
# Pan-mutant and isoform selective PI3Kα inhibitor, RLY-2608, demonstrates selective targeting in a first-in-human study of *PIK3CA*-mutant solid tumor patients: ReDiscover trial

Andreas Varkaris,[1] Komal Jhaveri,[2] Cesar A. Perez,[3] Janice S. Kim,[1] Jason T. Henry,[4] Vivek Subbiah,[5] Alexander I. Spira,[6] Lucía Sanz Gómez,[7] Angel I. Guerrero-Zotano,[8] Kari B. Wisinski,[9] Xiaoyan Li,[10] Gege Tan,[10] Ramin Samadani,[10] Tamieka Lauz Hunter,[10] Wei Guo,[10] Alison Timm,[10] Djuro Karanovic,[10] Beni B. Wolf,[10] Erika P. Hamilton,[11] Alison M. Schram[2]

[1]Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Memorial Sloan Kettering Cancer Center, New York, New York, USA; [3]Sarah Cannon Research Institute /Florida Cancer Specialists, Orlando, Florida, USA; [4]Sarah Cannon Research Institute/HealthOne Denver, Denver, Colorado, USA; [5]MD Anderson Cancer Center, Houston, Texas, USA; [6]Virginia Cancer Specialists, Fairfax, Virginia, USA; [7]Vall d'Hebron Instituto de Oncología, Barcelona, Spain; [8]Instituto Valenciano de Oncología, Valencia, Spain; [9]University of Wisconsin, Madison, Carbone Cancer Center, Madison, Wisconsin, USA; [10]Relay Therapeutics, Cambridge, Massachusetts, USA; [11]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee, USA

Presentation CT017

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# Disclosure Information

Andreas Varkaris, M.D., Ph.D.

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# Mutant PI3Kα is a Validated Cancer Target with Significant Unrealized Therapeutic Potential

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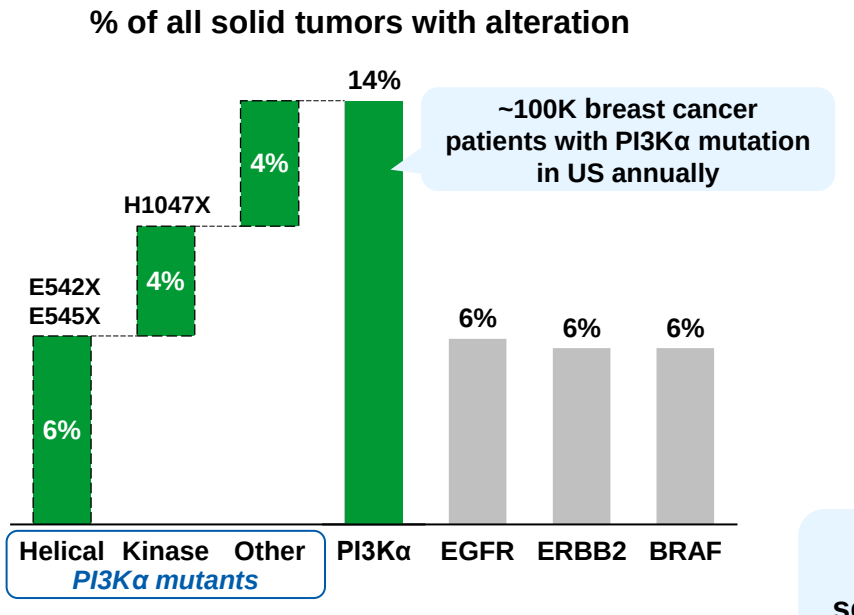
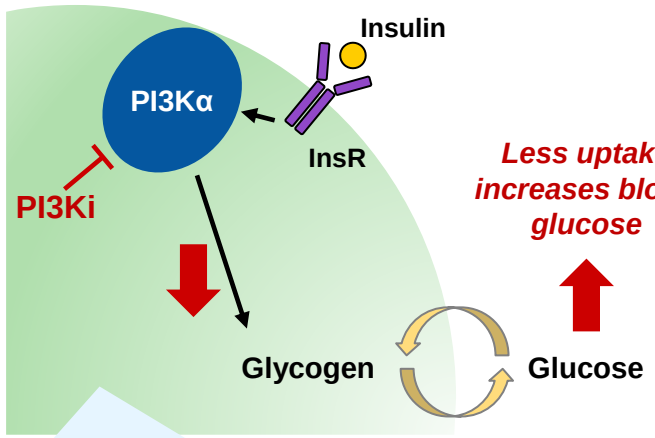
## PI3Kα is the most frequently mutated kinase in solid tumors




## PI3Kα regulates glucose homeostasis




Alpelisib, the only FDA-approved PI3Kα inhibitor for solid tumors, is not mutant-selective and disrupts glucose metabolism, causing hyperglycemia

## WT PI3Kα and off-isoform toxicity limit the clinical benefit of alpelisib

**AEs frequently leading to treatment discontinuation for alpelisib**

| AE | All Gr (Gr3+) |
|---|---|
| Hyperglycemia | 65% (37%) |
| Diarrhea | 60% (7%) |
| Rash | 36% (10%) |

Adapted from Hanker et al, *Cancer Disc* 2019; Adapted from Helsten et al, *Clin Cancer Res* 2016;22:259-267.; SEER; SOLAR-1 (long-term follow up): Andre et al, *Ann Oncol* 2021;32:208.

