Prelude
THERAPEUTICS

Precision Oncology **Redefined**

Q3 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, PRT3645 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, 2022 and in our 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

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

~$246M cash & marketable securities (6/30/22)

Experienced Management Team: Proven Track Records

Founding member

Kris Vaddi, PhD

Founder & Chief Executive Officer

Jane Huang M.D.

President and Chief Medical Officer

Laurent Chardonnet

Chief Financial Officer

Andrew Combs, PhD

Executive Vice President and Head of Chemistry

Peggy Scherle, PhD

Chief Scientific Officer

Board of Directors

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

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

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

David Bonita, MD
- OrbiMed — *General Partner*

Julian C. Baker

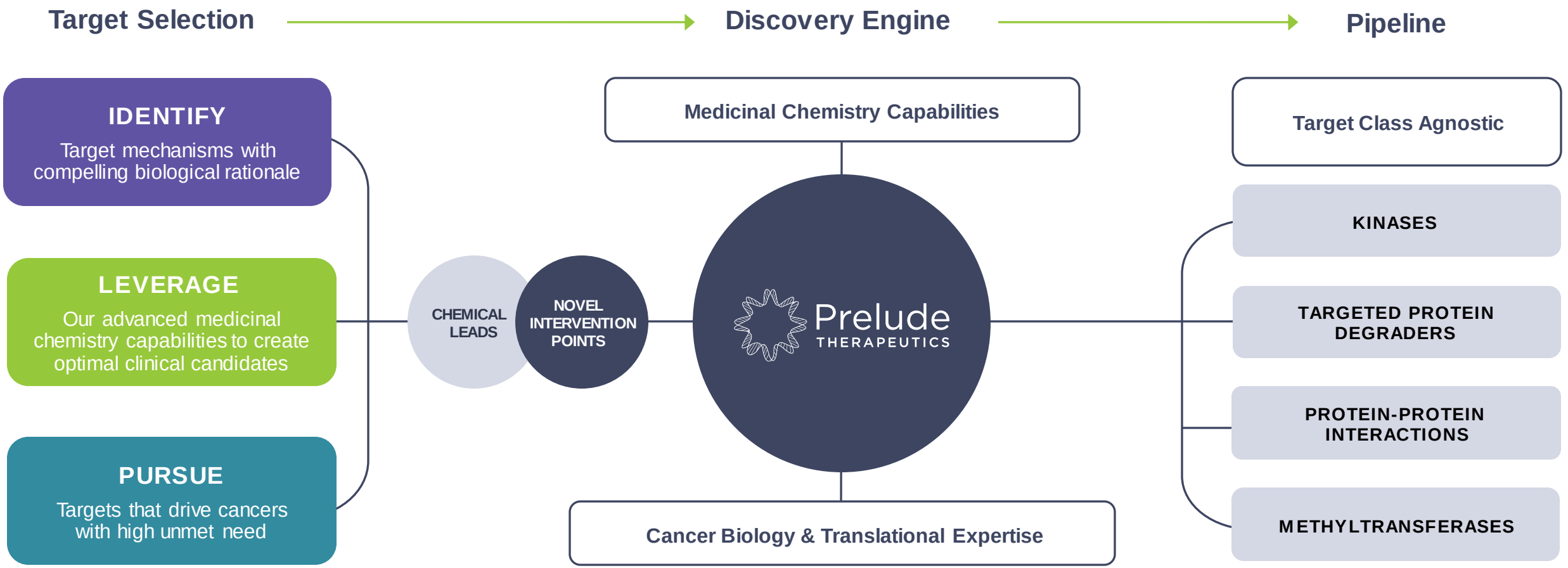
Managing Member
Baker Brothers Investments

Kris Vaddi, PhD

Founder & Chief Executive Officer

Martin Babler
- PRINCIPIA BIOPHARMA — *Former CEO*

Prelude Discovery and Development Approach



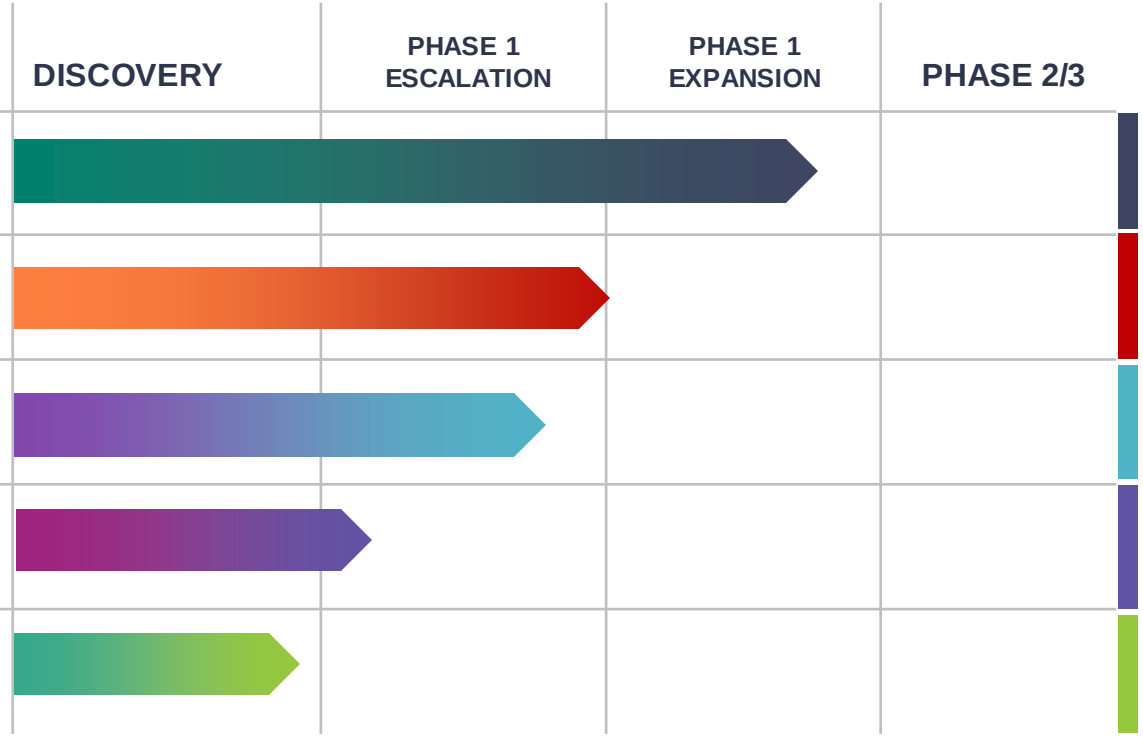
Precision Oncology: Targeting Clinically Relevant Pathways

TARGET	PRMT5*	MCL1	CDK9	SMARCA2 (BRM)	CDK4/6 (BBB)
MOA	mRNA Splicing & DNA Repair	Apoptosis	Transcriptional Regulation	Synthetic Lethality	Cell cycle Regulation
SELECTABLE PATIENTS	Spliceosome Mutations	Venetoclax Resistant	MYC Amplified	SMARCA4 (BRG1) Mutations	Multiple indications targeting brain mets
CANCERS	High Grade Glioma, Uveal Melanoma	AML, MDS, CLL	Sarcoma, Prostate, AML	NSCLC, Endometrial	Metastatic Cancers with CNS Metastases

*PRT543 ongoing; enrollment concluded

Diversified Precision Oncology Pipeline

PROGRAM	CANCER INDICATIONS
PRT811 (Brain Penetrant PRMT5)	IDH+ high grade glioma, uveal melanoma
PRT1419 (MCL1)	Selected hematologic malignancies and solid tumors
PRT2527 (CDK9)	Selected solid and hematologic malignancies
PRT3645 (Brain Penetrant CDK4/6)	Solid tumors
PRT-SCA2 (SMARCA2)	Multiple genomically-selected cancers



