UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 5, 2021

Prelude Therapeutics Incorporated

(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-39527**	**81-1384762**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

200 Powder Mill Road	
Wilmington, Delaware	**19803**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (302) 467-1280

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, $0.0001 par value per share	PRLD	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition.

On November 12, 2021, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing its financial results for the three months ended September 30, 2021. A copy of the press release is attached as Exhibit 99.1 to this report.

The information in this Item 2.02, including Exhibit 99.1 to this report, shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section or Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended (the "Securities Act"). The information contained in this Item 2.02 and in the accompanying Exhibit 99.1 shall not be incorporated by reference into any other filing under the Exchange Act or under the Securities Act, except as shall be expressly set forth by specific reference in such filing.

Item 5.02 Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers

Departure of Chief Financial Officer

On November 5, 2021, Brian Piper, the Chief Financial Officer of the Company, notified the Company that he will be resigning from the Company, effective November 19, 2021, to pursue other opportunities. On November 5, 2021, the Board of Directors of the Company (the "Board") appointed Laurent Chardonnet as the Chief Financial Officer of the Company, including as the "principal financial officer" and "principal accounting officer" of the Company within the meaning of Rule 16a-1(f) under the Securities Exchange Act of 1934, as amended, effective on or about November 29, 2021 (the "Appointment Date").

Before joining the Company, Mr. Chardonnet, age 57, served as Senior Vice President and Chief Financial Officer of Axcella Health Inc. from November 2019 until November 2021. From 2004 to November 2019, Mr. Chardonnet served in various positions at Incyte Corporation, including Vice President, Treasurer and Principal Accounting Officer, Head of Finance and Administration for the Incyte's European division; and as Vice President of Alliances Prior to Incyte, Mr. Chardonnet served as Controller, Vice President of Finance and acting Chief Financial Officer of Drug Abuse Sciences, a privately held biotechnology company, and as a senior consultant at PricewaterhouseCoopers LLP. Mr. Chardonnet received his Master of Business Administration from Vanderbilt University and his initial business degree from the Institut Superieur de Gestion in Paris.

In connection with Mr. Chardonnet's appointment as Chief Financial Officer, the Compensation Committee of the Board approved the Company's entry into an employment agreement (the "Employment Agreement") with Mr. Chardonnet, which includes the following terms: (i) an initial annual base salary of $400,000 per year (the "Initial Base Salary"), (ii) an annual discretionary bonus of up to 40% of the Initial Base Salary (the "Target Bonus"), (iii) an option to purchase up to 180,000 shares of Company's common stock ("Common Stock") (the "Option Award") with 1/4th of the shares underlying the Option Award vesting and becoming exercisable on the one-year anniversary of the Appointment Date, and 1/48th of the shares underlying the Option Award vesting and becoming exercisable on a monthly basis thereafter, among other benefits. Additionally, in the event Mr. Chardonnet experiences a termination of his employment without "cause" or he resigns for "good reason" (each as defined in the Employment Agreement), provided that he executes and makes effective a release of claims against the Company and its affiliates, Mr. Chardonnet will become entitled to (i) continued base salary for twelve months, payable in accordance with the Company's standard payroll practices; and (ii) premium payments for continued healthcare coverage for up to nine months. In the event Mr. Chardonnet experiences a termination without "cause" or he resigns for "good reason" during the 12-month period following a change in control, then in lieu of the foregoing, Mr. Chardonnet would become entitled to (a) continued base salary for 12 months, payable in accordance with the Company's standard payroll practices; (b) 100% of his annual target bonus, payable in a single lump-sum; (c) premium payments for continued healthcare coverage for up to 12 months; and (d) 100% accelerated vesting his then-outstanding equity awards. Mr. Chardonnet will also receive a one-time signing bonus of $160,000 in January 2022.

The foregoing summary of the Employment Agreement does not purport to be complete and is subject to, and qualified in its entirety by, the Employment Agreement, which will be filed as an exhibit to the Company's Annual Report on Form 10-K for the fiscal year ending December 31, 2021.

The Company expects to enter into its standard form of indemnification agreement for directors and executive officers with Mr. Chardonnet. The form of the indemnification agreement was previously filed by the Company as Exhibit 10.1 to the Company's Registration Statement on Form S-1 filed with the Securities and Exchange Commission on September 4, 2020 and incorporated by reference herein.

There are no arrangements or understandings between Mr. Chardonnet and any other persons, pursuant to which he was appointed as Chief Financial Officer, no family relationships among any of the Company's directors or executive officers and Mr. Chardonnet and he has no direct or indirect material interest in any transaction required to be disclosed pursuant to Item 404(a) of Regulation S-K.

Changes to Executive Compensation

On November 5, 2021, the Compensation Committee of the Board of the Company approved a one-time cash bonus (the "Retention Bonus") to Deborah Morosini, the Company's Executive Vice President and Chief of Clinical Affairs, in the amount of $200,000 to be paid on November 30, 2022 (the "Award Date"), so long as Dr. Morosini remains employed by the Company on the Award Date.

Item 7.01 Regulation FD Disclosure

The Company has prepared investor presentation materials with information about the Company, which it intends to use as part of investor presentations. A copy of the investor presentation materials to be used by management for presentations is attached as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information furnished with this report, including Exhibit 99.2, shall not be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference into any other filing under the Exchange Act or the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press release issued by Prelude Therapeutics Incorporated regarding its financial results for the three months ended September 30, 2021, dated November 12, 2021.
99.2	Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRELUDE THERAPEUTICS INCORPORATED

Date: November 12, 2021

By: /s/ Brian Piper
Brian Piper
Chief Financial Officer

Exhibit 99.1

Prelude Therapeutics Announces Third Quarter 2021 Financial Results and Operations Update

PRT543 and PRT811 Demonstrate Favorable Safety Profile, Tolerability and Evidence of Preliminary Clinical Activity in Phase 1 Dose Escalation in Unselected Patients

Phase 1 Dose Expansion Ongoing in Biomarker-Selected Solid Tumor and Hematologic Malignancy Expansion Cohorts for PRT543; Dose Expansion Portion of Phase 1 Trial of PRT811 to Commence 4Q21 with Data Readouts Anticipated for Both Programs in 2022

PRT2527 IND Cleared by FDA; Phase 1 Clinical Trial Evaluating IV Monotherapy in Patients with Selected Solid Tumors Anticipated to Begin by Year-End

Strong Cash, Cash Equivalents and Marketable Securities Position of $320 Million to Support Clinical and Discovery Pipeline Advancement

Wilmington, DE – November 12, 2021 – Prelude Therapeutics Inc. (Nasdaq: PRLD), a clinical-stage precision oncology company, today announced its financial results for the third quarter ended September 30, 2021 and provided an update on recent clinical and development pipeline progress.

“We continue to make significant progress advancing our novel pipeline of therapeutic candidates, most notably with the recent presentation of dose escalation data from the Phase 1 trials of our lead PRMT5 inhibitors, PRT543 and PRT811,” said Kris Vaddi, PhD, Chief Executive Officer. “We were pleased by these initial data in unselected patients, which demonstrated key points of differentiation for our molecules, including good tolerability and potency, and a desirable therapeutic window. In addition, evidence of preliminary clinical activity was observed in multiple tumor types displaying preclinically validated genomic features. We look forward to leveraging learnings from these data as we execute on the dose escalation portion of the trials and evaluate PRT543 and PRT811 in biomarker-selected patient populations, with data readouts from these cohorts anticipated in 2022. Beyond our PRMT5 inhibitors, the balance of our pipeline continues to advance. During the quarter we received IND clearance from the FDA for PRT2527, our CDK9 inhibitor, positioning us to commence a Phase 1 study of this molecule before year-end.”

Recent Highlights and Upcoming Milestones

PRT543

- **Phase 1 Dose Escalation Study Data Presented at the AACR-NCI-EORTC Annual Meeting; Data from Expansion Cohorts to be Presented in 2022**: In October 2021, the Company presented data from the dose escalation portion of its Phase 1 trial of PRT543, which is designed to be a potent and selective inhibitor of PRMT5, in unselected patient populations. PRT543 demonstrated target engagement and inhibition of PRMT5 functional activity, as well as preliminary clinical activity. PRT543 was generally well tolerated. Patient enrollment is ongoing in specific biomarker-selected solid tumor and hematologic malignancy expansion cohorts. The Company expects to present data from the expansion cohorts in 2022.

- **Phase 1 Dose Escalation Data for PRT543 in Patients with Myeloid Malignancies to be Presented at the 63rd American Society of Hematology (ASH) Annual Meeting**: Data from the dose escalation portion of the ongoing Phase 1 clinical trial of PRT543 in patients with

myelodysplastic syndrome (MDS) and myelofibrosis (MF), including safety, pharmacokinetics, pharmacodynamics, and preliminary clinical activity, will be featured during a poster session at the 63rd ASH Annual Meeting and Exposition being held December 11-14, 2021.

PRT811

- **Phase 1 Dose Escalation Study Data Presented at the AACR-NCI-EORTC Annual Meeting; Dose Expansion Portion of Phase 1 Trial to Commence 4Q21:** In October 2021, the Company presented data from the dose escalation portion of its Phase 1 trial of PRT811, which is designed to be a potent, selective, and brain penetrant PRMT5 inhibitor, in patients with unselected advanced solid tumors. PRT811 demonstrated dose dependent inhibition of PRMT5 activity and demonstrated signs of preliminary clinical activity. PRT811 was generally well-tolerated. Prelude will shortly commence the dose expansion portion of the Phase 1 trial in selected patients with central nervous system cancers (CNS) and non-CNS cancers. The Company expects to present data from the expansion cohorts in 2022.