# RLY-2608 is First Allosteric Mutant Selective PI3Kα Inhibitor

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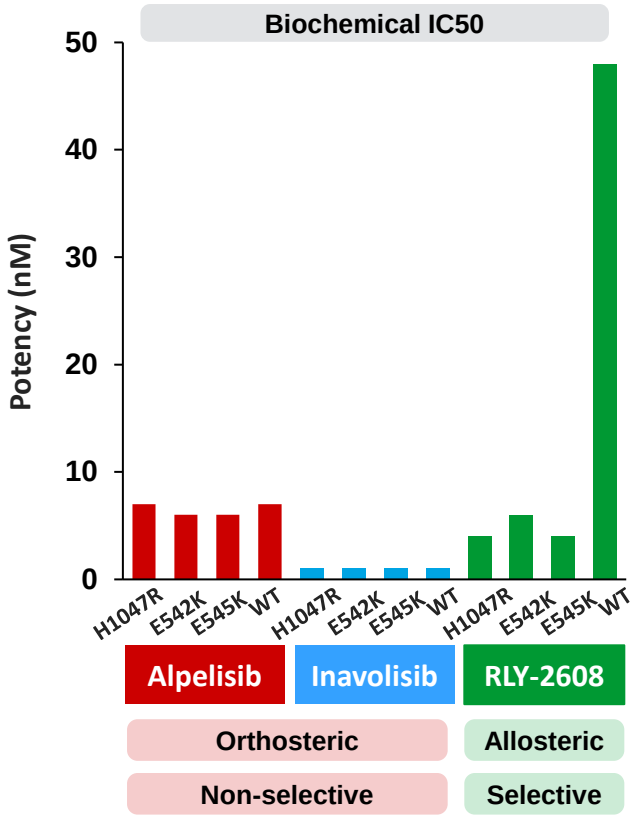
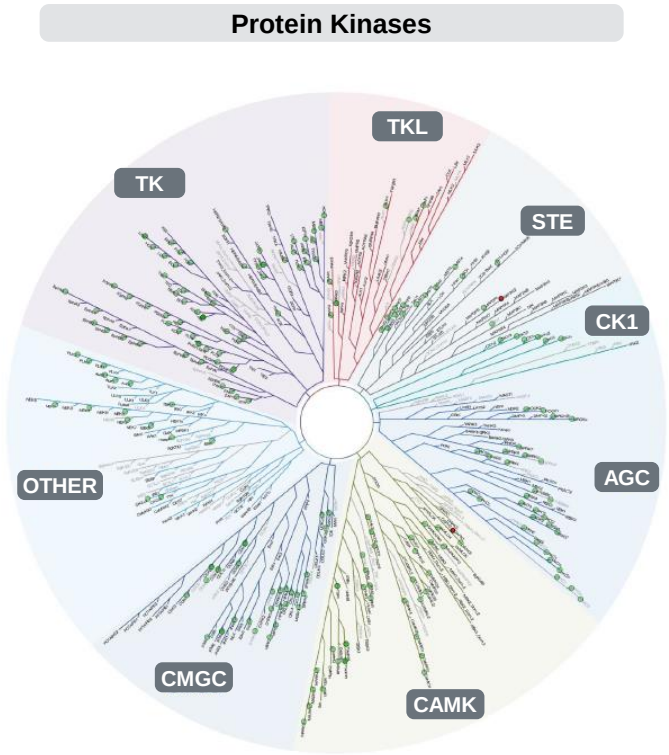
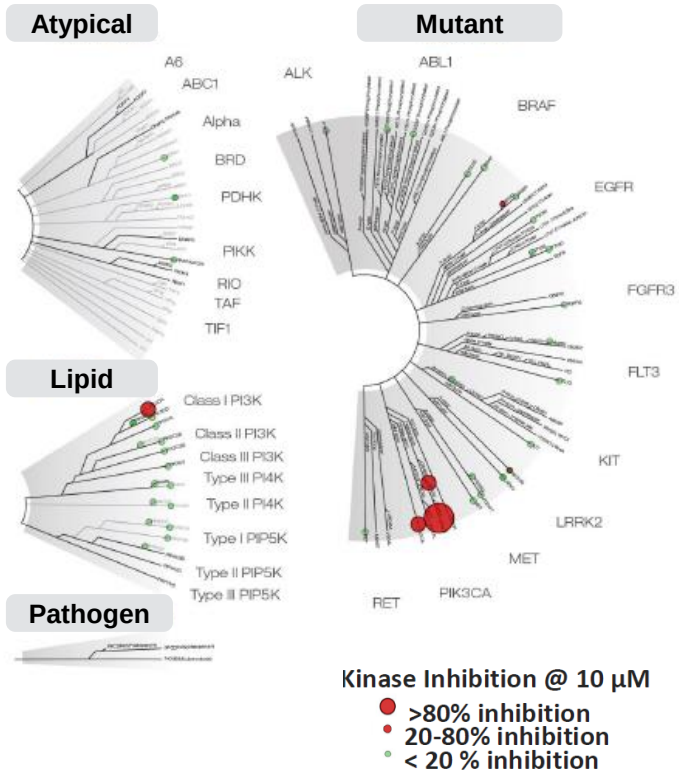
## RLY-2608 selectively inhibits mutant PI3Kα




## High selectivity over the kinome and within PI3K family




Pazolli M, Discovery and characterization of RLY-2608, the first allosteric, mutant, and isoform-selective inhibitor of PI3Kα. Oral presentation at: AACR-NCI-EORTC Virtual International Conference on Molecular Targets Conference; October 7-10, 2021; Virtual.

# RLY-2608 - Robust Efficacy with Limited Impact on Glucose Homeostasis in Preclinical Models

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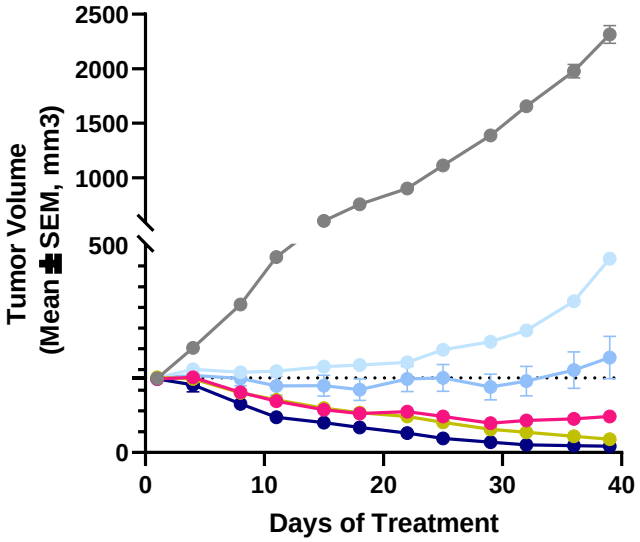
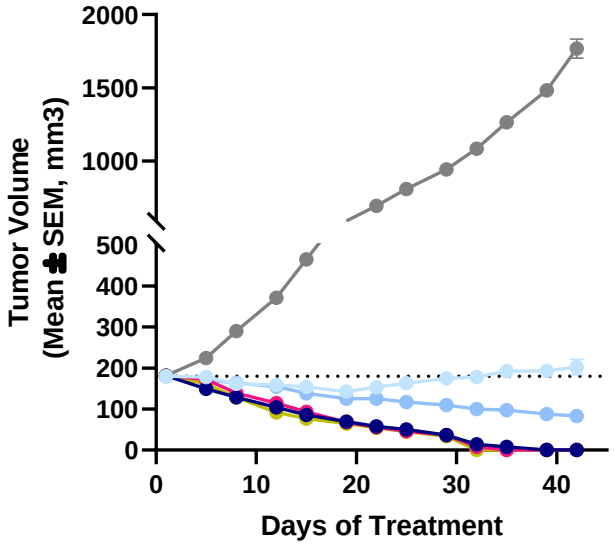
## Tumor regression in mutant *PIK3CA* mouse breast cancer models

H1047R (Kinase mutant)
(HCC1954)

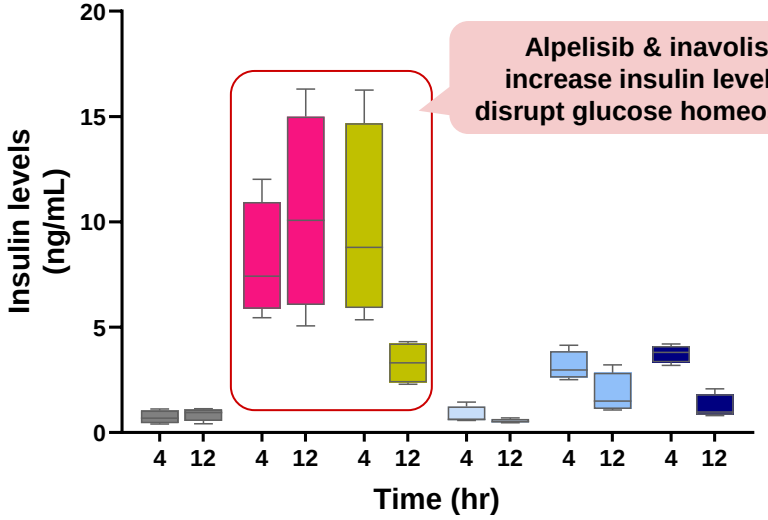



E545K (Helical mutant)
(MDAMB361[1])




## Minimal perturbation of insulin levels

Insulin levels at steady state exposure in tumor-bearing mice[2]




Vehicle
Alpelisib 50mg/kg QD
Inavolisib 25mg/kg QD
RLY-2608 25mg/kg BID
RLY-2608 50mg/kg BID
RLY-2608 100mg/kg BID

Higher doses/exposures lead to increased modulation of pAKT across *PIK3CA* mutant models

Pazolli M, Discovery and characterization of RLY-2608, the first allosteric, mutant, and isoform-selective inhibitor of PI3Kα. Oral presentation at: AACR-NCI-EORTC Virtual International Conference on Molecular Targets Conference; October 7-10, 2021; Virtual.
1. This model also carries a second mutation at K567R; 2. HSC2 model

