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.

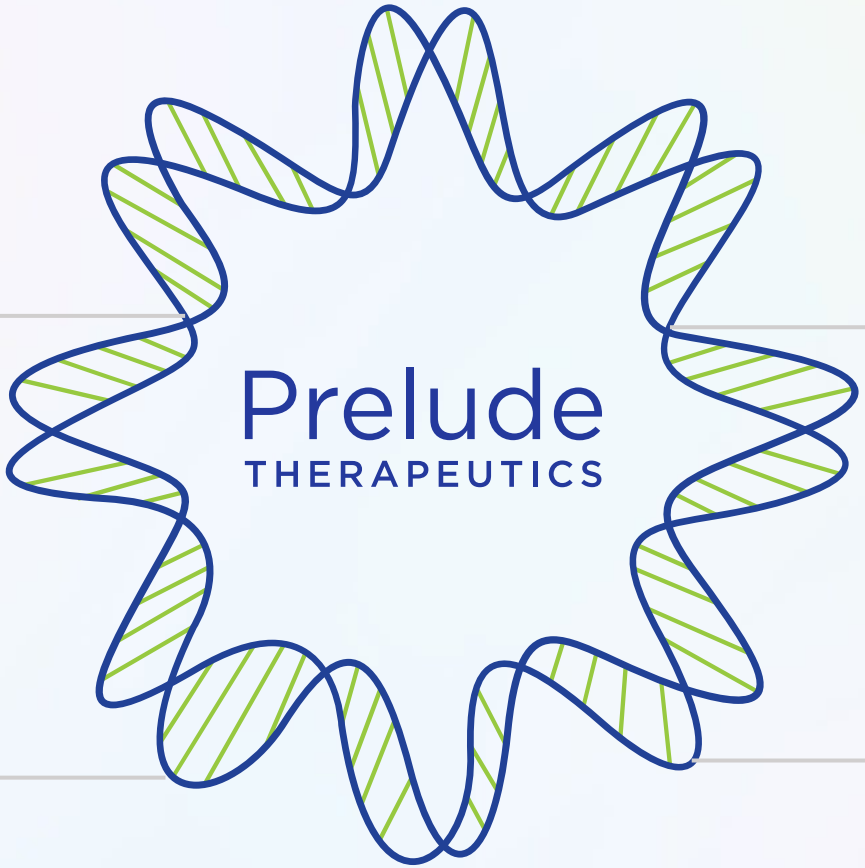
These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will 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

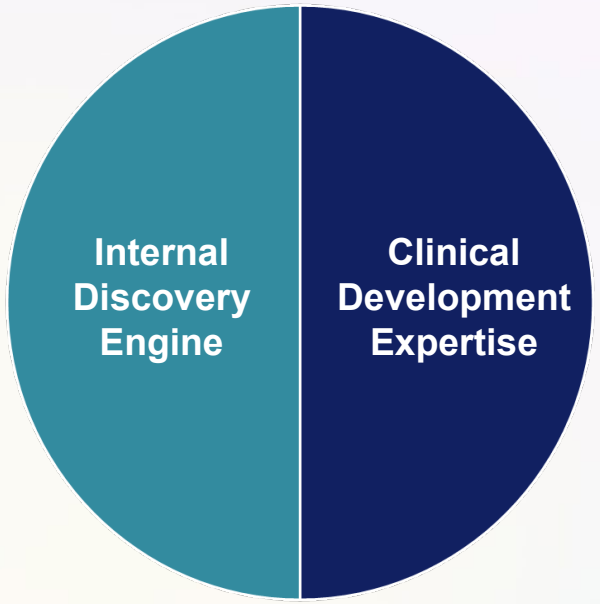


Exceptional Team

Well Capitalized

Prelude Discovery and Development Engine: Positioned to Succeed

R&D ENGINE



APPROACH

Target

Mechanisms that drive meaningful benefit in patients with cancer

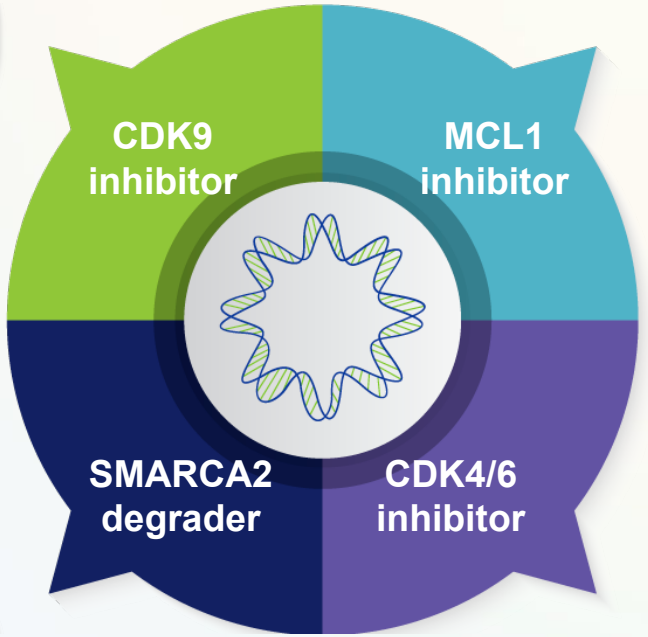
Discover

Optimized molecules that overcome the limitations of current treatments

Translate

Science into meaningful treatments for patients

DIFFERENTIATED PIPELINE



Experienced Management Team: Proven Track Records

Kris Vaddi, PhD

Founder &
Chief Executive Officer

Jakafi ruxolitinib (tablets)
olumiant (baricitinib) tablets 2 mg
TABRECTA (capmatinib) tablets
VELCADE (bortezomib)

Jane Huang M.D.

President and Chief Medical Officer

Brukinsa zanubrutinib 80 mg capsules
CALQUENCE (acalabrutinib) 100 mg capsules
VENCLEXTA venetoclax tablets
GAZYVA obinutuzumab injection 1,000mg/40mL
Kadcyla ado-trastuzumab emtansine
AVASTIN bevacizumab

Andrew Combs, PhD

Executive Vice President and Head of Chemistry

Jakafi ruxolitinib (tablets)
olumiant (baricitinib) tablets 2 mg

Laurent Chardonnet

Chief Financial Officer

sanofi
Incyte
axcella

Peggy Scherle, PhD

Chief Scientific Officer

Jakafi ruxolitinib (tablets)
olumiant (baricitinib) tablets 2 mg
Pemazyre pemigatinib (tablets)
TABRECTA (capmatinib) tablets

