Prelude Therapeutics Provides Clinical Update and Announces Presentation of New Preclinical Data at the Upcoming 2022 AACR Annual Meeting

March 9, 2022

Announces strategic prioritization within lead programs targeting PRMT5 and MCL1

Describes new pipeline candidate, PRT3645, a highly brain penetrant CDK4/6 inhibitor; IND submission planned mid-2022

Advances PRT2527, a highly selective CDK9 inhibitor, with the goal of establishing a recommended Phase 2 dose in 2H/2022

Progresses its highly selective potential first-in-class SMARCA2/BRM degrader with IND submission planned by year-end 2022

Data from all of Prelude's portfolio programs to be presented at the upcoming AACR Annual Meeting

WILMINGTON, Del., March 09, 2022 (GLOBE NEWSWIRE) -- Prelude Therapeutics Inc. (Nasdaq: PRLD), a clinical-stage precision oncology company, today provided a clinical update on its diverse and growing pipeline and announced that new preclinical data have been accepted for presentation at the upcoming 2022 American Association for Cancer Research (AACR) Annual Meeting being held April 8-13 in New Orleans, Louisiana.

"Through disciplined and effective execution, Prelude made meaningful progress across all of our portfolio programs in 2021," said Kris Vaddi, Ph.D., Chief Executive Officer. "Because of these efforts, we now have five distinct precision oncology programs with four internally discovered molecules in clinical development. One of our key objectives in 2022 is to focus our development efforts and generate the clinical data necessary to prioritize these programs. For the PRMT5 program, which includes PRT543 and PRT811, we are concentrating our efforts on PRT811 because of its superior safety profile, higher level of target engagement, and unique brain penetrant properties. Our development efforts for PRT811 are focused on specific indications, including splicing mutated myeloid malignancies and solid tumors, including uveal melanoma, and IDH1 mutated high grade glioma. We anticipate reporting data from the ongoing dose expansion cohorts in 2H/2022."

"For our MCL1 program, in which we have both an oral and intravenous formulation for PRT1419 currently in clinical development, our priority is to advance the intravenous formulation in combination with venetoclax to rapidly establish proof-of-concept in myeloid malignancies. Provided this combination is well-tolerated, we believe PRT1419 has the potential to be a best-in-class MCL1 inhibitor. We look forward to reporting data from the combination study in 2H/2022."

Dr. Vaddi added, "We are particularly excited to announce the newest addition to our pipeline, PRT3645, a novel, highly brain penetrant CDK4/6 inhibitor. Despite the success of approved CDK4/6 inhibitors in HR+ breast cancer, their utility in breast cancer with brain metastasis and other CNS cancers remains limited because of their low brain penetration. We have also made significant progress in our SMARCA2/BRM protein degrader program and have identified highly selective, potential first-in-class lead molecules. An IND submission for PRT3645 is planned for mid-year, with a second IND submission for our SMARCA2/BRM candidate by year-end 2022."

Data from all of Prelude's portfolio programs will be presented at the upcoming AACR annual meeting, underscoring the strength of the Company's internal discovery engine to produce differentiated, optimal small molecule therapies for cancer patients in key areas of unmet need.

Clinical Update

PRMT5 (PRT543/PRT811)

PRMT5 plays essential roles in promoting cancer cell growth and survival. Overexpression of PRMT5 is associated with poor outcomes and decreased survival in several cancers. Prelude's PRMT5 program includes two lead compounds, PRT543 and PRT811.

Based on data from the ongoing Phase 1 dose expansion studies of both PRT543 and PRT811, Prelude is concentrating its further development efforts on PRT811 in biomarker-selected patients in specific cancer types. While the Company believes that both PRT811 and PRT543 are high quality, clinically active compounds, PRT811 was selected based on its superior safety profile, higher level of target engagement, and unique brain penetrant properties.

Specifically Prelude intends to:

- Focus clinical development in select patient populations where clinical activity has been observed, including splicing mutated myeloid malignancies and solid tumors, including uveal melanoma, and IDH1 mutated high grade gliomas
- Complete data analysis of the ongoing expansion cohort of adenoid cystic carcinoma (ACC) by mid-year to determine if further development is warranted
- Report data from the ongoing dose expansion cohorts in 2H/2022

- Determine appropriate development options for PRT811 based on emerging data from ongoing expansion cohorts

MCL1 (PRT1419): MCL1 is a member of the anti-apoptotic BCL2 family of proteins and has also been implicated in mediating resistance to chemotherapeutic agents and targeted therapies. PRT1419 is a potent, selective inhibitor of MCL1 currently in Phase 1 development as oral and intravenous (IV) formulations.

