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): January 4, 2021

Prelude Therapeutics Incorporated
(Exact Name of Registrant as Specified in its Charter)

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

200 Powder Mill Road **Wilmington, Delaware**	**19803**
(Address of principal executive offices)	**(Zip Code)**

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

Not Applicable
(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 per share	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 2.02 Results of Operations and Financial Condition.

On January 4, 2020, Prelude Therapeutics Incorporated (the "***Company***") filed a registration statement on Form S-1 (the "***Registration Statement***") with the Securities and Exchange Commission (the "***SEC***") in connection with a proposed public offering of shares of the Company's common stock by the Company (the "***Offering***"), which contained information regarding the Company's preliminary estimates of certain financial metrics for the three months and fiscal year ended December 31, 2020. In the Registration Statement, the Company disclosed that it expects to report that the Company had cash and cash equivalents of approximately $218.3 million as of December 31, 2020.

The Company's audited financial statements for the fiscal year ended December 31, 2020 are not yet available. Accordingly, the preliminary financial metrics and results included in the Registration Statement are estimates subject to the completion of the Company's financial closing procedures and any adjustments that may result from the completion of the audit of the Company's financial statements. The preliminary results may differ materially from the actual results that will be reflected in the Company's audited financial statements when they are completed and publicly disclosed.

In accordance with General Instruction B.2. of Form 8-K, the information in this Item 2.02 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 liability of that section, nor shall it be deemed incorporated by reference in any of the Company's filings under the Securities Act of 1933, as amended (the "***Securities Act***"), whether made before or after the date hereof, regardless of any incorporation language in such a filing, except as expressly set forth by specific reference in such a filing.

Item 7.01 Regulation FD Disclosure.

The Company is furnishing its corporate presentation which it intends to use in conferences and meetings. The full copy of the Company's corporate presentation is filed as Exhibit 99.1 hereto.

The information furnished in Exhibit 99.1 shall not be deemed "filed" for purposes of Section 18 of 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 except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Corporate Presentation dated January 2021

Forward-Looking Statements

This Current Report on Form 8-K contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995 and other federal securities laws. Any statements contained herein that do not describe historical facts, including, but not limited to, statements regarding the Company's expected cash and cash equivalents as of December 31, 2020, are forward-looking statements that involve risks and uncertainties that could cause actual results to differ materially from those discussed in such forward-looking statements. Such risks and uncertainties include, among others, the risks identified in the Company's filings with the SEC, including its Quarterly Report on Form 10-Q for the quarter ended September 30, 2020, filed with the SEC on November 10, 2020, the Registration Statement related to the Offering, and subsequent filings with the SEC. Any of these risks and uncertainties could materially and adversely affect the Company's results of operations, which would, in turn, have a significant and adverse impact on the Company's stock price. The Company cautions you not to place undue reliance on any forward-looking statements, which speak only as of the date they are made. The Company undertakes no obligation to update publicly any forward-looking statements to reflect new information, events or circumstances after the date they were made or to reflect the occurrence of unanticipated events.

SIGNATURES

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 thereunto duly authorized.

Date: January 4, 2021

PRELUDE THERAPEUTICS INCORPORATED

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

Exhibit 99.1

Prelude THERAPEUTICS

Corporate Presentation

January 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).

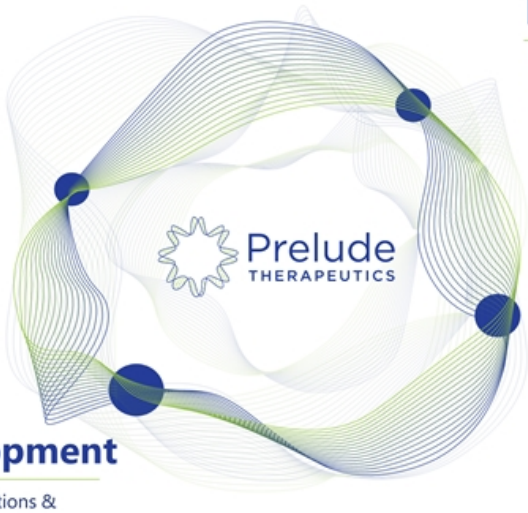
These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will 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 Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission for the fiscal quarter ended September 30, 2020.

Prelude Therapeutics Vision

Building a patient-focused precision oncology company

Discovery Engine

Powered by scientists with proven ability to deliver precision oncology medicines



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

Clinical Development

Highly selected patient populations & cancers with significant unmet need

Senior Management & Board of Directors

Experienced. Proven. Focused.

Kris Vaddi
PhD
Founder &
Chief Executive Officer

Founding member Incyte

Jakafi · olumiant · VELCADE · TABRECTA

Peggy Scherle PhD
Chief Scientific Officer

Incyte · Jakafi · olumiant · Pemazyre · TABRECTA

Andrew Combs PhD
EVP and
Head of Chemistry

Incyte · Jakafi · Parsaclisib

David Mauro MD, PhD
Chief Medical Officer

Bristol Myers Squibb · MERCK · ERBITUX · Pegintron · SPRYCEL

Deborah Morosini MD, MSW
EVP and
Chief of Clinical Affairs

LOXO ONCOLOGY · FOUNDATION MEDICINE · AstraZeneca · FOUNDATION MEDICINE · TAGRISSO osimertinib · Retevmo selpercatinib · VITRAKVI

Christopher Pierce MBA
EVP and
Chief of Business
Operations

LOXO ONCOLOGY · Pfizer · MILLENNIUM · VELCADE · XALKORI · Retevmo selpercatinib · VITRAKVI

Brian Piper MBA
Chief Financial Officer

aevi genomic medicine · Shire

Board of Directors

Paul Friedman, MD
CEO Madrigal
Former CEO Incyte

Mardi Dier
CFO ultragenyx
Former CFO, CBO PORTOLA

Victor Sandor, MD
Former CMO ARRAY

David Bonita, MD
General Partner OrbiMed

Kelvin Neu, MD
Partner
Baker Brothers Investments

Kris Vaddi, PhD
Founder & Chief Executive Officer

Prelude Therapeutics Corporate Highlights

3 INDs approved in 3 years; 3 clinical stage molecules

Highly productive target class agnostic discovery engine

Pipeline focused on differentiated and validated targets
- 1 IND filed each year in 2018, 2019, and 2020
- At least 1 additional IND anticipated in 2021
- 1 IND planned every 12 – 18 months

