A Novel SOS1 Inhibitor, HM99462, Demonstrates Antitumor Activity against KRAS-Mutant Cancers

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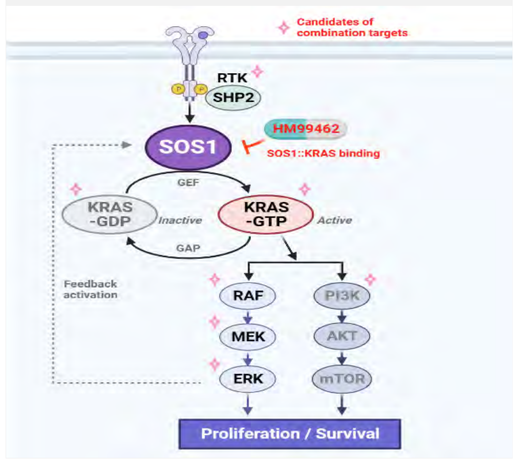
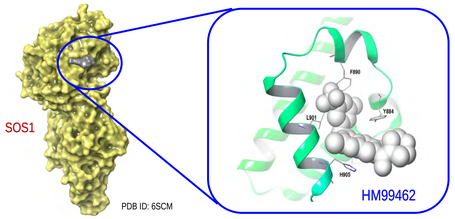
Introduction

KRAS is one of the well-known oncogenic driver and most commonly mutated gene in various cancers. KRAS cycles between GDP-loaded 'off' and GTP-loaded 'on' states inducing downstream signal transduction to promote cell proliferation and survival[1-2]. Interconversion between 'on' and 'off' states is modulated by SOS (Son of sevenless), a binary molecular switch of KRAS. SOS family as a guanine-nucleotide exchange factor (GEF) is composed of SOS1 and SOS2, but SOS1 is a node in the negative feedback regulation of the KRAS pathway while SOS2 is not[3]. Since SOS1 is a direct upstream of KRAS, SOS1 inhibitor has the potential to be a pan-KRAS inhibitor affecting various cancers harboring diverse KRAS mutations. Herein, we explored the novel SOS1 inhibitor, HM99462, in combination with KRAS G12Ci or MAPK pathway inhibitor resulted a significant increase of antitumor activity in KRAS-driven cancers.

Schematic Signaling Pathway of KRAS and SOS1[4]



Expected Binding Mode to SOS1



Pharmacological & Pharmacokinetic Profiles

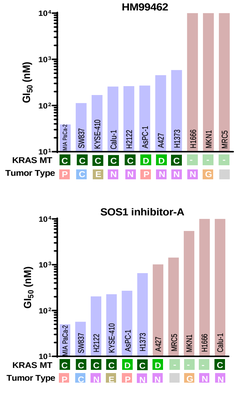
A. Target inhibition activity to SOS1-KRAS binding

Compounds	Target inhibition (IC_{50}, nM)		
	HM99462	SOS1i-A*	SOS1i-B**
SOS1::KRAS WT	30	43	50
SOS1::KRAS G12C	18	19	29
SOS1::KRAS G12D	13	N/A	N/A
SOS1::KRAS G12V	33	N/A	N/A
SOS2::KRAS G12C	5,321	~10,000	>10,000

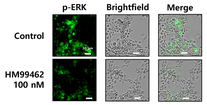
*A known clinical candidate of SOS1 inhibitor, **A tool compound of SOS1 inhibitor.

B. Anti-cancer activity of 3D spheroid growth and inhibition of ERK phosphorylation (IC_{50}) in KRAS mutant cancer cell lines

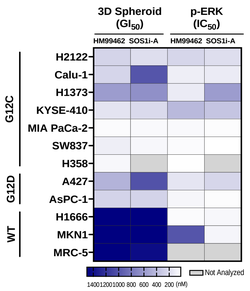
Cellular activity



In-cell western of p-ERK in H358



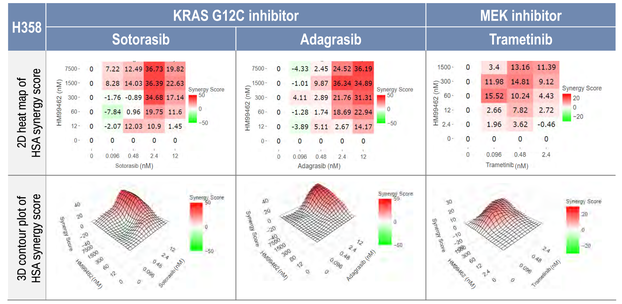
Positive correlation



C. Pharmacokinetic profiles

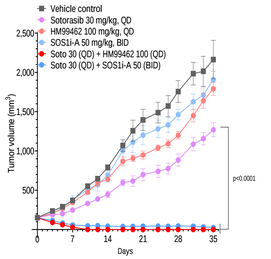
Compound		HM99462
In vitro	Microsomal stability (R% at 0.5h)	69 ~ 89 (quite stable for all species)
	Plasma stability (R% at 2h)	~ 100 (stable for all species)
	CYP isozyme inhibition (IC_{50}, μM)	> 30 (for 7 isozymes)
	PPB (%)	85.3 ~ 91.5 (for all species)
In vivo	Mouse / Rat / Dog (%F)	40 ~ 100

