A Novel SOS1-panKRAS Modulator, HM101207: Promising Combination for Treating KRAS-MAPK Driven Cancers

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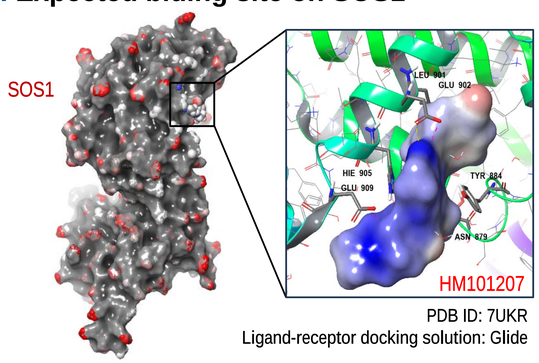
Introduction

KRAS is the most frequently mutated isoform, with a prevalence ranging from 35% to 90% in NSCLC, CRC and PDAC[1,2]. Functionally, KRAS alternates between an inactive GDP-bound "off" state and an active GTP-bound "on" state, thereby driving downstream signaling cascades that promote uncontrolled cell proliferation and survival. Son of Sevenless homolog 1 (SOS1) is a guanine nucleotide exchange factor (GEF) that facilitates this GDP-GTP exchange, acting as a binary molecular switch to activated KRAS[3]. Moreover, SOS1 serves as a critical node within the negative feedback loop of the RTK-KRAS-MAPK pathway. Therapeutically, targeting the SOS1-KRAS interaction provides an opportunity to modulate the GDP-bound state of pan-KRAS, thereby overcoming adaptive resistance and offering a promising strategy to suppress various KRAS-driven cancers.

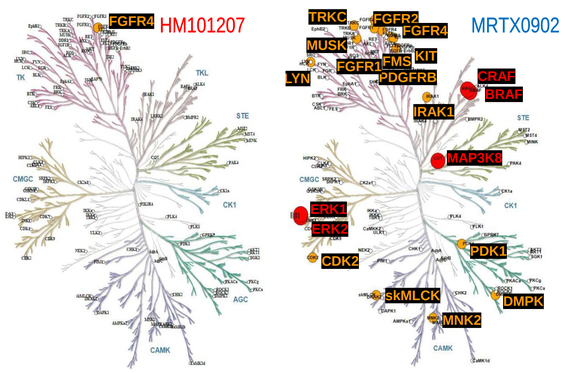
Biochemical Profiles of HM101207

A. Expected biding site on SOS1



PDB ID: 7UKR
Ligand-receptor docking solution: Glide

B. Kinase kinome tree

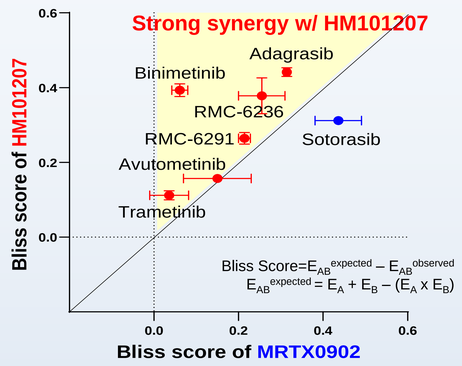


Inhibition ○ < 20% ● 20~50% ● >50%
Inhibition % at 10 μM, screened 118 kinases

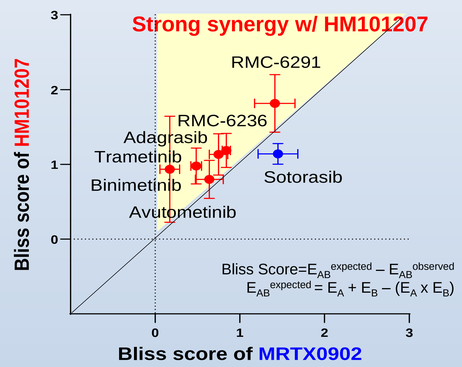
HM101207: A Potential Combination Partner for KRAS-MAPK Pathway Inhibitors

In Vitro: Strong synergism of HM101207 in combination with RAS-MAPK pathway inhibitors

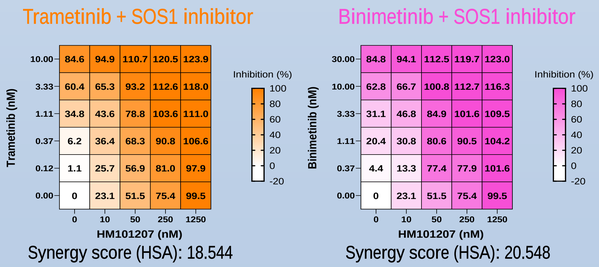
A. NCI-H2122 (KRAS^{G12C} NSCLC)



B. SNU-1411 (KRAS^{G12C} CRC)



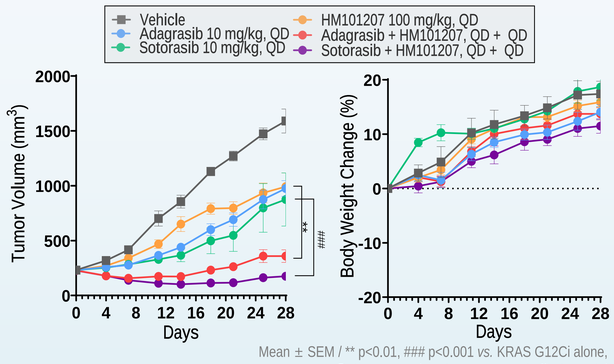
C. LN229 (PTPN11^{A72S} GBM)



Synergy score analysis by SynergyFinder.;
From -10 to 10: The interaction between two drugs is likely to be additive;
Larger than 10: The interaction between two drugs is likely to be synergistic

