

**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): March 17, 2021

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

Delaware
(State or other jurisdiction
of incorporation)

001-39527
(Commission
File Number)

81-1384762
(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

<u>Exhibit No.</u>	<u>Description</u>
99.1	Presentation

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: March 17, 2021

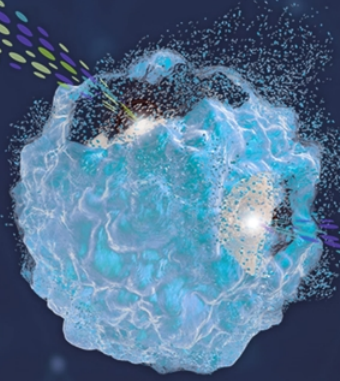
By: /s/ Brian Piper
Brian Piper
Chief Financial Officer



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

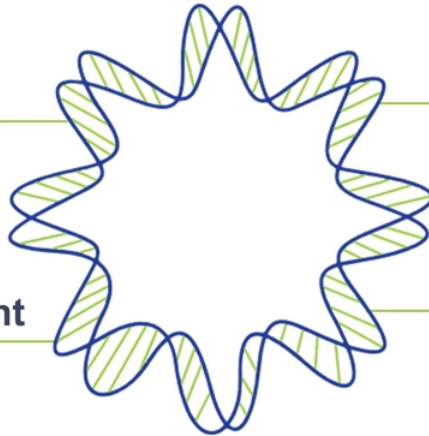
Building a patient-focused precision oncology company

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



Peggy Scherle, PhD
Chief Scientific Officer



Deborah Morosini, MD, MSW
Executive Vice President
and Chief of Clinical Affairs



Andrew Combs, PhD
Executive Vice President
and Head of Chemistry



Christopher Pierce, MBA
Executive Vice President
and Chief of Business
Operations



David Mauro, MD, PhD
Chief Medical Officer



Brian Piper, MBA
Chief Financial Officer



Board of Directors

- Paul Friedman, MD**
 CEO
 Former CEO
- Mardi Dier**
 CFO
 Former CFO, CBO
- Victor Sandor, MD**
 Former CMO
- David Bonita, MD**
 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

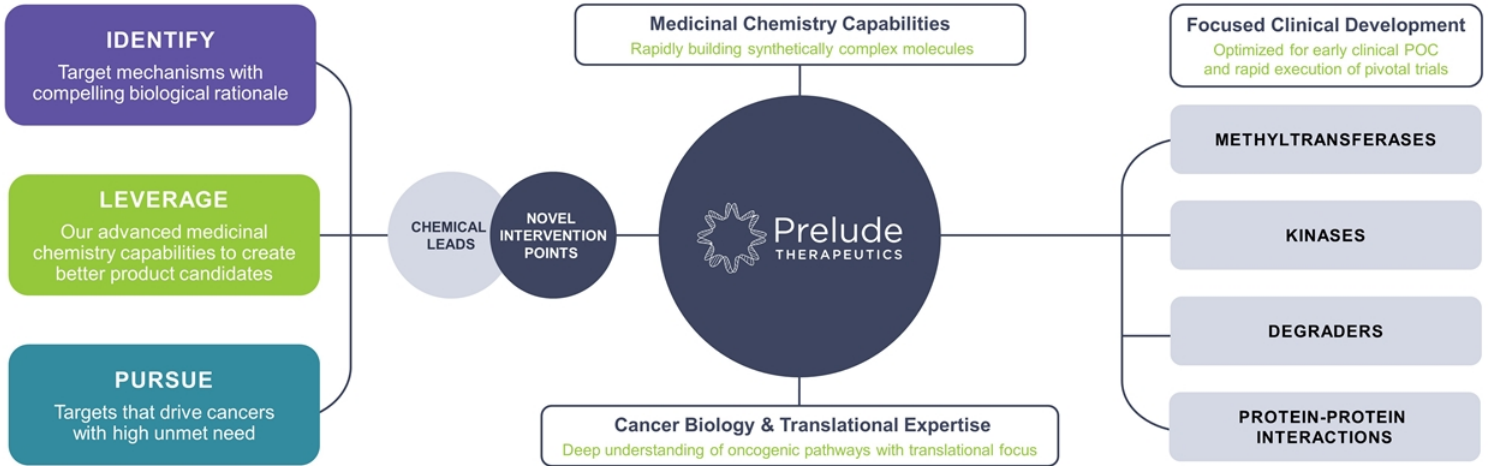


Experienced leadership team with marquee investors and board members

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

Prelude Discovery and Development Approach

Target Selection → Discovery Engine → Pipeline



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+)						<ul style="list-style-type: none"> Escalation complete; additional expansion cohorts early 2Q2021 Data presentation 2H2021 	
	Selected Myeloid Malignancies (incl. MF and MDS)							
PRT811 (Brain Penetrant PRMT5)	GBM and CNS Metastatic Cancers						<ul style="list-style-type: none"> Expansion cohorts mid-2021 Initial clinical data YE2021 	
PRT1419 (MCL1)	Selected Hematological Malignancies (oral formulation)						<ul style="list-style-type: none"> Addition of expansion cohorts expected 2H2021 	
	Solid Tumors (IV formulation)						<ul style="list-style-type: none"> Phase 1 trial to commence 1H2021 	
PRT2527 (CDK9)	Selected Solid and Hematological Malignancies						<ul style="list-style-type: none"> IND 2021 	
PRT-SCA2 (SMARCA2)	Multiple Genomically Selected Cancers						<ul style="list-style-type: none"> IND 2021/2022 	
PRT-K4 (Kinase)	Solid Tumors						<ul style="list-style-type: none"> IND-enabling 2021 	