In vitro Combination Synergy in KRAS G12C Mutant H358 Cells[5]



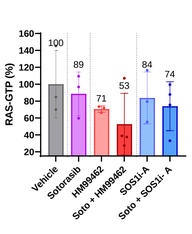
Combination Potential with KRAS G12Ci in KRAS G12C Mutant NSCLC

A. H1373 (NSCLC, $KRAS^{G12C}$)

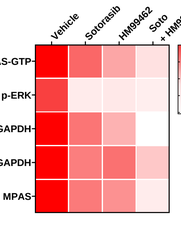


B. PD evaluation study (2 hour post-dose at 7 day)

RAS-GTP analysis

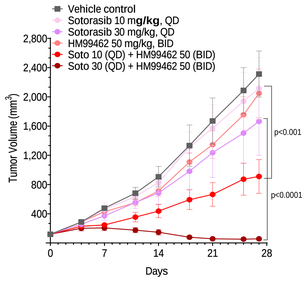


PD biomarker modulation

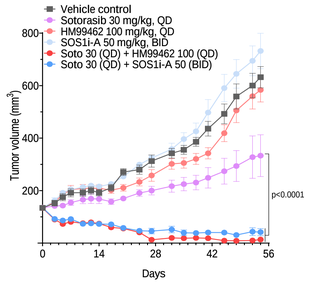


In vivo Efficacy in Combination with Sotorasib (KRAS G12Ci) in KRAS G12C Mutant Cancer Cell Xenograft Models

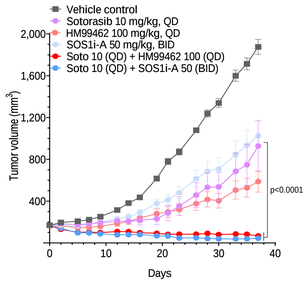
A. LU5191 PDX (NSCLC)



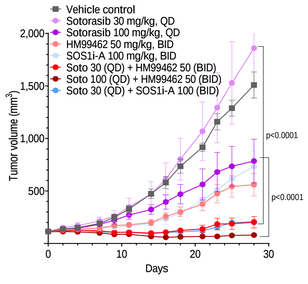
B. SW837 (CRC)



C. MIA PaCa-2 (PDAC)

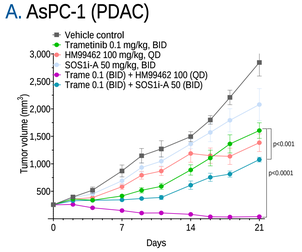


D. KYSE-410 (ESCC, insensitive to $KRAS^{G12C}$i)

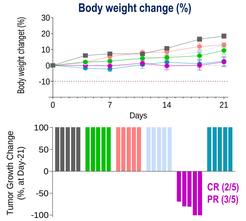


Combination with MEK Inhibitor in KRAS G12D Mutant Cancer

A. AsPC-1 (PDAC)



Body weight change (%)



Concluding Remarks

- HM99462, a SOS1 inhibitor, presents a druggable profile as pan-KRAS therapeutics in KRAS-mutated cancers.
- This study revealed HM99462 as a therapeutics in patients with KRAS-addicted cancers including NSCLC, PDAC, and CRCs by interruption of negative feedback loop as well as inhibition of KRAS signaling.
- *In vitro* and *in vivo* studies proved synergistic effects of SOS1 inhibitors combined with KRAS G12C and MEK inhibitors.
- Currently, HM99462 is undergoing GLP-toxicity studies for IND submission, planned to apply in 4Q 2023.

References

1) Huang L., et al., *Signal Transduct. Target Ther.* 2021, *6*, 386;
2) Punekar SR., et al., *Nat. Rev. Clin. Oncol.* 2022, *19*, 637;
3) Kessler D., et al., *Curr. Opin. Chem. Biol.* 2021, *62*, 109;
4) Schematic illustration was created with BioRender.com;
5) Yadav B., et al., *Comput. Struct. Biotechnol. J.* 2015, *13*, 504.