Farnesyl Transferase Inhibitors- Evolution from Targeting HRAS to Overcoming Adaptive Resistance to Targeted Therapies

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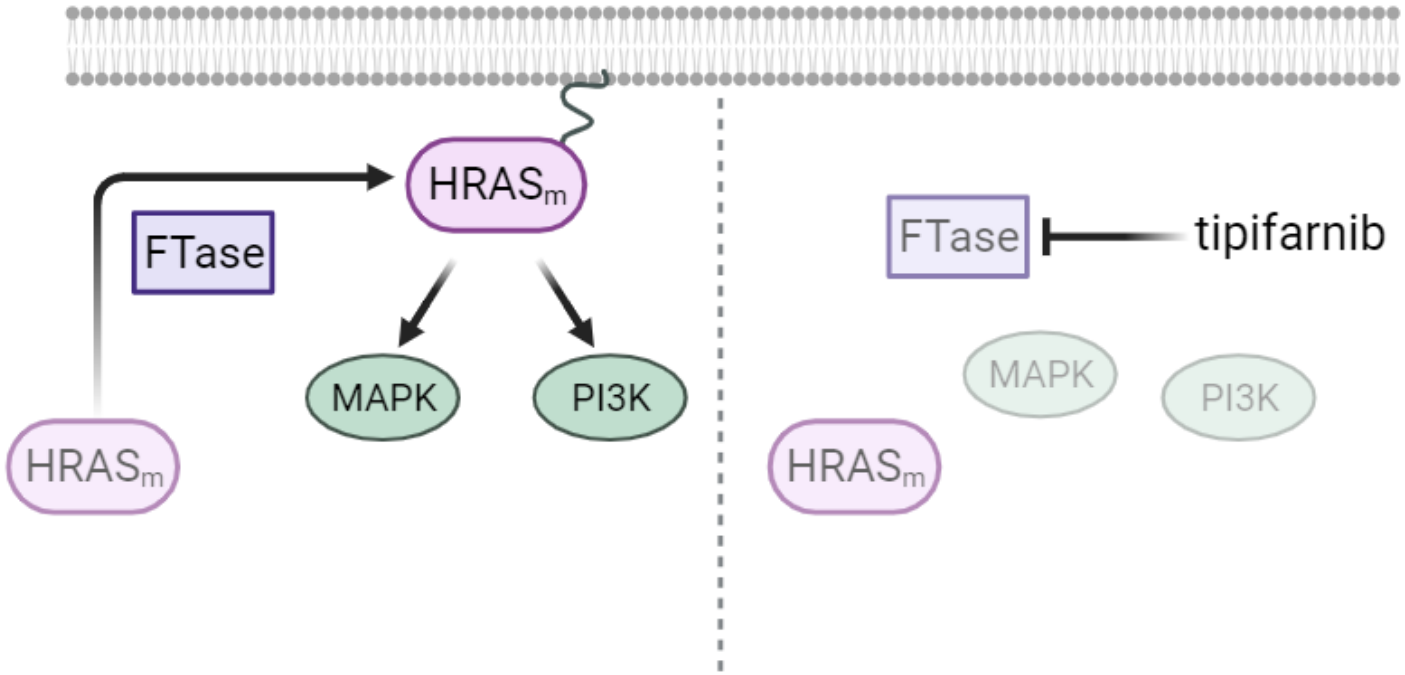
5th RAS-Targeted Drug Development Summit
September 26-28, 2023

Disclosures

-Employee of Kura Oncology, Inc.

FTIs and the RAS Family of Oncogenes

- Tipifarnib-first-in-class FTI, originally developed to target KRAS
- Upon farnesyl transferase inhibition, KRAS and NRAS become geranylgeranylated
- HRAS is an obligate farnesylation target-it lacks the geranylgeranylation rescue pathway

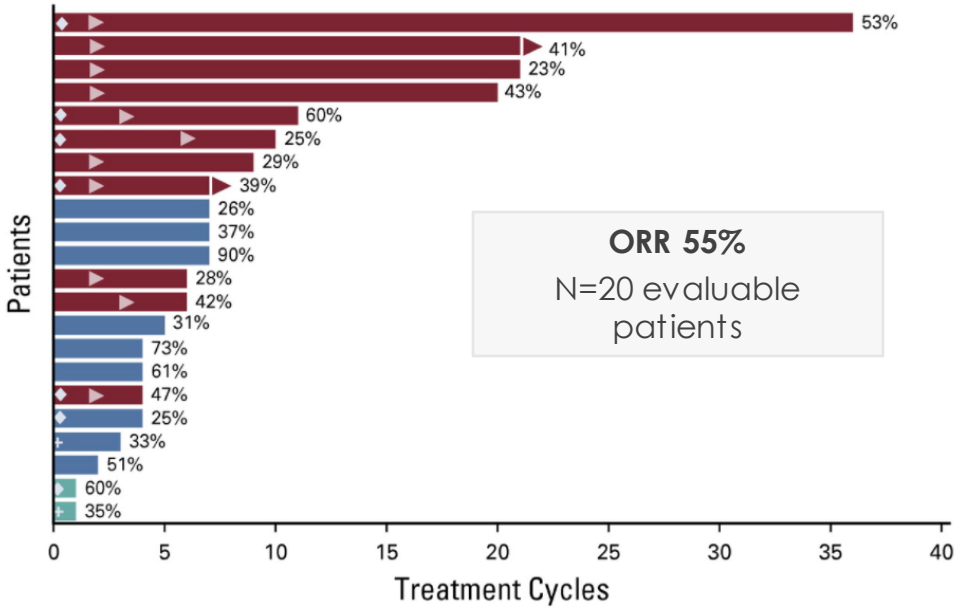


FTase- Farnesyl transferase
FTI- Farnesyl transferase inhibitor

Tipifarnib Demonstrates Durable Anti-Tumor Activity in Patients with Recurrent or Metastatic HRAS-Mutant HNSCC

RUN-HN
KO-TIP-001

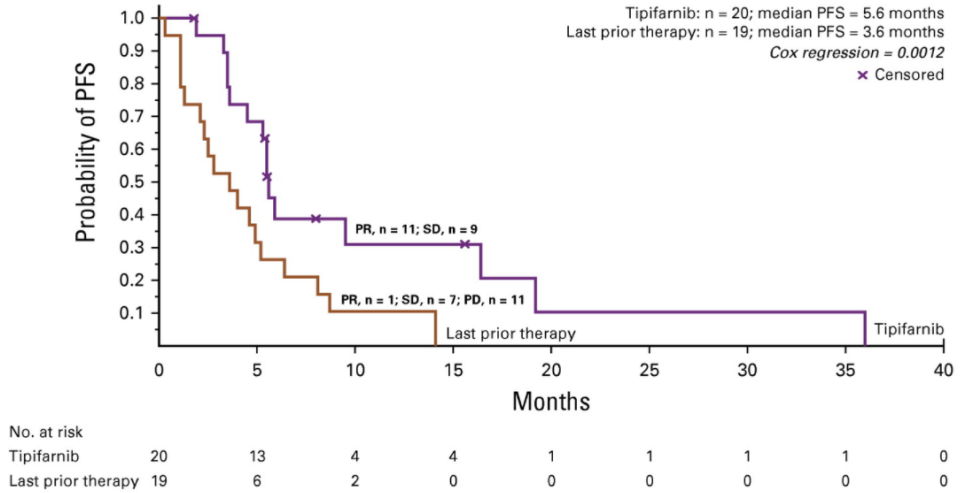
Patients with high variant allele frequency (VAF, ≥20%) m*HRAS* HNSCC

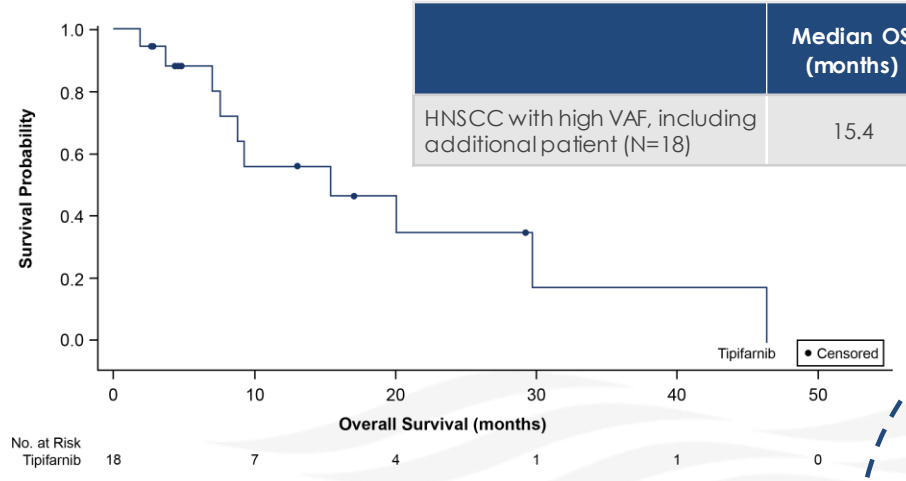


ORR 55%

N=20 evaluable patients

Red, PR; *blue*, SD; *green*, not evaluable for efficacy; *diamond*, patient initiated treatment at 600 mg twice a day; *cross*, patient withdrew consent; *arrow in bar*, start of response; *arrow*, active treatment. Numbers at the end of the bars represent VAF for each patient.



