Updated efficacy of mutant-selective PI3Kα inhibitor RLY-2608 in combination with fulvestrant in patients with *PIK3CA*-mutant HR+/HER2- advanced breast cancer: ReDiscover trial

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**research conducted while at this institution*

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INTRODUCTION

- Oncogenic *PIK3CA* mutations constitutively activate PI3Kα and drive ~40% of cases of HR+/HER2– BC[1,2]
- Approved 2L therapies (alpelisib, inavolisib, capivasertib) are nonselective PI3K pathway inhibitors with off-target toxicity that limits their tolerability (hyperglycemia, rash, diarrhea, stomatitis) and efficacy (mPFS of ~5.5-8 months with endocrine therapy)[3-9]
- RLY-2608 is the first pan-mutant-selective inhibitor designed to overcome these limitations
- RLY-2608 acts via binding a novel allosteric pocket, distinct from approved orthosteric inhibitors and emerging inhibitors that target only H1047R (Figure 1)[10]
- ReDiscover is a multi-arm, open-label, FIH study designed to evaluate RLY-2608 in patients with advanced solid tumors who have *PIK3CA* mutations present in blood and/or tumor per local assessment (Figure 2)[11]
- Here we present updated efficacy and safety of RLY-2608 + fulvestrant in patients with *PIK3CA*-mutant, HR+/HER2- advanced breast cancer post-CDK4/6i, treated at the recommended dose[11-13]

Figure 1. RLY-2608 Is the First Pan-Mutant-Selective PI3Kα Inhibitor

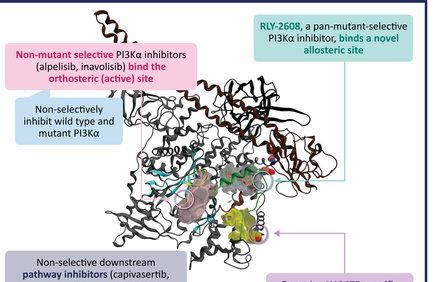

Figure 2. ReDiscover Study Design

METHODS

- Key inclusion criteria for the RLY-2608 + fulvestrant arm included[11]:
  - HR+/HER2- unresectable or metastatic breast cancer not amenable to curative therapy
  - ≥1 oncogenic *PIK3CA* mutation(s) in blood and/or tumor per local assessment
  - Evaluable disease per RECIST 1.1
  - 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
  - HbA1c <7%
- Key endpoints included determination of MTD and RP2D, safety and tolerability, PK/PD, and preliminary efficacy per RECIST 1.1
- 118 patients received RLY-2608 (100–1000 mg BID under fasting conditions) + fulvestrant in 28-day cycles
- Safety per CTCAE v.5 is presented for 118 patients across all doses with 64 patients receiving the RP2D (Tables 1 and 2)
- Efficacy (N=52) and ctDNA clearance are presented for patients without baseline *PTEN or AKT1 E17K* co-mutation who received the RP2D (Figure 3)