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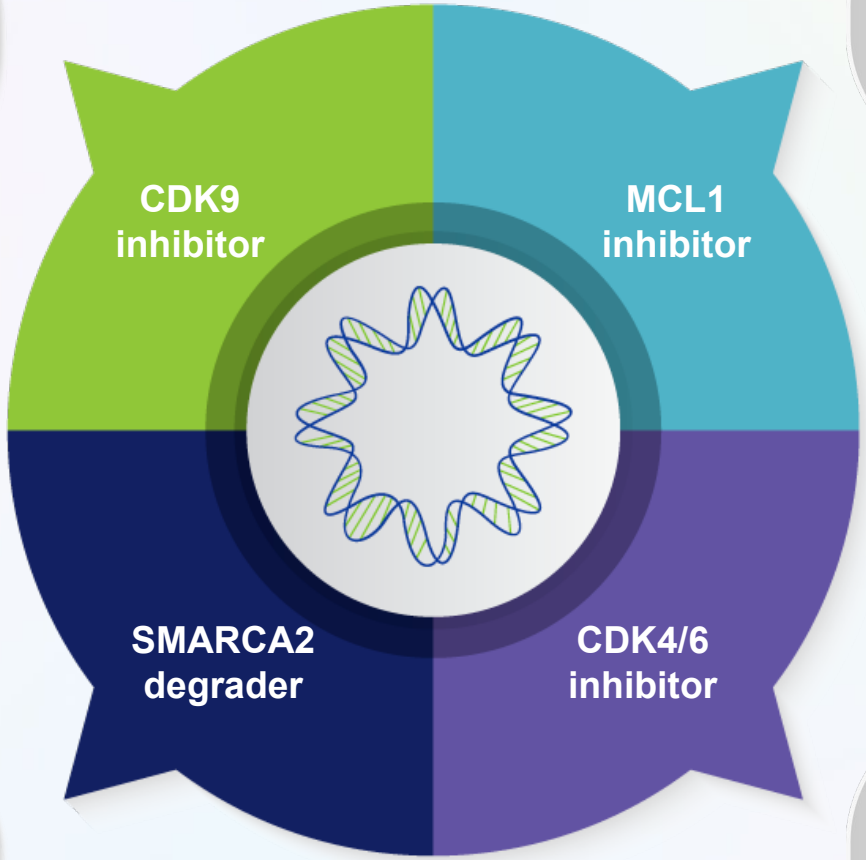
Prelude Precision Oncology Pipeline: Diversified and Differentiated

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 Degrader)	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



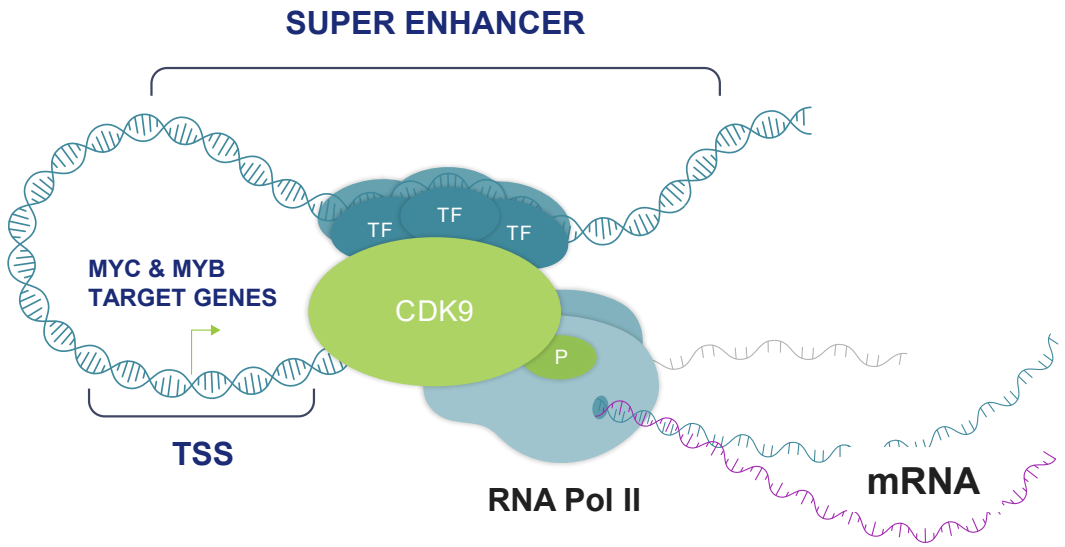
Potent and Selective Degrader
Potential to address major unmet need in biomarker-selected patients

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

PRT2527

CDK9 Inhibitor

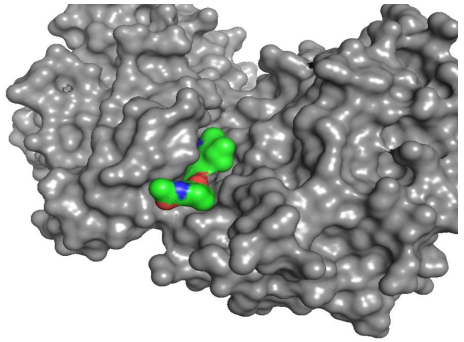
CDK9 Inhibition: Targeting Cancer by Regulating Oncogene Expression

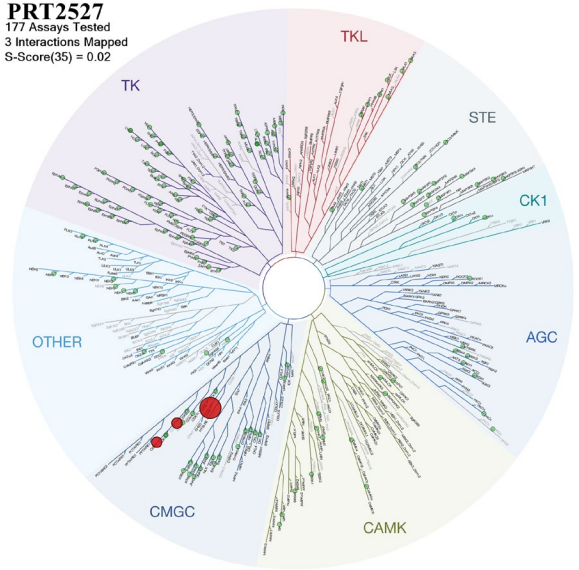


- CDK9 regulates expression of several **oncogenes that drive cancer cell growth and resistance** (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
- **Improving the selectivity** of CDK9 inhibitors may translate to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

PRT2527: Potent and Highly Selective CDK9 Inhibitor

Highly Selective, ATP Competitive CDK9 Inhibitor





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

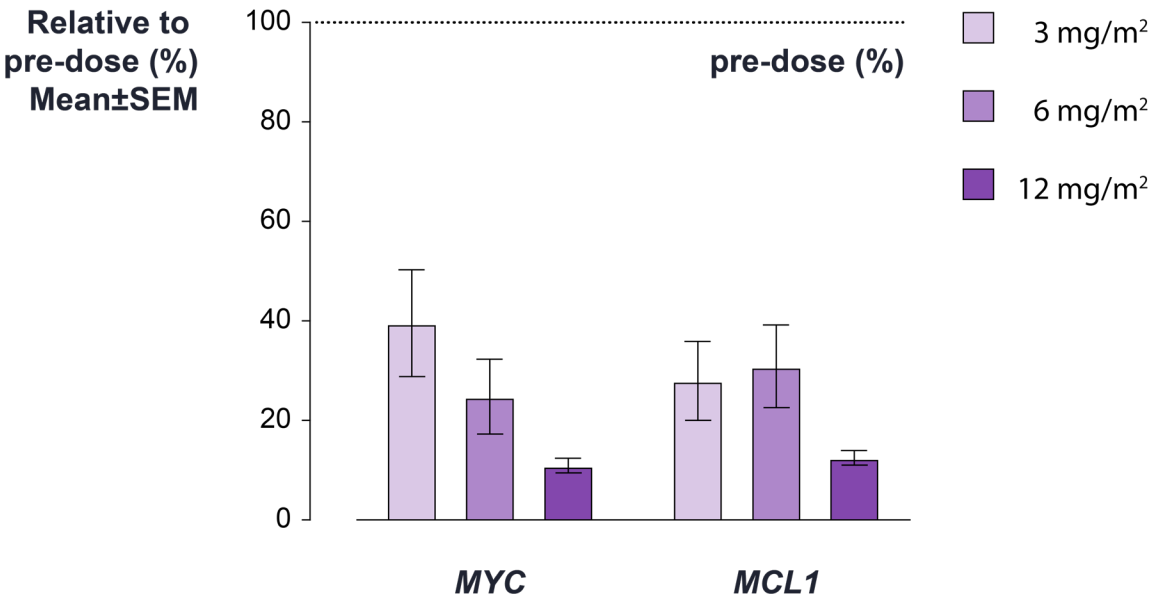
*Internal data; biochemical assay at 1 mM ATP, H929 CTG proliferation assay; **VIP151 was formerly BAY151 and licensed to Vincerx by Bayer

