HMPL-453, a highly selective inhibitor of fibroblast growth factor receptors 1, 2, and 3, displays potent activity in FGFR-altered tumor models


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INTRODUCTION

- Fibroblast growth factors (FGFs) and their receptors (FGFRs) regulate numerous cellular processes. Dysregulation of FGFR signaling due to receptor fusion, mutation or amplification is observed across multiple cancer types, making activated FGFRs an important therapeutic target.

- HMPL-453, discovered by HUTCHMED, is a highly potent and selective inhibitor of FGFR1, 2, and 3, currently being developed in phase II clinical trial (NCT04355375). Preclinical data of HMPL-453 are summarized in this poster.

METHODS

- **Cell viability assay**: Different tumor cell lines were treated with HMPL-453 in a serial diluted concentrations for 72 hours and cell viability was measured by CellTiter-Glo luminescent or CCK8 assay.

- **Signaling pathway**: Cells were incubated with a serial dilution of HMPL-453 for 1 hour and lysed for western blot assay.

- **Pharmacokinetics and pharmacodynamics (PK/PD) studies**: Subcutaneous tumor-bearing nude mice were treated with a single oral dose of HMPL-453 and euthanized at different time points. Tumor tissue was analyzed via IHC or IHC/FISH (FGFR3/164) and FGFR2 western blot assay. Meanwhile, plasma concentration of HMPL-453 was determined by LC/MS/MS method.

- **In vivo antitumor efficacy study**: Multiple tumor models with FGFR2 or FGFR3 alterations were used in nude mice to determine antitumor efficacy of HMPL-453 as a single agent or in combination with chemotherapy. The combination effect of HMPL-453 with antineoplastic PAI-1 antibody was evaluated in immunocompetent BALB/c mice inoculated with the constructed NCI-OT1 cells carrying FGFR2V564I fusion. All models were established by subcutaneously implating tumor cells into mice. Tumor volume was measured to assess tumor growth inhibition.

- **Immunohistochemistry (IHC) and immunofluorescence (IF) staining assay**: Paraffin-embedded tumor samples were sectioned and stained with primary antibodies followed by biotinylated or fluorescently conjugated secondary antibodies. For quantification, 35 images for each sample were randomly chosen, and staining signals were quantified by Image J software.

RESULTS

- **Figure 1. HMPL-453 is a highly potent and selective inhibitor of FGFR1, 2, and 3**

- **Figure 2. HMPL-453 selectively inhibited the growth of tumor cell lines with activation of FGFR signaling**

- **Figure 3. Oral administration of HMPL-453 demonstrated strong target inhibition in vivo**

- **Figure 4. HMPL-453 induced tumor regression in multiple FGFR-altered tumor models**

- **Figure 5. HMPL-453 enhanced anti-tumor effect of chemotherapy in an FGFR2 fusion model**

SUMMARY

- **HMPL-453 is a highly potent and selective inhibitor of FGFR 1, 2, and 3 with strong activity against FGFR-deregulated tumors in preclinical models.**

- **Combination with HMPL-453 significantly improved anti-tumor activity of chemotherapy as well as PD-1 blockade in an FGFR-altered tumor model.**

- **The preclinical studies support clinical evaluations of HMPL-453 as either a single agent or in combination with other therapeutic agents for the treatment of advanced solid tumors harboring FGFR alterations.**

References
