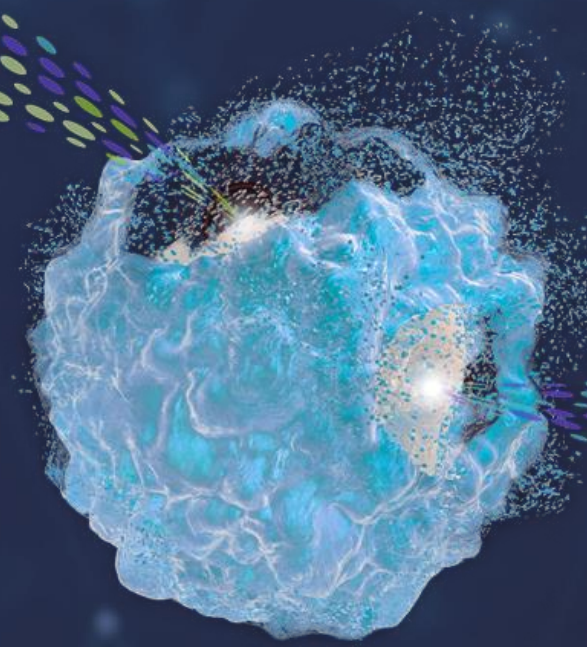
Prelude THERAPEUTICS

# Corporate Presentation

May 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 three months ended March 31, 2021.

# Prelude Therapeutics Vision

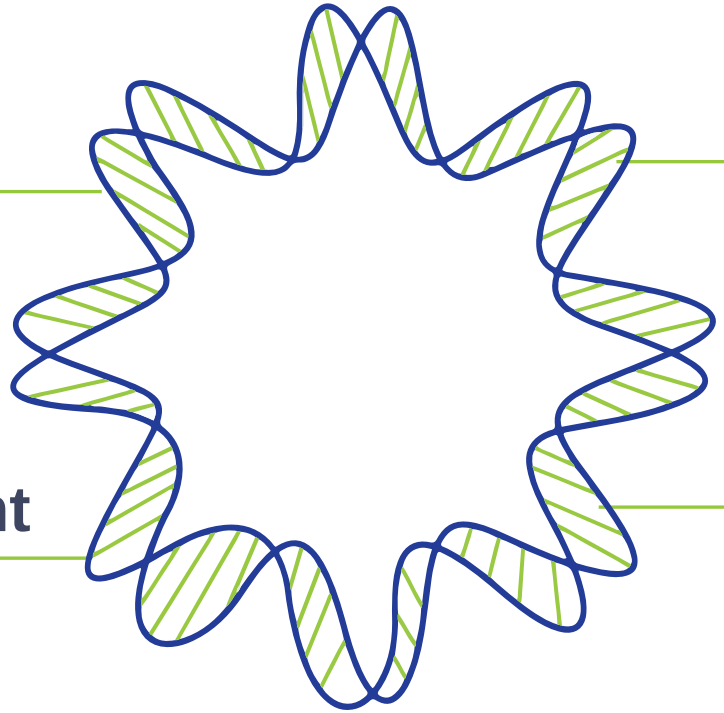
## Building a patient-focused precision oncology company

### Discovery Engine

Powered by scientists with a track record of delivering 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

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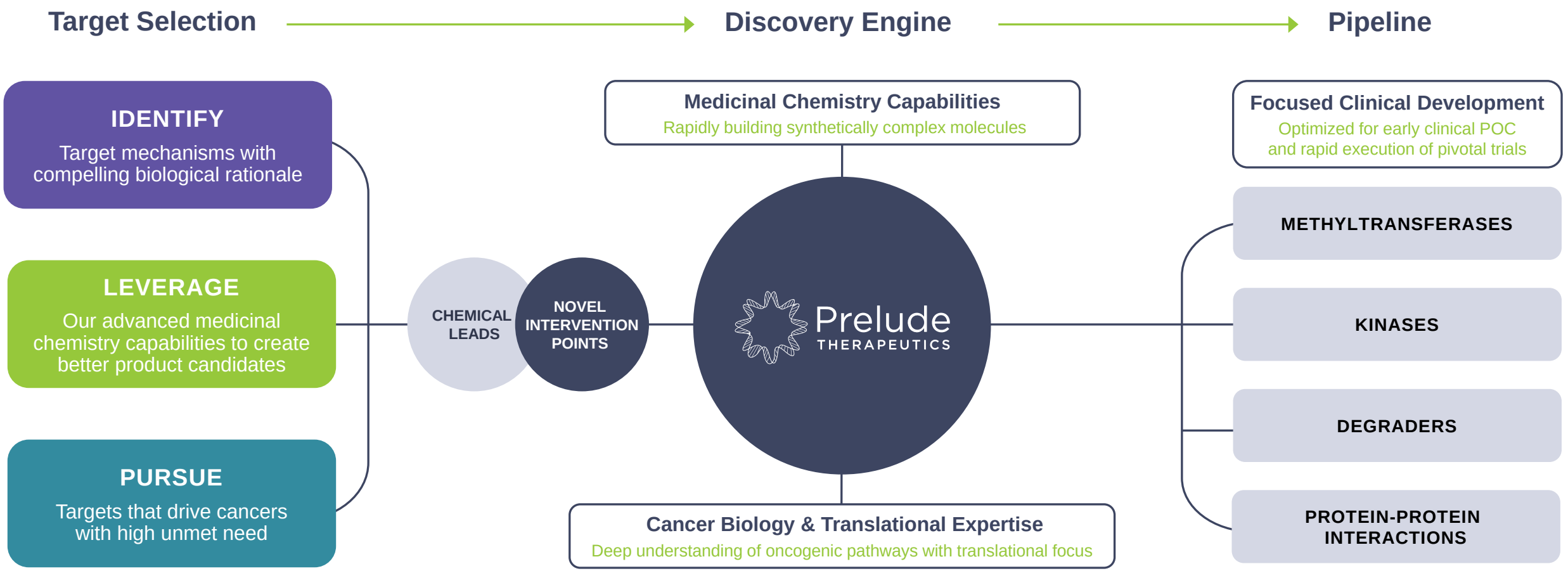
# Prelude Discovery and Development Approach



# 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+) | | | | | | • Multiple expansion cohorts ongoing<br>• Initial 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<br>• Initial clinical data 2H2021 | |
| **PRT1419** (MCL1) | Selected Hematological Malignancies *(oral formulation)* | | | | | | • Addition of expansion cohorts expected 2H2021 | |
| | Solid Tumors *(IV formulation)* | | | | | | • Phase 1 trial to commence mid-2021 | |
| **PRT2527** (CDK9) | Selected Solid and Hematological Malignancies | | | | | | • IND 2021 | |
| **PRT-SCA2** (SMARCA2) | Multiple Genomically Selected Cancers | | | | | | • IND 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

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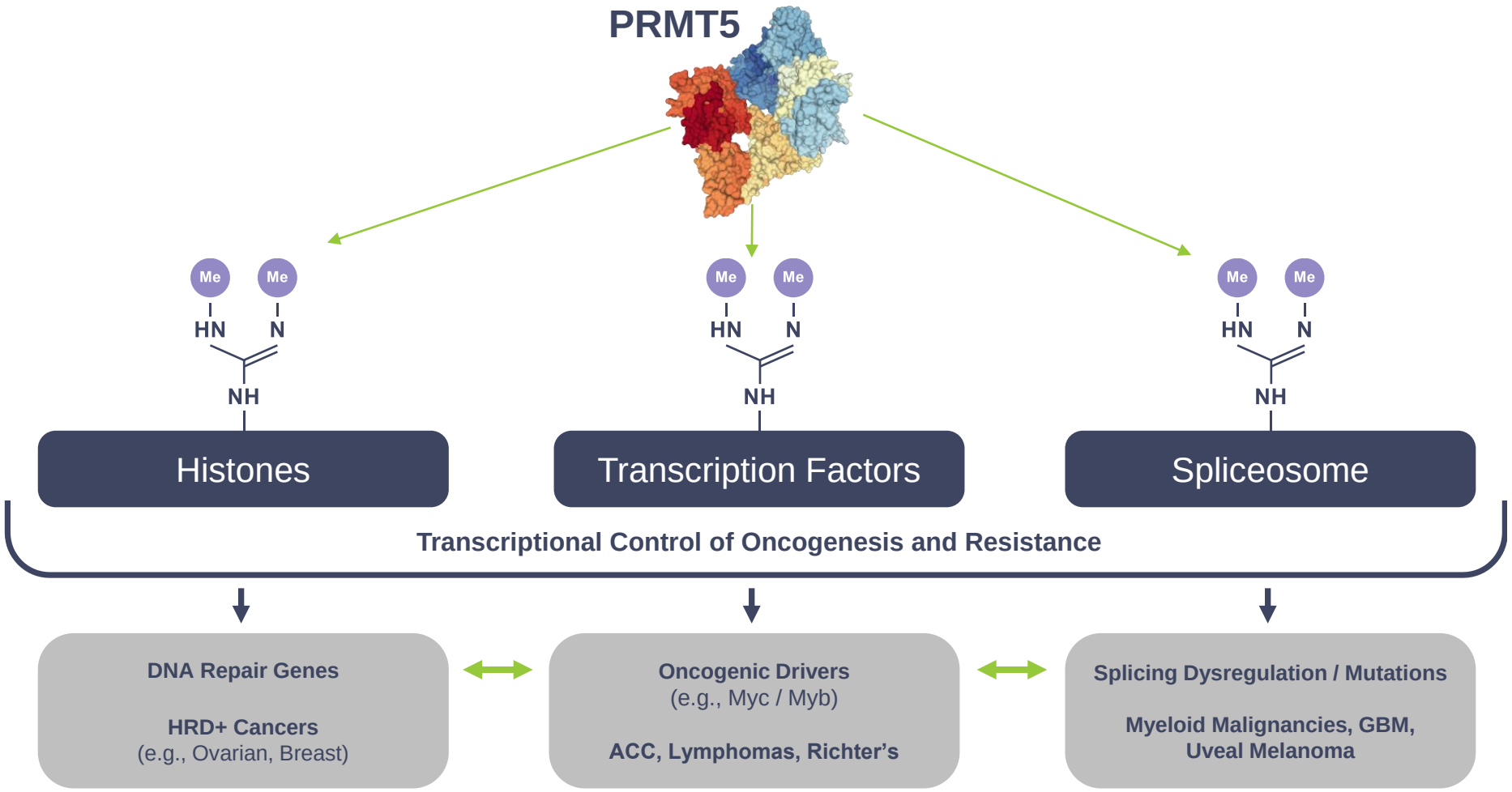
# PRMT5 Pathway Drives Oncogenesis and Resistance

