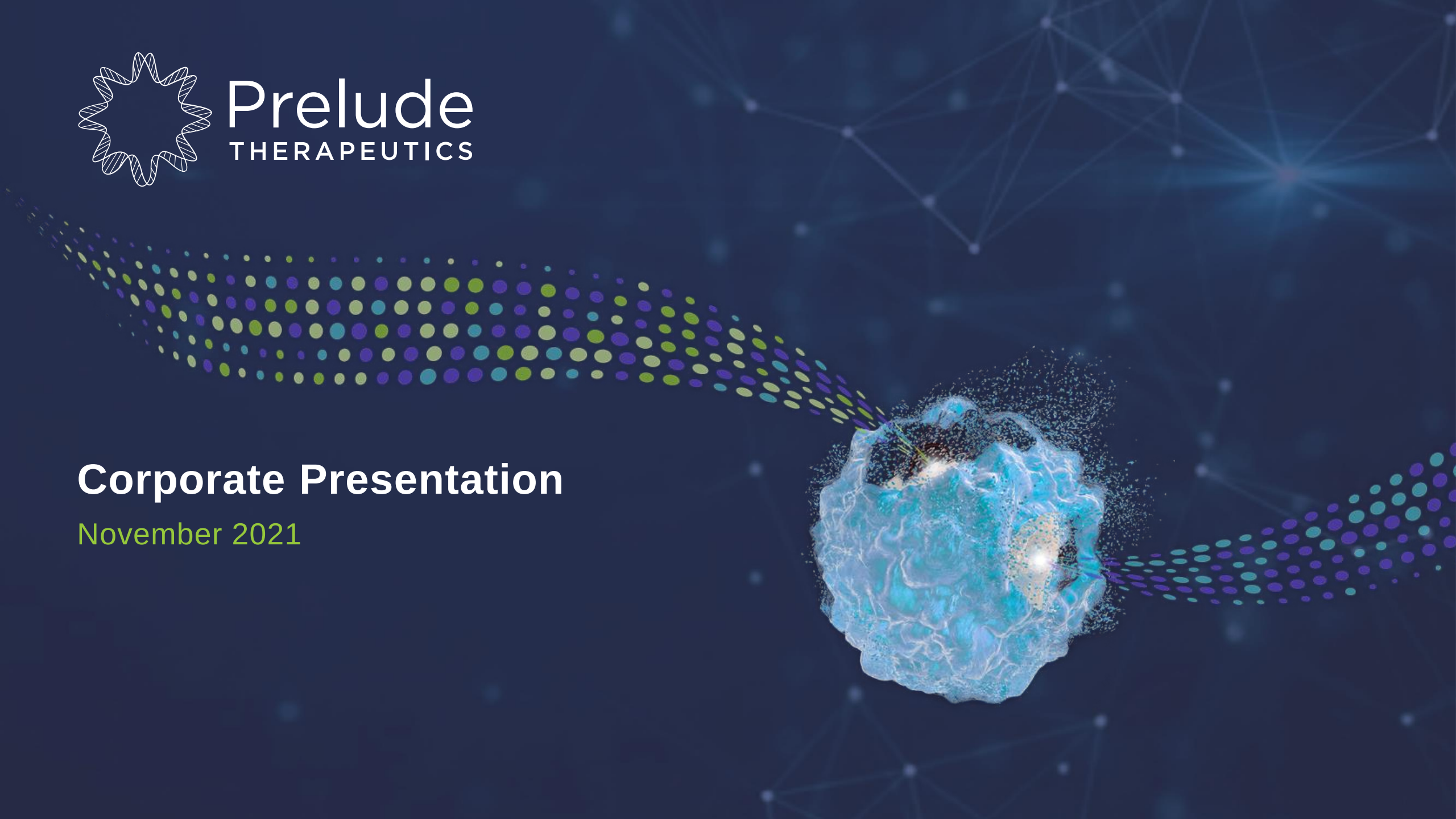
Prelude THERAPEUTICS

Corporate Presentation

November 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 June 30, 2021.

Prelude Therapeutics Vision

Discovery Engine

Powered by scientists with a track record of delivering precision oncology medicines

Clinical Development

Highly selected patient populations with significant unmet need

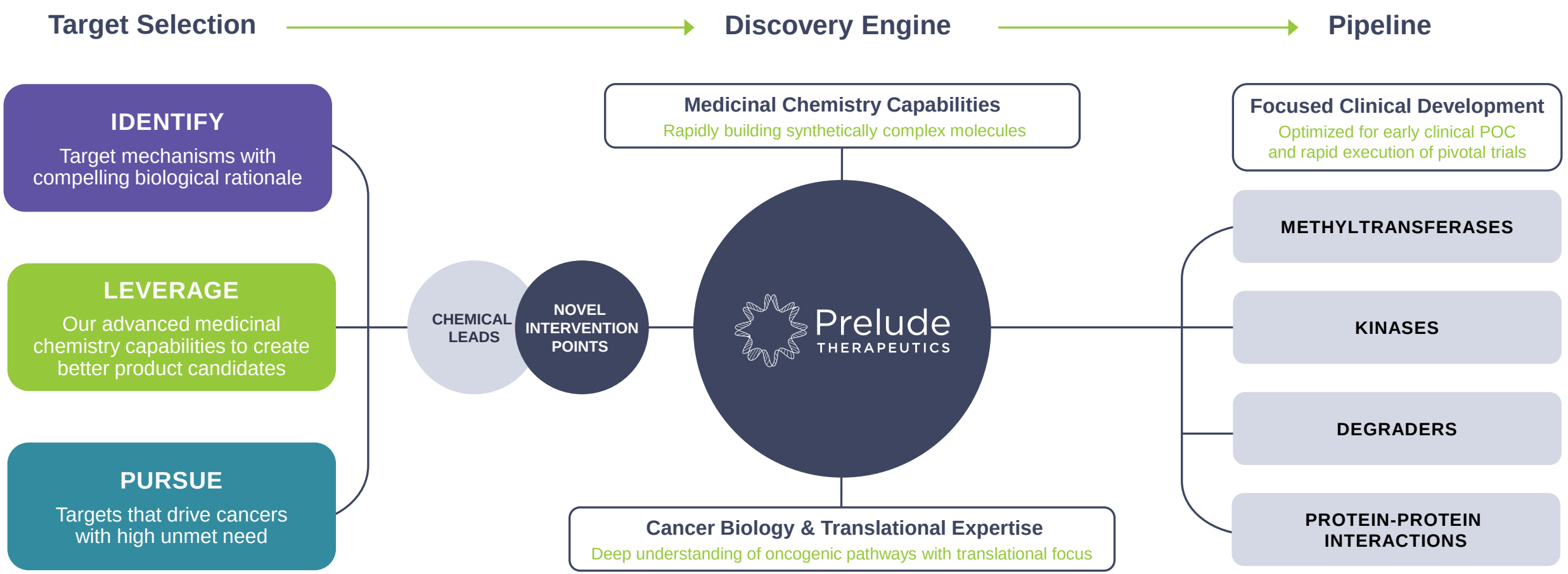
Regulatory Strategy

Efficient development path with potential for rapid regulatory approvals

Commercial Approach

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

Prelude Discovery and Development Approach



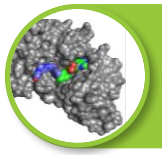
Prelude Therapeutics Pipeline

Program	Indications	Discovery/ Preclinical	IND Enabling	Phase 1	Phase 2/3	Worldwide Rights
PRT543 (PRMT5)	Selected Solid Tumors (incl. ACC, HRD+)					
	Selected Myeloid Malignancies (incl. MF and MDS)					
PRT811 (Brain Penetrant PRMT5)	CNS and Non-CNS Cancers					
PRT1419 (MCL1)	Selected Hematological Malignancies *(oral formulation)*					
	Solid Tumors *(IV formulation)*					
PRT2527 (CDK9)	Selected Solid Tumors					
PRT-SCA2 (SMARCA2)	Multiple Genomically Selected Cancers					
PRT-K4 (Kinase)	Solid Tumors					

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

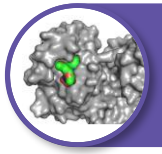
Prelude Roadmap for Value Creation

Anticipated 2021/2022 Milestones



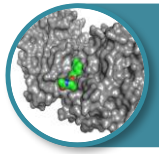
PRMT5

Report P1 dose expansion data
Generate POC in selected patients



MCL1

Complete dose escalation and initiate expansion/combination phase



CDK9

Initiate Phase 1 clinical trial in selected solid tumors

SMARCA2/ Kinase

Complete IND-enabling studies and file INDs

Future Strategy

Leverage initial POC clinical data to inform design of P2 registration studies

Advance multiple precision oncology clinical programs focusing on underserved cancers

