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): August 3, 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** **(Address of principal executive offices)**		**19803** **(Zip Code)**

Registrant's telephone number, including area code: (302) 467-1280

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	PRLD	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition

On August 3, 2023, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing its financial results for the three months ended June 30, 2023. A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K.

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 June 30, 2023, dated August 3, 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, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRELUDE THERAPEUTICS INCORPORATED

Date: August 3, 2023

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

Prelude Therapeutics Announces Second Quarter 2023 Financial Results and Provides Corporate Update

Four lead programs on track to deliver clinical data and to inform future development plans.

Recent equity financing extends cash runway into 2026,
enabling advancement of Prelude's pipeline through critical milestones

WILMINGTON, Del. – (Globe Newswire) August 3, 2023 – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today reported financial results for the second quarter ended June 30, 2023, and provided a corporate update.

Kris Vaddi, Ph.D., Chief Executive Officer of Prelude stated, "With the recent financing that extended our cash runway into 2026, we are in a strong position to advance our diverse pipeline of potentially best and/or first-in-class compounds to address the needs of patients with certain underserved cancers. Our focus remains on generating critical data for each of our molecules to make key strategic decisions. As disclosed recently, and based on additional data generated in this quarter, PRT2527 (CDK9 inhibitor) and PRT1419 (MCL1 inhibitor) demonstrated differentiated clinical safety profiles and strong target inhibition and are continuing to enroll patients with hematological malignancies, which is where we see the best opportunities for these molecules."

"Our first-in-class selective SMARCA2 degrader, PRT3789, and next generation CDK4/6 inhibitor, PRT3645, are progressing well in Phase 1 and are on track to reach confirmation doses in the first half of 2024 and by year end 2023, respectively," added Dr. Vaddi. "Based on meaningful progress made in the first half of the year, we look forward to sharing updates and clarity around strategic prioritization of our pipeline in the coming months."

Pipeline Updates

PRT2527- CDK9 Inhibitor Program

The Company believes its highly selective CDK9 inhibitor, PRT2527, has the potential to avoid off-target toxicities, achieve substantial clinical activity and become the best-in-class CDK9 inhibitor, making it amenable for combination with other therapies.

PRT2527 has completed a Phase 1 multi-dose escalation study (NCT05159518) in patients with solid tumors. In this trial, PRT2527 was shown to achieve high levels of target inhibition and the potential to be better tolerated than existing CDK9 inhibitors, specifically, manageable neutropenia and an absence of meaningful gastrointestinal events or hepatotoxicity. *

* AACR2023 Poster Presentation

A Phase 1 multi-dose escalation study (NCT05665530) is currently ongoing in hematologic malignancies. Patient recruitment for hematological clinical trials in the US is highly competitive and this trial has recently been expanded to include global sites to support patient recruitment.

The Company's objective is to establish a biologically active confirmation dose by Q1 2024. As part of this Phase 1 multi-dose escalation trial, the Company intends to expand the Phase 1 clinical trial and evaluate PRT2527 in combination with zanubrutinib.

Potential indications for PRT2527 include aggressive B-cell lymphoma subtypes, mantle cell lymphoma (MCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) including Richter syndrome, and T-cell lymphoma subtypes.

The Company intends to provide a program update by year end on the CDK9 inhibitor program and present initial results at a future scientific meeting.

PRT1419- MCL1 Inhibitor Program

PRT1419 is a potent and selective MCL1 inhibitor. With its optimized PK/PD profile, the Company believes PRT1419 has the potential to achieve greater target engagement and provide patients with better clinical outcomes as well as improved safety and tolerability, as compared to other MCL1 inhibitors in development.

PRT1419 has completed a Phase 1 multi-dose escalation study (NCT04837677) in patients with solid tumors. In this study, PRT1419 demonstrated an acceptable safety and tolerability profile in patients with advanced and metastatic solid tumors. No cardiac toxicity was observed. Pharmacokinetics/pharmacodynamics and safety data in the 80 mg/m2 QW dose cohort support further evaluation of this dose in future studies.

A Phase 1 multi-dose escalation clinical trial of PRT1419 in patients with hematologic malignancies is ongoing (NCT05107856). In this trial, PRT1419 is being evaluated as monotherapy for myeloid malignancies and in combination with azacitidine or venetoclax for patients with relapsed/refractory myeloid or B-cell malignancies.

The Company will provide a clinical update on PRT1419 by year end.

PRT3645- Next Generation CDK4/6 Inhibitor Program

PRT3645 is a highly potent and selective next generation CDK4/6 inhibitor with the potential to provide improved safety and tolerability outcomes and higher, more effective brain and tissue penetration than current CDK4/6 inhibitors.

In preclinical models *in vivo*, PRT3645 has been shown to be efficacious in multiple cancers as monotherapy as well as when combined with KRAS inhibitors, MEK inhibitors and with a brain penetrant HER2 receptor kinase inhibitor. Additionally, oral administration of PRT3645 has been shown to induce tumor regressions in preclinical models that are resistant to currently approved CDK4/6 inhibitors. Together, these data suggest that PRT3645 may extend the benefit of CDK4/6 inhibition beyond HR+ breast cancer.

A Phase 1 multi-dose escalation clinical trial of PRT3645 (NCT05538572) is underway and the Company expects to reach a biologically active dose confirmation in Q4 2023.

Potential indications for PRT3645 in combination with other therapies, in addition to breast cancer with or without brain metastases, include endometrial, sarcomas, glioblastomas, non-small cell lung cancer, head and neck cancers.

The Company intends to provide a program update by year end and present initial results at a future scientific meeting.

PRT3789- SMARCA2 Targeted Protein Degrader Program

PRT3789 is a first-in-class highly selective degrader of SMARCA2 protein, which along with SMARCA4 controls gene regulation through chromatin remodeling. Cancer cells with SMARCA4 mutations are dependent on SMARCA2 for their growth and survival and selectively degrading SMARCA2 induces cell death in cancer cells while sparing normal cells. PRT3789 is efficacious and well tolerated in preclinical models of SMARCA4 deleted/mutated cancers as monotherapy and in combination with standards of care. The Company believes a selective SMARCA2 degrader has the potential to be of benefit in up to 70,000 US/EU cancer patients with the SMARCA4 mutation.

Patients with SMARCA4 mutations or deletions may have poor clinical outcomes and limited treatment options. Therefore, mutated, or deleted SMARCA4 cancers provides a potential biomarker to select those patients most likely to respond to treatment with a highly selective SMARCA2 degrader.

A Phase 1 multi-dose escalation clinical trial of PRT3789 is ongoing (NCT05639751) in biomarker selected SMARCA4 mutated cancers. The Company intends to evaluate PRT3789 as monotherapy as well as in combination.

The Company intends to provide a program update by year end and expects to reach confirmation dose in the first half of 2024.

SMARCA2- Oral Program

The Company has also recently nominated a new chemical entity as a potent, orally bioavailable and highly selective SMARCA2 degrader candidate (>1000x over SMARCA4) and intends to file an IND early in 2024.

Second Quarter 2023 Financial Results

Cash, Cash Equivalents and Marketable Securities: In May 2023, the Company completed a public offering of common stock, raising gross proceeds of $113.0 million before deducting underwriting discounts, commissions and offering expenses. Net proceeds received, $110.4 million, will be focused on the continued development and expansion of the Company’s product pipeline.

Cash, cash equivalents, and marketable securities as of June 30, 2023, were $255.0 million. Prelude anticipates that its existing cash, cash equivalents and marketable securities will fund the Company's operations into 2026.

Research and Development (R&D) Expenses: For the second quarter of 2023, R&D expense increased to $25.0 million from $21.3 million for the prior year period. Research and development expenses increased 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 second quarter of 2023, G&A expenses decreased to $7.4 million from $8.2 million for the prior year period. General and administrative expenses decreased reflecting the Company's careful management of its G&A expenses.

Net Loss: For the three months ended June 30, 2023, net loss was $30.4 million, or $0.54 per share compared to $27.4 million, or $0.58 per share, for the prior year period. Included in the net loss for the quarter ended June 30, 2023, was $6.7 million of non-cash expense related to the impact of expensing share-based payments, including employee stock options, as compared to $6.0 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**,** PRT3789 an IV administered, potent and highly selective SMARCA2 degrader, and a preclinical oral candidate targeting SMARCA2.

