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

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Abstract #35050

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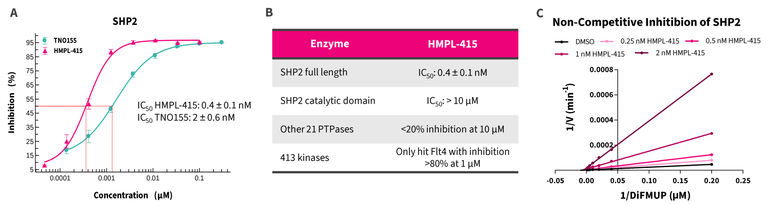
INTRODUCTION

- Oncogenic activation of the RAS/MAPK signaling pathway is one of the leading causes for driving a variety of cancers[1]. Src homology 2-containing protein tyrosine phosphatase 2 (SHP2) functions downstream of multiple RTKs, and integrates growth factor signals to promote RAS activation[2]. Preclinical evidences suggest that suppression of SHP2 activity displays strong activity against a wide spectrum of tumor models, especially those with $KRAS^{G12C}$, Class Ⅲ BRAF, NF1 loss of function mutations or RTK alterations[3].
- 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

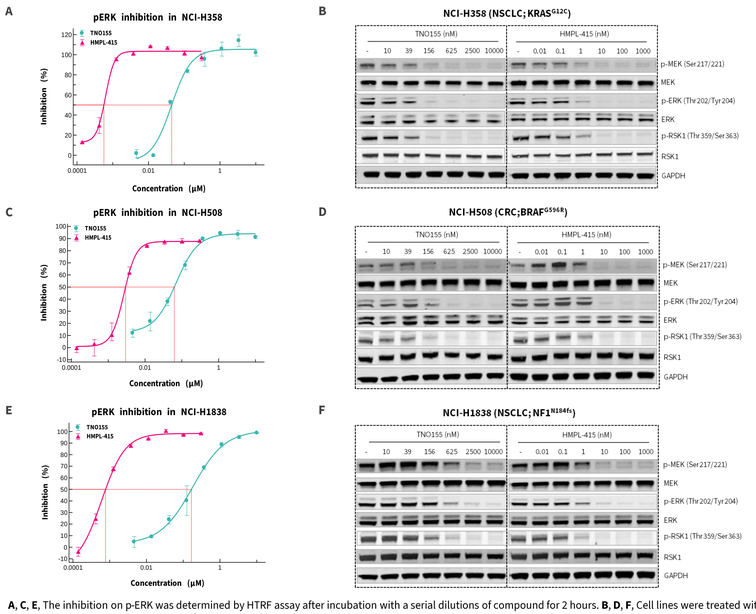
Figure 1. HMPL-415 is a potent, selective, and non-competitive inhibitor of human SHP2



Enzyme	HMPL-415
SHP2 full length	IC_{50}: 0.4 ± 0.1 nM
SHP2 catalytic domain	IC_{50}: > 10 μM
Other 21 PTPases	<20% inhibition at 10 μM
413 kinases	Only hit Flt4 with inhibition >80% at 1 μM

A-B, Inhibition of HMPL-415 on the full length (**A**) and catalytic domain (**B**) of SHP2 was detected by a biochemical DIFMUP pseudosubstracte-fluorgenic assay. The IC_{50} value was shown as mean ± SD, n=3. For selectivity, HMPL-415 was assessed against a panel of 413 kinases (at 1 μM) and 21 phosphatases (at 10 μM) by Eurofins. **C**, To characterize the competitiveness of HMPL-415, the inhibition on SHP2's catalyzed reaction rate was determined at various DIFMUP concentrations using biochemical assay. The velocity's reciprocal(1/V) was pooled and plotted against 1/[DIFMUP].

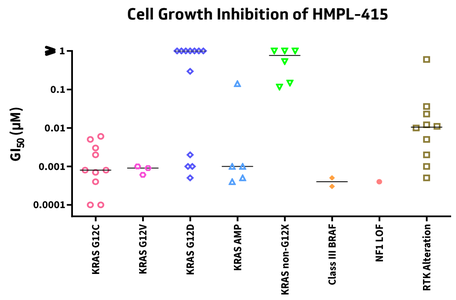
Figure 2. HMPL-415 potently inhibited RAS/MAPK pathway signaling



A, **C**, **E**, The inhibition on p-ERK was determined by HTRF assay after incubation with a serial dilutions of compound for 2 hours. **B**, **D**, **F**, Cell lines were treated with compound at indicated concentrations for 2 hours and lysed for western blot assay to assess the modulation on RAS/MAPK cascades.