2022 Goals: Aggressive with Clear Deliverables

PRMT5
PRT811

Complete dose expansion in select tumor types and provide update in 2H/2022

Demonstrate PoC in one or more indications

MCL1
PRT1419

Establish RP2D

Demonstrate safety of IV formulation in combinations

Provide update 2H/2022

CDK9
PRT2527

Complete dose escalation

Establish safety, target engagement, and RP2D by 2H/2022

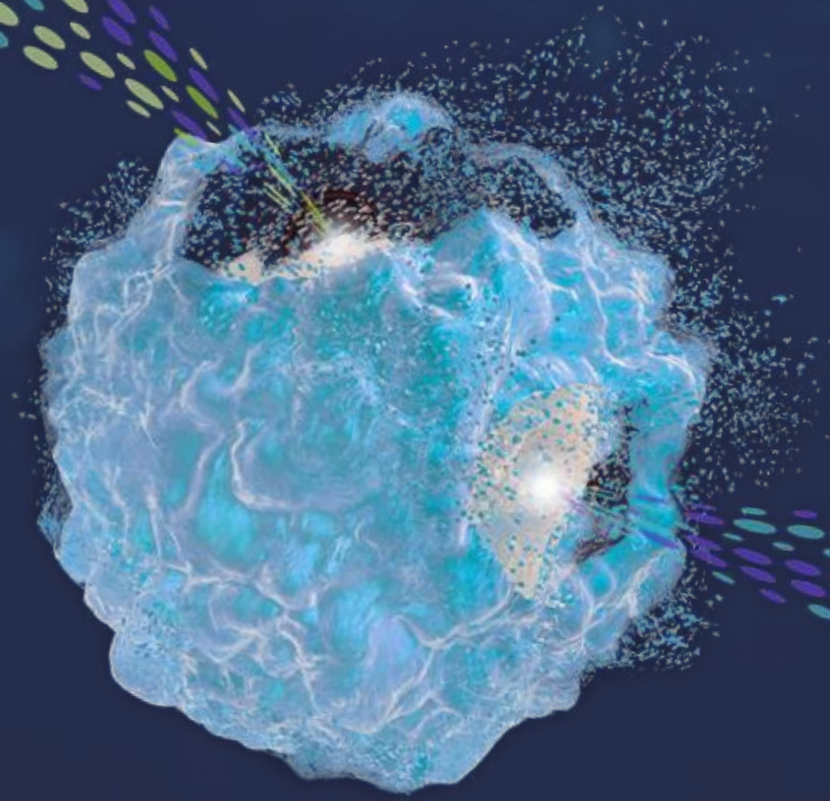
CDK4/6
PRT3645

File IND

Initiate dose escalation 2H/2022

SMARCA2
(BRM)
PRTSMA2

File IND



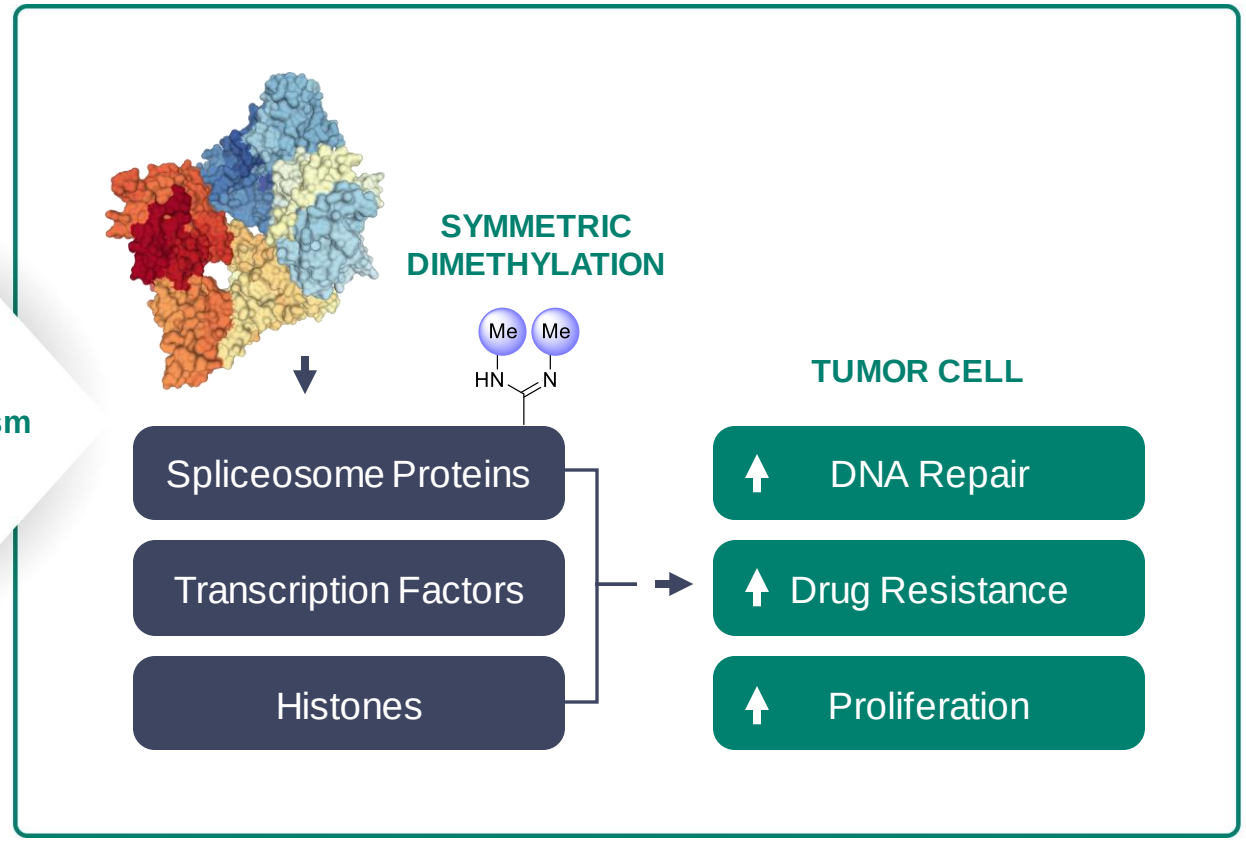
PRMT5 Program

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

PRT811

Potential Best-In-Class Brain Penetrant PRMT5 Inhibitor

Differentiated PRMT5 Inhibitor

- Highly selective, potent, oral
- High, sustained brain penetration in preclinical studies

Applicability in Both Solid Tumors and Heme

- Strong scientific rationale and robust preclinical activity across broad range of cancers
- Early clinical signals in biomarker selected patients

Optimized PK Profile

- High oral bioavailability and optimal half-life (4-6 hrs) to maximize therapeutic window
- Potential best-in-class safety profile

Potential in Patients with High Unmet Need

- Opportunity in multiple cancer types

Prelude THERAPEUTICS

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

PRMT5

Part 1
Dose Escalation
COMPLETED

PRT811

SOLID TUMORS,
MYELOID MALIGNANCIES

Part 2
Expansion Cohorts
ONGOING

PRT811
600 mg QD

Go/No Go Decision in 2H 2022

- Uveal Melanoma
- High Grade Glioma

PRMT5 Phase 1: Key Takeaways and Next Steps

PRMT5

FAVORABLE SAFETY PROFILE

Well tolerated

Potential best-in-class safety profile

Low incidence of dose-limiting toxicities at expansion doses

DESIRABLE PK & PD PROFILES

Dose-dependent increase in exposure

High levels of target inhibition

Wide therapeutic window

PRELIMINARY CLINICAL ACTIVITY

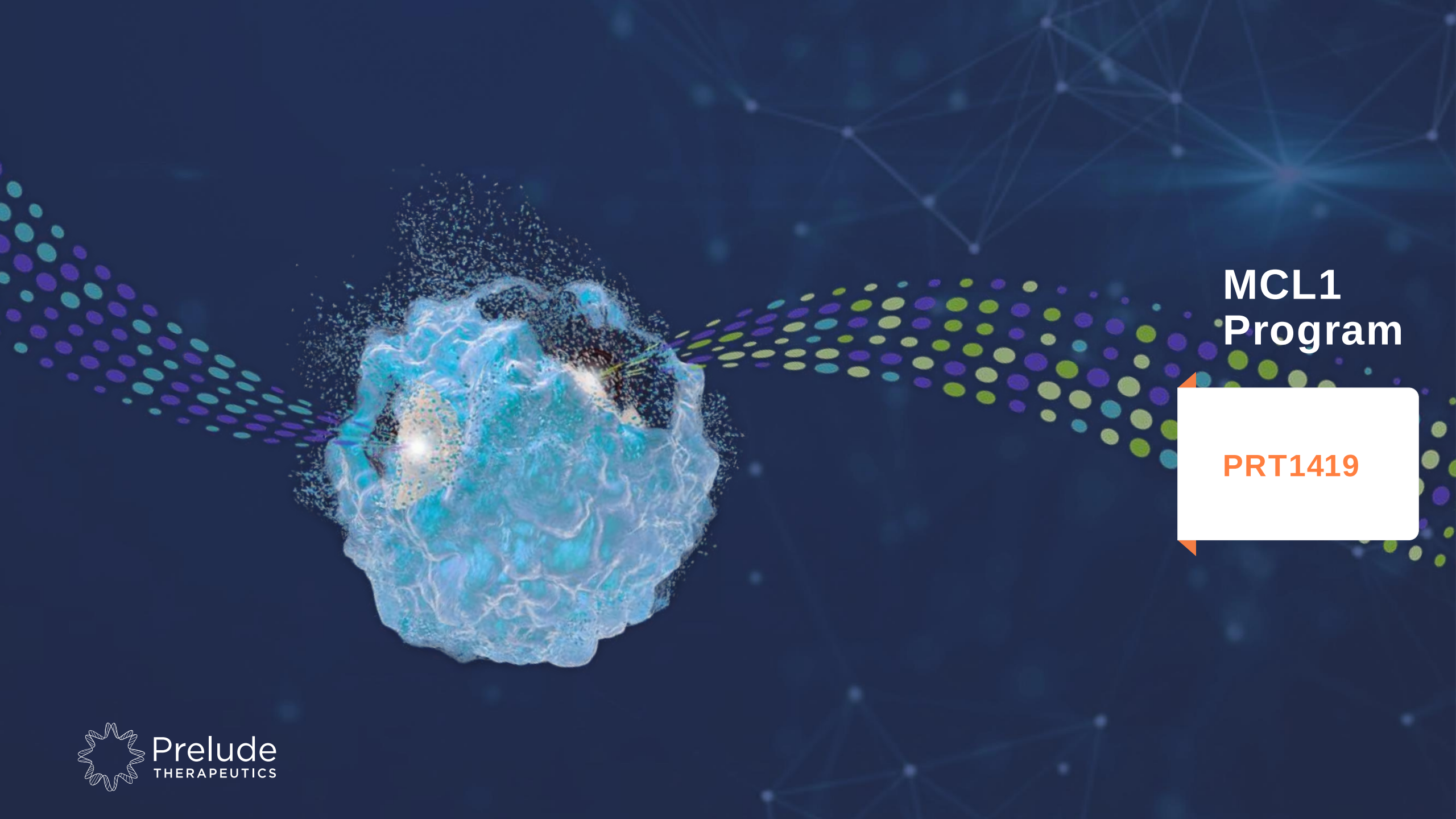
Anti-tumor activity observed in patients with target biomarker profile