PRMT5



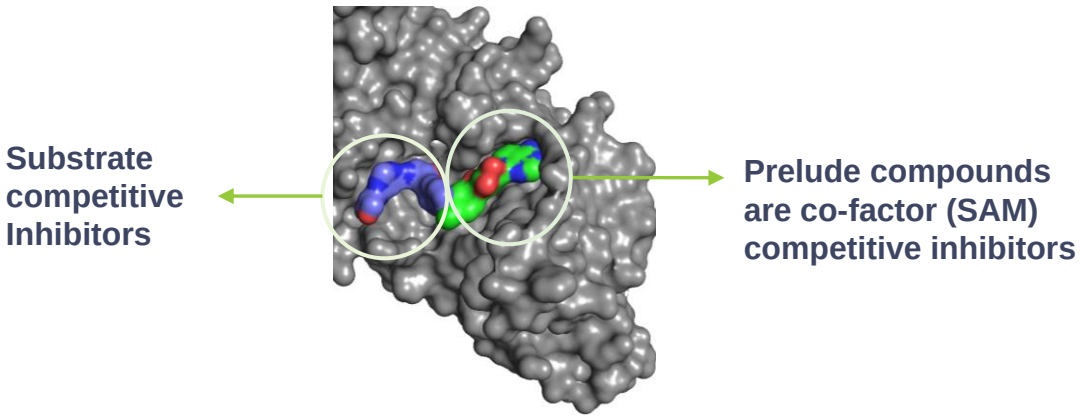

**PRMT5 inhibition can be leveraged to potentially treat a broad range of solid tumors and hematologic malignancies**

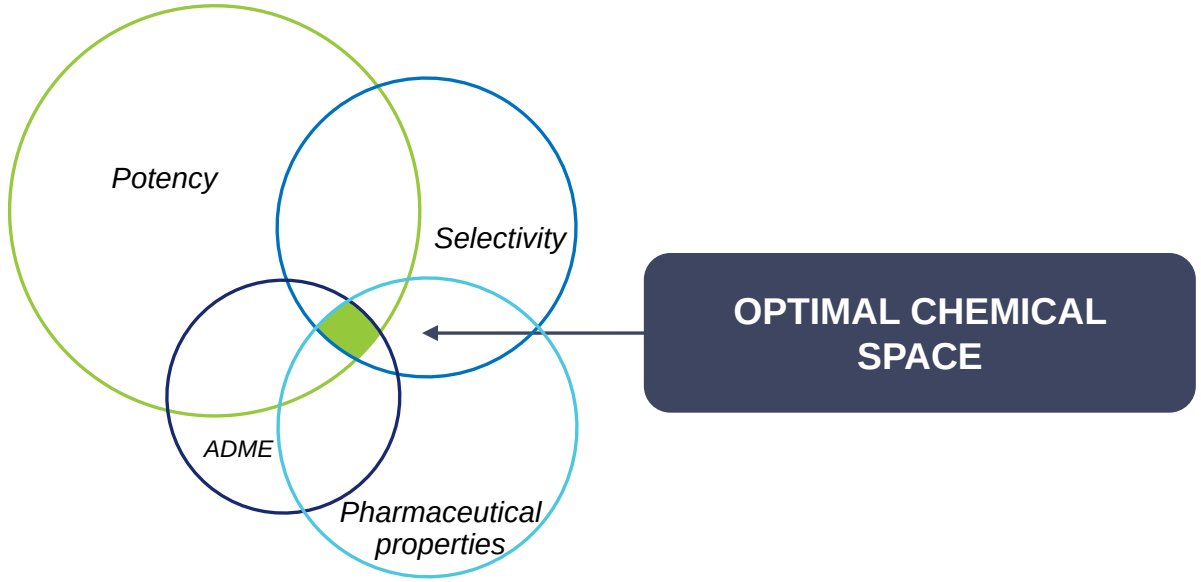
# Prelude PRMT5 Program

## 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

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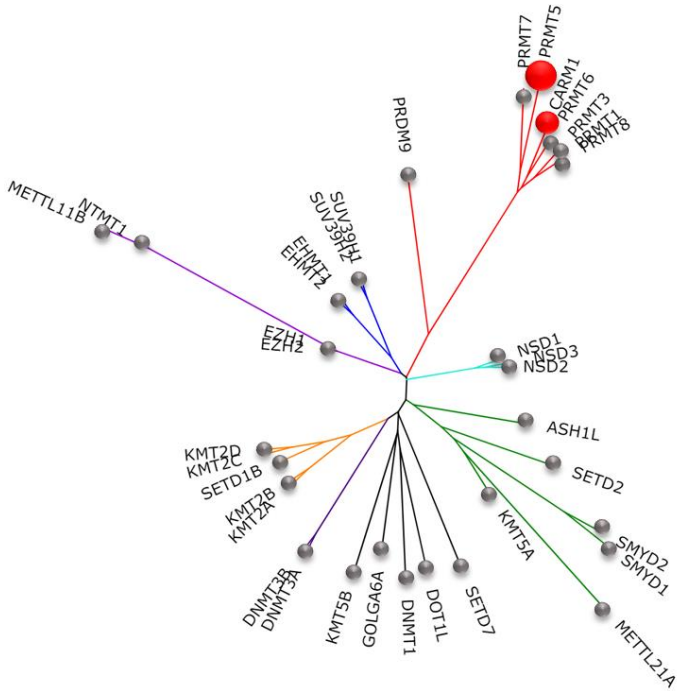
# PRT543 – A Potent, Selective and Oral PRMT5 Inhibitor Candidate

