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): February 16, 2022

Prelude Therapeutics Incorporated
(Exact name of registrant as specified in its charter)

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

200 Powder Mill Road
Wilmington, Delaware, 19803
(Address of principal executive offices, including zip code)

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

N/A
(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	**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 7.01. Regulation FD Disclosure

Prelude Therapeutics Incorporated (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 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information furnished with this report, including Exhibit 99.1, shall not be deemed "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, 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 No.	Description
99.1	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: February 16, 2022

By: /s/ Laurent Chardonnet
Laurent Chardonnet
Chief Financial Officer

Exhibit 99.1

Prelude THERAPEUTICS

Precision Oncology **Redefined**

February 2022

Forward-Looking Statements

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 September 30, 2021 and in our upcoming Annual Report on Form 10-K for the year ended December 31, 2021.

Prelude Therapeutics: Vision

Build a fully integrated oncology company on the foundation of drug discovery excellence to deliver novel precision cancer medicines to underserved patients

Prelude THERAPEUTICS

Experienced Management Team: Proven Track Records

Founding member

Kris Vaddi, PhD

Founder & Chief Executive Officer

Jakafi (ruxolitinib tablets) · olumiant (baricitinib tablets) · TABRECTA (capmatinib) tablets · VELCADE (bortezomib)

Laurent Chardonnet

Chief Financial Officer

Jakafi (ruxolitinib tablets) · olumiant (baricitinib tablets) · Pemazyre (pemigatinib tablets) · TABRECTA (capmatinib) tablets

Deborah Morosini, MD, MSW

Executive Vice President and Chief of Clinical Affairs

TAGRISSO osimertinib · Retevmo selpercatinib · VITRAKVI

Andrew Combs, PhD

Executive Vice President and Head of Chemistry

Jakafi (ruxolitinib tablets) · olumiant (baricitinib tablets)

Peggy Scherle, PhD

Chief Scientific Officer

Jakafi (ruxolitinib tablets) · olumiant (baricitinib tablets) · Pemazyre (pemigatinib tablets) · TABRECTA (capmatinib) tablets

Naveen Babbar, PhD

Senior Vice President of Translation Medicine

ZYKADIA ceritinib · KISQALI ribociclib · PIQRAY (alpelisib) tablets · TABRECTA (capmatinib) tablets

Board of Directors

Paul Friedman, MD
- Madrigal — *CEO*
- Incyte — *Former CEO*

Mardi Dier
- ultragenyx — *CFO*
- PORTOLA — *Former CFO, CBO*

Victor Sandor, MD
- ARRAY BIOPHARMA — *Former CMO*

David Bonita, MD
- OrbiMed — *General Partner*

Julian C. Baker

Managing Member
Baker Brothers Investments

Kris Vaddi, PhD

Founder & Chief Executive Officer

Martin Babler
- PRINCIPIA BIOPHARMA — *Former CEO*

Prelude Therapeutics: Key Reasons to Invest

Internal Discovery Engine

Scientists with proven track records

Effective R&D Approach

Seamless integration between biology and chemistry

Strong Execution

Proprietary diversified pipeline

Focused Clinical Development

Driving to 'go/no go' decisions with a sense of urgency

Well Capitalized

~$320M cash & marketable securities (9/30/21)

Precision Oncology: Targeting Clinically Relevant Pathways

TARGET	PRMT5	MCL1	CDK9	SMARCA2 (BRM)
MOA	mRNA Splicing & DNA Repair	Apoptosis	Transcriptional Regulation	Synthetic Lethality
SELECTABLE PATIENTS	Spliceosome Mutations, HRD+	Venetoclax Resistance	MYC Amplified	SMARCA4 (BRG1) Mutations
CANCERS	Glioma, Myeloid, Solid Tumors	AML, MDS, CLL	Sarcoma, Prostate, AML	NSCLC, Endometrial

Current Pipeline: Diversified and Growing

PROGRAM	CANCER INDICATIONS	IND ENABLING	PHASE 1 ESCALATION	PHASE 1 EXPANSION	PHASE 2/3 REGISTRATION
PRT543 (PRMT5)	Solid Tumors, Myeloid Cancers				
PRT811 (Brain Penetrant PRMT5)	IDH+ High Grade Glioma, Uveal Melanoma				
PRT1419 (MCL1)	AML, MDS, CLL				
PRT2527 (CDK9)	Sarcoma, Prostate, AML				
PRT-SCA2 (SMARCA2)	NSCLC, Endometrial				
PRT-K4 (Kinase)	Solid Tumors				

