A First-In-Human Study of LOXO-101, a Highly Selective Inhibitor of the Tropomyosin Receptor Kinase (TRK) Family

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Abstract

Background: The TRK family of neurotrophin receptors, TRKA, TRKB, and TRKC (encoded by NTRK1, NTRK2, and NTRK3 genes, respectively) and their neurotrophin ligands regulate growth, differentiation and survival of neurons. Translocations involving the NTRK1/2/3 kinase domain, mutations involving the TRK ligand-binding site, amplifications of ntrk, TRK splice variants, and autocrine/paracrine signaling have been described in a diverse number of tumor types and may contribute to tumorigenesis. Recently NTRK1 fusions were described in a subset of adenocarcinoma lung cancer patients (Vaishnavi, 2013) and NTRK2 and NTRK3 fusions have been described in multiple tumor types (Skalova, 2014; Ricarte-Filho, 2013; Vaishnavi, 2014). LOXO-101 is a potent, oral, ATP-competitive pan-TRK inhibitor with IC50 values in the low nanomolar range for inhibition of TRK family members in binding and cellular assays, with 100x selectivity over other kinases. LOXO-101 has demonstrated tumor inhibition in preclinical models.

Methods: This study (NCT02122913) is an ongoing phase Ia/Ib dose escalation plus expansion trial in adults with advanced solid tumors. The phase Ia component is an open-label, multicenter, dose escalation trial. Patients with solid tumors refractory to standard therapy, with normal hematopoietic and major organ function are eligible for study. LOXO-101 is administered orally QD or BID for continuous 28-day cycles. This component of the trial will determine the MTD for LOXO-101.

The phase Ib component is an open-label, multicenter, global, dose expansion study. In addition to the Phase Ia eligibility criteria, patients must have a demonstrated alteration in one of the three NTRK genes or three TRK proteins. The number of expansion cohorts will be determined by the molecular characteristics of the tumors in the patients enrolled. Data will provide initial evidence of tumor activity of LOXO-101, stratified by the type of NTRK or TRK alteration or tumor type, as well as further elucidation of the safety profile of LOXO-101 in cancer patients. Archival tissue is required for further characterization of molecular abnormalities.

Selected Inclusion Criteria

1. Adult patients with a locally advanced or metastatic solid tumor that has progressed or was nonresponsive to available therapies and for which no standard or available curative therapy exists.
2. Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2 and life expectancy of at least 3 months.
3. Archived tumor tissue sample available or tissue available for fresh biopsy if the archived sample is not available.
4. Adequate end organ function
5. Ability to swallow capsules.

Selection of Identified TRK Fusions

Study Objectives

To determine the safety of oral LOXO-101, including dose-limiting toxicity (DLT), in adult patients with an advanced solid tumor, characterize the pharmacokinetic (PK) properties, and to identify the maximum tolerated dose (MTD) and/or the appropriate dose of LOXO-101 for further clinical investigation.

Methods

Study Design
Phase 1, multicenter, open-label, 3+3 dose-escalation and safety study, with expansion cohorts for TRK-selected patients

Drug Treatment
LOXO-101 administered either QD or BID doses for continuous 28-day cycles. Individual patients will continue daily LOXO-101 dosing until disease progression, unacceptable toxicity, or other reason for treatment discontinuation

Pharmacokinetics
LOXO-101 concentrations quantified in plasma by a validated LC-MS/MS on Days 1 and 8 of Cycle 1

Currenty Recruiting Sites

University of Colorado Cancer Center, Aurora, Colorado
Massachusetts General Hospital, Boston, Massachusetts
University Hospitals Case Medical Center, Cleveland, Ohio

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Summary

Rearrangements in NTRK1, NTRK2, and NTRK3 that lead to constitutively-active TRKA, TRKB, and TRKC receptors are oncogenic and prevalent in a wide array of tumor types, including lung adenocarcinoma, thyroid, head and neck cancer, glioblastoma, and others

LOXO-101 demonstrates potent and highly-selective inhibition of TRKA, TRKB, and TRKC over other kinase- and non-kinase targets

LOXO-101 demonstrated robust inhibition of tumor growth in xenograft models, acceptable pharmaceutical properties, and safety in nonclinical models

The preclinical safety profile will be validated in this ongoing phase 1 trial. Further study of LOXO-101 will provide further information related to the efficacy of this highly-specific targeted therapy