Prelude THERAPEUTICS

Precision Oncology **Redefined**

Corporate Presentation
January 2022

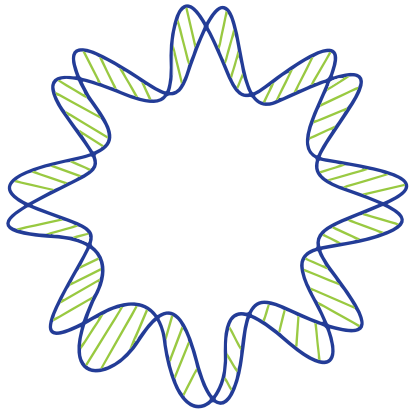
Forward Looking Statements

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).

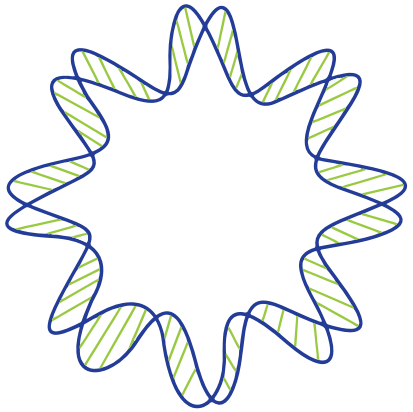
These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will 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.

Prelude Therapeutics: Vision



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

Prelude Therapeutics: Building for Success



Internal Discovery Engine

Powered by experienced drug developers with a *proven track record* of multiple successful oncology medicines

Differentiated R&D Approach

Effective *integration* between cancer biology and medicinal chemistry to rapidly iterate and discover optimized molecules in a target class agnostic fashion

Strong Execution and Commitment to Discovery

4 INDs approved in 4 years; 4 *differentiated* clinical candidates currently advancing through Phase 1 and into Phase 2/3 clinical development; 2 new additional INDs expected in 2022

Focused Clinical Development in Underserved Cancers

Clinical trial designs in selected cancer patients allowing *efficient 'go / no go' decisions* in caner types *with* potential for *rapid regulatory approval*

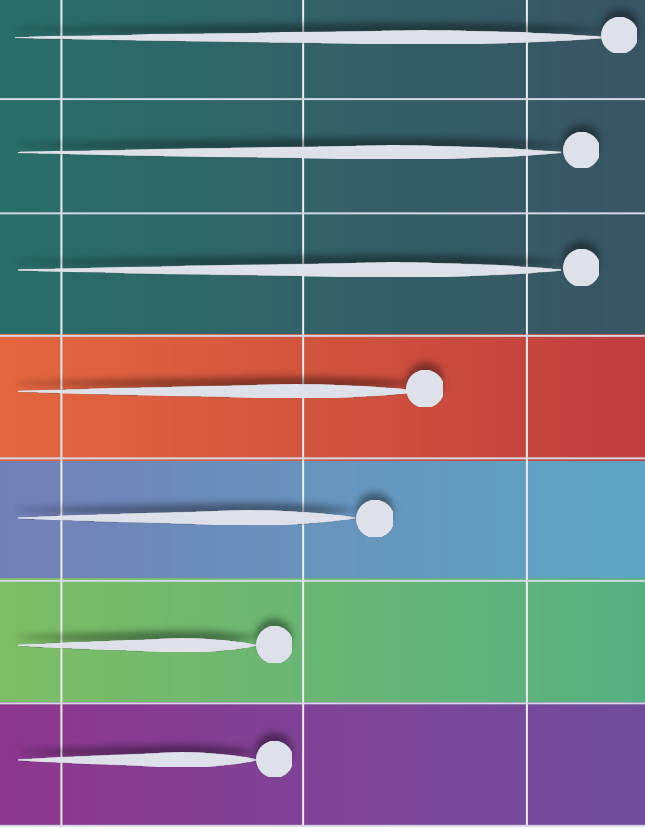
Strong Financial Position: ~$320M Cash & Marketable Securities (9/30/21)

Building a Deep Portfolio of Oncology Assets

Target	PRMT5	MCL1	CDK9	SMARCA2 (BRM)
MOA	mRNA Splicing & DNA Repair	Apoptosis	Transcriptional Regulation	Synthetic Lethality
Molecule(s)	**PRT543 & PRT811**	**PRT1419**	**PRT2527**	**PRT-SCA2**
Development Stage	Phase 1 Expansion	Phase 1 Escalation	Phase 1 Escalation	IND Target 2022
Target Cancers	Spliceosome Mutations Selected CNS HRD+	Venetoclax and TKI-Resistant Heme and Solid	MYC-driven Heme and Solid	SMARCA4 (BRG1) Deleted NSCLC and Others

Diversified Precision Oncology Pipeline

Program	Cancer Indications	IND Enabling	Phase 1 Escalation	Phase 1 Expansion	Phase 2/3	Upcoming Milestones
PRT543 (PRMT5)	ACC, HRD+, spliceosome mutations					Data readouts 2H22
	Selected myeloid malignancies (incl. MF and MDS)					
PRT811 (Brain Penetrant PRMT5)	IDH+ high grade glioma, uveal melanoma					Data readouts 2H22
PRT1419 (MCL1)	Selected hematological malignancies and solid tumors					Dose escalation data readout 2H22
PRT2527 (CDK9)	Selected solid and hematological malignancies					Dose escalation data YE 2022
PRT-SCA2 (SMARCA2)	Multiple genomically selected cancers					IND filing target 2022
PRT-K4 (Kinase)	Solid tumors					IND filing target 2022



2021 Accomplishments and 2022 Goals

PRMT5

2021

✓

PRT543
- Identified RP2D
- Demonstrated favorable safety profile and preliminary clinical activity
- Multiple expansions initiated

PRT811
- Identified RP2D
- Best-in-class potential demonstrated; Expansion phase initiated

2022

- Complete expansion phases for both molecules
- Demonstrate PoC in one or more indications
- Advance PRMT5 program into Phase 2

MCL1

✓

- Phase 1 dose escalation with oral formulation ongoing
- Phase 1 dose escalation with IV formulation initiated

- Establish RP2D
- Demonstrate safety in combination with Venetoclax/Azacitidine
- Demonstrate PoC

CDK9

✓

- Successfully filed IND
- Phase 1 Initiated

- Complete dose escalation
- Establish safety, target engagement and RP2D

Preclinical

✓

- PRT-SCA2 - IND Enabling Studies Initiated; IND target in 2022
- PRT-K4 - IND Enabling Studies Initiated; IND target in 2022