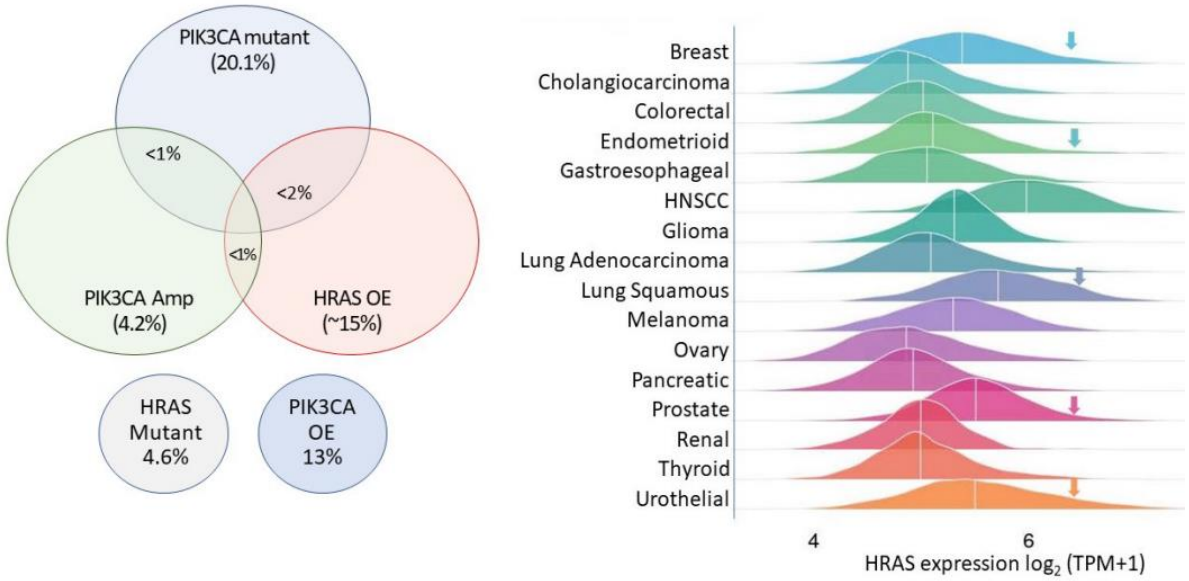


	Median OS (months)	95% CI	
		Lower	Upper
HNSCC with high VAF, including additional patient (N=18)	15.4	7.0	46.4

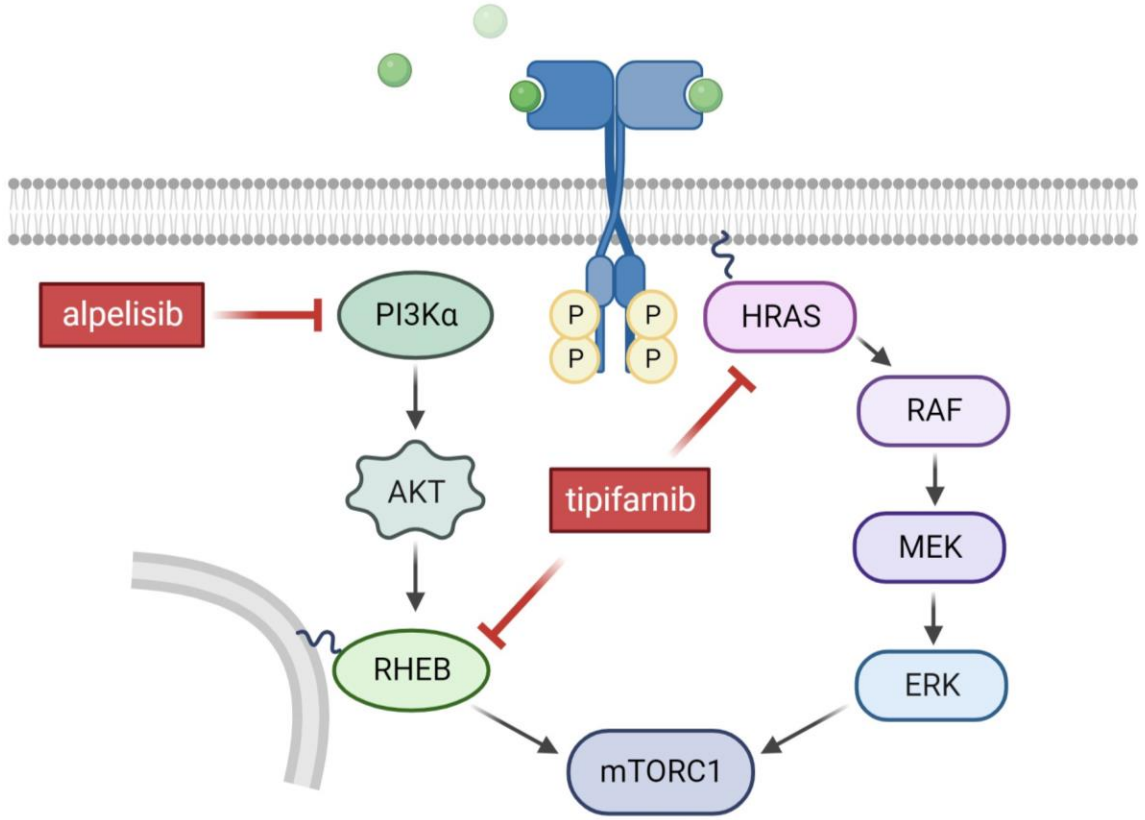
Ho, et al. *J Clin Oncol*. 2021 June 10;39(17):1856-1864. doi: 10.1200/JCO.20.02903.
Ho *et al*. ASCO 2020 #6504 (preliminary exploratory data as of 9/30/19)

Efficacy-evaluable patients with HRAS mutant variant allele frequency (VAF) ≥ 20% and serum albumin ≥ 3.5 g/dL, or HRAS VAF ≥ 35%
One patient treated off-protocol through compassionate use

Can FTIs Be Clinically Effective in a Broader HNSCC Population?

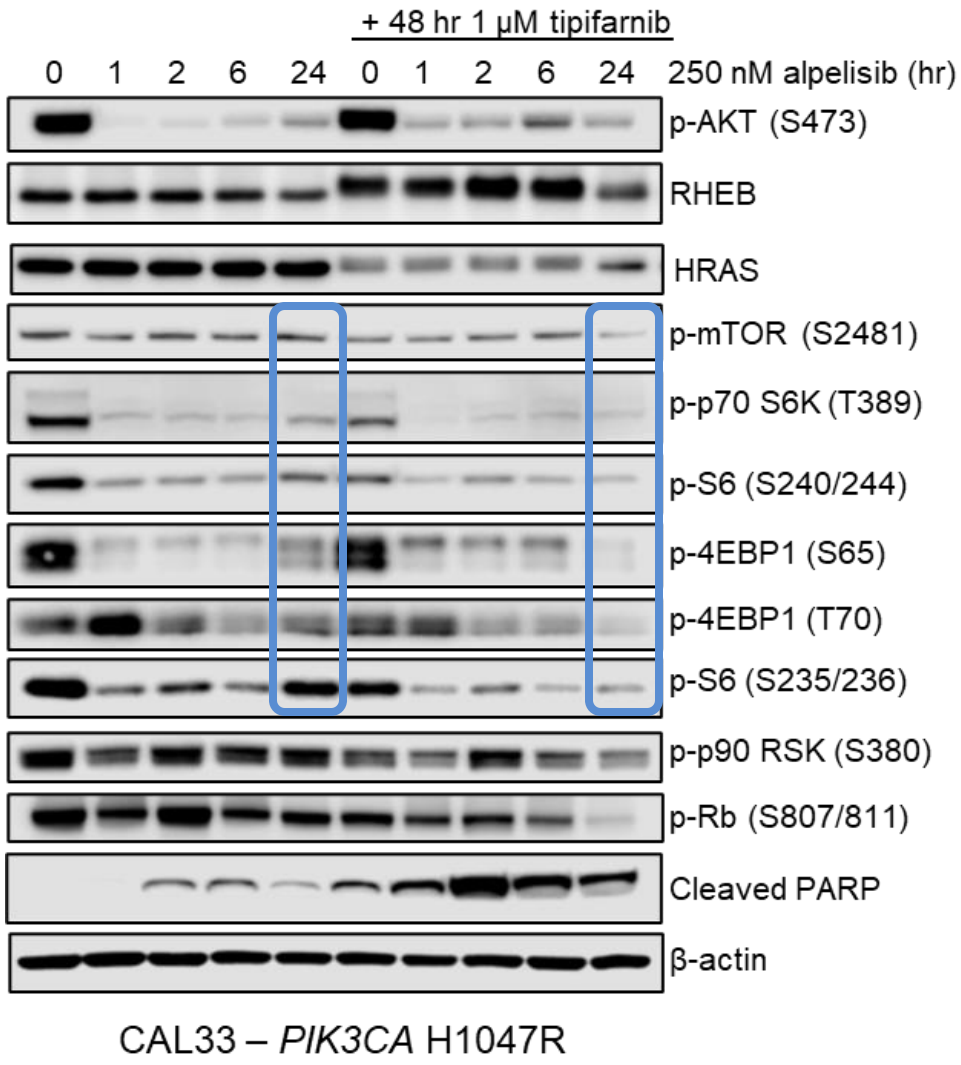


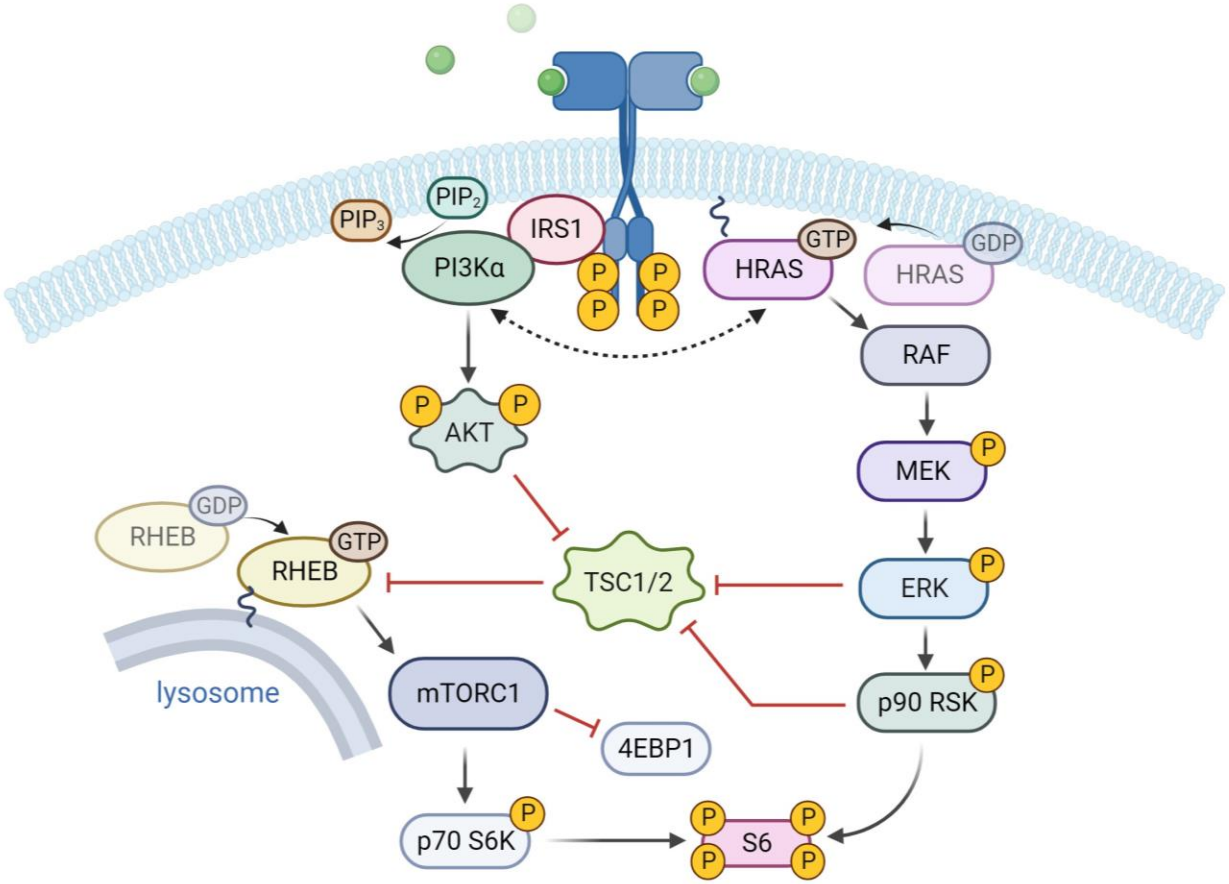
Comprehensive genomic profiling using Tempus XT reveals HRAS- and/or PIK3CA-dependence in HNSCC