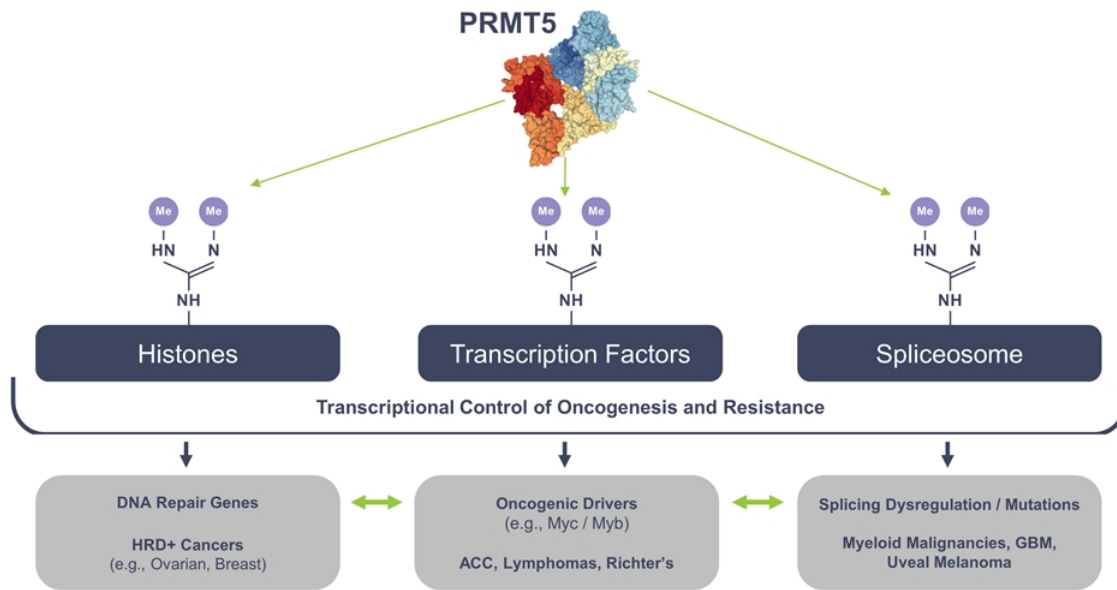
Wholly-owned patent portfolio covering composition of matter and method of use patents. Prior to possible extensions, PRT543 has IP coverage into at least H2 2038; PRT811 and PRT1419 until at least 2039



PRMT5 Programs

PRMT5 Pathway Drives Oncogenesis and Resistance

PRMT5



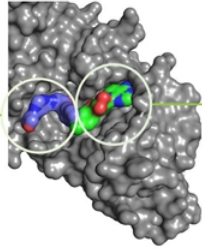
Prelude PRMT5 Program

Optimized for a well-balanced and differentiated profile

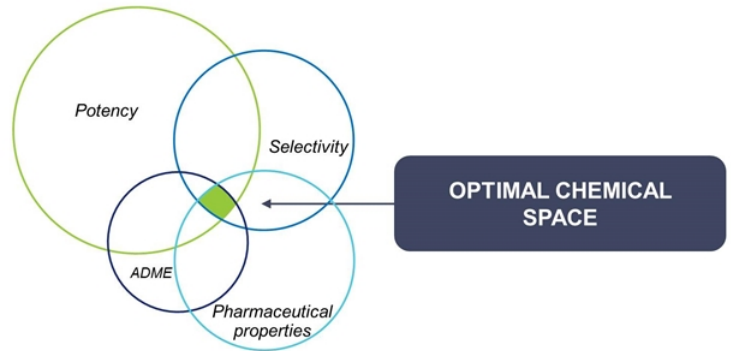
PRMT5

Differentiating Mechanism of Action

Substrate competitive Inhibitors



Prelude compounds are co-factor (SAM) competitive inhibitors



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

PRT543

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

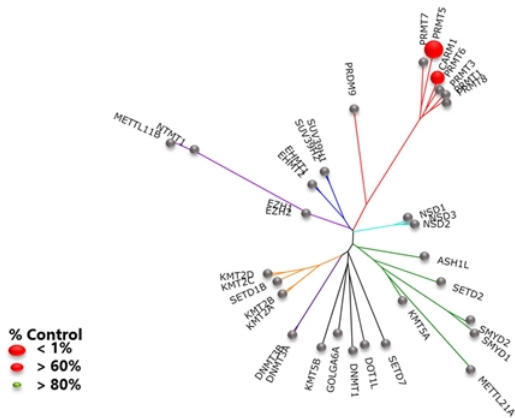
- Phase 1 ongoing
- Potential for accelerated approval pathway

