



Prelude
THERAPEUTICS

Corporate Presentation

January 2024

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, anticipated discovery, preclinical and clinical development activities for Prelude’s product candidates, the potential safety, efficacy, benefits and addressable market for Prelude’s product candidates, the expected timeline for proof-of-concept data and clinical trial results for Prelude’s product candidates, the sufficiency of Prelude’s cash runway into 2026, and Prelude’s planned prioritization of its SMARCA2 degrader molecule and CDK9 inhibitor programs in the near-term.

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 filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2023.

**What's Next in
Cancer remains
the biggest
challenge facing
patients**

Cancers evade, evolve and resist treatments through multiple mechanisms.

Precision medicines that selectively target mechanisms unique to each cancer can offer safe and effective options for patients.

Our mission is to discover, develop and commercialize precision medicines to deliver new treatment options for patients with cancer.

Our Mission: Deliver Precision Medicines for Patients with Cancer



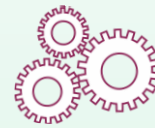
Platform

A team with experience of having done it and the passion to do it again



R&D Strategy

Discover potent and selective molecules with unique profiles regardless of target class- informed by patient need



Pipeline

Clinical and discovery pipeline of first/best-in-class molecules with attractive early clinical profiles



Commercialize

Advance the programs with the highest potential to significantly improve the lives of patients

Experienced Management Team: Proven Track Records



Kris Vaddi, PhD
*Founder &
Chief Executive Officer*

Jakafi[®]
ruxolitinib (tablets)

olumiant
(baricitinib) tablets
2 mg

TABRECTA
(capmatinib) tablets
100 mg - 200 mg

VELCADE
(bortezomib)



Jane Huang M.D.
*President and Chief
Medical Officer*

Brukina[®]
zanubrutinib
80 mg capsules

CALQUENCE
(acalabrutinib) 100 mg capsules

VENCLEXTA[®]
venetoclax tablets
10mg, 50mg, 100mg

GAZYVA[®]
obinutuzumab
injection 1,000mg/40mL

Kadcyla[®]
ado-trastuzumab emtansine

AVASTIN[®]
bevacizumab
VENEGAL INJECTION FOR IN-USE



Peggy Scherle, PhD
Chief Scientific Officer

Jakafi[®]
ruxolitinib (tablets)

olumiant
(baricitinib) tablets
2 mg

Pemazyre[®]
pemigatinib (tablets)

TABRECTA[®]
(capmatinib) tablets
100 mg - 200 mg



Andrew Combs, PhD
*Executive Vice President
and Head of Chemistry*

Jakafi[®]
ruxolitinib (tablets)

olumiant
(baricitinib) tablets
2 mg



Laurent Chardonnet, MBA
Chief Financial Officer

Incyte

axcella[®]

sanofi



Bryant Lim, J.D.
*Chief Legal Officer and
Corporate Secretary*

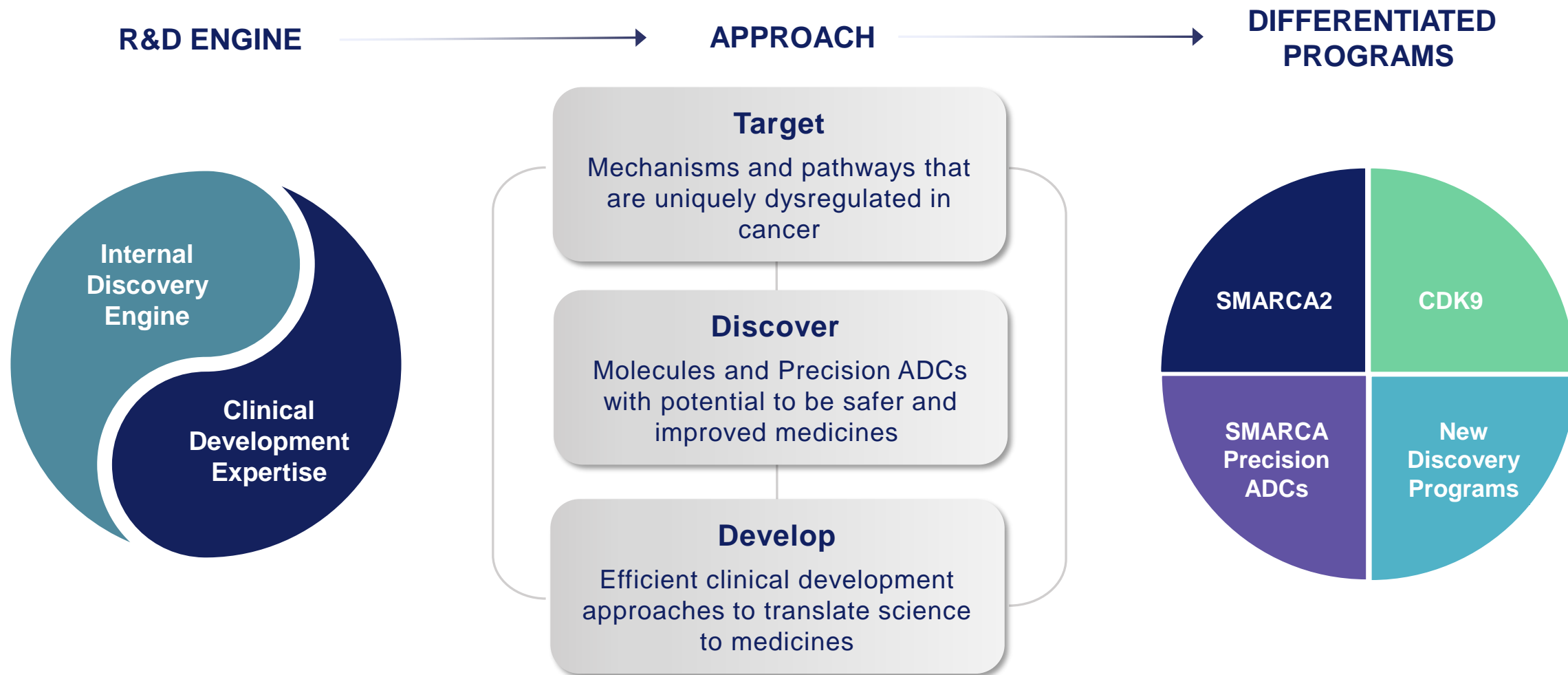
MERCK

VIROPHARMA
INCORPORATED









Incyte

Idera

Prelude Discovery and Development Engine



Strategic Pipeline With of Focus on POC in 2024

PROGRAM	CANCER INDICATIONS	DISCOVERY	PHASE 1	PHASE 2/3	Strategic Priorities
SMARCA2 PRT3789 (IV)	Patients with SMARCA4 mutated NSCLC and other cancers				Drive to POC in 2024
CDK9 PRT2527	Patients with B, T-cell malignancies and AML				Drive to POC in 2024
SMARCA2 (Oral)	Patients with SMARCA4 mutated NSCLC and other cancers				Target IND 1H 2024
SMARCA (Precision ADC)	Solid Tumors & Heme Malignancies not addressed by selective SMARCA2 degraders		 Partnership		Advance a Precision ADC Program with SMARCA Payload
New precision ADCs	Solid Tumors Heme Malignancies		 Partnership		Continue to build Precision ADC platform with novel payloads
Small Molecule Discovery	Solid Tumors Heme Malignancies				Advance a first-in-class small molecule program for a biomarker selected cancer

Key R&D Objectives and Strategic Priorities for 2024

PROGRAM

PRT3789

**SMARCA2
(IV)**

- Complete monotherapy escalation in patients with SMARCA4 mutations- mid-year
- Enroll 2 backfill cohorts (up to 10 patients each) mid-year
- Initiate docetaxel combination study in 1H
- Report initial phase 1 clinical results in 2H

PRT2527

CDK9

- Initiate zanubrutinib combination study in 1Q
- Complete monotherapy dose escalation in B-cell malignancies mid-year
- Initiate AML cohort in the existing phase 1 study in 1H
- Report initial heme phase 1 clinical results in 2H