HRAS-PIK3CA crosstalk in HNSCC - Tipifarnib blocks hyperactivated growth factor signaling at multiple nodes, including HRAS and RHEB

Combined Tipifarnib and Alpelisib Inhibits mTOR Reactivation for the Entire Dosing Interval

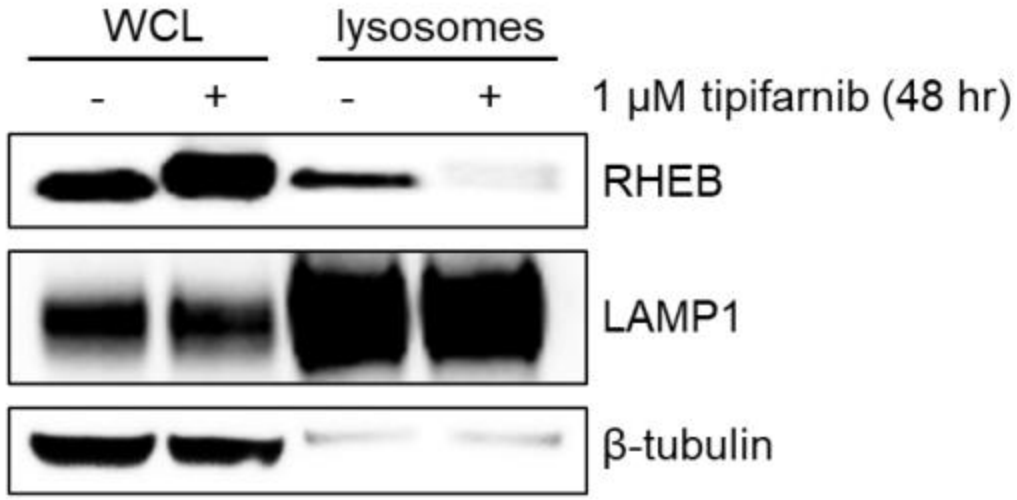




Reference: Smith et al., 2023, Tipifarnib potentiates the antitumor effects of PIK3Kα inhibition in PIK3CA- and HRAS- dysregulated HNSCC via convergent inhibition of mTOR activity. Cancer Res, CAN-23-0282

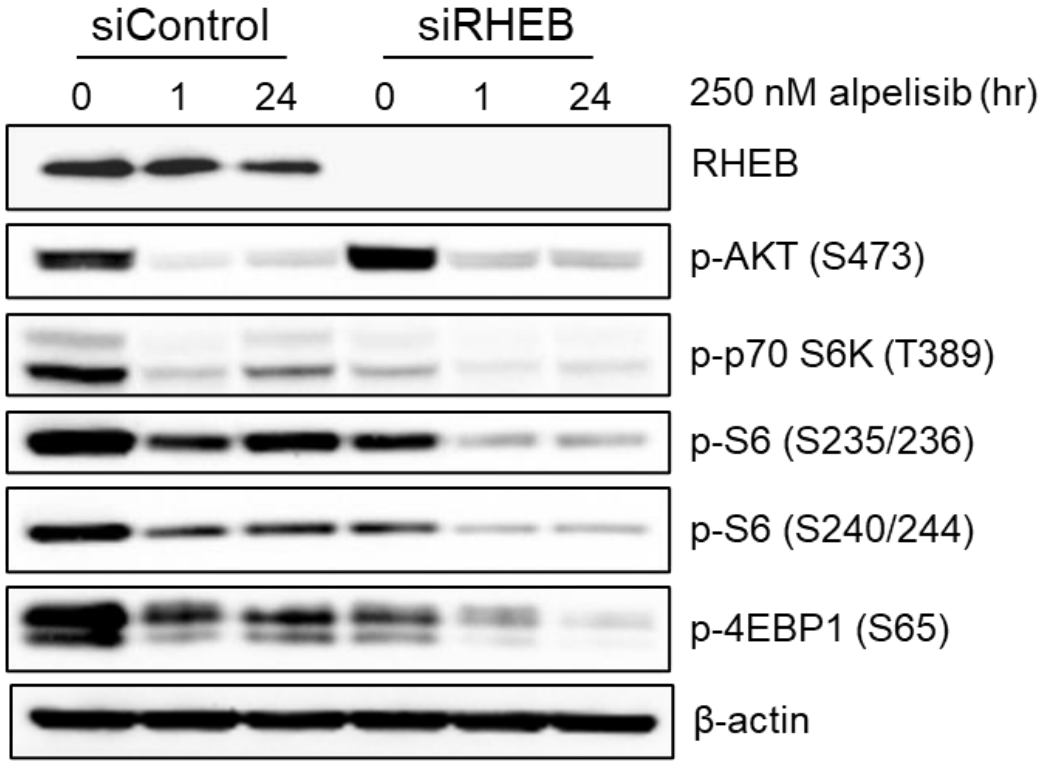
RHEB, An Obligately Farnesylated Protein, is a Key FTI Target

Tipifarnib blocks localization of RHEB to the lysosomes



CAL33 – *PIK3CA* H1047R

RHEB depletion enhances mTOR inhibition <u>when combined with alpelisib</u> in PIK3CA mutant HNSCC cells



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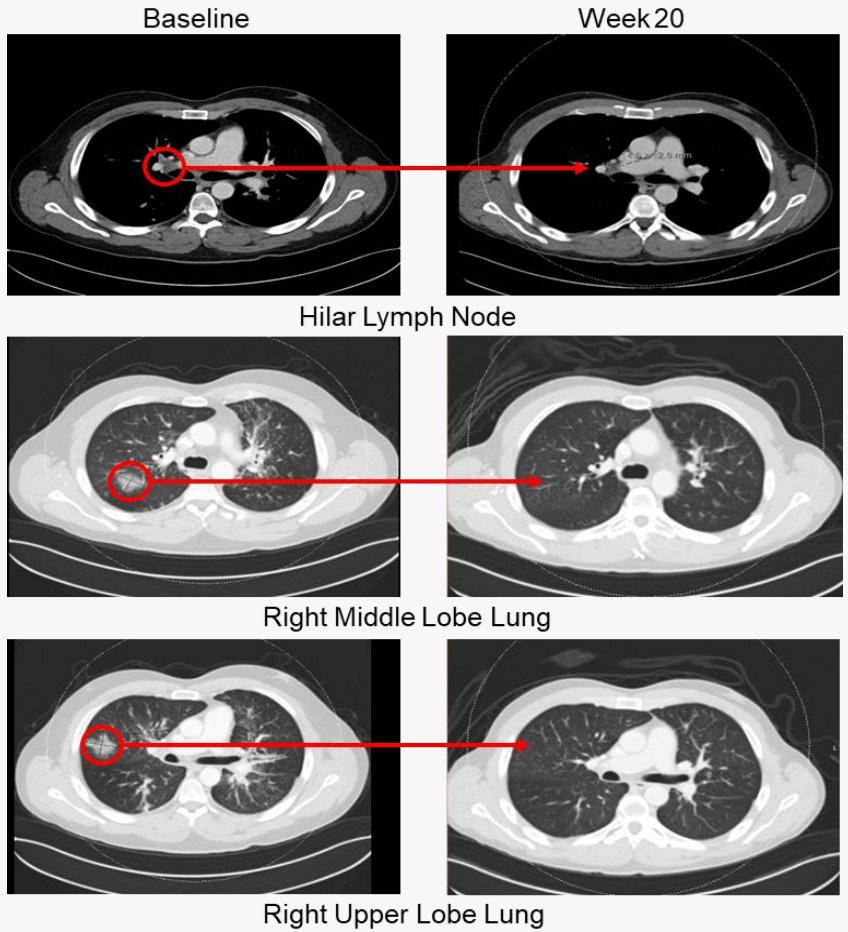
Reference: Smith et al., 2023, Tipifarnib potentiates the antitumor effects of PIK3Kα inhibition in PIK3CA- and HRAS- dysregulated HNSCC via convergent inhibition of mTOR activity. Cancer Res, CAN-23-0282

