ReDiscover-2, a phase III study of zovegalisib (RLY-2608) + fulvestrant versus capivasertib + fulvestrant as treatment for locally advanced or metastatic *PIK3CA*-mutant HR+/HER2- breast cancer following recurrence or progression on or after treatment with a CDK4/6 inhibitor (trial in progress)

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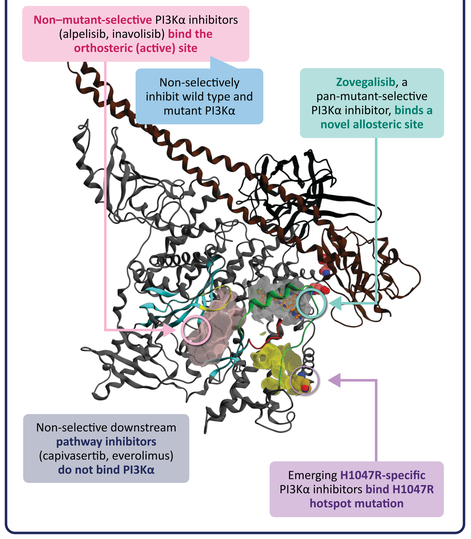
BACKGROUND

- Oncogenic *PIK3CA* mutations constitutively activate PI3Kα and drive approximately 40% of HR+/HER2- BC[1-3]
- Approved therapies for patients with *PIK3CA*-mutated HR+/HER2- ABC are non-mutant-selective PI3K pathway inhibitors, which have shown modest efficacy in combination with ET post-CDK4/6 inhibitor treatment (mPFS of ~5.5-8 months) and are limited by toxicities associated with broad inhibition of the PI3K pathway (hyperglycemia, rash, diarrhea, and stomatitis)[4-10]
- Zovegalisib (RLY-2608) is the first pan-mutant-selective inhibitor designed to overcome these limitations by selectively targeting mutated forms of PI3Kα while sparing wild type
- Zovegalisib binds a novel allosteric pocket of PI3Kα, distinct from approved inhibitors that bind the active orthosteric site, and emerging inhibitors that specifically target only the H1047R hotspot mutation (**Figure 1**)[11]

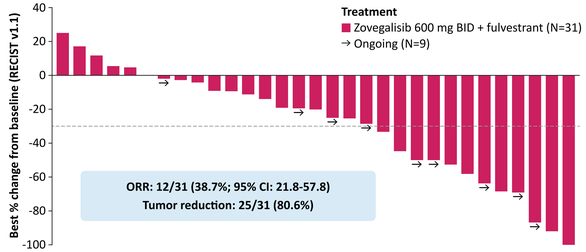
Figure 1: Zovegalisib Is the First Pan-Mutant-Selective PI3Kα Inhibitor



RATIONALE AND STUDY DESIGN

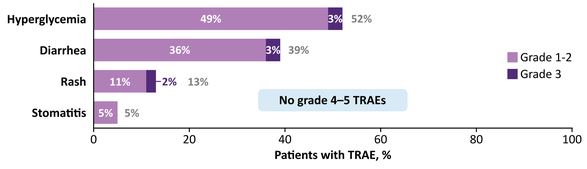
- The first-in-human ReDiscover study of zovegalisib demonstrated encouraging antitumor activity across a range of *PIK3CA* genotypes and a favorable safety profile when given in combination with fulvestrant in patients with *PIK3CA*-mutated HR+/HER2- ABC previously treated with a CDK4/6i[12]
  - 64 patients were dosed at the RP2D of 600 mg zovegalisib BID + fulvestrant
  - mPFS was 10.3 months (95% CI: 7.2-18.4) in the efficacy-evaluable population, excluding *PTEN/AKT* co-alterations (N=52)
  - In patients with measurable disease (N=31), ORR was 38.7% (95% CI: 21.8-57.8) and tumor reduction was observed in 80.6% of patients (**Figure 2**)
  - In the overall safety population (N=64), zovegalisib had a favorable safety profile consistent with wild-type sparing, mutant-selective PI3Kα inhibition and AEs were mostly low grade, reversible events (**Figure 3**)
- Based on these findings, zovegalisib in combination with fulvestrant is being studied in patients with *PIK3CA*-mutated HR+/HER2- ABC following recurrence or progression on or after a CDK4/6 inhibitor in this Phase III ReDiscover-2 study (NCT06982521)

Figure 2: Radiographic Tumor Reduction and Response per RECIST v1.1 (N=31)



Not shown: CR in patient with non-measurable disease.
Data as of 26 March 2025.

