KO-2806, a next-generation farnesyl transferase inhibitor, re-sensitizes KRAS^{G12C} NSCLC tumors to KRAS^{G12C} mutant-specific inhibitors through mTOR signaling inhibition

Abstract # 388

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BACKGROUND

- Approval of KRAS^{G12C} mutant-selective inhibitors sotorasib and adagrasib has revolutionized the clinical landscape of non-small cell lung cancer (NSCLC).
- However, adaptive resistance due to compensatory reactivation of mTOR and MAPK signaling pathways limits their clinical effectiveness.
- We have previously shown KO-2806, a next-generation farnesyl transferase inhibitor (FTI), to block adagrasib-induced mTORC1 compensation through inhibition of RHEB farnesylation.
- Consequently, in multiple previously untreated *KRAS^{G12C}* NSCLC preclinical models, the combination of KO-2806 with adagrasib showed significantly enhanced anti-tumor activity compared to adagrasib monotherapy.
- The rapidly evolving clinical landscape in the KRAS field calls for combinations that can benefit patients who have previously experienced a KRAS^{G12C} inhibitor.
- In this study, we evaluated the combination of KO-2806 with adagrasib in preclinical KRAS^{G12C} NSCLC xenograft models previously exposed to KRAS inhibitors and demonstrated that KO-2806 enhanced anti-tumor activity of the KRAS inhibitors.

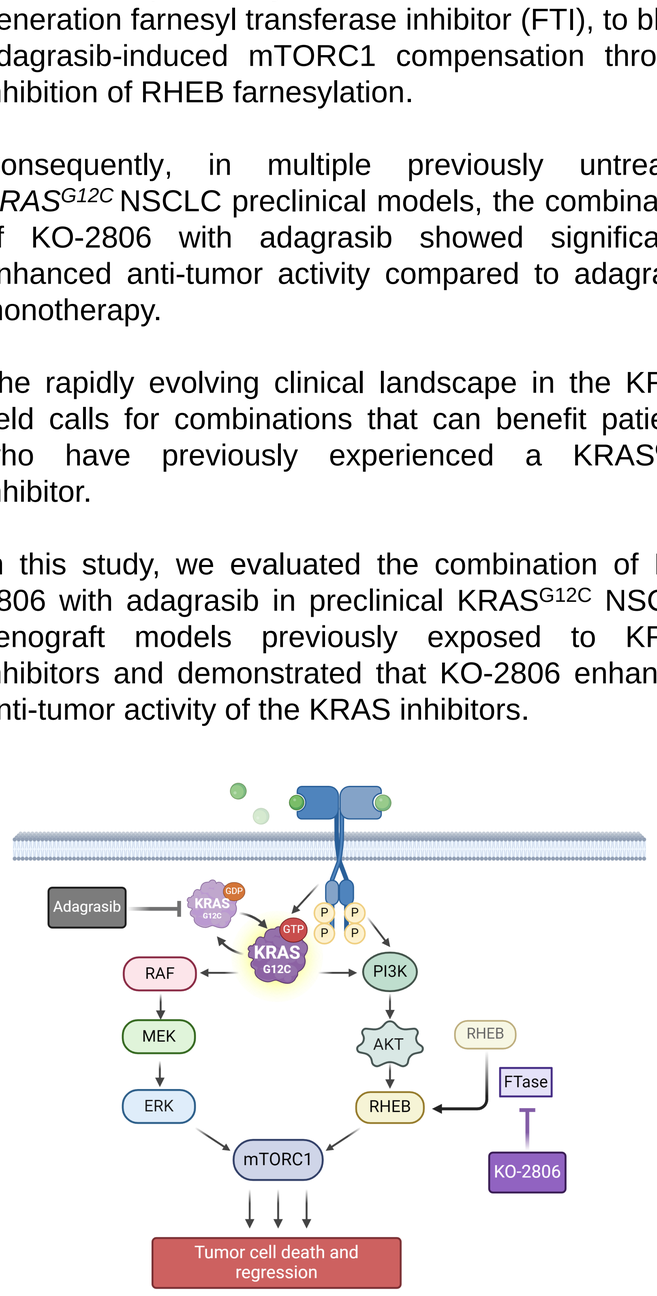

Figure 1. Graphical schematic of KRAS-mTORC1 signaling, including the farnesylated mTORC1 activator, RHEB. Combination of KO-2806, a next-generation FTI, and adagrasib, a KRAS^{G12C} inhibitor, causes tumor cell death and regression through compensatory mTOR pathway inhibition.