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/m^2 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

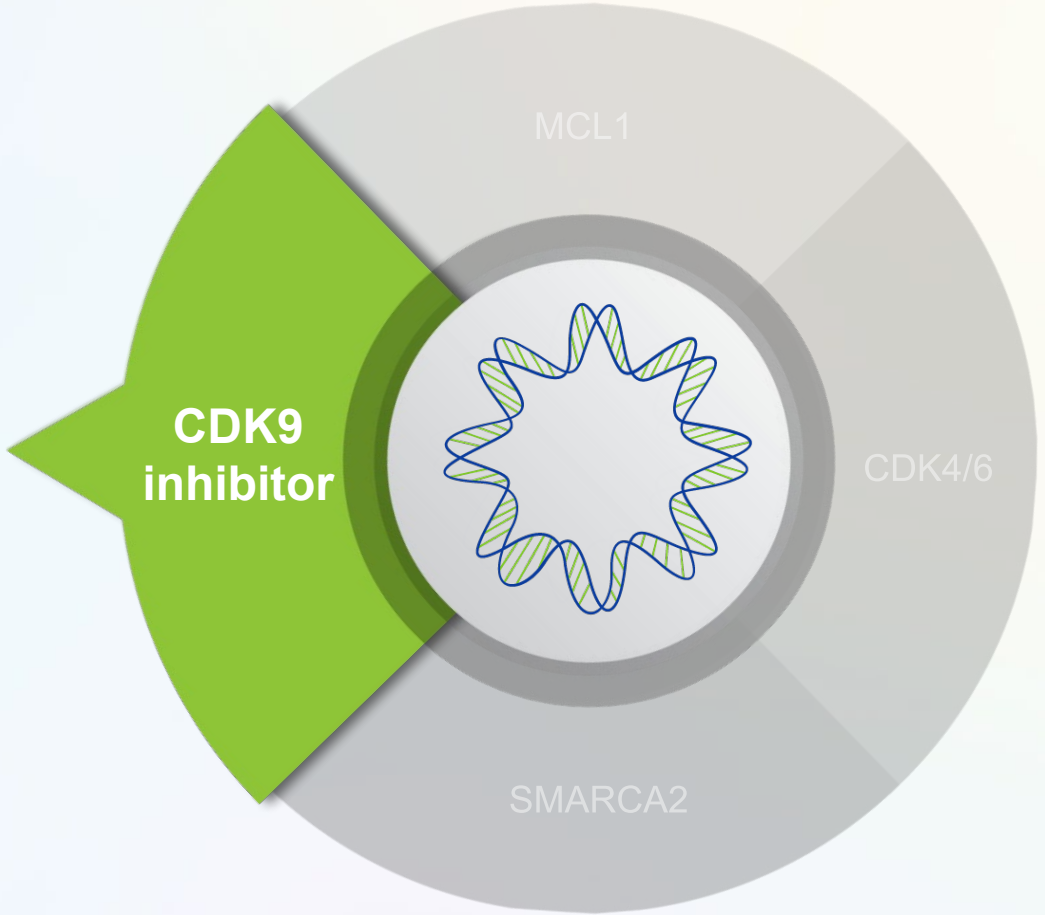
Potential for Improved Safety Based on Best-in-Class Kinome Selectivity

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

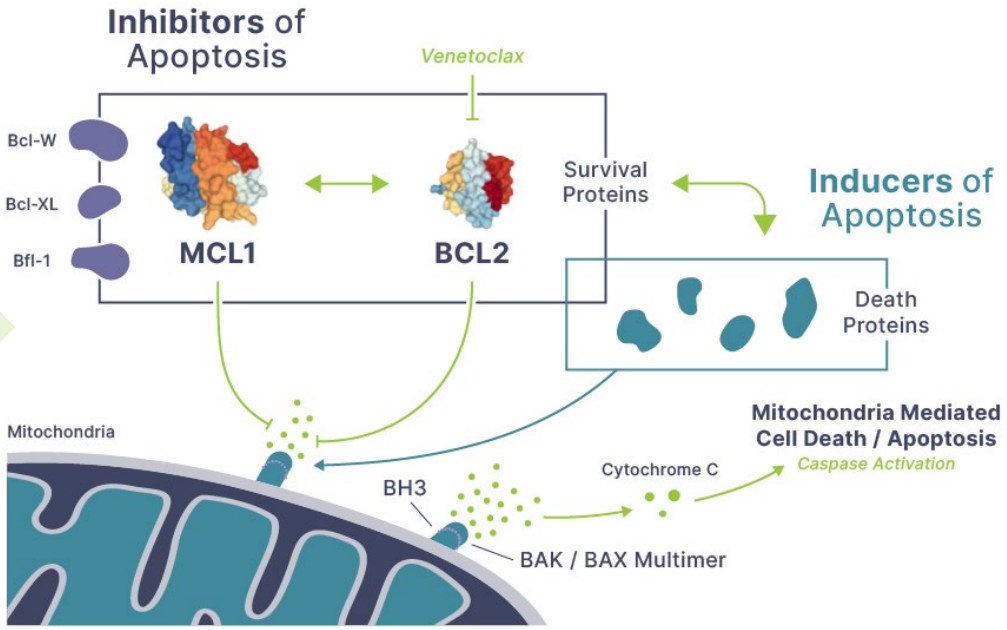


PRT1419

MCL1 Inhibitor

MCL1 inhibition: Targeting Cancer Cell Survival

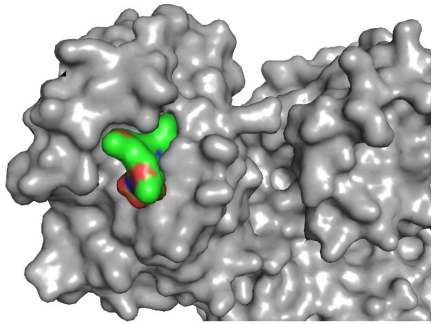
Mechanism



- 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**

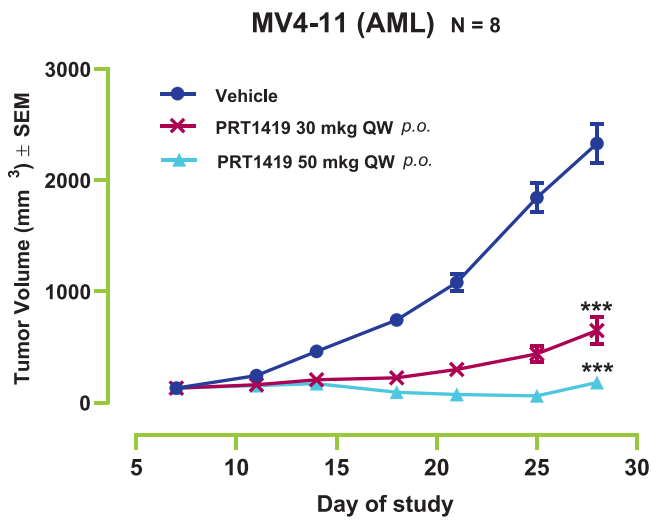
PRT1419: Potent MCL1 Inhibitor with Strong Preclinical Activity as Monotherapy and in Combination

