# 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): May 8, 2023**

# 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 May 8, 2023, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing its financial results for the three months ended March 31, 2023. 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 March 31, 2023, dated May 8, 2023 |
| 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: May 8, 2023

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

**Exhibit 99.1**

# Prelude Therapeutics Announces First Quarter 2023 Financial Results and Operations Update

*Eight abstracts presented at AACR 2023 demonstrate progress of the pipeline*

*Cash runway unchanged, supporting operations into the fourth quarter of 2024*

**WILMINGTON, Del.** – May 8, 2023 – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today reported financial results for the first quarter ended March 31, 2023, and provided an update on recent clinical and development pipeline progress.

"Our recent presentations at the 2023 AACR Annual Meeting highlight the meaningful progress we made across our clinical and preclinical pipeline programs. In addition to our clinical presentations on PRT2527 (CDK9 inhibitor) and PRT1419 (MCL-1 Inhibitor) that demonstrated differentiated and potential best-in-class PK/PD profiles of these molecules, our preclinical research demonstrated the promise of our pipeline in addressing unmet patient needs in cancer through combination approaches. Patient enrollment in the phase 1 dose escalation of PRT3789 (first-in-class SMARCA2 selective degrader) is now underway. Our teams are focused on advancing our pipeline to key milestones and we look forward to reporting further updates in the coming months," said **Kris Vaddi, Ph.D., Chief Executive Officer of Prelude**.

***Recent Highlights***

**2023 AACR Annual Meeting:** Prelude participated in the 2023 American Association for Cancer Research Annual Meeting, presenting two clinical and six preclinical poster presentations. Initial safety, pharmacokinetic and pharmacodynamic profiles in solid tumors for both PRT2527 and PRT1419 were presented. Preclinical data for both the Company's next generation CDK4/6 inhibitor, PRT3645, and the SMARCA2 degrader, PRT3789, in combination with other targeted therapies, demonstrated the combinability of these compounds with standard of care medicines and inform potential clinical development.

***Program Updates and Upcoming Milestones***

**PRT2527- CDK9 Inhibitor Program**
PRT2527, Prelude's potentially best in class CDK9 inhibitor, is completing a solid tumor dose escalation study. In adults with advanced solid tumors, PRT2527 was generally well-tolerated 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 making it potentially suitable for weekly administration without inducing significant toxicity. 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. The 15 m/mg2 QW dose of PRT2527 was selected for further evaluation in dose-confirmation cohort.

The overall safety profile observed in this study supports further development of PRT2527 in combination with other targeted therapies, including in hematologic malignancies. The Company is on track to establish a RP2D in hematological malignancies in 2H 2023.

**PRT1419- MCL1 Inhibitor Program**
PRT1419 demonstrated an acceptable safety and tolerability profile in patients with advanced and metastatic solid tumors, with the most common TRAEs of nausea, vomiting, and diarrhea. Neutropenia was deemed to be dose related. No cardiac toxicity was observed. Pharmacokinetics/pharmacodynamics and safety data in the 80 mg/m2 QW PRT1419 dose cohort support further evaluation of this dose in future studies. Induction of activated-BAX and cleaved caspase-3 was observed at 80 and 120 mg/m2 QW PRT1419, suggesting successful MCL-1 inhibition. No tumor reductions met response criteria. Further investigation of PRT1419 in patients with hematologic malignancy is ongoing. The Company is on track to determine the RP2D in hematological RP2D and will provide a clinical update at year end.

**PRT3645-Next Generation CDK4/6 Inhibitor Program**
Prelude showed that PRT3645 is highly efficacious when combined with KRAS/MEK inhibitors, and with a brain penetrant HER2 receptor kinase inhibitor in *in vivo* preclinical models.

Additionally, oral administration of PRT3645 induces tumor regression in palbociclib-resistant preclinical models. Dose escalation phase of PRT3645 is progressing per plan and the Company expects to provide an update by year end.

**PRT3789 SMARCA2 Targeted Protein Degrader Program**
Phase 1 dose escalation of PRT3789 (first-in-class selective SMARCA2 degrader) is ongoing. The Company recently presented preclinical data, showing that SMARCA2 selective degraders demonstrate anti-proliferation activity and promote cell differentiation in a wide range of indications demonstrating activity as monotherapy, as well as in combination with KRAS G12C inhibitors, chemotherapy and other targeted agents. Consistent with the Company's plans to nominate an orally bioavailable candidate in early 2024, preclinical data at AACR showed that oral administration of multiple internally developed compounds results in significant tumor growth inhibition of SMARCA4-deficient lung cancer xenografts at well-tolerated doses.

**First Quarter 2023 Financial Results**

**Cash, Cash Equivalents and Marketable Securities:** Cash, cash equivalents, and marketable securities as of March 31, 2023, were $172.3 million. Prelude anticipates that its existing cash, cash equivalents and marketable securities will fund the Company's operations into the fourth quarter of 2024.

**Research and Development (R&D) Expenses**: For the first quarter of 2023, R&D expense decreased to $21.8 million from $22.8 million for the prior year period. Research and development expenses decreased primarily due to the timing of our clinical research programs. We expect our R&D 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 first quarter of 2023, G&A expenses were relatively unchanged as compared to the three months ended March 31, 2022.

**Net Loss:** For the three months ended March 31, 2023, net loss was $27.7 million, or $0.58 per share compared to $29.5 million, or $0.63 per share, for the prior year period. Included in the net loss for the quarter ended March 31, 2023, was $6.3 million of non-cash expense related to the impact of expensing share-based payments, including employee stock options, as compared to $6.8 million for the same period in 2022.

**About Prelude Therapeutics**

Prelude Therapeutics is a clinical-stage precision oncology company developing innovative drug candidates targeting critical cancer cell pathways. The Company'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 next generation CDK4/6 inhibitor**,** and PRT3789 an IV administered, potent and highly selective SMARCA2 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, the timing and/or announcements relating to the reporting of expected findings for PRT1419, PRT2527, PRT3645 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 March 31, 2023 | 2022 |
|---|---|---|
| **Operating expenses:** | | |
| Research and development | $ 21,834 | $ 22,821 |
| General and administrative | 7,281 | 7,467 |
| Total operating expenses | 29,115 | 30,288 |
| Loss from operations | (29,115) | (30,288) |
| Other income, net | 1,397 | 823 |
| Net loss | $ (27,718) | $ (29,465) |
| **Per share information:** | | |
| Net loss per share of common stock, basic and diluted | $ (0.58) | $ (0.63) |
| Weighted average common shares outstanding, basic and diluted | 47,737,190 | 47,066,427 |
| **Comprehensive loss** | | |
| Net loss | $ (27,718) | $ (29,465) |
| Unrealized gain (loss) on marketable securities, net of tax | 1,294 | (1,602) |
| Comprehensive loss | $ (26,424) | $ (31,067) |

**PRELUDE THERAPEUTICS INCORPORATED**

**BALANCE SHEETS**
**(UNAUDITED)**

| (in thousands, except share data) | March 31, 2023 | December 31, 2022 |
|---|---|---|
| **Assets** | | |
| **Current assets:** | | |
| Cash and cash equivalents | $ 18,201 | $ 30,605 |
| Marketable securities | 154,054 | 171,123 |
| Prepaid expenses and other current assets | 3,008 | 2,652 |
| Total current assets | 175,263 | 204,380 |
| Restricted cash | 4,044 | 4,044 |
| Property and equipment, net | 5,371 | 4,908 |
| Right-of-use asset | 1,360 | 1,792 |
| Prepaid expenses and other non-current assets | 12,282 | 5,376 |
| Total assets | $ 198,320 | $ 220,500 |
| **Liabilities and stockholders' equity** | | |
| **Current liabilities:** | | |
| Accounts payable | $ 7,082 | $ 6,777 |
| Accrued expenses and other current liabilities | 11,190 | 13,093 |
| Operating lease liability | 1,390 | 1,832 |
| Total current liabilities | 19,662 | 21,702 |
| Other liabilities | 3,361 | 3,361 |
| Total liabilities | 23,023 | 25,063 |
| **Commitments** | | |
| **Stockholders' equity:** | | |
| Voting common stock, $0.0001 par value: 487,149,741 shares authorized; 36,514,218 and 36,496,994 shares issued and outstanding at March 31, 2023 and December 31, 2022, 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 March 31, 2023 and December 31, 2022, respectively | 1 | 1 |
| Additional paid-in capital | 537,966 | 531,682 |
| Accumulated other comprehensive loss | (398) | (1,692) |
| Accumulated deficit | (362,276) | (334,558) |
| Total stockholders' equity | 175,297 | 195,437 |
| Total liabilities and stockholders' equity | $ 198,320 | $ 220,500 |