Continue to resource discovery engine to expand our pipeline

Maximize portfolio value through strategic partnerships

PRMT5 Programs

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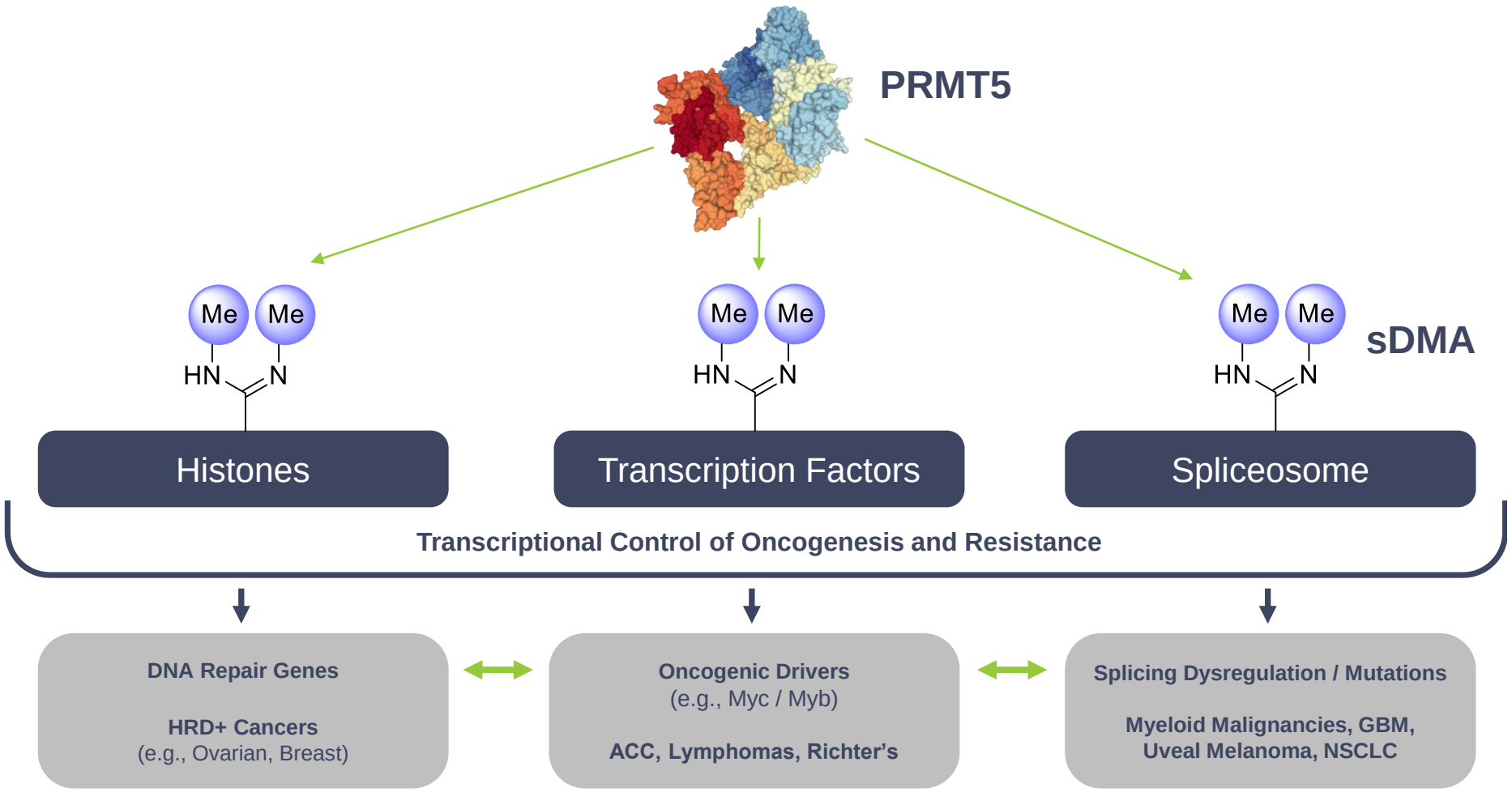
PRMT5 Pathway Drives Oncogenesis and Resistance

PRMT5



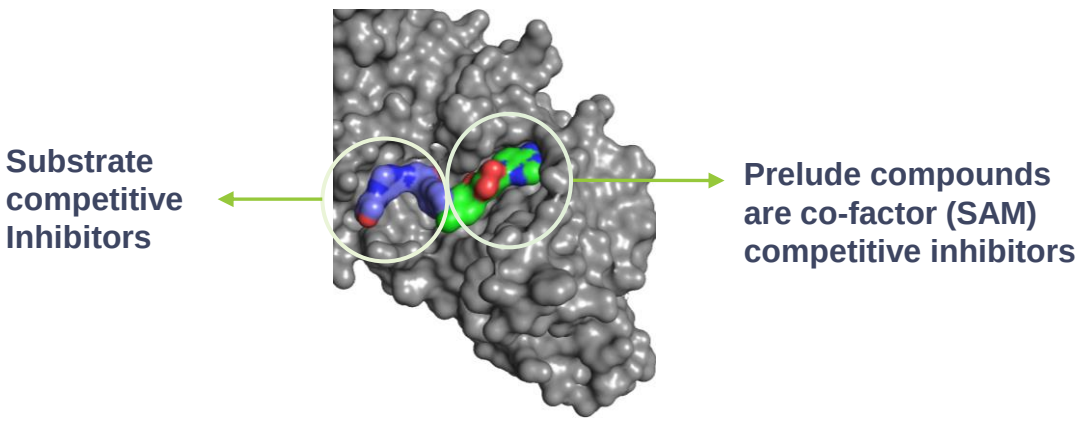
PRMT5 inhibition can be leveraged to potentially treat a broad range of solid tumors and hematologic malignancies

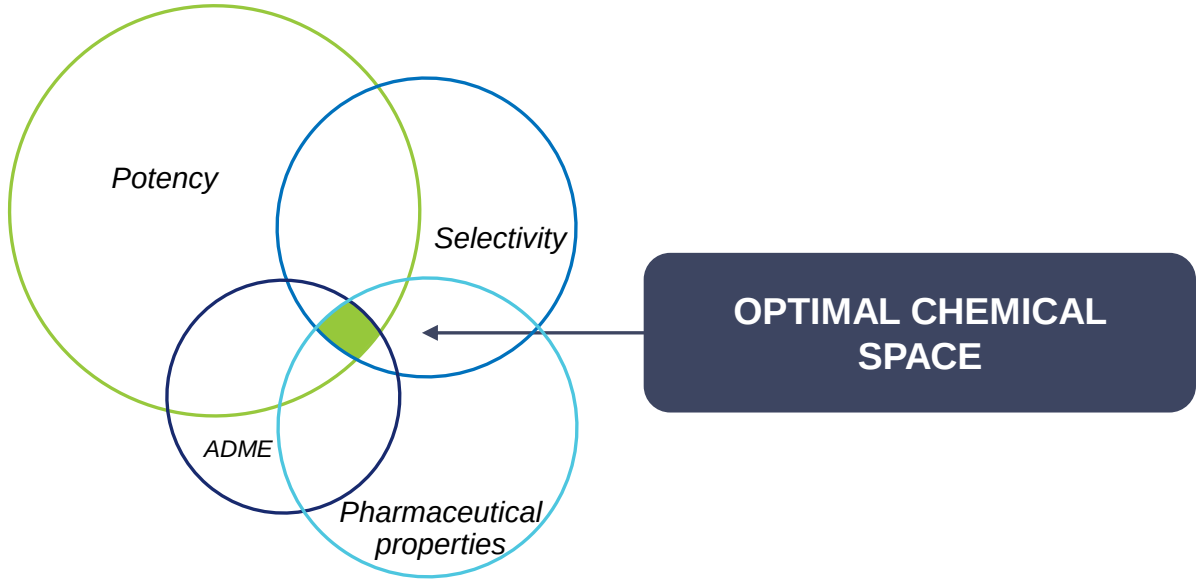
Prelude PRMT5 Program

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 / PRT811

Differentiated Clinical Stage Oral PRMT5 Inhibitors

PRT543

- **Strong** scientific rationale for pathway
- Highly **selective** and **potent** oral candidate
- **Optimized** PK profile
  - Good oral bioavailability and long half-life (12+ hours)
- Applicability in both **solid tumors** and **heme malignancies**
- Completed **dose escalation;** Currently in **expansion phase in selected** patient cohorts

PRT811

- **Brain-penetrant** PRMT5 inhibitor
- **High/sustained** brain exposure in preclinical studies
- Highly **selective** and **potent** oral candidate
- **Optimized** PK profile
  - 5+ hours half-life; maximizing therapeutic window
- Completed **Dose escalation; Expansion phase** to begin

PRT543 /PRT811
Phase 1 Dose Escalation Data

Prelude
THERAPEUTICS

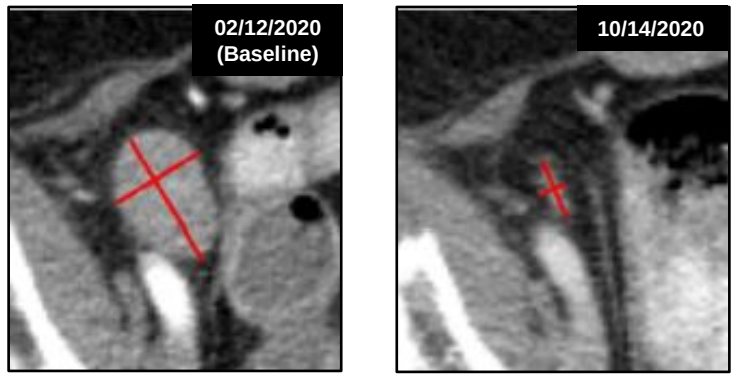
PRT543: Well-Tolerated with Evidence of Preliminary Clinical Activity in Phase 1 Dose Escalation Study*

Study Demographics & Safety

- 49 patients
  - Unselected patient population with 18 different diagnoses
  - 9 colon; 7 ACC; 6 uveal melanoma (2 patients SF3B1+); 5 ovarian cancer (2 patients HRD+)
  - Median of 3 prior lines of systemic therapy
- PRT543 was well-tolerated
  - Most common TRAEs of any grade in ≥ 5% of all patients: fatigue, thrombocytopenia, anemia, nausea
  - The most common Grade 3≥ AEs were thrombocytopenia and anemia
    - Reversible upon dose modification
  - Thrombocytopenia was only dose-limiting toxicity
  - No discontinuations due to toxicity

Preliminary Clinical Activity

- Stable disease for at least 6 months and tumor regressions (<30%) in 5 patients including ACC and uveal melanoma
- Durable CR in a patient with HRD+ ovarian cancer
  - Multiple lines of prior therapy, including PARPi
  - One target lesion per RECIST and CA125 level 37.8 U/mL at baseline
  - RECIST v1.1 CR at first follow-up tumor assessment (7 weeks), maintained throughout the study
  - CA125 reduced and remained below 5 U/mL at the last assessment
  - Patient remains on study following 18 months of treatment at 35 mg 5x/week



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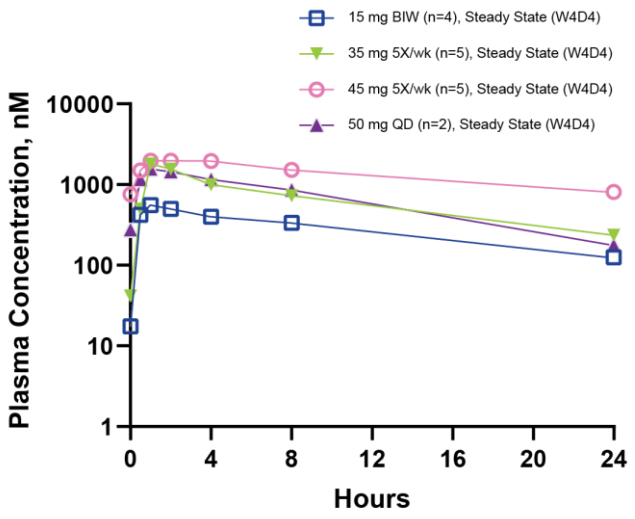
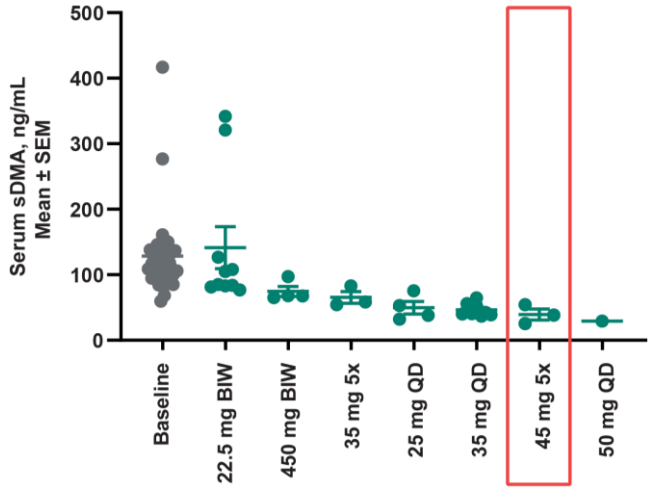
*Data as of August 6, 2021
Data presented at 2021 AACR-NCI-EORTC Annual Meeting

