

**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 9, 2023

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

Delaware
(State or other jurisdiction of
incorporation or organization)

001-39527
(Commission
File Number)

81-1384762
(I.R.S. Employer
Identification No.)

200 Powder Mill Road
Wilmington, Delaware
(Address of principal executive offices)

19803
(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 7.01 Regulation FD Disclosure

Prelude Therapeutics Incorporated (the "Company") has prepared investor presentation materials with information about the Company, which it intends to use as part of investor presentations. A copy of the investor presentation materials to be used by management for presentations is attached as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Current Report on Form 8-K and in Exhibit 99.1 attached hereto is being furnished, but shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended ("Exchange Act"), and is not incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

<u>Exhibit Number</u>	<u>Description</u>
99.1	Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRELUDE THERAPEUTICS INCORPORATED

Date: January 9, 2023

By: /s/ Laurent Chardonnet
Laurent Chardonnet
Chief Financial Officer



Prelude
THERAPEUTICS

Corporate Presentation
January 2023

Patient focused
Science driven
Precision oncology



Forward Looking Statements

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, present data and clinical results or updates, and to obtain regulatory approvals for PRT543, PRT811, PRT1419, PRT2527, PRT3645, PRT3789 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).

Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities or differences. This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.

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 September 30, 2022 and in our upcoming Annual Report on Form 10-K for the year ended December 31, 2022.