PRT543 – A Potent, Selective and Oral PRMT5 Inhibitor Candidate

PRMT5

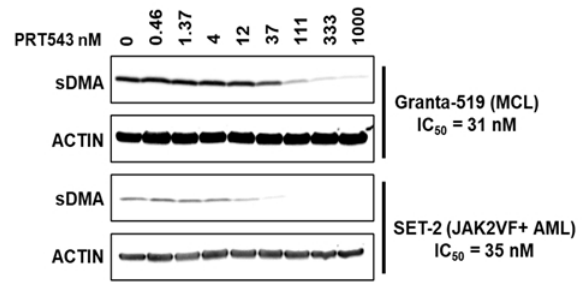
PRT543 is Highly-Selective

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

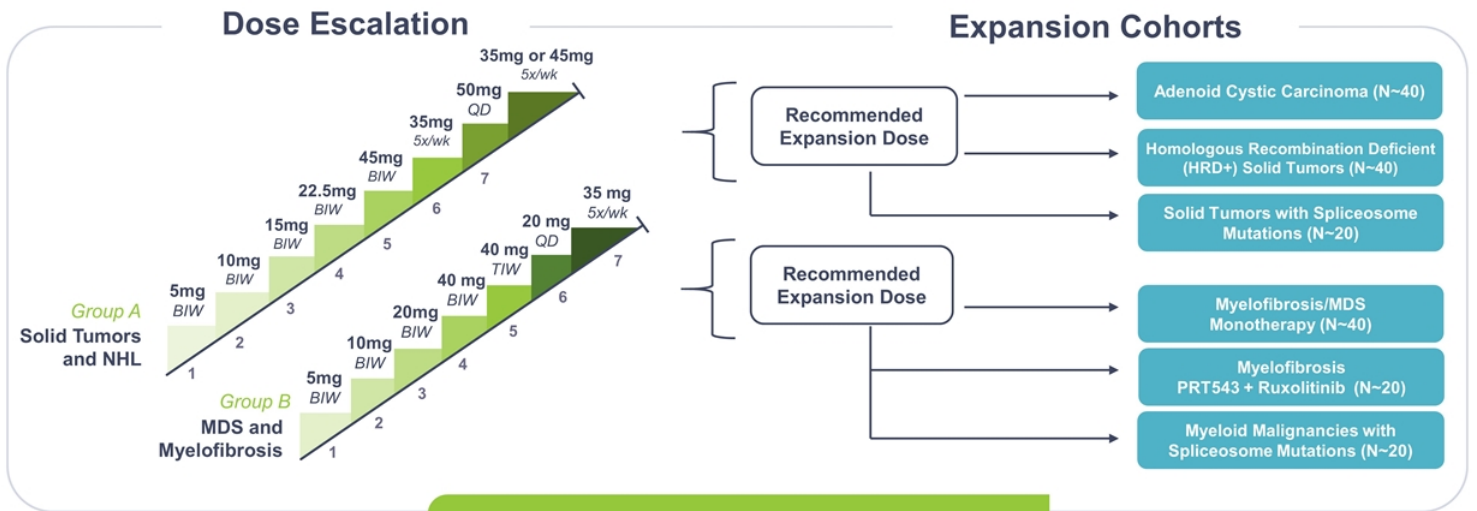


Dose-Dependent PD

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



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

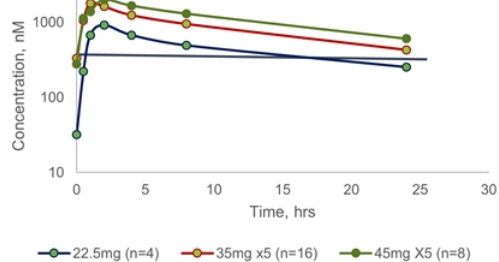


Potential for PoC in multiple cancers in 2H2021

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

PRMT5

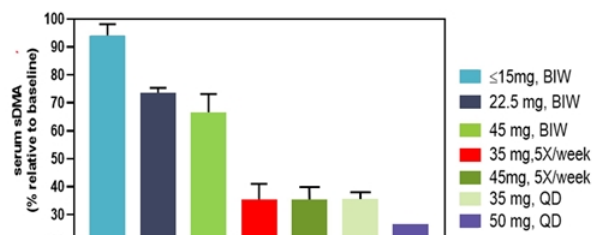
Dose-Proportional Increase in Exposure (Steady State)



Parameter	35 mg (5x)	45 mg (5x)
C_{max} (nM)	1792	1989
$T_{1/2}$ (h)	10.7	12.3
AUC ($\mu\text{M}\cdot\text{h}/\text{wk}$)	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

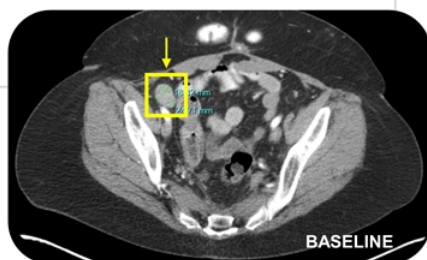
Status as of December 16, 2020

Durable Confirmed CR in HRD+ High Grade Serous Ovarian Cancer

PRMT5

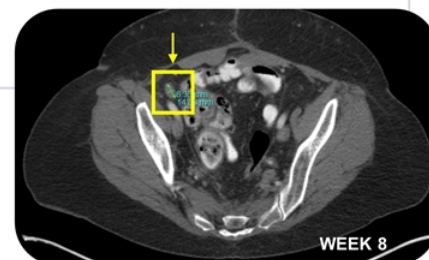
Patient History

- 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

Transcriptional
Regulation

Splicing
Dysregulation

Synthetic
Lethality

Tumor Types

Adenoid Cystic Carcinoma
HRD+ Tumors (Ovarian, TNBC, Others)

Uveal Melanoma

Myeloid Malignancies
(Myelofibrosis and MDS)

US Market Opportunity

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: 2,000 patients annually

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

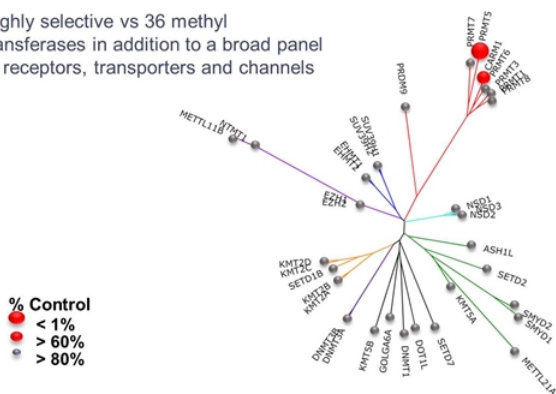
- Phase 1 ongoing
- Anticipated expansion in GBM and CNS metastatic cancers mid-2021

