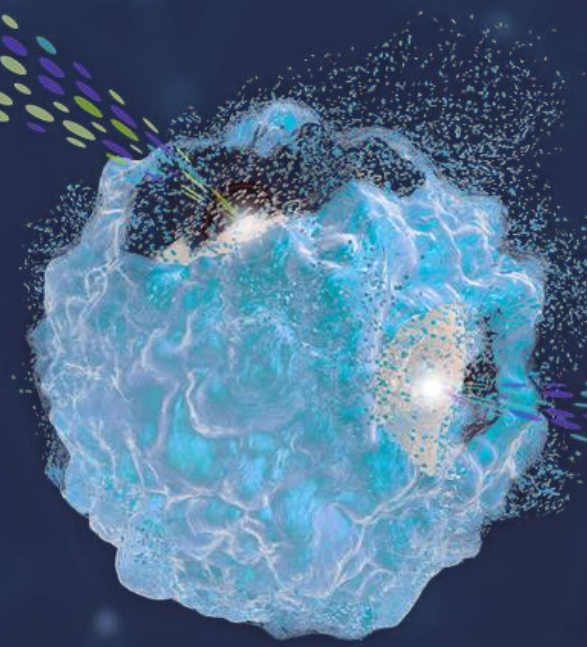
Prelude THERAPEUTICS

Corporate Presentation

March 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 Annual Report on Form 10-K filed with the Securities and Exchange Commission for the fiscal year ended December 31, 2020.

Prelude Therapeutics Vision

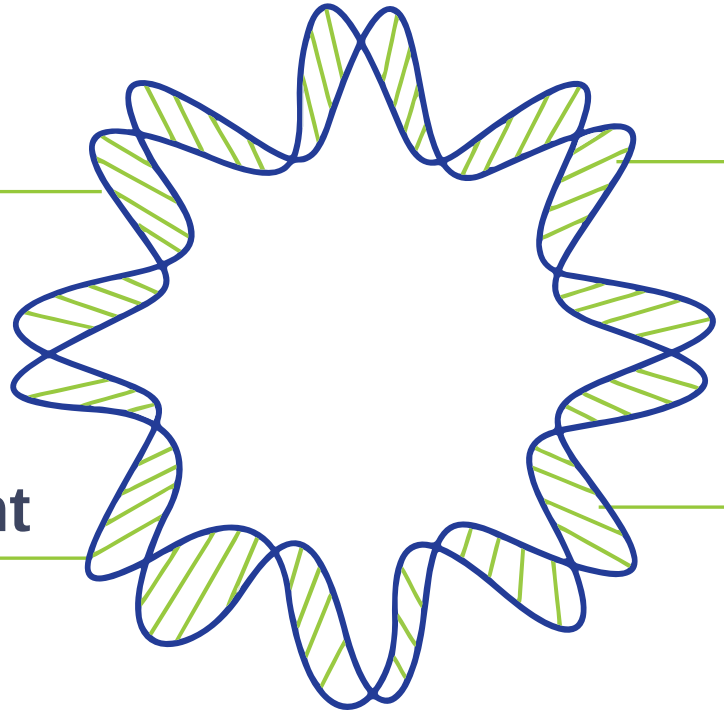
Building a patient-focused precision oncology company

Discovery Engine

Powered by scientists with proven ability to deliver precision oncology medicines

Clinical Development

Highly selected patient populations & cancers with significant unmet need



Regulatory Strategy

Efficient development path with potential for accelerated regulatory approvals

Commercial Approach

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

Senior Management & Board of Directors

Experienced. Proven. Focused.

Kris Vaddi, PhD

Founder &
Chief Executive Officer

Founding member

Incyte

Jakafi ruxolitinib (tablets)
olumiant (baricitinib) tablets 2 mg
VELCADE (bortezomib)
TABRECTA (capmatinib) tablets

Peggy Scherle, PhD

Chief Scientific Officer

Incyte
Jakafi ruxolitinib (tablets)
olumiant (baricitinib) tablets 2 mg
Pemazyre pemigatinib (tablets)
TABRECTA (capmatinib) tablets

Andrew Combs, PhD

Executive Vice President and Head of Chemistry

Incyte
Jakafi ruxolitinib (tablets)
Parsaclisib

David Mauro, MD, PhD

Chief Medical Officer

Bristol Myers Squibb
MERCK
ERBITUX cetuximab
PegIntron
SPRYCEL dasatinib

Deborah Morosini, MD, MSW

Executive Vice President and Chief of Clinical Affairs

LOXO ONCOLOGY
FOUNDATION MEDICINE
AstraZeneca
TAGRISSO osimertinib
Retevmo selpercatinib
VITRAKVI larotrectinib

Christopher Pierce, MBA

Executive Vice President and Chief of Business Operations

LOXO ONCOLOGY
Pfizer
Takeda MILLENNIUM THE TAKEDA ONCOLOGY COMPANY
VELCADE (bortezomib)
XALKORI crizotinib
Retevmo selpercatinib
VITRAKVI larotrectinib

Brian Piper, MBA

Chief Financial Officer

aevi genomic medicine
Shire

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 Healthcare Fund Management — *General Partner*

Julian C. Baker

Managing Member
Baker Brothers Investments

Kris Vaddi, PhD

Founder &
Chief Executive Officer

Prelude Therapeutics Corporate Highlights

4 INDs cleared to date;

3 Clinical stage programs;

3 Preclinical assets

Highly productive target class agnostic discovery engine

Pipeline focused on differentiated and validated targets

Compelling market opportunities across multiple tumor types

Patient-inspired drug development, regulatory, and commercial strategies to address high unmet need

Multiple wholly owned programs with fast-to-market potential

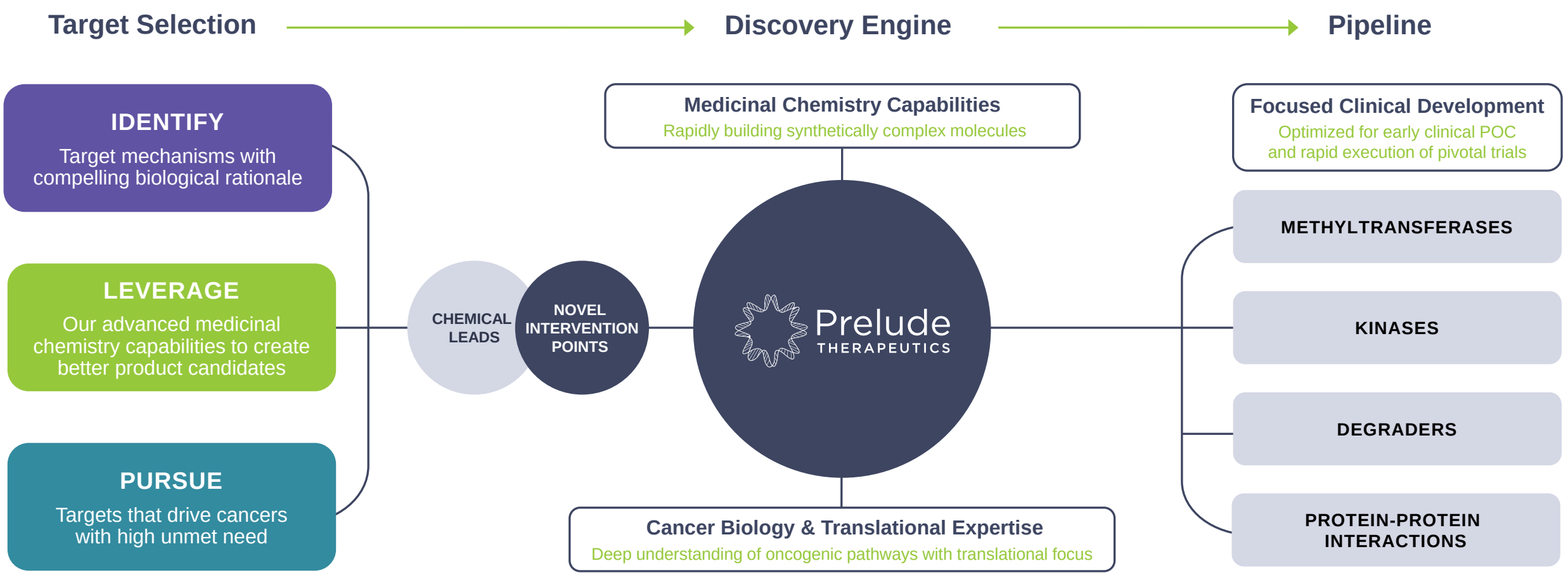
Lead programs, PRT543 & PRT811 (PRMT5) and PRT1419 (MCL1) target clinically validated mechanisms with differentiated product profile

Experienced leadership team with marquee investors and board members

Deeply experienced employee base that has worked on multiple approved targeted agents

Prelude THERAPEUTICS

Prelude Discovery and Development Approach



Prelude Therapeutics Pipeline

Program	Indications	Discovery/ Preclinical	IND Enabling	Phase 1	Phase 2	Phase 3	Upcoming Milestones	Worldwide Rights
PRT543 (PRMT5)	Selected Solid Tumors (incl. ACC, HRD+)						• Escalation complete; additional expansion cohorts early 2Q2021 • Data presentation 2H2021	Prelude THERAPEUTICS
	Selected Myeloid Malignancies (incl. MF and MDS)							
PRT811 (Brain Penetrant PRMT5)	GBM and CNS Metastatic Cancers						• Expansion cohorts mid-2021 • Initial clinical data YE2021	
PRT1419 (MCL1)	Selected Hematological Malignancies *(oral formulation)*						• Addition of expansion cohorts expected 2H2021	
	Solid Tumors *(IV formulation)*						• Phase 1 trial to commence 1H2021	
PRT2527 (CDK9)	Selected Solid and Hematological Malignancies						• IND 2021	
PRT-SCA2 (SMARCA2)	Multiple Genomically Selected Cancers						• IND 2021/2022	
PRT-K4 (Kinase)	Solid Tumors						• IND-enabling 2021	

