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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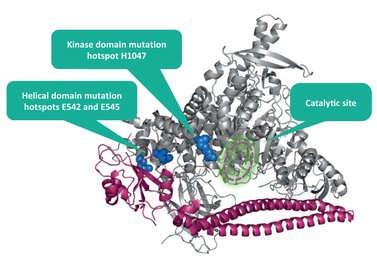
Poster OT3-22-01
San Antonio Breast Cancer Symposium®, December 6–10, 2022

BACKGROUND

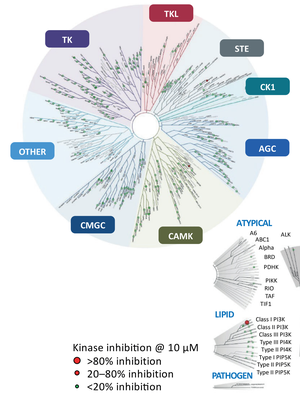
- Targeting constitutively active mutant kinases with selective small molecule inhibitors is a key therapeutic pillar of precision oncology
- *Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA)* mutations leading to oncogenic activation of phosphatidylinositol 3-kinase alpha (PI3Kα) represent the largest opportunity for this approach in solid tumors[1–2]
  - 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 orthosteric inhibitor, alpelisib, the only approved solid tumor PI3K inhibitor[3]

Figure 1. (a) RLY-2608 novel allosteric mechanism and (b) novel MOA enables selectivity for PI3Kα-mutants[4]

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



(b) RLY-2608 has exquisite selectivity over the kinome



Kinase inhibition @ 10 µM
- >80% inhibition
- 20–80% inhibition
- <20% inhibition

ABL1, ABL proto-oncogene 1; AGC, containing PKA, PKG, PKC families; ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BRD, bromodomains; CAMK, calcium/calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, containing CDK, MAPK, GSK3, CLK families; EGFR, epidermal growth factor receptor; FGFR3, fibroblast growth factor receptor 3; FLT3, fms-related tyrosine kinase 3; KIT, KIT proto-oncogene; LRRK2, leucine-rich repeat kinase; MET, MET proto-oncogene; MOA, mechanism of action; OTHER, divergent kinases not represented in other groups; PDHK, pyruvate dehydrogenase kinase; PI3K, phosphatidylinositol 3-kinase; PI4K, phosphatidylinositol 4-kinase; PIK3CA, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha; PIKK, phosphatidylinositol-3 kinase-related kinases; PIP5K, phosphatidylinositol 4-phosphate 5-kinase; RET, ret proto-oncogene; STE, homologs of yeast sterile 7, sterile 11, sterile kinases; TAF, tumor angiogenesis factor; TIF1, transcriptional intermediary factor 1; TK, tyrosine kinase; TKL, tyrosine kinase-like.

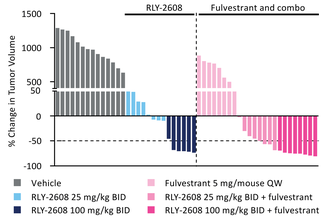
- To further investigate this target, we used our Dynamo™ platform that integrates computational and experimental techniques to gain insight into the dynamic conformations of WT and mutant PI3Kα
  - We designed RLY-2608, an oral, selective allosteric pan-mutant PI3Kα inhibitor, to bind to a novel allosteric site and overcome limitations of current inhibitors via mutant- and isoform-selective PI3Kα inhibition for greater target coverage, improved tolerability, and antitumor activity
- We initiated a first-in-human (NCT05216432) study to evaluate the safety and clinical activity of RLY-2608 as a single agent in advanced solid tumor patients with PI3KCA mutations and in combination with fulvestrant in patients with PIK3CA-mutant, hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) metastatic breast cancer (MBC)

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

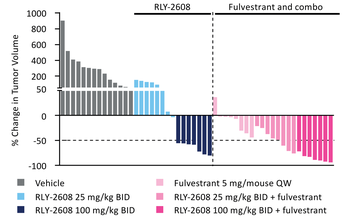
CLINICAL RATIONALE AND STUDY DESIGN

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[4]

