RLY-2608, A First-in-class Mutant-selective PI3Kα Inhibitor, Suppresses Aberrant PI3Kα Signaling and Induces Lesion Regressions in an *In Vivo* Experimental Model of *PIK3CA*-related Vascular Malformations

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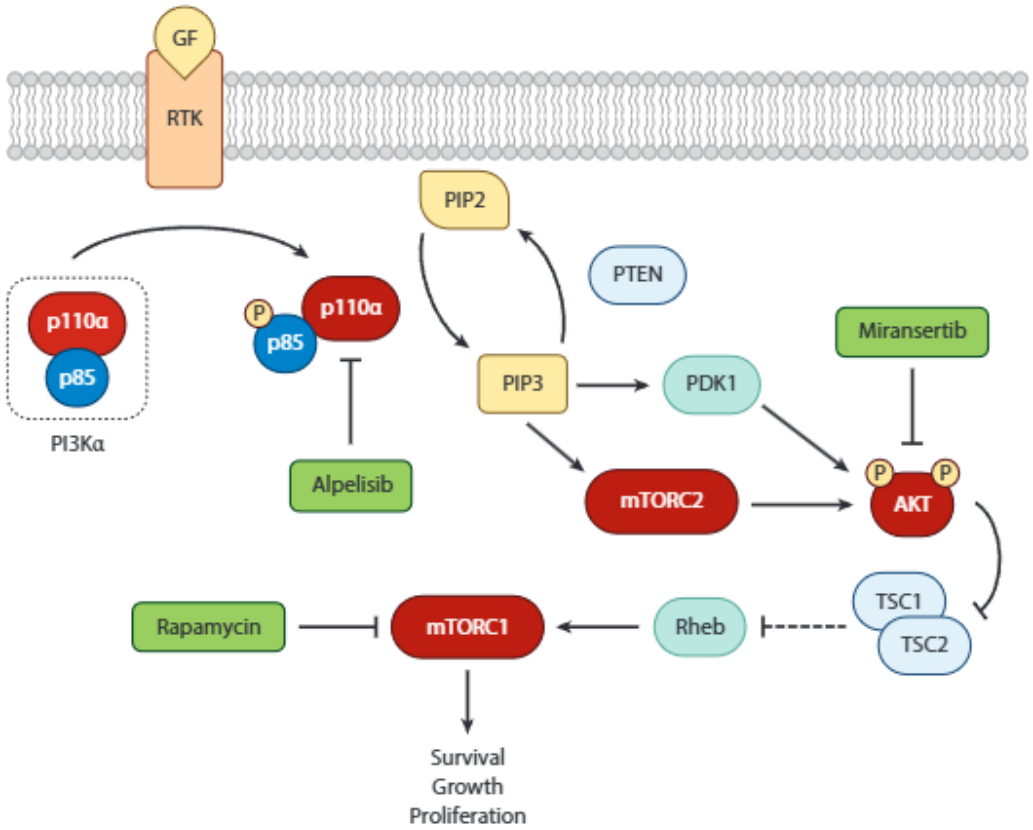
Disclosure

I am an employee and shareholder of Relay Therapeutics.

