

Updated efficacy of mutant-selective PI3K α inhibitor RLY-2608 in combination with fulvestrant in patients with *PIK3CA*-mutant HR+/HER2- advanced breast cancer: ReDiscover trial

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INTRODUCTION

- Oncogenic *PIK3CA* mutations constitutively activate PI3K α 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)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 PI3K α Inhibitor

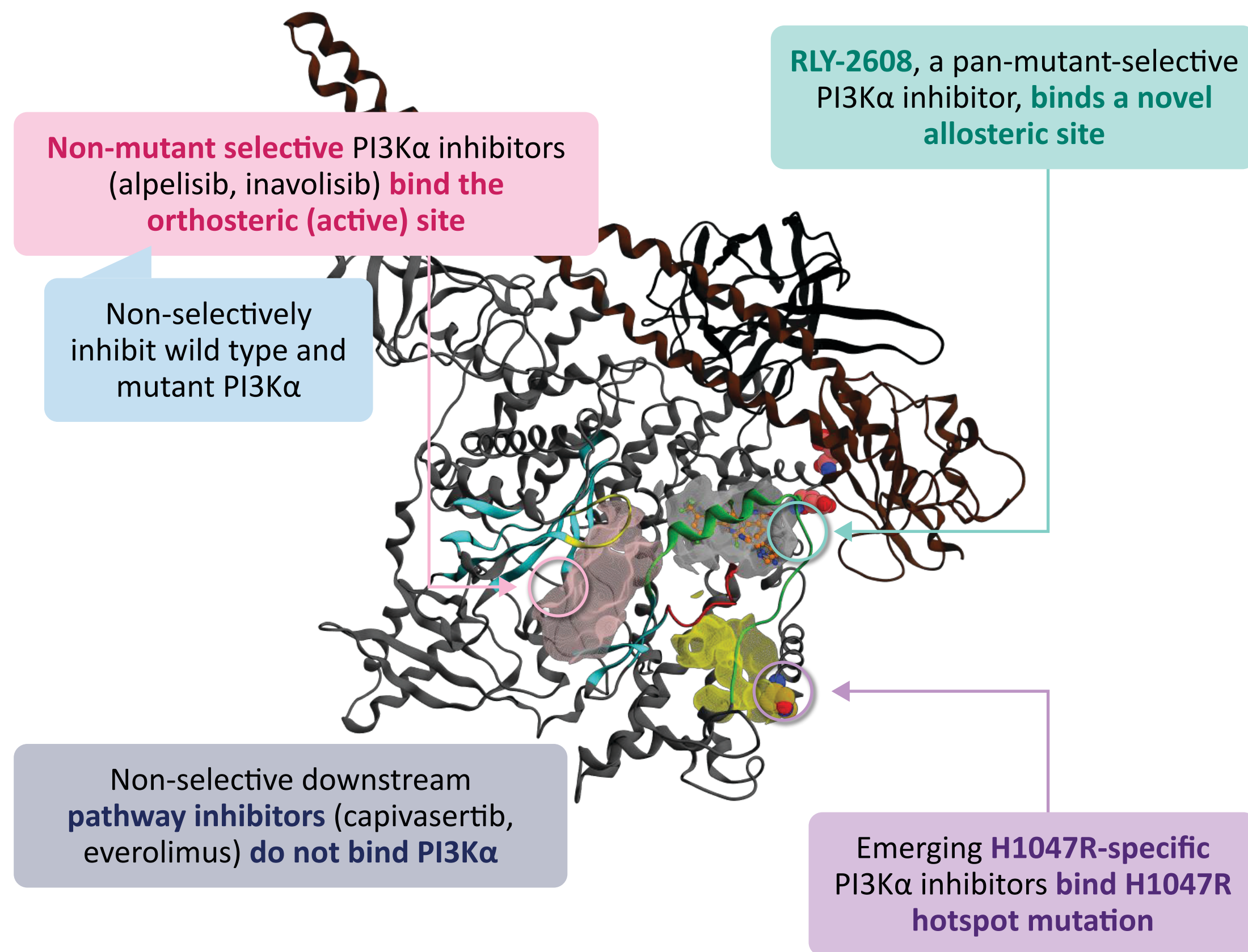
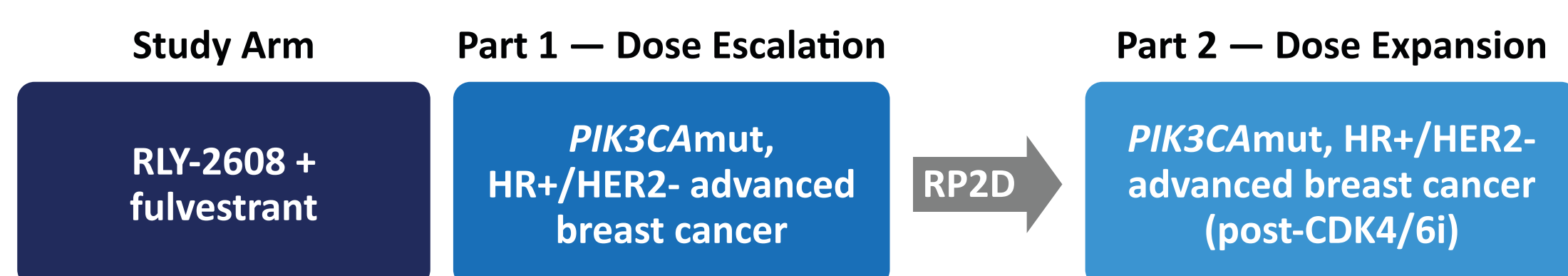