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RESULTS

Table 1. Patient Demographics and Baseline Characteristics

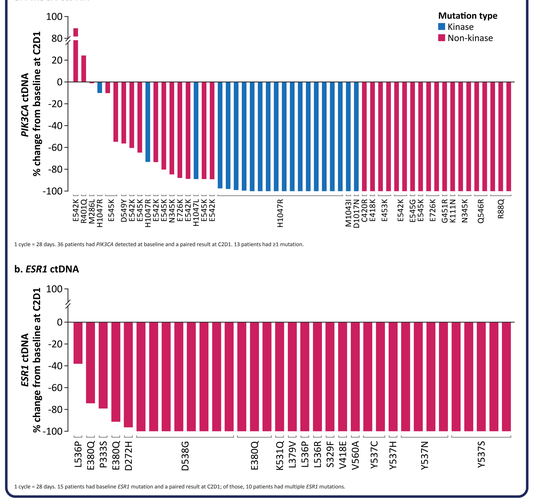
	RLY-2608 + fulvestrant	
	All patients (N=118)	600 mg BID (RP2D, N=64)
Median age (range), years	59.0 (34-85)	59.0 (34-80)
ECOG, n (%)		
0	69 (58.5)	38 (59.4)
1	49 (41.5)	26 (40.6)
Local *PIK3CA* baseline results		
Kinase mutation, n (%)	57 (48.3)	31 (48.4)
Non-kinase mutations, n (%)	61 (51.7)	33 (51.6)
BMI ≥30 or HbA1c ≥5.7%, n (%)	44 (37.3)	22 (34.4)
Measurable disease, n (%)	83 (70.3)	42 (65.6)
Patients with visceral metastases, n (%)*	75 (63.6)	38 (59.4)
Prior lines of therapy in advanced setting, n (%)		
1	59 (50.0)	36 (56.3)
2+	59 (50.0)	28 (43.8)
Prior therapies in advanced setting, n (%)		
CDK4/6i†	118 (100.0)	64 (100.0)
Fulvestrant or novel SERD	65 (55.1)	33 (51.6)
Chemo / ADC	33 (28.0)	18 (28.1)
***ESR1* mutation (central read),‡ n (%)**	40 (35.4)	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.

600 mg BID cohort (N=64)
Still on treatment: 18 (28.1%)
Discontinued: 46 (71.9%)

- Progressive disease: 39 (60.9%)
- Patient withdrew consent: 3 (4.7%)
- Due to AE: 2 (3.1%)
- Physician decision: 2 (3.1%)

Figure 3. Rapid Decline in *PIK3CA* and *ESR1* ctDNA at RP2D (600 mg BID) Across Mutations



1 cycle = 28 days. 36 patients had *PIK3CA* detected at baseline and a paired result at C2D1. 13 patients had ≥1 mutation.

1 cycle = 28 days. 15 patients had baseline *ESR1* mutation and a paired result at C2D1; of those, 10 patients had multiple *ESR1* mutations.

Table 2. RLY-2608 Has a Favorable Safety Profile Consistent With Mutant-Selective PI3Kα Inhibition

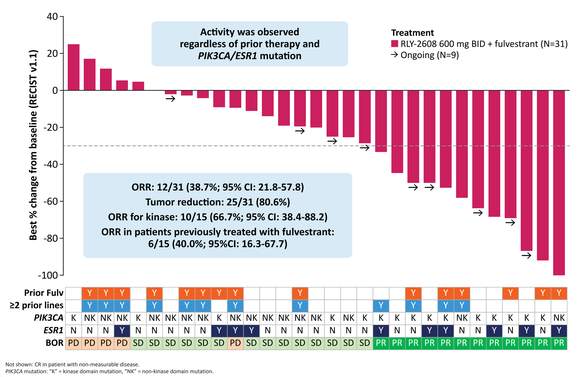
		All patients (N=118)		600 mg BID (RP2D, N=64)	
		All grade	Grade 3	All grade	Grade 3†
Any TRAE		**94.1%**	**27.1%**	**96.9%**	**35.9%**
TRAEs ≥15% of 600 mg BID	Hyperglycemia*	44.1%	2.5%	51.6%	3.1%
	Nausea	42.4%	0.8%	50.0%	1.6%
	Fatigue*	44.9%	8.5%	42.2%	9.4%
	Creatinine increased*	39.8%	1.7%	39.1%	3.1%
	Diarrhea	33.1%	1.7%	39.1%	3.1%
	Decreased appetite	18.6%	0%	23.4%	0%
	Headache	16.1%	0.8%	21.9%	0%
	Hypokalemia*	16.9%	4.2%	18.8%	4.7%
	Dysgeusia	15.3%	0%	15.6%	0%
	Vomiting	13.6%	0%	15.6%	0%
Other select TRAEs	Rash*	12.7%	0.8%	12.5%	1.6%
	Stomatitis	3.4%	0.8%	4.7%	0%

* Hyperglycemia includes the MedDRA v26.0 preferred terms (PTs): hyperglycemia, blood glucose increased, diabetes mellitus, glucose tolerance impaired. Fatigue includes the PTs: fatigue, asthenia, malaise. Creatinine increased includes the PTs: blood creatinine increased, hypercreatininemia. Hypokalemia includes the PTs: hypokalemia and blood potassium decreased. Rash includes the PTs: rash, rash macular, rash maculo-papular.
† No Grade 4 or Grade 5 TRAEs observed.