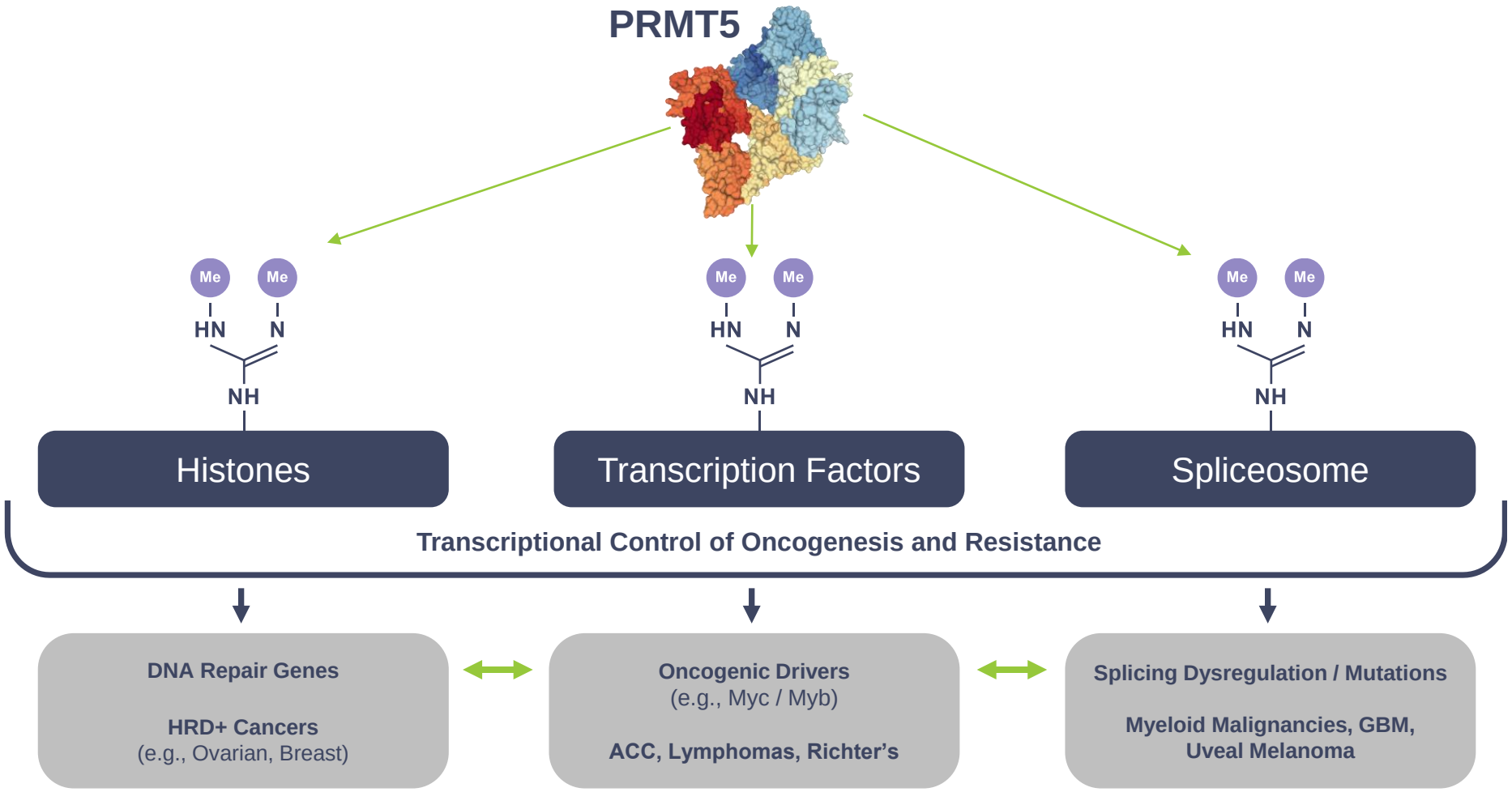
Wholly-owned patent portfolio covering composition of matter and method of use patents. Prior to possible extensions, PRT543 has IP coverage into at least H2 2038; PRT811 and PRT1419 until at least 2039

PRMT5 Programs

Prelude THERAPEUTICS

PRMT5 Pathway Drives Oncogenesis and Resistance

PRMT5



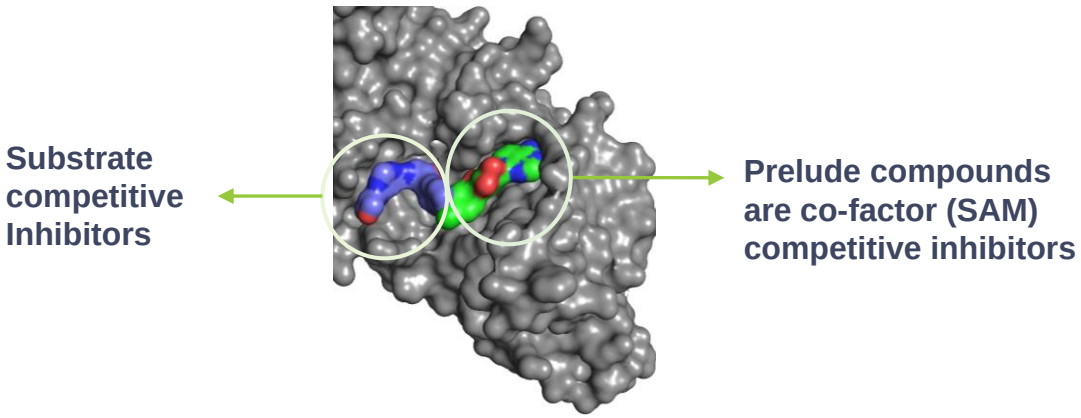
PRMT5 inhibition can be leveraged to potentially treat a broad range of solid tumors and hematologic malignancies

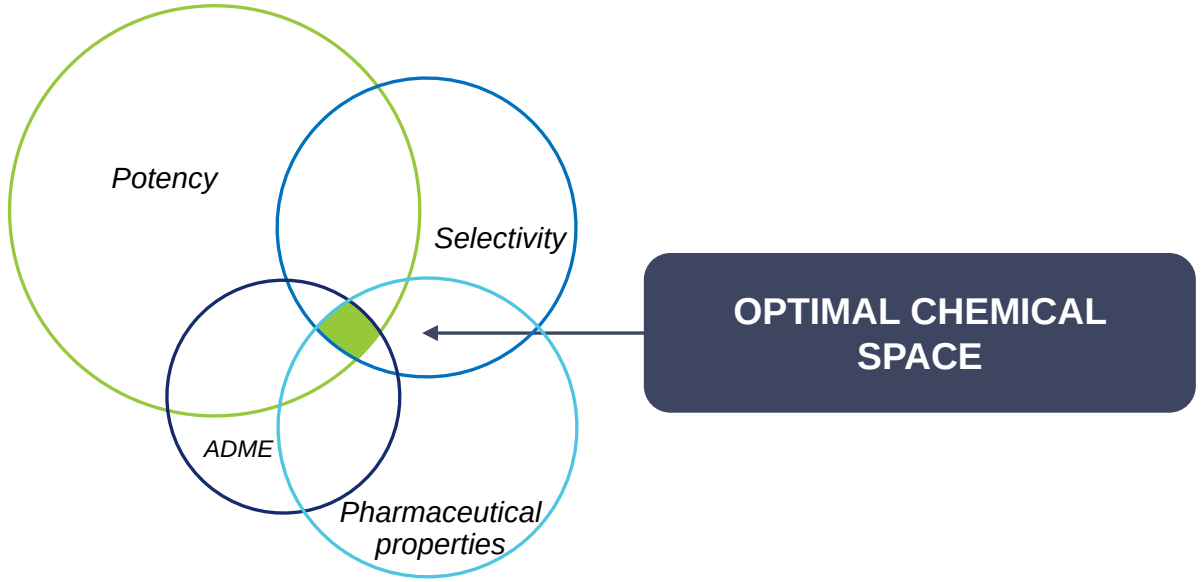
Prelude PRMT5 Program

Optimized for a well-balanced and differentiated profile

PRMT5

Differentiating Mechanism of Action





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

PRT543

Opportunity for Accelerated Development Path

Potential best-in-class PRMT5 inhibitor

Differentiated PRMT5 Inhibitor

- Highly selective and potent

Targets Selected Solid Tumors and Heme Malignancies

- Strong scientific rationale
- Clinical PoC for target

Optimized PK Profile

- High oral bioavailability and long half-life
- Differentiated safety and efficacy profile

Potential Rapid Path to Market

- Phase 1 ongoing
- Potential for accelerated approval pathway

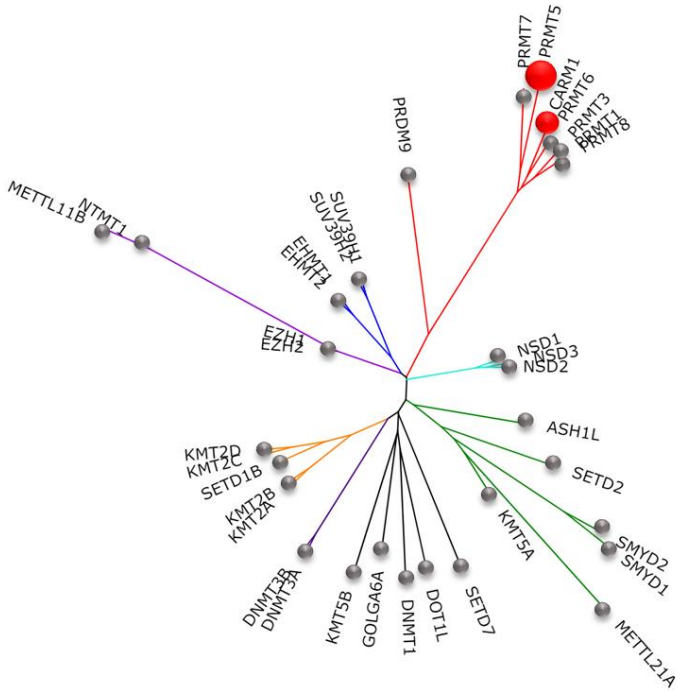
Prelude THERAPEUTICS

PRT543 – A Potent, Selective and Oral PRMT5 Inhibitor Candidate

PRMT5

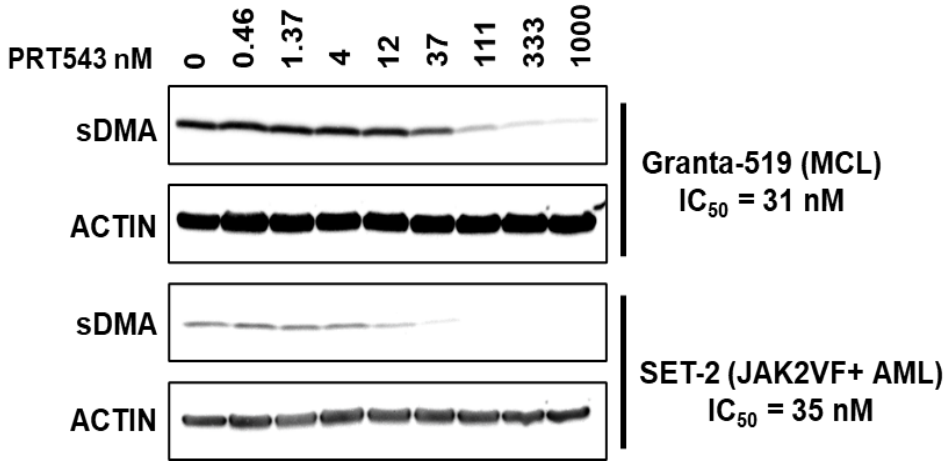
PRT543 is Highly-Selective

Vs 36 methyltransferases in addition to a broad panel of receptors, transporters and channels



Dose-Dependent PD

Modulation of sDMA (symmetric dimethylation) is a direct measure of PRMT5 activity



