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

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Abstract #82

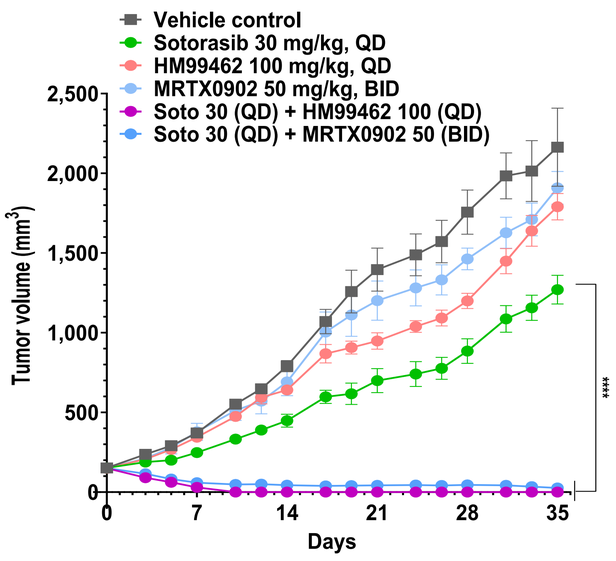
Introduction

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)]

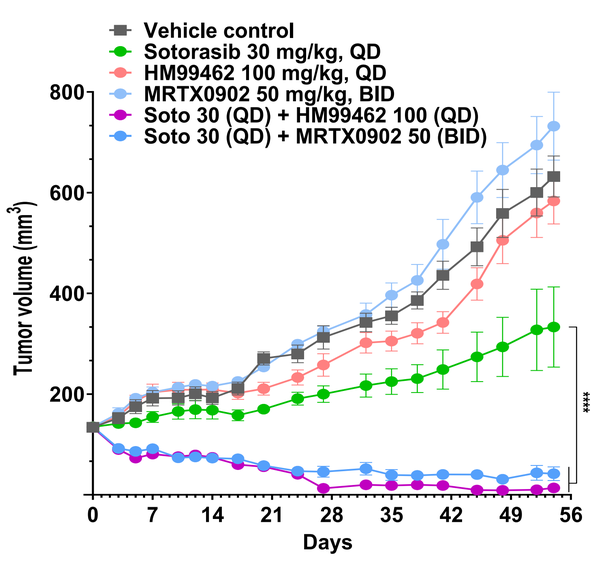
Previously, we demonstrated the synergistic effects of a SOS1 inhibitor, HM99462, with KRAS G12C or MEK inhibitors in *in vitro* and *in vivo* studies. Furthermore, HM99462 can suppress the development of resistance and induce tumor regression through combination with various EGFR inhibitors.

Antitumor Activity in Combination with KRAS G12C Inhibitor

❖ H1373 (KRAS^{G12C}, NSCLC)

