Prelude Therapeutics Presents New Data from SMARCA Degrader Portfolio at the 36th EORTC-NCI-AACR Symposium

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– Interim data from ongoing trial of PRT3789 showed additional clinical activity at higher doses in patients with non-small cell lung cancer (NSCLC)

– First safety data presented from combination study of PRT3789 and docetaxel demonstrated an acceptable safety profile

– First preclinical proof-of-concept data presented from precision antibody drug conjugate program deploying a novel SMARCA2/4 dual degrader payload

WILMINGTON, Del., Oct. 24, 2024 (GLOBE NEWSWIRE) -- Prelude Therapeutics Incorporated (Nasdaq: PRLD) ("Prelude" or the "Company"), a clinical-stage precision oncology company, today announced the presentation of additional data from its ongoing Phase 1 open-label, dose-escalation trial of PRT3789, a first-in-class, highly selective SMARCA2 degrader designed to treat cancer patients with a SMARCA4 mutation. The data were presented at a plenary session of the 36th Annual EORTC-NCI-AACR Symposium in Barcelona, Spain.

The study investigators reported, as of September 23, 2024 (the Cutoff Date), additional follow up data on 65 patients that were enrolled, treated, and safety evaluable. PRT3789 was generally well-tolerated through 8 dosing cohorts. The majority of adverse events reported by investigators have been mild to moderate.

Overall, of the 26 advanced, heavily pre-treated NSCLC or esophageal patients with Class 1 (loss of function) mutations evaluable for efficacy, now with additional follow up, RECIST partial responses (PRs) were confirmed in 4 patients, including 2 of 9 NSCLC patients with confirmed PRs at doses of 283 mg or higher. As anticipated, higher doses are resulting in deeper and more sustained SMARCA2 degradation in PBMCs. Additional patients demonstrated clinical benefit as measured by prolonged stable disease (SD) including one patient on treatment for more than a year.

"We, along with our study investigators, are encouraged by the promising activity shown to date by PRT3789 in this novel first-in-class mechanism for patients who have limited treatment options," stated Jane Huang, M.D., President and Chief Medical Officer of Prelude. "We look forward to further characterizing and understanding the full potential of PRT3789 through ongoing monotherapy dose escalation and in combination studies with both docetaxel and pembrolizumab."

PRT3789 Interim Phase 1 Results
PRT3789 is currently being evaluated in an ongoing dose-escalation Phase 1 trial in heavily pre-treated patients with advanced solid tumors harboring any SMARCA4 mutation who have relapsed/refractory disease. Sixty-five patients with advanced cancer were treated once weekly via intravenous infusion at eight dose levels (24 mg, 48 mg, 80 mg, 120 mg, 160 mg, 212 mg, 283 mg, 376 mg), and follow up data reported through to September 23, 2024. The median age of these patients was 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. Treatment emergent adverse events of any grade observed to date consisted of nausea (26.2%), fatigue (21.5%), anemia (20.0%), decreased appetite (20.0%), abdominal pain (18.5%), and constipation (18.5%). 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 (as measured by SMARCA2 protein levels in peripheral blood mononuclear cells) observed was more prolonged than PK half-life. Higher dose levels, above 212 mg, demonstrated a deeper, more consistent, and more prolonged PD effect. SMARCA2 degradation was observed in both peripheral blood mononuclear cells (PBMC) and in available tumor tissue as shown through biopsy.

Analysis of Initial Clinical Activity
Of the 26 advanced NSCLC or esophageal patients with Class 1 (loss of function) mutations who were evaluable for efficacy, RECIST confirmed partial responses (PRs) were observed in 4 patients (2 esophageal, 2 NSCLC), including 2 of 9 NSCLC patients with confirmed PRs at doses of 283 mg or higher. 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, including one advanced NSCLC patient who remains stable and on study having been treated for more than 1 year.

Initial observations of safety from evaluable patients in the PRT3789 plus docetaxel combination dose escalation arm of the trial were also presented. To date, PRT3789 in combination with docetaxel demonstrated an acceptable safety profile, with no dose limiting toxicities or study drug serious adverse events reported.

Additional SMARCA Degrader Presentations

The Company also provided two poster presentations at the conference.

The Selective SMARCA2 Degrader, PRT3789, Counteracts the Protective Cellular Stress Response to Chemotherapy and Enhances the Efficacy of Standard of Care Chemotherapeutic Agents in SMARCA4 Mutant NSCLC Models

The combination of PRT3789 with standard of care NSCLC chemotherapy agents significantly enhances anti-tumor activity in preclinical models of SMARCA4-mutated NSCLC. Downregulation of dominant gene pathways by PRT3789, specifically counters docetaxel-induced upregulation of the E2F and G2/M pathways, resulting in a more comprehensive cell cycle blockade and increased apoptosis in SMARCA4-mutated cells. This synergistic activity was observed with both Class I (loss of function) mutations and Class II (missense) mutations.

Discovery of First-in-Class Precision Antibody Drug Conjugates with a Potent SMARCA 2/4 Dual Degrader Payloads that Safely Achieve Maximal and Tumor Specific Degradation and Efficacy in Mouse Models

PRP0004 is a potent SMARCA2/4 dual degrader that robustly inhibits cancer cell growth and induces cell death. Conjugation of PRP0004 to clinically-validated antibodies yielded novel degrader antibody conjugates (DACs), which demonstrated potent and antigen-selective internalization and SMARCA2 and SMARCA4 degradation in cell lines derived from multiple cancers. Prostate cancer cell lines were among the most sensitive to the PRP0004 degrader payload. PRP0004 downregulated multiple drivers of prostate cancer cell growth and survival and resulted in cell death, rationalizing the use of PSMA-targeting antibodies for initial proof-of-concept studies in preclinical models.

As expected, dosing with PRP0004 on its own was highly efficacious in prostate cancer xenografts but displayed a narrow therapeutic window. However, when delivered as a payload on anti-PSMA antibodies, the anti-PSMA SMARCA2/4 DACs demonstrate robust SMARCA2 and SMARCA4 degradation and antigen-dependent efficacy in xenograft models while being well-tolerated. These data highlight the potential of this first-in-class precision ADC approach utilizing a highly potent SMARCA2/4 dual degrader payload to achieve maximal target degradation in tumors while sparing healthy tissues. This strategy has the potential to significantly expand the reach of Prelude's novel SMARCA degraders to treating patients without SMARCA4 mutations.

"Preclinical data presented today with our novel approach to develop degrader antibody conjugates by using potent dual degraders of SMARCA2 and 4 as payloads offers first proof-of-concept of effectively and safely targeting an important mechanism to treat cancers beyond those with SMARCA4 mutations" stated Peggy Scherle, Ph.D., Chief Scientific Officer of Prelude.

All of the above noted presentations can be found at Publications - Prelude Therapeutics (preludetx.com).

About PRT3789-01
PRT3789 is a first-in-class, potent and highly selective SMARCA2 degrader, in Phase 1 clinical development in SMARCA4-mutated patients. Enrollment remains on track, and the Company expects to conclude monotherapy dose escalation by year end 2024 and identify the biologically active dose to advance for future registrational trials. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations at higher dose levels is ongoing. The objective is to assess clinical activity in a more homogeneous group of patients with high unmet need to support planned discussions with regulatory agencies. A maximum tolerated dose has not yet been identified. Dose escalation continues, now in the 10^{th} dosing cohort (665 mg IV once weekly).

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 clinical trial results 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, 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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