- File INDs
- Initiate Phase 1 studies

PRMT5 Program

PRT543 & PRT811

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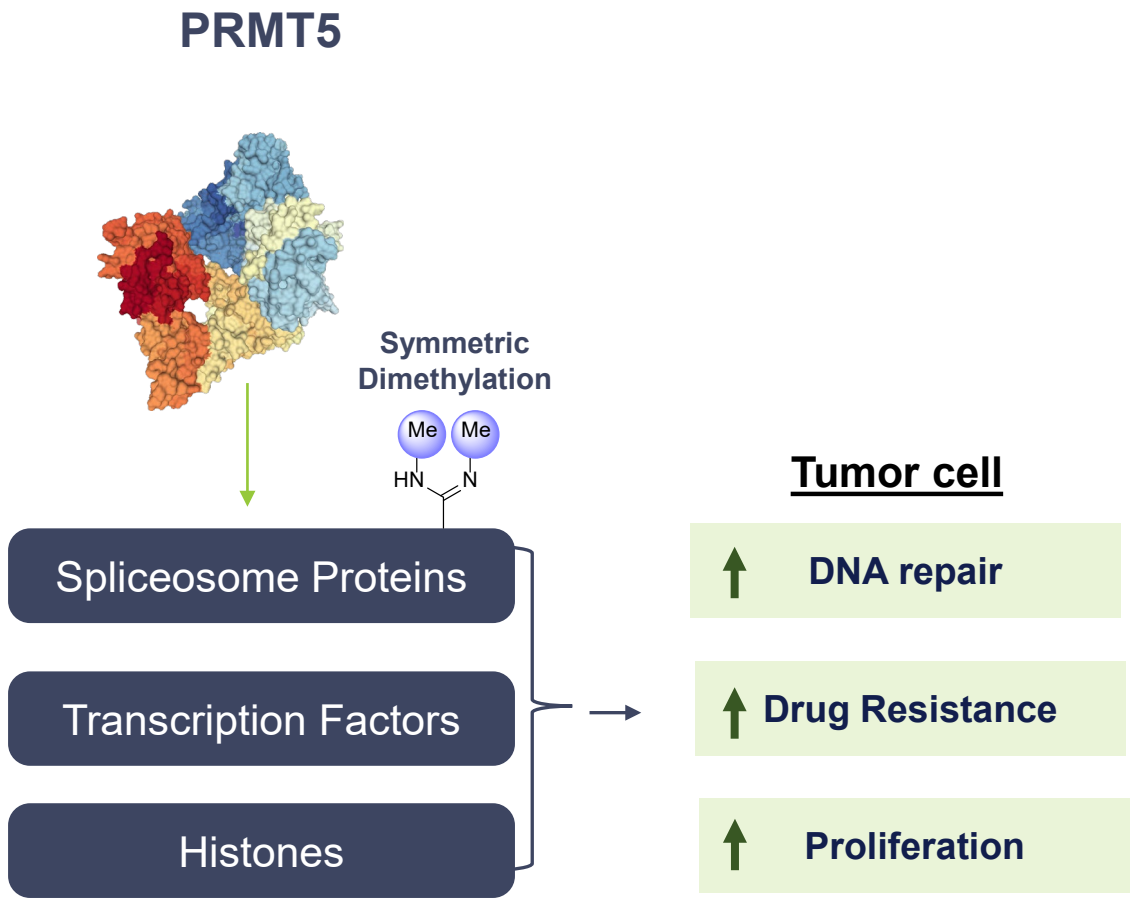
PRMT5 Pathway Drives Oncogenesis and Resistance

- 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

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

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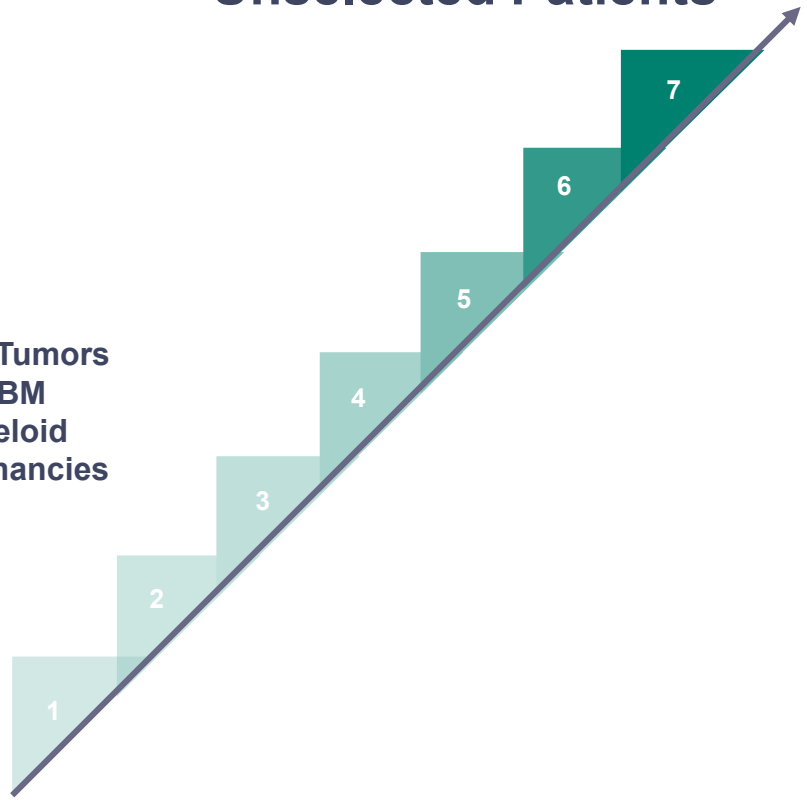
PRMT5: Phase 1 Overview

Dose Escalation Unselected Patients



Solid Tumors
GBM
Myeloid
Malignancies

Recommended Expansion Doses

PRT543
45 mg 5x/wk (solids)
35 mg 5x/wk (heme)

PRT811
600 mg QD

Expansion Cohorts Selected Patients

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

PRT543

- Uveal Melanoma
- High Grade Gliomas

PRT811

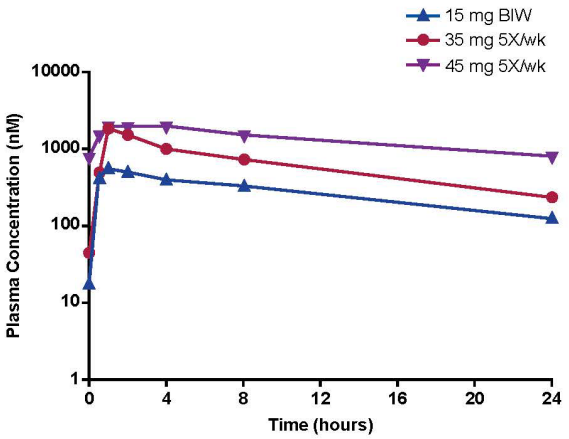
Completed

Ongoing

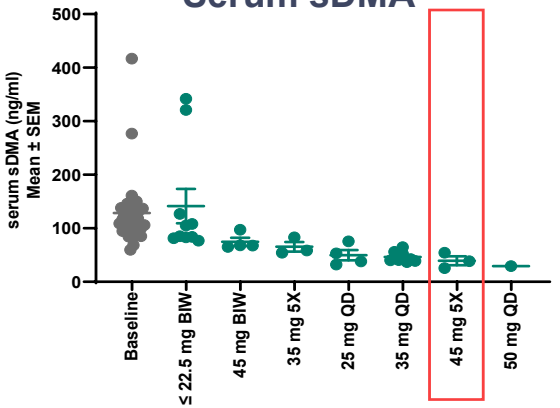
PRT543 and PRT811 Demonstrate Desirable PK and PD Properties

