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

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BACKGROUND

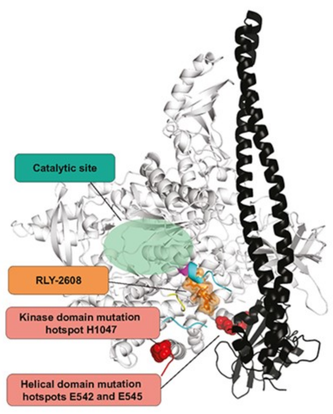
- Oncogenic mutations in *PIK3CA* are common driver events in solid tumors, particularly in breast cancer (BC), where mutations occur in up to ~35% of HR+, HER2– advanced BC patients[1,2]
- In BC, *PIK3CA* mutations in the kinase (i.e. H1047R) and helical (i.e. E542K, E545K) domains are the most common and contribute to resistance to endocrine therapy
- The approval of orthosteric PI3Kα inhibitors, like alpelisib (approved for HR+, HER2– advanced BC), validates PI3Kα as a therapeutic target. However, these inhibitors also potently inhibit WT PI3Kα, leading to significant hyperglycemia and rash, which limit dose intensity and potential for use in combination regimens[3]
- A PI3Kα mutant-selective inhibitor could avoid WT PI3Kα toxicity and potentially improve dose intensity, efficacy and tolerability, and be used in combinations, benefiting broader populations of patients

RATIONALE

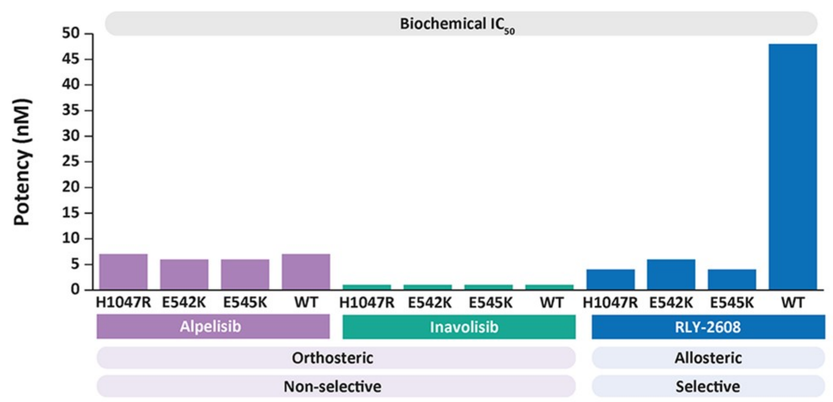
- RLY-2608 is the first oral, pan-mutant- and isoform-selective allosteric inhibitor of PI3Kα (**Figure 1a**)
- RLY-2608 demonstrates biochemical selectivity for both kinase and helical mutants over WT PI3Kα (**Figure 1b**) and kinome selectivity, including over other PI3K isoforms

Figure 1. Novel allosteric mechanism of RLY-2608 enables selectivity for PI3Kα mutants[4]

(a) RLY-2608 binds to a novel allosteric pocket in PI3Kα



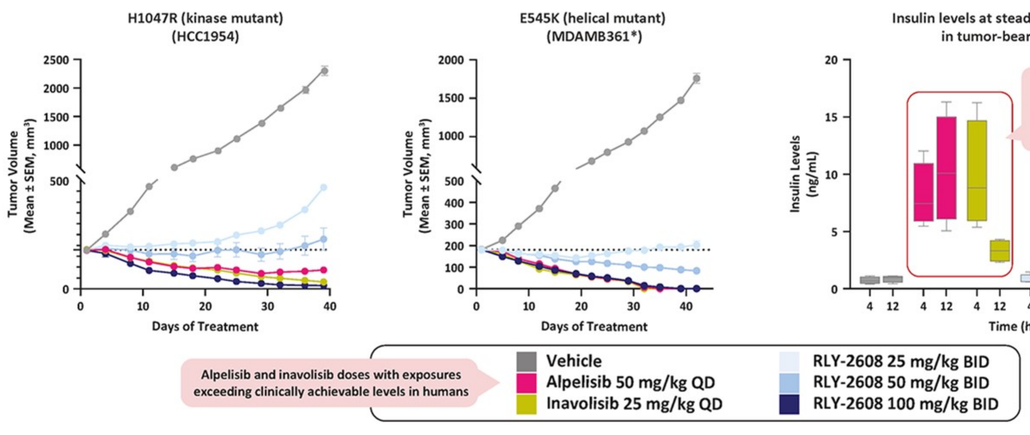
(b) RLY-2608 demonstrates pan-mutant selectivity in biochemical assays