Mutations in the PI3Kα Pathway Drive Subtypes of Vascular Malformations

Inhibitors of the PI3Kα pathway used in VMs



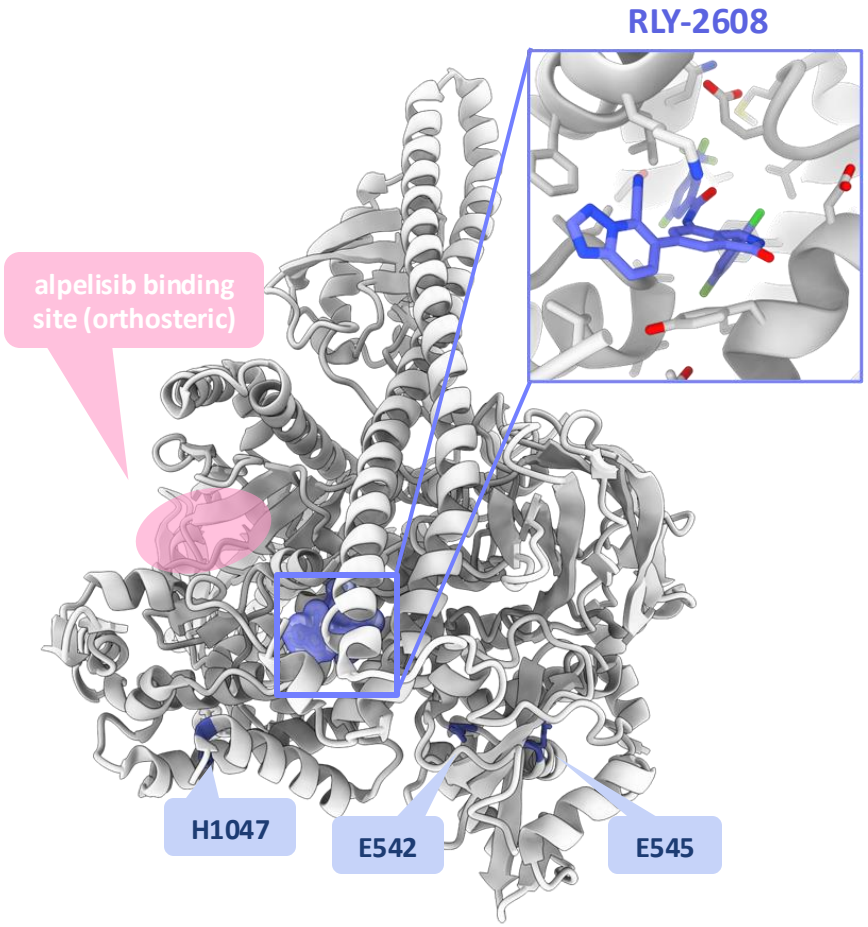
- Mosaic PIK3CA^{mut} are very frequent in syndromes such as CLOVES, KTS, MCAP (ie. PROS), lymphatic malformations and some venous malformations
- Current therapies are not mutant selective, inhibiting wild type PI3Kα pathway, leading to hyperglycemia, rash, diarrhea and stomatitis, limiting dose
- In 2022, alpelisib received FDA accelerated approval with retrospective data (EPIK-P1), but failed its primary endpoint in the prospective EPIK-P2 study (2024) with:
  - 17% ORR in adult pts (125mg QD)
  - 23% ORR in pediatric pts (50mg QD)
- Novel mutant-selective therapies are needed to more effectively target the disease driver with less toxicity

Morin et al. Annu. Rev. Genom. Hum. Genet. 2024

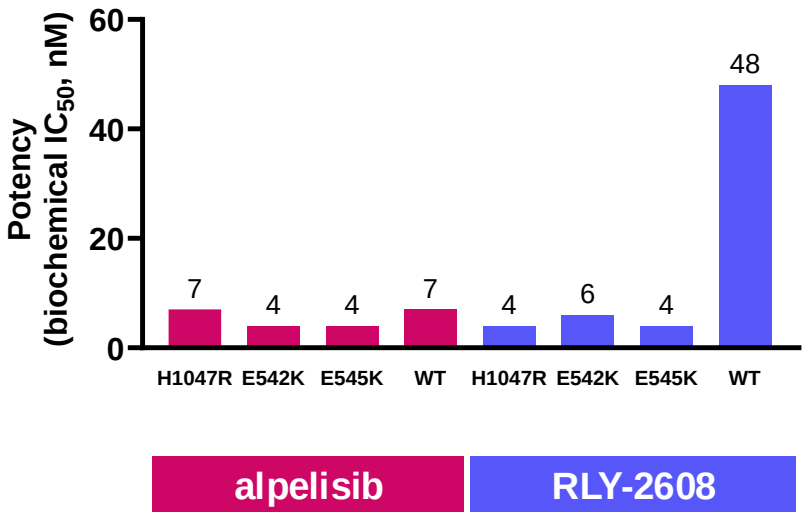
Vijoice USPI; Canaud et al. Blood 2024 Supplement

RLY-2608 Is a First-In-Class Mutant-Selective PI3Kα inhibitor That Targets PI3Kα Through a Novel Allosteric Mechanism

