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Discovery and characterization of RLY-2608, the first allosteric, mutant, and isoform-selective inhibitor of PI3Kα

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I have the following financial relationships to disclose:

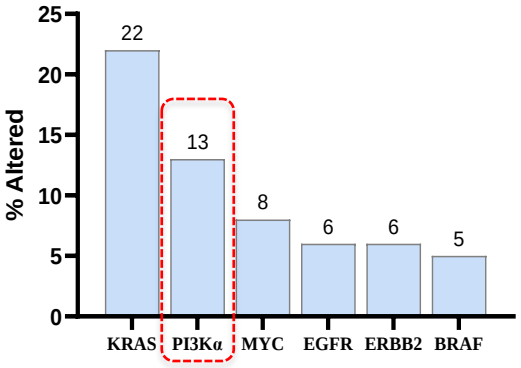
Stockholder in: Relay Therapeutics

Employee of: Relay Therapeutics

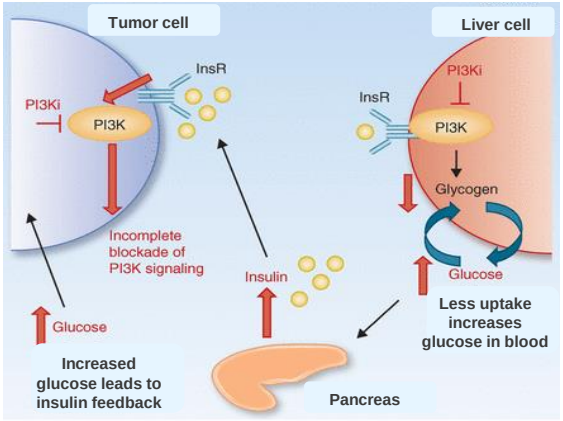
I will not discuss off label use and/or investigational use in my presentation.