PRT1419

- **Phase 1 Dose Escalation Portion of Oral and Intravenous (IV) PRT1419 Trial Ongoing**: The dose escalation portion of the Company's first-in-human Phase 1 study investigating both an oral and IV formulation of MCL-1 inhibitor, PRT1419, the Company's third clinical candidate, in patients with relapsed/refractory hematologic malignancies, including acute myeloid leukemia and high-risk myelodysplastic syndromes, and solid tumors, remains ongoing. The Company expects to add dose expansion and combination cohorts to the Phase 1 clinical trial in the first half of 2022.

PRT2527

- **Dose Escalation Phase 1 Trial of PRT2527 on Track to Begin by Year-End:** During the third quarter the Company received clearance for an Investigational New Drug (IND) application for PRT2527, which is designed to be a potent and selective CDK9 inhibitor. The Company anticipates beginning a Phase 1 trial of PRT2527 by year-end evaluating IV infusion monotherapy in patients with selected solid tumors.

- **Preclinical Data Presented at the AACR-NCI-EORTC Annual Meeting:** In October 2021, the Company presented new preclinical data demonstrating that intermittent intravenous administration of PRT2527 demonstrated strong efficacy in hematological malignancies and solid tumor models with *MYC* dysregulation.

Discovery Programs

- The Company continues to expect to initiate IND-enabling studies for PRT-SCA2, which is designed to be a SMARCA2 protein degrader, by year-end. The Company also continues to make progress in the PRT-K4 discovery program and expects to initiate IND-enabling studies by year-end.

Corporate Update

- On November 5, 2021, Brian Piper, our Chief Financial Officer, notified the Company that he will be resigning from the Company, effective November 19, 2021, to pursue other opportunities.

- The Company today announced the appointment of Laurent Chardonnet as its new Chief Financial Officer starting November 29, 2021. Mr. Chardonnet joins from Axcella Health where, since 2019, he served as Senior Vice President, CFO. Prior to Axcella, he spent 15 years at Incyte Corporation where he held roles of increasing responsibility including Vice President Finance, Treasurer and Principal Accounting Officer, Head of Finance and Administration for the company's European division, and Vice President of Alliances and Global Strategy. Mr. Chardonnet received his Master of Business Administration from Vanderbilt University and his initial business degree from the Institut Supérieur de Gestion in Paris

- The Company and Dr. David Mauro, the Company's Chief Medical Officer, mutually agreed that Dr. Mauro would depart from the Company to pursue other opportunities. Dr. Mauro's last day with the Company was on November 9, 2021. The Company has an ongoing search for a successor. Dr. Victor Sandor, former Chief Medical Officer of Array Biopharma and current board member and chair of the Science and Technology Committee, will provide strategic and operational oversight of clinical development during this time.

Third Quarter 2021 Financial Results

- **Cash, Cash Equivalents, and Marketable Securities:** Cash, cash equivalents, and marketable securities as of September 30, 2021 were $320.9 million.

- **Research and Development (R&D) Expenses**: For the third quarter of 2021, R&D expense increased by $7.4 million to $22.7 million for the three months ended September 30, 2021 from $15.3 million for the three months ended September 30, 2020. The increase was mainly due to increased clinical research costs to support the advancement of our clinical programs as well as an increase in discovery-stage program expenses. Our chemistry, manufacturing and other costs for the clinical trials also increased.

- **General and Administrative (G&A) Expenses**: For the third quarter of 2021, G&A expense increased by $5.2 million to $8.1 million for the three months ended September 30, 2021 from $2.9 million for the three months ended September 30, 2020. The increase was primarily due to an increase in personnel related expense due to an increase in employee headcount and an increase in our professional fees as we expanded our operations to support our research and development efforts and incurred additional costs to operate as a public company.

- **Net Loss:** For the third quarter of 2021, net loss was $30.7 million, or $0.66 per share, compared with a net loss of $16.8 million, or $5.25 per share, for the same period in 2020.

- **Financial Guidance:** The Company believes that its current cash, cash equivalents and marketable securities will be sufficient to fund operating expenses and capital expenditure requirements into the second half of 2023.

About Prelude Therapeutics

Prelude Therapeutics is a clinical-stage precision oncology company developing innovative, potential best-in-class molecules targeting critical cancer cell pathways involved in cancer pathogenesis. Prelude's initial clinical candidates, PRT543 and PRT811, are potent, selective, oral PRMT5 inhibitors in Phase 1 development for the treatment of advanced solid tumors, primary and secondary CNS cancers and select myeloid malignancies. PRT1419, a potent and selective MCL1 inhibitor, is in Phase 1 development for patients with relapsed/refractory hematologic malignancies and solid tumors. PRT2527, a highly selective CDK9 inhibitor, is anticipated to begin Phase 1 clinical development by year-end as a monotherapy in patients with selected solid tumors. In addition, the Company's pipeline includes PRT-SCA2, a SMARCA2 protein degrader, PRT-K4, a highly selective kinase inhibitor, and additional discovery stage programs.

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 Phase 1 clinical trial for PRT543, PRT811 and PRT1419, the timing of IND-related activities for PRT2527 and PRT-SCA2 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.

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(UNAUDITED)

(in thousands, except share and per share data)	Three Months Ended September 30, 2021	2020
Operating expenses:		
Research and development	$ 22,721	$ 15,293
General and administrative	8,115	2,851
Total operating expenses	30,836	18,144
Loss from operations	(30,836)	(18,144)
Other income, net	149	1,384
Net loss	$ (30,687)	$ (16,760)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (0.66)	$ (5.25)
Weighted average common shares outstanding, basic and diluted	46,330,794	3,194,471
Comprehensive loss		
Net loss	$ (30,687)	$ (16,760)
Unrealized gain(loss) on marketable securities, net of tax	(176)	—
Comprehensive loss	$ (30,863)	$ (16,760)

BALANCE SHEETS
(UNAUDITED)

(in thousands, except share data)	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 61,424	$ 218,309
Marketable securities	259,441	—
Prepaid expenses and other current assets	5,032	2,500
Total current assets	325,897	220,809
Property and equipment, net	3,213	2,480
Right-of-use asset	2,107	—
Deferred offering costs	—	301
Total assets	$ 331,217	$ 223,590
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 11,062	$ 3,920
Accrued expenses and other current liabilities	6,765	7,455
Operating lease liability	1,836	—
Total current liabilities	19,663	11,375
Other liabilities	—	32
Operating lease liability	312	—
Total liabilities	19,975	11,407
Stockholders' equity:		
Voting common stock, $0.0001 par value: 487,149,741 shares authorized; 35,789,759 and 32,595,301 shares issued and outstanding at September 30, 2021 and December 31, 2020, respectively	4	3
Non-voting common stock, $0.0001 par value; 12,850,259 shares authorized; 11,402,037 and 11,110,371 shares issued and outstanding at September 30, 2021 and December 31, 2020, respectively	1	1
Additional paid-in capital	497,691	319,605
Accumulated other comprehensive income (loss)	(176)	—
Accumulated deficit	(186,278)	(107,426)
Total stockholders' equity	311,242	212,183
Total liabilities and stockholders' equity	$ 331,217	$ 223,590

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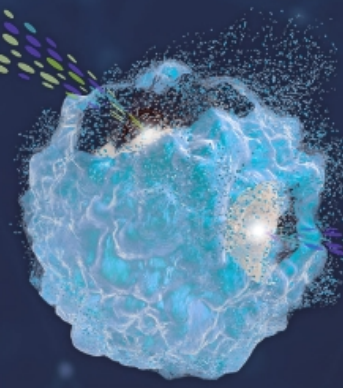
Exhibit 99.2

Prelude THERAPEUTICS

Corporate Presentation

November 2021



Disclaimer

This presentation 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: our plans to develop and commercialize small molecule therapies, our expectations about timing and ability to commence, enroll or complete clinical studies and to obtain regulatory approvals for PRT543, PRT811, PRT1419, PRT2527 and other candidates in development, the ability of our product candidates to treat various cancers, the ability to discover additional suitable candidates for regulatory approval, the potential impact of the COVID-19 pandemic and the sufficiency of our cash and cash equivalents to fund our operations.

Any statements contained herein or provided orally that are not statements of historical fact may be deemed to be forward-looking statements. In some cases, you can identify forward-looking statements by such terminology as “believe,” “may,” “will,” “potentially,” “estimate,” “continue,” “anticipate,” “intend,” “could,” “would,” “project,” “plan,” “expect” and similar expressions that convey uncertainty of future events or outcomes, although not all forward-looking statements contain these words. Statements, including forward-looking statements, speak only to the date they are provided (unless an earlier date is indicated).

These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. If such assumptions do not fully materialize or prove incorrect, the events or circumstances referred to in the forward-looking statements may not occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations, except as required by law. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. Additional risks and uncertainties that could affect our business are included under the caption “Risk Factors” in our Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission for the three months ended June 30, 2021.