~50% reduction in plasma sDMA correlates with efficacy in preclinical models

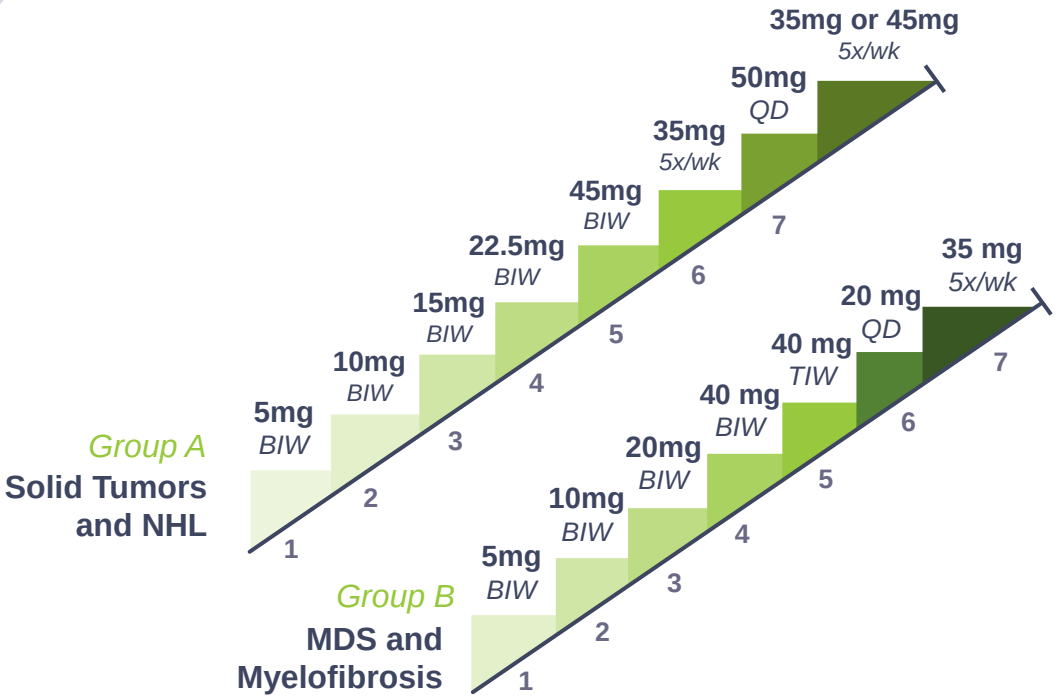
PRT543 demonstrated optimized potency, dose-dependent PD, and selectivity offering best-in-class potential

PRT543 Phase 1 Clinical Trial

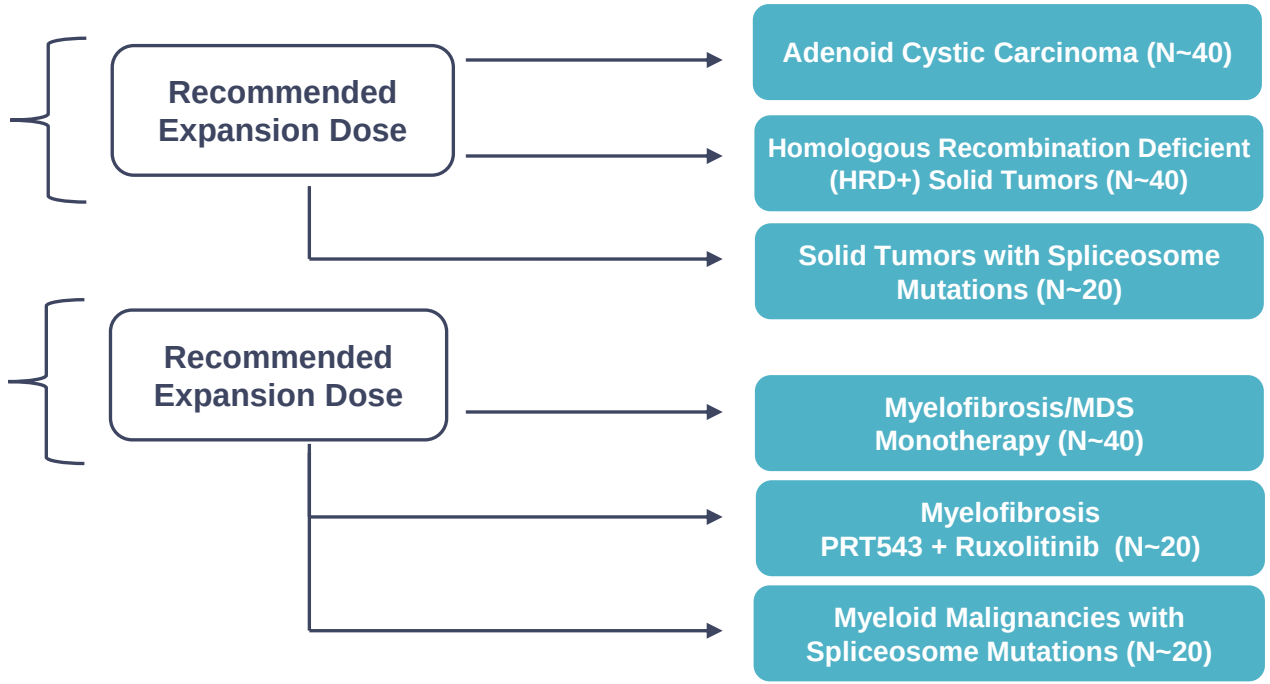
PRMT5

4Q2020 / EARLY 2021

Dose Escalation



Expansion Cohorts



Potential for PoC in multiple cancers in 2H2021

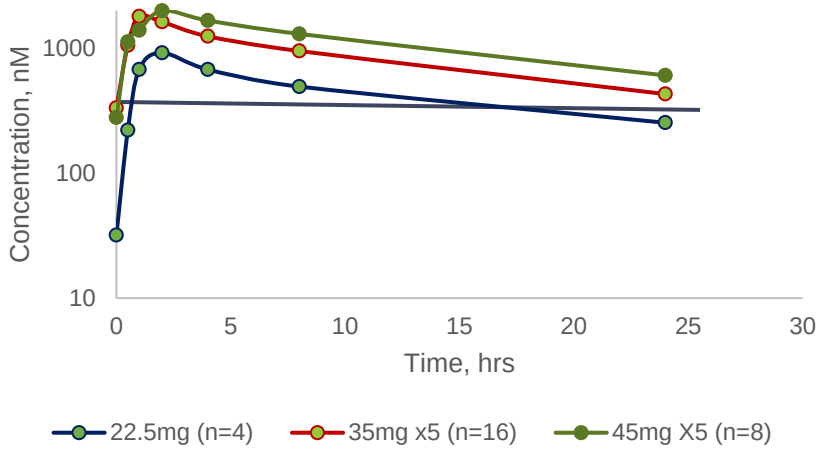
Prelude THERAPEUTICS

PRT543 Phase 1 – Interim PK/PD Results Demonstrated Predictable Profile

PRMT5

Dose-Proportional Increase in Exposure

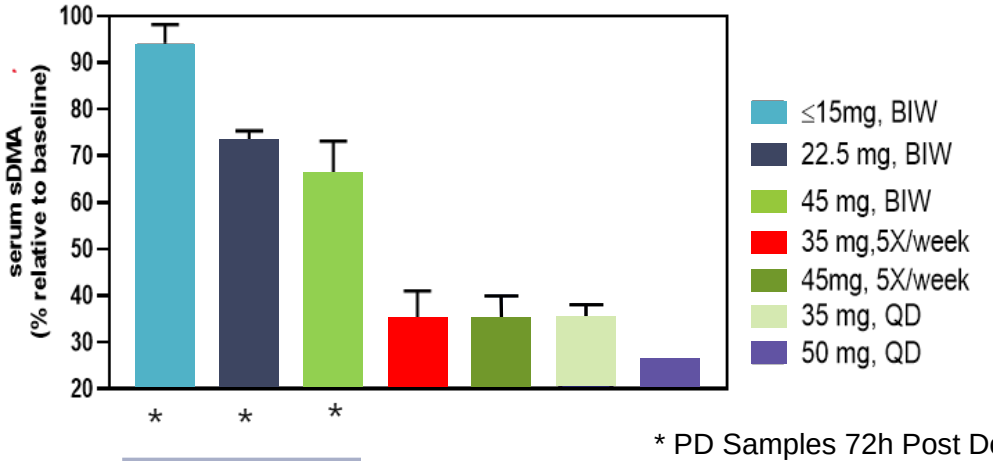
(Steady State)



Parameter	35 mg (5x)	45 mg (5x)
C_{max} (nM)	1792	1989
$T_{1/2}$ (h)	10.7	12.3
AUC (μM.h/wk)	13962	16542

Trough Level target based on Preclinical models

Dose-Dependent Decrease in Serum sDMA



* PD Samples 72h Post Dose

Serum was obtained from patients at various times following administration of PRT543 and analyzed for sDMA levels by LC/MS. The data are shown as % relative to pre-dose levels

PRT543 is currently in a dose range that provides target coverage predicted based on preclinical models

Data as of March 15, 2021

PRT543 Phase 1 Clinical Trial Safety Profile

- Phase 1 clinical trial of PRT543 enrolled 61 patients
  - 42 with advanced solid tumors (including two with HRD+ high grade serous ovarian cancer)
  - 11 with MF
  - Seven with MDS
  - One with NHL
- Overall safety profile consistent between both Groups A and B
  - Majority of drug related adverse events were Grade 1-2 with anemia and thrombocytopenia being the most common Grade 3-4 adverse events
  - 24 SAEs reported amongst 11 patients, with three individual SAEs deemed drug related
  - Thrombocytopenia remains only dose-limiting toxicity
  - No patients discontinued study due to adverse events

Status as of December 16, 2020

Durable Confirmed CR in HRD+ High Grade Serous Ovarian Cancer

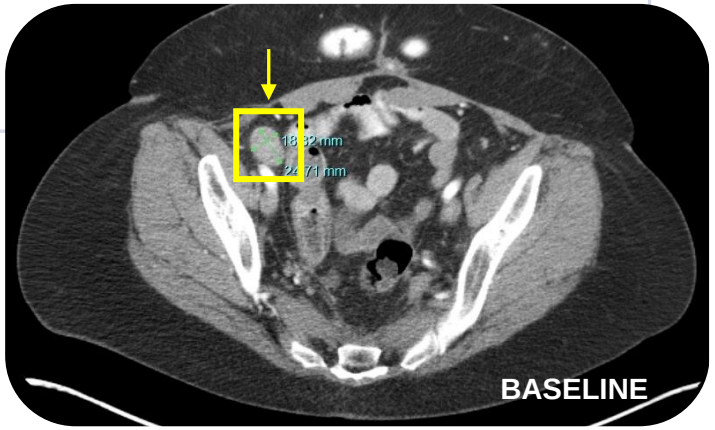
PRMT5

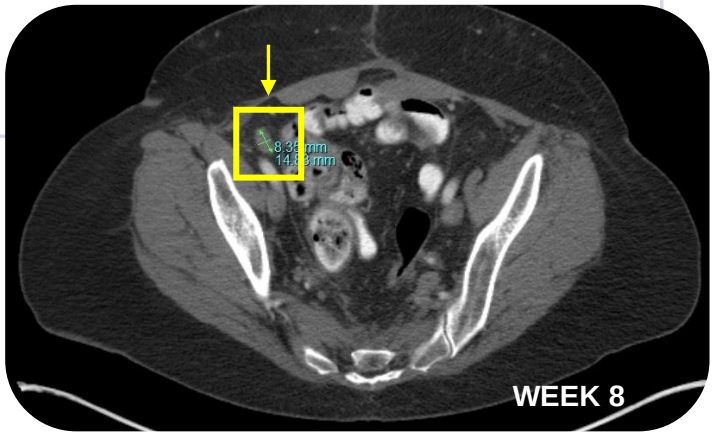
Patient History

- Diagnosed in 2014 with tumor origin in fallopian tube
- Seven prior lines of therapy including PARPi
- Enrolled in 35mg, 5x/week; currently ongoing
- Based on genomic analysis of archival tumor tissue, HRD+
  - Mutations in genes involved in DNA damage response (ATR, RAD51D, BRCA1)
  - Plans to confirm HRD status in validated clinical assay
- One target lesion per RECIST and CA125 level of 37.8 U/mL at baseline