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Prelude THERAPEUTICS

**Exhibit 99.2**

# Corporate Presentation

May 2023

**Patient focused.**
**Science driven.**
**Precision oncology.**

# Forward Looking Statements

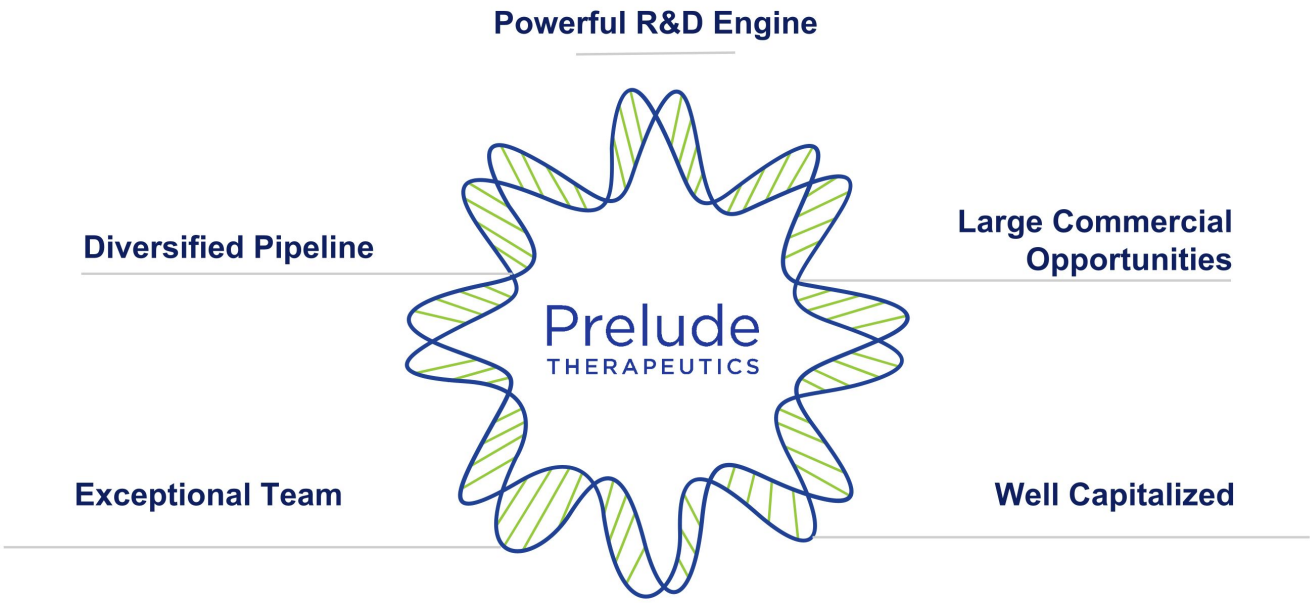
This presentation contains “forward-looking” statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: our plans to develop and commercialize small molecule therapies, our expectations about timing and ability to commence, enroll or complete clinical studies, present data and clinical results or updates, and to obtain regulatory approvals for PRT1419, PRT2527, PRT3645, PRT3789, our oral SMARCA2 candidate 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).

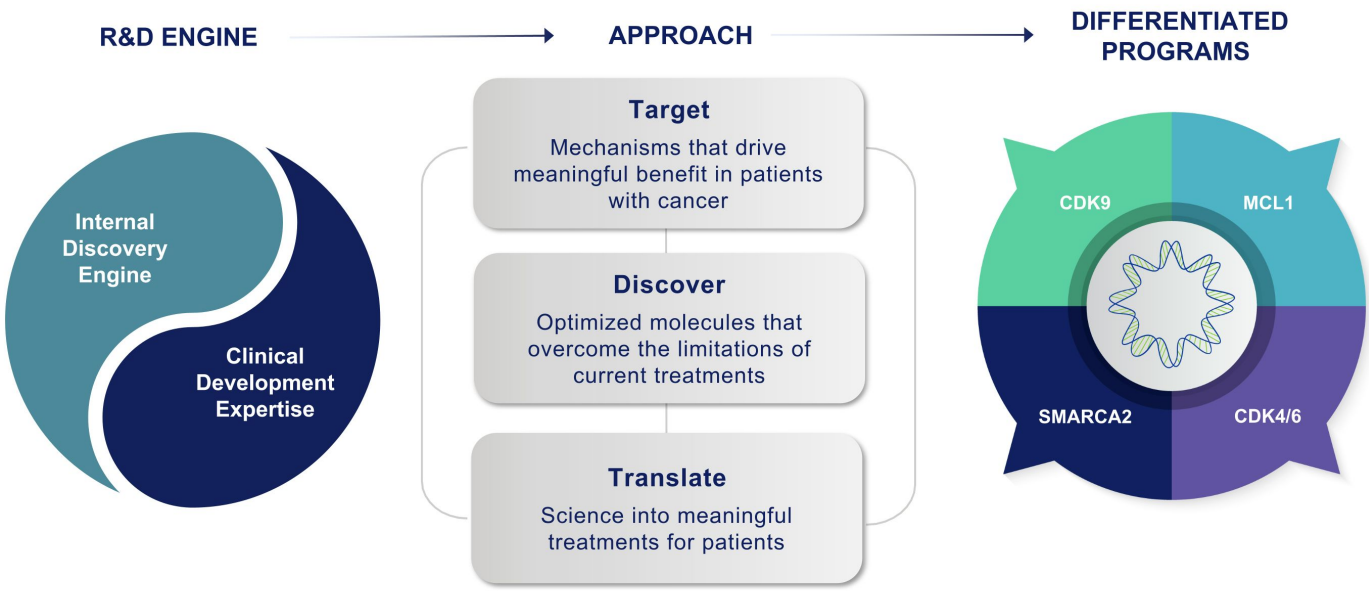
Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities or differences. This presentation shall not constitute an offer to sell or the solicitation 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 filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2022.

# Prelude Therapeutics: Delivering Precision Medicines to Patients with Cancer



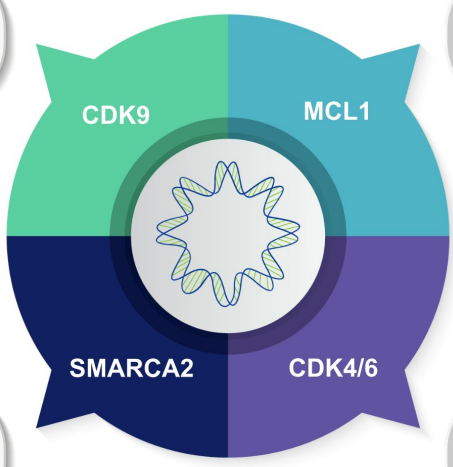
# Prelude Discovery and Development Engine: Positioned to Succeed



# Differentiated Programs with Transformative Potential for Patients with Cancer

**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 CDK4 Bias**
Potential for high tissue and brain penetration and better combinability

**Powerful Discovery Engine generating new INDs every 12-18 months**

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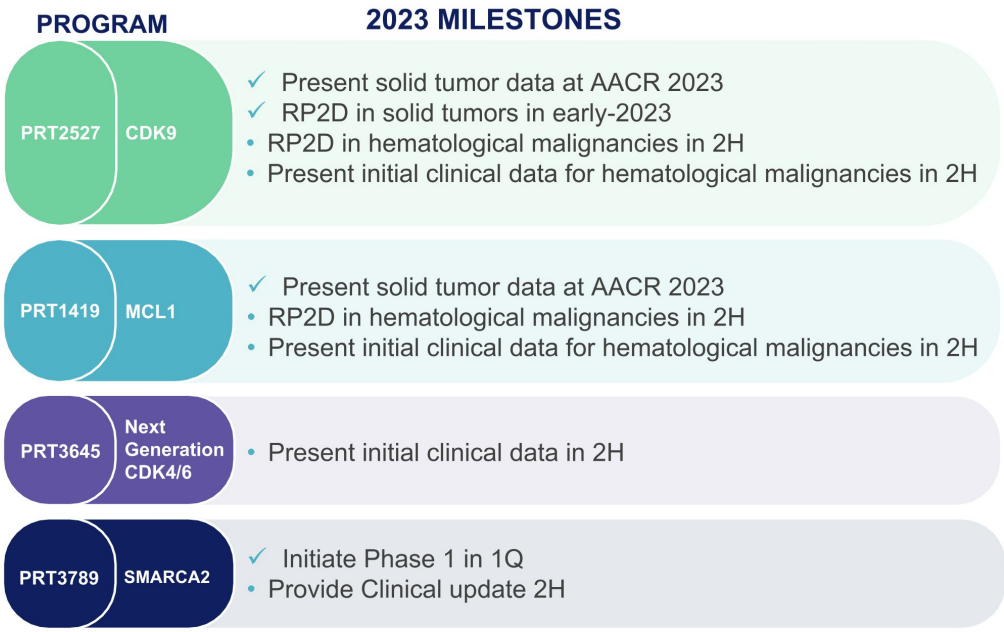
# Prelude Precision Oncology Pipeline: Diversified and Differentiated

| PROGRAM | CANCER INDICATIONS | DISCOVERY | PHASE 1 | PHASE 2/3 | AREAS OF CLINICAL FOCUS |
|---|---|---|---|---|---|
| **CDK9** PRT2527 | Selected solid and hematologic malignancies | | | | MCL, CLL, Lymphoma |
| **MCL1** PRT1419 | Selected hematologic malignancies and solid tumors | | | | AML, CLL, Lymphoma |
| **CDK4/6** PRT3645 | Selected solid tumors | | | | Breast Cancer, Gliomas, HNSCC, Lung cancers |
| **SMARCA2** PRT3789 (IV) | Multiple genomically-selected cancers | | | | SMARCA4 deleted NSCLC and Other cancers |
| **SMARCA2** (Oral) | Multiple genomically-selected cancers | | | | SMARCA4 deleted NSCLC and Other cancers |
| **New Programs** (Multiple targets) | Selected solid and hematologic malignancies | | | | Solid Tumors Heme Malignancies |

