Efficacy of RLY-2608, a mutant-selective PI3Kα inhibitor in patients with *PIK3CA*-mutant HR+/HER2– advanced breast cancer: ReDiscover trial

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INTRODUCTION

- Oncogenic *PIK3CA* mutations constitutively activate PI3Kα and drive ~40% of cases of HR+/HER2– BC[1,2]
- Approved therapies (alpelisib, inavolisib, everolimus, capivasertib) are non-selective 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 selectively targets mutant PI3Kα, via binding to a novel 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 that have *PIK3CA* mutations present in blood and/or tumor per local assessment (**Figure 2**)[11]
- Previously we demonstrated robust and continuous target coverage and promising initial efficacy in phase 1 dose escalation[12]
- Here we present the efficacy and safety of RLY-2608 + fulvestrant in patients with *PIK3CA*-mutant, HR+/HER2– BC treated at the RP2D
- Monotherapy and triplet (RLY-2608 + fulvestrant + ribociclib; RLY-2608 + fulvestrant + atirmociclib) arms are ongoing and will be presented separately

Figure 1. RLY-2608 is the first pan-mutant-selective PI3Kα inhibitor

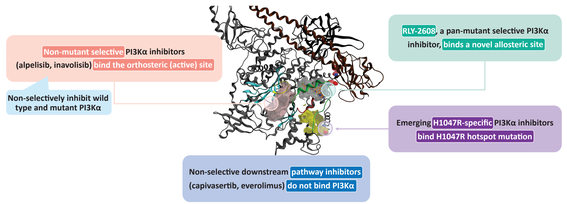
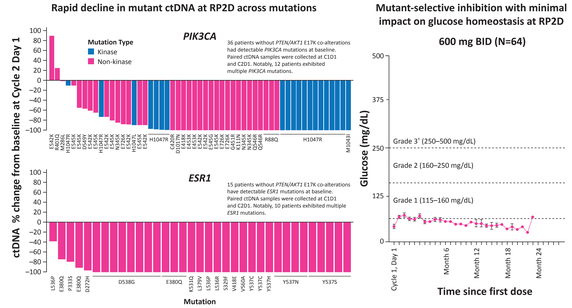


Figure 2. ReDiscover study design

METHODS

- 118 patients with advanced *PIK3CA*-mutant, HR+/HER2– BC received doublet therapy with RLY-2608 (100–1000 mg BID under fasting conditions) + fulvestrant in 28-day cycles: 64 patients received the RP2D across dose-escalation and -expansion phases (**Table 1**)
- Efficacy is presented for 52 patients without baseline *PTEN* or *AKT1* E17K co-mutation who received the RP2D
- Key endpoints included determination of MTD and RP2D, safety and tolerability, PK/PD, and preliminary efficacy per RECIST 1.1
- Key inclusion criteria for the RLY-2608 doublet therapy arm included[11]:
  - Histologically or cytologically confirmed HR+/HER2– unresectable or metastatic BC not amenable to curative therapy
  - One or more documented primary oncogenic *PIK3CA* kinase or non-kinase mutation(s) in blood and/or tumor per local assessment
  - Evaluable disease per RECIST 1.1
  - No prior PI3K/mTOR inhibitor
  - ≥1 CDK4/6i in either the adjuvant and/or metastatic setting
  - ≥1 anti-estrogen therapy
  - ≤1 line of chemotherapy in the metastatic setting

Figure 3. Potent and mutant-selective target inhibition at the recommended dose



*Per CTCAE version 4.0.