Prelude Therapeutics Vision

Discovery Engine

Powered by scientists with a track record of delivering precision oncology medicines

Clinical Development

Highly selected patient populations with significant unmet need

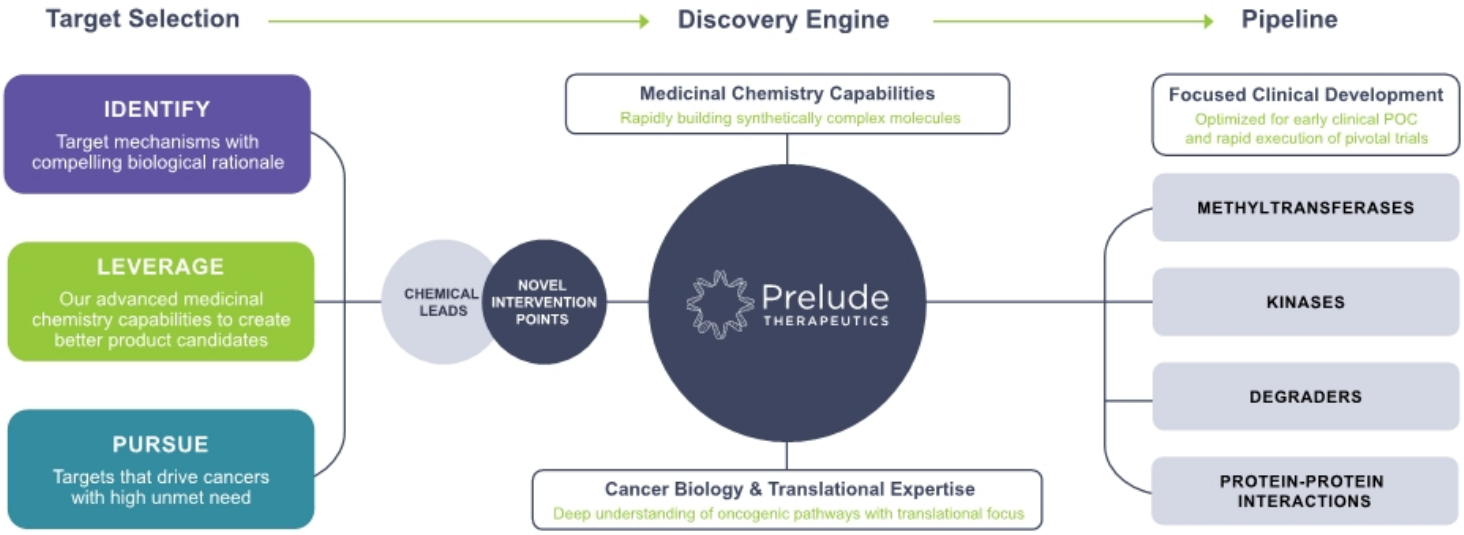
Regulatory Strategy

Efficient development path with potential for rapid regulatory approvals

Commercial Approach

Rapidly advancing potentially high value therapy candidates with a commitment to future patient access, awareness and support

Prelude Discovery and Development Approach



Prelude Therapeutics Pipeline

Program	Indications	Discovery/ Preclinical	IND Enabling	Phase 1	Phase 2/3	Worldwide Rights
PRT543 (PRMT5)	Selected Solid Tumors (incl. ACC, HRD+)			●		Prelude THERAPEUTICS
	Selected Myeloid Malignancies (incl. MF and MDS)			●		
PRT811 (Brain Penetrant PRMT5)	CNS and Non-CNS Cancers			●		
PRT1419 (MCL1)	Selected Hematological Malignancies *(oral formulation)*			●		
	Solid Tumors *(IV formulation)*			●		
PRT2527 (CDK9)	Selected Solid Tumors			●		
PRT-SCA2 (SMARCA2)	Multiple Genomically Selected Cancers	●				
PRT-K4 (Kinase)	Solid Tumors	●				

Wholly-owned patent portfolio covering composition of matter and method of use patents. Prior to possible extensions, PRT543 has IP coverage into at least H2 2038; PRT811 and PRT1419 until at least 2039

Prelude Roadmap for Value Creation

Anticipated 2021/2022 Milestones

PRMT5
Report P1 dose expansion data
Generate POC in selected patients

MCL1
Complete dose escalation and initiate expansion/combination phase

CDK9
Initiate Phase 1 clinical trial in selected solid tumors

SMARCA2/ Kinase
Complete IND-enabling studies and file INDs

Future Strategy

Leverage initial POC clinical data to inform design of P2 registration studies

Advance multiple precision oncology clinical programs focusing on underserved cancers

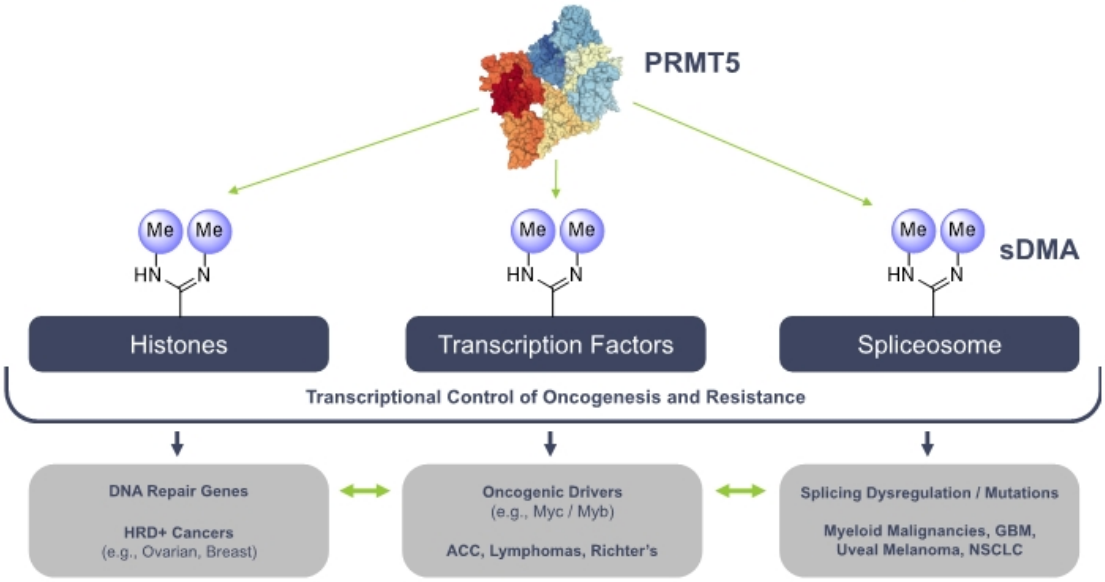
Continue to resource discovery engine to expand our pipeline

Maximize portfolio value through strategic partnerships


PRMT5 Programs
Prelude
THERAPEUTICS

PRMT5 Pathway Drives Oncogenesis and Resistance

PRMT5



PRMT5 inhibition can be leveraged to potentially treat a broad range of solid tumors and hematologic malignancies

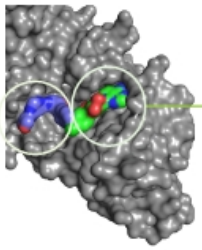
Prelude PRMT5 Program

Optimized for a well-balanced and differentiated profile

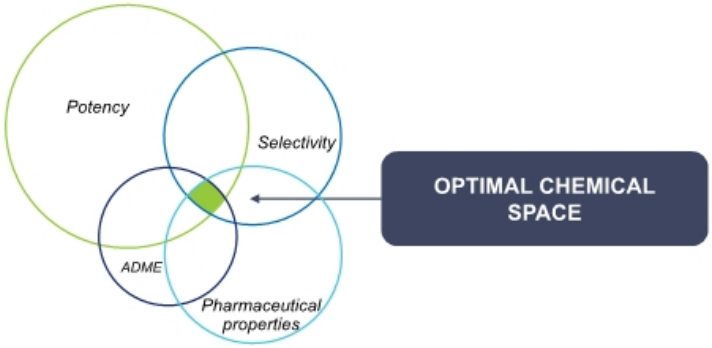
PRMT5

Differentiating Mechanism of Action

Substrate competitive Inhibitors



Prelude compounds are co-factor (SAM) competitive inhibitors



Designed and synthesized >600 compounds to select PRT543 and PRT811 for advancement

PRT543 / PRT811

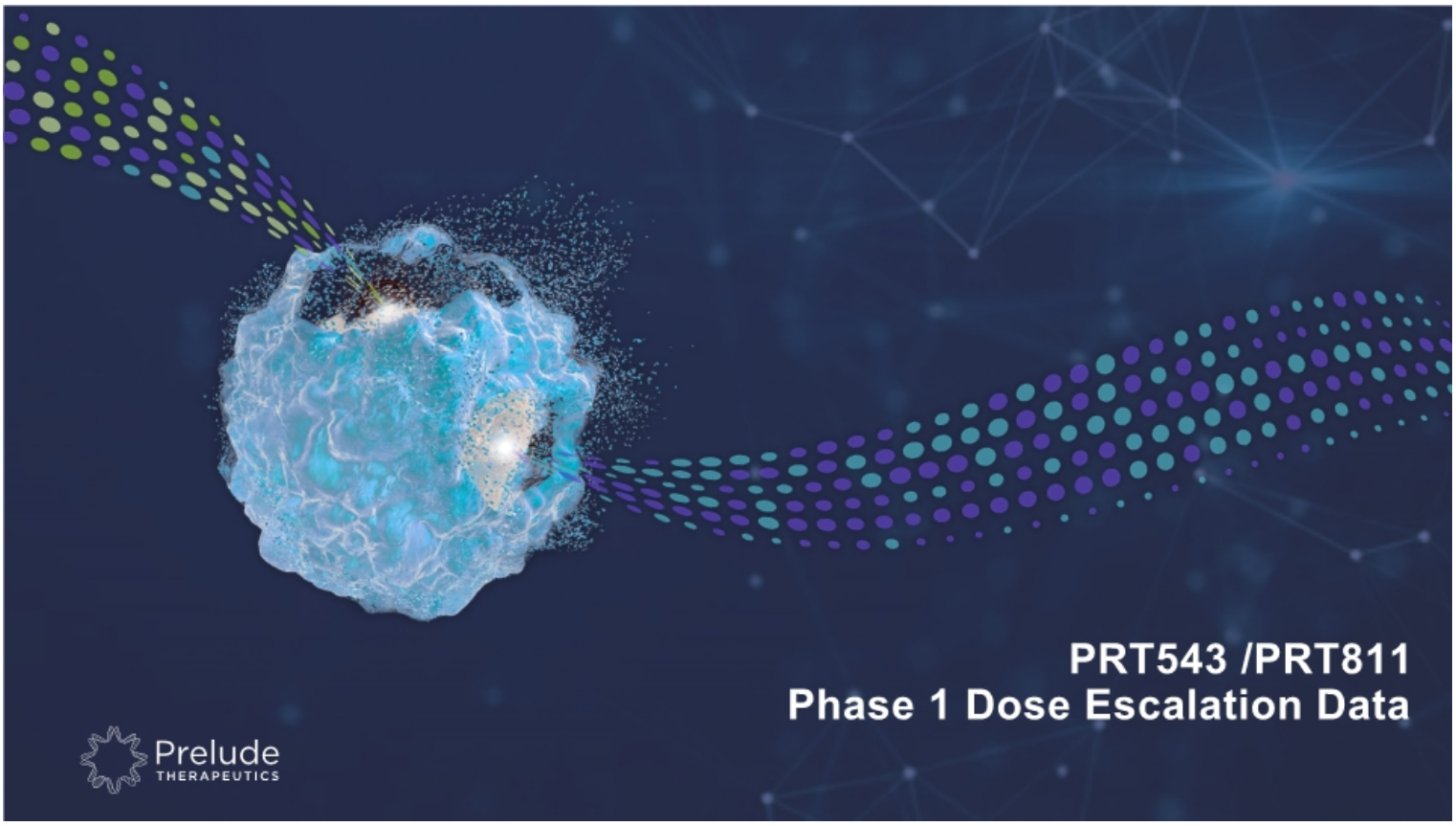
Differentiated Clinical Stage Oral PRMT5 Inhibitors