Prelude compounds are competitive inhibitors of BIM binding

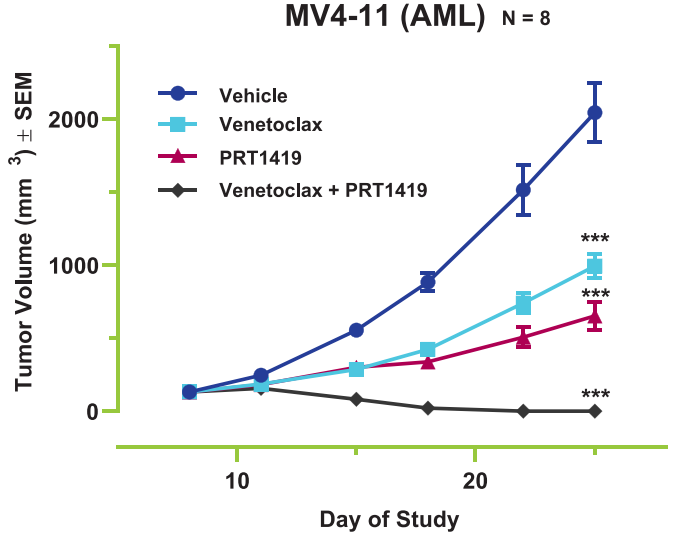


	Proliferation IC_{50} (nM)	Whole Blood IC_{50} (nM)
AMG176	150	1800
AZD5991	31	320
MIK665	4.5	430
PRT1419	**80**	**210**

Monotherapy



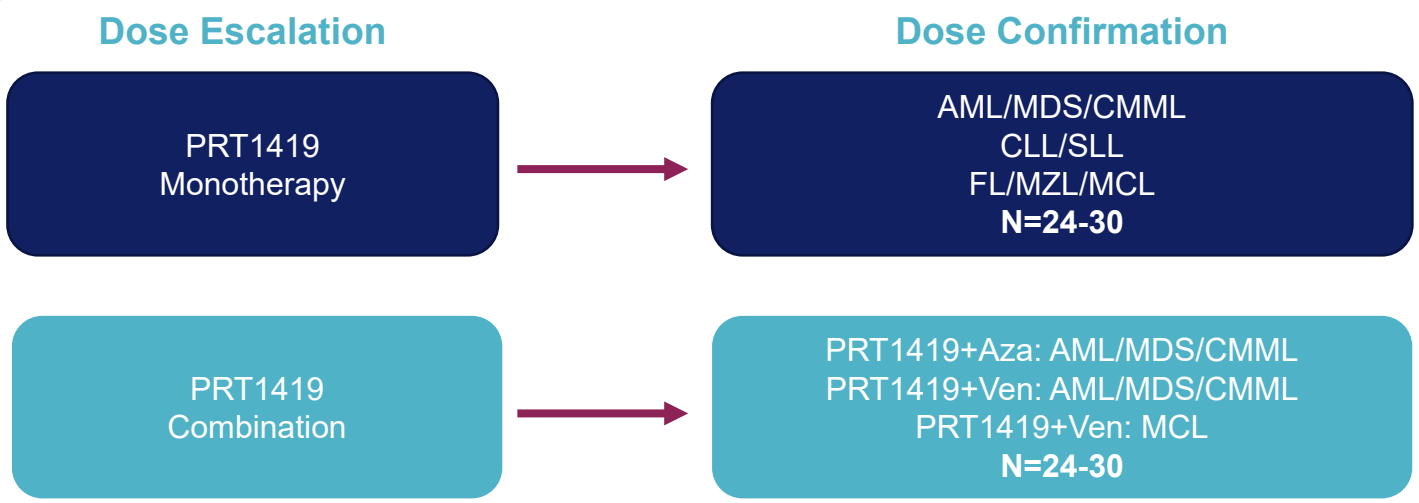
Combination



Robust monotherapy activity also seen in models of DLBCL & MM

MCL1 inhibitor: PRT1419

Phase 1 Study in Hematologic Malignancies



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

- 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 heme[1]

ClinicalTrials.gov Identifier: NCT05107856

[1] Ong et al. Cancer Drug Resist 2022;5:380-400

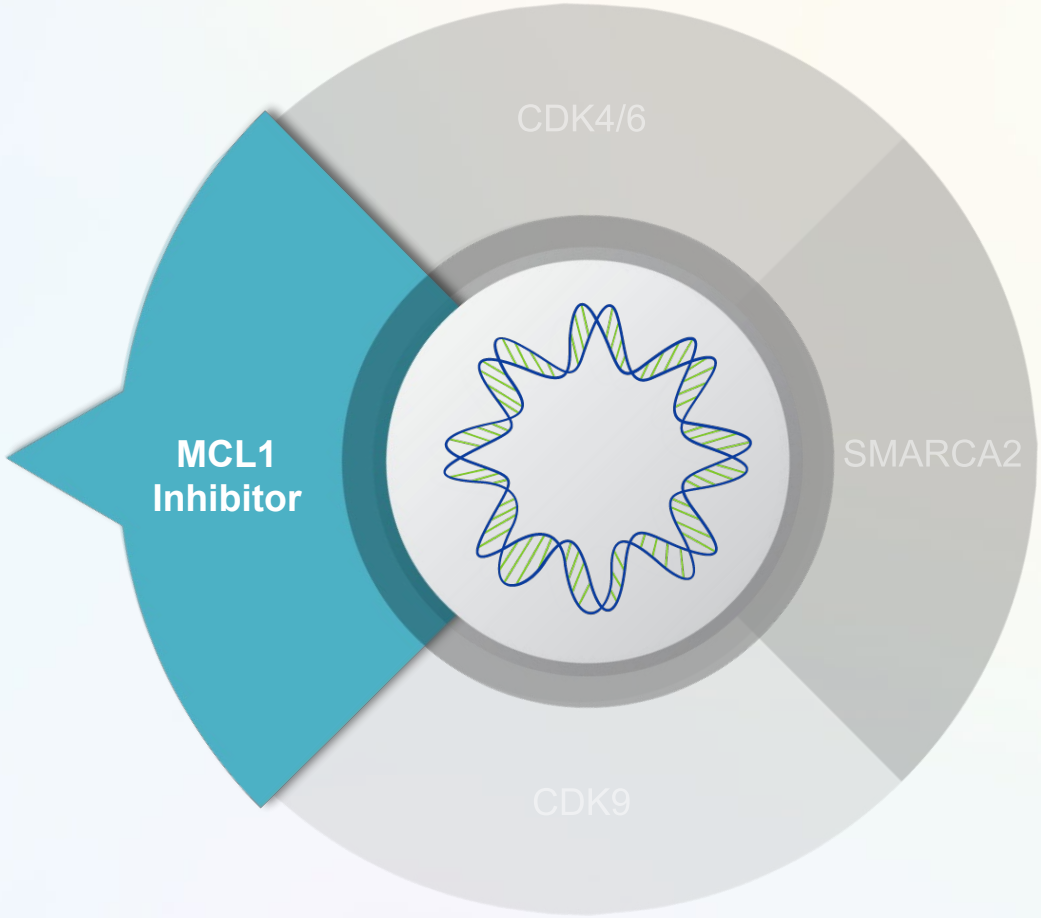
MCL1 Inhibitor Differentiation and Market Opportunity

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.