PRT-SCA2

**SMARCA2
(Oral)**

- IND in 1H
- Initiate Phase 1 in patients with SMARCA4 mutations in 2H

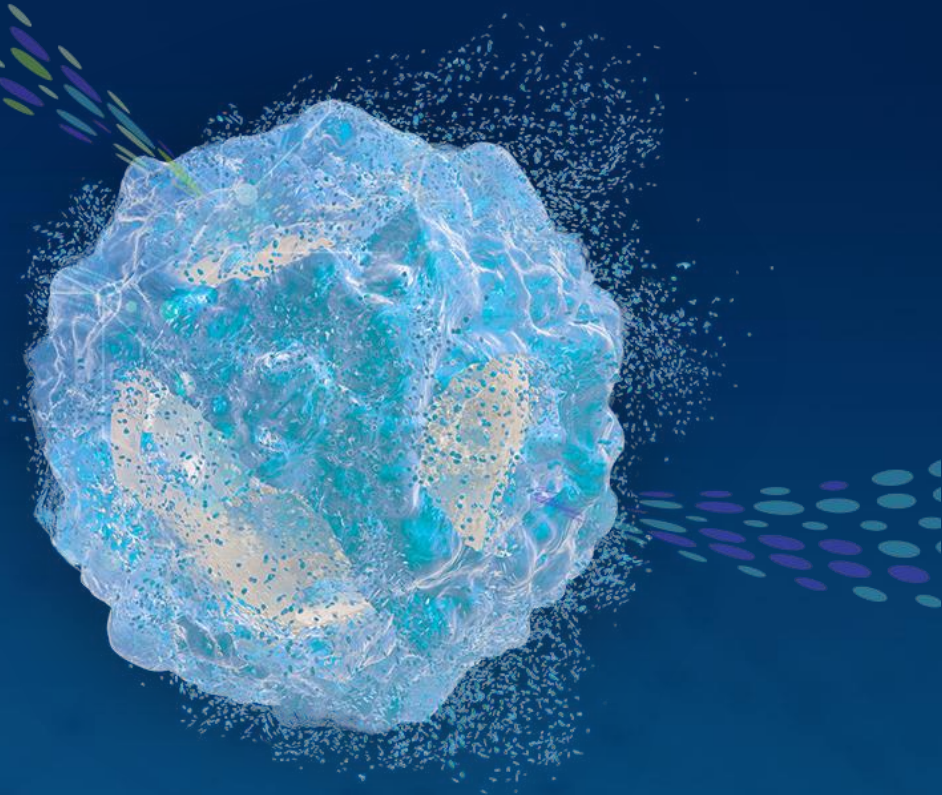
Discovery

**Small
molecule
and pADC**

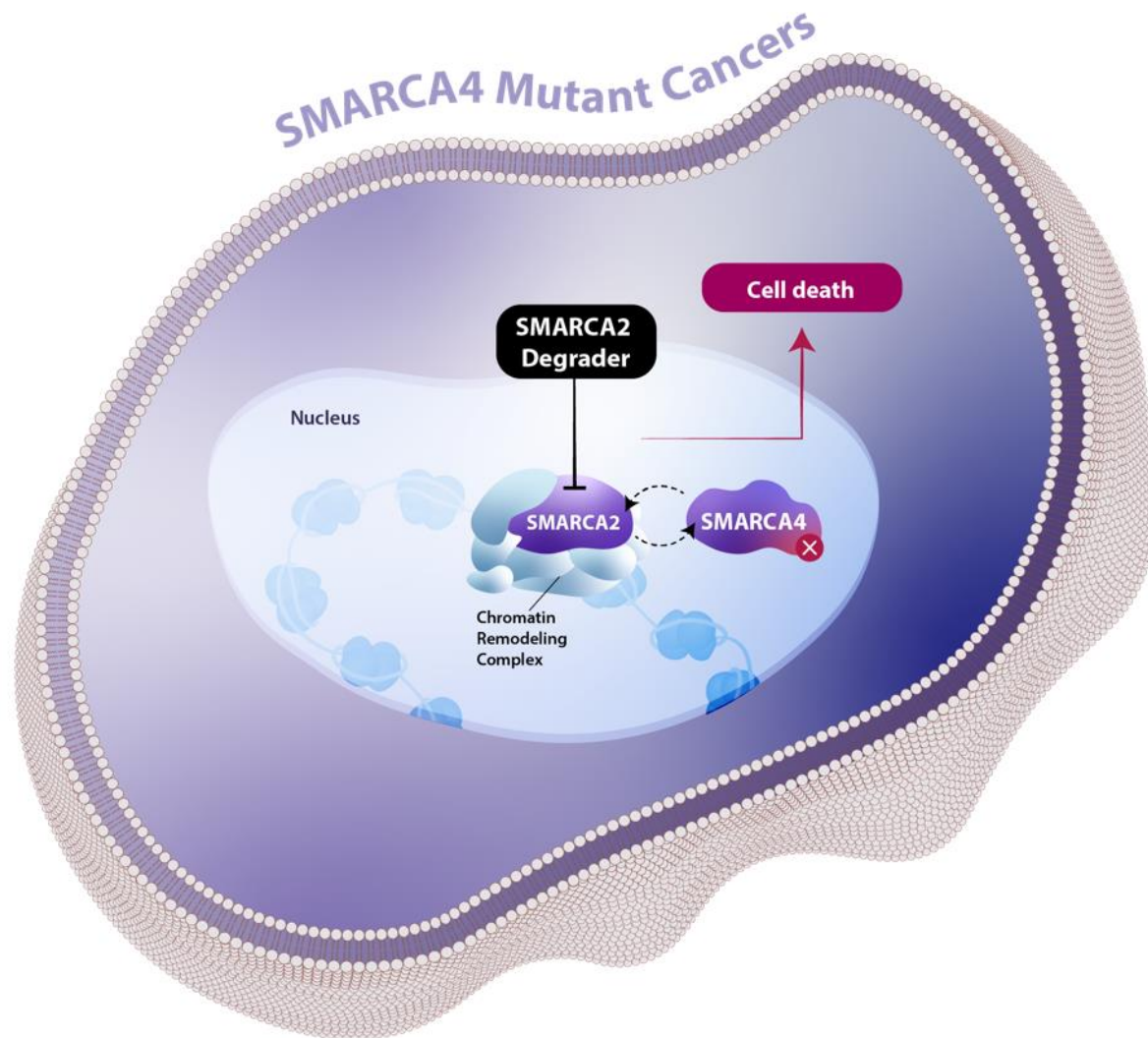
- Advance a small molecule discovery program
- Advance SMARCA degrader ADC program in partnership with AbCellera
- Build precision ADC (pADC) platform with novel payloads

PRT3789

SMARCA2 Degradator



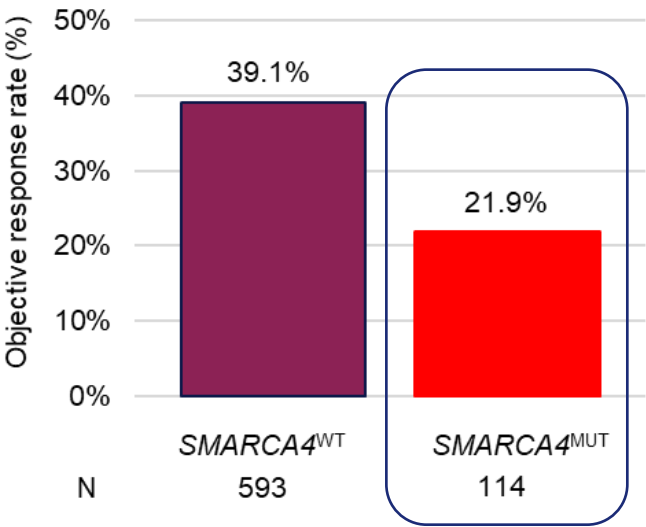
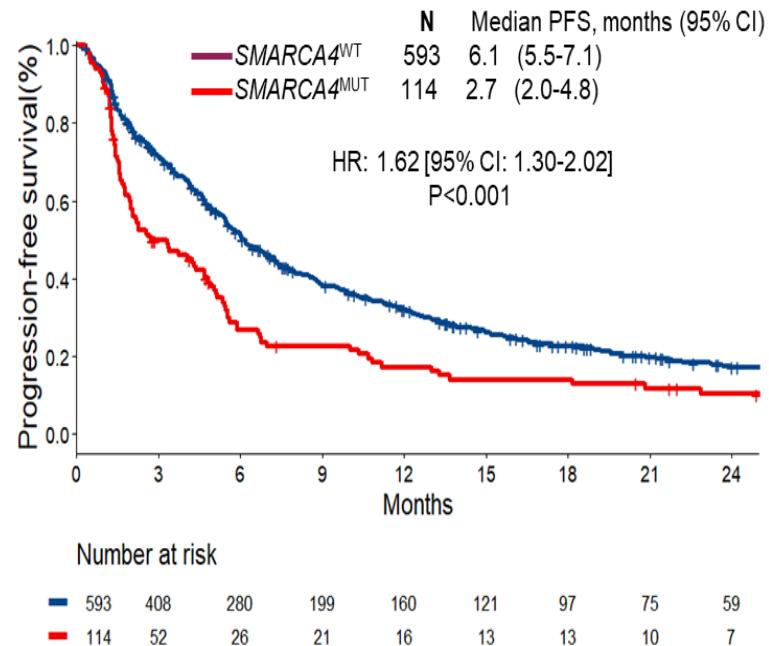
Selective Degradation of SMARCA2 (BRM) is a First-in-Class Opportunity to Treat SMARCA4 mutated Patients



- Mutations in the Chromatin Remodeling (CR) complex drive cancer growth and resistance and confer poor prognosis in many cancers
- SMARCA2 and SMARCA4 are subunits of the CR complex, required for its function
- Cancer cells with loss of SMARCA4 expression through mutations are highly dependent on SMARCA2 for survival
- Selective degradation of SMARCA2 offers a novel approach to develop treatments for patients with SMARCA4 mutated cancers

Patient outcomes with Firstline Advanced NSCLC: Harboring a SMARCA4 mutation highlights needs for improved therapies

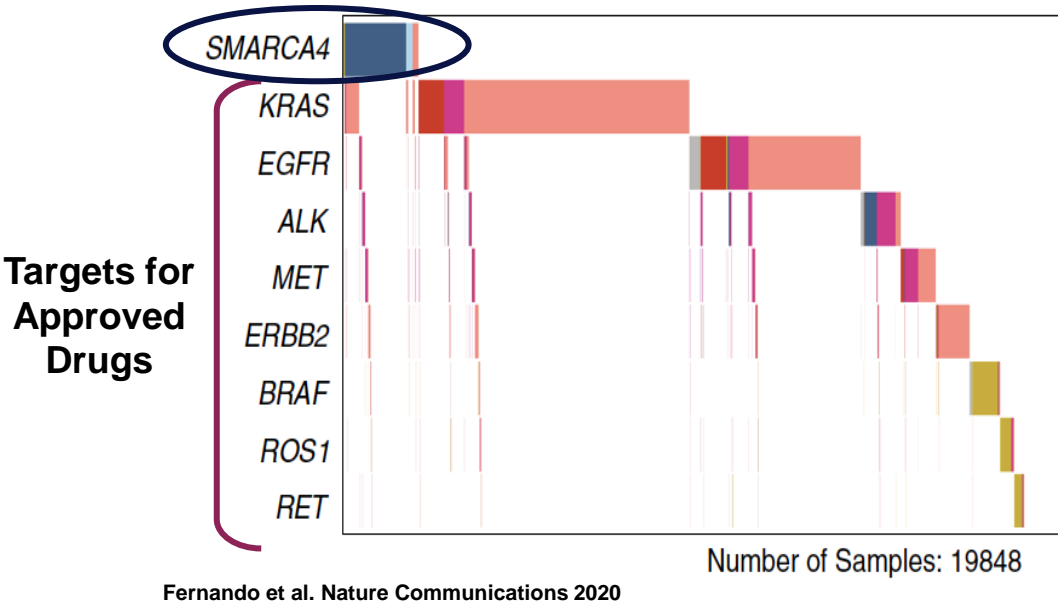
Patients treated with chemoimmunotherapy



Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193 (attached).

NSCLC Patients with SMARCA4 Mutations Do Not Harbor Overlapping Driver Mutations: Few Targeted Medicines are Available

SMARCA4 Mutation – A Potentially Novel Biomarker for NSCLC



SMARCA4 Prevalence Across Selected Solid Tumors

Indication	Any SMARCA4 Mutation ^{1,2,3} (%)
NSCLC	10
Esophageal	8.0
Gastric (stomach adeno)	8.3
Skin (invasive and in situ melanoma)*	21
Endometrial (uterine corpus)	13
Squamous cell lung	7.7
Urinary (bladder)	9.0
Colorectal	6.0
Pancreatic	2.9
Melanoma (invasive)	8.7

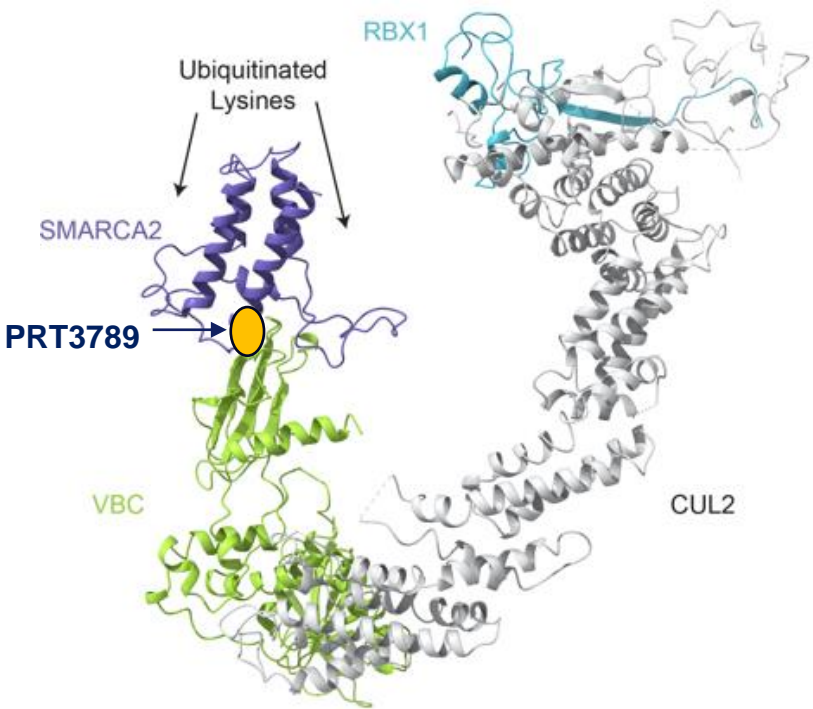
- Most patients with SMARCA4 mutations do not have other driver mutations that are targets for molecularly driven medicines in lung cancer

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: Highly Selective SMARCA2 Degradator – Clinical Candidate

VHL-Based Degradator for IV Dosing

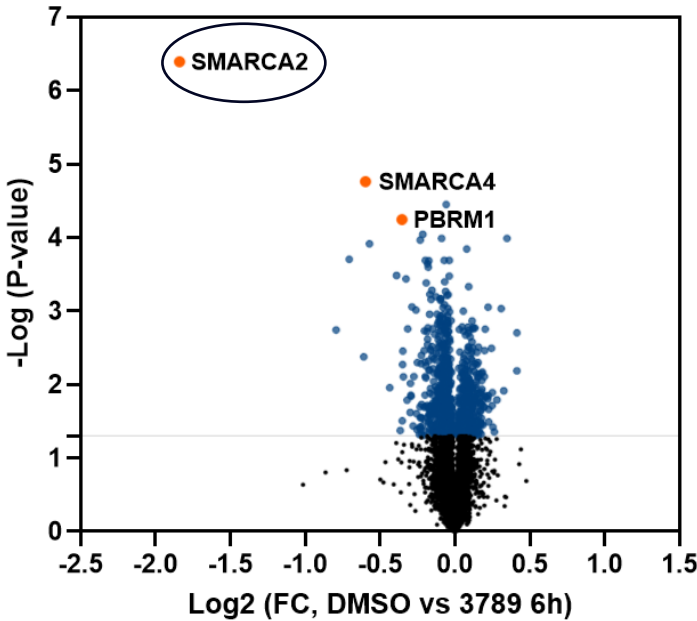
Tertiary Complex of SMARCA2/PRT3789/VHL E3 Ligase