Patient Response

- RECIST CR at first follow up tumor assessment with associated drop in CA-125 level to 2.6 U/mL
- A second follow up scan performed 8 weeks after first follow up confirmed the CR and CA-125 measured 4.6 U/mL
- A third follow up scan performed at 24 weeks demonstrated continued CR and CA-125 measured 3.3 U/mL
- As of December 16, 2020, patient received 9 months of study therapy and remained in CR





PRT543 Offers Broad Opportunity Across Tumor Types

PRMT5

Scientific Rationale	Tumor Types	US Market Opportunity
Transcriptional Regulation Splicing Dysregulation Synthetic Lethality	Adenoid Cystic Carcinoma HRD+ Tumors (Ovarian, TNBC, Others)	**ACC:** 10-15,000 patients **Ovarian:** 63% of ovarian tumors HRD+ **TNBC:** 55% of TNBC tumors HRD+ **Prostate:** 25% of mCRPC tumors HRD+
	Uveal Melanoma	**Uveal Melanoma:** 2,000 patients annually
	Myeloid Malignancies (Myelofibrosis and MDS)	**MF:** ~12,000 intermediate/high risk patients **MDS:** 10,000 patients annually

PRT811

Expanding PRMT5 Opportunity into CNS Cancers

Only clinical stage brain-penetrant PRMT5 inhibitor

Differentiated Brain-Penetrant PRMT5 Inhibitor

- Highly selective and potent

Targeting GBM and CNS Metastatic Brain Cancers

- High target engagement in the brain and preclinical activity

Optimized PK Profile

- High and sustained brain exposure in preclinical studies

Potential Rapid Path to Market

- Phase 1 ongoing
- Anticipated expansion in GBM and CNS metastatic cancers mid-2021

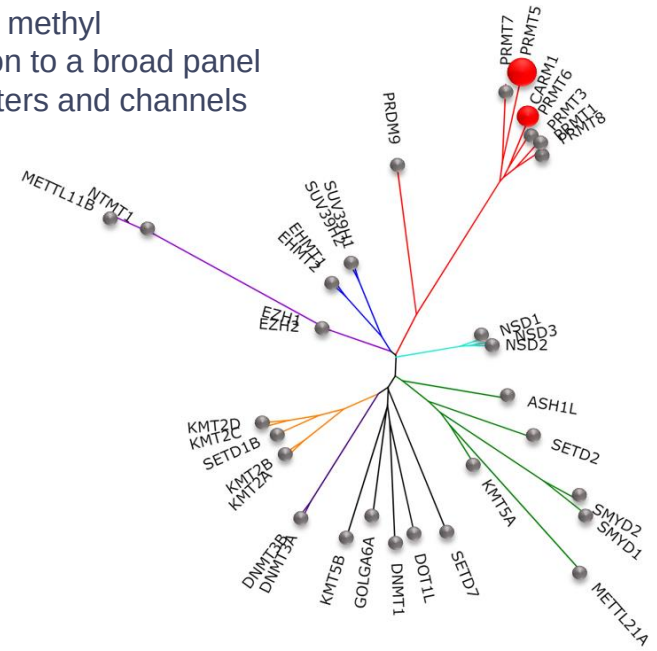
Prelude THERAPEUTICS

PRT811 – A Potent, Selective and Brain Penetrant PRMT5 Inhibitor Candidate

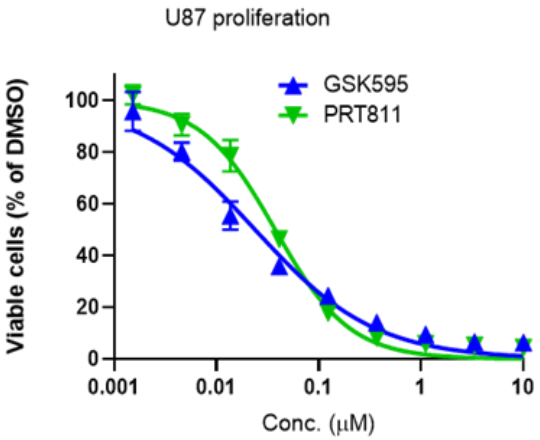
PRMT5

PRT811 is a Potent SAM-Competitive PRMT5 Inhibitor

Highly selective vs 36 methyl transferases in addition to a broad panel of receptors, transporters and channels



Equivalent Potency and 100-fold Higher Brain Exposure vs GSK'595



	GSK'595	PRT811
	Mean	*Mean*
Plasma concentration µmol/L	2.50	**2.02**
Brain concentration µmol/kg	0.722	**4.11**
Brain/plasma ratio	0.0293	**2.26**

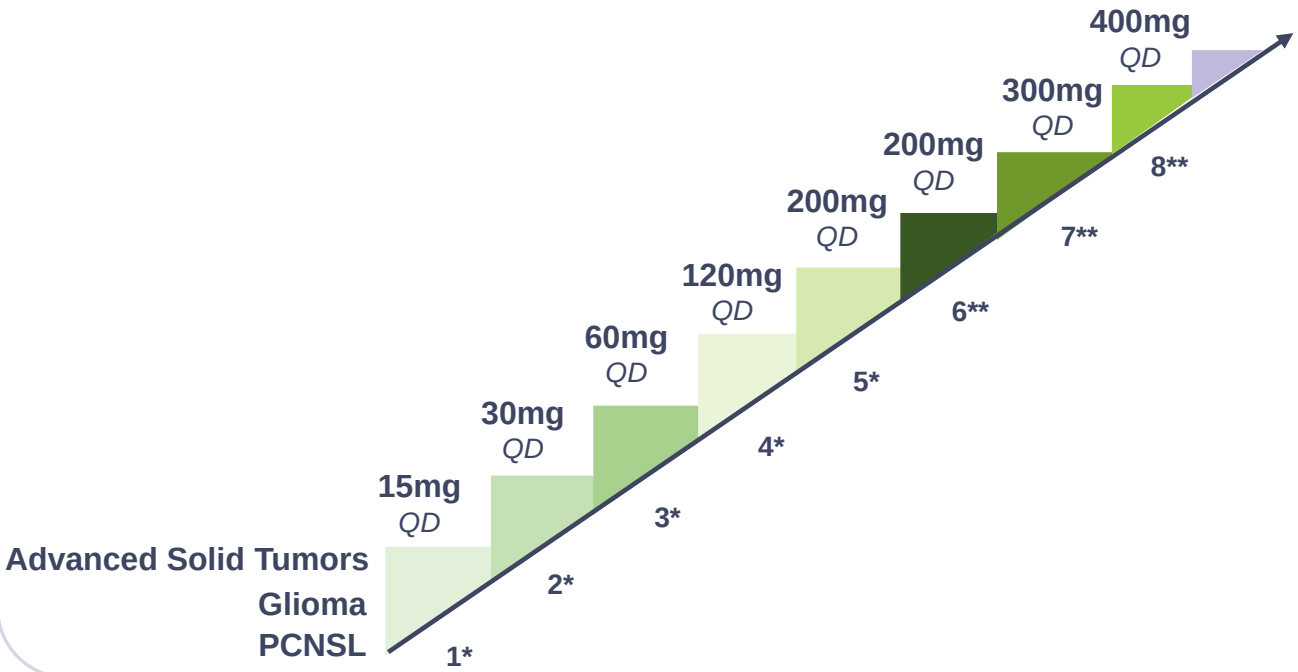
PRT811 has high oral bioavailability, high brain exposure, and no dose-limiting toxicities to date

PRT811 Phase 1 Clinical Trial

PRMT5

ANTICIPATED MID-2021

Dose Escalation



Expansion Cohorts

Recommended Expansion Dose

- Glioblastoma (N~20)
- Primary CNS Lymphoma (N~20)
- CNS Metastatic Disease (N~20)