PRT543

- **Strong** scientific rationale for pathway
- Highly **selective** and **potent** oral candidate
- **Optimized** PK profile
  - Good oral bioavailability and long half-life (12+ hours)
- Applicability in both **solid tumors** and **heme malignancies**
- Completed **dose escalation;** Currently in **expansion phase in selected** patient cohorts

PRT811

- **Brain-penetrant** PRMT5 inhibitor
- **High/sustained** brain exposure in preclinical studies
- Highly **selective** and **potent** oral candidate
- **Optimized** PK profile
  - 5+ hours half-life; maximizing therapeutic window
- Completed **Dose escalation; Expansion phase** to begin


PRT543 /PRT811
Phase 1 Dose Escalation Data
Prelude
THERAPEUTICS

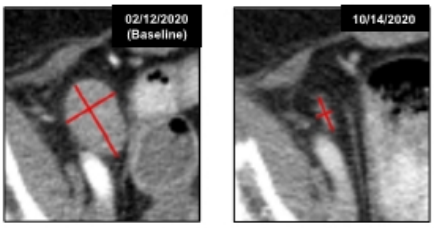
PRT543: Well-Tolerated with Evidence of Preliminary Clinical Activity in Phase 1 Dose Escalation Study*

Study Demographics & Safety

- 49 patients
  - Unselected patient population with 18 different diagnoses
  - 9 colon; 7 ACC; 6 uveal melanoma (2 patients SF3B1+); 5 ovarian cancer (2 patients HRD+)
  - Median of 3 prior lines of systemic therapy
- PRT543 was well-tolerated
  - Most common TRAEs of any grade in ≥ 5% of all patients: fatigue, thrombocytopenia, anemia, nausea
  - The most common Grade 3≥ AEs were thrombocytopenia and anemia
    - Reversible upon dose modification
  - Thrombocytopenia was only dose-limiting toxicity
  - No discontinuations due to toxicity

Preliminary Clinical Activity

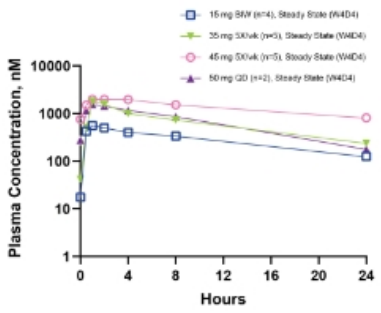
- Stable disease for at least 6 months and tumor regressions (<30%) in 5 patients including ACC and uveal melanoma
- Durable CR in a patient with HRD+ ovarian cancer
  - Multiple lines of prior therapy, including PARPi
  - One target lesion per RECIST and CA125 level 37.8 U/mL at baseline
  - RECIST v1.1 CR at first follow-up tumor assessment (7 weeks), maintained throughout the study
  - CA125 reduced and remained below 5 U/mL at the last assessment
  - Patient remains on study following 18 months of treatment at 35 mg 5x/week



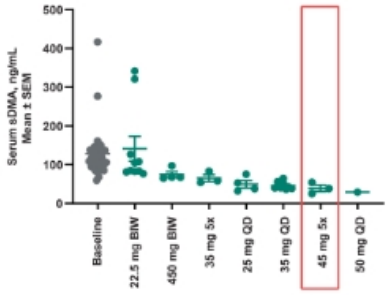
*Data as of August 6, 2021
Data presented at 2021 AACR-NCI-EORTC Annual Meeting

PRT543: Exhibited Target Engagement and Inhibited PRMT5 Activity in Phase 1 Dose Escalation Study

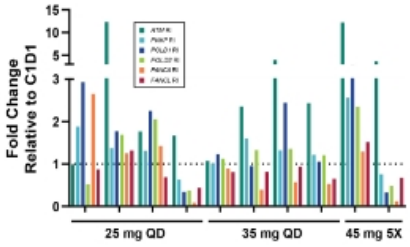
Dose-Dependent Increases in Cmax and AUC



Dose-Dependent Inhibition of Serum sDMA

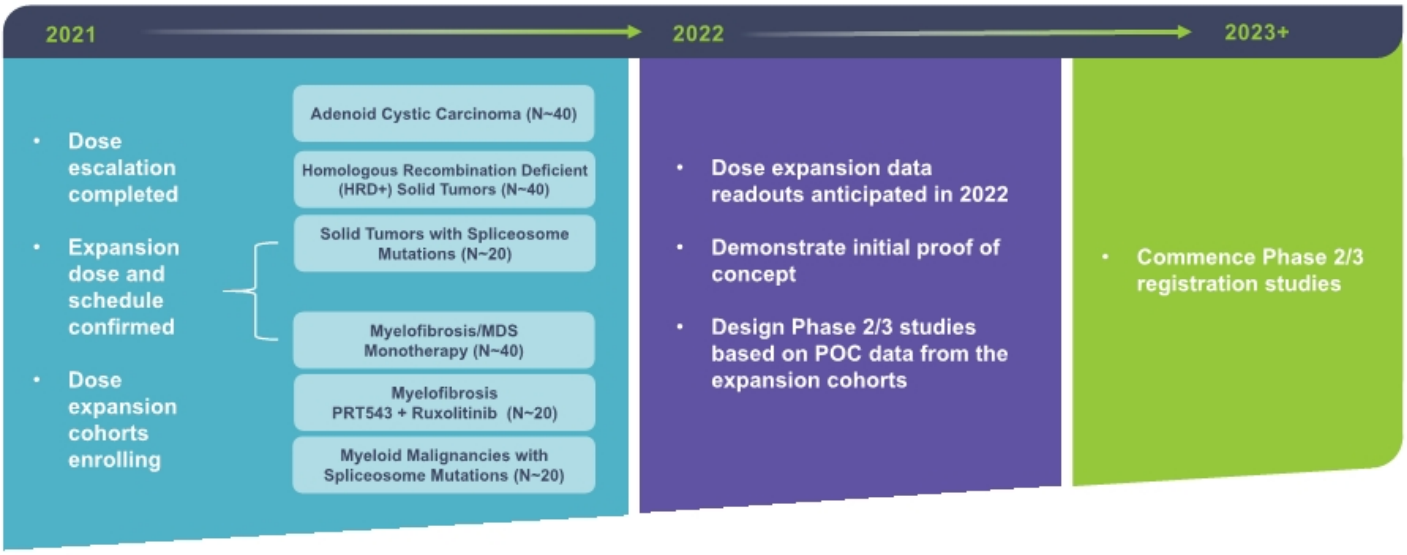


Intron Retention Observed at Higher Dose Levels



45 mg/5x week selected as recommended Phase 2 dose

PRT543 – Timeline and Clinical Plan



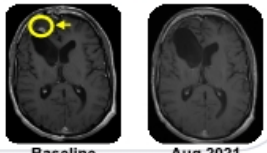
PRT811: Well-Tolerated with Evidence of Preliminary Clinical Activity in Phase 1 Dose Escalation Study

Study Demographics & Safety

- 45 patients
  - 27 across 16 unselected advanced solid tumors
  - 18 patients with high-grade glioma:
    - 17 relapsed/refractory GBM and 1 anaplastic astrocytoma
    - 1/17 patients with IDH1 mutated GBM
- PRT811 was well tolerated
  - Most common TRAEs of any grade in ≥ 5% of all patients: nausea, vomiting, fatigue, thrombocytopenia
  - Grade 3 ≥ AEs were uncommon occurring in 11% of patients
  - No DLTs at doses up to 600 mg QD

Preliminary Clinical Activity

- Two SF3B1+ uveal melanoma patients demonstrated anti tumor activity – both patients continuing on treatment
  - One patient had an uPR (47% decrease in target lesion) and continuing on therapy**
  - One patient had SD (25% decrease in target lesion for >6 months and continuing on therapy*
- One patient with triple negative breast cancer had a 27% decrease in target lesions**
- One patient with IDH1 mutated GBM experienced durable PR that evolved into CR*
  - Baseline: one target lesion per RANO
  - Prior treatment: surgery and chemoradiation + temozolomide
  - Nov/20: 77% reduction of target lesion, confirmed PR; August 2021: confirmed CR