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, PRT3789, and its preclinical oral SMARCA2 degrader, 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 2026. 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, clinical trial sites and our ability to enroll eligible patients, 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 June 30, 2023	2022
Operating expenses:		
Research and development	$ 24,966	$ 21,310
General and administrative	7,432	8,151
Total operating expenses	32,398	29,461
Loss from operations	(32,398)	(29,461)
Other income, net	1,967	2,087
Net loss	$ (30,431)	$ (27,374)
Per share information:		
Net loss per share of common stock, basic and diluted	$ (0.54)	$ (0.58)
Weighted average common shares outstanding, basic and diluted	56,240,491	47,276,684
Comprehensive loss		
Net loss	$ (30,431)	$ (27,374)
Unrealized (loss) gain on marketable securities, net of tax	(313)	19
Comprehensive loss	$ (30,744)	$ (27,355)

PRELUDE THERAPEUTICS INCORPORATED

BALANCE SHEETS
(UNAUDITED)

(in thousands, except share data)	June 30, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 26,446	$ 30,605
Marketable securities	228,543	171,123
Prepaid expenses and other current assets	5,221	2,652
Total current assets	260,210	204,380
Restricted cash	4,044	4,044
Property and equipment, net	6,082	4,908
Right-of-use asset	918	1,792
Prepaid expenses and other non-current assets	9,357	5,376
Total assets	$ 280,611	$ 220,500
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 5,585	$ 6,777
Accrued expenses and other current liabilities	8,667	13,093
Operating lease liability	938	1,832
Total current liabilities	15,190	21,702
Other liabilities	3,361	3,361
Total liabilities	18,551	25,063
Commitments (Note 8)		
Stockholders' equity:		
Voting common stock, $0.0001 par value: 487,149,741 shares authorized; 41,958,456 and 36,496,994 shares issued and outstanding at June 30, 2023 and December 31, 2022, respectively	4	4
Non-voting common stock, $0.0001 par value: 12,850,259 shares authorized; 12,850,259 and 11,402,037 shares issued and outstanding at June 30, 2023 and December 31, 2022, respectively	1	1
Additional paid-in capital	655,473	531,682
Accumulated other comprehensive loss	(711)	(1,692)
Accumulated deficit	(392,707)	(334,558)
Total stockholders' equity	262,060	195,437
Total liabilities and stockholders' equity	$ 280,611	$ 220,500

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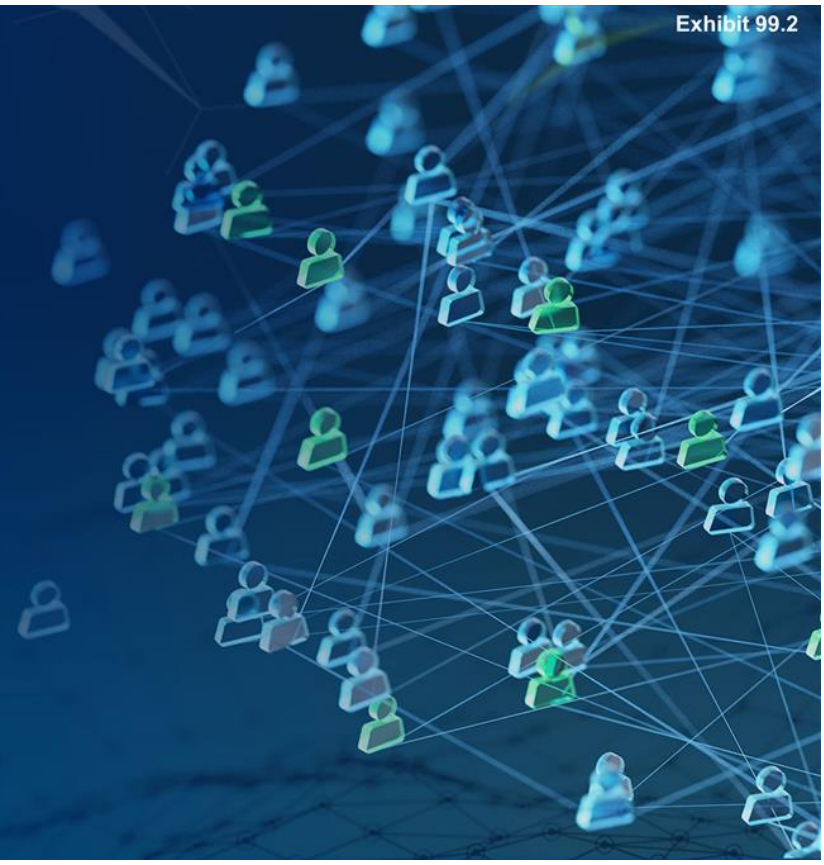
Exhibit 99.2

Prelude
THERAPEUTICS

Corporate Presentation

July 2023

Patient focused.
Science driven.
Precision oncology.



Forward Looking Statements

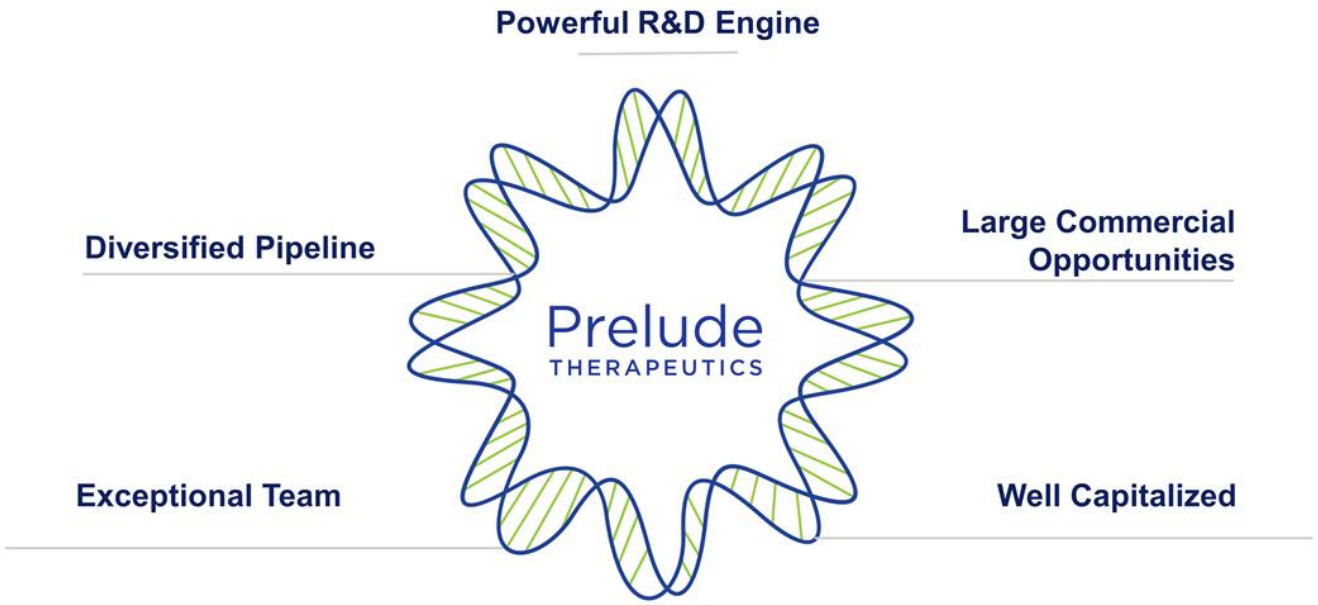
This presentation contains "forward-looking" statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: our plans to develop and commercialize small molecule therapies, our expectations about timing and ability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

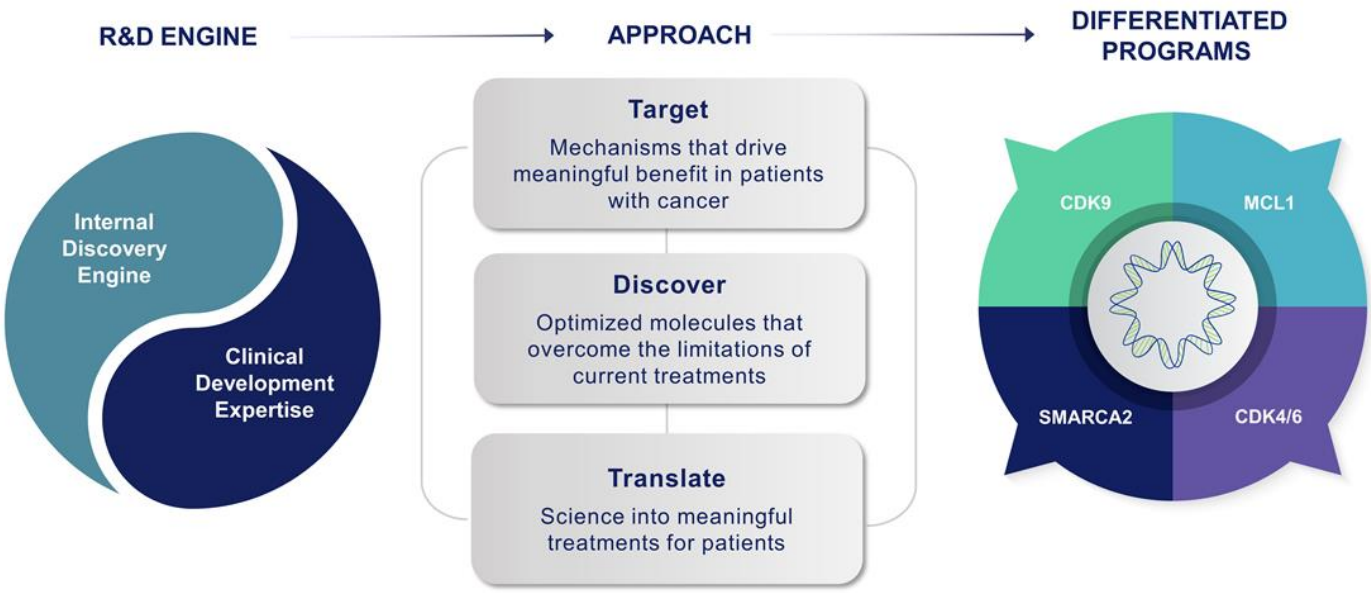
Certain data in this presentation are based on cross-study comparisons and are not based on any head-to-head clinical trials. Cross-study comparisons are inherently limited and may suggest misleading similarities or differences. This presentation shall not constitute an offer to sell or the solicitation 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: Aiming to Deliver Precision Medicines to Patients with Cancer