Mutant PI3Kα is a validated cancer target with unrealized therapeutic potential

PI3Ka is the most frequently mutated kinase in cancer



Inhibition of WT PI3Kα leads to hyperglycemia



Adapted from Hanker Cancer Disc 2019

Multiple generations of inhibitors

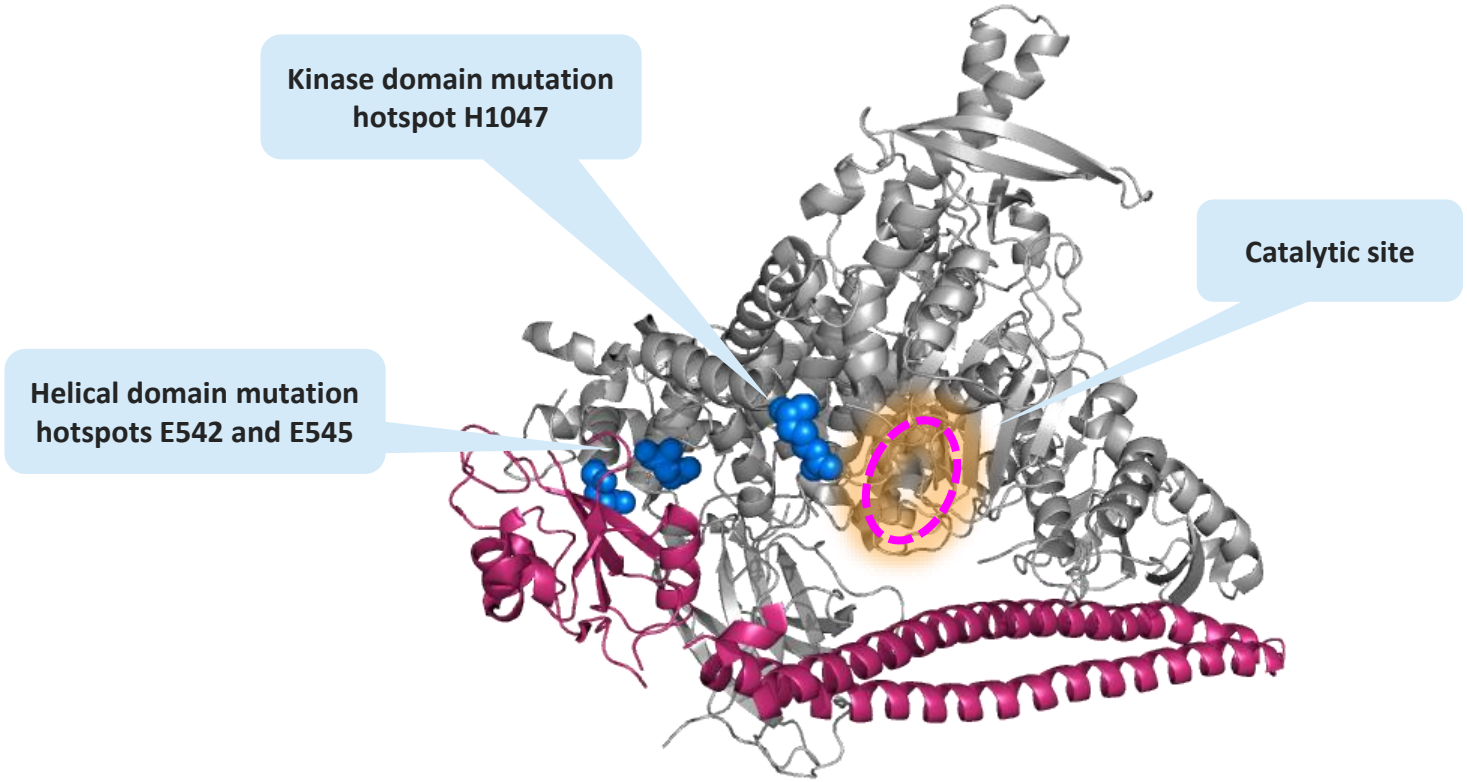
Prior — Pan-PI3K/mTOR inhibitors: Significant toxicity

2010s — Pan-PI3K inhibitors: Significant toxicity

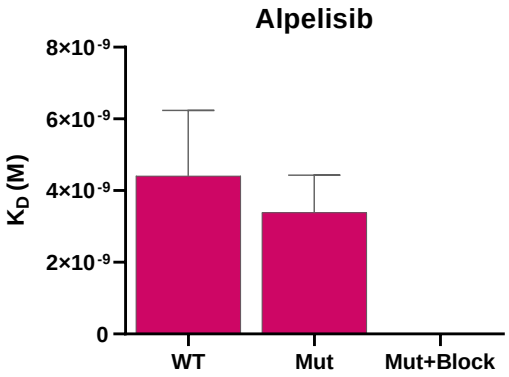
2019 — PI3Kα-predominant inhibitor (alpelisib): PFS benefit with limited TI

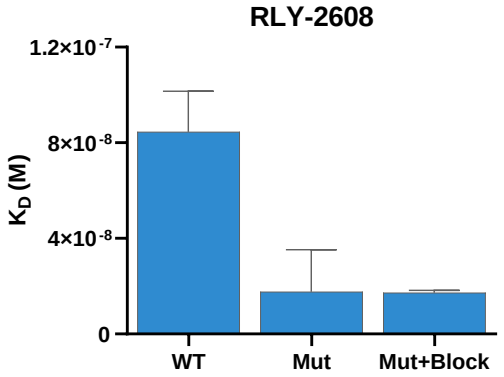
Currently no approved mutant-selective PI3Kα inhibitors