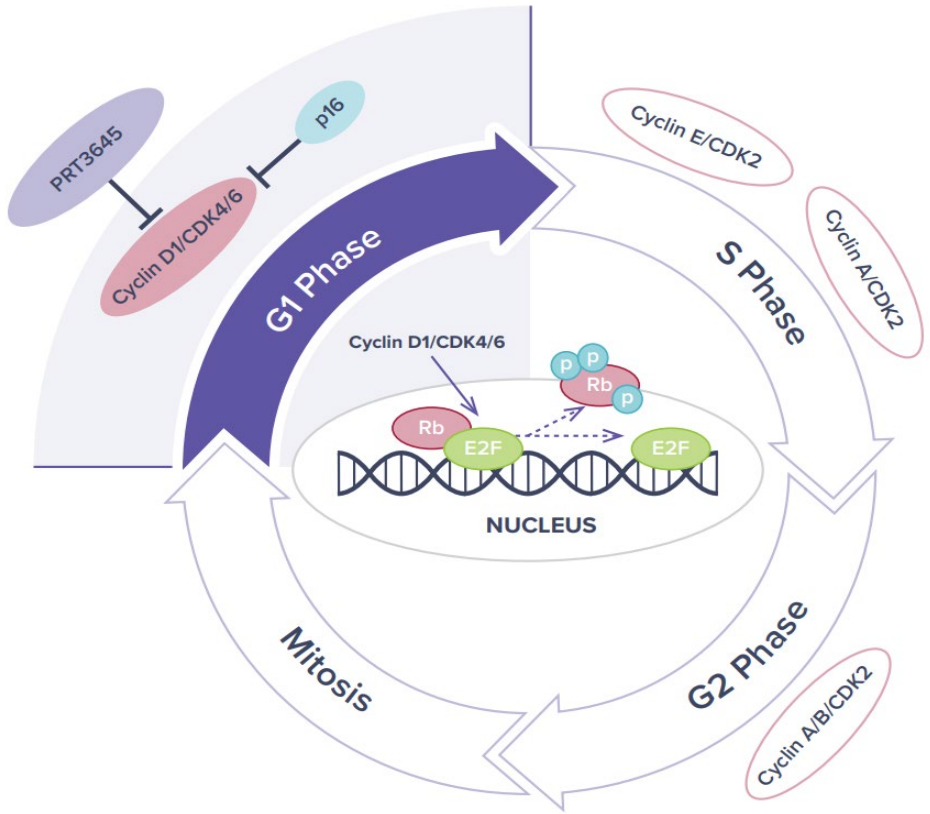


PRT3645

CDK4/6 Inhibitor

CDK4/6 Inhibition: Targeting Cancer Through Cell Cycle Regulation

Mechanism

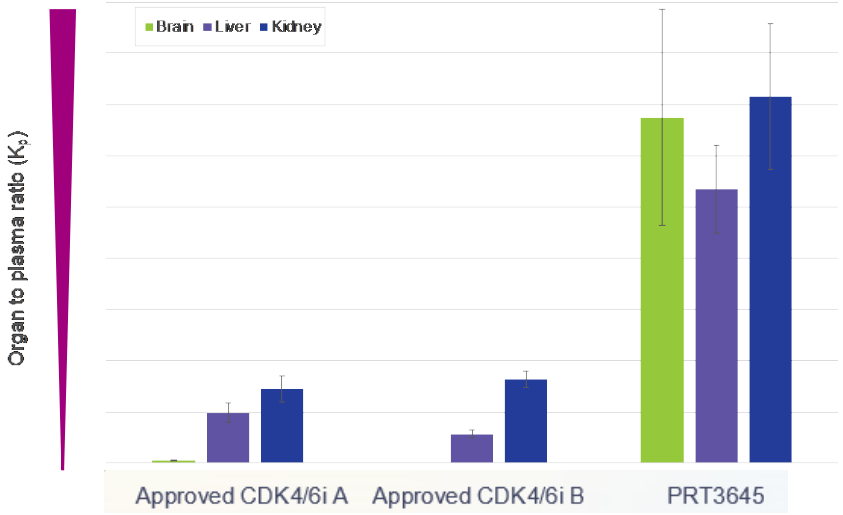


- **Validated mechanism** with approval of CDK4/6 inhibitors in HR+ breast cancer
- **Resistance mechanism** to other targeted therapies including KRAS G12C inhibitors
- Current CDK4/6 inhibitors limited by poor tolerability and lack broad tissue penetration
- Next generation CDK 4/6 inhibitor with **improved 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

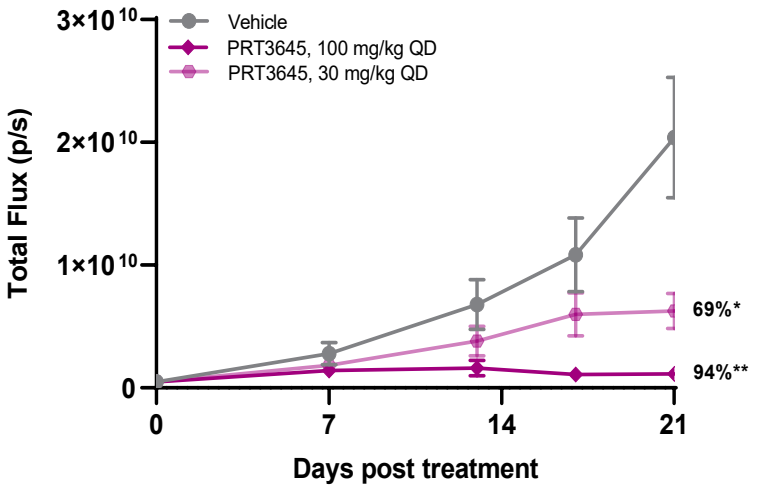
Improved Tissue Penetration and Robust Activity in Preclinical Models