Potent and Selective for SMARCA2 vs SMARCA4

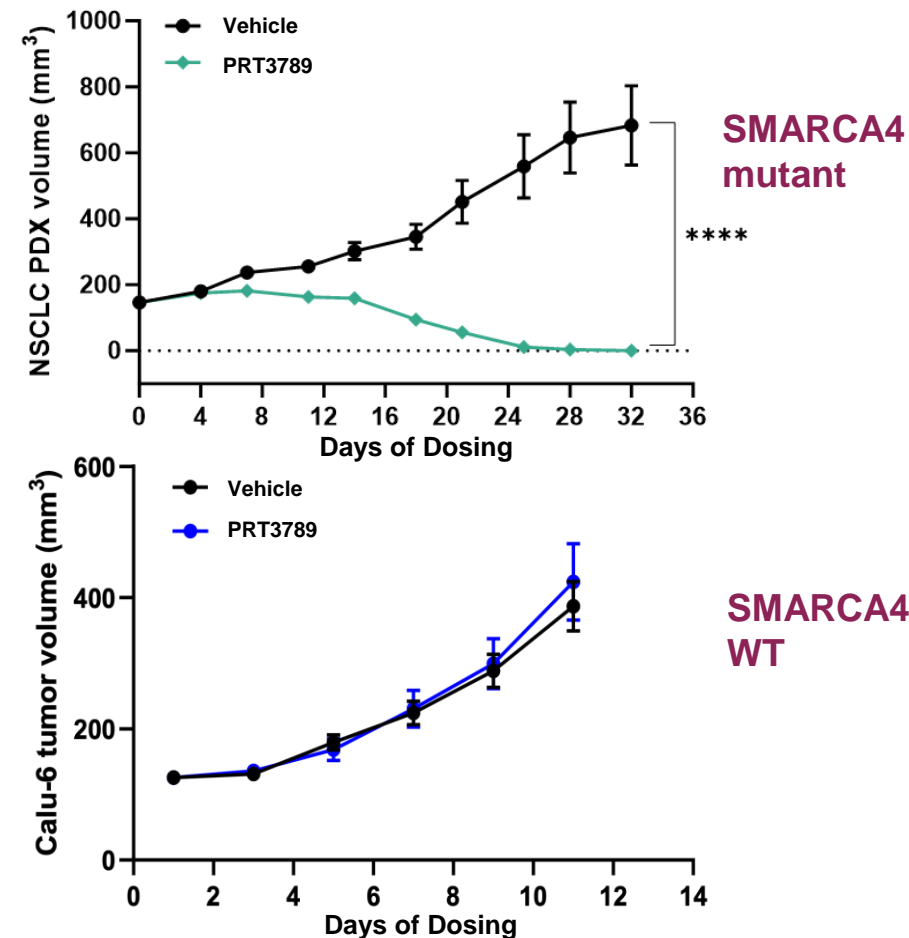
Assay	PRT3789
SMARCA2 Degradation (nM)	0.73
SMARCA4 Degradation (nM)	26
Selectivity: Degradation (SMARCA4/SMARCA2)	40X
Selectivity: Cell Proliferation (SMARCA4/SMARCA2)	>1000x

High Selectivity Across the Proteome

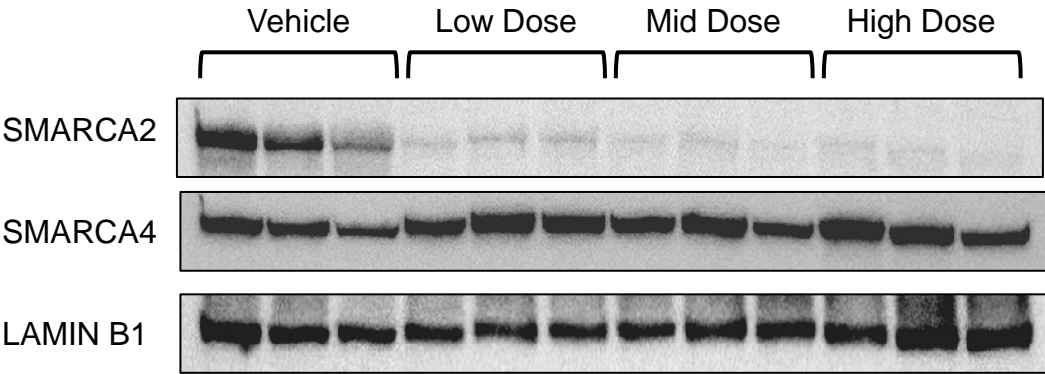


PRT3789: Potent and Selective SMARCA2 Degradator with *In Vivo* Activity

Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft



Significant Degradation of SMARCA2 Protein but not SMARCA4 in Preclinical Models



Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Hulse_SMARCA2_AACR-2023_Poster-6270_04APR23.pdf
Presented at AACR 2022; https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

Phase 1 Study in Biomarker (SMARCA4 mutations) Selected Cancers

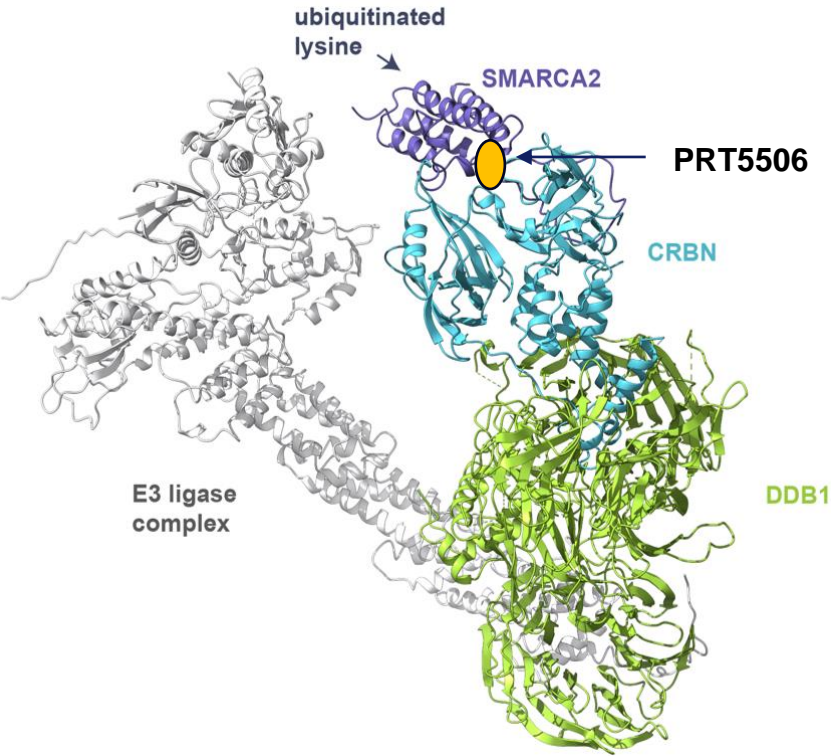


ClinicalTrials.gov Identifier: NCT05639751; ESMO 2023 Poster: <https://preludetx.com/wp-content/uploads/2023/10/Dagogo-Jack-ESMO-2023-PRT3789-01-TiP-Poster-Final-9Oct2023.pdf>

Highly Selective Orally Bioavailable SMARCA2 Degraders Identified

CRBN-Based Degraders for Oral Dosing

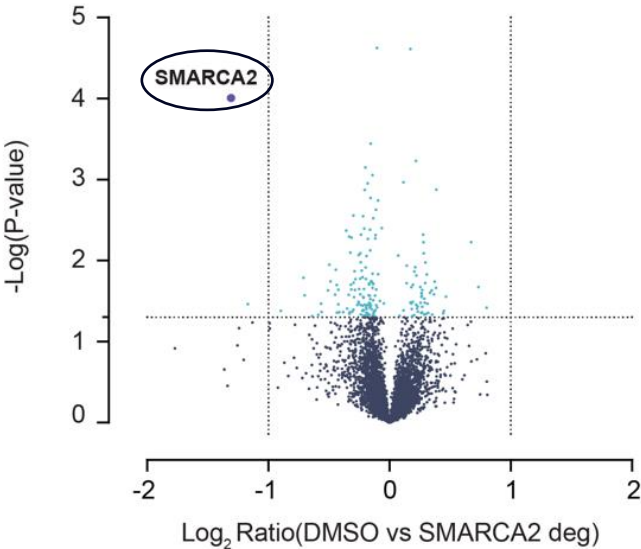
Tertiary Complex of SMARCA2/PRT5506/CRBN E3 Ligase



Potent, Selective and Orally Bioavailable

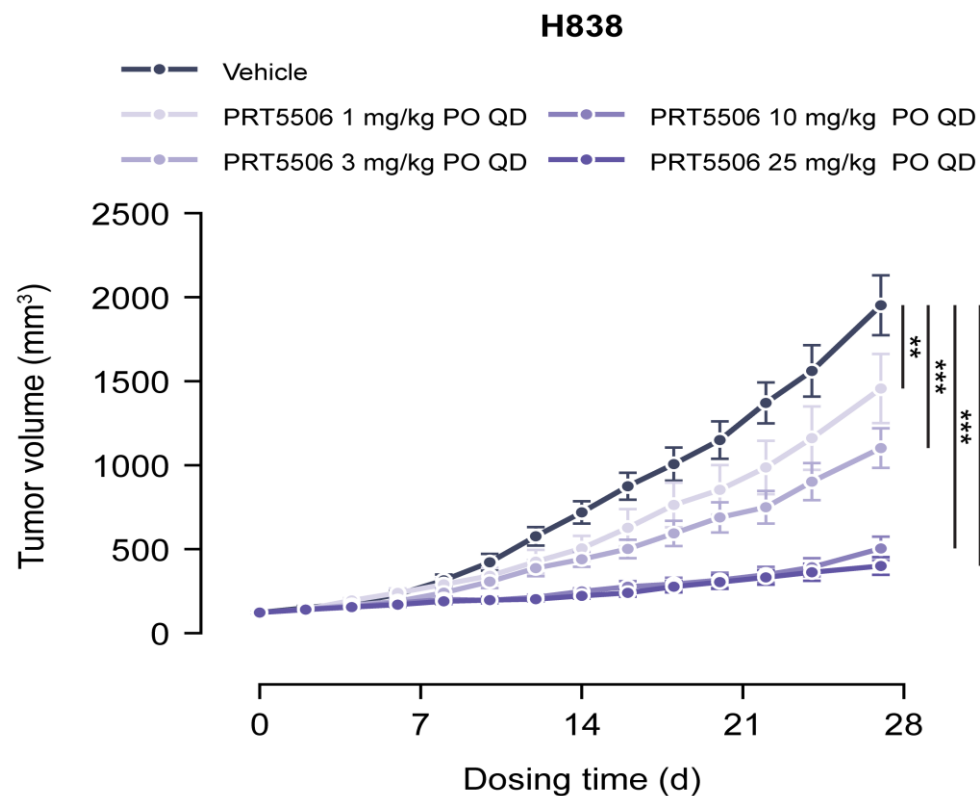
Assay	PRT5506
SMARCA2 Degradation (nM)	1
SMARCA4 Degradation (nM)	52
Selectivity SMARCA4/SMARCA2	52X
Selectivity Cell Proliferation (WT/SMARCA4 Mutant)	>1000x
PK	
mouse/dog (%F)	7, 12