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

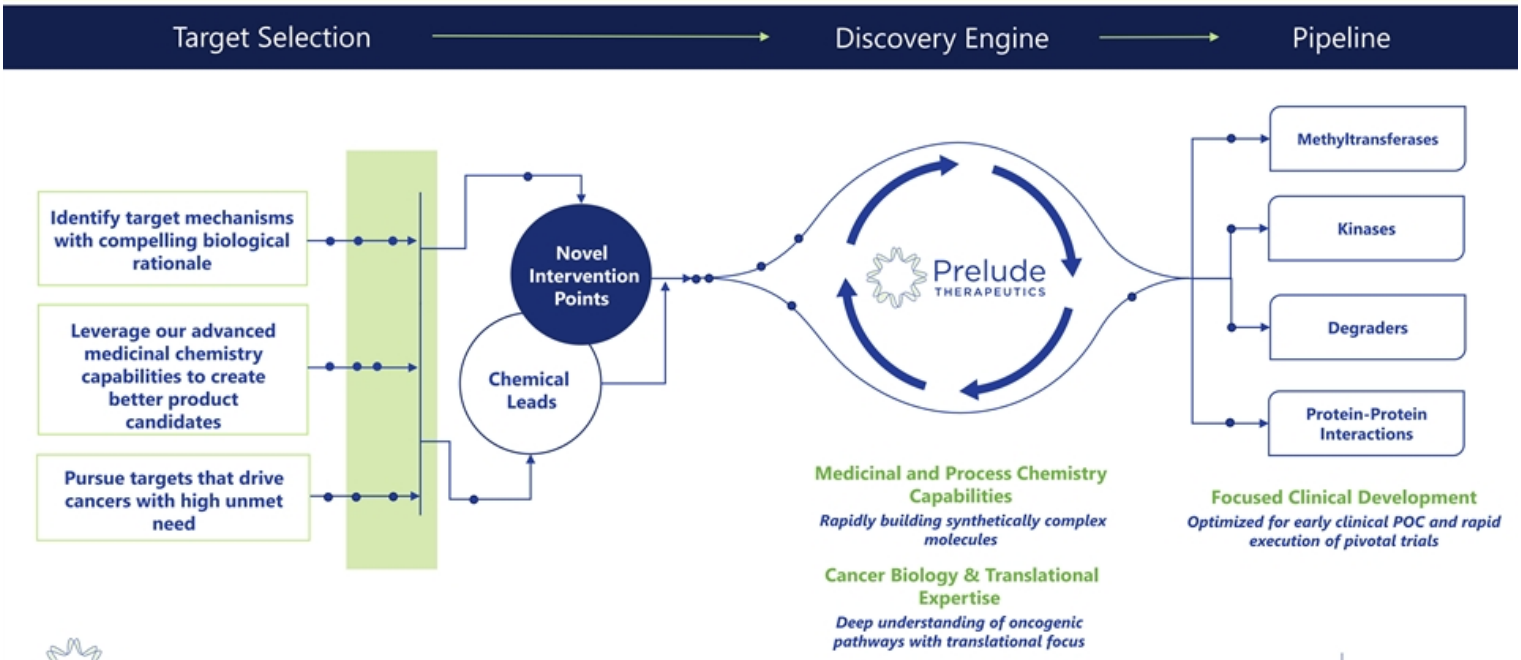
Compelling market opportunities across multiple tumor types

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

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



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+)						• Expansion cohorts 4Q2020/1H2021 • Data presentation 2H2021	Prelude THERAPEUTICS
	Selected Myeloid Malignancies (incl. MF and MDS)							
PRT811* (Brain Penetrant PRMT5)	GBM and CNS Metastatic Cancers						• Expansion cohorts 1H2021 • Initial clinical data YE2021	Prelude THERAPEUTICS
PRT1419* (MCL1)	Selected Hematological Malignancies						• Expansion cohorts 2H2021	Prelude THERAPEUTICS
PRT2527 (CDK9)	Selected Solid and Hematological Malignancies						• IND 2021	Prelude THERAPEUTICS
PRT-SCA2 (SMARCA2)	Multiple Genomically Selected Cancers						• IND 2021/2022	Prelude THERAPEUTICS
PRT-K4 (Kinase)	Solid Tumors						• IND-enabling 2021	Prelude THERAPEUTICS

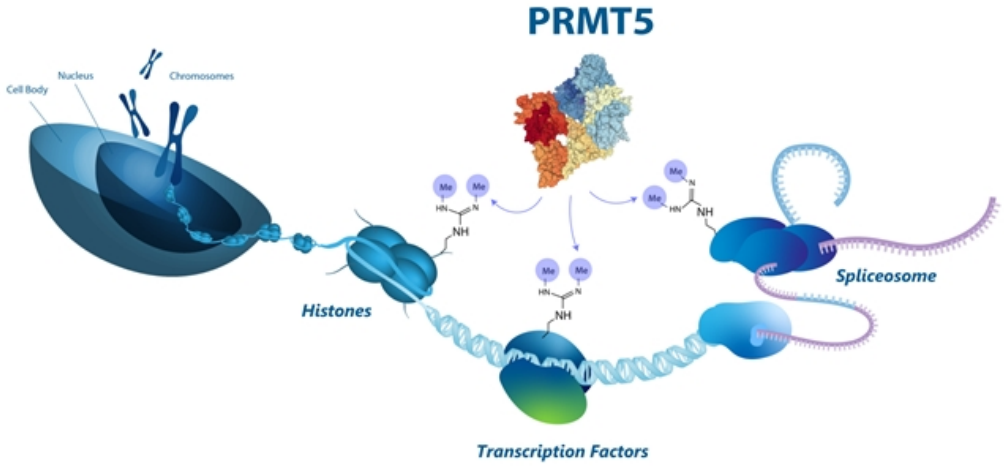
** Currently in Phase 1 dose escalation*

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

PRMT5 Programs

PRMT5 Pathway Drives Oncogenesis and Resistance

Regulates transcription of genes linked to cancer cell growth and proliferation



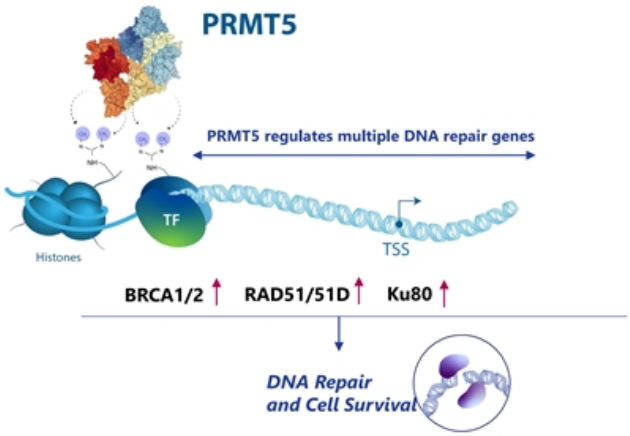
- ↑ Cell cycle genes
- ↑ Cancer metabolism
- ↓ Tumor suppressors
- ↑ Oncogenes
- ↑ Proliferative signaling

PRMT5

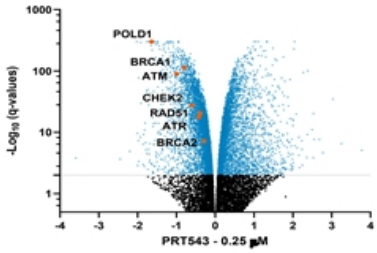
PRMT5 inhibition can be leveraged to potentially treat a broad range of solid tumors and hematologic malignancies

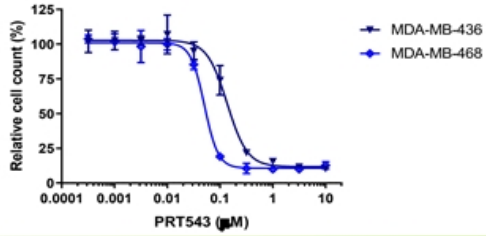
PRMT5 Regulates Drivers of DNA Damage Repair

