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


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Presentation CT017
Disclosure Information

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I have no financial relationships to disclose.
Mutant PI3Kα is a Validated Cancer Target with Significant Unrealized Therapeutic Potential

PI3Kα is the most frequently mutated kinase in solid tumors

PI3Kα regulates glucose homeostasis

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

% of all solid tumors with alteration

- H1047X: 14%
- E542X: 4%
- E545X: 4%
- 6% of all solid tumors

~100K breast cancer patients with PI3Kα mutation in US annually

PI3Kα mutants

Helical Kinase Other PI3Kα

AEs frequently leading to treatment discontinuation for alpelisib

- Hyperglycemia: 65% (37%)
- Diarrhea: 60% (7%)
- Rash: 36% (10%)

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

PI3Kα mutates

Less uptake increases blood glucose

Glucose

Glycogen

Insulin

InsR

PI3Ki

PI3Kα

RLY-2608 is First Allosteric Mutant Selective PI3Kα Inhibitor

**Biochemical IC50**

- **Orthosteric**
- **Non-selective**
- **Allosteric**
- **Selective**

**High selectivity over the kinome and within PI3K family**

**Protein Kinases**

- **Atypical**
- **Mutant**

**Lipid**

**Pathogen**

**Kinase Inhibition @ 10 μM**

- >80% inhibition
- 20-80% inhibition
- < 20% inhibition

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

Tumor regression in mutant PIK3CA mouse breast cancer models

Minimal perturbation of insulin levels

Insulin levels at steady state exposure in tumor-bearing mice

Alpelisib & inavolisib increase insulin levels & disrupt glucose homeostasis

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

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

**Part 1: Dose Escalations (ongoing)**
- RLY-2608
- PIK3CA-mutant advanced solid tumors

**Part 2: Dose Expansion**
- MTD/RP2D
- PIK3CA-mutant solid tumors (clear-cell ovarian cancer, HNSCC, cervical cancer, PIK3CA double-mutant, other)

**RLY-2608 + fulvestrant**
- PIK3CA-mutant, HR+, HER2– advanced / metastatic breast cancer

**PIK3CA-mutant, HR+, HER2– advanced breast cancer with no prior PI3Kα inhibitor**

**PIK3CA-mutant, HR+, HER2– advanced breast cancer intolerant to PI3Kα inhibitor**

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*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.

NCT05216432. PIK3CA mutations in Part 1 and Part 2 identified per local assessment. No prior PI3K inhibitor treatment allowed.

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

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

- Current enrollment focus
  - 300mg BID N=3
  - 200mg BID N=3
  - 100mg BID N=1
  - 50mg BID N=2