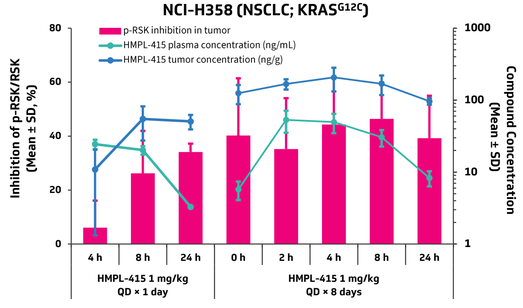
RESULTS

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



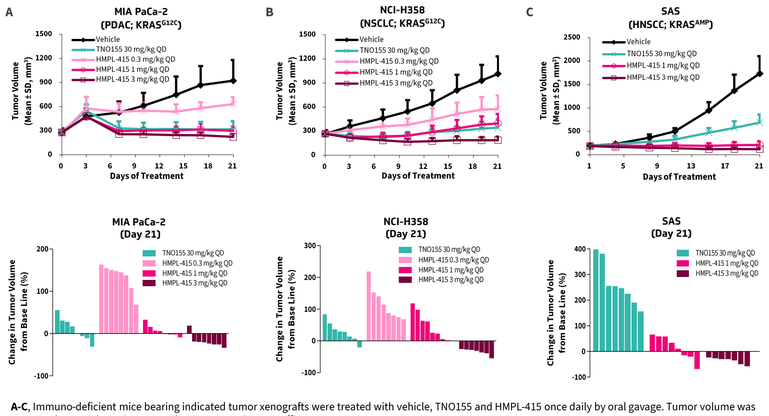
Forty-nine tumor cell lines with RAS/MAPK pathway activation were treated with HMPL-415 and anti-proliferation activity was determined by CellTiter-Glo luminescent assay. Cell lines with RTK alterations were cultured in standard 2-dimensional growth condition and treated with HMPL-415 for 72 hours. Cell lines with *KRAS* alterations, Class III BRAF and NF1 loss of function (LOF) mutations were cultured in 3D spheroid growth condition and treated with HMPL-415 for 120 hours.

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



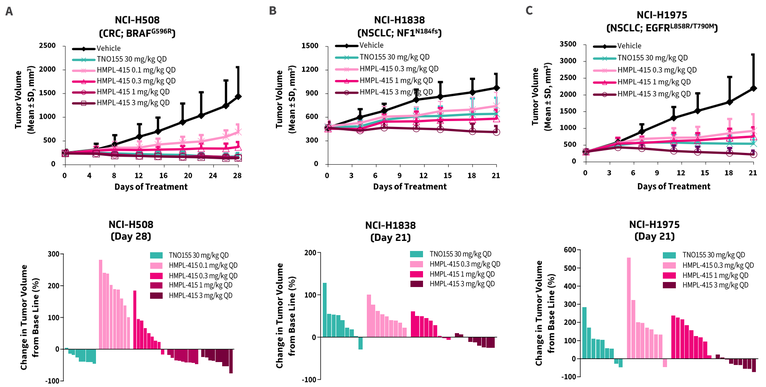
NCI-H358 xenograft-bearing mice were orally-dosed with 1 mg/kg HMPL-415 and euthanized at different time points post administration of the last dose. Tumor tissues were analyzed for p-RSK (Ser363/Thr359) and RSK by western blot assay. Meanwhile, tumor and plasma concentration of HMPL-415 was determined by LC-MS/MS .

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



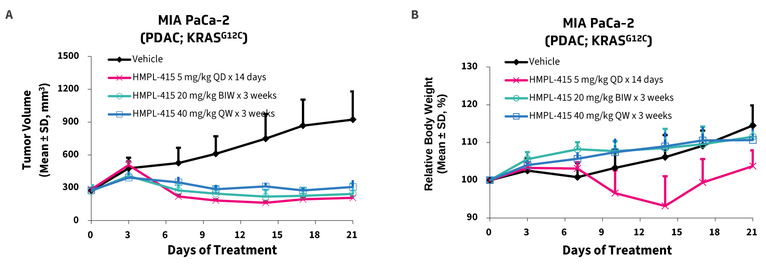
A-C, Immuno-deficient mice bearing indicated tumor xenografts were treated with vehicle, TNO155 and HMPL-415 once daily by oral gavage. Tumor volume was measured two or three times a week to assess anti-tumor efficacy.

Figure 6. HMPL-415 demonstrated anti-tumor activity in class Ⅲ BRAF, $NF1^{LOF}$ and EGFR mutant tumor models



A-C, Immuno-deficient mice bearing indicated tumor xenografts were treated with vehicle, TNO155 and HMPL-415 once daily by oral gavage. Tumor volume was measured two or three times a week to assess anti-tumor efficacy.

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



A-B, The MIA PaCa-2 tumor bearing nude mice were orally treated with vehicle, 5 mg/kg HMPL-415 (daily dosing for 14 days), 20 mg/kg HMPL-415 (twice a week for 3 weeks), and 40 mg/kg HMPL-415 (once a week for 3 weeks). Tumor volume was measured twice a week to assess 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 (NCT05886374).**

References

1. Dhillon AS et al. Oncogene. 2007 May 14;26(22):3279-90.
2. Prahallad A et al. Cell Rep. 2015 Sep 29;12(12):1978-85.
3. Nichols RJ et al. Nat Cell Biol. 2018 Sep;20(9):1064-1073.

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