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): October 24, 2024

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.)**

175 Innovation Boulevard **Wilmington, Delaware**	**19805**
(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 8.01 Other events

On October 24, 2024, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing updated interim clinical data from its ongoing Phase 1 trial of PRT3789 and preclinical data from its precision degrader antibody conjugate program deploying a novel SMARCA2/4 dual degrader payload. The press release was issued simultaneously with the previously announced plenary session of the 36th EORTC-NCI-AACR Symposium taking place in Barcelona, Spain. A copy of the press release is attached as Exhibit 99.1 to this report.

In connection with the presentation of the clinical data, the Company has updated its corporate presentation. A copy of the updated corporate presentation is attached as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press Release
99.2	Corporate 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: October 24, 2024

By: /s/ Bryant Lim
Bryant Lim
Chief Legal Officer, Corporate Secretary, and Interim Chief Financial Officer

Exhibit 99.1

Prelude Therapeutics Presents New Data from SMARCA Degrader Portfolio at the 36th EORTC-NCI-AACR Symposium

- *Interim data from ongoing trial of PRT3789 showed additional clinical activity at higher doses in patients with non-small cell lung cancer (NSCLC)*
- *First safety data presented from combination study of PRT3789 and docetaxel demonstrated an acceptable safety profile*
- *First preclinical proof-of-concept data presented from precision antibody drug conjugate program deploying a novel SMARCA2/4 dual degrader payload*

WILMINGTON, Del., Oct. 24, 2024 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD) ("Prelude" or the "Company"), a clinical-stage precision oncology company, today announced the presentation of additional data from its ongoing Phase 1 open-label, dose-escalation trial of PRT3789, a first-in-class, highly selective SMARCA2 degrader designed to treat cancer patients with a SMARCA4 mutation. The data were presented at a plenary session of the 36th Annual EORTC-NCI-AACR Symposium in Barcelona, Spain.

The study investigators reported, as of September 23, 2024 (the Cutoff Date), additional follow up data on 65 patients that were enrolled, treated, and safety evaluable. PRT3789 was generally well-tolerated through 8 dosing cohorts. The majority of adverse events reported by investigators have been mild to moderate.

Overall, of the 26 advanced, heavily pre-treated NSCLC or esophageal patients with Class 1 (loss of function) mutations evaluable for efficacy, now with additional follow up, RECIST partial responses (PRs) were confirmed in 4 patients, including 2 of 9 NSCLC patients with confirmed PRs at doses of 283 mg or higher. As anticipated, higher doses are resulting in deeper and more sustained SMARCA2 degradation in PBMCs. Additional patients demonstrated clinical benefit as measured by prolonged stable disease (SD) including one patient on treatment for more than a year.

"We, along with our study investigators, are encouraged by the promising activity shown to date by PRT3789 in this novel first-in-class mechanism for patients who have limited treatment options," stated Jane Huang, M.D., President and Chief Medical Officer of Prelude. "We look forward to further characterizing and understanding the full potential of PRT3789 through ongoing monotherapy dose escalation and in combination studies with both docetaxel and pembrolizumab."

PRT3789 Interim Phase 1 Results
PRT3789 is currently being evaluated in an ongoing dose-escalation Phase 1 trial in heavily pre-treated patients with advanced solid tumors harboring any SMARCA4 mutation who have relapsed/refractory disease. Sixty-five patients with advanced cancer were treated once weekly via intravenous infusion at eight dose levels (24 mg, 48 mg, 80 mg, 120 mg, 160 mg, 212 mg, 283 mg, 376 mg), and follow up data reported through to September 23, 2024. The median age of these patients was 62 and the median number of prior treatments was 3 (ranging from 1-10). 34 patients (52.3%) presented with a Class 1 (loss of function) SMARCA4 mutation, while 24 patients (36.9%) presented with a Class 2 (missense, VUS) SMARCA4 mutation and 7 (10.8%) had a loss of SMARCA4 protein.

Initial Safety Data
PRT3789 was generally well-tolerated. Treatment emergent adverse events of any grade observed to date consisted of nausea (26.2%), fatigue (21.5%), anemia (20.0%), decreased appetite (20.0%), abdominal pain (18.5%), and constipation (18.5%). No dose limiting toxicities were observed and no study drug-related serious adverse events were reported.

Pharmacokinetic (PK) and Pharmacodynamic (PD) Data
Preliminary PK data was available from 24 mg to 376 mg dose cohorts. A general trend of increases in exposure (Cmax, AUC) with dose was observed. Mean concentrations were observed above SMARCA2 plasma DC_{50} (21 nM) for approximately 8 hours at the 376 mg dose. No accumulation was observed with repeat dose administration, consistent with the half-life and once-weekly administration. PD effect (as measured by SMARCA2 protein levels in peripheral blood mononuclear cells) observed was more prolonged than PK half-life. Higher dose levels, above 212 mg, demonstrated a deeper, more consistent, and more prolonged PD effect. SMARCA2 degradation was observed in both peripheral blood mononuclear cells (PBMC) and in available tumor tissue as shown through biopsy.

Analysis of Initial Clinical Activity
Of the 26 advanced NSCLC or esophageal patients with Class 1 (loss of function) mutations who were evaluable for efficacy, RECIST confirmed partial responses (PRs) were observed in 4 patients (2 esophageal, 2 NSCLC), including 2 of 9 NSCLC patients with confirmed PRs at doses of 283 mg or higher. Tumor shrinkage was observed in patients with both Class 1 and Class 2 SMARCA4 mutations. Additional patients on-study demonstrated clinical benefit as measured by prolonged SD, including one advanced NSCLC patient who remains stable and on study having been treated for more than 1 year.

Initial observations of safety from evaluable patients in the PRT3789 plus docetaxel combination dose escalation arm of the trial were also presented. To date, PRT3789 in combination with docetaxel demonstrated an acceptable safety profile, with no dose limiting toxicities or study drug serious adverse events reported.

Additional SMARCA Degrader Presentations

The Company also provided two poster presentations at the conference.

The Selective SMARCA2 Degrader, PRT3789, Counteracts the Protective Cellular Stress Response to Chemotherapy and Enhances the Efficacy of Standard of Care Chemotherapeutic Agents in SMARCA4 Mutant NSCLC Models

The combination of PRT3789 with standard of care NSCLC chemotherapy agents significantly enhances anti-tumor activity in preclinical models of SMARCA4-mutated NSCLC. Downregulation of dominant gene pathways by PRT3789, specifically counters docetaxel-induced upregulation of the E2F and G2/M pathways, resulting in a more comprehensive cell cycle blockade and increased apoptosis in SMARCA4-mutated cells. This synergistic activity was observed with both Class I (loss of function) mutations and Class II (missense) mutations.

Discovery of First-in-Class Precision Antibody Drug Conjugates with a Potent SMARCA 2/4 Dual Degrader Payloads that Safely Achieve Maximal and Tumor Specific Degradation and Efficacy in Mouse Models

PRP0004 is a potent SMARCA2/4 dual degrader that robustly inhibits cancer cell growth and induces cell death. Conjugation of PRP0004 to clinically-validated antibodies yielded novel degrader antibody conjugates (DACs), which demonstrated potent and antigen-selective internalization and SMARCA2 and SMARCA4 degradation in cell lines derived from multiple cancers. Prostate cancer cell lines were among the most sensitive to the PRP0004 degrader payload. PRP0004 downregulated multiple drivers of prostate cancer cell growth and survival and resulted in cell death, rationalizing the use of PSMA-targeting antibodies for initial proof-of-concept studies in preclinical models.

As expected, dosing with PRP0004 on its own was highly efficacious in prostate cancer xenografts but displayed a narrow therapeutic window. However, when delivered as a payload on anti-PSMA antibodies, the anti-PSMA SMARCA2/4 DACs demonstrate robust SMARCA2 and SMARCA4 degradation and antigen-dependent efficacy in xenograft models while being well-tolerated. These data highlight the potential of this first-in-class precision ADC approach utilizing a highly potent SMARCA2/4 dual degrader payload to achieve maximal target degradation in tumors while sparing healthy tissues. This strategy has the potential to significantly expand the reach of Prelude's novel SMARCA degraders to treating patients without SMARCA4 mutations.