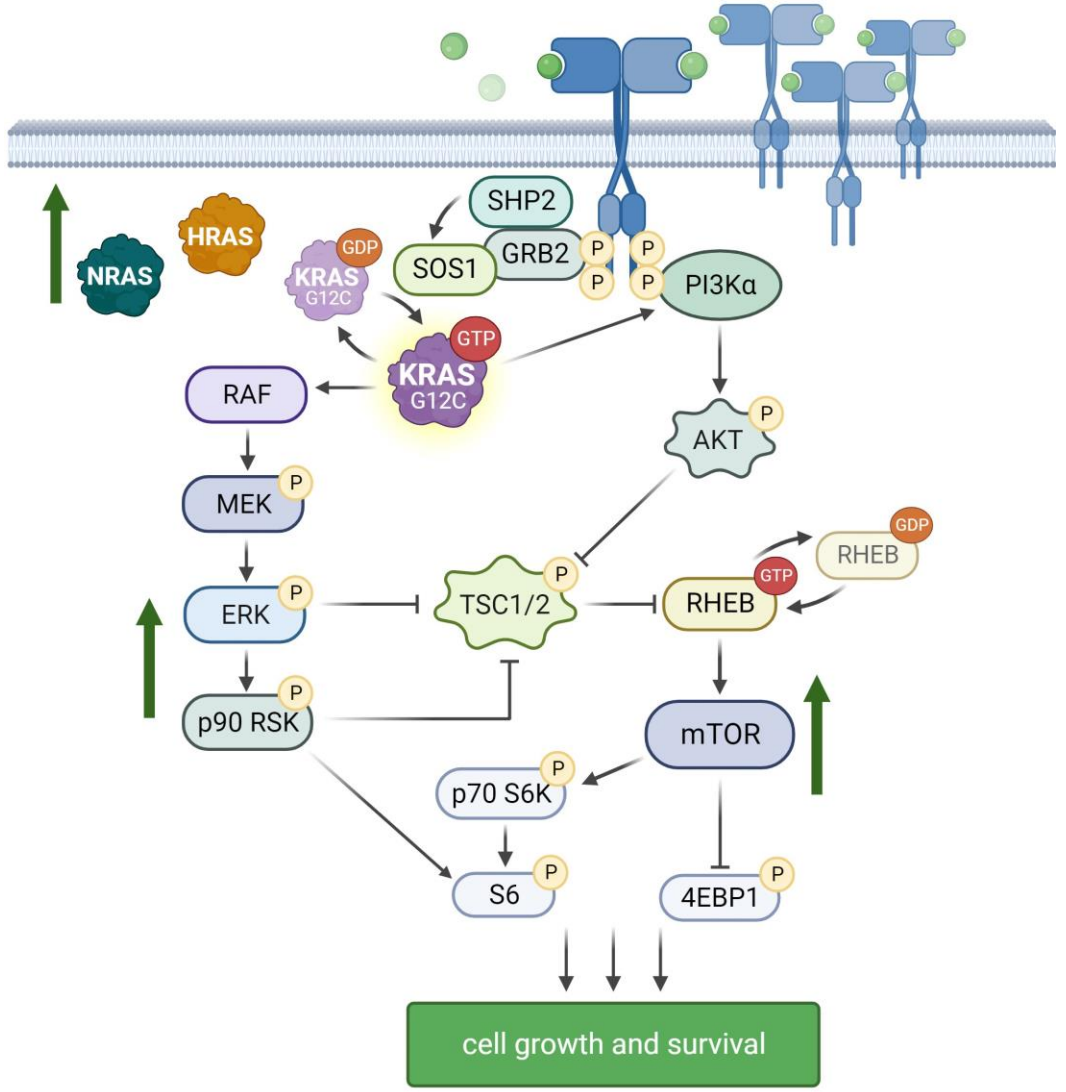
Durable Clinical Response Observed in Patient with *PIK3CA*-dependent HNSCC



- **35yo, male, nonsmoker, HPV16 positive**
- SCC of tonsil Stage III cT4N2M0; PD-L1 CPS = 60
- Prior Treatments
- CDDP/rad for 1 mo (Nov-Dec2019), BOR UNK
- Cemiplimab/ISA101b (Jun-Nov2021), BOR PD
- **PIK3CA R88Q mutation** (44%) and HRAS OE (3+ staining in 100% of tumor cells) by IHC from May 2021 biopsy
- DL1 tipifarnib, DL2 alpelisib; completed 6 cycles
- G1/2 TRAE, G3 lipase elevation; presented clinical benefit and improvement in respiratory symptoms
- 81% reduction in target lesions after 1 cycle of treatment
- **84% reduction in target lesions** after 3 cycles (BOR)
- **Continued on-study for >27 weeks** maintaining QoL

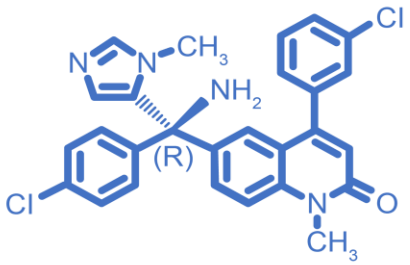
Soifer H et al, ENA 2022 PB041; Data cut as of 14Sep2022; Preliminary raw data

Mechanism-Based Combinations Needed to Fully Realize the Potential of Breakthrough KRAS^{G12C} Inhibitors



pERK inhibition by KRAS^{G12C} inhibitors hyperactivates RTK signaling leading to ERK-RSK and/or mTOR-S6 pathway activation

Next-Generation FTI



Tipifarnib

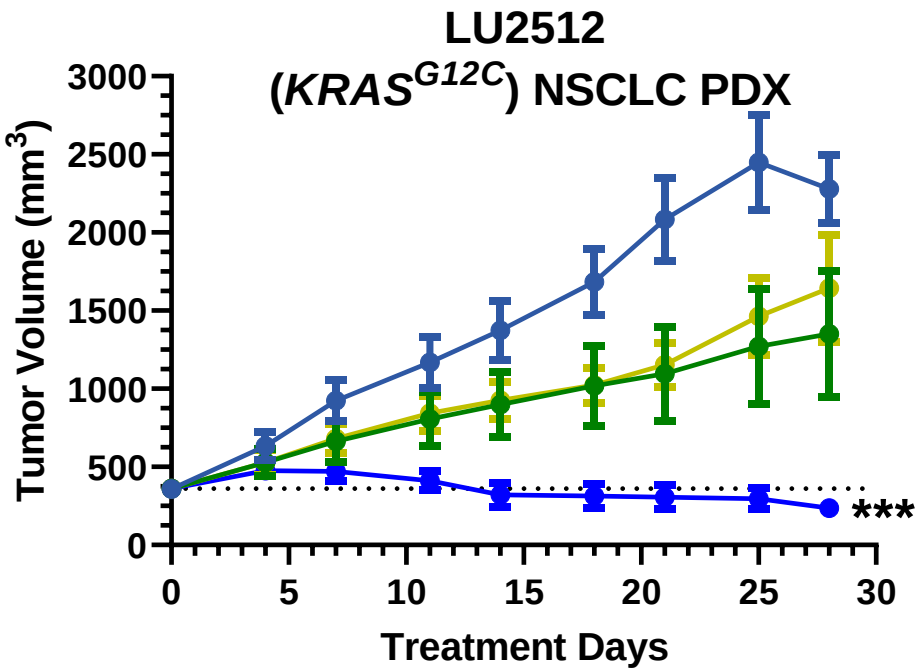
Potency: Good
Selectivity: Excellent
Dose: 600 mg
Frequency: BID

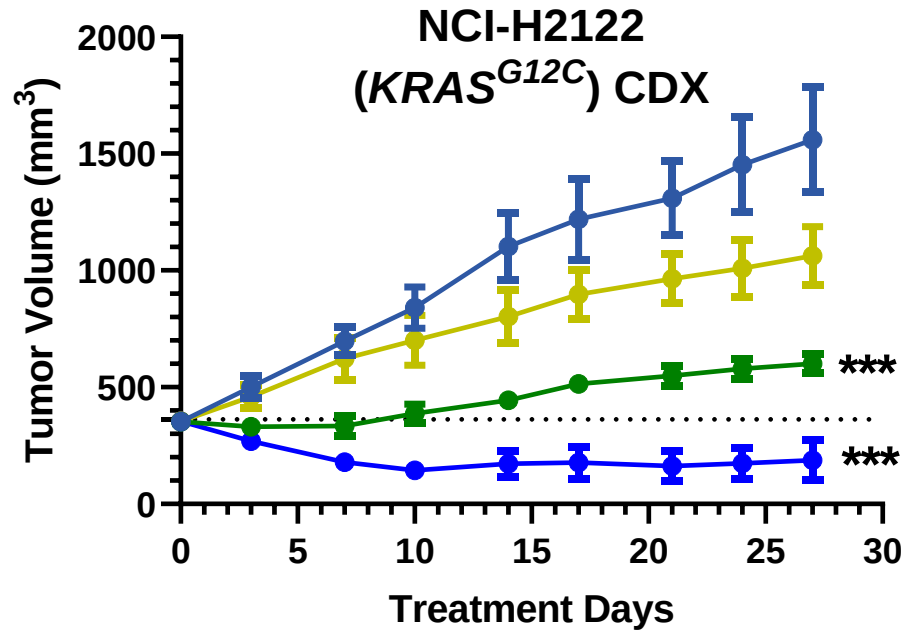
KO-2806

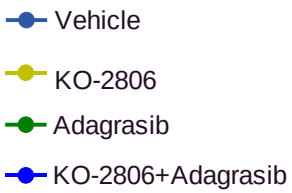
Improved potency, pharmacokinetic and physicochemical properties

- FTIs represent an attractive therapeutic and commercial opportunity in oncology with compelling options in combination with other targeted therapies
- KO-2806 is a potent next-generation FTI designed to improve upon potency, pharmacokinetic and physicochemical properties of earlier FTI drug candidates
- IND application cleared by FDA; on track to initiate Phase 1 study of KO-2806 in 2H 2023