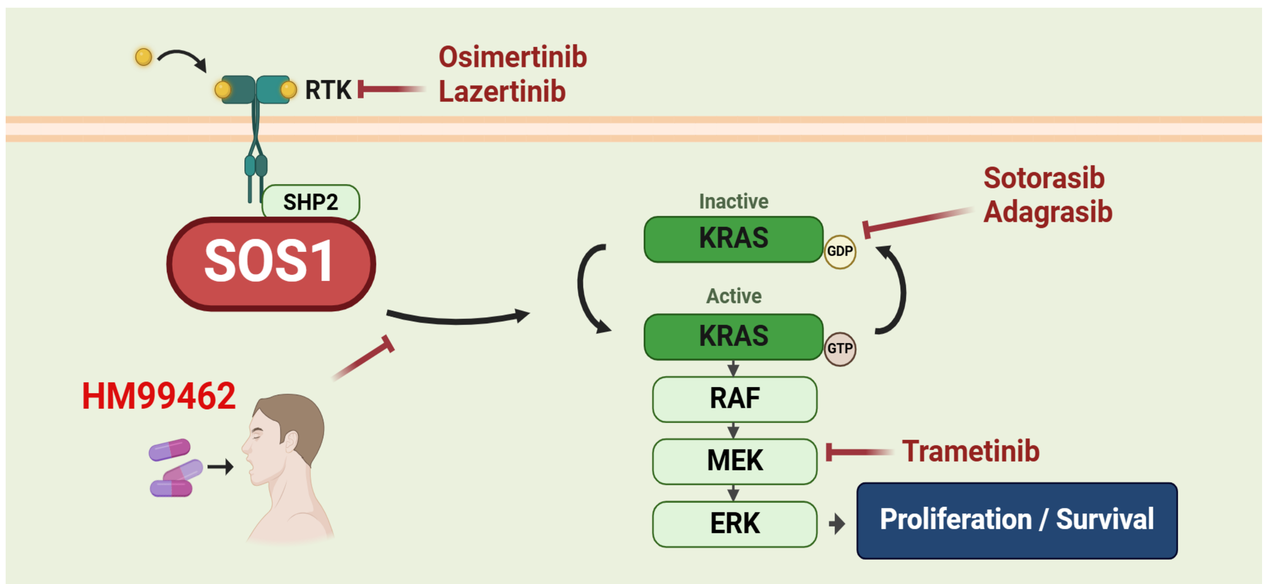


❖ SW837(KRAS^{G12C}, CRC)



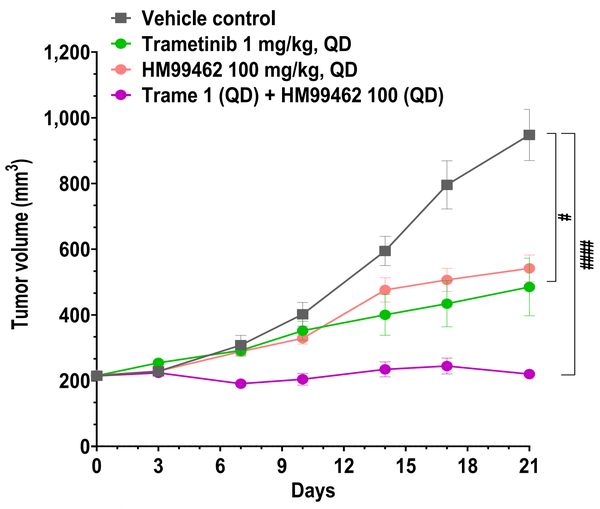
****p<0.0001 *vs* Sotorasib 30 mg/kg group; mixed-effect model with Tukey's multiple comparison test.

Signaling Pathway of SOS1 and RTK-KRAS-MAPK[7)]

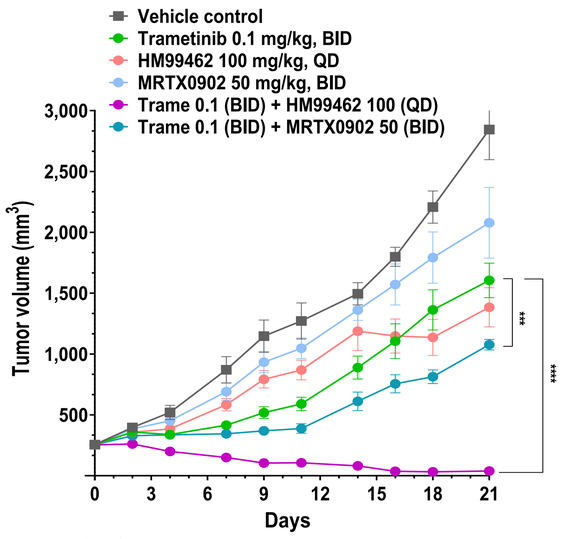


Antitumor Activity in Combination with MEK Inhibitor

❖ MIA PaCa-2 (KRAS^{G12C}, PDAC)



❖ AsPC-1 (KRAS^{G12D}, PDAC)



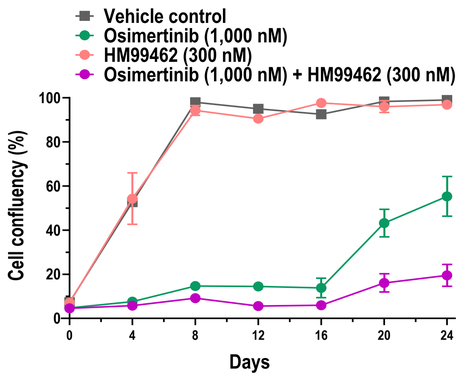
#p<0.05, ####p<0.001 *vs* Vehicle control group; ***p<0.001, ****p<0.0001 *vs* Trametinib 0.1 mg/kg group; mixed-effect model with Tukey's multiple comparison test.