Figure 3. Zovegalisib Has a Favorable Safety Profile Consistent With Mutant-Selective PI3Kα Inhibition (N=64)



Data as of 26 March 2025.

STUDY DESIGN AND OBJECTIVES

Figure 4. ReDiscover-2 (RLY-2608-102): Phase III Registrational Trial for Post-CDK4/6 Inhibitor HR+/HER2- Advanced Breast Cancer With a *PIK3CA* Mutation (NCT06982521)[13]

Inclusion Criteria

- *PIK3CA*-mutated HR+/HER2- ABC
- No concomitant *PTEN* or *AKT* tumor alterations
- Measurable disease or evaluable bone-only disease
- Progression in ABC or adjuvant[a] setting on or after:
  - 1-2 lines ET, and
  - 1 line CDK4/6i

Exclusion Criteria

- Prior PI3Ki, AKTi, mTORi, ADC, IO, or investigational CDKi, CDK2i, CDK4i
- Progression on ≤6 mo of ET-based regimen for ABC
- Type 1 diabetes, or type 2 diabetes requiring antihyperglycemic medication
- Fasting plasma glucose ≥140 mg/dL, or HbA1c ≥7.0% (≥53 mmol/mol)

R 1:1 N=540

- Zovegalisib (400 mg BID[b]) + fulvestrant
- Capivasertib (400 mg BID[c] 4 days on, 3 days off) + fulvestrant

Stratification:
- *PIK3CA* mutation type
- Visceral disease
- Geography

- Primary endpoint: PFS (kinase, overall population)
- Key secondary endpoint: OS (kinase, overall population)
- Additional secondary endpoints: ORR, DoR, CBR, QoL

[a] Disease progression during or within 12 mo of completing adjuvant therapy.
[b] Zovegalisib administered with food.
[c] Capivasertib administered with or without food.

ReDiscover-2 is a global, multicenter, open-label, randomized Phase III study comparing the efficacy and safety of zovegalisib + fulvestrant to capivasertib + fulvestrant in adult patients with HR+/HER2- locally advanced or metastatic BC with *PIK3CA* mutation (**Figure 4**)

- Primary objective is to compare the efficacy of zovegalisib + fulvestrant relative to capivasertib + fulvestrant by assessment of PFS within the kinase domain mutation and overall populations by BICR
- Key secondary objective is to compare the efficacy of zovegalisib + fulvestrant relative to capivasertib + fulvestrant by assessment of OS within the kinase domain mutation and overall population
- Additional secondary endpoints include safety and tolerability, ORR, DoR, CBR, and QoL

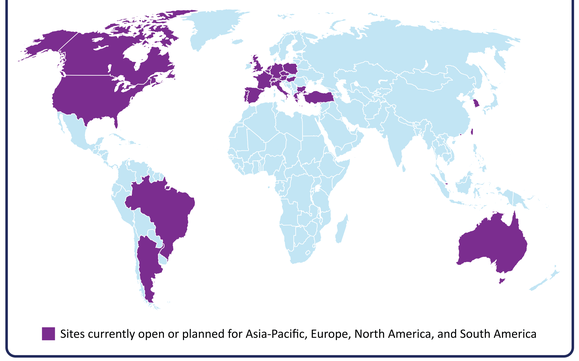
ASSESSMENTS

- Tumor response is assessed in accordance with RECIST v1.1
- The primary endpoint of PFS is assessed by BICR
- Study visits for assessments of safety (including adverse events, vital signs, laboratory tests, and electrocardiograms), pharmacokinetics, and circulating tumor DNA are conducted periodically throughout study treatment

REDISCOVER-2 (RLY-2608-102) STATUS

- This pivotal, registrational Phase III clinical trial plans to open in >250 study centers globally
- Study enrollment began in July 2025 and recruitment is currently ongoing (**Figure 5**)

Figure 5. ReDiscover-2 Sites



Sites currently open or planned for Asia-Pacific, Europe, North America, and South America

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Abbreviations

2L, second-line; ABC, advanced breast cancer; ADC, antibody-drug conjugate; AE, adverse event; AKT, protein kinase B; BC, breast cancer; BICR, blinded independent central review; BID, twice daily; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HbA1c, glycosylated hemoglobin; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor positive; I, inhibitor; IO, immuno-oncology therapy; mo, months; mTOR, mammalian target of rapamycin; NR, not reached; ORR, objective response rate; OS, overall survival; (m)PFS, (median) progression-free survival; PI3Kα, phosphatidylinositol 3-kinase alpha; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin homolog; QoL, quality of life; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TRAE, treatment-related adverse event.

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