PRMT5 promotes DNA repair and cell survival



PRMT5 inhibition suppresses DNA repair gene expression & growth of HRD+ cell lines





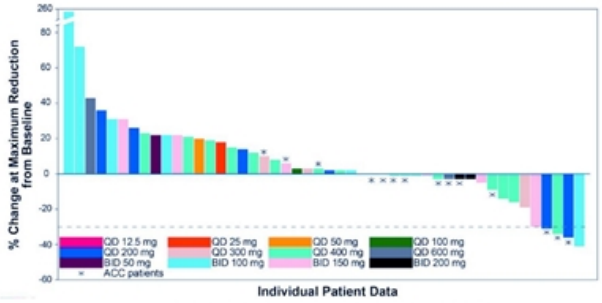
PRMT5

PRMT5 inhibition potentially drives synthetic lethality in HRD+ cancers

PRMT5 Pathway Is Clinically Validated in Multiple Cancers by GSK'595

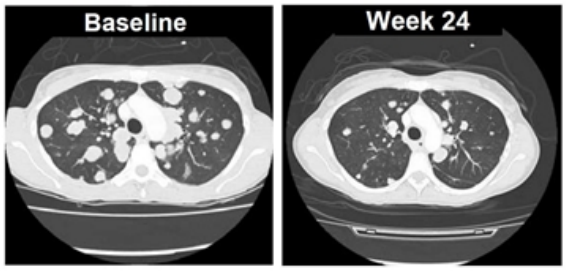
- **21% OR and mPFS of 11.2 mos observed with GSK'595 in Adenoid cystic carcinoma (ACC)**
  - Highly underserved cancer in which typical OR is <10% and PFS is 4 – 6 mos
- **Objective responses reported in other cancers; currently in dose expansion phase in multiple tumors**

PRMT5 Inhibition Demonstrated Objective Responses



Siu, Lillian L., et al. Annals of Oncology 30:Supplement_5 (2019): mdz244.

Confirmed PR in ACC



Source: GSK595, ESMO 2019

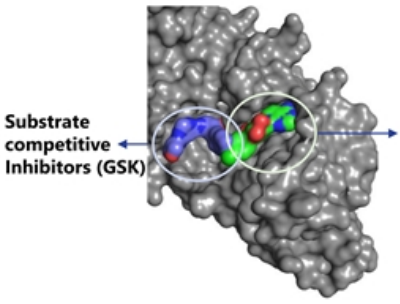
PRMT5

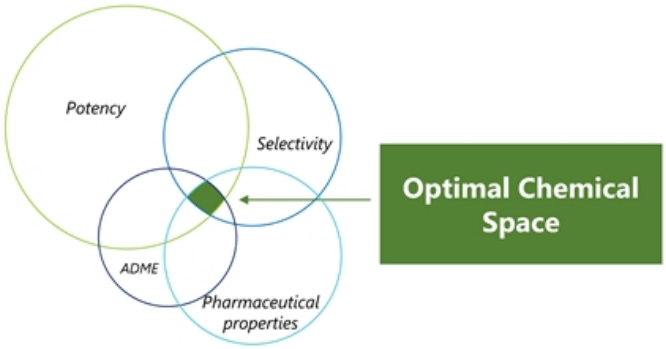
ACC offers potential fast-to-market opportunity for Prelude PRMT5 inhibitors

Prelude PRMT5 Program

Optimized for a well-balanced and differentiated profile

Differentiating Mechanism of Action





PRMT5

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

PRT543 – Opportunity for Accelerated Development Path

Potential best-in-class PRMT5 inhibitor

PRMT5

Differentiated PRMT5 Inhibitor

Highly selective

Highly 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

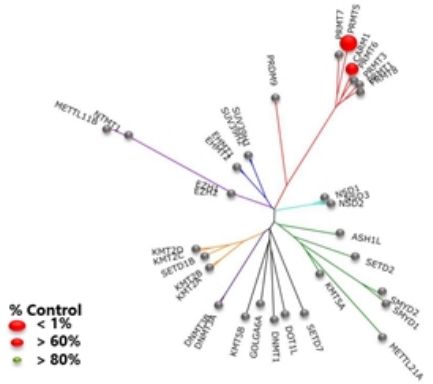
Enrollment began in select solid tumor expansion cohorts in 4Q2020 and expect to commence in select myeloid malignancies in early 2021

Potential for accelerated approval pathway

PRT543 – A Potent, Selective and Oral PRMT5 Inhibitor Candidate

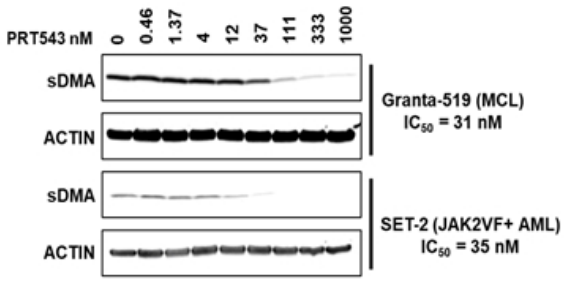
PRT543 is Highly-Selective

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



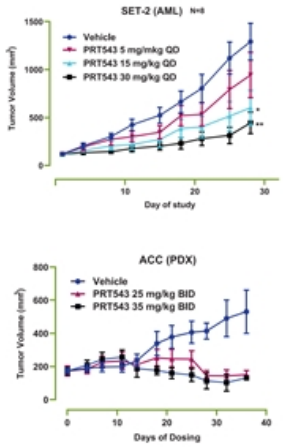
~50% reduction in plasma sDMA correlates with efficacy in preclinical models

PRMT5

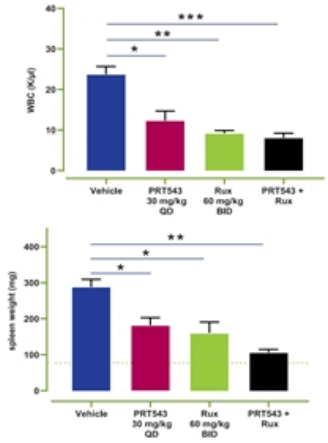
PRT543 demonstrated optimized potency, dose-dependent PD, and selectivity offering best-in-class potential

PRT543 Demonstrated Broad Preclinical Activity

Monotherapy



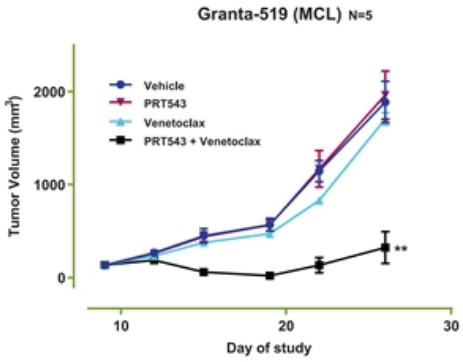
JAK2V617F MPN Model



Oral administration of PRT543 as monotherapy and in combination with ruxolitinib led to significant decrease in spleen size in the JAK2VF bone marrow transplant model of MF. Data represent mean ± SEM. Dotted line indicates mean spleen weight of WT transplanted mice.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. vehicle by Mann-Whitney U test.