High Selectivity Across the Proteome

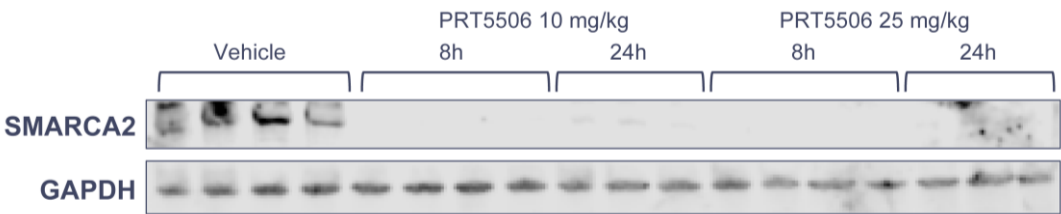


Oral SMARCA2 Degraders Candidates Provide Proof-of-Concept in Preclinical Models

Robust Tumor Growth Inhibition of SMARCA4 Mutated Xenograft with Oral Dosing



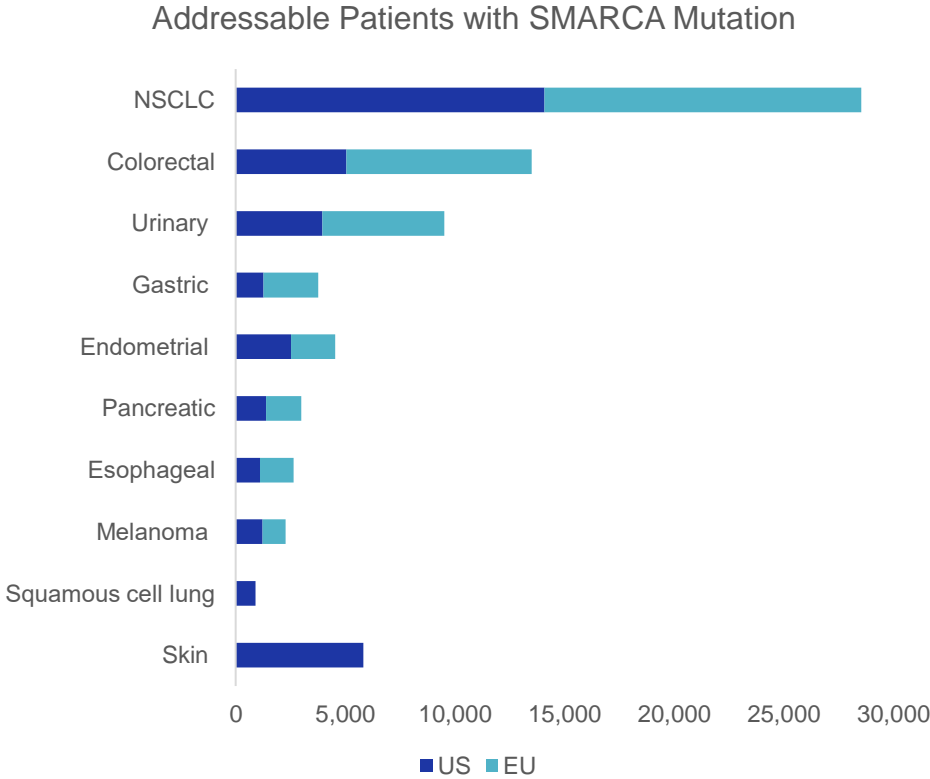
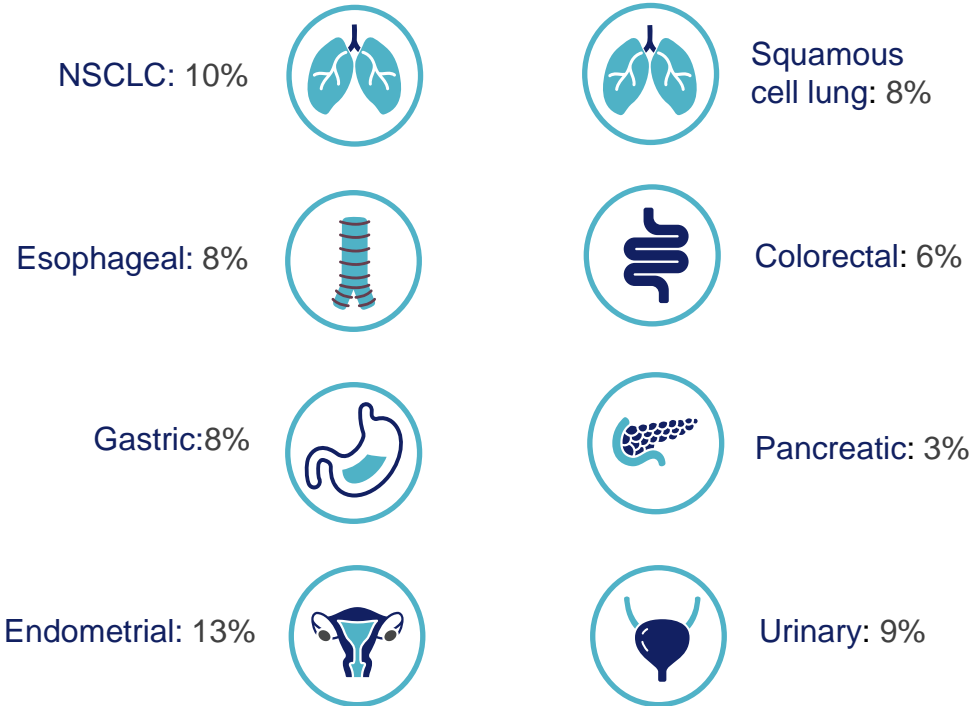
SMARCA2 Degradation In Vivo with Oral Dosing of PRT5506



- Development Candidate Identified and IND Filing expected in 1H24

Pan-Tumor Unmet Need in Patients with SMARCA4 Mutations

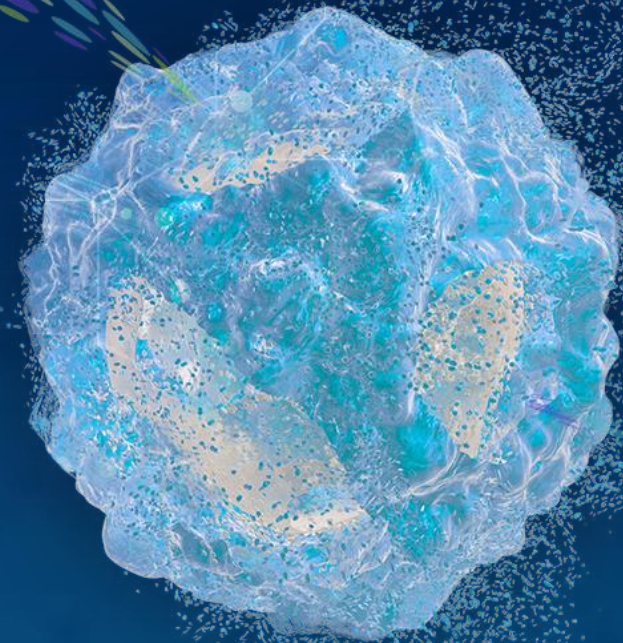
At least 70K patients across multiple tumors have a SMARCA4 mutation, for which there is no targeted treatment approved (US+EU).^{1,2}



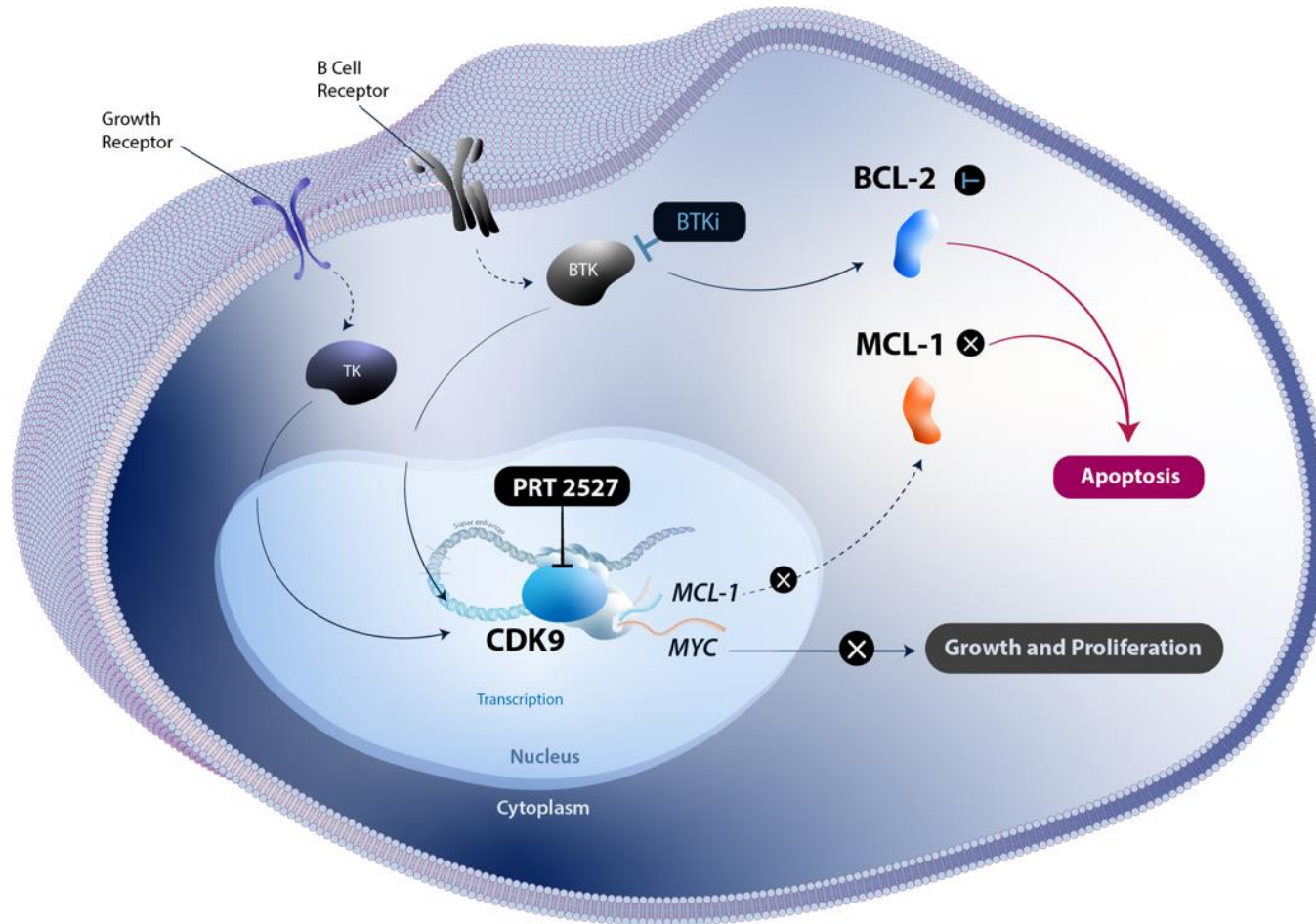
¹Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine data set; ²US tumor incidence based on SEER 2022; EU5 tumor incidence based on Globocan

PRT2527

CDK9 Inhibitor



CDK9 Inhibition: Targets Two Major Validated Pathways (MYC and MCL-1)

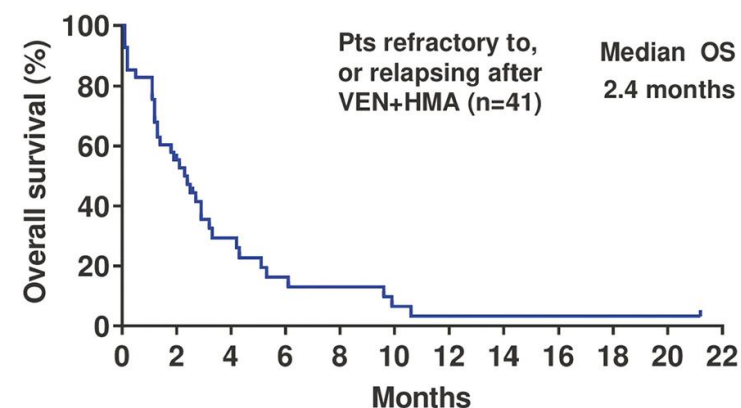


- CDK9 is the primary transcriptional regulator of a major oncogene MYC and an apoptosis inducer MCL-1
- Dysregulated pathways involving MYC and MCL-1 drive pathogenesis and resistance in hematological cancers including lymphoid and myeloid cancers
- PRT2527, a potent and highly selective CDK9 inhibitor, represents a major advance over previous CDK inhibitors and has the potential to address a broad range of hematological cancers