# ReDiscover: First-in-Human Study of RLY-2608

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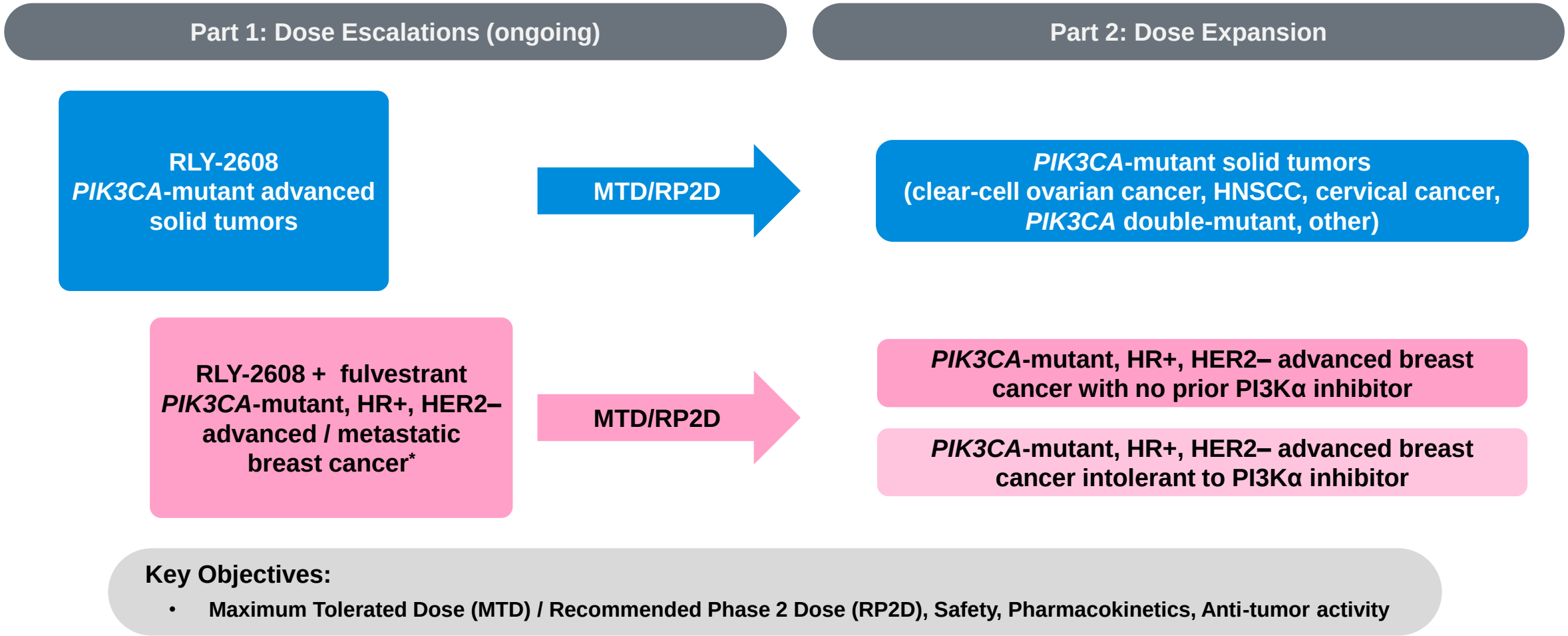


**Key Objectives:**

- **Maximum Tolerated Dose (MTD) / Recommended Phase 2 Dose (RP2D), Safety, Pharmacokinetics, Anti-tumor activity**

NCT05216432. *PIK3CA* mutations in Part 1 and Part 2 identified per local assessment. No prior PI3K inhibitor treatment allowed.
*Patients must have previous treatment with ≥1 chemotherapy, ≥1 CDK 4/6 inhibitor, and ≥1 anti-estrogen therapy.**Double mutation defined as one major PIK3CA mutation (E542K, E545X or H1047X) and ≥1 additional PIK3CA mutation.
BOIN, Bayesian Optimal Interval; CDK, cyclin-dependent kinase; HER2–, human epidermal growth factor receptor 2-negative; HNSCC, head and neck squamous cell carcinoma; HR+, hormone receptor-positive; MTD, maximum tolerated dose; mut, mutated; PI3Kα, phosphatidylinositol 3-kinase alpha; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit alpha; RP2D, recommended Phase 2 dose; RECIST, Response Evaluation Criteria in Solid Tumors.

# ReDiscover: Interim Part 1 Results

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**Part 1: Dose Escalations – Bayesian optimal interval design with cohort enrichment**
**RLY-2608 daily via continuous oral administration**

**RLY-2608**
***PIK3CA*-mutant advanced solid tumors (N=19)**

***Start: Dec 2021***

- *Ongoing*
- 400mg BID N=4
- 300mg BID N=3
- 200mg BID N=3
- 400mg QD N=3
- 100mg BID N=1
- 200mg QD N=3
- 50mg BID N=2

**RLY-2608 + fulvestrant**
***PIK3CA*-mutant, HR+, HER2– advanced / metastatic breast cancer (N=23)**

***Start: April 2022***

- *Ongoing*
- 800mg BID N=6
- 600mg BID N=7
- 400mg BID N=4
- 200mg BID N=3
- 100mg BID N=3

Current enrollment focus

**Across both dose escalation cohorts:**
- **No dose limiting toxicities (DLTs)**
- **MTD not reached & dose escalation continues**
- **Cohort enrichment ongoing**

Preliminary data as of 03/09/2023

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# Baseline Demographics



| | RLY-2608 (N=19) | RLY-2608 + fulvestrant (N=23) | Total (N=42) |
|---|---|---|---|
| Age, median (range), years | 63 (42-85) | 57 (40-83) | 60 (40-85) |
| Female, n (%) | 11 (58%) | 23 (100%) | 34 (81%) |
| Ethnicity, % | | | |
| White / Asian / American Indian / Black / Unknown | 95% / 0% / 0% / 0% / 5% | 78% / 4% / 4% / 4% / 9% | 86% / 2% / 2% / 2% / 7% |
| ECOG, % | | | |
| 0 / 1 | 42% / 58% | 57% / 39% | 50% / 48% |
| BMI, kg/m$^2$, median (range) | 25 (16-44) | 25 (18-38) | 25 (16-44) |
| <30 / ≥30, % | 74% / 26% | 74% / 26% | 74% / 26% |
| Prior regimens of therapy in metastatic setting, median (range) | 3 (0,12) | 1 (1, 12) | 2 (0,12) |
| 0 | 1 (5%) | 0 | 1 (2%) |
| 1 | 4 (21%) | 12 (52%) | 16 (38%) |
| 2 | 2 (11%) | 3 (13%) | 5 (12%) |
| 3+ | 12 (63%) | 8 (35%) | 20 (48%) |
| Type of prior therapy, n (%) | | | |
| Endocrine therapy + CDK4/6 inhibitor | NA | 23 (100%) | NA |
| Chemotherapy / ADC | 12 (63%) | 6 (26%) | 18 (43%) |
| mTOR / AKT inhibitor | 0 | 4 (17%) | 4 (10%) |
| *PIK3CA* genotype, % | | | |
| Helical / Kinase / Other | 63% / 16% / 21% | 43% / 48% / 9% | 52% / 33% / 14% |

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# Favorable RLY-2608 PK Profile Optimizes Mutant-Selective Inhibition

