrials.gov number NCT04211337), are currently underway.

Another investigational RET inhibitor, Blueprint Medicines’ pralsetinib (formerly known as BLU-667) has also demonstrated good activity in an early study, with overall response rates of 60% for NSCLC patients who used prior platinum-based chemotherapy and 71% for previously untreated people.

The availability of RET inhibitors underscores the need for genetic testing to determine which patients have gene mutations or fusions that could make them eligible for these new targeted therapies. Next-generation sequencing of a tumor tissue biopsy sample or liquid biopsy using a blood sample can reveal multiple actionable genetic alterations. However, there is currently no FDA-approved companion test specifically for RET alterations.

“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,” Andrea Ferris, president and chief executive officer of LUNGevity, said in the Lilly press release. “We urge patients to ask their doctors about broad biomarker tests that include RET alterations.”

Click here for full prescribing information for Retevmo.
Click here to learn more about lung cancer.
Click here to learn more about thyroid cancer.