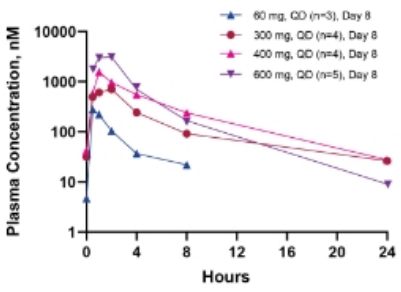


Baseline Aug 2021

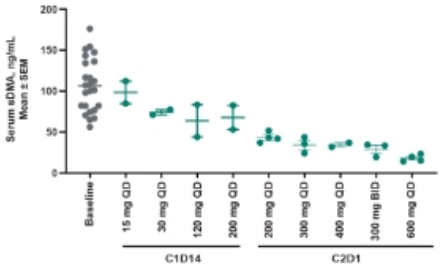
*Data as of August 13, 2021
**Data as of September 20, 2021

PRT811: Exhibited Target Engagement and Inhibited PRMT5 Activity in Phase 1 Dose Escalation Study

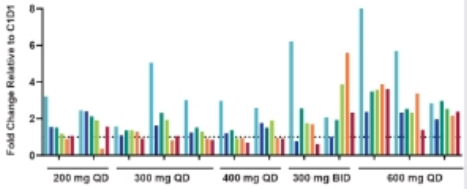
Dose-Dependent Increases in Cmax and AUC



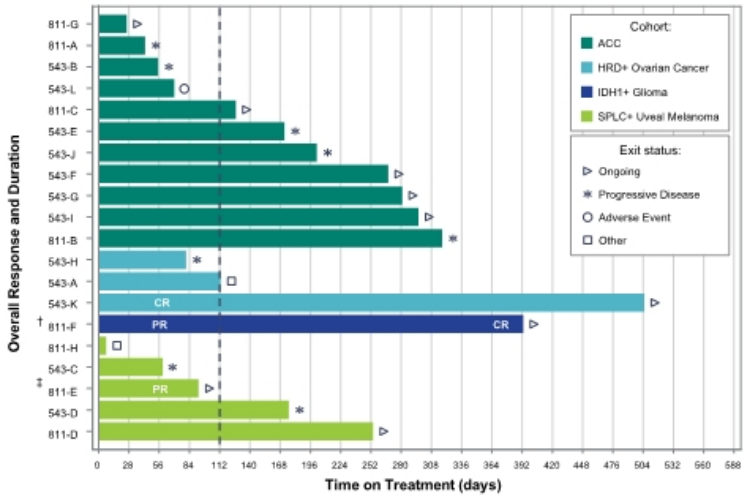
Dose-dependent Inhibition of Serum sDMA



Intron Retention Observed at Higher Dose Levels

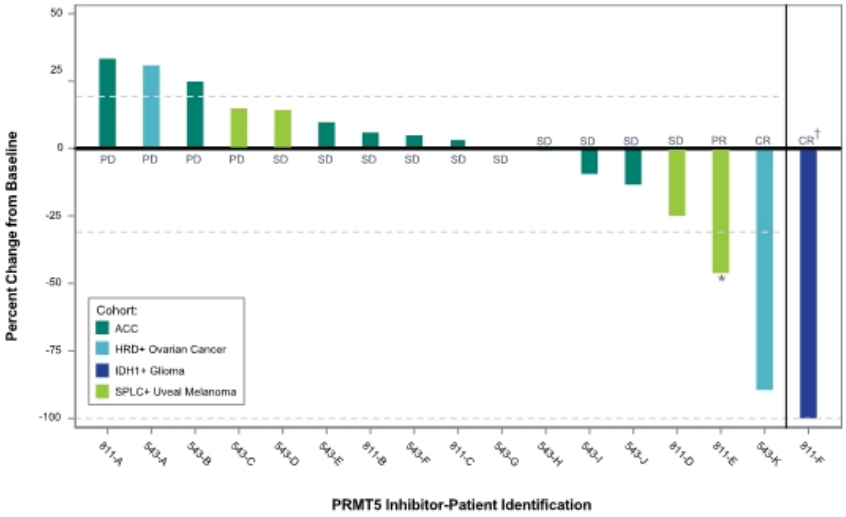


PRT543 and PRT811: Overall Response and Response Duration in Select Patient Cohorts From Dose Escalation Phase



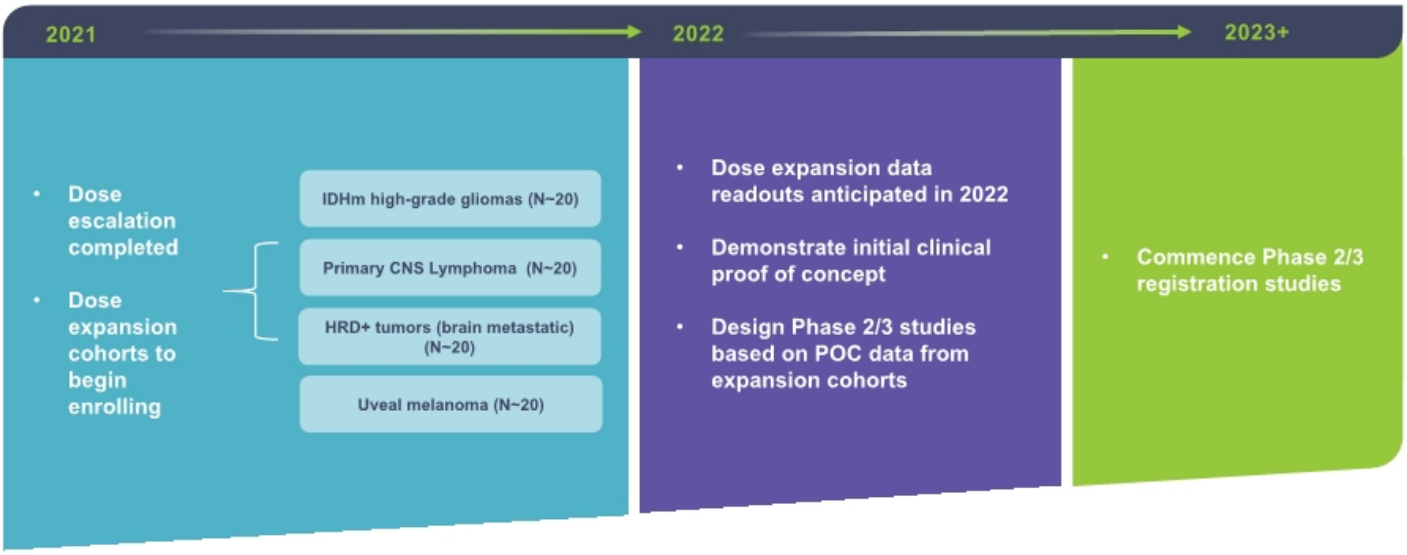
†Target lesions assessed using RECIST, except for patient 811-F with glioma assessed by RANO.
‡Data cutoff for PRT543 was 8.6.21, for PRT811 was 8.13.21, and for patient 811-E was 10.8.21.
ACC, adenoid cystic carcinoma; CR, complete response; HRD, homologous recombination deficiency; IDH, isocitrate dehydrogenase; PD, progressive disease; PR, partial response; PRMT, protein arginine methyltransferase; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SPLC, splicing mutation.

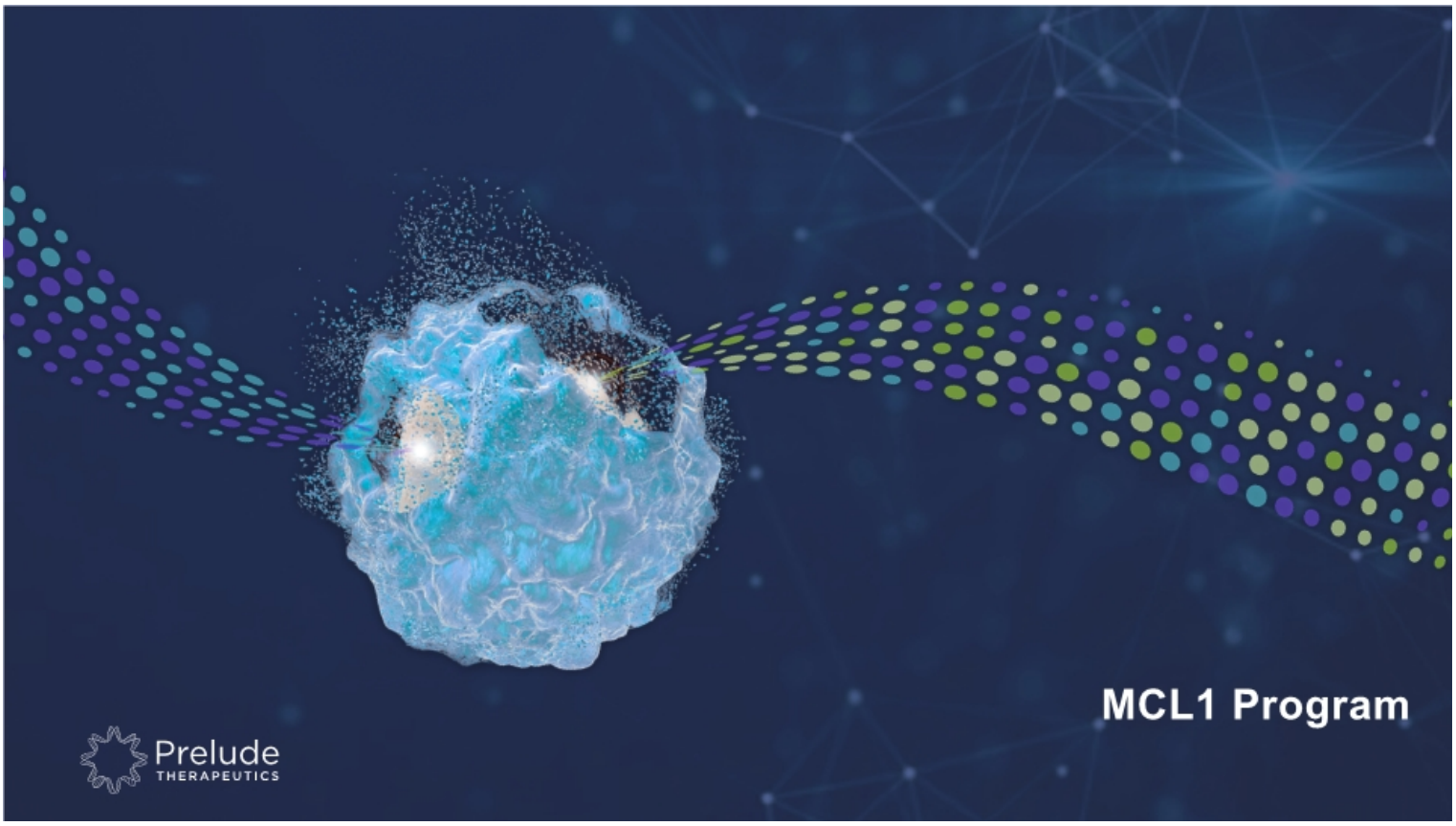
PRT543 and PRT811: Overall Response of Target Lesions (RECIST or RANO) in Select Patient Cohorts From Dose Escalation Phase