2022 Goals: Aggressive with Clear Deliverables

PRMT5
PRT543/PRT811

Complete expansion phases for both molecules

Demonstrate PoC in one or more indications

MCL1
PRT1419

Establish RP2D

Demonstrate safety in combination with venetoclax / azacitidine

Demonstrate PoC

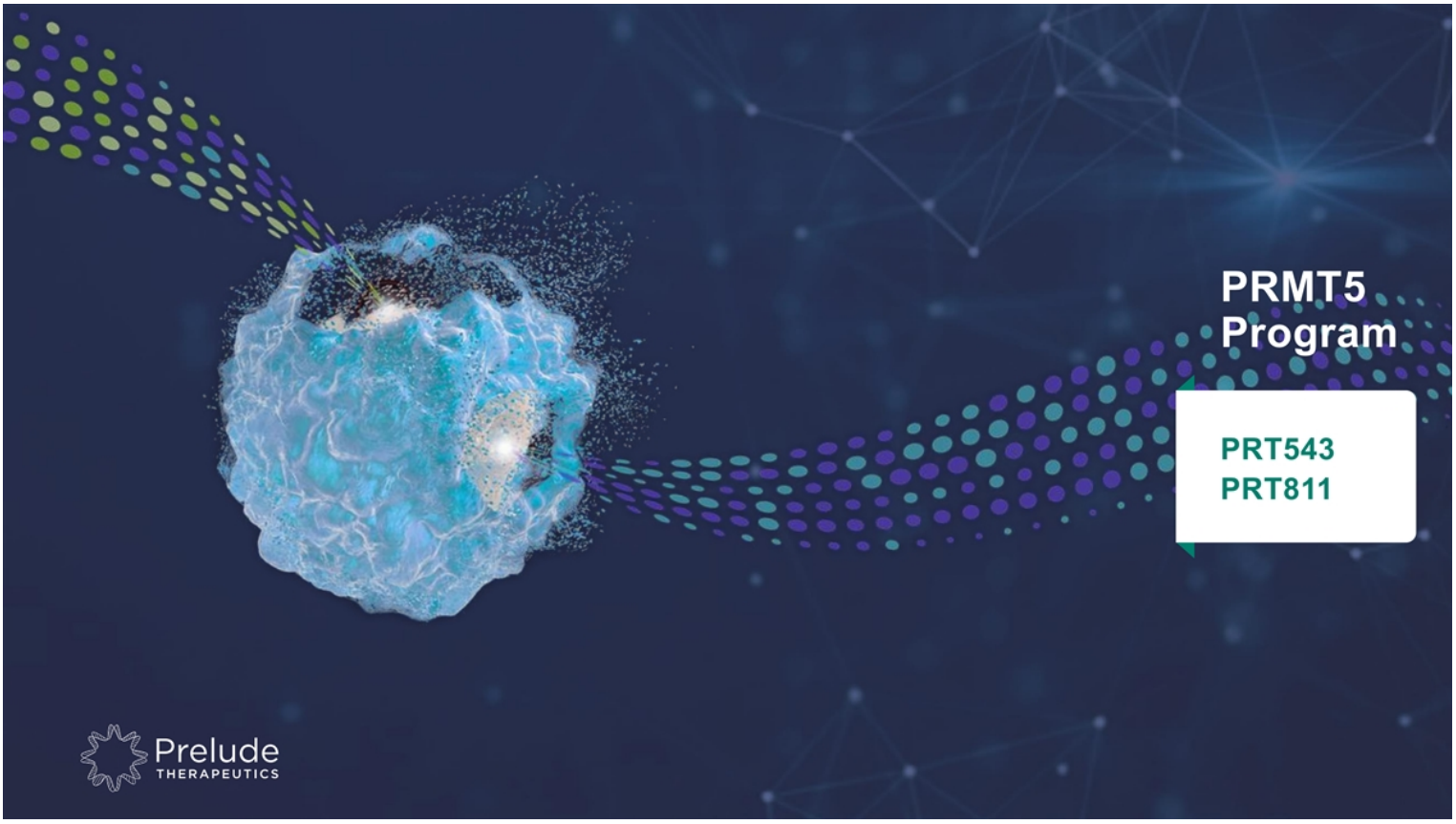
CDK9
PRT2527

Complete dose escalation

Establish safety, target engagement, and RP2D

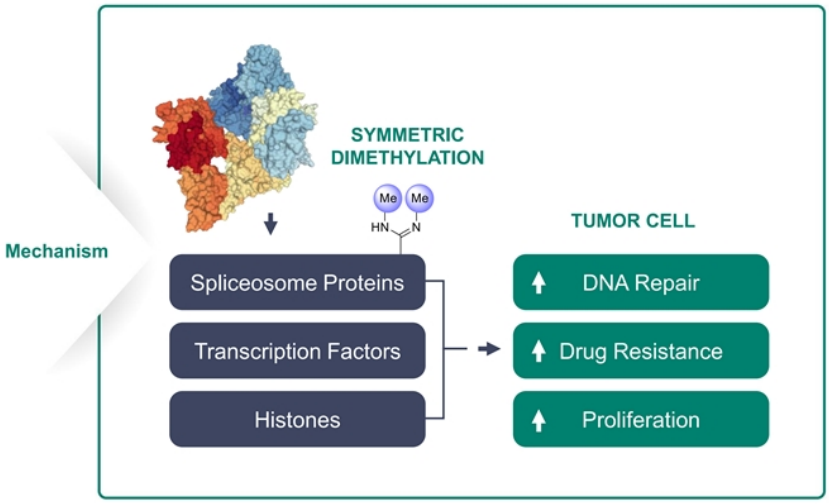
SMARCA (BRM)
PRT-SCA2

File IND


PRMT5
Program
PRT543
PRT811
Prelude
THERAPEUTICS

PRMT5 Pathway Drives Oncogenesis and Resistance

PRMT5



- PRMT5 catalyzes symmetric arginine dimethylation (sDMA) of protein substrates including histones, transcription factors, and spliceosome proteins
- Dimethylated substrates of PRMT5 control key oncogenic and resistance mechanisms
- PRMT5 inhibition is highly efficacious in models with mutations in DNA repair or mRNA-splicing pathways in preclinical models
- PRMT5 inhibition can be leveraged to target genetically selected patient populations in the clinic

PRT543
PRT811

Potential Best-In-Class PRMT5 Inhibitors

Prelude THERAPEUTICS

Differentiated PRMT5 Inhibitors

- Highly selective and potent oral candidates
- PRT811 is highly differentiated in the class with high brain penetration potential

Applicability in Both Solid Tumors and Heme

- Strong scientific rationale and robust preclinical activity across broad range of cancers
- Early clinical signals in multiple cancer types

Optimized PK Profile

- High oral bioavailability and optimal half-life to maximize therapeutic window
- Differentiated safety and clinical activity profile

Potential Rapid Path to Market

- Potential for accelerated approval pathway
- Opportunity in multiple cancer types

PRMT5: Phase 1 Data Will Drive Phase 2/3 Indication Selection

PRMT5

Part 1
Dose Escalation
COMPLETED

PRT543

PRT811

SOLID TUMORS, GBM,
MYELOID MALIGNANCIES

Part 2
Expansion Cohorts
ONGOING

RECOMMENDED EXPANSION DOSES

PRT543
45 mg 5x/wk
(solid tumors)
35 mg 5x/wk
(hematologic malignancies)

- Adenoid Cystic Carcinoma (N~40)
- Homologous Recombination Deficient (HRD+) Solid Tumors (N~40)
- Splicing mutated Solid and Myeloid Malignancies (N~40)