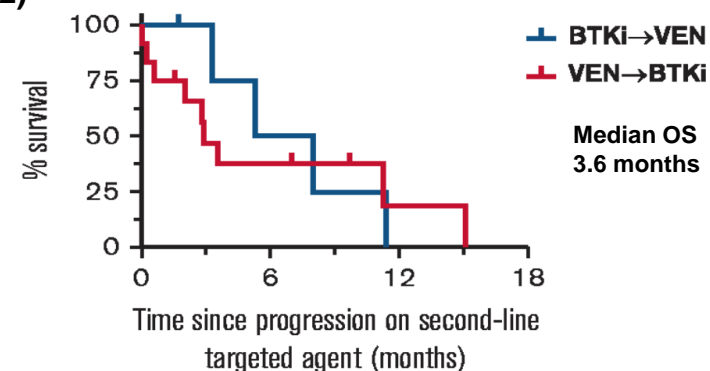
Outcomes in Patients with Hematologic Malignancies Refractory to Current Treatments are Poor after SoC

- Venetoclax + hypomethylating agent (HMA) is the most widely used treatment for AML patients ineligible to receive intensive chemotherapy. After venetoclax + HMA, patients have very poor outcomes with a median overall survival of 2.4 months
- Double class (BTKi and BCL2i) resistant CLL is another emerging high unmet need population. Median overall survival after the second targeted agent was 3.6 months
- CDK9 is key driver of pathogenesis and resistance in B-cell and myeloid malignancies. CDK9i downregulates several oncogenes, including MYC, MYB and MCL-1 which are known resistance factors in hematologic malignancies

(1)



(2)



Source:

1) Maiti A et al. Haematologica 2021. <https://doi.org/10.3324/haematol.2020.252569>

2) Low TE et al. Blood Advances 2021. <https://doi.org/10.1182/bloodadvances.2021005083>

PRT2527: Potent and Highly Selective CDK9 Inhibitor

Depletes MCL-1 and MYC Proteins

Highly Isoform Selective CDK9 Inhibitor

Compound		PRT2527
Biochemical* IC ₅₀ (nM)	CDK9	0.95
Proliferation* IC ₅₀ (nM)		18
Plasma* IC ₅₀ (nM)		196
Fold Selectivity CDK9 vs Other Isoforms	CDK1	73x
	CDK2	340x
	CDK3	35x
	CDK4	250x
	CDK5	>1000x
	CDK6	>1000x
	CDK7	>1000x

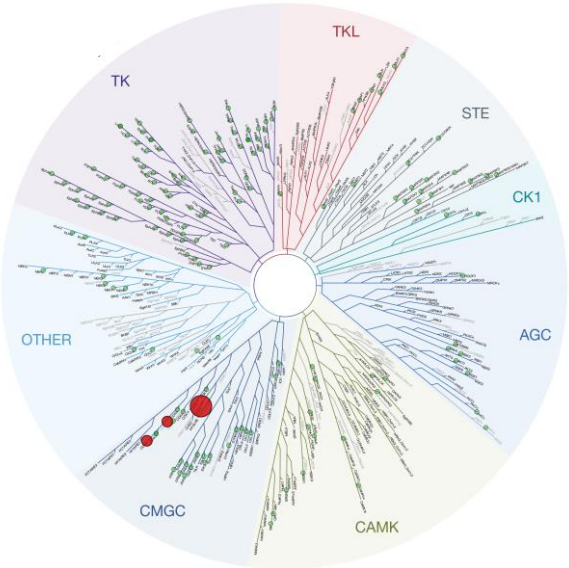


10 -100x



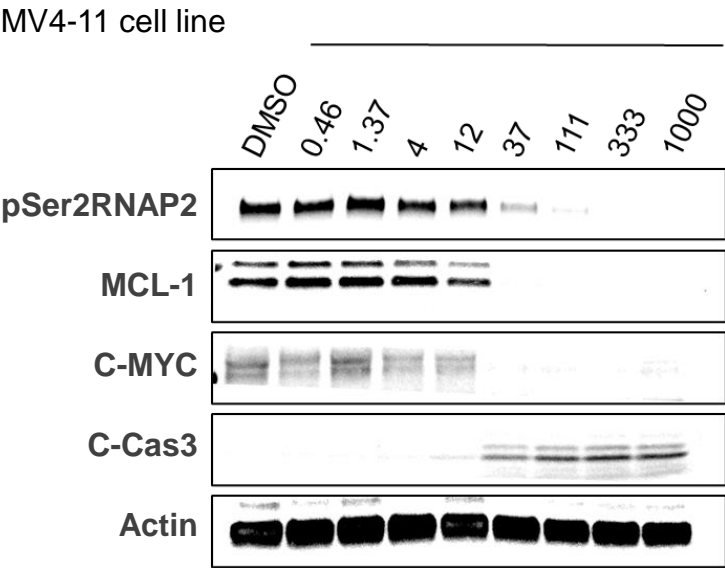
>100x

Highly Selective in Kinome



PRT2527
177 Assays tested
3 Interactions Mapped
S-Score(35) = 0.02

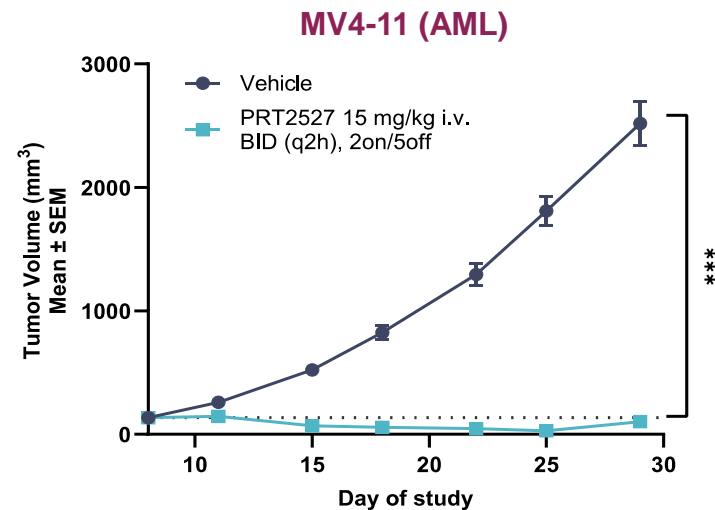
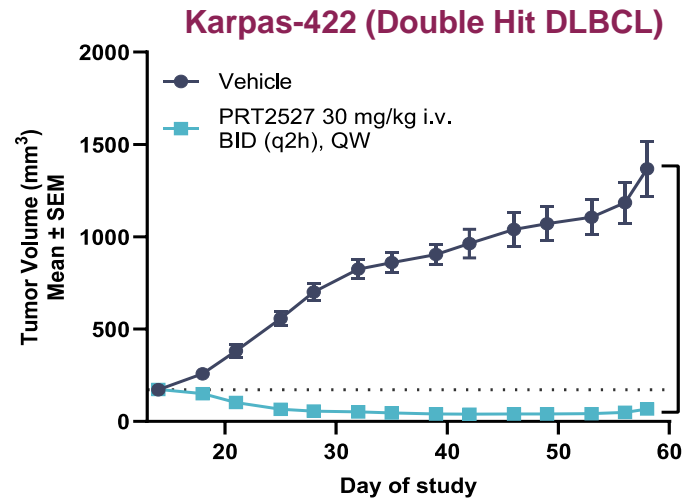
PRT2527 Treatment Depletes MCL-1 and MYC Proteins



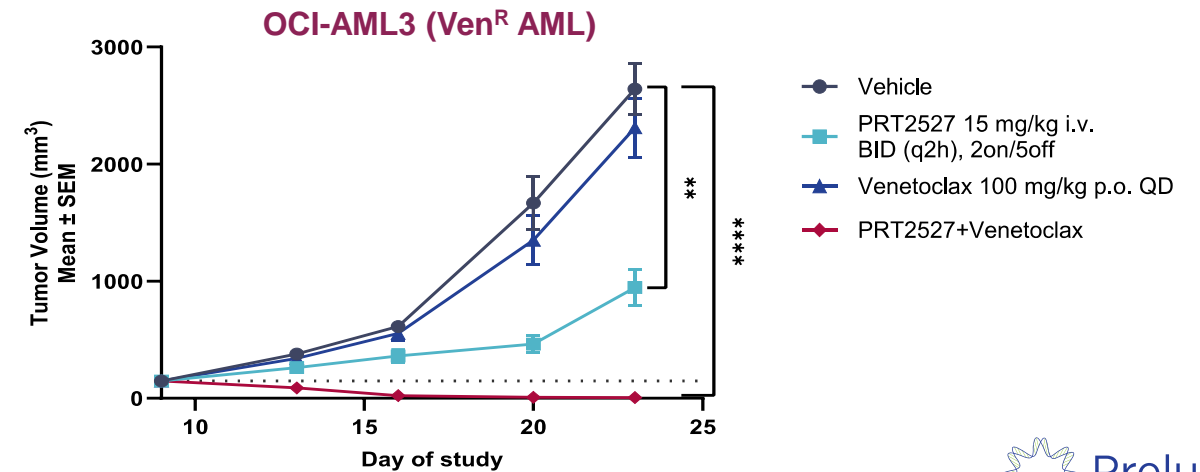
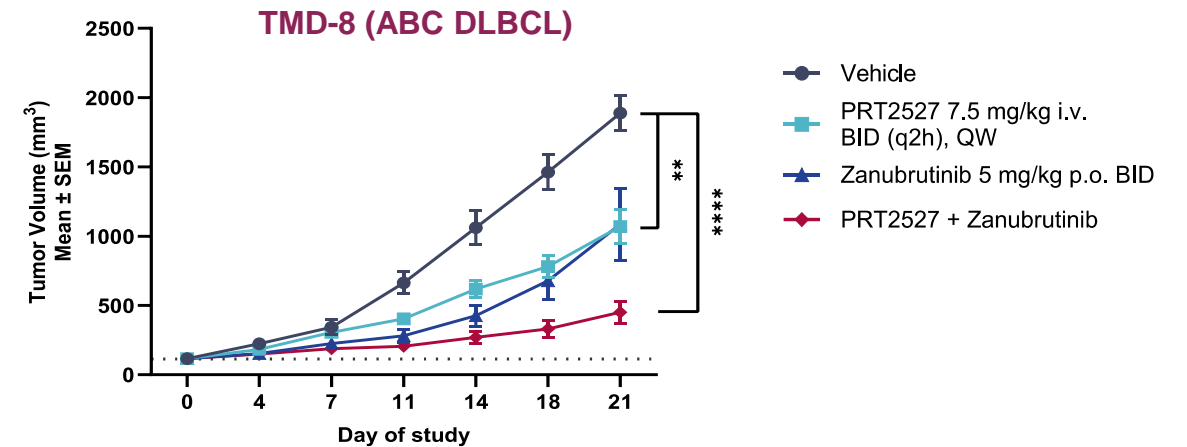
*Internal data; biochemical assay at 1 mM ATP, H929 CTG proliferation assay
Presented at ASH 2022; https://preludetx.com/wp-content/uploads/2023/03/ASH-2022_PRT2527-Presentation.pdf