Oncogenic mutations in PI3Kα are located distal to the active site

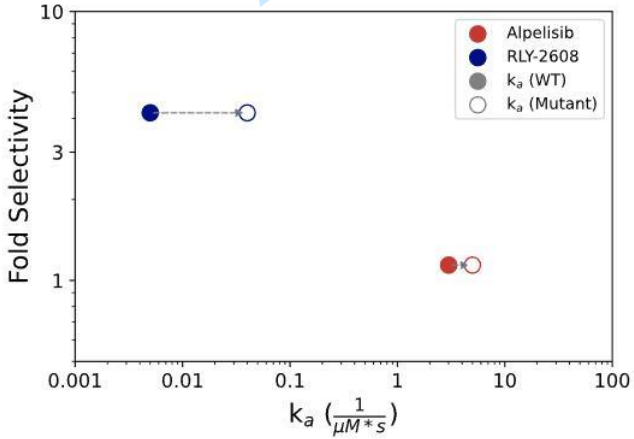


RLY-2608 binds preferentially to mutant PI3Kα at a novel allosteric site



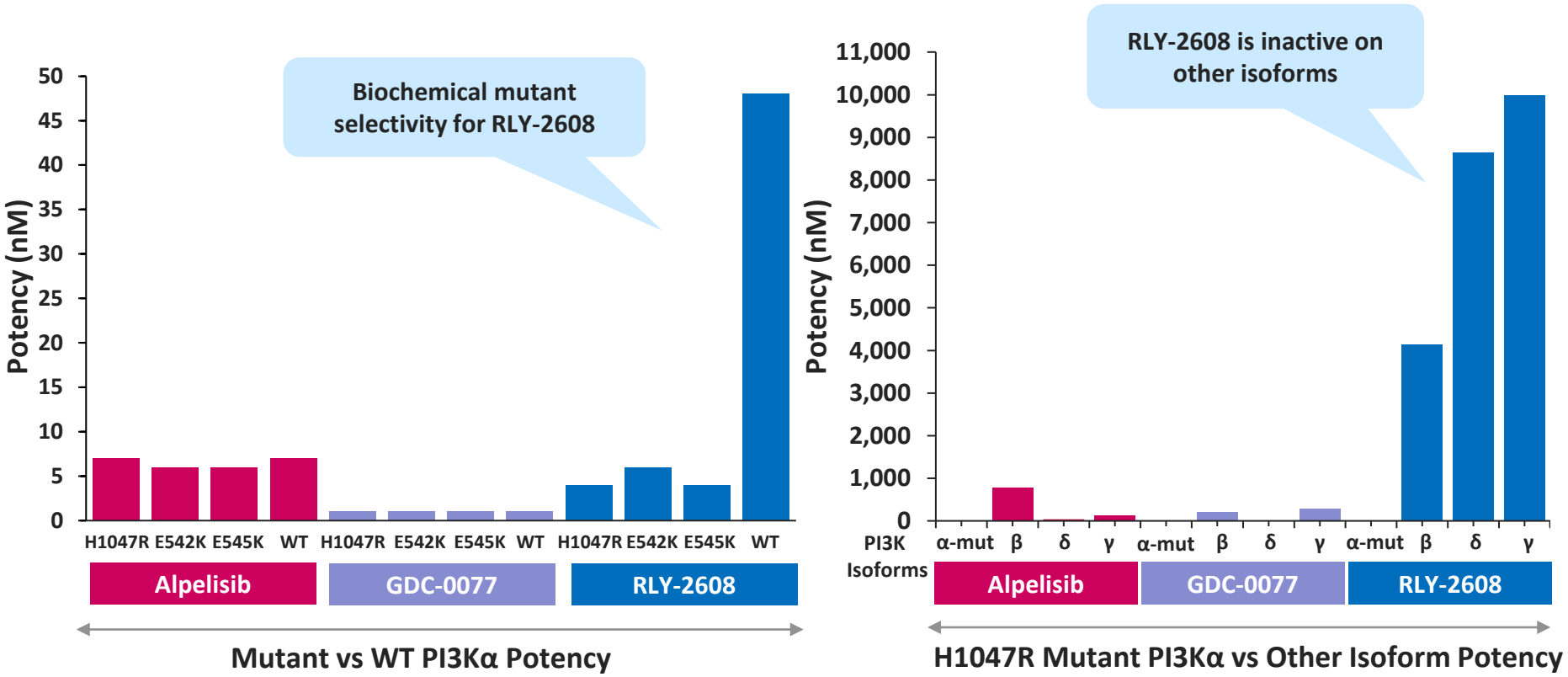


Faster binding to mutant vs WT

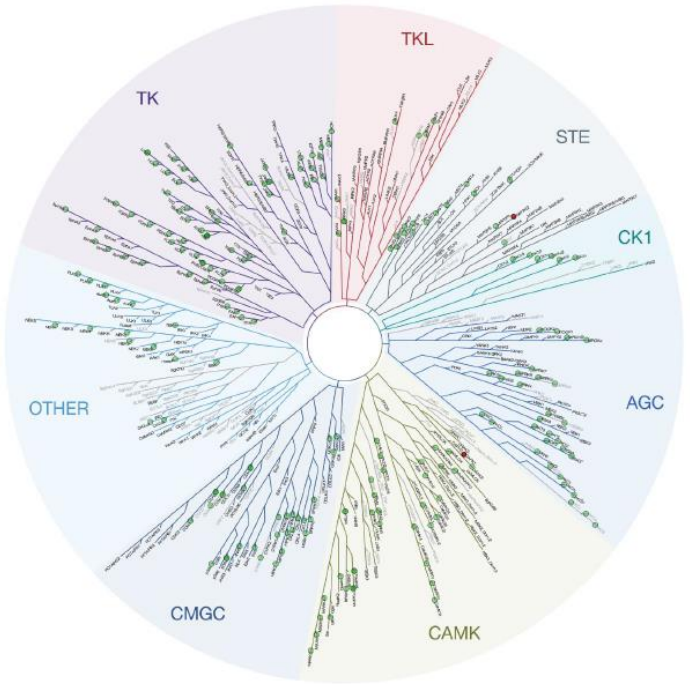


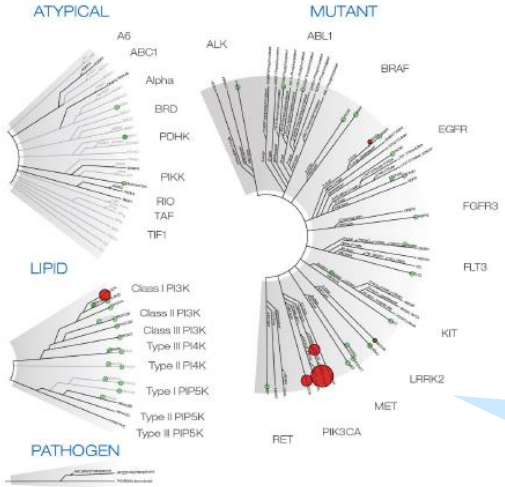
Mutant-favored binding, not impacted by blocking the orthosteric site

