Efficacy of mutant-selective PI3Kα inhibitor zovegalisib (RLY-2608) in combination with fulvestrant in patient subset populations, including pts with *PIK3CA*-mutant HR+/HER2- advanced breast cancer (BC) pre-treated with fulvestrant or other SERD

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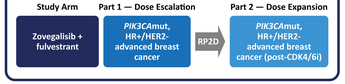
INTRODUCTION

- Oncogenic *PIK3CA* mutations drive approximately 40% of HR+/HER2- breast cancer (BC) and define a validated target for therapeutic inhibition in this setting[1,2]
- Approved targeted therapies for this patient population yield modest efficacy in combination with endocrine therapy (ET) due to dose-limiting toxicities associated with broad, nonselective inhibition of the PI3K pathway such as hyperglycemia, rash, diarrhea, and stomatitis[3-9]
- Zovegalisib (RLY-2608) is the first oral, pan-mutant-selective, allosteric α-selective PI3K inhibitor (PI3Kαi) designed to overcome these limitations by selectively targeting a broad range of mutated forms of the PI3Kα enzyme while sparing wild-type[10]
- The FIH ReDiscover (NCT05216432) study investigated zovegalisib + fulvestrant (F) at the recommended Phase 2 dose (RP2D) in patients with *PIK3CA*-mutated HR+/HER2- advanced BC previously treated with CDK4/6i and ET (**Figure 1**)[11]
- Here, we report subgroup efficacy analyses of this arm according to baseline characteristics, including prior selective estrogen receptor degrader (SERD) treatment and *ESR1* mutation status[11-14]

Figure 1. ReDiscover Study Design



METHODS

- As of 15 October 2025, 64 adult patients with *PIK3CA*-mutated HR+/HER2-advanced BC previously treated with CDK4/6i and ET received the RP2D of zovegalisib (600 mg BID fasted) + standard-dose F
- Key inclusion criteria included:
  - HR+/HER2- unresectable or metastatic BC not amenable to curative therapy
  - ≥1 oncogenic *PIK3CA* mutation(s) in blood and/or tumor per local assessment
  - Evaluable disease per RECIST v1.1
  - No prior PI3Kα, AKT, or mTOR inhibitors
  - ≥1 CDK4/6i in the adjuvant and/or metastatic setting
  - ≥1 anti-estrogen therapy
  - ≤1 line of chemotherapy in the metastatic setting
- Key objectives were investigator-assessed efficacy per RECIST v1.1 and adverse events (AEs) per CTCAE v5.0
  - Objective response rate (ORR) is defined as the rate of any confirmed complete or partial response (CR or PR)
  - Duration of response (DOR) is calculated among responders as time from CR or PR until time of first documented progressive disease (PD) per RECIST v1.1 or death by any cause
  - Progression-free survival (PFS) is defined as the time from date of first dose to the date of progression per RECIST v1.1 or death by any cause in the absence of progression
- Baseline demographics are presented for 64 patients who received the RP2D
- Tumor response in patients with measurable disease (N=31) and PFS in patients with evaluable disease (N=52), without detectable *PTEN/AKT* co-alterations, were assessed according to baseline characteristics including prior treatment history (prior SERD or no prior SERD) and presence of *ESR1* mutation
- *PIK3CA* and *ESR1* ctDNA were assessed at baseline and at C2D1 of study treatment as a pharmacodynamic marker of biologic activity

RESULTS

Summary

- Efficacy was evaluated in patients without detectable *PTEN/AKT* co-alterations
- In 31 patients with measurable disease, ORR was 38.7% (95% CI: 21.8%-57.8%); responders achieved a durable median DOR of 12.9 months (95% CI: 4.4-NR; **Figure 3**)
- Among 52 patients with evaluable disease
  - Overall mPFS (**Figure 4**) was 10.3 months (95% CI: 7.2-16.5)
  - mPFS was 8.8 months (95% CI: 3.0-NR) in patients with detectable *ESR1* mutations and 11.0 months (95% CI: 6.2-22.0) for those without (**Figure 5**)
  - mPFS in patients who received a prior SERD was 11.4 months (95% CI: 5.6-NR) and 9.2 months (95% CI: 5.8-22.0) for those naïve to SERDs (**Figure 5**)
  - mPFS was 11.4 months (95% CI: 7.3-22.0) in patients receiving zovegalisib as 2L treatment and 9.2 months (95% CI: 5.4-NR) for ≥3L treatment (**Figure 6**)
- At longer follow up, the safety profile of zovegalisib was consistent with previous reports[13,14]
  - AEs associated with targeting PI3K were mostly low grade and reversible
  - Relative dose intensity was high with a median of 90%
  - There were no Grade 4 or 5 TRAEs