PRT543: Exhibited Target Engagement and Inhibited PRMT5 Activity in Phase 1 Dose Escalation Study

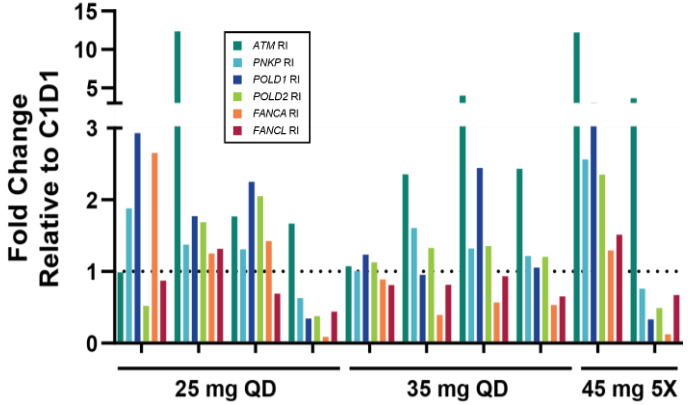
Dose-Dependent Increases in Cmax and AUC



Dose-Dependent Inhibition of Serum sDMA

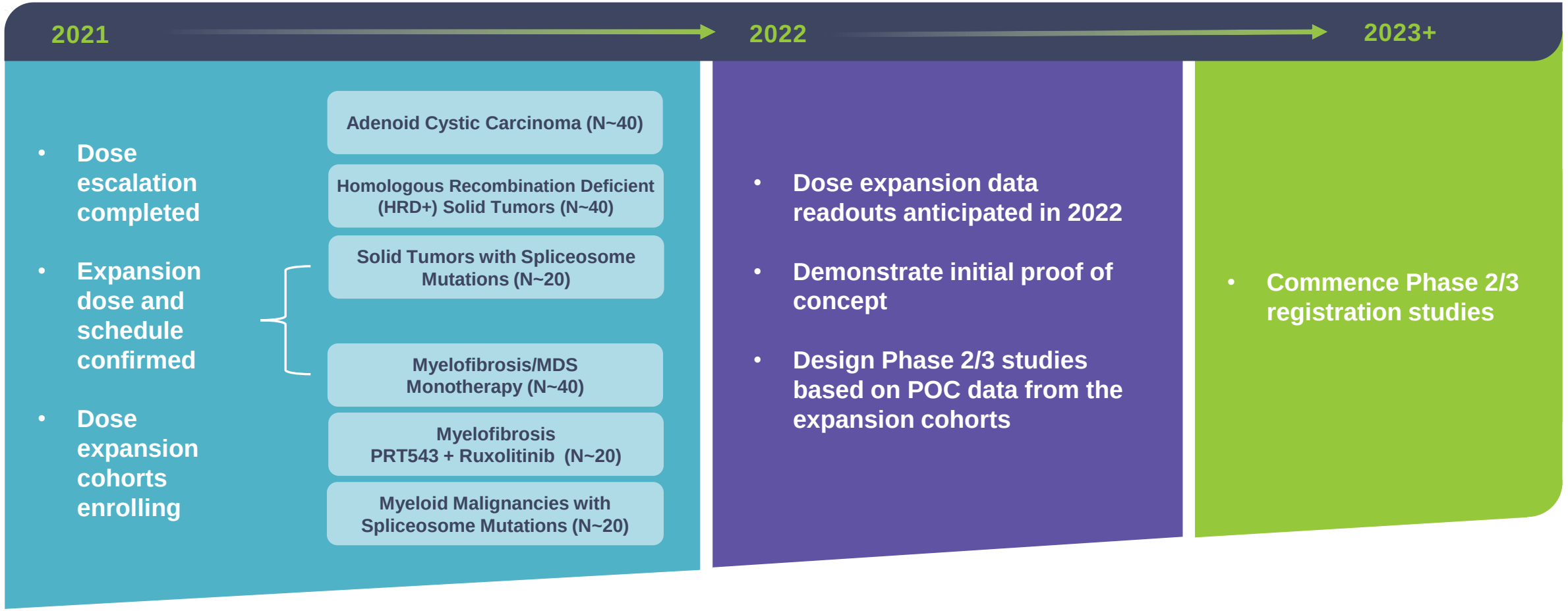


Intron Retention Observed at Higher Dose Levels



45 mg/5x week selected as recommended Phase 2 dose

PRT543 – Timeline and Clinical Plan



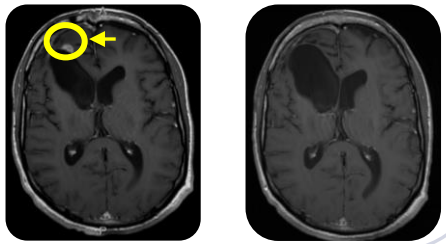
PRT811: Well-Tolerated with Evidence of Preliminary Clinical Activity in Phase 1 Dose Escalation Study

Study Demographics & Safety

- 45 patients
  - 27 across 16 unselected advanced solid tumors
  - 18 patients with high-grade glioma:
    - 17 relapsed/refractory GBM and 1 anaplastic astrocytoma
    - 1/17 patients with IDH1 mutated GBM
- PRT811 was well tolerated
  - Most common TRAEs of any grade in ≥ 5% of all patients: nausea, vomiting, fatigue, thrombocytopenia
  - Grade 3 ≥ AEs were uncommon occurring in 11% of patients
  - No DLTs at doses up to 600 mg QD

Preliminary Clinical Activity

- Two SF3B1+ uveal melanoma patients demonstrated anti tumor activity – both patients continuing on treatment
  - One patient had an uPR (47% decrease in target lesion) and continuing on therapy**
  - One patient had SD (25% decrease in target lesion for >6 months and continuing on therapy*
- One patient with triple negative breast cancer had a 27% decrease in target lesions**
- One patient with IDH1 mutated GBM experienced durable PR that evolved into CR*
  - Baseline: one target lesion per RANO
  - Prior treatment: surgery and chemoradiation + temozolomide
  - Nov/20: 77% reduction of target lesion, confirmed PR; August 2021: confirmed CR



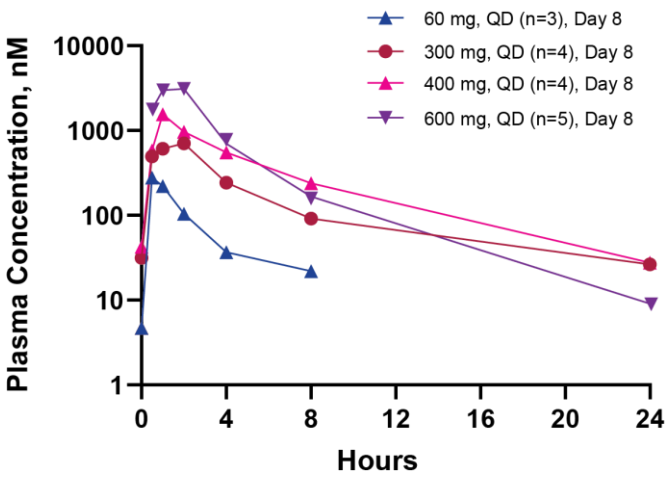
Baseline | Aug 2021

Data presented at 2021 AACR-NCI-EORTC Annual Meeting

*Data as of August 13, 2021
**Data as of September 20, 2021

PRT811: Exhibited Target Engagement and Inhibited PRMT5 Activity in Phase 1 Dose Escalation Study