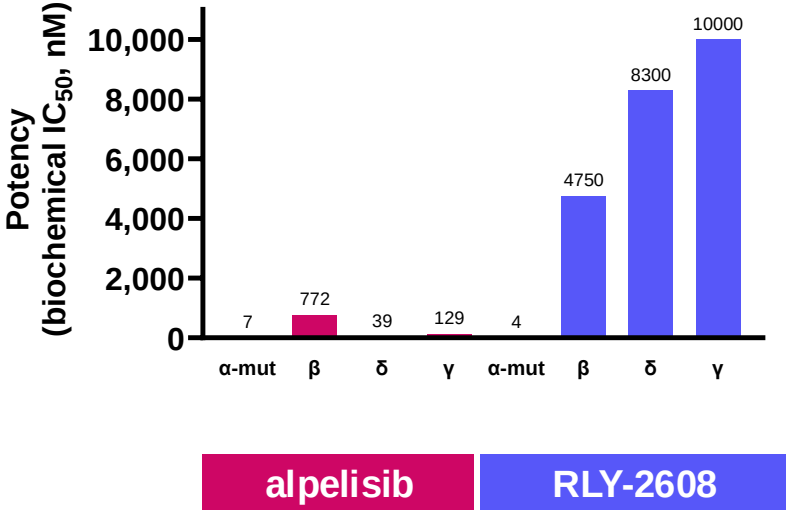
RLY-2608 binds in a novel allosteric binding site in PI3Ka



Mutant vs WT PI3Kα Selectivity



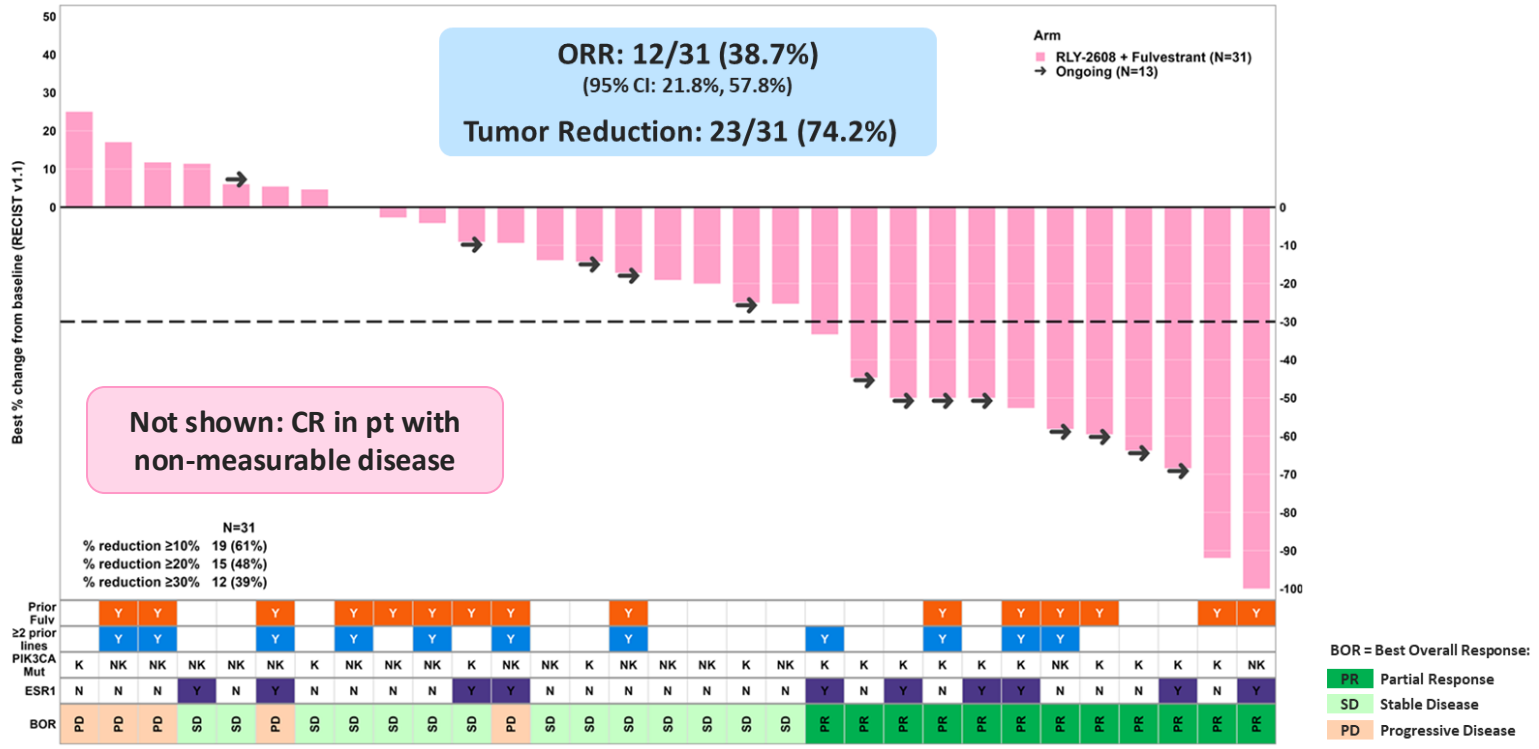
Mutant PI3Kα vs. other PI3K Isoforms Selectivity



