Pharmacokinetics (PK) of LOXO-101 During the First-in-Human Phase I Study in Patients with Advanced Solid Tumors - Interim Update

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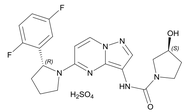
Introduction

TRKA, TRKB, and TRKC Receptors in Cancer

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 TRK kinase domain, mutations involving the TRK ligand-binding site, amplifications of NTRK, TRK splice variants, and autocrine/paracrine signaling are described in diverse tumor types, and may contribute to tumorigenesis (Vaishnavi, Cancer Discov 5:25, 2015).

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.



Structure of LOXO-101

Here we report the first safety and pharmacokinetic data of LOXO-101 in patients.

Study Objectives

Primary

Safety, maximum-tolerated dose (MTD), and recommended dose for further investigation

Secondary

Pharmacokinetic parameters

Methods

Study Design

Phase 1, multicenter, open-label, 3+3 dose-escalation and safety study

Key Eligibility Criteria

Locally advanced or metastatic adult solid tumor that has progressed or was nonresponsive to available therapies and for which no standard or available curative therapy exists; ECOG score of 0 or 1; adequate hematologic, hepatic, and renal function

Drug Treatment

LOXO-101 administered orally for a single day, between 3 and 7 days prior to the start of Cycle 1, followed by QD or BID doses for continuous 28-day cycles

Pharmacokinetics

LOXO-101 concentrations quantified in plasma by a validated LC-MS/MS assay after the single-day dose, and on Days 1 and 8 of Cycle 1

Data cut-off

March 26, 2015

Results

Baseline Characteristics

Characteristics		Subjects (n=15)
Median age (range), years		57, (38-76)
Sex	Male	8
	Female	7
Race	White	12
	Black	3
Tumor Type	Colorectal carcinoma	2
	Head and neck (MASC, synovial sarcoma, squamous cell)	3 (1,1,1)
	Lung (NSCLC, mesothelioma)	3 (2,1)
	Appendiceal peritoneal carcinomatosis	1
	Anal	1
	Thyroid (follicular)	1
	Thymus	1
	Pancreatic	1
	Melanoma	1
	Soft tissue sarcoma	1
ECOG Status	0	7
	1	8
Prior systemic anticancer therapy alone, n (%)		10 (67%)
Prior radiation and systemic anticancer therapy, n (%)*		4 (27%)
Median number of regimens (range)*		3 (0-6)
TRK-fusion positive		1 (*NTRK1*-fusion soft tissue sarcoma)**

*One patient received radiation therapy alone
**Patient enrolled March 10, 2015 and remained on study as of data cut-off

Dose Escalation Summary

Cohort	LOXO-101 Dose Level Achieved	Subjects (n)
1	50 mg QD	4
2	100 mg QD	5
3	100 mg BID	6*

* One patient dose-reduced to 100 mg QD

Summary of Phase 1 Study Status

Status		Subjects (n=15)
On Treatment		4
Off Treatment		11
Reason for discontinuation	Progressive disease	10
	Adverse event	1