Table 1. Patient Demographics and Baseline Characteristics

	Zovegalisib + Fulvestrant
	600 mg BID (RP2D, N=64)
Median age (range), years	59.0 (34-80)
ECOG 0/1, n (%)	38 (59.4)/26 (40.6)
BMI ≥30 or HbA1c >5.7%, n (%)	22 (34.4)
Measurable disease, n (%)	42 (65.6)
Patients with visceral metastases, n (%)*	40 (62.5)
Prior lines of therapy in advanced setting, n (%)	
1	35 (54.7)
2+	29 (45.3)
Prior therapies in advanced setting, n (%)	
CDK4/6i†	64 (100.0)
SERD (fulvestrant or oral SERD)	33 (51.6)
Chemo/ADC	17 (26.6)
***ESR1* mutation, n (%)‡**	18 (28.6)

* Visceral metastatic sites include brain, lung, liver, pleural, peritoneal involvement. † Three patients received prior CDK4/6i in the adjuvant setting which is allowed per protocol. ‡ Percentage was based on patients with evaluable ctDNA data at baseline.

Still on treatment: 13 (20%)
Discontinued: 51 (80%)
- Progressive disease: 45 (70%)
- Patient withdrew consent: 3 (5%)
- Due to AE: 2 (3%)
- Physician decision: 1 (2%)

Figure 2. Rapid Decline in *PIK3CA* and *ESR1* ctDNA at RP2D (600 mg BID) Across Mutations

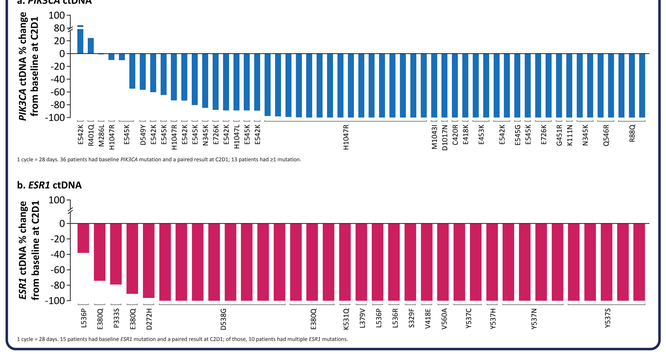
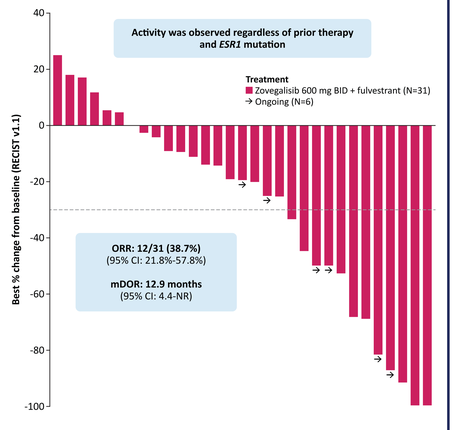


Figure 3. Radiographic Tumor Reduction and Response per RECIST v1.1 (N=31)



mDOR includes CR in patient with non-measurable disease who is not shown. Prior SERD includes prior treatment in the advanced setting with fulvestrant (N=11), an oral SERD (N=1), or both (N=4).

Figure 4. Progression-Free Survival (N=52)

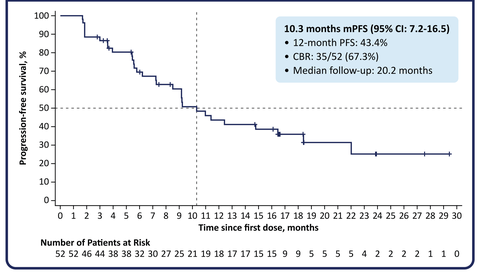
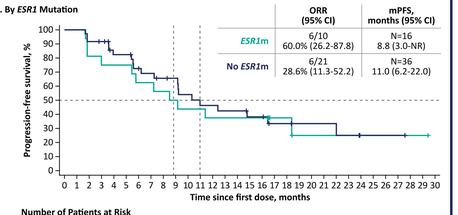
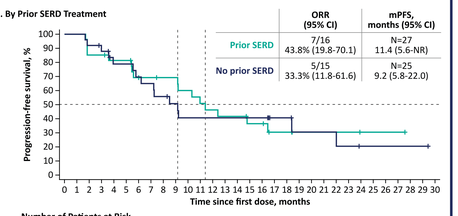


Figure 5. Progression-Free Survival by *ESR1*m and Prior SERD (N=52)

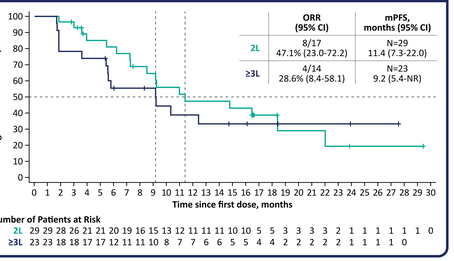


One patient had unknown *ESR1* mutation at baseline and was included within the group without *ESR1*m.