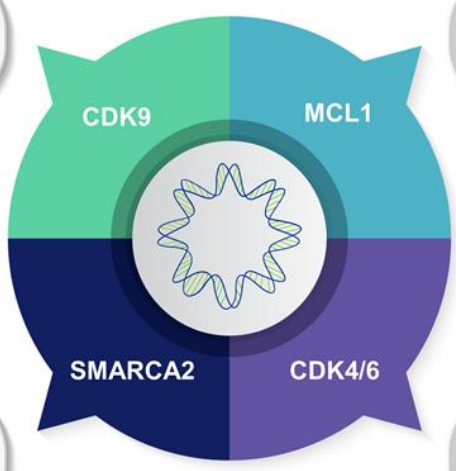
Prelude Discovery and Development Engine



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



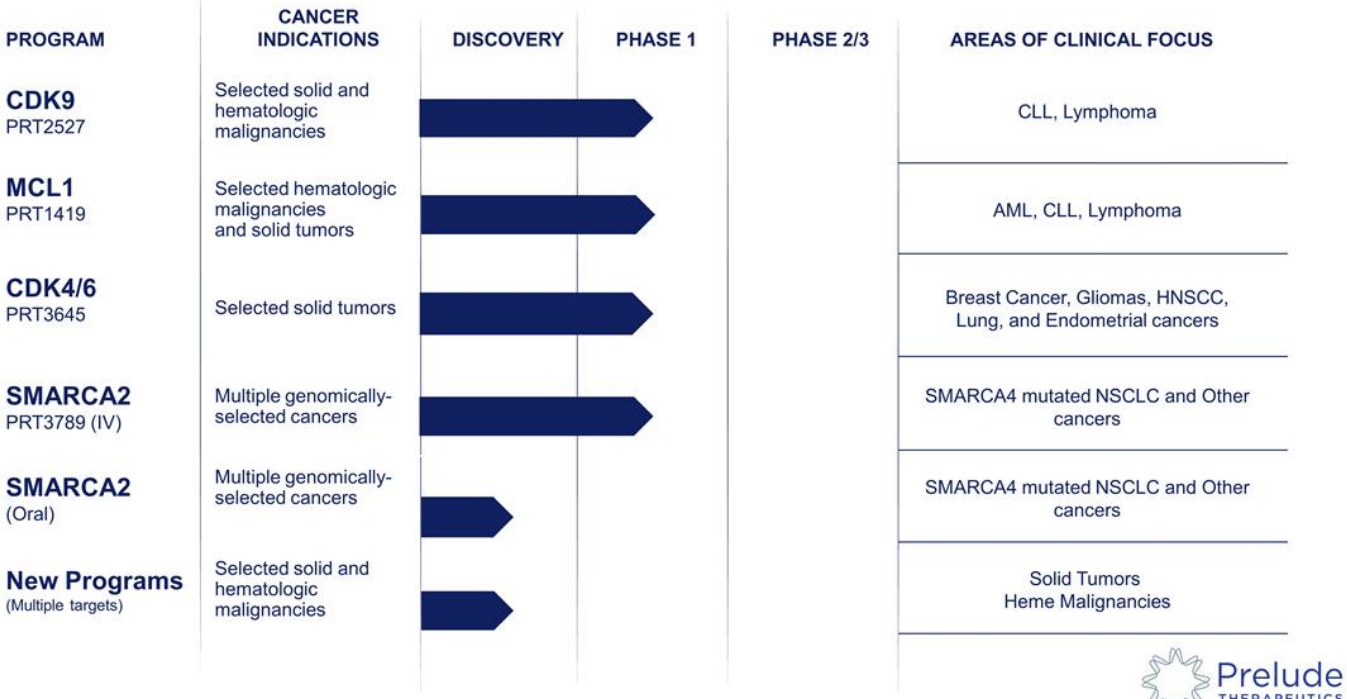
Potent and Selective Degrader
Potential to address major unmet need in biomarker-selected patients

Highly Selective CDK4 Bias
Potential for high tissue and brain penetration and better combinability

Powerful Discovery Engine expected to generate new INDs every 12-18 months

Prelude THERAPEUTICS

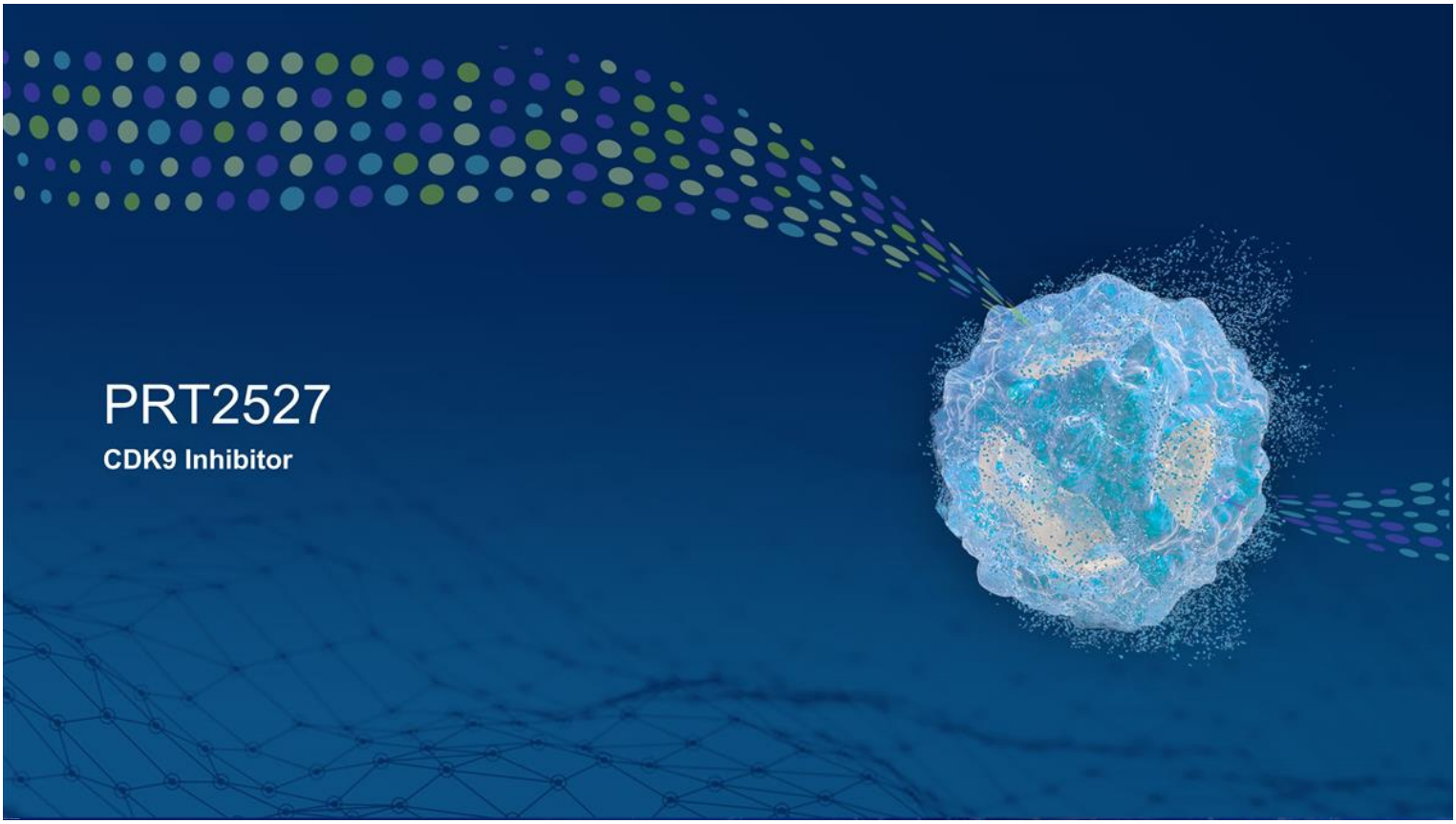
Prelude Precision Oncology Pipeline: Diversified and Differentiated



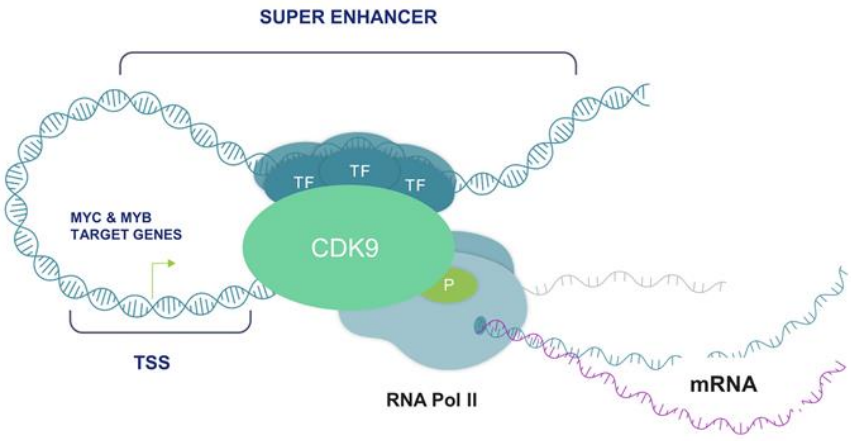
Prelude THERAPEUTICS

Driving The Programs to Key Milestones and Value Creation

Prelude THERAPEUTICS


PRT2527
CDK9 Inhibitor

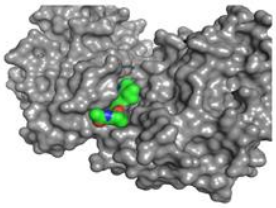
CDK9 Inhibition: Targeting Cancer by Regulating Oncogene Expression