At RP2D:

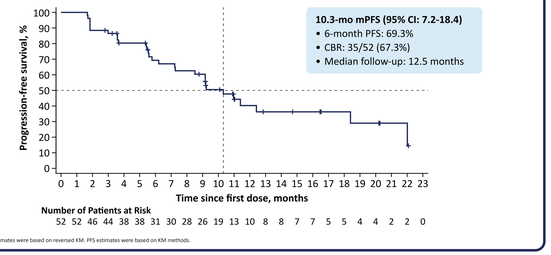
- Relative dose intensity was high with a median of 92%
- Discontinuation rate was low at 2%
- AEs were mostly low-grade, reversible events
- Hyperglycemia was mostly Grade 1 (31%), with no intervention needed

Figure 4. Radiographic Tumor Reduction and Response per RECIST v1.1 (N=31)



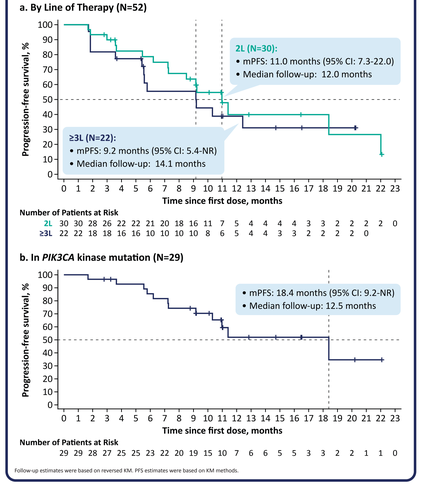
Not shown: CR in patient with non-measurable disease.
PIK3CA mutation: "K" = kinase domain mutation, "NK" = non-kinase domain mutation.

Figure 5. Median Progression-Free Survival (N=52)



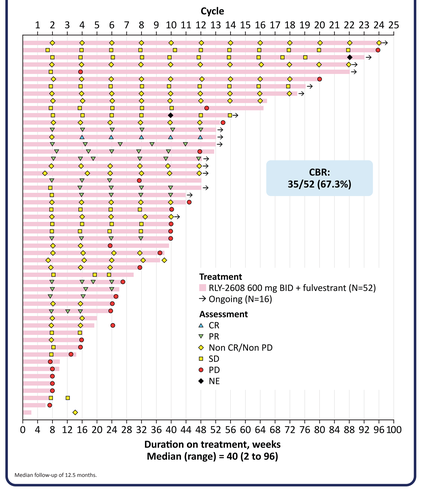
Follow-up estimates were based on reversed KM. PFS estimates were based on KM methods.

Figure 6. Median Progression-Free Survival by Subgroups



Follow-up estimates were based on reversed KM. PFS estimates were based on KM methods.

Figure 7. Durable Efficacy Across *PIK3CA* Mutations (N=52)



Median follow-up of 12.5 months.

