First-in-human global multi-center study of RLY-2608, a pan mutant and isoform selective PI3Kα inhibitor, as a single agent in advanced solid tumor patients and in combination with fulvestrant in patients with advanced breast cancer

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Background

- Targeting constitutively active mutant kinases with selective small molecule inhibitors is a key therapeutic pillar of precision oncology.
- Phosphatidylinositol-4,5-bisphosphate-3 kinase, catalytic subunit alpha (PIK3CA) mutations leading to oncogenic activation of PI3Kα represent the largest opportunity for this approach in solid tumors1-2
  - However, no known selective inhibitor targets mutant PI3Kα in the clinic.
  - Toxicities related to inhibition of WT PI3Kα (hyperglycemia) and other PI3K isoforms limit the tolerability, dosing, and efficacy of the orthosteric inhibitor, alpelisib, the only approved solid tumor PI3K inhibitor3.
- To further investigate this target, we used our Dynamo4 platform that integrates computational and experimental techniques to gain insight into the dynamic configurations of WT and mutant PI3Kα.
- We designed RLY-2608, an oral, selective allosteric pan-mutant PI3Kα inhibitor, to bind to a novel allosteric site and overcome limitations of current inhibitors via mutant- and isoform-selective PI3Kα inhibition for greater target coverage, improved tolerability, and antitumor activity.

RLY-2608 is the first known allosteric PI3Kα mutant and isoform selective inhibitor

Figure 1. (a) RLY-2608 novel allosteric mechanism (b) and novel MOA enables selectivity for PI3Kα-mutants

(a) Alpelisib binds orthosteric (catalytic) site. RLY-2608 binds proprietary allosteric site (not disclosed).

STUDY DESIGN

This is a global, multi-center, dose escalation/expansion study of RLY-2608 as a single agent in adults who have advanced solid tumors that are refractory, intolerant, or declined standard therapy and RLY-2608 in combination with fulvestrant in previously treated patients with HR+/HER2- metastatic breast cancer.

Figure 2. (a, b) In-vivo tumor regression observed in H1047R and E545K mutant models with (c) less insulin at active doses of RLY-2608 than orthosteric inhibitors

Figure 3. Study Design (NCT0216432)

Part 1: Dose Escalation

- PK3CAmut Clear Cell OvCa (N = 15)
- PK3CAmut HHNSC (N = 15)
- PK3CAmut Cervical CA (N = 15)
- PIK3CA double mutant advanced solid tumors (N=15)

Part 2: Dose Expansion

- PK3CAmut, HR+, HER2- advanced breast cancer, with NO prior PI3K inhibitor (N = 15)
- PK3CAmut, HR+, HER2- advanced breast cancer, intolerant to PI3K inhibitor (N = 15)

Figure 4. Active sites

Key Objectives

- Superior operating characteristics relative to traditional 3+3 design and continual reassessment designs
- Bayesian toxicity assessment coupled with option to accelerate dose titration and enrich accrual to dose level determined to be tolerable and pharmacologically active
- Permits rigorous assessment of safety, pharmacokinetics, and anti-tumor activity to define optimal dose and schedule
- More accurately determines maximum tolerated dose via isotonic regression of observed dose-limiting toxicities rate across all cohorts

BAYESIAN OPTIMAL INTERVAL DOSE ESCALATION

- The target enrollment for RLY-2608 is 190 patients. Recruitment is ongoing in 6 study centers in the USA.
- USA enrollment began December 2021 and study start-up ex-USA is under way.

ELIGIBILITY CRITERIA

- ≥ 18 years of age
- Documented primary oncogenic PIK3CA mutation per local assessment (tumor or blood)
- ECOG performance status 0 – 1
- Part 1: Evaluable disease per RECIST v1.1
- Part 2: Measurable disease per RECIST v1.1
- No prior PI3K inhibitor (except Part 2 RLY-2608 + Fulvestrant combination group intolerant to a inhibitors)
- For RLY-2608+Fulvestrant combination, patients must have previous treatment with ≤ 1 chemotherapy, ≥1 CDK4/6 inhibitor and ≥1 anti-estrogen therapy

References

4. Pazdil, et al. Poster presented at SABCS; 2021; San Antonio, TX, USA.

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