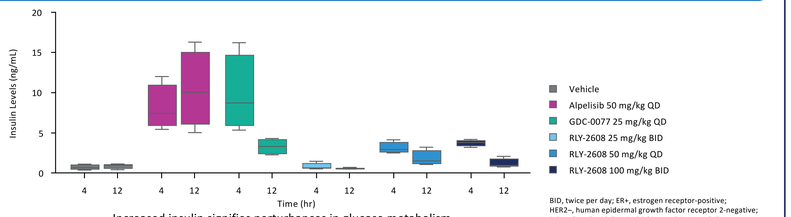
(a) ST1056 (ER+/HER2–; H1047R)



(b) ST986 (ER+/HER2–; E542K)



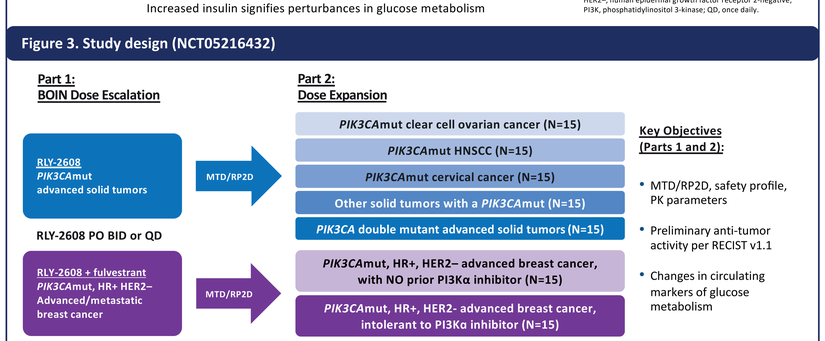
(c) Insulin levels after repeat dosing in tumor-bearing animals



Increased insulin signifies perturbances in glucose metabolism

BID, twice per day; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; PI3K, phosphatidylinositol 3-kinase; QD, once daily.

Figure 3. Study design (NCT05216432)



Key Objectives (Parts 1 and 2):

- MTD/RP2D, safety profile, PK parameters
- Preliminary anti-tumor activity per RECIST v1.1
- Changes in circulating markers of glucose metabolism

BID, twice per day; BOIN, Bayesian Optimal INterval; HER2–, human epidermal growth factor receptor 2-negative; HNSCC, head and neck squamous cell carcinoma; HR+, hormone receptor-positive; MTD, maximum tolerated dose; mut, mutations; PI3Kα, phosphatidylinositol 3-kinase alpha; PIK3CA, phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha; PO, by mouth; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase 2 dose; RECIST, Response Evaluation Criteria in Solid Tumors.

KEY ELIGIBILITY CRITERIA

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, intolerant or who declined standard therapy) and RLY-2608 in combination with fulvestrant in previously treated patients with HR+/HER2– metastatic breast cancer.

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
- Part 1: Evaluable disease per Response Evaluation Criteria in Solid Tumors (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 α inhibitors)
- For RLY-2608+fulvestrant combination, patients must have previous treatment with ≤1 chemotherapy, ≥1 cyclin-dependent kinase 4 and 6 inhibitor, and ≥1 anti-estrogen therapy

Figure 4. Active sites

- **Spain**
  - VHIO Vall d'Hebron Instituto de Oncología, Barcelona
  - Institut Valencia D'Oncologia, Valencia
- **United States**
  - The University of Arizona Cancer Center, Tucson, Arizona
  - HealthONE/SCRI, Denver, Colorado
  - BRCR Global, Plantation, Florida
  - Lake Nona/SCRI Florida Cancer Specialists, Orlando, Florida
  - Massachusetts General Hospital, Boston, Massachusetts
  - Columbia University Herbert Irving Comprehensive Cancer Center, New York, New York
  - Memorial Sloan Kettering Cancer Center, New York, New York
  - Tennessee Oncology/SCRI, Nashville, Tennessee
  - The University of Texas M.D. Anderson Cancer Center, Houston, Texas
  - Virginia Cancer Specialists/NEXT Virginia, Fairfax, Virginia
  - The University of Wisconsin Carbone Cancer Center, Madison, Wisconsin

As of November 2022

- The target enrollment for RLY-2608 is 190 patients. Recruitment is ongoing in 14 study centers in the USA and Spain
- USA enrollment began in December 2021 for the single arm, and in April 2022 for the breast cancer combination arm. Ex-USA enrollment began in November 2022

References

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Acknowledgments

The authors would like to thank the patients, their families, and all study team members involved in this study.

Presented at the 2022 San Antonio Breast Cancer Symposium, December 6–10, 2022, San Antonio, Texas, USA. For more information, please contact: ClinicalTrials@relaytx.com.