KO-2806, a Farnesyl Transferase Inhibitor, Re-sensitizes $KRAS^{G12C}$ NSCLC Tumors to $KRAS^{G12C}$ Mutant-Specific Inhibitors

Hetika Vora Patel

6th Annual RAS-Targeted Drug Development Summit
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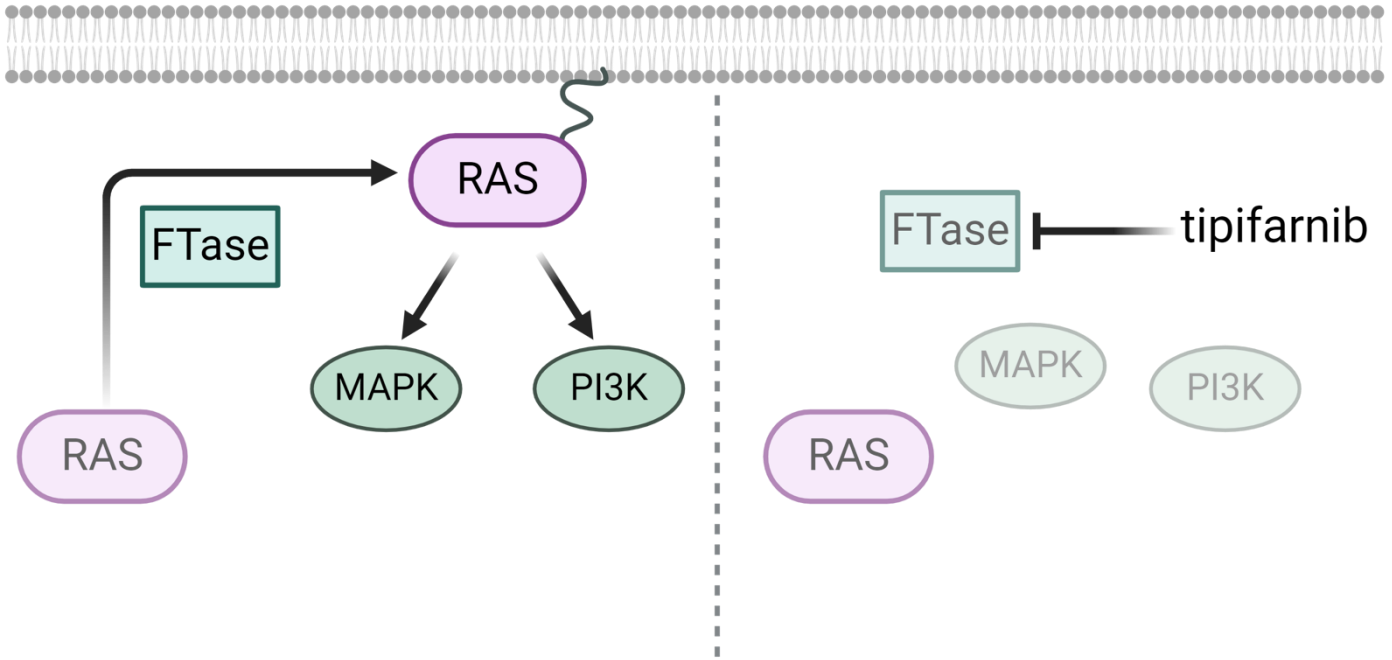
Disclosure Information

-Employee and Stockholder of Kura Oncology, Inc.

Evolution of farnesyl transferase inhibitors (FTIs)

Tipifarnib, a FTI, is developed to indirectly target RAS proteins

1997



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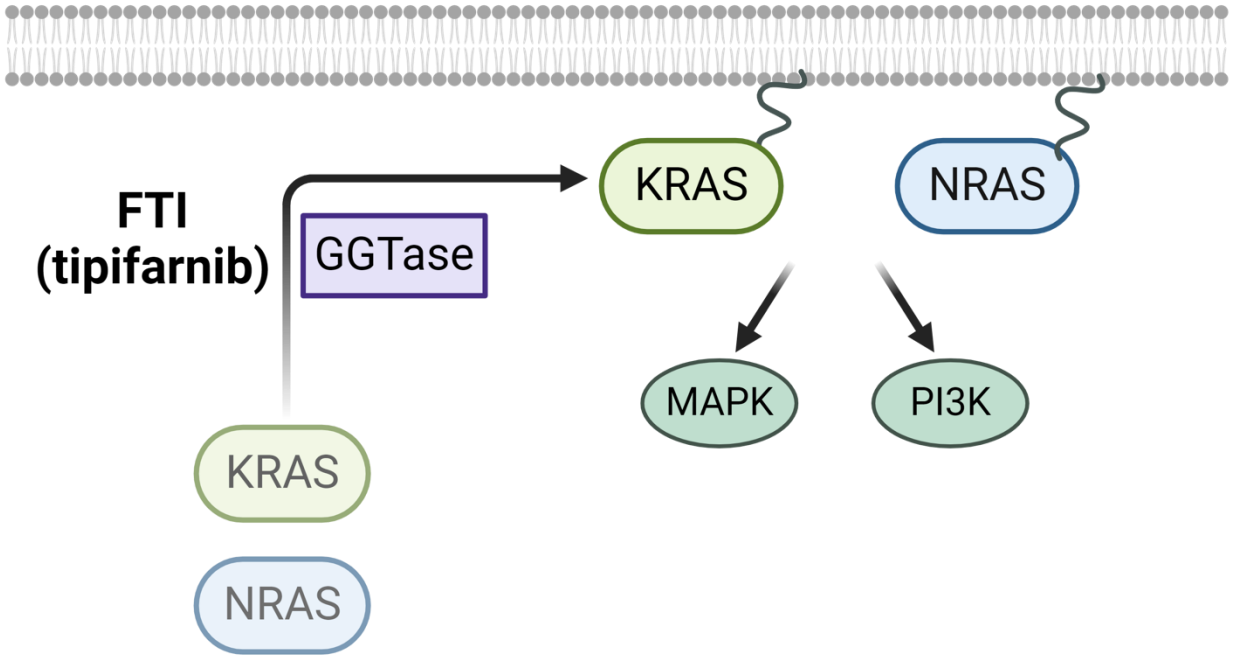

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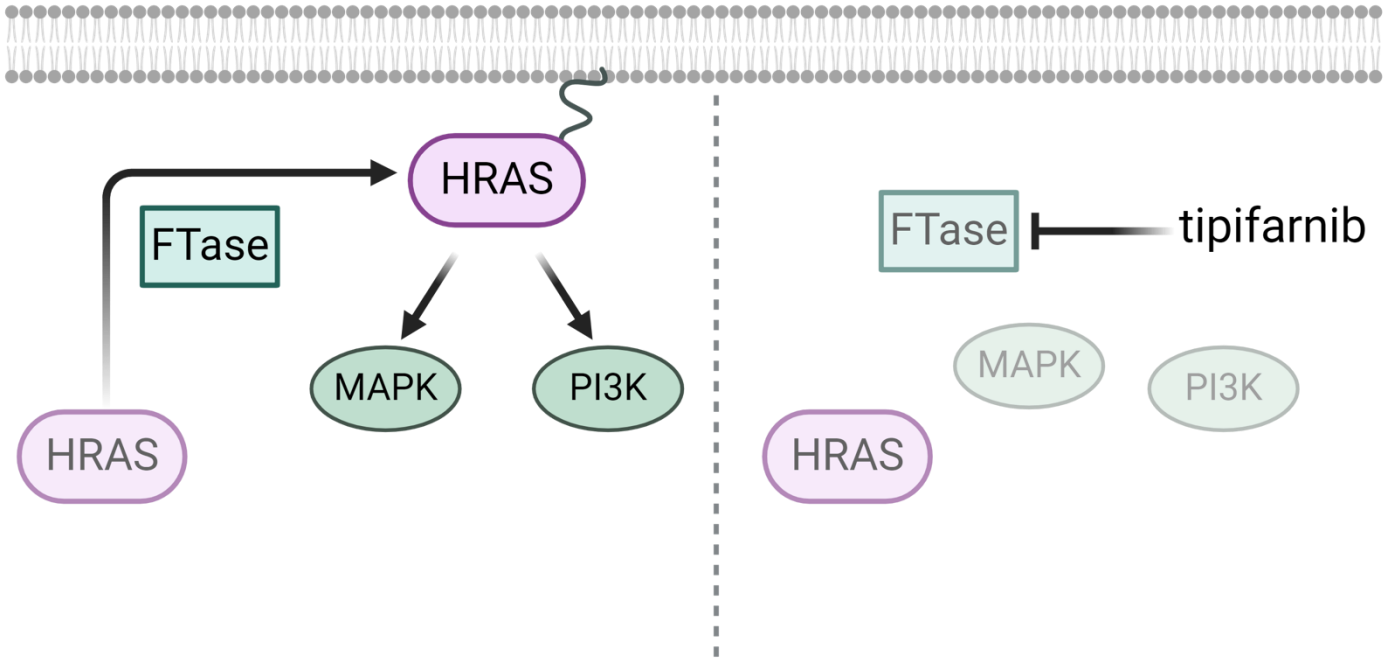
Kura Oncology in-licenses tipifarnib to target HRAS-driven cancers