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

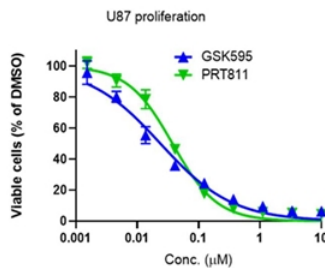
PRMT5

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

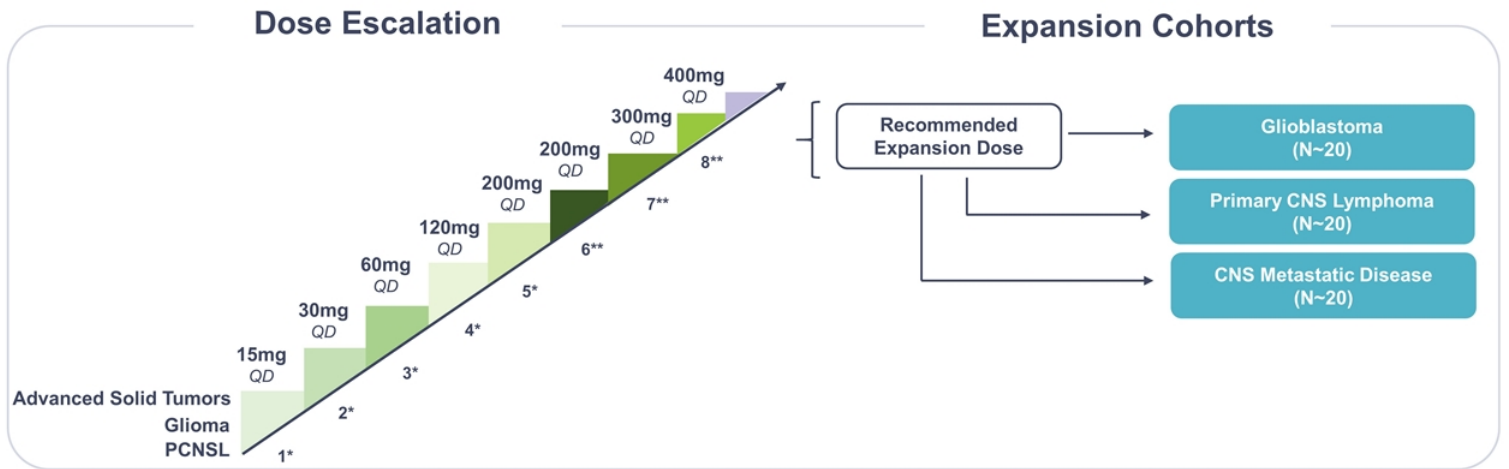


	GSK'595	PRT811
	Mean	Mean
Plasma concentration µmol/L	2.50	2.02
Brain concentration µmol/kg	0.722	4.11
Brain/plasma ratio	0.0293	2.26



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

ANTICIPATED MID-2021

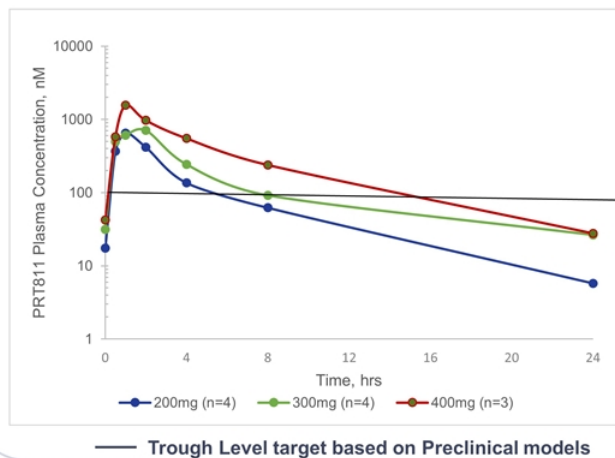


* (2 weeks on/1 week off) 21-day cycles
** (Continuous 3 weeks on) 21-day cycles

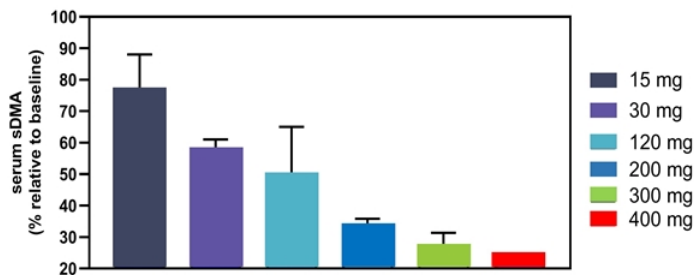
PRT811 Phase 1 – Interim Results Demonstrated Dose-Dependent PK/PD

PRMT5

PRT811 Pharmacokinetic Profile (Steady State)



