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): November 14, 2022

Prelude Therapeutics Incorporated

(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-39527**	**81-1384762**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

200 Powder Mill Road **Wilmington, Delaware**	**19803**
(Address of principal executive offices)	**(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 2.02 Results of Operations and Financial Condition.

On November 14, 2022, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing its financial results for the three months ended September 30, 2022. A copy of the press release is attached as Exhibit 99.1 to this report.

Item 7.01 Regulation FD Disclosure

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 99.2 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 Exhibits 99.1 and 99.2 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

Exhibit Number	Description
99.1	Press release issued by Prelude Therapeutics Incorporated regarding its financial results for the three months ended September 30, 2022, dated November 14, 2022.
99.2	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: November 14, 2022

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

Exhibit 99.1

Prelude Therapeutics Announces Third Quarter 2022 Financial Results and Provides Business Update

FDA clearance of two new INDs: PRT3789 (First-in-class Selective SMARCA2 degrader) and PRT3645 (next generation CDK4/6 inhibitor)

Company to reprioritize clinical pipeline and discontinue PRMT5 program for internal development

Strong cash, cash equivalents and marketable securities of $224.0 million as of September 30, 2022, expected to fund multiple data catalysts with a runway into the fourth quarter of 2024

WILMINGTON, Del. – November 14, 2022 – Prelude Therapeutics Incorporated (Prelude) (Nasdaq: PRLD), a clinical-stage precision oncology company, today reported financial results for the third quarter ended September 30, 2022 and provided an update on recent clinical and development pipeline progress.

"We made meaningful advancements in the third quarter and to date in the fourth quarter, including FDA clearance for two new INDs, one for PRT3645, a next generation, brain penetrant CDK4/6 inhibitor and one for PRT3789, a novel, first-in-class selective SMARCA2 degrader. We've also made good progress in the clinical development of our CDK9 inhibitor, PRT2527 and PRT1419, the MCL1 inhibitor," stated Kris Vaddi, Ph.D., Chief Executive Officer of Prelude.

"We continue to expand our highly innovative clinical pipeline. In order to focus resources on bringing compounds with the highest likelihood of success forward, we have decided to discontinue the internal development of our PRMT5 program. While PRT811 demonstrated a best-in-class safety profile and evidence of clinical activity in biomarker-selected patients with glioma and splicing mutated uveal melanoma, our prioritization reflects the high benchmark we set for clinical and regulatory success," Dr. Vaddi added. "We are committed to delivering impactful medicines to patients and building significant and sustainable value."

"Since joining Prelude, I have had the opportunity to critically review and to assess each program and identify clear next steps for clinical development," said Jane Huang, M.D., President and Chief Medical Officer of Prelude. "With this prioritization, we believe we can generate proof-of-concept clinical data in the next 12 to 24 months to guide our future regulatory pathways to approval. Our CDK9 and MCL1 inhibitors are selective and potent, with potentially superior safety profiles. PRT3645 was specifically designed to be a brain penetrant CDK4/6 inhibitor and our SMARCA2 molecule is a unique, first-in-class degrader, targeting specific patient populations. I believe these programs offer the best chance to improve patient outcomes and I share our investigators' excitement in our highly differentiated molecules."

Recent Highlights and Upcoming Objectives

- **CDK9 Inhibitor Program**: Given the compelling clinical activity recently reported with CDK9 inhibitors, PRT2527, as a more selective compound, has the potential to be best-in-class, with a favorable toxicity profile, allowing for rapid development in combinations. The PRT2527 Phase 1 dose escalation study in solid tumors has enrolled 11 patients to date. Dose dependent increases in exposure and target engagement were observed as evidenced by MYC and MCL1 depletion to levels associated with tumor regression in preclinical models. No adverse events leading to dose reduction or discontinuation have been reported. The Company remains on track to select a recommended Phase 2 dose by year-end. Prelude will use these safety data to continue cohort expansion in solid tumors, as well as to inform and rapidly progress the hematology trial.
    - *ASH 2022: oral preclinical presentation*

        - *Session Name: 605. Molecular Pharmacology and Drug Resistance: Lymphoid Neoplasms: Targeting BH3, BTK, and CDK: PRT2527, a Novel Highly Selective Cyclin-Dependent Kinase 9 (CDK9) Inhibitor, Has Potent Anti-Leukemic Activity in Preclinical Primary Models of Human B-ALL, T-ALL, and CLL*
        - *Session Date: Saturday, December 10, 2022*
        - *Session Time: 2:00 PM - 3:30 PM*
        - *Presentation Time: 3:15 PM*
        - *Room: Ernest N. Morial Convention Center, 388-390*
    - *Present solid tumor dose escalation data at a medical conference in 1H 2023*
    - *RP2D in hematological malignancies in 2H 2023*
    - *Present initial clinical results for hematological malignancies at a medical conference in 2H 2023*

- **MCL1 Inhibitor Program:** To date, 26 patients have been enrolled in the PRT1419 Phase 1 solid tumor dose escalation and confirmation cohorts, including 15 patients at the recommended expansion dose of 80 mg/m^2. PRT1419 has demonstrated a differentiated profile with no cardiotoxicity observed in patients to date. Cardiovascular parameters including troponin levels and ejection fraction changes were evaluated, in addition to standard safety, pharmacokinetics and target engagement metrics. The clinical pharmacodynamic profile of PRT1419 demonstrates the desired level of target engagement, as measured by caspase activation in peripheral mononuclear cells and reduction of CD14+ monocytes to levels associated with tumor regressions in preclinical models of hematological cancers. Advancement in hematological cancers will include monotherapy expansions in CLL and NHL based on a strong rationale for MCL1 inhibition and the need for novel treatments in second line.
    - *Solid tumor data is expected to be presented at a medical conference 1H 2023*
    - *RP2D expected in hematological malignancies in 2H 2023*
    - *Hematological malignancy data expected to be presented in 2H 2023*

- **Brain Penetrant CDK4/6:** Phase 1 clinical trial is being initiated for PRT3645 in 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.
    - *Present initial clinical results at a medical conference in 2H 2023*
    - *RP2D in solid tumors in 2H 2024*

- **SMARCA2/BRM Protein Degrader Program**: Prelude received IND clearance in October for PRT3879. Prelude plans to dose the first patient in Q1 2023. SMARCA2 inhibition has the greatest potential in patients with SMARCA4 deficient cancers, including up to 10% of all non-small cell lung cancers.
    - *Provide Clinical update 2H 2023*

- **PRMT5 Programs:** In the Phase 1 trials for PRT543 and PRT811, both molecules were generally well tolerated. In the PRT811 clinical trial, a total of 82 patients across multiple tumor types were enrolled in dose escalation and expansion, of whom 57 had glioma or uveal melanoma. Out of 38 glioma patients (16 IDH+ and 22 IDH-), two complete responses were observed in IDH+ glioma. These responses remain ongoing for 62 and 21 weeks, respectively. In addition, out of 19 uveal melanoma patients (8 SPLC+ and 11 SPLC-), one confirmed PR (duration of response of 42 weeks) and a second ongoing unconfirmed PR were observed, both in patients who were SPLC+. The most common adverse events of any grade, with an incidence of >20% were nausea (57.3%), vomiting (41.5%) fatigue (31.7%), constipation (25.6%), and thrombocytopenia (24.4%), and were predominantly grade 1-2. The most common adverse events (grade ≥3), occurring >5% were thrombocytopenia (9.76%), anemia (7.32%), and fatigue (7.32%). Full results from the two clinical trials will be shared in the first half of 2023.

Third Quarter 2022 Financial Results

Cash, Cash Equivalents and Marketable Securities: Cash, cash equivalents, and marketable securities as of September 30, 2022, were $224.0 million. Prelude anticipates that its existing cash, cash equivalents and marketable securities will be sufficient to fund Prelude's operations into the fourth quarter of 2024.