*Data cutoff for PRT543 was 8.6.21, for PRT811 was 8.13.21, and for patient 811-E was 10.8.21.
†Target lesions assessed using RECIST, except for patient 811-F with glioma assessed by RANO.
ACC, adenoid cystic carcinoma; CR, complete response; HRD, homologous recombination deficiency; IDH, isocitrate dehydrogenase; PD, progressive disease; PR, partial response; PRMT, protein arginine methyltransferase; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SPLC, splicing mutation.

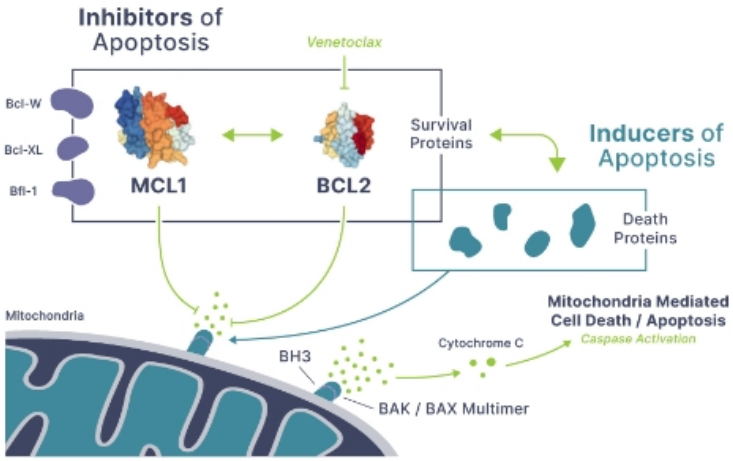
PRT811 – Timeline and Clinical Plan




MCL1 Program
Prelude
THERAPEUTICS

Prelude MCL1 Program

MCL1



- Dysregulated MCL1 expression occurs frequently in cancer
- MCL1 is a member of BCL2 family of proteins involved in blocking cell death proteins
- MCL1 is a validated bypass and resistance mechanism for venetoclax (BCL2 inhibitor) and TKIs
- Currently active competitor compounds are IV candidates
- Challenging medicinal chemistry target that requires disruption of protein-protein interaction

Significant opportunity in post-venetoclax setting

PRT1419

Differentiated Clinical-Stage
MCL1 Inhibitor Candidate

Prelude THERAPEUTICS

MCL1 Inhibitor

- Potent and selective
- Oral and IV formulations

Targeting Selected Heme and Solid Cancers

- Robust activity in preclinical models with once weekly dosing
- Synergistic with venetoclax in AML Models

Optimized PK Profile Maximizes Therapeutic Window

- High oral bioavailability and optimized physicochemical properties

Potential Rapid Path to Market

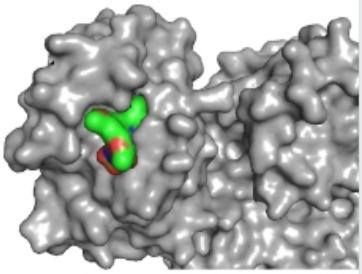
- Phase 1 dose escalation ongoing for both oral and IV formulations

PRT1419: Potential Leading MCL1 Inhibitor

MCL1

Highly Potent Binding to MCL1

Prelude compounds are competitive inhibitors of BIM binding



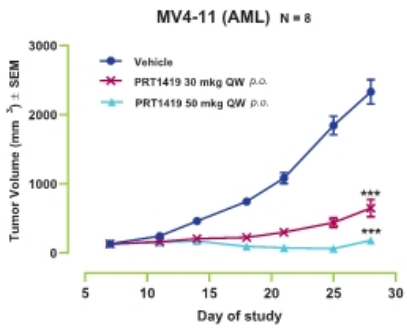
Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC_{50} (nM)	150	31	4.5	**80**
Whole Blood IC_{50} (nM)	1800	320	430	**210**
Caco-2 ($x10^{-6}$ cm/s)	6	<0.1	0.2	**11**
Human Hepat. Cl (%HBF)	42	ND	ND	**71**
Solubility at pH 7.4 (µg/mL)	13	ND	ND	**>1000**
Route of Administration	IV	IV	IV	**Oral/IV**

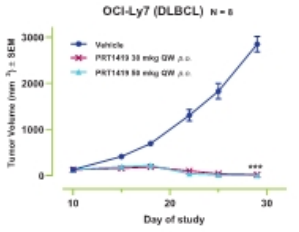
PRT1419 is a potent MCL1 inhibitor candidate with no preclinical evidence of cardiac toxicity

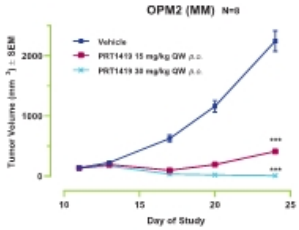
PRT1419 Demonstrated Preclinical Activity as Monotherapy and in Combination

MCL1

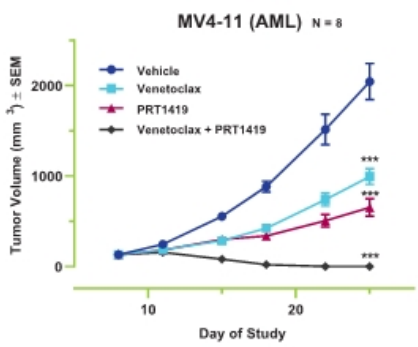
Monotherapy







Combination



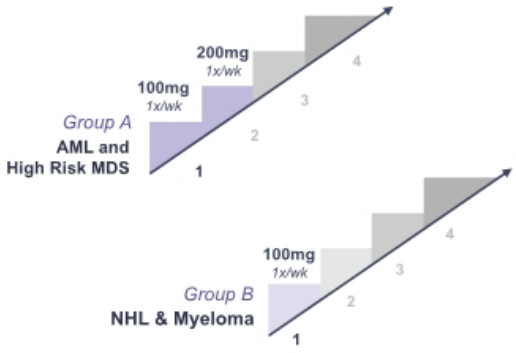
Dose-dependent activity with tumor regression at once-weekly, oral dosing in hematological tumor models

Oral PRT1419 Phase 1 Clinical Trial

MCL1

CURRENT → 2021

Dose Escalation



Expansion Cohorts

Recommended Expansion Dose

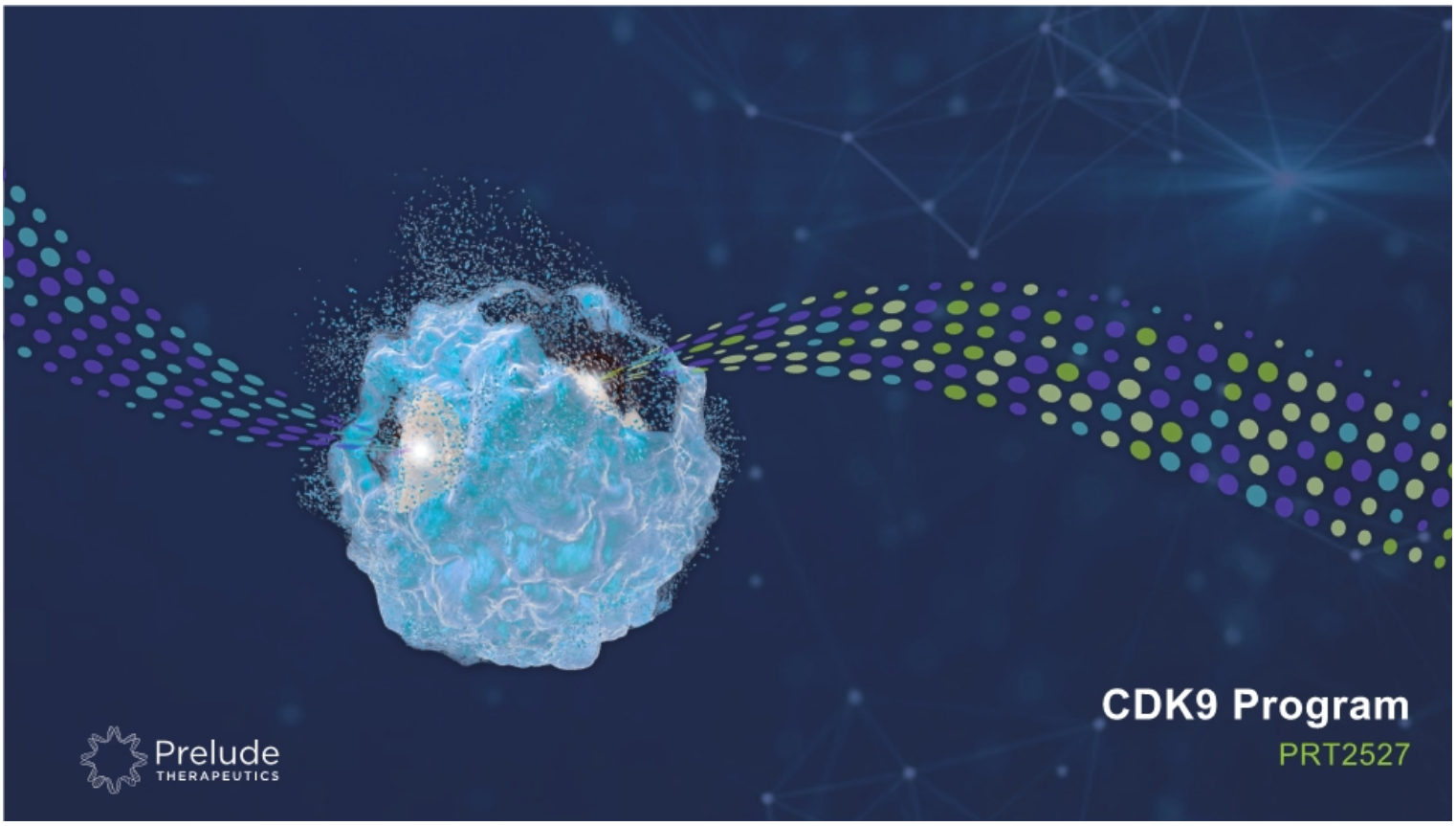
- AML (N~20)
- AML or MDS PRT1419 + Venetoclax or Aza (N~20)
- High Risk MDS (N~20)