"Preclinical data presented today with our novel approach to develop degrader antibody conjugates by using potent dual degraders of SMARCA2 and 4 as payloads offers first proof-of-concept of effectively and safely targeting an important mechanism to treat cancers beyond those with SMARCA4 mutations" stated Peggy Scherle, Ph.D., Chief Scientific Officer of Prelude.

All of the above noted presentations can be found at Publications - Prelude Therapeutics (preludetx.com).

About PRT3789-01
PRT3789 is a first-in-class, potent and highly selective SMARCA2 degrader, in Phase 1 clinical development in SMARCA4-mutated patients. Enrollment remains on track, and the Company expects to conclude monotherapy dose escalation by year end 2024 and identify the biologically

active dose to advance for future registrational trials. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations at higher dose levels is ongoing. The objective is to assess clinical activity in a more homogeneous group of patients with high unmet need to support planned discussions with regulatory agencies. A maximum tolerated dose has not yet been identified. Dose escalation continues, now in the 10th dosing cohort (665 mg IV once weekly).

About Prelude Therapeutics

Prelude Therapeutics is a leading precision oncology company developing innovative medicines in areas of high unmet need for cancer patients. Our pipeline is comprised of several novel drug candidates including first-in-class, highly selective IV and oral SMARCA2 degraders, and a potentially best-in-class CDK9 inhibitor. We are also leveraging our expertise in targeted protein degradation to discover, develop and commercialize next generation degrader antibody conjugates (Precision ADCs) with partners. We are on a mission to extend the promise of precision medicine to every cancer patient in need. For more information, visit preludetx.com.

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 for Prelude's product candidates, the potential safety, efficacy, benefits and addressable market for Prelude's product candidates, and clinical trial results for Prelude's product candidates. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. The words "believes," "anticipates," "estimates," "plans," "expects," "intends," "may," "could," "should," "potential," "likely," "projects," "continue," "will," "schedule," and "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements are predictions based on the Company's current expectations and projections about future events and various assumptions. 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 Prelude's Annual Report on Form 10-K for the year ended December 31, 2023, its Quarterly Reports on Form 10-Q and other documents that 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, except as may be required by law.

Investor Contact:
Robert A. Doody Jr.
Senior Vice President, Investor Relations
484.639.7235
rdoody@preludetx.com

Exhibit 99.2

Corporate Presentation

October 2024

Forward Looking Statements

This presentation contains “forward-looking” statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to, anticipated discovery, preclinical and clinical development activities for Prelude’s product candidates, the potential safety, efficacy, benefits and addressable market for Prelude’s product candidates, the expected timeline for clinical trial results for Prelude’s product candidates including its SMARCA2 degrader molecules.

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).

This presentation shall not constitute an offer to sell or the solicitation of an offer to buy, nor shall there be any sale of these securities in any state or other jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or other jurisdiction.

These forward-looking statements are based on the beliefs of our management as well as assumptions made by and information currently available to us. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. If such assumptions do not fully materialize or prove incorrect, the events or circumstances referred to in the forward-looking statements may not occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations, except as required by law. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. Additional risks and uncertainties that could affect our business are included under the caption “Risk Factors” in our filings with the Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2023.

Prelude THERAPEUTICS

Prelude THERAPEUTICS

We are on a mission to extend the promise of precision medicine to every cancer patient in need

Strive for first- or best-in-class and anchor to patient unmet need

Select the best modality to precisely target oncogenic mechanisms

Draw on decades of experience and proven leadership to drive innovation

Experienced Leadership Team With Proven Track Records in Precision Oncology

Kris Vaddi, PhD

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 80mg capsules)
CALQUENCE (acalabrutinib 100 mg capsules)
VENCLEXTA (venetoclax tablets 10mg, 50mg, 100mg)
GAZYVA (obinutuzumab injection 1000mg/40mL)
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

Chief Chemistry Officer

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

Sean Brusky, MBA

Chief Business Officer

Genentech
A Member of the Roche Group
VERTEX
BAIN & COMPANY
Pardes Biosciences

Bryant Lim, J.D.

Chief Legal Officer, Corporate Secretary and Interim CFO

MERCK
ViroPharma Incorporated
Incyte
idera

Prelude THERAPEUTICS

Prelude's Evolution

2016 – 2022	2022 – 2025	2025+
Establish Leading Precision Oncology Discovery Engine	**Expand Development Capabilities, *Strategic Focus on SMARCA***	**Advance to Registrational Trials, Demonstrate Value**
• Assembled team to create a highly productive discovery engine • Delivered initial wave of first- or potentially best-in-class clinical development candidates: – PRMT5i, MCL1i, CDK9i, CDK4/6i, SMARCA2 degraders	• Advancing clinical programs including IV SMARCA2 degrader (PRT3789), oral SMARCA2 degrader (PRT7732) and CDK9 inhibitor (PRT2527) towards PoC • Developing SMARCA as 'Pipeline in Program' with IV, Oral and 'Precision ADC' Approaches	• Continue to grow R&D team while adding key capabilities for future growth • Expand global clinical development footprint and capabilities • Advance lead clinical development candidates to registrational trials
Strategic Priorities		
• **~1 new IND every 12-18 months** • **Successfully advance programs into early clinical development**	• **Continue to build SMARCA leadership** • **Generate proof-of-concept data** • **Prepare for global registrational trials**	• **Advance SMARCA "Pipeline in a Program"** • **Explore collaborations to accelerate trials and global capabilities**

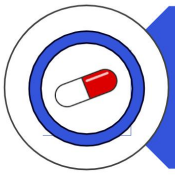
Prelude's Precision Medicine Pipeline & Discovery Engine

PROGRAM	POTENTIAL INDICATIONS	DISCOVERY / PHASE 1 / PHASE 2/3	UPCOMING MILESTONES
Lead SMARCA2 Degrader (IV)	SMARCA4-mutated NSCLC & other cancers	*PRT3789*	**Dose Confirmation by YE2024; Phase 2 Pembrolizumab Combo Trial Start in Q4 2024**
Oral SMARCA2 Degrader	SMARCA4-mutated NSCLC & other cancers	*PRT7732*	**Phase I Trial Initiated**
SMARCA2/4 Precision ADCs*	Broad range of cancers (heme & solid tumors)		**First Pre-clinical PoC Data Presented at ENA; Additional Data in 2025**
Next-Gen CDK9 Selective Inhibitor	Myeloid and Lymphoid malignancies	*PRT2527*	**Interim Phase 1 Data Anticipated in Q4 2024**
Discovery Engine	Hard-to-treat cancers, "undruggable" targets, high unmet need		**Deliver a First- or Best-in-Class New Program Every 12-18 Months**
Precision ADCs*	Broad range of cancers (heme & solid tumors)		**Advance Additional Novel Payload-Antibody Pairings**

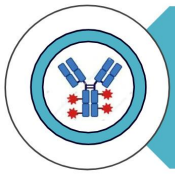
* Precision ADCs are the focus of our strategic collaboration with AbCellera

Developing an Industry Leading Portfolio of SMARCA-Targeted Precision Medicines

Lead SMARCA2 Degrader (PRT3789)



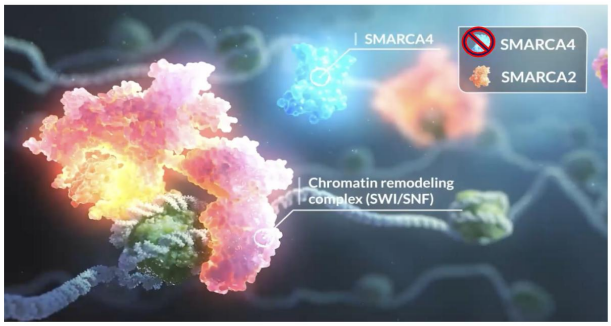
Oral SMARCA2 Degrader (PRT7732)



