



Relay Therapeutics Announces Initial Clinical Data Demonstrating that RLY-2608 Selectively Targets Multiple PI3K α Mutations

April 18, 2023

Multiple doses achieved sustained target exposure of ~80%+ mutant PI3K α inhibition

No Grade 3 hyperglycemia, rash or diarrhea observed at target exposures

Favorable initial safety profile at target exposures

Confirmed partial response in breast cancer patient with 12 prior lines of therapy

Initial anti-tumor activity in breast cancer patients observed across range of doses

Relay Therapeutics to host a conference call today, April 18, at 1:30 p.m. ET

ORLANDO, Fla., April 18, 2023 (GLOBE NEWSWIRE) -- [Relay Therapeutics, Inc.](#) (Nasdaq: RLY), a clinical-stage precision medicine company transforming the drug discovery process by combining leading-edge computational and experimental technologies, today announced initial clinical data for RLY-2608, the first known investigational allosteric, pan-mutant and isoform-selective inhibitor of PI3K α . The data support initial clinical proof of mechanism, demonstrating that RLY-2608 achieved selective target engagement at multiple predicted efficacious doses with a favorable initial safety and tolerability profile. These data are being presented today at the American Association for Cancer Research (AACR) Annual Meeting 2023.

"While early, these data suggest that by selectively inhibiting mutant PI3K α and avoiding key off-target toxicities that typically limit the use of non-selective PI3K α pathway inhibitors, RLY-2608 has the potential to transform treatment for patients with a broad range of PI3K α mutations," said Don Bergstrom, M.D., Ph.D., President of R&D at Relay Therapeutics. "At doses achieving target exposure, there was no observed Grade 3 hyperglycemia, rash or diarrhea – the three most common adverse events leading to discontinuation of existing investigational and approved treatments, and radiographic tumor reductions were seen across multiple dose levels. We are continuing dose escalation and expect to initiate expansion cohorts in the second half of 2023."

ReDiscover – RLY-2608 First-in-Human Trial

RLY-2608 is currently being evaluated in an ongoing dose-escalation portion of ReDiscover, a first-in-human trial, which was designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary antitumor activity across two separate arms. The monotherapy arm started in December 2021 and enrolled 19 patients with unresectable or metastatic solid tumors with a PI3K α mutation. This arm included a broad diversity of solid tumors, predominantly tumor types not predicted to be sensitive to single agent PI3K α inhibition. The RLY-2608 + fulvestrant combination arm started April 2022 and enrolled 23 patients with PI3K α -mutant, HR+, HER2– locally advanced or metastatic breast cancer. Across both arms of the study, enrolled patients had received a significant level of prior therapy, including all breast cancer patients who had received at least one prior endocrine therapy and CDK4/6 inhibitor. The cut-off date for data reported at AACR was March 9, 2023.

Broad Range of PI3K α Mutations Represented in Enrolled Patients

Among the 27 patients with breast cancer (4 mono + 23 combo), 12 had kinase mutations, 10 had helical mutations and nine had other mutations.

Sustained Target Exposure of ~80%+ Mutant PI3K α Inhibition Achieved at Multiple Doses

In the monotherapy arm, patients received seven different doses, ranging from 50mg twice daily (BID) to 400mg BID. In the combination arm, patients received five different BID doses, ranging from 100mg to 800mg BID.

RLY-2608 reached selective target exposure at multiple doses, with target exposure being defined as continuous inhibition of mutant PI3K α of approximately 80 percent or greater. This was reached at 400mg BID monotherapy and at 600mg BID and 800mg BID combination doses.

Selective PI3K α Inhibition Demonstrated

RLY-2608 demonstrated mutant selective PI3K α target engagement at multiple doses. There was limited observed impact on glucose homeostasis overall and no Grade 3 hyperglycemia was observed. Glucose homeostasis is believed to be an important indicator of both RLY-2608's clinical selectivity profile and its potential ability to avoid this key off-target toxicity associated with wild-type inhibition.

Declines of PI3K α mutations in ctDNA from patient samples support initial clinical validation of RLY-2608's ability to selectively inhibit a wide range PI3K α mutations in a dose-dependent manner.

Initial Safety Analysis Supports a Meaningfully Differentiated Profile

RLY-2608 has been generally well tolerated in the 42 patients treated as of the cut-off date:

- The overall safety profile consisted of mostly low-grade adverse events (AEs) that were manageable and reversible

- Across all doses, there were no dose-limiting toxicities, no AEs leading to treatment discontinuation and no Grade 4-5 AEs

Among patients receiving doses at target exposures (mono: 400mg BID; combo: 600mg BID & 800mg BID; n=17), AEs were mostly low-grade events that were manageable and reversible:

- No Grade 3 hyperglycemia, diarrhea, or rash, which are the AEs most commonly associated with treatment discontinuation for existing investigational and approved therapies
- No dose reductions or discontinuations due to AEs

The low rate of AE-related dose modifications allowed for median dose intensity of at least 98 percent across all dose levels.

Partial Response Achieved with Monotherapy in Breast Cancer Patient with 12 Prior Lines of Therapy

A patient with metastatic HR+/HER2- breast cancer, with two PI3K α mutations (H1047R, E453K), who progressed following 12 lines of prior therapy, including chemotherapy (including Enhertu®), endocrine and HER2-directed therapies, received RLY-2608 400mg BID monotherapy. An unconfirmed partial response by Response Evaluation Criteria in Solid Tumors (RECIST) was recorded at 8 weeks. Subsequent to the data cut-off, this partial response was confirmed, and the patient remains on treatment with no AEs reported as of April 4, 2023.