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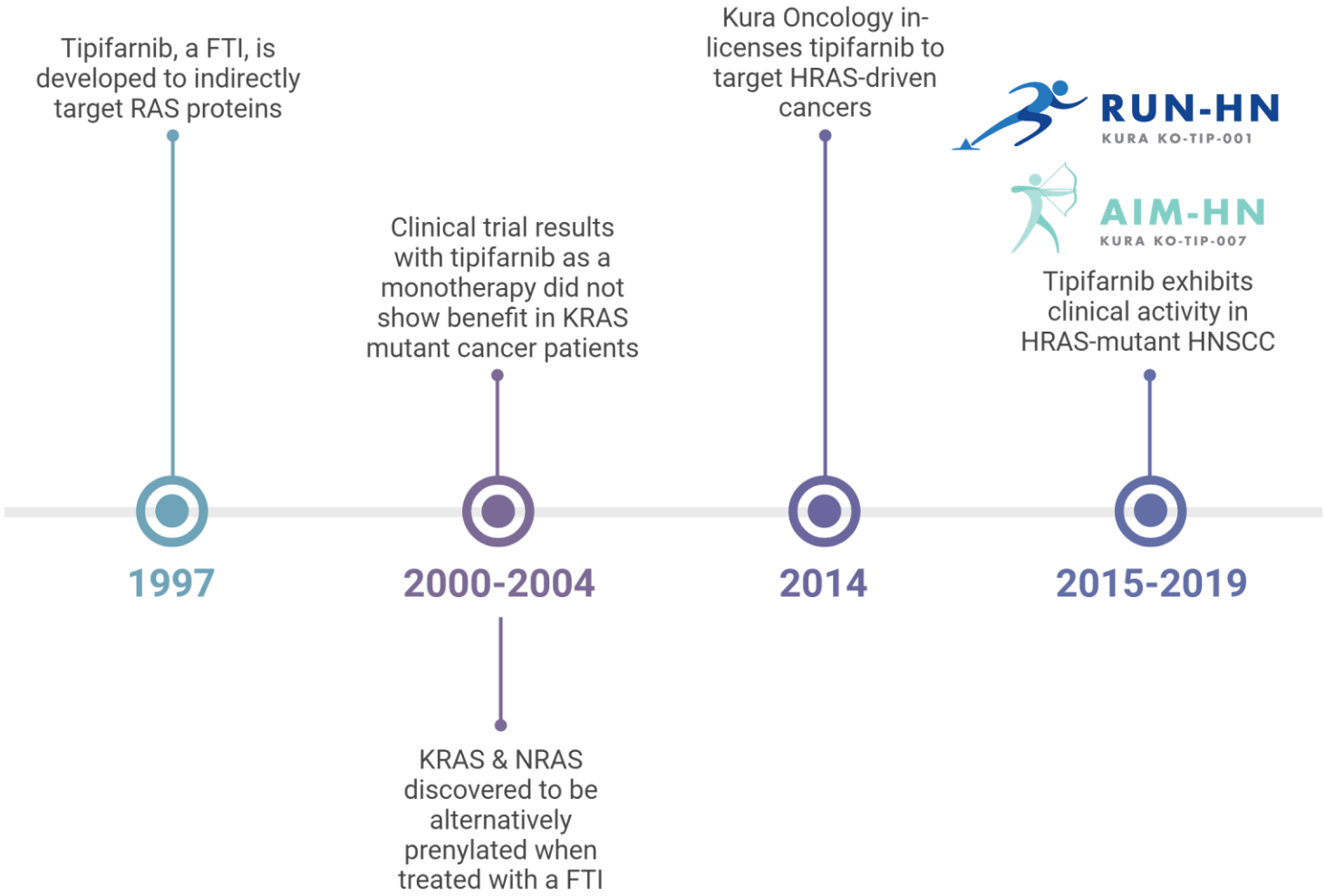

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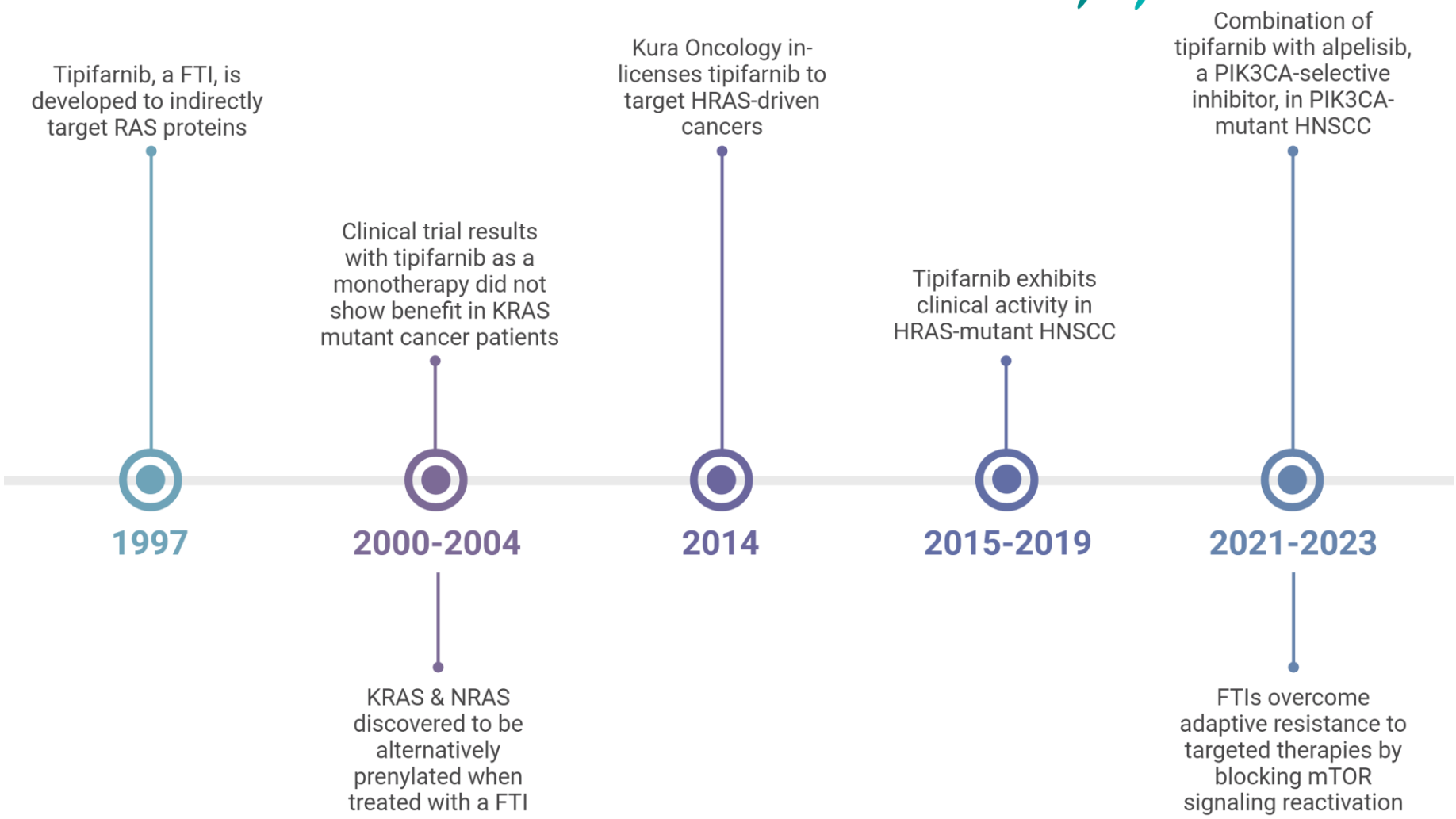
KURRENT-HN
KURA KO-TIP-013



Smith et al. *Cancer Res* (2023) 83 (19): 3252–3263.