Combination



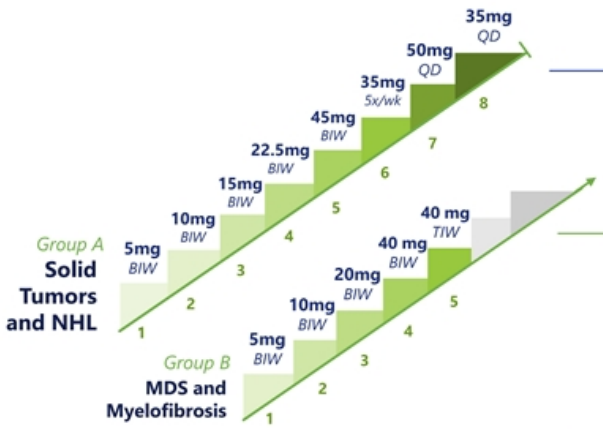
PRMT5

Dose-dependent activity as single agent and in combination in heme and solid tumor models

PRT543 Phase 1 Clinical Trial as of September 1, 2020

4Q2020 / Early 2021

Dose Escalation



Expansion Cohorts

Recommended Expansion Dose

Recommended Expansion Dose

Expansion cohorts in selected patients

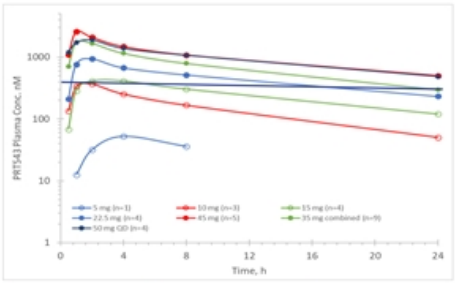
- Adenoid Cystic Carcinoma (N~20)
- Homologous Recombination Deficient (HRD+) Solid Tumors (N~20)
- Solid Tumors with Spliceosome Mutations (N~20)
- Myelofibrosis Monotherapy (N~20)
- Myelofibrosis PRT543 + Ruxolitinib (N~20)
- Myeloid Malignancies with Spliceosome Mutations (N~20)

PRMT5

Potential for PoC in multiple cancers in 2021

PRT543 Phase 1 – Interim PK/PD Results Demonstrated Predictable Profile as of September 1, 2020

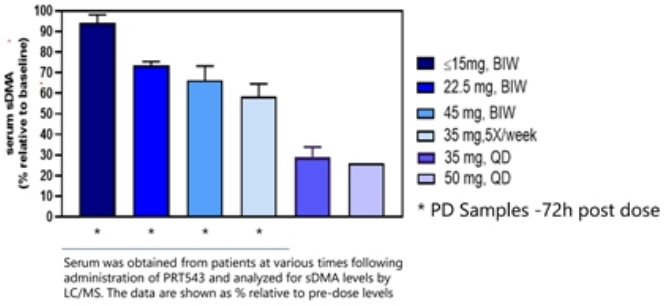
Dose-Proportional Increase in Exposure
(Day 1)



Parameter	35 mg (5x)	50 mg QD
C_{max} (nM)	1976	2130
$T_{1/2}$ (h)	7	16
AUC (μM.h/wk)	96	243

Trough Level target based on Preclinical models

Dose-Dependent Decrease in Serum sDMA



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

PRMT5

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

PRT543 Favorable Phase 1 Safety Profile as of September 1, 2020

- **Interim Safety data available for 41 patients**
  - 30 in Group A (solid tumors and NHL); 11 in Group B (myeloid malignancies)
- **AE profiles similar between patient groups**
  - Primarily GI and manageable with standard treatments
    - Diarrhea, nausea and fatigue
    - Mostly Grade 1-2
- **Discontinuations: No patients discontinued study therapy due to adverse events**
- **Reversible thrombocytopenia is the most common hematological toxicity**
  - Dose limiting in solid tumor cohort at 50 mg QD
  - No DLTs were seen at the 35mg QD dose; however, 3 of 5 patients experienced Grade 3 thrombocytopenia and were dose reduced to 35mg 5x weekly dose
  - Only 1 of 8 patients has experienced Grade 3 thrombocytopenia at 35 mg 5x weekly dose
- **1 SAE related to study therapy (grade 4 thrombocytopenia)**
  - Platelets recovered to baseline levels after a one to two week drug holiday
- **Deaths: No drug-related deaths reported, 9 deaths reported total on study**

PRMT5

PRT543 demonstrated good tolerability at doses up to 35 mg

PRT543 Preliminary Efficacy Data as of September 1, 2020

Group A (Solid Tumors)

- Thirteen patients have received doses ≥35 mg 5x/week and are response evaluable per RECIST 1.1:
  - One patient demonstrated durable confirmed complete response (CR) in HRD+ high grade serous ovarian cancer
  - Four patients demonstrated stable disease (including an additional patient with HRD+ ovarian cancer)
  - Four patients showed progressive disease
  - Seven patients remain on study, of whom four are awaiting their first response assessment

Group B (Myeloid Malignancies)

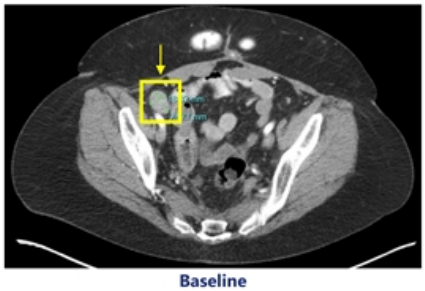
- Eleven patients have enrolled into Group B (nine MF and two MDS) and all are evaluable for response assessments as per IWG criteria:
  - One MF patient at the 20 mg b.i.w. dose level has demonstrated an objective response of clinical improvement and continues to receive therapy beyond one year to date
  - A second MF patient at the 40 mg t.i.w. dose level demonstrated ~66% decrease in TSS
  - Eight patients achieved a best response of SD; two additional patients remained on study for ~1 year

PRMT5

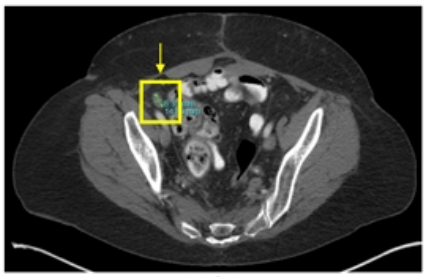
Durable Confirmed CR in HRD+ High Grade Serous Ovarian Cancer

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



Baseline



Week 8

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
- Patient has received 9 months of study therapy as of December 16, 2020 and remains in CR

PRMT5

Commencement of select solid tumor expansion cohorts began in 4Q2020 and additional solid tumor and myeloid malignancies cohorts expected to begin in early 2021

PRT543 Clinical Update as of December 16, 2020

- Phase 1 clinical trial of PRT543 has enrolled 61 patients (42 with advanced solid tumors, one with NHL, 11 with MF, and seven with MDS)
- Overall safety profile unchanged from the September 1, 2020 data cutoff and consistent between both Groups A and B
  - Majority of drug related adverse events continue to be grade 1-2 with anemia and thrombocytopenia being the most common grade 3-4 adverse events
  - 24 SAEs have been reported amongst 11 patients, with 3 individual SAEs deemed drug related
  - Thrombocytopenia remains only dose-limiting toxicity
  - No patients have discontinued study due to adverse events
- ACC expansion cohort initiated at a dose/schedule of 35mg 5x weekly, with opportunity for intra-patient dose adjustment
- Both 25mg QD and 50mg 5x weekly doses/schedules explored in the escalation phase, which may enable a dose titration algorithm in expansion
- Enrollment into additional solid tumor and myeloid malignancies cohorts is planned in early 2021

