The farnesyl transferase inhibitor KO-2806 constrains mTORC1 activity to enhance the antitumor efficacy of mutant-selective PI3Kα inhibitors

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BACKGROUND

- Mutant-selective PI3Kα inhibitors may have improved therapeutic indices compared to their isoform-selective predecessors but feedback reactivation of PI3K-AKT-mTORC1 signaling may hinder their efficacy as monotherapies.
- We have previously demonstrated that farnesyl transferase inhibitors (FTIs) enhance the antitumor activity of multiple targeted therapies, including the α-selective PI3K inhibitor alpelisib, by blocking RHEB-mediated mTORC1 activation.
- We hypothesized the FTI darlifarnib (KO-2806) could potentiate the efficacy of mutant-selective PI3Kα inhibitors via sustained inhibition of mTORC1 signaling.
- **In this study, we assessed the potential therapeutic utility of combining KO-2806 with the mutant-selective PI3Kα inhibitors STX-478 or RLY-2608 in a panel of in vitro cell line and in vivo xenograft models spanning the breadth of solid tumor indications with the highest frequency of PIK3CA mutation.**

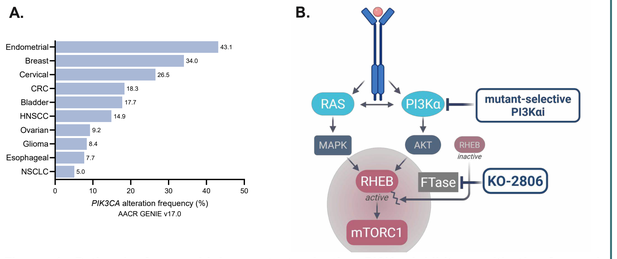


Figure 1. Rationale for combining mutant-selective PI3Kα inhibitors with the farnesyl transferase inhibitor darlifarnib (KO-2806). A. Frequency of activating *PIK3CA* mutations across solid tumor indications in the AACR GENIE dataset. **B.** Farnesyl transferase inhibitors block mTORC1 activation by preventing farnesylation of RHEB, thereby potentially enhancing the signaling inhibition and antitumor activity of PI3Kα inhibitors.

RESULTS

Darlifarnib (KO-2806) enhances the mTORC1 inhibition and antitumor activity of mutant-selective PI3Kα inhibitors in preclinical models of *PIK3CA*-mutant HR+ breast cancer

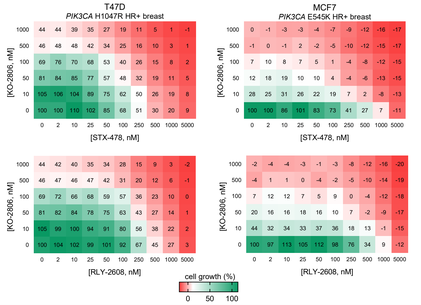


Figure 2. KO-2806 deepens the antiproliferative activity of mutant-selective PI3Kα inhibitors in *PIK3CA*-mutant HR+ breast cancer cell lines *in vitro.* Growth of T47D and MCF7 cells exposed to the indicated concentrations of STX-478 or RLY-2608 ± KO-2806 for 5 days. Data are % cell growth from day 0, normalized to DMSO and represent 3 biological replicates.

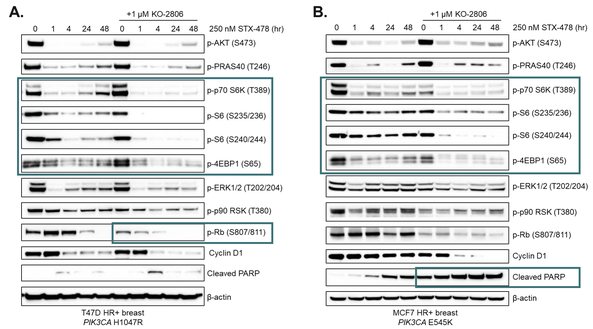


Figure 3. KO-2806 enhances the depth and durability of mTORC1 inhibition following exposure to STX-478 in HR+ breast cancer cell lines. Immunoblots of the indicated signaling proteins in (**A**) T47D or (**B**) MCF7 cells exposed to 250 nM STX-478 for 0, 1, 4, 24, or 48 hours in the presence or absence of 1μM KO-2806.

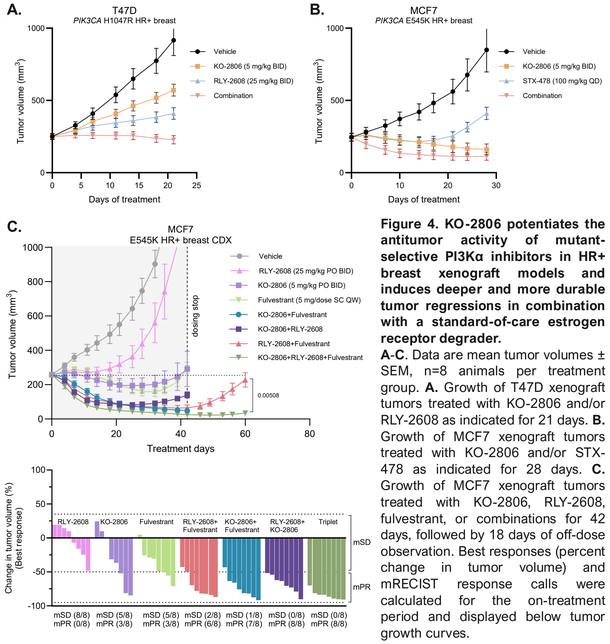
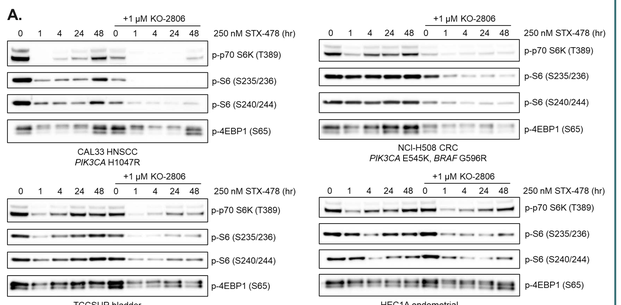