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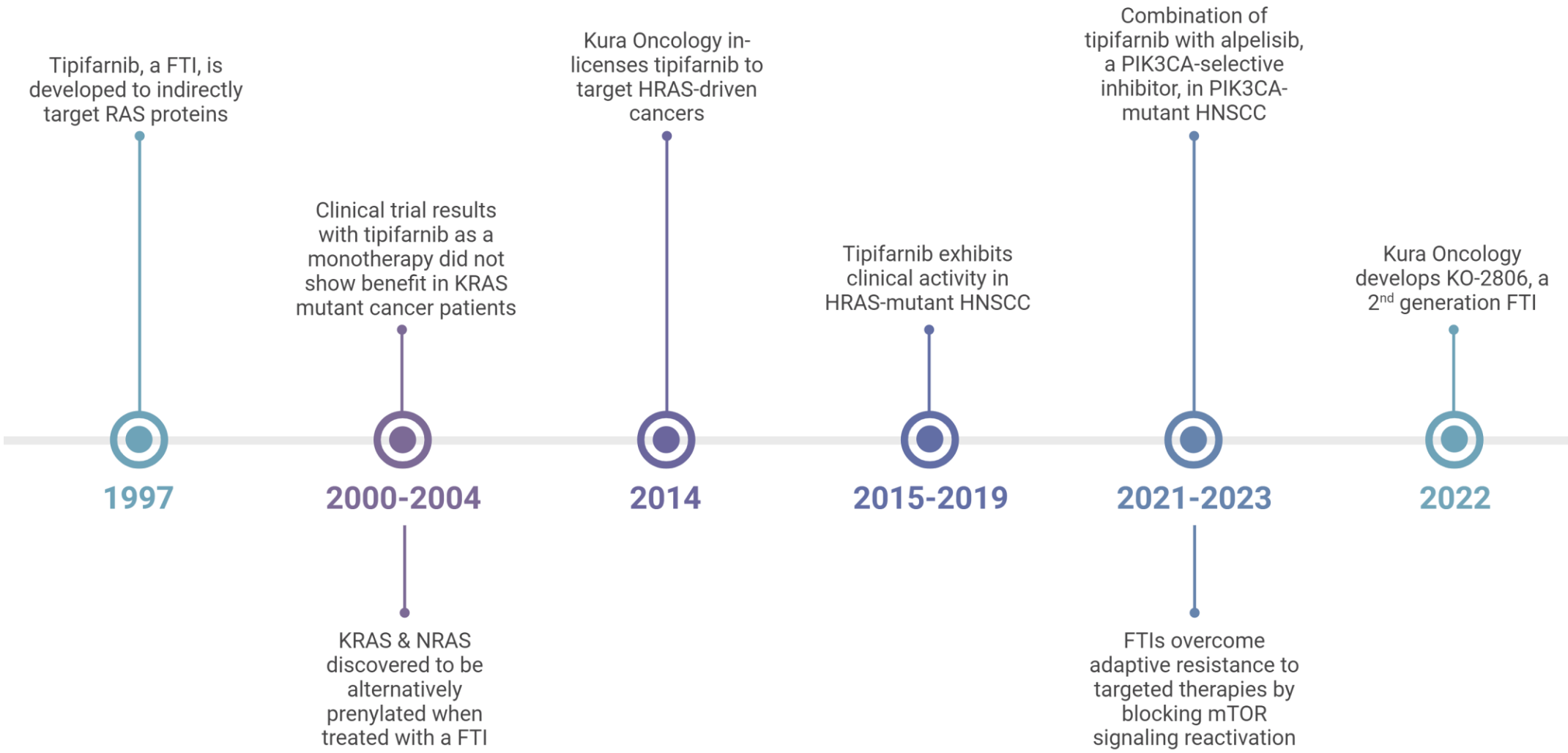

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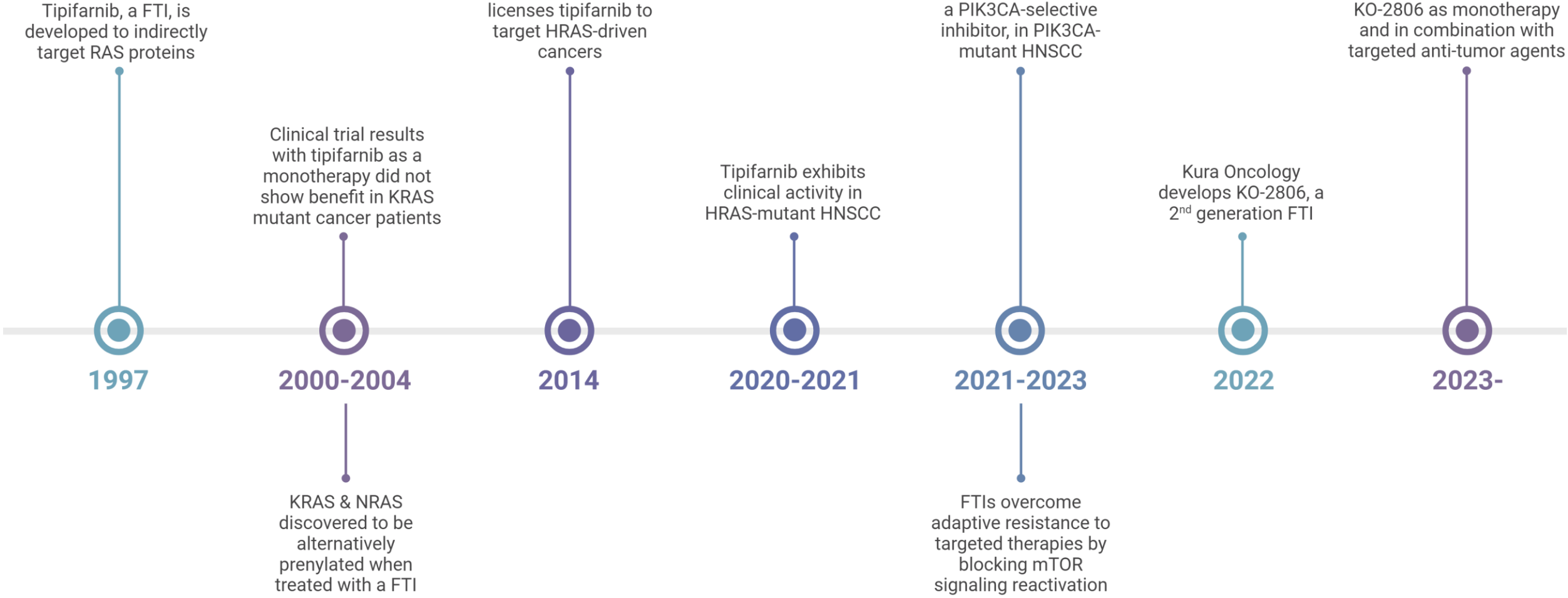
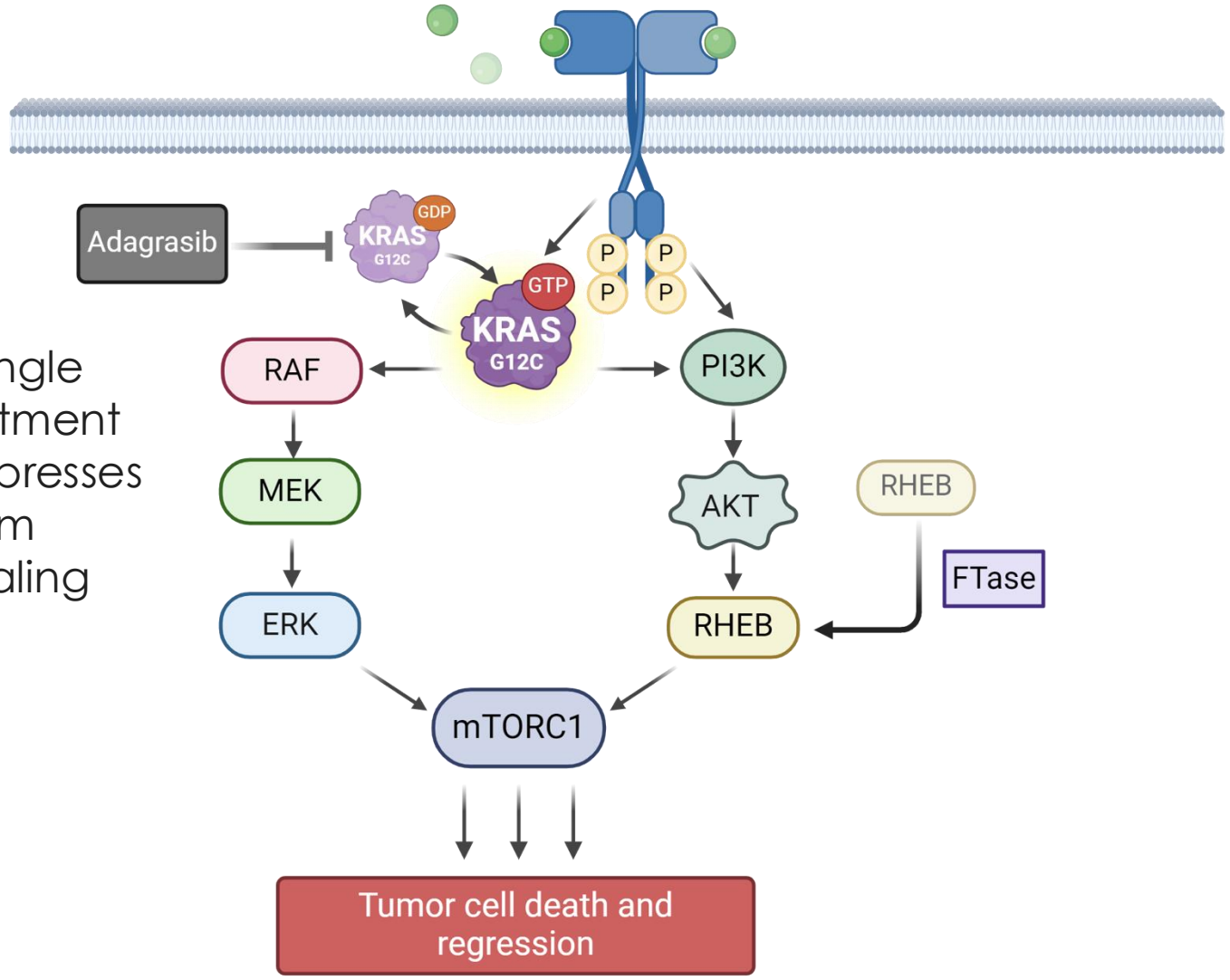