Figure 2. ReDiscover Study Design



METHODS

- Key inclusion criteria for the RLY-2608 + fulvestrant arm included²¹:
 - 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)

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 <i>PIK3CA</i> 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 (%)		
CDK4/6 ⁱ	118 (100.0)	64 (100.0)
Fulvestrant or novel SERD	65 (55.1)	33 (51.6)
Chemo / ADC	33 (28.0)	18 (28.1)
<i>ESR1</i> mutation (central read), ^a n (%)	40 (35.4)	18 (28.6)

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

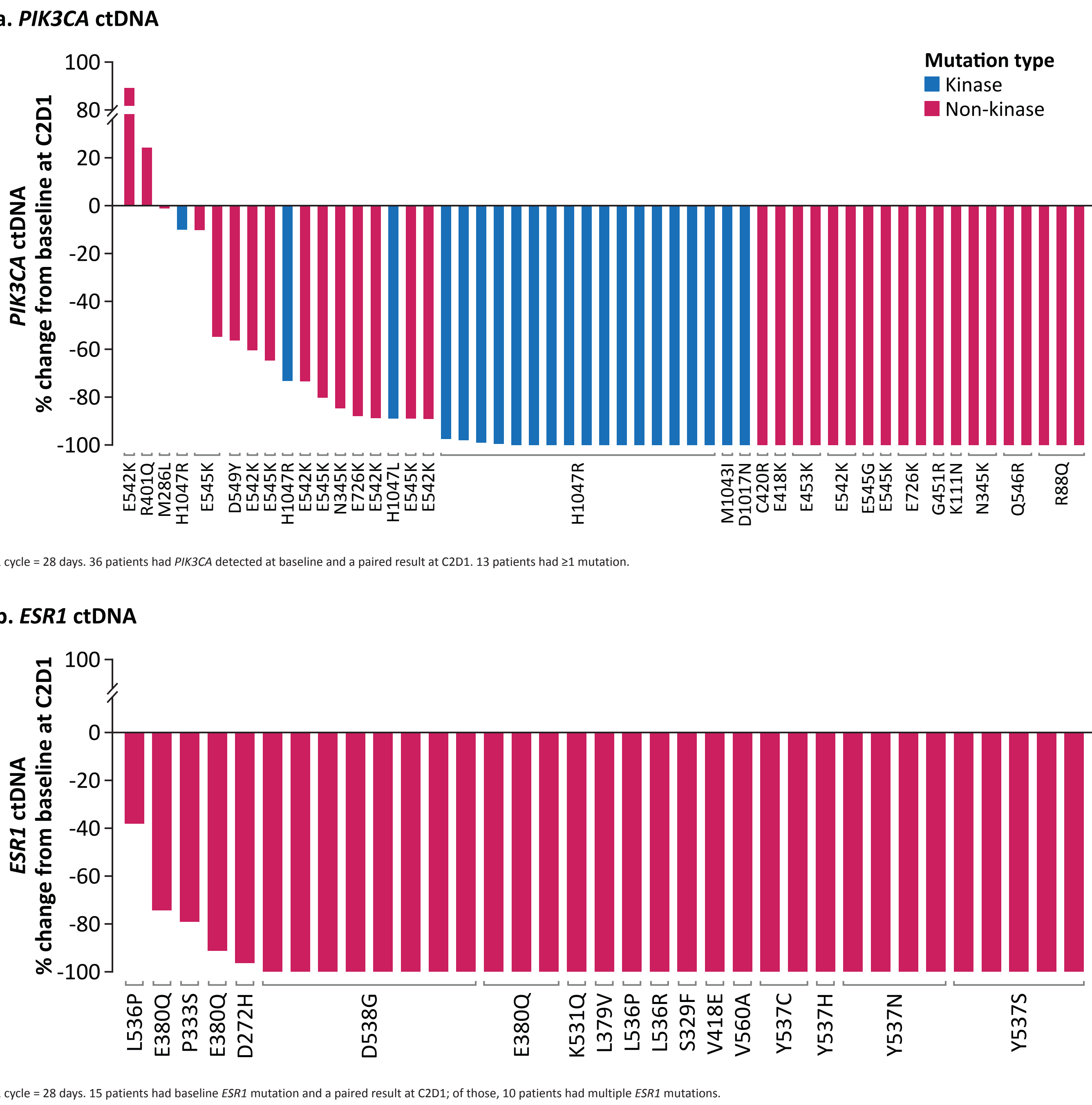


Table 2. RLY-2608 Has a Favorable Safety Profile Consistent With Mutant-Selective PI3K α Inhibition

		All patients (N=118)		600 mg BID (RP2D, N=64)	
Any TRAE		All grade	Grade 3	All grade	Grade 3 ^a
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%

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)