RESULTS

KO-2806 deepens the anti-tumor effects of adagrasib monotherapy in *KRAS^{G12C}* inhibitor-naïve preclinical models of NSCLC

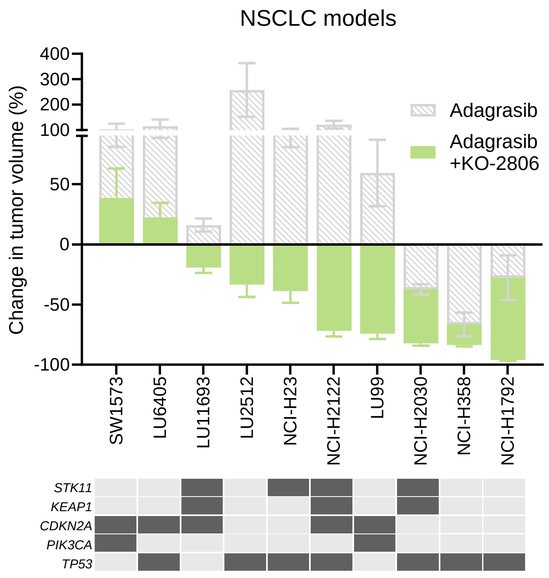

Figure 2. Tumor growth inhibition waterfall plots in *KRAS^{G12C}* NSCLC xenograft models. A range of cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models, which have previously been shown to be either adagrasib-resistant, -partially sensitive, or -sensitive, were treated with adagrasib (30 or 100 mg/kg, PO, QD) as monotherapy or in combination with KO-2806. There was enhanced tumor growth inhibition in the combination-treated groups compared to adagrasib-treated groups, regardless of sensitivity or co-mutational status of the xenograft models. Each bar represents the mean percent change in tumor volume at treatment day 25-35 relative to baseline (day 0), ± SEM, *n* = 6-8 animals per group. Oncoplots illustrating the mutational status of key driver genes in each model are shown below each waterfall plot. Mutations are indicated by dark shading.

Enhanced tumor growth inhibition with the combination of adagrasib plus KO-2806 vs. SHP2 & SOS1 inhibitors in *KRAS^{G12C}* NSCLC

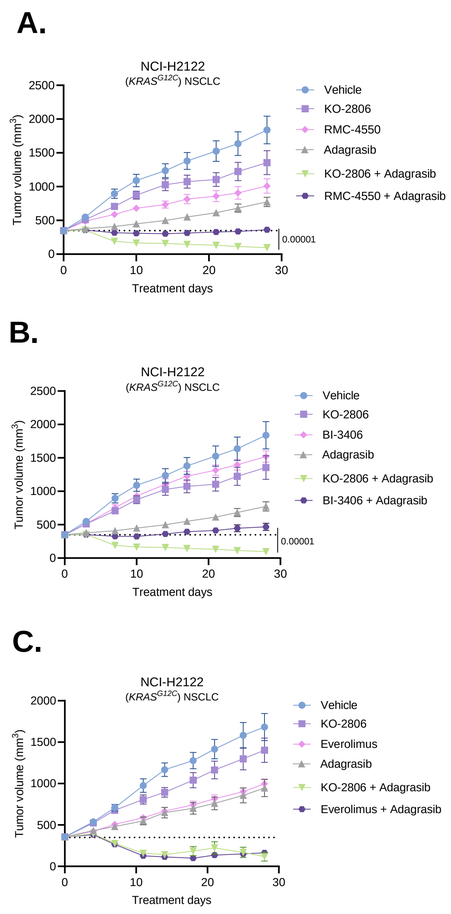

Figure 3. Head-to-head comparisons of adagrasib combined with KO-2806 and various combination partners based on mechanistic rationale. NCI-H2122 NSCLC CDX mice were treated with adagrasib (100 mg/kg, QD, PO) plus (A) FTI KO-2806, (B) SHP2 inhibitor RMC-4550 (30 mg/kg, QD, PO), (C) SOS1 inhibitor BI-3406 (50 mg/kg, BID, PO), or (D) mTOR inhibitor everolimus (10 mg/kg, QD, PO). Anti-tumor activity was improved with the KO-2806 combination compared to the SHP2 or SOS1 inhibitor combinations and comparable to the mTOR inhibitor combination, as expected based on similar mechanisms of blocking mTOR vs. MAPK signaling. Statistical significance was determined by unpaired Student's t-test, p-values as indicated on plots.