PRT3645 demonstrates higher brain penetration than approved CDK4/6 inhibitors

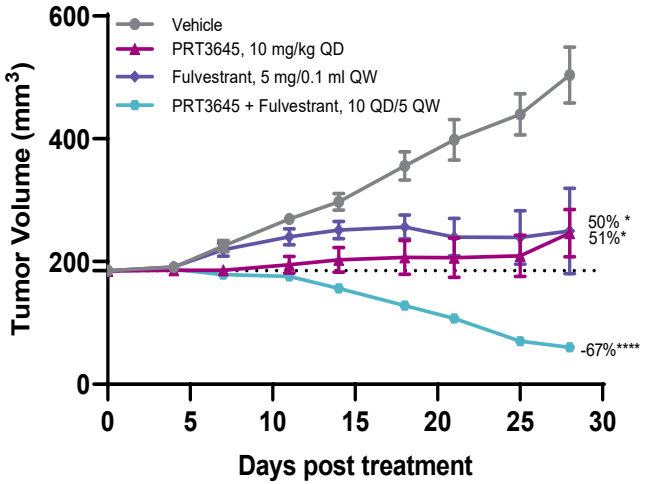


PRT3645 shows robust activity in vivo as monotherapy and in combination

U87 glioblastoma model

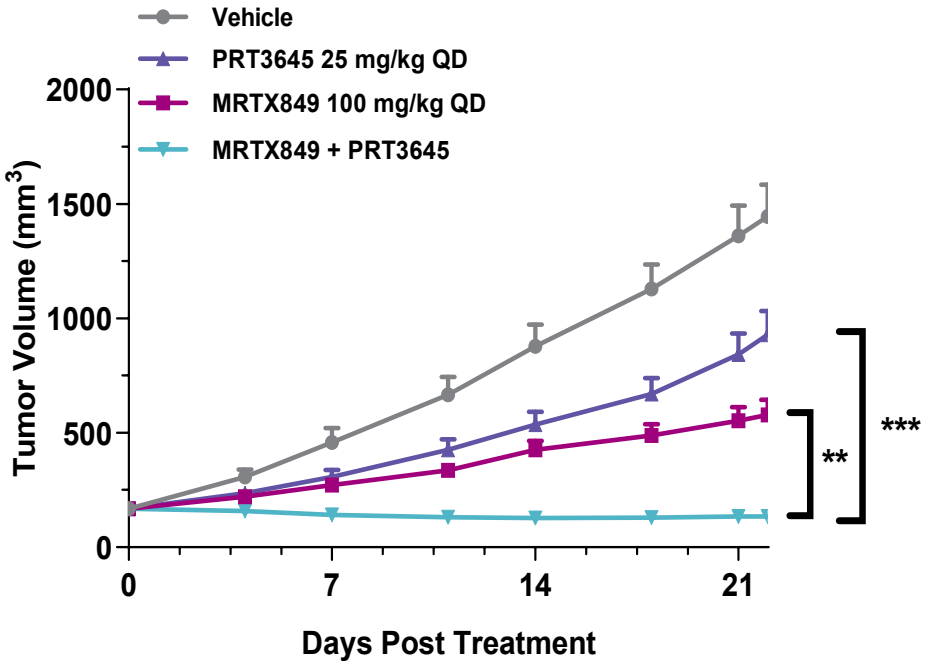


MCF7 breast cancer model

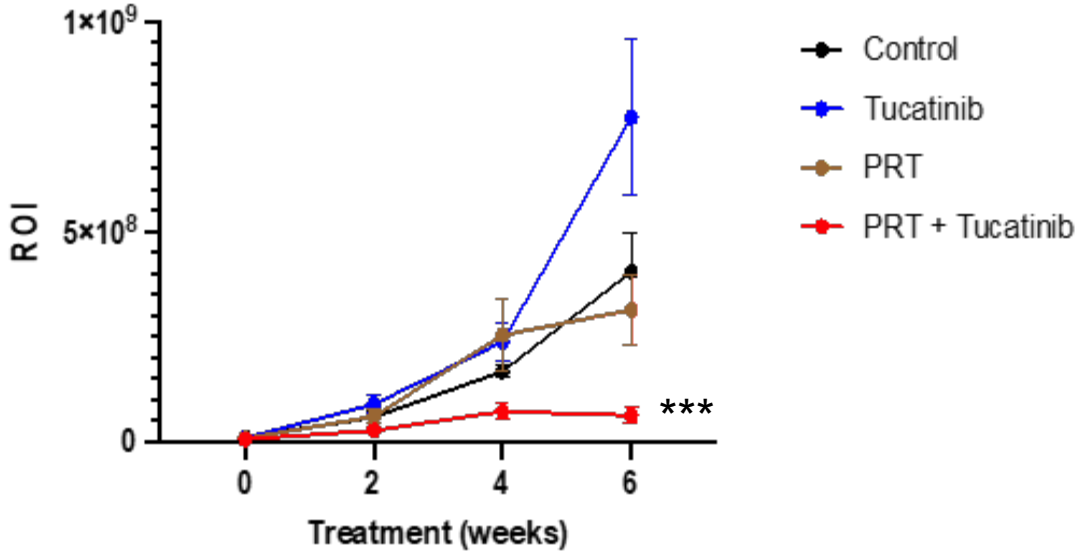


Novel Combinations to Extend the Potential of CDK4/6 Inhibition

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

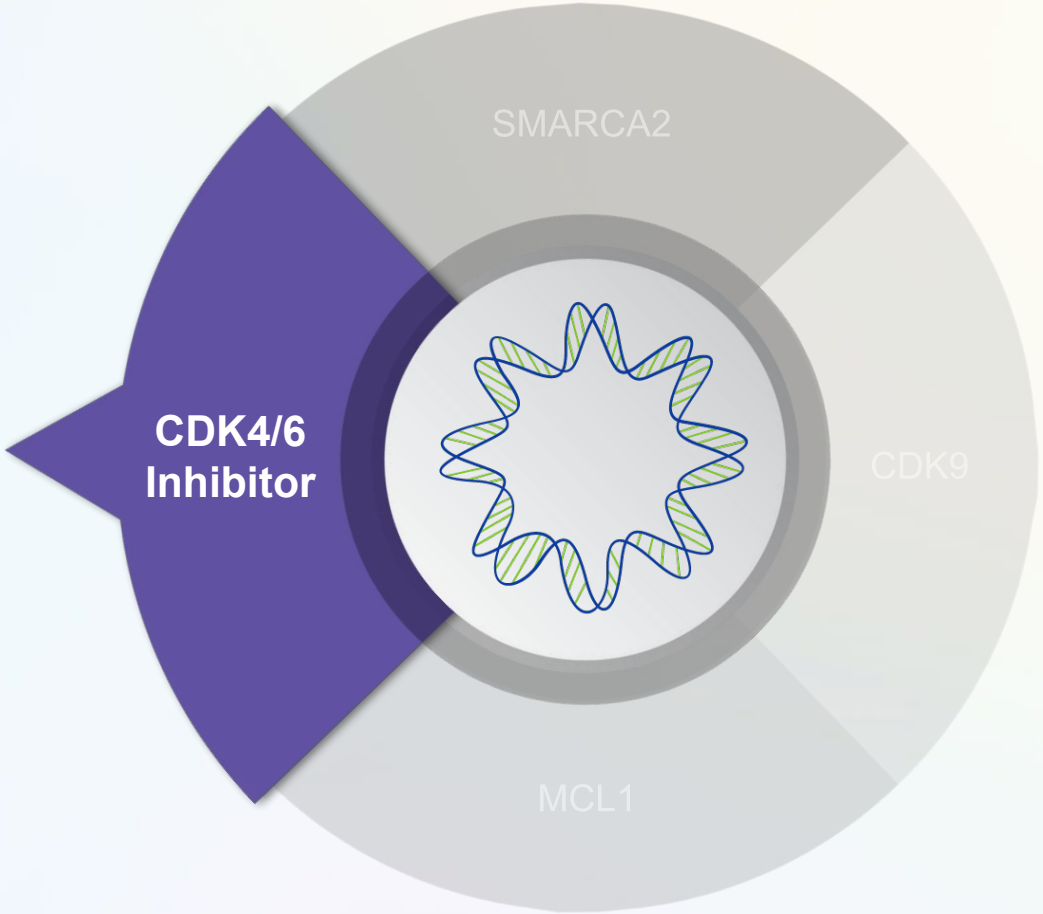
CDK4/6 Inhibitor Differentiation and Market Opportunity