Research and Development (R&D) Expenses: For the third quarter of 2022, R&D expenses increased to $22.9 million for the three months ended September 30, 2022, from $22.7 million for the three months ended September 30, 2021. Included in research and development expenses for the quarter ending September 30, 2022, was $3.2 million of non-cash expense related to stock-based compensation expense, including employee stock options, compared to $3.3 million for the three months ended September 30, 2021. Research and development expenses remain steady as our clinical pipeline advances into clinical trials. We expect our research and development expenses to vary from quarter to quarter, primarily due to the timing of our clinical development activities.

General and Administrative (G&A) Expenses: For the third quarter of 2022, G&A expenses decreased to $7.5 million for the three months ended September 30, 2022, from $8.1 million for the three months ended September 30, 2021. Included in the general and administrative expenses for the quarter ended September 30, 2022, was $3.2 million of non-cash expense related to stock-based compensation expense, including employee stock options, as compared to $3.8 million for the same period in 2021. The decrease in general and administrative expenses was primarily due to non-cash stock-based compensation expense and prudent management of expenses.

Net Loss: For the three months ended September 30, 2022, net loss was $30.0 million, or $0.63 per share of common stock, basic and diluted compared to $30.7 million, or $0.66 per share, respectively, for the prior year period. Included in the net loss for the quarter ended September 30, 2022, was $6.4 million of non-cash expense related to the impact of expensing share-based payments, including employee stock options, as compared to $7.1 million for the prior year period.

About Prelude

Prelude is a clinical-stage precision oncology company developing innovative drug candidates targeting critical cancer cell pathways. Prelude's diverse pipeline is comprised of highly differentiated, potentially best-in-class proprietary small molecule compounds aimed at addressing clinically validated pathways for cancers with selectable underserved patients. Prelude's pipeline includes four candidates currently in clinical development: PRT1419, a potent, selective inhibitor of MCL1; PRT2527, a potent and highly selective CDK9 inhibitor, PRT3645, a brain penetrant CDK4/6 inhibitor, and PRT3879 a first-in-class SMARCA2/BRM protein degrader.

For more information, visit our website and follow us on LinkedIn and Twitter.

Cautionary Note Regarding Forward-Looking Statements

This press release 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, timing of availability and announcements of clinical results for PRT1419 and PRT3645, the timing of reporting expected findings related to PRT1419, PRT2527, PRT2645 and PRT3789, the potential benefits of Prelude's product candidates and platform, and the sufficiency of cash and cash equivalents to fund operating expenses and capital expenditures into the fourth quarter of 2024. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Although Prelude believes that the expectations reflected in such forward-looking statements are reasonable, Prelude cannot guarantee future events, results, actions, levels of activity, performance or achievements, and the timing and results of biotechnology development and potential regulatory approval is inherently uncertain. Forward-looking statements are subject to risks and uncertainties that may cause Prelude's actual activities or

results to differ significantly from those expressed in any forward-looking statement, including risks and uncertainties related to Prelude's ability to advance its product candidates, the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, the impact of the COVID-19 pandemic on Prelude's business, clinical trial sites, supply chain and manufacturing facilities, Prelude's ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of preclinical and clinical trials, Prelude's ability to fund development activities and achieve development goals, Prelude's ability to protect intellectual property, and other risks and uncertainties described under the heading "Risk Factors" in documents Prelude files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and Prelude undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(UNAUDITED)

(in thousands, except share and per share data)	Three Months Ended September 30, 2022	2021
Operating expenses:		
Research and development	$ 22,889	$ 22,721
General and administrative	7,517	8,115
Total operating expenses	30,406	30,836
Loss from operations	(30,406)	(30,836)
Other income, net	448	149
Net loss	$ (29,958)	$ (30,687)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (0.63)	$ (0.66)
Weighted average common shares outstanding, basic and diluted	47,449,811	46,330,794
Comprehensive loss		
Net loss	$ (29,958)	$ (30,687)
Unrealized gain (loss) on marketable securities, net of tax	(69)	(176)
Comprehensive loss	$ (30,027)	$ (30,863)

PRELUDE THERAPEUTICS INCORPORATED

BALANCE SHEETS
(UNAUDITED)

(in thousands, except share data)	September 30, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 52,022	$ 31,828
Marketable securities	172,021	259,405
Prepaid expenses and other current assets	2,850	3,882
Total current assets	226,893	295,115
Restricted cash	4,044	4,044
Property and equipment, net	5,110	3,929
Right-of-use asset	1,354	1,707
Other assets	4,926	303
Total assets	$ 242,327	$ 305,098
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 10,250	$ 7,840
Accrued expenses and other current liabilities	9,922	9,621
Operating lease liability	1,388	1,740
Total current liabilities	21,560	19,201
Other liabilities	3,360	—
Total liabilities	24,920	19,201
Commitments		
Stockholders' equity:		
Voting common stock, $0.0001 par value: 487,149,741 shares authorized; 36,444,776 and 36,200,299 shares issued and outstanding at September 30, 2022 and December 31, 2021, respectively	4	4
Non-voting common stock, $0.0001 par value; 12,850,259 shares authorized; 11,402,037 and 11,402,037 shares issued and outstanding at September 30, 2022 and December 31, 2021, respectively	1	1
Additional paid-in capital	525,682	505,723
Accumulated other comprehensive income (loss)	(2,363)	(711)
Accumulated deficit	(305,917)	(219,120)
Total stockholders' equity	217,407	285,897
Total liabilities and stockholders' equity	$ 242,327	$ 305,098

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Vice President, Investor Relations
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ltrickett@preludetx.com

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Shik Communications
617.510.4373
Helen@ShikCommunications.com

Exhibit 99.2


Prelude
THERAPEUTICS
PRELUDE Corporate Presentation
NOVEMBER 2022
Patient focused
Science driven
Precision oncology

Forward Looking Statements

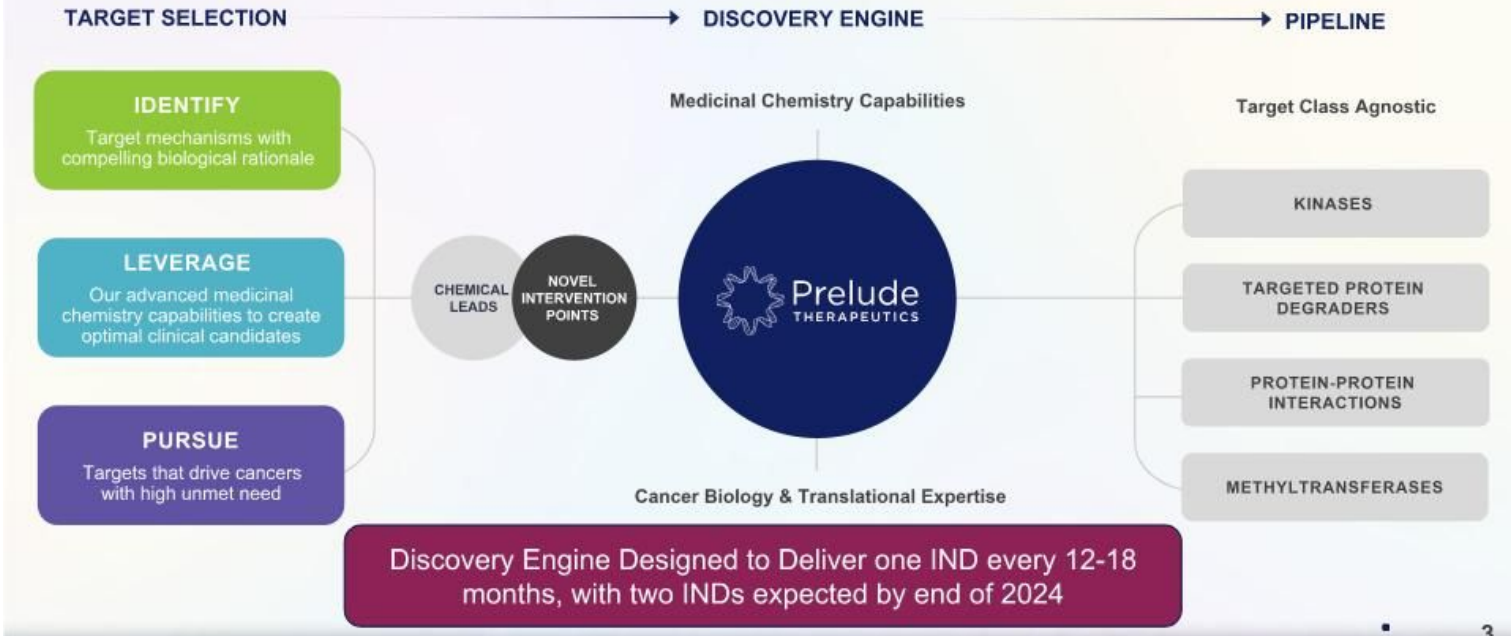
This presentation contains "forward-looking" statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: our plans to develop and commercialize small molecule therapies, our expectations about timing and ability to commence, enroll or complete clinical studies 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, 2021.

