Relay Therapeutics Announces Preclinical Data that Support Clinical Development of RLY-2608 as Both a Single Agent and in Combination

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RLY-2608 combines with standard of care therapies to drive regressions in ER+/HER2- breast cancer models

CAMBRIDGE, Mass., Dec. 10, 2021 (GLOBE NEWSWIRE) -- Relay Therapeutics, Inc. (Nasdaq: RLAY), a clinical-stage precision medicine company transforming the drug discovery process by combining leading-edge computational and experimental technologies, today shared additional preclinical data at the 2021 San Antonio Breast Cancer Symposium for RLY-2608, the first known allosteric, pan-mutant and isoform-selective PI3Kα inhibitor. The data presented in the poster help support the clinical development of RLY-2608 both in single agent and combination clinical trials for patients with PIK3CA (PI3Kα) mutant tumors, including PI3Kα-mutant, HR+/HER2- breast cancer.

The data indicate RLY-2608 synergizes with fulvestrant and the CDK4/6 inhibitor abemaciclib in cell viability assays in PIK3CAmut/ER+/HER2- cell lines. Oral administration of RLY-2608 in combination with fulvestrant or abemaciclib led to improved efficacy compared to either agent alone in ER+/HER2- xenograft models representing the most commonly observed PIK3CA mutations in breast cancer (H1047R, E542K, E545K). The triple combination of all three agents resulted in deep regressions across all models. Additionally, the combination arms had similar tolerability to monotherapy arms.

“We continue to validate our novel allosteric approach for PI3Kα inhibition and believe that RLY-2608 has the potential to overcome many of the toxicity limitations seen with non-selective orthosteric inhibition of PI3K that lead to frequent discontinuations and challenges combining with standard of care inhibitors,” said Don Bergstrom, M.D., Ph.D., executive vice president of R&D at Relay Therapeutics. “This preclinical profile supports the clinical development of RLY-2608 as what we believe is a truly differentiated molecule that can be safe and effective both as a single agent and in combination, and has the potential to address a major unmet medical need for patients with PI3Kα mutant tumors, PI3Kα-mutant, HR+/HER2- breast cancer.”

The data presented at the conference also include previously presented preclinical data, showing RLY-2608 preferentially binds to the mutant protein, and binding occurs in a novel allosteric pocket and thus is not abrogated by buparlisib, an orthosteric site inhibitor. The data show that RLY-2608 binds faster to the mutant protein and demonstrates biochemical selectivity for mutant PI3Kα over wild type (WT) and other family member isoforms in addition to exquisite selectivity over the rest of the kinome. RLY-2608 is shown to inhibit phosphorylated AKT (pAKT) in PI3Kα mutant cancer cell lines independent of the hotspot mutation and inhibit proliferation. Finally, the data show that RLY-2608 demonstrates potent tumor growth inhibition in a dose-dependent manner leading to full regressions at doses associated with minimal impact on insulin levels, in contrast to non-selective orthosteric inhibitors.

These results support clinical investigation of RLY-2608 as a differentiated mechanism of mutant PI3Kα inhibition with the first-in-human study anticipated to start in the first half of 2022.

The poster presentation from the 2021 San Antonio Breast Cancer Symposium is available on the Relay Therapeutics website at https://relaytx.com/publications.

About RLY-2608

RLY-2608 is the lead program of multiple preclinical efforts to discover and develop mutant selective inhibitors of PI3Kα. PI3Kα is the most frequently mutated kinase in all cancers, with oncogenic mutations detected in about 13% of patients with solid tumors. Traditionally, the development of PI3Kα 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 WT PI3Kα and off-isoform activity. Toxicity related to inhibition of WT PI3Kα and other PI3K isoforms results in sub-optimal inhibition of mutant PI3Kα with reductions in dose intensity and frequent discontinuation. The Dynamo™ platform enabled the discovery of RLY-2608, the first known allosteric, pan-mutant (H1047X, E542X and E545X), and isoform-selective PI3Kα inhibitor designed to overcome these limitations. Relay Therapeutics solved the full-length cryo-EM structure of PI3Kα, performed computational long time-scale molecular dynamic simulations to elucidate conformational differences between WT and mutant PI3Kα, and leveraged these insights to support the design of RLY-2608. RLY-2608 is on path to initiate a first-in-human clinical trial in the first half of 2022, subject to submission of an investigational new drug application and acceptance by the FDA.

About Relay Therapeutics

Relay Therapeutics (Nasdaq: RLAY) is a clinical-stage precision medicines company transforming the drug discovery process by combining leading-edge computational and experimental technologies with the goal of bringing life-changing therapies to patients. Relay Therapeutics is the first of a new breed of biotech created at the intersection of disparate technologies. Relay Therapeutics’ 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 plans and timelines for the clinical development of RLY-2608, including the timing of initiation of a first-in-human clinical trial of RLY-2608, potential therapeutic effects and anticipated clinical benefits of RLY-2608, as a monotherapy and in combination; the potential of RLY-2608 to be a differentiated molecule; the potential of RLY-2608 to address a major unmet medical need; whether preclinical results of RLY-2608 will be predictive of future clinical trials of RLY-2608; and Relay Therapeutics' strategy, business plans and focus. The words "may," "might," "will," "could," "would," "should," "expect," "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 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 and future operations; the delay of any current or planned clinical trials or the development of Relay Therapeutics' drug candidates; the risk that the results of its clinical trials may not be predictive of future results in connection with future clinical trials; Relay Therapeutics' ability to successfully demonstrate the safety and efficacy of its drug candidates; the timing and outcome of Relay Therapeutics' 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 or 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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