RLY-2608 - Clinical Proof of Concept in Metastatic Breast Cancer

RLY-2608 600 mg BID (RP2D) + Fulvestrant

Excluding PTEN / AKT Co-Mutations – Measurable Disease (N=31)



Post-CDK4/6 mBC Phase 3 trial initiation expected in 2025

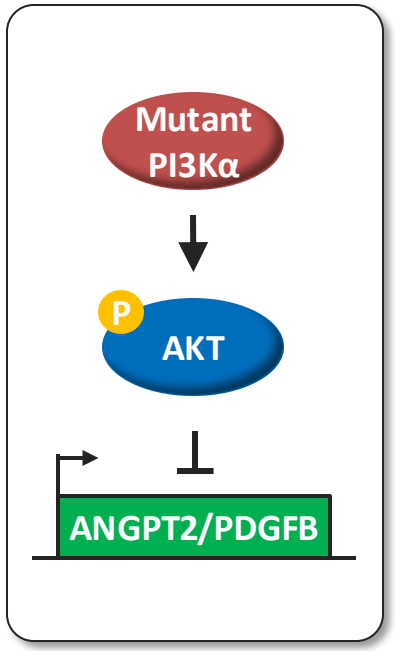
PIK3CA mutation: "K" = Kinase domain mutation, "NK" = Non-Kinase domain mutation; CR = Complete Response

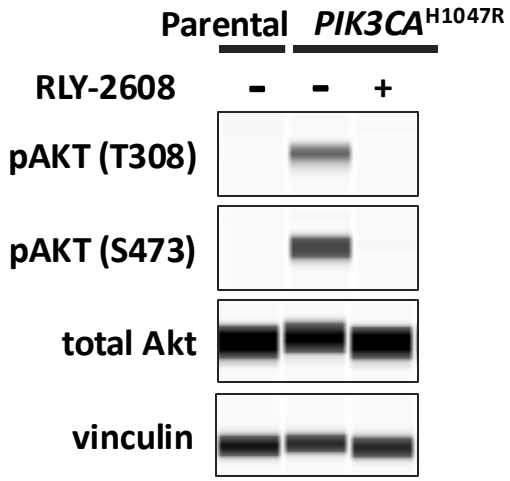
ReDiscover preliminary data as of 11/04/2024

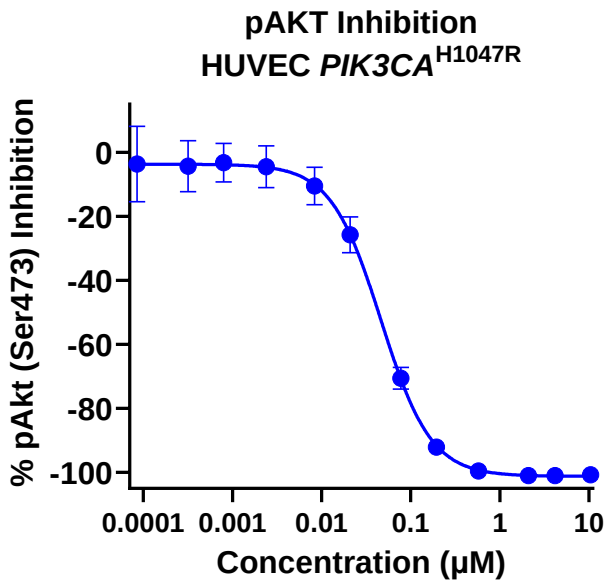
RLY-2608 Fully Suppresses Aberrant AKT Phosphorylation and Restores Expression of the Endothelial Genes ANGPT2 and PDGFB to Physiological Levels