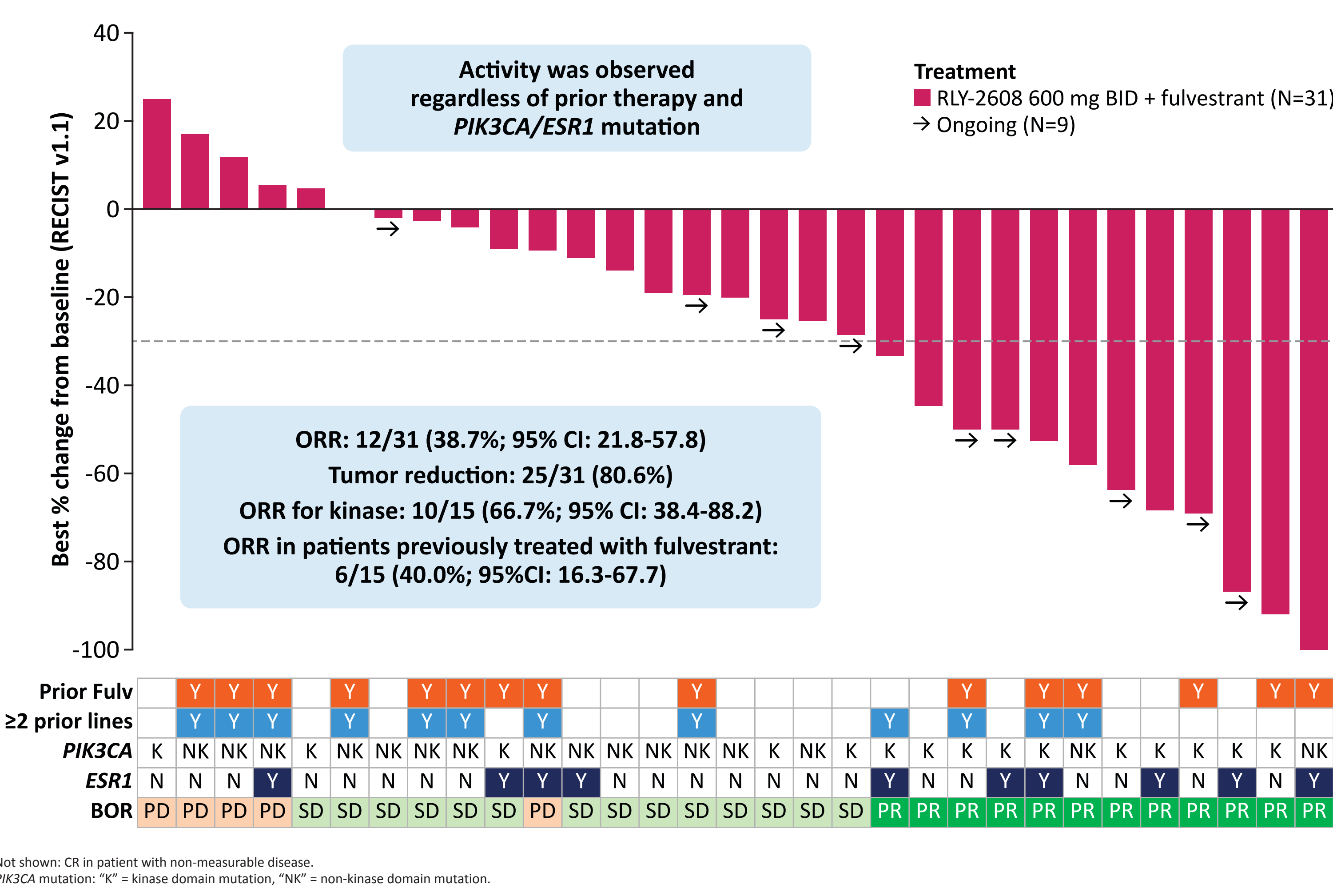


Figure 5. Median Progression-Free Survival (N=52)