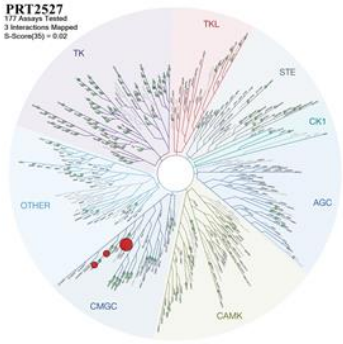


- CDK9 regulates expression of several **oncogenes that drive cancer cell growth and resistance** (i.e. MYC, MYB, MCL1)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
- **Improving the selectivity** of CDK9 inhibitors may translate to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

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

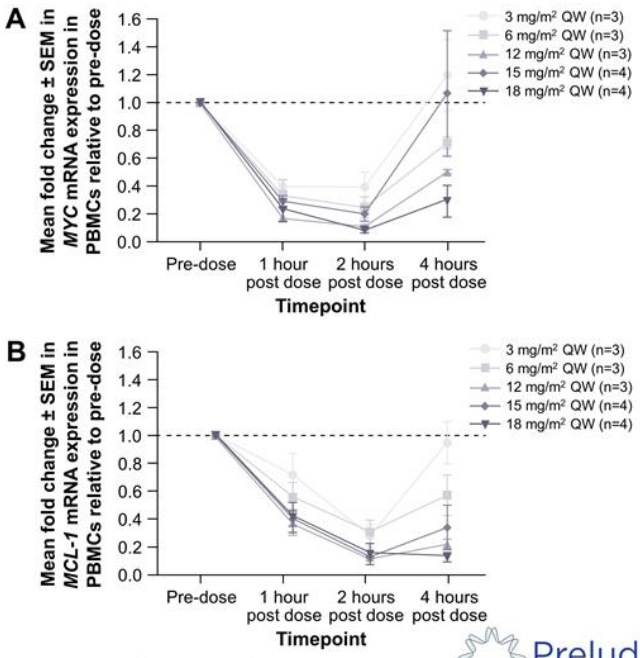
*Internal data; biochemical assay at 1 mM ATP, H929 CTG proliferation assay; **VIP151 was formerly BAY151 and licensed to Vincerx by Bayer

Prelude THERAPEUTICS

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 was generally well tolerated 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



ClinicalTrials.gov Identifier: NCT05159518

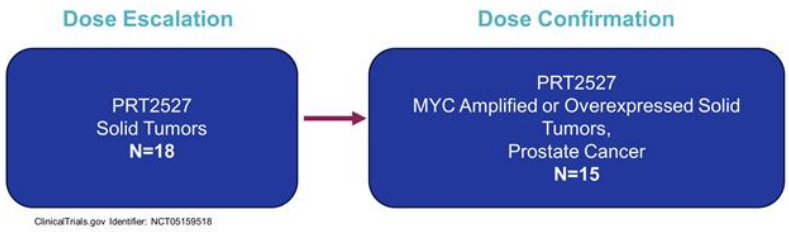
HR+ Hormone receptor positive; HER2- Human epidermal growth factor negative

Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Henry_2527-01_AACR-CT173-poster_23MAR23.pdf

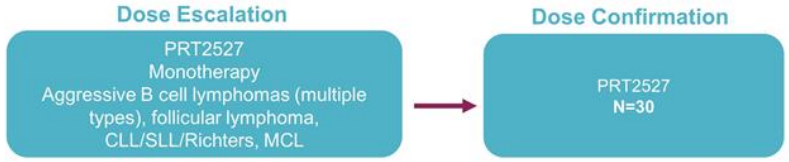
Prelude THERAPEUTICS

CDK9 Inhibitor: PRT2527

Phase 1 Studies in Solid Tumors and Hematologic Malignancies



Solid Tumor data at AACR 2023



Present clinical update in 2H 2023
Confirmation dose in hematological malignancies in Q1 2024

ClinicalTrials.gov Identifier: NCT05665530

Solid Tumors

- Dose dependent increases in drug concentrations 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

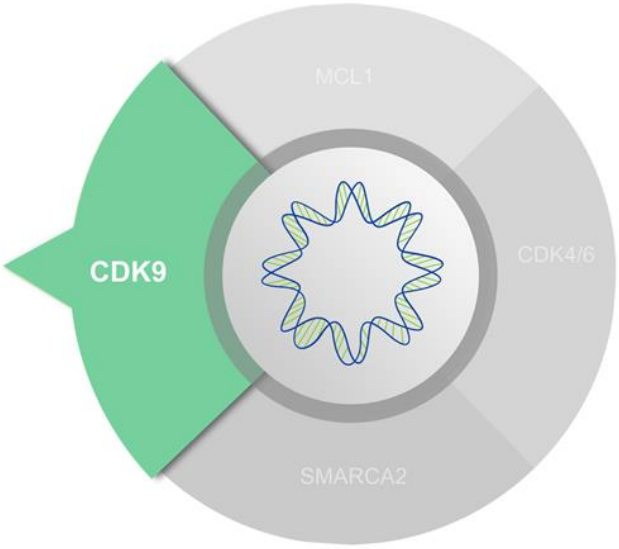
Potential for Improved Safety Based on Best-in-Class Kinome Selectivity

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

- Designed to have an **optimized PK profile** to maximize therapeutic window
- **Highly active** in pre-clinical models at **well-tolerated doses**
- **High levels of inhibition** of CDK9 dependent genes in Phase 1

Market Opportunity

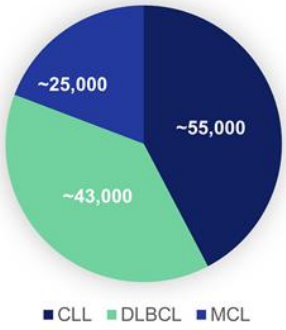
- CDK9 inhibitors in lymphomas, including CLL, Mantle cell and DLBCL may address areas of high unmet need



PRT2527: Broad Potential to Address areas of High Unmet Need

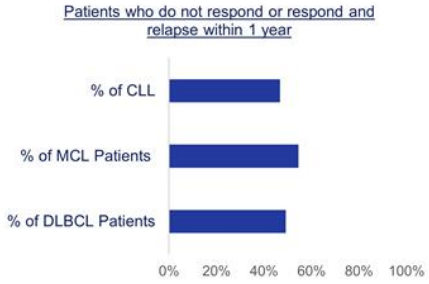
Broad Opportunity:

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



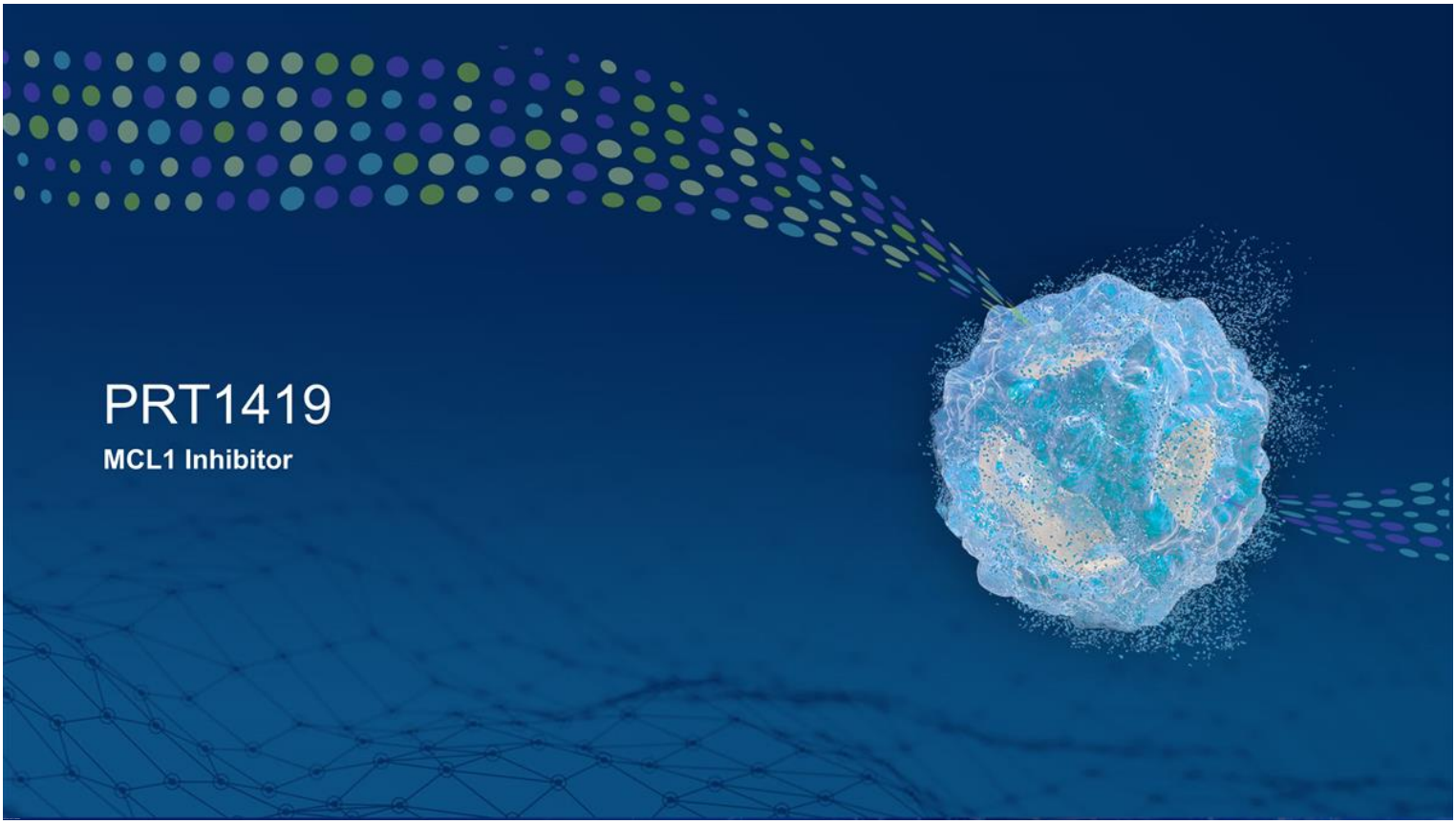
Limited Treatment Options:

