Introduction

The fusion ROS1 and ALK have been identified as oncogene drivers in small portions of many malignancies, especially in non-small cell lung cancer (NSCLC). ALK/ROS1 inhibitors have been approved by the US Food and Drug Administration for the treatment of ALK or ROS1-positive non-small cell lung cancer in 2016 and 2017, respectively. The emergence of drug resistance presents a major issue for targeted therapy. Although crizotinib, alelectinib and brigatinib have been approved for crizotinib-refractory ALK+ patients with NSCLC, treatment options for patients with ROS1+ NSCLC are limited, especially for crizotinib-refractory patients. Centrinib and entrectinib demonstrated clinical efficacy only in crizotinib-naïve ROS1+ patients. The most common resistance mechanisms to crizotinib treatment in ROS1+ NSCLC are the solvent front mutation ROS1 G2032R and gatekeeper mutation ROS1 L2026M. TPX-0005, a novel triple domain macrocyclic with a much smaller size than current ROS1 inhibitors in the clinic, was designed to overcome clinical resistance mutations systematically. TPX-0005 potently inhibited both wild type and mutant ROS1s including solvent front mutants and gatekeeper mutants. TPX-0005 showed pro-motor activity against ROS1 kinase (IC50 0.706 nM) in Reactivation Biology kinase assay. The comparison of TPX-0005 with other ROS1 inhibitors in Ba/F3 cell proliferation assays is presented in the table. In the xenograft tumor model studies, TPX-0005 dramatically caused tumor regression in the tumors carrying WT or solvent-front mutated ROS1 fusion gene. Overall, TPX-0005 demonstrated desired drug-like properties, good safety profile, and is a supreme ROS1 inhibitor against WT and various mutated ROS1s. A Phase 1/2 clinical trial of TPX-0005 is actively pursued (NCT03093116).

TPX-0005 is designed to overcome resistances systematically

- TPX-0005 is a polypharmacology kinase inhibitor
- TPX-0005 kinase selectivity profile over 395 non-mutant kinases (screened at DiscoveRx)

ROS1 mutations and ROS1 inhibitor structures

Conclusions

- The compact three dimensional structure of TPX-0005 allows it to bind WITHIN the ATP binding pocket with high affinity and be able to target both wild type and mutant kinases.
- TPX-0005 potently inhibited WT and mutant ROS1s in vitro and in vivo, especially the solvent front mutations which render common resistances to ROS1 inhibitors that are currently in clinic.
- TPX-0005 has good drug like properties, and is able to address the unmet medical needs for patients that are resistant to ROS1 inhibitors.
- A Phase 1/2 clinical trial is on-going for TPX-0005 for cancer patients with solid tumors harboring ALK+ or NTRK fusion gene (NCT01309316).

Reference