Prelude Therapeutics: Delivering Precision Medicines to Patients

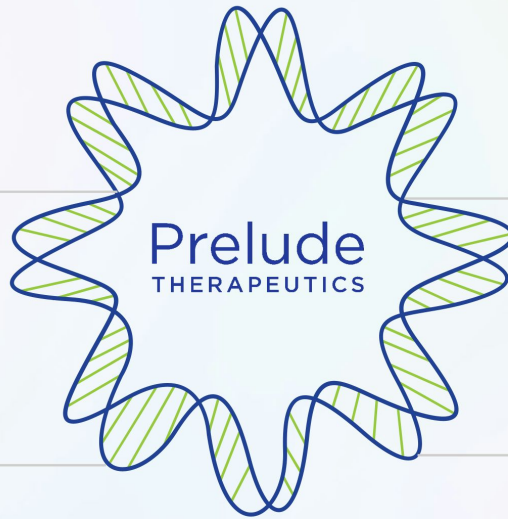
Powerful R&D Engine

Diversified Pipeline

Large Commercial Opportunities

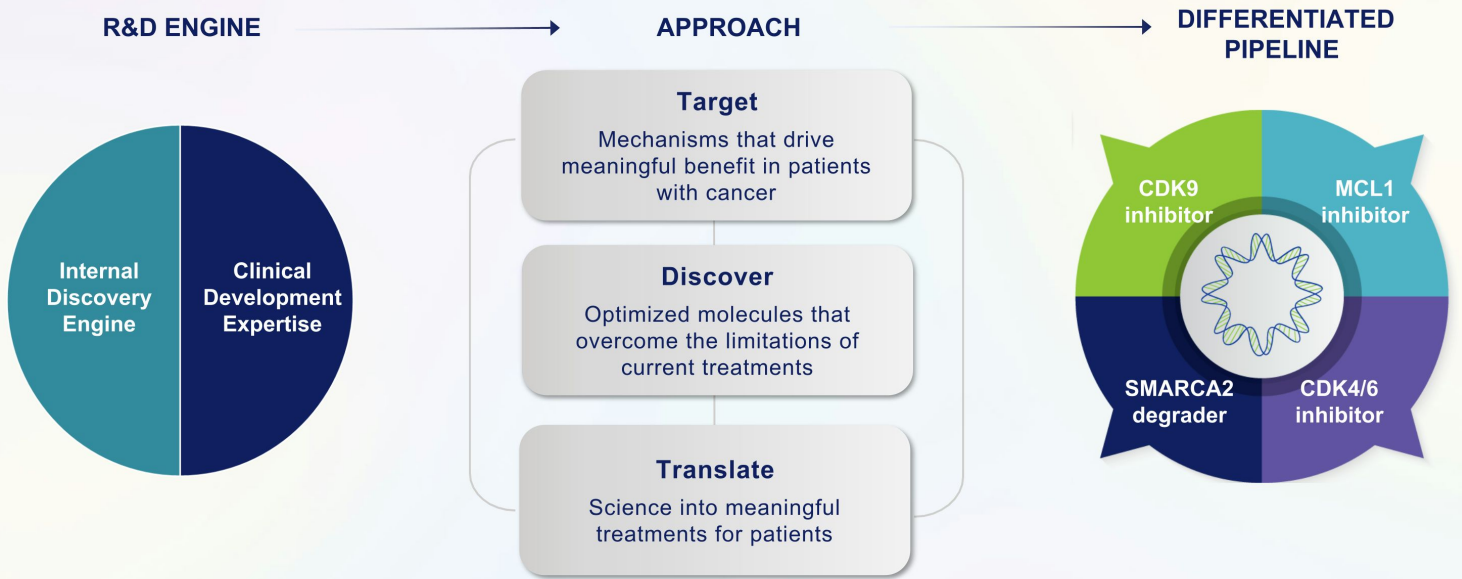
Exceptional Team

Well Capitalized





Prelude Discovery and Development Engine: Positioned to Succeed





Experienced Management Team: Proven Track Records



Kris Vaddi, PhD
Founder &
Chief Executive Officer



Jane Huang M.D.
President and Chief
Medical Officer



Andrew Combs, PhD
Executive Vice President
and Head of Chemistry



Laurent Chardonnet
Chief Financial Officer



Peggy Scherle, PhD
Chief Scientific Officer



Board of Directors

Paul Friedman, MD



CEO



Former CEO

Mardi Dier



Former CFO



Former CFO,
CBO

Victor Sandor, MD



Former CMO

David Bonita, MD



General Partner

Julian C. Baker

Managing Member
Baker Brothers Investments

Kris Vaddi, PhD

Founder &
Chief Executive Officer

Martin Babler



Former CEO



Prelude Precision Oncology Pipeline: Diversified and Differentiated

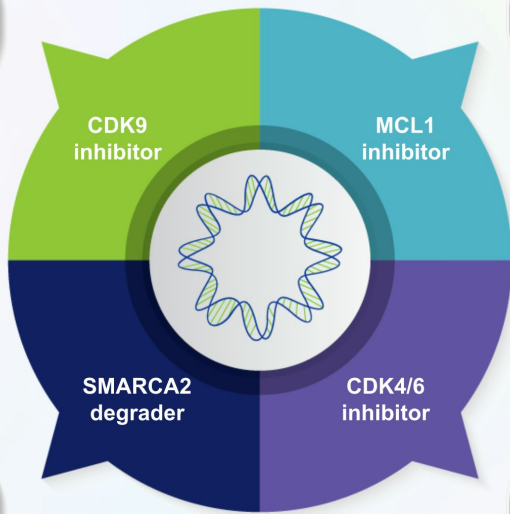
PROGRAM	CANCER INDICATIONS	DISCOVERY	IND ENABLING	PHASE 1	PHASE 2/3	Anticipated Milestones
PRT2527 (CDK9 Inhibitor)	Selected solid and hematologic malignancies					Report Clinical Data in Solid Tumors and Hematological Malignancies – 2023
PRT1419 (MCL1 Inhibitor)	Selected hematologic malignancies and solid tumors					Report Clinical Data in Solid Tumors and Hematological Malignancies – 2023
PRT3645 (Next Generation CDK4/6 Inhibitor)	Selected Solid tumors					Report Phase 1 Dose Escalation – 2023 Expansion Cohorts – 2024
PRT3789 (SMARCA2 Degradar)	Multiple genomically-selected cancers					Report Phase 1 Dose Escalation – 2023 Expansion Cohorts – 2024
New Programs (Multiple targets)	Selected solid and hematologic malignancies					Selection of Development Candidate



Differentiated Pipeline with Transformative Potential

Potentially Best-in-Class Selectivity
Potential to avoid off-target toxicity and higher clinical activity

Optimized PK Profile
Potential for maximal target engagement and improved cardiac safety



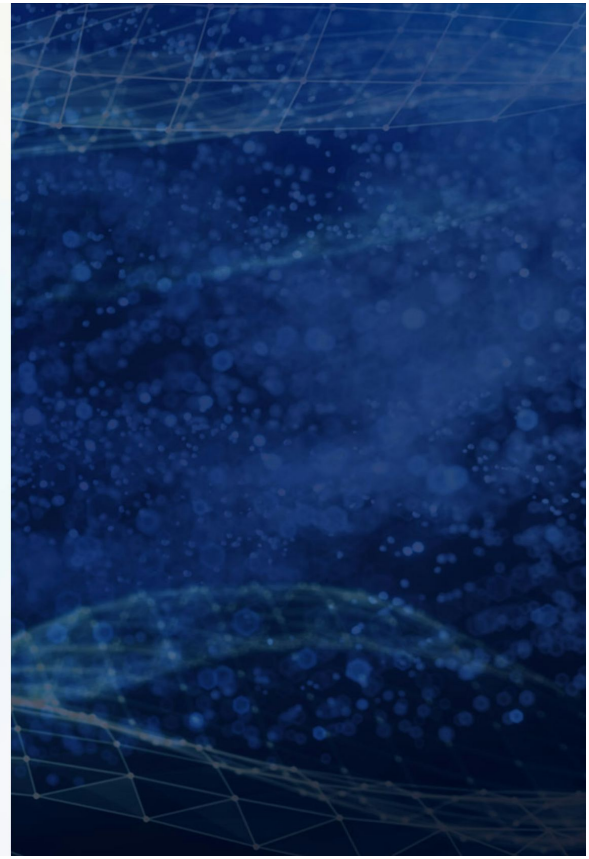
Potent and Selective Degraders
Potential to address major unmet need in biomarker-selected patients

Highly Selective Differentiated Metabolic Profile
Potential for high tissue and brain penetration and better combinability

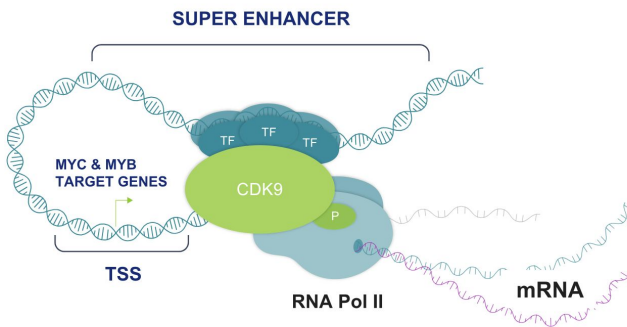


PRT2527

CDK9 Inhibitor



CDK9 Inhibition: Targeting Cancer by Regulating Oncogene Expression

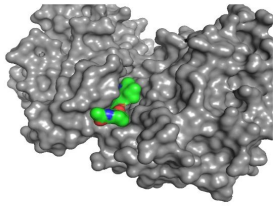


- CDK9 regulates expression of several **oncogenes that drive cancer cell growth and resistance** (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
- **Improving the selectivity** of CDK9 inhibitors may translate to **better activity and safety**