** (2 weeks on/1 week off) 21-day cycles*
*** (Continuous 3 weeks on) 21-day cycles*

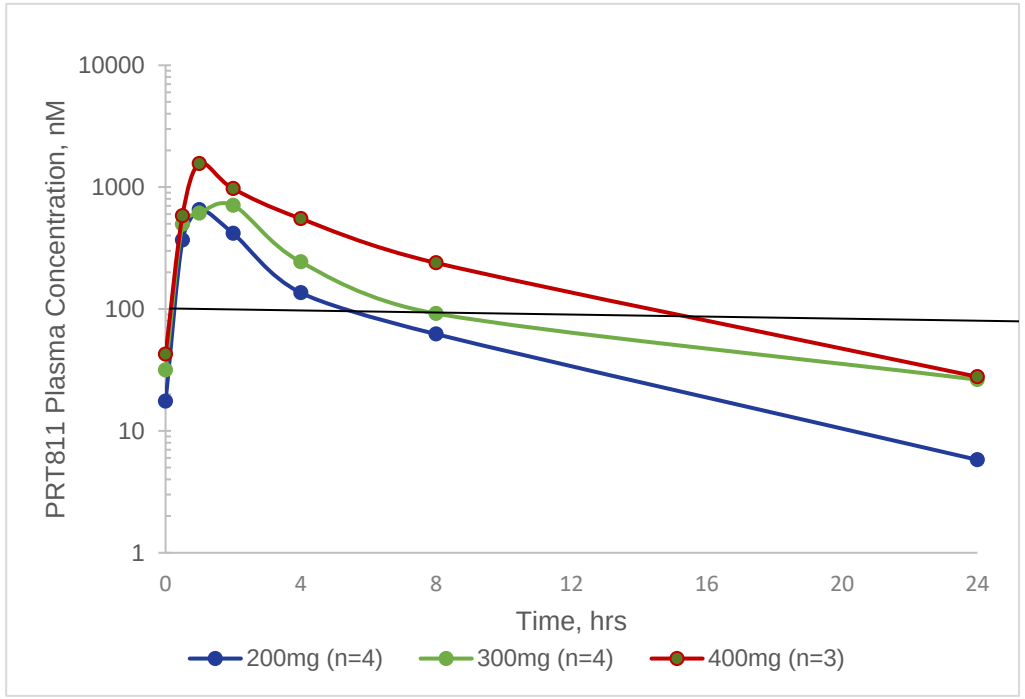
Potential PoC in CNS cancers in 2H2021

PRT811 Phase 1 – Interim Results Demonstrated Dose-Dependent PK/PD

PRMT5

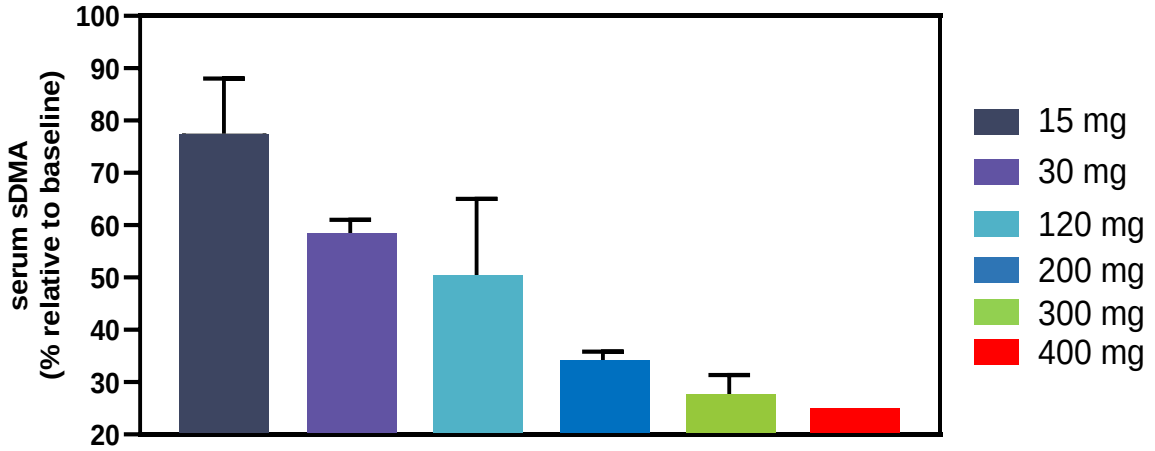
PRT811 Pharmacokinetic Profile

(Steady State)



Trough Level target based on Preclinical models

PRT811 Pharmacodynamic Profile Serum sDMA



Data as of March 15, 2021

PRT811 offers the potential to achieve desired levels of PRMT5 inhibition in tissues including brain

PRT811 Phase 1 Clinical Trial Safety Profile

- Phase 1 clinical trial of PRT811 enrolled 24 patients
  - 16 with advanced solid tumors
  - Eight with GBM
- Overall safety profile
  - Four patients each experienced one SAE, none of which was attributed to study therapy
  - No dose limiting toxicities observed
  - One patient discontinued study therapy due to transient Grade 2 nausea

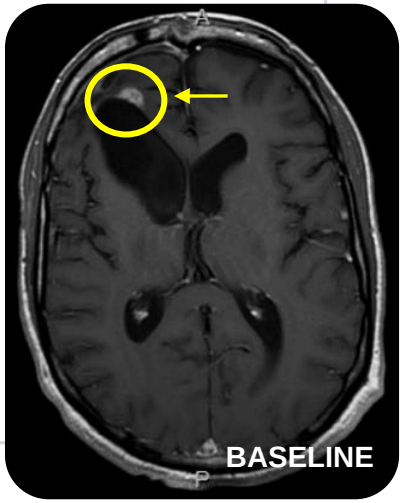
Status as of December 16, 2020

Confirmed PR in Glioblastoma Multiforme

PRMT5

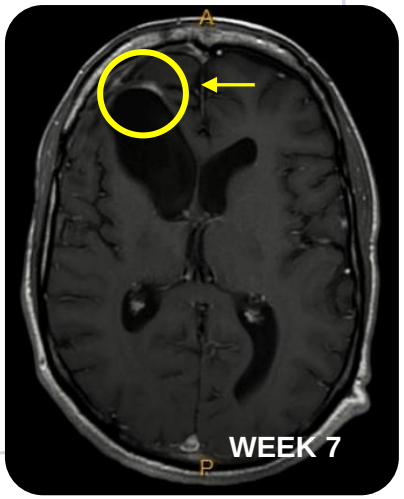
Patient History

- Diagnosed with recurrent GBM and originally treated with surgery and chemoradiation with Temodar in July 2019
- Patient has not been treated with steroids or Avastin, and clinical status is stable
- Presented with progressive disease in June 2020
- Enrolled in **200 mg (q.d. two weeks on/one week off)** in July 2020
- Patient's tumor is:
  - IDH1+
  - MGMT unmethylated
- One target lesion per RANO (response assessment in neuro-oncology) measuring 23 mm x 10 mm



Study Follow-Up

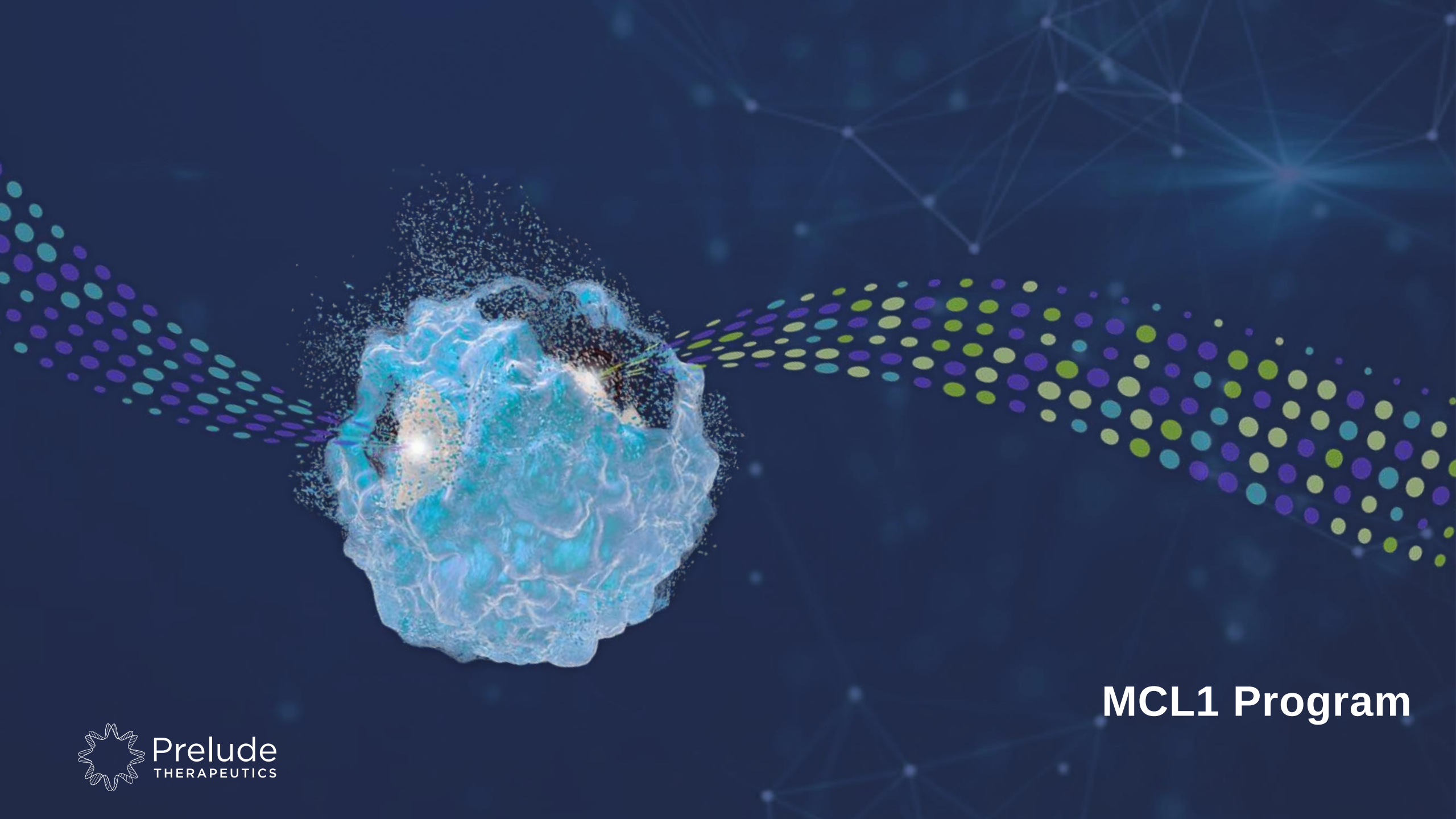
- In September 2020, at patient's first follow-up MRI evaluation (week 7) lesion measured 13 mm x 6 mm (**66% reduction**)
- Follow-up MRI at week 18 confirmed a partial response (PR) per RANO criteria and an **improved regression of 77% from baseline**
- As of December 16, 2020, patient received five months of study therapy and remained in PR and is clinically stable



PRT811 Expands PRMT5 Opportunity into CNS Cancers

PRMT5

Scientific Rationale	Tumor Types	US Market Opportunity
Transcriptional Regulation	Glioblastoma Multiforme	10,000 patients annually
Splicing Dysregulation	Primary CNS Lymphoma	~2,000 -~2,500 patients annually
Synthetic Lethality	CNS Metastatic Disease	PRMT5i-sensitive subset of 200,000 CNS metastatic patients annually



