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
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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**

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<th>% Altered</th>
<th>KRAS</th>
<th>PI3Kα</th>
<th>MYC</th>
<th>EGFR</th>
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**Inhibition of WT PI3Kα leads to hyperglycemia**

- Increased glucose leads to insulin feedback
- Less uptake increases glucose in blood
- Incomplete blockade of PI3K signaling
- Inhibition of WT PI3Kα leads to hyperglycemia

**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 TIs

Currently no approved mutant-selective PI3Kα inhibitors

Adapted from Hanks Cancer Disc 2019
Oncogenic mutations in PI3Kα are located distal to the active site

- **Kinase domain mutation hotspot H1047**
- **Helical domain mutation hotspots E542 and E545**
- **Catalytic 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.

Biochemical mutant selectivity for RLY-2608

RLY-2608 is inactive on other isoforms

Mutant vs WT PI3Kα Potency

H1047R Mutant PI3Kα vs Other Isoform Potency
RLY-2608 is exquisitely selective across the kinome

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

In 28-day repeat dose dog study, RLY-2608 achieves max efficacy with less insulin than orthosteric inhibitors. Throughout the dosing interval, RLY-2608 covers mutant IC90.

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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