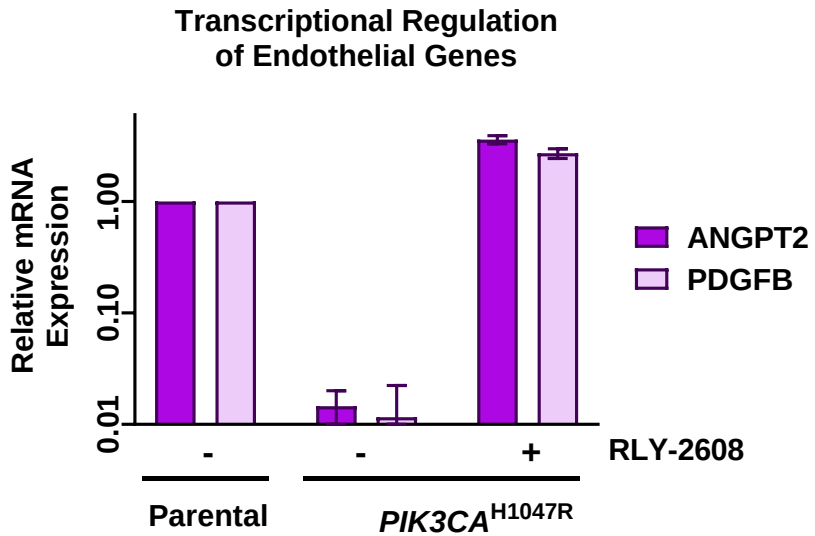
pAKT Inhibition in *PIK3CA*^{H1047R} HUVEC cells

Endothelial Genes Transcriptional Regulation





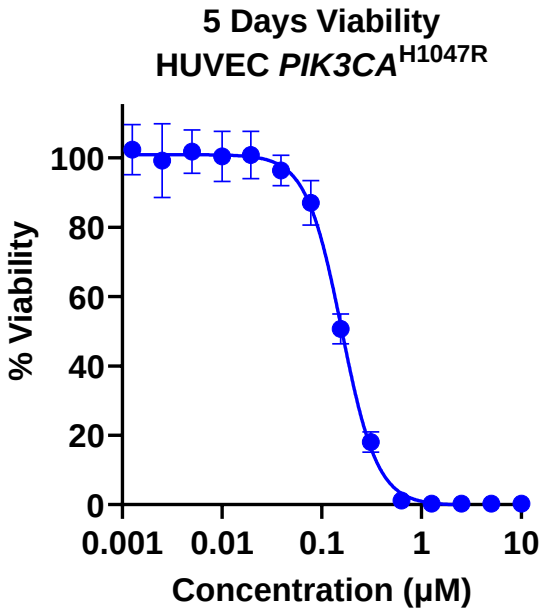




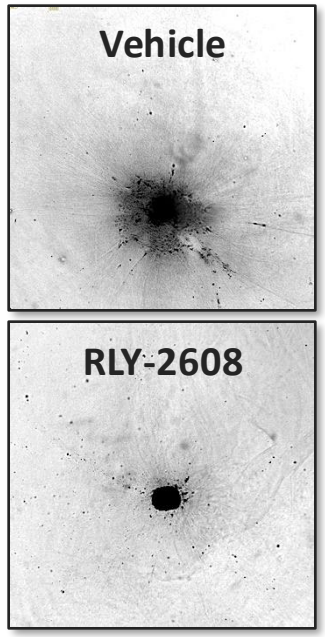
HUVEC cells

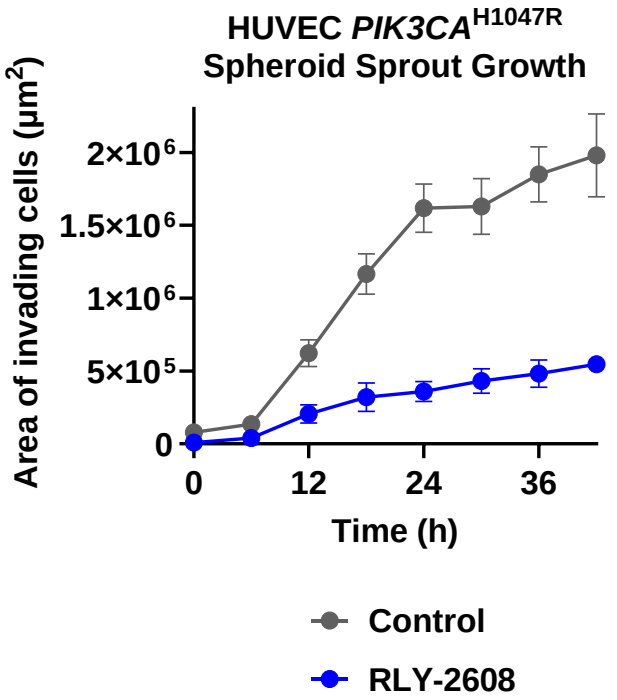
RLY-2608 Inhibits Mutant *PIK3CA* Endothelial Cell Proliferation and Invasiveness