MCL1 Program

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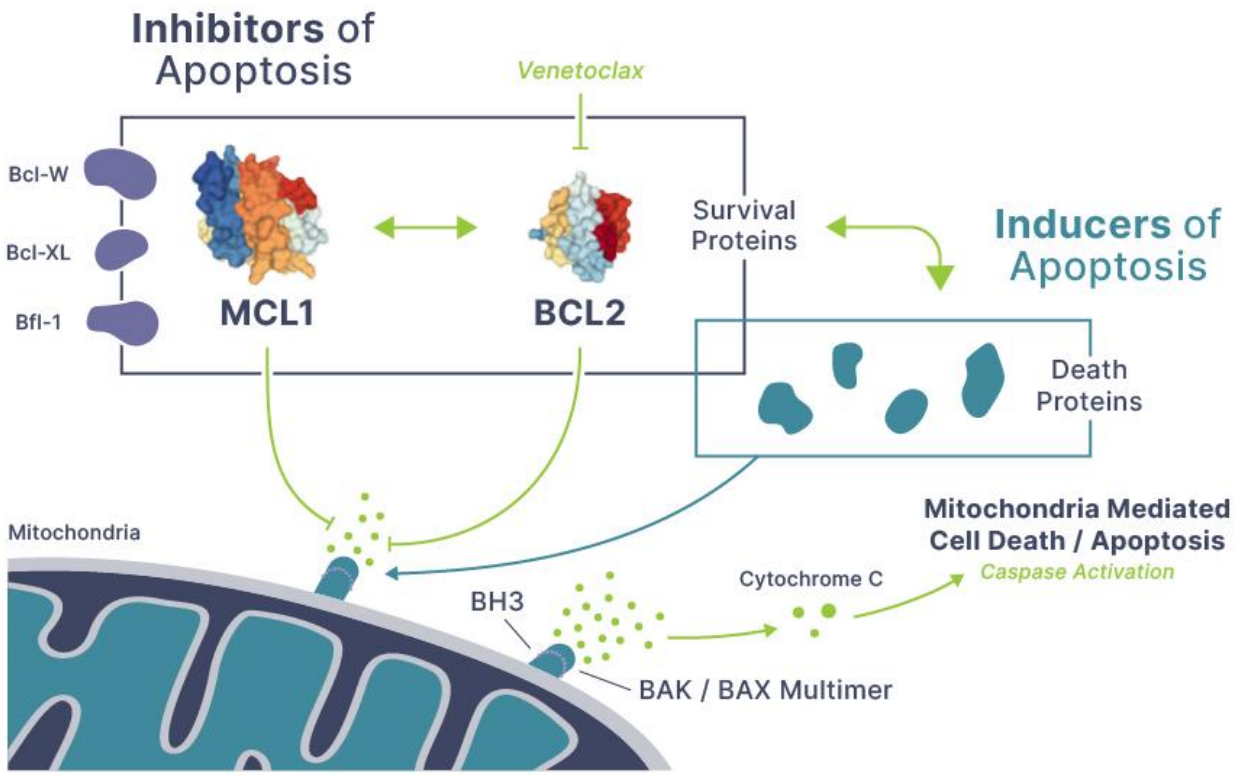
Prelude MCL1 Program

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

MCL1 Inhibitor

- Potent and selective
- Oral and IV formulations

Targeting Selected Heme Cancers

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

Optimized PK Profile Maximizes Therapeutic Window

- High oral bioavailability and optimized physicochemical properties

Potential Rapid Path to Market

- Phase 1 dose escalation ongoing; expansion cohorts expected 2H2021 (oral)
- Phase 1 in solid tumors to commence 1H2021 (IV)

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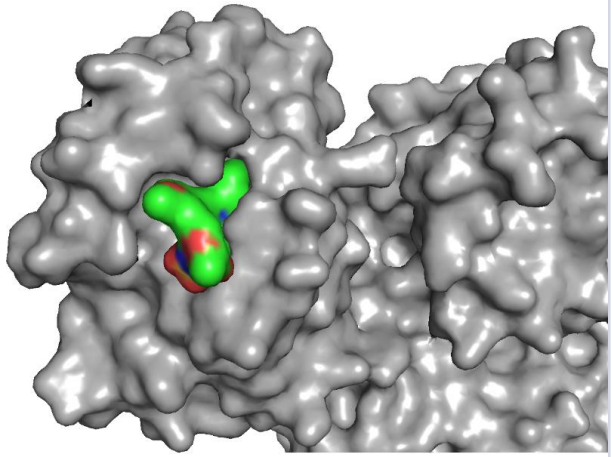
PRT1419: Potential Leading MCL1 Inhibitor

MCL1

Highly Potent Binding to MCL1

Prelude compounds are competitive inhibitors of BIM binding



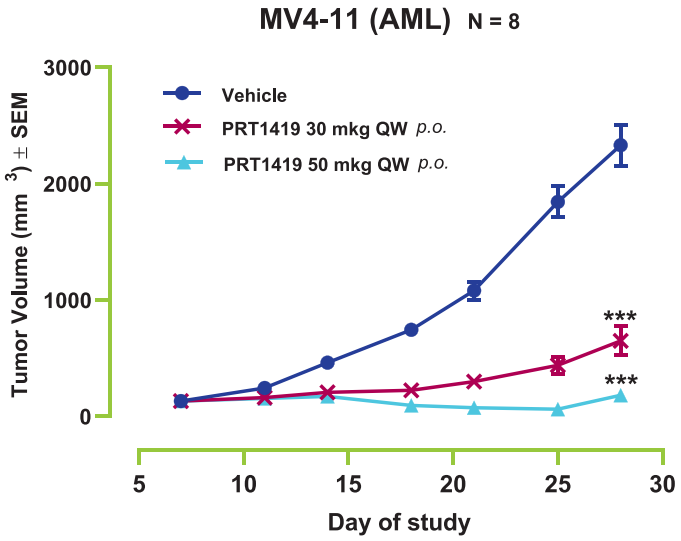
Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC_{50} (nM)	150	31	4.5	**80**
Whole Blood IC_{50} (nM)	1800	320	430	**210**
Caco-2 ($x10^{-6}$ cm/s)	6	<0.1	0.2	**11**
Human Hepat. Cl (%HBF)	42	ND	ND	**71**
Solubility at pH 7.4 (μg/mL)	13	ND	ND	**>1000**
Route of Administration	IV	IV	IV	**Oral/IV**

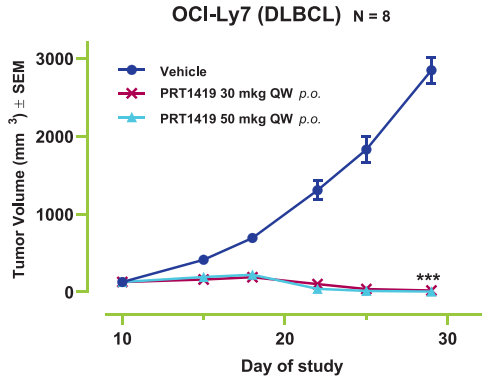
PRT1419 is a potent MCL1 inhibitor candidate with no preclinical evidence of cardiac toxicity

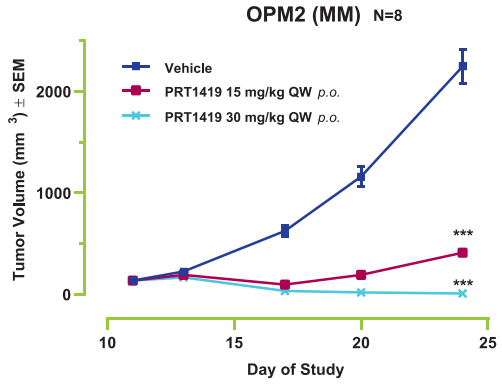
PRT1419 Demonstrated Preclinical Activity as Monotherapy and in Combination

MCL1

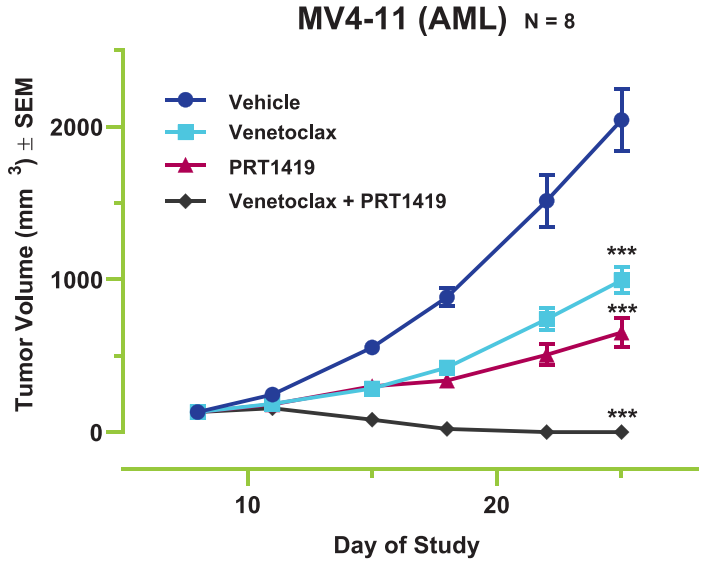
Monotherapy







Combination



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

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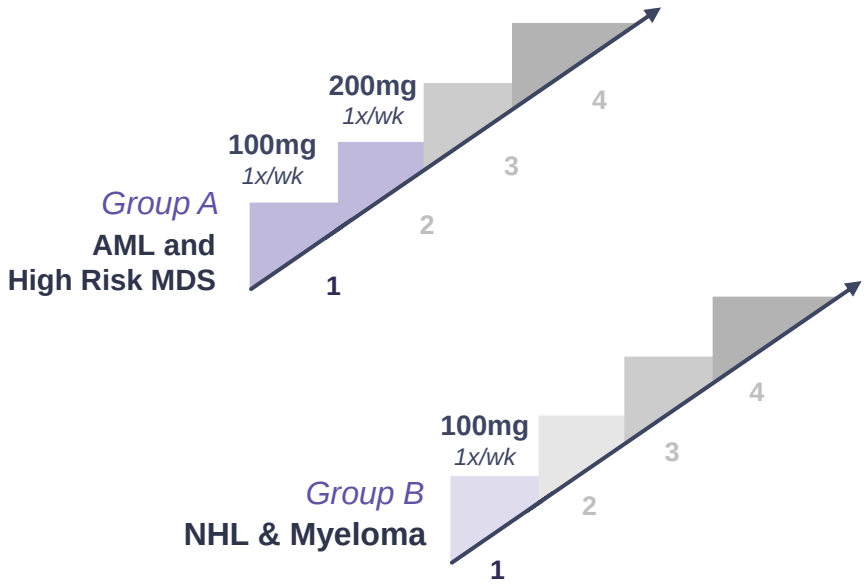
Oral PRT1419 Phase 1 Clinical Trial