# Driving The Programs to Key Milestones and Value Creation

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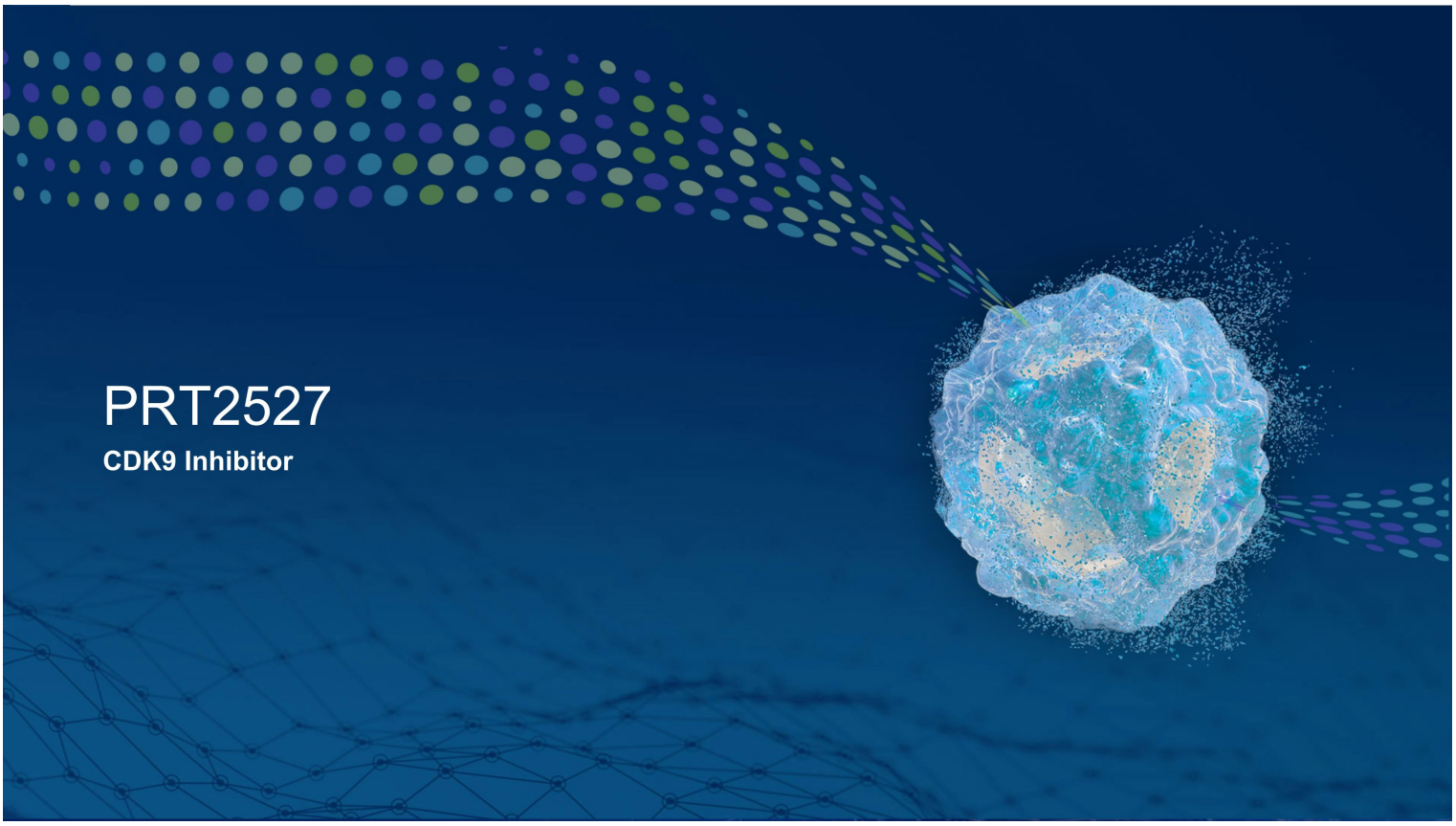
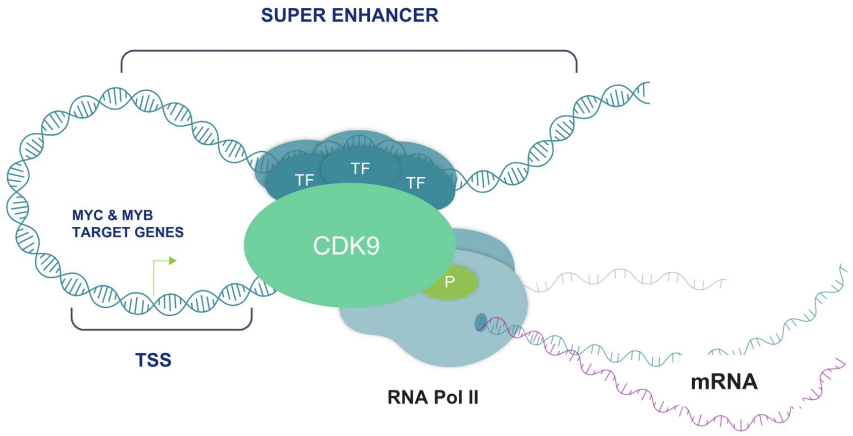

PRT2527
CDK9 Inhibitor

# 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**

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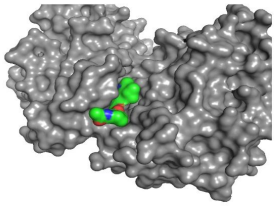
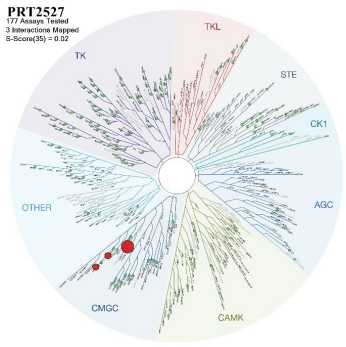
# PRT2527: Potent and Highly Selective CDK9 Inhibitor

**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

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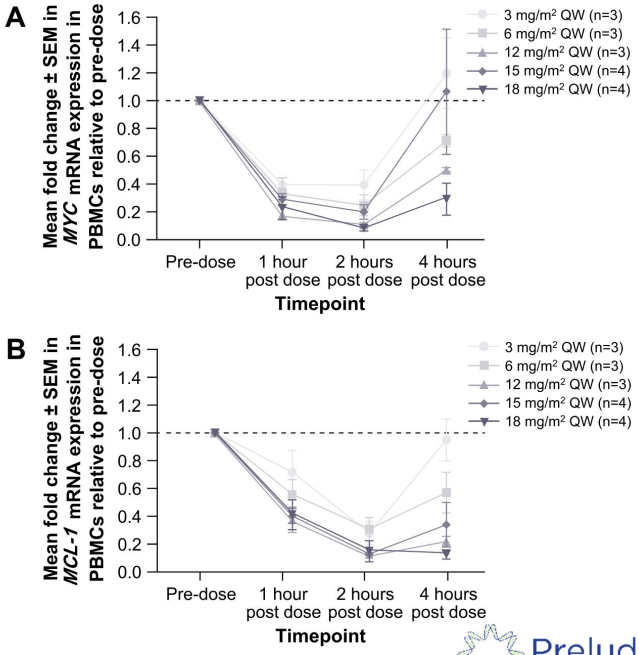
# CDK9 inhibitor: PRT2527

*Phase 1 Dose-Escalation Study in Advanced Solid Tumors*

- Phase 1 dose escalation study of PRT2527 is ongoing and enrolling the 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
- In the 18 patients treated in dose escalation, PRT2527 demonstrated favorable tolerability with manageable neutropenia and absence of significant gastrointestinal events or hepatotoxicity
- The 15 m/mg2 QW dose of PRT2527 was selected for further evaluation in a dose-confirmation cohort
- Dose-dependent inhibition of CDK9 transcription targets observed in PBMCs