Recommended Expansion Dose

- Multiple Myeloma (N~20)
- NHL (B or T cell Lymphoma) (N~20)

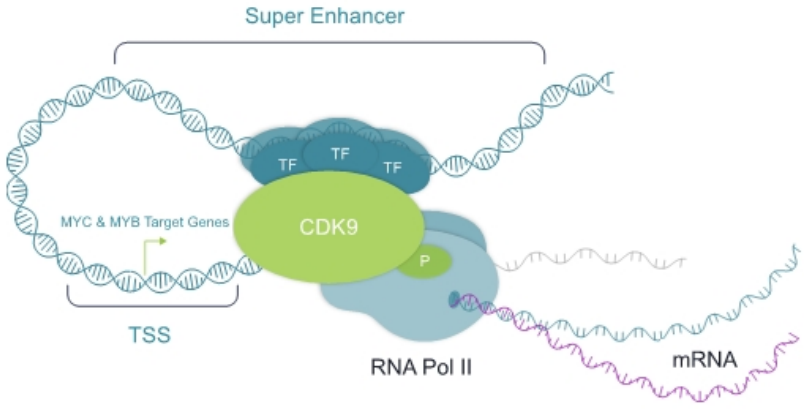
Status as of December 16, 2020

Phase 1 dose escalation ongoing; only Grade 1-2 AEs observed


Prelude
THERAPEUTICS
CDK9 Program
PRT2527

Prelude CDK9 Program

CDK9



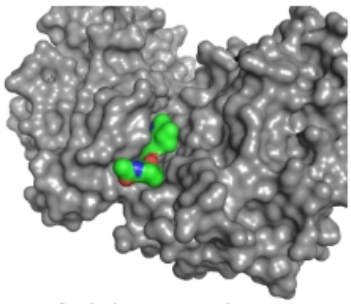
- CDK9 phosphorylates RNA Pol II and regulates transcription
- Regulates expression of several immediate early genes driving oncogenesis and resistance (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
  - Lack of selectivity and potency vs other CDK9s is believed to contribute to low therapeutic window

Highly-selective CDK9 inhibitors believed to have broad applicability in hematological and solid malignancies

PRT2527: Potent and Highly Selective CDK9 Inhibitor Candidate

CDK9

Highly Selective CDK9 Inhibitor Candidate



Prelude compounds are ATP competitive inhibitors

Compound		AZD4573	KB0742	VIP152**	PRT2527
Biochemical* IC_{50} (nM)	CDK9	1.9	483	16	0.95
Proliferation* IC_{50} (nM)		11	915	84	18
Plasma* IC_{50} (nM)		192	1056	923	196
Fold Selectivity CDK9 *vs* Other Isoforms	CDK1	23x	>20x	371x	73x
	CDK2	35x	>20x	147x	340x
	CDK3	2x	>20x	37x	35x
	CDK4	53x	>20x	38x	250x
	CDK5	37x	>20x	>600x	>1000x
	CDK6	79x	>20x	296x	>1000x
	CDK7	150x	>20x	>600x	>1000x

*Internal data; biochemical assay at 1 mM ATP, H929 CTG proliferation assay; **VIP151 was formerly BAY151and licensed to Vincera by Bayer

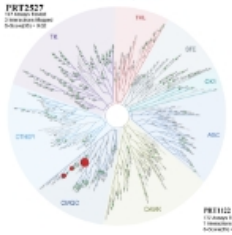
PRT2527 demonstrated improved potency and kinase selectivity relative to competitor compounds in preclinical studies

CDK9 Inhibitor Candidate: PRT2527

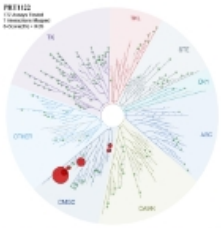
CDK9

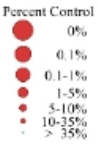
Improved Selectivity

PRT2527

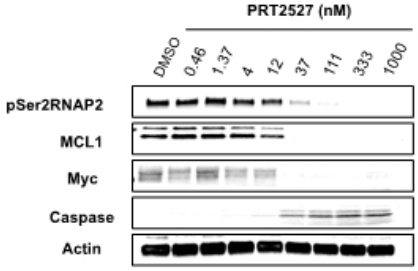


AZD4573



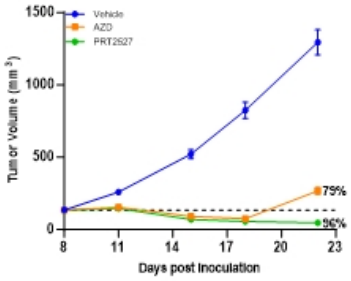


Potent in Vitro Activity

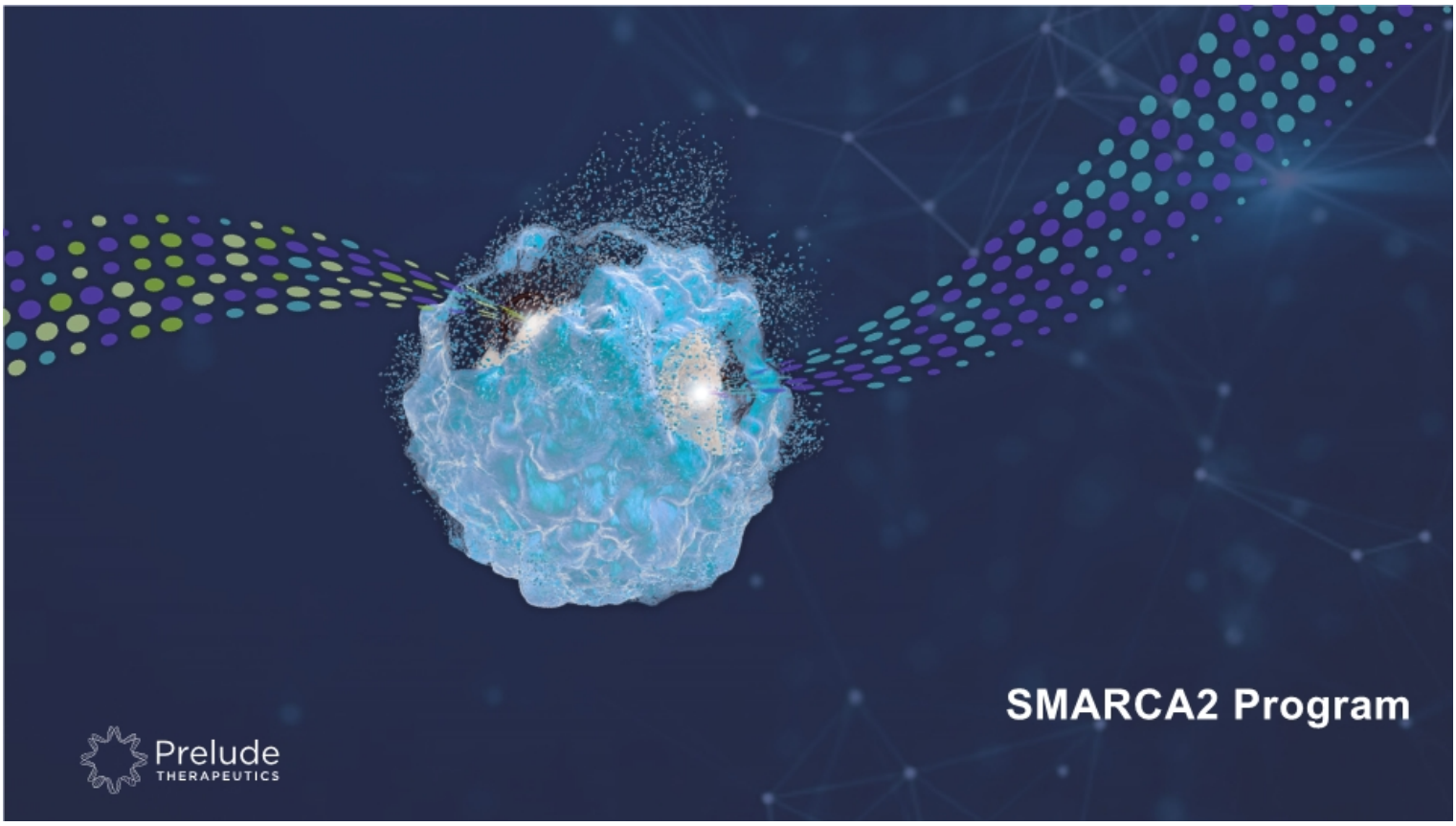


Sustained Regressions at Well-Tolerated Doses in Vivo

MV4-11 (AML)