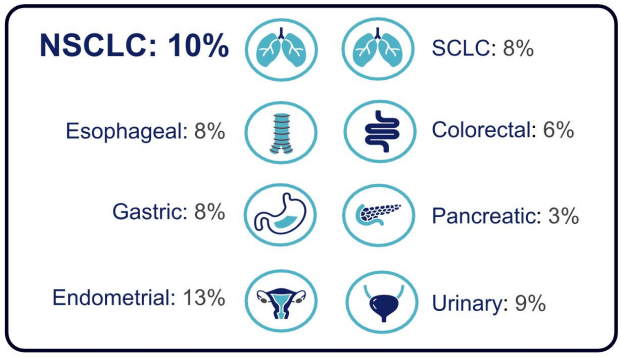
Precision ADCs with SMARCA2/4 Degrader Payload

Targeting SMARCA4-*mutated* Cancer By Selectively Degrading SMARCA2

Mutations in the chromatin remodeling complex drive cancer growth and resistance



SMARCA4 (BRG1) mutations occur in approximately 5% of all cancers



Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine Dataset

Cancer cells with deleterious SMARCA4 mutations become highly dependent on SMARCA2 for survival

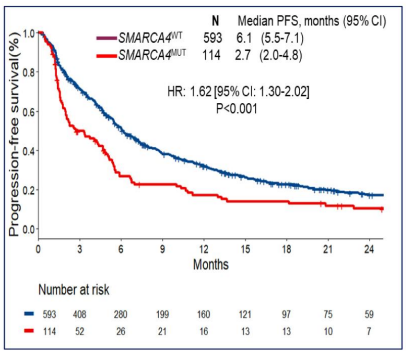
Selectively degrading SMARCA2 induces "synthetic lethality" in SMARCA4-*deficient* cancers

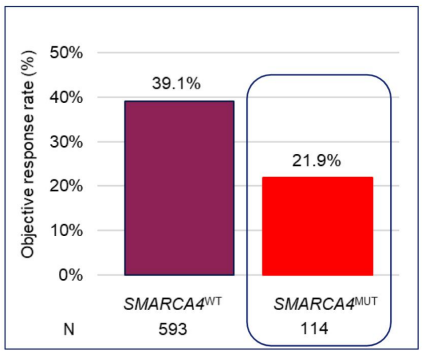
Patients with SMARCA4 mutations are not typically eligible for other targeted therapies

Currently treated with standard of care chemotherapy or chemo-immunotherapy

Outcomes for Patients with SMARCA4-*mutated* NSCLC are Poor with Current Standard of Care

Patients treated with first-line chemoimmunotherapy





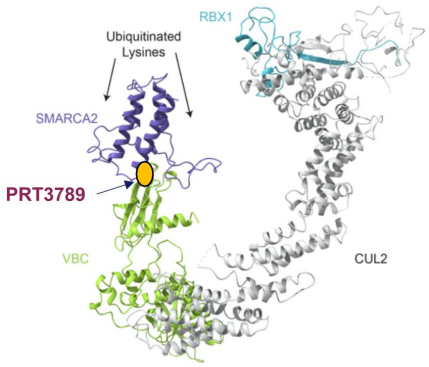
Median progression free survival for <u>first-line</u> SMARCA4-mutated NSCLC treated with chemoimmunotherapy is 2.7 months and response rates approximately 22%

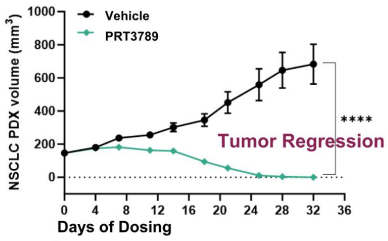
There is even greater unmet need in <u>second-line and beyond</u>

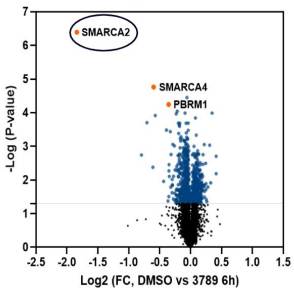
Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. PMID: 36775193.

PRT3789: A Highly Potent SMARCA2 Degrader with >1000-fold Selectivity Over SMARCA4

Preclinical Assay	PRT3789
SMARCA2 Degradation (nM)	0.73
Selectivity: Cell Proliferation (SMARCA4 / SMARCA2)	>1000 fold







Hulse et al. *Cancer Res*. (2022); 82 (12_Suppl) :3263.
AACR 2022 Poster (http://www.preludetx.com/science/publications)

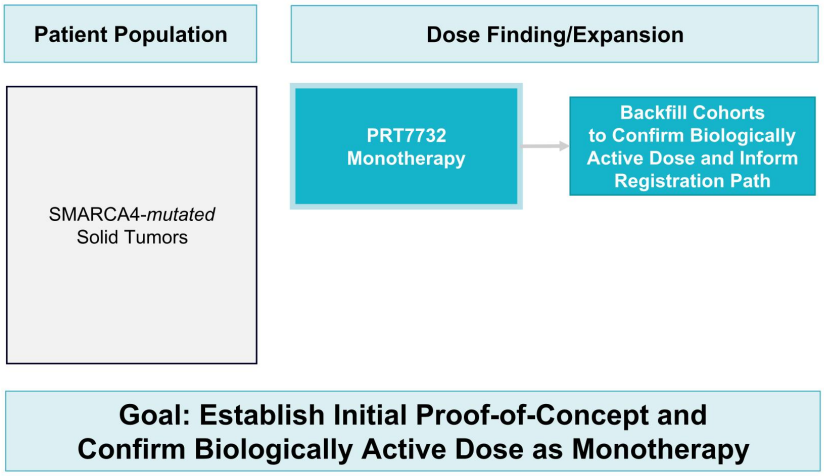
Sub-nanomolar SMARCA2 degradation potency in cell lines

Anti-tumor activity, including regressions, in SMARCA4 mutant models *in vivo*

Highly selective for SMARCA2 vs SMARCA4 (>1000 fold) and selective across the proteome

PRT7732: First-in-Class, Highly Selective Oral SMARCA2 Degrader – *Phase I Trial Initiated*

Assay	PRT7732
SMARCA2 Degradation (nM)	0.98
Selectivity: Degradation (SMARCA4 / SMARCA2)	>3000 fold
Selectivity: Cell Proliferation (SMARCA4 / SMARCA2)	>1000 fold



Goal: Establish Initial Proof-of-Concept and Confirm Biologically Active Dose as Monotherapy

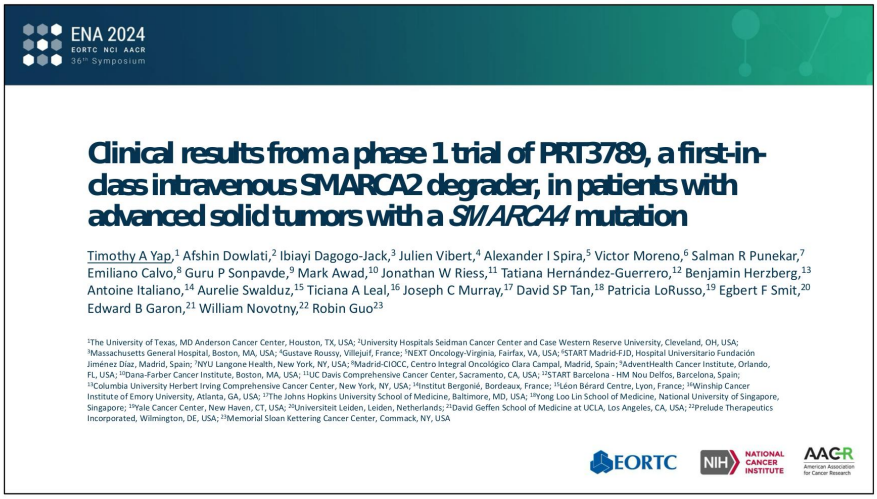
ClinicalTrials.gov Identifier: NCT06560645

Sub-nanomolar SMARCA2 degradation potency in cell lines

Very high selectivity for SMARCA2 over SMARCA4

Good oral bioavailability observed across species supports projected once-daily human dose

Interim Update from PRT3789-01 Presented at Plenary Session of the 2024 ENA Symposium



ENA 2024
EORTC NCI AACR
36th Symposium

Clinical results from a phase 1 trial of PRT3789, a first-in-class intravenous SMARCA2 degrader, in patients with advanced solid tumors with a *SMARCA4* mutation