RLY-2608 shows potent, mutant and isoform selective, biochemical inhibition



RLY-2608 is exquisitely selective across the kinome



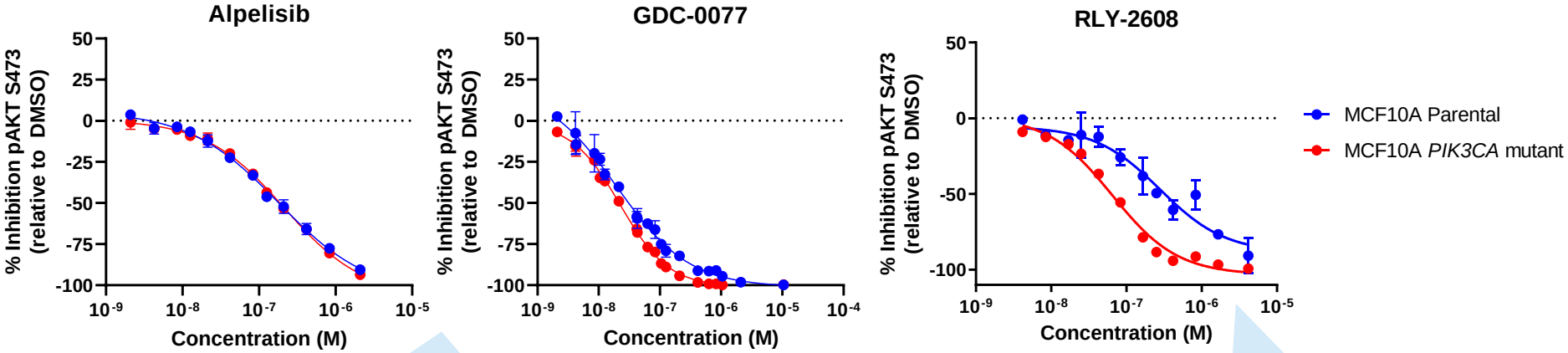


RLY-2608 inhibits only PI3Kα, with preferential inhibition of mutant

Kinase Inhibition @ 10 µM

- **>80% inhibition**
- **20-80% inhibition**
- **< 20 % inhibition**

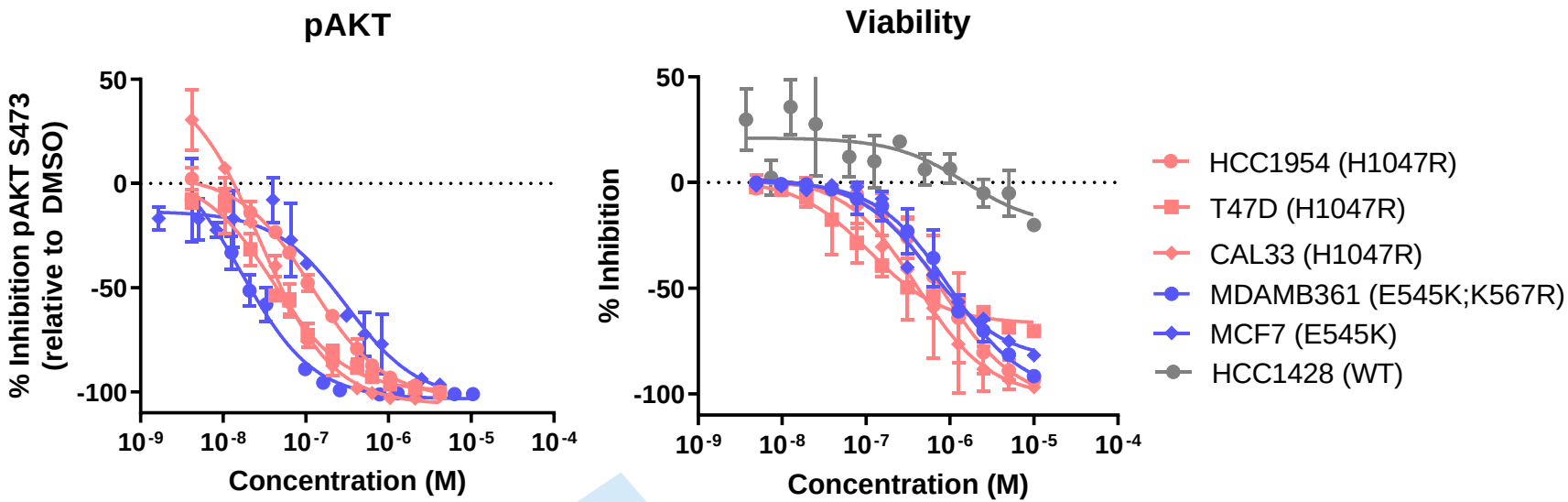
RLY-2608 inhibits mutant PI3Kα more potently in cells