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



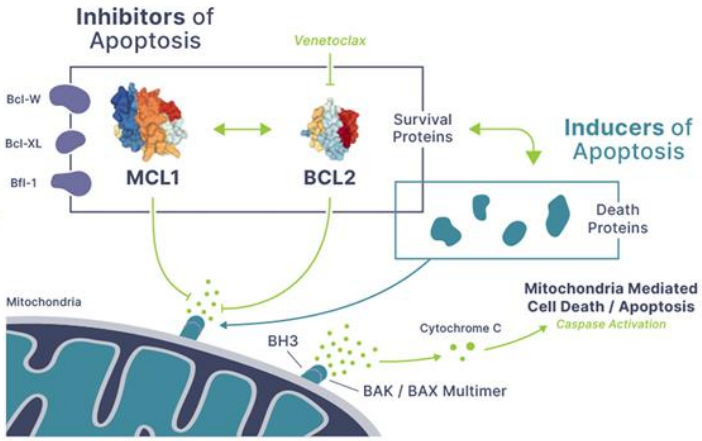
1. SEER Cancer Stat Facts: https://seer.cancer.gov/statfacts/html/clyl.html; 2. Gena Kanas, et. al. Epidemiology of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) in the United States and Western Europe 3. CancerMPact® Treatment Architecture, Non-Hodgkin US, 4. CancerMPact® Treatment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

Prelude THERAPEUTICS


PRT1419
MCL1 Inhibitor

MCL1 inhibition: Targeting Cancer Cell Survival

Mechanism

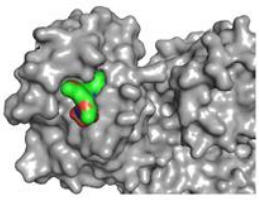


- MCL1 is a member of the **BCL2 family of inhibitors** of apoptosis
- Emerged as a **resistance mechanism** to the BCL2 inhibitor Venetoclax
- Prolonged depletion of MCL1 is undesirable and may be associated with cardiac toxicity
- Optimizing the PK profile of an MCL1 inhibitor may **maximize the therapeutic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

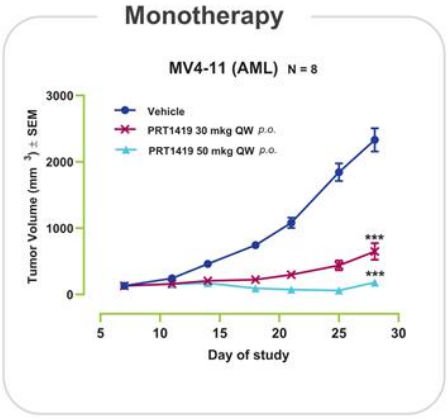
Prelude THERAPEUTICS

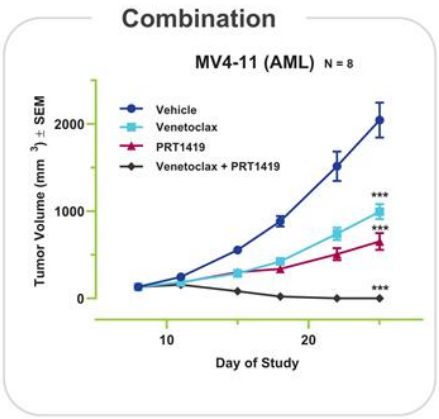
PRT1419 is Potent MCL1 Inhibitor with Demonstrated Preclinical Activity as Monotherapy and in Combination

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

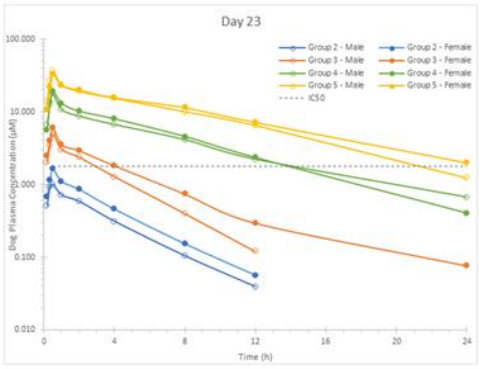




Robust monotherapy activity also seen in models of DLBCL & MM

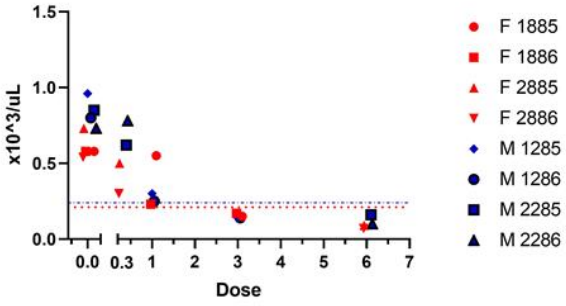
PRT1419: Not Observed to Cause Cardiac Injury in Preclinical Toxicology Studies

Pharmacokinetics



Pharmacodynamics

Absolute Monocytes

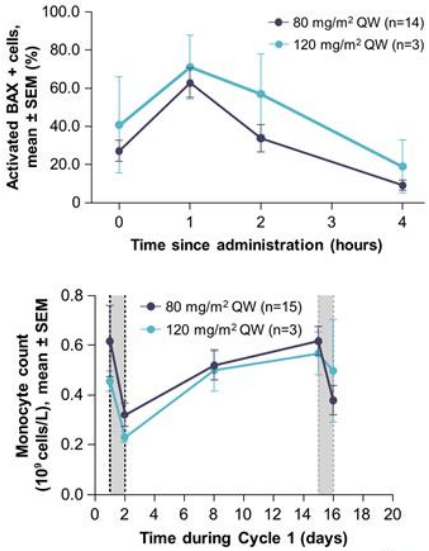


- Doses: 0.3, 1, 3 and 6 mg/m2; once weekly
- Linear increases in exposure
- No troponin elevations observed at any doses, even high dose which covered EC90 for 24h
- No histopathological evidence of cardiac injury

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

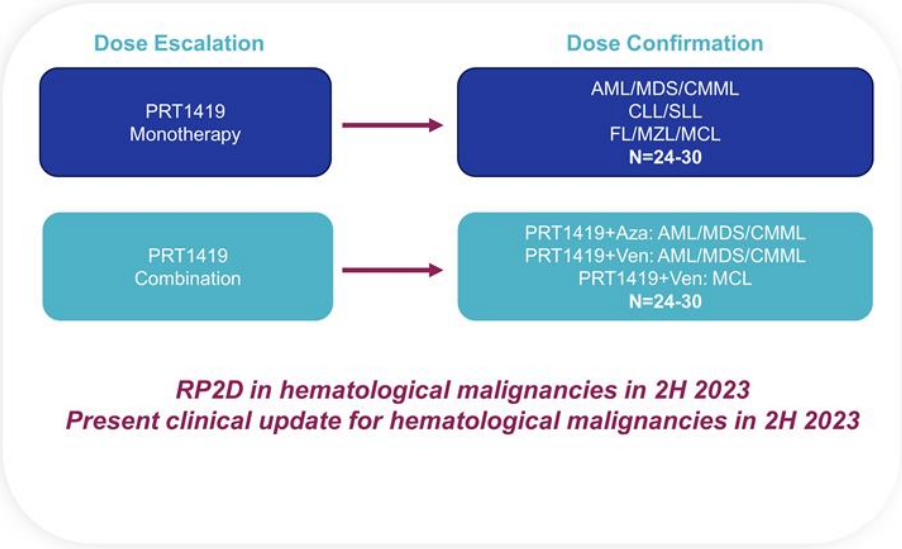


Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Falchook_1419-02_AACR-CT172-poster-23MAR23.pdf

Prelude THERAPEUTICS

MCL1 inhibitor: PRT1419

Phase 1 Study in Hematologic Malignancies



ClinicalTrials.gov Identifier: NCT05107856

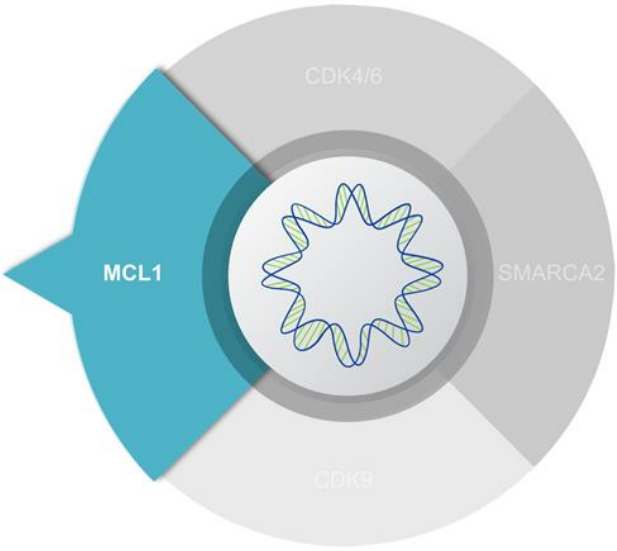
MCL1 Inhibitor Differentiation and Market Opportunity