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

AACR 2023 Poster Section 45

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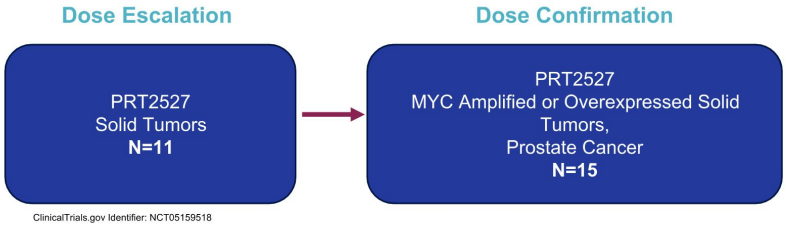
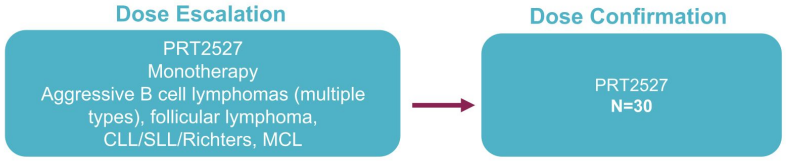
# CDK9 Inhibitor: PRT2527

*Phase 1 Studies in Solid Tumors and Hematologic Malignancies*




***Solid Tumor data at AACR 2023***




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

ClinicalTrials.gov Identifier: NCT05665530

### 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

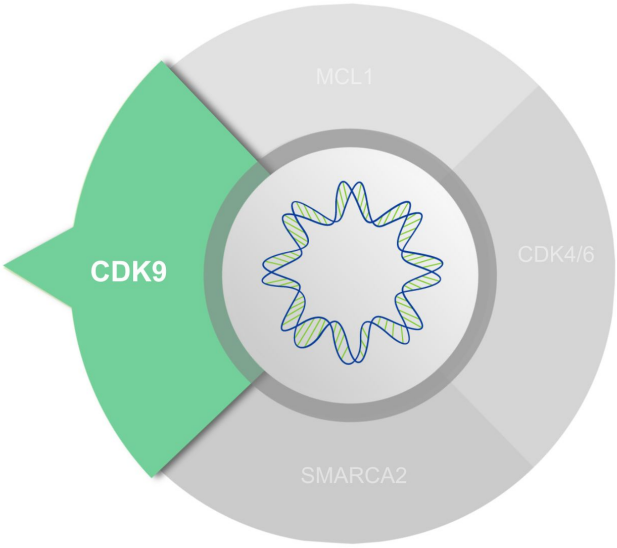
*Potential for Improved Safety Based on Best-in-Class Kinome Selectivity*

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

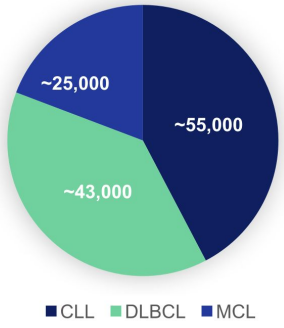



Prelude THERAPEUTICS

# PRT2527: Broad Potential Addressing areas of High Unmet Need

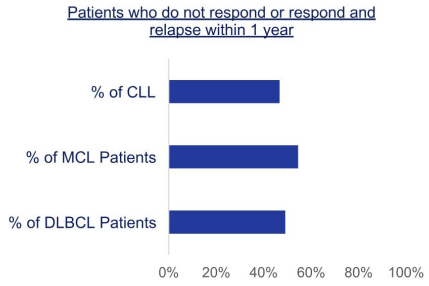
## Broad Opportunity:

*~125K patients treated annually(US): CLL, MCL and DLBCL*[1,2,3,4,5]



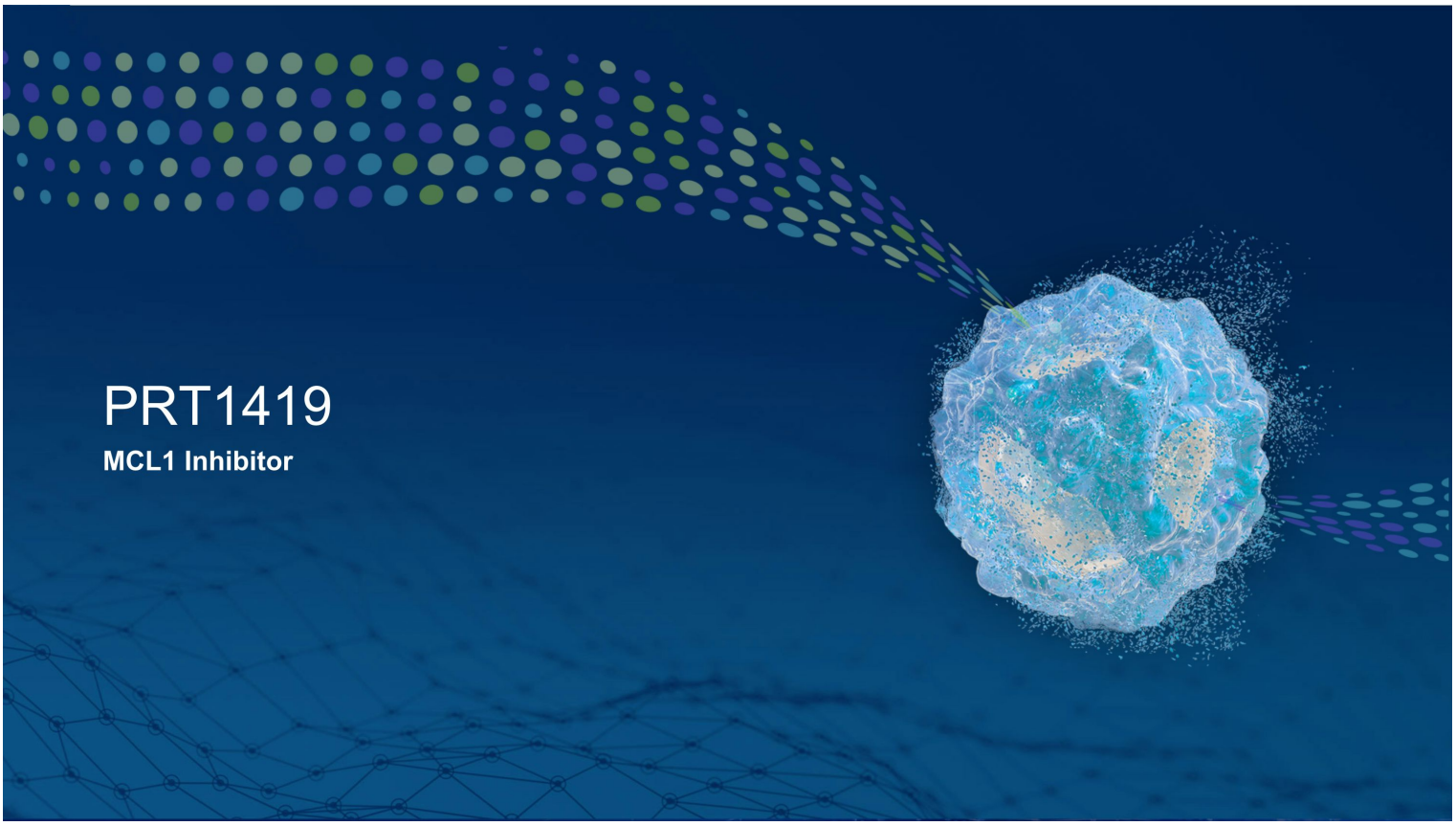

## Limited Treatment Options:

***>50%** of High Risk CLL, MCL and DLBCL patients are refractory/relapsed within 1 year after 2L Treatment* [2,3]



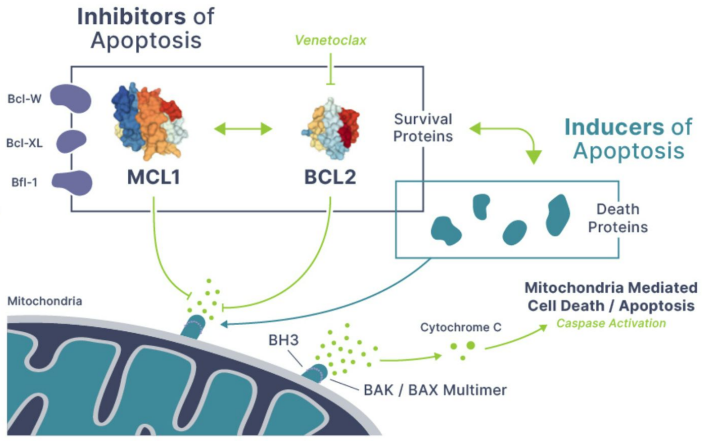

1. SEER Cancer Stat Facts: https://seer.cancer.gov/statfacts/html/clyl.html; 2. Gena Kanas, et. al. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe 3. CancerMPact® Treatment Architecture, Non-Hodgkin US, 4. CancerMPact® Treatment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

