SOS1-panKRAS modulator, HM101207: A top candidate to control KRAS-MAPK-driven cancers through strong synergy with vertical inhibitors

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Abstract #A066

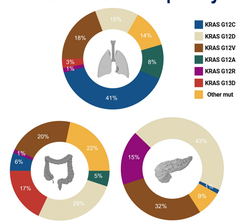
Introduction

KRAS, the most frequently mutated member of the RAS gene family, acts as a molecular switch between off (inactive) and on (active) states.[2] KRAS-driven cancers, including non-small cell lung, colorectal, and pancreatic cancers, are challenging due to their high prevalence and poor outcomes.[3] Although KRAS was once considered "undruggable," the recent approval of KRAS G12C inhibitors[4] has brought hope, particularly for NSCLC and CRC patients with the G12C mutation. However, the clinical benefit of KRAS G12C inhibitors remains limited, largely due to the emergence of resistance mechanisms including secondary KRAS mutations, KRAS wt amplification, RTK bypass signaling, and activation of upstream regulators such as SOS1. Particularly, the key mechanism is ERK pathway reactivation through the relief of negative feedback triggered by KRAS inhibition.[5]

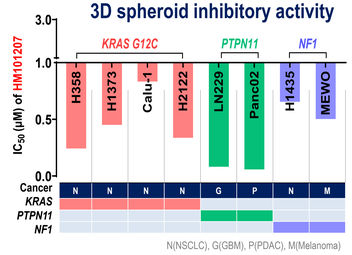
SOS1 is a guanine nucleotide exchange factor that plays a pivotal role in converting KRAS from its GDP-bound (inactive) state to its GTP-bound (active) form. Beyond being a key activator of RAS, SOS1 itself is embedded in a complex network of feedback regulation.[6] In the tumor environment, inhibition of the KRAS-MAPK pathway relieves ERK-dependent negative feedback on SOS1, enabling SOS1 to hyperactivate KRAS signaling, which ultimately promotes uncontrolled cell growth. In this aspect, targeting of SOS1 provides a promising therapeutic strategy to overcome the resistance of KRAS inhibitor and drive the durable anticancer effects.

In Vitro Pharmacological Profiles

KRAS mutation frequency[7]

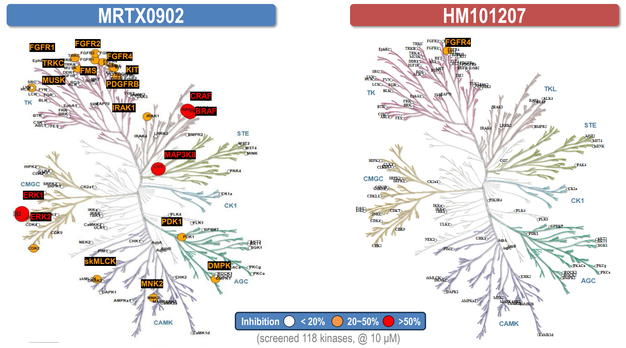


3D spheroid inhibitory activity



N(NSCLC), G(GBM), P(PDAC), M(Melanoma)

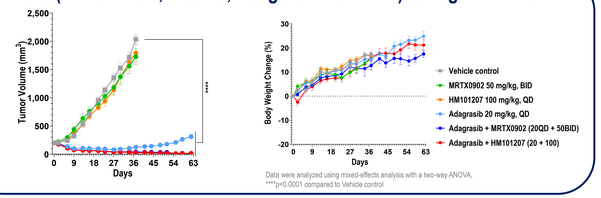
Off-Target Kinase Panel Inhibition



(screened 118 kinases, @ 10 μM)

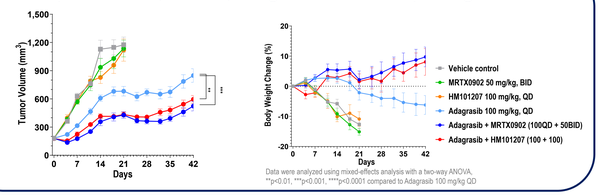
Synergistic Effect in Combination with Various KRAS G12C Inhibitors

H1373 (KRAS G12C, NSCLC, Adagrasib-sensitive) xenograft model



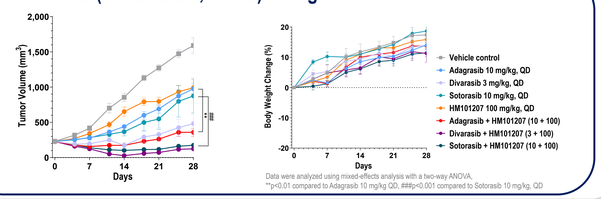
Data were analyzed using mixed-effects analysis with a two-way ANOVA,
****p<0.0001 compared to Vehicle control

H2122 (KRAS G12C, NSCLC, Adagrasib-insensitive) xenograft model



Data were analyzed using mixed-effects analysis with a two-way ANOVA,
**p<0.01, ****p<0.0001 compared to Adagrasib 100 mg/kg QD

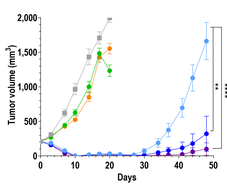
Mia PaCa-2 (KRAS G12C, PDAC) xenograft model



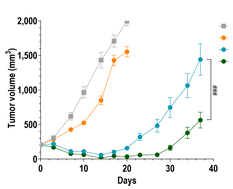
Data were analyzed using mixed-effects analysis with a two-way ANOVA,
**p<0.01 compared to Adagrasib 10 mg/kg QD, ###p<0.001 compared to Sotorasib 10 mg/kg, QD