Designed to have PK Profile to Achieve Desired Target Engagement

- PRT1419 is designed to be 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, CLL and MCL patients need additional treatment options

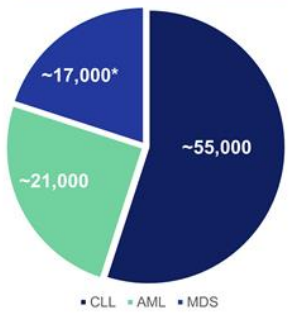


PRT1419: MCL1 Inhibitor Offers Potential Benefit for Patients with Poor Outcomes

Broad Opportunity:

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

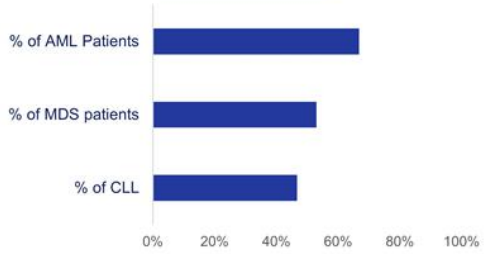
Annual Treated Patients (US Only)



Outcomes for relapsed / refractory patients are poor:

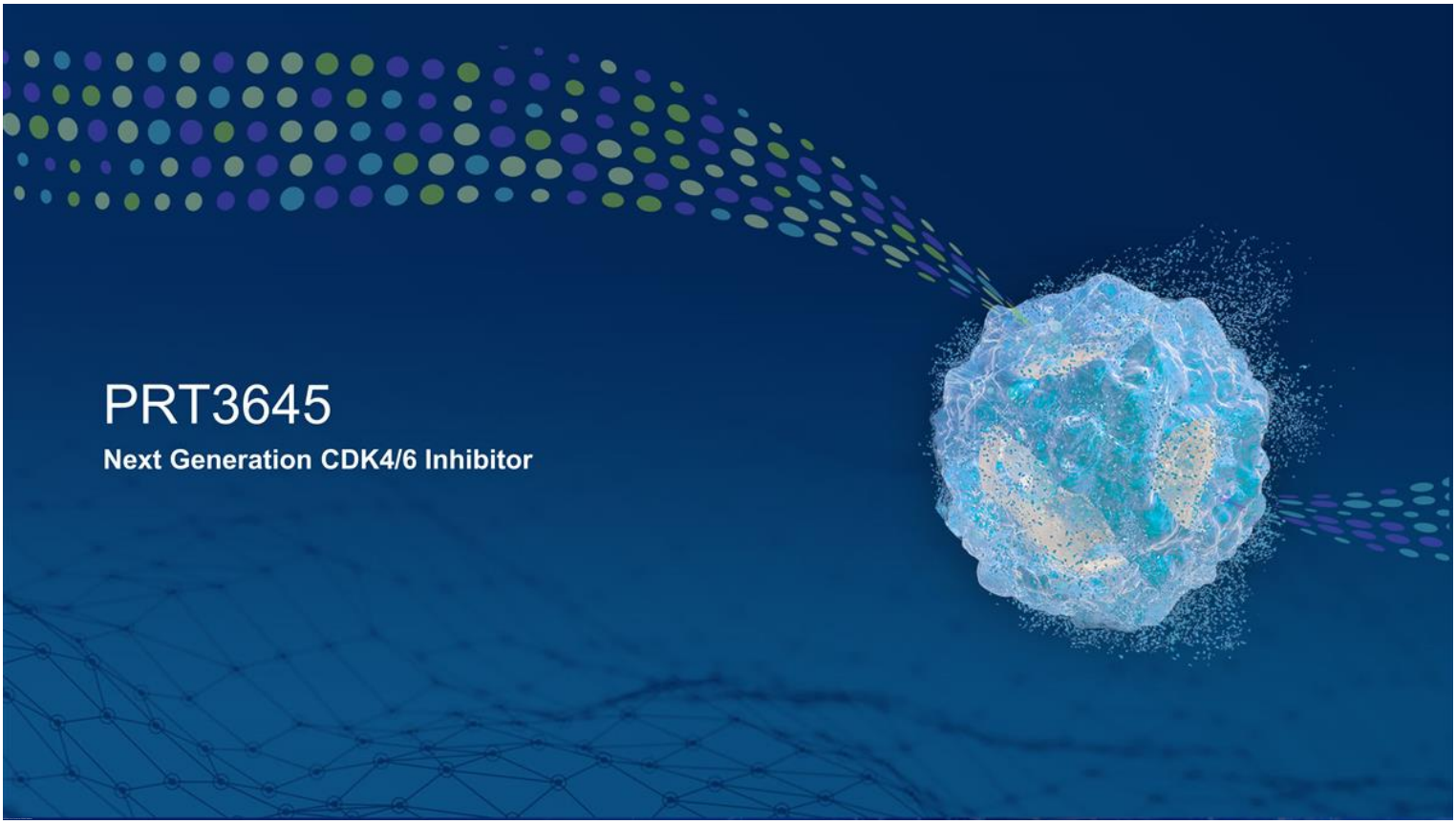
***>50%** of CLL, High Risk MDS and Unfit AML patients are refractory/relapsed within 1 year after second relapse*[2,3,4]

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



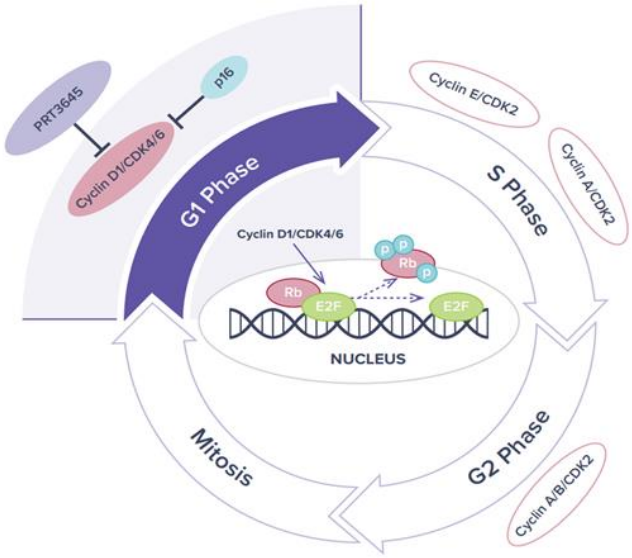
1. SEER Cancer Stat Facts: Chronic Lymphocytic Leukemia. National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/statfacts/html/clyl.html; 2. CancerMPact® Treatment Architecture, Non-Hodgkin US May 2022 3, CancerMPact® Treatment Architecture, Chronic Lymphocytic Leukeimia, US May 2022 4. CancerMPact® Treatment Architecture, MDS, US., August 2022 * MDS number represents annual incident patients, treated patient number may be higher.

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 inhibitors of the RAS and HER2 pathways, including KRAS G12C
- Inability of current inhibitors to **penetrate the blood-brain barrier** (BBB)
- Next generation CDK4/6 inhibitor with **improved tolerability and tissue penetrance** could translate into **activity in areas of unmet need** beyond HR+ breast cancer
- Sequential use of Next Generation CDK4/6 inhibitors in breast cancer may also improve outcomes

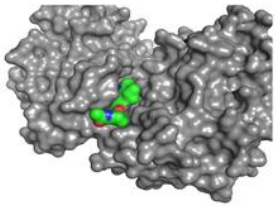
ASCO 2022 reference: A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor–positive (HR+), HER2-negative metastatic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

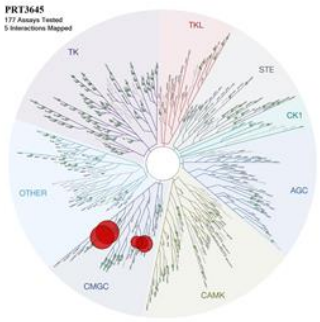
Prelude THERAPEUTICS

PRT3645 – Designed to be a 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

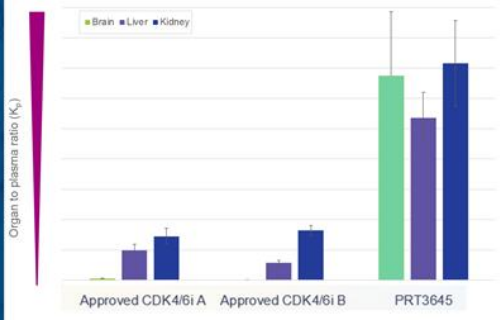
*Internal data; biochemical assay at 1 mM ATP, MCF7 CTG proliferation assay; MCF7 pRB

Prelude THERAPEUTICS

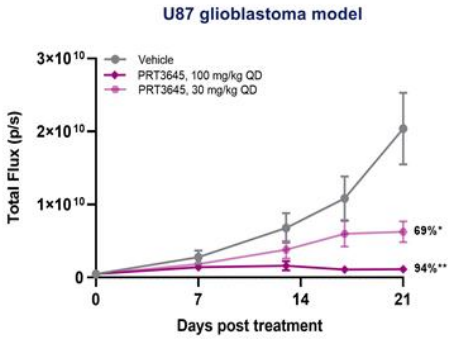
PRT3645: Next Generation CDK4/6 inhibitor

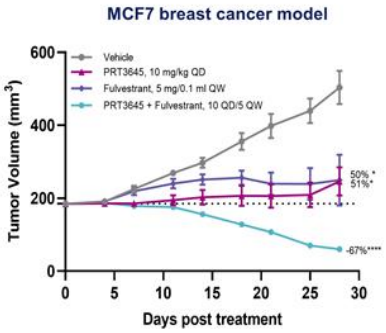
Improved Tissue Penetration and Favorable Activity in Preclinical Models