PRT543

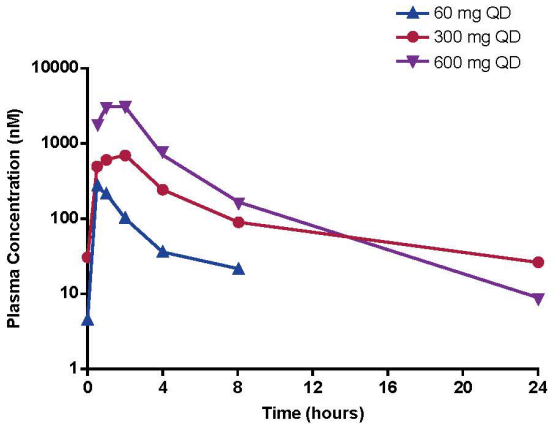
Dose-Dependent Increases in Cmax and AUC

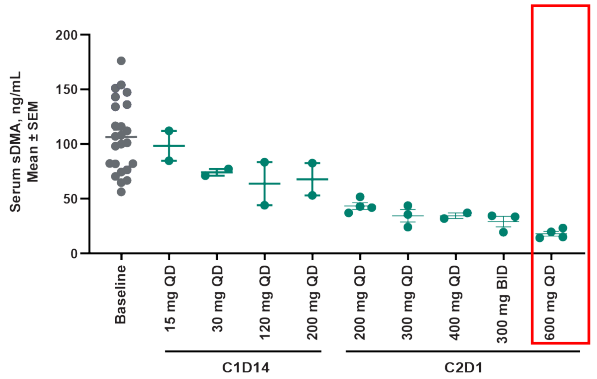


Dose-dependent Inhibition of Serum sDMA



PRT811





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Data presented at 2021 AACR-NCI-EORTC Annual Meeting

PRMT5 - Phase 1 Dose Escalation: Safety and Clinical Activity*

PRT543

Study Demographics & Safety

- Unselected patient population with advanced solid tumors and myeloid malignancies

Safety

- Most common Grade ≥ 3 AEs were thrombocytopenia and anemia
- Thrombocytopenia is the only DLT
- Reversible upon dose modification
- Low incidence (≤20%) at expansion doses

Preliminary Clinical Activity

- Durable CR in a patient with HRD+ ovarian cancer (35 mg 5x/wk; still on Rx)
- Stable disease and tumor regressions (<30%) in 5 patients including ACC and uveal melanoma
- Sustained hemoglobin and anemia improvements in multiple patients with myeloid malignancies

PRT811

Study Demographics & Safety

- Unselected patient population with advanced cancers including GBM

Safety

- Grade ≥ 3 AEs were uncommon (occurring in 11% of patients)
- No DLTs up to 600 mg QD

Preliminary Clinical Activity

- One patient with IDH1 mutated GBM experienced durable PR that evolved into CR (still on Rx)
- Two splicing mutated uveal melanoma patients demonstrated anti-tumor activity including a uPR and a 25% tumor regression

*Data presented at 2021 AACR-NCI-EORTC and ASH Annual Meetings

PRMT5 Phase 1: Key Takeaways and Next Steps

Favorable Safety Profile

- PRT543 and PRT811 well tolerated
- Favorable safety properties
- Low incidence of dose-limiting toxicities at expansion doses

Desirable PK & PD Profiles

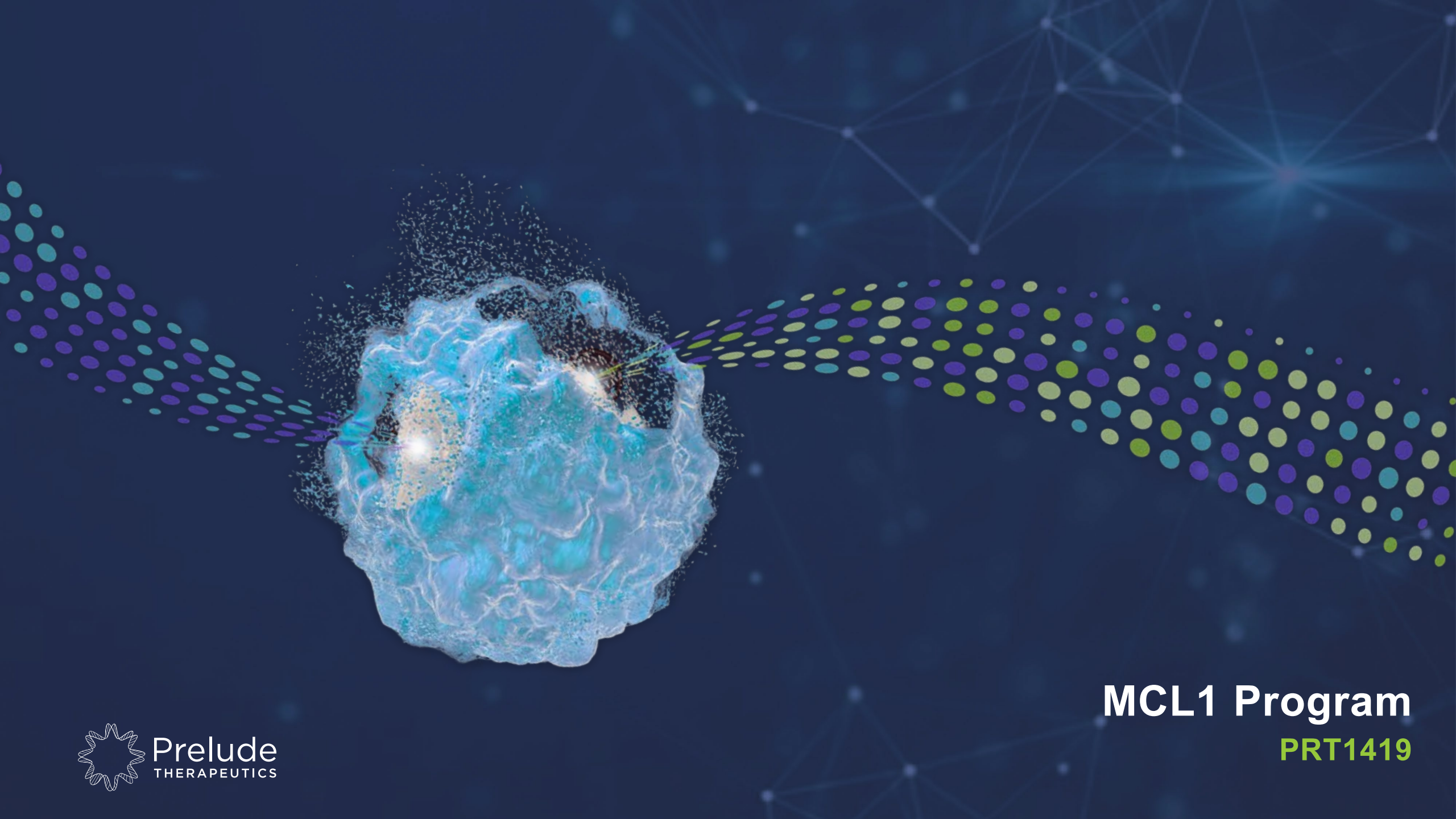
- Dose-dependent increase in exposure
- High levels of target inhibition
- PRT811 demonstrated best-in-class profile with wide therapeutic window

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

- Dose expansion ongoing
- Data readouts from multiple cohorts in 2022
- Prioritize indications for advancement into P2