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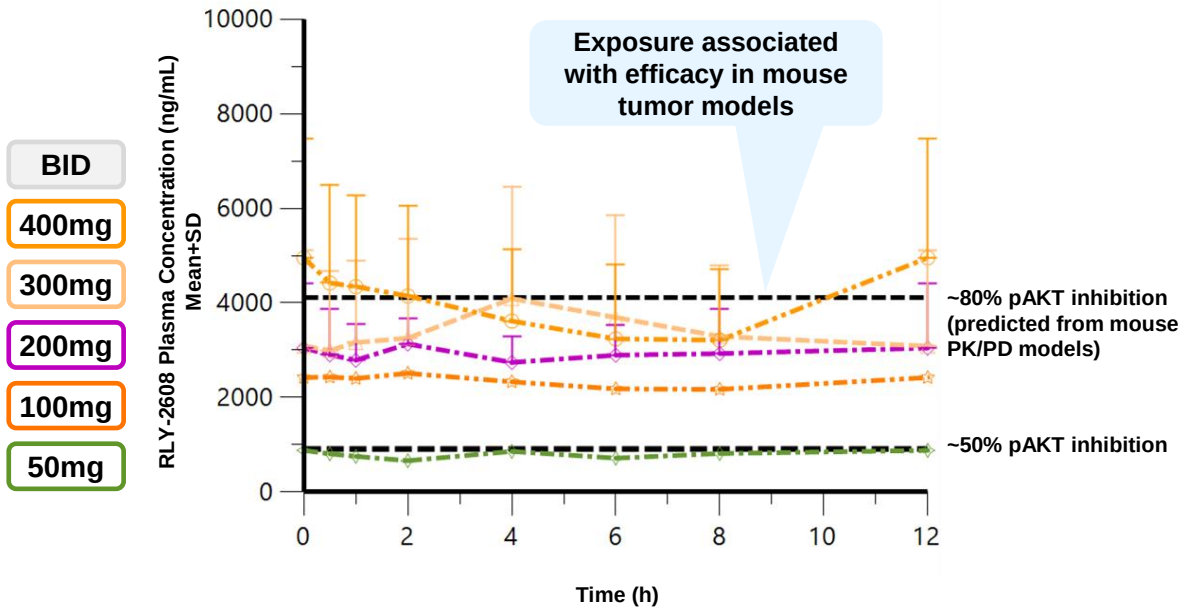
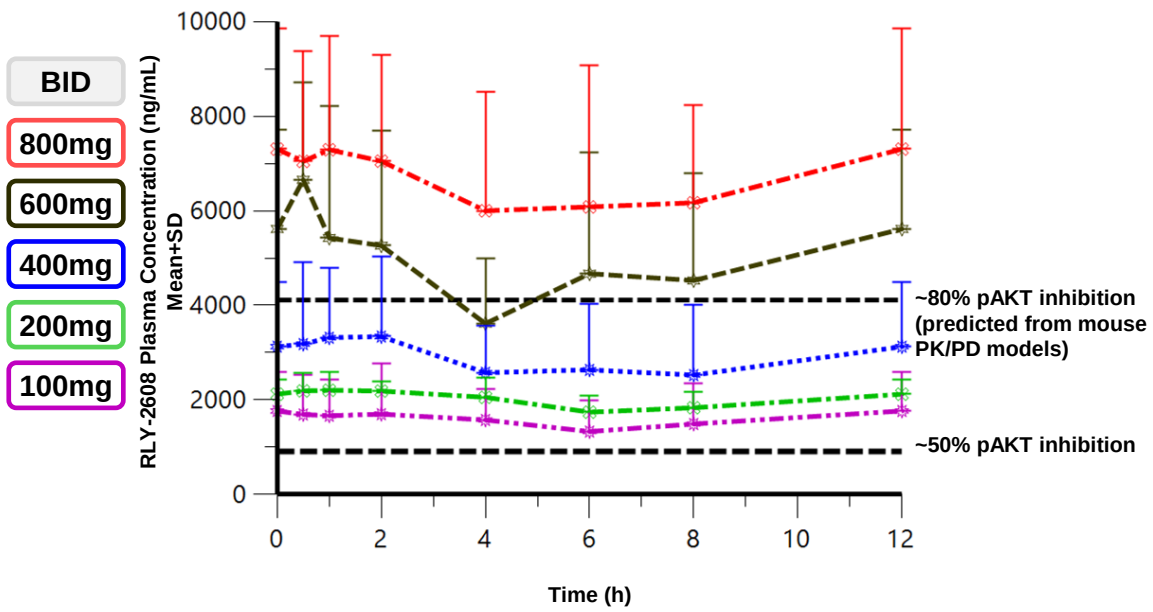
## RLY-2608 C1D15




## RLY-2608 + fulvestrant C1D15




**Dose-dependent increase in exposure and low peak to trough fluctuations across dose levels**

**Continuous exposure over IC80 correlates with efficacy in preclinical models***

**Constant coverage at IC80 across dosing interval at 400mg BID mono and 600mg and 800mg BID**

* Fritsch et al *Mol Can Therapeutics* 2014 13(5) 1117-1129. Piqray - European Medicines Agency Public Assessment Report 28 May 2020

Preliminary data as of 03/09/2023

# Ex Vivo Target Inhibition Shows Concentration-Dependent Pathway Suppression

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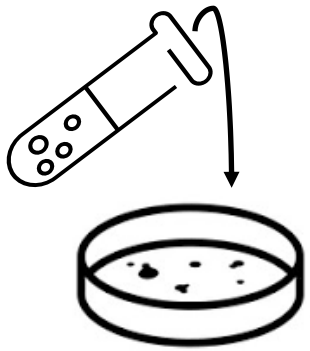
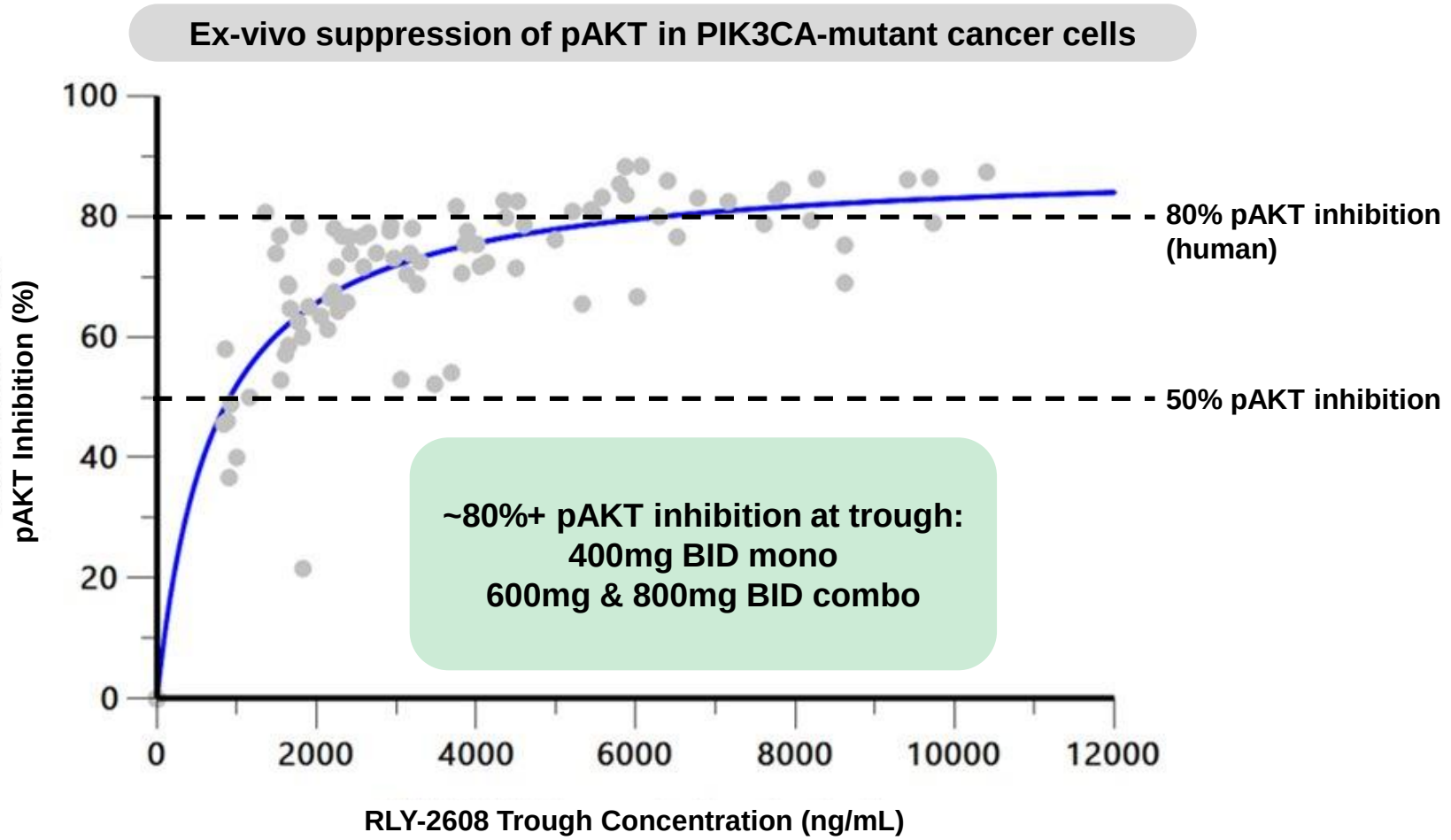
Patient Plasma Sample*
(Pre-dose)