Prelude Discovery and Development Approach



Discovery Engine Designed to Deliver one IND every 12-18 months, with two INDs expected by end of 2024

Prelude Therapeutics: Key Highlights

Internal Discovery Engine

Scientists with proven track records

Strong Execution

Rapidly advancing a diversified proprietary pipeline

Effective Research

Seamless integration between biology and chemistry

Focused Clinical Development

Developing meaningful medicines for patients with cancer

Well Capitalized

$224M cash, cash equivalents & marketable securities (9/30/22)

Experienced Management Team: Proven Track Records

Kris Vaddi, PhD

Founder & Chief Executive Officer

Jakafi
olumiant
TABRECTA (capmatinib) tablets
VELCADE

Jane Huang M.D.

President and Chief Medical Officer

VENCLEXTA
Brukinsa
GAZYVA obinutuzumab

Laurent Chardonnet

Chief Financial Officer

sanofi
Incyte
axcella

Andrew Combs, PhD

Executive Vice President and Head of Chemistry

Jakafi
olumiant

Peggy Scherle, PhD

Chief Scientific Officer

Jakafi
olumiant
Pemazyre (pemigatinib tablets)
TABRECTA (capmatinib) tablets

Board of Directors

Paul Friedman, MD
Madrigal — *CEO*
Incyte — *Former CEO*

Mardi Dier
ultragenyx — *Former CFO*
PORTOLA — *Former CFO, CBO*

Victor Sandor, MD
ARRAY BIOPHARMA — *Former CMO*

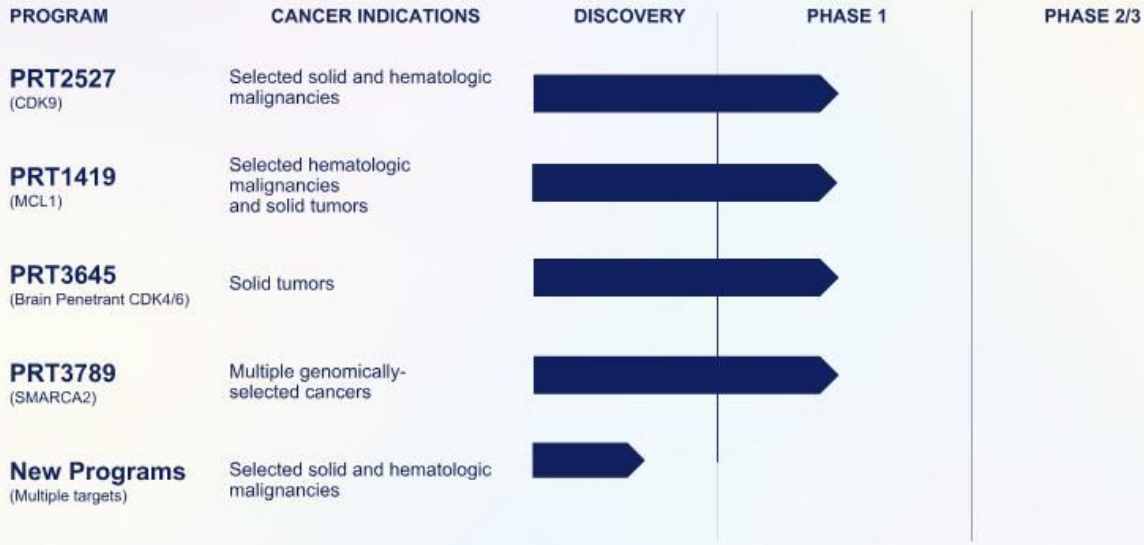
David Bonita, MD
OrbiMed — *General Partner*

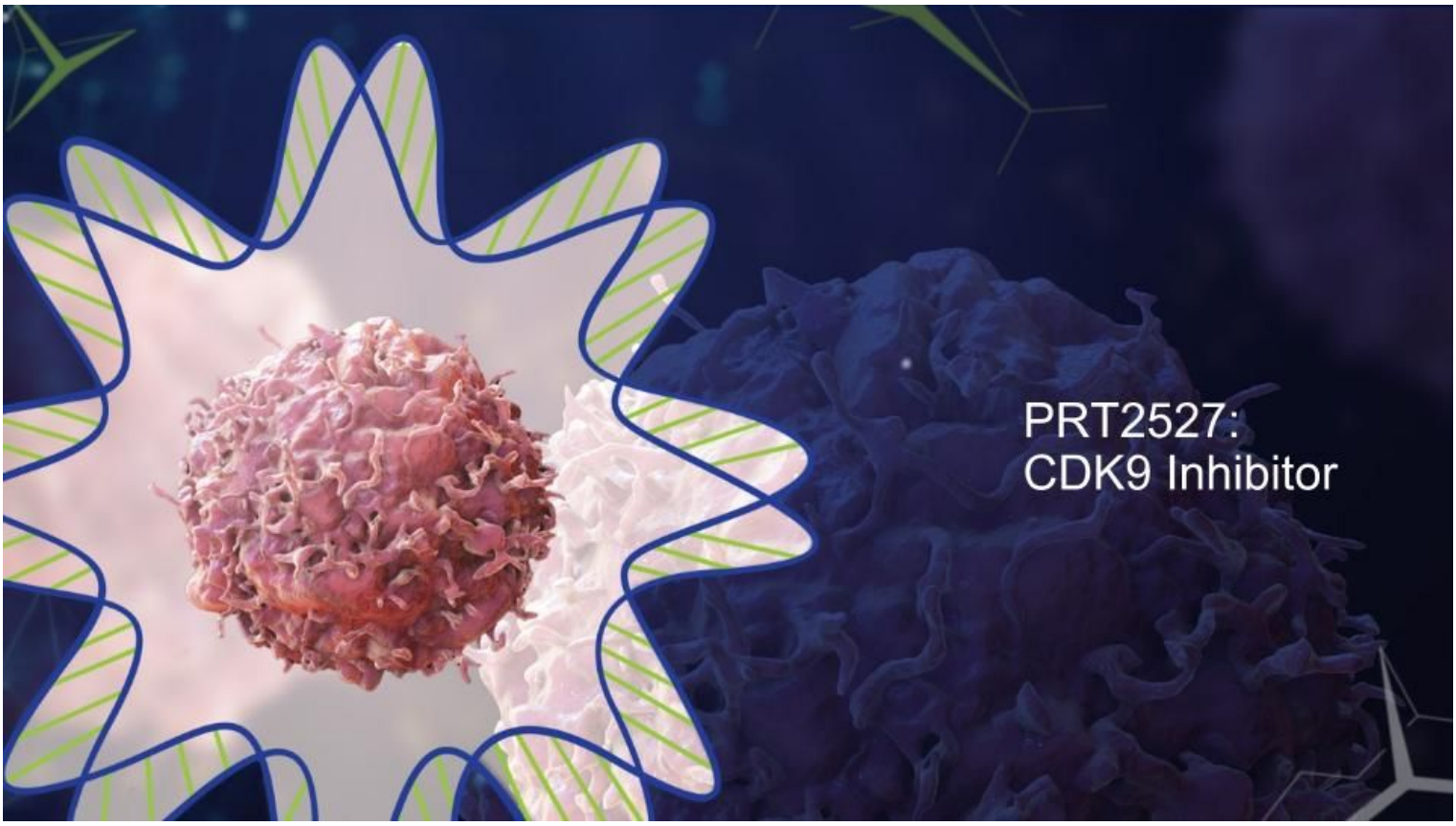
Julian C. Baker
Managing Member
Baker Brothers Investments