Dose-Dependent Increases in Cmax and AUC



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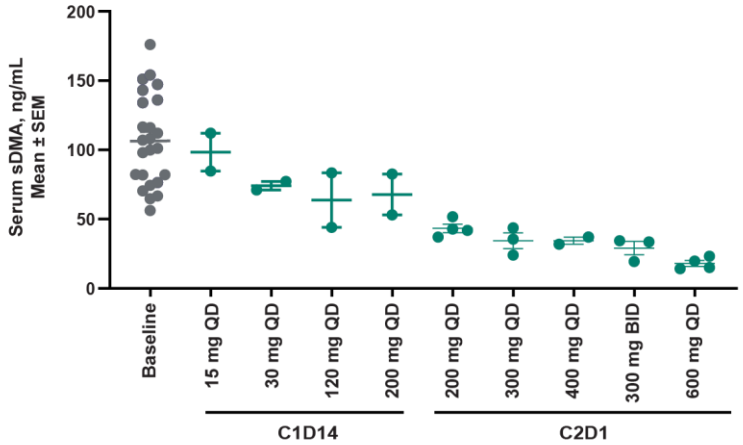
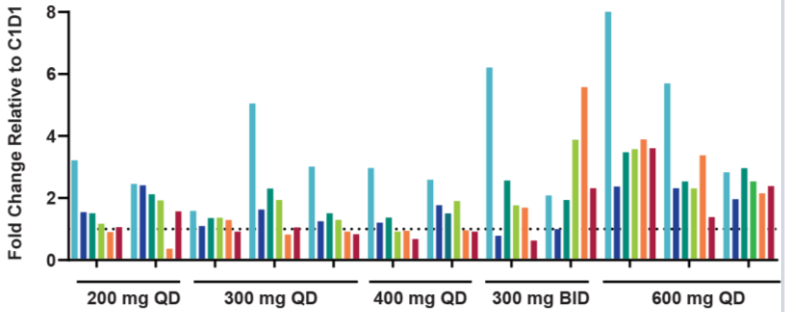
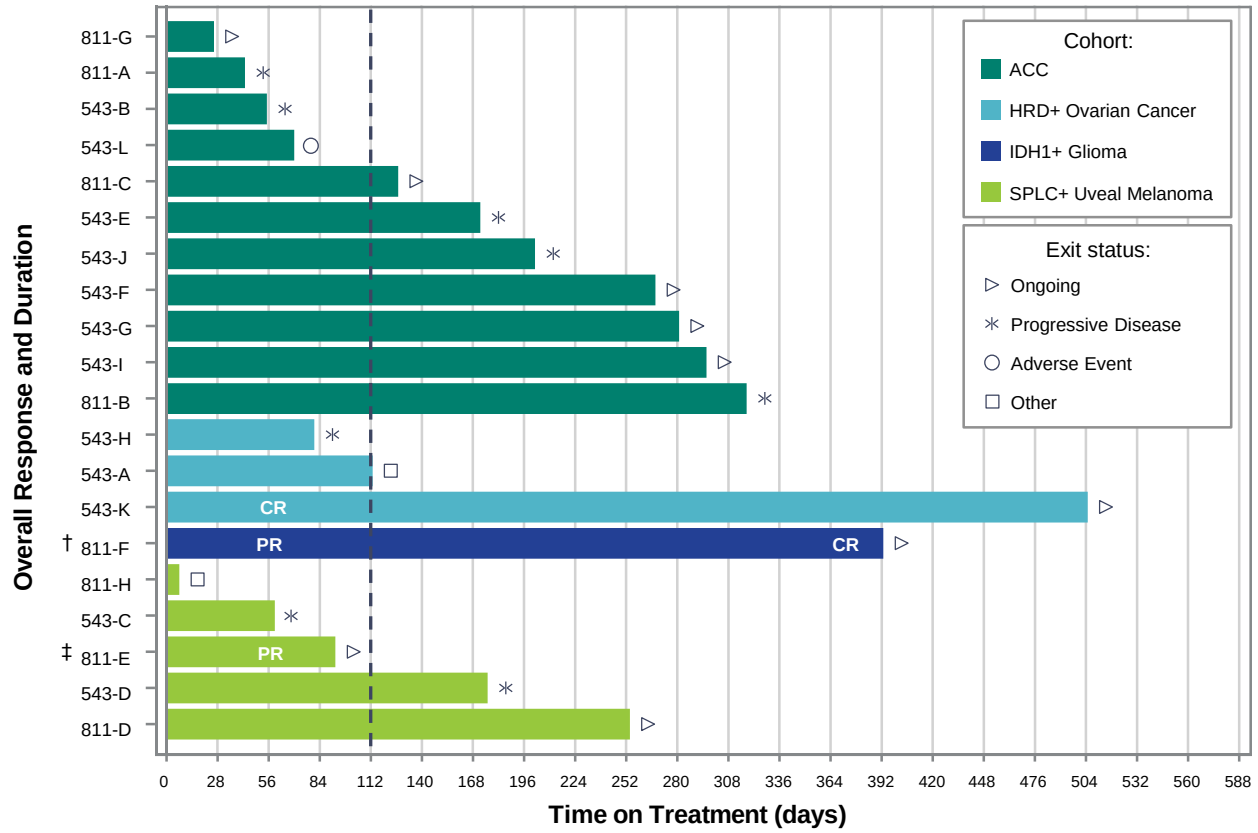


Intron Retention Observed at Higher Dose Levels

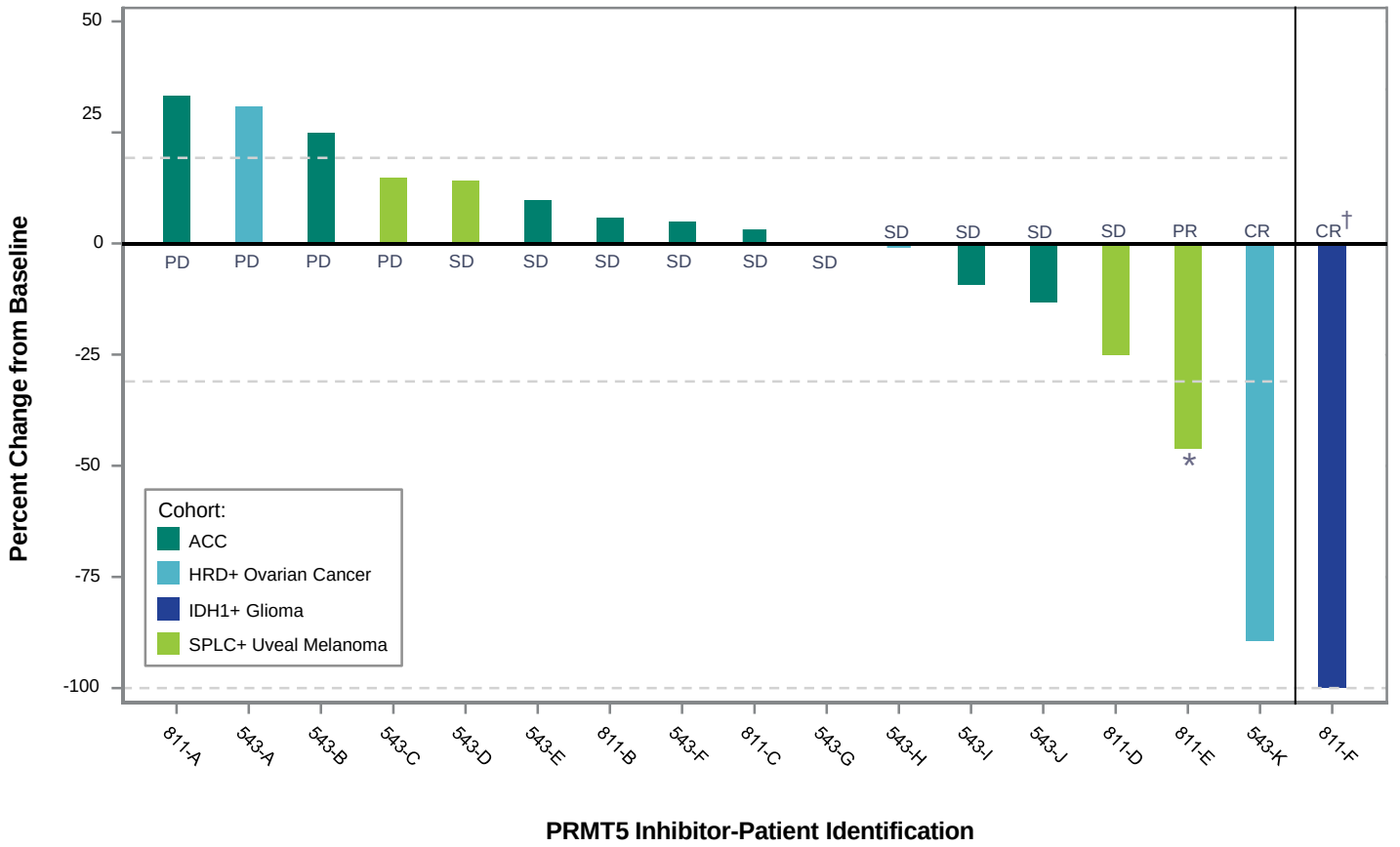


PRT543 and PRT811: Overall Response and Response Duration in Select Patient Cohorts From Dose Escalation Phase



†Target lesions assessed using RECIST, except for patient 811-F with glioma assessed by RANO.
‡Data cutoff for PRT543 was 8.6.21, for PRT811 was 8.13.21, and for patient 811-E was 10.8.21.
ACC, adenoid cystic carcinoma; CR, complete response; HRD, homologous recombination deficiency; IDH, isocitrate dehydrogenase; PD, progressive disease; PR, partial response; PRMT, protein arginine methyltransferase; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SPLC, splicing mutation.

PRT543 and PRT811: Overall Response of Target Lesions (RECIST or RANO) in Select Patient Cohorts From Dose Escalation Phase