Prelude THERAPEUTICS


PRT1419
MCL1 Inhibitor

# MCL1 inhibition: Targeting Cancer Cell Survival

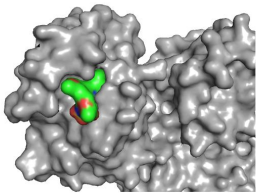
Mechanism



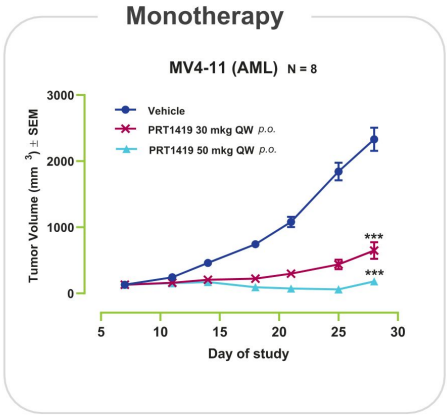

- MCL1 is a member of the **BCL2 family of inhibitors** of apoptosis
- **Established resistance** mechanism to the BCL2 inhibitor Venetoclax
- Prolonged depletion of MCL1 is undesirable and may be associated with cardiac toxicity
- Optimizing the PK profile of an MCL1 inhibitor may **maximize the therapeutic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

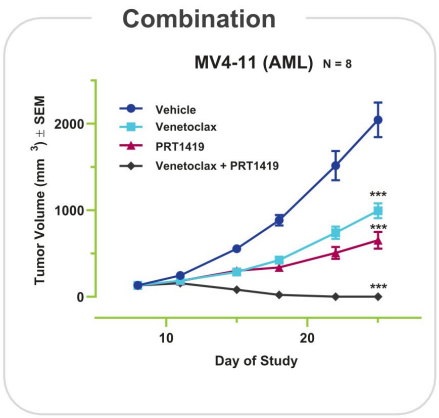
# PRT1419 is Potent MCL1 Inhibitor with Demonstrated Preclinical Activity as Monotherapy and in Combination

Prelude compounds are competitive inhibitors of BIM binding



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




Robust monotherapy activity also seen in models of DLBCL & MM

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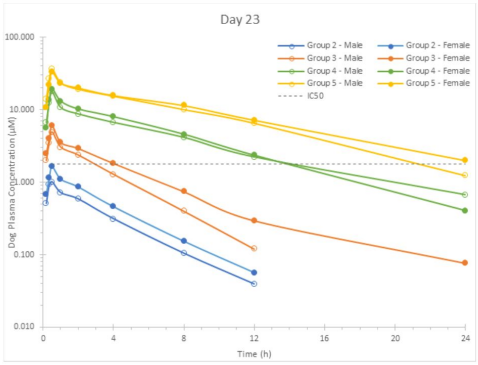
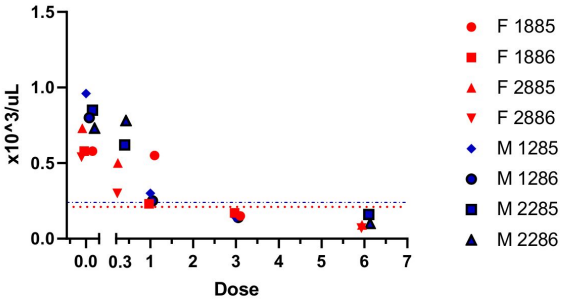
# PRT1419 Does Not Cause Cardiac Injury in Preclinical Toxicology Studies

**Pharmacokinetics**




**Pharmacodynamics**

**Absolute Monocytes**




- 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

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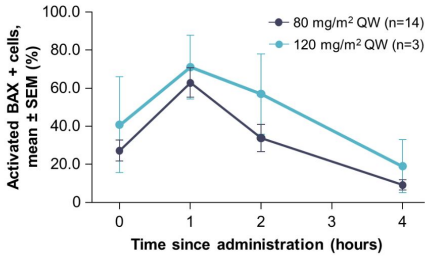
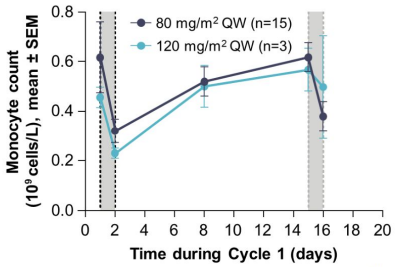
# MCL-1 inhibitor: PRT1419
# Phase 1 Dose-Escalation Study in Advanced Solid Tumors

- PRT1419 demonstrated acceptable safety and tolerability in patients with advanced metastatic solid tumors, with the most common TRAEs of nausea, vomiting and diarrhea
  - Neutropenia was deemed to be dose related
  - No cardiac toxicity was observed
- Induction of activated-BAX and cleaved caspase-3 was observed at 80 and 120 mg/m2: QW PRT1419, suggesting optimal MCL-1 inhibition
- Upregulation of MCL1 is a mechanism of resistance to BCL2 inhibition, particularly in CLL and AML; Strong preclinical hypothesis in heme

**Phase 1 Target Engagement**

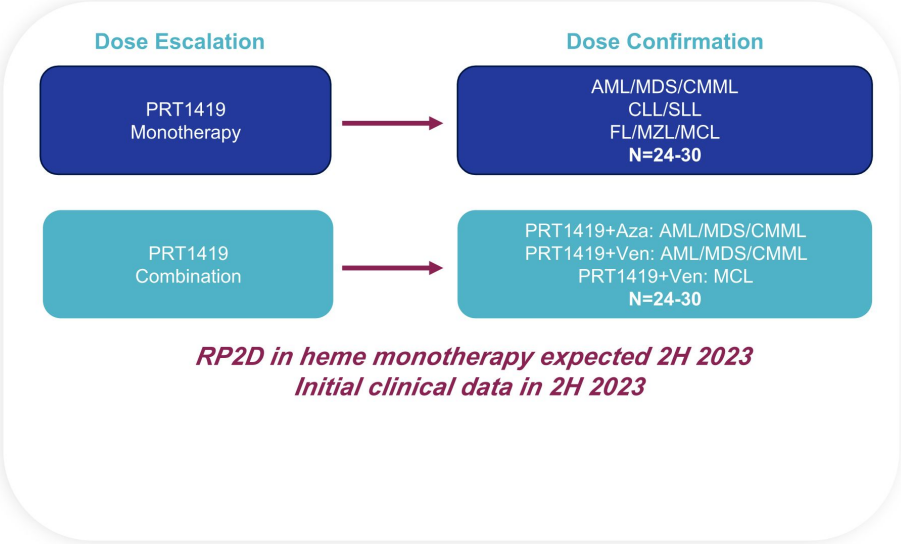



Prelude THERAPEUTICS

# MCL1 inhibitor: PRT1419

*Phase 1 Study in Hematologic Malignancies*




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

ClinicalTrials.gov Identifier: NCT05107856

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

Prelude THERAPEUTICS

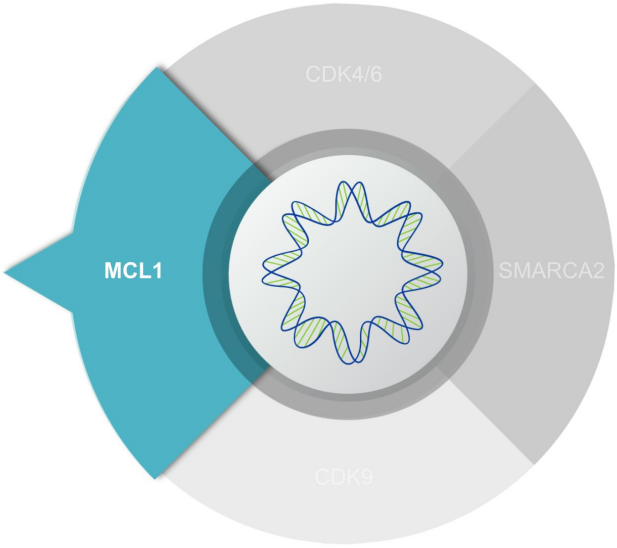
# MCL1 Inhibitor Differentiation and Market Opportunity

*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



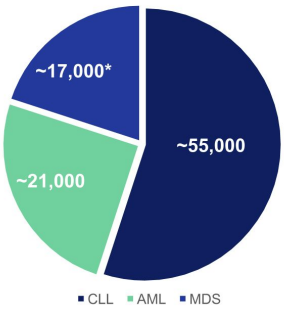

Prelude THERAPEUTICS

# PRT1419: MCL1 Inhibitor Offers Potential Benefit for Patients with Poor Outcomes

## Broad Opportunity:

*~95K patients treated annually(US): CLL, AML, MDS* [1,2,3,4]

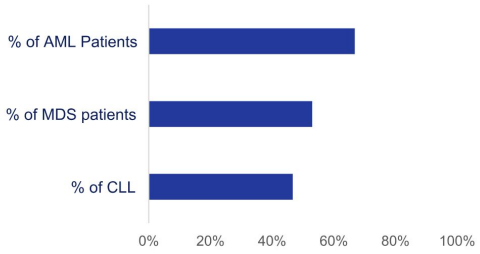
Annual Treated Patients (US Only)