IDH1 mutated GBM
Splicing mutated uveal melanoma

NEXT STEPS

Complete dose expansion in select cohorts

Demonstrate PoC in one or more indications



MCL1 Program

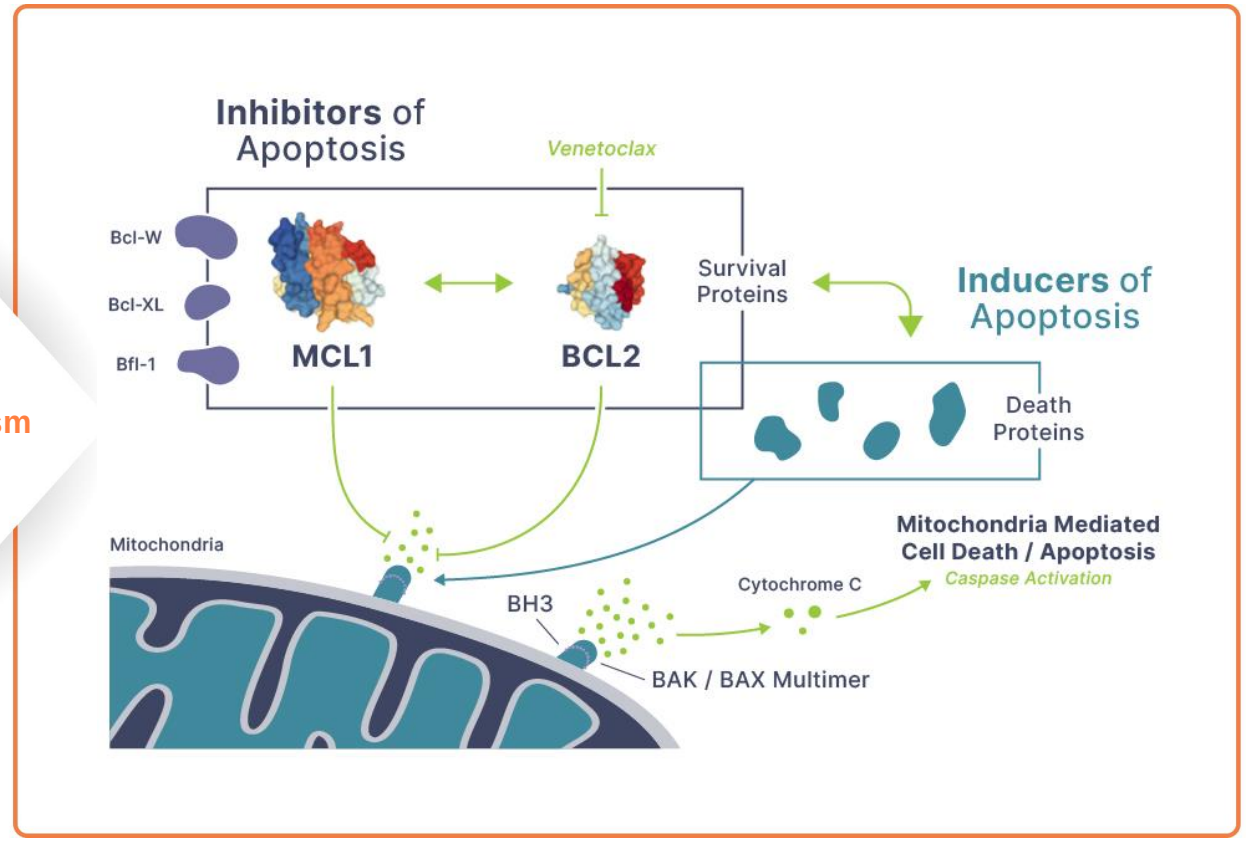
PRT1419

Prelude THERAPEUTICS

MCL1: Targeting Cancer Cell Survival

MCL1

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

Prioritizing PRT1419 IV Formulation

MCL1

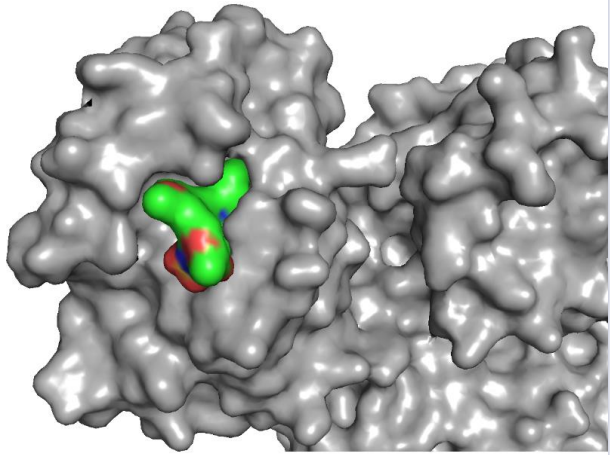
- PRT1419 designed to provide optimal coverage of the pathway to induce apoptosis but allows time off to mitigate potential toxicities
- No evidence of cardiac tox with PRT1419 in preclinical models
- Cardiac toxicity has been a challenge for the MCL1 class and was observed in clinical trials with other MCL1 inhibitors
- Program objective: Evaluate combination PRT1419 IV formulation and venetoclax
- Ability to combine safely could position PRT1419 as a leader in the class and addresses a critical opportunity in frontline therapy

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

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 others

Optimized PK Profile Maximizes Therapeutic Window

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

Potential in Patients with High Unmet Need

- Venetoclax-resistant cancers offer opportunity for accelerated approval
- Proof-of-concept to be pursued with IV formulation

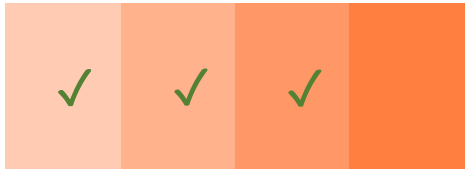
Prelude THERAPEUTICS

MCL1: Phase 1 Overview

MCL1

Phase 1 Dose Escalation

Monotherapy (mg/m2)



1H 2022

Dose Escalation Combination

Combination (Ven + Aza)