PRT811
600 mg QD

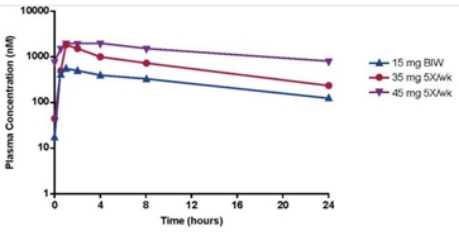
- Uveal Melanoma
- High Grade Gliomas

PRT543 and PRT811 Demonstrate Desirable PK and PD Properties

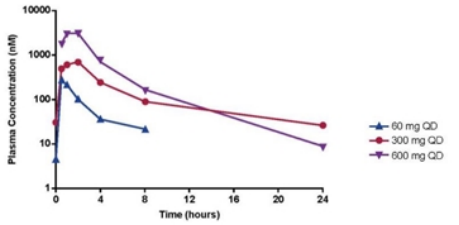
PRMT5

Dose-Dependent Increases in Cmax and AUC

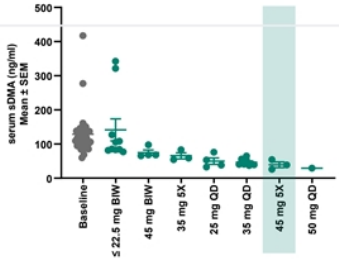
PRT543

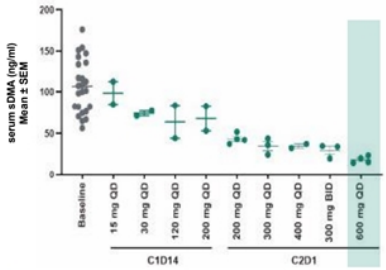


PRT811



Dose-dependent Inhibition of Serum sDMA





PRMT5 Phase 1: Key Takeaways and Next Steps

PRMT5

FAVORABLE SAFETY PROFILE

PRT543 and PRT811 well tolerated

Favorable safety properties

Low incidence of dose-limiting toxicities at expansion doses

DESIRABLE PK & PD PROFILES

Dose-dependent increase in exposure

High levels of target inhibition

PRT811 demonstrated best-in-class profile with wide therapeutic window

PRELIMINARY CLINICAL ACTIVITY

Objective responses in solid tumors

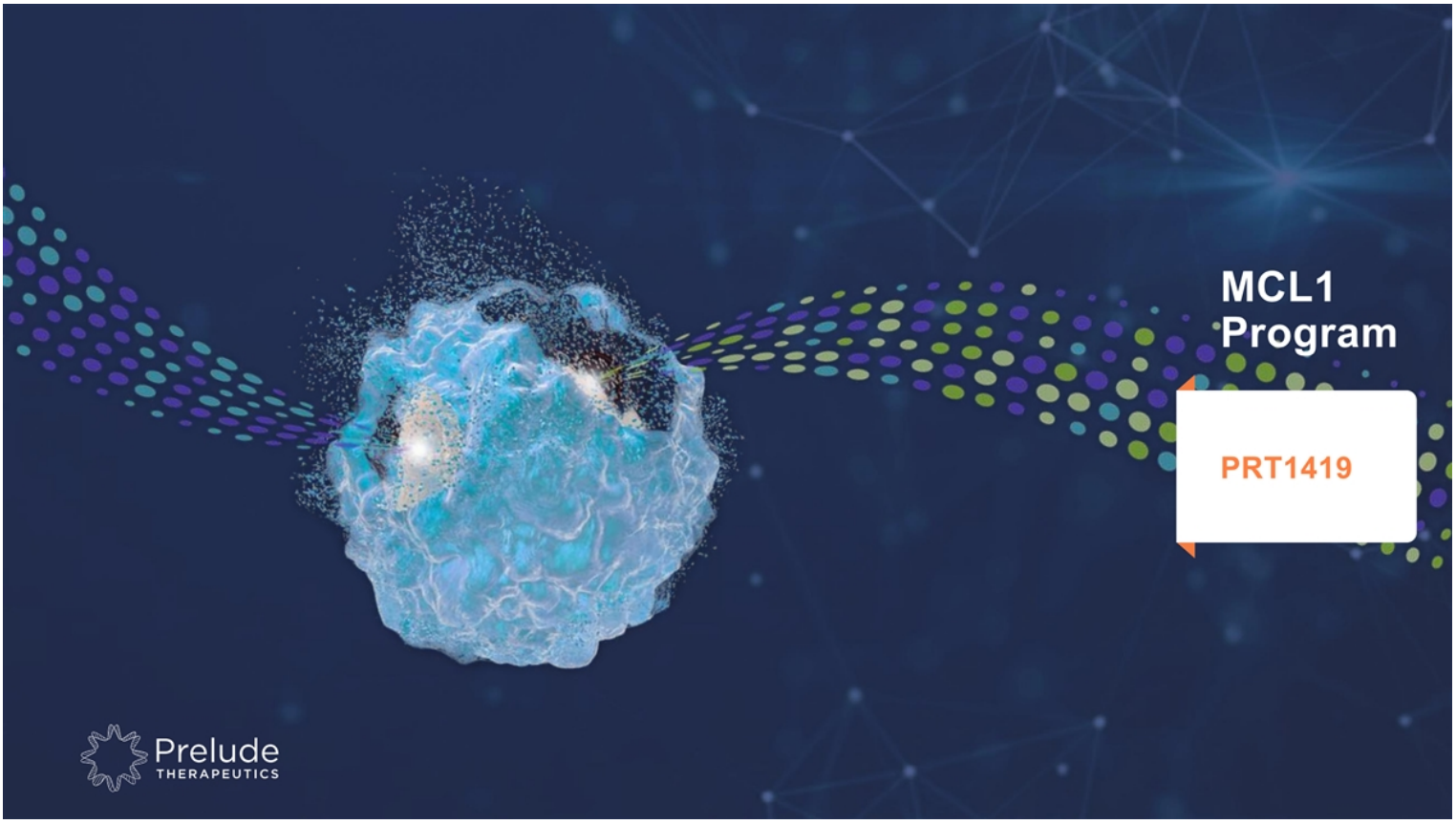
IWG anemia benefit in myeloid malignancies