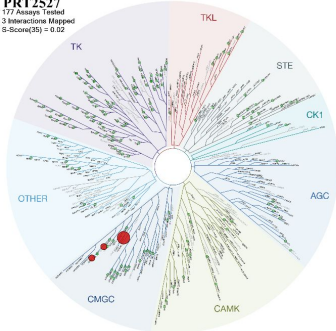


PRT2527: Potent and Highly Selective CDK9 Inhibitor

Highly Selective, ATP Competitive
CDK9 Inhibitor



PRT2527
177 Proteins Tested
3 Interactions Mapped
S-Score(75) = 0.22



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 BAY151 and licensed to Vincerx by Bayer

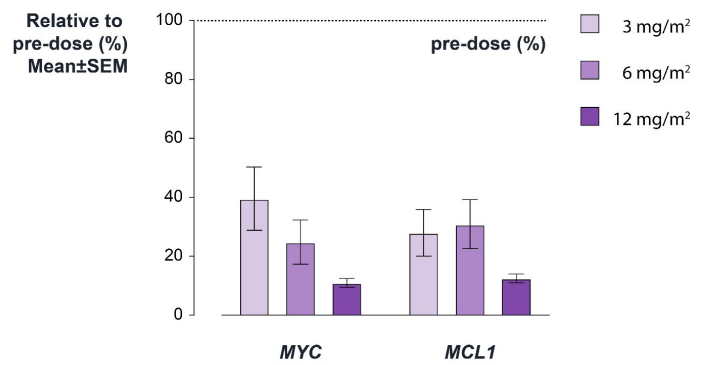


CDK9 inhibitor: PRT2527

Phase 1 Dose-Escalation Study in Advanced Solid Tumors

- Phase 1 dose escalation study of PRT2527 is ongoing and enrolling following tumor types
 - Selected sarcomas displaying a gene fusion
 - Castrate resistant prostate cancer
 - HR+ HER2- breast cancer
 - Non-small cell lung cancer
 - Solid tumors with MYC amplification
- Nine patients have been treated in the first three dose levels (3, 6 and 12 mg/m² I.V. weekly), with no dose-limiting toxicities and acceptable tolerability to date

Dose-dependent inhibition of CDK9 transcription targets observed in PBMCs



ASH Annual Meeting 2022 Abstract No. 210

HR+ Hormone receptor positive; HER2- Human epidermal growth factor negative
ClinicalTrials.gov Identifier: NCT05159518



CDK9 Inhibitor: PRT2527

Phase 1 Studies in Solid Tumors and Hematologic Malignancies

Dose Escalation

PRT2527
Solid Tumors
N=11



Dose Confirmation

PRT2527
MYC Amplified or Overexpressed Solid
Tumors,
Prostate Cancer
N=15

ClinicalTrials.gov Identifier: NCT05159518

Solid Tumor data in 1H 2023

Dose Escalation

PRT2527
Monotherapy
Aggressive B cell lymphomas (multiple
types), follicular lymphoma,
CLL/SLL/Richters, MCL



Dose Confirmation

PRT2527
N=30

*RP2D in hematological malignancies 2H 2023
Initial clinical data in 2H 2023*

Solid Tumors

- Dose dependent increases in exposure and target engagement observed in Phase 1
- Clinical MYC and MCL1 depletion to levels consistent with tumor regression in preclinical models
- Generally well tolerated

Hematologic Malignancies

- ASH 2022 preclinical oral presentation
- CDK9 as a target externally validated in aggressive lymphoma and other heme malignancies



CDK9 Inhibitor Differentiation and Market Opportunity

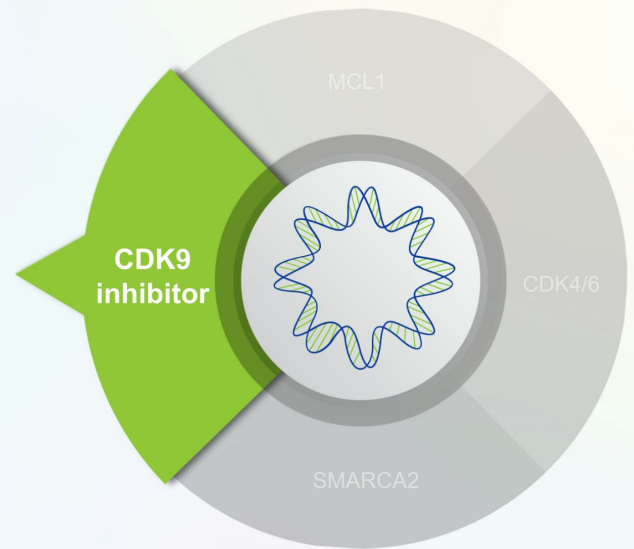
Potential for Improved Safety Based on Best-in-Class Kinome Selectivity

PRT2527 is a highly potent CDK9 inhibitor with **best-in-class kinome selectivity** compared to competitor compounds

- **Optimized PK profile** to maximize therapeutic window
- **Well-tolerated in GLP preclinical studies** at doses exceeding those required for efficacy
- **High levels of inhibition** of CDK9 dependent genes in Phase 1