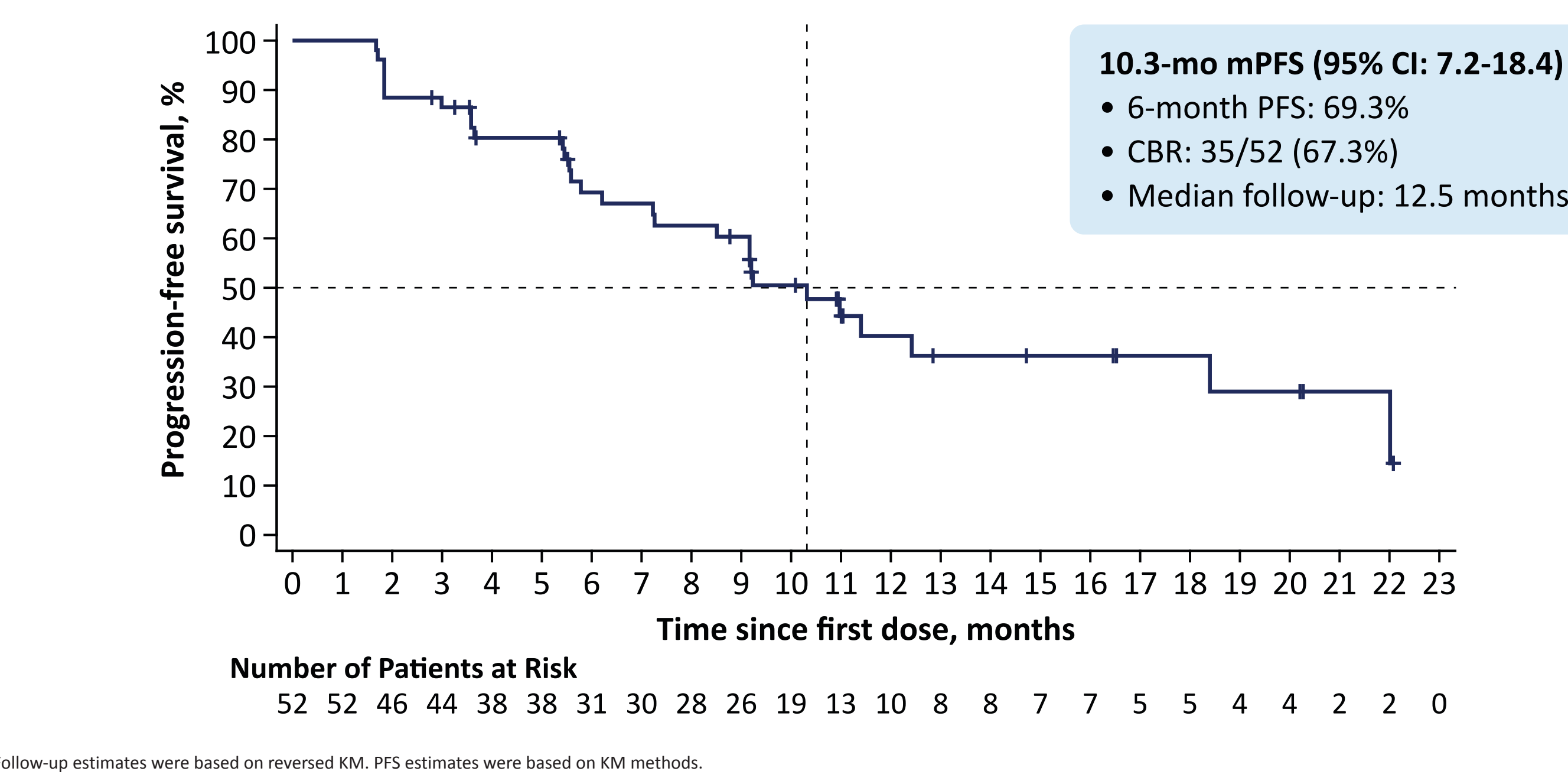


Figure 6. Median Progression-Free Survival by Subgroups

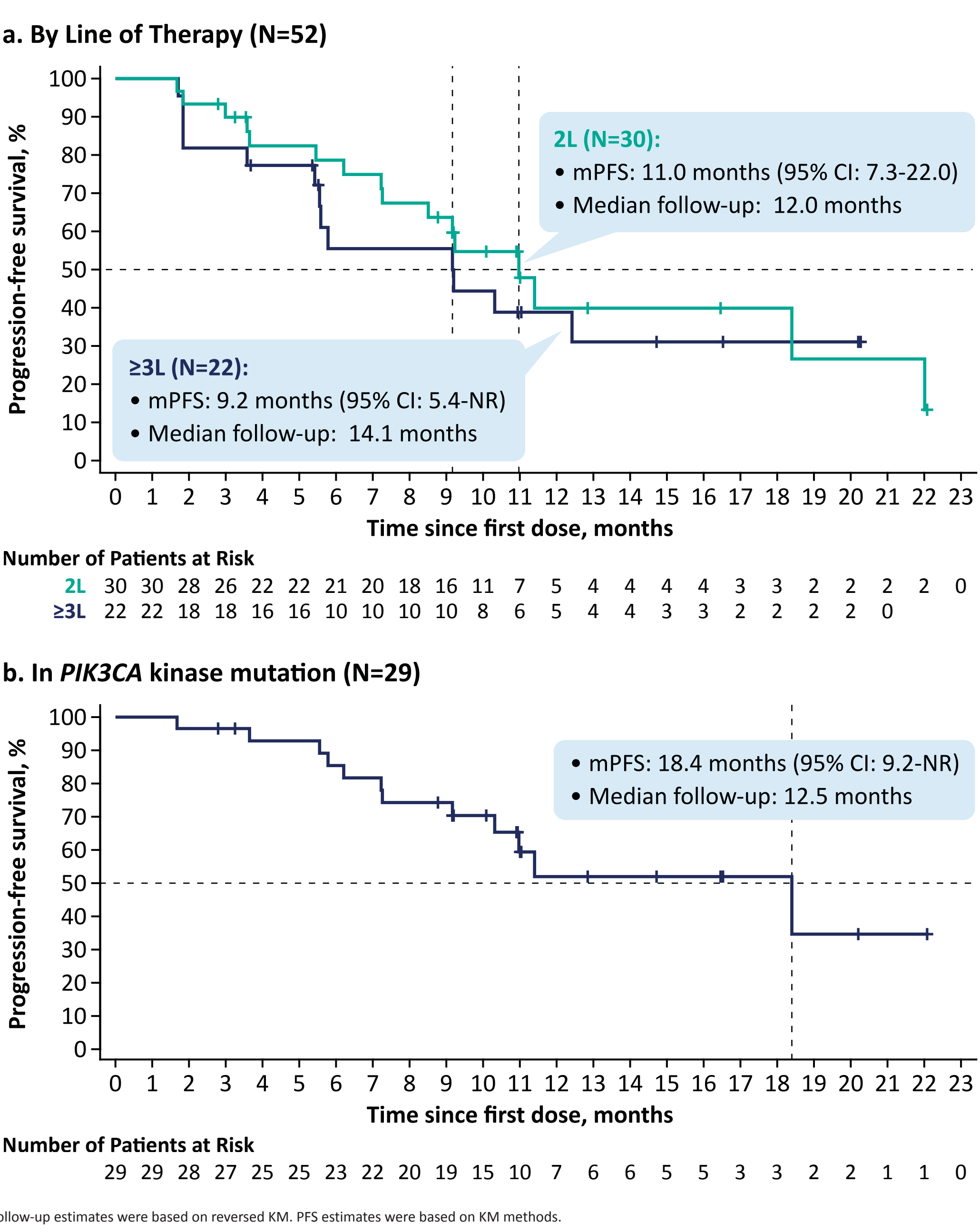