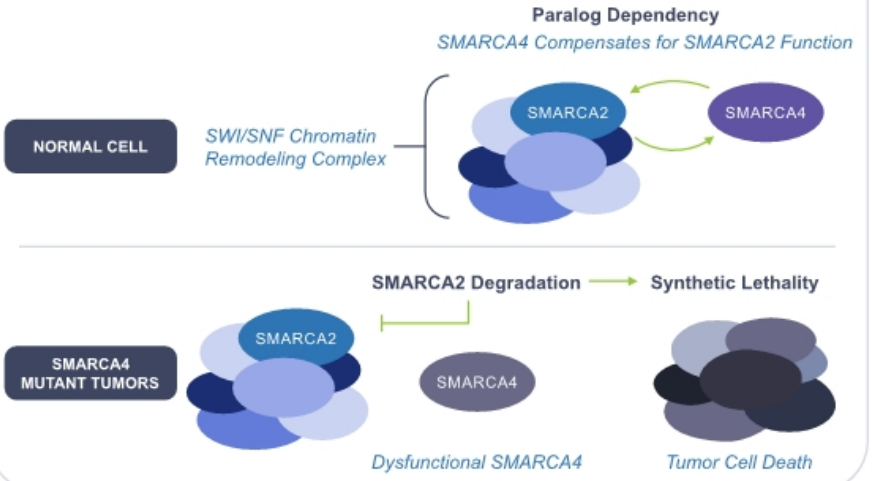
PRT2527 IND expected to be filed in 2021


SMARCA2 Program
Prelude
THERAPEUTICS

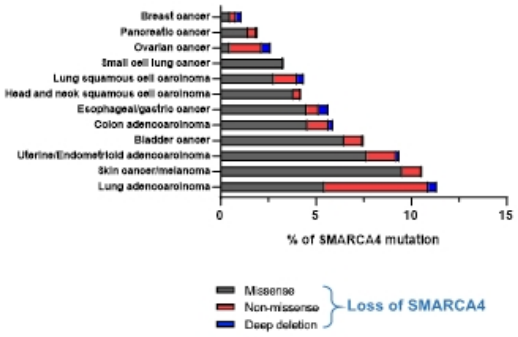
SMARCA2 Targeted Degrader Program

SMARCA2

SMARCA4 and SMARCA2 Regulate Chromatin Accessibility and Gene Expression



Loss of SMARCA4 Leads to SMARCA2 Dependency

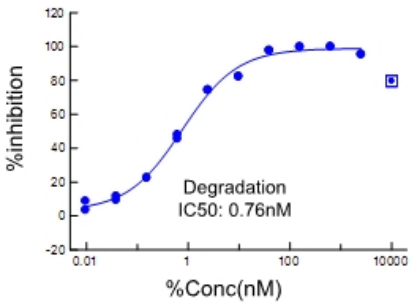


Opportunity to target 10 – 12% NSCLC with SMARCA4 deletions

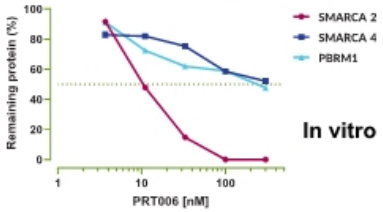
PRT-SCA2: Potent Selective SMARCA2 Degraders with In Vivo Activity

SMARCA2

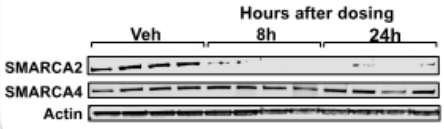
Sub-Nanomolar Potency for SMARCA2 Degradation



Highly Selective for SMARCA2 Degradation

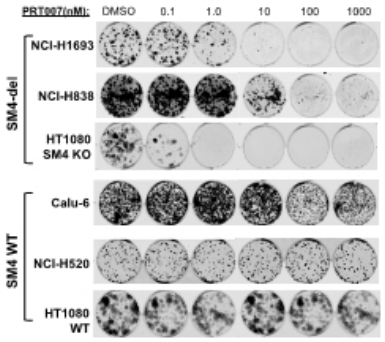


In vitro

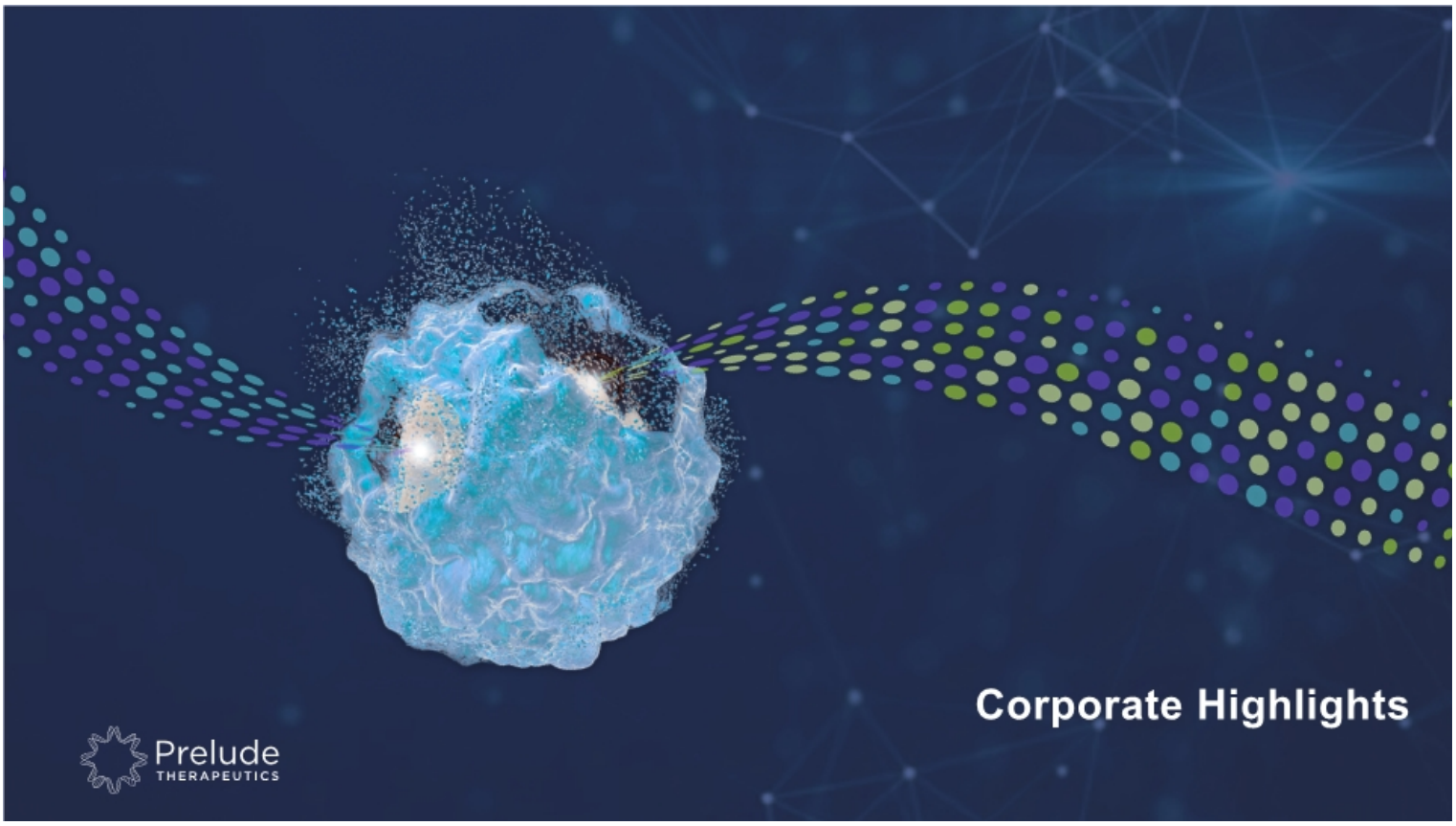


In vivo

Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality



IND expected to be filed 2022


Prelude
THERAPEUTICS
Corporate Highlights

Financial Summary

Shares Outstanding

- 47.0 million shares voting and non-voting common stock as of Nov 8, 2021
- 61.0 million shares fully diluted

Cash, Cash Equivalents and Marketable securities

- $320.9 million as of Sept 30, 2021
- The Company believes that its current cash, cash equivalents and marketable securities will be sufficient to fund operating expenses and capital expenditure requirements into the second half of 2023

Prelude THERAPEUTICS

Prelude Roadmap for Value Creation

Anticipated 2021/2022 Milestones

PRMT5 — Report P1 dose expansion data
Generate POC in selected patients

MCL1 — Complete dose escalation and initiate expansion/combination phase

CDK9 — Initiate Phase 1 clinical trial in selected solid tumors

SMARCA2/ Kinase — Complete IND-enabling studies and file INDs

Future Strategy

Leverage initial POC clinical data to inform design of P2 registration studies

Advance multiple precision oncology clinical programs focusing on underserved cancers

Continue to resource discovery engine to expand our pipeline

Maximize portfolio value through strategic partnerships

Prelude
THERAPEUTICS

Thank You