PRT3645 demonstrated higher brain penetration than approved CDK4/6 inhibitors



PRT3645 showed favorable activity in vivo as monotherapy and in combination

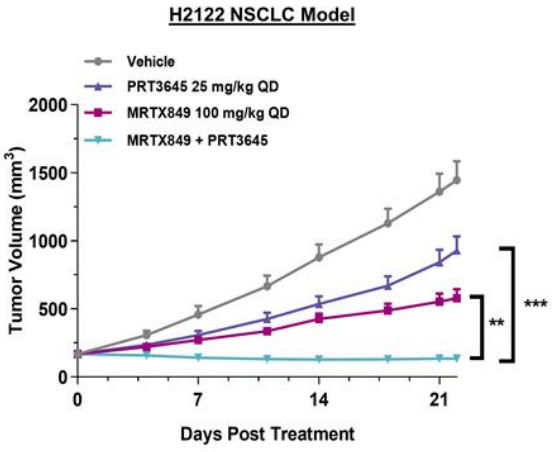


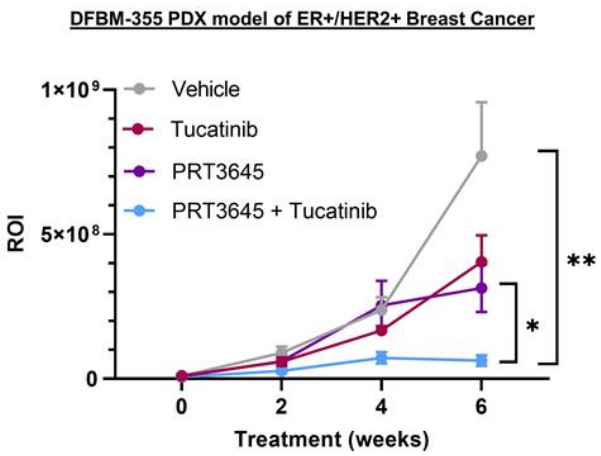


Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Juvekar-CDK4-FINAL-28Mar2022.pdf

Prelude THERAPEUTICS

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





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

Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Zou_CDK46_AACR-2023_Poster-5973_04APR23.pdf

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

Present program update in 2H 2023
Confirmation dose in Q4 2023

- A potentially 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

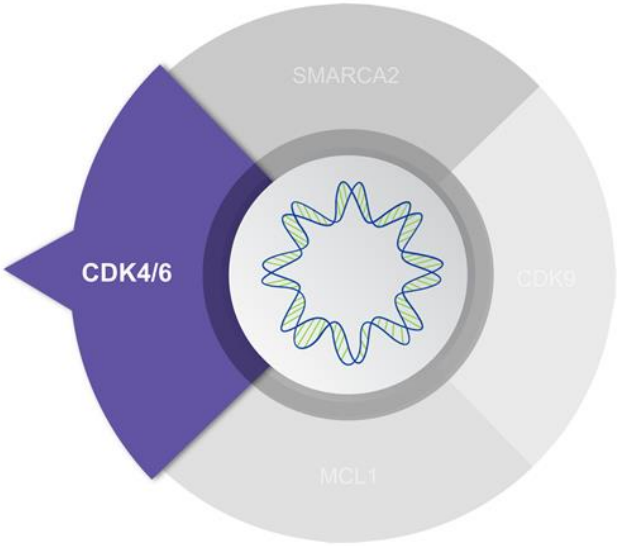
Next Generation CDK4/6 Inhibitor Differentiation and Market Opportunity

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

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

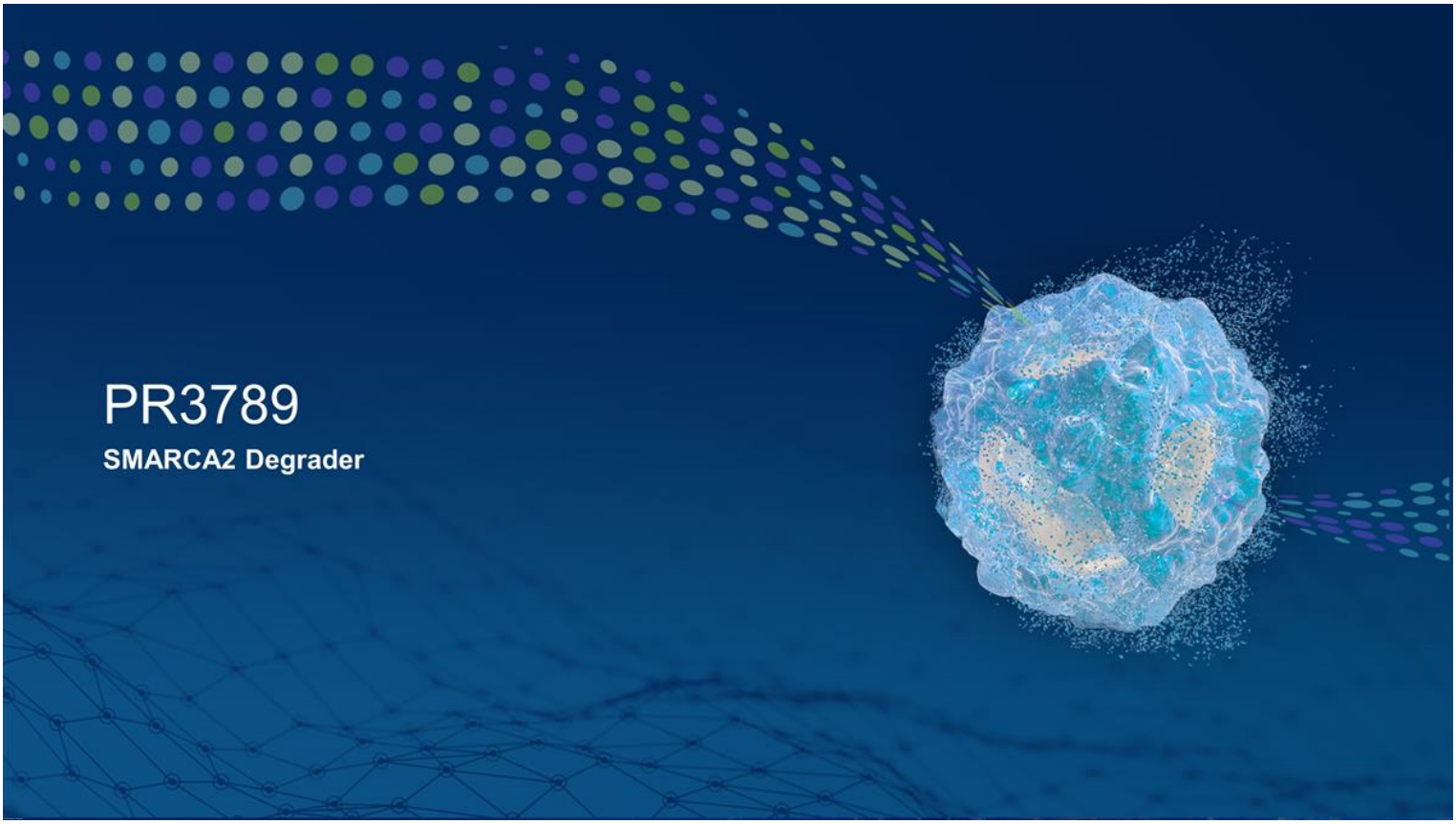
Market Opportunity:

- 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



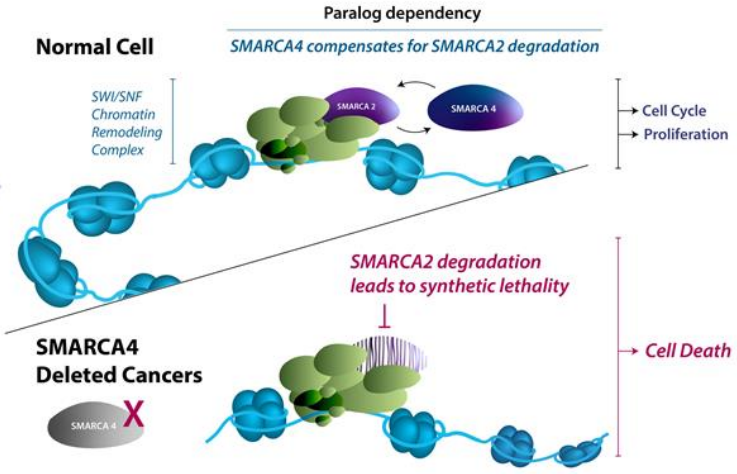
PRT3645 Module 2.6 IND PK written summary; ASCO 2022 reference: A randomized, phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus cyclin-dependent kinase 4/6 inhibition (CDK 4/6i) in patients (pts) with unresectable or hormone receptor–positive (HR+), HER2-negative metastatic breast cancer (MBC): MAINTAIN trial. and See AACR 2023; https://preludetx.com/wp-content/uploads/2023/04/Zou_CDK46_AACR-2023_Poster-5973_04APR23.pdf