PRMT5

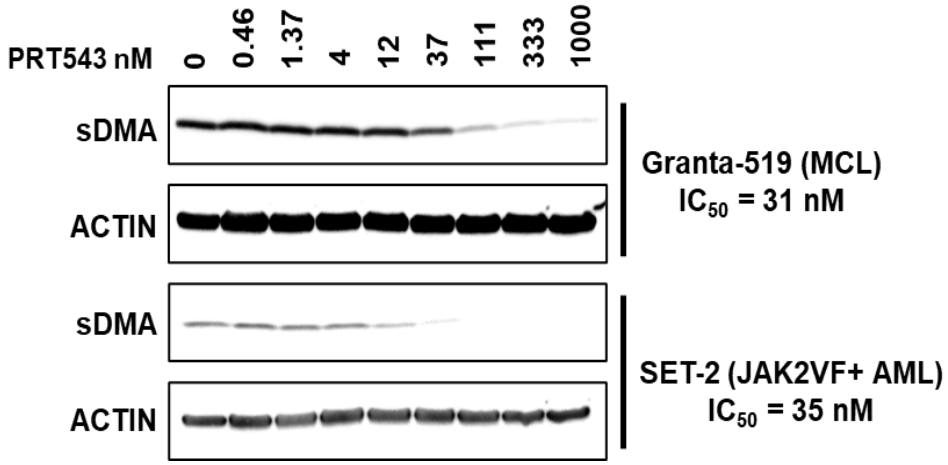
## PRT543 is Highly-Selective

**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**



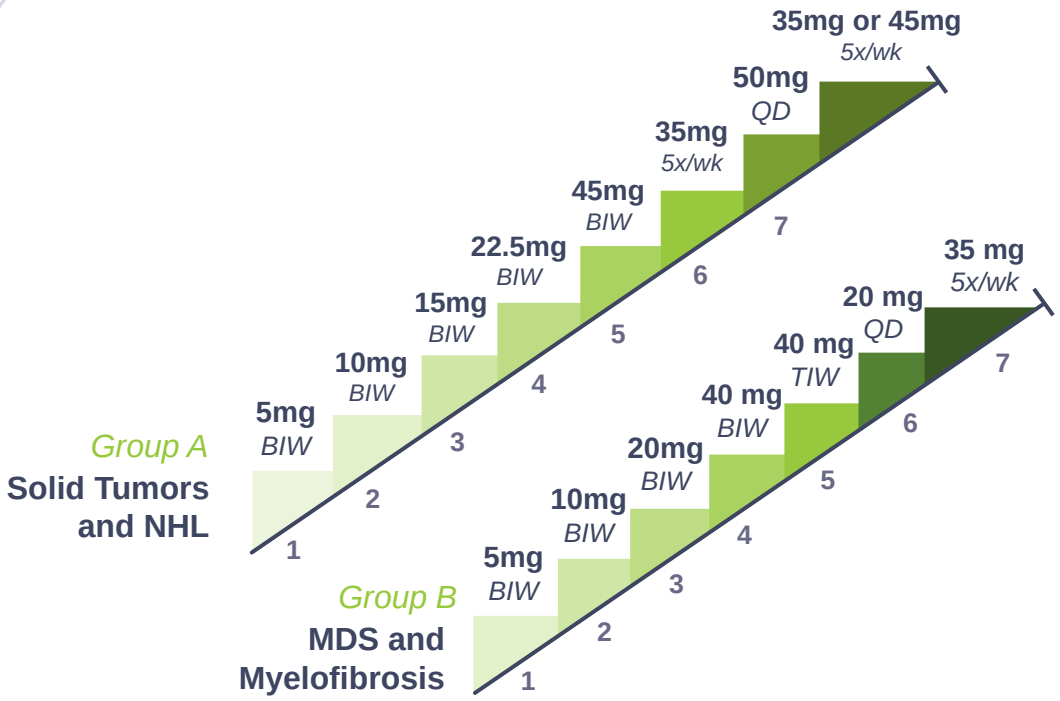

*~50% reduction in plasma sDMA correlates with efficacy in preclinical models*

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

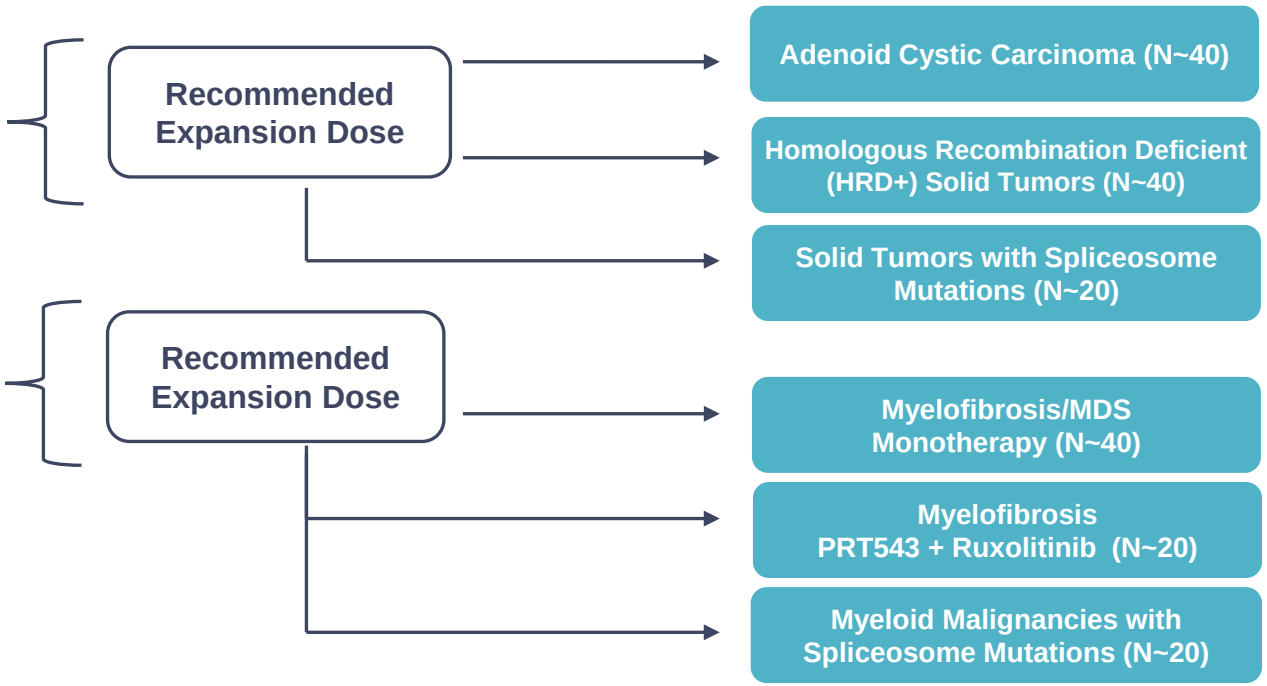
# PRT543 Phase 1 Clinical Trial

PRMT5

## Dose Escalation




## Expansion Cohorts

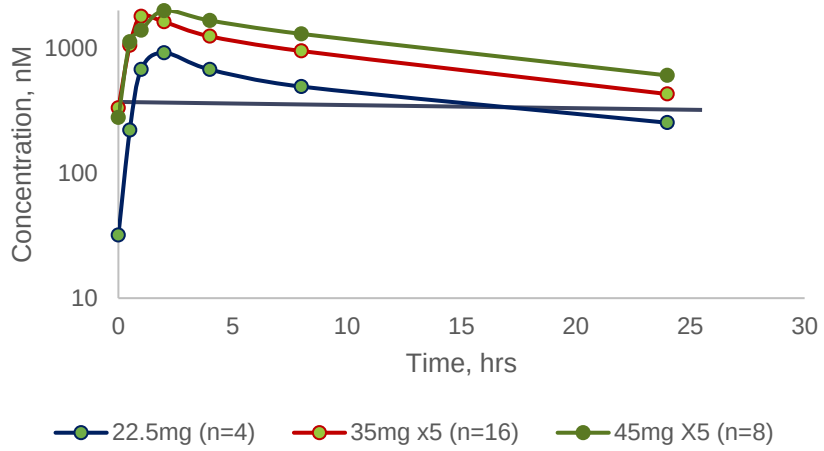


# PRT543 Phase 1 – Interim PK/PD Results Demonstrated Predictable Profile

PRMT5

## Dose-Proportional Increase in Exposure

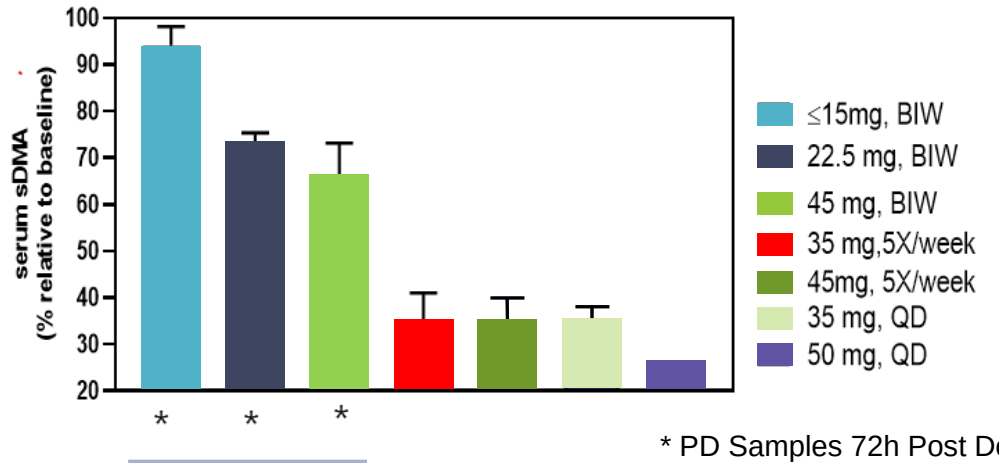
(Steady State)




| 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 doses selected for expansion cohorts provide optimal target coverage 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

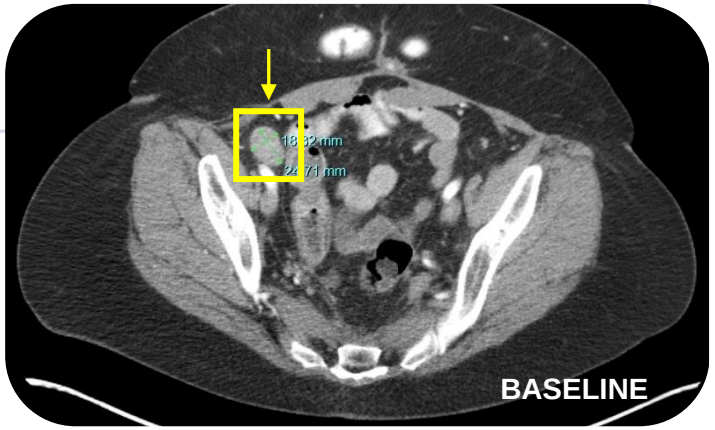
PRMT5

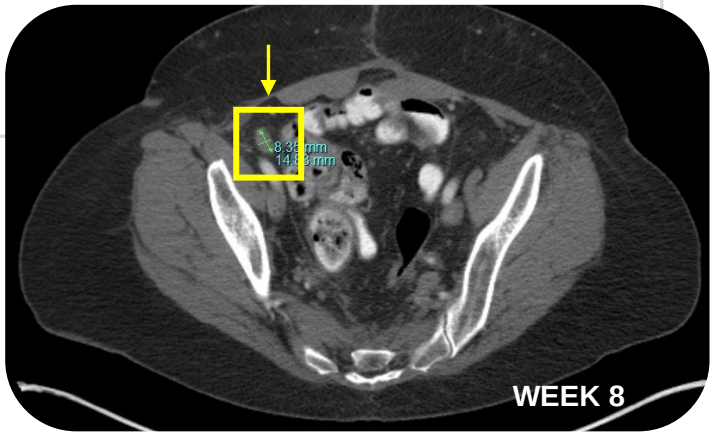
## Patient History

- 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<br>Splicing Dysregulation<br>Synthetic Lethality | Adenoid Cystic Carcinoma<br>HRD+ Tumors (Ovarian, TNBC, Others) | **ACC:** 10-15,000 patients<br>**Ovarian:** 63% of ovarian tumors HRD+<br>**TNBC:** 55% of TNBC tumors HRD+<br>**Prostate:** 25% of mCRPC tumors HRD+ |
| | Uveal Melanoma | **Uveal Melanoma:** 2,000 patients annually |
| | Myeloid Malignancies<br>(Myelofibrosis and MDS) | **MF:** ~12,000 intermediate/high risk patients<br>**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