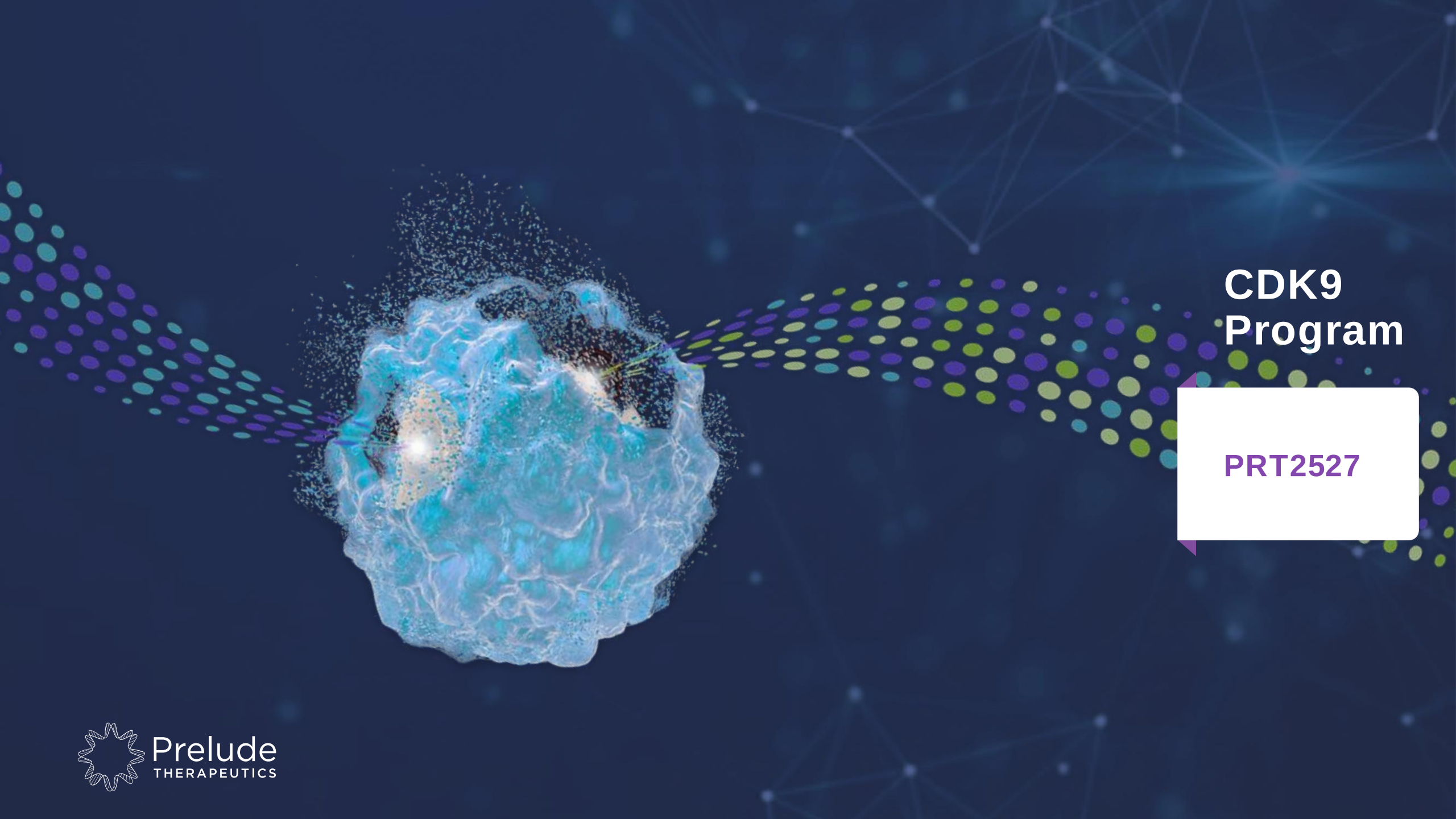
2H 2022

Dose Expansion

1419 VEN+ AZA
R/R AML/MDS

1419 + AZA
R/R AML/MDS

1H 2023



CDK9 Program

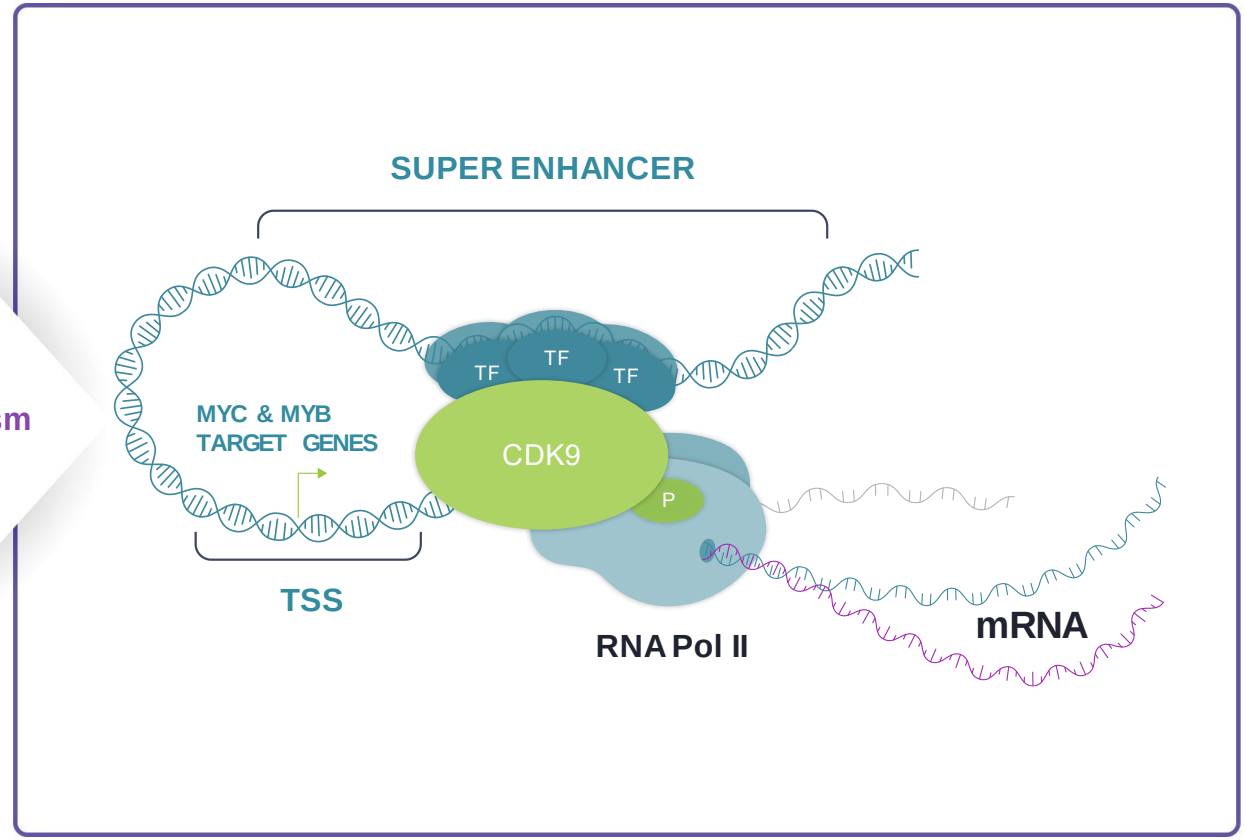
PRT2527

Prelude THERAPEUTICS

CDK9: Targeting Cancer Through Transcriptional Regulation

CDK9

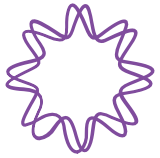
Mechanism



- 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



CDK9 Inhibitor

- Potent and selective compared to other in class

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

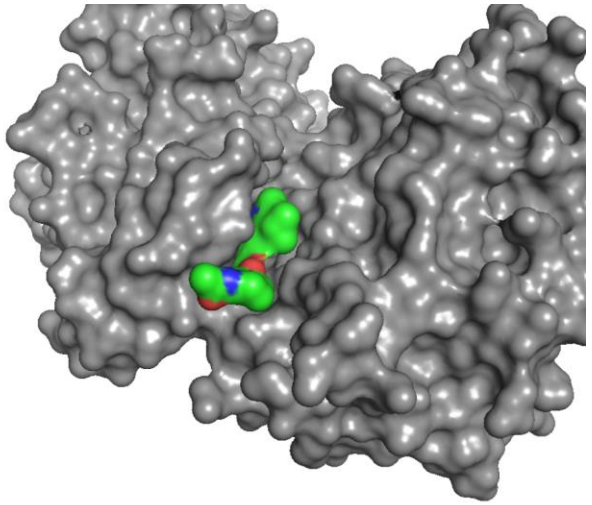
- Higher clearance built in to maximize therapeutic window

Prelude THERAPEUTICS

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 BAY151 and licensed to Vincerx by Bayer

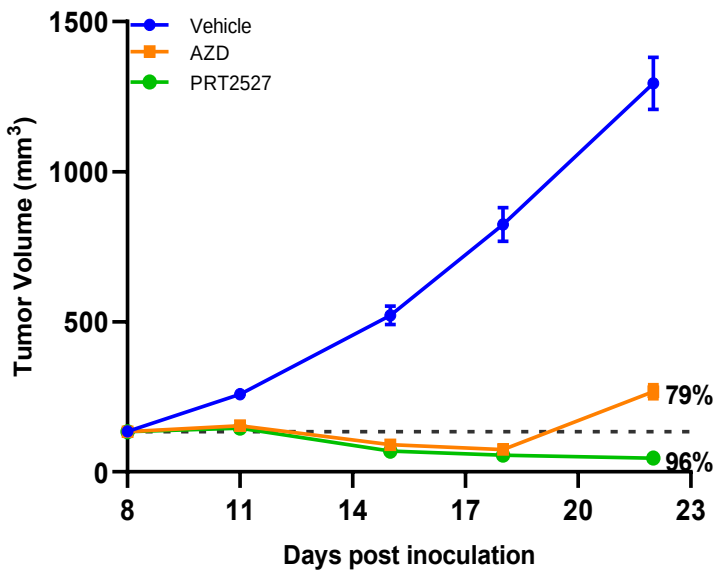
PRT2527 demonstrated improved potency and kinase selectivity relative to competitor compounds in preclinical studies

Robust Activity in Preclinical Models at Well-Tolerated Doses

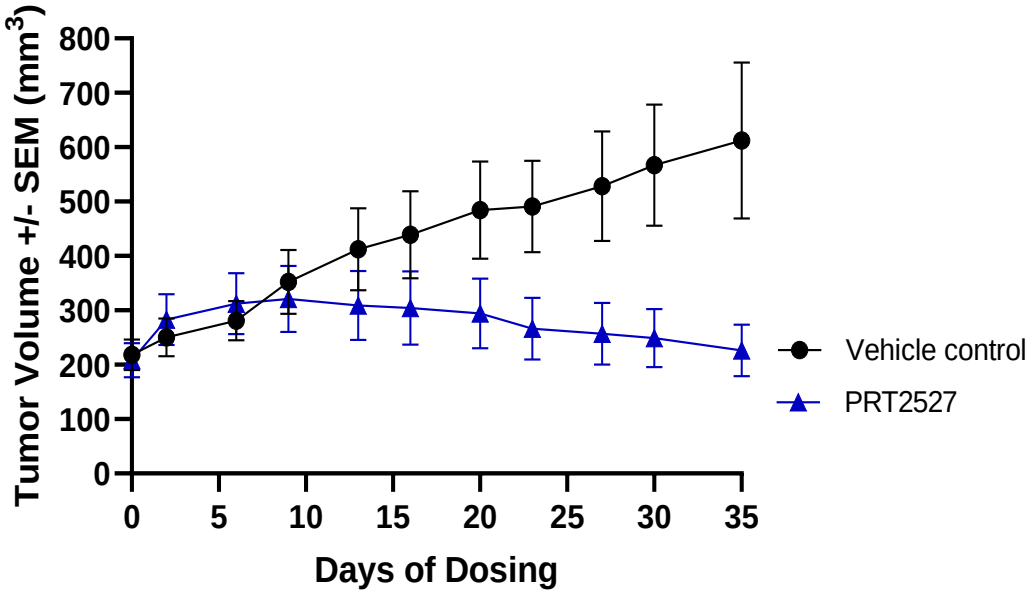
CDK9

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

MV4-11 (AML)