Anti-tumor activity observed in relapsed/refractory patients with target biomarker profile

NEXT STEPS

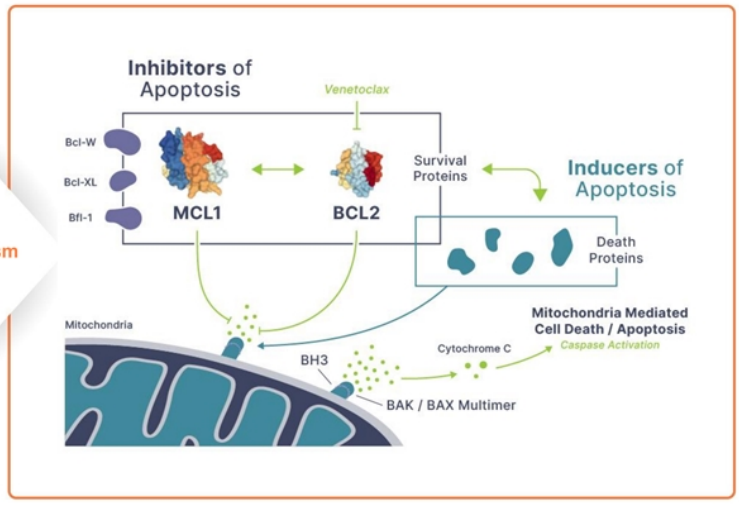
Complete expansion phases for both molecules

Demonstrate PoC in one or more indications


MCL1
Program
PRT1419
Prelude
THERAPEUTICS

MCL1: Targeting Cancer Cell Survival

Mechanism



- MCL1 is a member of family inhibitors of apoptosis (BCL2); often overexpressed in cancers
- BCL2 family is clinically validated – Venetoclax approved for lymphoid and myeloid malignancies
- MCL1 is a bypass and resistance mechanism for Venetoclax and multiple TKIs
- Challenging medicinal chemistry target that requires disruption of protein-protein interaction

PRT1419

Differentiated Clinical-Stage MCL1 Inhibitor Candidate

Prelude THERAPEUTICS

MCL1 Inhibitor

- Potent and selective
- No cardiotoxicity signal in GLP-toxicology studies

Targeting Selected Heme and Solid Cancers

- Robust activity in preclinical models with once weekly dosing
- Potential combination strategy with Venetoclax and/or HMAs in Hematological malignancies

Optimized PK Profile Maximizes Therapeutic Window

- Higher clearance built in to achieve desirable duration of target inhibition
- Optimal physicochemical properties

Potential Rapid Path to Market

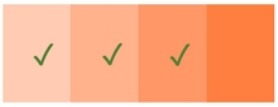
- Venetoclax-resistant cancers offer opportunity for accelerated approval

MCL1: Phase 1 Overview

MCL1

Phase 1
Dose Escalation

Monotherapy (mg/m2)



1H 2022

Dose Escalation
Combination

Combination (Ven + Aza)