Market Opportunity

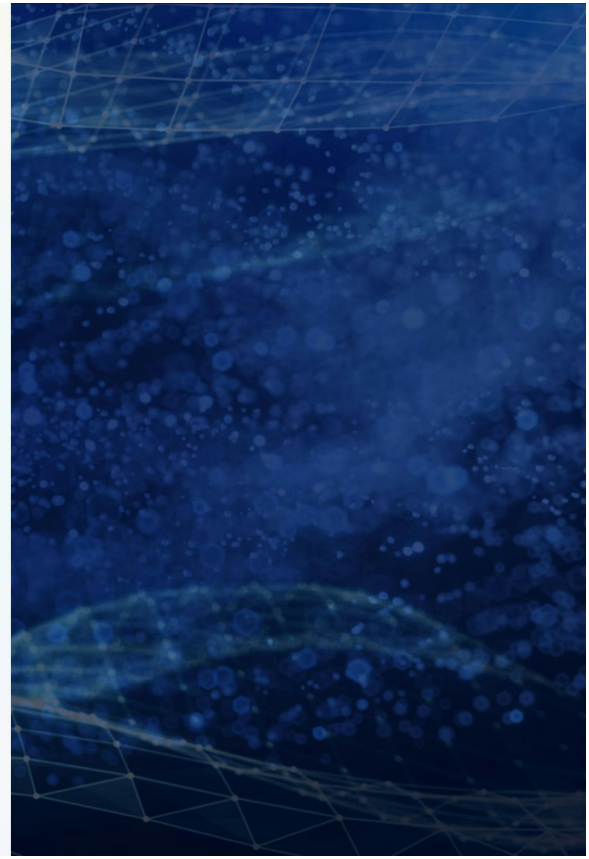
- CDK9 inhibitors in CLL, Mantle cell lymphoma, and DLBCL may address areas of high unmet need
- There are ~ 50,000 DLBCL patients , 55,000 CLL patients, and 25,000 mantle cell patients treated each year in the US





PRT1419

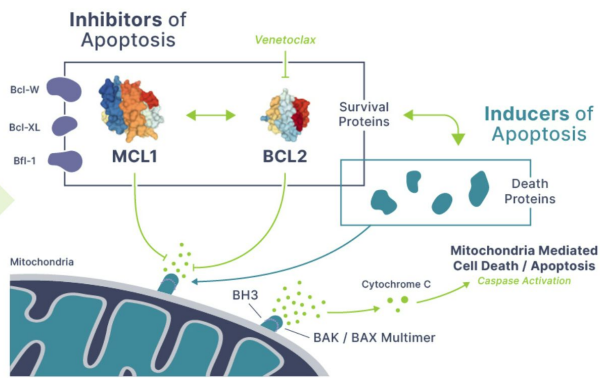
MCL1 Inhibitor





MCL1 inhibition: Targeting Cancer Cell Survival

Mechanism

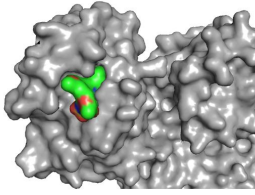


- MCL1 is a member of the **BCL2 family of inhibitors** of apoptosis
- **Established resistance** mechanism to the BCL2 inhibitor Venetoclax
- Prolonged depletion of MCL1 is undesirable and may be associated with cardiac toxicity
- Optimizing the PK profile of an MCL1 inhibitor may **maximize the therapeutic window**

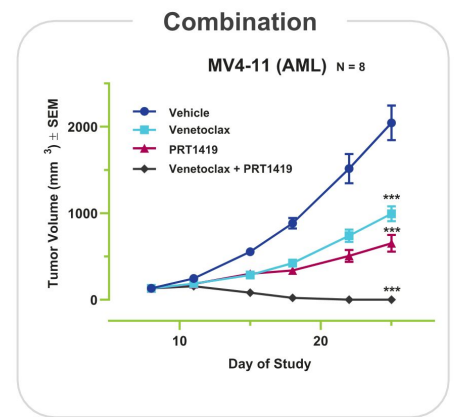
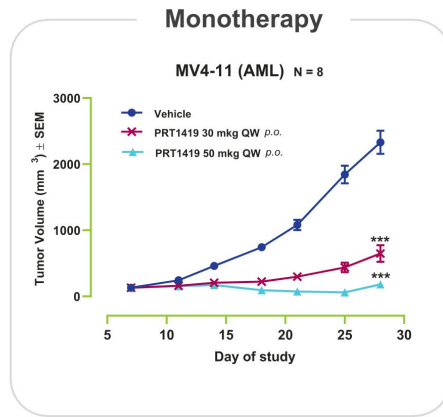


PRT1419: Potent MCL1 Inhibitor with Strong Preclinical Activity as Monotherapy and in Combination

Prelude compounds are competitive inhibitors of BIM binding



	Proliferation IC ₅₀ (nM)	Whole Blood IC ₅₀ (nM)
AMG176	150	1800
AZD5991	31	320
MIK665	4.5	430
PRT1419	80	210



Robust monotherapy activity also seen in models of DLBCL & MM



MCL1 inhibitor: PRT1419

Phase 1 Study in Hematologic Malignancies

Dose Escalation

PRT1419
Monotherapy



Dose Confirmation

AML/MDS/CMML
CLL/SLL
FL/MZL/MCL
N=24-30

PRT1419
Combination



PRT1419+Aza: AML/MDS/CMML
PRT1419+Ven: AML/MDS/CMML
PRT1419+Ven: MCL
N=24-30

RP2D in heme monotherapy expected 2H 2023
Initial clinical data in 2H 2023

ClinicalTrials.gov Identifier: NCT05107856

- In the solid tumor PRT1419 dose escalation Phase 1, 26 patients have been treated and 15 patients @ RP2D
- No cardiac toxicity seen @ RP2D as measured by ejection fraction decline/troponin elevation
- Solid tumor data to be presented 1H 2023
- Upregulation of MCL1 is a mechanism of resistance to BCL2 inhibition, particularly in CLL and AML; Strong preclinical hypothesis in heme¹