NSCLC PDX (MYC Amplified)

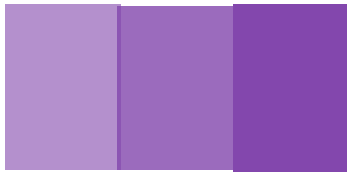


CDK9: Clinical Overview

CDK9

Phase 1 Dose Escalation (Bayesian Design)
ONGOING

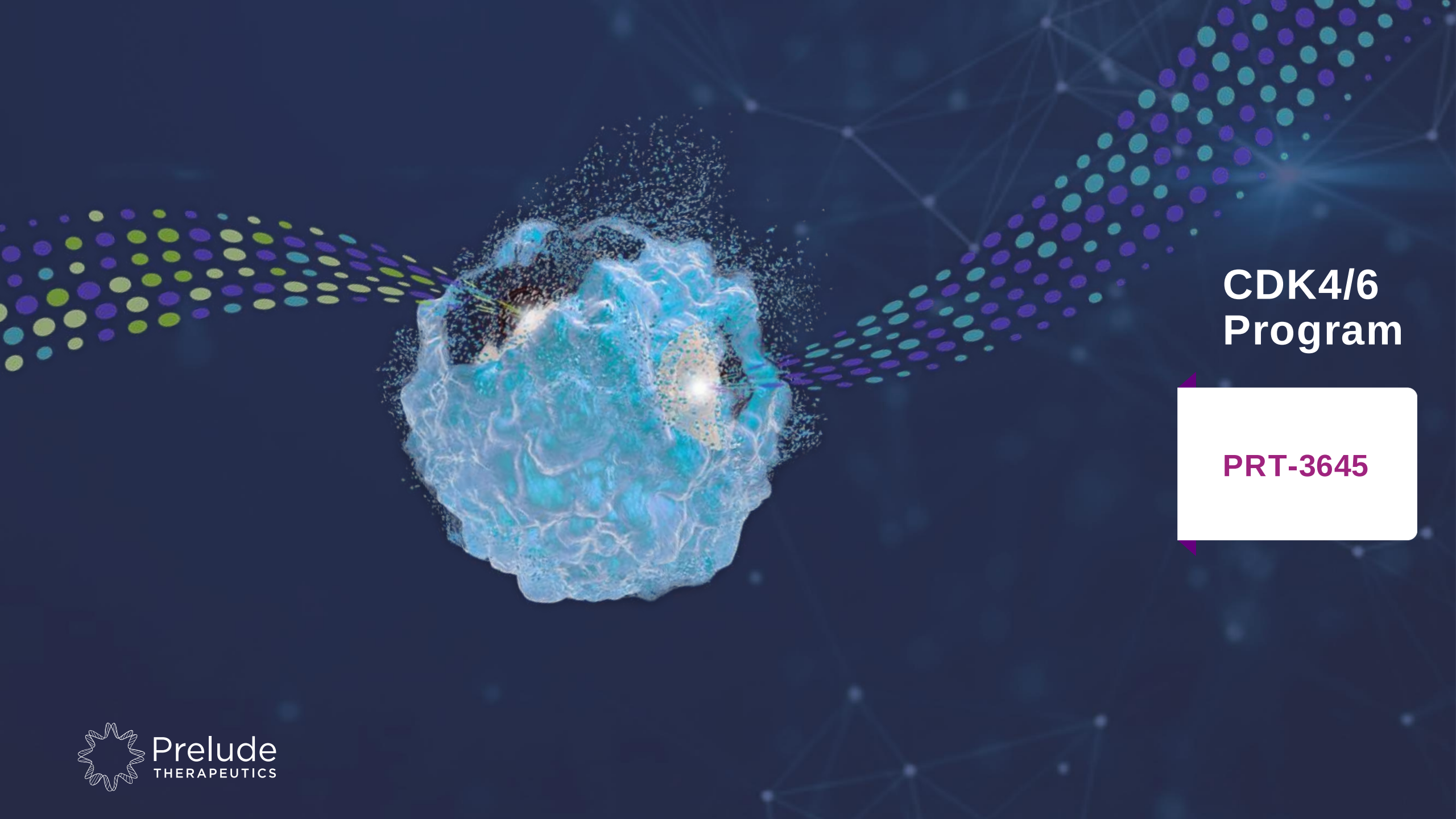
MYC-dependent solid tumors



Hematologic Malignancies

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

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



CDK4/6 Program

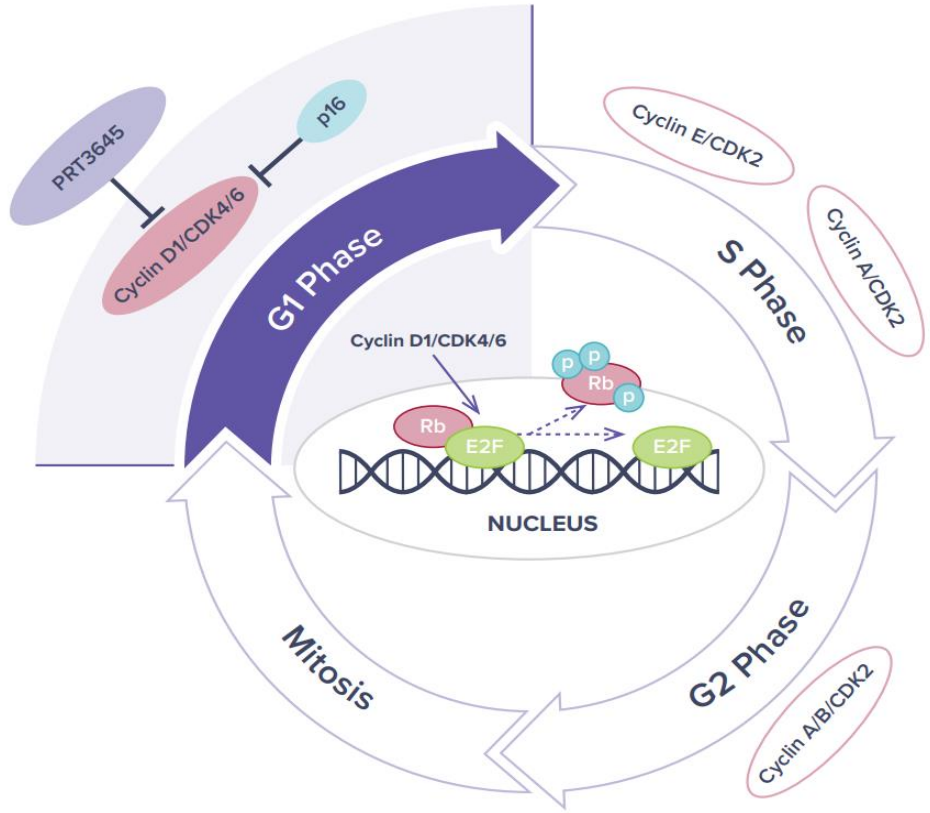
PRT-3645

Prelude THERAPEUTICS

CDK4/6: Targeting Brain Cancer Through Cell Cycle Regulation

CDK4/6

Mechanism



- Cell cycle entry controlled by cyclin dependent kinases, CDK4 and CDK6
  - Validated mechanism with multiple CDK4/6 inhibitors approved for HR+ breast cancer
- Current CDK4/6 inhibitors are ineffective in treating brain metastasis and other CNS cancers likely due to insufficient brain penetration
  - Brain penetrant TKIs to other oncogenic targets shown to be more effective in treating brain metastasis
- A potent and selective **brain penetrant** CDK4/6 inhibitor could more effectively treat brain metastasis associated with HR+ breast cancer as well as glioblastoma

PRT3645

Differentiated Brain Penetrant CDK4/6 Inhibitor

Differentiated Brain Penetrant CDK4/6 Inhibitor

- Highly potent and selective
- >10x higher brain penetration than currently approved CDK4/6 inhibitors in preclinical models

Targeting Breast Cancer with Brain Metastasis and GBM

- Improved monotherapy activity in preclinical models of breast cancer with brain metastasis and GBM at well-tolerated doses
- Combined activity with hormonal therapy in preclinical models

Validated Mechanism with Potential to Further Optimize

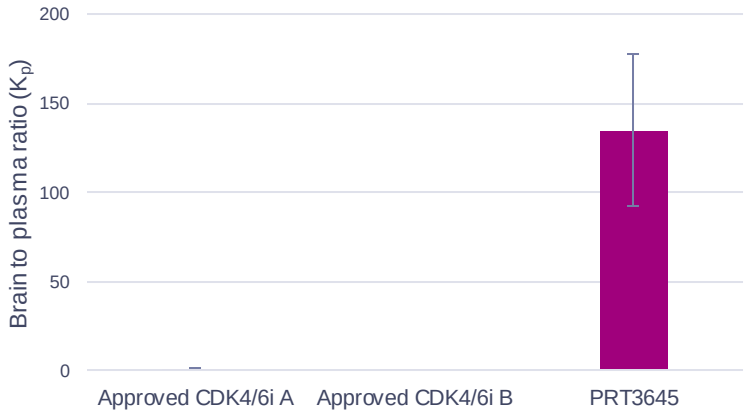
- Approved CDK4/6 inhibitors lack sufficient brain penetration to be effective in patients with CNS cancers or brain metastasis

