TPX-0046 is a novel and potent RET/SRC inhibitor for RET-driven cancers.

**INTRODUCTION**

- Oncogenic activation of the receptor tyrosine kinase (RTK) rearranged during transfection (RET) via point mutation or genomic rearrangement has been identified in multiple cancers, including medullary and papillary thyroid cancers, and non-small cell lung cancer (NSCLC).

- Two multi-kinase inhibitors with demonstrated RET activity, vandetanib and cabozantinib, have been approved for thyroid cancer.

- Current investigational selective RET inhibitors BLU-667 and LOXO-292 have demonstrated efficacy in RET aberrant NSCLC and thyroid cancers.

- TPX-0046 is designed with a macrocyclic structure targeting the RET active conformation (Figure 1D).

**KINASE SELECTIVITY OF TPX-0046**

- TPX-0046, with a molecular weight (MW) < 430, is much more compact than BLU-667 (MW 533.6) and LOXO-292 (MW 529.6).

- Based on our modeling, TPX-0046 is structurally distinguished from BLU-667 and LOXO-292, and was designed to overcome potential RET TKI resistant mutations that we predict may develop after either BLU-667 or LOXO-292 treatment.

**KINASE SELECTIVITY OF TPX-0046 (CONTINUED)**

- TPX-0046 had potent inhibition against RET and SRC family kinases (highlighted in red).

- TPX-0046 is potent against wildtype (WT) and mutant RET in comparison with BLU-667 and LOXO-292 in the enzymatic assay (Table 2).

- The results of the Ba/F3 cell proliferation assays and western blots are presented in Table 3 and Figure 2, respectively.

**EVALUATION OF TPX-0046 IN VITRO ASSAYS**

- In comparison with BLU-667 and LOXO-292, TPX-0046 has comparable activity against KIF5B-RET WT and Y806N.

- TPX-0046 is more potent against SMFs KIF5B-RET (G810S and G810R; TT (C634W) cell-derived models and the lung cancer PDX model harboring RET (V804M). TPX-0046 is less potent against gatekeeper mutation KIF5B-RET V804M.

**EVALUATION OF TPX-0046 IN VIVO TUMOR MODELS**

- TPX-0046 demonstrates marked antitumor effects in xenograft tumor models, including Ba/F3 KIF5B-RET WT and G810R, TT (E634W) cell-derived models and the lung cancer PDX model harboring KIF5B-RET fusion and papillary cancer (FCX-RET fusion) harboring NCOA4-RET fusion (Figure 3).

- Dose-dependent inhibition of RET phosphorylation was observed in the Ba/F3 KIF5B-RET cell-derived tumor model.

**CONCLUSIONS**

- TPX-0046 has potent activity against a broad array of disease-relevant RET mutations including the solvent front mutation G810R, which is predicted to cause resistance to current RET TKIs including BLU-667 and LOXO-292.

- TPX-0046 has promising drug-like properties and a unique pharmacology profile that warrant clinical studies in advanced solid tumors with RET gene alterations.

- IND has been submitted.

**REFERENCES & DISCLOSURES**

- TPX-0046 is a novel and potent RET/SRC inhibitor for RET-driven cancers. Turning Point Therapeutics – employment/consultancy.

**ACKNOWLEDGMENTS**

- Turning Point Therapeutics – employment/consultancy.

**DISCLOSURE**

- TPX-0046 is a novel and potent RET/SRC inhibitor for RET-driven cancers. Turning Point Therapeutics – employment/consultancy.

**Author Contributions**

- TPX-0046 is a novel and potent RET/SRC inhibitor for RET-driven cancers. Turning Point Therapeutics – employment/consultancy.

**Funding**

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