RESULTS

Table 1. Patient demographics and baseline characteristics

	RLY-2608 + Fulvestrant	
	All Patients (N=118)	600 mg BID (RP2D, N=64)
Age, Median (Range), Years	59.0 (34, 85)	59.0 (34, 80)
ECOG, 0 / 1, n (%)	69 (58.5) / 49 (41.5)	38 (59.4) / 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		
1, n (%)	62 (52.5)	38 (59.4)
2+, n (%)	56 (47.5)	26 (40.6)
Prior Therapies in Advanced Setting		
CDK4/6 inhibitor, n (%)†	118 (100.0)	64 (100.0)
Fulvestrant or Novel SERD, n (%)	66 (55.9)	33 (51.6)
Chemo / ADC, n (%)	30 (25.4)	16 (25.0)
ESR1 Mutation (Central Read), n (%)‡	40 (35.4)	18 (28.6)
PTEN or *AKT1* E17K Mutation, n (%)	25 (21.2)	12 (18.8)

600 mg BID cohort (N=64)
Still on treatment: 28 (43.8%)
Discontinued: 36 (56.3%)
- Progressive disease: 30 (46.9%)
- Patient withdrew consent: 3 (4.7%)
- Due to adverse event: 2 (3.1%)
- Physician decision: 1 (1.6%)

*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.

Table 2. RLY-2608 has a favorable safety profile consistent with mutant-selective PI3Kα inhibition

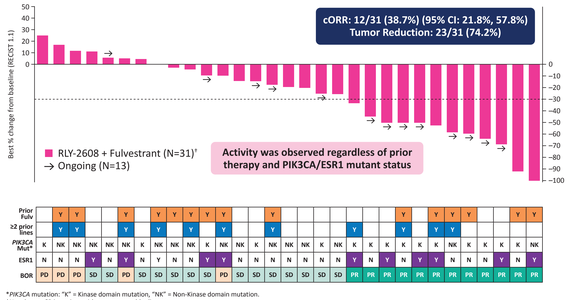
		All Patients (N=118)		600mg BID (RP2D, N=64)	
		All Grades	Grade 3	All Grades	Grade 3
Any TRAE, %		92.4	25.4	93.8	31.3
TRAEs ≥15% of 600 mg BID	Hyperglycemia*	42.4	2.5	46.9	3.1
	Nausea	41.5	0.8	50.0	1.6
	Fatigue*	40.7	8.5	35.9	9.4
	Creatinine Increased	34.7	0.8	34.4	1.6
	Diarrhea	30.5	1.7	35.9	3.1
	Decreased Appetite	16.9	0	20.3	0
	Headache	15.3	0.8	20.3	0
	Hypokalemia*	15.3	1.7	17.2	1.6
	Vomiting	12.7	0	15.6	0
Other select TRAEs	Rash*	11.9	0.8	10.9	1.6
	Stomatitis	3.4	0.8	4.7	0
No Grade 4–5 TRAEs					

27% Grade 1 hyperglycemia (no intervention required)

No Grade 4/5 TRAEs observed

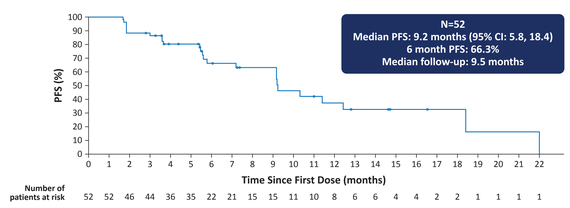
*Hyperglycemia includes the MedDRA v26.0 Preferred Terms (PT): Hyperglycemia, Blood Glucose Increased, Glucose Tolerance Impaired; Fatigue includes the PTs: Fatigue, Asthenia; Hypokalemia includes the PTs: Hypokalemia and blood potassium decreased; Rash includes the PTs: Rash, Rash Macular, Rash Maculo-Papular.

Figure 4. Radiographic tumor reduction and response per RECIST 1.1



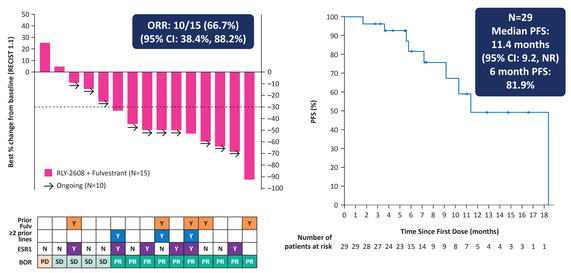
*PIK3CA mutation: "K" = Kinase domain mutation, "NK" = Non-Kinase domain mutation.
†Not shown: CR in patient with non-measurable disease.