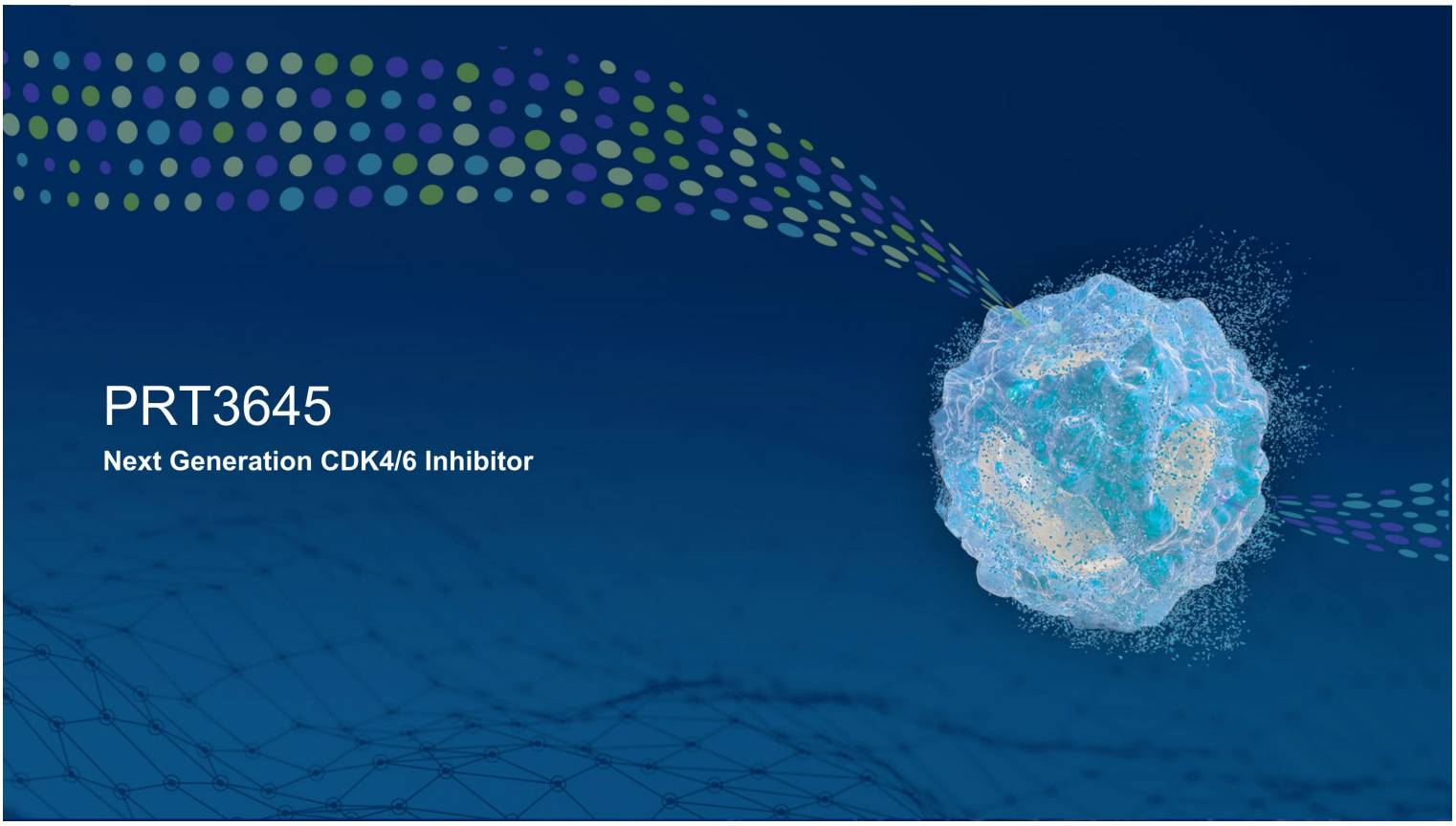

## Outcomes for relapsed / refractory patients are poor:

***>50%*** *of CLL, High Risk MDS and Unfit AML patients are refractory/relapsed within 1 year after second relapse*[2,3,4]

Patients who do not respond or respond and relapse within 1 year

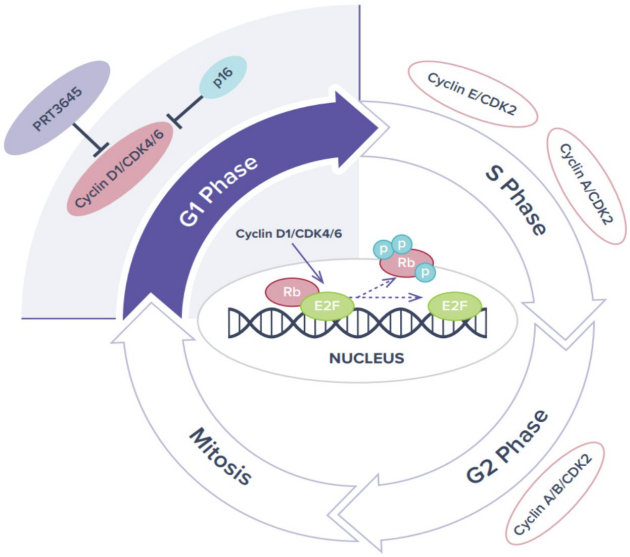



Prelude THERAPEUTICS


PRT3645
Next Generation CDK4/6 Inhibitor

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

Mechanism



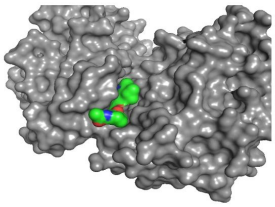

- **Validated mechanism** with approval of Next Generation CDK4/6 inhibitors in HR+ breast cancer
- **Resistance mechanism** to other targeted therapies including KRAS G12C inhibitors
- Current CDK4/6 inhibitors limited by poor tolerability and lack broad tissue penetration
- Next generation CDK4/6 inhibitor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

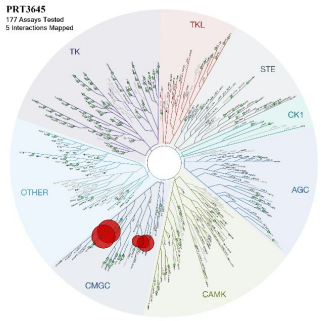
Prelude THERAPEUTICS

# PRT3645 – Highly Selective Next Generation CDK4/6 Inhibitor

## Bias towards CDK4 over CDK6

**Highly Selective, ATP Competitive**






| 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 |

>500x  500-50x  50-5x  <2x

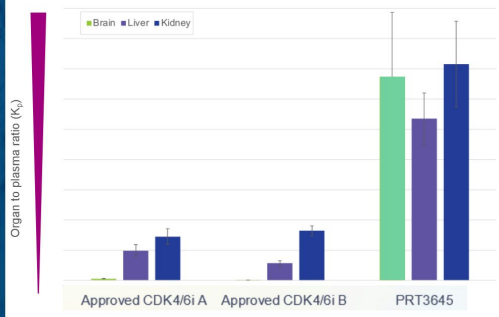
*Internal data; biochemical assay at 1 mM ATP, MCF7 CTG proliferation assay; MCF7 pRB

Prelude THERAPEUTICS

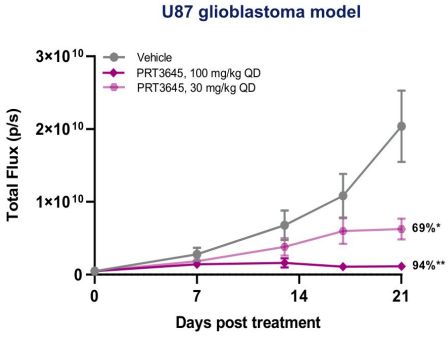
# Next Generation CDK4/6 inhibitor PRT3645

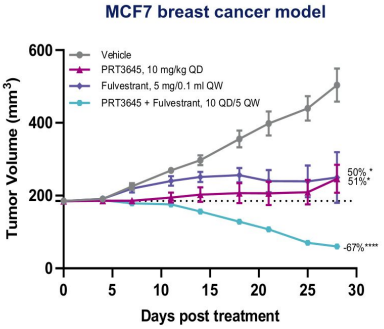
*Improved Tissue Penetration and Robust Activity in Preclinical Models*