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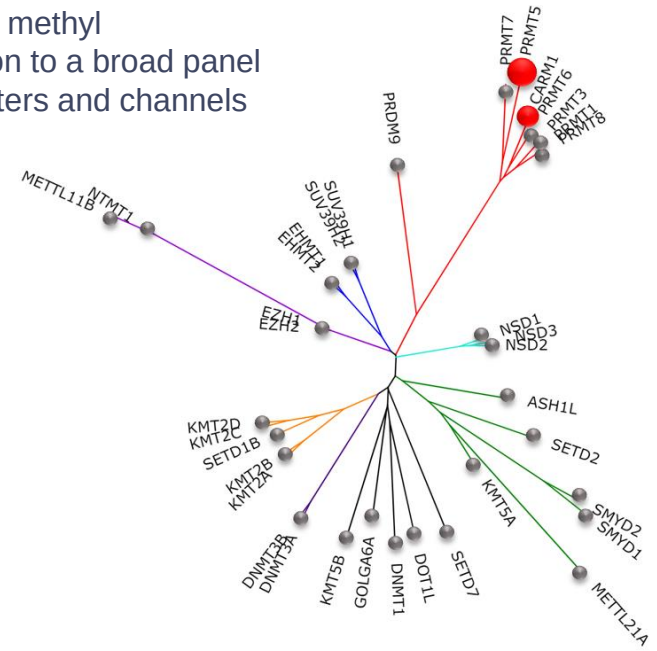
# PRT811 – A Potent, Selective and Brain Penetrant PRMT5 Inhibitor Candidate

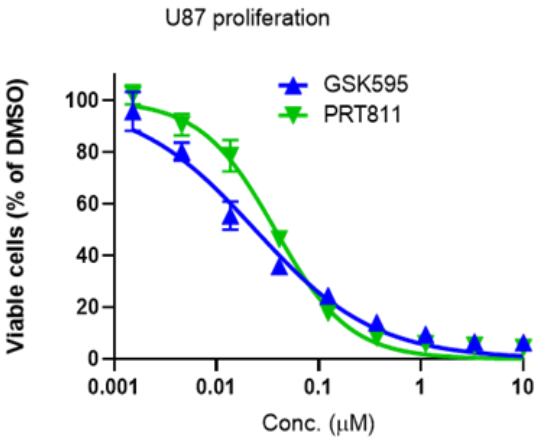
PRMT5

## 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** |

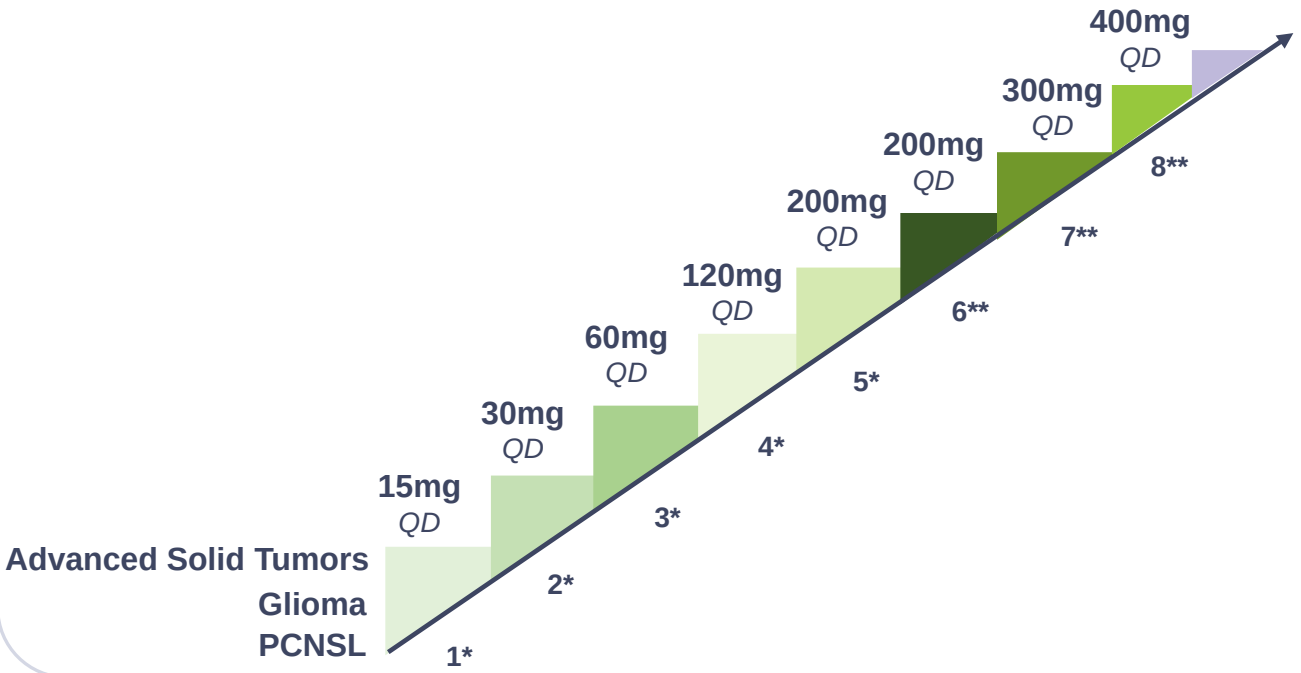
**PRT811 has high oral bioavailability, high brain exposure, and no dose-limiting toxicities to date**

# PRT811 Phase 1 Clinical Trial

PRMT5

ANTICIPATED MID-2021

## Dose Escalation




## Expansion Cohorts

Recommended Expansion Dose

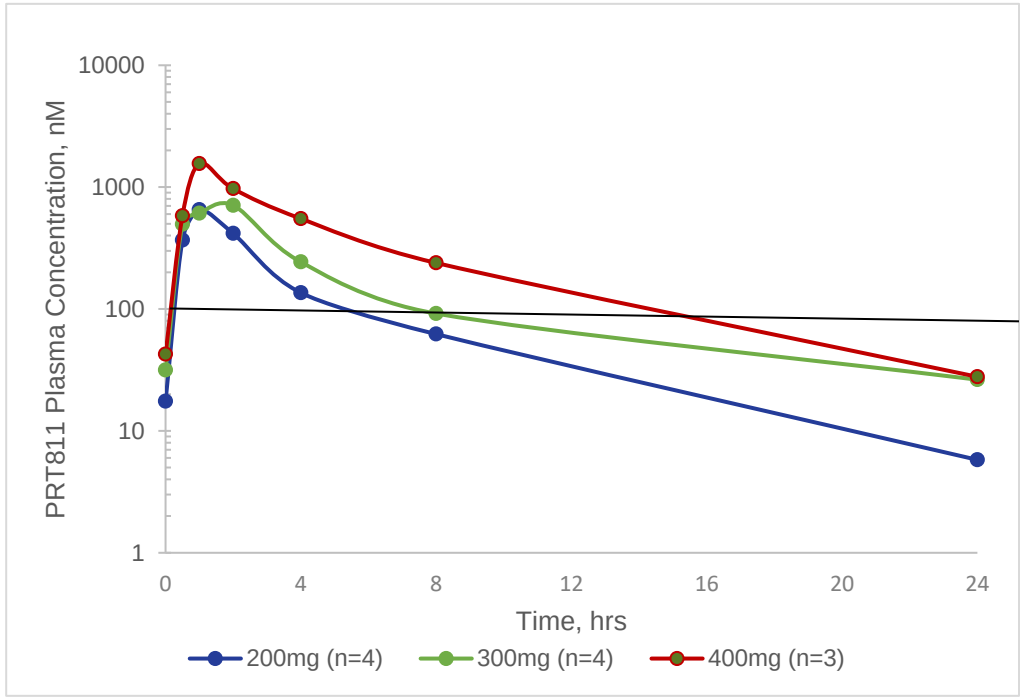
- Glioblastoma (N~20)
- Primary CNS Lymphoma (N~20)
- CNS Metastatic Disease (N~20)