Mechanistic rationale to combine FTI with KRAS^{G12C} inhibitor

KRAS^{G12C} single agent treatment initially suppresses downstream MAPK signaling



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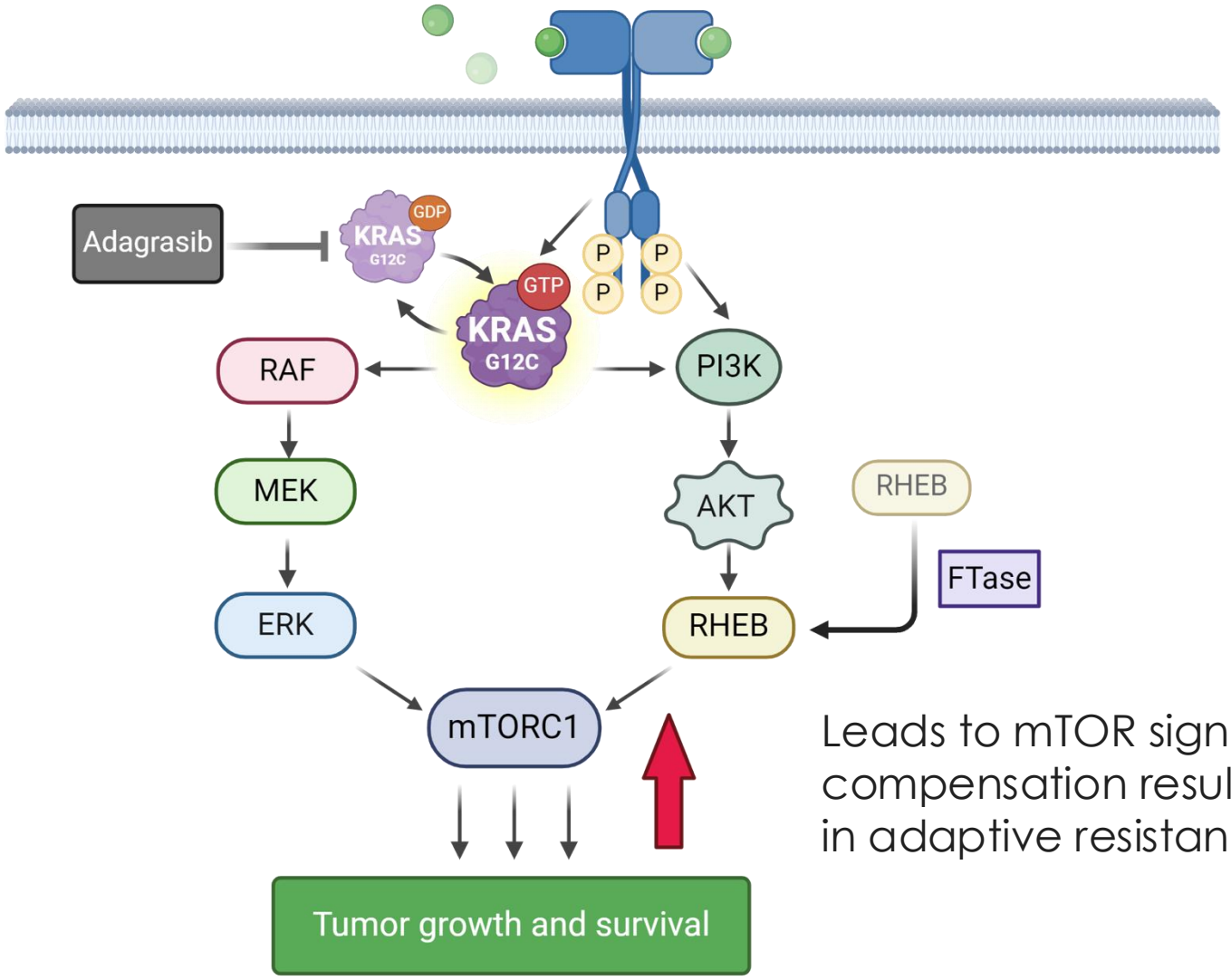

Leads to mTOR signaling compensation resulting in adaptive resistance

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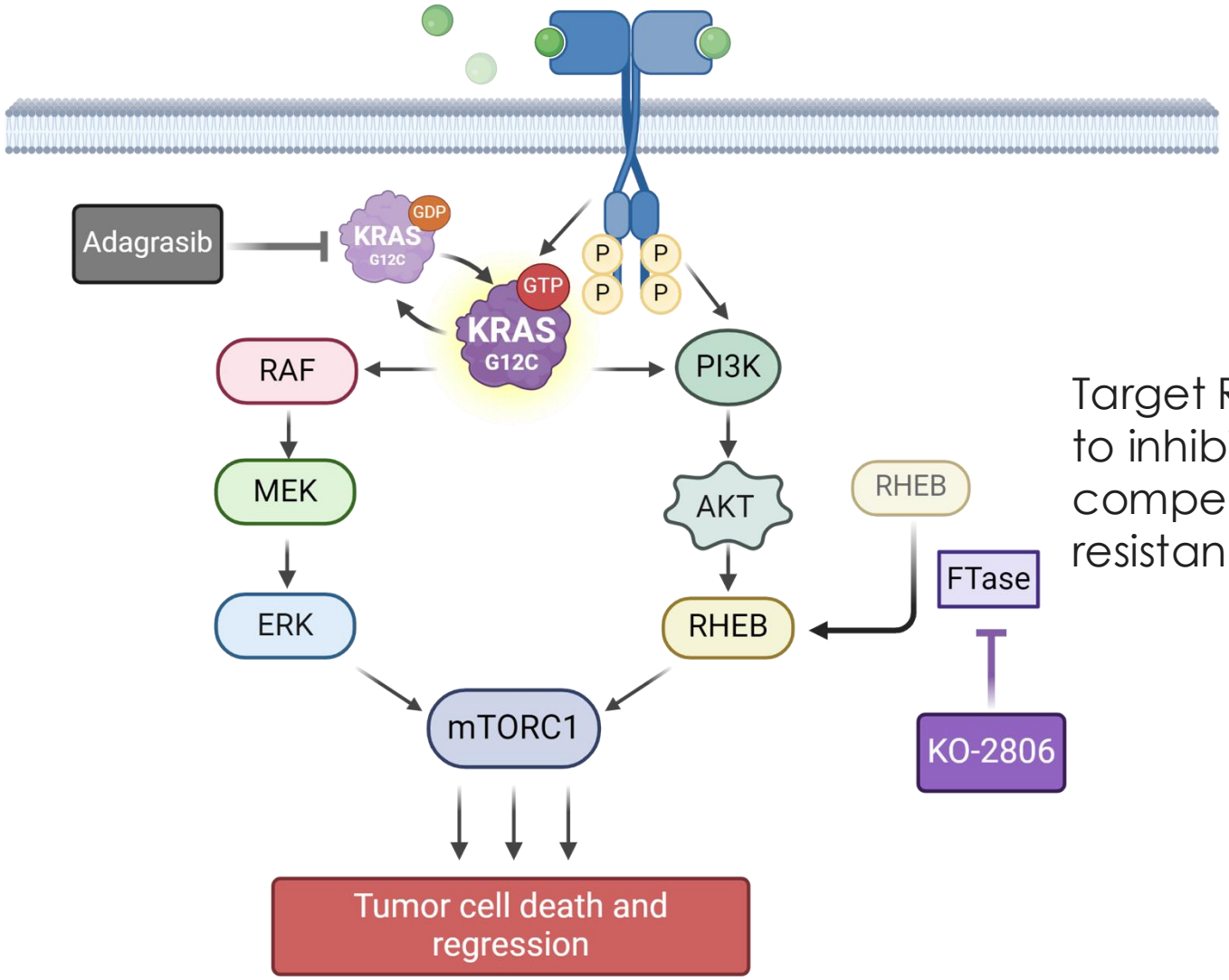