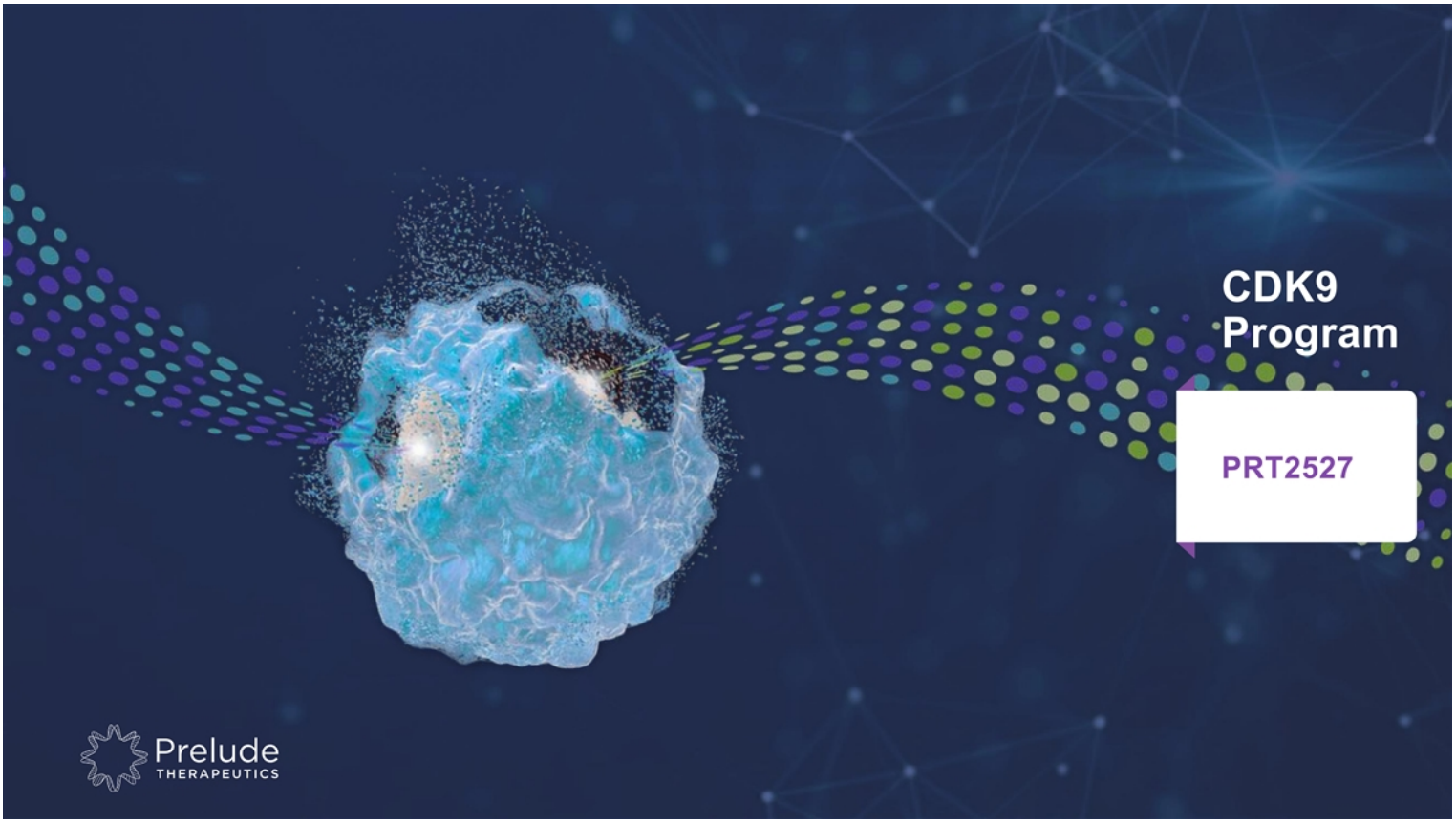
2H 2022

Dose Expansion

1419 VEN+ AZA
R/R AML/MDS

1419 + AZA
R/R AML/MDS

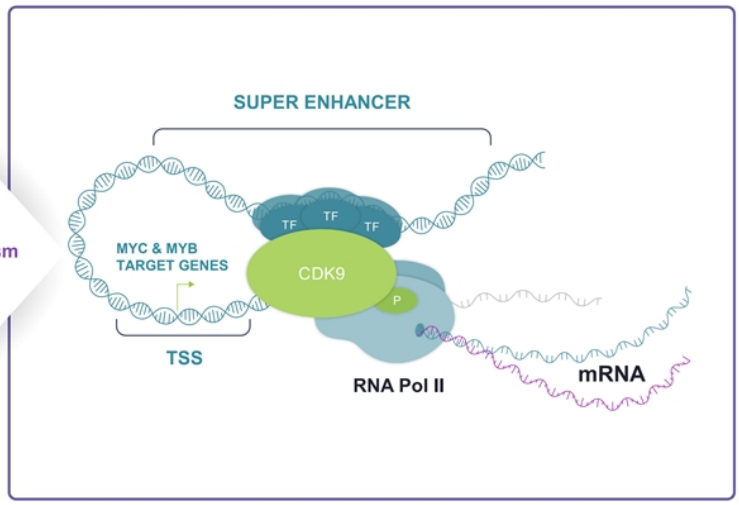
1H 2023


CDK9
Program
PRT2527
Prelude
THERAPEUTICS

CDK9: Targeting Cancer Through Transcriptional Regulation

CDK9

Mechanism



- 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

PRT2527

Potential Best-in-Class Selectivity and Potency

Prelude THERAPEUTICS

CDK9 Inhibitor

- Most selective in the class vs CDK family and across the kinome
- Low nanomolar potency in blocking tumor cell proliferation

Targeting Selected Heme and Solid Cancers

- Robust activity in preclinical models at well-tolerated doses
- Enhanced sensitivity in tumors that are MYC-dependent
- Provides patient selection strategy in clinic

Optimized PK Profile

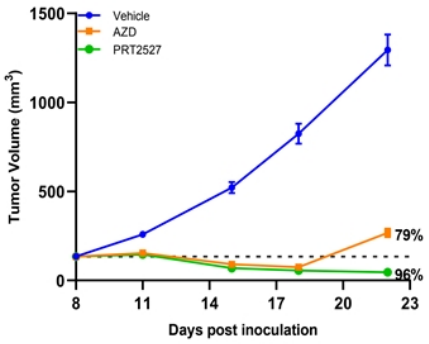
- Higher clearance built in to maximize therapeutic window

Robust Activity in Preclinical Models at Well-Tolerated Doses

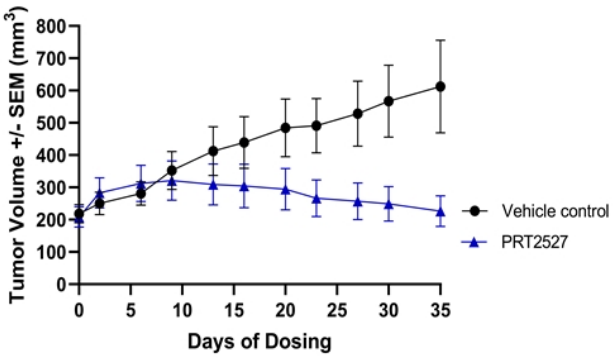
CDK9

Sustained Regression at Well-Tolerated Doses *In Vivo* in both Heme and Solid Tumor Models

MV4-11 (AML)



NSCLC PDX
(MYC Amplified)