Prelude THERAPEUTICS


PR3789
SMARCA2 Degrader

Targeting SMARCA2 (BRM): Leveraging Synthetic Lethality

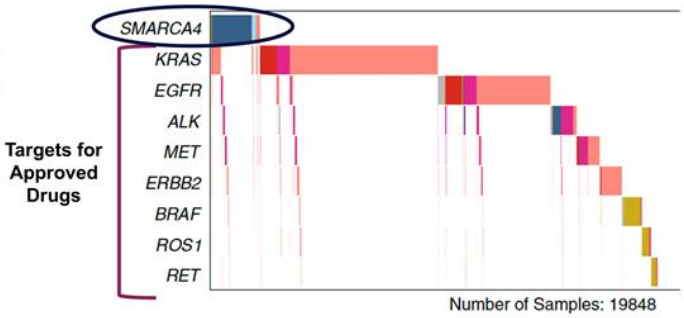
Mechanism



- The chromatin remodeling (SWI/SNF) complex is frequently mutated in cancer making it a **potential therapeutic target**
  - Activation 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 Mutation – A Potentially Novel Biomarker for NSCLC



Fernando et al. Nature Communications 2020

SMARCA4 Prevalence across selected Solid Tumors

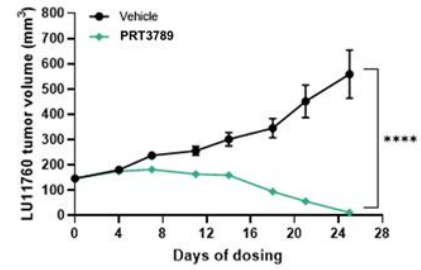
Indication	Any SMARCA4 Mutation[1,2,3]
NSCLC	10.0%
Esophageal	8.0%
Gastric (stomach adeno)	8.3%
Skin (invasive and in situ melanoma)*	21.0%
Endometrial (uterine corpus)	13.3%
Squamous cell lung	7.7%
Urinary (bladder)	9.0%
Colorectal	6.0%
Pancreatic	2.9%
Melanoma (invasive)	8.7%

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

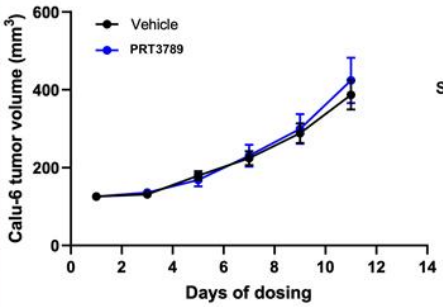
Prelude THERAPEUTICS

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

Robust Tumor Growth Inhibition of SMARCA4 mutated but not WT Xenograft

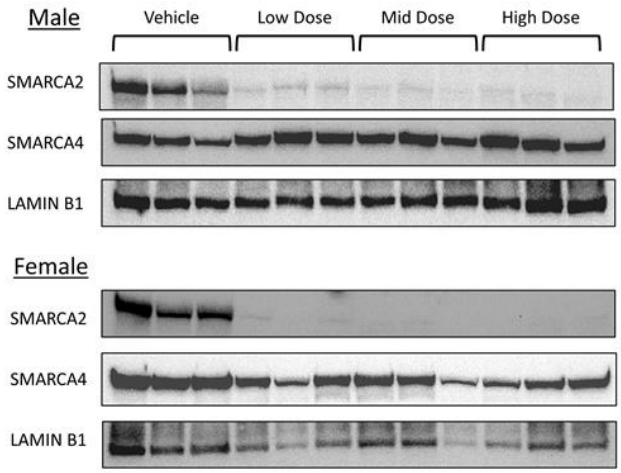


SMARCA4 mutant



SMARCA4 WT

Significant Degradation of SMARCA2 Protein but not SMARCA4 in Preclinical Models



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

Prelude THERAPEUTICS

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

Expected to provide program update 2H 2023
Confirmation dose in 1H 2024

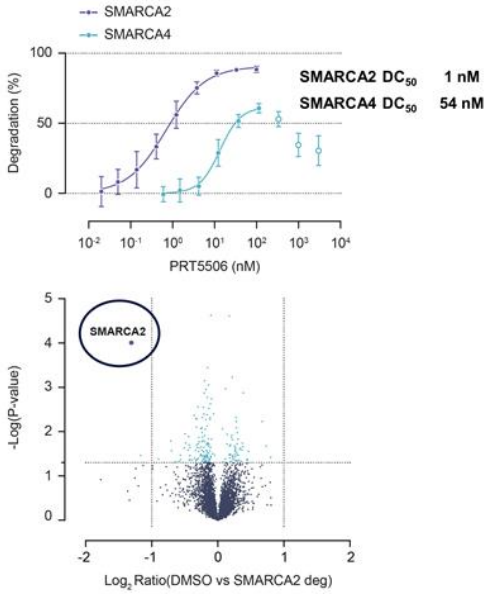
- SMARCA2 inhibition has the greatest potential in patients with SMARCA4 deficient cancers, including approximately 10% of all non-small cell lung cancers
- SMARCA2 degradation to be evaluated in Phase 1
- Study population: advanced, recurrent, or metastatic disease, with loss of SMARCA4 due to truncating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

ClinicalTrials.gov Identifier: NCT05639751

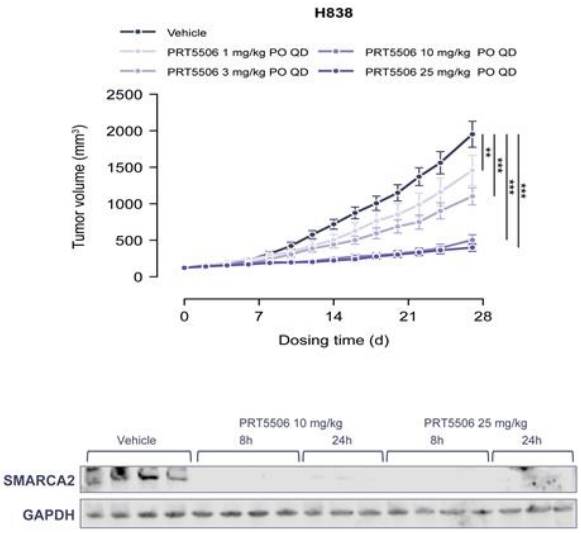
Selective Orally Bioavailable SMARCA2 Degrader Program

PRT5506 - Preclinical Lead to Demonstrate Proof-of-Concept

Potent and Highly Selective SMARCA2 Degradation



Robust Tumor Growth Inhibition of SMARCA4 Mutated Xenograft with Oral Dosing



Presented at AACR 2023; https://preludetx.com/wp-content/uploads/2023/05/Ito_SMARCA2_AACR-2023_Poster_6277_01MAY23_CORRECTION.pdf

Prelude THERAPEUTICS

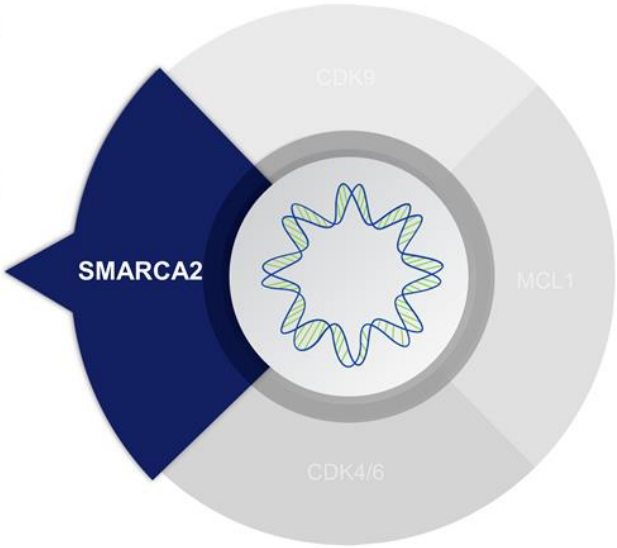
SMARCA2 Differentiation and Market Opportunity

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

- PRT3789 is **a potential first-in-class** SMARCA2 Degrader
- **Potentially potent and selective** SMARCA2 targeted protein degrader approach
- We believe SMARCA2 selectivity may provide a **favorable toxicity profile**
- Observed **favorable efficacy** in SMARCA4 mutant preclinical models, we believe provides path for **patient selection strategy** in the clinic

***Market Opportunity**:*

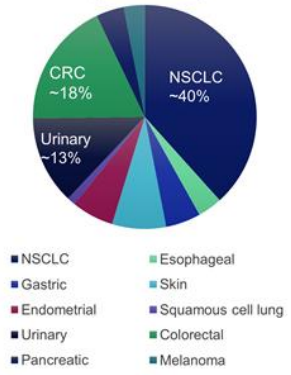
- 70,000 patients with SMARCA4 mutation in the US/EU5



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.

Prelude THERAPEUTICS

Prelude Therapeutics: Key Takeaways

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 demonstrated the potential for **class-leading opportunities**

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

We expect our cash, cash equivalents and marketable securities as of June 30, 2023 will enable us to fund operating expenses and capital expenditure requirements into 2026

Prelude THERAPEUTICS

Experienced Management Team: Proven Track Records

Kris Vaddi, PhD

Founder & Chief Executive Officer

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

Jane Huang M.D.

President and Chief Medical Officer

Brukinsa (zanubrutinib)
CALQUENCE (acalabrutinib)
VENCLEXTA (venetoclax tablets)
GAZYVA (obinutuzumab)
Kadcyla (ado-trastuzumab emtansine)
AVASTIN (bevacizumab)

Peggy Scherle, PhD

Chief Scientific Officer

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

Andrew Combs, PhD

Executive Vice President and Head of Chemistry

Jakafi (ruxolitinib tablets)
olumiant (baricitinib tablets)

Laurent Chardonnet, MBA

Chief Financial Officer

Incyte
axcella
sanofi

Bryant Lim, J.D.

Chief Legal Officer and Corporate Secretary

MERCK
ViroPharma Incorporated
Incyte
idera