PRMT5

PRT543 Offers Broad Opportunity Across Tumor Types

Scientific Rationale	Tumor Types	US Market Opportunity
Transcriptional Regulation	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+
Splicing Dysregulation	Uveal Melanoma	**Uveal Melanoma:** 2,000 patients annually
Synthetic Lethality	Myeloid Malignancies (Myelofibrosis and MDS)	**MF:** ~12,000 intermediate/high risk patients **MDS:** 10,000 patients annually

PRMT5

PRT811 – Expanding PRMT5 Opportunity into CNS Cancers

Only clinical stage brain-penetrant PRMT5 inhibitor

PRMT5

Differentiated Brain-Penetrant PRMT5 Inhibitor

Highly selective

Highly 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

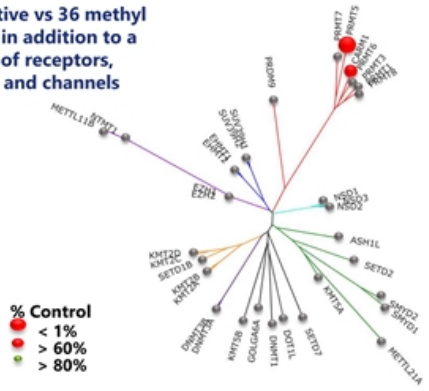
Phase 1 ongoing

Anticipated expansion in GBM and PCNSL 1H 2021

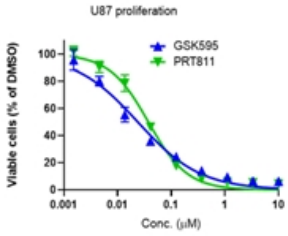
PRT811 – A Potent, Selective and Brain Penetrant PRMT5 Inhibitor Candidate

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**

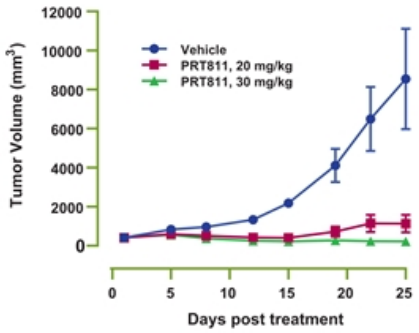
PRMT5

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

PRT811 – Strong Activity Demonstrated in GBM Models

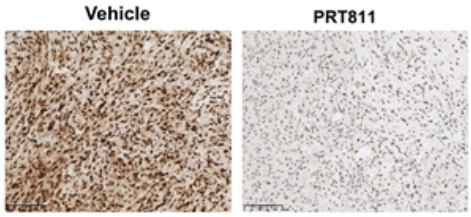
PRT811 in GBM Model

PRT811 Inhibited Tumor Growth in GBM Model



GBM Orthotopic Model - sDMA

PRT811 Decreased sDMA Levels in Orthotopic Brain Tumor Model



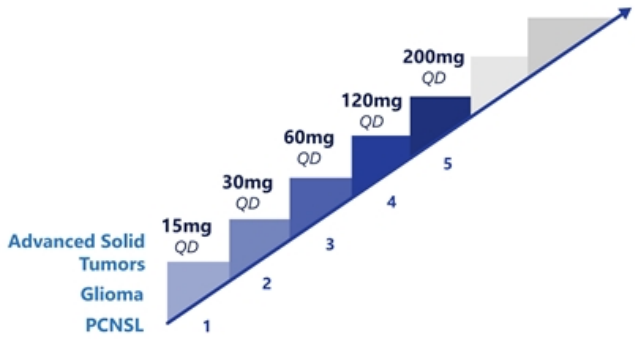
PRMT5

We believe PRT811 is uniquely positioned to potentially treat PRMT5 sensitive CNS cancers

PRT811 Phase 1 Clinical Trial as of September 1, 2020

Anticipated 1H2021

Dose Escalation*



PRMT5

* (2 wks on/1 wk off) 21 day cycles

Expansion Cohorts

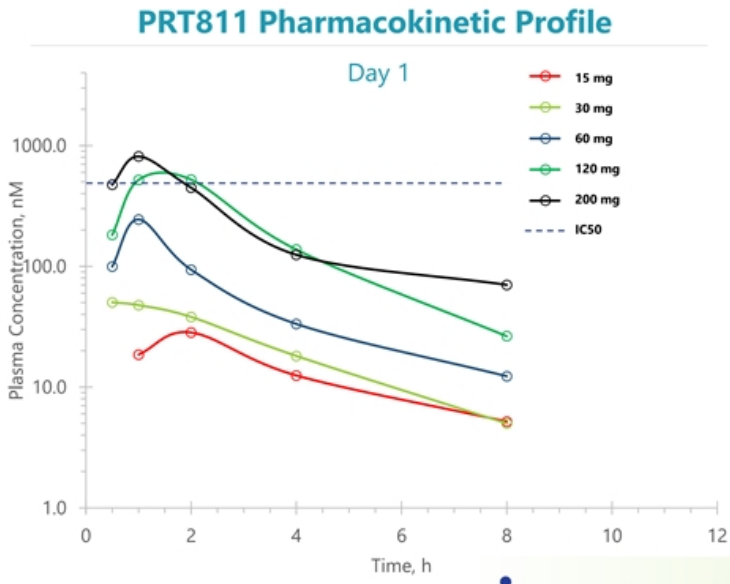
Recommended Expansion Dose

Expansion cohorts In selected patients

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

Potential PoC in CNS cancers in 2021

PRT811 Phase 1 Interim Results Demonstrated Dose-Dependent PK as of September 1, 2020



- Dose-dependent exposure
- Dose-dependent sDMA Inhibition; ~50% at 200 mg dose
- No unexpected AEs or drug-related SAEs
- Dose escalation ongoing

PRMT5

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

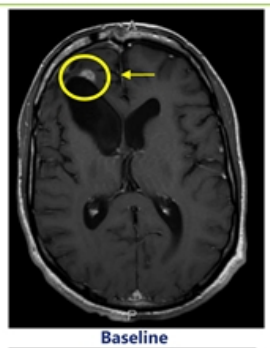
Confirmed PR in Glioblastoma Multiforme

Patient History

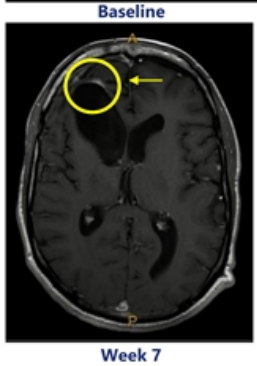
- Diagnosed with recurrent GBM and originally treated with surgery and chemoradiation with Temodar in July 2019
  - Patient has not been treated with steroids or Avastin, and clinical status is stable
- Presented with progressive disease in June 2020
- Enrolled in **200 mg (q.d. two weeks on/one week 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**
- Patient has received 5 months of study therapy as of December 16, 2020 and remains in PR and is clinically stable