Figure 4. KO-2806 potentiates the antitumor activity of mutant-selective PI3Kα inhibitors in HR+ breast xenograft models and induces deeper and more durable tumor regressions in combination with a standard-of-care estrogen receptor degrader.

A-C. Data are mean tumor volumes ± SEM, n=8 animals per treatment group. **A.** Growth of T47D xenograft tumors treated with KO-2806 and/or RLY-2608 as indicated for 21 days. **B.** Growth of MCF7 xenograft tumors treated with KO-2806 and/or STX-478 as indicated for 28 days. **C.** Growth of MCF7 xenograft tumors treated with KO-2806, RLY-2608, fulvestrant, or combinations for 42 days, followed by 18 days of off-dose observation. Best responses (percent change in tumor volume) and mRECIST response calls were calculated for the on-treatment period and displayed below tumor growth curves.

The darlifarnib/PI3Kα inhibitor combination shows preclinical activity across PIK3CA-mutant solid tumor indications



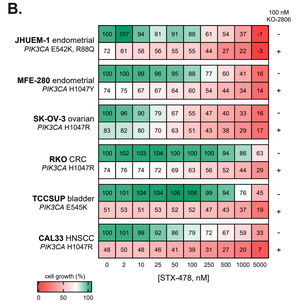


Figure 5. The combination of KO-2806 and STX-478 inhibits proliferation and mTORC1 activity in cell lines representative of solid tumor indications with high *PIK3CA* mutation rates. A. Immunoblots of phosphorylated mTORC1 substrates in the indicated cell lines treated with 250 nM STX-478 for 0, 1, 4, 24, or 48 hours in the presence or absence of 1 μM KO-2806. **B.** Proliferation of *PIK3CA*-mutant cell lines exposed to increasing concentrations of STX-478 ± 100 nM KO-2806 for 5 days. Data are % cell growth from day 0, normalized to DMSO

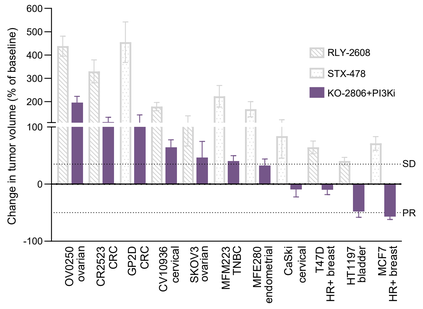


Figure 6. KO-2806 enhances the antitumor activity of mutant-selective PI3Kα inhibitors in *PIK3CA*-mutant xenograft models. Waterfall plots of xenograft models treated with 25-100 mg/kg PO BID RLY-2608 or 50-100 mg/kg PO QD STX-478 as monotherapy (gray bars) or in combination with 5 mg/kg PO BID KO-2806 (purple bars). Each bar represents the mean percent change in tumor volume at day 21-28 (endpoint) relative to day 0, ± SEM, n=8 animals per treatment group.

CONCLUSIONS

- (Re)activation of downstream mTORC1 signaling remains a factor limiting the activity of mutant selective PI3Kα inhibitors that is targetable with FTIs.
- The combination of darlifarnib (KO-2806) and STX-478 or RLY-2608 inhibited growth across models of multiple solid *PIK3CA*-mutant tumor indications *in vitro* and *in vivo,* with HR+ breast models demonstrating the greatest sensitivity.
- Darlifarnib can synergize with PI3K inhibitors and standard-of-care therapies, leading to deeper and more durable responses in xenograft models.
- These data suggest darlifarnib holds promise as a partner agent for mutant-selective PI3Kα inhibitors across a broad range of PIK3CA-mutant solid tumor indications, owing to its ability to constrain mTORC1 signaling.

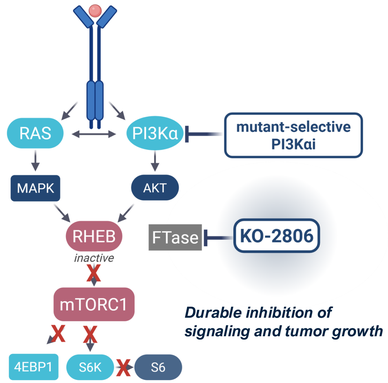


Figure 6. The FTI darlifarnib (KO-2806) controls persistent mTORC1 signaling to enhance the antitumor activity of mutant-selective PI3Kα inhibitors in *PIK3CA*-mutant solid tumor models.

Acknowledgements

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Disclosures

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