Kris Vaddi, PhD
Founder & Chief Executive Officer

Martin Babler
PRINCIPIA — *Former CEO*

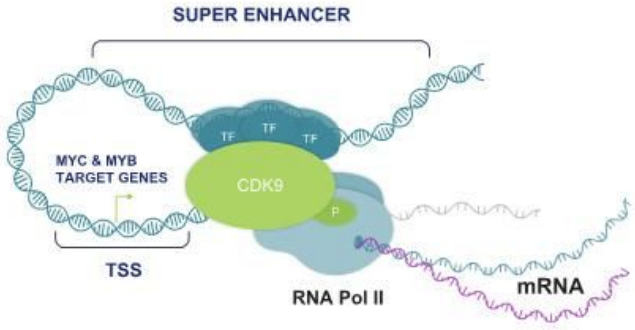
Diversified Precision Oncology Pipeline




PRT2527:
CDK9 Inhibitor

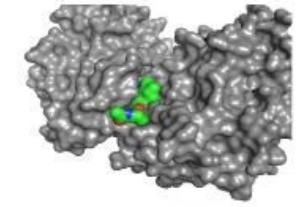
CDK9 – Targeting Cancer Through Transcriptional Regulation

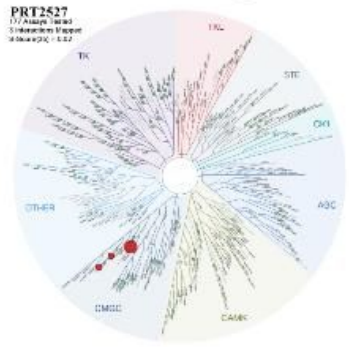
- CDK9 phosphorylates RNA Pol II and regulates transcription
- Regulates expression of several immediate early genes driving oncogenesis and resistance (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
  - Lack of selectivity and potency vs other CDK9s is believed to contribute to low therapeutic window



PRT2527: Potent and Highly Selective CDK9 Inhibitor Candidate

Highly Selective, ATP Competitive CDK9 Inhibitor Candidate





Compound		AZD4573	KB0742	VIP152**	PRT2527
Biochemical* IC_{50} (nM)	**CDK9**	1.9	483	16	0.95
Proliferation* IC_{50} (nM)		11	915	84	18
Plasma* IC_{50} (nM)		192	1056	923	196
Fold Selectivity CDK9 *vs* Other Isoforms	**CDK1**	23x	>20x	371x	73x
	CDK2	35x	>20x	147x	340x
	CDK3	2x	>20x	37x	35x
	CDK4	53x	>20x	38x	250x
	CDK5	37x	>20x	>600x	>1000x
	CDK6	79x	>20x	296x	>1000x
	CDK7	150x	>20x	>600x	>1000x

>100x 100-10x <10x

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

PRT2527: CDK9 Inhibitor Phase 1 Studies

Dose Escalation

PRT2527
Solid Tumors
N=11

Dose Confirmation

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

Dose escalation data at a medical conference in 1H 2023

Solid Tumors

- Dose dependent increases in exposure and target engagement were observed
- MYC and MCL1 depletion to levels consistent with tumor regression in preclinical models
- No adverse events leading to dose reduction or discontinuation have been reported as of 9/2022
- ClinicalTrials.gov Identifier: NCT05159518

Dose Escalation

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

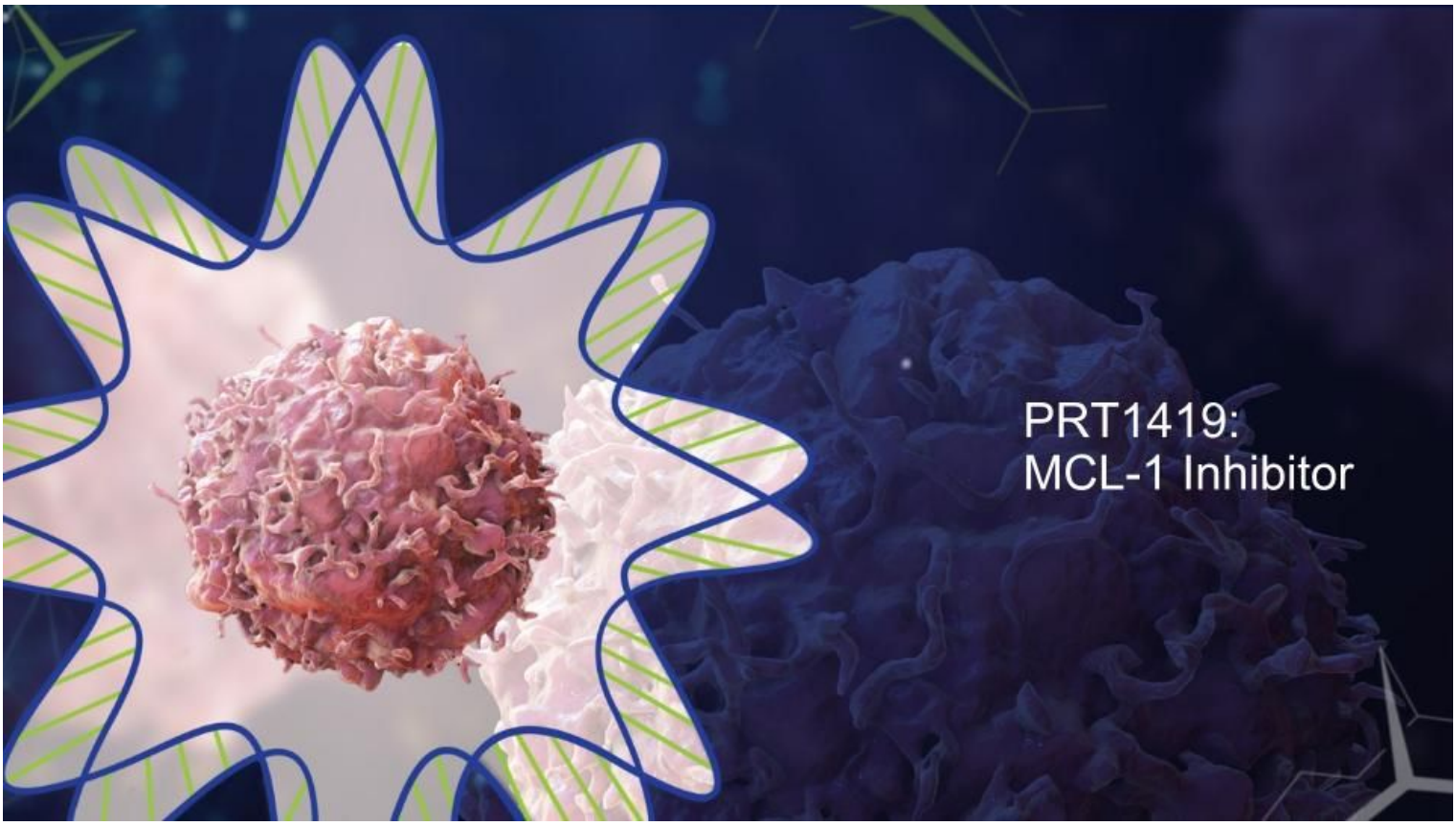
Dose Confirmation

PRT2527
N=30

RP2D in hematological malignancies in 2H 2023
Initial clinical results for hematological malignancies at a medical conference in 2H 2023

