Breaking the KRAS Inhibitor Induced Resistance-Wall: Targeting KRAS-SOS1 to Disarm Hypoxic Survival

Jongmin Hong, Heesun Moon, Soye Jeon, Yongjae Park, Seung Hyun Jung, Jaeyul Choi, Young Gil Ahn, Jooyun Byun, and In Young Choi
Hanmi R&D Center, Hanmi Pharm. Co., Ltd., Gyeonggi-do, Republic of Korea

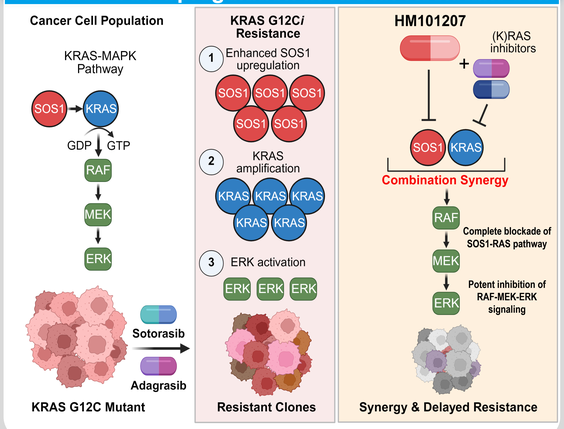
Hanmi

Abstract #441

Introduction

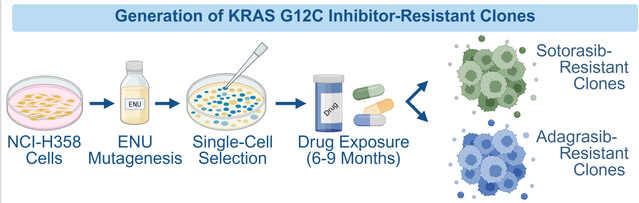
- $KRAS^{G12C}$ inhibitors such as Sotorasib and Adagrasib have shown only modest clinical benefit (ORR 28–43%, median PFS ~6 months), underscoring the need to overcome intrinsic and acquired resistance in $KRAS^{G12C}$–driven cancers[1,2]. Resistance mechanisms include KRAS amplification, secondary RAS alterations, and ERK reactivation through disruption of ERK-mediated negative feedback[3,4,5]. Thus, identification of optimal combination partners is essential to improve efficacy and delay resistance.
- We established Sotorasib- and Adagrasib–resistant clones from the NCI-H358 cell line. Resistant clones exhibited significantly increased SOS1 expression, elevated KRAS and ERK levels, indicating reinforcement of KRAS-MAPK pathway activity. These findings suggest that adaptive rewiring toward sustained RAS pathway activation contributes to resistance development in $KRAS^{G12C}$–mutant cells.
- HM101207 emerged as a potent combination partner, preventing ERK reactivation and showing marked synergistic anti-tumor activity with $KRAS^{(ON)}$ and $KRAS^{(OFF)}$ inhibitors in $KRAS^{G12C}$–mutant cancer cells. Notably, in xenograft models, combination with $KRAS^{G12C}$ or $RAS^{(ON)}$ inhibitors produced superior anti-tumor efficacy and markedly delayed resistance onset, supporting its potential to improve therapeutic durability. RNA-seq analysis revealed that HM101207 treatment resulted in a marked downregulation of hypoxia-associated gene expression signatures. These findings highlight that combination with SOS1 inhibitors enables more robust and sustained control of KRAS-driven malignancies through co-targeting of the RAS signaling network.
- Collectively, HM101207, a pan-RAS modulator targeting the SOS1–RAS signaling pathway, represents a promising therapeutic approach in RAS-driven tumors, addressing the intrinsic and acquired limitations of KRAS inhibitor monotherapy.