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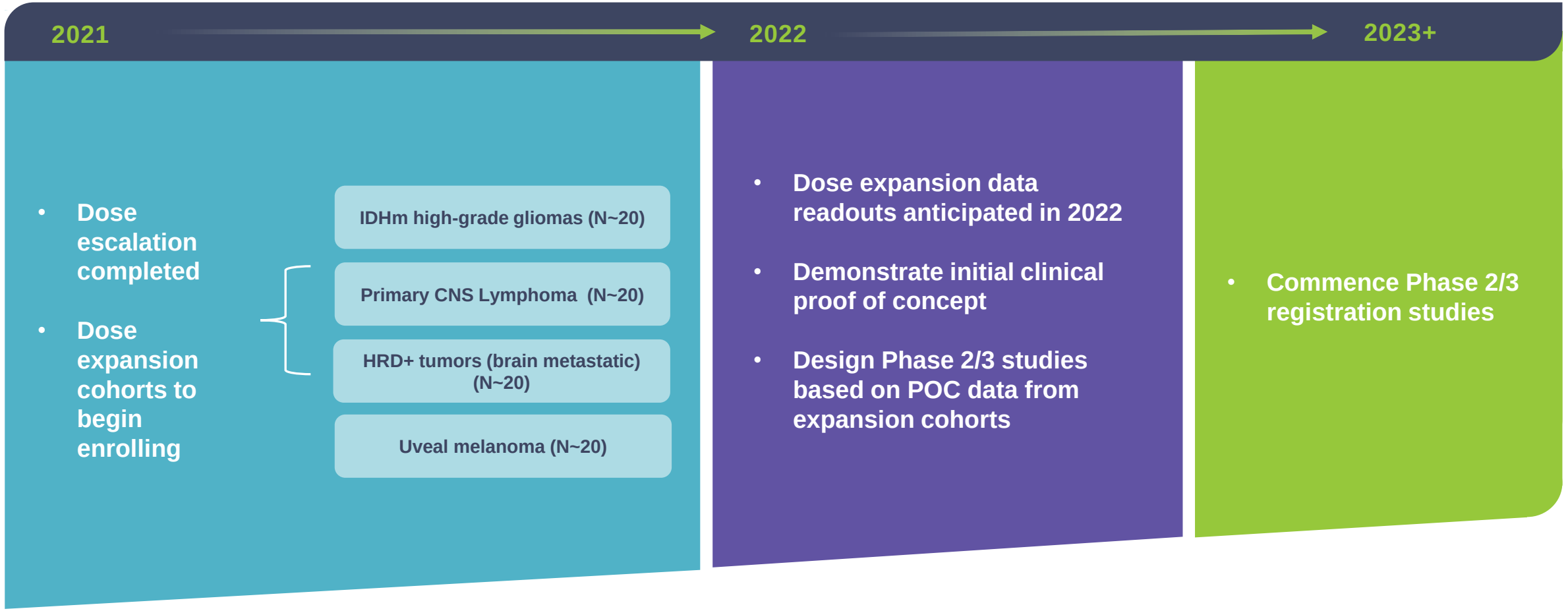
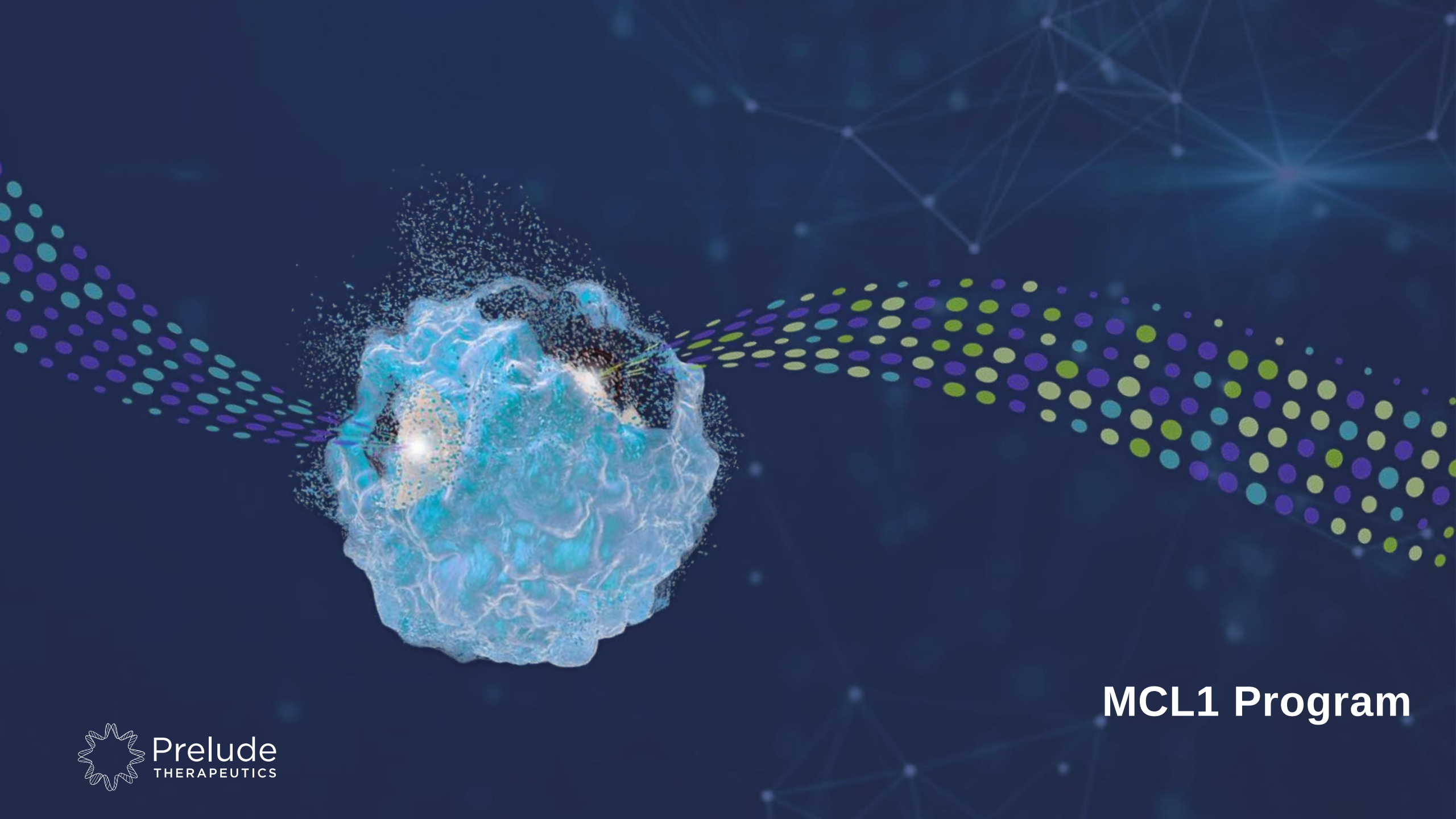
ACC, adenoid cystic carcinoma; CR, complete response; HRD, homologous recombination deficiency; IDH, isocitrate dehydrogenase; PD, progressive disease; PR, partial response; PRMT, protein arginine methyltransferase; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; SPLC, splicing mutation.

PRT811 – Timeline and Clinical Plan





MCL1 Program

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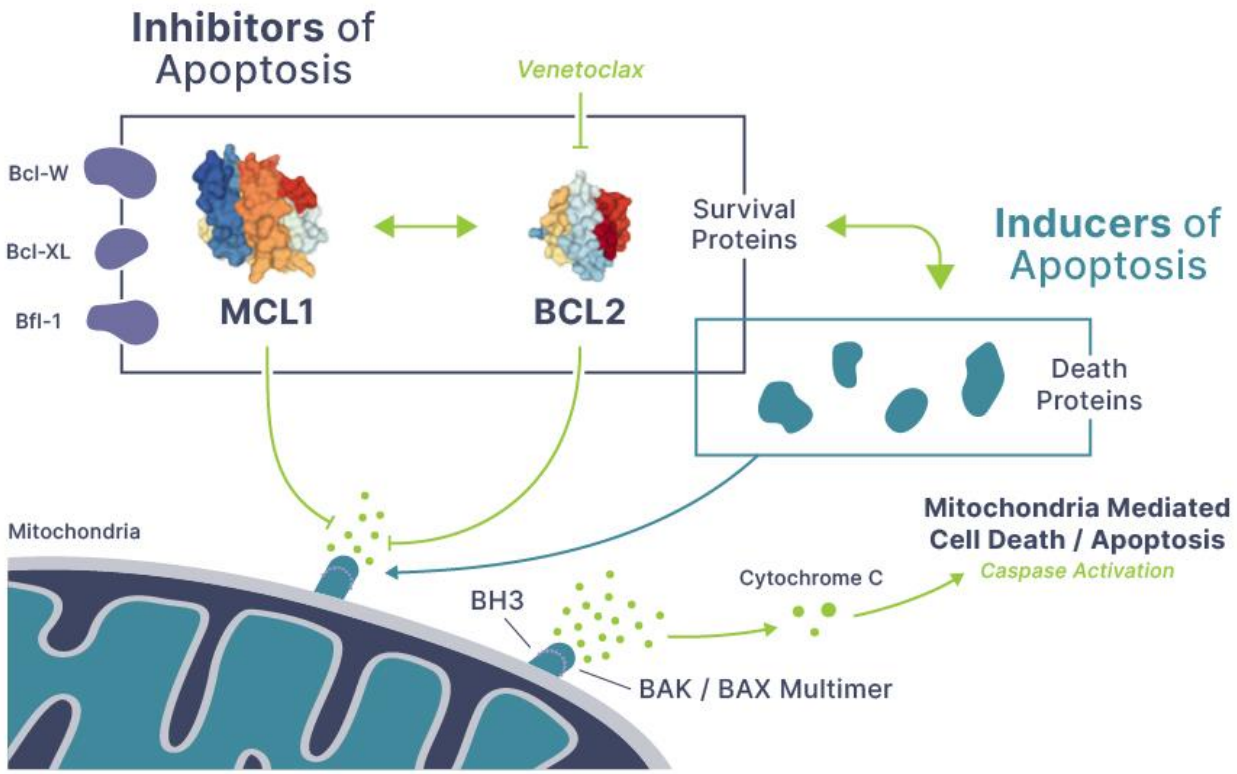
Prelude MCL1 Program

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 and Solid Cancers

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

Optimized PK Profile Maximizes Therapeutic Window

- High oral bioavailability and optimized physicochemical properties

Potential Rapid Path to Market

- Phase 1 dose escalation ongoing for both oral and IV formulations

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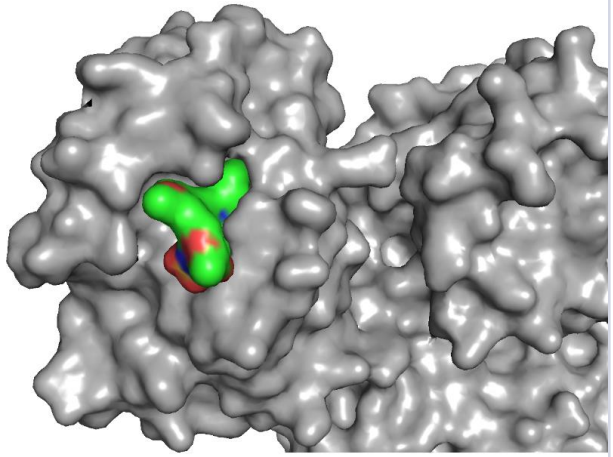
PRT1419: Potential Leading MCL1 Inhibitor

MCL1

Highly Potent Binding to MCL1

Prelude compounds are competitive inhibitors of BIM binding



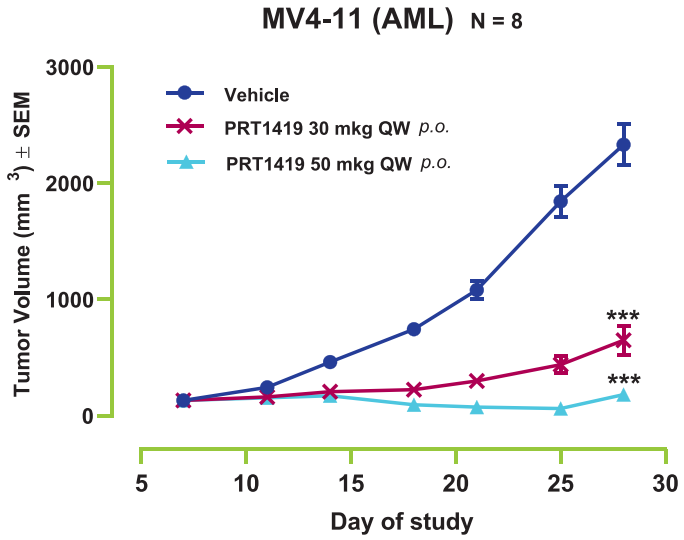
Assay	AMG176	AZD5991	MIK665	PRT1419
Proliferation IC_{50} (nM)	150	31	4.5	**80**
Whole Blood IC_{50} (nM)	1800	320	430	**210**
Caco-2 ($x10^{-6}$ cm/s)	6	<0.1	0.2	**11**
Human Hepat. Cl (%HBF)	42	ND	ND	**71**
Solubility at pH 7.4 (μg/mL)	13	ND	ND	**>1000**
Route of Administration	IV	IV	IV	**Oral/IV**

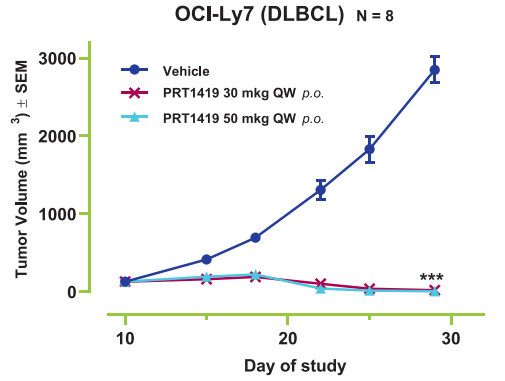
PRT1419 is a potent MCL1 inhibitor candidate with no preclinical evidence of cardiac toxicity