## PRT3645 demonstrates higher brain penetration than approved CDK4/6 inhibitors



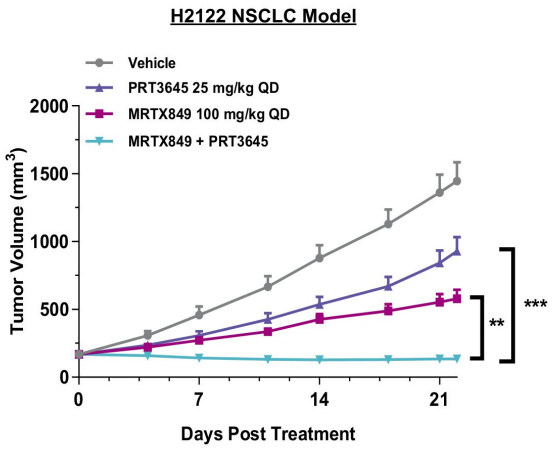

## PRT3645 shows robust activity in vivo as monotherapy and in combination

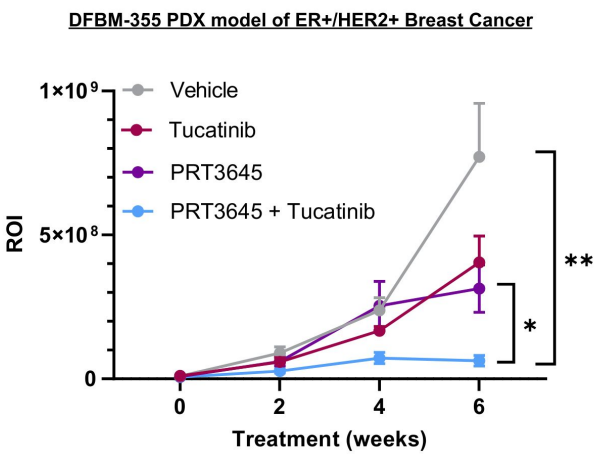



Prelude THERAPEUTICS

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




PRT3645 significantly enhances 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*

**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***

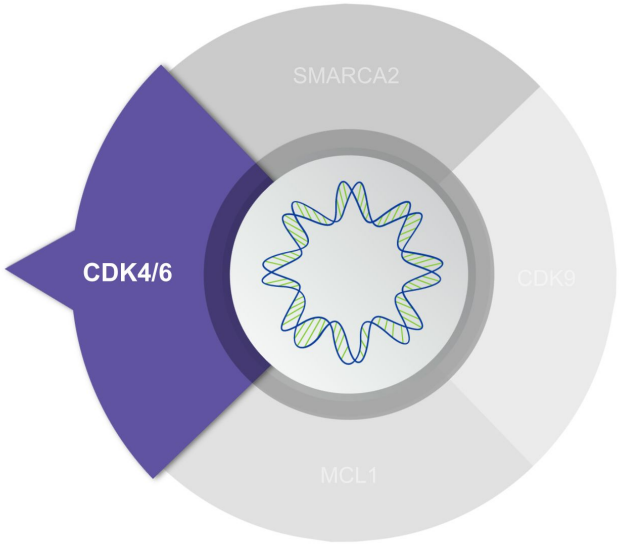
- A differentiated and highly brain penetrant Next Generation CDK4/6 inhibitor
- Potential to extend the reach of CDK4/6 inhibition beyond HR+ breast cancers, for which the first generation CDK4/6 inhibitors were approved

ClinicalTrials.gov Identifier: NCT05538572

# Next Generation CDK4/6 Inhibitor Differentiation and Market Opportunity

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

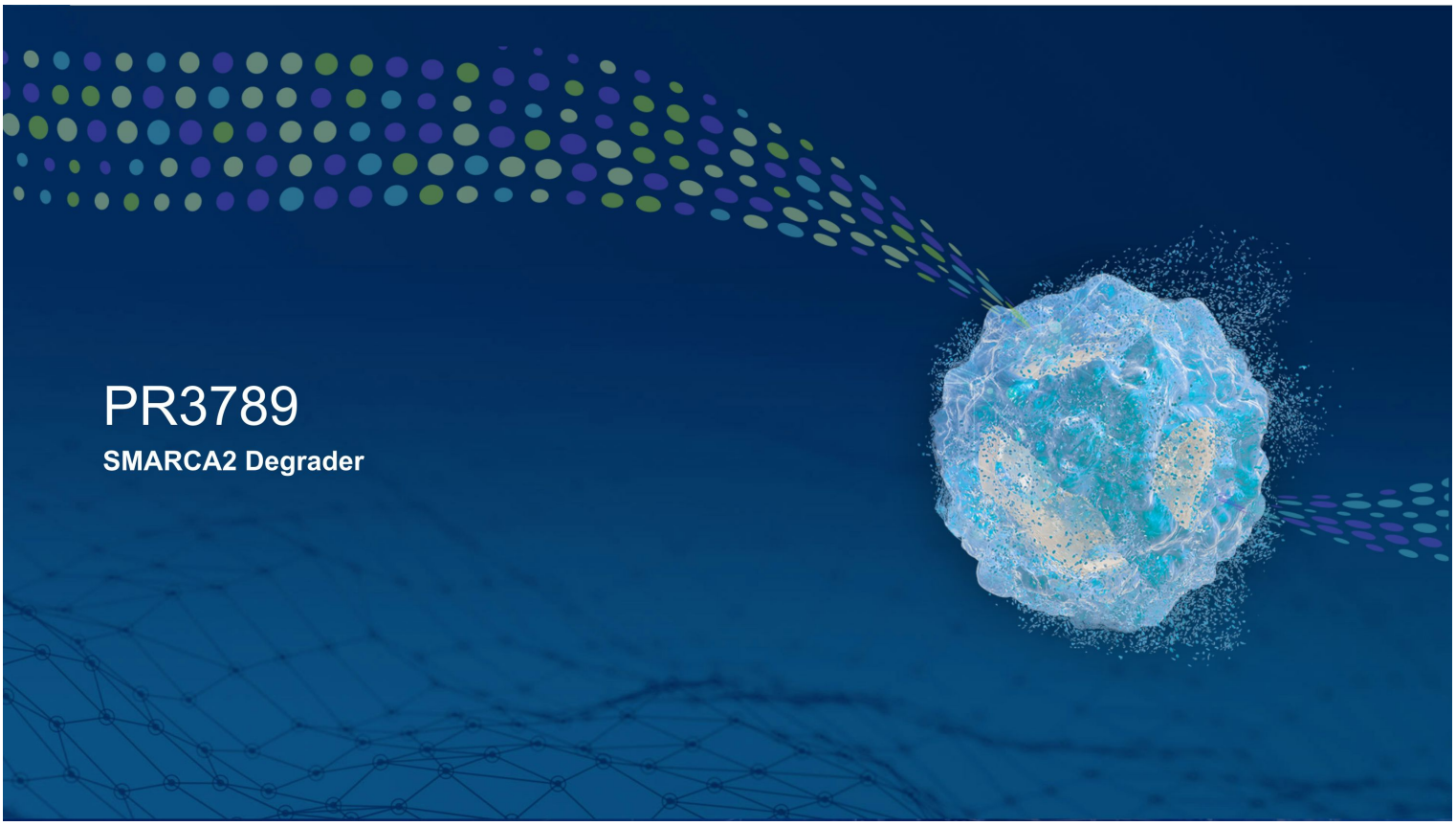
- PRT3645 is a **highly potent and selective** Next Generation CDK4/6 inhibitor
- Optimized to demonstrate **deep tissue penetration including brain penetrance**
- **Improved metabolic profile** to allow for combination treatment in diseases beyond breast cancer
- **Reduced toxicity** in preclinical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




***Market Opportunity:***

- Breast cancer patients may benefit from sequential CDK4/6 inhibitors treatment
- There are estimated to be 65,000 breast cancer patients treated with CDK4/6 inhibitors in 2023 in the U.S.
- Other solid tumors (lung cancer, glioma, HER2+ breast cancer) may demonstrate activity in combination

Prelude THERAPEUTICS

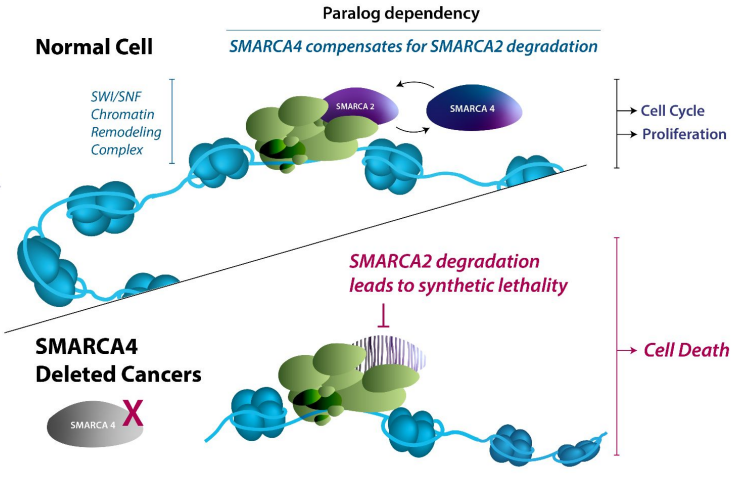


# PR3789

**SMARCA2 Degrader**

# Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

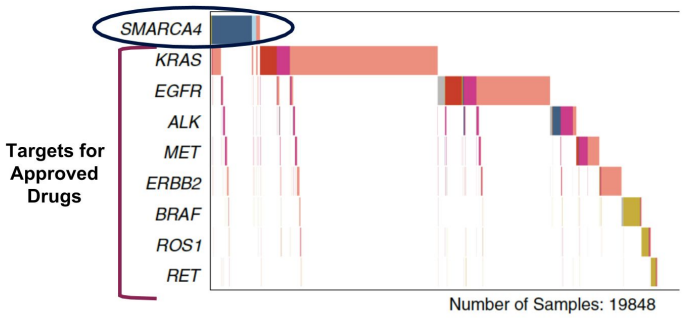
Mechanism




- 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

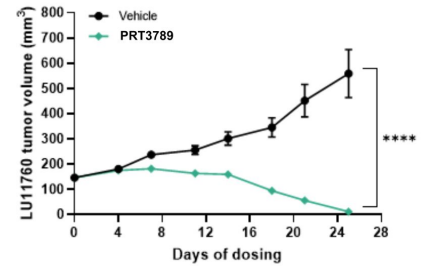
**SMARCA4 Prevalence across selected Solid Tumors**