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

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

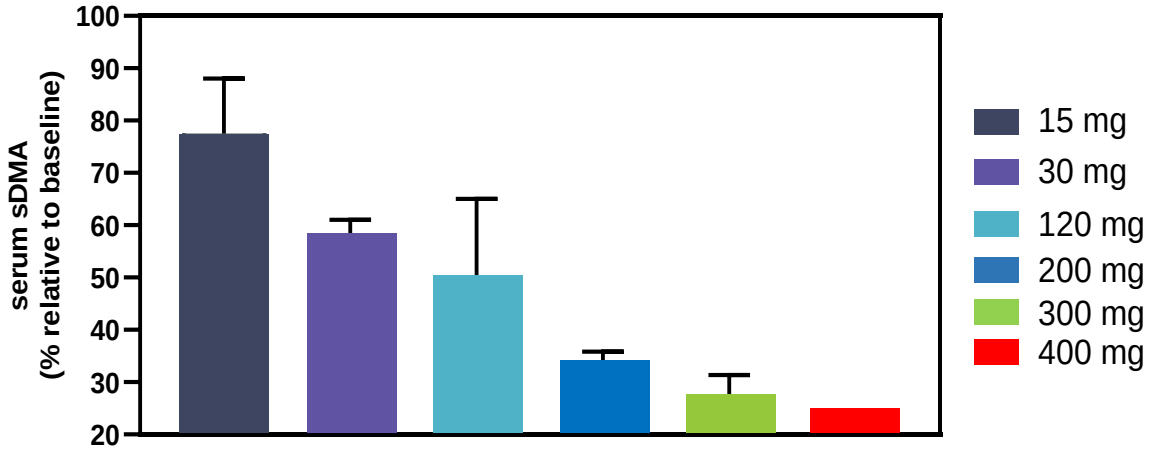
PRMT5

## 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

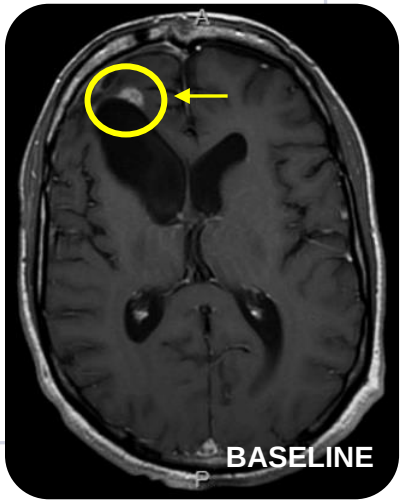
*Status as of December 16, 2020*

# Confirmed PR in Glioblastoma Multiforme

PRMT5

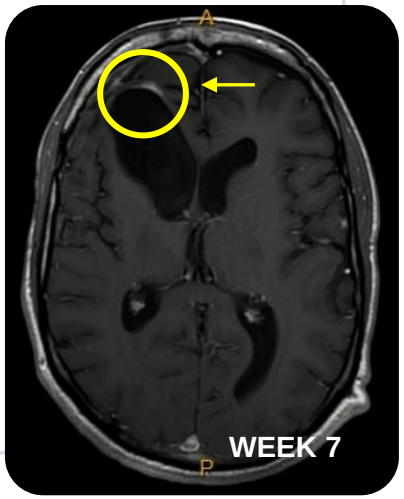
## Patient History

- 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

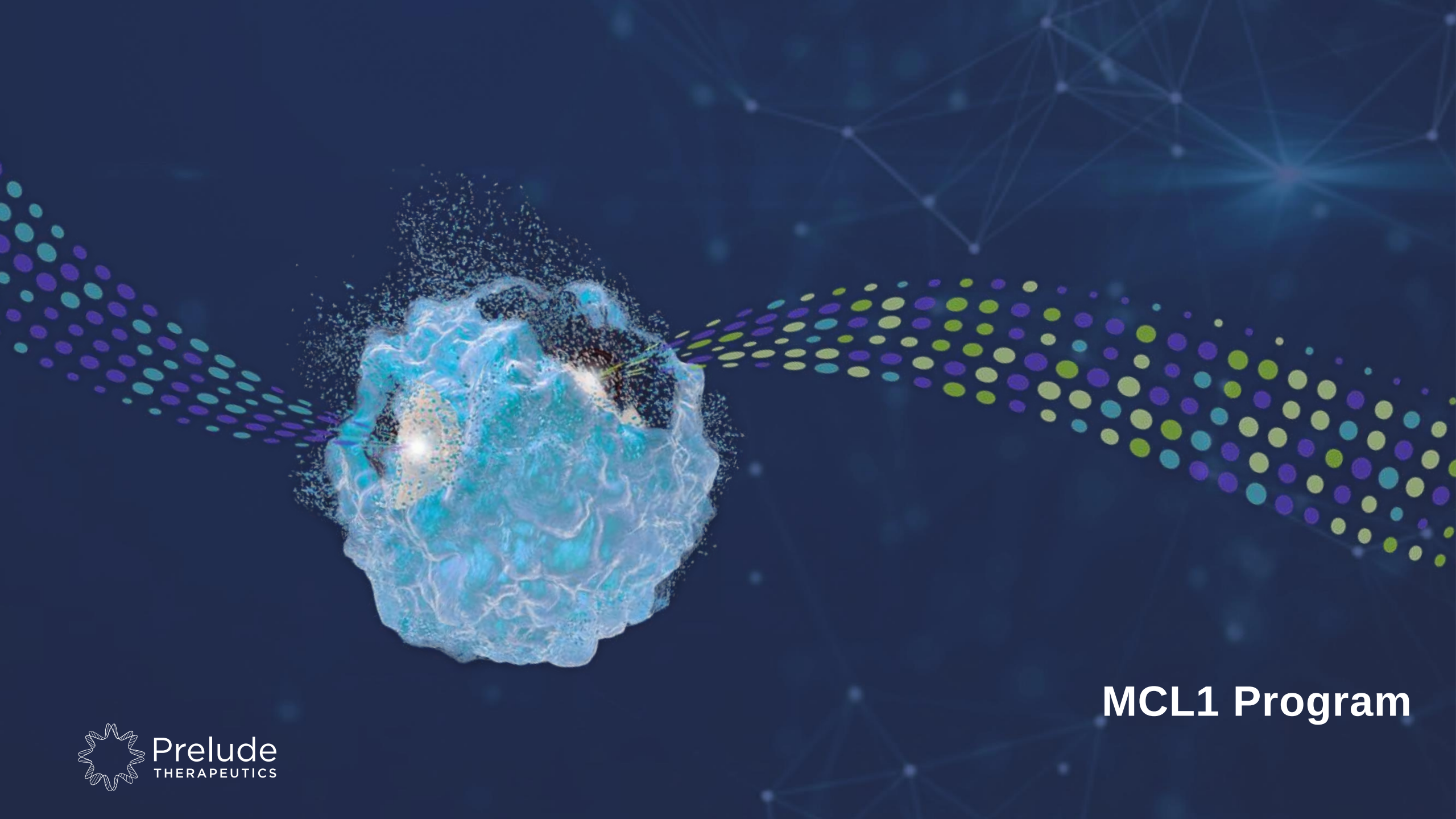
- In September 2020, at patient's first follow-up MRI evaluation (week 7) lesion measured 13 mm x 6 mm (**66% reduction**)
- Follow-up MRI at week 18 confirmed a partial response (PR) per RANO criteria and an **improved regression of 77% from baseline**
- As of December 16, 2020, patient received five 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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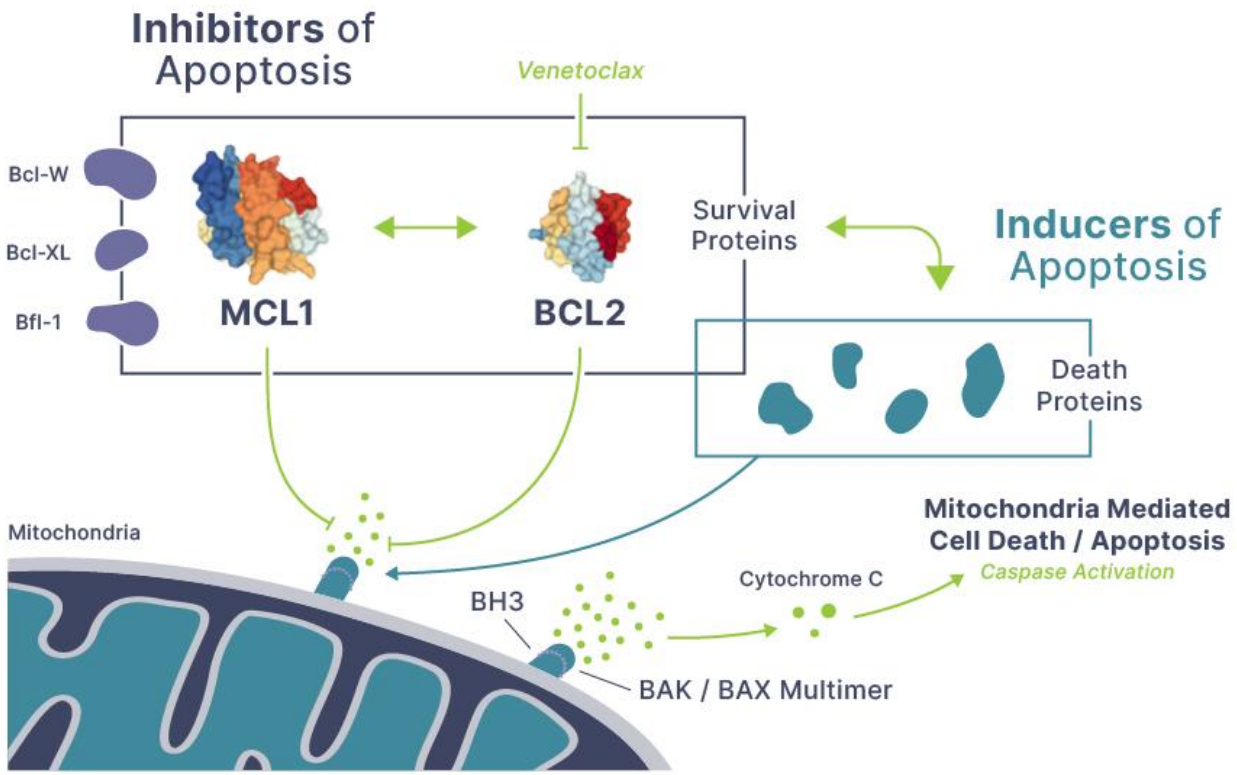
# Prelude MCL1 Program

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 mid-2021 (IV)

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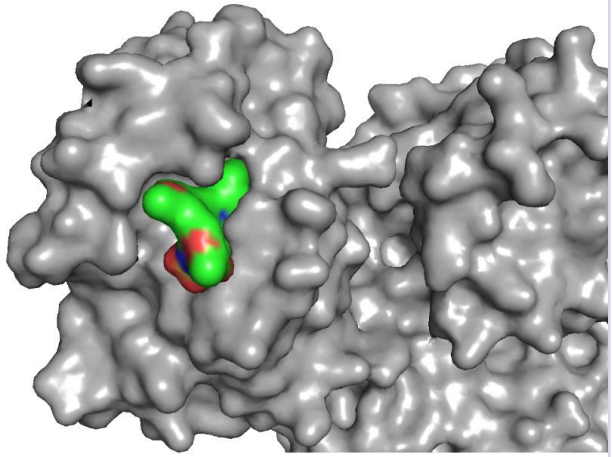
# PRT1419: Potential Leading MCL1 Inhibitor