Phase 1 Initiated in 2H2020

MCL1

2021

Dose Escalation



Expansion Cohorts

Recommended Expansion Dose

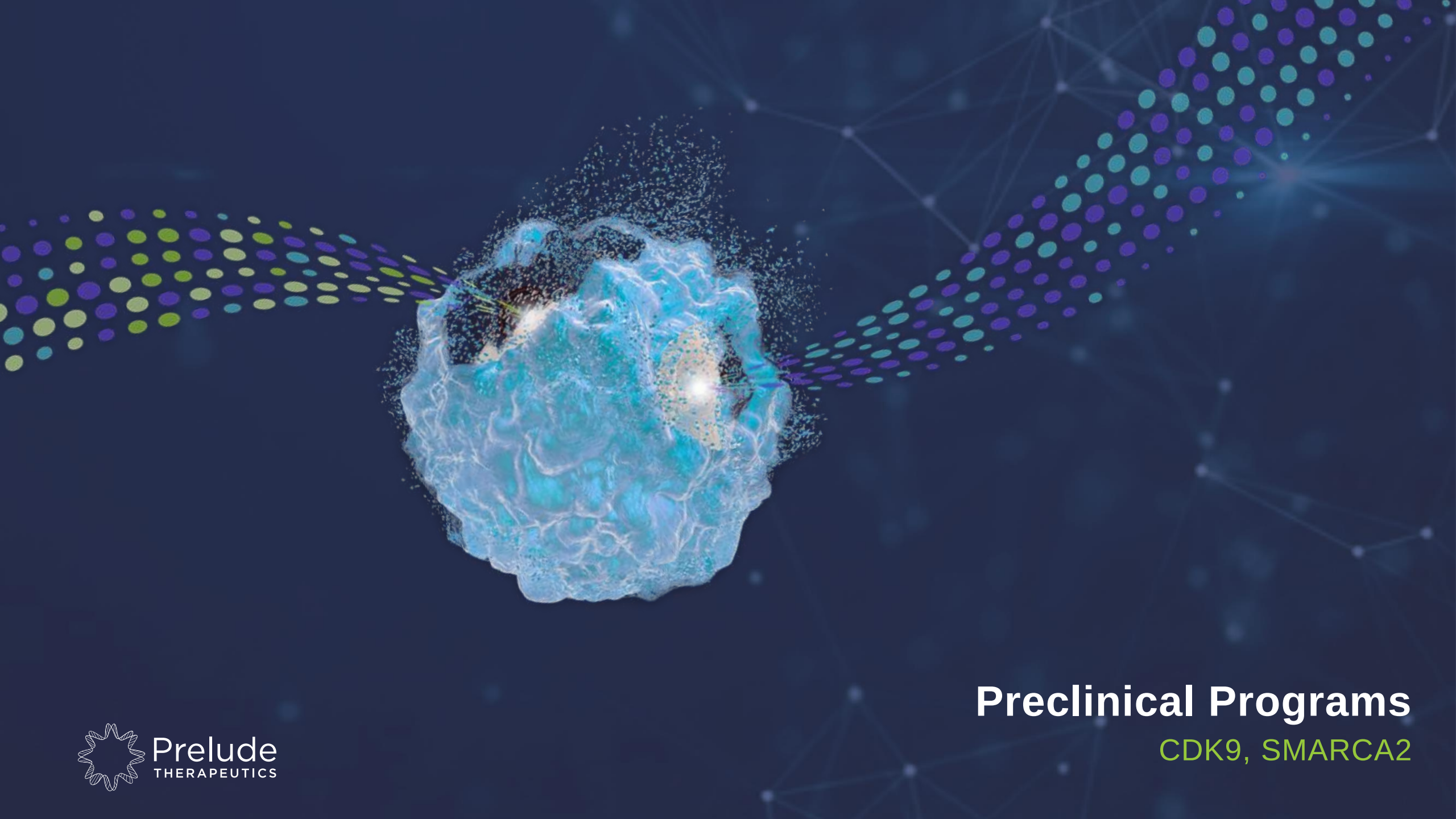
- AML (N~20)
- AML or MDS
  PRT1419 + Venetoclax or Aza
  (N~20)
- High Risk MDS (N~20)

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



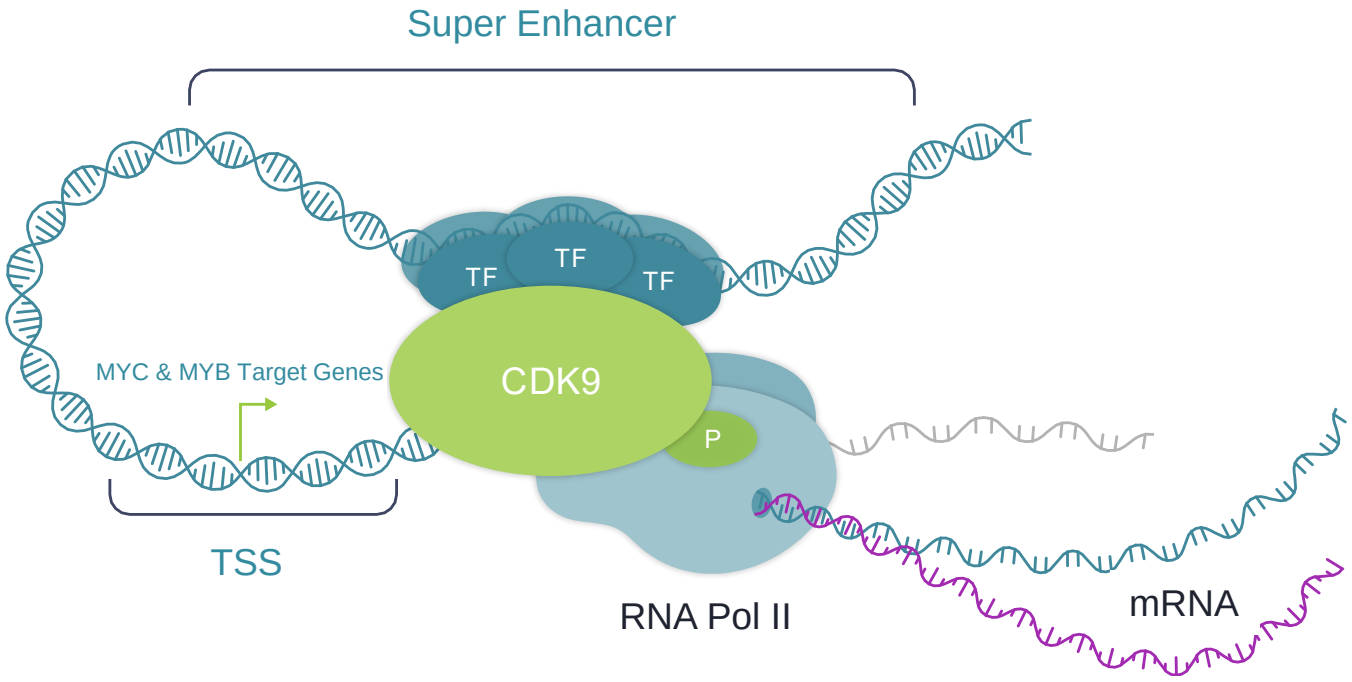
Preclinical Programs

CDK9, SMARCA2

Prelude THERAPEUTICS

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

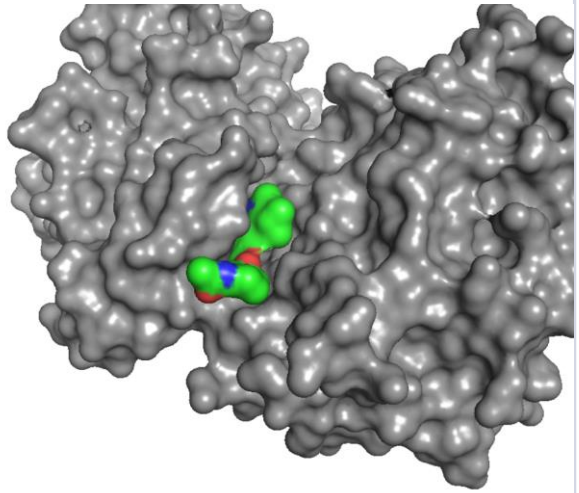
Highly-selective CDK9 inhibitors believed to have broad applicability in hematological and solid malignancies

PRT2527: Potent and Highly Selective CDK9 Inhibitor Candidate

CDK9

Highly Selective CDK9 Inhibitor Candidate

Prelude compounds are ATP competitive inhibitors



Compound		Dinaciclib	AZD4573	PRT2527
Biochemical IC_{50} (nM)	**CDK9**	4.4	1.9	0.95
Proliferation IC_{50} (nM)			11	18
WB IC_{50} (nM)			192	196
Fold Selectivity CDK9 *vs* Other Isoforms	**CDK1**	98x	23x	73x
	CDK2	7x	35x	340x
	CDK3	0.5x	2x	35x
	CDK4	13x	53x	250x
	CDK5	17x	37x	>1000x
	CDK6	59x	79x	>1000x
	CDK7	34x	150x	>1000x

>100x 100-10x <10x

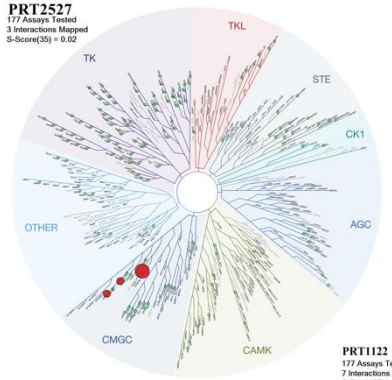
PRT2527 demonstrated improved potency and kinase selectivity relative to competitor compounds in preclinical studies

CDK9 Inhibitor Candidate: PRT2527

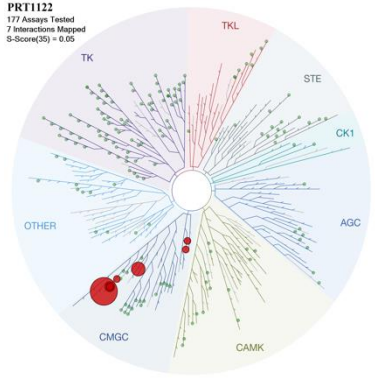
CDK9

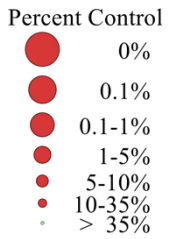
Improved Selectivity

PRT2527

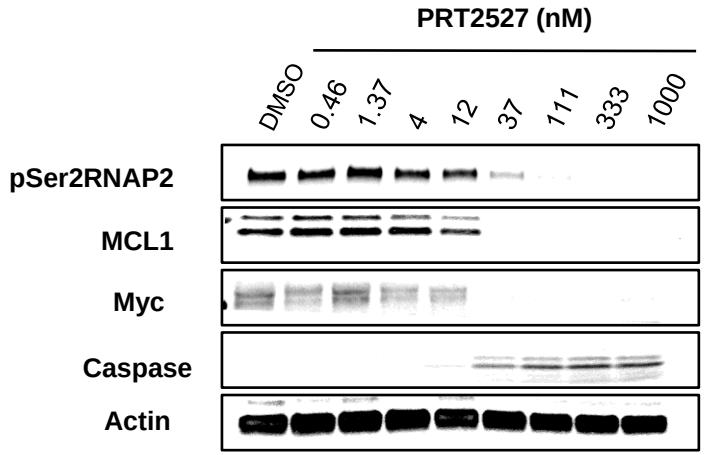


AZD4573



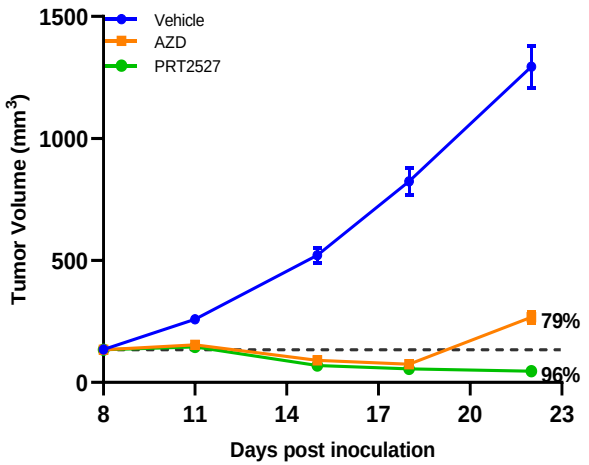


Potent in Vitro Activity



Sustained Regressions at Well-Tolerated Doses in Vivo

MV4-11 (AML)



