Lorlatinib

is an investigational agent and has not been approved for marketing by any regulatory agency at this time.

ABOUT LORLATINIB

Lorlatinib is an investigational next-generation ALK/ROS1 tyrosine kinase inhibitor that has been shown to be highly active in preclinical lung cancer models harboring chromosomal rearrangements of both ALK and ROS1.

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]

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.[4]

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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.[5]
- 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.[6]
  - 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.
- The Phase 2 study has completed the accruals and is currently recruiting patients.

The Phase 3 CROWN study (NCT03052608) recently began enrolling patients. CROWN is an ongoing, open label, randomized, two-arm study comparing lorlatinib to crizotinib in the first-line treatment of patients with metastatic ALK-positive NSCLC.

- For additional information on the CROWN study (NCT03052608), please visit: https://ClinicalTrials.gov

REGULATORY MILESTONE

In April 2017, lorlatinib received Breakthrough Therapy designation from the U.S. Food and Drug Administration (FDA) for the treatment of patients with ALK-positive metastatic NSCLC, previously treated with one or more ALK inhibitors.

CONTACT & ADDITIONAL INFORMATION

Pfizer Media Relations Contact

Sally Beatty – Pfizer Oncology Global Media Relations
Phone: 212-733-6566
Mobile: 347-330-7867
Sally.Beatty@Pfizer.com

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