RET Inhibitor Shows High Response Rate for Lung Cancer

Selpercatinib shrank tumors in 68% of patients previously treated with chemotherapy.

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An experimental therapy that targets tumors with RET gene alterations demonstrated durable activity in people with non-small-cell lung cancer (NSCLC), and it appeared particularly active against cancer that had spread to the brain, researchers reported today at the World Conference on Lung Cancer (WCLC) in Barcelona.

Selpercatinib led to tumor shrinkage in 68% of previously treated participants and 85% of those starting treatment for the first time. What's more, it shrank cancer in the brain in 91% of study participants with brain metastasis.

Several targeted therapies have been developed to treat non-small-cell lung cancer with various gene alterations, including EGFR, ALK and ROS1 mutations or fusions. Yet a majority of people with NSCLC do not have any mutations that can be treated with existing medications.

Alexander Drilon, MD, of Memorial Sloan Kettering Cancer Center in New York, presented the latest findings from the Phase I/II LIBRETTO-001 trial, an international study evaluating an experimental drug for cancer harboring RET mutations or gene fusions.

Selpercatinib is a selective inhibitor of the receptor tyrosine kinase known as RET. Although some multikinase inhibitors (drugs with multiple targets) have weak activity against RET, there are currently no approved medications aimed specifically at this target. The RET protein plays a role in cell proliferation, and mutations or fusions in the RET gene can trigger the development of cancer. 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 (for example, 60% of medullary thyroid tumors).

Formerly called LOXO-292, selpercatinib was discovered by Loxo Oncology, which was acquired by Eli Lilly earlier this year. Loxo is best known for developing Vitrakvi (larotrectinib), the first site-agnostic, or pancancer, therapy designed to work against cancer with a specific genetic alteration anywhere in the body; Bayer acquired Vitrakvi as part of the Lilly acquisition.

Drilon presented earlier results from LIBRETTO-001 at the 2018 American Society of Clinical Oncology annual meeting. In that analysis, 82 participants with various types of cancer received

escalating oral doses of selpercatinib. The overall response rate, meaning complete or partial tumor shrinkage, was 77% for people with RET fusion cancers (mostly NSCLC) and 45% for those with RET-mutated medullary thyroid cancer; none of the four patients without RET alterations saw a response.

Based on these early findings, the Food and Drug Administration granted selpercatinib a breakthrough therapy designation for certain patients with NSCLC and thyroid cancer with RET fusions or mutations, meaning the drug is expected to fill an unmet medical need.

At WCLC, Drilon presented further results from an expanded cohort of 105 people with RET fusion-positive NSCLC who were previously treated with platinum-based chemotherapy. About 60% were women and the median age was 61. Nearly half had tried at least one multikinase inhibitor, and 55% had used checkpoint inhibitor immunotherapy. All received 160 milligrams of selpercatinib twice daily.

In this group, the overall response rate was 68%, including complete responses in 2%, and the likelihood of response was similar regardless of the type of prior treatment. An additional 26% had stable disease, and only 2% experienced cancer progression.

RET fusion-positive NSCLC commonly spreads to the brain. In this analysis, 10 of the 11 patients with brain metastasis (91%) experienced cancer regression in the brain, known as an intracranial or central nervous system (CNS) response, including 18% with complete remission.

The median duration of response was 20.3 months. The median progression-free survival (PFS), meaning participants were still living without worsening of disease, was 18.4 months. The overall survival rate cannot yet be determined because a majority of participants are still alive.

Drilon also reported findings from a smaller cohort of 34 NSCLC patients being treated for the first time. In this group, the overall response rate was 85%. The median duration of response and PFS data are not yet available because most participants are still doing well.

Treatment was generally safe and well tolerated. Looking at all 531 patients with various cancer types enrolled in the study to date, only nine people (1.7%) stopped treatment because of side effects. The most common adverse events (not necessarily treatment-related) were dry mouth, diarrhea, constipation, fatigue, headache, high blood pressure and elevated liver enzymes.

“In this large cohort, selpercatinib’s response rate, durability, robust CNS activity and safety show promise,” Drilon said in a WCLC press release. “Furthermore, this continues to confirm that RET fusions are clinically targetable alterations, placing them in the company of activating EGFR/ALK/ROS1 alterations.”

Lilly indicated that it plans to submit a new drug application for selpercatinib by the end of the year. A Phase III trial comparing selpercatinib versus platinum chemotherapy with or without the checkpoint inhibitor Keytruda (pembrolizumab) is expected to start soon.

Another experimental drug targeting RET, 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 chemotherapy and 71% for previously untreated people.

If these two oncogene-targeted therapies continue to do well in larger trials, they could become part of an emerging paradigm of treating cancer based on genetic characteristics regardless of where it occurs in the body.

Discussing the results after Drilon's presentation, Robert Doebele, MD, of the University of Colorado, a co-investigator for studies of the recently approved site-agnostic NTRK inhibitor Rozlytrek (entrectinib), questioned whether it is ethical to continue running Phase III trials comparing these new highly active targeted therapies against standard chemotherapy.

The results also raise the issue of the need for genetic testing to determine which patients have mutations and gene fusions that could make them eligible for these new therapies.

With these kinds of responses, "you have to be checking for RET, and the need for [next-generation sequencing] is even more pressing for the proper management of NSCLC," Stephen Liu, MD, of Georgetown University's Lombardi Comprehensive Cancer Center, commented on Twitter.

Click here for the WCLC conference program (this study was presented Monday as part of a Presidential Symposium highlighting the seven top abstracts from the meeting).