Target RHEB farnesylation to inhibit mTOR pathway compensation and prevent resistance to adagrasib

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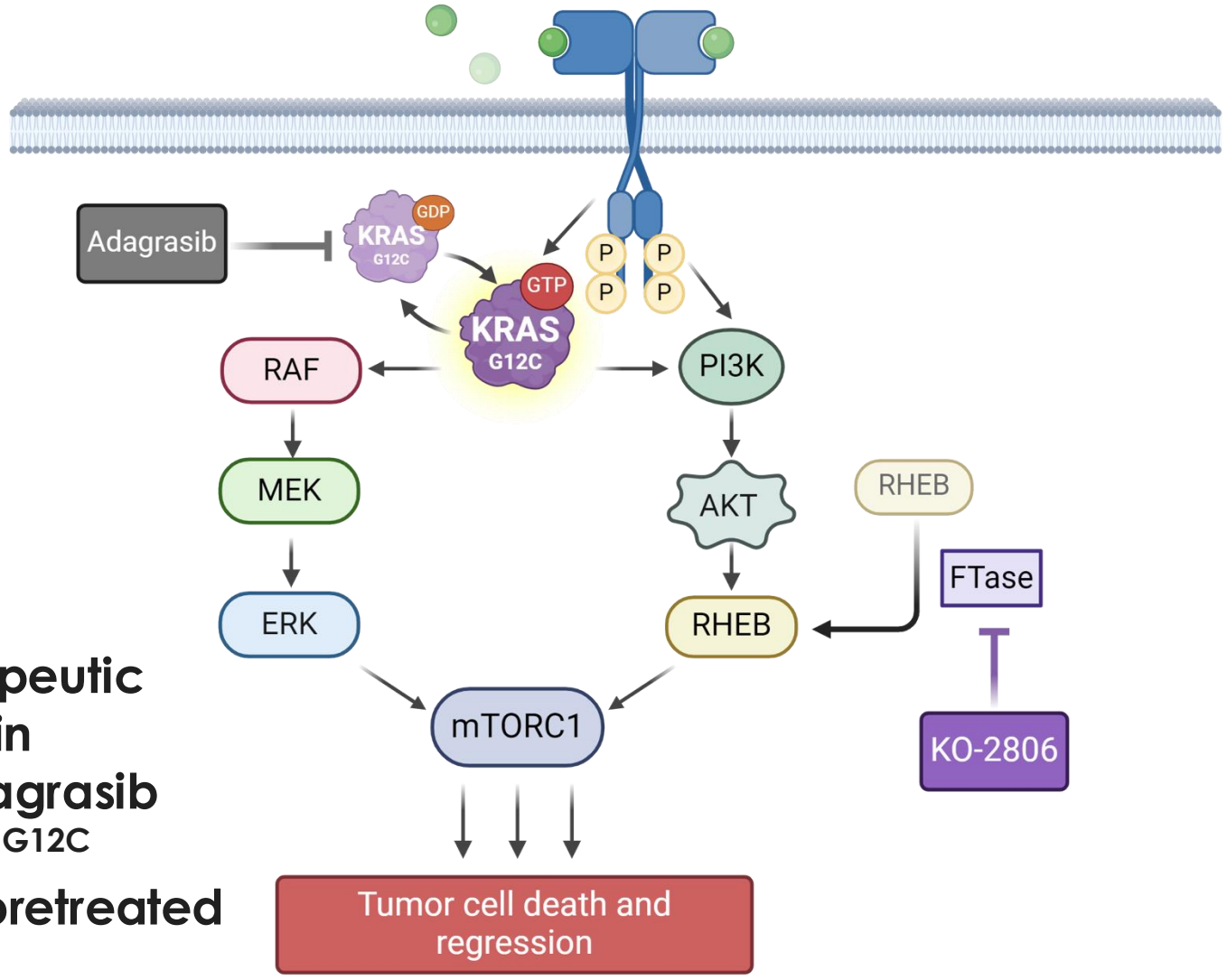
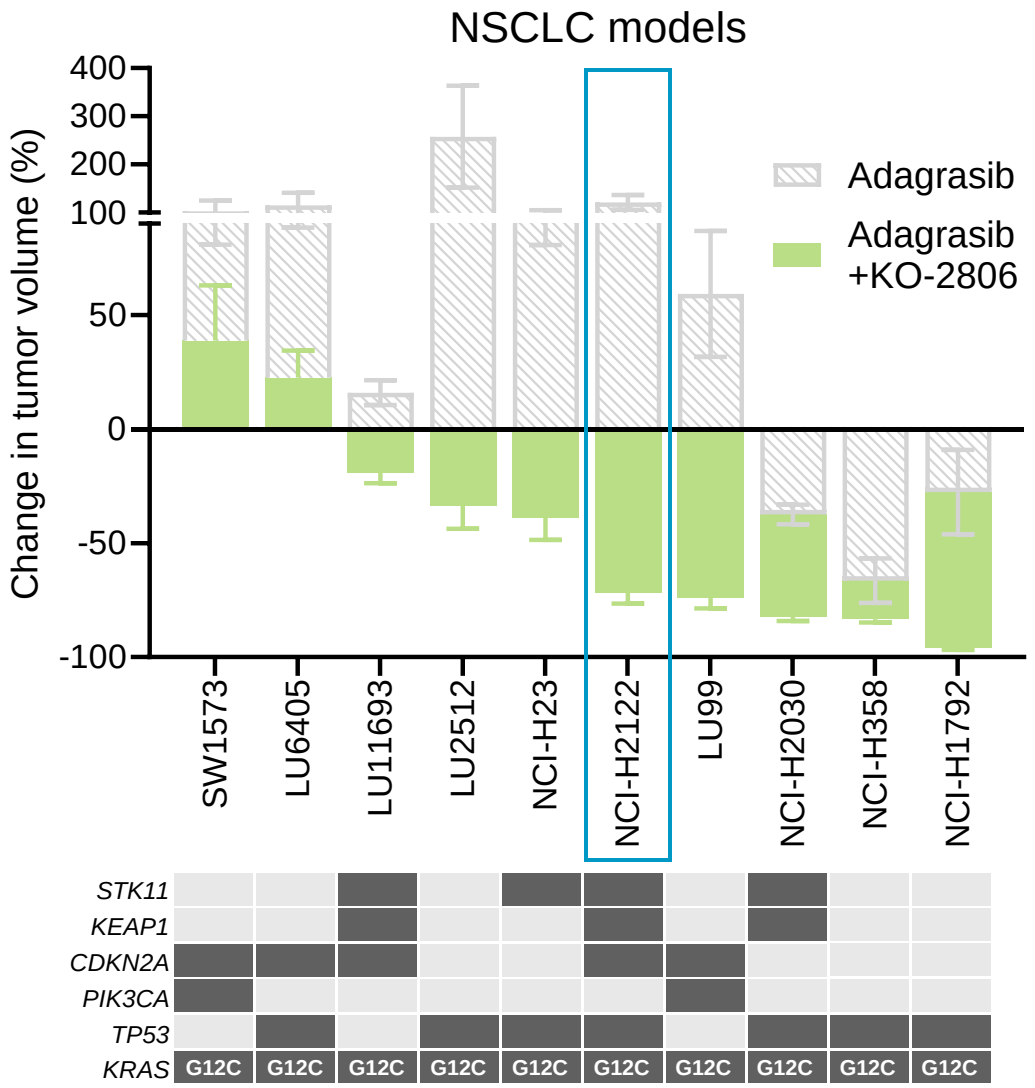