| 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% |

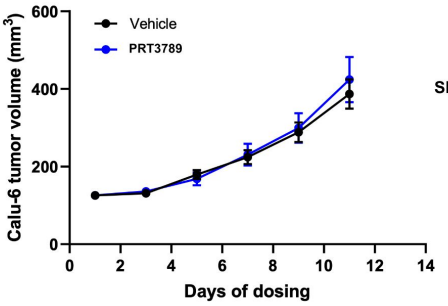
1.cBioPortal; FoundationCore; 2.SMARCA4 LOF mutations included homozygous missense, hotspot mutations with LOF, and damaging mutations; 3.SEER 2022; Globocan; * Source: American Cancer Society – Cancer Facts & Figures 2022

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

## Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft

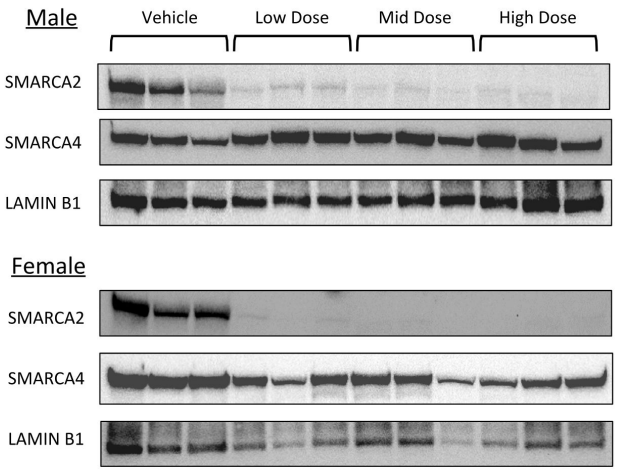



SMARCA4 mutant




SMARCA4 WT

## Significant Degradation of SMARCA2 Protein but not SMARCA4 in Preclinical Models

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# 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***
***Clinical update expected 2H 2023***

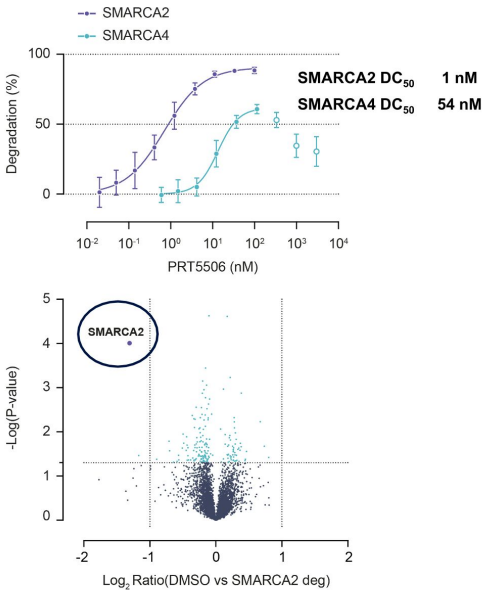
- SMARCA2 inhibition has the greatest potential in patients with SMARCA4 deficient cancers, including approximately 10-20% of all non-small cell lung cancers
- SMARCA2 degradation to be evaluated in Phase 1
- Study population: advanced, recurrent, or metastatic disease, with loss of SMARCA4 due to truncating mutation and/or deletion
- Biomarker selected by local NGS or IHC in tumor tissue or blood

ClinicalTrials.gov Identifier: NCT05639751

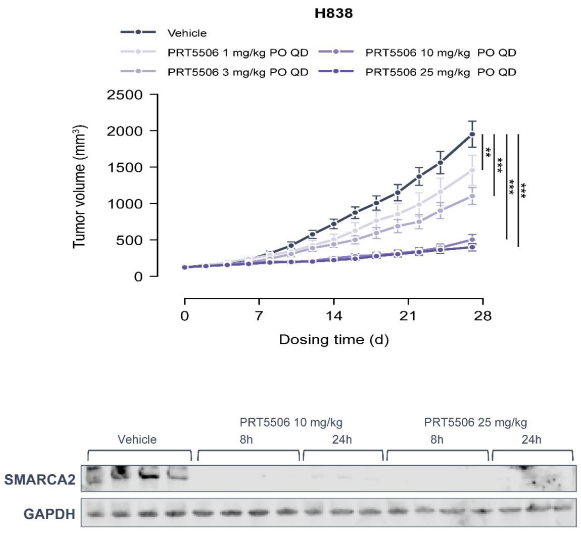
# Selective Orally Bioavailable SMARCA2 Degrader Program

*PRT5506 - a Preclinical POC Molecule*

## Potent and Highly Selective SMARCA2 Degradation




## Robust Tumor Growth Inhibition of SMARCA4 Mutated Xenograft with Oral Dosing







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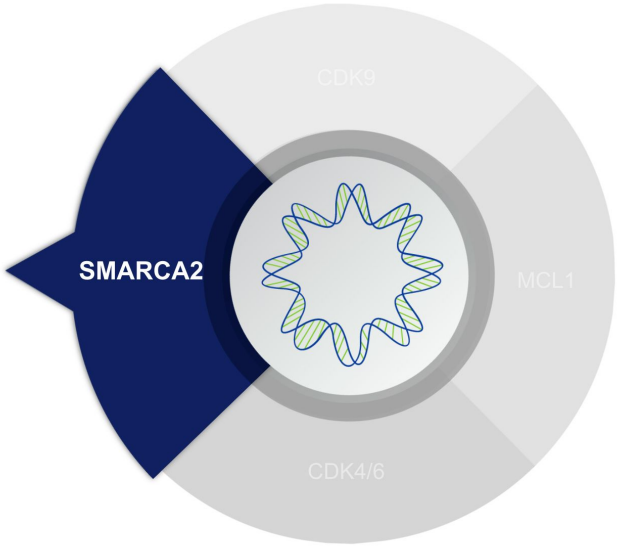
# SMARCA2 Differentiation and Market Opportunity

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

- PRT3789 is **a first-in-class** SMARCA2 Degrader
- **Potent and selective** 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***:

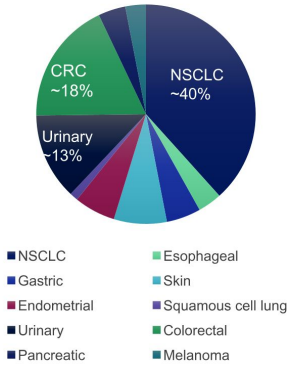
- 70,000 patients with SMARCA4 mutation in the US/EU5



# PRT3789: Large Pan-Tumor Unmet Need in Patients with SMARCA4 Mutation

## Broad Opportunity:

Distribution of Patients with SMARCA4 mutation by Tumor, based on study of ~130k patients[1,2,3]




## Improvement vs SoC:

*Most common 2L mNSCLC regimen offers minimal benefit and significant toxicity* [4]

**mPFS ~ 4.5 months**

**docetaxel + ramucirumab**

## SMARCA 4 Degrader offers:

First in Class Treatment Option in patients with no approved drugs

1. Fernando, T.M., Piskol, R., Bainer, R. *et al.* Functional characterization of *SMARCA4* variants identified by targeted exome-sequencing of 131,668 cancer patients..https://doi.org/10.1038/s41467-020-19402-8; 2. https://www.mycancergenome.org/content/gene/smarca4/ 3. US SEER Database 4. CancerMPact® Treatment Architecture, NSCLC – Non Driver Mutation.

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# 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**
- Potentially **first-in-class SMARCA2 degrader program** with a significant lead over competitors and offers transformational potential for the company
- Current cash runway expected into **Q4 2024**

Prelude THERAPEUTICS

# Experienced Management Team: Proven Track Records

**Kris Vaddi, PhD**

*Founder & Chief Executive Officer*

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

**Jane Huang M.D.**

*President and Chief Medical Officer*

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

**Peggy Scherle, PhD**

*Chief Scientific Officer*

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

**Andrew Combs, PhD**

*Executive Vice President and Head of Chemistry*

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

**Laurent Chardonnet, MBA**

*Chief Financial Officer*

Incyte
axcella
sanofi

**Bryant Lim, J.D.**

*Chief Legal Officer and Corporate Secretary*

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ViroPharma Incorporated
Incyte
idera