Prior SERD includes prior treatment in the advanced setting with fulvestrant (N=21), an oral SERD (N=2), or both (N=4).

Figure 6. Progression-Free Survival by Line of Therapy (N=52)



CONCLUSIONS

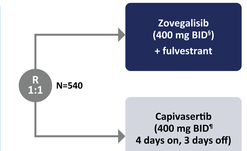
- Zovegalisib (RLY-2608) at the RP2D (600 mg BID) + F demonstrates promising efficacy in patients with *PIK3CA*-mutated HR+/HER2- advanced BC who have progressed on CDK4/6i including those with *ESR1*m or prior exposure to SERD
- These findings underscore the importance of mutated PI3Kα as a key driver of HR+/HER2– BC and highlight the need for effective therapies that selectively inhibit oncogenic PI3Kα in combination with anti-estrogen approaches
- Encouraging mPFS was observed particularly in patients treated in the 2L setting, with patients treated in the ≥3L setting also experiencing durable benefit
- These FIH ReDiscover data highlight the activity of zovegalisib + F irrespective of *ESR1*m status or prior SERD exposure and support the ongoing investigation of zovegalisib in ReDiscover-2, a pivotal Phase III global study of zovegalisib + F vs capivasertib + F in patients previously treated with CDK4/6i and ET, which is currently open for enrollment (NCT06982521; **Figure 7**)

Figure 7. ReDiscover-2 (RLY-2608-102): Phase III Registrational Trial for Post-CDK4/6 Inhibitor HR+/HER2– Advanced Breast Cancer With a *PIK3CA* Mutation (NCT06982521)[*,†]

Key Eligibility Criteria:

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[‡] 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 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)



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

* Relay Therapeutics, data on file. † https://clinicaltrials.gov/study/NCT06982521. ‡ Disease progression during or within 12 months of completing adjuvant therapy. § Zovegalisib administered with food. ¶ Capivasertib administered with or without food.

References

1. Vasan N, Cantley LC. *Nat Rev Clin Oncol.* 2022;19(7):471-485.
2. Kobold DC, et al. *Nature.* 2012;490(7418):61-70.
3. Piqray [Prescribing information]. Novartis Pharmaceuticals Corporation; 2025.
4. Itovebi [Prescribing information]. Genentech, Inc.; 2025.
5. Truqap [Prescribing information]. AstraZeneca Pharmaceuticals LP; 2025.
6. Rugo HS, et al. *Ann Oncol.* 2020;31(8):1001-1010.
7. Turner NC, et al. *N Engl J Med.* 2023;388(22):2058-2070.
8. Chia S, et al. *J Clin Oncol.* 2023;41(suppl 16):TPS1078.
9. Juric D, et al. *Cancer Res.* 2022;82(suppl 4):PS-17-05.
10. Varkaris A, et al. *Cancer Discov.* 2024;14(2):240-257.
11. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05216432. Accessed November 2, 2025.
12. Saura C, et al. *J Clin Oncol.* 2024;42(suppl 16):TPS1128.
13. Saura C, et al. *Clin Cancer Res.* 2025;31(suppl 12):PS7-01.
14. Sammons SL, et al. *J Clin Oncol.* 2025;43(suppl 16):1086.

Abbreviations

2L, second-line; 3L third-line; ABC, advanced breast cancer; ADC, antibody-drug conjugate; AE, adverse event; AKT, protein kinase B; BC, breast cancer; BID, twice per day; BMI, body mass index; BOR, best overall response; C2D1, cycle 2 day 1; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; ctDNA, circulating tumor DNA; (m)DOR, (median) duration of response; ECOG, Eastern Cooperative Oncology Group; ER+, estrogen receptor alpha gene; ET, endocrine therapy; F, fulvestrant; FIH, first in human; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; I, inhibitor; IO, immuno-oncology therapy; KM, Kaplan-Meier; MedDRA, Medical Dictionary for Regulatory Activities; mTOR, mammalian target of rapamycin; ORR, objective response rate; OS, overall survival; PD, progressive disease; (m)PFS, (median) progression-free survival; PI3K, phosphoinositide 3-kinase; PI3Kα, phosphatidylinositol 3-kinase alpha; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PR, partial response; PT, preferred term; PTEN, phosphatase and tensin homolog; QoL, quality of life; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose; SD, stable disease; SERD, selective estrogen receptor degrader; TRAE, treatment-related adverse event.

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