Tumors progressing on a KRAS^{G12C} inhibitor regress when switched to KO-2806+adagrasib combination

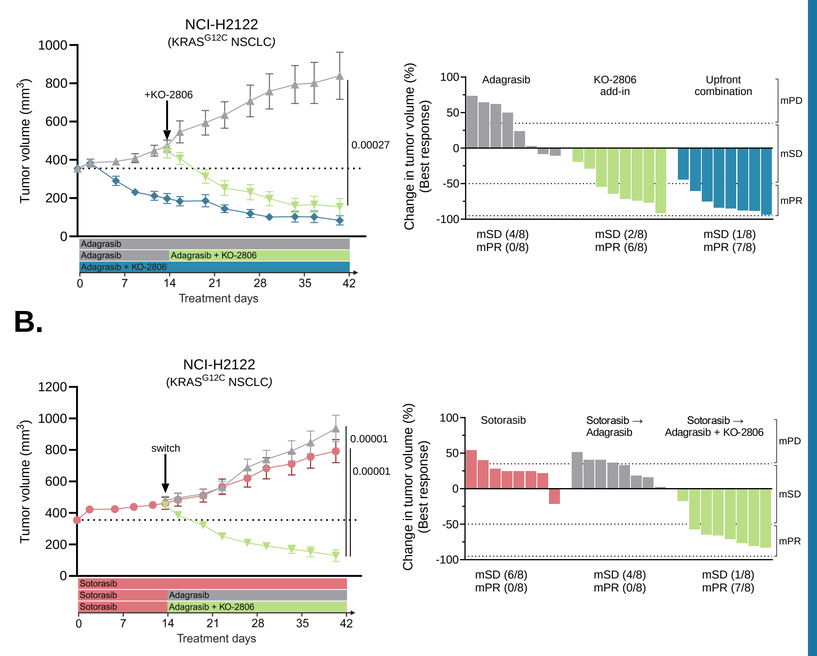

Figure 4. Combination of KO-2806+adagrasib after prior KRAS^{G12C} inhibitor monotherapy causes tumor regressions comparable to the upfront combination of KO-2806+adagrasib. NCI-H2122 NSCLC CDX mice were treated with KO-2806 plus adagrasib after 14 days on either (A) adagrasib (100 mg/kg, QD, PO) or (B) sotorasib (100 mg/kg, QD, PO). Statistical significance was determined by unpaired Student's t-test, p-values as indicated on plots. The changes in tumor volume were calculated using Day 0 as baseline, and best responses of individual xenograft mice in each treatment group are displayed in the waterfall plots. Modified RECIST (mRECIST) response calls using the best responses were calculated and are shown below the plots.

Combination of KO-2806+adagrasib, irrespective of prior KRAS^{G12C} inhibitor treatment, inhibits mTOR signaling through defarnesylation of RHEB

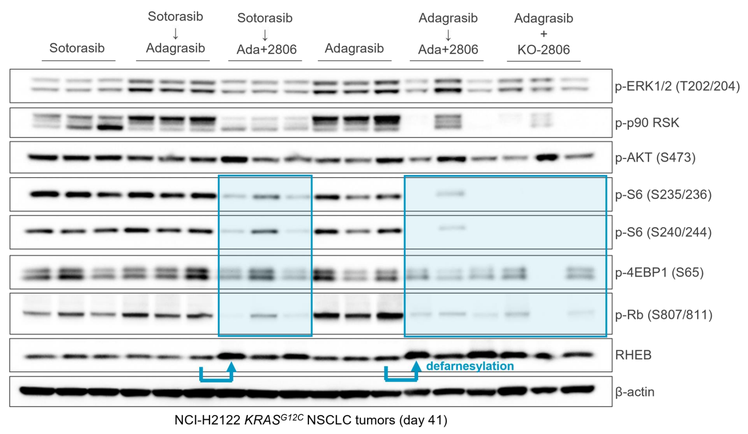

Figure 5. Immunoblot of indicated signaling proteins from tumors in Figures 4A and 4B. NCI-H2122 tumors were collected at endpoint on Day 41 and analyzed using western blot. Addition of KO-2806+adagrasib to either KRAS^{G12C} inhibitor treatment resulted in robust inhibition of mTOR signaling (phosphorylation of S6 and 4EBP1) and induction of cell cycle arrest (phosphorylation of Rb), comparable to the upfront combination of KO-2806+adagrasib. Mobility gel shift (arrows) of the farnesylated mTORC1 activator RHEB was shown to depict defarnesylation with KO-2806 treatment.