PRT811 Pharmacodynamic Profile Serum sDMA



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

Data as of March 15, 2021

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

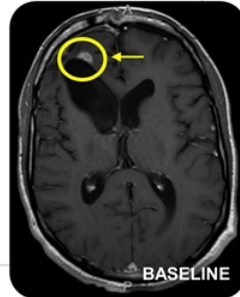
Status as of December 16, 2020

Confirmed PR in Glioblastoma Multiforme

PRMT5

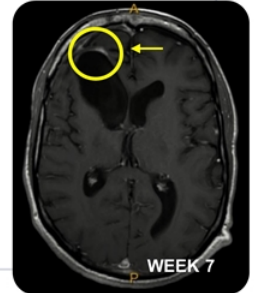
Patient History

- 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

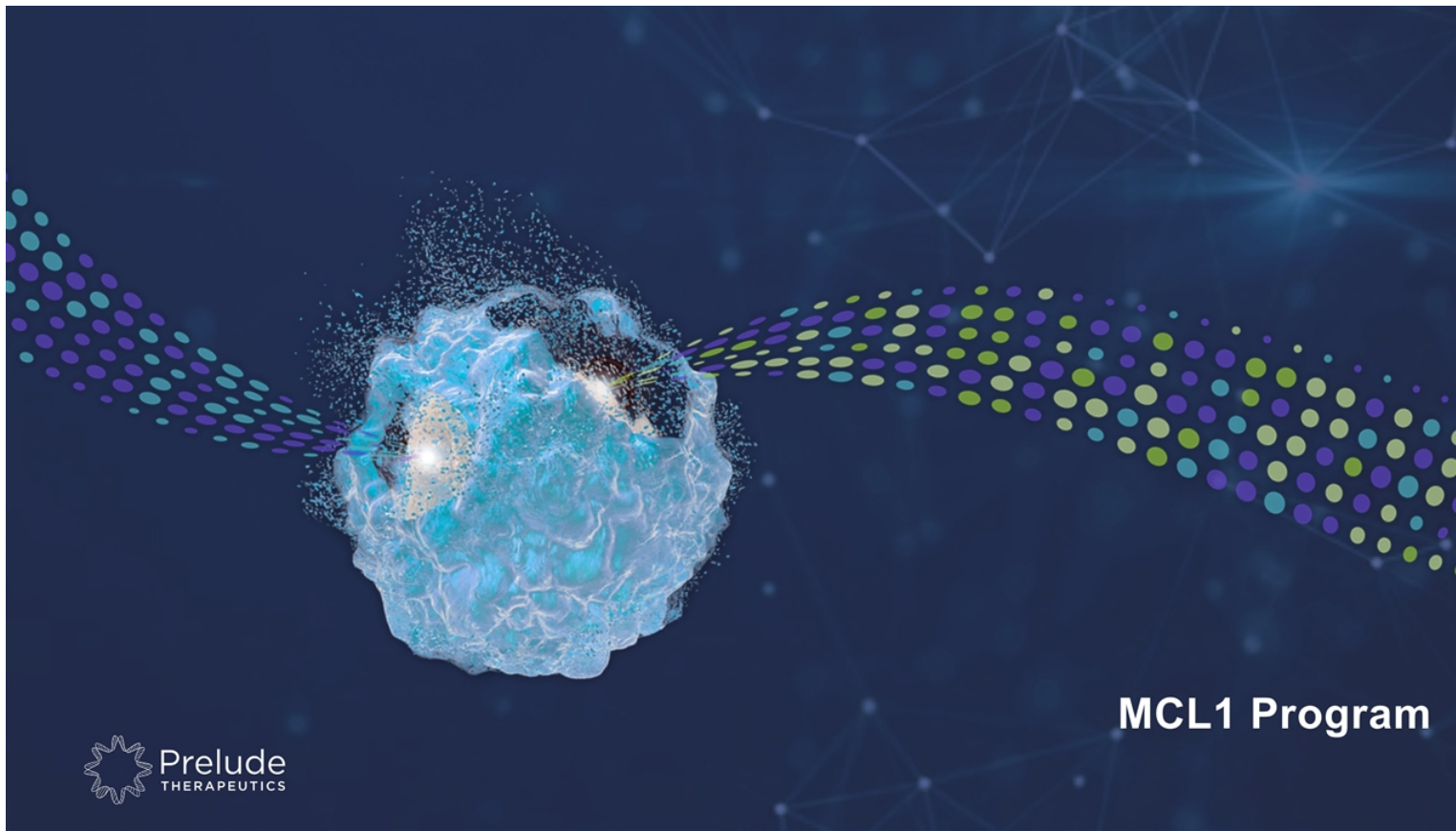
- In September 2020, at patient's first follow-up MRI evaluation (week 7) lesion measured 13 mm x 6 mm (**66% reduction**)
- Follow-up MRI at week 18 confirmed a partial response (PR) per RANO criteria and an **improved regression of 77% from baseline**
- As of December 16, 2020, patient received five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



PRT811 Expands PRMT5 Opportunity into CNS Cancers

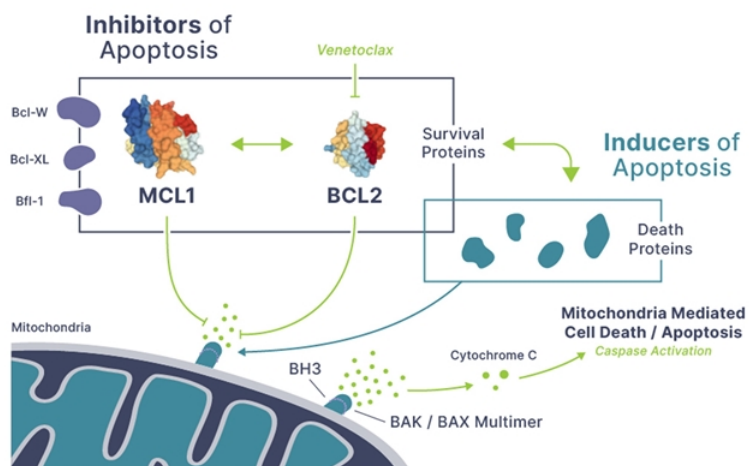
PRMT5

		US Market Opportunity
Scientific Rationale	Tumor Types	
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





- 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

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

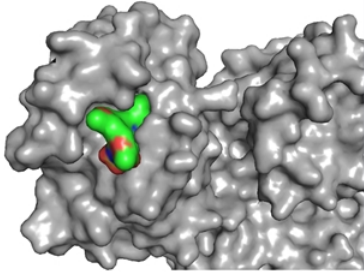
- Phase 1 dose escalation ongoing; expansion cohorts expected 2H2021 (oral)
- Phase 1 in solid tumors to commence 1H2021 (IV)

