Repotrectinib, a new generation ROS1 inhibitor, is highly potent against fusion ROS1s and emerging resistance mutations

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Introduction

ROS1 gene fusions (ROS1+) have been identified as oncogenic drivers in many malignancies, especially in non-small cell lung cancer (NSCLC). ALK/ROS1/MET inhibitor crizotinib is the only drug approved for the treatment of ROS1+ NSCLC. 1 The efficacy of crizotinib in ROS1+ NSCLC varied among different types of ROS1 fusion partners and patients with the most dominant fusion CD74-ROS1+ had a higher brain metastasis rate and shorter overall survival. 2 In addition, the emergence of drug resistance presents a major obstacle for targeted therapy. The most common resistance mutations to crizotinib treatment in ROS1+ NSCLC are the solvent front mutation (SFM) ROS1 G2032R and the gatekeeper mutation ROS1 L2026M. Repotrectinib (TPX-0005) was designed to overcome clinical resistance mutations systematically. The activity of repotrectinib against ROS1 fusions with different partner genes and also with additional ROS1 resistance mutations was investigated. Repotrectinib potently inhibited both wildtype (WT) and mutant ROS1 fusions including SFMs and gatekeeper mutations. In cell growth assays using engineered Ba/F3 cells expressing ROS1 fusions with several partners, such as CD44, C0D4, TPRM3 and E2R, repotrectinib demonstrated superior potency in comparison to other ROS1 inhibitors against multiple ROS1 mutations, especially SFMs and gatekeeper mutations. In xenograft tumor model studies, repotrectinib treatment resulted in pronounced regression of the tumors harboring WT or SFM ROS1 fusion genes. Overall, repotrectinib demonstrated a profound inhibition profile against WT and various mutated ROS1 fusions with several partners. A Phase 1/2 clinical trial of repotrectinib is currently ongoing (TRIDENT 1, NCT03081116).

Repotrectinib is a highly potent ROS1 inhibitor

- Repotrectinib potently inhibited wildtype and mutant ROS1s at 10 μM ATP

- Inhibition of cell proliferation in Ba/F3 cell lines by ROS1 inhibitors

Ba/F3 Cell Proliferation IC50 (nM)

<table>
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<th>Inhibitor</th>
<th>CD74-ROS1</th>
<th>ROS1 G2032R</th>
<th>TPRM3-ROS1</th>
<th>CD74-ROS1</th>
<th>ROS1 G2032R</th>
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Efficacy of repotrectinib in xenograft tumor models

- Antitumor effect of repotrectinib in a Ba/F3 cell-derived xenograft model with the CD74-ROS1 fusion gene

- Antitumor effect of repotrectinib in a patient-derived xenograft model of lung cancer with the CD74-ROS1 fusion gene

Conclusions

- The compact, 3-dimensional macroscopic structure of repotrectinib allows it to bind completely inside the ATP pocket of the target kinase with greater precision and affinity and be able to target both wildtype and mutant kinases with high potency
- Repotrectinib potently inhibited multiple WT and mutant ROS1 fusions, regardless of fusion partners
- Repotrectinib is the most potent Type I ROS1 inhibitor against the SFM G2032R that is the major resistant mechanism developed after crizotinib treatment
- Repotrectinib has been well tolerated in the on-going Phase 1 portion of the TRIDENT-1 clinical trial and this preclinical data support that repotrectinib has great potential to address the unmet medical need for patients that are resistant to first generation ROS1 inhibitors
- A Phase 1/2 clinical trial of repotrectinib is on-going for patients with advanced solid tumors harboring ROS1, NTRK1-3, or ALK fusion (NCT03093116)

Reference