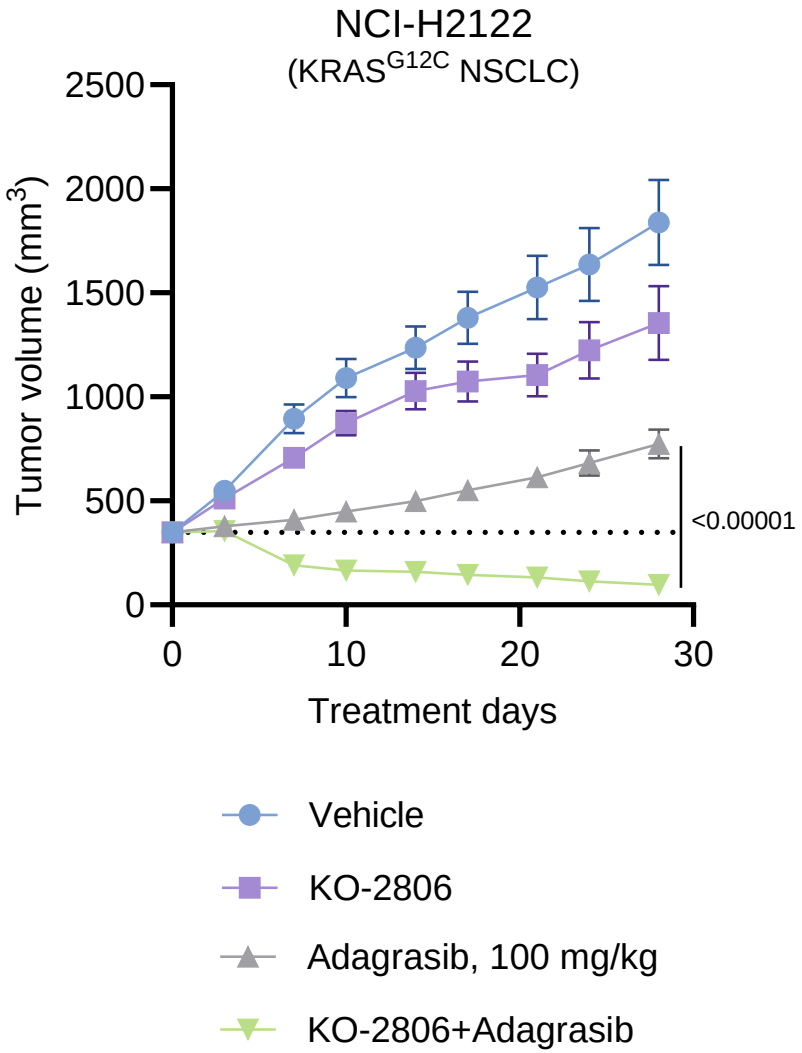
In this work, the therapeutic potential of KO-2806 in combination with adagrasib was assessed in KRAS^{G12C} inhibitor-naïve and -pretreated preclinical models

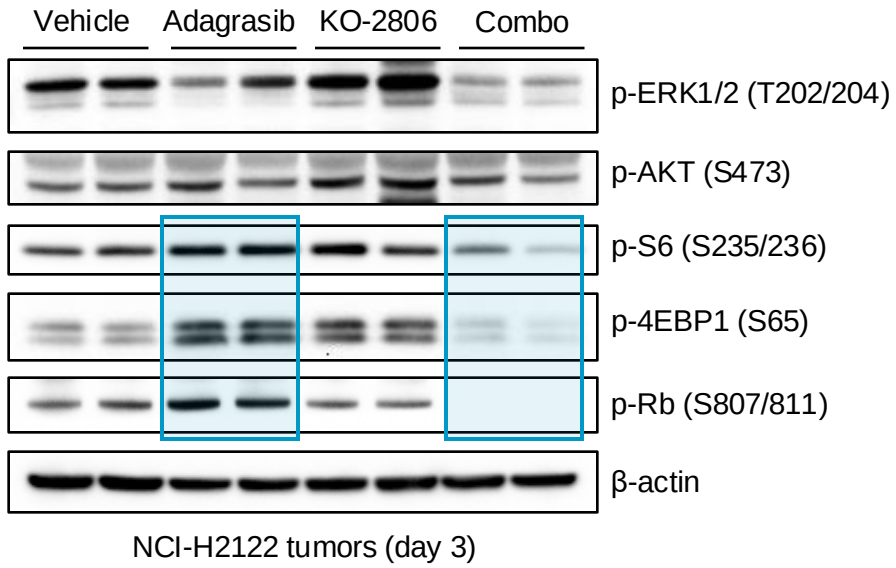
KO-2806 deepens anti-tumor responses to adagrasib monotherapy



*Adagrasib doses = 30 mg/kg or 100 mg/kg

KO-2806 enhances anti-tumor effects through mTOR signaling inhibition





mTOR signaling inhibition and cell cycle arrest with upfront combination

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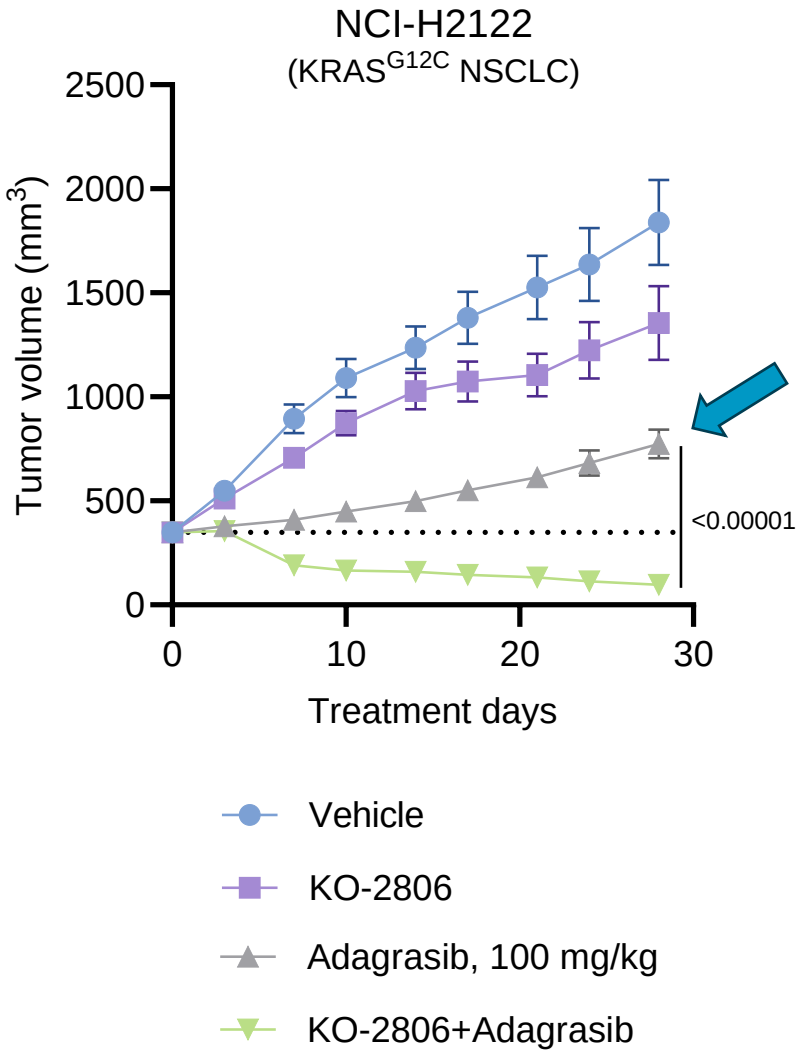
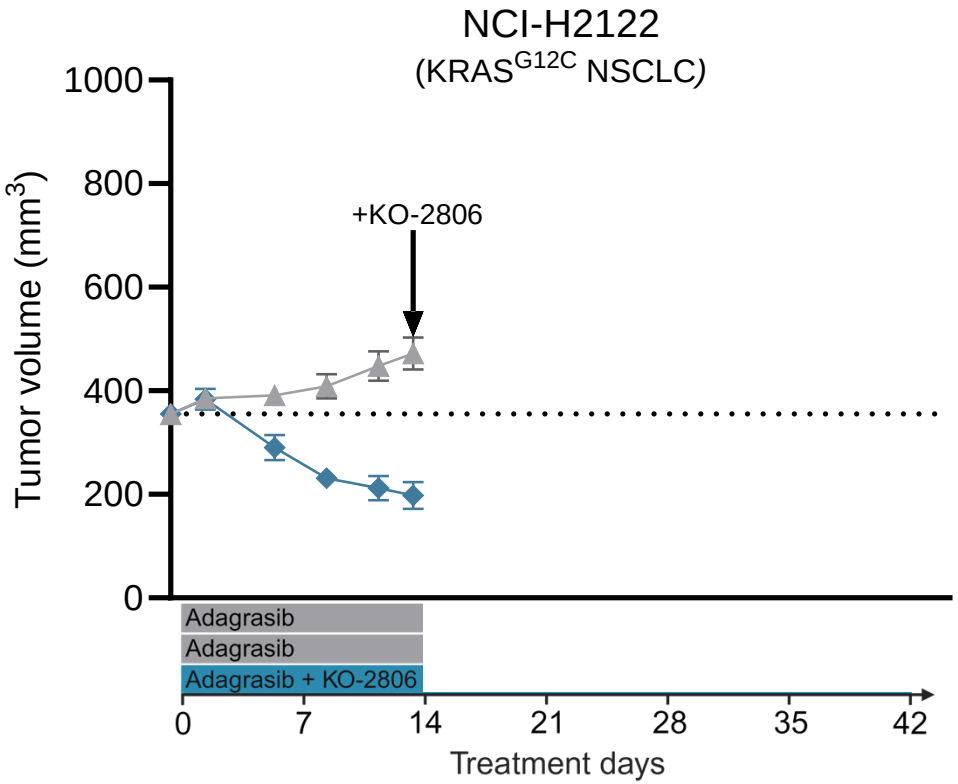


Can tumors that are progressing on KRAS^{G12C} inhibitor monotherapy benefit from the combination of KO-2806 with adagrasib?