PRT1419: Potential Leading MCL1 Inhibitor

MCL1

Highly Potent Binding to MCL1

Prelude compounds are competitive inhibitors of BIM binding

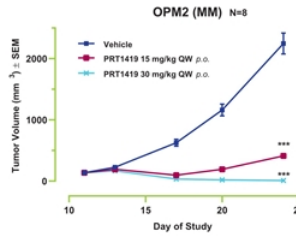
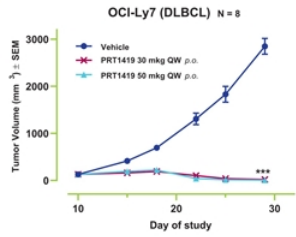
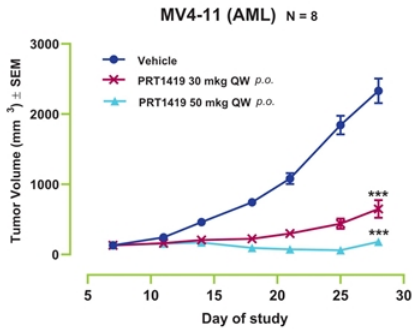


Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC ₅₀ (nM)	150	31	4.5	80
Whole Blood IC ₅₀ (nM)	1800	320	430	210
Caco-2 (x10 ⁻⁶ cm/s)	6	<0.1	0.2	11
Human Hepat. Cl (%HBF)	42	ND	ND	71
Solubility at pH 7.4 (µg/mL)	13	ND	ND	>1000
Route of Administration	IV	IV	IV	Oral/IV

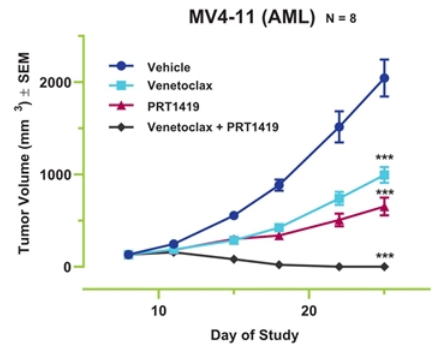
PRT1419 Demonstrated Preclinical Activity as Monotherapy and in Combination

MCL1

Monotherapy



Combination



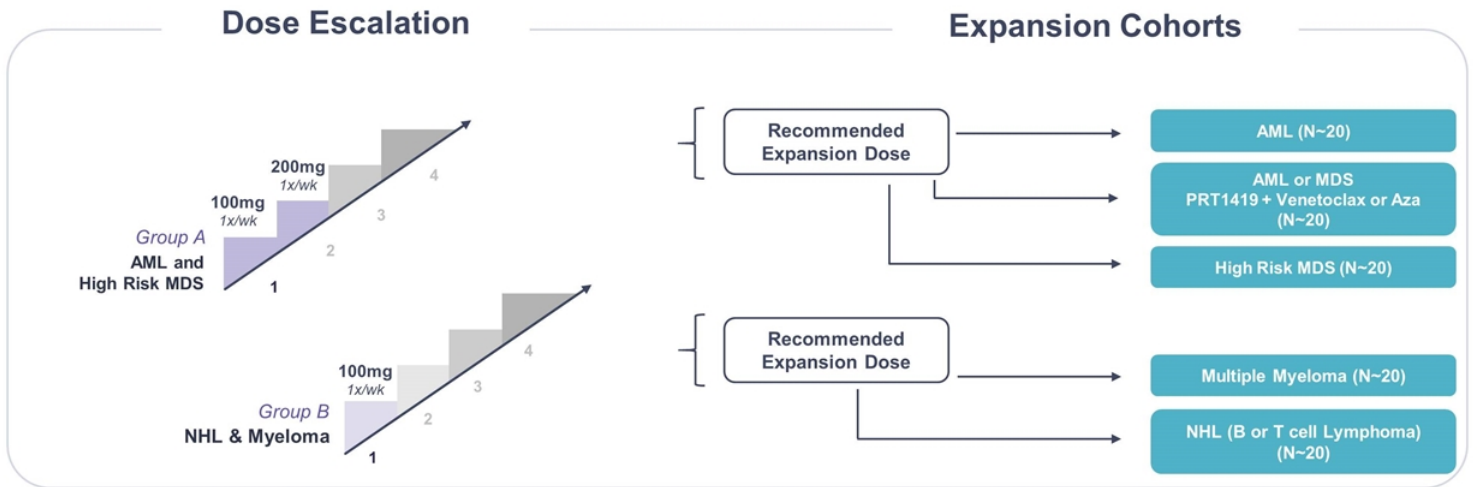
Dose-dependent activity with tumor regression at once-weekly, oral dosing in hematological tumor models