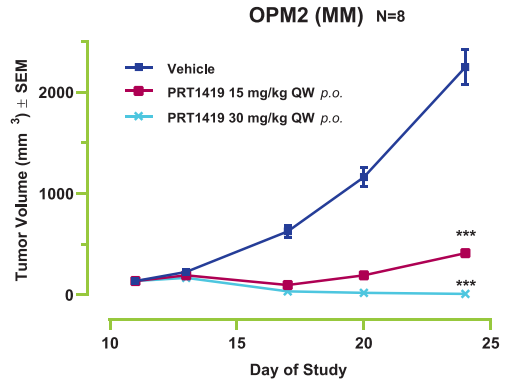
PRT1419 Demonstrated Preclinical Activity as Monotherapy and in Combination

MCL1

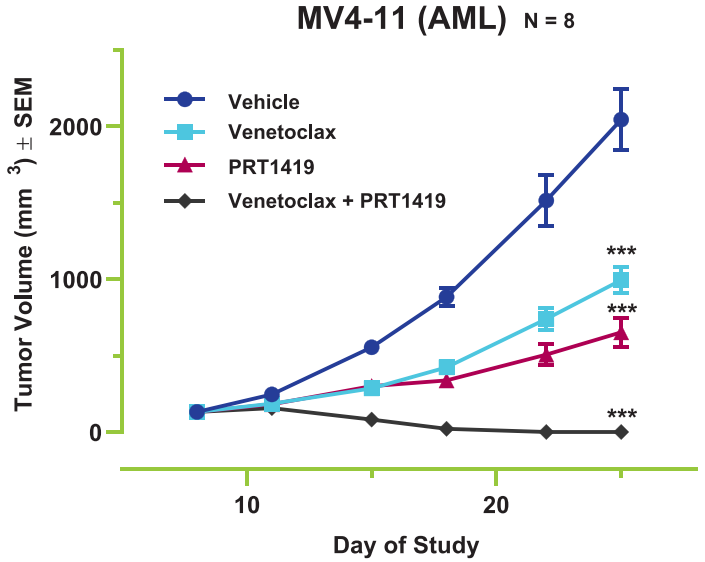
Monotherapy







Combination



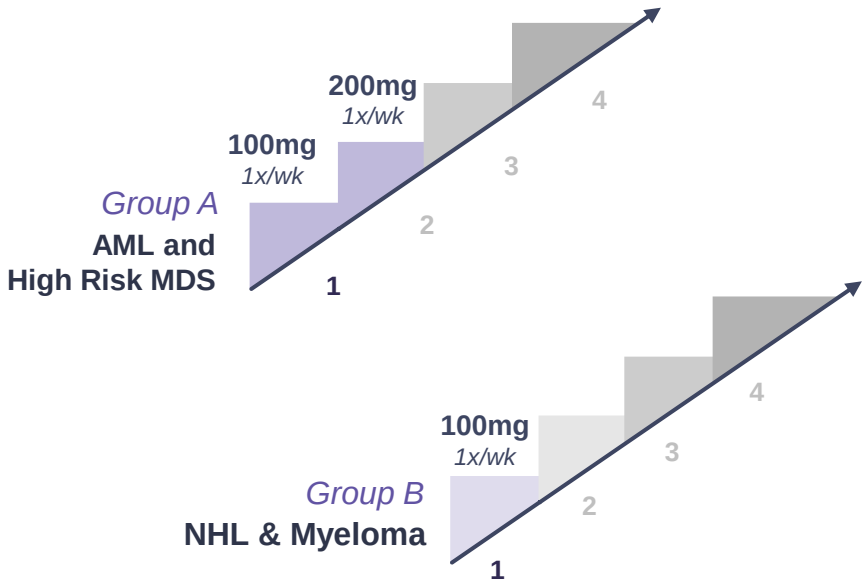
Dose-dependent activity with tumor regression at once-weekly, oral dosing in hematological tumor models

Oral PRT1419 Phase 1 Clinical Trial

MCL1

CURRENT → 2021

Dose Escalation



Expansion Cohorts

Recommended Expansion Dose

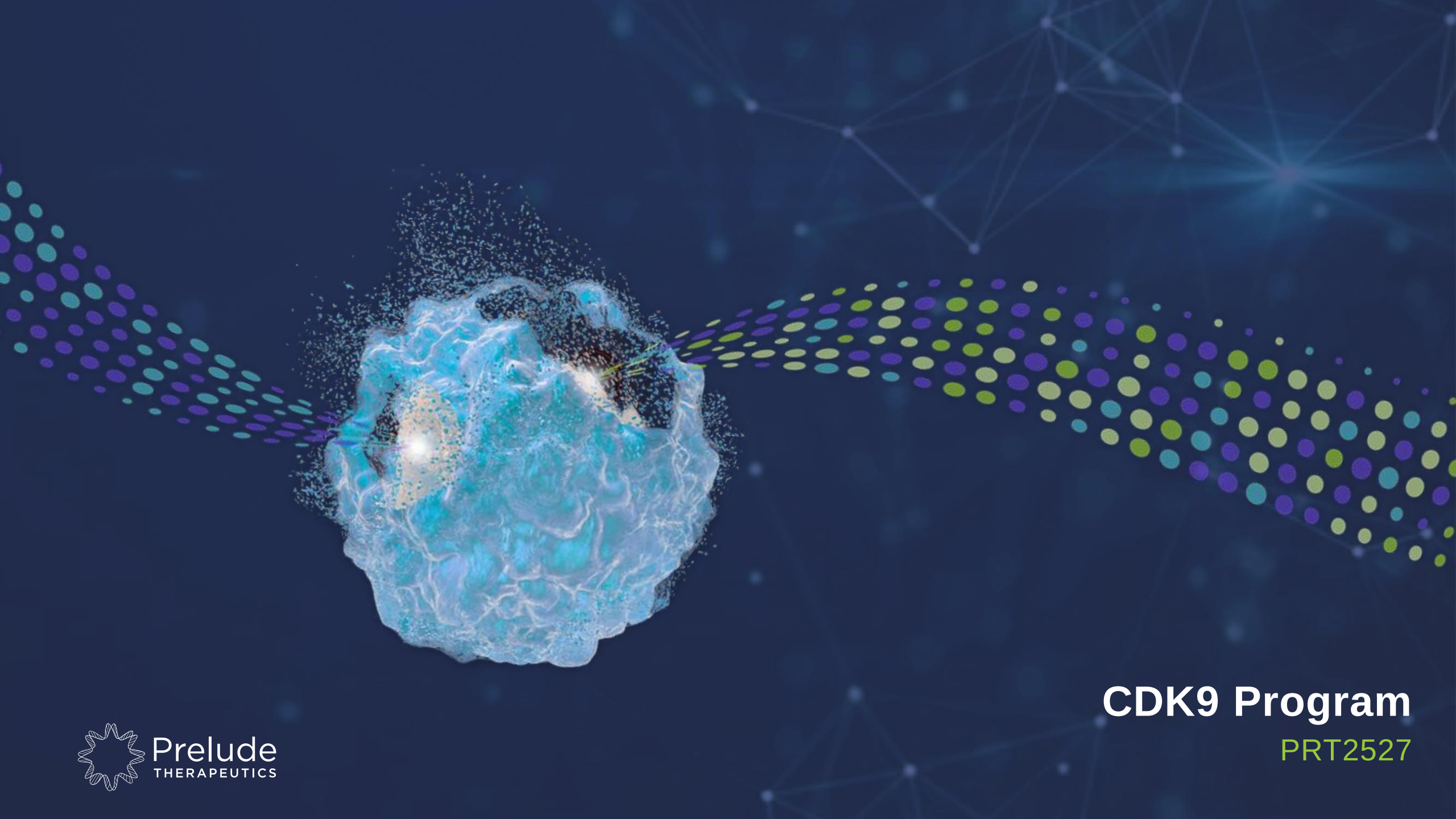
- AML (N~20)
- AML or MDS
  PRT1419 + Venetoclax or Aza
  (N~20)
- High Risk MDS (N~20)

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



CDK9 Program

PRT2527

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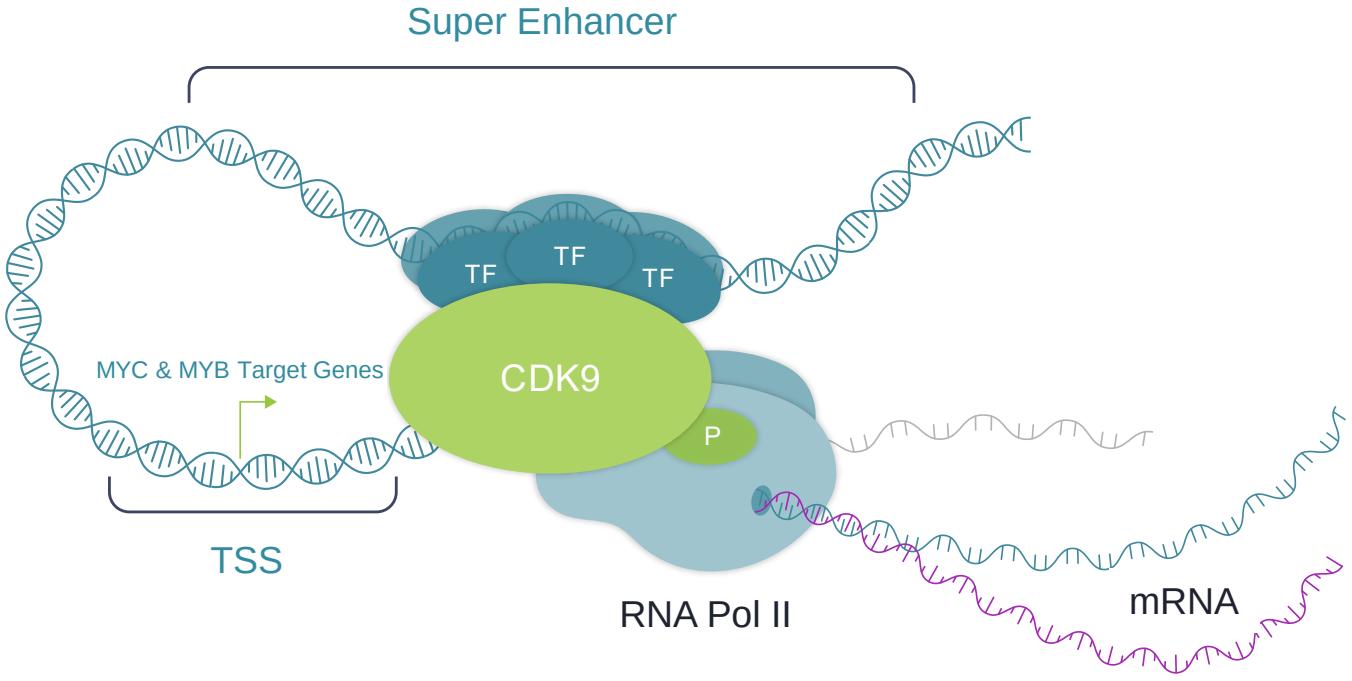
Prelude CDK9 Program