Baseline



Week 7

PRMT5

PRT811 Clinical Update as of December 16, 2020

- Phase 1 clinical trial of PRT811 has enrolled 24 patients (eight with GBM and 16 with advanced solid tumors)
- Overall safety profile unchanged from the September 1, 2020 data cutoff
  - Four patients have each experienced one SAE, none of which attributed to study therapy
  - No dose limiting toxicities have been observed
  - One patient discontinued study therapy due to transient Grade 2 nausea
- 300mg QD dose cohort currently ongoing
- Remain on track to complete the dose escalation phase 1H21 and initiate expansion phase in cancers including GBM, PCNSL, and CNS metastatic solid tumors in the second half of 2021

PRMT5

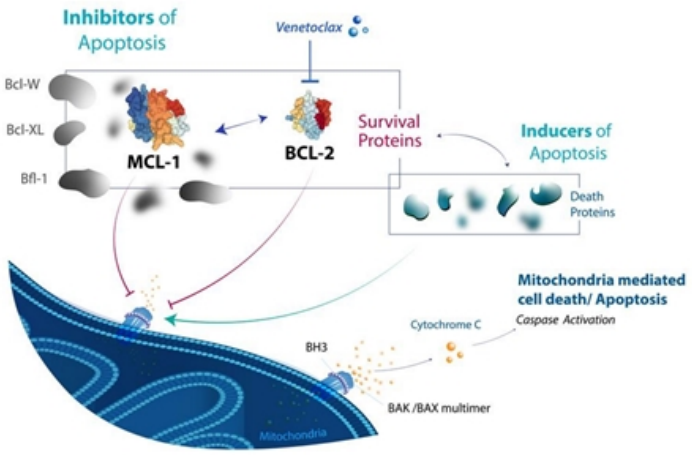
PRT811 Expands PRMT5 Opportunity into CNS Cancers

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

PRMT5

MCL1 Program

Prelude 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

MCL1

Significant opportunity in post-venetoclax setting

PRT1419: Oral Differentiated Clinical-Stage MCL1 Inhibitor Candidate

MCL1

MCL1 Inhibitor

Potent

Selective

Oral

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, permeability and intrinsic clearance

Potential Rapid Path to Market

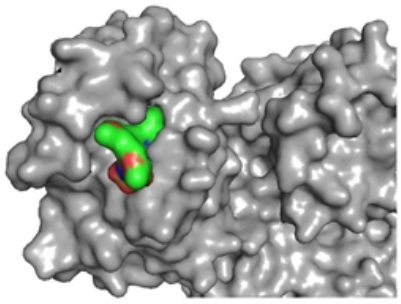
Phase 1 dose escalation ongoing

Anticipated expansion in MDS/AML with Venetoclax/Aza

PRT1419: Potential Leading Oral MCL1 Inhibitor

Highly Potent Binding to MCL1

Prelude compounds are competitive inhibitors of BIM binding



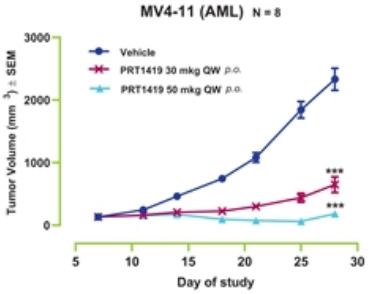
Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC_{50} (nM)	150	31	4.5	**80**
Whole Blood IC_{50} (nM)	1800	320	430	**210**
Caco-2 ($x10^{-6}$ cm/s)	6	<0.1	0.2	**11**
Human Hepat. Cl (%HBF)	42	ND	ND	**71**
Solubility at pH 7.4 (μg/mL)	13	ND	ND	**>1000**
Route of Administration	IV	IV	IV	**Oral/IV**

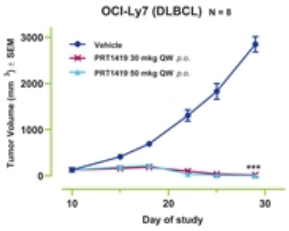
MCL1

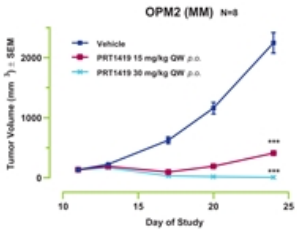
PRT1419 is a potent oral MCL1 inhibitor candidate with no preclinical evidence of cardiac toxicity