MCL1

## Highly Potent Binding to MCL1

Prelude compounds are competitive inhibitors of BIM binding



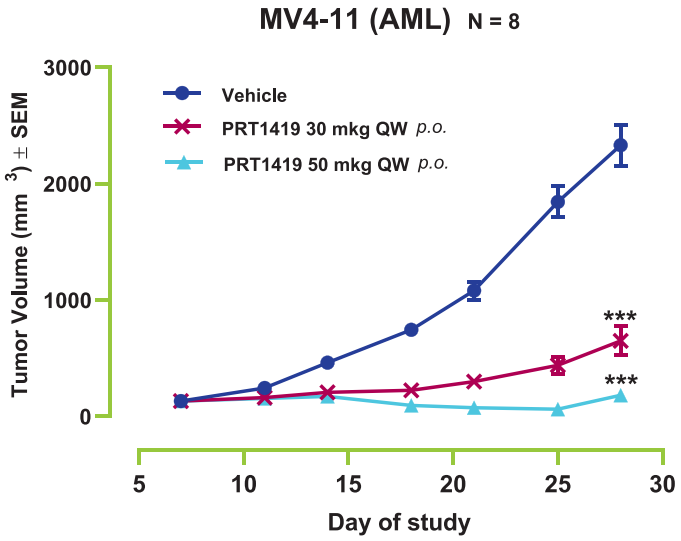
| Assay | AMG176 | AZD5991 | MIK665 | PRT1419 |
|---|---|---|---|---|
| **Proliferation $IC_{50}$ (nM)** | 150 | 31 | 4.5 | **80** |
| **Whole Blood $IC_{50}$ (nM)** | 1800 | 320 | 430 | **210** |
| **Caco-2 ($x10^{-6}$ cm/s)** | 6 | <0.1 | 0.2 | **11** |
| **Human Hepat. Cl (%HBF)** | 42 | ND | ND |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

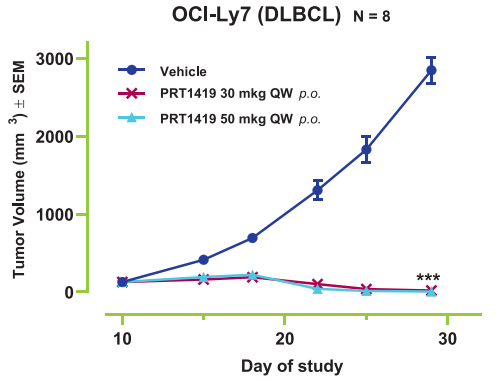
**PRT1419 is a potent MCL1 inhibitor candidate with no preclinical evidence of cardiac toxicity**

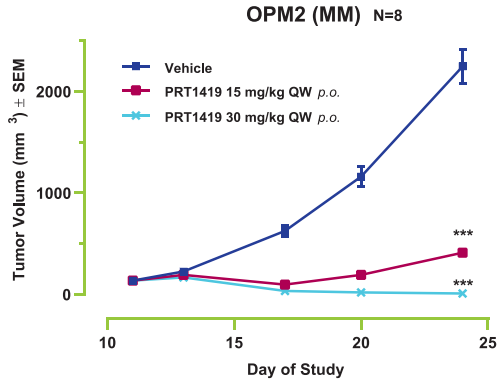
# PRT1419 Demonstrated Preclinical Activity as Monotherapy and in Combination

MCL1

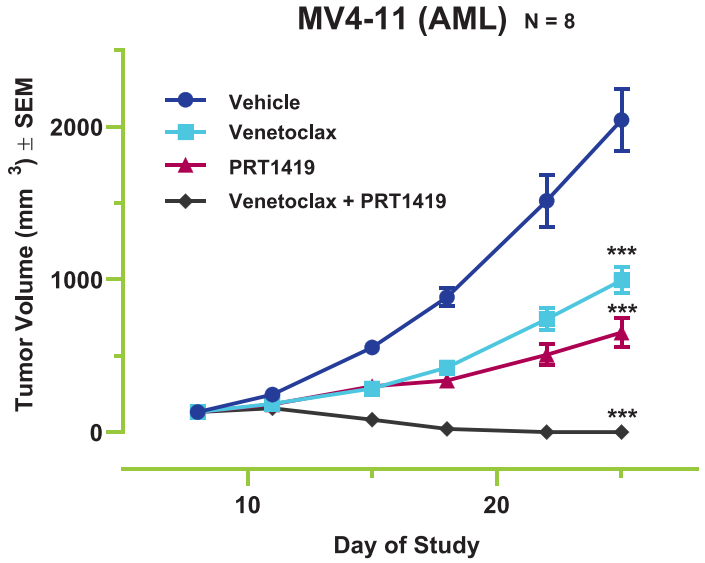
## Monotherapy




## Combination




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

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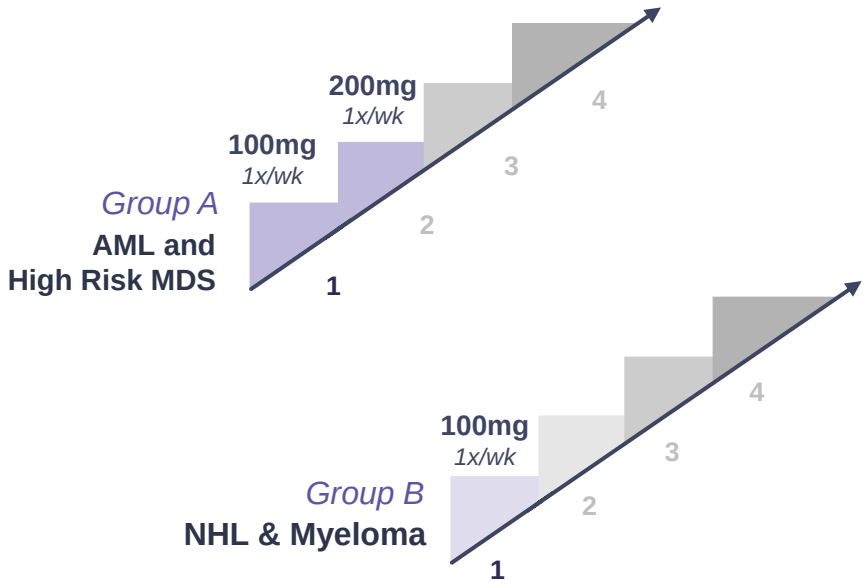
# Oral PRT1419 Phase 1 Clinical Trial

## Phase 1 Initiated in 2H2020

MCL1

2021

### Dose Escalation




### Expansion Cohorts

Recommended Expansion Dose

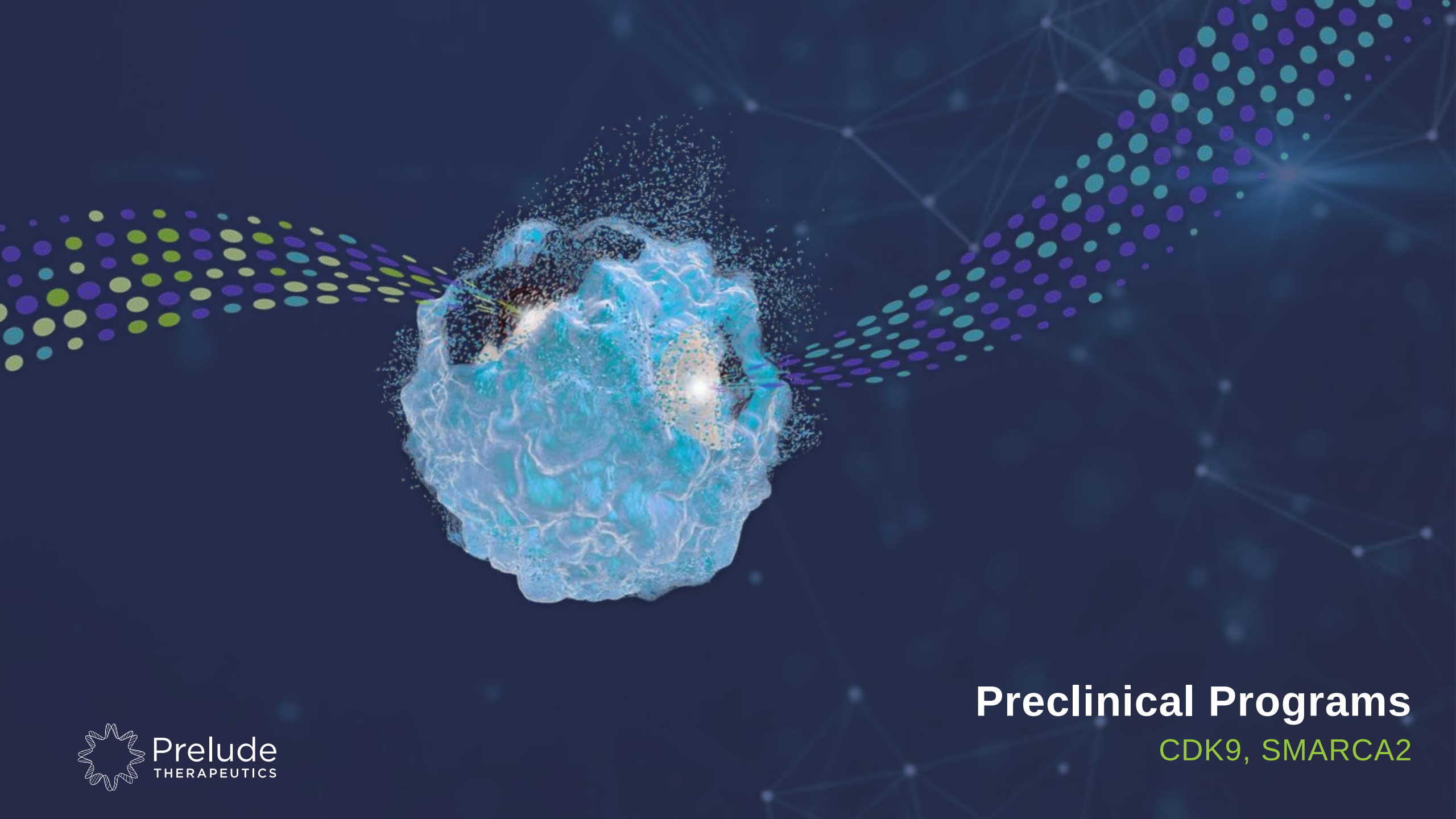
- AML (N~20)
- AML or MDS
  PRT1419 + Venetoclax or Aza
  (N~20)
- High Risk MDS (N~20)