Tumors progressing on adagrasib are re-sensitized by KO-2806 addition



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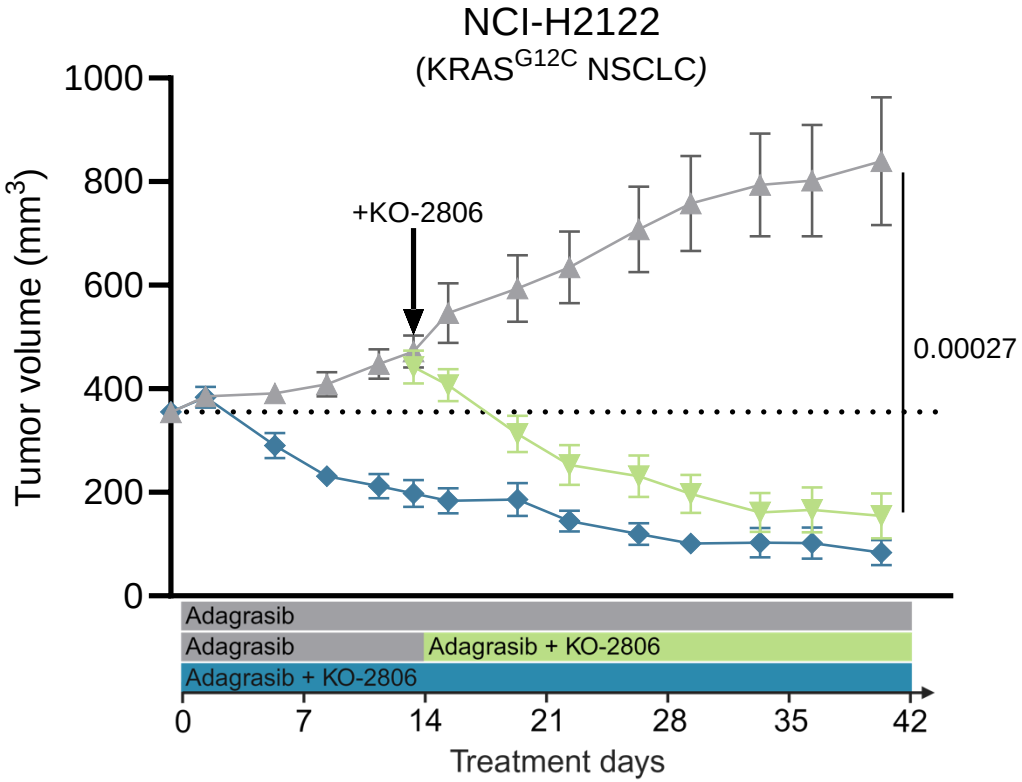
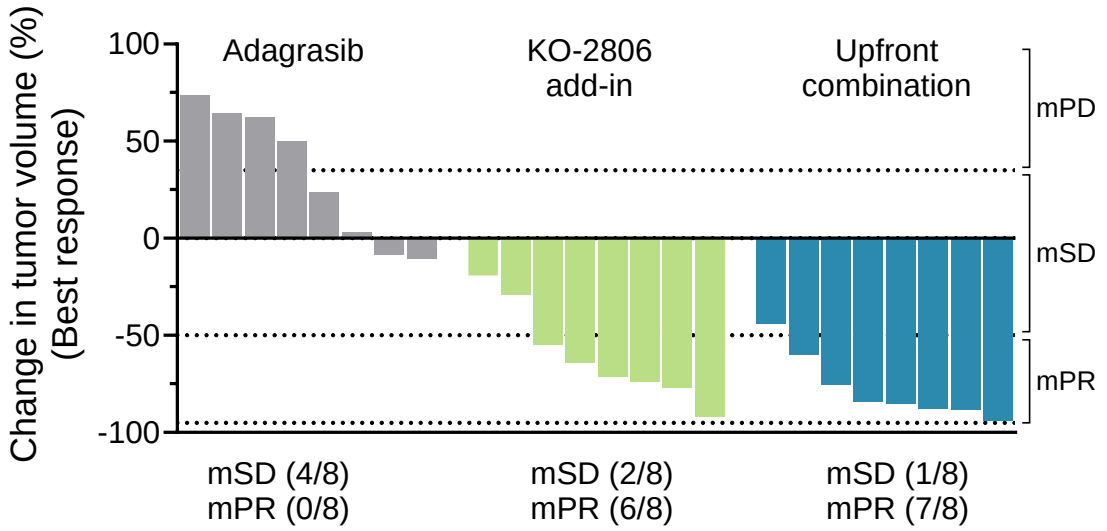
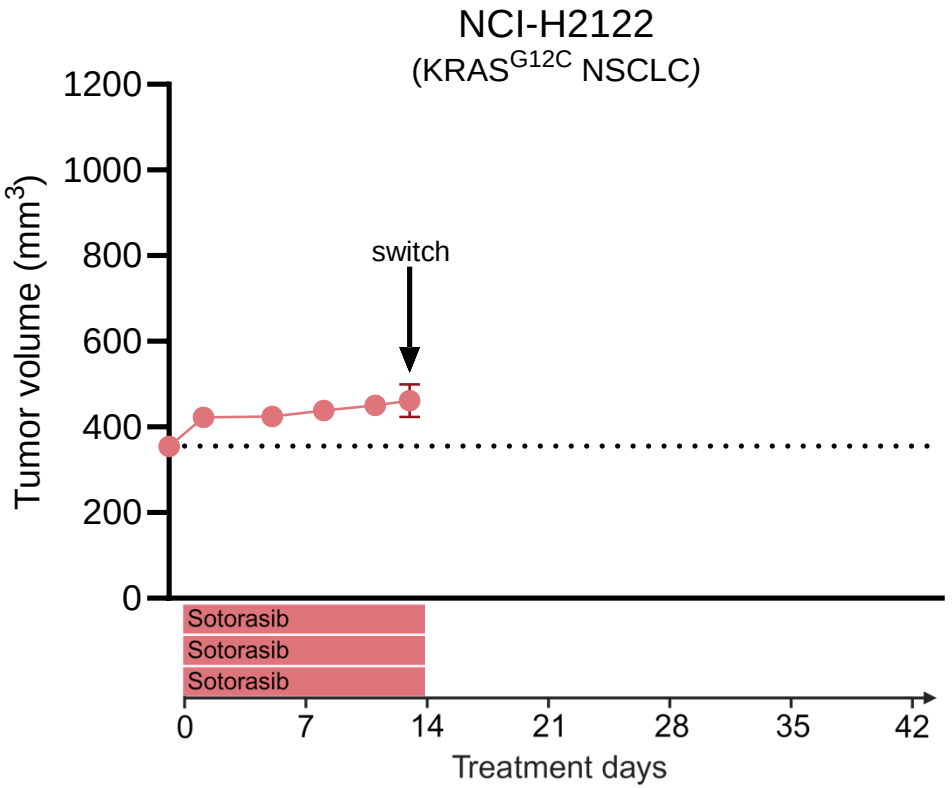




Tumor regressions in KO-2806 add-in group were comparable to upfront combination of KO-2806 with adagrasib

Tumors progressing on sotorasib regress when switched to combination of KO-2806 with adagrasib