Prelude THERAPEUTICS

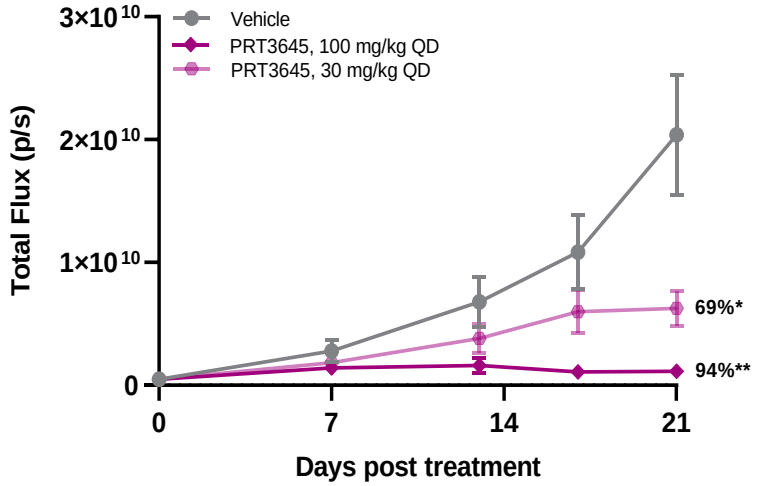
PRT3645 Has High Brain Exposure and Demonstrates Robust Activity in Preclinical Models at Well-Tolerated Doses

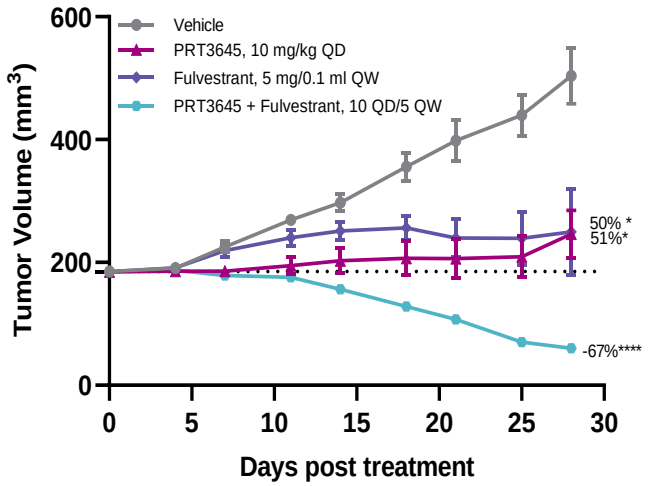
CDK4/6

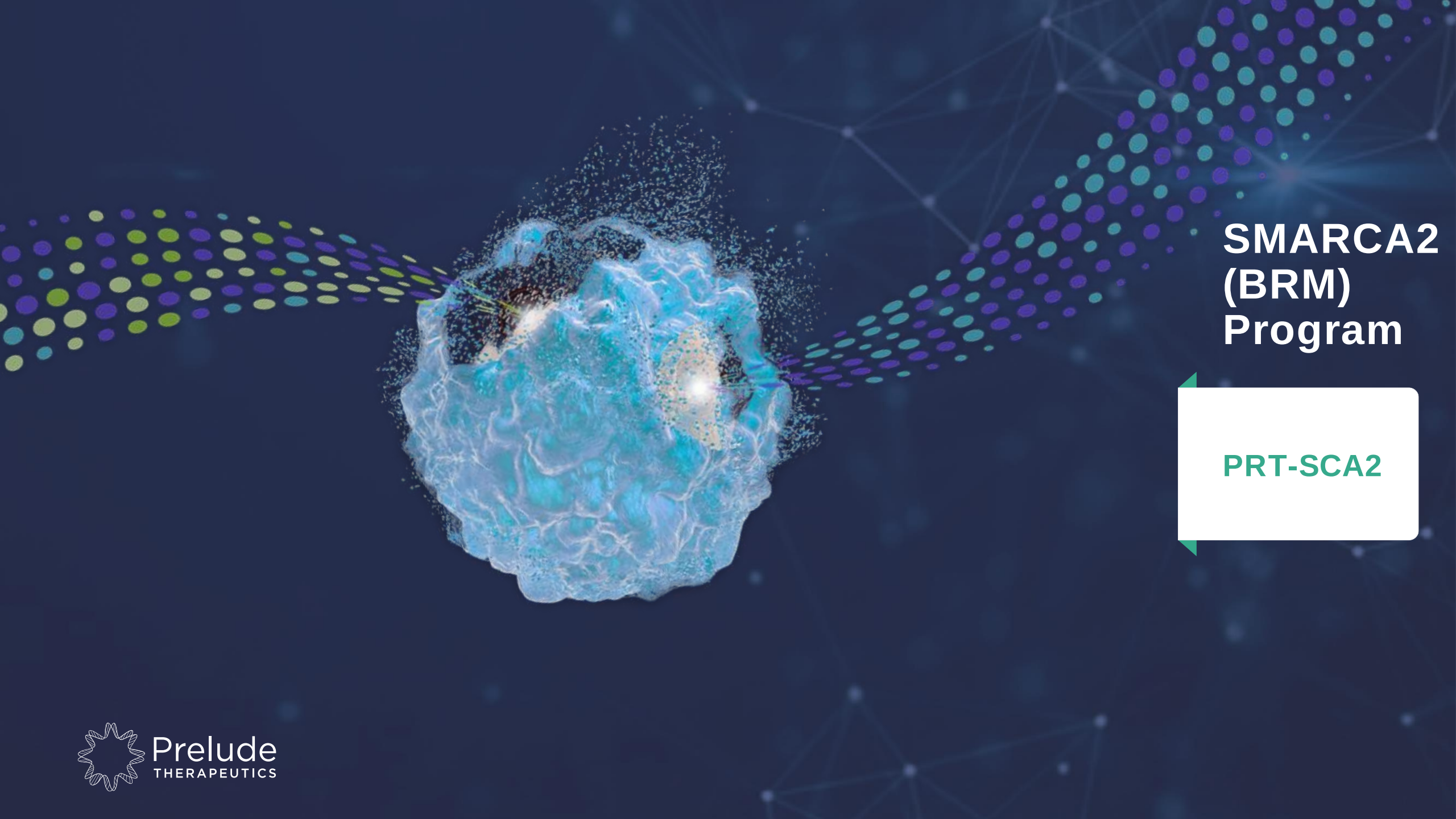
PRT3645 demonstrates >10x higher brain penetration than approved CDK4/6 inhibitors



