TPX-0022, a polypharmacology inhibitor of MET/CSF1R/SRC for treatment of cancers with abnormal HGF/MET signaling

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Poster #1321

Introduction

Aberrant activation of the HGF-MET pathway has frequently been observed in human cancers including MET mutation, gene amplification and translocation, as well as paracrine or autocrine HGF upregulation. The abnormal HGF-MET signaling not only acts as an oncogenic driver but also confers resistance to many cancer therapies, such as EGFR targeted therapy in NSCLC.1,2 One key downstream effector of activated MET is SRC, which is also involved in malignancy formation, tumor metastasis and drug resistance.3 The tumor microenvironment, CSF1R plays an important role in regulation of tumor associated macrophages, which promote tumor progression and angiogenesis.4 Therefore, the polypharmacological inhibition of MET/ CSF1R/SRC has great potential to target cancers with abnormal HGF/MET signaling more effectively by simultaneously targeting tumor intrinsic signaling and the tumor microenvironment.

TPX-0022, a novel macrocyclic compound, has been designed based on the unique autocrine crystal structure of MET and optimized to inhibit MET/CSF1R/SRC with enzymatic kinase inhibition IC50 of 0.14, 0.71 and 0.12 nM, respectively. TPX-0022 potently inhibited cell proliferation of the MET-amplified MKN45 and SNU-5 gastric cancer cells, with IC50 of 0.2 nM, which ranks it as one of the most potent MET inhibitors. TPX-0022 suppressed MET auto-phosphorylation at an IC50 of approximately 0.3 nM in the MKN45 cell line. TPX-0022 also potently suppressed the phosphorylation of MET downstream signaling effectors, including AKT, ERK, STAT3 and PLCγ2 in a dose-dependent manner. In the cancer cell line and patient-derived xenograft tumor models from gastric, lung and liver cancers harboring MET amplification or MET exon14 skipping (Δex14) mutations, TPX-0022 treatment resulted in marked tumor regression and tumor growth inhibition (up to 85.3% tumor regression), without overt abnormality and body weight loss in treated mice.

Overall, TPX-0022 is a novel and potent MET inhibitor with desirable drug-like properties, a good preclinical safety profile, that warrants further clinical development and an IND submission is currently planned. The activity of TPX-0022 against CSF1R in vitro and in vivo will be presented at Poster # 1325 (Abstract #3749).

TPX-0022 potent inhibition of MET in cell-based assays

- Novel structure as first MET macrocyclic kinase inhibitor
- Modeling of TPX-0022 in the complex with MET kinase domain (PDB ID 2W4L)
- Hinge hydrogen bond with Y1230
- Strong α-helix interaction with Y1230
- Hydrogen bond with D1222
  - Kinase inhibition IC50 of TPX-0022 on MET, CSF1R and SRC at 10 µM of ATP

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<thead>
<tr>
<th>Enzyme</th>
<th>IC50 (nM)</th>
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<tr>
<td>MET</td>
<td>0.14</td>
</tr>
<tr>
<td>SRC</td>
<td>0.12</td>
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<tr>
<td>CSF1R</td>
<td>0.71</td>
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<tr>
<td>TPX-0022</td>
<td>0.20</td>
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<tr>
<td>Capmatinib</td>
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<td>Crizotinib</td>
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TPX-0022 potently inhibited MET in cell-based assays

- TPX-0022 inhibited cell proliferation in MKN45 and SNU-5 cell lines with potency that is comparable to capmatinib and is more than 10 fold more potent than crizotinib
- TPX-0022 inhibited MET phosphorylation in MKN45 and SNU-5 cell lines
- TPX-0022 suppressed the phosphorylation of MET downstream effectors in MKN45 cells
- TPX-0022 demonstrated a dose-dependent inhibition of MKN-45 tumor growth in nude mice
- Treatment with TPX-0022 at 15 mg/kg/BID resulted in 85.3% tumor regression in LU2503 Huvaxi® lung cancer PDX mouse tumor model, which has MET Δex14 mutation and MET gene amplification
- No body weight loss and overt abnormality were observed

TPX-0022 Inhibited tumor growth in PDX models

- TPX-0022 achieved 82.1% tumor growth inhibition and 17.6% tumor regression when dosed at 5 and 15 mg/kg BID, respectively, in LOVo12 Huvaxi® hepatocellular carcinoma PDX mouse model with MET gene amplification
- No body weight loss and overt abnormality were observed

TPX-0022 Inhibited MKN-45 tumor growth In vivo

- TPX-0022, a novel compact three-dimensional macrocyclic molecule, designed based on the unique crystal structure of MET to efficiently target the MET kinase in the autocrine signaling pathway
- In biochemical and cell based assays, TPX-0022 is one of the most potent MET inhibitors in clinical development
- TPX-0022 demonstrated marked antitumor effect in the MKN-45 gastric cancer xenograft tumors with MET gene amplification, lung cancer PDX tumors harboring ME7αex14 mutation and MET gene amplification and HCC PDX tumors with MET amplification
- TPX-0022 has promising drug-like properties, and the novel polypharmacological profile inhibiting MET/CSF1R/SRC that has the potential to inhibit MET as an oncogenic driver and alter the tumor microenvironment to affect anti-tumor activity via inhibition of CSF1R
- TPX-0022 IND submission is planned for the first half of this year and a Phase 1 clinical trial initiated in the second half of this year

Conclusions

- TPX-0022, a novel compact three-dimensional macrocyclic molecule, designed based on the unique crystal structure of MET to efficiently target the MET kinase in the autocrine signaling pathway
- In biochemical and cell based assays, TPX-0022 is one of the most potent MET inhibitors in clinical development
- TPX-0022 demonstrated marked antitumor effect in the MKN-45 gastric cancer xenograft tumors with MET gene amplification, lung cancer PDX tumors harboring ME7αex14 mutation and MET gene amplification and HCC PDX tumors with MET amplification
- TPX-0022 has promising drug-like properties, and the novel polypharmacological profile inhibiting MET/CSF1R/SRC that has the potential to inhibit MET as an oncogenic driver and alter the tumor microenvironment to affect anti-tumor activity via inhibition of CSF1R
- TPX-0022 IND submission is planned for the first half of this year and a Phase 1 clinical trial initiated in the second half of this year

Reference


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