Orthosteric binders are equipotent between WT and mutant

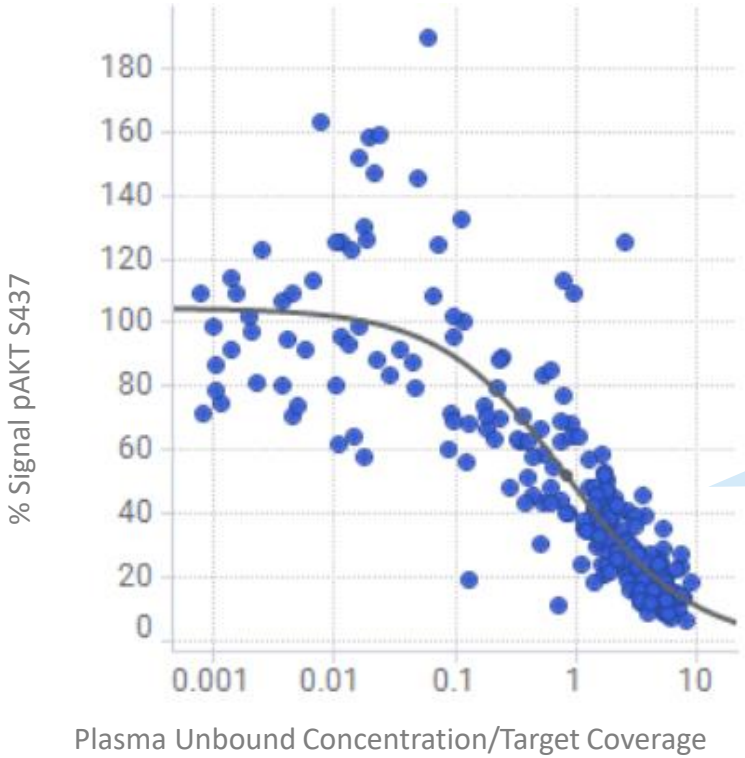
RLY-2608 is more potent against mutant cells

RLY-2608 potently inhibits signaling and viability in *PIK3CA* mutant cancer cell lines



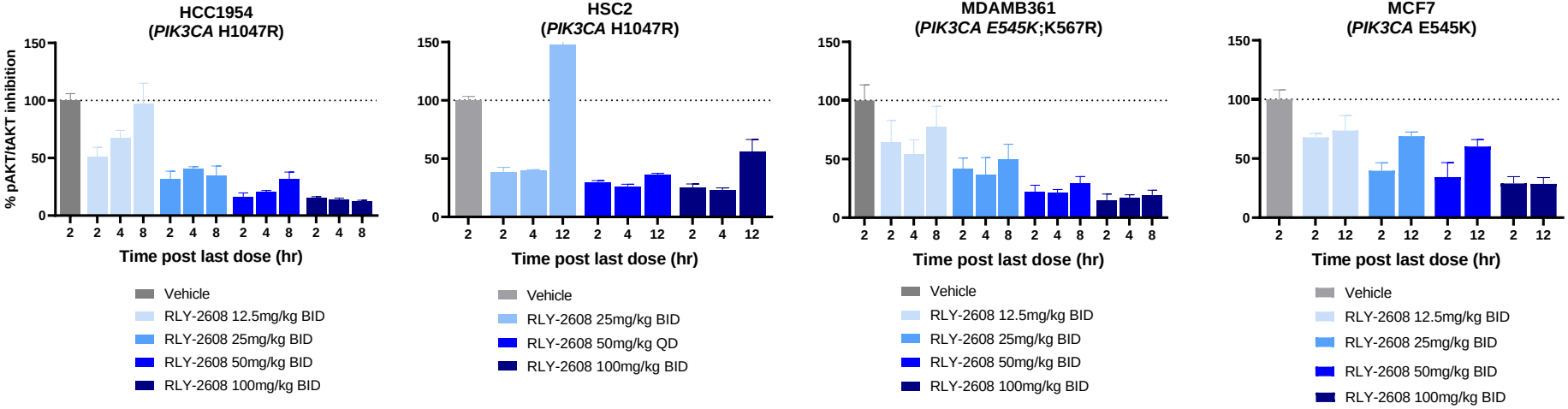
Activity observed in both kinase and helical domain mutant cell lines