Tumor Growth Inhibition in *KRAS*^{G12C}-Mutant NSCLC PDX & CDX Models





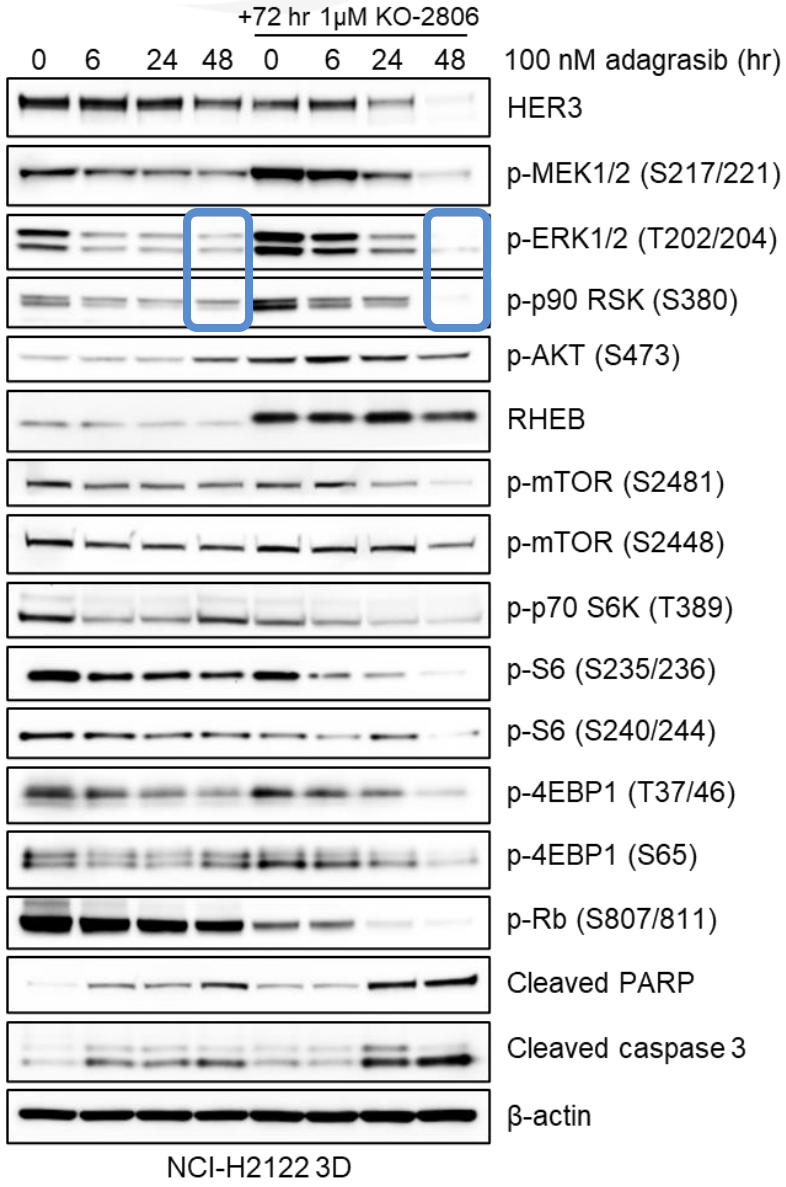


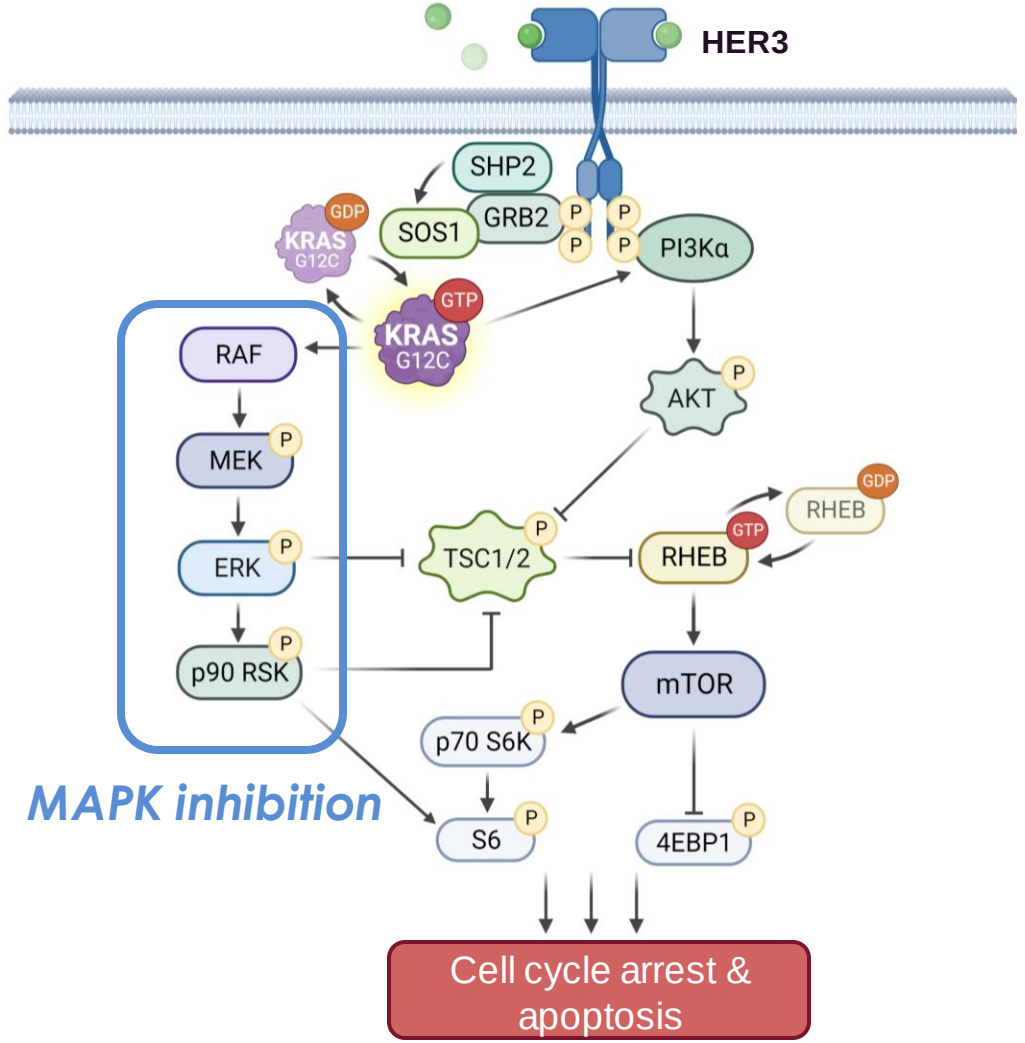
Adagrasib - 100mg/kg, QD

***- $p<0.001$

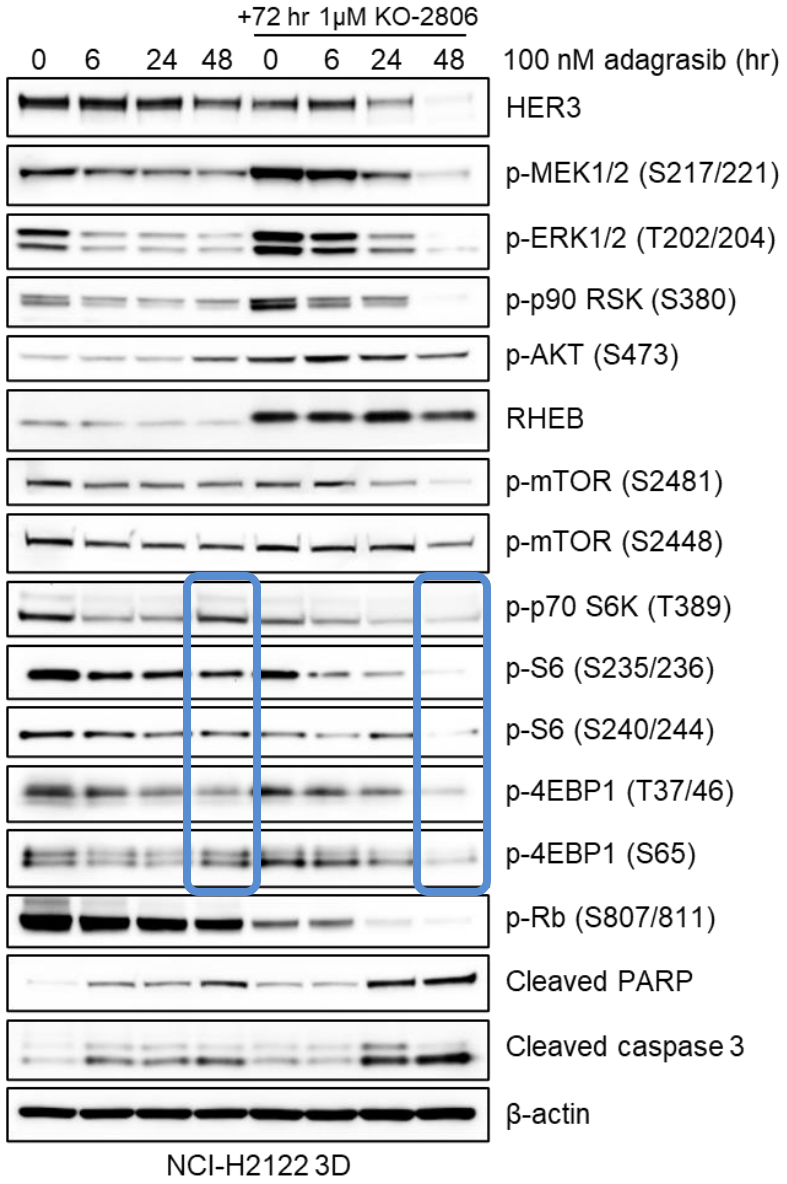
Combination of KO-2806 and adagrasib has superior antitumor effect compared with adagrasib monotherapy

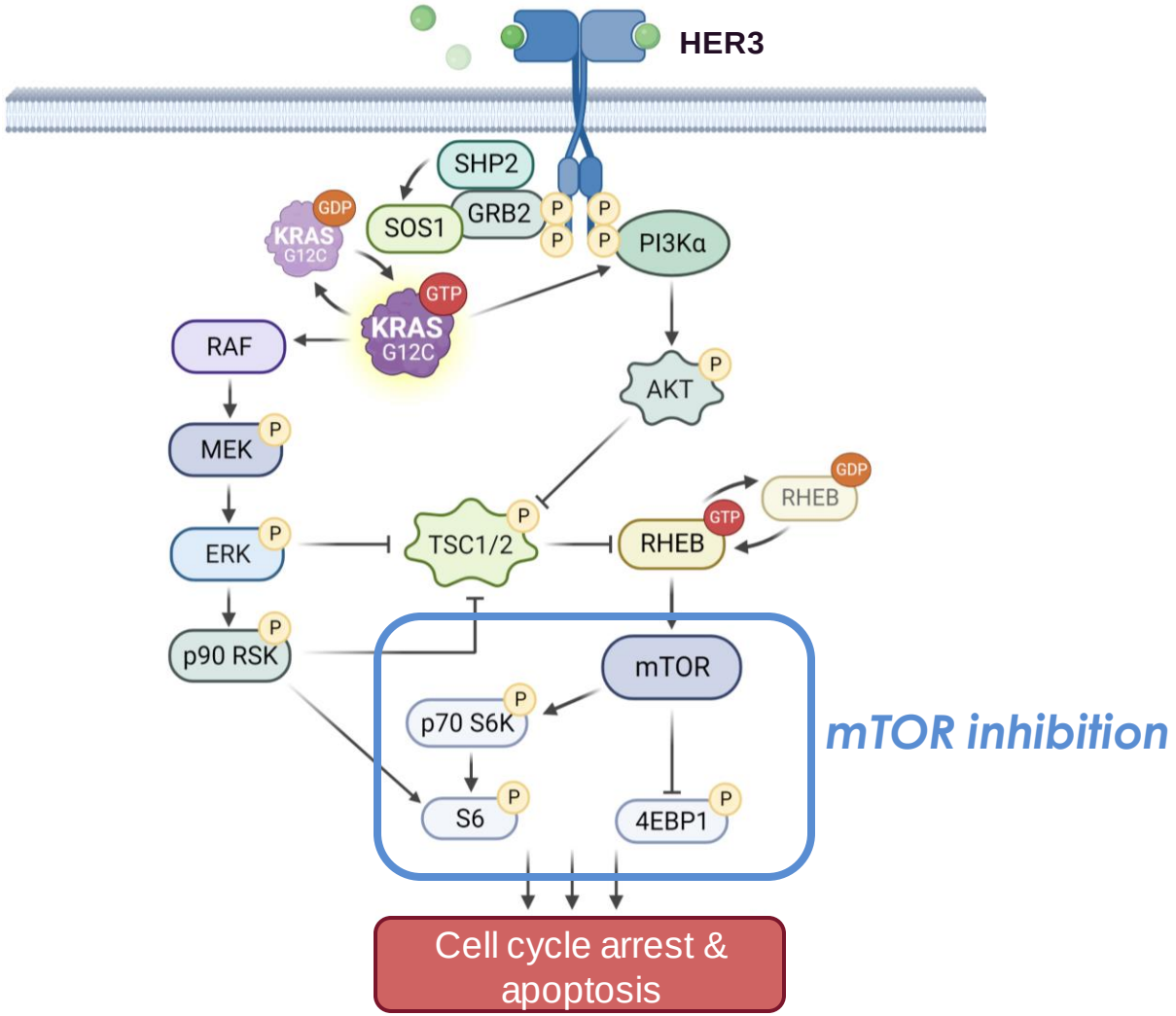
KO-2806 Deepens Signaling Inhibition by Adagrasib in *KRAS*^{G12C}-Mutant NSCLC Tumor Spheroids: Inhibition of MAPK Signaling