Tumors progressing on adagrasib are re-sensitized by KO-2806 through mTOR signaling inhibition

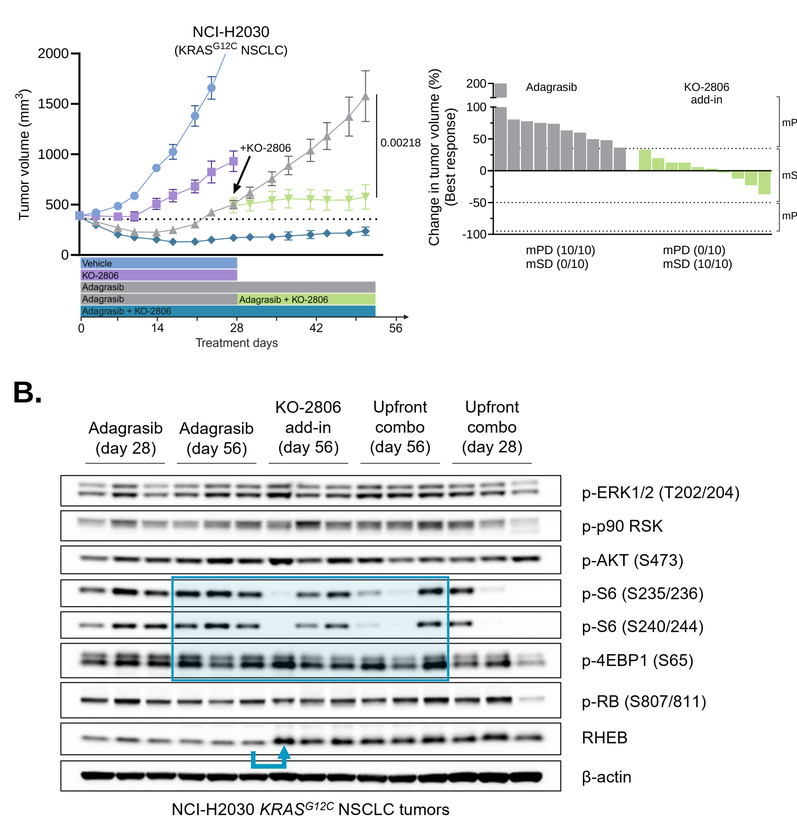

Figure 6. KO-2806 addition to tumors progressing on adagrasib monotherapy causes inhibition of tumor growth and mTOR signaling. (A) NCI-H2030 NSCLC CDX mice were treated with KO-2806 plus adagrasib after 28 days on adagrasib (100 mg/kg, QD, PO). The changes in tumor volume were calculated using Day 28 as baseline, and best responses of individual xenograft mice in each treatment group are displayed in the waterfall plots. (B) NCI-H2030 tumors were collected prior to KO-2806 addition on Day 28 or at endpoint on Day 56 and analyzed using western blot. Addition of KO-2806 to adagrasib, whether added upfront or later, caused a decrease in the phosphorylation of mTOR signaling substrates (S6 and 4EBP1) compared to adagrasib alone. Mobility gel shift (arrow) of RHEB was shown to depict defarnesylation with KO-2806 treatment.