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

- Start: April 2022

- Current enrollment focus
  - 800mg BID N=6
  - 600mg BID N=7
  - 400mg BID N=4

- 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
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>RLY-2608 (N=19)</th>
<th>RLY-2608 + fulvestrant (N=23)</th>
<th>Total (N=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), years</strong></td>
<td>63 (42-85)</td>
<td>57 (40-83)</td>
<td>60 (40-85)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>11 (58%)</td>
<td>23 (100%)</td>
<td>34 (81%)</td>
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<tr>
<td><strong>Ethnicity, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White / Asian / American Indian / Black / Unknown</td>
<td>95% / 0% / 0% / 0% / 5%</td>
<td>78% / 4% / 4% / 4% / 9%</td>
<td>86% / 2% / 2% / 2% / 7%</td>
</tr>
<tr>
<td><strong>ECOG, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 / 1</td>
<td>42% / 58%</td>
<td>57% / 39%</td>
<td>50% / 48%</td>
</tr>
<tr>
<td><strong>BMI, kg/m², median (range)</strong></td>
<td>25 (16-44)</td>
<td>25 (18-38)</td>
<td>25 (16-44)</td>
</tr>
<tr>
<td>&lt;30 / ≥30, %</td>
<td>74% / 26%</td>
<td>74% / 26%</td>
<td>74% / 26%</td>
</tr>
<tr>
<td><strong>Prior regimens of therapy in metastatic setting, median (range)</strong></td>
<td>3 (0,12)</td>
<td>1 (1, 12)</td>
<td>2 (0,12)</td>
</tr>
<tr>
<td>0</td>
<td>1 (5%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>1</td>
<td>4 (21%)</td>
<td>12 (52%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (11%)</td>
<td>3 (13%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>3+</td>
<td>12 (63%)</td>
<td>8 (35%)</td>
<td>20 (48%)</td>
</tr>
<tr>
<td><strong>Type of prior therapy, n (%)</strong></td>
<td>NA</td>
<td>23 (100%)</td>
<td>NA</td>
</tr>
<tr>
<td>Endocrine therapy + CDK4/6 inhibitor</td>
<td>NA</td>
<td>23 (100%)</td>
<td>NA</td>
</tr>
<tr>
<td>Chemotherapy / ADC</td>
<td>12 (63%)</td>
<td>6 (26%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>mTOR / AKT inhibitor</td>
<td>0</td>
<td>4 (17%)</td>
<td>4 (10%)</td>
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<tr>
<td><strong>PIK3CA genotype, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helical / Kinase / Other</td>
<td>63% / 16% / 21%</td>
<td>43% / 48% / 9%</td>
<td>52% / 33% / 14%</td>
</tr>
</tbody>
</table>

Preliminary data as of 03/09/2023
Favorable RLY-2608 PK Profile Optimizes Mutant-Selective Inhibition

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


Preliminary data as of 03/09/2023
Ex Vivo Target Inhibition Shows Concentration-Dependent Pathway Suppression

Patient Plasma Sample* (Pre-dose)

PIK3CA-mutant cancer cells

Ex-vivo suppression of pAKT in PIK3CA-mutant cancer cells

~80%+ pAKT inhibition at trough:
400mg BID mono
600mg & 800mg BID combo

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

Preliminary data as of 03/09/2023
Minimal Impact on Glucose Homeostasis Confirms Mutant Selective Targeting

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*

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

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

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

Per protocol all combo patients previously treated with endocrine therapy and CDK4/6

BOR = Best Overall Response:
- **PD** Progressive Disease
- uPR* Unconfirmed Partial Response*
- SD Stable Disease

*Response confirmed after data cut-off

Preliminary data as of 03/09/2023

**Arm**
- RLY-2608 (N=2)
- RLY-2608 + Fulvestrant (N=14)
- Ongoing (N=11)
RLY-2608 Induces Declines in Mutant PIK3CA ctDNA

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

1. Patients with paired evaluable ctDNA

Patients with paired evaluable ctDNA
RLY-2608 9
RLY-2608 + fulvestrant 10

Patients with paired evaluable ctDNA
RLY-2608 2
RLY-2608 + fulvestrant 10

Preliminary data as of 03/09/2023
Disease Stabilization Across PIK3CA Breast Cancer Genotypes

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

Preliminary data as of 03/09/2023

*Response confirmed after data cut-off
RLY-2608-101 Monotherapy – Other tumor types

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

**Assessment**
- Non-CR/Non-PD
- SD
- PD

**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

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

- **RLY-2608 Mono + Combo (N=42)**
  - Nausea: 31%
  - Blood Creatinine Increased: 24%
  - Fatigue: 24%
  - Headache: 24%
  - Hypokalaemia: 21%
  - Decreased Appetite: 17%
  - Diarrhea: 17%
  - Hyperglycemia: 17%

- **RLY-2608 + Fulvestrant (N=23)**
  - Nausea: 44%
  - Blood Creatinine Increased: 30%
  - Fatigue: 22%
  - Headache: 30%
  - Hypokalaemia: 17%
  - Decreased Appetite: 17%
  - Diarrhea: 17%
  - Hyperglycemia: 17%

**AEs leading to alpelisib discontinuation observed with RLY-2608**
(for 400mg BID mono, ≥600mg BID combo; N=17)

- 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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