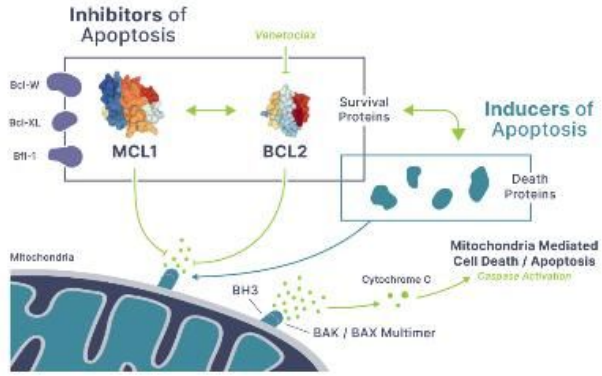
Hematologic Malignancies

- ASH 2022 preclinical oral presentation
- CDK9 inhibitor class validates and provides proof of concept and opportunity in hematology combinations with BTK inhibitors


PRT1419:
MCL-1 Inhibitor

MCL1: Targeting Cancer Cell Survival

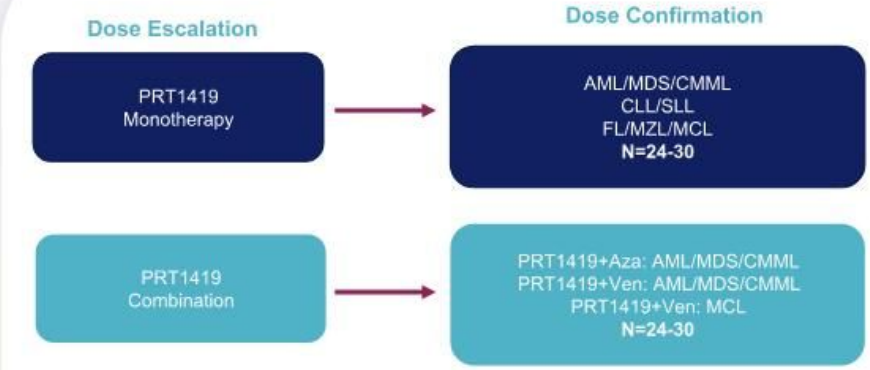
Mechanism



- MCL1 is a member of family inhibitors of apoptosis (BCL2); often overexpressed in cancers
- BCL2 family is clinically validated – Venetoclax approved for lymphoid and myeloid malignancies
- MCL1 is a bypass and resistance mechanism for Venetoclax and multiple TKIs
- Challenging medicinal chemistry target that requires disruption of protein-protein interaction

In Phase 1 clinical trial, PRT1419 demonstrates target engagement, as measured by caspase activation in peripheral mononuclear cells and reduction of CD14+ monocytes to levels consistent with tumor regressions in preclinical models of hematological cancers

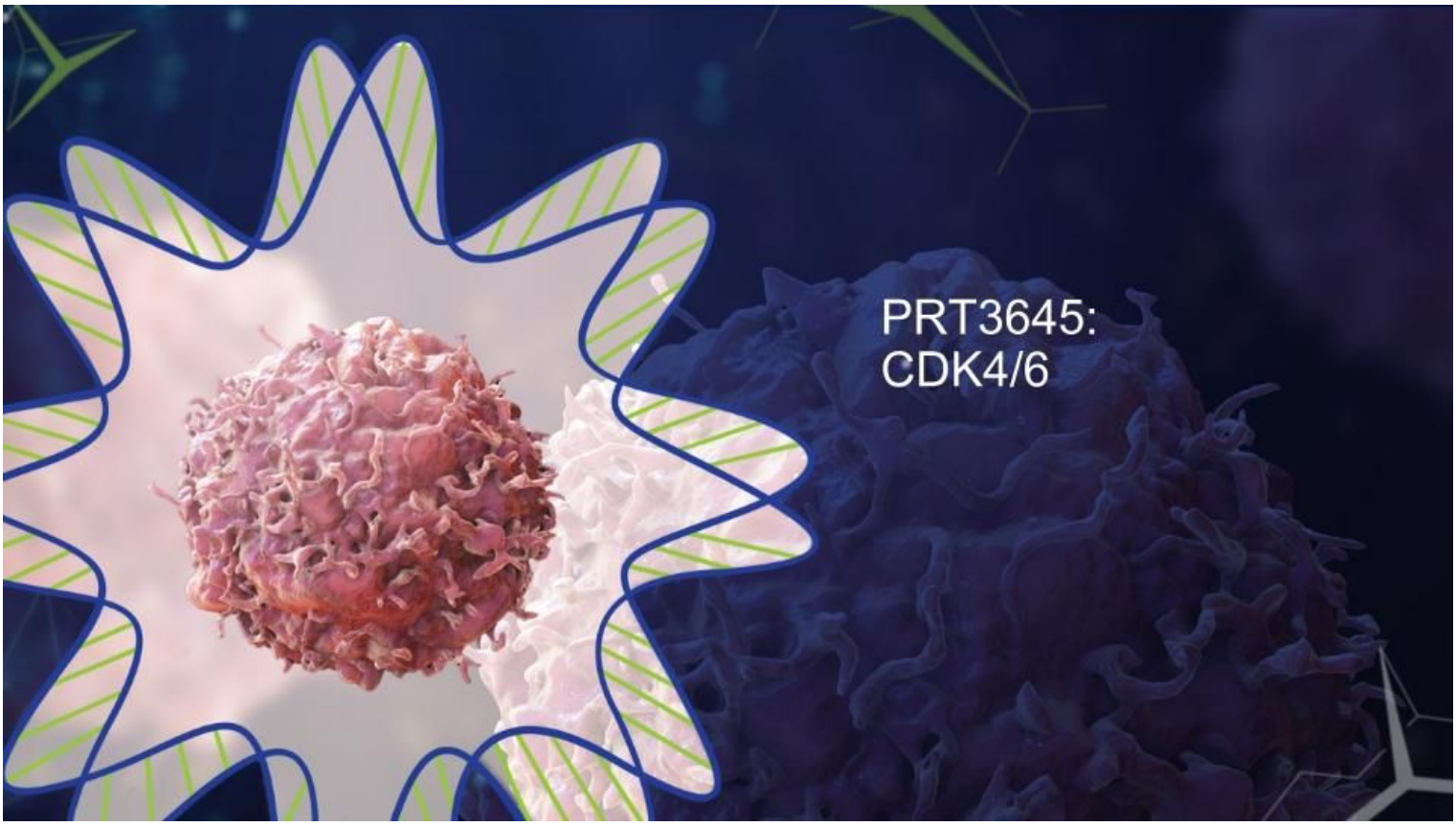
PRT1419: Phase 1 Study in Hematologic Malignancies



RP2D expected in hematological malignancies in 2H 2023
Hematological malignancy data expected to be presented in 2H 2023

