Characterization of TRK Fusions in Papillary Thyroid Carcinomas

An analysis of publicly-available TCGA gene expression data (NTRK) from 513 papillary thyroid cancer tumors revealed the presence of NTRK1-4 (NTRK3) fusions in 30% of tumors. NTRK3 fusions were also observed in three thyroid samples from different patients. NTRK1, NTRK2, and NTRK3 fusions were detected in 12% of tumors.

Study Design

Phase 1, multicenter, open-label, 3+3 dose-escalation and safety study. Three patients will be enrolled at each dose level, with separation cohorts for TRK-fusion patients enrolled at the MTD.

Drug Treatment

LOXO-101 will be administered orally either QD or BID in doses of 40, 80, 100, 200, 300, 400, and 600 mg per day. The maximum tolerated dose (MTD) will be determined based on the incidence of dose-limiting toxicities (DLTs).

Study Objectives

To determine the safety of oral LOXO-101, including dose-limiting toxicity (DLT), in adult patients with an advanced solid tumor that has been identified as harboring a TRK fusion. LOXO-101 will be administered at the MTD or the highest dose level tolerated by patients who do not experience DLTs.

Assessment of Efficacy

Tumor response will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients will be evaluated for response every 3 cycles or sooner if disease progression occurs.

Prophylactic Chemotherapy

Antidepressant

Anxiolytic

Antipsychotic

Mood Stabilizer

Benzodiazepine

Anticonvulsant

Tricyclic antidepressant

Selective serotonin reuptake inhibitor

Extracted Text:

LOXO-101, A Selective Pan-TRK Inhibitor for patients with TRK-alterations

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Abstract

TRK fusion-positive cancers include the fusion of TRK with various partner genes and are mutually exclusive of other known oncogenic mutations (TCGA, 2014 and others). LMNA-NTRK1 and LMNA-NTRK2 fusions have been described in 30% of papillary thyroid carcinomas and are mutually exclusive of other known oncogenic mutations. LOXO-101 is an orally bioavailable, potent, ATP-competitive inhibitor of TRKA, TRKB, and TRKC. LOXO-101 has IC50 values in the low nM range for inhibition of TRK family members in binding and cellular assays, with 100x selectivity over other kinases and the shown acceptable pharmacokinetic properties and safety in preclinical and clinical models.

Results:

NTRK1, NTRK2, and NTRK3 fusions are present in 30% of papillary thyroid cancer tumors and 9% of other cancers. LOXO-101 is a potent, ATP-competitive inhibitor of TRKA, TRKB, and TRKC with 100x selectivity over other kinases.

Methods:

An analysis of publically-available TCGA gene expression data (NTRK) from 513 papillary thyroid cancer tumors revealed the presence of NTRK1-4 (NTRK3) fusions in 30% of tumors. NTRK3 fusions were also observed in three thyroid samples from different patients. NTRK1, NTRK2, and NTRK3 fusions were detected in 12% of tumors.

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Selection of Identified TRK Fusions

One patient received radiation therapy alone (7%) and another received chemotherapy (13%). The most common regimen included carboplatin, paclitaxel, and bevacizumab (20%).

Conclusion

LOXO-101 is a selective pan-TRK inhibitor with promising clinical activity in patients with advanced solid tumors harboring TRK fusions. LOXO-101 is orally bioavailable and has demonstrated acceptable pharmacokinetic properties and safety in preclinical and clinical models.

Dose-Response and Schedule-Dependent Inhibition of Tumor Growth in SK-N-SH Allografts

LOXO-101 caused inhibition of tumor growth at doses of 200 µg/kg/day in either single dose or split dosing.

Conclusions

LOXO-101 is a selective pan-TRK inhibitor with promising clinical activity in patients with advanced solid tumors harboring TRK fusions. LOXO-101 is orally bioavailable and has demonstrated acceptable pharmacokinetic properties and safety in preclinical and clinical models.