Timothy A Yap,[1] Afshin Dowlati,[2] Ibiayi Dagogo-Jack,[3] Julien Vibert,[4] Alexander I Spira,[5] Victor Moreno,[6] Salman R Punekar,[7] Emiliano Calvo,[8] Guru P Sonpavde,[9] Mark Awad,[10] Jonathan W Riess,[11] Tatiana Hernández-Guerrero,[12] Benjamin Herzberg,[13] Antoine Italiano,[14] Aurelie Swalduz,[15] Ticiana A Leal,[16] Joseph C Murray,[17] David SP Tan,[18] Patricia LoRusso,[19] Egbert F Smit,[20] Edward B Garon,[21] William Novotny,[22] Robin Guo[23]

[1]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [2]University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [3]Massachusetts General Hospital, Boston, MA, USA; [4]Gustave Roussy, Villejuif, France; [5]NEXT Oncology-Virginia, Fairfax, VA, USA; [6]START Madrid-FJD, Hospital Universitario Fundación Jiménez Diaz, Madrid, Spain; [7]NYU Langone Health, New York, NY, USA; [8]Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [9]AdventHealth Cancer Institute, Orlando, FL, USA; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [12]START Barcelona - HM Nou Delfos, Barcelona, Spain; [13]Columbia University Herbert Irving Comprehensive Cancer Center, New York, NY, USA; [14]Institut Bergonié, Bordeaux, France; [15]Léon Bérard Centre, Lyon, France; [16]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [17]The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [18]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [19]Yale Cancer Center, New Haven, CT, USA; [20]Universiteit Leiden, Leiden, Netherlands; [21]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [22]Prelude Therapeutics Incorporated, Wilmington, DE, USA; [23]Memorial Sloan Kettering Cancer Center, Commack, NY, USA

EORTC NIH NATIONAL CANCER INSTITUTE AACR American Association for Cancer Research

2024 Triple Meeting Update

Additional clinical activity observed in NSCLC patients with Class I mutations treated with PRT3789 monotherapy at doses ≥ 283 mg

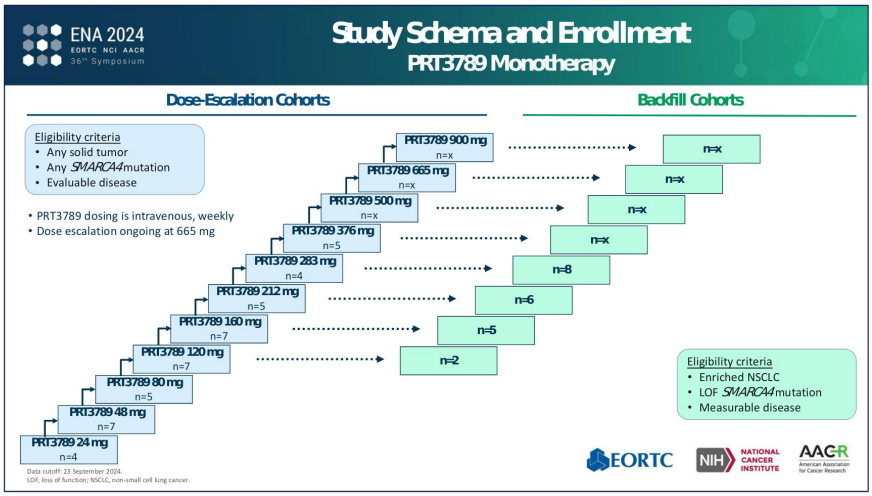
First look at safety and PK data from PRT3789 + docetaxel in combination demonstrate acceptable safety profile, with no dose limiting toxicities to date

ClinicalTrials.gov Identifier: NCT05639751

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: Study Schema and Enrollment



2024 Triple Meeting Update

Study is enrolling patients with evaluable disease, any solid tumors, and any type of SMARCA4 mutation

Dose escalation is on-going, now at cohort 10 (665 mg)

Data presented includes additional follow-up on 65 patients treated in escalating doses from 24 to 376 mg, including backfills enriched for NSCLC with Class 1 (LOF) mutations

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: Demographics and Disease Characteristics, PRT3789 Monotherapy

Characteristics	Patients (N=65)
Age (years)	
Median	62
Sex, n (%)	
Male	36 (55.5)
Female	29 (44.6)
Prior lines of systemic anti-cancer therapy, n	
Median (min, max)	3 (1, 10)
Tumor type, n (%)	
Non-small cell lung cancer	30 (46.2)
Pancreatic cancer	6 (9.2)
Breast cancer	4 (6.2)
Gastric cancer/small intestine cancer	3 (4.6)
Thoracic undifferentiated	3 (4.6)
Cholangiocarcinoma	2 (3.1)
Colorectal cancer	2 (3.1)
Esophageal cancer	2 (3.1)
Other	13 (20.0)
Type of SMARCA4 mutation, n (%)	
Class 1 (loss of function)	34 (52.3)
Class 2 (missense, VUS)	24 (36.9)
Loss of SMARCA4 protein (BRG1) by IHC	7 (10.8)

Note: For the ENA analysis, 4 patients previously listed as NSCLC were reclassified as "thoracic undifferentiated" or "other". Patients with at least 7 weeks of follow-up are included.

VUS, variant of uncertain significance; IHC, immunohistochemistry.

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

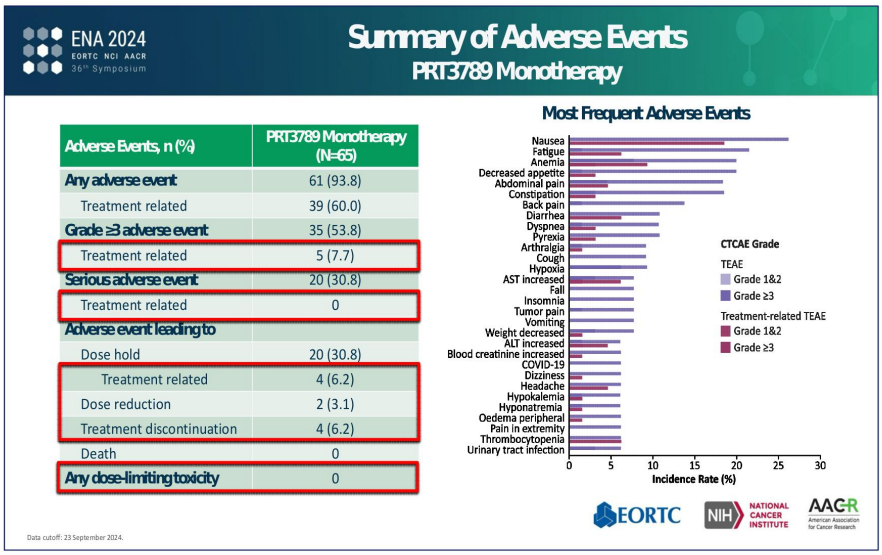
2024 Triple Meeting Update

65 patients with additional follow-up included in the analysis were treated and safety evaluable at time of data cutoff

The primary tumor type, as characterized by investigators, was NSCLC (n = 30) along with other solid tumors

34 patients had Class 1 (loss of function) mutations and an additional 7 patients had loss of SMARCA4 protein by IHC

PRT3789-01: Summary of Adverse Events



Adverse Events, n (%)	PRT3789 Monotherapy (N=65)
Any adverse event	61 (93.8)
Treatment related	39 (60.0)
Grade ≥3 adverse event	35 (53.8)
Treatment related	5 (7.7)
Serious adverse event	20 (30.8)
Treatment related	0
Adverse event leading to	
Dose hold	20 (30.8)
Treatment related	4 (6.2)
Dose reduction	2 (3.1)
Treatment discontinuation	4 (6.2)
Death	0
Any dose-limiting toxicity	0