CONCLUSIONS

- The ReDiscover study validates RLY-2608 as the first allosteric, pan-mutant and isoform-selective PI3Kα inhibitor
- Across *PIK3CA* genotypes without concurrent *PTEN* or *AKT1 E17K* co-mutations, RLY-2608 at the recommended dose + fulvestrant demonstrates durable efficacy in patients with advanced HR+/HER2- breast cancer, confirming potent, pan-mutant targeting
  - Tumor reduction was observed in 80.6% of patients, and ORR was 38.7% across *PIK3CA* genotypes (Figure 4), including rapid clearance of *PIK3CA / ESR1* mutations
    - ORR of 66.7% observed in patients with kinase domain mutations (Figure 4)
  - Encouraging PFS observed in patients with *PIK3CA*-mutated HR+/HER2- advanced breast cancer previously treated with CDK4/6i
    - mPFS of 10.3 months (95% CI: 7.2-18.4) across mutation types (Figure 5)
    - mPFS of 11.0 months (95% CI: 7.3-22.0) in patients receiving RLY-2608 as 2L treatment and 18.4 months (95% CI: 9.2-NR) in all kinase patients (Figure 6)
- RLY-2608 has a favorable safety profile that minimizes AEs
- The promising efficacy and safety data observed in this FIH study suggest that RLY-2608 has broad therapeutic potential in *PIK3CA*-mutant, HR+/HER2- breast cancer
- A pivotal phase 3 study will open July 2025: RLY-2608 + fulvestrant vs capivasertib + fulvestrant in patients previously treated with CDK4/6i and endocrine therapy (Figure 8)

Figure 8. ReDiscover 2 – RLY-2608 Pivotal Phase 3 Study Schema in *PIK3CA*-Mutated HR+/HER2- Advanced Breast Cancer Post-CDK4/6i (NCT06982521)

Target population: Post-CDK4/6i; estrogen sensitive

Locally advanced/metastatic *PIK3CA*mut breast cancer

Inclusion Criteria
- ECOG 0-1
- *PIK3CA* mutation*
- Measurable disease per RECIST v1.1 or evaluable bone-only disease
- >10% IHC estrogen receptor positivity
- Progression after 1 prior CDK4/6i

Exclusion Criteria
- Prior treatment with PI3Ki, AKTi, mTORi; ADC
- Progression after ≤6 mo on ET-based regimen for locally advanced/metastatic breast cancer
- Type 1 or type 2 diabetes requiring antihyperglycemic medication, or HbA1c ≥7%
- Concurrent *PTEN* or *AKT E17K* co-mutations

Stratification Factors:
- *PIK3CA* genotype
- Visceral disease
- Geography

N=540 1:1
- RLY-2608† + fulvestrant
- Capivasertib‡ + fulvestrant

Endpoints:
- Primary endpoints: PFS in the kinase and overall populations
- Key secondary endpoints: OS in the kinase and overall populations
- Secondary endpoints: ORR, DOR, CBR, safety, PROs

* Kinase: H1047R, H1047L, H1047Y, M1043V, M1043I, and G1049R; non-kinase: E542K, E545A, E545D, E545G, E545K, E545Q, E545K, E726K, Q546E, Q546K, Q546P, R88Q, N345K, and C420R.
† RLY-2608 400 mg BID administered with food provides exposures similar to 600 mg BID dosed fasted, informed by results of a separate food effect study.

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Abbreviations

2L, second line; ADC, antibody-drug conjugate; AE, adverse event; AKT1, serine/threonine protein kinase 1; AKTi, AKT inhibitor; BID, twice per day; BMI, body mass index; BOR, best overall response; C2D1, cycle 2 day 1; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; Chemo, chemotherapy; CR, complete response; ctDNA, circulating tumor DNA; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; ESR1, estrogen receptor 1 gene; ET, endocrine therapy; FH, first in human; Fulv, fulvestrant; HbA1c, hemoglobin A1c; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; IHC, immunohistochemistry; KM, Kaplan-Meier; MedDRA, Medical Dictionary for Regulatory Activities; MTD, maximum tolerated dose; mTOR, mechanistic target of rapamycin; mut, mutation; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; (m)PFS, (median) Progression-Free Survival; PI3Kα, phosphatidylinositol 3-kinase alpha; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PK, pharmacokinetics; PR, partial response; PRO, patient-reported outcome; RECIST, 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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