Anti-tumor Activity in Combination with MEK Inhibitors

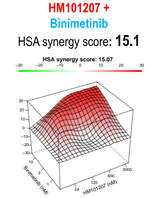
AsPC-1 (KRAS G12D, PDAC) xenograft model

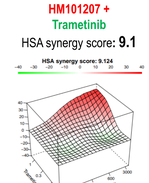


Data were analyzed using mixed-effects analysis with a two-way ANOVA,
###p<0.001 compared to Trametinib 0.1 mg/kg, QD



Data were analyzed using mixed-effects analysis with a two-way ANOVA,
**p<0.01, ***p<0.001 compared to Binimetinib 30 mg/kg, QD

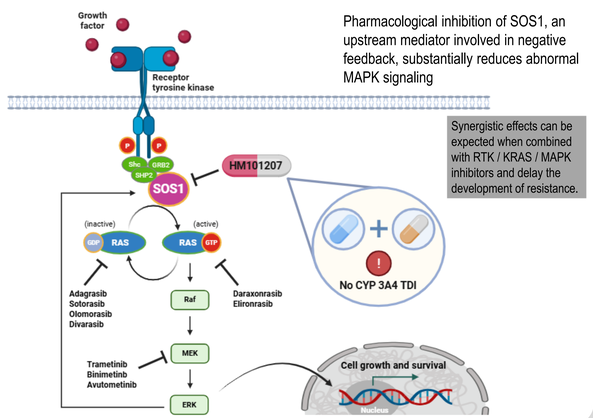




Concluding Remarks

- HM101207 is a highly selective SOS1-panKRAS modulator and suppressed GTP exchange of KRAS wild-type and multiple mutant variants.
- No potential for CYP3A4 TDI for HM101207 (data not shown)
- *In vitro*, HM101207 exhibited stronger synergism than of MRTX0902 when combined with RTK/KRAS/MAPK pathway inhibitors including pan-RAS inhibitor, KRAS G12C inhibitor, RAF/MEK inhibitor or MEK inhibitor.
- *In vivo*, synergistic antitumor effects were observed in combination of HM101207 including various KRAS G12C inhibitors, RTK and MEK inhibitor.
- Collectively, these results suggest HM101207 as a promising combination strategy to enhance KRAS-targeted therapies and overcome adaptive resistance in KRAS-MAPK driven cancers.
- HM101207 is currently undergoing IND enabling GLP-toxicity studies and expected to begin FIH studies in 2Q 2026.

Schematic Signaling Pathway of SOS1 to KRAS-MAPK

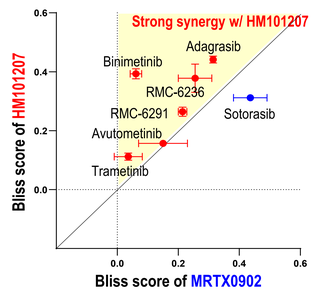


Pharmacological inhibition of SOS1, an upstream mediator involved in negative feedback, substantially reduces abnormal MAPK signaling

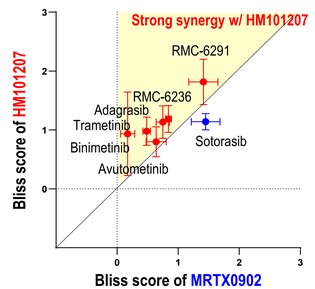
Synergistic effects can be expected when combined with RTK / KRAS / MAPK inhibitors and delay the development of resistance.

Strong Synergism of HM101207 with RAS-MAPK Pathway Inhibitors

NCI-H2122 (KRAS G12C, NSCLC)



SNU-1411 (KRAS G12C, CRC)

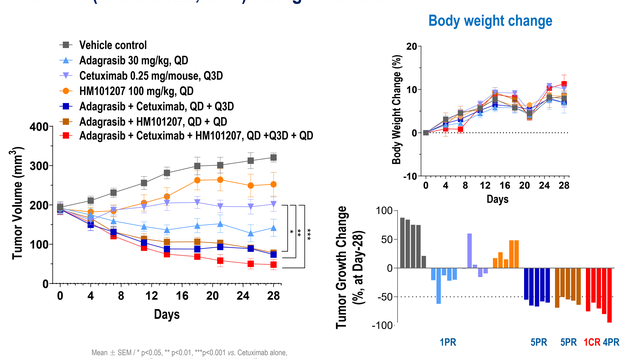


- KRAS G12C inhibitor: Adagrasib (BMS), Sotorasib (Amgen), RMC-6291 (Revolution medicines)
- RAS(ON) inhibitor: RMC-6236 (Revolution medicines)
- MEK inhibitor: Trametinib (Novartis), Binimetinib (Pfizer)
- RAF/MEK dual inhibitor: Avutometinib (Verastem)

Bliss Score=$E_{AB}^{expected} - E_{AB}^{observed}$; $E_{AB}^{expected} = E_A + E_B - (E_A \times E_B)$

Supported the Feasibility of a Triplet Combination Regimen Approach

SW837 (KRAS G12C, CRC) xenograft model



Mean ± SEM / * p<0.05, ** p<0.01, ***p<0.001 vs. Cetuximab alone,
Data were analyzed using a mixed-effects model

References

1. The graphical representations were generated with BioRender.com
2. Yang, X., et al. *Journal of Hematology & Oncology*. **2024** 17;108
3. Singhal, A., et al. *Nature medicine*. **2024** 30:969-983
4. Isermann, T., et al. *Trends in Cancer*. **2025** 11;2:91-116
5. Sattler, M., et al. *Trends in Cancer*. **2023** 9;1:42-54
6. Lake, D., et al. *Cell. Mol. Life Sci.* **2016** 73:4397-4413
7. Zhu, C., et al. *Molecular Cancer*. **2022** 21;159