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

Howard A. Burris, III[1], Marcia S. Brose[2], Alice T. Shaw[3], Todd M. Bauer[1,4], Anna F. Farago[3], Robert C. Doebele[5], Steven Smith[6], Michele Fernandes[6], Scott Cruickshank[6], Jennifer A. Low[6]
[1]Sarah Cannon Research Institute, Nashville, TN; [2]University of Pennsylvania, Philadelphia, PA
[3]Massachusetts General Hospital, Boston, MA; [4]Tennessee Oncology, PLLC, Nashville, TN; [5]University of Colorado, Aurora, CO; [6]Loxo Oncology, South San Francisco, CA;

Abstract

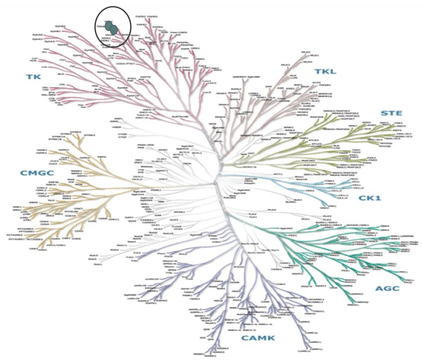
Background: The TRK family of neurotrophin receptors, TRKA, TRKB, and TRKC (encoded by *NTRK1, NTRK2,* and *NTRK3* genes, respectively) and their neurotrophin ligands regulate growth, differentiation and survival of neurons. Translocations involving the *NTRK1/2/3* kinase domain, mutations involving 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 IC_{50} 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.

LOXO-101

LOXO-101 is an orally bioavailable, potent, ATP-competitive inhibitor of TRKA, TRKB, and TRKC. LOXO-101 has IC_{50} values in the low nanomolar range for inhibition of all three TRK family members in binding and cellular assays, with 100x selectivity over other kinases, and has shown acceptable pharmaceutical properties and safety in nonclinical models.



LOXO-101 is highly selective for TRKA, TRKB, and TRKC

- **No inhibition of >200 other kinases at 1000 nM**
- **Weak inhibition of TNK2 (IC_{50} > 1000 nM)**
- **>100-fold selective for other kinases**
- **1,000-fold selective for >75 non-kinase targets**

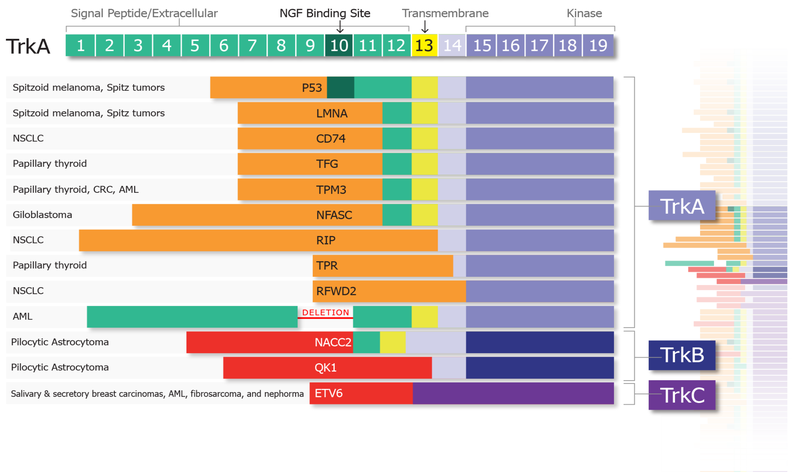
Selected Inclusion Criteria

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.**

Selected Exclusion Criteria

1. **Investigational agent or anticancer therapy within 2 weeks prior to planned start of LOXO-101.**
2. **Major surgery within 4 weeks prior to planned start of LOXO-101.**
3. **Patients with primary CNS tumors or metastasis and a documented *NTRK* 1, 2, or 3 gene translocation may be enrolled if they are neurologically stable and have not required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms. Patients with primary CNS tumors or metastasis who do not have a documented *NTRK* 1, 2, or 3 gene translocation are also permitted, but must have no evidence of active CNS disease for at least 4 weeks prior to first dose, as documented by appropriate imaging studies.**
4. **Malabsorption syndrome or other condition affecting oral absorption.**
5. **Current treatment with a strong CYP3A4 inhibitor or inducer.**

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

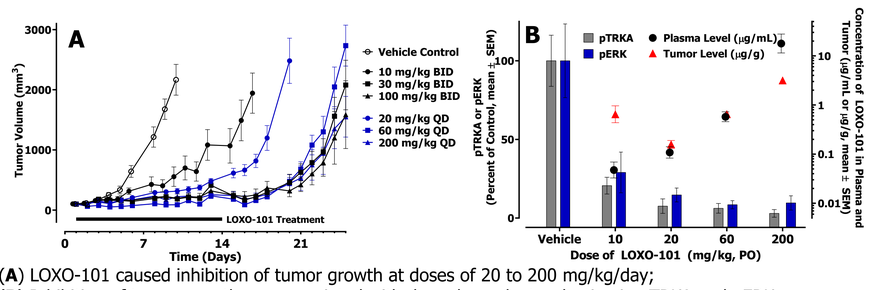
Drug Treatment

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

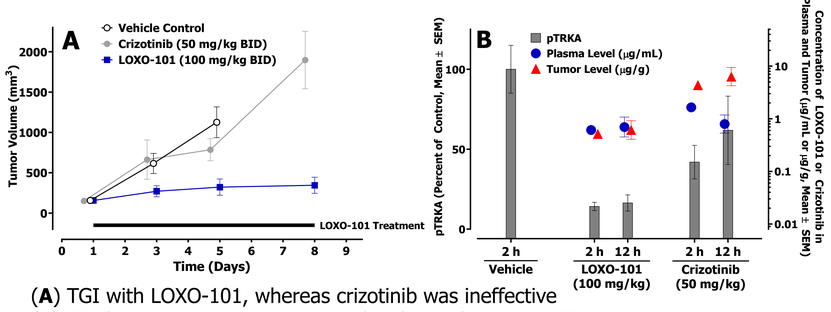
LOXO-101 concentrations quantified in plasma by a validated LC-MS/MS on Days 1 and 8 of Cycle 1

Dose- and Schedule-Dependent Inhibition of Tumor Growth and pTRKA in 3T3-TRKA Allografts



(**A**) LOXO-101 caused inhibition of tumor growth at doses of 20 to 200 mg/kg/day;
(**B**) Inhibition of tumor growth was associated with dose-dependent reduction in pTRKA and pERK

LOXO-101 Demonstrates Greater Tumor Growth Inhibition and pTRKA Reduction than Crizotinib



(**A**) TGI with LOXO-101, whereas crizotinib was ineffective
(**B**) TGI by LOXO-101 was associated with a reduction in pTRKA

Currently Recruiting Sites

University of Colorado Cancer Center, Aurora, Colorado

University of Pennsylvania, Philadelphia, Pennsylvania

Massachusetts General Hospital, Boston, Massachusetts

Sarah Cannon Research Institute, Nashville, Tennessee

University Hospitals Case Medical Center, Cleveland, Ohio

MD Anderson Cancer Center, Houston, Texas

Sponsors and Collaborators: Loxo Oncology, Inc.
Contact: Carol Hill +1 (650) 392-0004 Hill@loxoconcology.com

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 I trial. Further study of LOXO-101 will provide further information related to the efficacy of this highly-specific targeted therapy