PRT2527 is Highly Efficacious In Vivo in Models of Hematologic Malignancies

Monotherapy



Combination

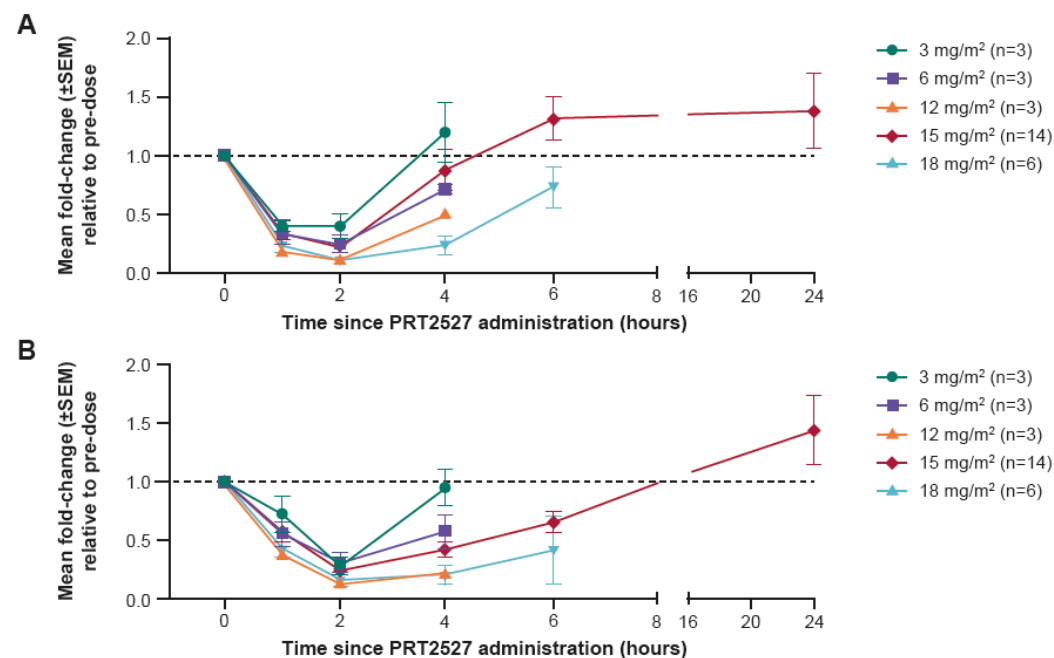


CDK9 Inhibitor: PRT2527

Phase 1 Studies in Solid Tumors

- In adults with advanced solid tumors, PRT2527 demonstrated favorable tolerability with manageable neutropenia and absence of significant gastrointestinal events or hepatotoxicity.
- The short half-life of PRT2527 enables acute CDK9 inhibition over a defined period.
- The observed dose-dependent downregulation of CDK9 transcriptional targets – MYC and MCL-1 mRNA expression in PBMCs isolated from patients treated with PRT2527 – was consistent with the degree of target engagement required for preclinical efficacy.
- As predicted by the preclinical model, 12 mg/m² QW dosing and higher showed optimal target inhibition.
- The overall safety profile observed in this study supports further development of PRT2527 in hematologic malignancies (NCT05665530).

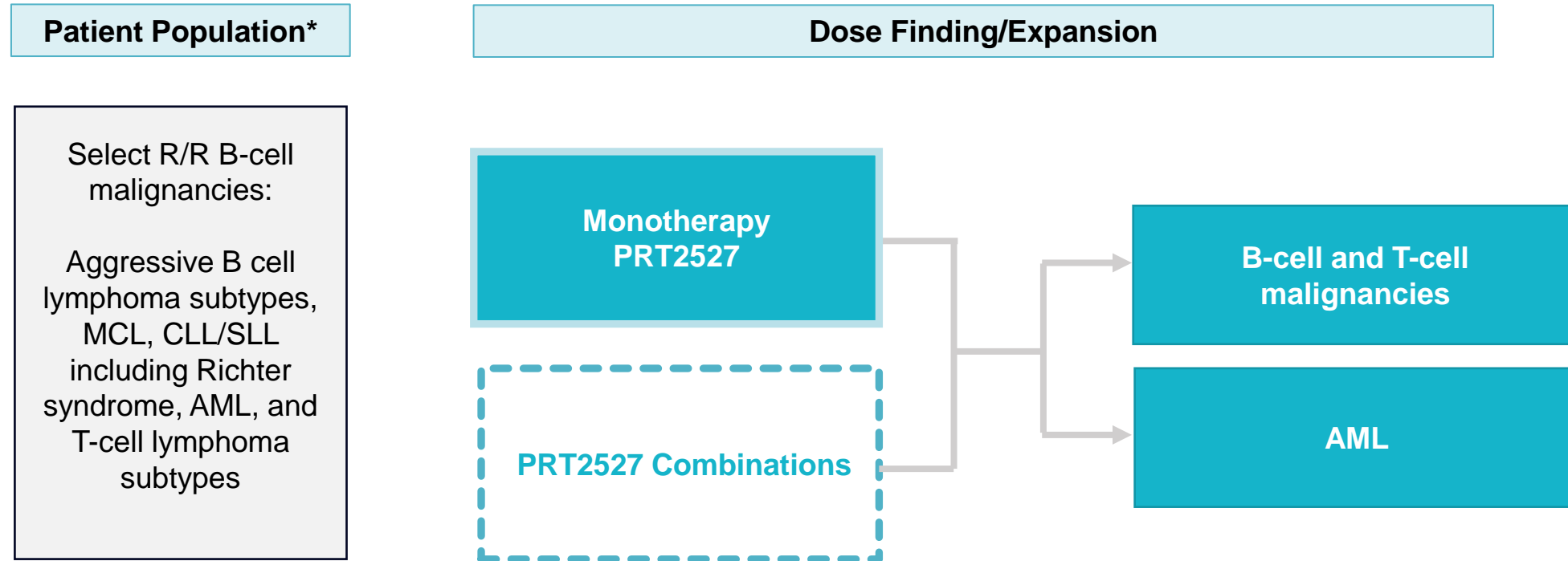
PRT2527-Associated Inhibition of CDK9 Transcriptional Targets MYC (A), MCL1 (B) in PBMCs



The dotted line represents pre-dose baseline levels.

CDK9 Inhibitor: PRT2527

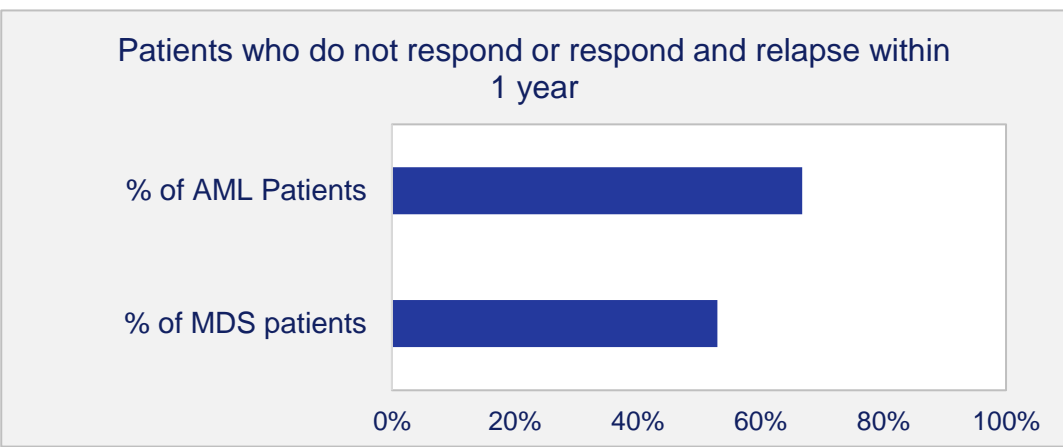
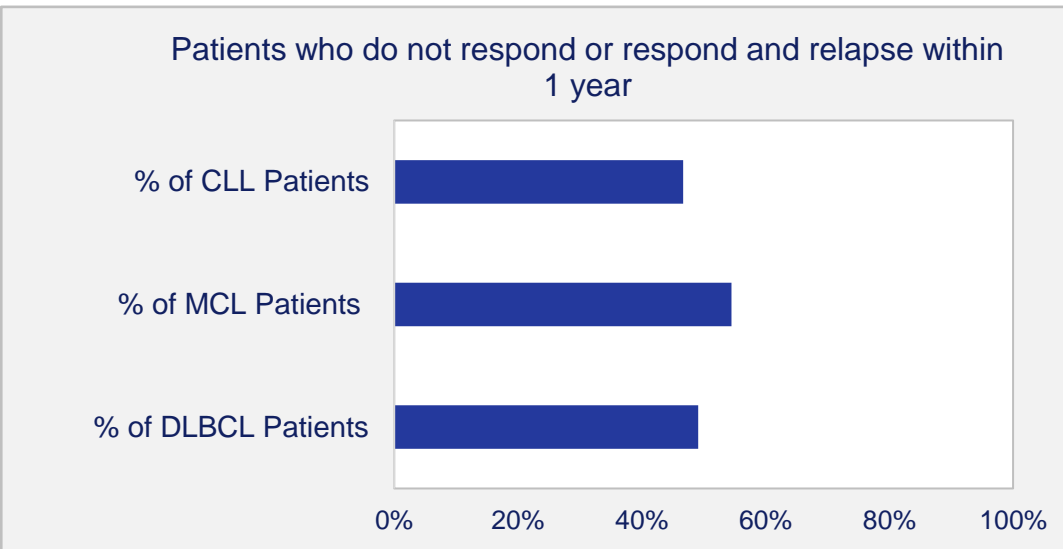
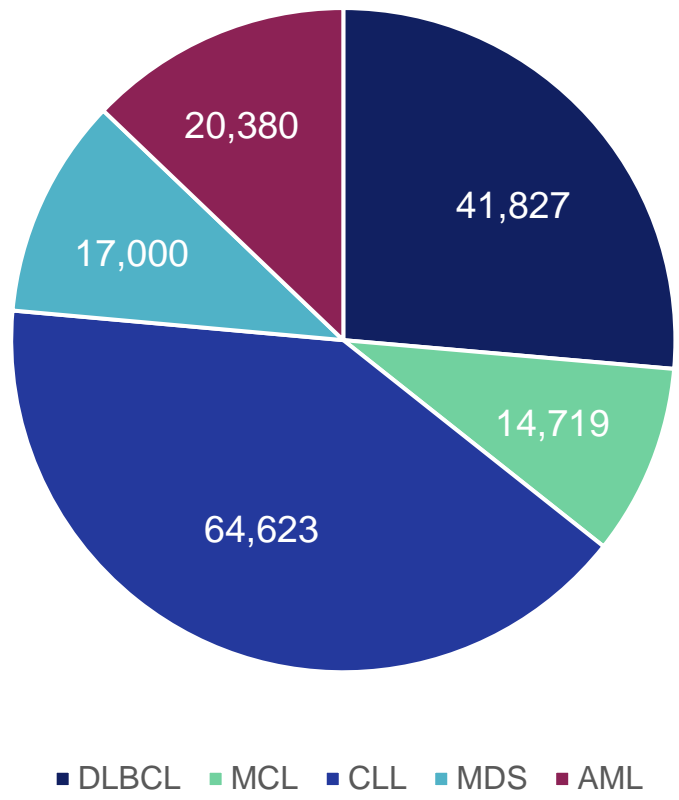
Phase 1 Studies in Hematologic Malignancies



*R/R disease following: At least 1 prior systemic therapy for aggressive BCL subtypes, MCL and Richter's syndrome; At least 2 prior therapies including a BTK inhibitor and venetoclax for CLL.
ClinicalTrials.gov Identifier: NCT05665530

PRT2527: Broad Potential to Address Areas of High Unmet Need

>150K Treatable Patients across 5 tumor types^{1,2,3,4,5}



1. SEER Cancer Stat Facts: <https://seer.cancer.gov/statfacts/html/clyl.html>; 2. Gena Kanas, et. al. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe 3. CancerMPact® Treatment Architecture, Non-Hodgkin US, 4. CancerMPact® Treatment Architecture, Chronic Lymphocytic Leukeimia, US, 5. CLL Patient Based Forecast, Datamonitor Healthcare

Precision ADC Partnership with AbCellera



Precision ADCs: The Next Generation of ADCs

- Multi-year global collaboration to jointly discover, develop and commercialize novel oncology medicines for up to five programs.
 - First program focusing on a SMARCA degrader
- AbCellera will lead manufacturing activities and Prelude will lead clinical development and global commercialization, subject to AbCellera's option to co-promote any resulting commercial products in the U.S.