PRT3546 shows robust activity in vivo as monotherapy and in combination







SMARCA2 (BRM) Program

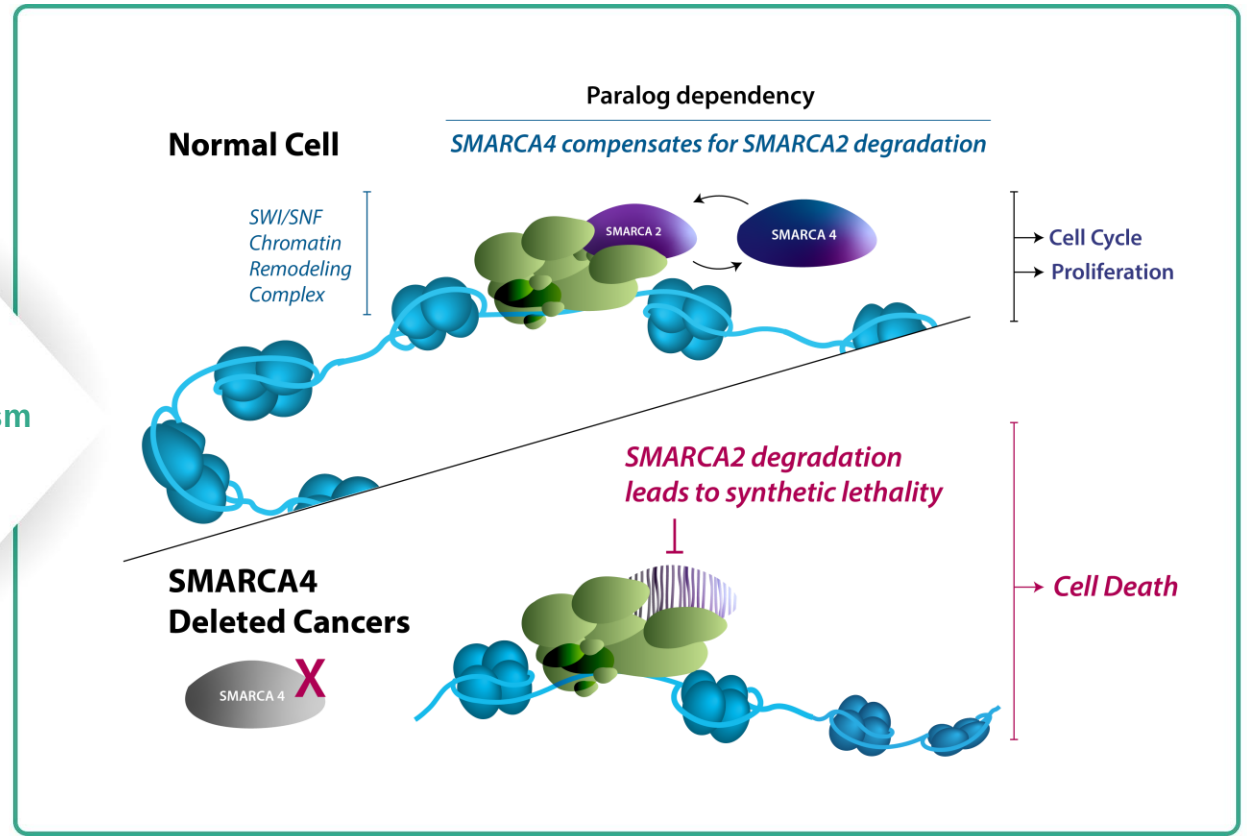
PRT-SCA2

Prelude THERAPEUTICS

Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

SMARCA2

Mechanism

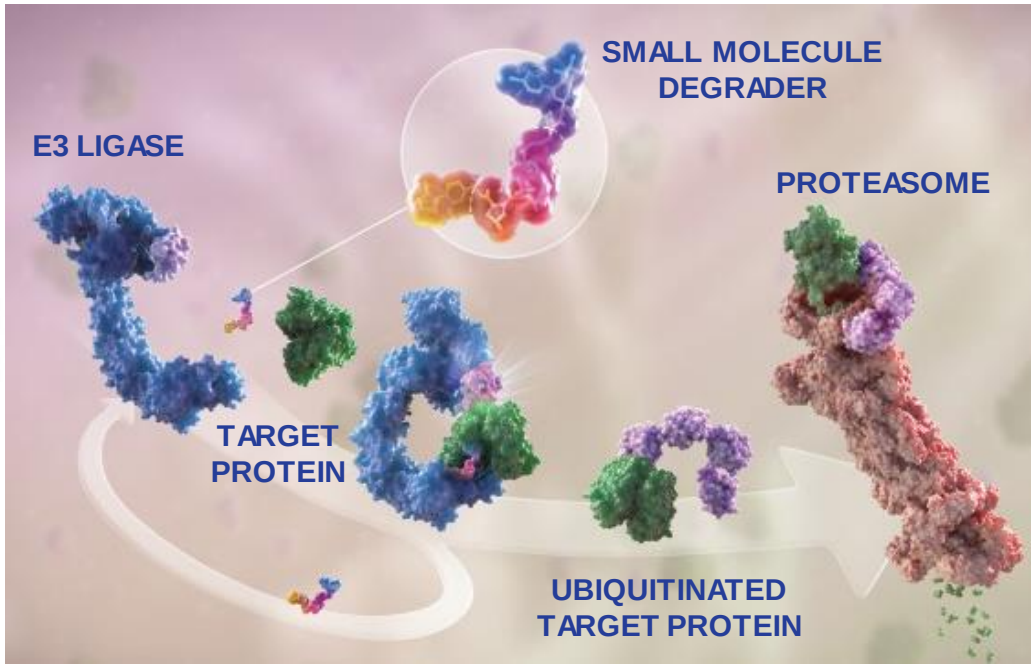


- The chromatin remodeling (SWI/SNF) complex is frequently mutated in cancer making it a potential therapeutic target
  - Activity of the SWI/SNF complex requires either SMARCA4 (BRG1) or SMARCA2 (BRM)
  - Loss of SMARCA4 (BRG1) through mutation leads to dependency on SMARCA2 (BRM)
  - Subsets of solid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



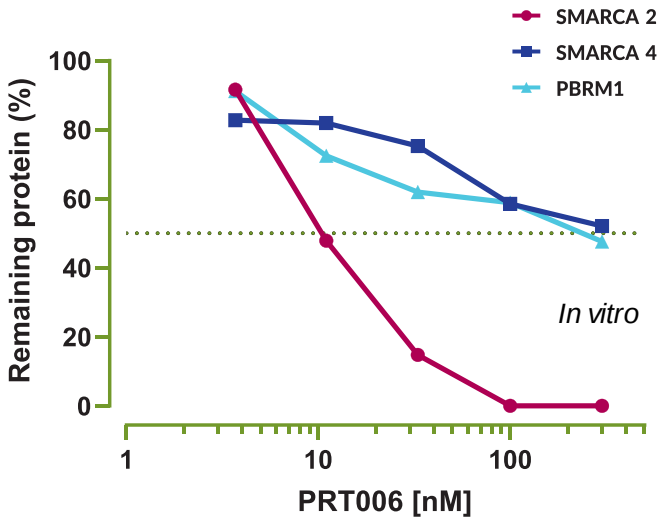
Mullard A. Nat Rev Drug Discov. 2019

- 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

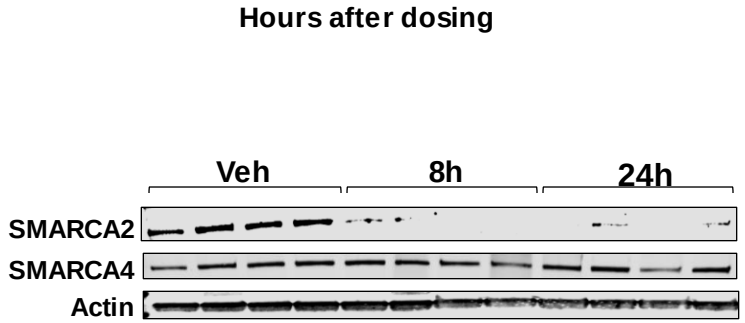
PRT-SCA2: Potent and Selective SMARCA2 Degrader with *In Vivo* Activity

SMARCA2

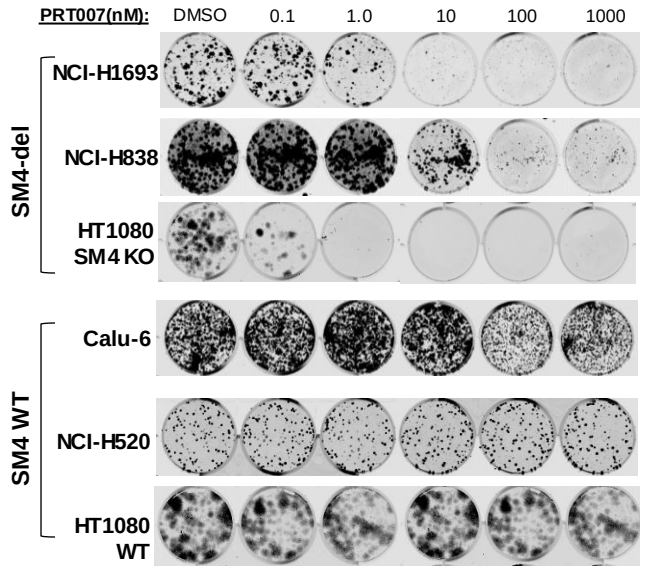
Highly Selective for SMARCA2 Degradation *In Vitro*



Highly Selective for SMARCA2 Degradation *In Vivo*



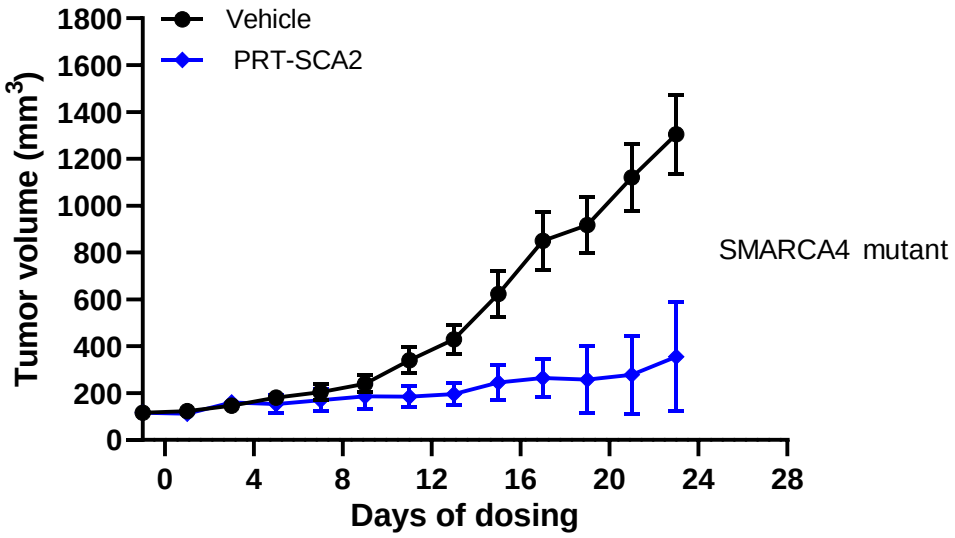
Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality