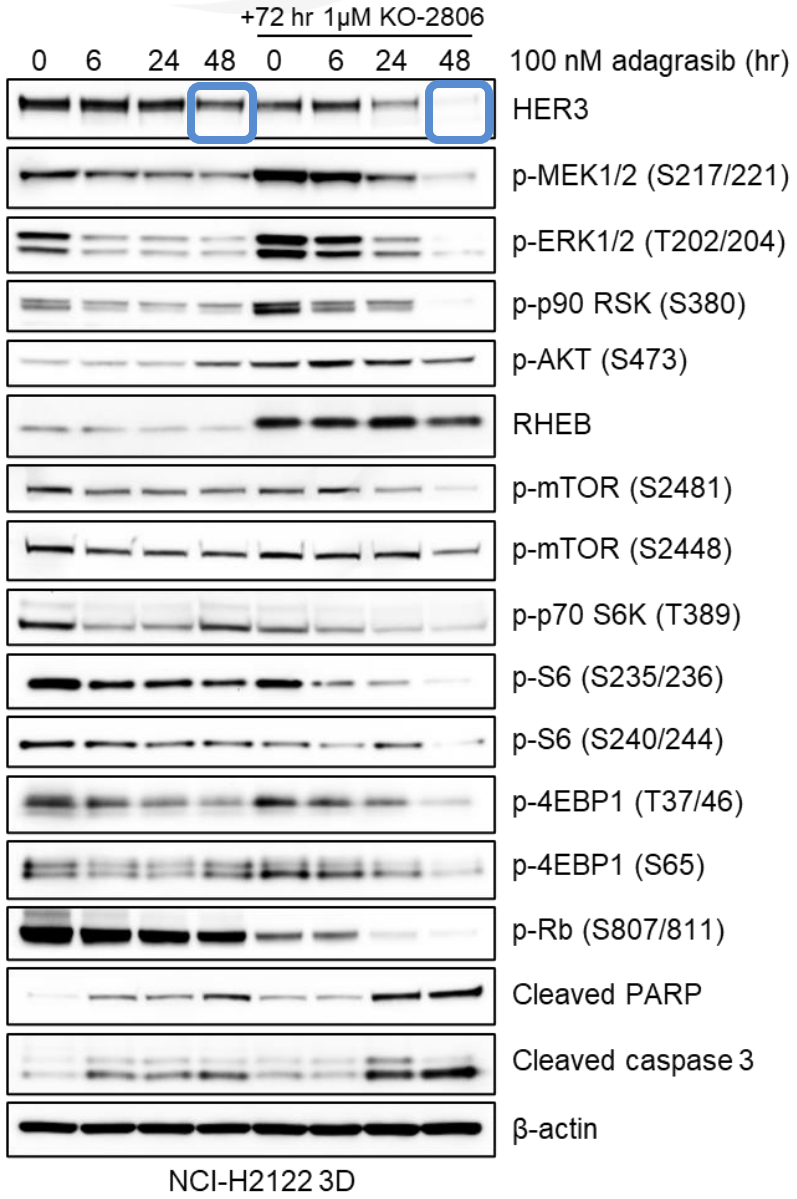


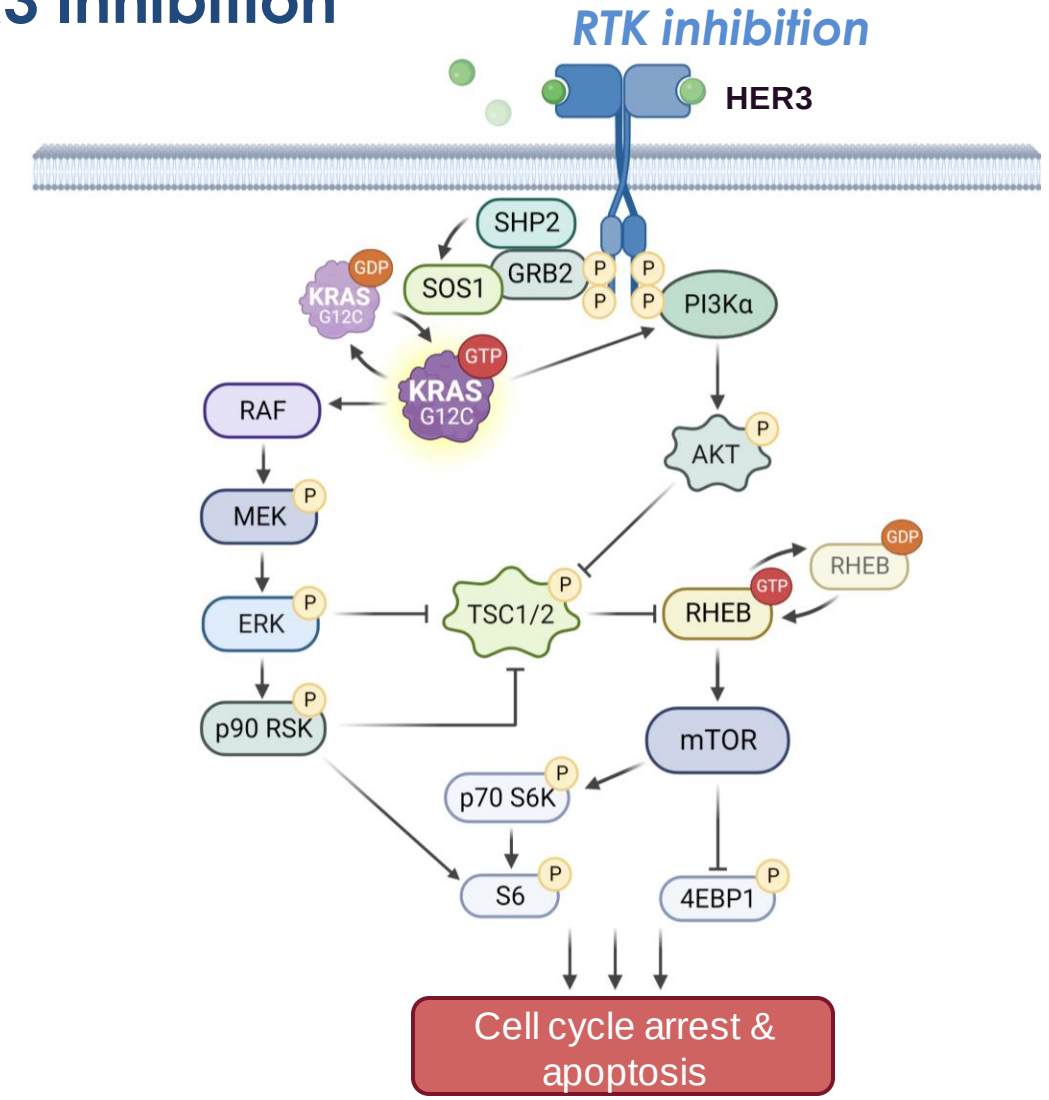
KO-2806 Deepens Signaling Inhibition by Adagrasib in *KRAS*^{G12C}-Mutant NSCLC Tumor Spheroids: Strong Inhibition of mTOR Signaling