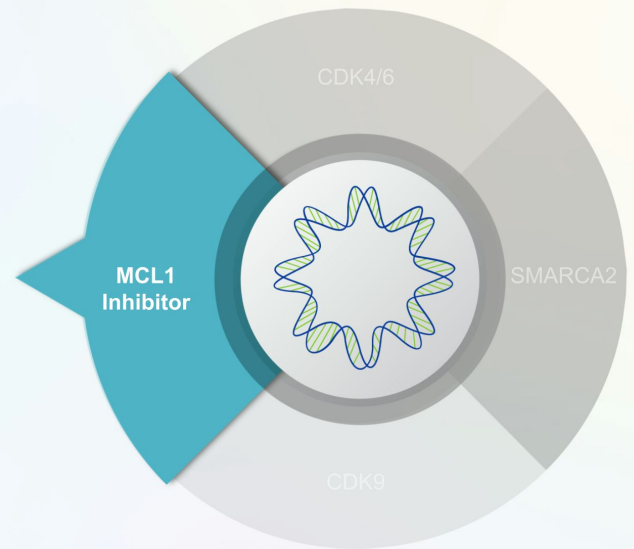
MCL1 Inhibitor Differentiation and Market Opportunity

Optimized PK Profile to Achieve Desired Target Engagement

- PRT1419 is a **highly potent and selective** MCL1 inhibitor
- Designed to have a PK profile with **high clearance** to provide desired target engagement with **improved safety**
- **No cardiotoxicity or troponin changes** in GLP preclinical studies at doses exceeding those required for efficacy
- **No evidence of cardiotoxicity** in the solid tumor Phase 1 at the recommended Phase 2 dose

Market Opportunity

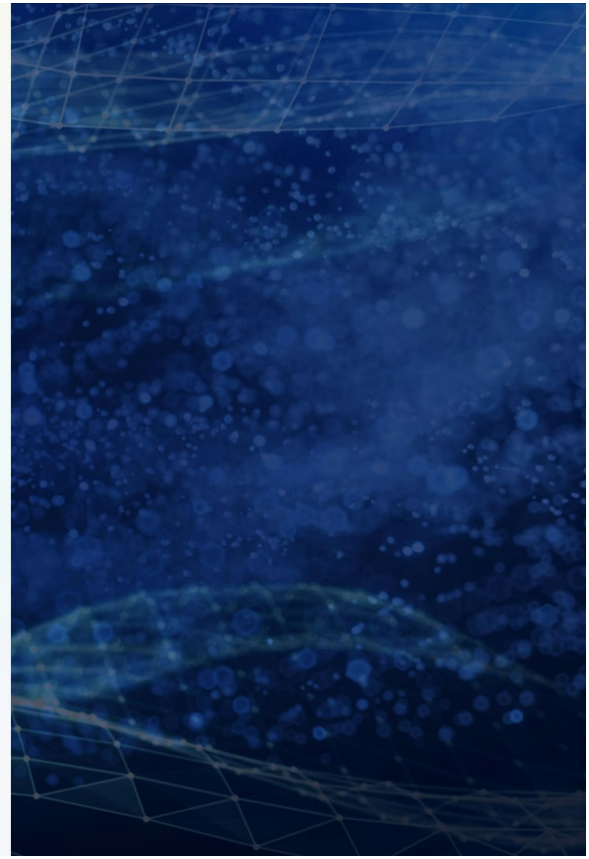
- AML, MDS, CLL, MCL patients need additional treatment options
- There are ~ 37,000 AML patients , 55,000 CLL patients, and 25,000 mantle cell lymphoma patients treated each year in the U.S.





PRT3645

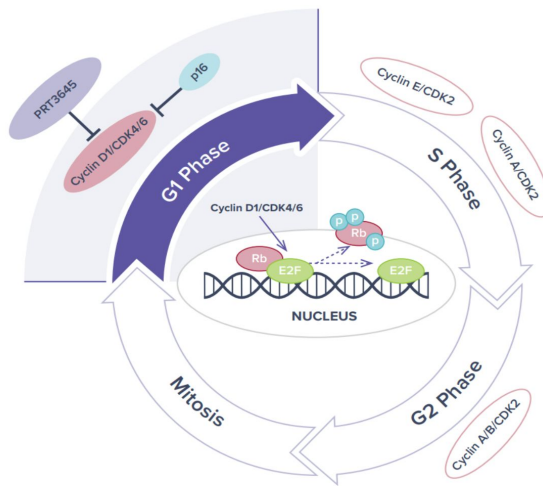
CDK4/6 Inhibitor





CDK4/6 Inhibition: Targeting Cancer Through Cell Cycle Regulation

Mechanism



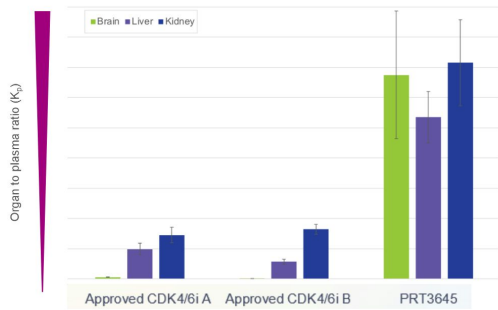
- **Validated mechanism** with approval of CDK4/6 inhibitors in HR+ breast cancer
- **Resistance mechanism** to other targeted therapies including KRAS G12C inhibitors
- Current CDK4/6 inhibitors limited by poor tolerability and lack broad tissue penetration
- Next generation CDK 4/6 inhibitor with **improved tolerability and tissue penetrance** could translate into **activity in areas of unmet need** beyond HR+ breast cancer
- Sequential use of CDK 4/6 inhibitors in breast cancer may also improve outcomes