MCL1 Program

PRT1419

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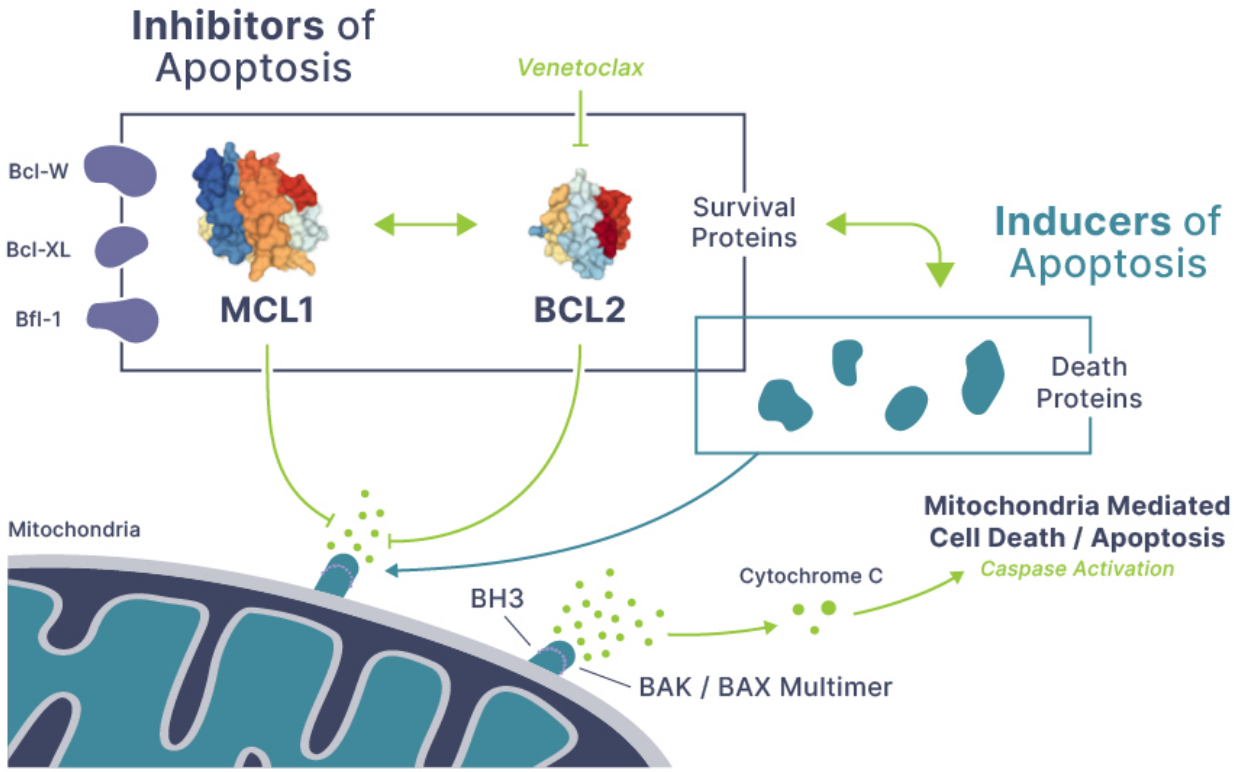
MCL1: Targeting Cancer Cell Survival



- 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 malignacies
- MCL-1 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

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

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Status

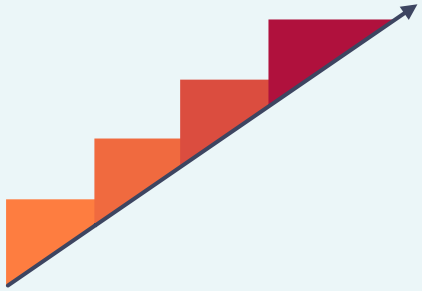
- **Dose escalation (monotherapy) ongoing**
  - Oral – Myeloid malignancies
  - IV – Solid tumors

Next Steps

- **Combination cohorts**
  - Venetoclax and/or HMA
- **Identify RP2D and initiate expansion phase**
- **Report dose escalation data (2H2022)**

Phase 1 Overview

Dose Escalation (ongoing)



AML and High Risk MDS (Oral)

Solid Tumors (IV)

Recommended Expansion Dose

Expansion Phase (Target 2H2022)

AML & High Risk MDS
PRT1419 + Venetoclax or Aza (N~20)
Potential Solid Tumors (N~20)

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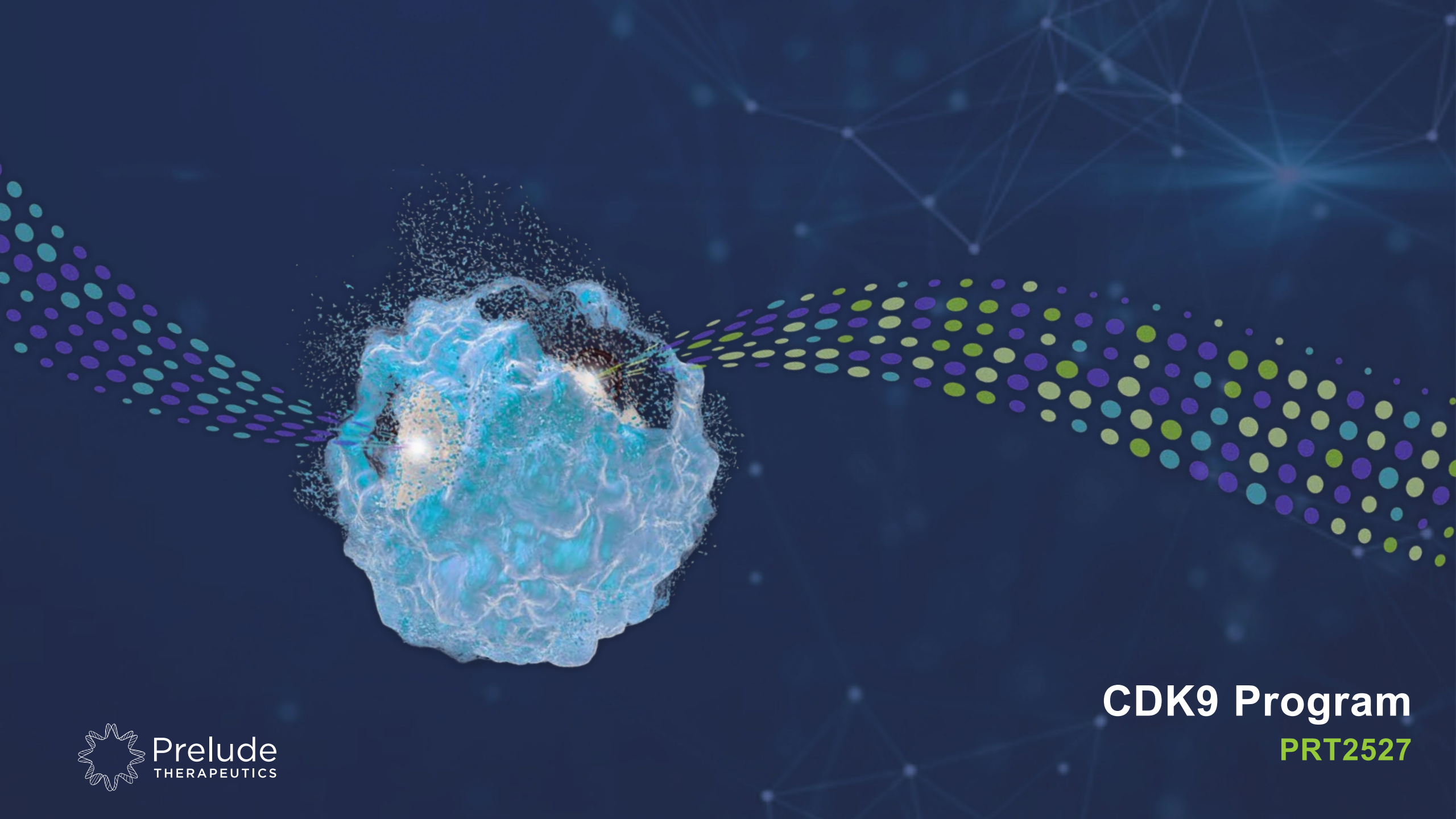