Figure 5. Encouraging mPFS across *PIK3CA* genotypes



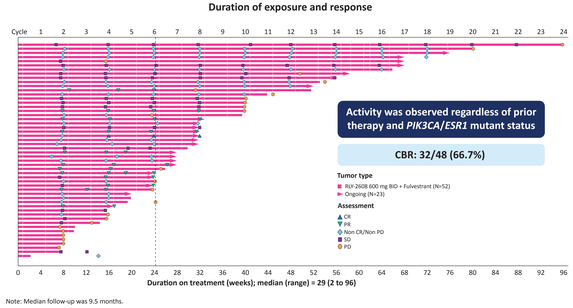
Note: Follow-up estimated based on reverse KM. PFS estimates based on KM methods.

Figure 6. Radiographic response and PFS in patients with *PIK3CA* kinase mutations



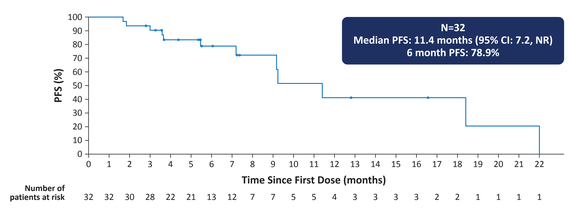
Note: Not shown: CR in patient with non-measurable disease.

Figure 7. Durable efficacy across *PIK3CA* mutations



Note: Median follow-up was 9.5 months.

Figure 8. PFS in patients treated with RLY-2608 + fulvestrant as 2L therapy



Note: Follow-up estimated based on reverse KM. PFS estimates based on KM methods.

CONCLUSIONS

- The ReDiscover study validates RLY-2608 as the first allosteric, pan-mutant and isoform-selective PI3Kα inhibitor
- Durable initial efficacy was demonstrated at the recommended dose (600 mg BID) across *PIK3CA* genotypes in patients with advanced HR+/HER2– breast cancer, confirming potent, pan-mutant targeting
  - Tumor reduction observed in 74% of patients and ORR was 39% across *PIK3CA* genotypes
    - An ORR of 67% observed in patients with kinase domain mutations
  - Highest-ever PFS observed in patients with *PIK3CA*-mutated HR+/HER2– advanced BC previously treated with CDK4/6i
    - Median PFS 9.2 months (95% CI: 5.8–18.4) across mutation types
    - Median PFS 11.4 months (95% CI: 7.2–NR) in patients receiving RLY-2608 as 2L treatment
    - Forty-four percent of patients (23/52) remain ongoing with SD or response (one treated beyond progression)
- PK/PD and differentiated safety profile confirm pan-mutant selectivity
  - Target inhibition was robust and continuous
  - The favorable safety profile eliminates or minimizes AEs commonly seen with non-selective pathway inhibitors (alpelisib, inavolisib, capivasertib, and everolimus)
- 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 initiate in 2025: RLY-2608 + fulvestrant vs capivasertib + fulvestrant in patients with HR+/HER2– breast cancer previously treated with CDK4/6i and endocrine therapy

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Abbreviations

2L, second-line; ADC, antibody-drug conjugate; AE, adverse event; BC, breast cancer; BID, twice per day; BMI, body mass index; C2D1, cycle 2 day 1; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CR, complete response; ctDNA, circulating tumor DNA; DCR, disease control rate; DoR, duration of response; ESR1, estrogen receptor alpha gene; FIH, first-in-human; HbA1c, hemoglobin A1c; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; KM, Kaplan Meier; MedDRA, Medical Dictionary for Regulatory Activities; MTD, maximum tolerated dose; mut, mutations; 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; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended Phase 2 dose; SD, stable disease; SERD, selective estrogen receptor degrader; SOC, standard-of-care; TRAE, treatment-related adverse event.

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