Initial Anti-Tumor Activity Observed in Breast Cancer Patients Across Range of Doses

Early anti-tumor activity was seen across a range of doses and across helical, kinase and other mutations, demonstrating selective target engagement of mutant PI3K α .

Among the 16 breast cancer patients with measurable disease:

- Nine experienced radiographic tumor reductions (3 helical, 4 kinase, and 3 other)
- 12 exhibited a best overall response of stable disease and 1 partial response (4 helical, 7 kinase, and 4 other)
- 11 remain on treatment as of the cut-off date

Median duration of treatment for all breast cancer patients was approximately 4 months:

- 70 percent (19/27) remain on treatment as of the cut-off date
- 600mg BID dose: approximately 4-month median follow-up
 - Six of seven 600mg BID patients remain on treatment

To date, a maximum tolerated dose has not been reached and dose exploration is ongoing to determine the recommended dose(s) for the dose expansion cohorts (part 2), which Relay Therapeutics anticipates initiating in the second half of 2023.

RLY-5836 First-in-Human Trial

In April 2023, Relay Therapeutics initiated a first-in-human trial of RLY-5836, the Company's second investigational allosteric, pan-mutant, isoform-selective PI3K α inhibitor, which is chemically distinct from RLY-2608. The trial design is similar to the first-in-human trial of RLY-2608 and can be found [here](#).

Conference Call Information

Relay Therapeutics will host a conference call and live webcast today, April 18, 2023, at 1:30 p.m. ET. Registration and dial-in for the conference call may be accessed through Relay Therapeutics' website under Events in the News & Events section through the following link: <https://ir.relaytx.com/news-events/events-presentations>. An archived replay of the webcast will be available following the event.

The data presentation from the AACR Annual Meeting is also available on the Relay Therapeutics website in the "Publications/Presentations" section through the following link: <https://relaytx.com/pipeline/>.

About RLY-2608 & RLY-5836

RLY-2608 is the lead program of multiple efforts to discover and develop mutant selective inhibitors of PI3K α . RLY-5836 is Relay Therapeutics' second pan-mutant, isoform-selective PI3K α inhibitor, which is chemically distinct from RLY-2608. PI3K α is the most frequently mutated kinase in all cancers, with oncogenic mutations detected in about 14% of patients with solid tumors. RLY-2608 and RLY-5836 have the potential to address more than 100,000 patients per year in the United States, one of the largest patient populations for a precision oncology medicine.

Traditionally, the development of PI3K α inhibitors has focused on the active, or orthosteric, site. The therapeutic index of orthosteric inhibitors is limited by the lack of clinically meaningful selectivity for mutant versus wild-type (WT) PI3K α and off-isoform activity. Toxicity related to inhibition of WT PI3K α and other PI3K isoforms results in sub-optimal inhibition of mutant PI3K α with reductions in dose intensity and frequent discontinuation. The Dynamo™ platform enabled the discovery of RLY-2608, the first known allosteric, pan-mutant, and isoform-selective PI3K α inhibitor and RLY-5836, both designed to overcome these limitations. Relay Therapeutics solved the full-length cryo-EM structure of PI3K α , performed computational long time-scale molecular dynamic simulations to elucidate conformational differences between WT and mutant PI3K α , and leveraged these insights to support the design of RLY-2608 and RLY-5836. RLY-2608 and RLY-5836 are currently being evaluated in first-in-human trials designed to treat patients with advanced solid tumors with a PIK3CA (PI3K α) mutation. For more information on RLY-2608, please visit [here](#), and for more information on RLY-5836, please visit [here](#).

About Relay Therapeutics

Relay Therapeutics is a clinical-stage precision medicine company transforming the drug discovery process by combining leading-edge computational and experimental technologies with the goal of bringing life-changing therapies to patients. As the first of a new breed of biotech created at the intersection of complementary techniques and technologies, Relay Therapeutics aims to push the boundaries of what's possible in drug discovery. Its Dynamo™ platform integrates an array of leading-edge computational and experimental approaches designed to drug protein targets that have previously been intractable or inadequately addressed. Relay Therapeutics' initial focus is on enhancing small molecule therapeutic discovery in targeted oncology and genetic disease indications. For more information, please visit www.relaytx.com or [follow us on Twitter](#).

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding the potential of RLY-2608 or RLY-5836 to address a major unmet medical need; whether initial clinical results of RLY-2608 or RLY-5836 will be predictive of final results in future clinical trials; potential therapeutic effects and anticipated clinical benefits of RLY-2608 or RLY-5836; Relay Therapeutics' strategy, business plans and focus; the progress and timing of updates on the clinical development of the programs across Relay Therapeutics' portfolio, including RLY-2608; and expected therapeutic benefits of its programs. The words "may," "might," "will," "could," "would," "should," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: the impact of global economic uncertainty, geopolitical instability, or public health epidemics or outbreaks of an infectious disease, such as COVID-19, on countries or regions in which Relay Therapeutics has operations or does business, as well as on the timing and anticipated results of its clinical trials, strategy, future operations and profitability; the delay of any current or planned clinical trials or the development of Relay Therapeutics' drug candidates; the risk that the preliminary results of its preclinical or clinical trials, including ReDiscover, may not be predictive of future or final results in connection with future clinical trials of its product candidates; Relay Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of its planned interactions with regulatory authorities; and obtaining, maintaining and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in Relay Therapeutics' most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Relay Therapeutics' views only as of today and should not be relied upon as representing its views as of any subsequent date. Relay Therapeutics explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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