CDK9



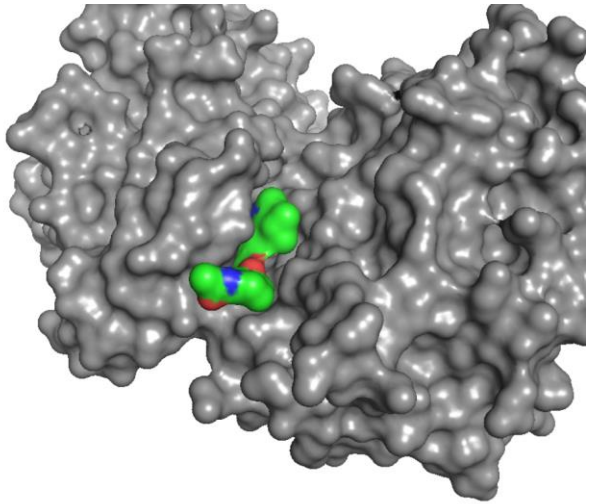
- CDK9 phosphorylates RNA Pol II and regulates transcription
- Regulates expression of several immediate early genes driving oncogenesis and resistance (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
  - Lack of selectivity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

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

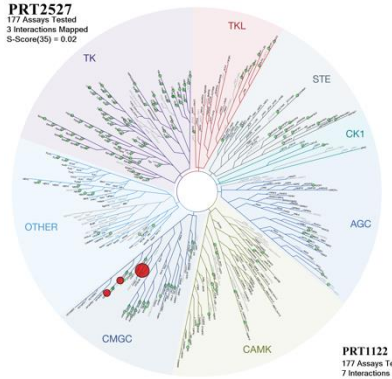
PRT2527 demonstrated improved potency and kinase selectivity relative to competitor compounds in preclinical studies

CDK9 Inhibitor Candidate: PRT2527

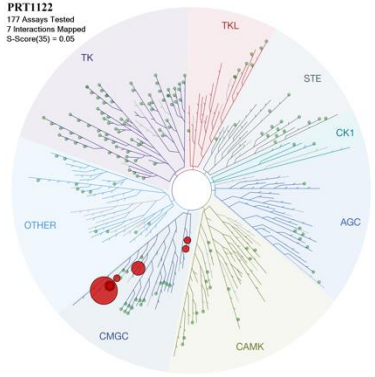
CDK9

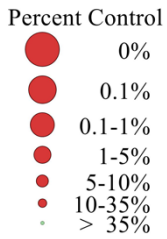
Improved Selectivity

PRT2527

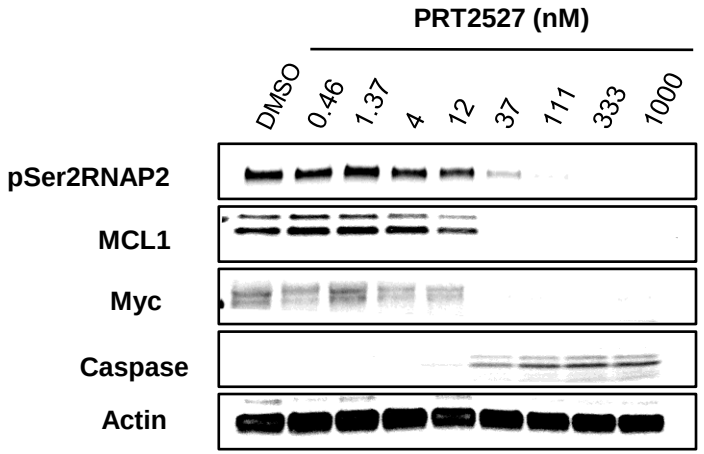


AZD4573



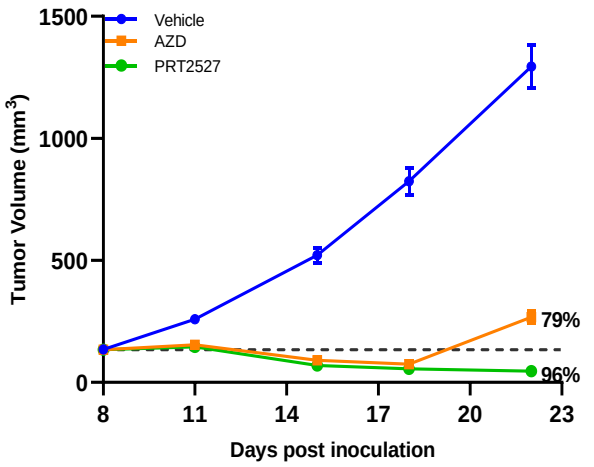


Potent in Vitro Activity



Sustained Regressions at Well-Tolerated Doses in Vivo

MV4-11 (AML)



PRT2527 IND expected to be filed in 2021

SMARCA2 Program

Prelude THERAPEUTICS

SMARCA2 Targeted Degrader Program

SMARCA2

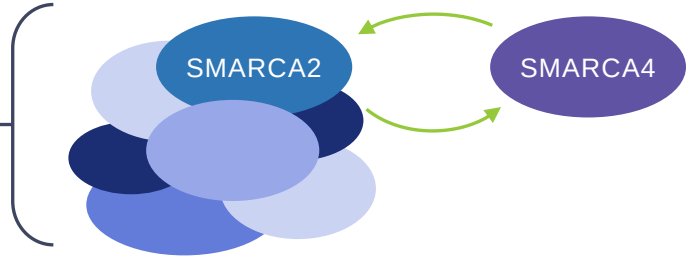
SMARCA4 and SMARCA2 Regulate Chromatin Accessibility and Gene Expression

Paralog Dependency

SMARCA4 Compensates for SMARCA2 Function

NORMAL CELL

SWI/SNF Chromatin Remodeling Complex



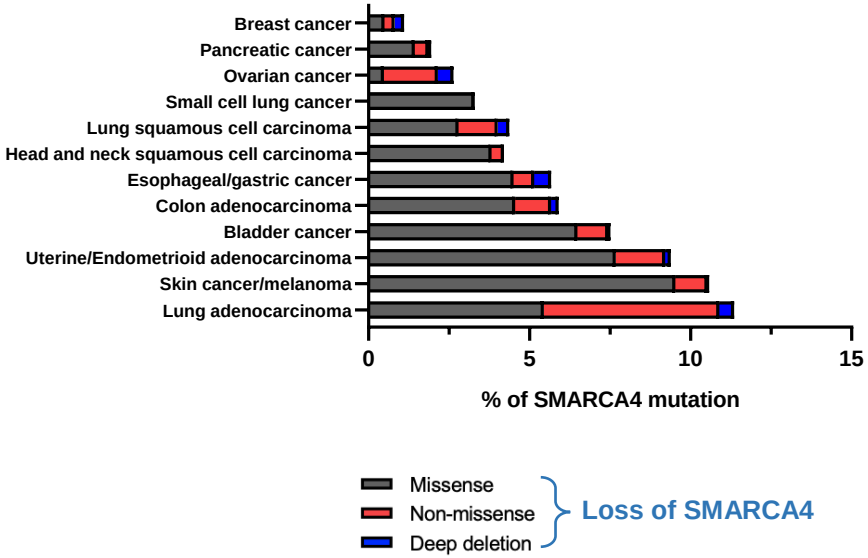
SMARCA4 MUTANT TUMORS

SMARCA2 Degradation → **Synthetic Lethality**

Dysfunctional SMARCA4

Tumor Cell Death

Loss of SMARCA4 Leads to SMARCA2 Dependency

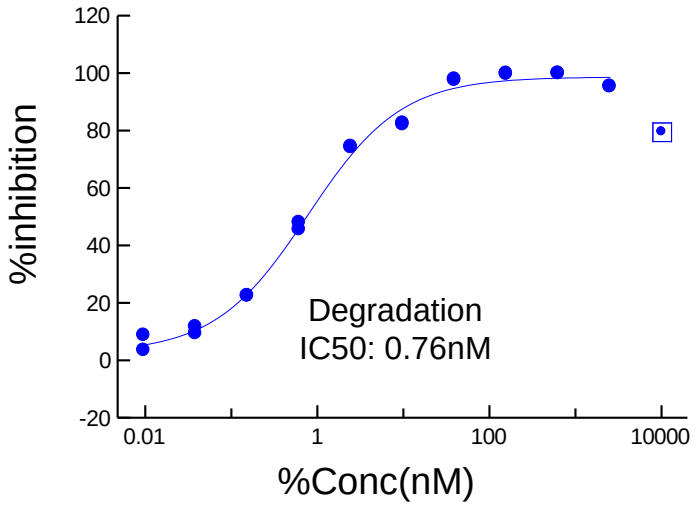


Opportunity to target 10 – 12% NSCLC with SMARCA4 deletions

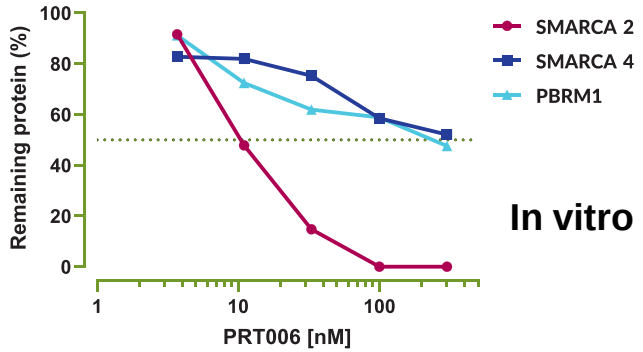
PRT-SCA2: Potent Selective SMARCA2 Degraders with In Vivo Activity

SMARCA2

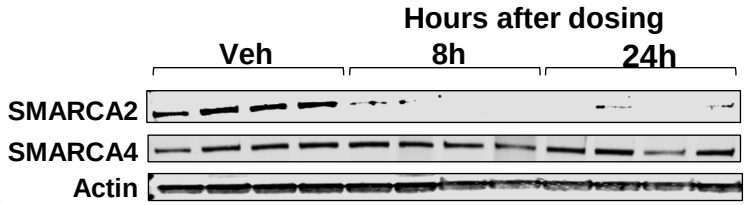
Sub-Nanomolar Potency for SMARCA2 Degradation