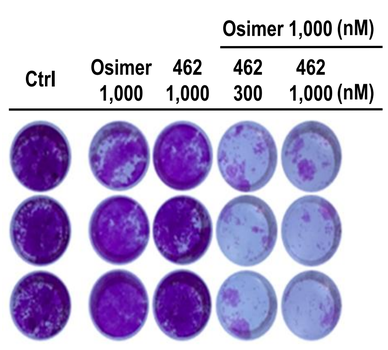
SOS1::KRAS Protein-Protein Interaction Assay

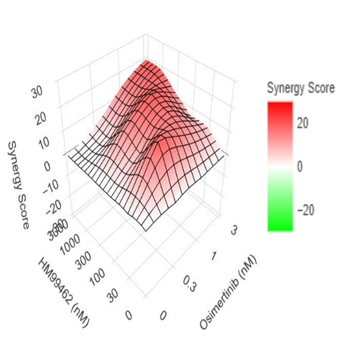
SOS1::KRAS mutant	Target inhibition (IC_{50}, nM)	
	HM99462	MRTX0902
SOS1::KRAS WT	9.9	9.3
SOS1::KRAS G12C	18	17
SOS1::KRAS G12D	15	14
SOS2::KRAS G12C	5,321	~10,000

Possibility to Overcome Osimertinib Resistance by HM99462

❖ Overcoming Resistance of Osimertinib-persistent H1975 Cells ❖ *In vitro* Combination*







*The synergistic effect was evaluated using a 3D spheroid assay and HSA modeling in the H1975 cell line.

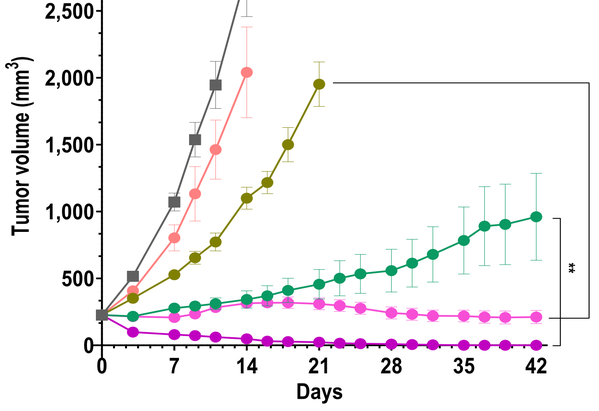
Inhibition of 3D Spheroid in KRAS-driven Cancer Cell Lines

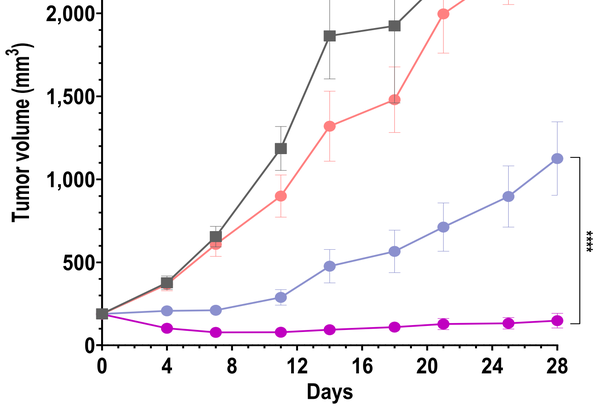
Cell line	Cancer type	Mutation												3D (IC_{50}, nM)*	
		KRAS	EGFR	ERBB2-4	RAF	PIK3C	TP53	APC	CDKN2A	SMAD4	STK11	KEAP1	NF1	HM99462	MRTX0902
H1373	NSCLC	G12C													
SW837	CRC	G12C													
MIA PaCa-2	PDAC	G12C													
AcPC-1	PDAC	G12D													

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

Antitumor Activity in Combination with EGFR Inhibitors

❖ NCI-H1975 (EGFR$^{L858R/T790M}$, NSCLC)





**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.

Concluding Remarks

- 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

1) Huang, L., *et al*., *Signal Transduct. Target Ther.* **2021**, *6*, 386;
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3) Yaeger, R., *et al*., *Cancer Discovery*. **2023**, *13*, 41;
4) Stewart, Erin L., *et al*., *Transl. Lung. Cancer. Res.* **2015**, *4*, 67;
5) He, Yan, *et al*., *Signal Transduct. Target Ther.* **2021**, *6*, 425;
6) Hirotaka Miyashita., *et al*., *Frontiers in Oncology.* **2024**, *14*, 1380584;
7) Schematic illustration was created with BioRender.com.