CDK9 Program

PRT2527

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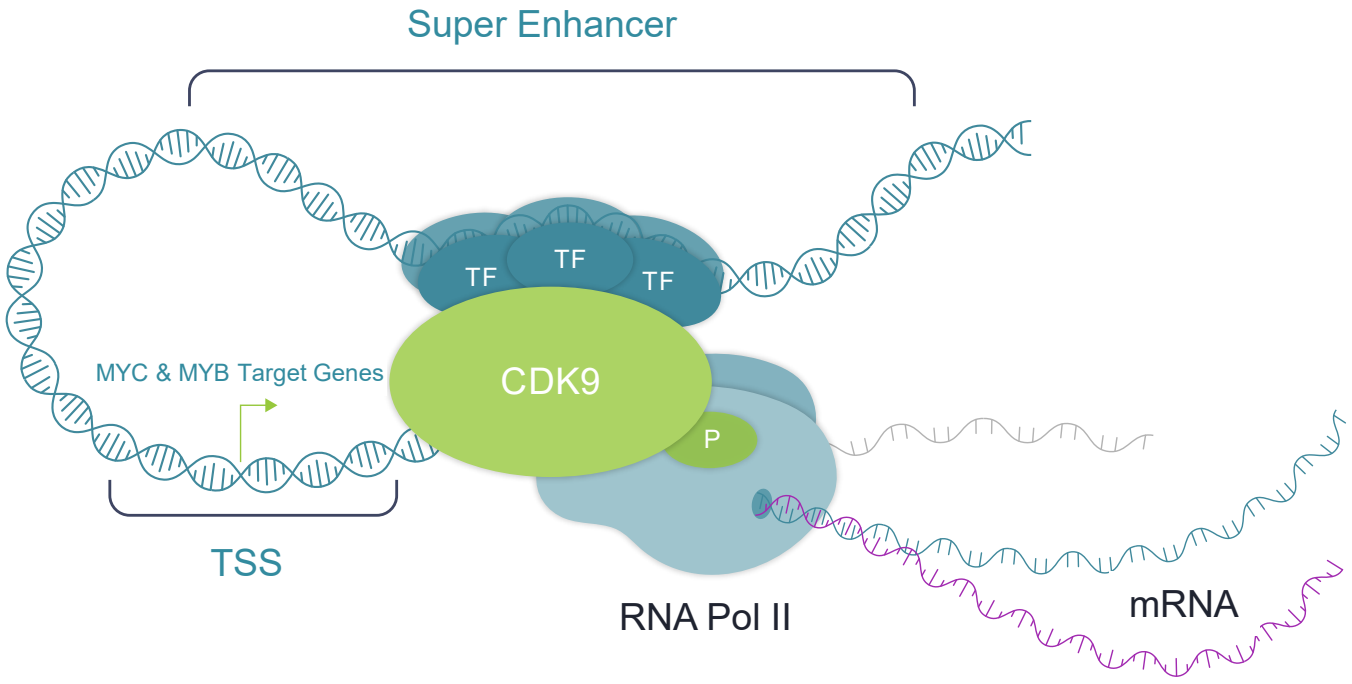
CDK9: Targeting Cancer Through Transcriptional Regulation



- 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

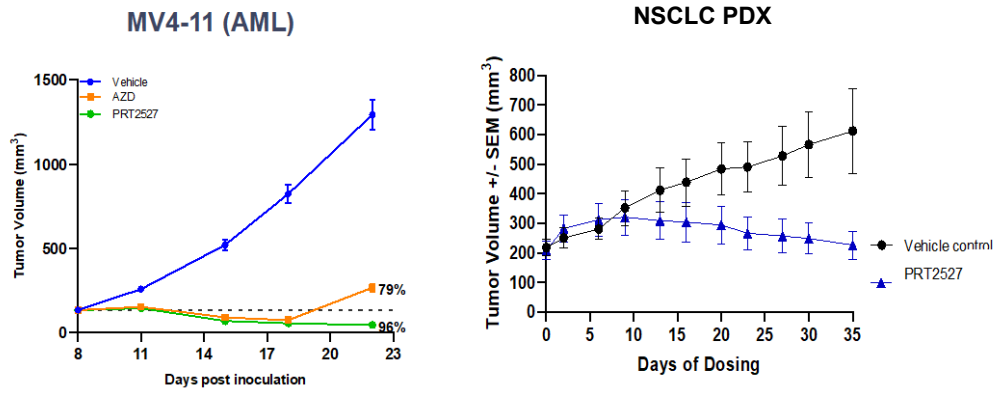
CDK9 Inhibitor

- 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

Sustained Regressions at Well-Tolerated Doses in Vivo in both Heme and Solid Tumor Models



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Phase 1 Overview

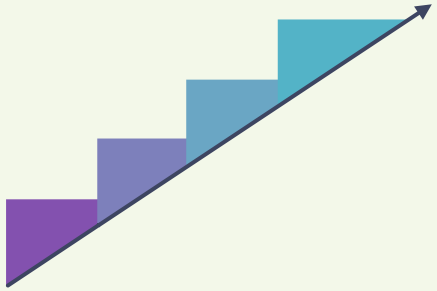
Status

- Dose Escalation
  - Solid tumors
  - Hematological malignancies

Next Steps

- Complete Phase 1
- Select RP2D
- Initiate Phase 2

Phase 1 Baysian Design (ongoing)



MYC-dependent Solid Tumors and Hematologic Malignancies

PoC

Phase 2 (Target 1H 2023)