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**



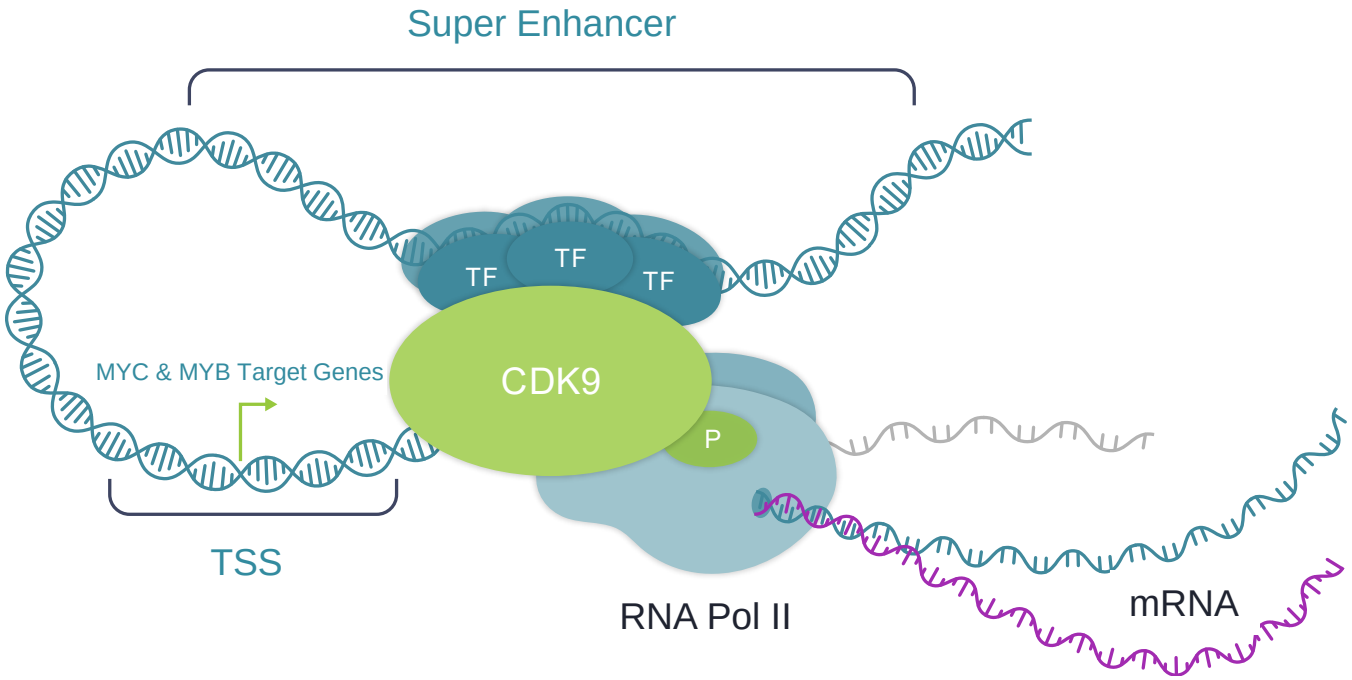
# Preclinical Programs

CDK9, SMARCA2

Prelude THERAPEUTICS

# Prelude CDK9 Program

CDK9



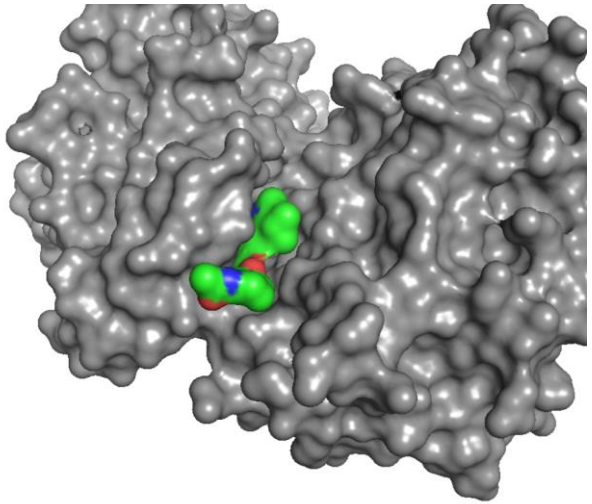

- CDK9 phosphorylates RNA Pol II and regulates transcription
- Regulates expression of several immediate early genes driving oncogenesis and resistance (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
  - Lack of selectivity 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 | | AZD4573 | KB0742 | VIP152** | PRT2527 |
|---|---|---|---|---|---|
| Biochemical* $IC_{50}$ (nM) | **CDK9** | 1.9 | 483 | 16 | 0.95 |
| Proliferation* $IC_{50}$ (nM) | | 11 | 915 | 84 | 18 |
| Plasma* $IC_{50}$ (nM) | | 192 | 1056 | 923 | 196 |
| Fold Selectivity CDK9 *vs* Other Isoforms | **CDK1** | 23x | >20x | 371x | 73x |
| | **CDK2** | 35x | >20x | 147x | 340x |
| | **CDK3** | 2x | >20x | 37x | 35x |
| | **CDK4** | 53x | >20x | 38x | 250x |
| | **CDK5** | 37x | >20x | >600x | >1000x |
| | **CDK6** | 79x | >20x | 296x | >1000x |
| | **CDK7** | 150x | >20x | >600x | >1000x |

>100x  100-10x  <10x

*Internal data; biochemical assay at 1 mM ATP, H929 CTG proliferation assay; **VIP151 was formerly BAY151and licensed to Vincera by Bayer

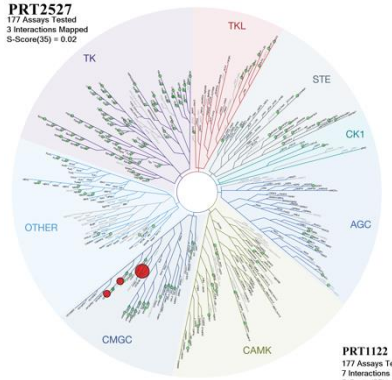
**PRT2527 demonstrated improved potency and kinase selectivity relative to competitor compounds in preclinical studies**

# CDK9 Inhibitor Candidate: PRT2527

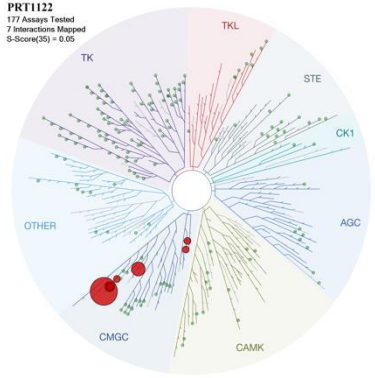
CDK9

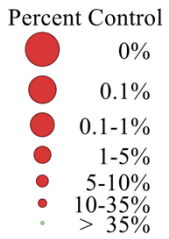
## Improved Selectivity

### PRT2527

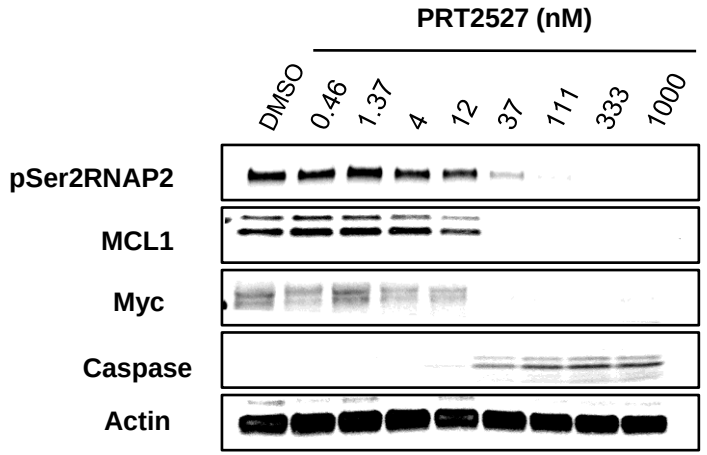



### AZD4573



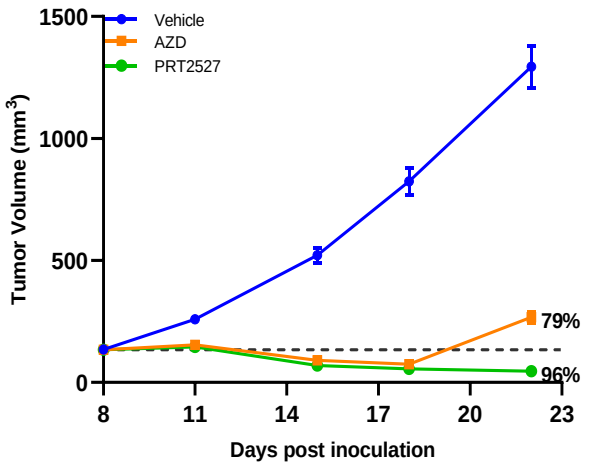




## Potent in Vitro Activity




## Sustained Regressions at Well-Tolerated Doses in Vivo

### MV4-11 (AML)




**PRT2527 IND expected to be filed in 2021**

# SMARCA2 Targeted Degrader Program

SMARCA2

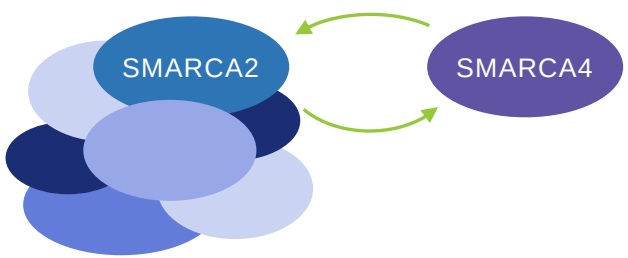
## SMARCA4 and SMARCA2 Regulate Chromatin Accessibility and Gene Expression