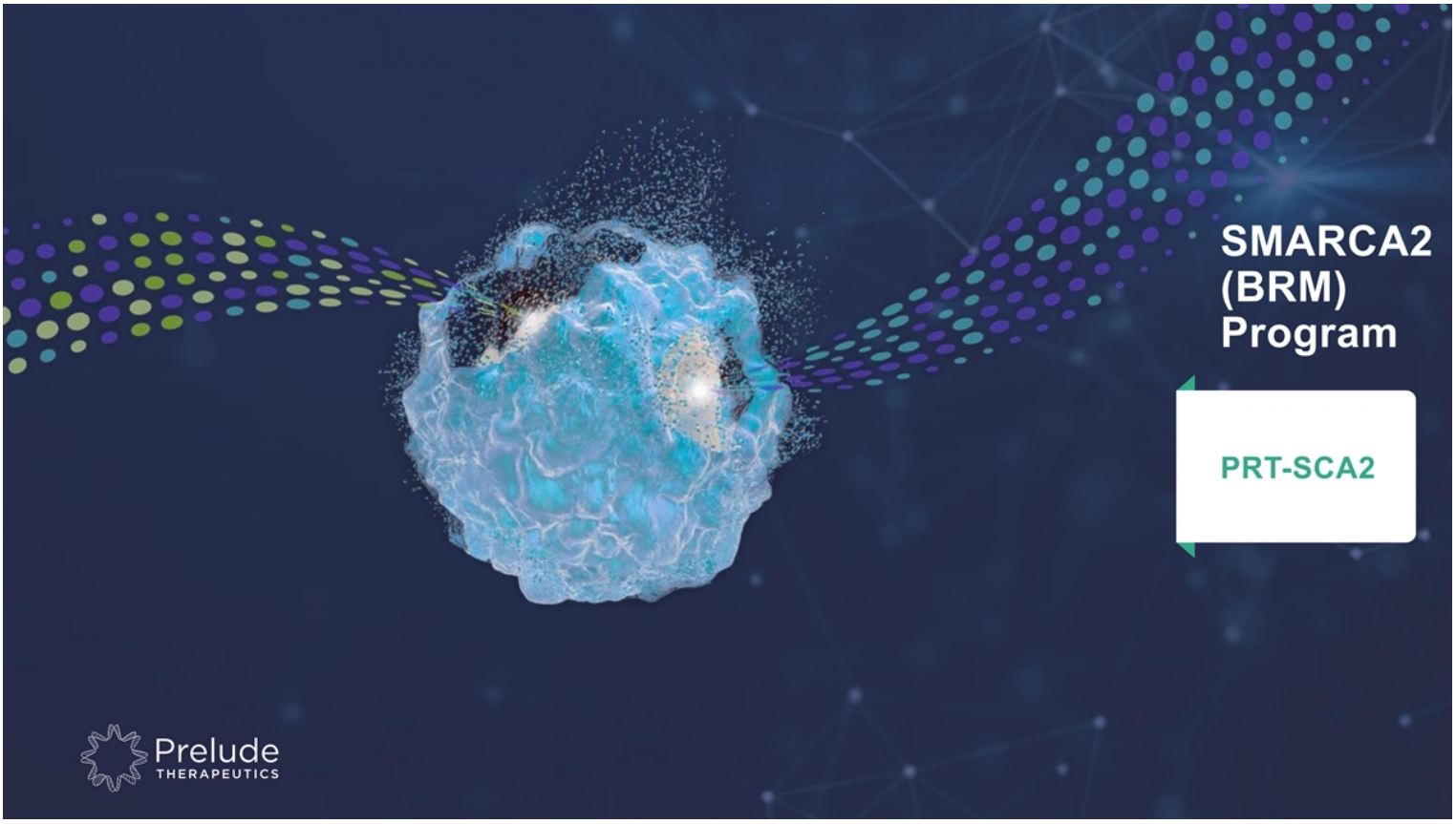


CDK9: Clinical Overview

Phase 1 Dose Escalation
(Bayesian Design)
ONGOING

Phase 2 With Recommended Dose From Completed Phase 1 Trial
(TARGET 1H 2023)

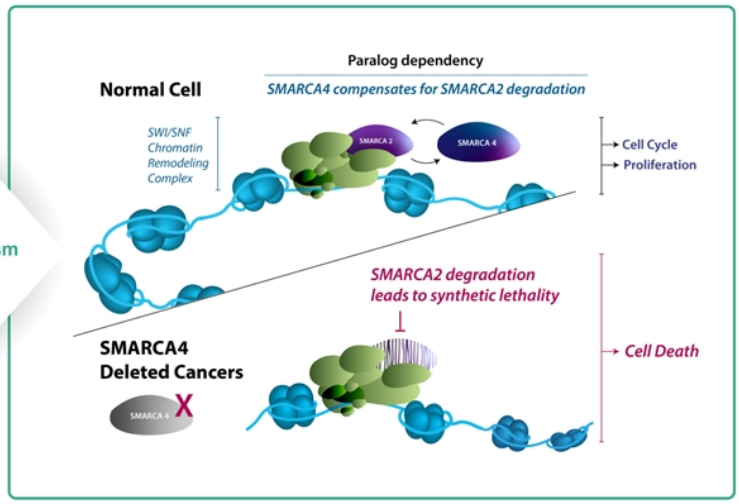
- MYC-Dependent Solid Tumors (NSCLC, Prostate)
- Sarcoma
- Hematologic Malignancies


SMARCA2
(BRM)
Program
PRT-SCA2
Prelude
THERAPEUTICS

Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

SMARCA2

Mechanism

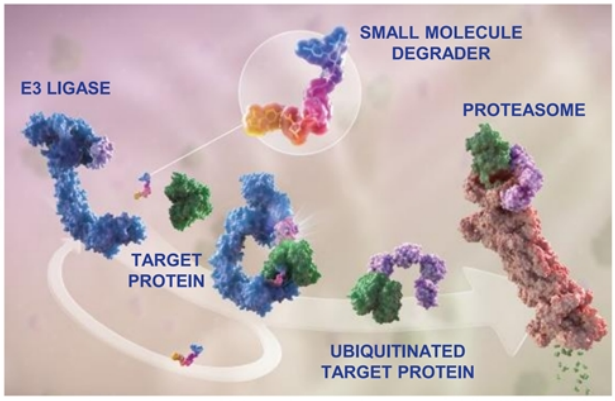


- The chromatin remodeling (SWI/SNF) complex is frequently mutated in cancer making it a potential therapeutic target
  - Activity of the SWI/SNF complex requires either SMARCA4 (BRG1) or SMARCA2 (BRM)
  - Loss of SMARCA4 (BRG1) through mutation leads to dependency on SMARCA2 (BRM)
  - Subsets of solid tumors express SMARCA4 (BRG1) mutations
  - Selectively inhibiting SMARCA2 (BRM) offers an attractive approach to target SMARCA4 (BRG1) mutant tumors