"By leveraging our combined capabilities and expertise in rapidly discovering and advancing novel candidates into the clinic, this collaboration provides an opportunity to build a pipeline of first-in-class ADCs targeting clinically validated pathways in oncology"

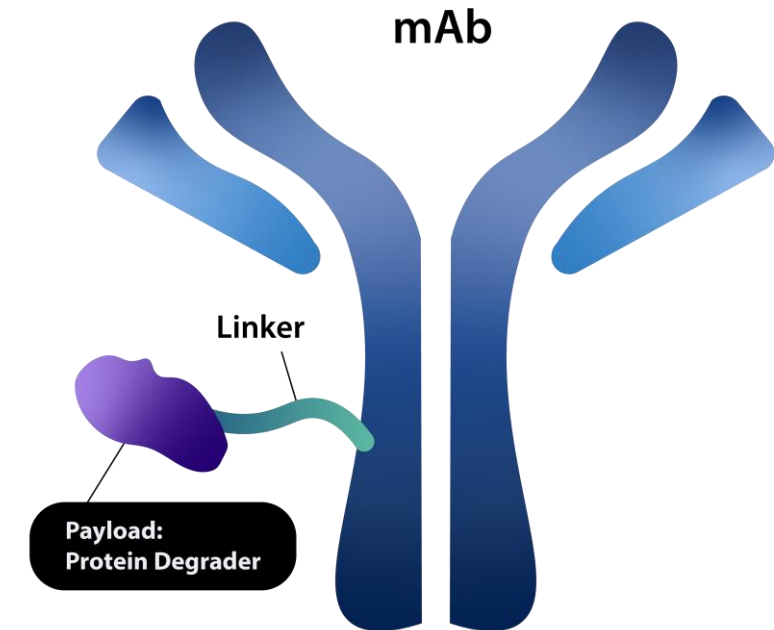
Kris Vaddi, Ph.D.
CEO of Prelude

"Through this strategic partnership we are combining deep expertise in antibody and small molecule development to create precision ADC therapies for patients in need"

Carl Hansen, Ph.D.
Founder and CEO of AbCellera

Prelude and AbCellera Partnership: Creating Novel First-in-Class 'Precision ADCs' Together

- Combines Prelude's expertise in medicinal chemistry, targeted protein degradation and clinical development capabilities with AbCellera's antibody discovery engine to develop novel 'Precision ADCs'.
- Diversifies Prelude's portfolio by adding 'Precision ADCs' to our pipeline
 - Expands the reach of SMARCA degraders to cancers beyond those with SMARCA4 mutations



Key R&D Objectives and Strategic Priorities for 2024

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PRT3789

SMARCA2
(IV)

- Complete monotherapy escalation in patients with SMARCA4 mutations- mid-year
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PRT2527

CDK9

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PRT-SCA2

SMARCA2
(Oral)

- IND in 1H
- Initiate Phase 1 in patients with SMARCA4 mutations in 2H

Discovery

Small
molecule
and pADC

- Advance a small molecule discovery program
- Advance SMARCA degrader ADC program in partnership with AbCellera
- Build precision ADC (pADC) platform with novel payloads



Prelude
THERAPEUTICS

Corporate Presentation - Appendix

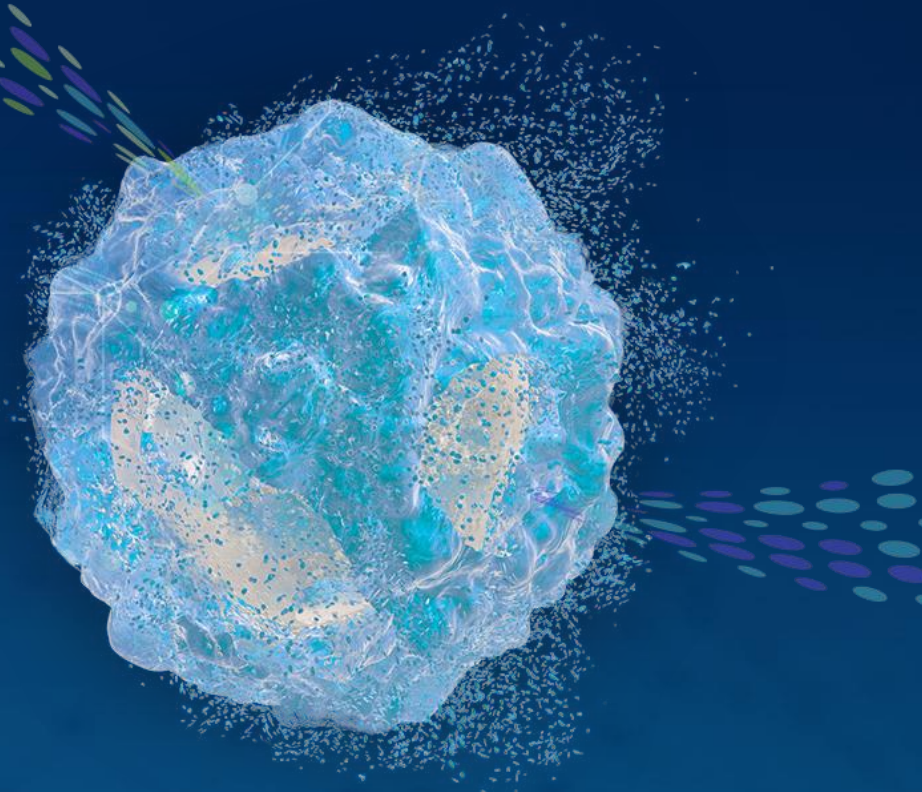
November 2023

Patient focused.
Science driven.
Precision oncology.

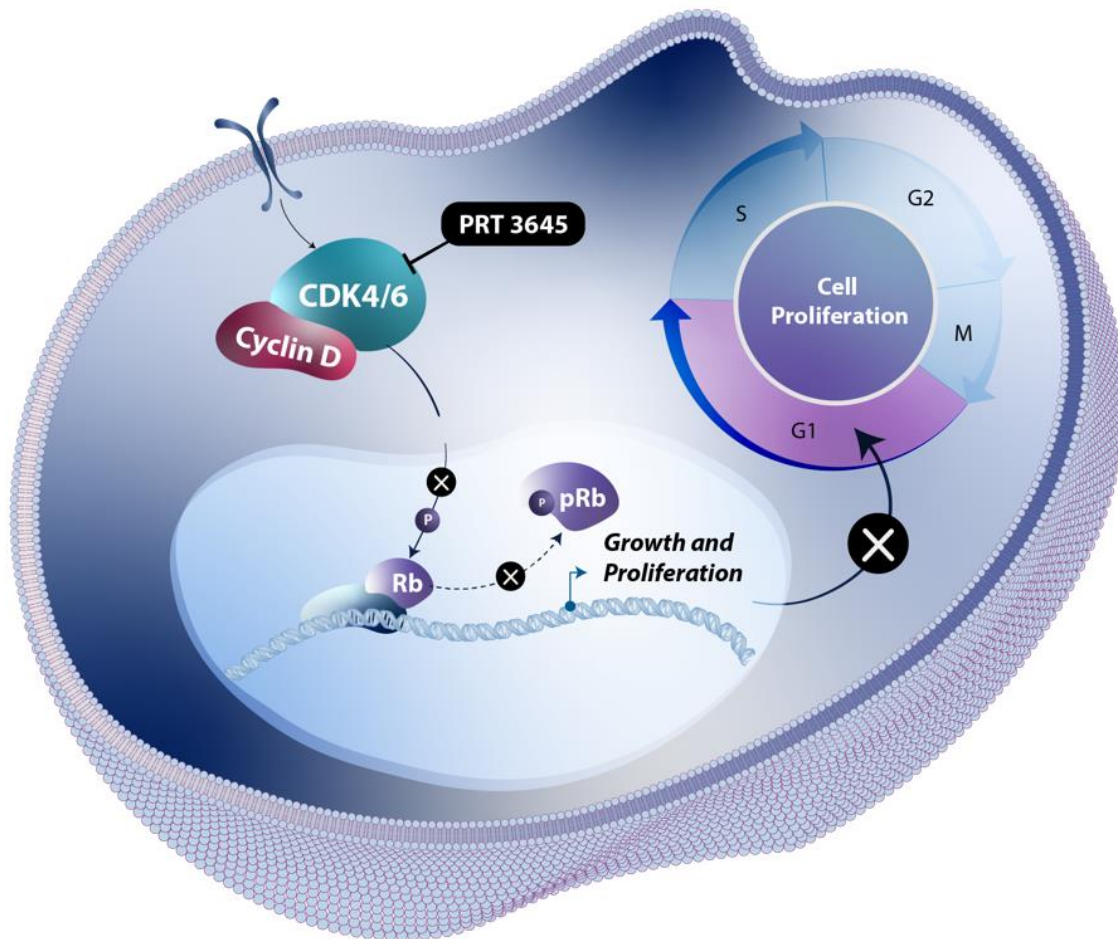


PRT3645

Next Generation CDK4/6 Inhibitor



Next Generation CDK4/6 Inhibition: Targeting Cancer Through Cell Cycle Regulation



- **Validated mechanism** with approval of Next Generation CDK4/6 inhibitors in HR+ breast cancer
- **Resistance mechanism** to other inhibitors of the RAS and HER2 pathways, including KRAS G12C
- Next generation CDK4/6 inhibitor with **improved tolerability and tissue penetrance** could translate into **activity in areas of unmet need** beyond HR+ breast cancer
- Sequential use of Next Generation CDK4/6 inhibitors in breast cancer may also improve outcomes

ASCO 2022 reference: A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor-positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN trial. and See AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Zou_CDK46_AACR-2023_Poster-5973_04APR23.pdf

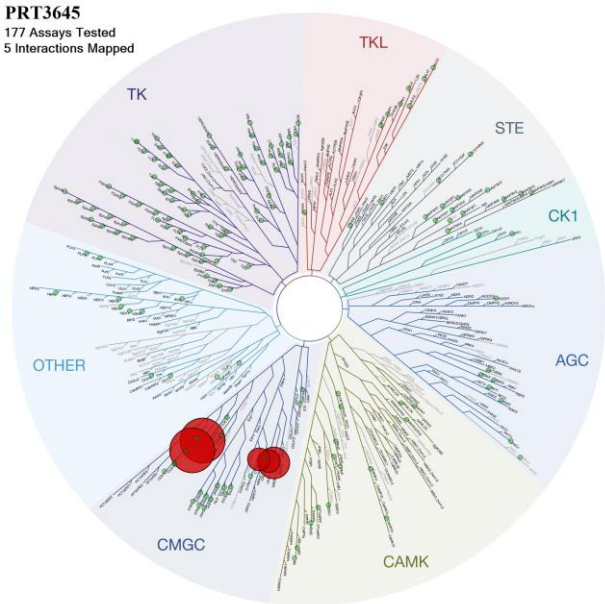
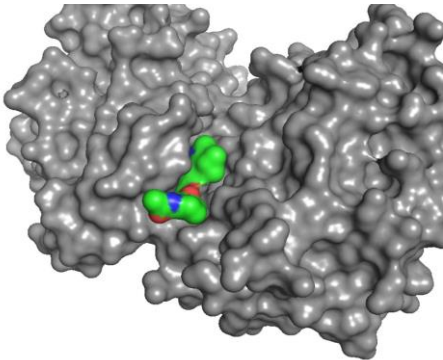
PRT3645: Designed to be the Next Generation Highly Selective CDK4/6 Inhibitor

Bias towards CDK4 over CDK6 to improve tolerability

Compound		Palbociclib	Abemaciclib	PRT3645
Biochemical* IC ₅₀ (nM)	CDK4	25	5	3
Proliferation* IC ₅₀ (nM)		52	70	47
Phospho-Rb* IC ₅₀ (nM)		28	30	16
Fold Selectivity CDK4 vs Other Isoforms	CDK6	1x	6x	5x
	CDK1	>500x	>500x	>500x
	CDK2	>500x	173x	>500x
	CDK3	>500x	212x	>500x
	CDK5	>500x	>500x	>500x
	CDK7	>500x	>500x	>500x
	CDK9	209x	59x	>500x