Proliferation



Spheroid Sprout Growth





RLY-2608 treatment reverts mutant phenotypes in HUVEC cells

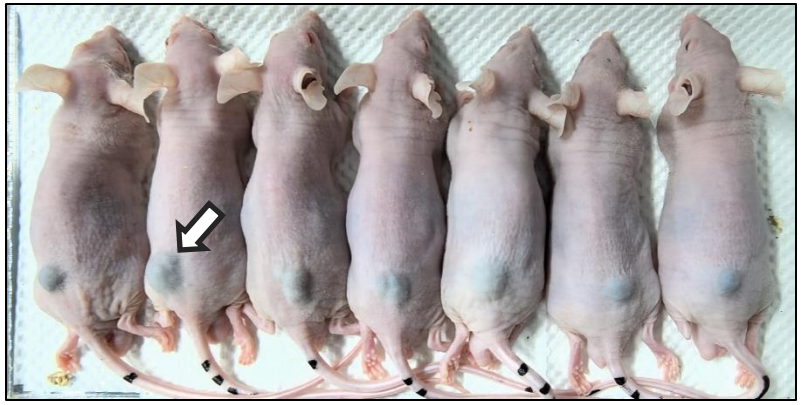
Development of a *PIK3CA*^{H1047R} HUVEC Xenograft Model to Assess WT and Mutant PI3Kα Inhibition *In Vivo*

PIK3CA^{H1047R} *HUVEC xenograft (~ 14 days)*

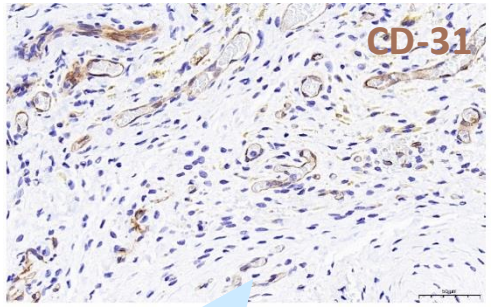
Daily oral dosing (42 days)

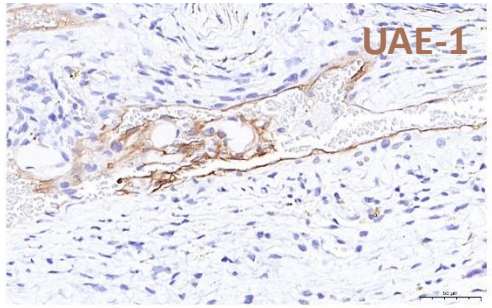
- Lesion growth (measurement of mutant PI3Kα inhibition)
- Insulin production (measurement of WT PI3Kα inhibition)

Highly vascularized lesions



Histopathology (Untreated Animals)