*PIK3CA*-mutant cancer cells




* Plasma samples taken at C1D1, C1D15, C2D1, C3D1, C4D1, then odd cycles starting at C5D1 until end of treatment

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# Minimal Impact on Glucose Homeostasis Confirms Mutant Selective Targeting

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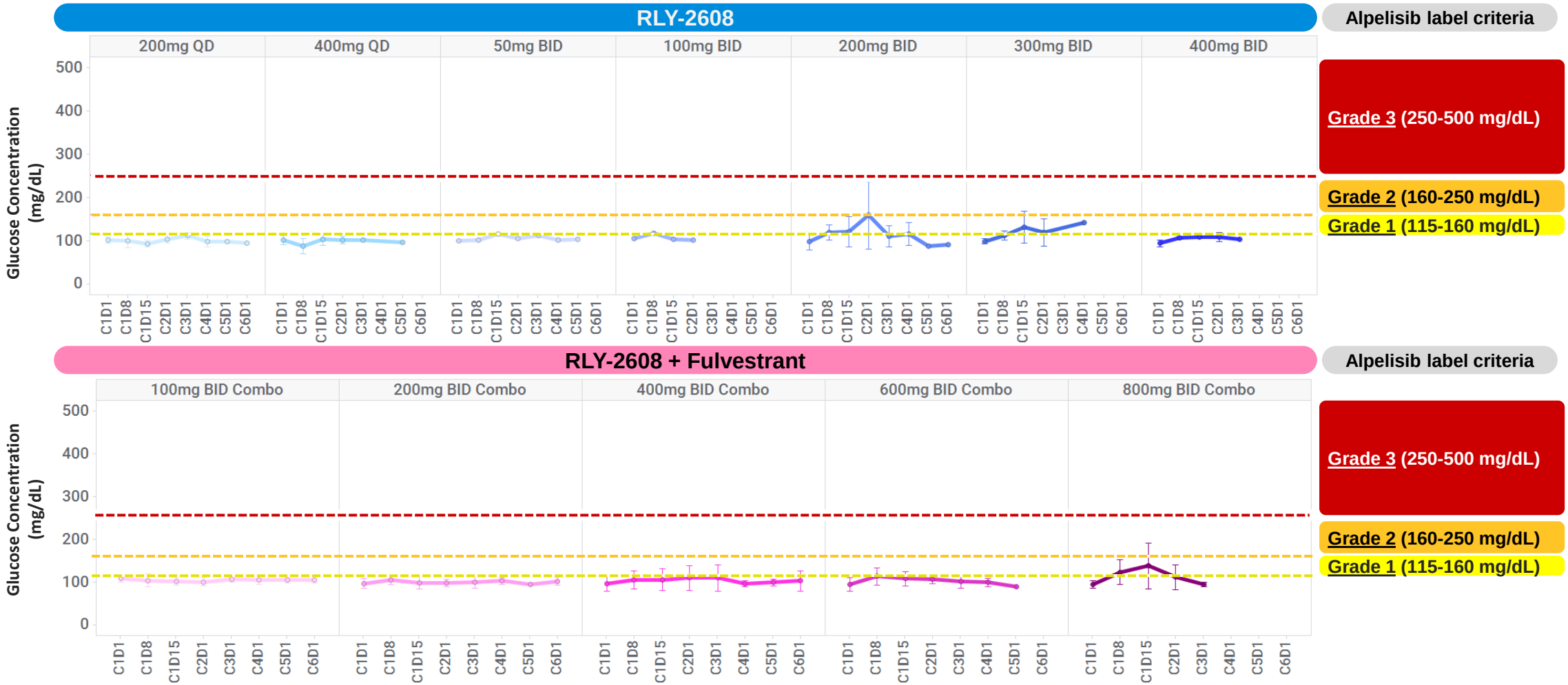
**No Grade 3 hyperglycemia per CTCAE v5.0**
**No dose interruptions or dose reductions due to hyperglycemia**




* Data represent mean per cohort +/- standard deviation

Preliminary data as of 03/09/2023

# Partial Response per RECIST in *PIK3CA*-Mutant Breast Cancer*

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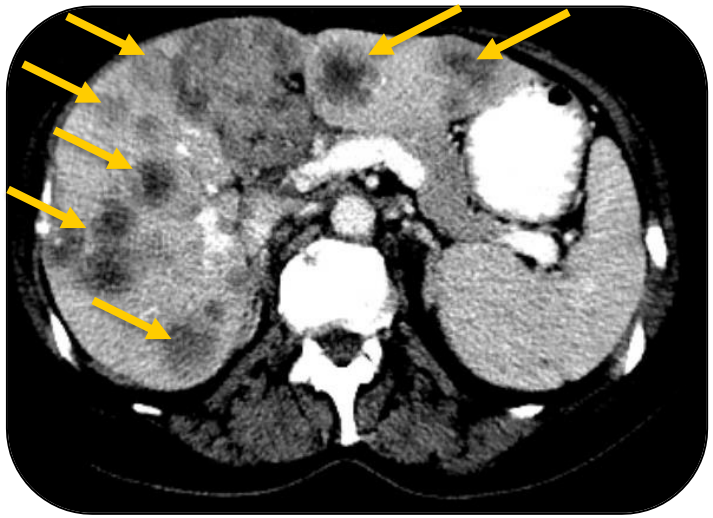
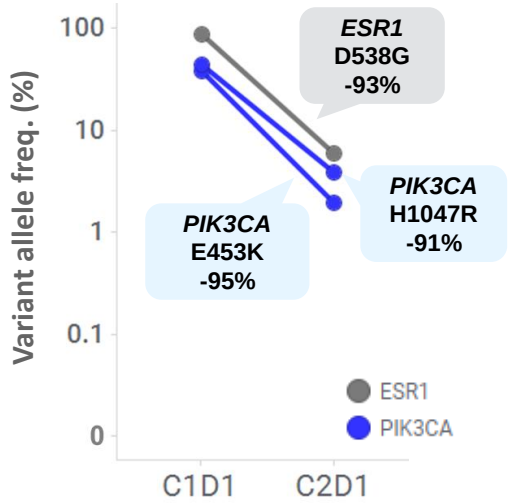
**uPR* with -36% tumor reduction per RECIST**
**Marked regression of multiple liver metastases**
**No adverse events reported**

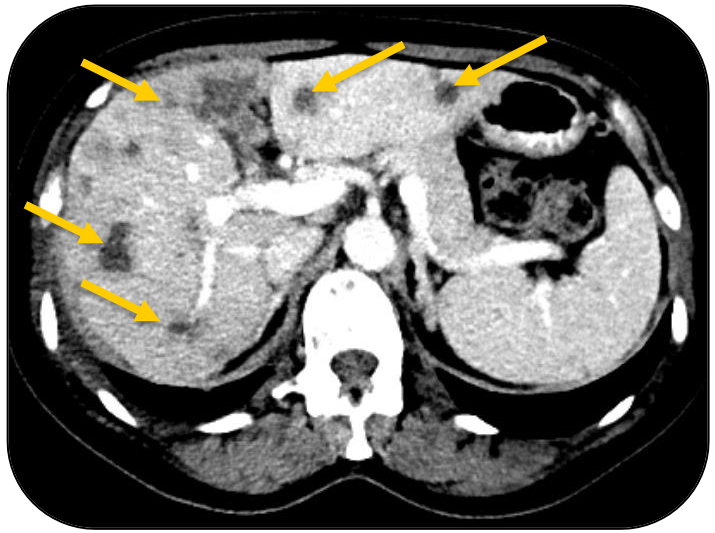
## Baseline



## ctDNA at 4 weeks




## First Assessment (8 weeks)



**58 y/o female, *PIK3CA* H1047R + E453K mutations, HR+ HER2- (IHC2+FISH-)**
**12 prior lines of therapy (chemo, endocrine, multiple HER2-directed, including Enhertu)**
**RLY-2608 400mg BID monotherapy, ongoing in response as of data cut-off**