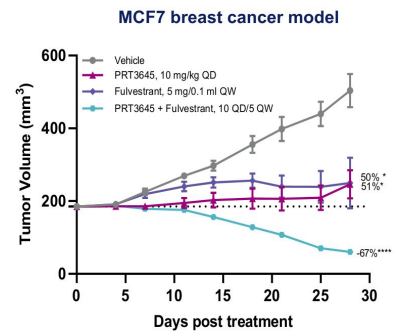
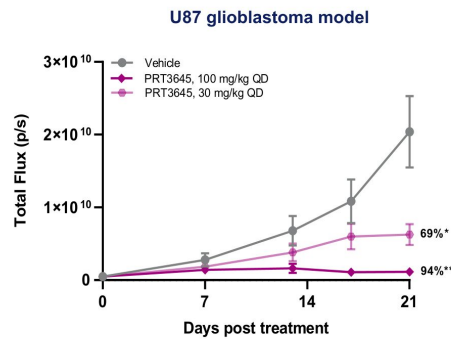
CDK 4/6 inhibitor PRT3645

Improved Tissue Penetration and Robust Activity in Preclinical Models

PRT3645 demonstrates higher brain penetration than approved CDK4/6 inhibitors



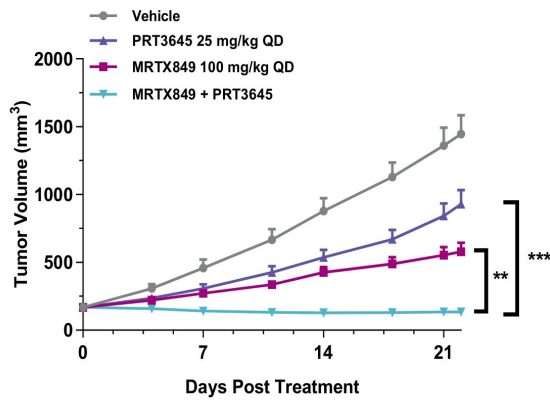
PRT3645 shows robust activity in vivo as monotherapy and in combination



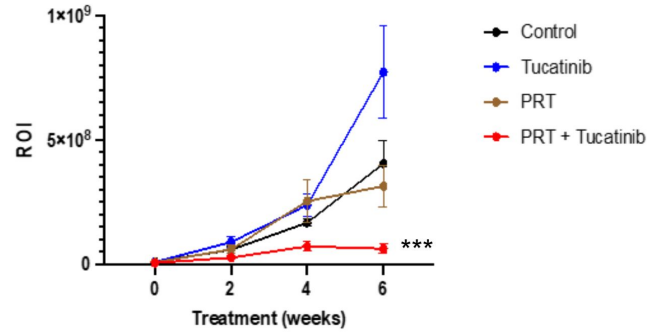


Novel Combinations to Extend the Potential of CDK4/6 Inhibition

H2122 NSCLC Model



DFBM-355 PDX model of ER+/HER2+ Breast Cancer



PRT3645 significantly enhances the activity of KRAS G12C inhibitor in NSCLC models and with HER2 kinase inhibitor in ER+/HER2+ BC models



CDK4/6 Inhibitor: PRT3645

Phase 1 Study in Solid Tumors

Dose Escalation and Confirmation

PRT3645

Biomarker enriched patients with select tumor types including sarcomas, mesothelioma, gliomas, head and neck cancers and non-small cell lung cancer, in addition to breast cancer with or without brain metastases

Initial clinical data in 2H 2023
RP2D in solid tumors in 2H 2024

- A differentiated and highly brain penetrant CDK4/6 inhibitor
- Potential to extend the reach of CDK4/6 inhibition beyond HR+ breast cancers, for which the first generation CDK4/6 inhibitors were approved

ClinicalTrials.gov Identifier: NCT05538572



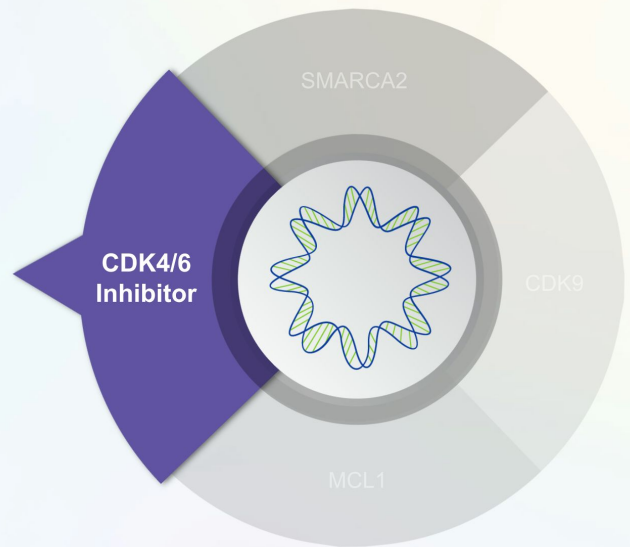
CDK4/6 Inhibitor Differentiation and Market Opportunity

Deep Tissue Penetration with Potential for Activity in Areas of Unmet Need

- PRT3645 is a **highly potent and selective** CDK4/6 inhibitor
- Optimized to demonstrate **deep tissue penetration including brain penetrance**
- **Improved metabolism profile** to allow for combination treatment in diseases beyond breast cancer
- **Reduced toxicity** in preclinical GLP studies with **potential for improved tolerability** in the clinic

Market Opportunity:

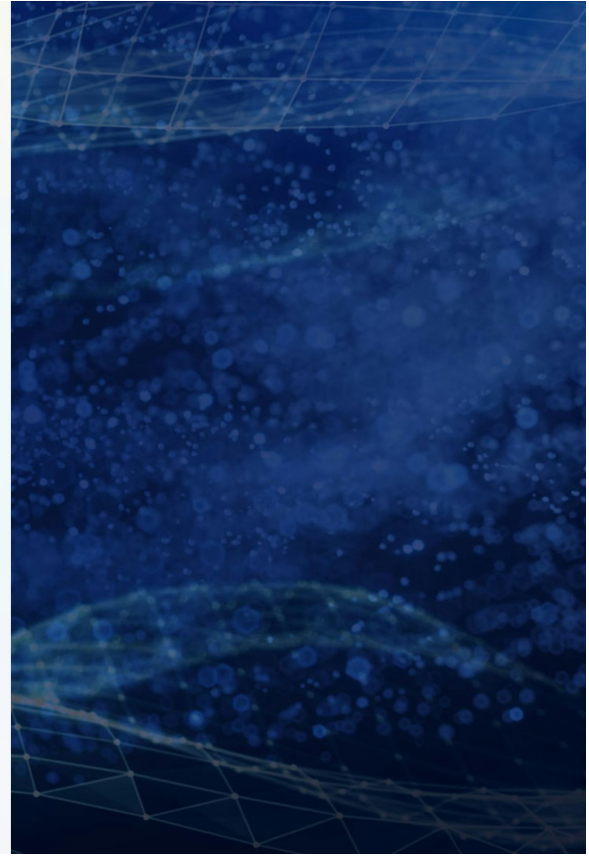
- Breast cancer patients may benefit from sequential CDK 4/6 inhibitors treatment
- There are estimated to be 65,000 breast cancer patients treated with CDK 4/6 inhibitors in 2023 in the U.S.
- Other solid tumors (lung cancer, glioma, HER2+ breast cancer) may demonstrate activity in combination





PRT3789

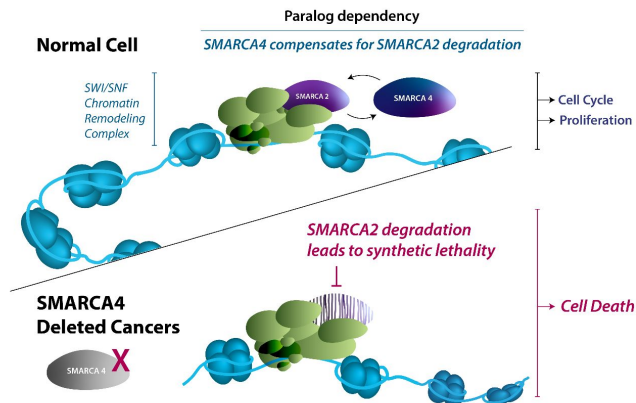
SMARCA2 Degradar





Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

Mechanism

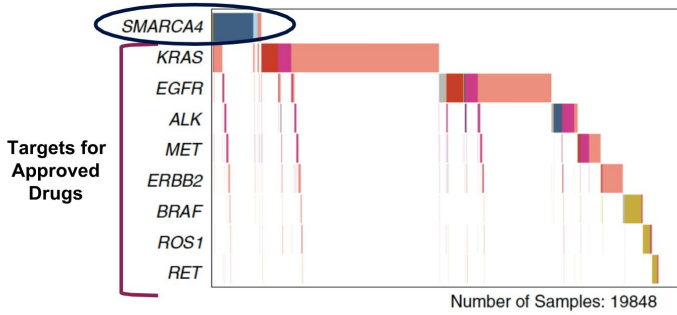


- The chromatin remodeling (SWI/SNF) complex is frequently mutated in cancer making it a **potential therapeutic target**
 - Activity of the SWI/SNF complex requires either SMARCA4 (BRG1) or SMARCA2 (BRM)
 - Loss of SMARCA4 (BRG1) through mutation leads to dependency on SMARCA2 (BRM)
 - Subsets of solid tumors express SMARCA4 (BRG1) mutations
 - Selectively inhibiting SMARCA2 (BRM) offers an attractive approach to target SMARCA4 (BRG1) mutant tumors



SMARCA4 Mutations in NSCLC: An Opportunity with No Approved Therapies

SMARCA4 Deletion – A Novel Biomarker for NSCLC



Fernando et al. Nature Communications 2020

SMARCA4 Prevalence across selected Solid Tumors

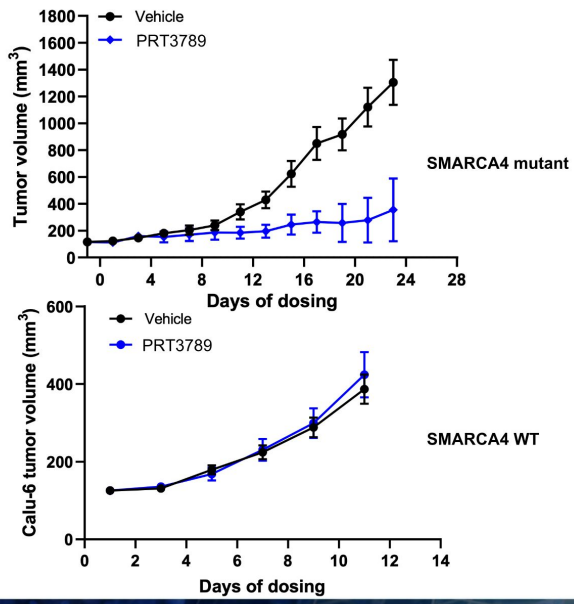
Indication	Any SMARCA4 Mutation ¹
NSCLC	10.0%
Esophageal	8.0%
Gastric (stomach adeno)	8.3%
Skin (invasive and in situ melanoma)*	21.0%
Endometrial (uterine corpus)	13.3%
Squamous cell lung	7.7%
Urinary (bladder)	9.0%
Colorectal	6.0%
Pancreatic	2.9%
Melanoma (invasive)	8.7%

1. cBioPortal; FoundationCore; 2. SMARCA4 LOF mutations included homozygous missense, hotspot mutations with LOF, and damaging mutations; 3. SEER 2022; Globocan; * Source: American Cancer Society – Cancer Facts & Figures 2022