2024 Triple Meeting Update

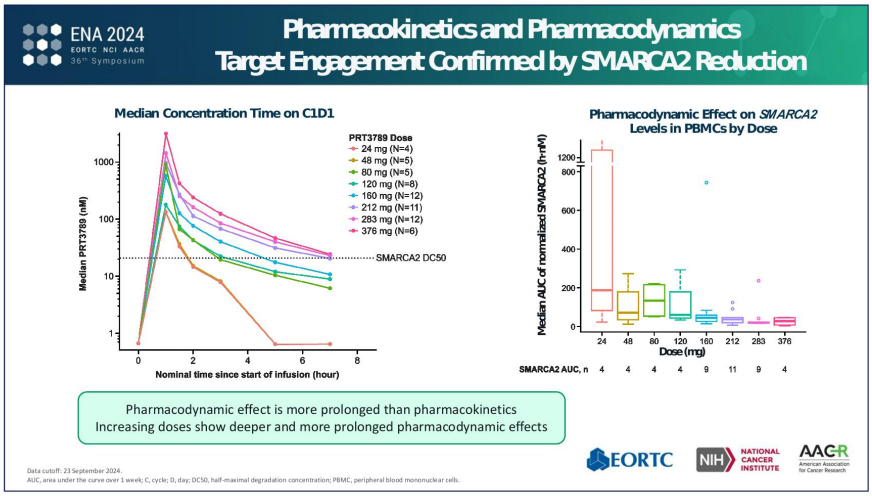
PRT3789 was generally well tolerated at doses studied with no treatment related SAEs or dose-limiting toxicities reported

Of all Treatment Emergent Adverse Events (TEAEs) of any grade, nausea, fatigue, anemia and decreased appetite had the highest incidence

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: Phase 1 Interim PK Findings



2024 Triple Meeting Update

Preliminary PK data are available from 24 mg to 376 mg

General trend of increases in exposure (Cmax, AUC) with higher doses was observed

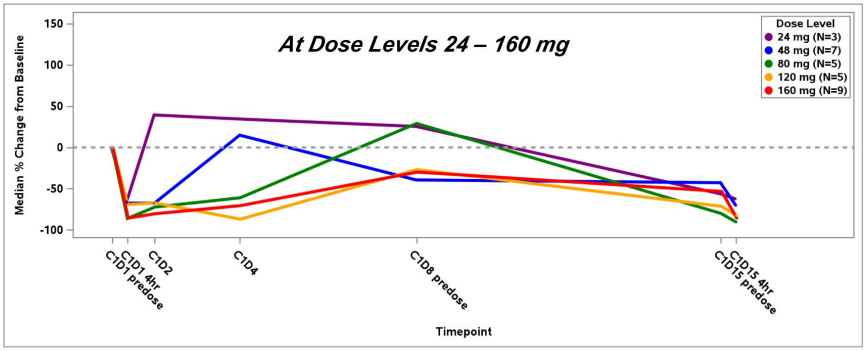
At the 376 mg dose level, mean concentrations were above SMARCA2 plasma DC50 (21 nM) for approximately 8 hours

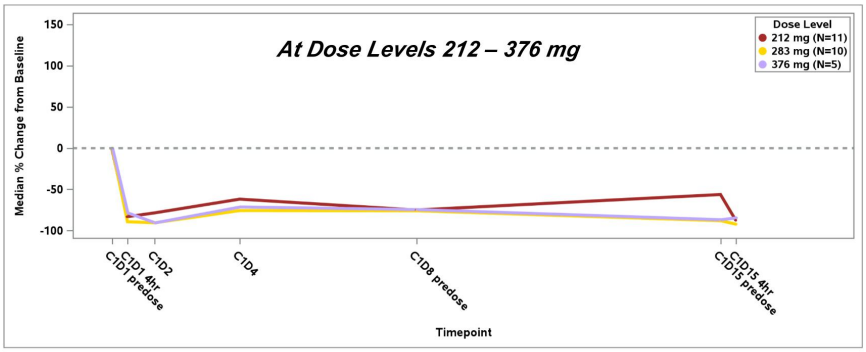
As expected with a potent degrader, the observed pharmacodynamic effect was more prolonged than pharmacokinetic half-life

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: SMARCA2 Protein Levels in PBMCs





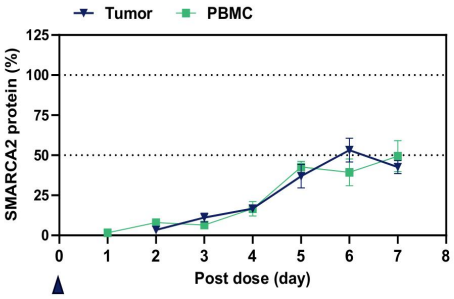
Note: LLQ (Lower Limit of Quantification) values were used for any value BLQ (Below Limit of Quantification).
Source: Data on file. PBMC, peripheral blood mononuclear cells.

At dose levels up to 160 mg, degradation of SMARCA2 was observed in PBMCs at early time points, but recovered or was above baseline by the end of the dosing interval (7 days)

At dose levels 212 – 376 mg, greater consistency, dose dependency, and sustained degradation of SMARCA2 were observed throughout the treatment cycle

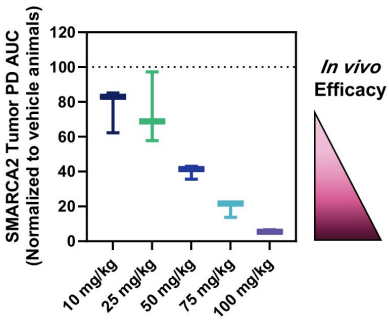
PD Correlates with Efficacy in Preclinical Models

SMARCA2 Levels over Time After a Single IV Dose of PRT3789



Tumor levels from mouse xenograft model and PBMC levels from normal rat after single doses that provide equivalent and efficacious exposure

PD AUC/Efficacy Correlation



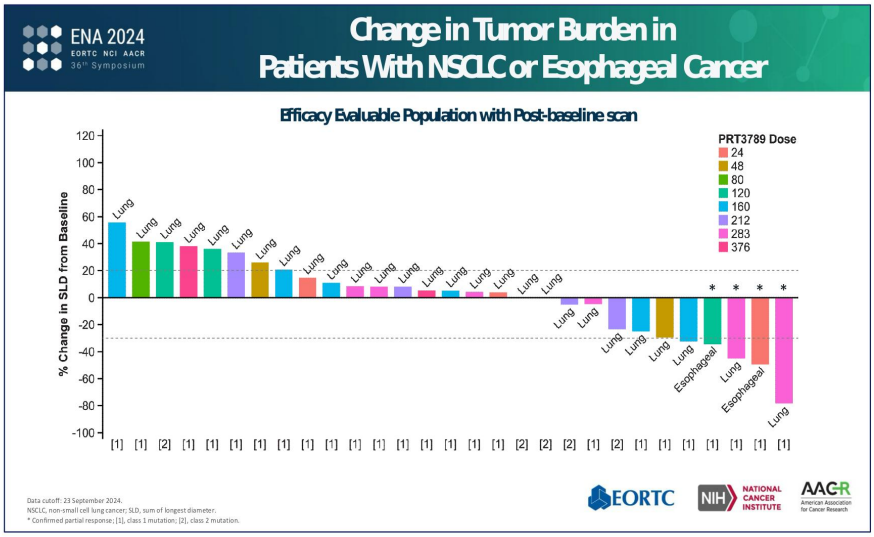
50 mg/kg = 243 human dose equivalent
75 mg/kg = 365 mg human dose equivalent
100 mg/kg = 487 mg human dose equivalent

In preclinical models, correlation was observed between PBMC and tumor SMARCA2 degradation levels at efficacious doses

Increasing doses resulted in increased reduction in SMARCA2 PD AUC in tumors and were associated with higher efficacy

AUC, area under curve; PBMC, peripheral blood mononuclear cells.
Source: Wang et. al. ENA 2023 Poster (http://www.preludetx.com/science/publications); Data on file

PRT3789-01: Phase 1 Interim Clinical Activity



2024 Triple Meeting Update

Of the 29 patients with NSCLC or esophageal cancer evaluable for efficacy at time of data cutoff, 8 experienced tumor shrinkage

RECIST confirmed partial responses (PRs) were observed in 4 patients (2 esophageal, 2 NSCLC)