Summary of Treatment-Emergent Adverse Events

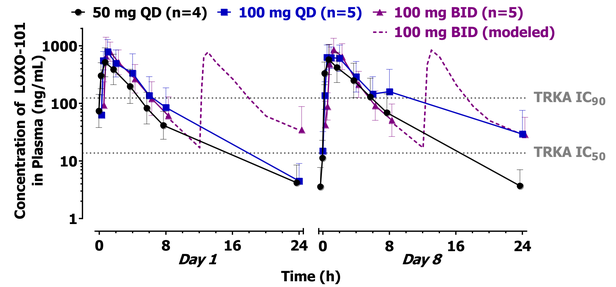
Dose:	50 mg QD (n=4)		100 mg QD (n=5)		100 mg BID (n=6)		Total (n=15)	
Adverse Events (AEs)*	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Fatigue	2 (50%)	1 (25%)	3 (60%)	0	2 (33%)	0	7 (47%)	1 (7%)
Dizziness	2 (50%)	0	0	0	2 (33%)	0	4 (27%)	0
Anemia	2 (50%)	1 (25%)	1 (20%)	1 (20%)	2 (33%)	0	5 (33%)	2 (13%)
Constipation	1 (25%)	0	2 (40%)	0	0	0	3 (20%)	0
Dry mouth	1 (25%)	0	2 (40%)	0	1 (17%)	0	3 (20%)	0
Diarrhea	0	0	1 (20%)	0	1 (17%)	0	2 (13%)	0
Nausea	1 (25%)	0	1 (20%)	0	0	0	2 (13%)	0
Vomiting	1 (25%)	0	1 (20%)	0	0	0	2 (13%)	0
Chills	1 (25%)	0	0	0	1 (17%)	0	2 (13%)	0
Pyrexia	0	0	1 (20%)	0	1 (17%)	0	2 (13%)	0
ALP increased	0	0	0	0	2 (33%)	0	2 (13%)	0
Hyper-glycemia	0	0	1 (20%)	0	1 (17%)	0	2 (13%)	0
Hypokalemia	0	0	1 (20%)	0	1 (17%)	0	2 (13%)	0
Peripheral edema	1 (25%)	0	1 (20%)	0	0	0	2 (13%)	0
Syncope	1 (25%)	1 (25%)	1 (20%)	1 (20%)	0	0	2 (13%)	2 (13%)
Cough	1 (25%)	0	0	0	1 (17%)	0	2 (13%)	0
Rash	2 (50%)	0	0	0	0	0	2 (13%)	0
AST increased	0	0	0	0	1 (17%)	1 (17%)	1 (7%)	1 (7%)
Delirium	0	0	0	0	1 (17%)	1 (17%)	1 (7%)	1 (7%)
Pneumonia	0	0	0	0	1 (17%)	1 (17%)	1 (7%)	1 (7%)

*Treatment-emergent adverse events (reported by > 10% of total subjects) or any Grade 3-4 events; patients were on study between 8 to 64 days

Seven SAEs were reported in four patients and were considered unrelated to study drug: pneumonia, bile duct obstruction, malignant neoplasm progression, pleural effusion, syncope

At the 100-mg BID dose level, one DLT occurred, delirium (Grade 3, deemed unrelated to study drug), which resolved within 72 hours; dose was reduced to 100 mg QD without recurrence

Plasma Concentration-versus-time Profiles



The horizontal line representing TRKA IC_{90} refers to the total plasma concentration of LOXO-101 that is associated with an unbound concentration of LOXO-101 that is equal to its IC_{50} for inhibition of NGF-stimulated activity in a cellular assay. The TRKA IC_{90} is modeled from IC_{50} data. The IC_{50} and IC_{90} values for TRKB and TRKC are not shown, but are similar to those of TRKA.

Pharmacokinetic Parameters of LOXO-101

Day 8 Steady-State PK Parameter (Mean ± SD)	50 mg QD (n=4)	100 mg QD (n=5)	100 mg BID (n=5)
C_{max} (ng/mL)	642 ± 418	925 ± 375	905 ± 552
T_{max} (h)	0.88 ± 0.25	0.90 ± 0.65	0.90 ± 0.22
AUC_{0-24} (ng•h/mL)	2580 ± 2290	4190 ± 3710	5220 ± 3200
$T_{1/2}$ (h)	2.2 ± 0.5	1.8 ± 0.7	1.6 ± 0.3
Cl/F (L/h/kg)	0.42 ± 0.35	0.52 ± 0.31	0.84 ± 0.64
V/F (L/kg)	1.2 ± 1.0	1.2 ± 0.6	1.9 ± 1.3

Non-compartmental pharmacokinetic parameters were calculated by conventional methods. For BID dosing, the AUC between 0 and 12 hours was calculated by log-linear extrapolation of the measured concentrations at 6 and 8 hours through 12 hours. The extrapolated AUC was ≤9% of the AUC in all cases. For BID dosing, AUC_{0-24} was calculated as 2 x AUC_{0-12}.

Summary

In this ongoing first-in-human study of LOXO-101, a total of 15 patients have been evaluated across 3 dose cohorts

LOXO-101 was generally well tolerated with the most common adverse events being Grade 1 and 2 fatigue, dizziness and anemia; no study drug related SAEs have been reported; the MTD has not yet been reached

Pharmacokinetics show good systemic exposure of LOXO-101 after oral dosing

At doses tested thus far, drug levels of LOXO-101 are already at biologically relevant concentrations and support the therapeutic potential of this highly selective inhibitor of TRKA, TRKB, and TRKC