Preclinical characterization of HMPL-415, a second-generation SHP2 inhibitor

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INTRODUCTION

- Oncogenic activation of the RAS/MAPK signaling pathway is one of the leading causes for driving a variety of cancers.1,2 SeroLogic: containing protein tyrosine phosphatase 2 (SHP2) functions downstream of multiple RTKs, and integrates growth factor signals to promote RAS activation.3 Preclinical evidences suggest that suppression of SHP2 activity displays strong activity against a wide spectrum of tumor models, especially those with KRAS41, BRAF42, or NRAS43 alterations.

- Herein, we present the preclinical characterization of HMPL-415, a highly potent, selective, and non-competitive SHP2 inhibitor, discovered and is being developed by HUTCHMED.

RESULTS

Figure 1. HMPL-415 is a potent, selective, and non-competitive inhibitor of human SHP2

Figure 2. HMPL-415 potently inhibited RAS/MAPK pathway signaling

Figure 3. HMPL-415 exhibited anti-proliferation activity in RAS/MAPK pathway-dysregulated cell lines

Figure 4. HMPL-415 showed prolonged and high tumor exposure with sustained pathway inhibition after repeat dosing

Figure 5. HMPL-415 demonstrated anti-tumor activity in tumor models with KRAS alterations

Figure 6. HMPL-415 demonstrated anti-tumor activity in class III BRAF, NF1LOF and EGFR mutant tumor models

Figure 7. Intermittent dosing of HMPL-415 also achieved strong anti-tumor efficacy

 SUMMARY

- HMPL-415 is a potent, selective, and non-competitive SHP2 inhibitor with strong activity against multiple RAS/MAPK activated tumor models.

- HMPL-415 monotherapy is currently being evaluated in the Phase I clinical study in patients with advanced malignant solid tumors (NCT0586374).

REFERENCES


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