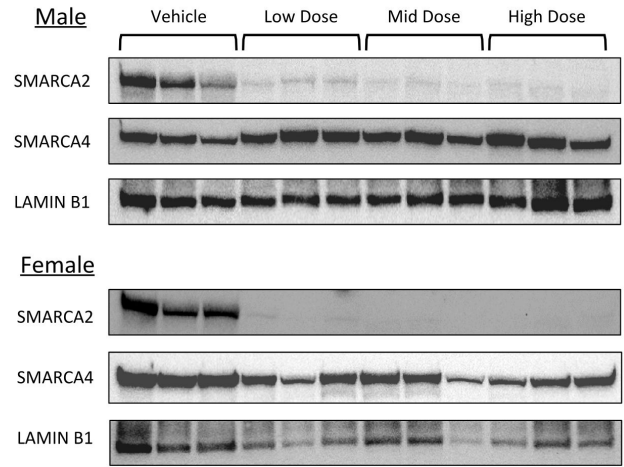


PRT3789: Potent and Selective SMARCA2 Degrader with *In Vivo* Activity

Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft



Significant Degradation of SMARCA2 Protein but not SMARCA4 in Preclinical Models





SMARCA2 Degradator: PRT3789

Phase 1 Study in Solid Tumors

Dose Escalation and Confirmation

PRT3789
Solid Tumors with loss of SMARCA4
Backfill: up to 10 participants with a minimum of 6 NSCLC
participants with loss of SMARCA4

IND cleared Q4 2022
Provide Clinical update 2H 2023

- SMARCA2 inhibition has the greatest potential in patients with SMARCA4 deficient cancers, including approximately 5-10% of all non-small cell lung cancers
- SMARCA2 degradation to be evaluated in Phase 1
- Study population: advanced, recurrent, or metastatic disease, with loss of SMARCA4 due to truncating mutation and/or deletion
- Biomarker selected by local NGS or IHC in tumor tissue or blood



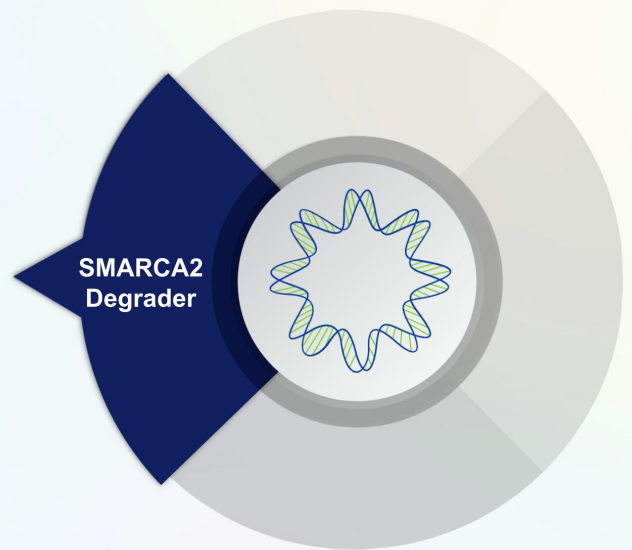
SMARCA2 Differentiation and Market Opportunity

Potential First-in-Class SMARCA2 (BRM) Targeted Protein Degradator

- PRT3789 is a **potent and highly selective** first-in-class SMARCA2 Degradator
- Designed to achieve the **requisite high selectivity** for SMARCA2 over the related isoform, SMARCA4, through a targeted protein degrader approach
- **Improved tolerability** compared to non-selective SMARCA2 inhibition
- **Robust efficacy** in SMARCA4 mutant preclinical models, providing **clear patient selection strategy** in the clinic

Market Opportunity:

- 70,000 patients with SMARCA4 mutation in the US/EU5





Prelude Therapeutics: Key Takeaways and Reasons to Invest



Deep clinical pipeline with unique and potentially **best-in-class or first-in-class molecules**



Opportunity to drive programs to key inflection points in the next **12 – 24 months**



Emerging clinical data on CDK9 and MCL-1 programs demonstrate the potential for **class-leading opportunities**

-CDK9 as a target externally validated in DLBCL with significant clinical and commercial potential



Potentially **first-in-class SMARCA2 degrader program** with a significant lead over competitors and offers transformational potential for the company



Current cash runway expected through **Q4 2024**



BACK UP





We Continue to Advance our Pipeline of Highly Innovative Oncology Medicines

PROGRAM	2022 ACHIEVEMENTS	2023 MILESTONES
PRT2527 CDK9	<ul style="list-style-type: none">Phase 1 dose escalation completed; RP2D solid tumors anticipated in early 2023Dose dependent target engagement and exposure observedNo adverse events leading to discontinuation observedOral presentation on preclinical hematologic malignancies at ASH 2022	<ul style="list-style-type: none">Present solid tumor data in 1HRP2D in solid tumors in early-2023RP2D in hematological malignancies in 2HPresent initial clinical data for hematological malignancies in 2H
PRT1419 MCL1	<ul style="list-style-type: none">Solid tumor RP2D determinedNo cardiac toxicity observed in patients @ RP2D (as measured by ejection fraction decline/troponin elevation)Clinical markers of MCL-1 inhibition demonstrated	<ul style="list-style-type: none">Present solid tumor data in 1HRP2D in hematological malignancies in 2HPresent initial clinical data for hematological malignancies in 2H
PRT3645 CDK4/6	<ul style="list-style-type: none">IND filed and acceptedFPI for Phase 1	<ul style="list-style-type: none">Present initial clinical data in 2H
PRT3789 SMARCA2	<ul style="list-style-type: none">IND application filed and accepted	<ul style="list-style-type: none">Initiate Phase 1 in 1QProvide Clinical update 2H