Oral PRT1419 Phase 1 Clinical Trial

Phase 1 Initiated in 2H2020

MCL1

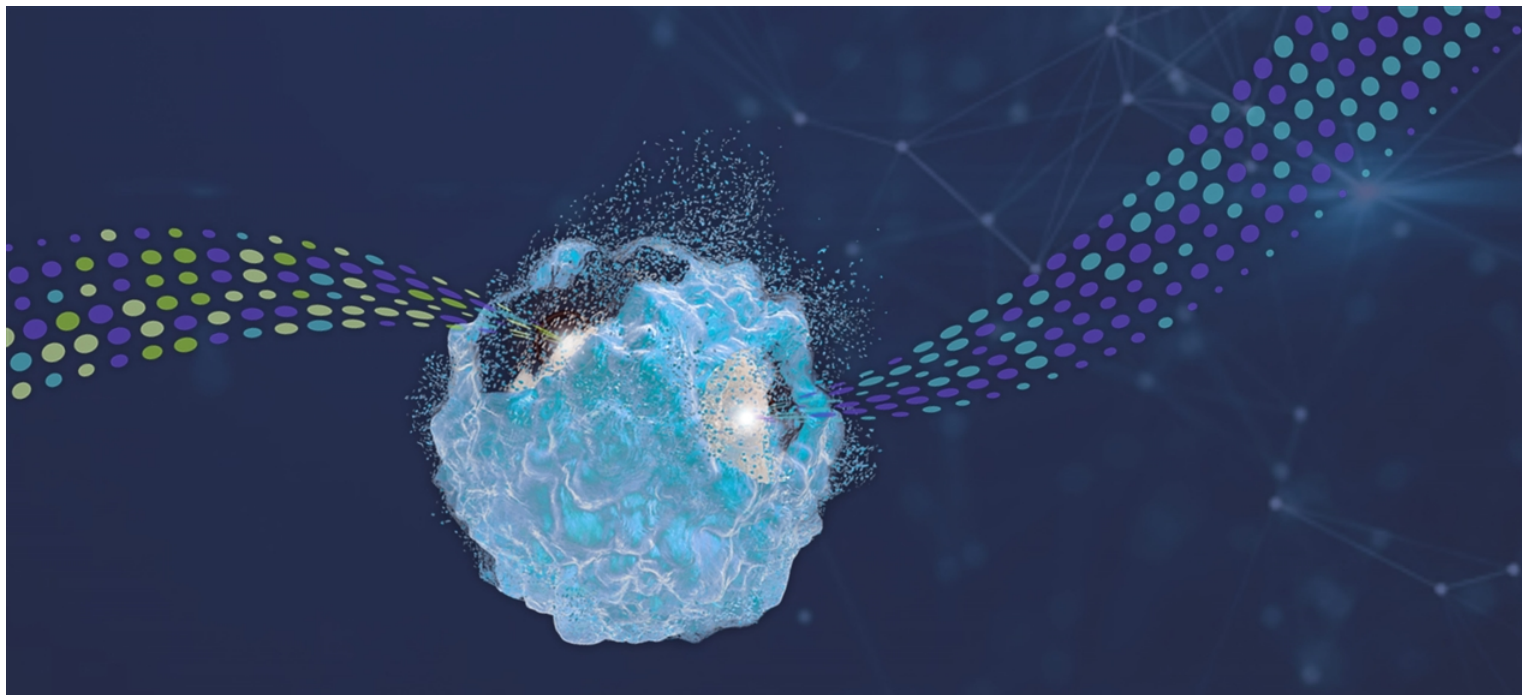
2021



Status as of December 16, 2020

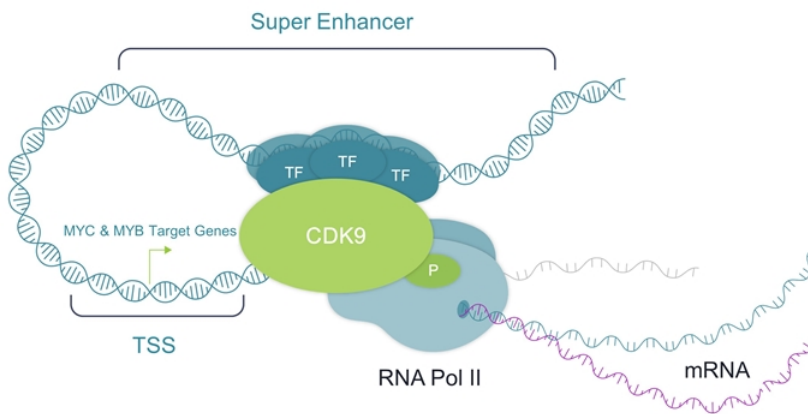


Phase 1 dose escalation ongoing; only Grade 1-2 AEs observed



Preclinical Programs

CDK9, SMARCA2



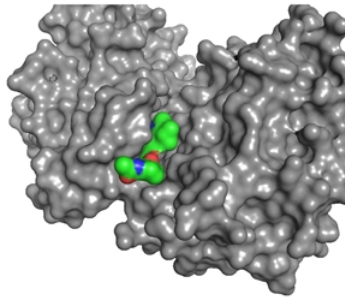
- CDK9 phosphorylates RNA Pol II and regulates transcription
- Regulates expression of several immediate early genes driving oncogenesis and resistance (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
 - Lack of selectivity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

PRT2527: 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



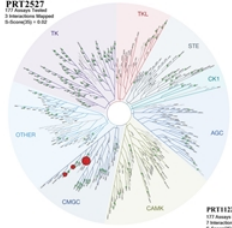
PRT2527 demonstrated improved potency and kinase selectivity relative to competitor compounds in preclinical studies

CDK9 Inhibitor Candidate: PRT2527

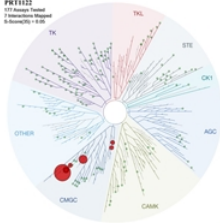
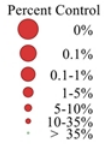
CDK9

Improved Selectivity

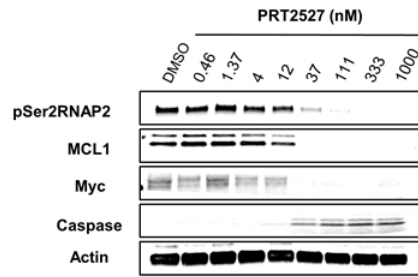
PRT2527



AZD4573

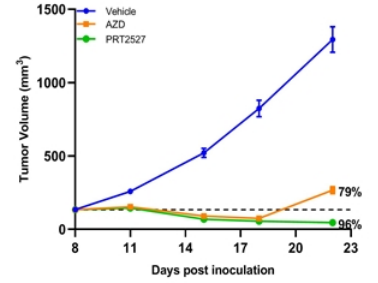


Potent in Vitro Activity



Sustained Regressions at Well-Tolerated Doses in Vivo

MV4-11 (AML)