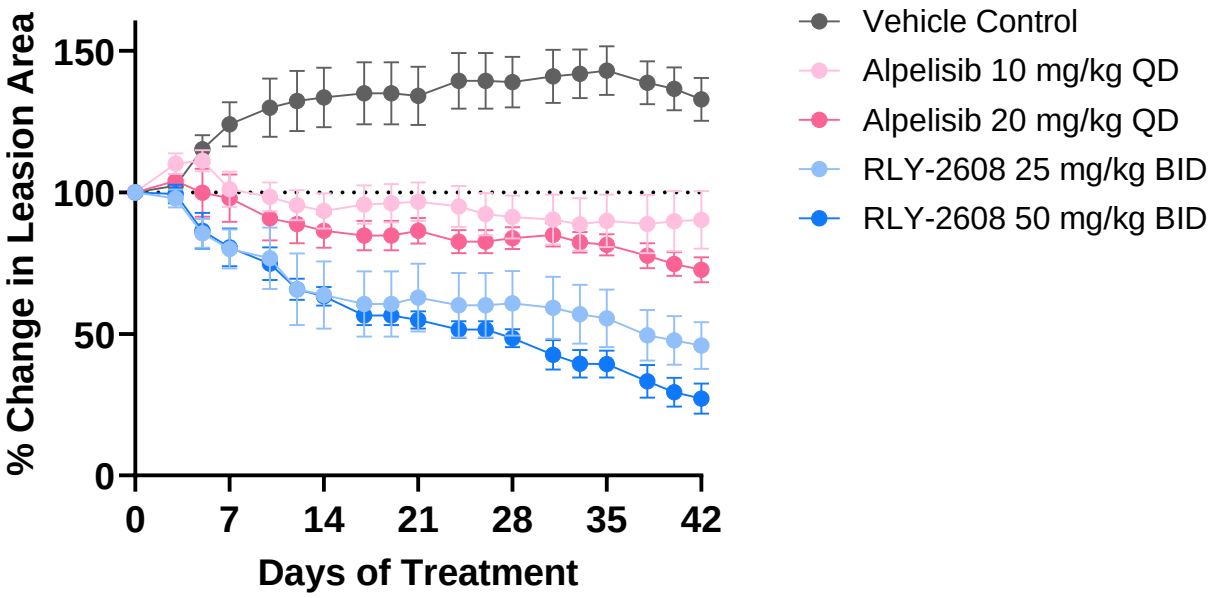


Human Endothelial Markers

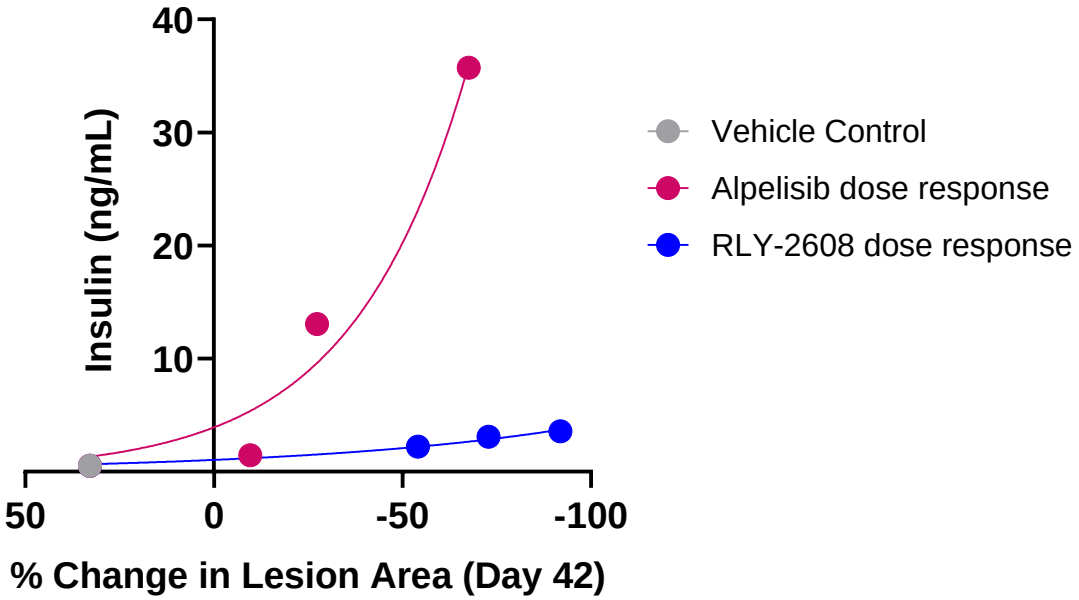
PIK3CA^{H1047R} HUVECs Populate Only a Fraction of the In Vivo Xenograft Lesions