- BC xenograft models with *PIK3CA* kinase and helical mutations demonstrate anti-tumor activity of RLY-2608 monotherapy, while maintaining glucose homeostasis (**Figure 2**)
- We initiated the first-in-human ReDiscover study (NCT05216432) to evaluate the safety and clinical activity of RLY-2608 as a single agent in patients with advanced solid tumors with *PIK3CA* mutations and in combination with fulvestrant and fulvestrant + a CDK4/6 inhibitor in patients with *PIK3CA*-mutant, HR+, HER2– metastatic BC
- To date, RLY-2608 plus fulvestrant has completed dose escalation; RP2Ds have been identified based on safety, PK, PD, and anti-tumor activity, and are being investigated in the combination regimens

Figure 2. RLY-2608 leads to tumor growth inhibition in HR+ BC mouse xenograft models with *PIK3CA* kinase and helical mutations while maintaining glucose homeostasis[5]

Tumor regression in PI3Kα mouse BC models



Minimal perturbation of insulin levels

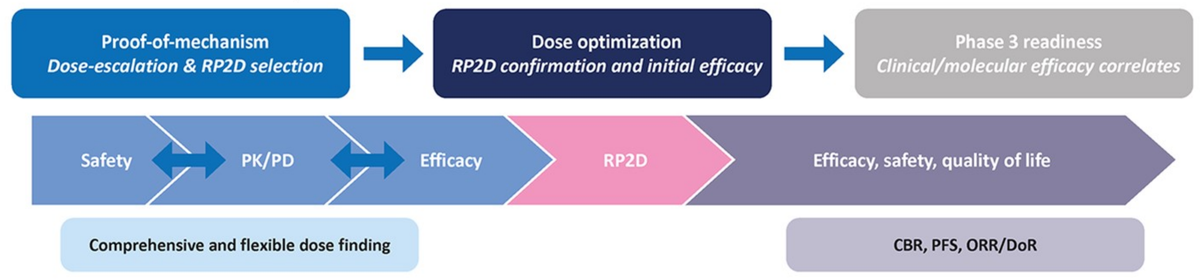
Dotted horizontal line: starting tumor size
*This model also carries a second mutation at K567R; †HSC2 model; ‡Juric D, et al. *J Clin Oncol*. 2018;36:1291–1299 and Juric D, et al. Presented at San Antonio Breast Cancer Symposium 2019, San Antonio, TX, USA. Abstract OT1-08-04; poster P5-17-05.

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 (refractory or intolerant to, or who decline, standard therapy) and RLY-2608 in combination with fulvestrant ± ribociclib in previously treated patients with HR+, HER2– metastatic BC (**Figure 3**)

Figure 3. Study design

ReDiscover first-in-human study overview



RLY-2608 PO BID or QD

RLY-2608 *PIK3CA*mut advanced solid tumors (complete)	MTD/RP2D	Advanced solid tumors*
RLY-2608 + fulvestrant *PIK3CA*mut, HR+, HER2– advanced /metastatic BC (complete)	MTD/RP2D range	*PIK3CA*mut, HR+, HER2– advanced BC, with NO prior PI3Kα inhibitor
RLY-2608 + fulvestrant + CDK4/6 inhibitor† *PIK3CA*mut, HR+, HER2– advanced/metastatic BC	MTD/RP2D range	*PIK3CA*mut, HR+, HER2– advanced BC, with NO prior PI3Kα inhibitor

- RLY-2608 is administered PO QD in 4-week cycles
- AEs per CTCAE v5, PK, biomarkers (pAKT, mutant ctDNA and insulin pathway markers) and anti-tumor activity are assessed serially
- Dose escalation employs a BOIN design to identify the MTD. Following dose escalation, expansion cohorts are enrolling patients with select *PIK3CA*-mutated solid tumors for treatment with RLY-2608 monotherapy and patients with HR+, HER2– metastatic BC for treatment with RLY-2608 plus fulvestrant ± ribociclib

*Includes *PIK3CA*mut clear cell ovarian cancer, *PIK3CA*mut HNSCC, and *PIK3CA*mut cervical cancer; †Triple combination arms will include the CDK4/6 inhibitor ribociclib.