Highly Selective for SMARCA2 Degradation

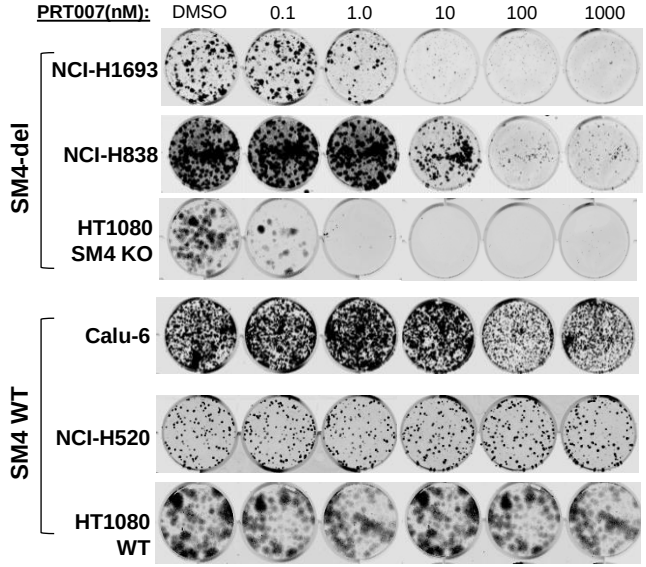


In vitro

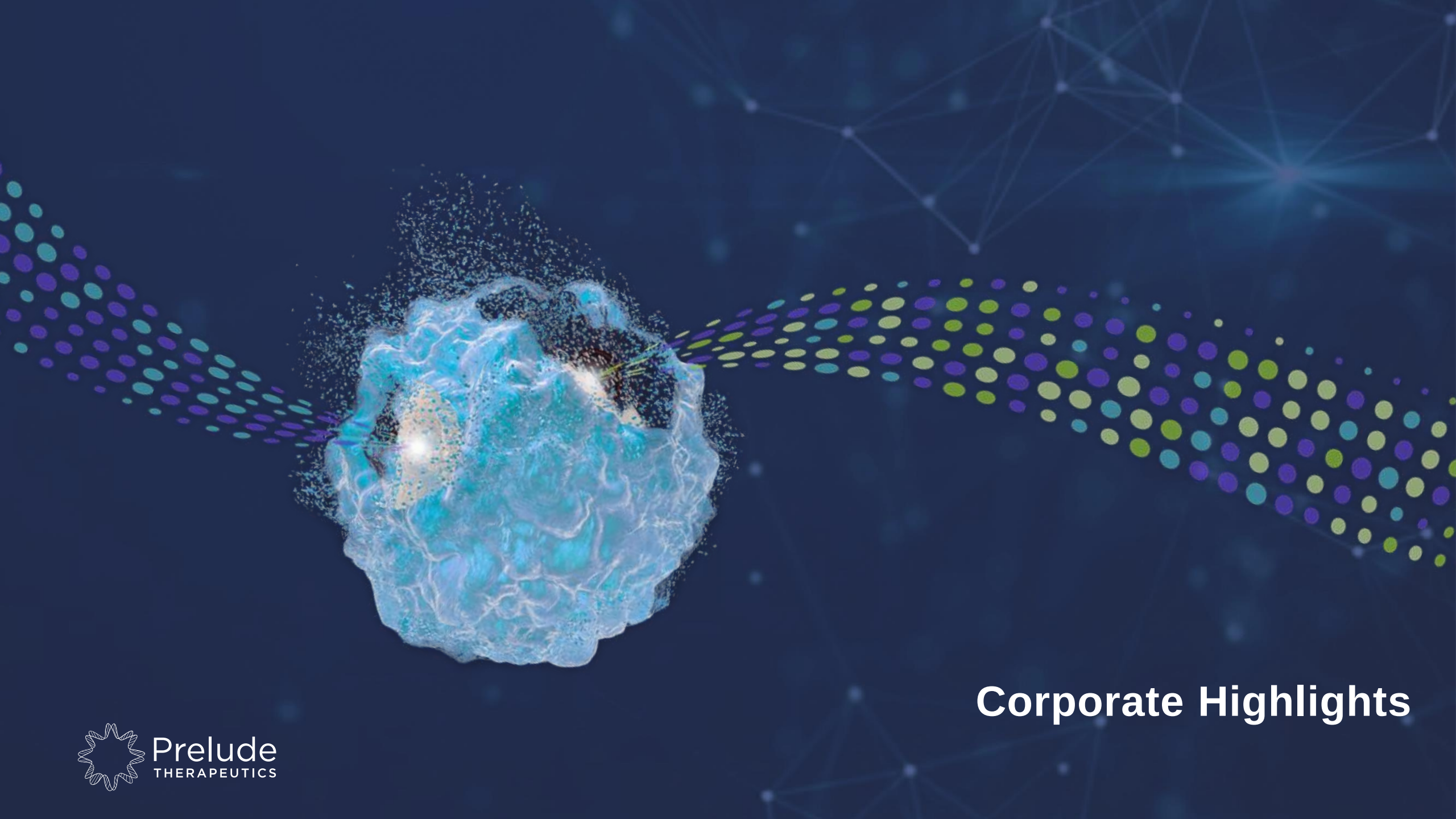


In vivo

Prelude SMARCA2 Degraders Replicate Genetic Synthetic Lethality



IND expected to be filed 2022



Corporate Highlights

Prelude THERAPEUTICS

Financial Summary

Shares Outstanding

- 47.0 million shares voting and non-voting common stock as of Nov 8, 2021
- 61.0 million shares fully diluted

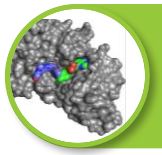
Cash and Cash Equivalents

- $320.9 million as of Sept 30, 2021
- The Company believes that its current cash, cash equivalents and marketable securities will be sufficient to fund operating expenses and capital expenditure requirements into the second half of 2023

Prelude THERAPEUTICS

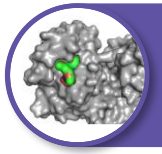
Prelude Roadmap for Value Creation

Anticipated 2021/2022 Milestones



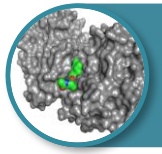
PRMT5

Report P1 dose expansion data
Generate POC in selected patients



MCL1

Complete dose escalation and initiate expansion/combination phase



CDK9

Initiate Phase 1 clinical trial in selected solid tumors

SMARCA2/ Kinase

Complete IND-enabling studies and file INDs

Future Strategy

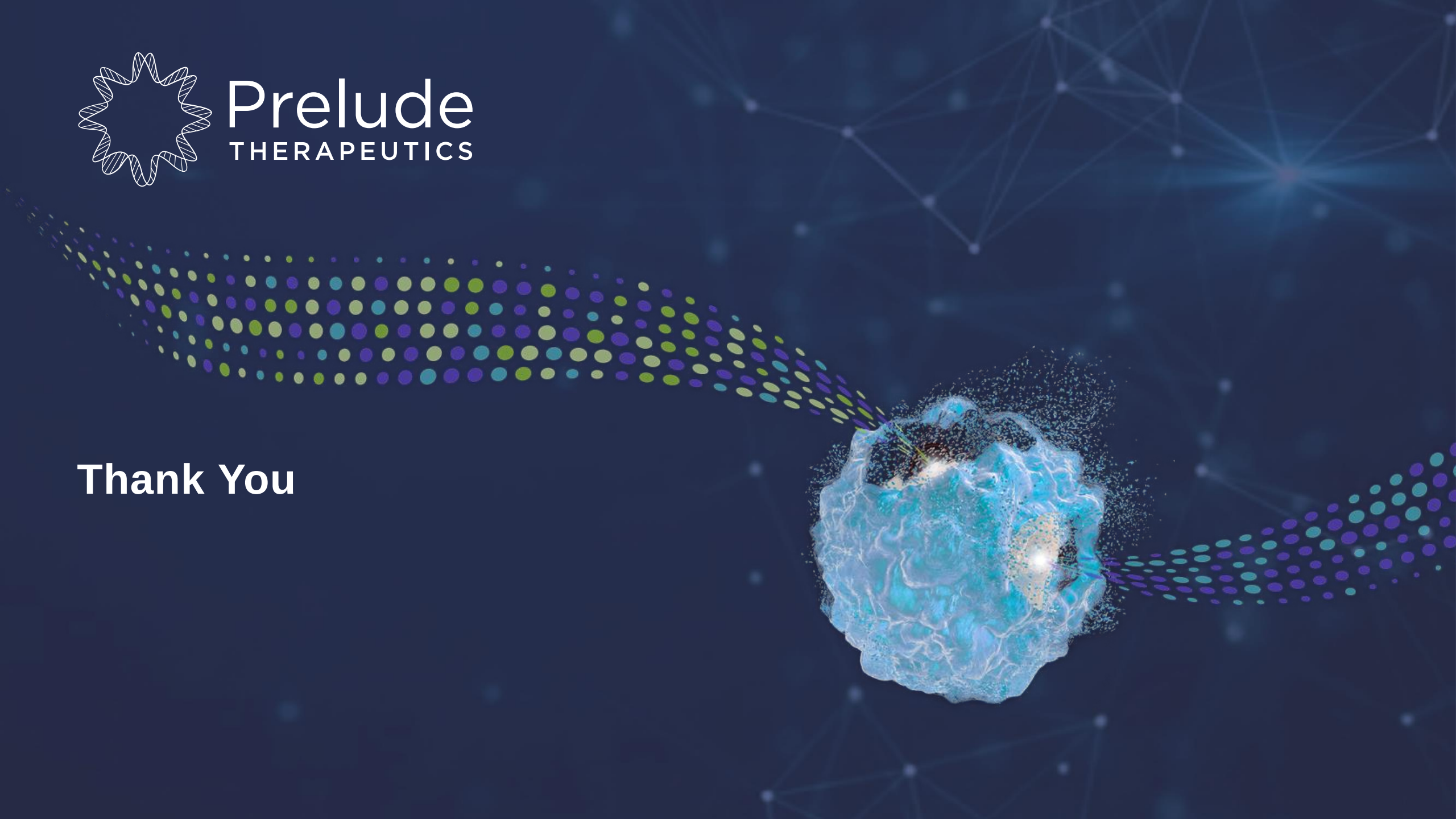
Leverage initial POC clinical data to inform design of P2 registration studies

Advance multiple precision oncology clinical programs focusing on underserved cancers

Continue to resource discovery engine to expand our pipeline

Maximize portfolio value through strategic partnerships

Prelude
THERAPEUTICS



Thank You