RLY-2608 modulates pAKT in vivo



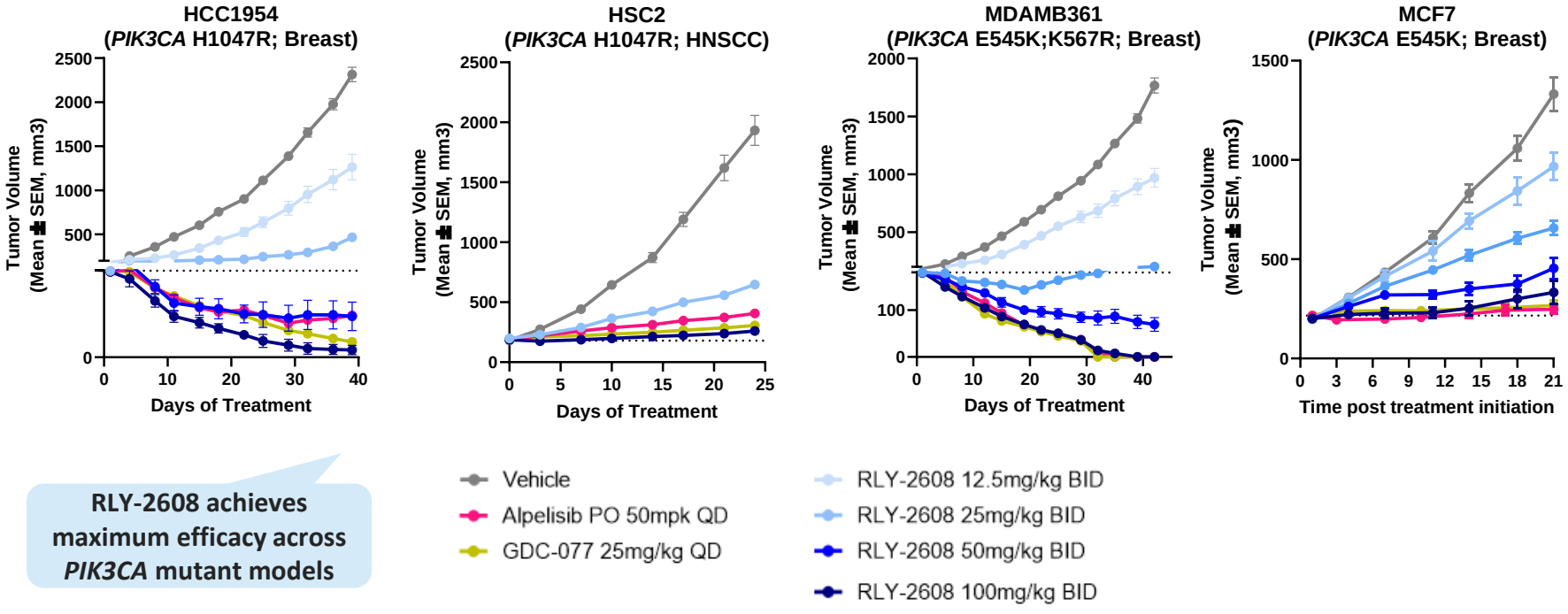
Exposure dependent inhibition of pAKT in tumors

RLY-2608 modulates pAKT in vivo



Higher doses/exposures lead to increased modulation of pAKT across *PIK3CA* mutant models