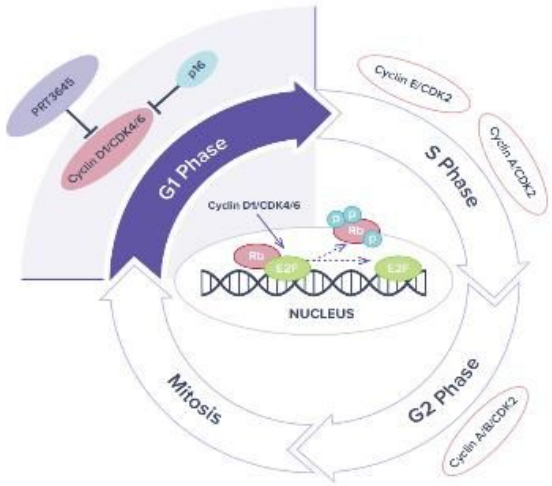
- 26 patients received ≥1 dose of PRT1419 with 15 patients @ 80 mg/m2 in the solid tumor study as of Sept 2022
- No cardiac toxicity seen @RP2D as measured by ejection fraction decline/troponin elevation
- Acceptable safety and tolerability in advanced or metastatic solid tumors, with primary toxicities of neutropenia, diarrhea, nausea, and vomiting
- Solid tumor data expected at a medical conference 1H 2023
- Advancement in hematological cancers to include expansions in CLL and NHL
- Strong rationale for MCL1 inhibition in second line CLL and NHL

ClinicalTrials.gov Identifier: NCT05107856


PRT3645:
CDK4/6

CDK4/6: Targeting Cancer Through Cell Cycle Regulation

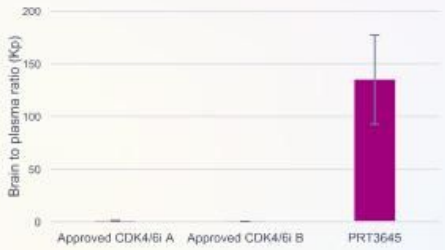
Mechanism



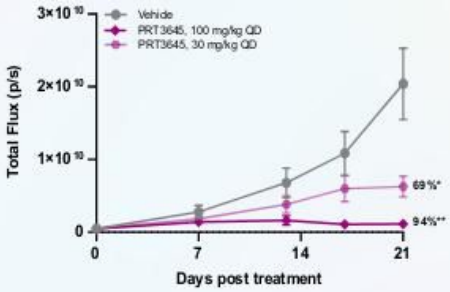
- Cell cycle entry controlled by cyclin dependent kinases, CDK4 and CDK6
  - Validated mechanism with multiple CDK4/6 inhibitors approved for HR+ breast cancer
- Current CDK4/6 inhibitors are ineffective in treating brain metastasis and other CNS cancers likely due to insufficient brain penetration
  - Brain penetrant TKIs to other oncogenic targets shown to be more effective in treating brain metastasis
- A potent and selective **brain penetrant** CDK4/6 inhibitor could more effectively treat brain metastasis associated with HR+ breast cancer as well as glioblastoma

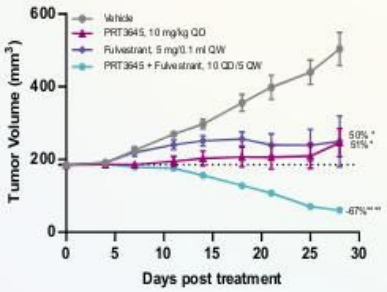
PRT3645 Has High Brain Exposure and Demonstrates Robust Activity in Preclinical Models at Well-Tolerated Doses

PRT3645 demonstrates >10x higher brain penetration than approved CDK4/6 inhibitors



PRT3546 shows robust activity in vivo as monotherapy and in combination





PRT3645: CDK4/6 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 results at a medical conference in 2H 2023
RP2D in solid tumors expected in 2H 2024

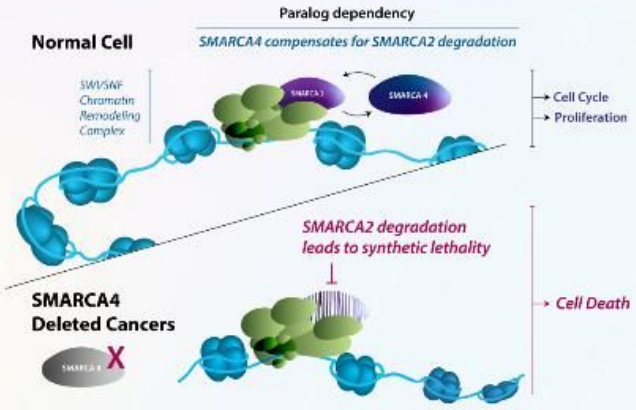
ClinicalTrials.gov Identifier: NCT05538572

- 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
- First patient planned by YE
- Opportunities in non-breast cancer indications and second line breast cancer after progression on a CDK4/6i
- Potential to address KRAS G12C resistance in NSCLC


PRT3789:
SMARCA2 Degrader

Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

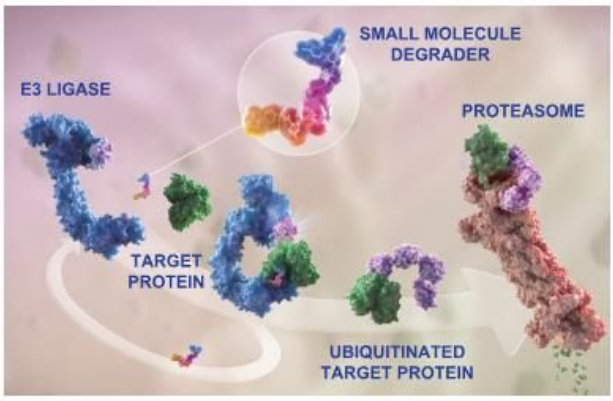
Mechanism



- 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

Achieving SMARCA2 Selectivity Through Degrader Approach

Mechanism

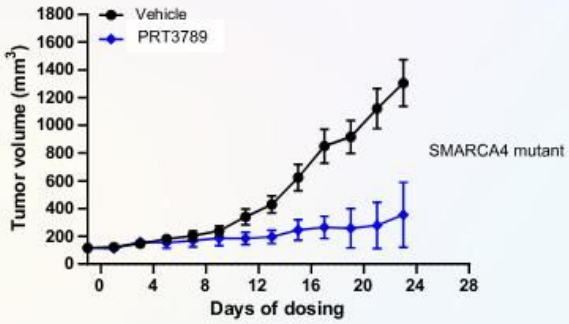


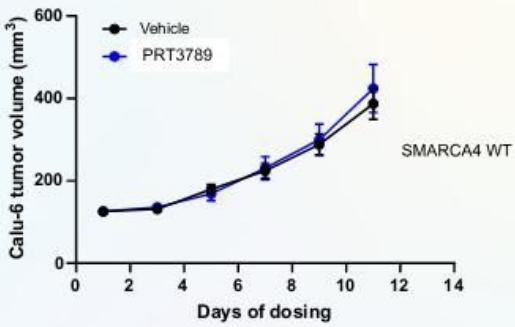
Mullard A. Nat Rev Drug Discov. 2019

- SMARCA2 selectively over highly homologous SMARCA4 isoform has been a challenging medical chemistry problem with traditional small molecule approaches
- Target Protein Degradation (TPD) of SMARCA2 selectively over SMARCA4 is possible through differences in ternary complexes
- Prelude scientists identified the molecular basis for achieving high degree of selectivity for SMARCA2 over SMARCA4
- Lead molecules from multiple chemical scaffolds with sub-nanomolar potency and selectivity have been discovered