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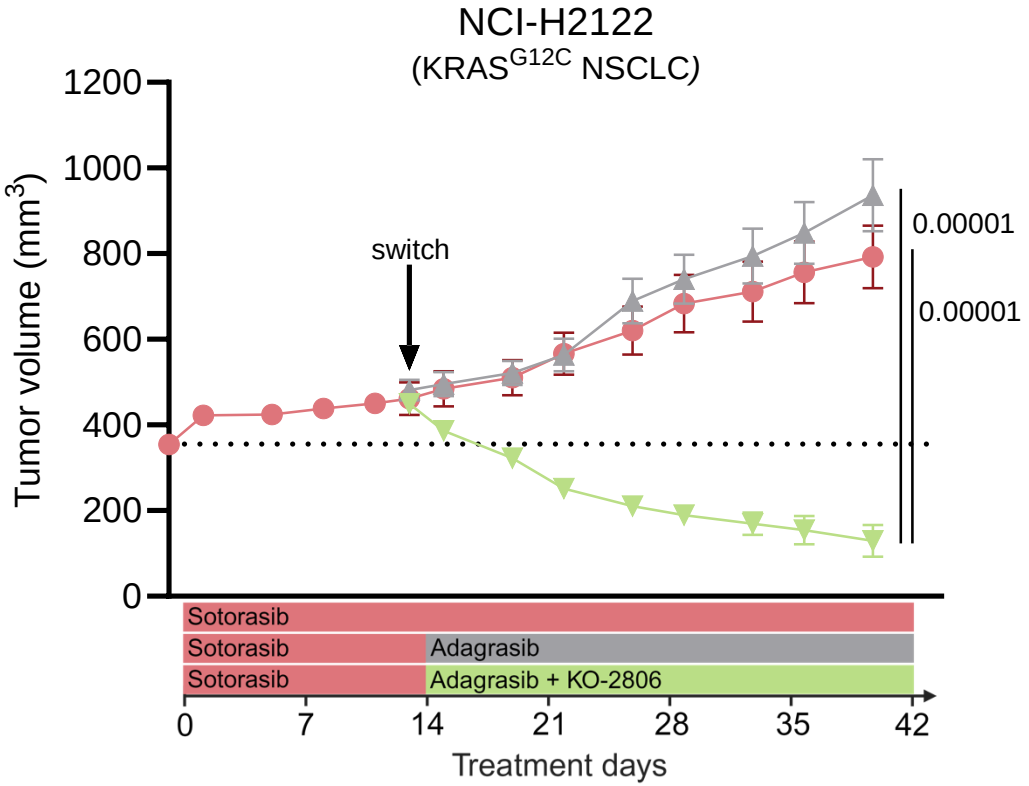
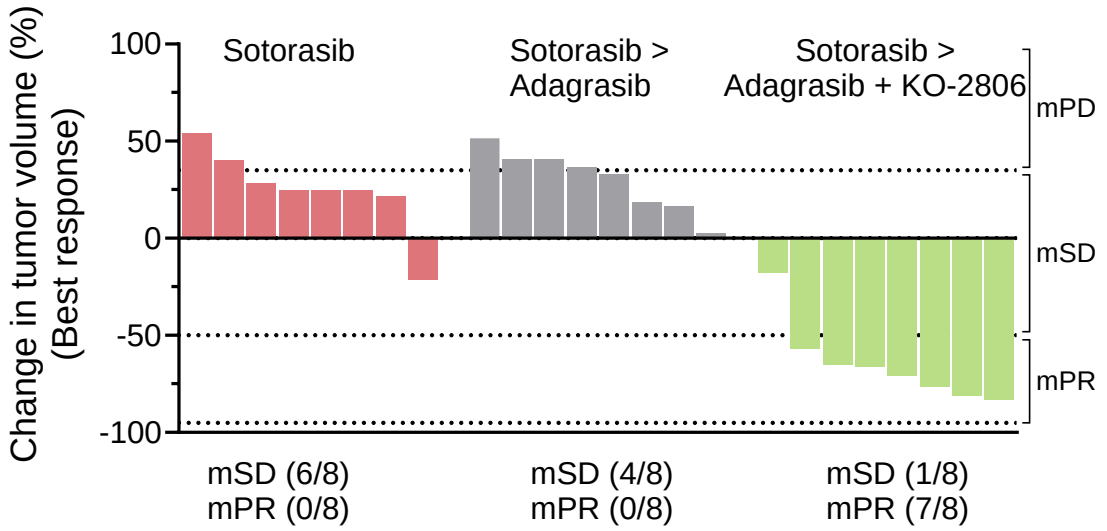
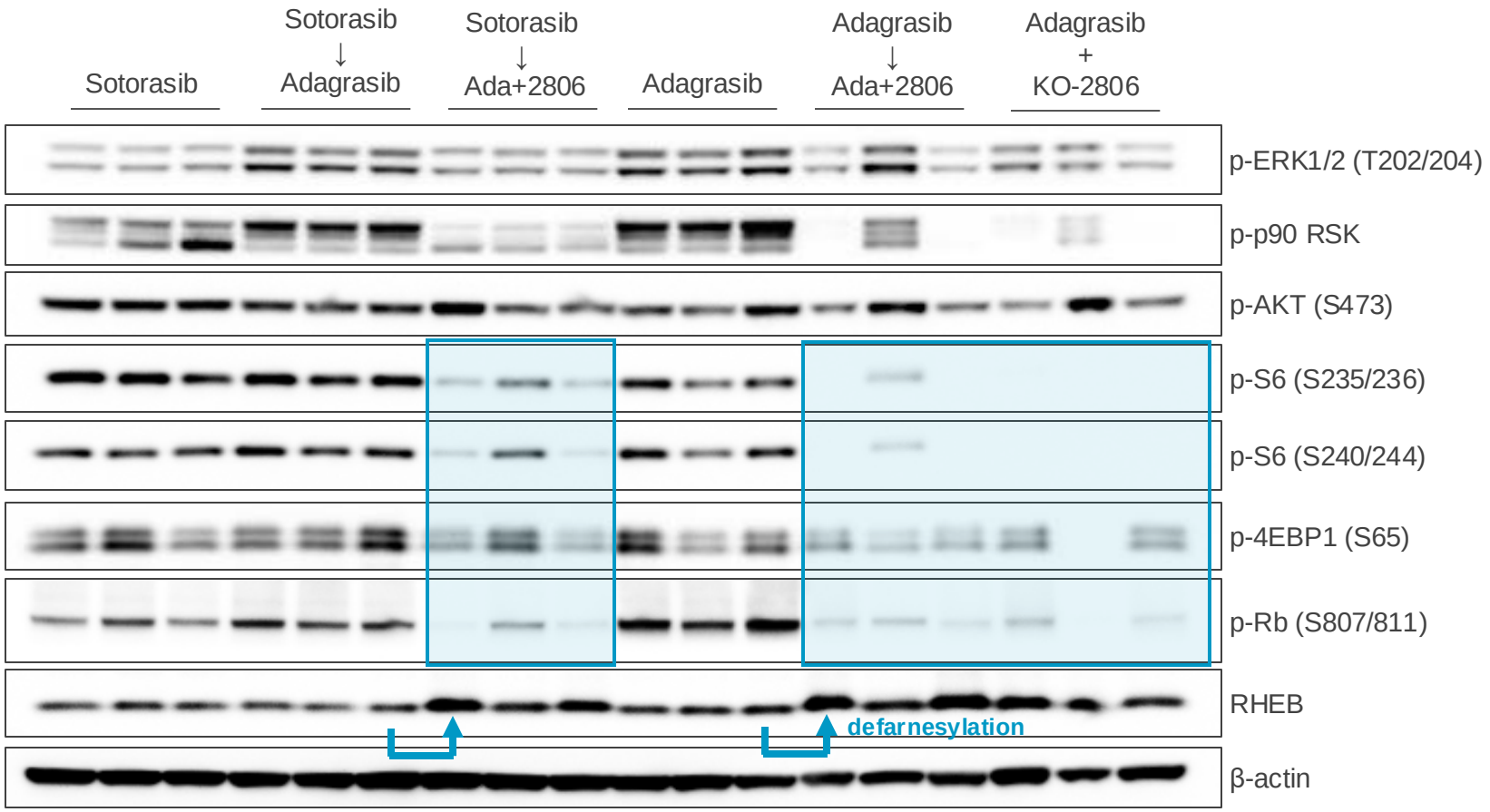




Tumor regressions were observed irrespective of prior KRAS^{G12C} inhibitor treatment

KO-2806-adagrasib combination, regardless of prior KRAS^{G12C} inhibitor treatment, inhibits mTOR signaling and induces cell cycle arrest



NCI-H2122 *KRAS*^{G12C} NSCLC tumors (day 41)

Summary

- The next-generation FTI, KO-2806, in combination with adagrasib enhances anti-tumor efficacy 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

- This study demonstrates the potential of KO-2806 as a combination partner to prevent or reverse adaptive resistance to $KRAS^{G12C}$ inhibitor monotherapy, supporting FIT-001 clinical trial assessing KO-2806 in combination with adagrasib

Acknowledgements

The patients and their families

Kura Oncology
Translational Research Team

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