RLY-2608 leads to significant tumor growth inhibition in *PIK3CA* mutant models

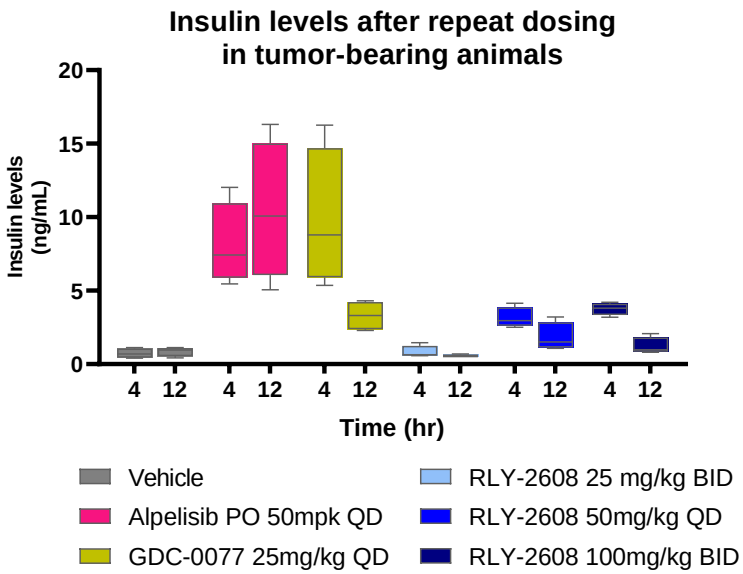


RLY-2608 achieves maximum efficacy across *PIK3CA* mutant models

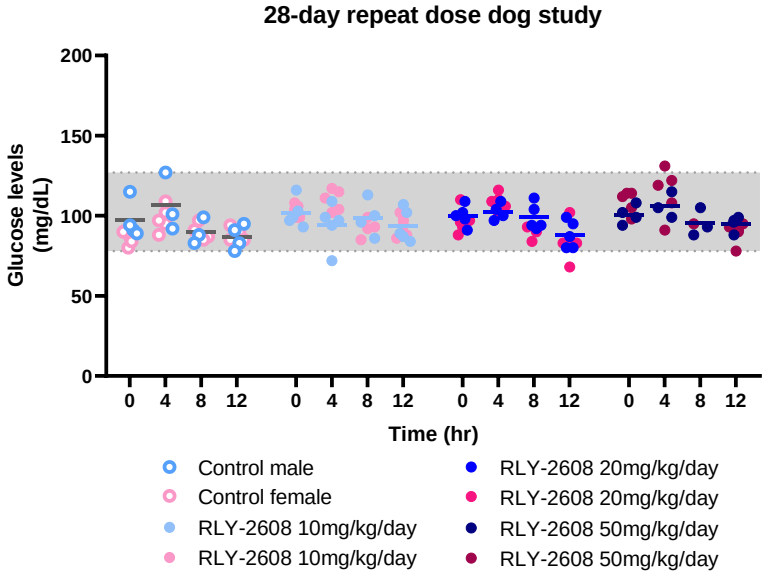
* Separate inoculation

RLY-2608 has reduced impact on glucose homeostasis

RLY-2608 achieves max efficacy with less insulin than orthosteric inhibitors



Repeat dosing of RLY-2608 does not cause hyperglycemia in tox species



Covers mutant IC90 throughout the dosing interval

Conclusions

- RLY-2608 preferentially binds mutant PI3Kα at a novel allosteric site
- In biochemical assays, RLY-2608 inhibits both kinase and helical domain mutant PI3Kα activity more potently than WT, and is highly selective against other PI3K family members and across the kinome
- RLY-2608 achieves maximum efficacy in both kinase and helical domain *PIK3CA* mutant in vivo xenograft models with significantly reduced elevation of insulin levels compared to orthosteric inhibitors
- In higher species, dosing of RLY-2608 results in exposures exceeding mutant PI3Kα cellular PD IC90 without resulting in elevated glucose levels or histopathological changes associated with dysregulation of glucose metabolism
- Results support clinical investigation of RLY-2608 as a differentiated mechanism of mutant PI3Kα inhibition with the first-in-human study anticipated to start in 1H22

Reach out with questions/comments:

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