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

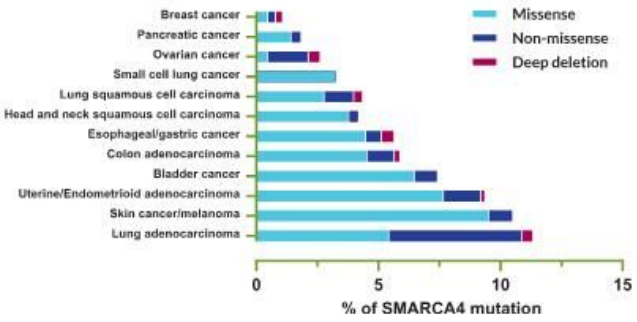
Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft



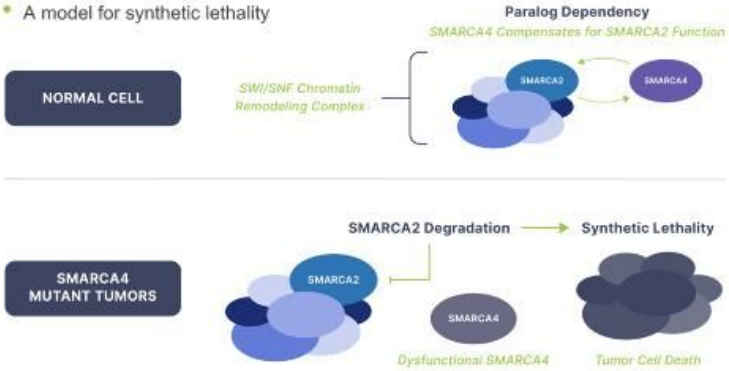


Targeting SMARCA2 induces synthetic lethality in SMARCA4 mutated cancers

- Frequency of *SMARCA4* mutation in cancer



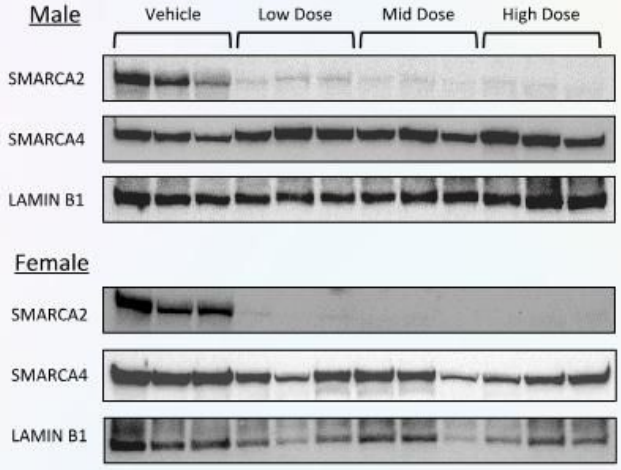
- A model for synthetic lethality



- Subsets of solid tumors express *SMARCA4* damaging mutations or gene deletion, resulting in loss of SMARCA4 protein expression
  - NSCLC (5-6%), Uterine/Endometrioid (2-3%), Colon Adenocarcinoma (1-2%)
- SMARCA2 gene knockout induces synthetic lethality in SMARCA4 deleted cancers

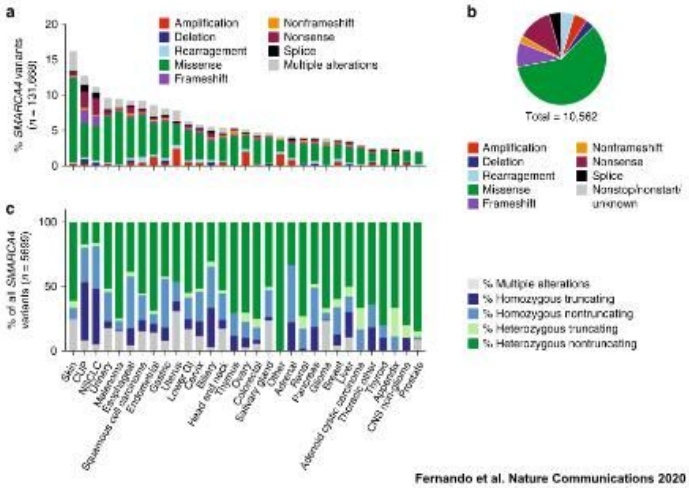
Source: Ito K et al. Abstract 1139; Vol. 81, Cancer Research. AACR; 2021. p. 1139–1139.

Significant Degradation of SMARCA2 Protein but not SMARCA4 in Rat PBMCs with PRT3789 –PD Marker in Clinic



Frequency of SMARCA4 Mutations

SMARCA4 Mutational Spectrum in 131,668 Cancer Patients



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

PRT3789: SMARCA2 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
- Selective SMARCA2 degradation can be demonstrated 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

Summary

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

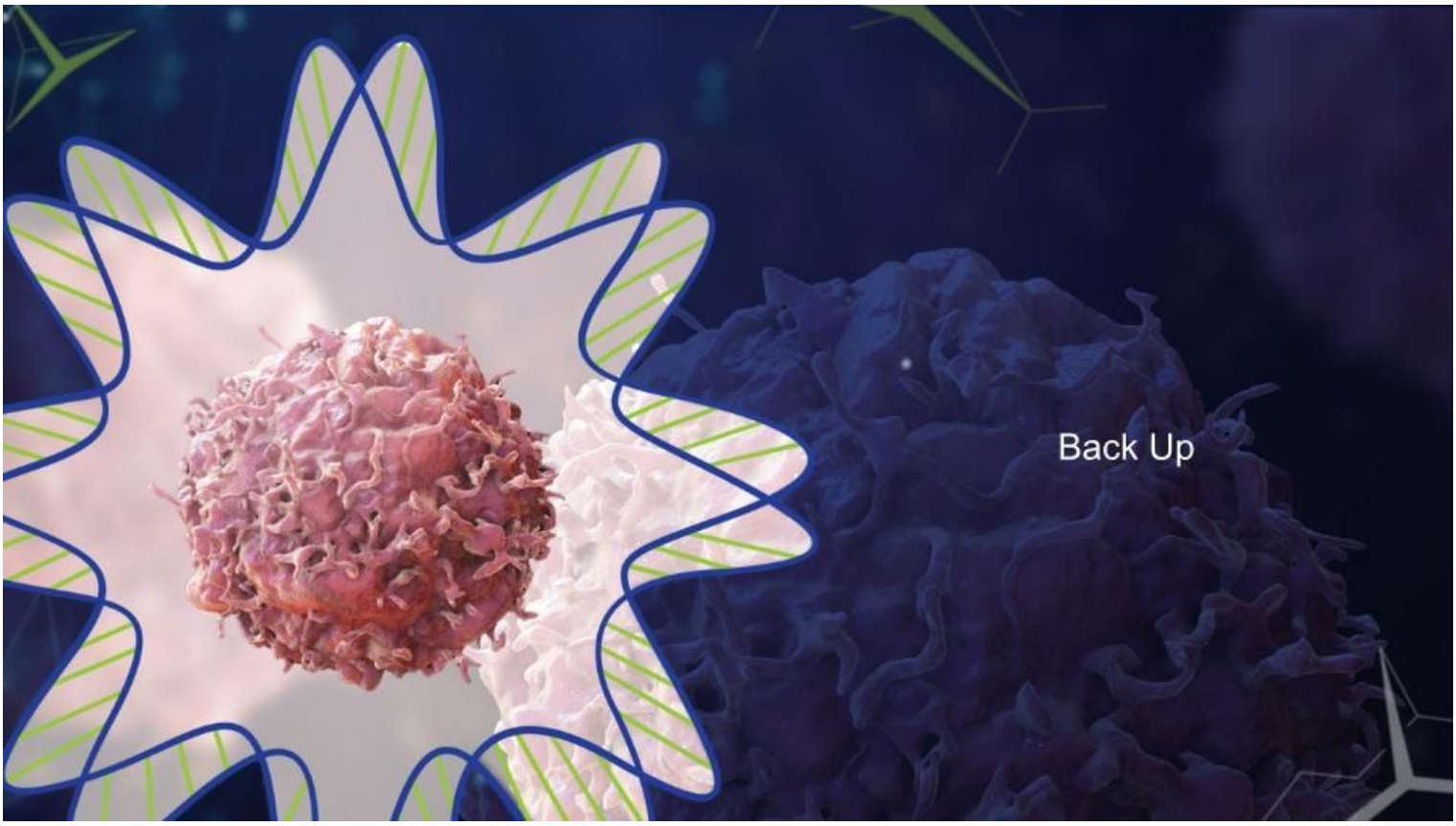
Opportunity to drive the programs to key inflection points in the next **12 – 24 months**