* Response confirmed after data cut-off
Courtesy Varkaris, MGH

Preliminary data as of 03/09/2023

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# Radiographic Tumor Regression & Response Across *PIK3CA* Breast Cancer Genotypes

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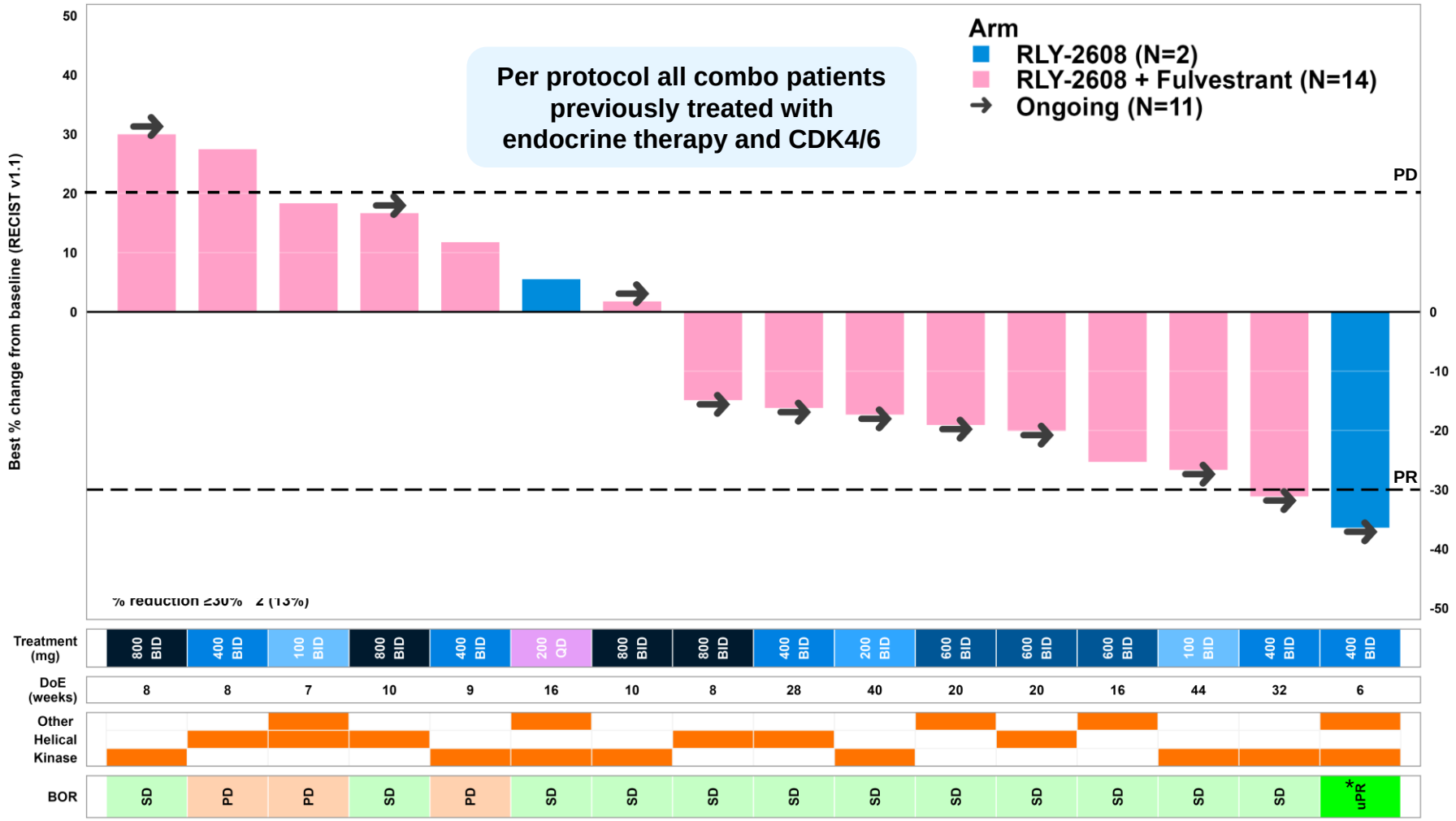
## Breast Cancer Patients (RECIST Measurable Disease) *N=16*




**56% of patients (9/16) exhibit radiographic tumor reductions**

**81% of patients (13/16) with SD/uPR* across genotypes**

**11/16 patients ongoing**

**BOR = Best Overall Response:**

- **SD** Stable Disease
- **uPR*** Unconfirmed Partial Response*
- **PD** Progressive Disease

*Response confirmed after data cut-off

Preliminary data as of 03/09/2023

# RLY-2608 Induces Declines in Mutant *PIK3CA* ctDNA

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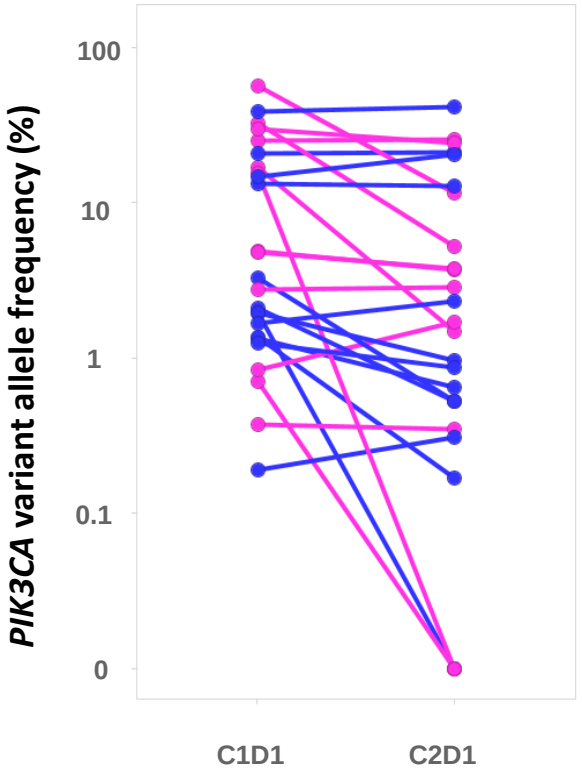
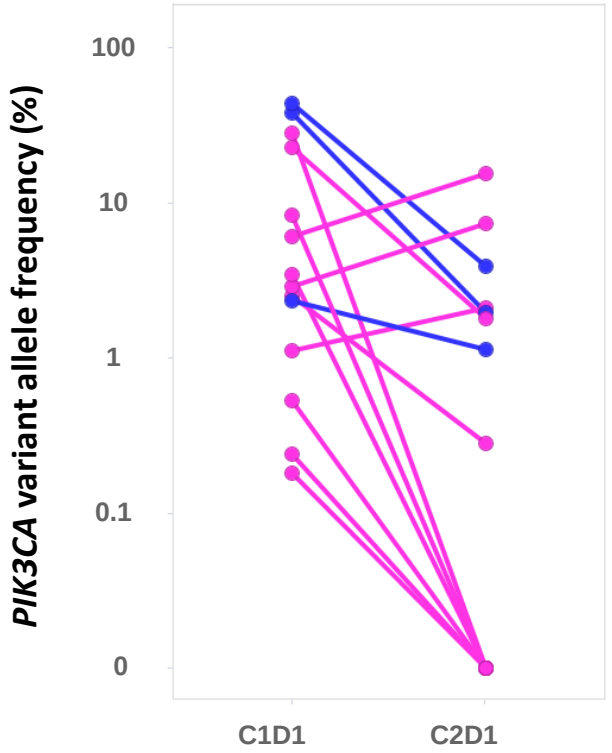
**400mg BID Combo, <400mg Mono**




| Patients with paired evaluable ctDNA[1] | | |
|---|---|---|
| | RLY-2608 | 9 |
| | RLY-2608 + fulvestrant | 10 |