Eligibility criteria

- ≥18 years of age
- ≥1 documented primary oncogenic *PIK3CA* mutation per local assessment (tumor or blood)
- Eastern Cooperative Oncology Group performance status 0–1
- Evaluable disease per RECIST v1.1
- No prior PI3Kα inhibitor*
- For the RLY-2608 combination and triplet arms, patients must have previous treatment with ≤1 chemotherapy, ≥1 CDK4/6 inhibitor, and ≥1 anti-estrogen therapy, and no prior treatment with PI3Kα, AKT, or mTOR inhibitors*
- No Type 1 or Type 2 diabetes requiring antihyperglycemic medication, or fasting plasma glucose ≥140 mg/dL and HbA1c ≥7.0%

*Except Part 2 RLY-2608 + fulvestrant combination group intolerant to PI3Kα inhibitors.

ENROLLMENT

- The target enrollment for RLY-2608 is 400 patients. Recruitment is ongoing in **24** study centers in the USA and Europe
- Study enrollment began in December 2021 and is ongoing in all study arms

Active sites

France
- Gustave Roussy, Villejuif Cedex
- Institut Bergonié, Bordeaux Cedex

Italy
- Istituto Europeo di Oncologia, Milan

Spain
- VHIO Vall d'Hebron Instituto de Oncología, Barcelona
- Hospital Universitario 12 de Octubre, Madrid
- South Texas Accelerated Research Therapeutics (START) Madrid - Hospital Fundacion Jimenez Diaz, Madrid
- Instituto Valenciano de Oncología, Valencia
- Institut Català d'Oncología – Badalona, Barcelona

United States
- The University of Arizona Cancer Center, Tucson, Arizona
- Sarah Cannon Research Institute/ HealthONE Denver, Denver, Colorado
- BRCR Medical Center, Plantation, Florida
- Sarah Cannon Research Institute/Florida Cancer Specialists, Orlando, Florida
- The University of Chicago Medical Center, Chicago, Illinois
- Community Health Network, Indianapolis, Indiana
- Dana-Farber Cancer Institute, Boston, Massachusetts
- Massachusetts General Hospital, Boston, Massachusetts
- University of Michigan, Ann Arbor, Michigan
- Columbia University Herbert Irving Comprehensive Cancer Center, New York, New York
- Memorial Sloan Kettering Cancer Center, New York, New York
- Sarah Cannon Research Institute/ Tennessee Oncology, Nashville, Tennessee
- The University of Texas Southwestern Medical Center, Dallas, Texas
- The University of Texas MD Anderson Cancer Center, Houston, Texas
- Virginia Cancer Specialists Research Institute and NEXT Oncology, Virginia, Fairfax, Virginia
- The University of Wisconsin Carbone Cancer Center, Madison, Wisconsin

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Abbreviations

AE, adverse event; BC, breast cancer; BID, twice per day; BOIN, Bayesian Optimal Interval; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinases 4/6; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; DoR, duration of response; HbA1c, glycosylated hemoglobin; HER2–, human epidermal growth factor receptor 2-negative; HNSCC, head and neck squamous cell carcinoma; HR+, hormone receptor-positive; IC50, half-maximal inhibitory concentration; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; mut, mutations; ORR, objective response rate; pAKT, phosphorylated AKT; PD, pharmacodynamics; PFS, progression-free survival; PI3Kα, phosphatidylinositol 3-kinase alpha; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PK, pharmacokinetics; PO, by mouth; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose; SEM, standard error of the mean; WT, wild type.

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