PRT1419 Demonstrated Preclinical Activity as Monotherapy and in Combination

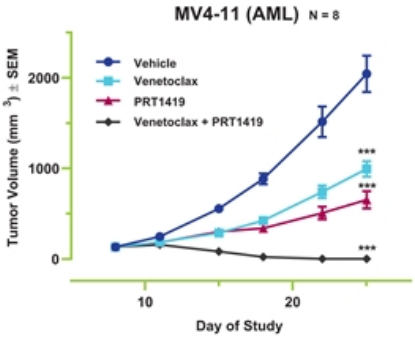
Monotherapy







Combination

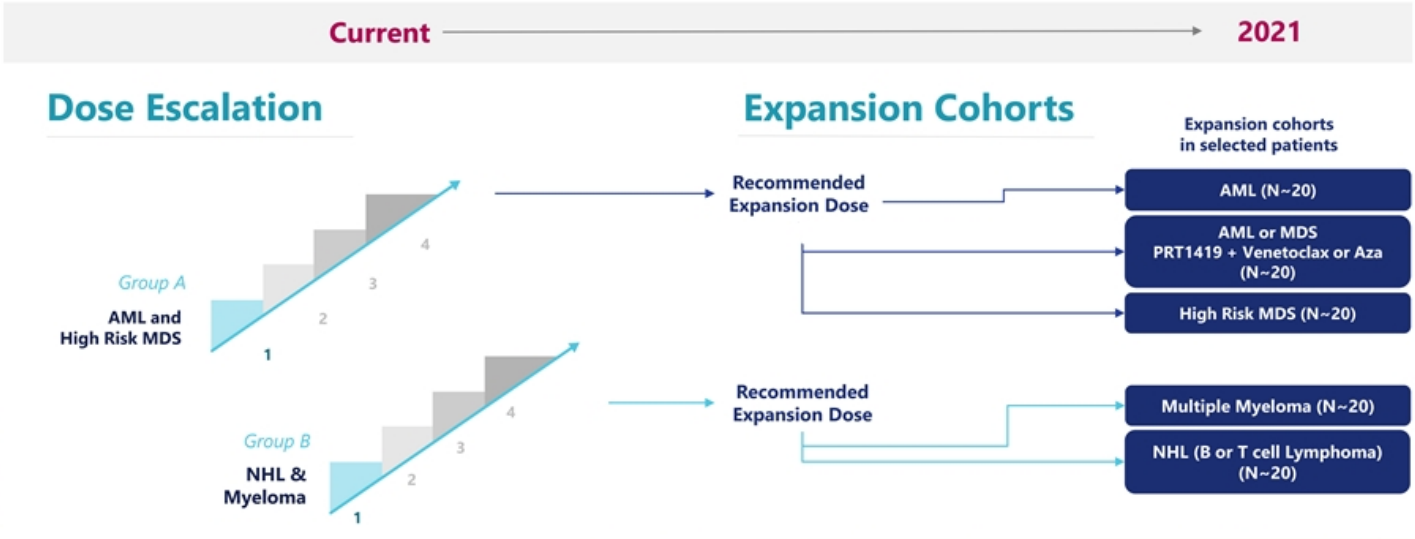


MCL1

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

PRT1419: Clinical Trial Program

Phase 1 Initiated in 2H2020



MCL1

Phase 1 escalation cohorts underway

PRT1419 Clinical Update as of December 16, 2020

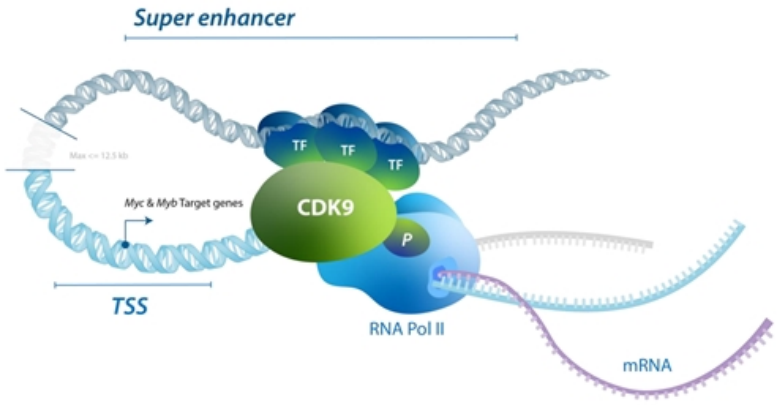
- Phase 1 clinical trial of PRT1419 has enrolled four patients with various hematological malignancies
- No adverse events above Grades 1 or 2 and no serious adverse events have been observed
- Currently enrolling AML and high-risk MDS patients into the second dose escalation cohort (200mg 1x weekly)

MCL1

Preclinical Programs

CDK9, SMARCA2

Prelude CDK9 Program



- **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

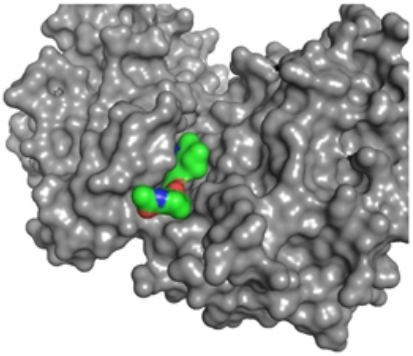
CDK9

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

PRT2527: Potent and Highly Selective CDK9 Inhibitor Candidate

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

CDK9

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

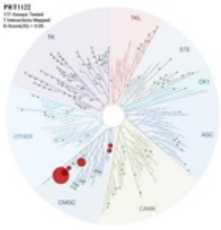
CDK9 Inhibitor Candidate: PRT2527

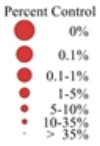
CDK9

Improved Selectivity

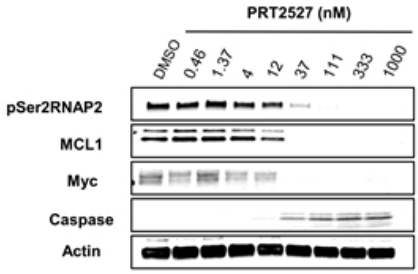
PRT2527

AZD4573

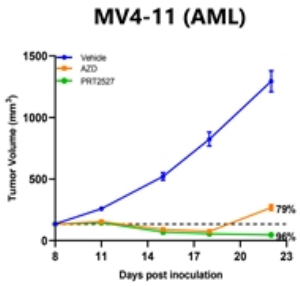




Potent in Vitro Activity



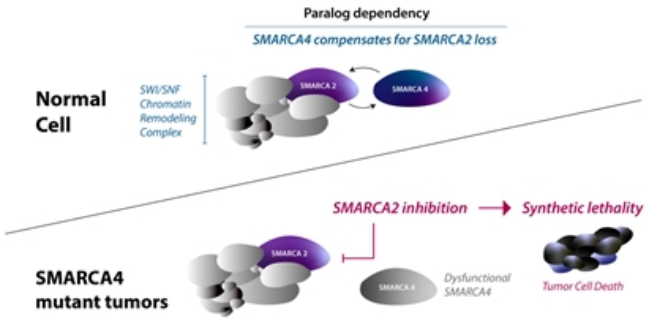
Sustained Regressions at Well-Tolerated Doses in Vivo



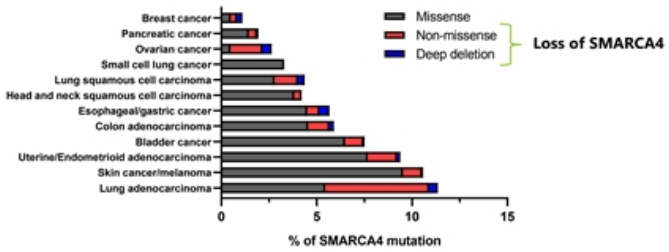
PRT2527 IND expected to be filed in 2021

SMARCA2 Targeted Degrader Program

SMARCA4 and SMARCA2 Regulate Chromatin Accessibility and Gene Expression



Loss of SMARCA4 Leads to SMARCA2 Dependency

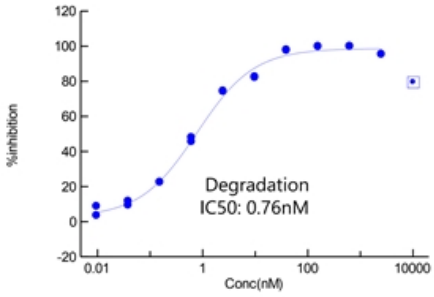


SMARCA2

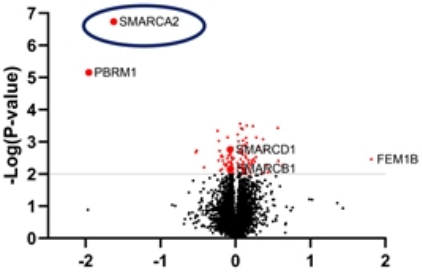
Opportunity to target 10 – 12% NSCLC with SMARCA4 deletions

Prelude Discovered Selective sub-nM SMARCA2 Degraders

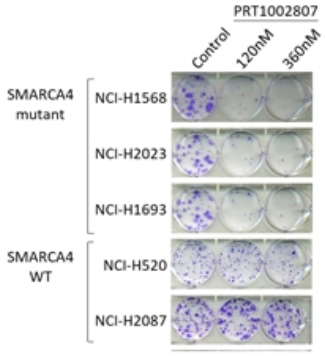
Sub-Nanomolar Potency for SMARCA2 Degradation