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

- Recent validating data on CDK9 in DLCBCL 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

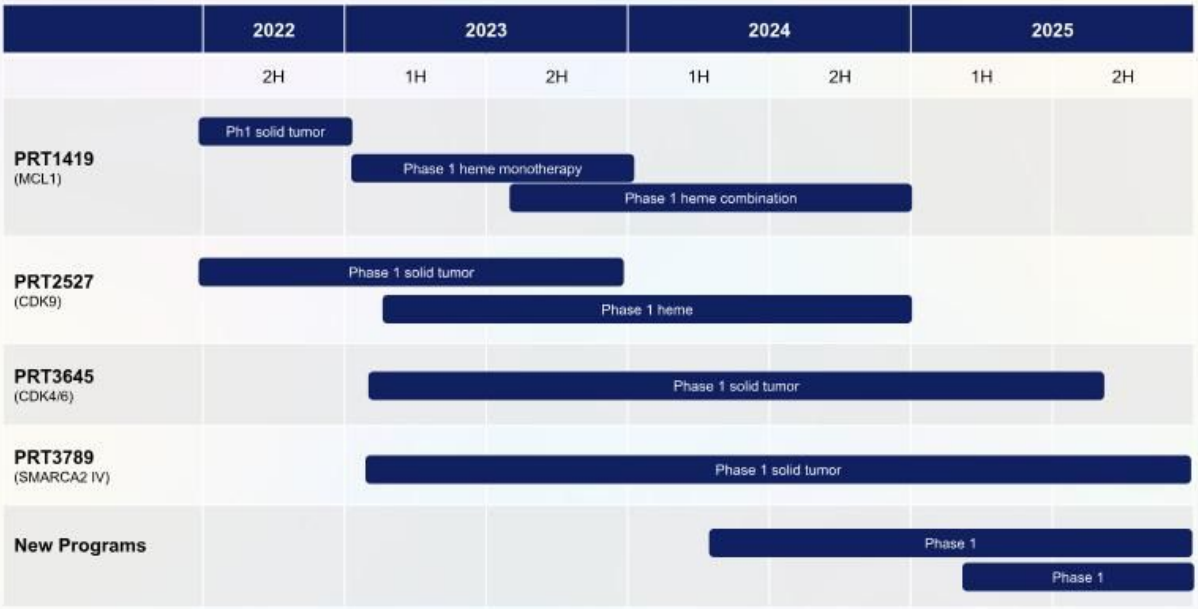
Current cash runway expected through **Q4 2024** pending data and program updates


Back Up

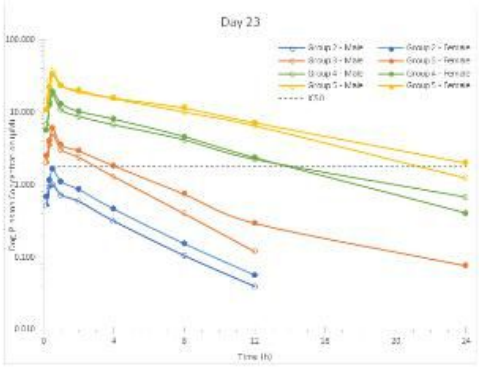
Expected Data Catalysts by Mid-2024

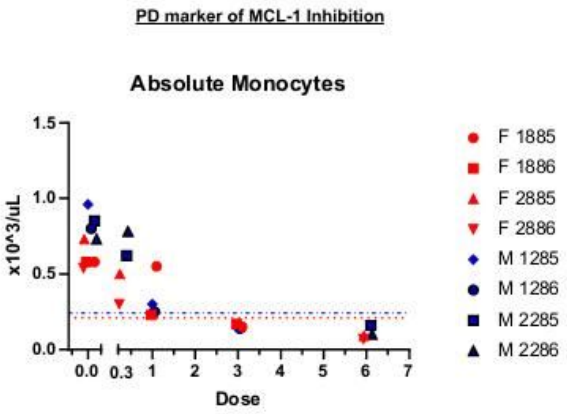
- PRT2527 (CDK9)
  - Hematology program POA
- PRT1419 (MCL-1) monotherapy activity in CLL
  - Program Update in 2H 2023
- PRT3645 (CDK4/6)
  - Monotherapy Recommended Phase 2 Dose
  - Potential for strategic partnership
- PRT3789
  - Demonstration of selective degradation of SMARCA2
  - Dose escalation safety, PK and clinical activity

Potential Development Timelines



Maximal Inhibition of MCL-1 in Sensitive Species (dog) did not cause cardiac injury in GLP Tox studies





- Doses: 0.3, 1, 3 and 6 mg/m2; once weekly
- Linear increases in exposure
- No troponin elevations observed at any doses, even high dose which covered EC90 for 24h
- No histopathological evidence of cardiac injury

PRT1419 Plans for Heme Malignancies

- CLL and NHL patients can improve dose escalation and give faster clarity on activity
- Expected benchmarks to demonstrate activity

R/R AML:

- CR/CRi rate for venetoclax monotherapy is 19% (Konopleva et al 2016)
- r/r AML CR/CRi rate for HMA monotherapy is 16-17% (Itzykson et al 2015; Stahl M et al 2018)
- cCR rate for VEN + HMAs or low dose cytarabine in R/R AML is about 33% (Brewersdorf et al 2020).

R/R CLL:

- 10-50% ORR after failure of all approved available therapies

R/R Mantle-cell lymphoma:

- After failure of BTKi, the ORR for VEN monotherapy was 53% (including 18% CRs)

PRMT5

- Decision to discontinue internal development of PRMT5 program, despite demonstration of a best-in-class safety profile and evidence of clinical activity in biomarker-selected patients with glioma and splicing mutated uveal melanoma
- Prioritization reflects the high benchmark we set for clinical and regulatory success
- **PRMT5 Results:** In the Phase 1 trials for PRT543 and PRT811, both molecules were generally well tolerated. In the PRT811 clinical trial, a total of 82 patients across multiple tumor types were enrolled in dose escalation and expansion, of whom 57 had glioma or uveal melanoma. Out of 38 glioma patients (16 IDH+ and 22 IDH-), two complete responses were observed in IDH+ glioma These responses remain ongoing for 62 and 21 weeks, respectively. In addition, out of 19 uveal melanoma patients (8 SPLC+ and 11 SPLC-), one confirmed PR (duration of response of 42 weeks) and a second ongoing unconfirmed PR were observed, both in patients who were SPLC+. The most common adverse events of any grade, with an incidence of >20% were nausea (57.3%), vomiting (41.5%) fatigue (31.7%), constipation (25.6%), and thrombocytopenia (24.4%), and were predominantly grade 1-2. The most common adverse events (grade ≥3), occurring >5% were thrombocytopenia (9.76%), anemia (7.32%), and fatigue (7.32%). Full results from the two clinical trials will be shared in the first half of 2023.