Achieving SMARCA2 Selectivity Through Degrader Approach

SMARCA2

Mechanism



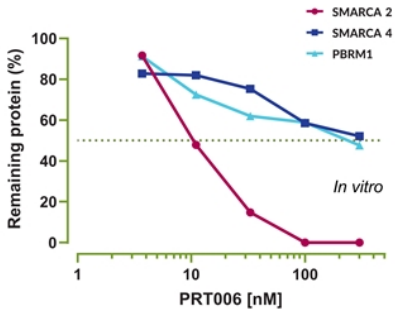
Mullard A. Nat Rev Drug Discov. 2019

- SMARCA2 selectively over highly homologous SMARCA4 isoform has been a challenging medical chemistry problem with traditional small molecule approaches
- Target Protein Degradation (TPD) of SMARCA2 selectively over SMARCA4 is possible through differences in ternary complexes
- Prelude scientists identified the molecular basis for achieving high degree of selectivity for SMARCA2 over SMARCA4
- Lead molecules from multiple chemical scaffolds with sub-nanomolar potency and selectivity have been discovered

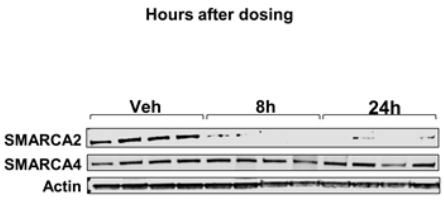
PRT-SCA2: Potent and Selective SMARCA2 Degrader with *In Vivo* Activity

SMARCA2

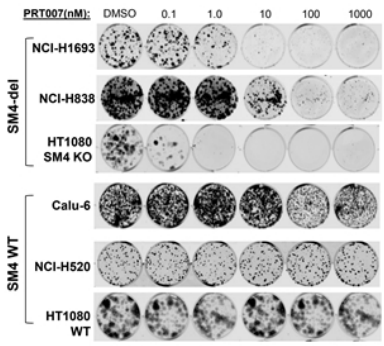
Highly Selective for SMARCA2 Degradation *In Vitro*



Highly Selective for SMARCA2 Degradation *In Vivo*



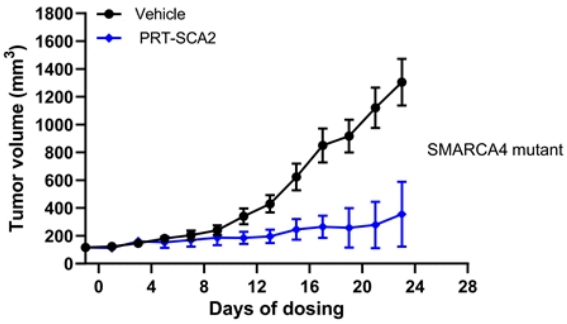
Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality

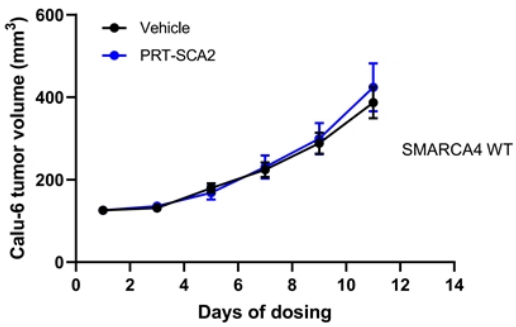


PRT-SCA2: Potent and Selective SMARCA2 Degrader with *In Vivo* Activity

SMARCA2

Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft





SMARCA2: Degrader Program Overview

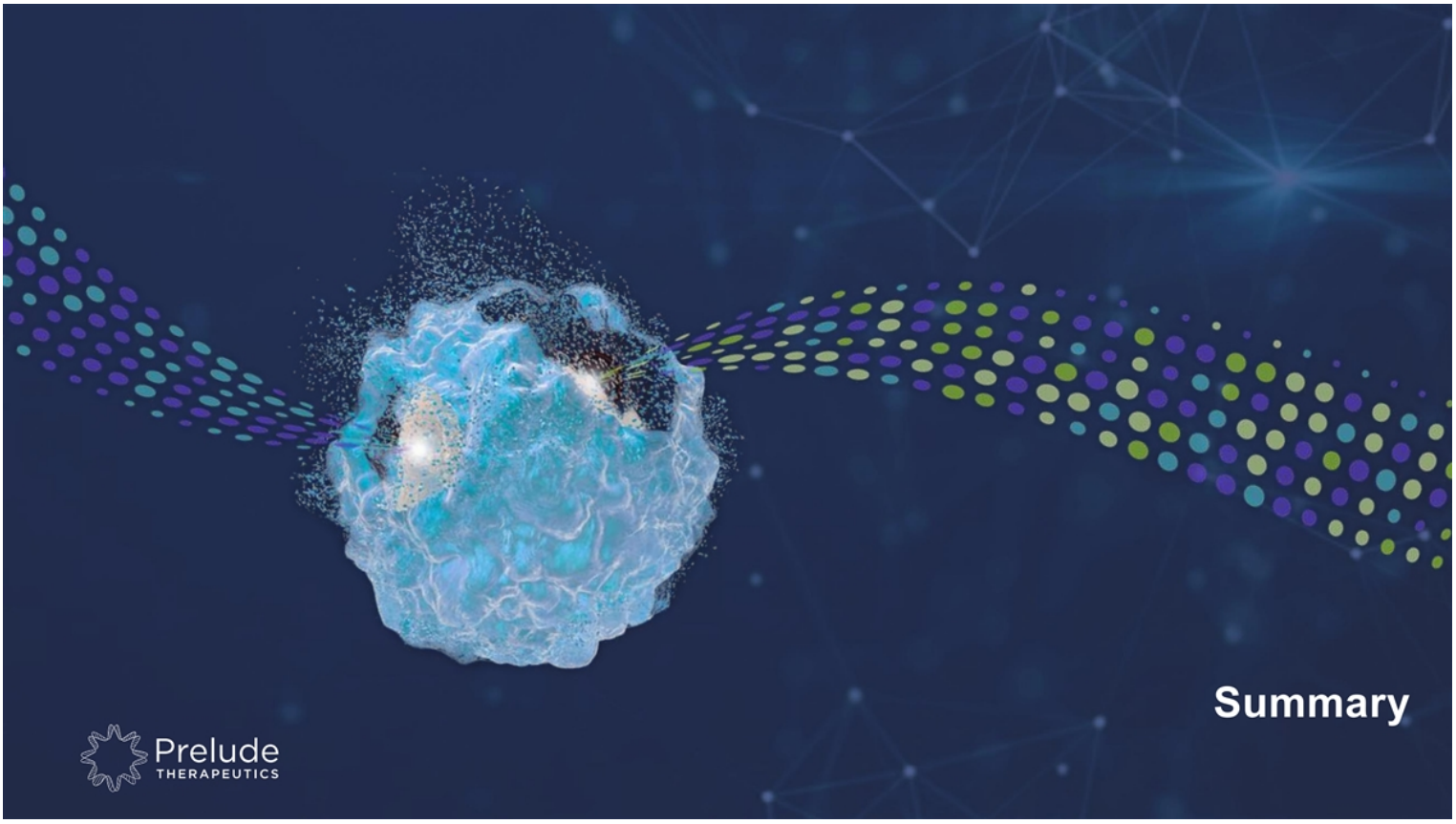
SMARCA2

Candidate molecule(s) identified
IND enabling studies initiated

- IND Enabling Studies
- IND Filing 2H 2022

Phase 1 Dose Escalation
TARGET 1Q 2023

SMARCA4-MUTATED NSCLC AND
OTHER TUMOR TYPES


Prelude
THERAPEUTICS
Summary

2022 Goals: Aggressive with Clear Deliverables

PRMT5
PRT543/PRT811

Complete expansion phases for both molecules

Demonstrate PoC in one or more indications

MCL1
PRT1419

Establish RP2D

Demonstrate safety in combination with venetoclax / azacitidine

Demonstrate PoC

CDK9
PRT2527

Complete dose escalation

Establish safety, target engagement, and RP2D

SMARCA (BRM)
PRT-SCA2

File IND

Prelude Therapeutics: Key Reasons to Invest

Internal Discovery Engine

Scientists with proven track records

Effective R&D Approach

Seamless integration between biology and chemistry

Strong Execution

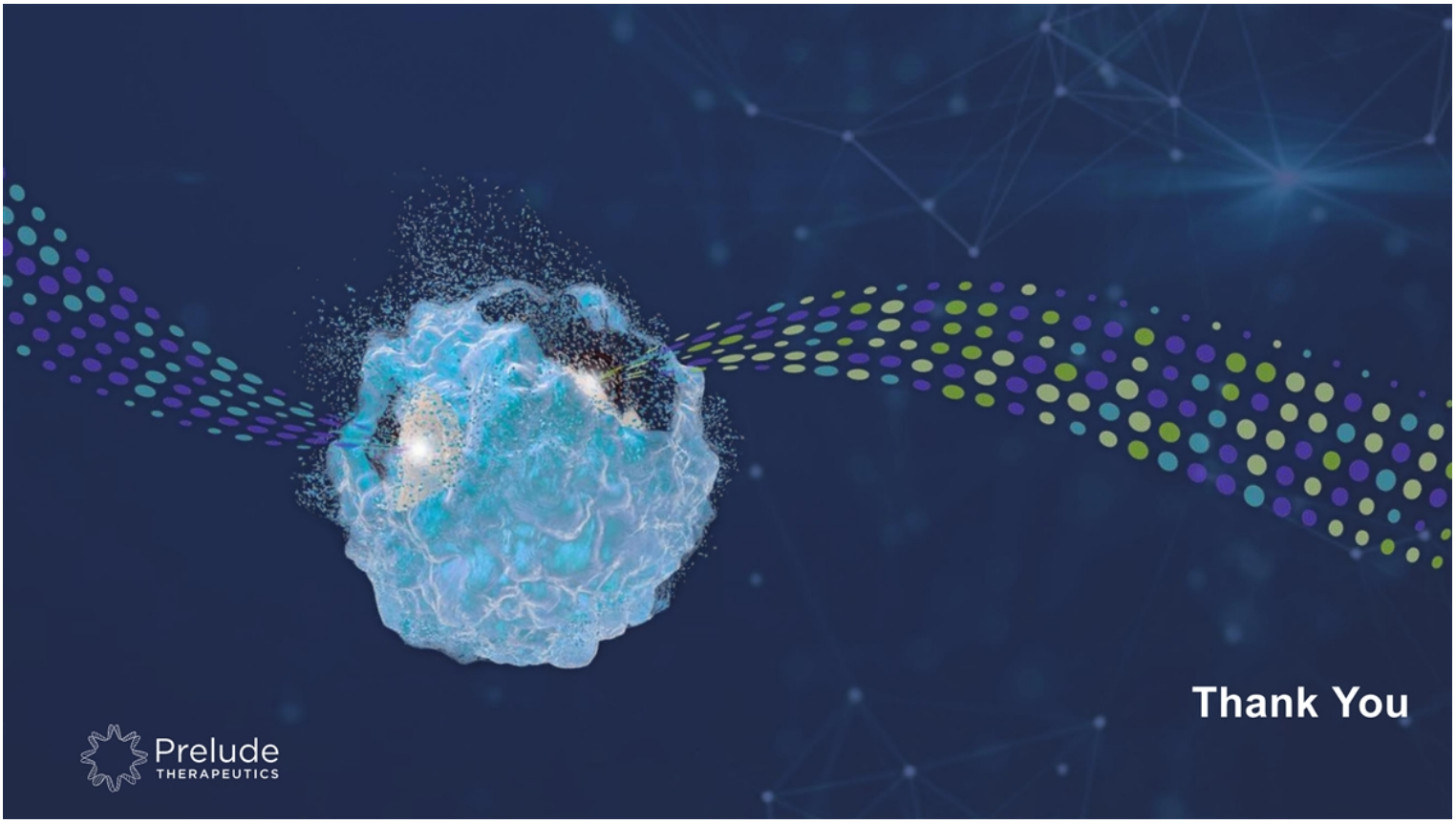
Proprietary diversified pipeline

Focused Clinical Development

Driving to 'go/no go' decisions with a sense of urgency

Well Capitalized

~$320M cash & marketable securities (9/30/21)


Thank You
Prelude
THERAPEUTICS