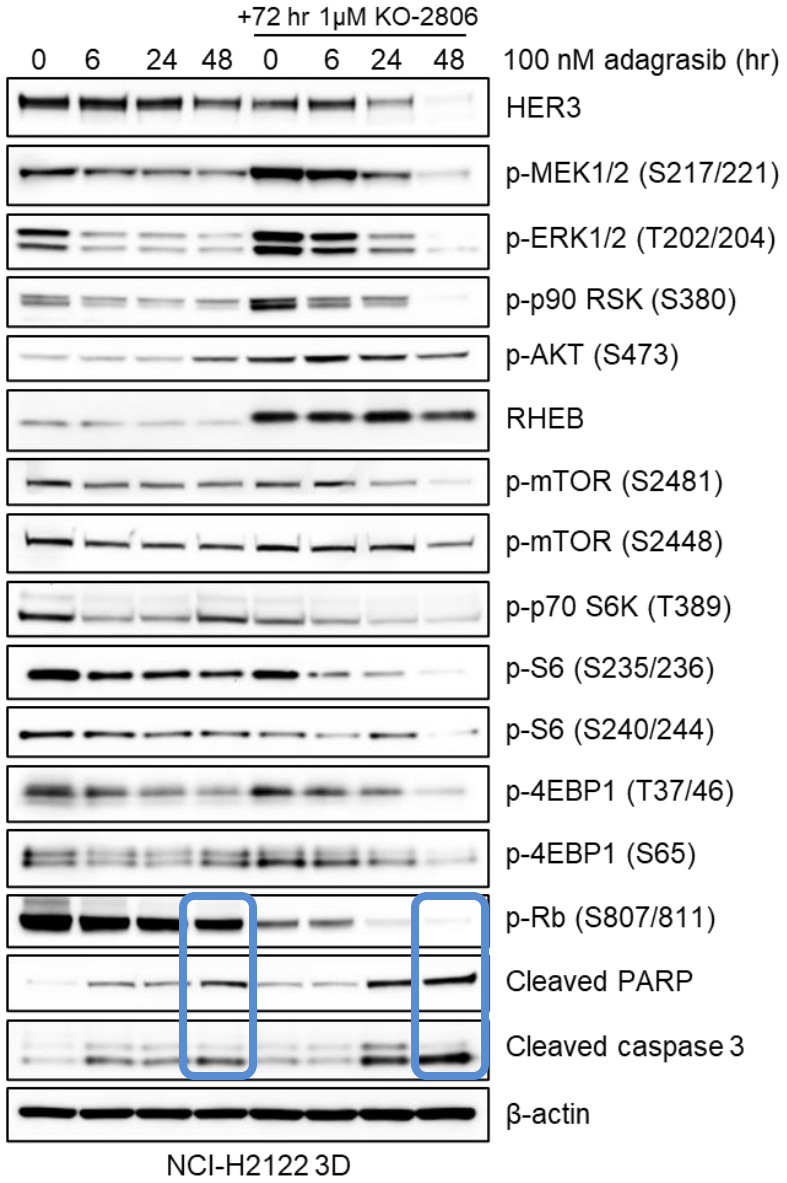


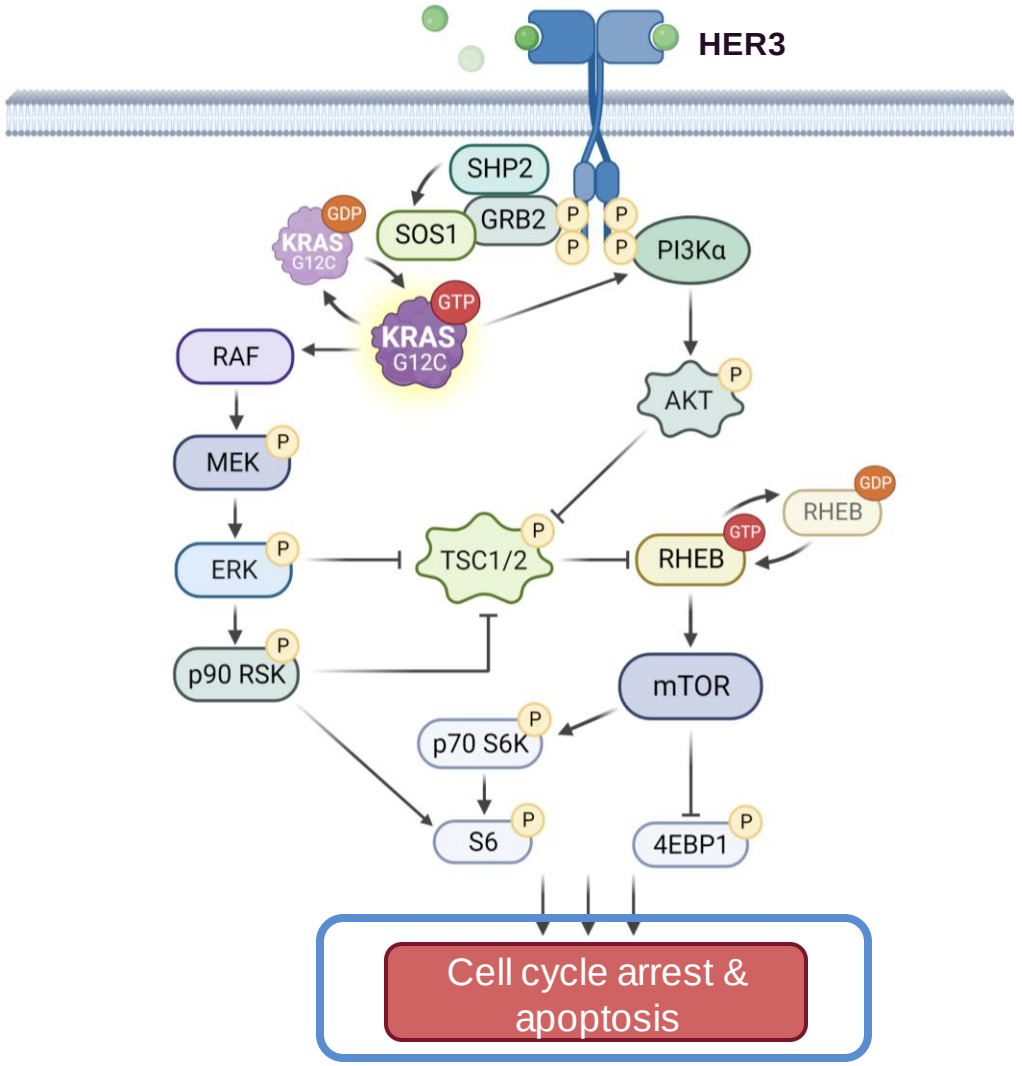
KO-2806 Deepens Signaling Inhibition by Adagrasib in *KRAS*^{G12C}-Mutant NSCLC Tumor Spheroids: HER3 Inhibition



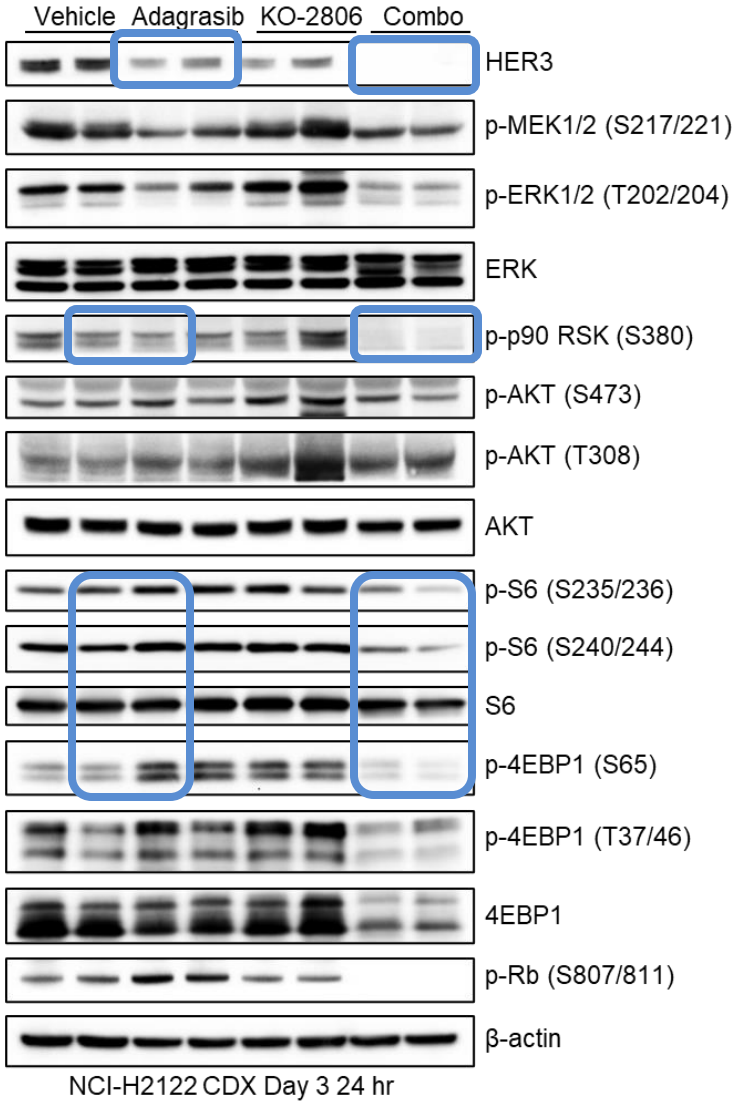


KO-2806 Deepens Signaling Inhibition by Adagrasib in *KRAS*^{G12C}-Mutant NSCLC Tumor Spheroids: Induction of Cell Cycle Arrest and Apoptosis