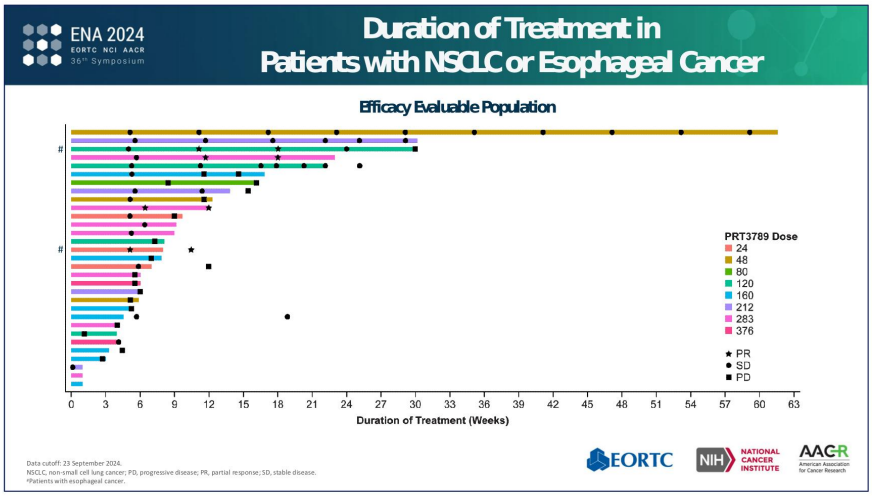
The two NSCLC responders had Class I mutations and were treated at the 283 mg dose level

Stable disease was observed in patients with both Class 1 and Class 2 SMARCA4 mutations

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: Phase 1 Interim Clinical Activity



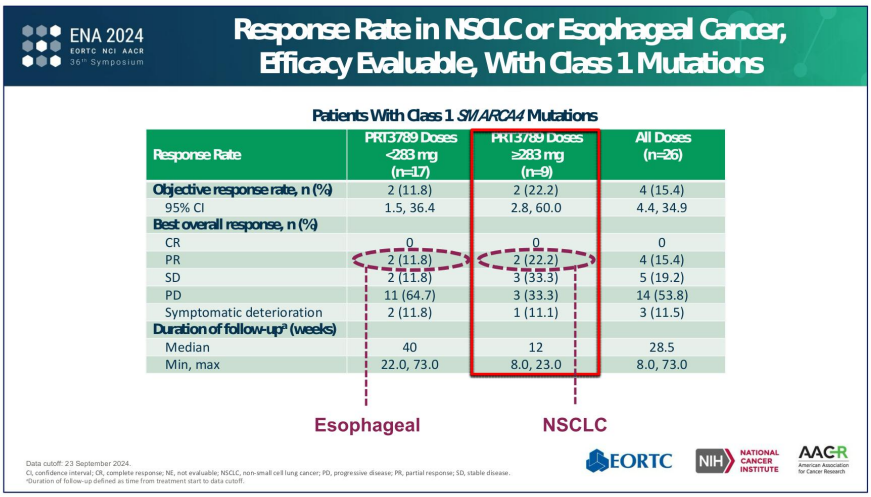
2024 Triple Meeting Update

As reported by Alessi *et al.*, the median PFS for <u>first-line</u> SMARCA4-*mutated* NSCLC treated with chemoimmunotherapy was 2.7 months [1]

Several patients had prolonged stable disease (SD) including a NSCLC patient who remains on treatment for more than a year

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

PRT3789-01: Response Rate By Dose Level



Note: Table includes all efficacy evaluable patients with NSCLC or esophageal cancer with Class 1 mutations, with or without a post-baseline scan

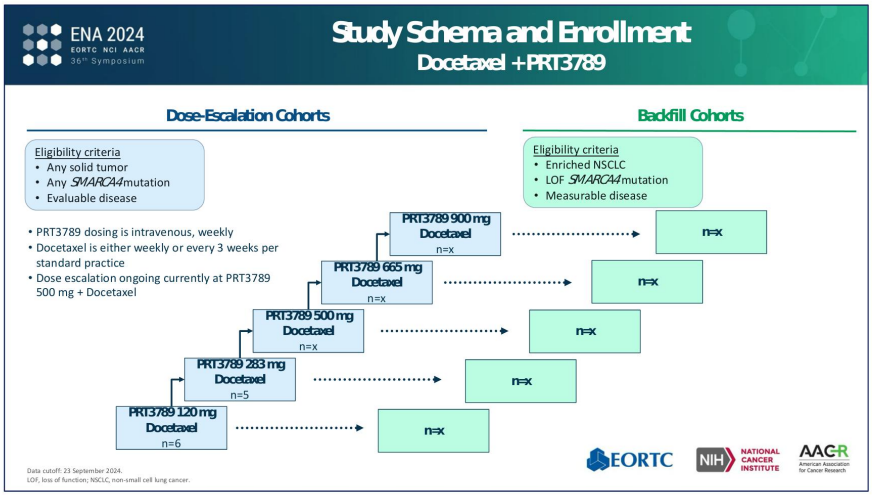
2024 Triple Meeting Update

As reported by Alessi *et al.*, the objective response rate (ORR) for first-line SMARCA4-*mutated* NSCLC treated with chemoimmunotherapy was 21.9% [1]

At doses ≥ 283 mg, as monotherapy, an interim ORR of 22.2% was observed in NSCLC patients with Class I SMARCA4-mutations

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

PRT3789-01: Docetaxel Combination Study Schema



2024 Triple Meeting Update

At time of data cutoff, 11 patients treated at 120 mg (n=6) and 283 mg (n=5) were evaluable for preliminary safety and PK assessment

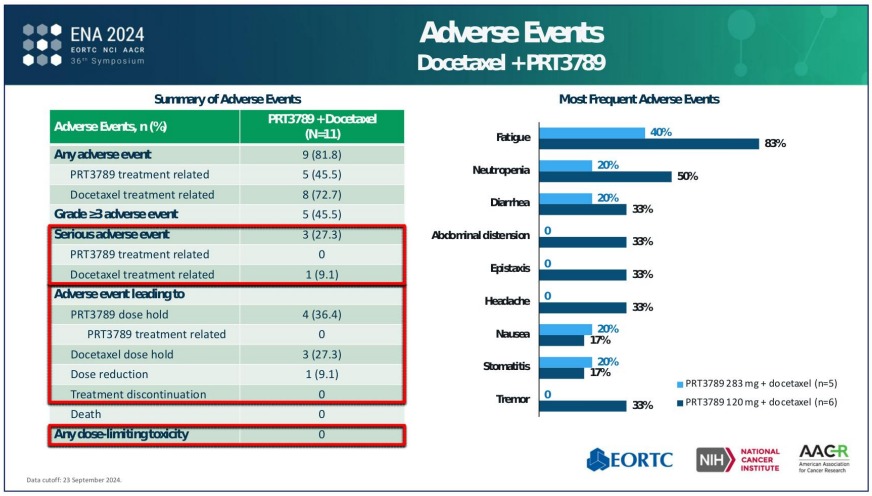
Enrollment continues with no dose limiting toxicities observed to date and is now enrolling at 500 mg

Backfill cohorts enriched for NSCLC and Class I LOF mutations are also enrolling

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: Preliminary Safety and Adverse Event Summary in Combination with Docetaxel



Adverse Events, n (%)	PRT3789 + Docetaxel (N=11)
Any adverse event	9 (81.8)
PRT3789 treatment related	5 (45.5)
Docetaxel treatment related	8 (72.7)
Grade ≥3 adverse event	5 (45.5)
Serious adverse event	3 (27.3)
PRT3789 treatment related	0
Docetaxel treatment related	1 (9.1)
Adverse event leading to	
PRT3789 dose hold	4 (36.4)
PRT3789 treatment related	0
Docetaxel dose hold	3 (27.3)
Dose reduction	1 (9.1)
Treatment discontinuation	0
Death	0
Any dose-limiting toxicity	0

2024 Triple Meeting Update

In combination with docetaxel, PRT3789 was generally well tolerated at doses studied with no treatment related SAEs or dose-limiting toxicities reported

Most frequent treatment emergent AEs of any grade included fatigue, neutropenia and diarrhea

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

PRT3789-01: Preliminary PK Assessment in Combination with Docetaxel

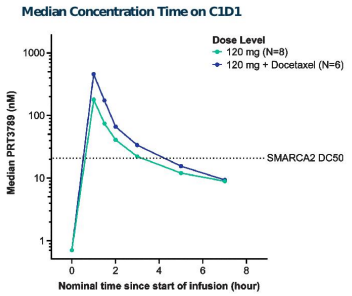
ENA 2024 EORTC NCI AACR 36th Symposium

Pharmacokinetics of PRT3789 + Docetaxel

- Preliminary PK data is available from 6 patients in the 120 mg combination cohort
- PRT3789 PK in combination with docetaxel appears to be consistent with monotherapy at 120 mg

Mean (SD) of PK PRT3789 parameters

Cohort	N	C_{max} (nM)	AUC_{last} (h·nM)	Half-life (hour)
120 mg combination	6	645 (546)	765 (633)	2.27 (0.46)
120 mg monotherapy	8	564 (734)	797 (821)	2.30 (0.48)



AUC_{last}, area under the curve from the time of dosing to the last measurable concentration; C, cycle; C_{max}, maximum concentration; D, day; DC50, half-maximal degradation concentration; PK, pharmacokinetic; SD, standard deviation.