Based on the data to date, the Company plans to:

- Prioritize development of the IV formulation of PRT1419, which demonstrated a desirable pharmacokinetic, pharmacodynamic and safety profile with potential for differentiation from competitor compounds
- Initiate combination trial with venetoclax by mid-year, with the goal of establishing safety, clinical activity and a recommended Phase 2 dose by 2H/2022

CDK9 (PRT2527): CDK9 is a cyclin dependent kinase and an essential regulator of cancer-promoting transcriptional programs and an important driver in *Myc*-driven solid tumors and myeloid malignancies. PRT2527 is a potent and highly selective CDK9 inhibitor currently being evaluated in a Phase 1 dose escalation study in patients whose cancers are likely to be dependent on CDK9.

The key objective for PRT2527 in 2022 is to:

- Complete enrollment in the Phase 1 dose escalation study of PRT2527 with the goal of identifying a recommended Phase 2 dose by 2H/2022

CDK4/6 (PRT3645): CDK4 and CDK6 are validated targets in HR+ breast cancers. Approved CDK4/6 inhibitors have limited utility in breast cancers with brain metastases and other central nervous system (CNS) cancers, including glioblastoma multiforme (GBM). PRT3645 is a highly potent, selective and brain penetrant CDK4/6 inhibitor that demonstrated greater than 10x brain penetration compared to approved CDK4/6 agents in preclinical models. Prelude intends to develop PRT3645 in these underserved cancers.

For PRT3645, Prelude plans to:

- Complete investigational new drug (IND)-enabling studies, file IND and initiate Phase 1 in 2H/2022

SMARCA2/BRM Protein Degrader: SMARCA2 (BRM) and SMARCA4 (BRG1) are the core catalytic subunits of the SWI/SNF complexes that control gene transcription. When SMARCA4 is lost because of mutations, cancer cells become highly dependent on SMARCA2 for their survival. Prelude has identified a number of highly selective SMARCA2 degraders that have the potential to be first-in-class for SMARCA4-deleted cancers.

During 2022, Prelude intends to:

- Complete IND-enabling studies and submit an IND application by year-end 2022

Summary of AACR Accepted Abstracts

Title: PRT2527, a novel highly selective cyclin-dependent kinase 9 (CDK9) inhibitor, is active in preclinical models of prostate cancer
Abstract: 5471
Date and Time: Friday, April 8, 2022, 12:00 pm CT – 1:00 pm CT
Session Title: Small Molecule Therapeutic Agents
Presenter: Dr. Elisa Federici, Institute of Oncology Research, Università della Svizzera Italiana

- Conclusion: PRT2527 was evaluated in prostate cancer models to assess its effects on cell proliferation, stem-cell-like properties, and tumor growth. Collectively, the data demonstrate that PRT2527 had potent antitumor activity in multiple models of castration-sensitive and castration-resistant prostate cancer, inhibited *Myc* transcriptional activity and reduced tumor stem-like cells.

Title: Combination of the MCL1 inhibitor PRT1419 and SMARCA2 degrader PRT3789 shows combinatorial benefit in SMARCA4 deleted lung cancer
Abstract: 420
Date and Time: Sunday, April 10, 2022, 1:30 pm CT – 5:00 pm CT
Session Title: Protein Degraders and Proteasome Inhibitors
Presenter: Norman Fultang, Prelude Therapeutics

- Conclusion: The abstract highlights new preclinical data demonstrating synergistic benefit when PRT1419 was combined with the Company's novel and selective SMARCA2 degrader, PRT3789, in SMARCA4 deleted lung cancer models. Potent synergistic interaction in SMARCA4 deleted cell lines was observed *in vitro*, whereas no additive benefit was seen in SMARCA4 WT lines. Combining PRT1419 and PRT3789 *in vivo* in cell line-derived xenograft models resulted in significant tumor growth inhibition, including tumor regressions.