MYC-dependent solid tumors
Sarcoma
Hematologic malignancies

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SMARCA2 (BRM) Program

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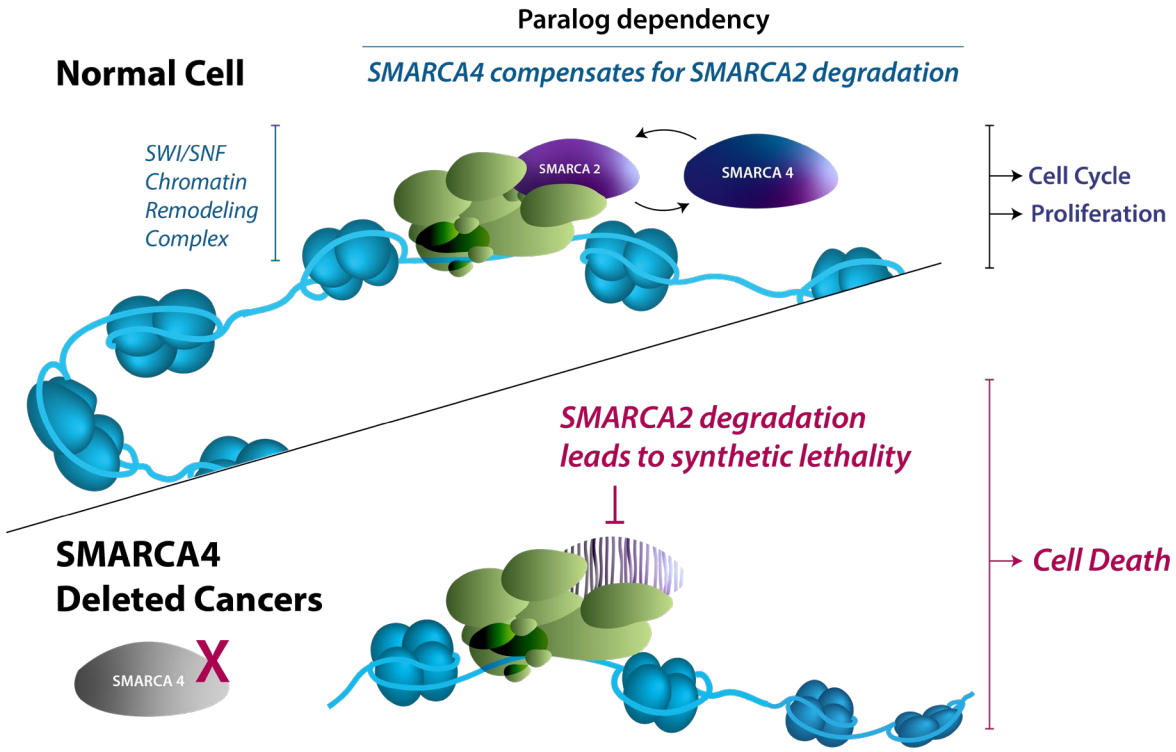
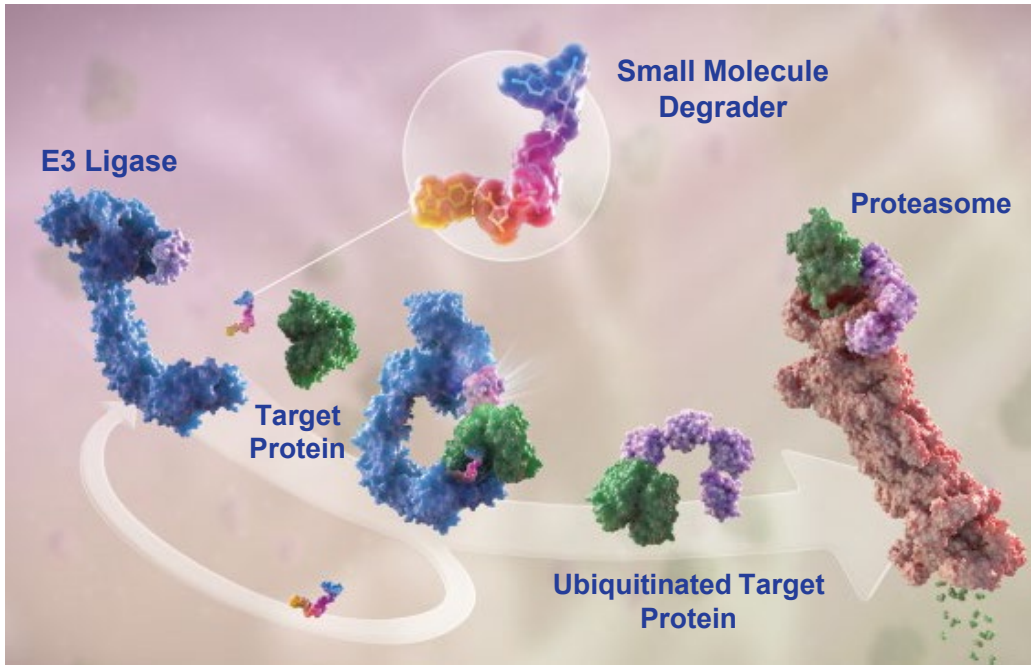
Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality



- 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

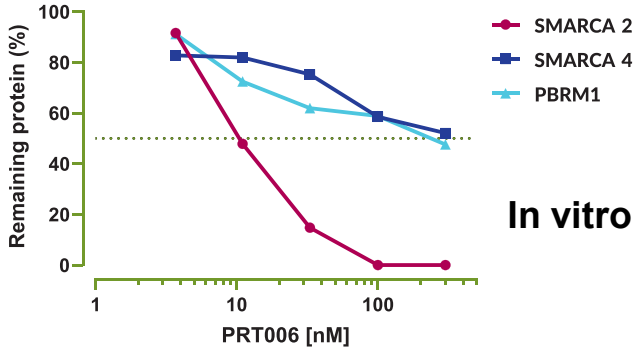


Mullard A. Nat Rev Drug Discov. 2019

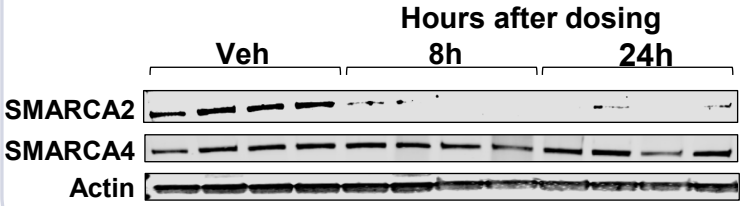
- SMARCA2 selectivity over highly homologous SMARCA4 isoform has been a challenging medicinal chemistry problem with traditional small molecule approaches
- Targeted Protein Degradation (TPD) of SMARCA2 selectively over SMARCA4 is possible through differences in ternary complexes
- Prelude scientists 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