Tumors progressing on a KRAS-mutant or pan-RAS inhibitor regress when switched to KO-2806+RMC-6236 (pan-RAS inhibitor) combination

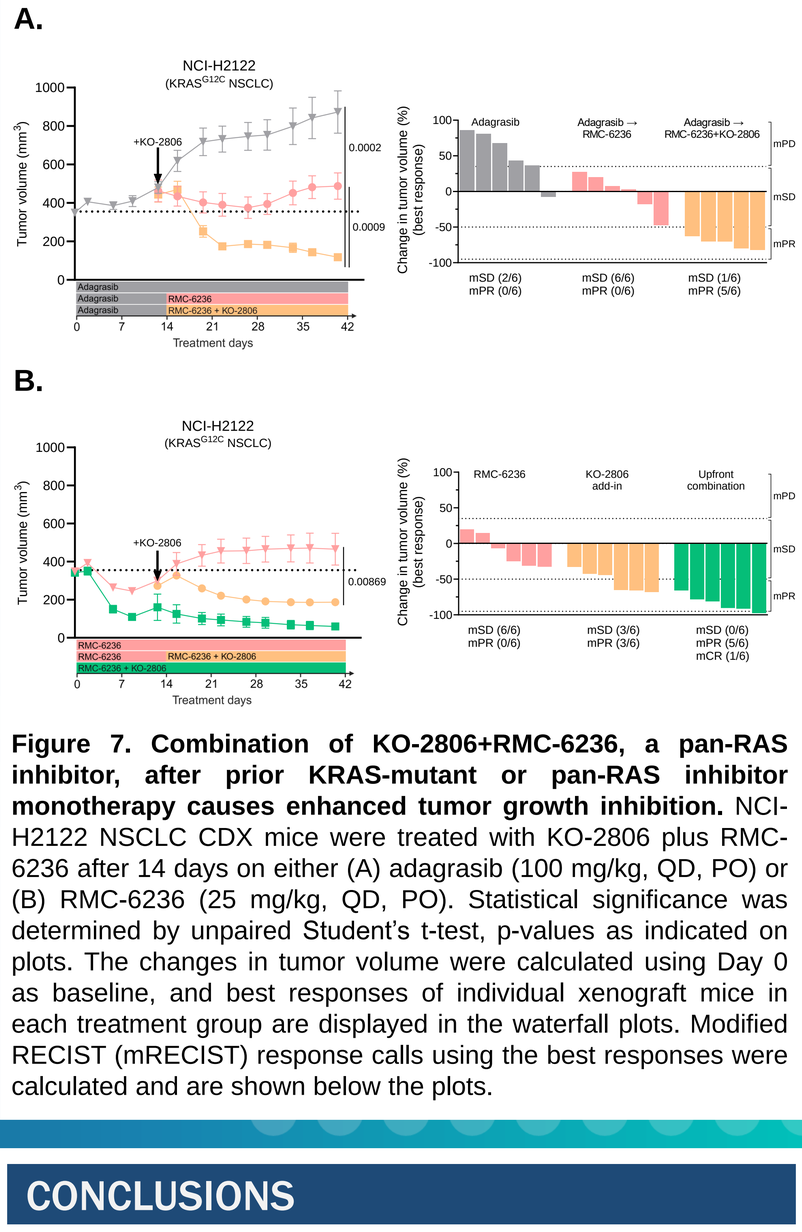

Figure 7. Combination of KO-2806+RMC-6236, a pan-RAS inhibitor, after prior KRAS-mutant or pan-RAS inhibitor monotherapy causes enhanced tumor growth inhibition. NCI-H2122 NSCLC CDX mice were treated with KO-2806 plus RMC-6236 after 14 days on either (A) adagrasib (100 mg/kg, QD, PO) or (B) RMC-6236 (25 mg/kg, QD, PO). Statistical significance was determined by unpaired Student's t-test, p-values as indicated on plots. The changes in tumor volume were calculated using Day 0 as baseline, and best responses of individual xenograft mice in each treatment group are displayed in the waterfall plots. Modified RECIST (mRECIST) response calls using the best responses were calculated and are shown below the plots.

CONCLUSIONS

- The next-generation FTI, KO-2806, in combination with adagrasib enhances anti-tumor activity in both KRAS^{G12C} inhibitor-naïve and -prior treated preclinical models of NSCLC.
- KO-2806 blocks KRAS inhibitor-induced mTORC1 compensation through the inhibition of RHEB farnesylation.
- Based on this mechanistic rationale, the combination of KO-2806+adagrasib showed improved tumor growth inhibition compared to the combinations with a SHP2 or SOS1 inhibitors.
- This study demonstrates the potential of KO-2806 as a combination partner to prevent or reverse adaptive resistance to KRAS^{G12C} inhibitor monotherapy.
- These preclinical results support the FIT-001 phase 1 first-in-human clinical trial assessing KO-2806 in combination with adagrasib (NCT06026410).