CLINICAL RATIONALE AND STUDY DESIGN

**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.
- Phosphorylated/activated 4–kinases, known as cellular signal molecules and regulators, are known targets of kinase inhibitors.
- Phosphorylated/activated 3–kinases (PI3Ks) represent the largest opportunity for this approach in solid tumors.6–8
- However, no known selective inhibitor targets mutant PI3Kα in the clinic.
- Toxicities related to inhibition of wild-type (WT) PI3Kα (hyperglycemia) and other PI3K isoforms limit the tolerability, dosing, and efficacy of the orthotopic kinase inhibitor, alpelisib, the only approved solid tumor PI3K inhibitor.9

**Figure 1. (a) RLY-2008 novel allosteric mechanism and (b) novel NDA enables selectivity for PI3Kα-mutants**

- Alpelisib binds orthosteric (EATC) 3p, RLY-2008 binds proximal kinase (site not disclosed)
- (b) RLY-2008 has exquisite selectivity over the known

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

**Figure 2. RLY-2608 anti-tumor activity (a) as a single agent, (b) in combination with fulvestrant, and (c) with minimal perturbation in glucose metabolism compared to other PI3K inhibitors**

**Figure 3. Study design (NCT03216422)**

**Figure 4. Active sites**

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

**Figure 5. RLY-2608 pharmacodynamics and efficacy in preclinical models**

**Figure 6. RLY-2608 clinical development**

**RLY-2008 + fulvestrant**

**Part 1: Proof of concept**

**Part 2: Dose expansion**

**RLY-2608 clinical trial overview (N=15)**

**Key objectives**

- Anti-TIM, safety profile, PK parameters
- Preliminary and tumor activity per RECIST v1.1
- Changes in circulating markers of glucose metabolism

**RLY-2608 in mut HNSCC (N=15)**

**RLY-2608 + fulvestrant in mut cervical cancer (N=15)**

**Key eligibility criteria**

- **16 years of age**
- **E2 - I**
- **Eastern Cooperative Oncology Group performance status 0-1**
- **Part 1: Exclusion criteria**
- **Part 2: Dose escalation per BEC/40 V3.1**
- **No prior PI3K inhibitor (except Part 2 RLY-2608 + Fulvestrant combination group intent to enroll to a randomization)**
- **For RLY-2608 + Fulvestrant combinations, patients must have previous treatment with chemotherapy, CRT, tyrosine-dependent kinase inhibitor 4, and 6 inhibitor, and is an anti-endocrine therapy**

- **RLY-2608 + Fulvestrant in mut HNSCC (N=15)**
- **RLY-2608 + Fulvestrant in mut cervical cancer (N=15)**
- **RLY-2608 + Fulvestrant in mut breast cancer (N=15)**
- **RLY-2608 + Fulvestrant in mut melanoma (N=15)**

**Figure 7. RLY-2608 anti-tumor activity (a) as a single agent, (b) in combination with fulvestrant, and (c) with minimal perturbation in glucose metabolism compared to other PI3K inhibitors**

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

**Figure 8. RLY-2608 pharmacodynamics and efficacy in preclinical models**

**RLY-2608 clinical trial overview (N=15)**

**Key objectives**

- Anti-TIM, safety profile, PK parameters
- Preliminary and tumor activity per RECIST v1.1
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**RLY-2608 in mut HNSCC (N=15)**

**RLY-2608 + fulvestrant in mut cervical cancer (N=15)**

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**RLY-2608 + fulvestrant in mut breast cancer (N=15)**

**RLY-2608 + fulvestrant in mut melanoma (N=15)**

**Figure 9. RLY-2608 anti-tumor activity (a) as a single agent, (b) in combination with fulvestrant, and (c) with minimal perturbation in glucose metabolism compared to other PI3K inhibitors**

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

**Figure 10. RLY-2608 pharmacodynamics and efficacy in preclinical models**

**RLY-2608 clinical trial overview (N=15)**

**Key objectives**

- Anti-TIM, safety profile, PK parameters
- Preliminary and tumor activity per RECIST v1.1
- Changes in circulating markers of glucose metabolism

**RLY-2608 in mut HNSCC (N=15)**

**RLY-2608 + fulvestrant in mut cervical cancer (N=15)**

**Key eligibility criteria**

- **16 years of age**
- **E2 - I**
- **Eastern Cooperative Oncology Group performance status 0-1**
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**RLY-2608 + fulvestrant in mut breast cancer (N=15)**

**RLY-2608 + fulvestrant in mut melanoma (N=15)**

**Figure 11. RLY-2608 in mut HNSCC (N=15)**

**RLY-2608 + fulvestrant in mut cervical cancer (N=15)**

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**RLY-2608 + fulvestrant in mut breast cancer (N=15)**

**RLY-2608 + fulvestrant in mut melanoma (N=15)**

**Figure 12. RLY-2608 in mut HNSCC (N=15)**

**RLY-2608 + fulvestrant in mut cervical cancer (N=15)**

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**RLY-2608 + fulvestrant in mut breast cancer (N=15)**

**RLY-2608 + fulvestrant in mut melanoma (N=15)**

**Figure 13. RLY-2608 in mut HNSCC (N=15)**

**RLY-2608 + fulvestrant in mut cervical cancer (N=15)**

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**RLY-2608 + fulvestrant in mut breast cancer (N=15)**

**RLY-2608 + fulvestrant in mut melanoma (N=15)**