Highly Selective for SMARCA2 Degradation

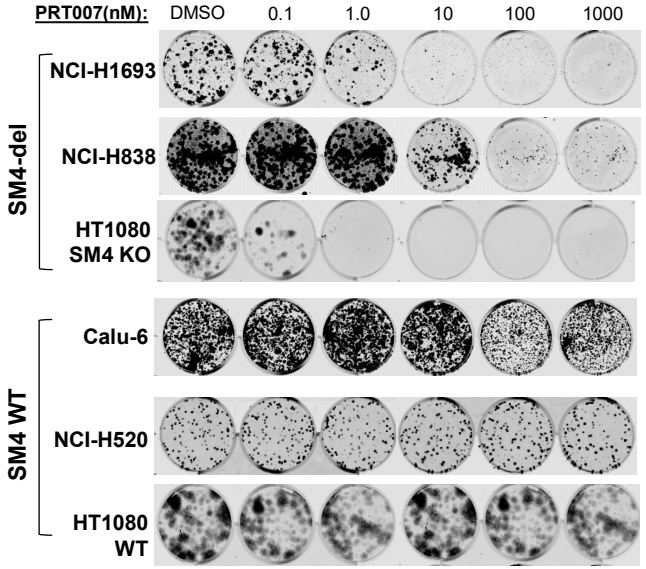


In vitro

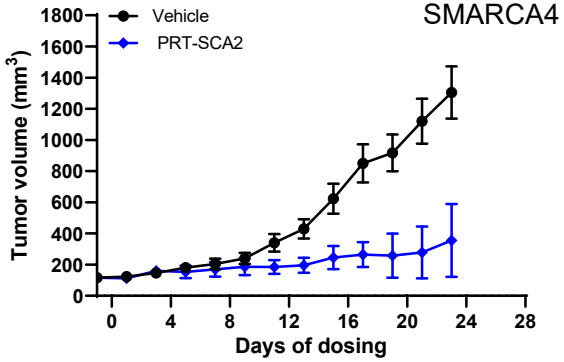


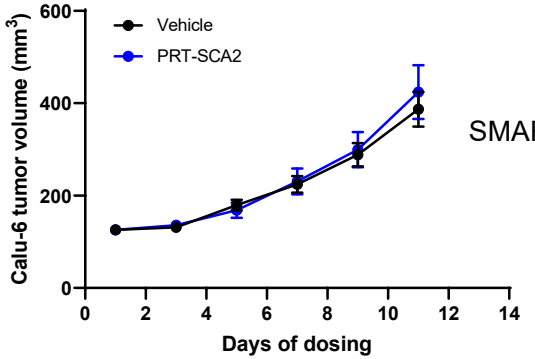
In vivo

Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality



Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft





SMARCA4 WT

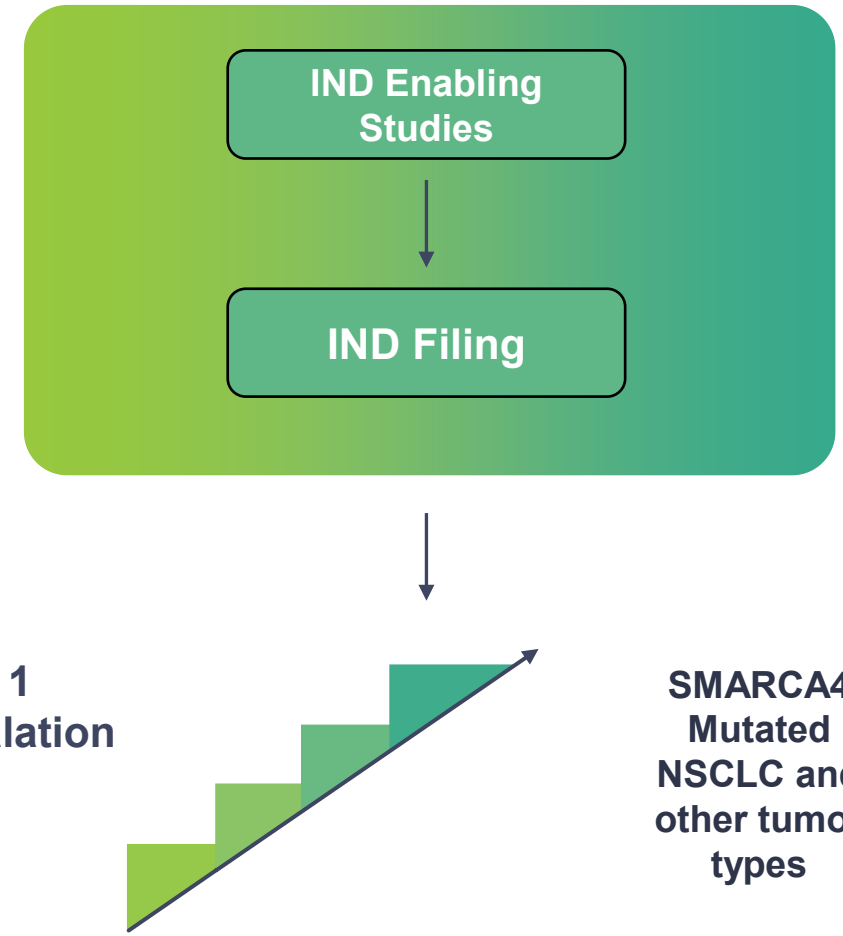
SMARCA2 Degrader Program Overview

Status

- Candidate molecule(s) identified
- IND enabling studies initiated

Next Steps

- File IND 2022
- Initiate Phase 1 escalation study in SMARCA4 mutant cancers



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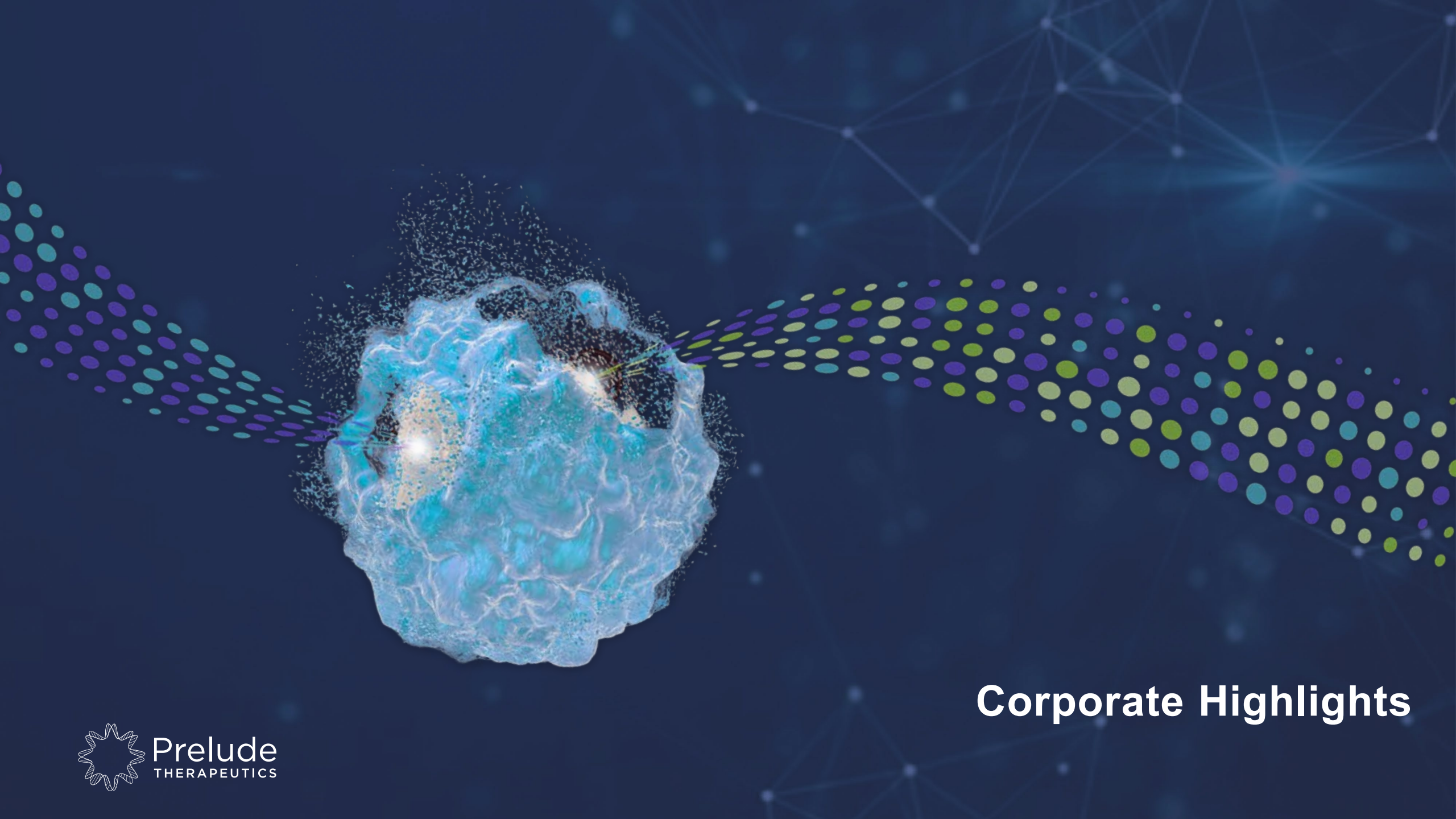