SMARCA2 Targeted Degradator 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

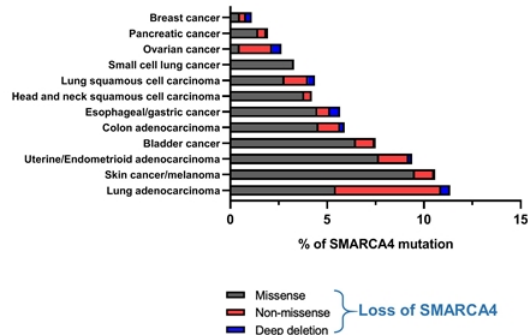
SMARCA4

Dysfunctional SMARCA4



Tumor Cell Death

Loss of SMARCA4 Leads to SMARCA2 Dependency

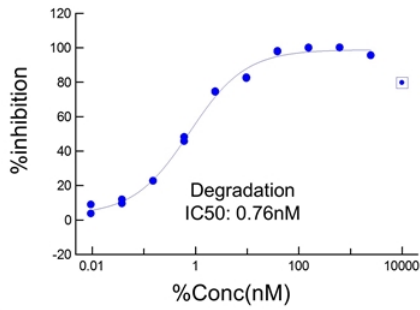


Opportunity to target 10 – 12% NSCLC with SMARCA4 deletions

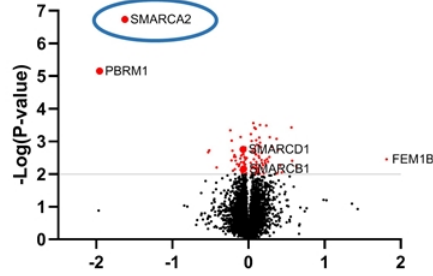
Prelude Discovered Selective sub-nM SMARCA2 Degraders

SMARCA2

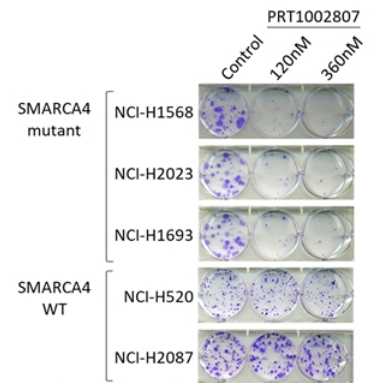
Sub-Nanomolar Potency for SMARCA2 Degradation



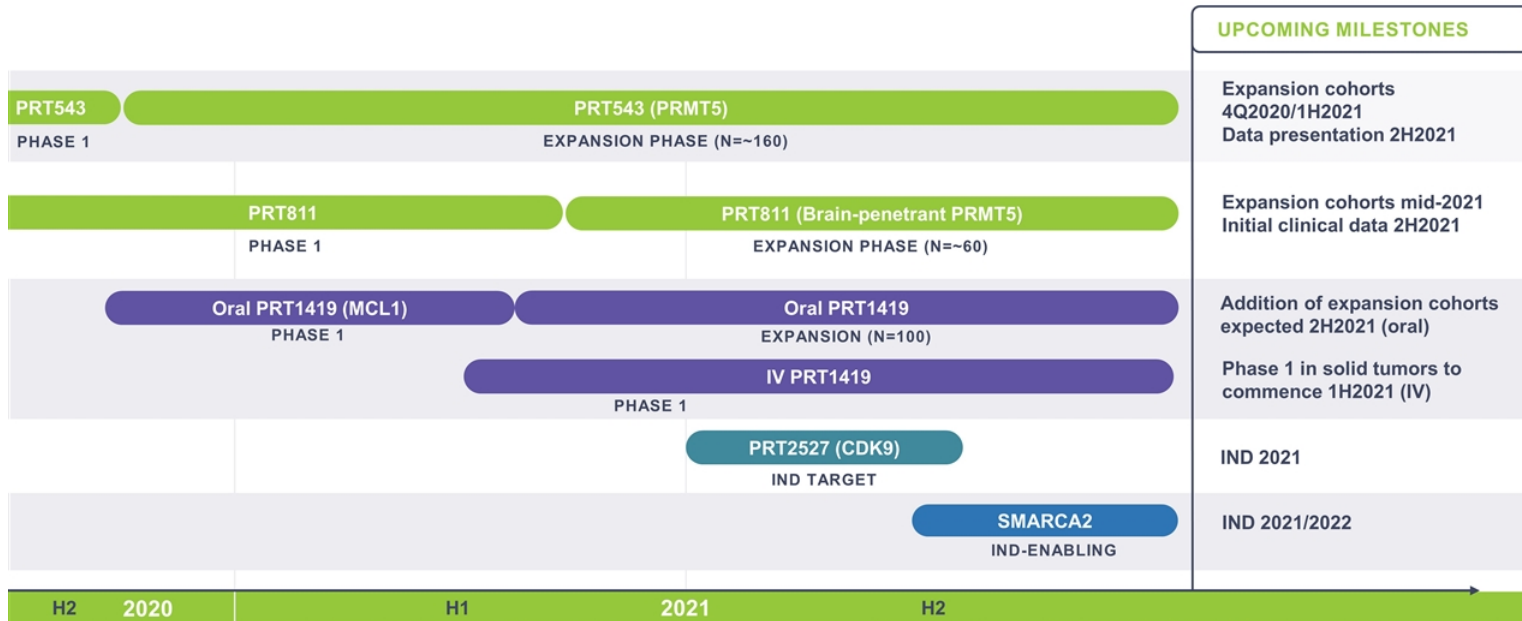
Highly Selective for SMARCA2 Degradation



Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality



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



Prelude
THERAPEUTICS

Thank You

