Abstract # 34968

The next generation farnesyltransferase inhibitor, KO-2806, blocks oncogenic signaling at multiple nodes to enhance the antitumor efficacy of KRAS^{G12C} inhibitor adagrasib in KRAS^{G12C} non-small cell lung carcinoma

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BACKGROUND

Emerging clinical and preclinical data have shown that responses to KRAS^{G12C} inhibition are limited by the activation of compensatory signaling proteins, including receptor tyrosine kinases (RTKs) and mTOR. Combination therapeutic strategies co-targeting these nodes are needed to fully realize the potential of breakthrough KRAS^{G12C}-selective inhibitors. We propose that, given its multipronged mechanism of action, KO-2806, a next-generation farnesyltransferase inhibitor (FTI), is a uniquely suited combination partner for KRAS^{G12C} inhibitors. Here, we evaluate the therapeutic potential and mechanistic basis of combined KO-2806 and adagrasib in preclinical models of KRAS^{G12C} non-small cell lung cancer (NSCLC).

RESULTS

Combination of KO-2806 with adagrasib causes tumor regressions in cell-derived and patient-derived *KRAS^{G12C}* NSCLC xenografts

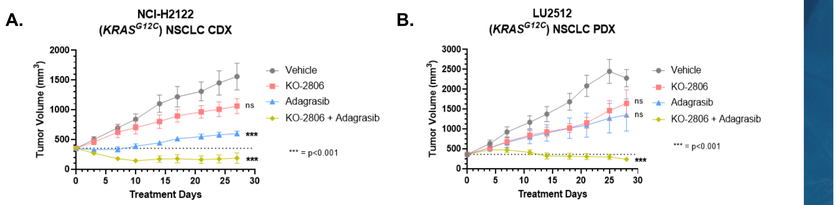


Figure 1. Antitumor efficacy in *KRAS^{G12C}* NSCLC xenograft models with combination of KO-2806 with KRAS^{G12C} inhibitor adagrasib. (A) NCI-H2122 CDX and (B) LU2512 PDX NSCLC models had significant tumor regressions with KO-2806 + 100 mg/kg adagrasib compared to vehicle control.

Combination of KO-2806 with adagrasib enhances duration & depth of antitumor response compared with adagrasib monotherapy

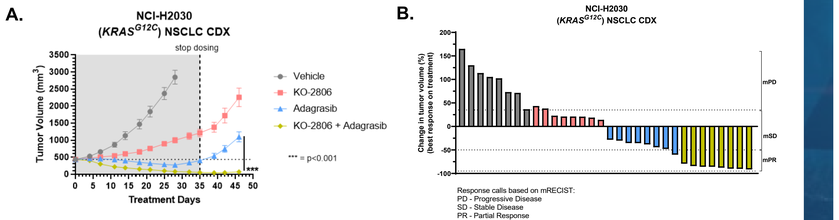
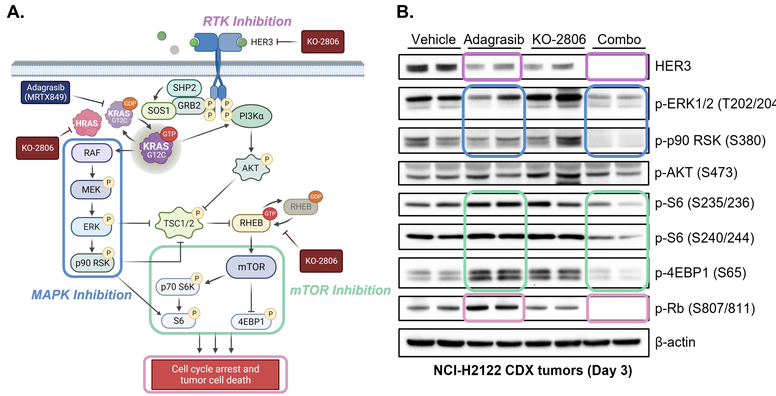


Figure 2. Antitumor efficacy in NCI-H2030 *KRAS^{G12C}* NSCLC xenograft model. (A) Tumor regressions observed with KO-2806 + 100 mg/kg adagrasib were maintained even when treatment was stopped. (B) Combination of KO-2806 with adagrasib had deeper tumor regressions than single-agent adagrasib.

KO-2806 enhances suppression of mTOR and MAPK signaling and decreases proliferation by adagrasib in *KRAS^{G12C}* NSCLC