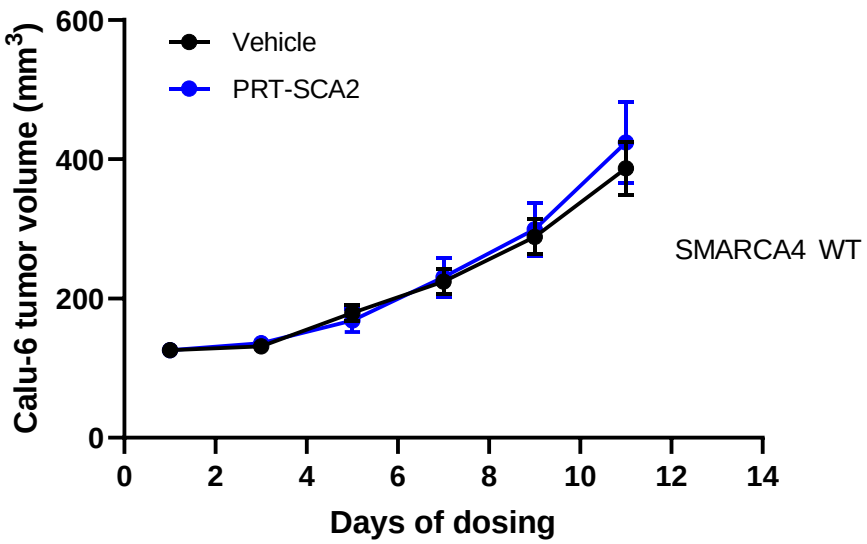


PRT-SCA2: Potent and Selective SMARCA2 Degrader with *In Vivo* Activity

SMARCA2

Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft





SMARCA2: Degrader Program Overview

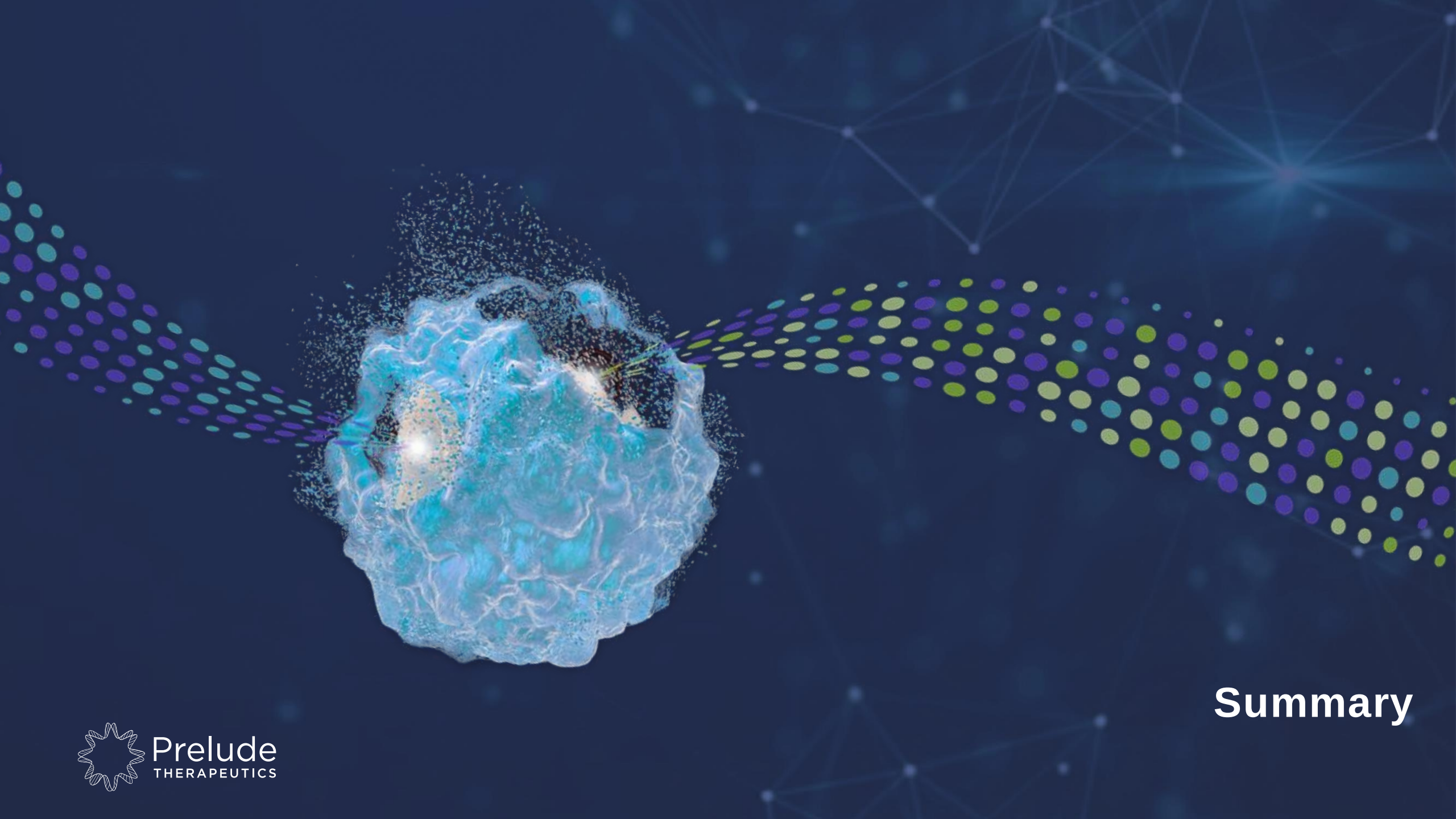
SMARCA2

IND Expected in 2H 2022

- IND Enabling Studies
- IND Filing 2H 2022

Phase 1 Dose Escalation
TARGET 1Q 2023

SMARCA4-MUTATED NSCLC AND OTHER TUMOR TYPES



Summary

Prelude THERAPEUTICS

2022 Goals: Aggressive with Clear Deliverables

PRMT5
PRT811

Complete dose expansion in select tumor types and provide update in 2H/2022

Demonstrate PoC in one or more indications

MCL1
PRT1419

Establish RP2D

Demonstrate safety of IV formulation in combinations

Provide update 2H/2022

CDK9
PRT2527

Complete dose escalation

Establish safety, target engagement, and RP2D by 2H/2022

CDK4/6
PRT3645

File IND

Initiate dose escalation 2H/2022

SMARCA2
(BRM)
PRTSMA2

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

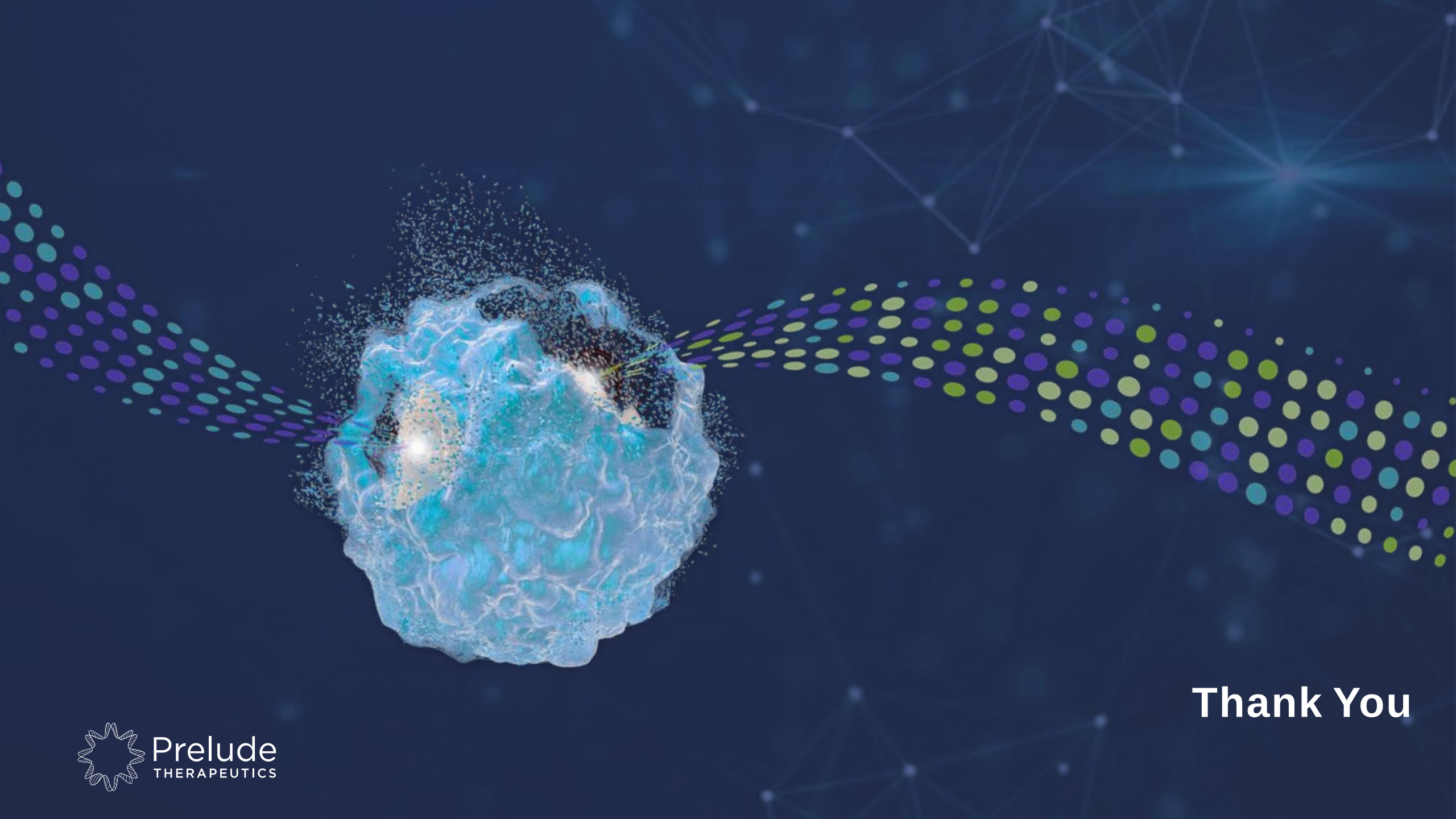
Proprietary diversified pipeline

Focused Clinical Development

Driving to ‘go/no go’ decisions with a sense of urgency

Well Capitalized

~$246M cash & marketable securities (6/30/22)



Thank You

Prelude
THERAPEUTICS