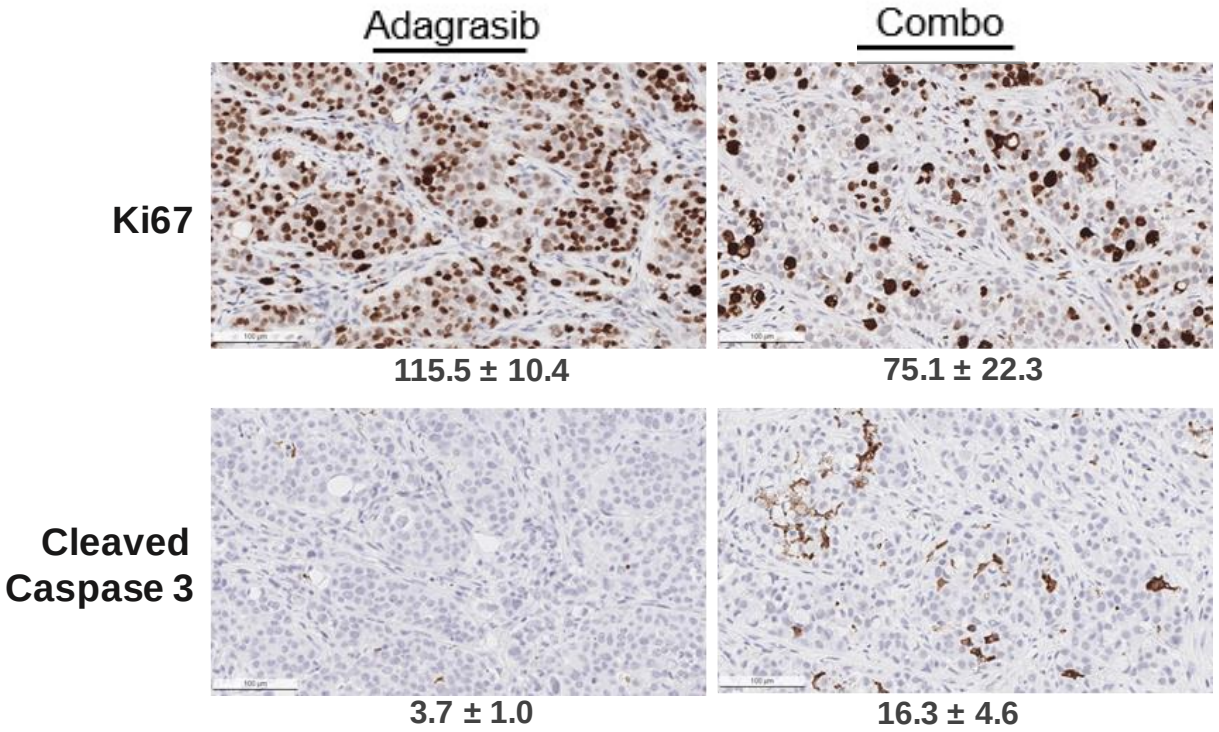




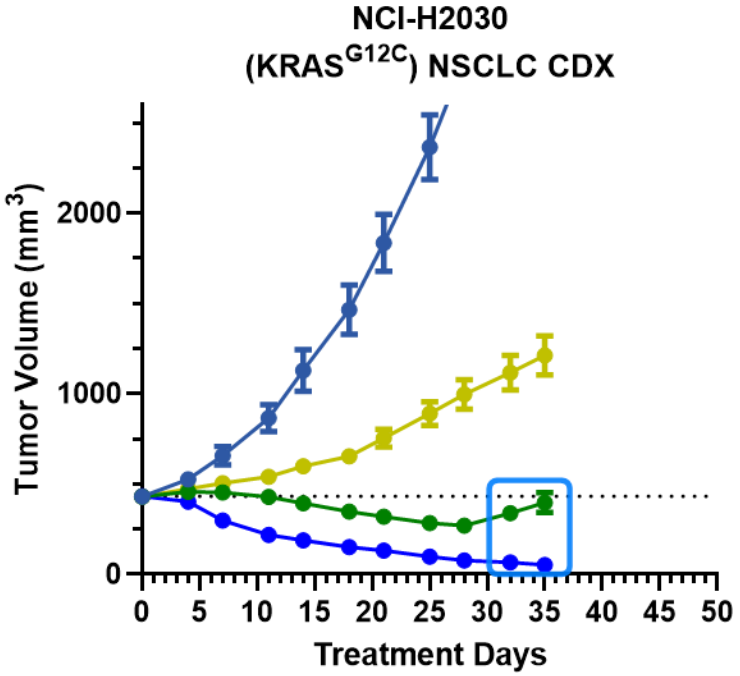
KO-2806-Adagrasib Combination Reduces mTOR and RSK Activation, Increases Apoptosis and Blocks Proliferation *in vivo*



NCI-H2122 CDX Day 3 24 hr

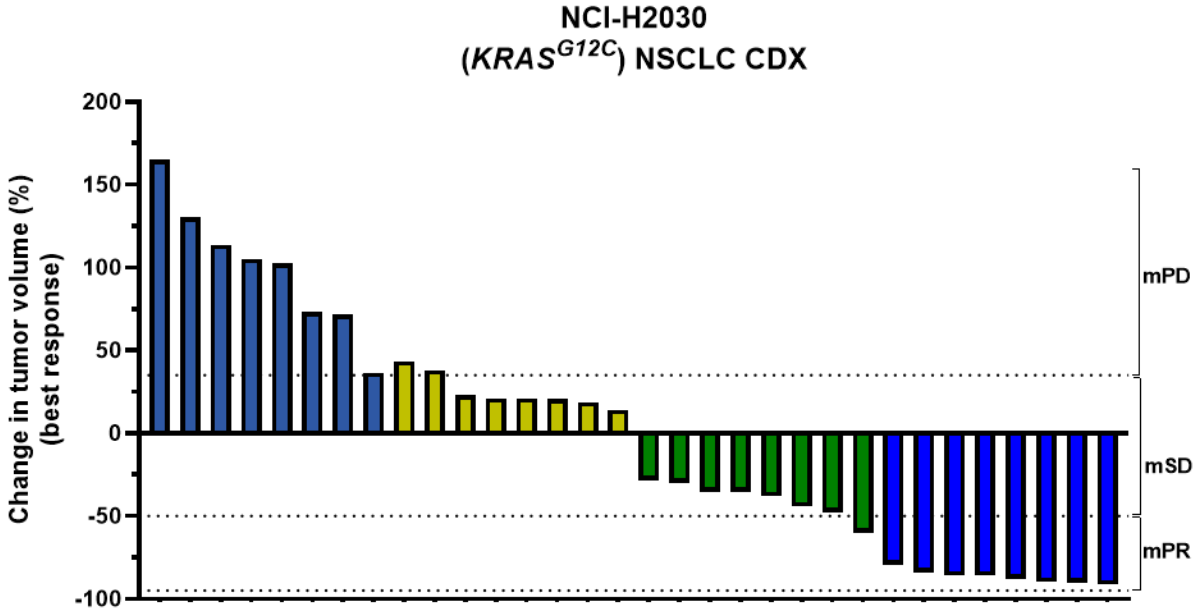


KO-2806-Adagrasib Combination Increases the Depth of Response Compared to Adagrasib Monotherapy



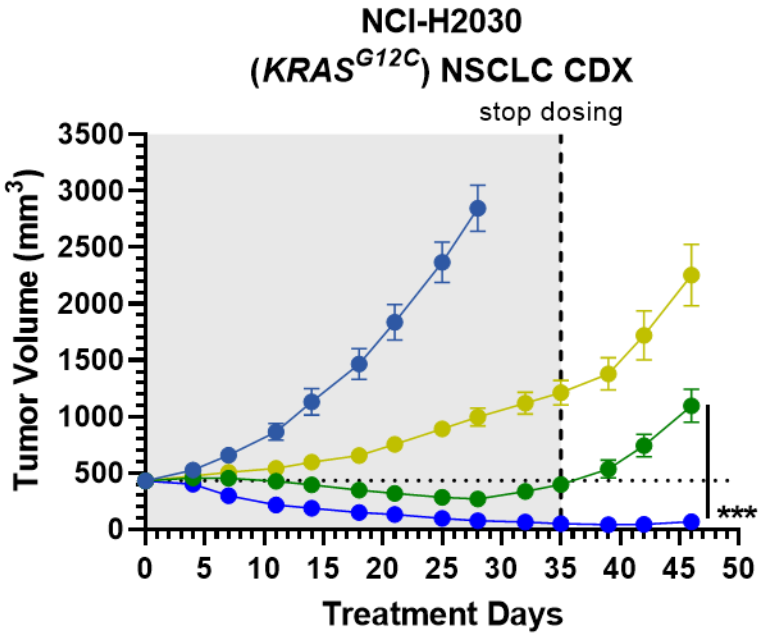
Adagrasib - 100mg/kg, QD

Vehicle
KO-2806
Adagrasib
KO-2806+Adagrasib

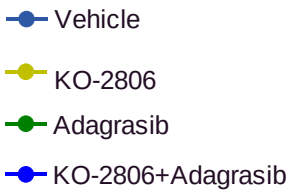


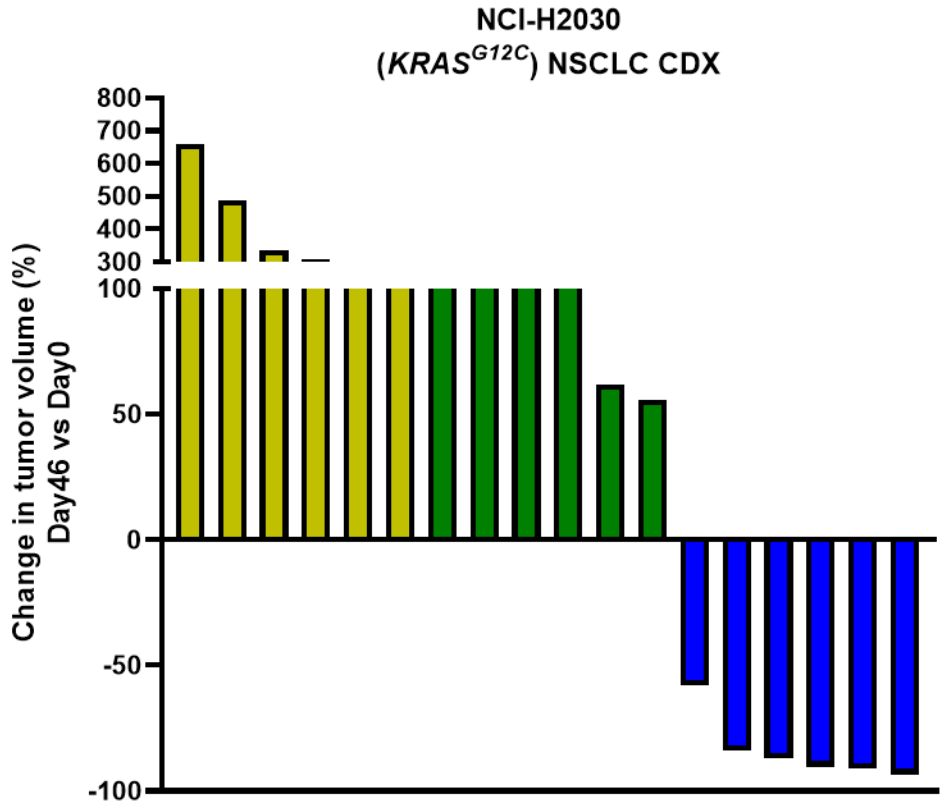
Response calls based on mRECIST
PD-Progressive disease
SD-Stable disease
PR-Partial response

KO-2806-Adagrasib Combination Increases the Duration of Response Compared to Adagrasib Monotherapy



***- $p<0.001$





Summary

- **FTIs have the promise to enhance antitumor activity of targeted therapies in solid tumors**
  - FTIs in combination with $KRAS^{G12C}$ inhibitors drive tumor regressions and durable responses in preclinical NSCLC models
  - First demonstration of a durable clinical response with combination of FTI tipifarnib with alpelisib in patient with *PIK3CA*-mutant HNSCC
- **FTIs are efficacious and tolerable and work by blocking oncogenic signaling at multiple nodes to enhance antitumor efficacy in combinations**
  - FTIs potently inhibit adaptive mTORC1 signaling (S6K and 4EBP1) when combined with appropriate partner drugs in biomarker-defined tumors.
  - In addition to mTOR, FTIs target additional key oncogenic nodes in the adaptive response to KRAS inhibitors, including upstream RTK signaling and HRAS
  - FTIs are likely to exhibit less on-target toxicity compared to both mTOR kinase inhibitors and rapalogs by sparing mTORC2

Acknowledgements

The patients and their families

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Yahu Liu
Asako McCloskey
Quinn Reilley
Betsy Gonzalez

Patel H et al. 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} NSCLC (B025)

Smith A et al. The next-generation farnesyltransferase inhibitor KO-2806 constrains compensatory signaling reactivation to deepen responses to KRAS^{G12D} inhibition (B023)

Gatchalian J et al. KO-2806, a next-generation farnesyltransferase inhibitor, potentiates the antitumor activity of cabozantinib in RCC (B024)