Hanmi HM99462, a Novel SOS1 Inhibitor, Induces Tumor Regression and Synergistic Effect with KRAS or EGFR Targeted Therapy in Solid Tumors

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Introduction

KRAS and EGFR mutations are prevalent in solid tumors.^{1),2)} Targeting these mutations with mutant-selective inhibitors can lead to significant tumor regression. However, approved KRAS and EGFR inhibitors have shown limited responses and adaptive resistance.^{3),4)} Currently, combinatorial strategies are being explored to overcome resistance mechanisms.⁵⁾ SOS1, a guanine nucleotide exchange factor (GEF) that activates KRAS, has been targeted to prevent RTK-KRAS-MAPK mediated bypass signaling and delay resistance. Several pharmaceutical companies are currently testing the combination of KRAS and EGFR inhibitors with SOS1 inhibitors in preclinical studies to overcome resistance and achieve durable responses.⁶⁾

Previously, we demonstrated the synergistic effects of a SOS1 inhibitor, HM99462, with

Antitumor Activity in Combination with KRAS G12C Inhibitor

✤ H1373 (KRAS^{G12C}, NSCLC)



KRAS G12C or MEK inhibitors in *in vitro* and *in vivo* studies. Furthermore, HM99462 can suppress the development of resistance and induce tumor regression through combination with various EGFR inhibitors.

****p<0.0001 vs Sotorasib 30 mg/kg group; mixed-effect model with Tukey's multiple comparison test.

SW837(KRAS^{G12C}, CRC)

Abstract #82



#p<0.05, ####p<0.001 vs Vehicle control group; ***p<0.001, ****p<0.0001 vs Trametinib 0.1 mg/kg group; mixed-effect model with Tukey's multiple comparison test.

SOS1::KRAS Protein-Protein Interaction Assay

Possibility to Overcome Osimertinib Resistance by HM99462

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*The maximum IC_{50} value of the bar graph is 1,000 nM.

Concluding Remarks



^{**}p<0.01, ****p<0.0001 vs Osimertinib 1 mg/kg or Lazertinib 1 mg/kg group; mixed-effect model with Tukey's multiple comparison test.

- HM99462 shows potential as a therapeutic agent for cancers associated with the hyperactivation of oncogenic KRAS or RTK signaling.
- *In vitro* and *in vivo* studies have demonstrated the synergistic effects of HM99462 when combined with RTK-KRAS-MAPK signaling inhibitors, highlighting its potential to enhance treatment responses in NSCLC patients with EGFR mutations.
- HM99462 is currently preparing IND dossiers for clinical study.

References

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- 7) Schematic illustration was created with BioRender.com.

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