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

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**BACKGROUND**

Emerging clinical and preclinical data have shown that responses to KRAS<sup>G12C</sup> 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<sup>G12C</sup>-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<sup>G12C</sup> inhibitors. Here, we evaluate the therapeutic potential and mechanistic basis of combined KO-2806 and adagrasib in preclinical models of KRAS<sup>G12C</sup> non-small cell lung cancer (NSCLC).

**RESULTS**

Combination of KO-2806 with adagrasib causes tumor regressions in cell-derived and patient-derived KRAS<sup>G12C</sup> NSCLC xenografts

**CONCLUSIONS**

- Combination of the next generation FTI, KO-2806, with the KRAS<sup>G12C</sup> inhibitor, adagrasib, caused significant tumor regressions in KRAS<sup>G12C</sup> NSCLC xenografts.
- 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 in KRAS<sup>G12C</sup> NSCLC tumors.
- Knockdown of RHEB partially mimics the effects of KO-2806 in combination with adagrasib.