>200x 200-20x 20-2x <2x

Highly Selective, ATP Competitive

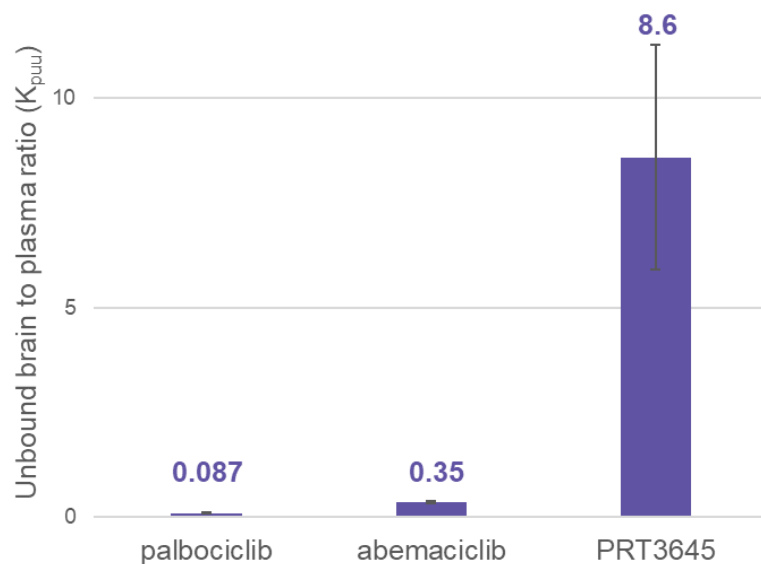


*Internal data; biochemical assay at 1 mM ATP, MCF7 CTG proliferation assay; MCF7 pRB

PRT3645: Next Generation CDK4/6 Inhibitor

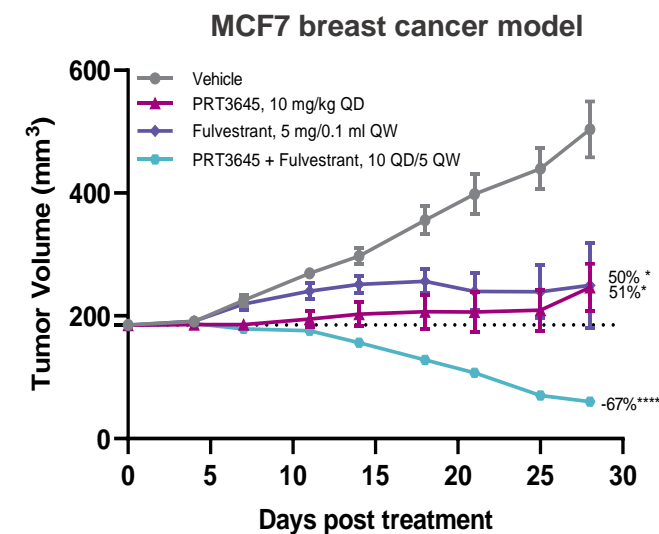
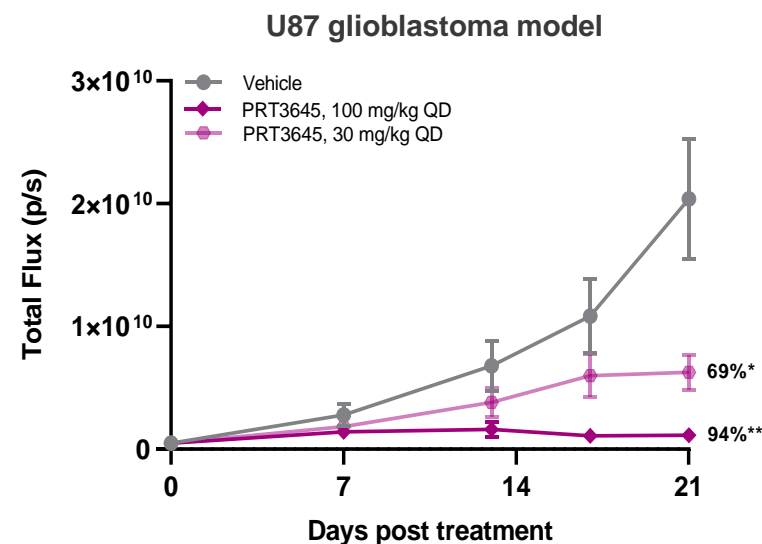
Improved Tissue Penetration and Favorable Activity in Preclinical Models

PRT3645 demonstrated higher tissue penetration than approved CDK4/6 inhibitors*



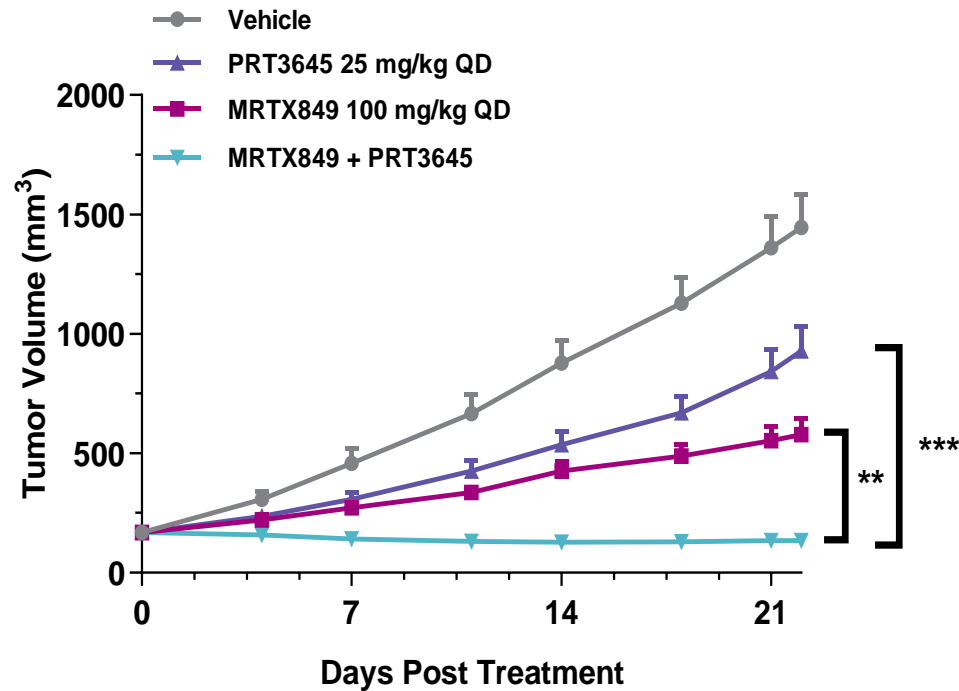
*IV infusion study in rats

PRT3645 showed favorable activity in vivo as monotherapy and in combination

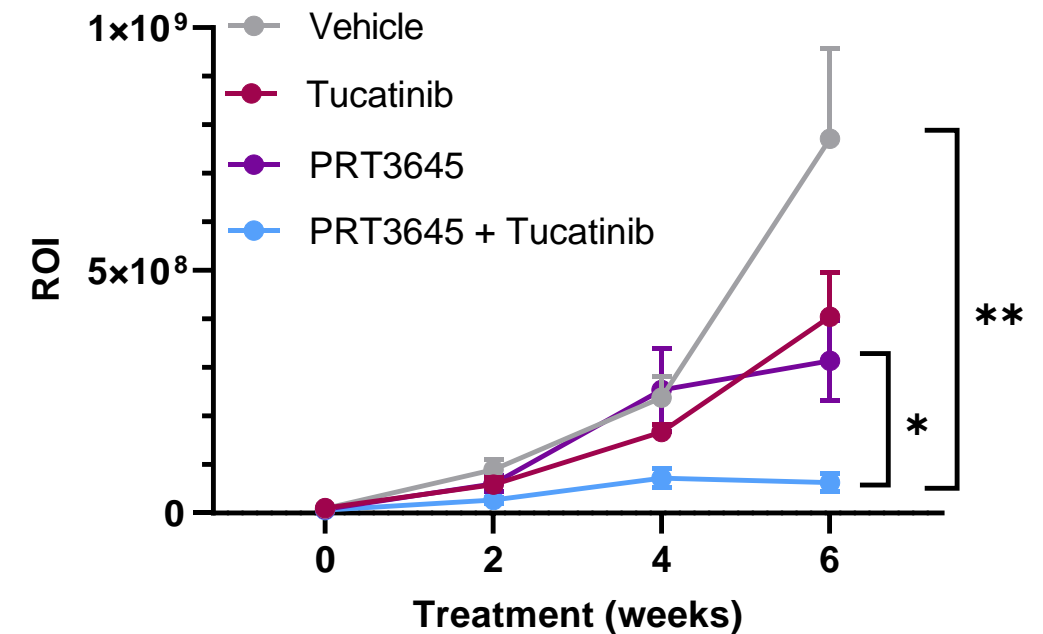


Potential for Novel Combinations to Extend the Reach of CDK4/6 Inhibition Beyond ER+ Breast Cancer

H2122 NSCLC Model



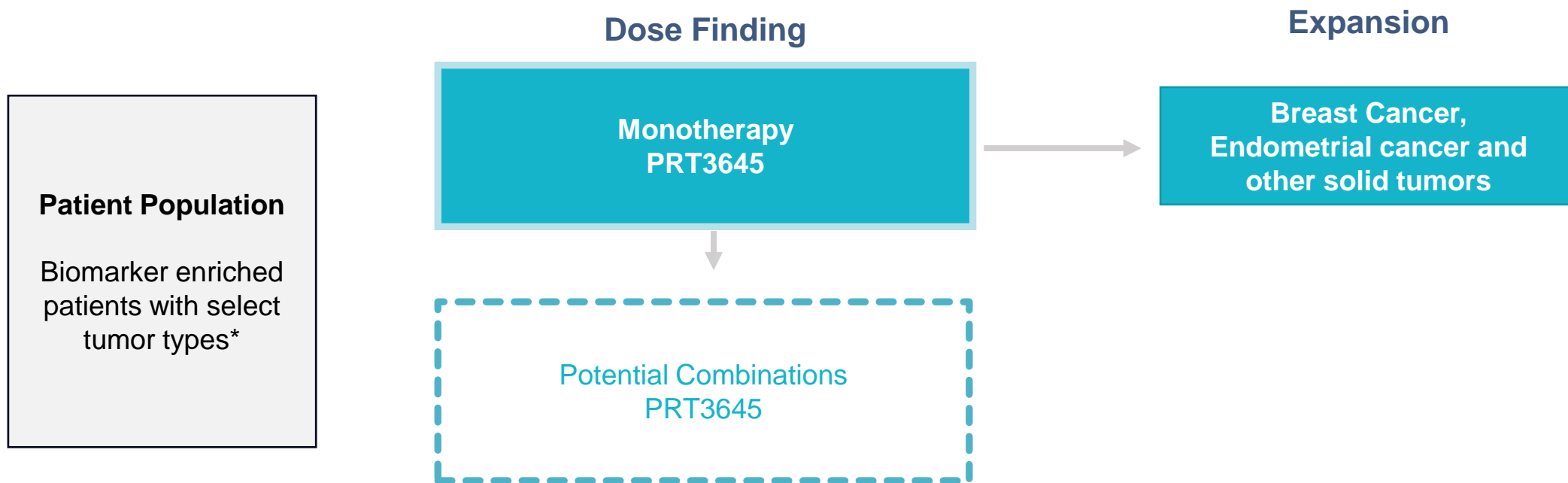
DFBM-355 PDX model of ER+/HER2+ Breast Cancer



PRT3645 observed to enhance the activity of KRAS G12C inhibitor in NSCLC models and with HER2 kinase inhibitor in ER+/HER2+ BC models.

Next Generation CDK4/6 Inhibitor: PRT3645

Phase 1 Study in Solid Tumors



Preliminary data presented at AACR-NCI-EORTC 2023 Poster B160:

https://preludetx.com/wp-content/uploads/2023/10/Patnaik_PRT3645-01_AACR-NCI-EORTC_poster_Oct2023.pdf

*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
ClinicalTrials.gov Identifier: NCT05538572