Title: PRMT5 inhibitor PRT543 displays potent antitumor activity in U2AF1^{S34F} and RBM10^{LOF} spliceosome-mutant non-small cell lung cancer *in vitro* and *in vivo*
Abstract: 2159
Date and Time: Monday, April 11, 2022, 3:50 pm CT – 4:05 pm CT
Session Title: Emerging New Anticancer Agents
Presenter: Jack Carter, Prelude Therapeutics

- Conclusion: The abstract highlights *in vitro* and *in vivo* activity of PRT543 in cancer cells harboring mutations in spliceosome factors such as U2AF1 and RBM10, which occur in ~5-10% of all NSCLC. Both U2AF1 and RBM10 mutant cell lines were significantly more sensitive to PRT543 compared to wild-type cell lines. PRT543 increased the effectiveness of chemotherapeutic agents both *in vitro* and *in vivo*. These results suggest PRMT5 inhibitors may be beneficial in cancers with these mutations.

Title: Brain penetrant CDK4/6 inhibitor PRT3645 demonstrates anti-tumor activity and enhances survival in glioblastoma and breast cancer brain metastasis models
Abstract: 2300
Date and Time: Tuesday, April 12, 2022, 9:00 am CT - 12:30 pm CT
Session Title: Cell Cycle Control and Cell Cycle Regulators as Therapeutic Targets
Presenter: Ashish Juvekar, Prelude Therapeutics

- Conclusion: This abstract highlights data from multiple preclinical studies showing that PRT3645 exhibits the desired balance of potency, selectivity, and brain penetration compared to approved CDK4/6 inhibitors. *In vivo*, oral administration of PRT3645 was highly efficacious in orthotopic human breast cancer brain metastasis (BCBM) and GBM preclinical models and demonstrated a combinatorial benefit with hormonal therapy as well as HER2 kinase inhibition.

Title: Preclinical characterization of PRT3789, a potent and selective SMARCA2 targeted degrader
Abstract: 3263
Date and Time: Tuesday, April 12, 2022, 1:30 pm CT – 5:00 pm CT
Session Title: Epigenetic Targets
Presenter: Michael Hulse, Prelude Therapeutics

- Conclusion: The abstract describes the characterization of PRT3789, one of Prelude's potent and selective SMARCA2 targeted degraders. Treatment with PRT3789 demonstrated robust inhibition of SMARCA4-deleted non-small cell lung cancer cell growth but not SMARCA4 WT cancer cells, both in vitro and in vivo at well-tolerated doses.

About Prelude Therapeutics

Prelude Therapeutics is a clinical-stage precision oncology company developing innovative drug candidates targeting critical cancer cell pathways. The Company's diverse pipeline is comprised of highly differentiated, potentially best-in-class proprietary small molecule compounds aimed at addressing clinically validated pathways for cancers with selectable underserved patients. Prelude's pipeline includes four candidates currently in clinical development: PRT543 and PRT811, highly selective, potent, orally bioavailable PRMT5 inhibitors; PRT1419, a potent, selective inhibitor of MCL1; and PRT2527, a potent and highly selective CDK9 inhibitor. Additionally, the Company is progressing two novel preclinical candidates, PRT3645, a brain penetrant CDK4/6 inhibitor; and a potential first-in-class SMARCA2/BRM protein degrader.

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, timing of availability and announcements of clinical results, the timing of the expansion portion for its clinical trials for PRT543, PRT811, PRT1419 and PRT 2527, the timing of IND-related activities for PRT3645, SMARCA2 and SMARCA4, and the potential benefits of the Company's product candidates and platform. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Although the Company believes that the expectations reflected in such forward-looking statements are reasonable, the Company 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 the Company's actual activities or results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to the Company's ability to advance its product candidates, the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, the impact of the COVID-19 pandemic on the Company's business, clinical trial sites, supply chain and manufacturing facilities, the Company's ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of preclinical and clinical trials, the Company's ability to fund development activities and achieve development goals, the Company's ability to protect intellectual property, and other risks and uncertainties described under the heading "Risk Factors" in documents the Company 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 the Company undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

Investor Contacts:
Stacey Jurchison
Executive Director, Corporate Affairs
sjurchison@preludetx.com

Melissa Forst
Argot Partners
212.600.1902
prelude@argotpartners.com

Media Contact:
Paige Donnelly
Argot Partners
212.600.1902
prelude@argotpartners.com