**400mg BID Mono, 600mg & 800mg BID Combo**




| Patients with paired evaluable ctDNA[1] | | |
|---|---|---|
| | RLY-2608 | 2 |
| | RLY-2608 + fulvestrant | 10 |

**31 patients with evaluable paired C1D1-C2D1 ctDNA samples**

**6 patients have ≥2 *PIK3CA* mutations**

**23 patients had declines in *PIK3CA* ctDNA**

**9 patients completely cleared mutant *PIK3CA* ctDNA by C2D1**

RLY-2608
RLY-2608 + fulvestrant

1. 6 patients are represented by more than one *PIK3CA* mutation in the ctDNA graphs shown

Preliminary data as of 03/09/2023

# Disease Stabilization Across *PIK3CA* Breast Cancer Genotypes

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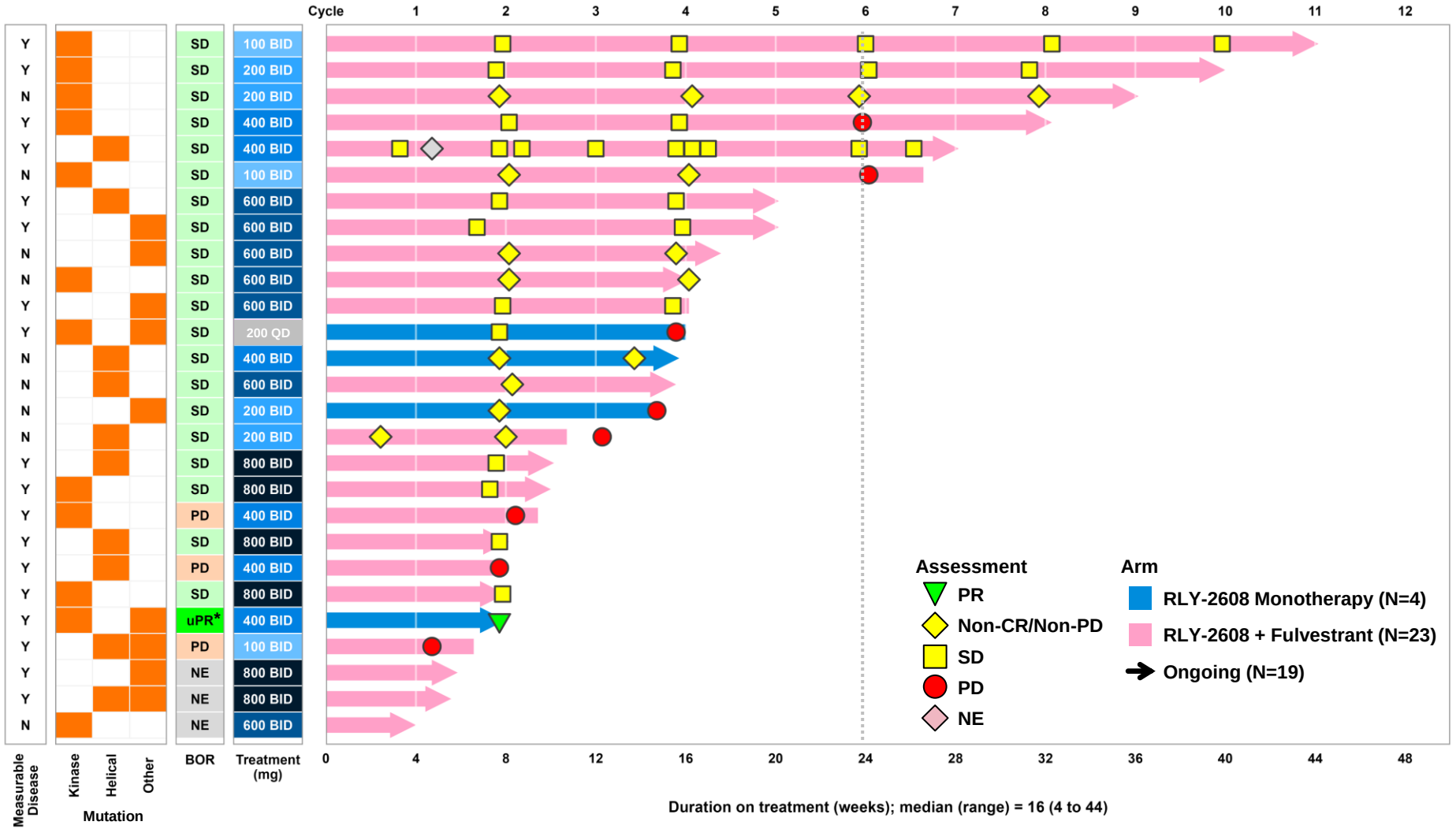
## Breast Cancer Patients (Measurable and Non-Measurable Disease) *N=27*




**19/27 patients (70%) ongoing**

**Duration on treatment:**
- **Median: 16 weeks**
- **Range: 4 – 44 weeks**

**21/24 RECIST evaluable patients (88%) had non-CR/non-PD, SD or response**

**Most patients (7/8) discontinued due to progressive disease**
- **No AEs leading to treatment discontinuation**

*Response confirmed after data cut-off

Preliminary data as of 03/09/2023

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# RLY-2608-101 Monotherapy – Other tumor types

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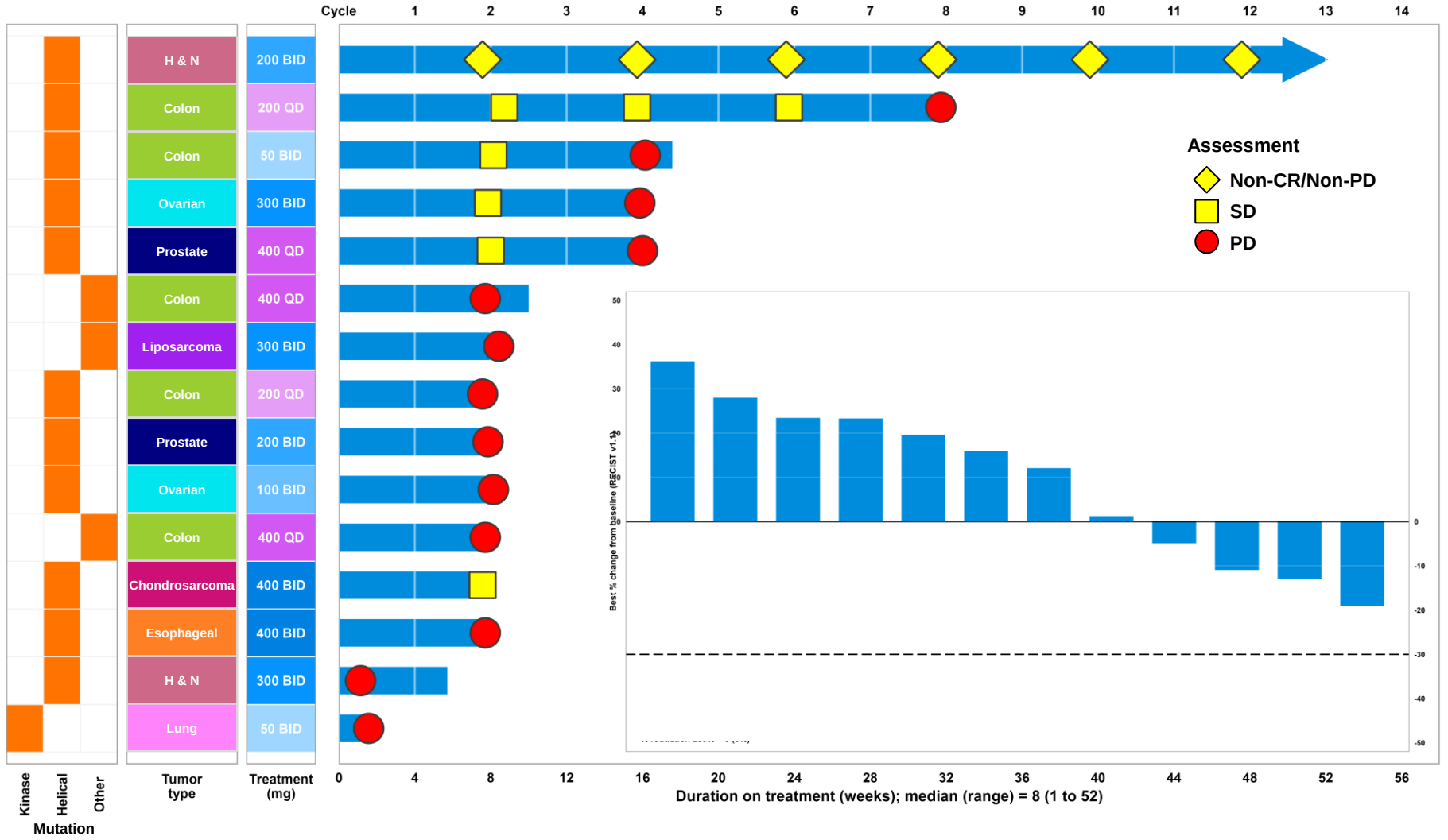
## RLY-2608 Non-Breast Cancer Patients *N=15*




