Pfizer Oncology

Lorlatinib, the proposed generic name for PF-06463922, is an investigational agent and has not been approved for marketing by any regulatory agency at this time.

ABOUT LORLATINIB

Lorlatinib is an investigational medicine that inhibits the anaplastic lymphoma kinase (ALK) and ROS1 proto-oncogene.

Due to tumor complexity and development of resistance to treatment, disease progression is a challenge in patients with ALK-positive metastatic non-small cell lung cancer (NSCLC). A common site for progression in metastatic NSCLC is the brain.

Lorlatinib was specifically designed to inhibit tumor mutations that drive resistance to other ALK inhibitors and to penetrate the blood brain barrier.

ALK in NSCLC

Originally discovered as an oncogenic driver in a type of lymphoma, ALK gene alterations were also found to be among key drivers of tumor development in cancers, such as NSCLC.[1]

In ALK-positive lung cancer, a normally inactive gene called ALK is fused with another gene. This genetic alteration creates the ALK fusion gene and ultimately, the production of an ALK fusion protein, which is responsible for tumor growth.[1,2] This genetic alteration is present in 3-5% of NSCLC patients.[3,4,5]

ROS1 in NSCLC

Another gene that can fuse with other genes is called ROS1. Sometimes a ROS1 fusion protein can contribute to cancer-cell growth and tumor survival. This genetic alteration is present in approximately 1% of NSCLC patients.[5]

PRECLINICAL DATA

Preclinical data showed lorlatinib is capable of overcoming resistance to existing ALK inhibitors and penetrated the blood brain barrier in ALK-driven tumor models.[2] Specifically, in these preclinical models, lorlatinib had activity against all tested clinical resistance mutations in ALK.

CLINICAL STUDIES

A Phase 1/2 clinical trial of lorlatinib in patients with ALK-positive or ROS1-positive advanced NSCLC is currently ongoing.

- The primary objective of the Phase 1 portion was to assess safety and tolerability of single-agent lorlatinib at increasing dose levels in patients with ALK-positive or ROS1-positive advanced NSCLC.[6]
- Data from the Phase 1 study showed that lorlatinib had promising clinical activity in patients with ALK-positive or ROS1-positive advanced NSCLC. Most of these patients had developed CNS metastases and had received ≥1 prior tyrosine kinase inhibitor.[7]
    - The most common treatment-related adverse events (AEs) were hypercholesterolemia (69%) and peripheral edema (37%). Hypercholesterolemia was the most common (11%) grade 3 or higher treatment-related AE and the most frequent reason for dose delay or reduction. No patients discontinued due to treatment-related AEs. At the recommended Phase 2 dose, 4 out of 17 patients (24%) experienced a treatment-related AE of any grade that led to a dose delay or hold.

CLINICAL STUDIES (CONTINUED)

- Based on the results of this study, the recommended Phase 2 dose has been declared at 100mg once-daily. The primary objective of the Phase 2 trial is to evaluate safety and overall and intracranial efficacy of lorlatinib.
- The ongoing Phase 2 study is expected to enroll a total of 240 patients across six cohorts (five for ALK-positive and one for ROS1-positive patients with NSCLC), defined by degree and type of prior treatment.

For additional information on the lorlatinib clinical trial (NCT01970865), please visit: https://clinicaltrials.gov/ct2/show/NCT01970865?term=PF-+06463922&rank=1

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