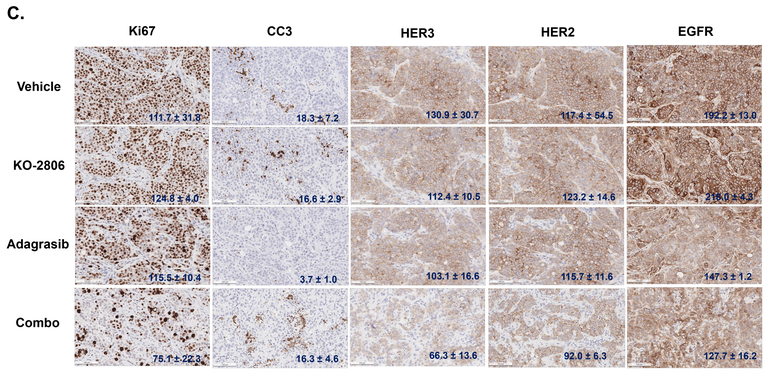


Figure 3. Signaling inhibition with combination of KO-2806 and adagrasib in NCI-H2122 *KRAS^{G12C}* NSCLC CDX model. (A) Schematic of signaling inhibition at multiple nodes with combination of FTI, KO-2806, and KRAS^{G12C} inhibitor, adagrasib. NCI-H2122 tumors were collected at Day 3 and analyzed using (B) western blot and (C) immunohistochemistry (IHC). (B) Combination of KO-2806 with adagrasib resulted in strong reduction of HER3 protein expression, enhanced inhibition of MAPK signaling (ERK1/2 and p90 RSK phosphorylation), increased suppression of mTOR activity (S6 and 4EBP1 phosphorylation), and induction of cell cycle arrest (Rb phosphorylation) compared with single-agent adagrasib treatment. (C) Combination of KO-2806 with adagrasib caused a decrease in the cell proliferation marker Ki67 and an increase in the apoptotic marker cleaved caspase 3 (CC3) compared to single-agent adagrasib. Additionally, there was a reduction in HER3 levels, while HER2 and EGFR levels were mostly unchanged with the combination treatment compared with single-agent adagrasib treatment. HALO was used for IHC image analysis and to quantify H-scores with n=3.

Depletion of RHEB phenocopies antiproliferative effects and mTOR signaling inhibition of KO-2806 when combined with adagrasib

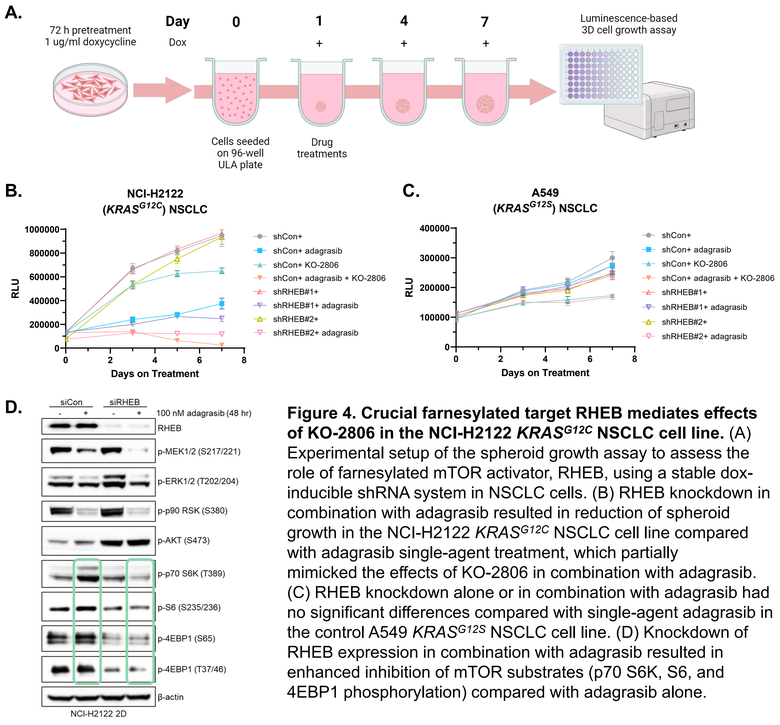


Figure 4. Crucial farnesylated target RHEB mediates effects of KO-2806 in the NCI-H2122 *KRAS^{G12C}* NSCLC cell line. (A) Experimental setup of the spheroid growth assay to assess the role of farnesylated mTOR activator, RHEB, using a stable dox-inducible shRNA system in NSCLC cells. (B) RHEB knockdown in combination with adagrasib resulted in reduction of spheroid growth in the NCI-H2122 *KRAS^{G12C}* NSCLC cell line compared with adagrasib single-agent treatment, which partially mimicked the effects of KO-2806 in combination with adagrasib. (C) RHEB knockdown alone or in combination with adagrasib had no significant differences compared with single-agent adagrasib in the control A549 *KRAS^{G12S}* NSCLC cell line. (D) Knockdown of RHEB expression in combination with adagrasib resulted in enhanced inhibition of mTOR substrates (p70 S6K, S6, and 4EBP1 phosphorylation) compared with adagrasib alone.

CONCLUSIONS

- Combination of the next generation FTI, KO-2806, with the KRAS^{G12C} inhibitor, adagrasib, caused significant tumor regressions in *KRAS^{G12C}* NSCLC xenograft models.
- Combination of KO-2806 with adagrasib enhances the depth and duration of response compared with single-agent adagrasib treatment.
- KO-2806 deepens signaling inhibition by adagrasib through inhibiting MAPK and mTOR signaling, reducing HER3, and blocking proliferation in *KRAS^{G12C}* NSCLC tumors.
- Knockdown of RHEB partially mimics the effects of KO-2806 in combination with adagrasib by decreasing spheroid growth and inhibiting mTOR signaling in *KRAS^{G12C}* NSCLC cells.