RLY-2608 Achieves Superior Efficacy with More Selectivity Over WT Signaling

Lesion Regression at Clinically Relevant Doses

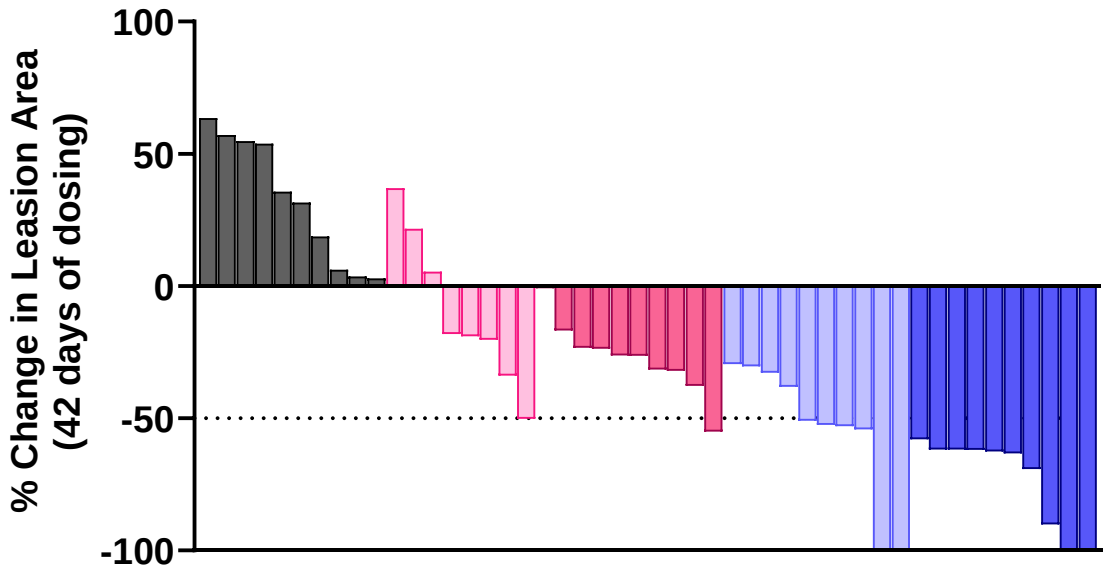


Efficacy vs. Insulin Induction



RLY-2608 Leads to Deeper Lesion Regression Than Alpelisib at Clinically Relevant Concentrations

Individual lesion comparison at clinically relevant doses



- Vehicle control
- Alpelisib 10 mg/kg QD ~ *125 mg QD in patients (EPIK-P2 dose)*
- Alpelisib 20 mg/kg QD ~ *250-300 mg QD in patients (Adult PROS/Oncology dose)*
- RLY-2608 25 mg/kg BID ~ *300 mg BID in patients*
- RLY-2608 50 mg/kg BID ~ *600 mg BID in patients*

% of mice with lesions area change

	≥50% reduction
Vehicle	0%
alpelisib 10 mg/kg QD	12.5%
alpelisib 20 mg/kg QD	10%
RLY-2608 25 mg/kg BID	60%
RLY-2608 50 mg/kg BID	100%

Conclusions and Acknowledgements

- **RLY-2608 is a first-in-class allosteric mutant-selective PI3Kα inhibitor.**
- **RLY-2608 potently inhibits aberrant PI3Kα signaling driven by expression of *PIK3CA*^{H1047R} and restores gene expression to a physiological non-disease state in endothelial cells.**
- ***In vivo*, RLY-2608 induces greater lesion regression than alpelisib at clinically relevant concentrations.**
- **These greater lesion reductions are associated with sustained PI3Kα pathway suppression without hyperinsulinemia.**

Thank You to Relay Tx Team

Amanda Iskandar, Claire Soave, Eric Sanford, Fabien Llambi, Hongtao Zeng, Jim Watters, Jonathan LaRochelle, Lakshmi Miller-Vedam, Matt Crowe, Ermira Pazolli, Olivia Orozco, Sean Eckley, Sweta Swaminathan

A Phase 2 Study of Mutant-selective PI3Kα Inhibitor, RLY-2608, in Adults and Children with *PIK3CA* Related Overgrowth Spectrum (PROS) and Malformations Driven by *PIK3CA* Mutation

Study Drug – RLY-2608

RLY-2608 is a novel, allosteric, pan-mutant and isoform selective, oral PI3Kα inhibitor.

The selectivity of RLY-2608 for mutant PI3Kα provides the opportunity for greater target coverage, leading to the potential of improved efficacy and chronic tolerability.

The trial will evaluate RLY-2608 in patients with PI3Kα-driven Vascular Malformations. Clinical start in 2025.

Learn More about the Phase 2 Trial

NCT Listing:
NCT06789913

Clincaltrials.gov Link:
https://clinicaltrials.gov/study/NCT06789913

Contact Relay Therapeutics:
clinicaltrials@relaytx.com

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