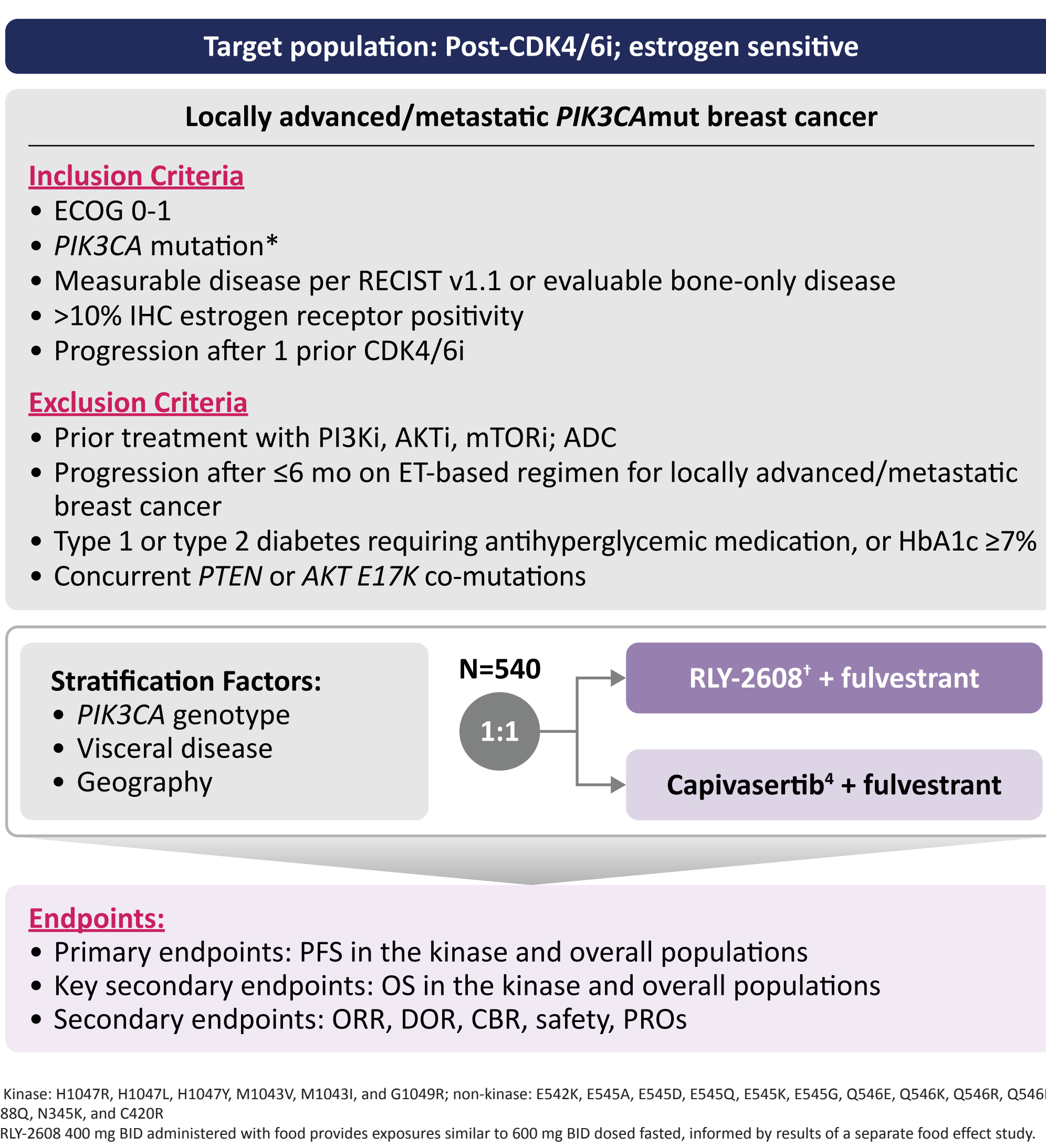
Figure 7. Durable Efficacy Across *PIK3CA* Mutations (N=52)



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)



References

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