EORTC NIH NATIONAL CANCER INSTITUTE AACR American Association for Cancer Research

2024 Triple Meeting Update

At time of data cutoff, preliminary PK data was available from 6 patients in the 120 mg combination cohort

PRT3789 PK in combination with docetaxel appears to be consistent with monotherapy at 120 mg

Early signs of anti-tumor activity reported by investigators

Additional data to be presented at a major medical meeting in 2025

Yap, T. *et al.*, ENA (EORTC, NCI, AACR) 36th Symposium, October 24th 2024

Data cutoff: 23 September 2024

What's Next for PRT3789?

'3789 Monotherapy Dose Confirmation

- Currently enrolling patients in dose escalation cohort 10 (665 mg QW)
- Backfill cohorts continue to enroll
  - Enriching for NSCLC and esophageal cancer w/ Class I LOF mutations
- Expecting dose confirmation by YE24
- Additional information on clinical activity at higher doses to be presented in 2025

'3789 + Docetaxel

- Docetaxel combination cohorts continue to enroll
- Goal is to assess safety and clinical activity in combination
- Docetaxel is the chemotherapy most often used in 2L+ NSCLC
- Seeking to improve upon poor outcomes observed with current standard of care

'3789 + KEYTRUDA®

- Phase 2 pembrolizumab combination trial is initiated
- Subject of collaboration agreement with Merck
- Goal is to assess safety and clinical activity in combination

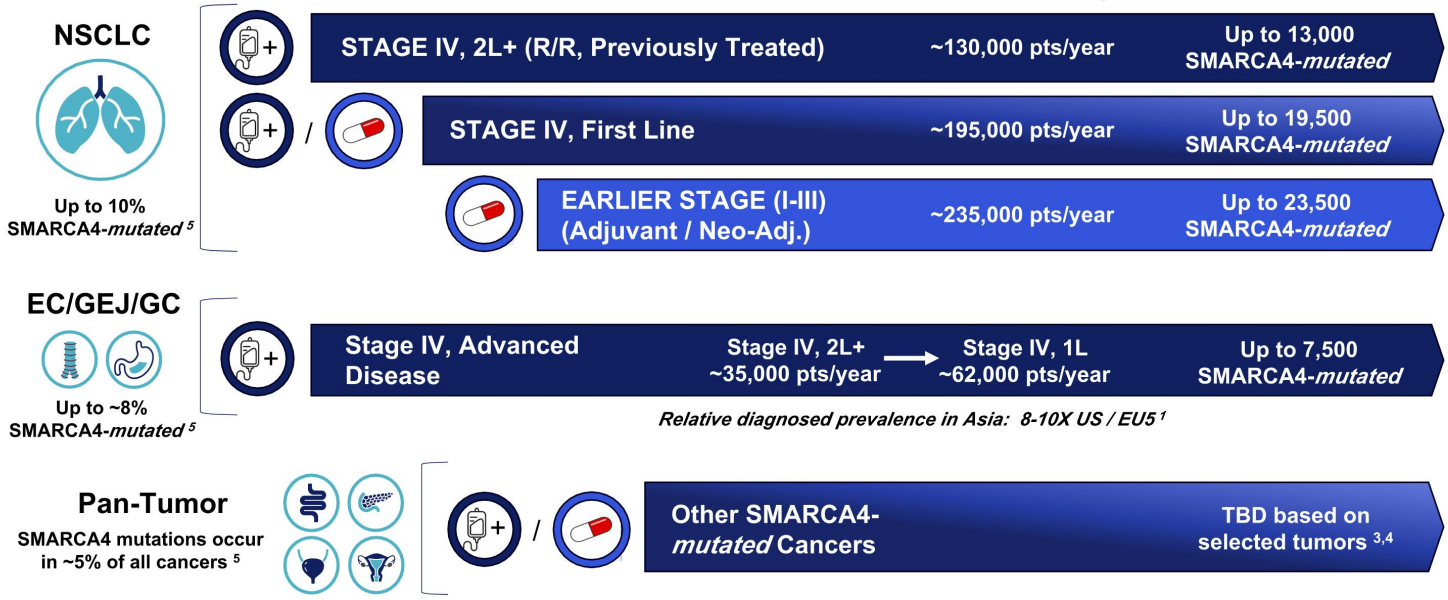
'3789 Program Priorities:

- Confirm biologically active dose as monotherapy
- Further characterize activity in Class 1 (LOF) vs. Class 2 patients at biologically active doses
- Share initial clinical activity data on combination with docetaxel in 2025

KEYTRUDA® is a registered trademark of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
LOF = "Loss-of-function"; QW, once weekly; YE, year end; NSCLC, non-small cell lung cancer; 2L+, second-line and beyond.

Prelude's SMARCA2 Degrader Portfolio Addresses a Significant Unmet Need

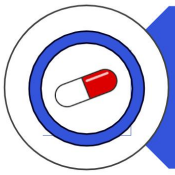
Potential Addressable Patient Populations US and EU5 [1-5]



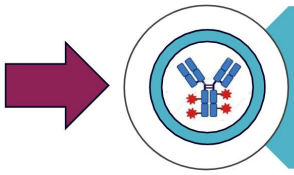
US & EU5 only (2030 *proj.*): [1] GlobalData (SEER), Earlier Stage (I-III) includes incidence only, Stage IV includes drug-treated prevalence only, with progression from earlier stages; all three factor-out patients treated with targeted therapies for driver mutations; [2] Datamonitor 2023 Lung Cancer Report; [3] Cerner CancerMpact Tumor Type Reports 2024 [4] Schoenfeld et al. *Clin Cancer Res.* (2020); 26(21):5701-5708. [5] Dagogo-Jack et al. *J Thorac Oncol.* (2020); 15(5):766-776.; Analysis on File.

Expanding Our Portfolio of SMARCA-Targeted Precision Medicines

Lead SMARCA2 Degrader (PRT3789)



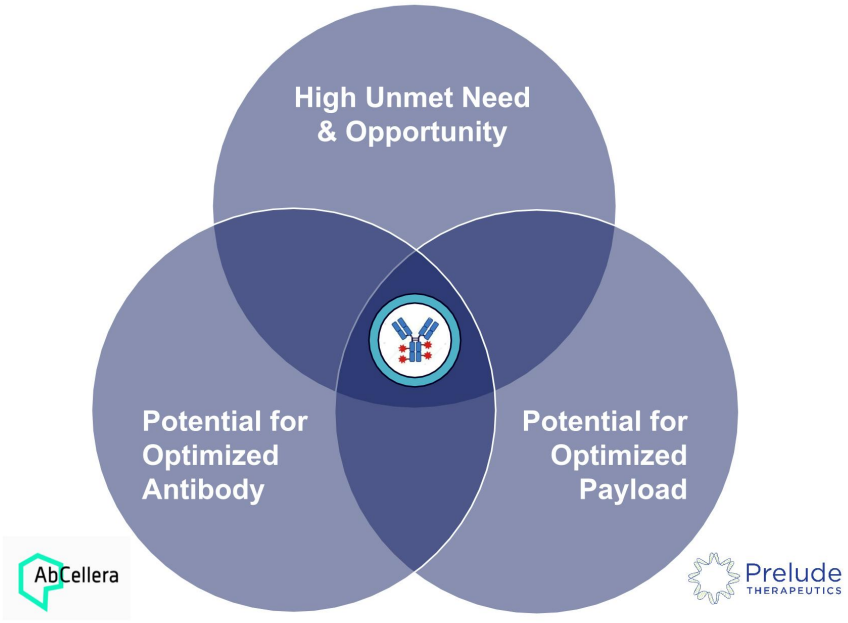
Oral SMARCA2 Degrader (PRT7732)