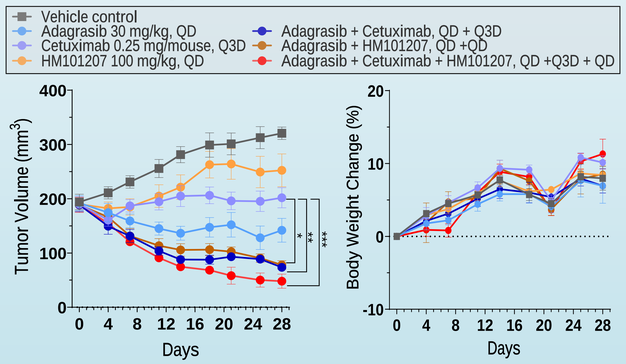
In Vivo: Synergistic antitumor effect of HM101207 combining with RAS-MAPK inhibitors

A. MIA PaCa2 (KRAS^{G12C} PDAC)



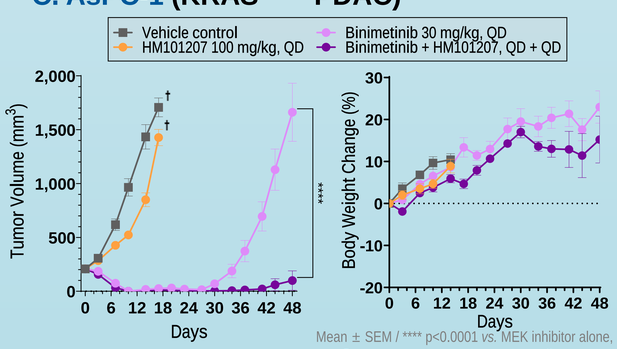
Mean ± SEM / ** p<0.01, ### p<0.001 *vs.* KRAS G12Ci alone,
Data were analyzed using a mixed-effects model

B. SW837 (KRAS^{G12C} CRC)



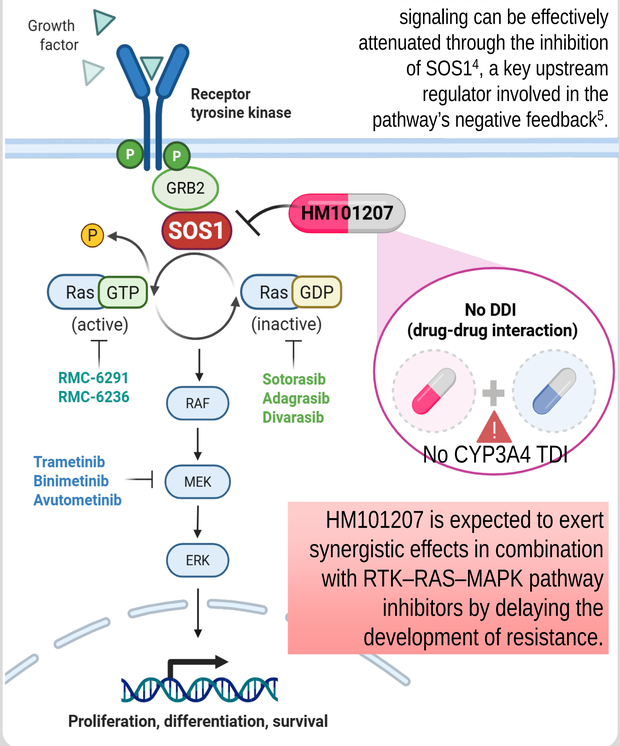
Mean ± SEM / * p<0.05, ** p<0.01, ***p<0.001 *vs.* Cetuximab alone,
Data were analyzed using a mixed-effects model

C. AsPC-1 (KRAS^{G12D} PDAC)



Mean ± SEM / **** p<0.0001 *vs.* MEK inhibitor alone,
Data were analyzed using a mixed-effects model
† Tumors exceeding 2000 mm³ in size were excluded according to IACUC guidelines

Therapeutic Combination Strategies



Aberrant activation of MAPK signaling can be effectively attenuated through the inhibition of SOS1[4], a key upstream regulator involved in the pathway's negative feedback[5].

HM101207 is expected to exert synergistic effects in combination with RTK–RAS–MAPK pathway inhibitors by delaying the development of resistance.

Concluding Remarks

- HM101207 is a highly selective SOS1-panKRAS modulator and suppressed GTP exchange of KRAS wild-type as well as various mutant forms (data not shown).
- HM101207 exhibited stronger synergism than of MRTX0902 when combined with RTK/KRAS/MAPK pathway inhibitors including pan-RASi, KRAS G12Ci, RAF/MEKi or MEKi.
- Synergistic antitumor effects were observed in combination of HM101207 with RTK/RAS/MAPK pathway inhibitors especially in overcoming the acquired resistance.
- Collectively, these results highlight HM101207 as a promising combination strategy to potentiate KRAS-targeted therapies and overcome adaptive resistance in KRAS-MAPK driven cancers.
- No potential for CYP3A4 TDI for HM101207 (data not shown)
- HM101207 is currently undergoing IND enabling GLP-toxicity studies and expected to begin FIH studies in 2Q 2026.

References

1) Uprety D, *et al*., *Cancer Treatment Reviews.*, 89, 2020, 102070;
2) Herdeis L, *et al*., *Current Opinion in Structural Biology.*, 71, 2021, 136–147;
3) Lamei H, et al., *Signal Transduction and Targeted Therapy*., 6, 2021, 386;
4) Schematic illustration was created with BioRender.com;
5) Marasco M, *et al*., *Cell Reports Medicine*, 5, 2024, 101818;