Robust SOS1 Upregulation in KRAS*i* Resistant Cell

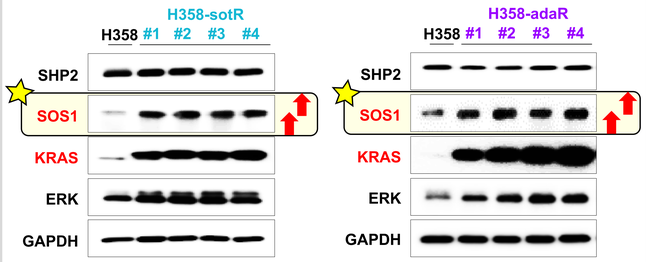


SOS1-Mediated Adaptive Resistance to KRAS G12C Inhibitors

A. Establishment of Resistant Clones to Sotorasib / Adagrasib

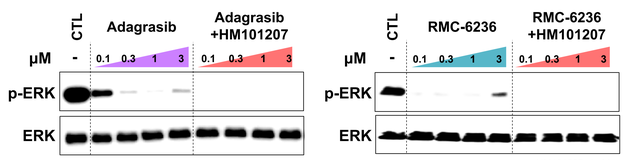


B. Robust SOS1 Upregulation in KRAS*i* Acquired Resistance

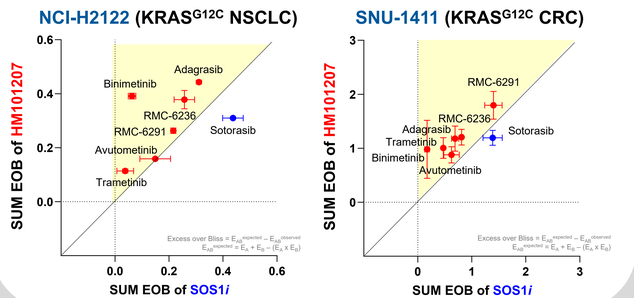


sotR: sotorasib-resistant clones; adaR: adagrasib-resistant clones

C. Preventing ERK Reactivation Through HM101207 Combination

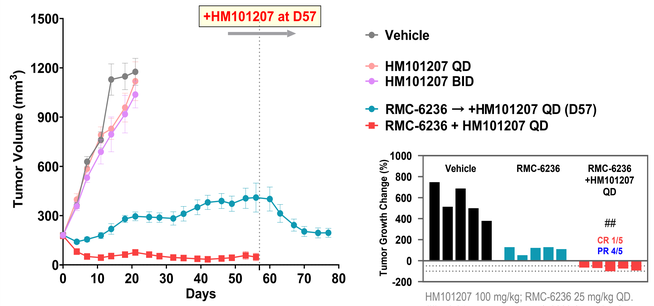


D. *in vitro* Strong Synergism of HM101207 with RAS-MAPK Inhibitors

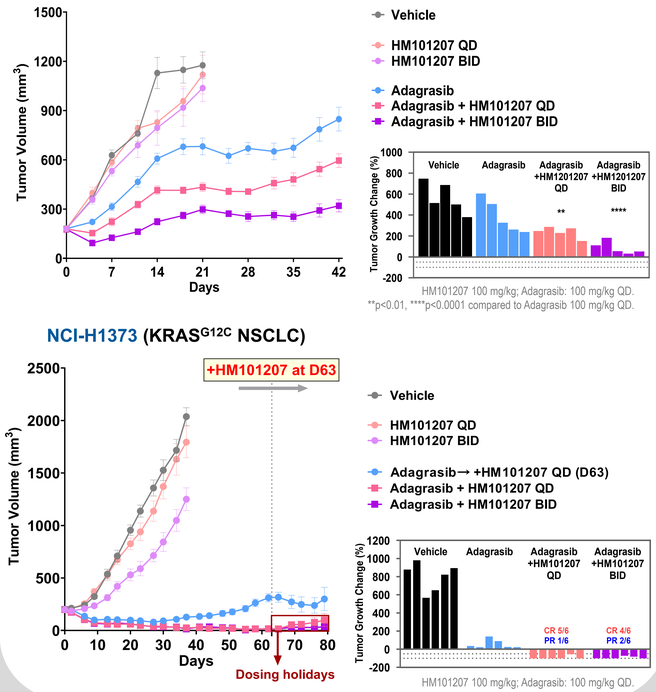


Anti-tumor Synergism of HM101207 with (K)RAS Inhibitors

A. Delaying Progression of $RAS^{(ON)}$ Inhibitor in NSCLC

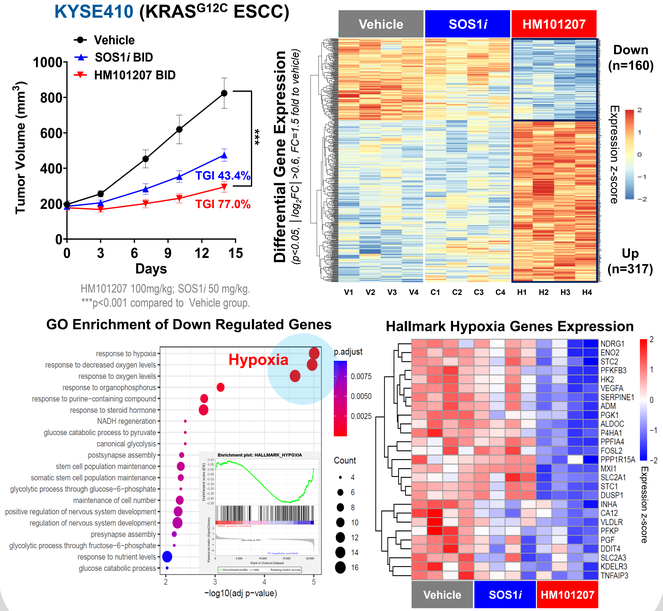


B. Delaying Progression of $KRAS\ G12C^{(OFF)}$ Inhibitor in NSCLC



Suppression of Hypoxia-Related Gene Expression by HM101207

A. Hypoxia Gene Regulation by HM101207 in $KRAS^{G12C}$ ESCC



Concluding Remarks

- KRAS G12C inhibitor resistance is associated with enhanced KRAS signaling, including SOS1 overexpression.
- HM101207 combined with (K)RAS or MEK inhibitors show synergistic effects and delay drug resistance *in vitro* and *in vivo*.
- This study revealed HM101207 as a potential pan-RAS modulator for KRAS-addicted cancers, acting through the inhibition of KRAS signaling and the modulation of hypoxia-related gene expression.
- HM101207 is currently conducting IND enabling GLP-toxicity studies and is expected to obtain results in the first half of 2026.

References

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