**Duration on treatment:**
- **Median: 8 weeks**
- **Range: 1 – 52 weeks**

**14/14 discontinued due to progressive disease**
- **No AEs leading to treatment discontinuation**

Preliminary data as of 03/09/2023

# Favorable Safety Profile Consistent with Mutant-Selective Inhibition

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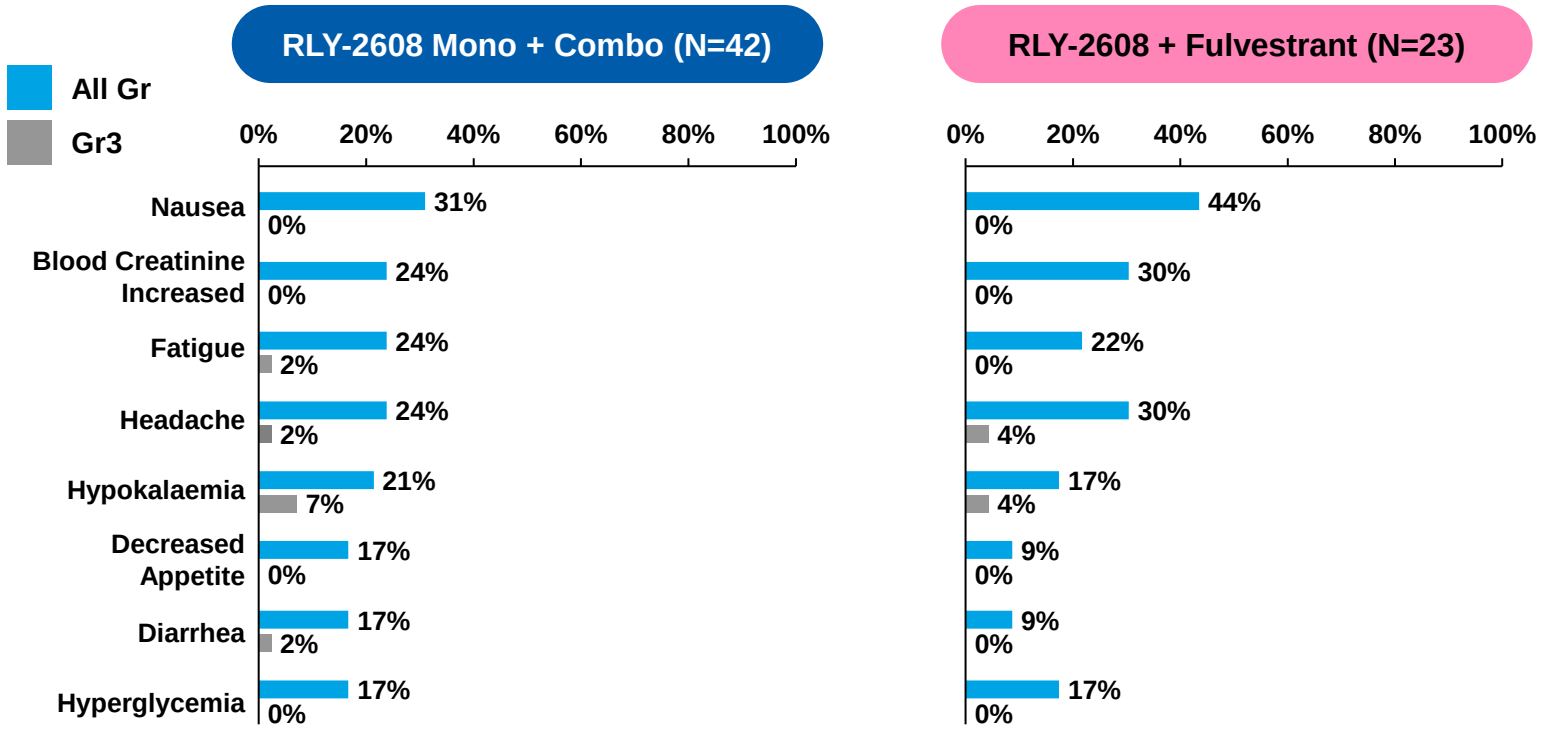
## Treatment Emergent Adverse Events (TEAEs) ≥15% Across All Doses (N=42)




### AEs leading to alpelisib discontinuation observed with RLY-2608

*(for 400mg BID mono, ≥600mg BID combo; N=17)*

| AE | All Gr (Gr3+) |
|---|---|
| Hyperglycemia | 18% (0%) |
| Diarrhea | 0% |
| Rash | 12% (0%) |

**Most AEs low grade, manageable, reversible**
**Grade 3 TEAEs 10/42 (24%); No Grade 4-5 AEs**
**Dose modifications due to AE: Interruptions 31%; Reductions 2%; Discontinuations 0%**
**Median Relative Dose Intensity: 98%**

Preliminary data as of 03/09/2023

# Conclusions



**ReDiscover data validate proof of mechanism for RLY-2608 as the first allosteric, pan-mutant- and isoform-selective PI3Kα inhibitor**

**Favorable PK-PD provides sustained target inhibition (~80%+) with minimal impact on glucose homeostasis**

- **Dose-dependent increase in exposure with low peak-to-trough fluctuation & pharmacologic activity across a wide dose range**

**Differentiated and favorable safety profile confirms mutant- and isoform-selectivity**

- **Most common adverse events were low grade, manageable events**
  - **Low rates of hyperglycemia, diarrhea, rash**
  - **No grade 3 hyperglycemia**
- **No DLTs and no AEs leading to treatment discontinuation with median dose intensity of 98%**

**Encouraging anti-tumor activity across PIK3CA genotypes in HR+HER2- breast cancer**

- **Declines in tumor markers and mutant ctDNAs with radiographic tumor reductions & response in RECIST-measurable patients**

**ReDiscover dose escalation and cohort enrichment continues with expected start of dose expansion 2H 2023**

Preliminary data as of 03/09/2023

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- BRCR Global, Plantation, Florida
- Lake Nona/SCRI Florida Cancer Specialists, Orlando, Florida
- Massachusetts General Hospital, Boston, Massachusetts
- Columbia University Herbert Irving Comprehensive Cancer Center, New York, New York
- Memorial Sloan Kettering Cancer Center, New York, New York
- Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee
- The University of Texas M.D. Anderson Cancer Center, Houston, Texas
- Virginia Cancer Specialists/NEXT Virginia, Fairfax, Virginia
- The University of Wisconsin Carbone Cancer Center, Madison, Wisconsin


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