Prelude Therapeutics' SMARCA2 Degrader PRT3789 Demonstrated Promising Initial Clinical Activity and Safety Profile in Phase 1 Trial

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- *Encouraging signs of anti-tumor activity including objective responses observed in patients with SMARCA4-mutated non-small cell lung cancer (NSCLC) and esophageal cancer in early PRT3789 monotherapy dose escalation*

- *At doses studied to date, PRT3789 was generally well-tolerated with no dose-limiting toxicities or study drug-related serious adverse events*

- *Company to host investor conference call and webcast on Friday, September 13, 2024 at 12:00 PM EST*

WILMINGTON, Del., Sept. 13, 2024 (GLOBE NEWSWIRE) -- Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today announced the first interim clinical data from its ongoing Phase 1 open-label, dose-escalation trial of PRT3789, a first-in-class SMARCA2 degrader, highly selective for SMARCA2 and designed to treat cancer patients with a SMARCA4 mutation. The data were presented at the European Society for Medical Oncology (ESMO) Congress 2024 in Barcelona, Spain.

The study investigators reported that, as of the August 5, 2024 data cutoff date (the Cutoff Date), 65 patients were safety evaluable, enrolled and treated. This included 46 efficacy evaluable patients (with a post-baseline scan) with any tumor type harboring any SMARCA4 mutation.

As reported today by the study investigators, PRT3789 was generally well-tolerated through 8 dosing cohorts. Dose escalation continues, now in the 9th dosing cohort. The majority of adverse events reported by investigators have been mild to moderate. A maximum tolerated dose has not yet been identified.

Overall, of the 26 advanced, heavily pre-treated NSCLC or esophageal patients evaluable for efficacy, 7 had tumor shrinkage. RECIST confirmed partial responses (PRs) were observed in 3 patients. Additional patients demonstrated clinical benefit as measured by prolonged stable disease (SD) including one patient on treatment for more than 1 year.

"For cancer patients harboring a SMARCA4 mutation, the disease is particularly aggressive and prognosis with current standard of care is quite poor," stated Robin Guo, M.D., Memorial Sloan Kettering Cancer Center. "The observation of durable stable disease and tumor regressions in Phase I monotherapy dose escalation, coupled with a tolerable emerging safety profile, is encouraging. This is what we hope to see with a first-in-class new therapy for a novel target in patients with a high unmet need."

"We are encouraged by the early clinical activity and emerging safety profile observed to date with PRT3789," stated Jane Huang, M.D., President and Chief Medical Officer of Prelude. "These data represent initial proof of concept that selective SMARCA2 degradation can yield antitumor activity in certain SMARCA4 mutated cancers."

Continued Dr. Huang, "Monotherapy dose escalation continues, now at cohort 9 (500mg once weekly) with backfill cohorts continuing to enroll enriched for NSCLC and esophageal cancer patients with Class 1 mutations. We intend to confirm the biologically active dose for PRT3789 as monotherapy by year-end and continue to advance monotherapy and docetaxel combination studies in parallel to best position PRT3789 as a new treatment option for patients suffering from this aggressive type of cancer."

PRT3789 Interim Phase 1 Results
PRT3789 is currently being evaluated in an ongoing dose-escalation Phase 1 trial in patients with solid tumors harboring any SMARCA4 mutation refractory to standard of care and generally multiple lines of therapy in most patients. As of the Cutoff Date, 65 patients with advanced cancer have been treated at eight dose levels (24 mg QW, 48 mg QW, 80 mg QW, 120 mg QW, 160 mg QW, 212 mg QW, 283 mg QW, 376 mg QW). The median age of these patients is 62 and the median number of prior treatments was 3 (ranging from 1-10). 34 patients (52.3%) presented with a Class 1 (loss of function) SMARCA4 mutation, while 24 patients (36.9%) presented with a Class 2 (missense, VUS) SMARCA4 mutation and 7 (10.8%) had a loss of SMARCA4 protein.

Initial Safety Data
PRT3789 was generally well-tolerated in the 65 patients treated as of the Cutoff Date. Adverse events are reported regardless of attribution to study drug. Adverse events of any grade observed to date consisted of nausea (24.5%), decreased appetite (18.5%), fatigue (18.5%), abdominal pain (16.9%), anemia (16.9%) and constipation (15.4%). No dose limiting toxicities were observed and no study drug-related serious adverse events were reported.