Corporate Highlights

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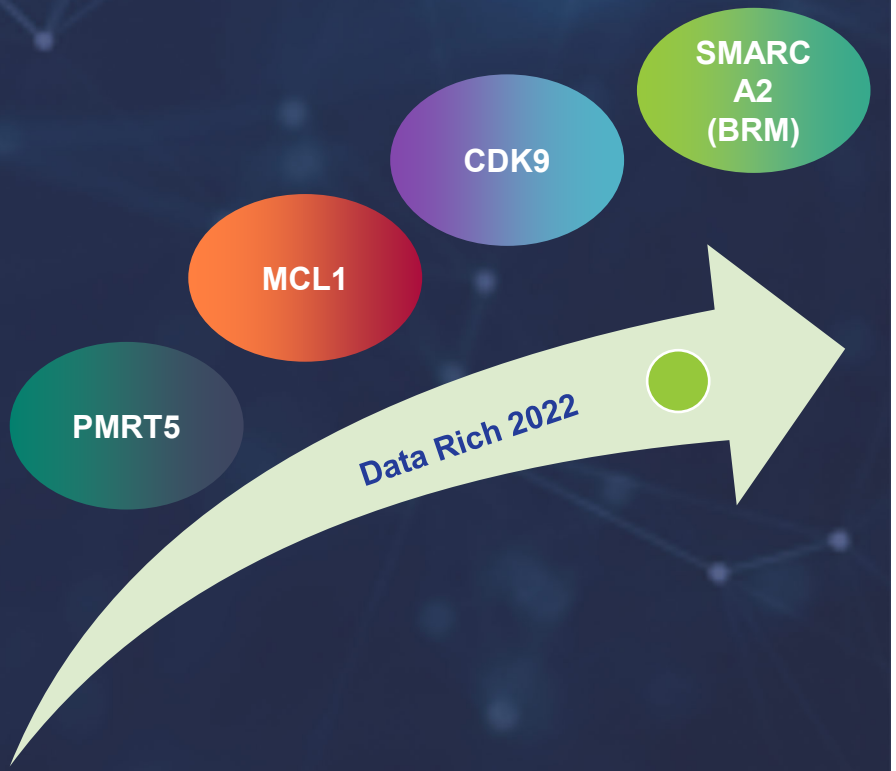
Our Investment Thesis



- Internal discovery engine
- Differentiated R&D approach
- Strong execution and commitment to discovery
- Focused clinical development in underserved cancers
- Strong financial position: ~$320M cash and marketable securities at 9/30/21

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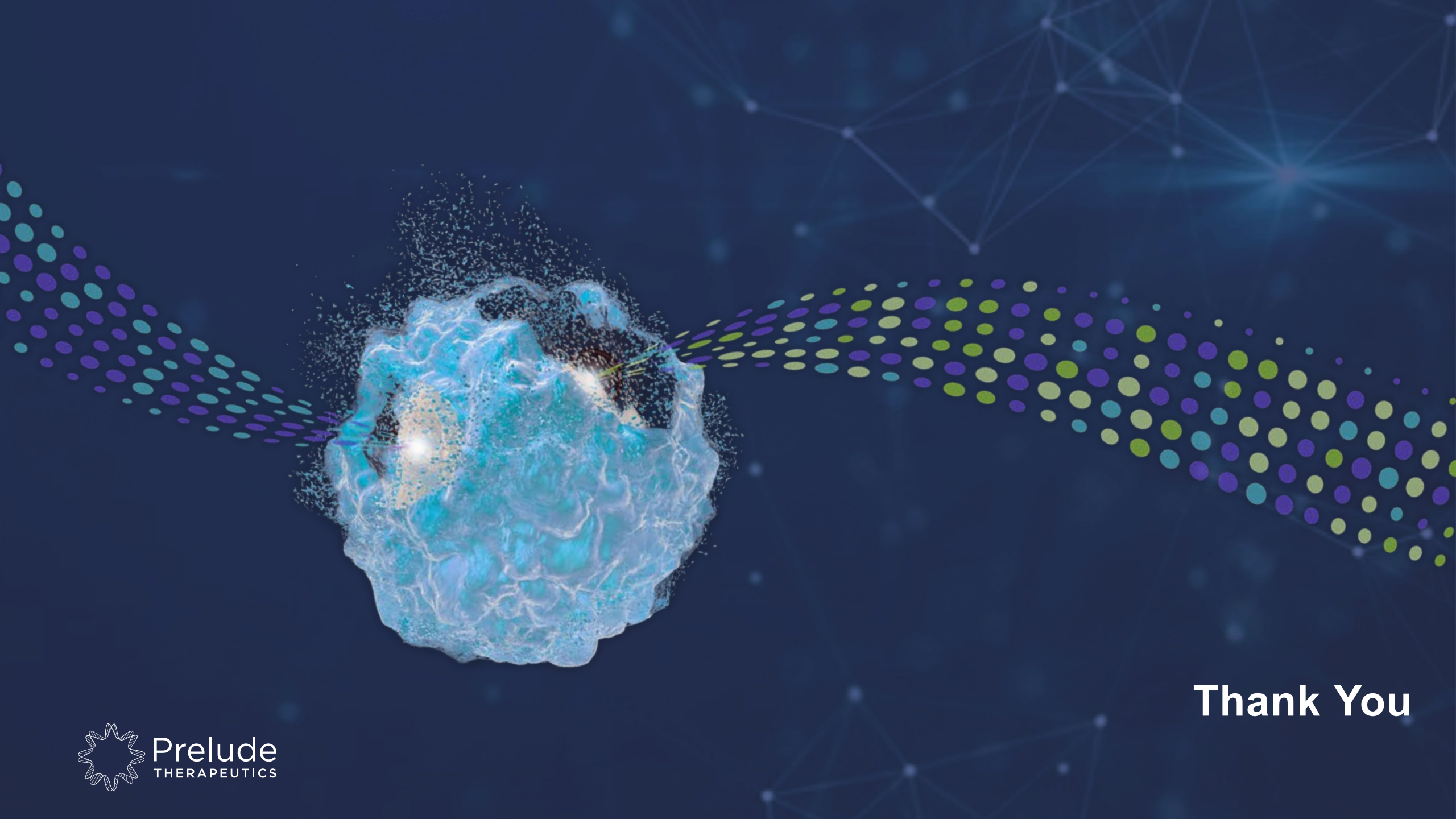

Thank You

Prelude THERAPEUTICS