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

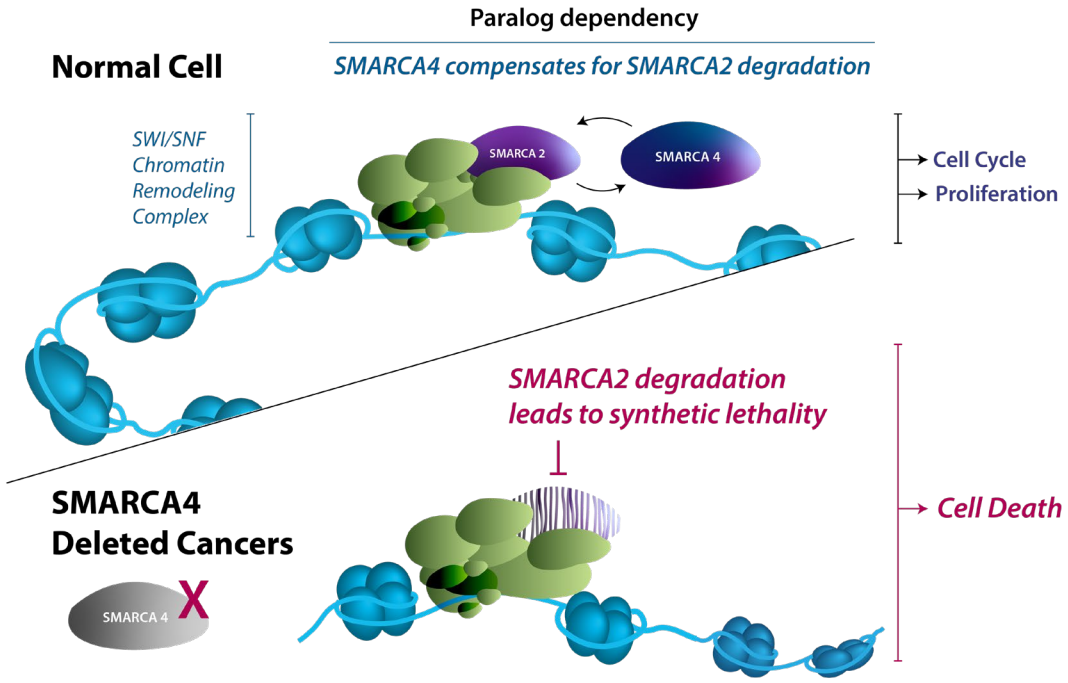


PRT3789

SMARCA2 Degrader

Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

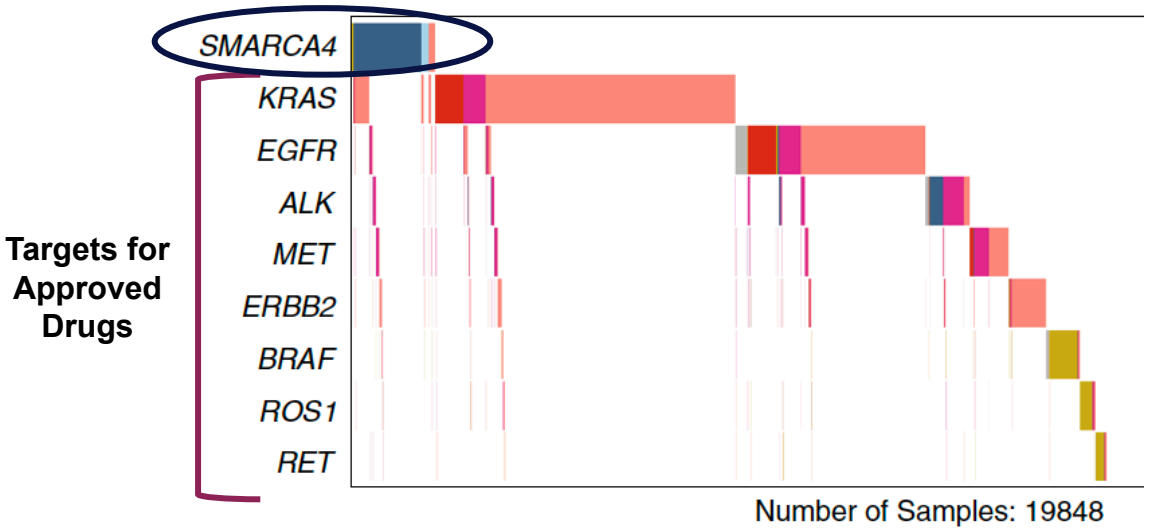
Mechanism



- 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

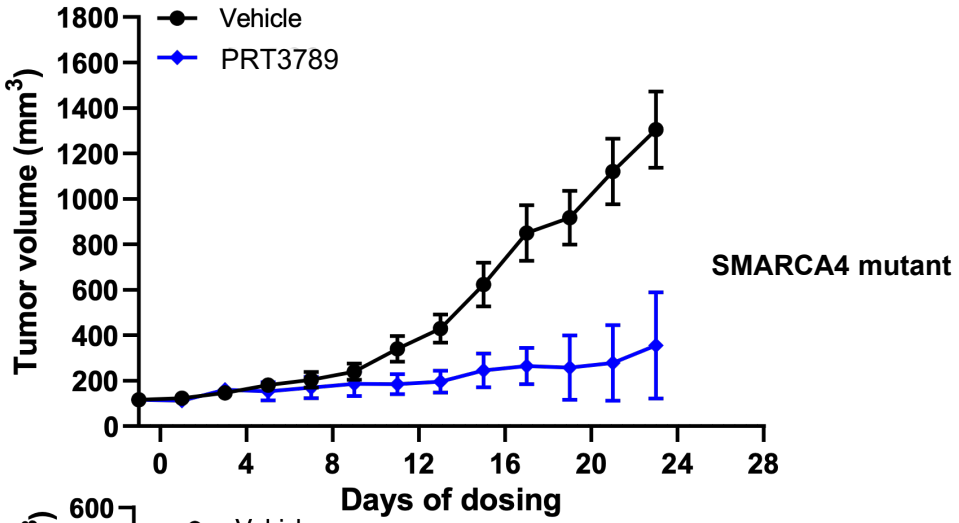
SMARCA4 Prevalence across selected Solid Tumors

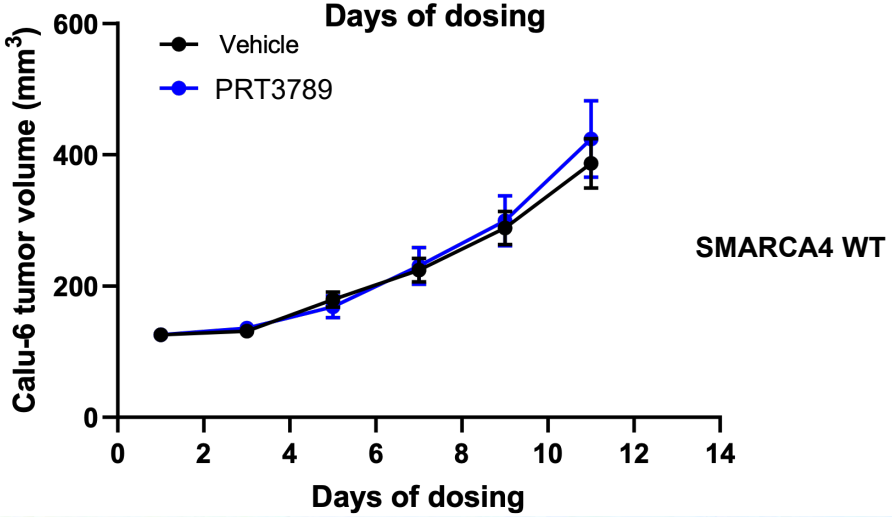
Indication	Any SMARCA4 Mutation[1]
NSCLC	10.0%
Esophageal	8.0%
Gastric (stomach adeno)	8.3%
Skin (invasive and in situ melanoma)*	21.0%
Endometrial (uterine corpus)	13.3%
Squamous cell lung	7.7%
Urinary (bladder)	9.0%
Colorectal	6.0%
Pancreatic	2.9%
Melanoma (invasive)	8.7%