Pharmacokinetic (PK) and Pharmacodynamic (PD) Data
Preliminary PK data was available from 24 mg to 376 mg dose cohorts. A general trend of increases in exposure (Cmax, AUC) with dose was observed. Mean concentrations were observed above SMARCA2 plasma DC_{50} (21 nM) for approximately 8 hours at the 376 mg dose. No accumulation was observed with repeat dose administration, consistent with the half-life and once-weekly administration. PD effect observed was more prolonged than PK half-life, reaching trough inhibition of 70-75% at higher doses. Increasing doses demonstrated a deeper and more prolonged PD effect. Evaluation of the AUC of PD (SMARCA2 and SMARCA4) demonstrated a dose dependent decrease of SMARCA2 but not SMARCA4, demonstrating the high selectivity of PRT3789.

Analysis of Initial Clinical Activity
As of the Cutoff Date, there were 46 efficacy evaluable patients with a post-baseline scan across all tumor types with any SMARCA4 mutation. Of the 26 advanced, heavily pre-treated NSCLC or esophageal patients who were evaluable for efficacy, 7 had tumor shrinkage. RECIST confirmed partial responses (PRs) were observed in 3 patients (2 esophageal, 1 NSCLC). Tumor shrinkage was observed in patients with both Class 1 and Class 2 SMARCA4 mutations. Additional patients on study demonstrated clinical benefit as measured by prolonged SD. One patient remains on study having

been treated for more than 1 year. Of the 20 patients with tumor types other than NSCLC and esophageal cancer, none demonstrated tumor shrinkage at dose levels studied to date.

Conference Call and Webcast Information
Prelude Therapeutics management team will host a conference call, live webcast with slides and a Q&A on Friday, September 13, 2024 at 12:00 PM ET. A live webcast of the presentation will be available at Events & Presentations - Prelude Therapeutics (preludetx.com). A replay of the webcast will be available shortly after the conclusion of the call at Events & Presentations - Prelude Therapeutics (preludetx.com) and archived on the Company's website for 60 days following the call.

Interim Phase 1 data selected for Plenary Session at upcoming EORTC-NCI-AACR Symposium
Interim Phase 1 data for PRT3789 was also selected for a Plenary Session oral presentation at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. The presentation titled, *"First Clinical Results from a Phase 1 Trial of PRT3789, a First-in-Class SMARCA2 Degrader, in Patients with Advanced Solid Tumors with a SMARCA4 Mutation*," will be presented by Timothy Yap, M.D. from University of Texas MD Anderson Cancer Center. The presentation is scheduled for October 24, 2024 at 10:00 AM CEST (4:00 AM EST) as part of the Proffered Papers: Advancing Patient Care Through Novel Clinical Trials session.

About PRT3789 – A first-in-class, highly selective, intravenous SMARCA2 degrader

PRT3789 is a first-in-class SMARCA2 degrader, highly selective for SMARCA2 and designed to treat patients with a SMARCA4 mutation. Cancer patients whose tumors have SMARCA4 mutations have a poor prognosis and as a result, this is an area of high unmet medical need.

PRT3789 is in Phase 1 clinical development in biomarker selected SMARCA4 mutant patients. Enrollment remains on track, and the Company expects to conclude monotherapy dose escalation in 2024 and identify a recommended Phase 2 dose. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations is ongoing, as is enrollment of the docetaxel combination cohort.

Objectives for this first Phase 1 clinical trial are to establish the safety and tolerability profile of PRT3789 as both monotherapy and in combination with docetaxel, evaluate activity, pharmacokinetics and pharmacodynamics and determine a dose and potential indications for advancement into registrational clinical trial(s).

Prelude launched an educational video series focused on the science of SMARCA biology, the discovery of first-in-class, highly selective SMARCA2 degraders and the unmet medical need for patients with SMARCA4 mutated cancer. This series can be found on the Company's website under Highly Selective SMARCA2 Degraders - Prelude Therapeutics (preludetx.com).

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 IV and oral SMARCA2 degraders, and a potentially best-in-class CDK9 inhibitor. 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. 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, the potential safety, efficacy, benefits and addressable market for Prelude's product candidates, and the expected timeline for concluding the monotherapy dose escalation and identifying the biologically active dose, and expected ongoing work on and development of PRT3789. 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, 2023, 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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