**Paralog Dependency**

*SMARCA4 Compensates for SMARCA2 Function*

**NORMAL CELL**

*SWI/SNF Chromatin Remodeling Complex*



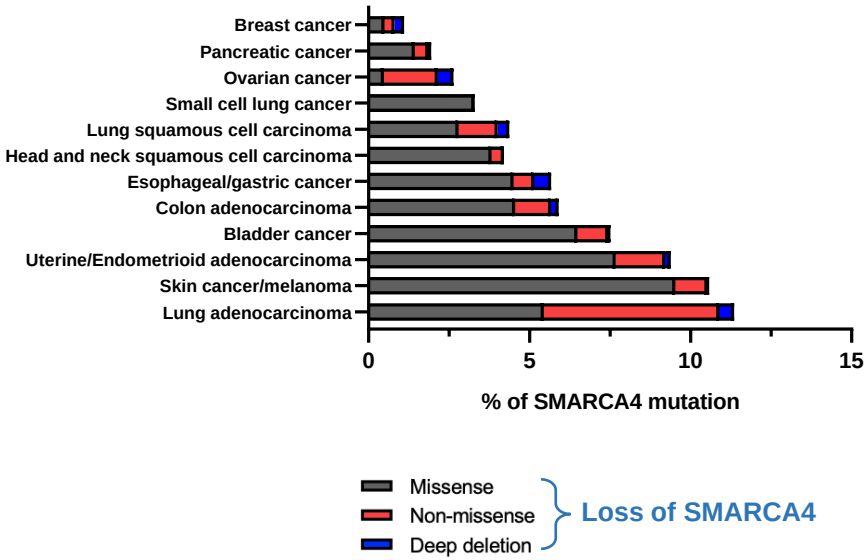

**SMARCA4 MUTANT TUMORS**

**SMARCA2 Degradation** → **Synthetic Lethality**


*Dysfunctional SMARCA4*

*Tumor Cell Death*

## Loss of SMARCA4 Leads to SMARCA2 Dependency

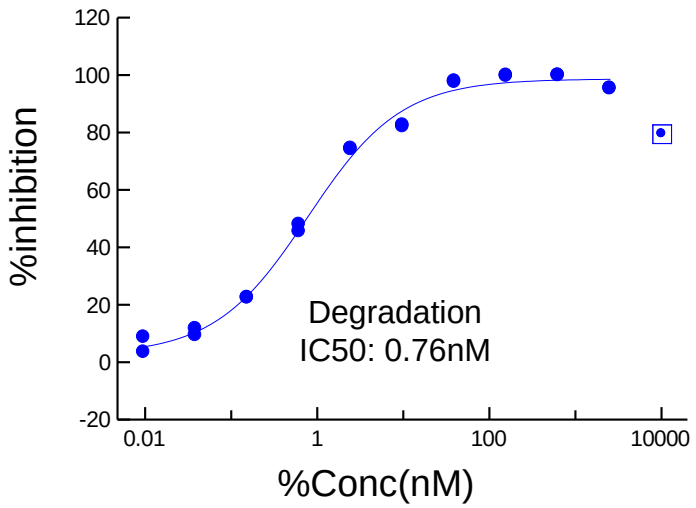



**Opportunity to target 10 – 12% NSCLC with SMARCA4 deletions**

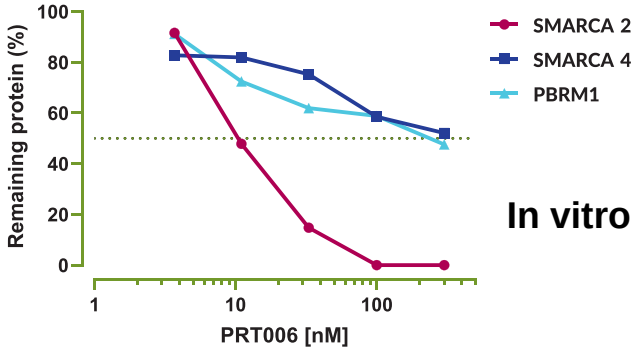
# PRT-SCA2: Potent Selective SMARCA2 Degraders with In Vivo Activity

SMARCA2

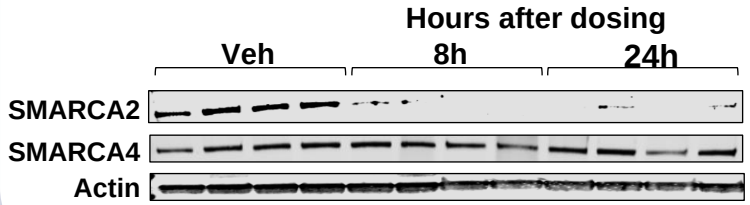
## Sub-Nanomolar Potency for SMARCA2 Degradation




## Highly Selective for SMARCA2 Degradation

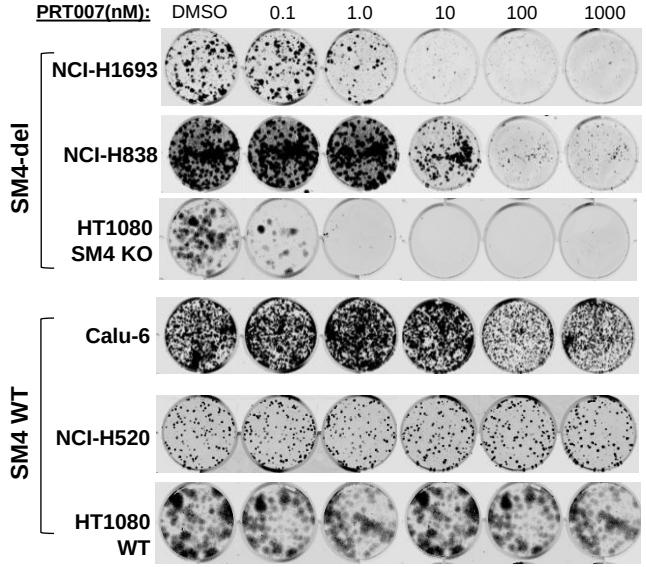



In vitro



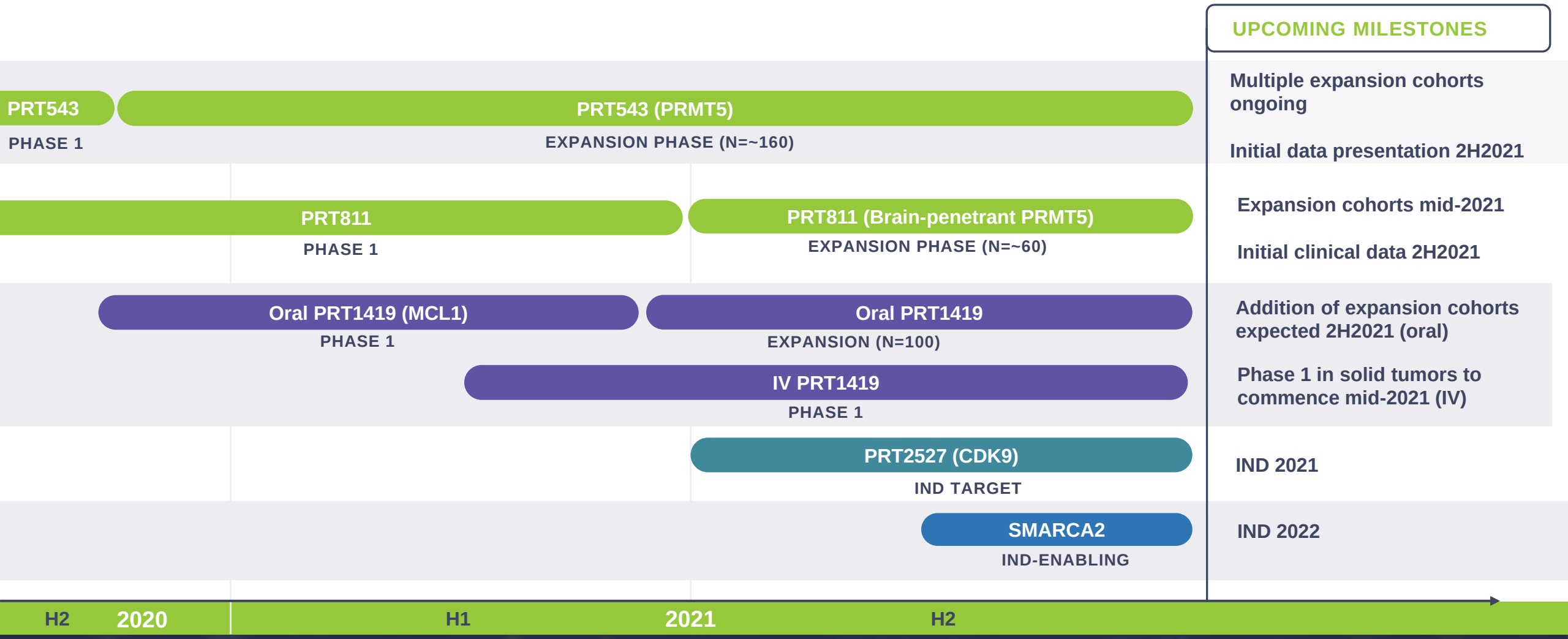

In vivo

## Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality




**IND expected to be filed 2022**

# Prelude Therapeutics Projected Milestones



# Financial Highlights

## Shares Outstanding

- 46.8 million shares voting and non-voting common stock as of March 31, 2021
- 61.0 million shares fully diluted

## Cash and Cash Equivalents

- $363.0 million as of March 31, 2021
- Current cash and cash equivalents will be sufficient to fund operating expenses and capital expenditure requirements into 2023

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# 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