Highly Selective for SMARCA2 Degradation



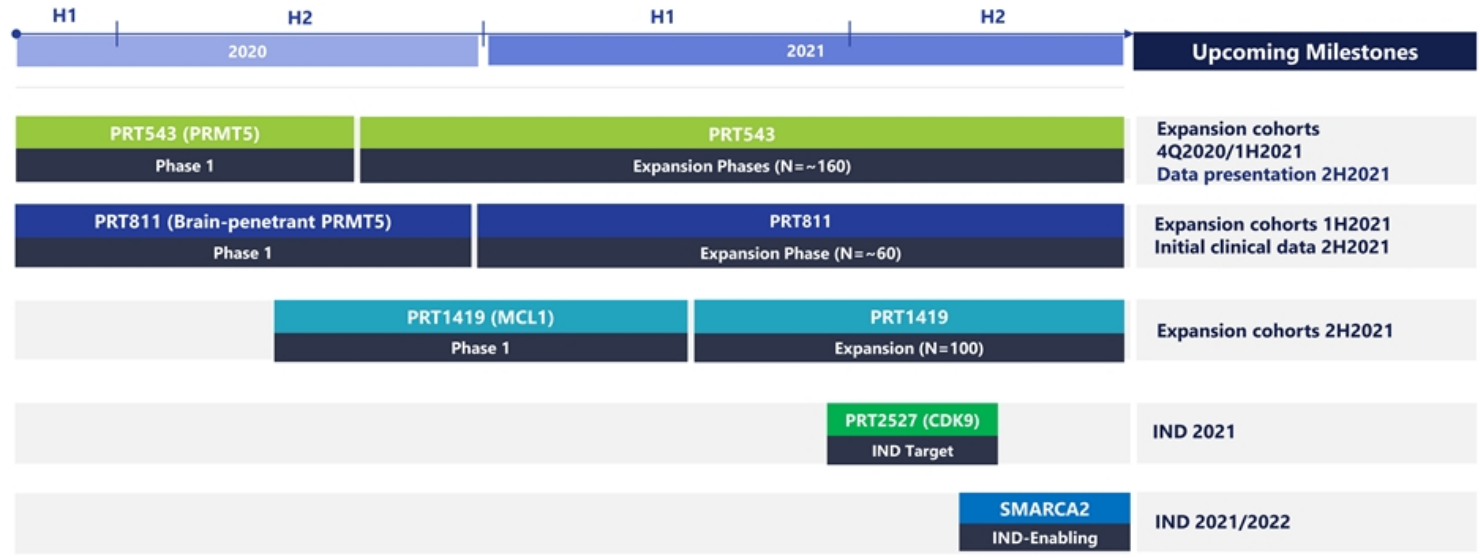
Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality



SMARCA2

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

Prelude Therapeutics Projected Milestones



Financial Highlights

Cash and Cash Equivalents

- $218.3 million as of December 31, 2020 (unaudited)
  - Includes $166.6 million net proceeds raised in September 2020 IPO

Shares Outstanding

- 43.7 million shares voting and non-voting common stock as of September 30, 2020
- 55.5 million shares fully diluted

Prelude Therapeutics Corporate Highlights

3 INDs approved in 3 years; 3 clinical stage molecules

Highly productive target class agnostic discovery engine

Pipeline focused on differentiated and validated targets
- 1 IND filed each year in 2018, 2019, and 2020
- At least 1 additional IND anticipated in 2021
- 1 IND planned every 12 – 18 months

Multiple wholly owned programs with fast-to-market potential

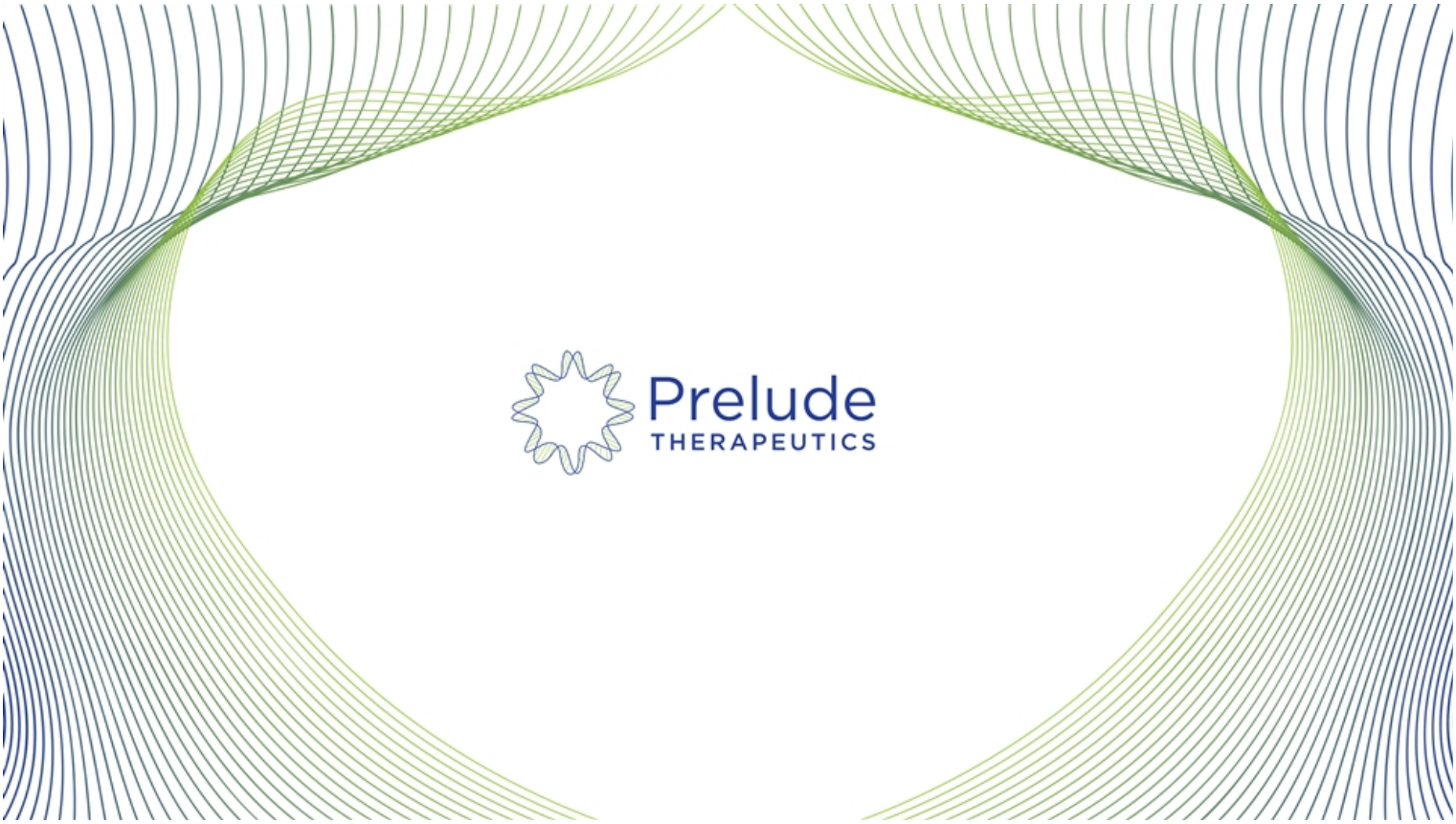
Lead programs, PRT543 & PRT811 (PRMT5) and PRT1419 (MCL1) target clinically validated mechanisms with differentiated product profile

Compelling market opportunities across multiple tumor types

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

Experienced leadership team with marquee investors and board members

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


Prelude
THERAPEUTICS