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

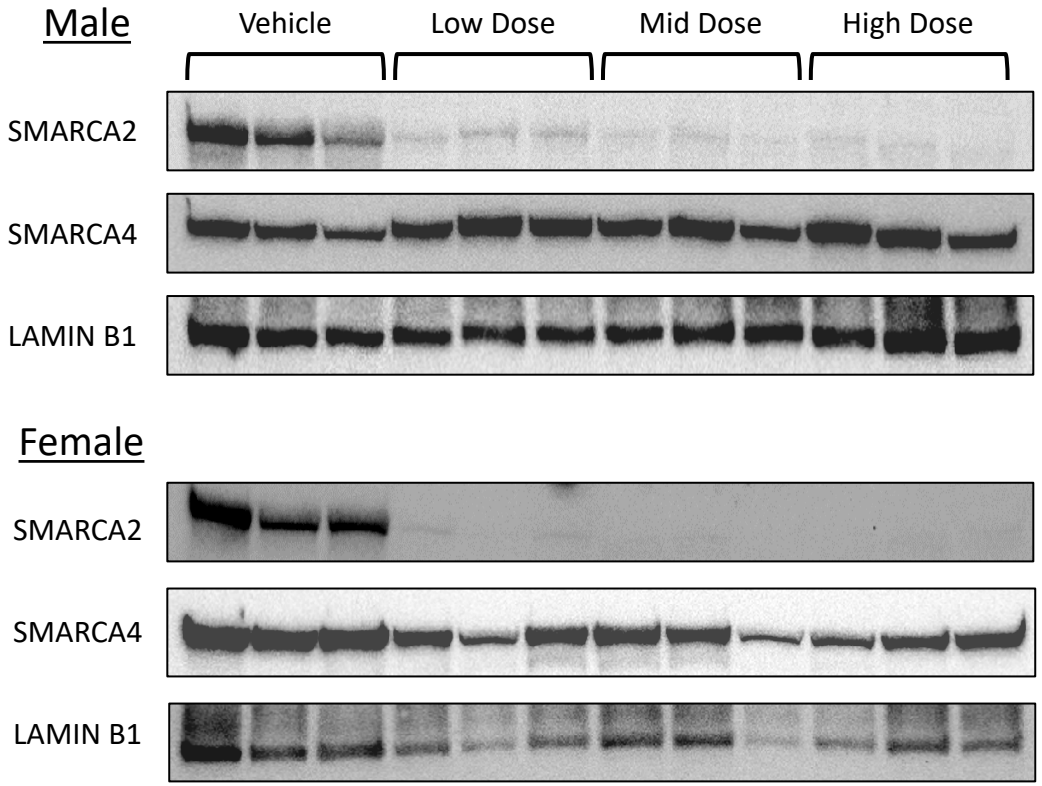
PRT3789: Potent and Selective SMARCA2 Degrader with *In Vivo* Activity

Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft





Significant Degradation of SMARCA2 Protein but not SMARCA4 in Preclinical Models



SMARCA2 Degrader: 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

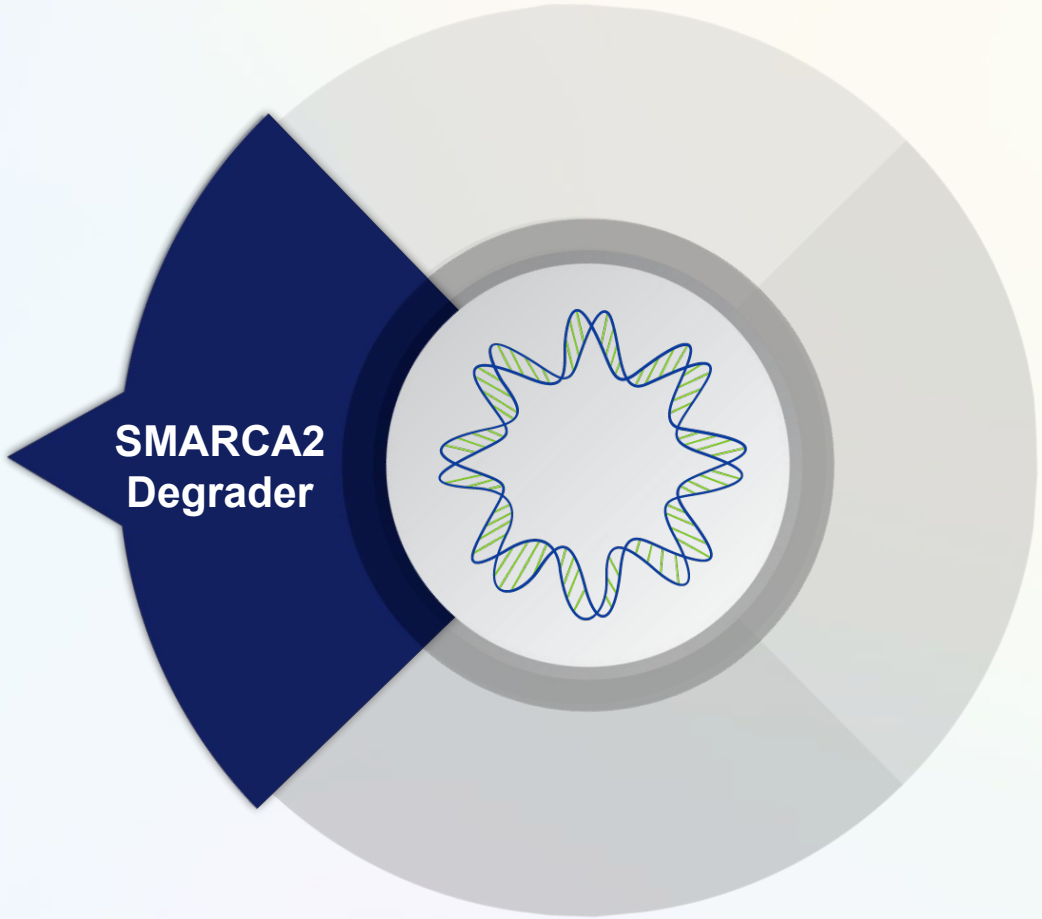
SMARCA2 Differentiation and Market Opportunity

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

- PRT3789 is **a potent and highly selective** first-in-class SMARCA2 Degrader
- 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	• Phase 1 dose escalation completed; RP2D solid tumors anticipated in early 2023 • Dose dependent target engagement and exposure observed • No adverse events leading to discontinuation observed • Oral presentation on preclinical hematologic malignancies at ASH 2022	• Present solid tumor data in 1H • RP2D in solid tumors in early-2023 • RP2D in hematological malignancies in 2H • Present initial clinical data for hematological malignancies in 2H
PRT1419 MCL1	• Solid tumor RP2D determined • No cardiac toxicity observed in patients @ RP2D (as measured by ejection fraction decline/troponin elevation) • Clinical markers of MCL-1 inhibition demonstrated	• Present solid tumor data in 1H • RP2D in hematological malignancies in 2H • Present initial clinical data for hematological malignancies in 2H
PRT3645 CDK4/6	• IND filed and accepted • FPI for Phase 1	• Present initial clinical data in 2H
PRT3789 SMARCA2	• IND application filed and accepted	• Initiate Phase 1 in 1Q • Provide Clinical update 2H