Prelude Announces Presentations at 2025 AACR Annual Meeting

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Preclinical data elucidating the mechanism of action of PRT3789, Prelude's first-in-class, highly selective SMARCA2 degrader currently in early clinical development

Highlights from Prelude's efforts to discover and develop selective KAT6A degraders, including preclinical data, demonstrating potential for a differentiated efficacy and safety profile

WILMINGTON, Del., April 25, 2025 (GLOBE NEWSWIRE) -- Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today announced the presentation of new preclinical data at the American Association for Cancer Research (AACR) Annual Meeting for its highly selective IV SMARCA2 degrader and its highly selective KAT6A degraders.

Peggy Scherle, Ph.D., Chief Scientific Officer of Prelude, stated, "We are pleased to provide further preclinical data on the discovery of our lead selective SMARCA2 degrader PRT3789, currently advancing in early clinical development for patients with SMARCA4 mutated cancers. We are also delighted to report initial preclinical data from our selective KAT6A degrader discovery program. These data demonstrate that selectively degrading KAT6A results in robust anti-cancer activity in various pre-clinical models of breast cancer and other solid tumors. We believe that our first-in-class, highly potent KAT6A selective degraders have the potential to expand the therapeutic reach of KAT6A/B inhibitors currently advancing in the clinic, while addressing safety challenges associated with non-selective approaches to this clinically validated target."

Details on the presentations are as follows:

Title: Elucidating the Molecular Mechanism of Action of the First-in-Human SMARCA2 Selective Degrader PRT3789

Summary:

- PRT3789 is a first-in-human SMARCA2 degrader that selectively induces deep and sustained SMARCA2 degradation in preclinical and clinical studies.
- PRT3789 achieves high selectivity by inducing a more stable ternary complex between SMARCA2 and VHL than SMARCA4 and VHL.
- K1405 loop in SMARCA2 provides a unique lysine residue to enable selective ubiquitination and also stabilizes the SMARCA2:PRT3789:VHL complex.
- SMARCA2 resynthesis rate is 2-3 times slower than SMARCA4 thereby enhancing the selectivity profile and contributing to the broad therapeutic index and favorable safety profile observed with PRT3789 in clinical studies to date.
- PRT3789 is currently under evaluation in Phase 1 and Phase 2 studies in patients with advanced solid tumors with loss of SMARCA4 (NCT05639751 and NCT06682806).

Link: Publications – Prelude Therapeutics (preludetx.com)

Title: Discovery of First-in-Class Potent and Selective Oral Degraders of KAT6A that Demonstrate Anti-cancer Activity in Pre-clinical Models

Summary:

- KAT6A expression is associated with cancer growth and is recurrently amplified in breast, lung, ovarian and other cancers.[1]
- KAT6 is a clinically validated target with a dual KAT6A/B inhibitor recently demonstrating promising efficacy in heavily pre-treated patients with ER+/HER2- breast cancer, albeit with potential on-target safety considerations including neutropenia.[2]
- Prelude hypothesized that a targeted protein degradation approach could enable discovery of KAT6A selective candidates with potential for improved hematological safety and more robust single agent activity relative to other KAT6-targeted approaches.
- Prelude believes that it has identified a series of first-in-class, sub-nanomolar, selective and readily orally bioavailable KAT6A degraders now advancing to candidate nomination.

- Pre-clinical data presented demonstrate that Prelude's selective KAT6A degraders:
  - Drive significantly deeper anti-cancer responses compared to non-selective KAT6A/B inhibitors across multiple KAT6A-amplified tumors.
  - Disrupt the histone acetyltransferase (HAT) complex resulting in a deeper biological effect on ERα expression.
  - Show sustained activity in *ESR1*- and *Pi3Kalpha*-mutated cells, as well as endocrine therapy- and CDK4/6i-resistant cells.
  - Exhibit robust combination benefit with SoC and potential synergy with next generation breast cancer therapies.
  - Deliver robust *in vivo* target engagement and deep tumor regressions, including complete regressions, in breast and lung cancer xenografts as a monotherapy at low oral daily doses.
  - Display reduced hematologic toxicity compared to KAT6A/B inhibitors.

Link: Publications – Prelude Therapeutics (preludetx.com)

1. White J, et al., Histone lysine acetyltranferase inhibitors: an emerging class of drugs for cancer therapy. Trends Pharmacol Sci 45 (3): 243-254 (2024).
2. Sharma S, et al., Discovery of a highly potent, selective, orally bioavailable inhibitor of KAT6A/B histone acetyltransferases with efficacy against KAT6A-high ER+ breast cancer. Cell Chem Biol 30 (10):1191- 1210 (2023).

About Prelude Therapeutics
Prelude Therapeutics is a leading precision oncology company developing innovative medicines in areas of high unmet need for cancer patients. Our pipeline is comprised of several novel drug candidates including first-in-class, highly selective SMARCA2 and KAT6A degraders, and ongoing research into other precision oncology targets. We are also leveraging our expertise in targeted protein degradation to discover, develop and commercialize next generation degrader antibody conjugates (Precision ADCs) with partners. We are on a mission to extend the promise of precision medicine to every cancer patient in need. Our corporate presentation can be found at Events & Presentations – Prelude Therapeutics. For more information, visit preludetx.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, anticipated discovery, preclinical and clinical development activities for Prelude's product candidates, and the potential safety, efficacy, benefits and addressable market for Prelude's product candidates. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. The words "believes," "anticipates," "estimates," "plans," "expects," "intends," "may," "could," "should," "potential," "likely," "projects," "continue," "will," "schedule," and "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are predictions based on the Company's current expectations and projections about future events and various assumptions. Although Prelude believes that the expectations reflected in such forward-looking statements are reasonable, Prelude cannot guarantee future events, results, actions, levels of activity, performance or achievements, and the timing and results of biotechnology development and potential regulatory approval is inherently uncertain. Forward-looking statements are subject to risks and uncertainties that may cause Prelude's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to Prelude's ability to advance its product candidates, the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, clinical trial sites and our ability to enroll eligible patients, supply chain and manufacturing facilities, Prelude's ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of preclinical and clinical trials, Prelude's ability to fund development activities and achieve development goals, Prelude's ability to protect intellectual property, and other risks and uncertainties described under the heading "Risk Factors" in Prelude's Annual Report on Form 10-K for the year ended December 31, 2024, its Quarterly Reports on Form 10-Q and other documents that Prelude files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and Prelude undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof, except as may be required by law.

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