PRT2527 IND expected to be filed in 2021

SMARCA2 Targeted Degrader Program

SMARCA2

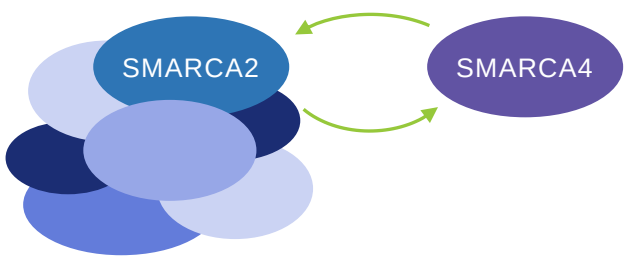
SMARCA4 and SMARCA2 Regulate Chromatin Accessibility and Gene Expression

Paralog Dependency

SMARCA4 Compensates for SMARCA2 Function

NORMAL CELL

SWI/SNF Chromatin Remodeling Complex



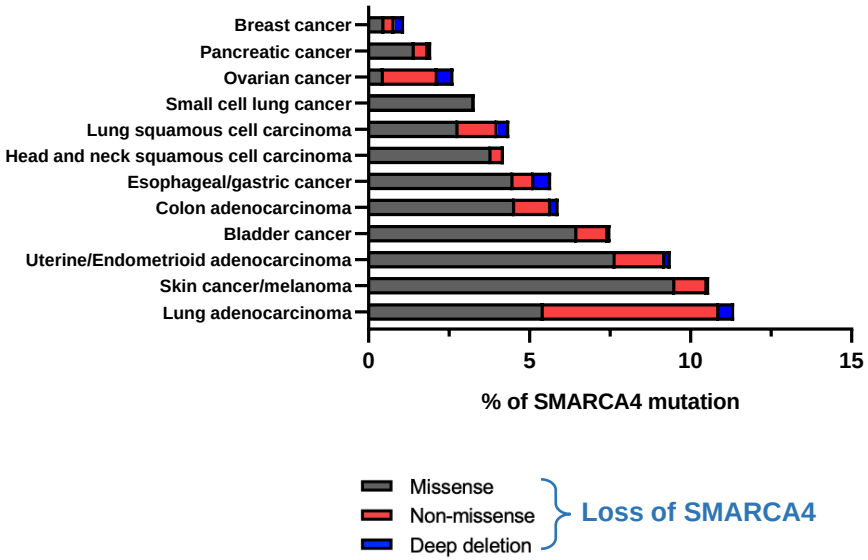
SMARCA4 MUTANT TUMORS

SMARCA2 Degradation → **Synthetic Lethality**

Dysfunctional SMARCA4

Tumor Cell Death

Loss of SMARCA4 Leads to SMARCA2 Dependency

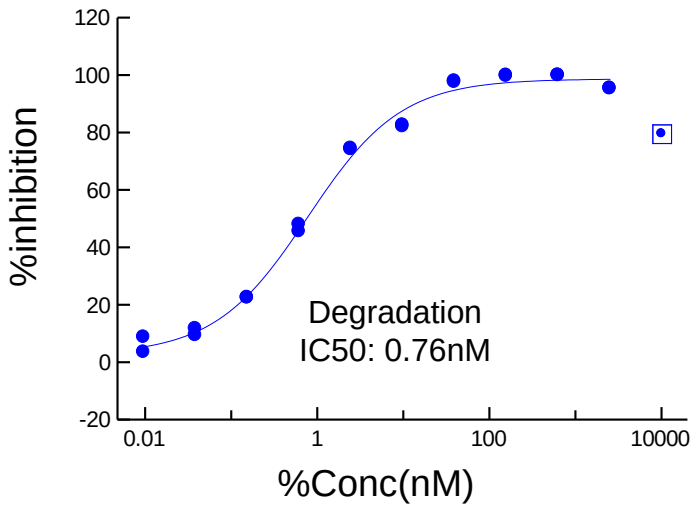


Opportunity to target 10 – 12% NSCLC with SMARCA4 deletions

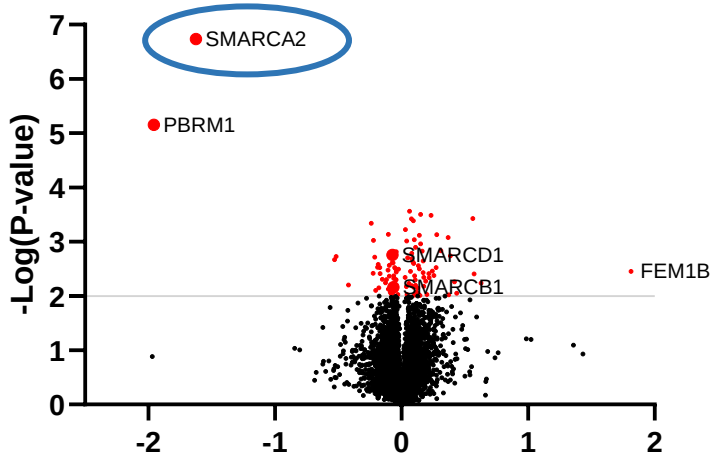
Prelude Discovered Selective sub-nM SMARCA2 Degraders

SMARCA2

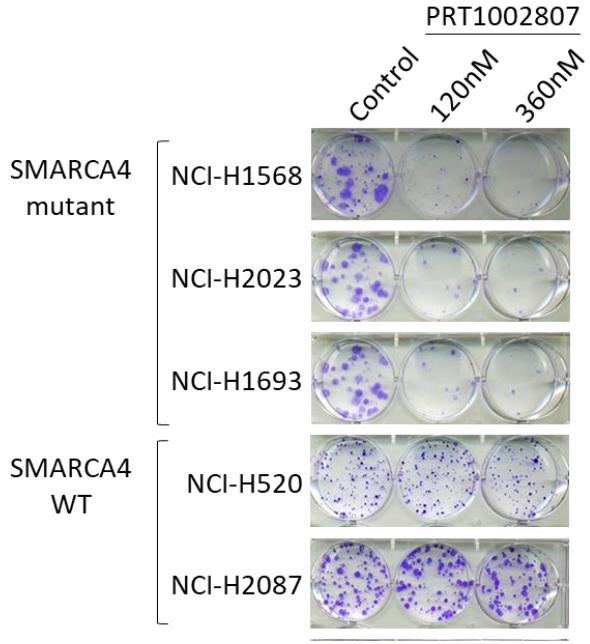
Sub-Nanomolar Potency for SMARCA2 Degradation



Highly Selective for SMARCA2 Degradation

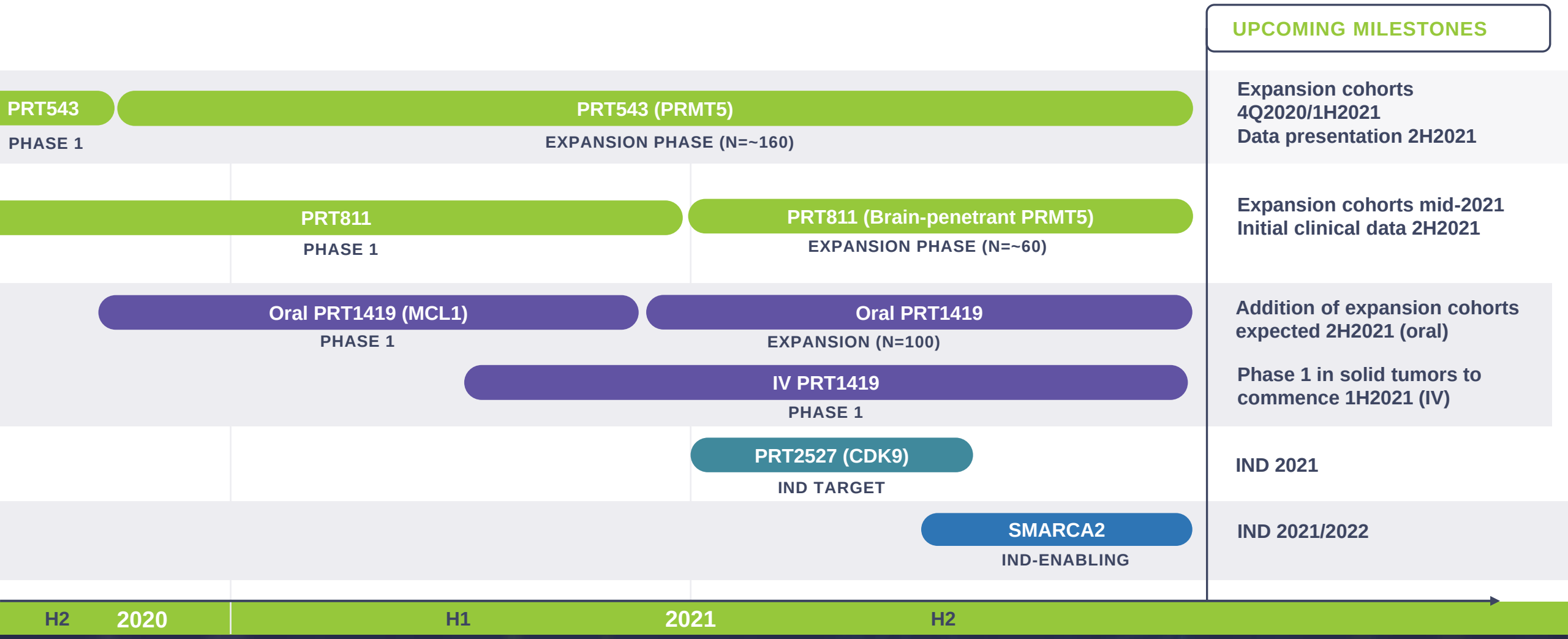


Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality



Lead optimization in progress – IND-enabling anticipated in the first half of 2021

Prelude Therapeutics Projected Milestones



Financial Highlights

Shares Outstanding

- 43.7 million shares voting and non-voting common stock as of December 31, 2020
- 60.5 million shares fully diluted
  - Excludes 2.9 million shares voting and non-voting common stock issued in January 2021 follow-on offering

Cash and Cash Equivalents

- $218.3 million as of December 31, 2020
  - Excludes $172.5 million gross proceeds raised in January 2021 follow-on offering
- Current cash and cash equivalents will be sufficient to fund operating expenses and capital expenditure requirements into 2023

Prelude Therapeutics Corporate Highlights

4 INDs cleared to date;

3 Clinical stage programs;

3 Preclinical assets

Highly productive target class agnostic discovery engine

Pipeline focused on differentiated and validated targets

Compelling market opportunities across multiple tumor types

Patient-inspired drug development, regulatory, and commercial strategies to address high unmet need

Multiple wholly owned programs with fast-to-market potential

Lead programs, PRT543 & PRT811 (PRMT5) and PRT1419 (MCL1) target clinically validated mechanisms with differentiated product profile

Experienced leadership team with marquee investors and board members

Deeply experienced employee base that has worked on multiple approved targeted agents

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Thank You