Precision ADCs with SMARCA2/4 Degrader Payload

- Cancers highly sensitive to SMARCA dysregulation
- Independent of SMARCA4 mutation status
- Initial focus of Prelude/AbCellera collaboration

Together, Prelude and AbCellera Are Creating Novel, First-in-Class Precision ADCs



*** Antibody target and tumor type(s) for initial candidates remain undisclosed at this time**

2024 Triple Meeting Update

Data presented describe the first preclinical proof-of-concept of a novel, highly potent SMARCA2/4 dual degrader as a "Precision Payload" conjugated to multiple antibodies

Prelude's SMARCA2/4 dual degraders have shown picomolar potency with potential for increased efficacy, selectivity and improved therapeutic index

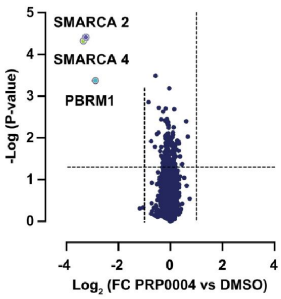
Precision ADCs have potential to expand the reach of SMARCA degrader technology to cancers without SMARCA4 mutations

Identification of Selective SMARCA2/4 Dual Degraders with Potent Anti-Cancer Activity

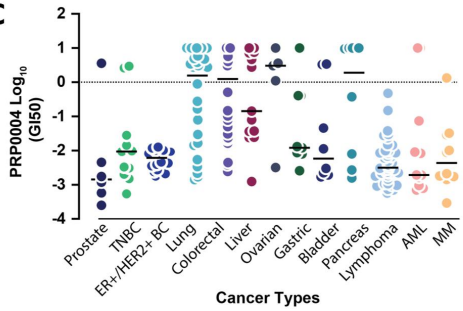
A

Cellular Potency & Selectivity			
Payload	**PRP 0004**	**PRP 0005**	**PRP 0006**
SMARCA2 DC_{50} (nM)	0.37	0.26	0.04
SMARCA4 DC_{50} (nM)	2.72	1.18	0.09
Fold Selectivity SMARCA4/SMARCA2	7	5	2

B



C



(A) SMARCA2/4 degradation potency of 3 payloads in a HeLa HiBiT cell-based assay. (B) Global proteomics analysis following treatment of LNCaP human prostate cancer cells with 25 nM PRP0004 for 1h. (C) GI_{50} of a panel of cancer cell lines treated with PRP0004, assessed by CellTiter-Glo® assay.

Carter J.,. *et al.*, 2024 EORTC, NCI, AACR Symposium Poster (http://www.preludetx.com/science/publications)

2024 Triple Meeting Update

Prelude has optimized several highly potent and selective SMARCA2/4 dual degraders for use as novel payloads in degrader antibody conjugates (DACs)

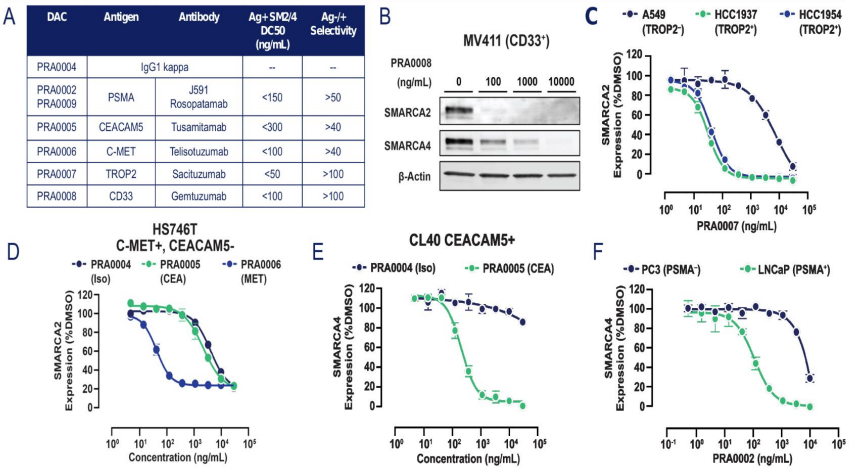
PRP0004 is a potent SMARCA2/4 dual degrader that is highly selective for SMARCA2 and SMARCA4 across the proteome

PRP0004 robustly inhibits cancer growth and induces cell death across a range of cancer cell lines tested

Conjugation of Clinically-Validated Antibodies to SMARCA2/4 Degrader Payloads Drives Antigen-Dependent Internalization and Target Engagement

A

DAC	Antigen	Antibody	Ag+SMD/4 DC50 (ng/mL)	Ag-/+ Selectivity
PRA0004	IgG1 kappa		--	--
PRA0002 PRA0009	PSMA	J591 Rosopatamab	<150	>50
PRA0005	CEACAM5	Tusamitamab	<300	>40
PRA0006	C-MET	Telisotuzumab	<100	>40
PRA0007	TROP2	Sacituzumab	<50	>100
PRA0008	CD33	Gemtuzumab	<100	>100



Carter J.,. *et al.*, 2024 EORTC, NCI, AACR Symposium Poster (http://www.preludetx.com/science/publications)

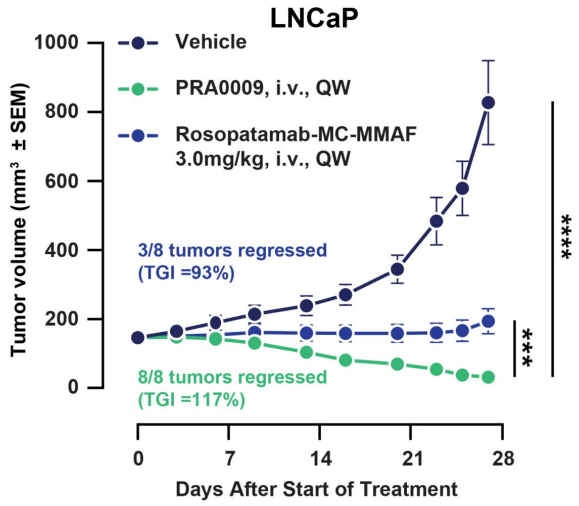
2024 Triple Meeting Update

Conjugation of PRP0004 to clinically-validated antibodies including PSMA, CEACAM5, C-MET, TROP2, and CD33

These DACs demonstrated potent and antigen-selective internalization and target engagement across multiple cancer types

Prostate cancer was amongst the most sensitive cell lines to SMARCA2/4 degradation rationalizing the use of PSMA-targeting antibodies for further proof-of-concept studies

Anti-PSMA SMARCA2/4 DAC Demonstrated Tumor Regression and Significantly Better Efficacy Compared to a Traditional PSMA-Targeted Cytotoxic ADC



Carter J.,. *et al.*, 2024 EORTC, NCI, AACR Symposium Poster (http://www.preludetx.com/science/publications)

2024 Triple Meeting Update

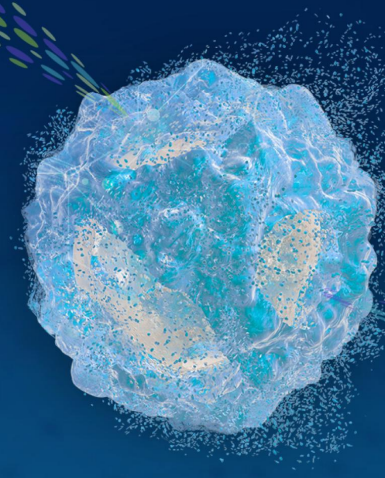
Anti-PSMA SMARCA2/4 DACs demonstrated robust target engagement and antigen-dependent efficacy in xenograft models while being well-tolerated

These data highlight the potential of utilizing a SMARCA2/4 degrader payload to achieve maximal target degradation in tumors while sparing healthy tissues

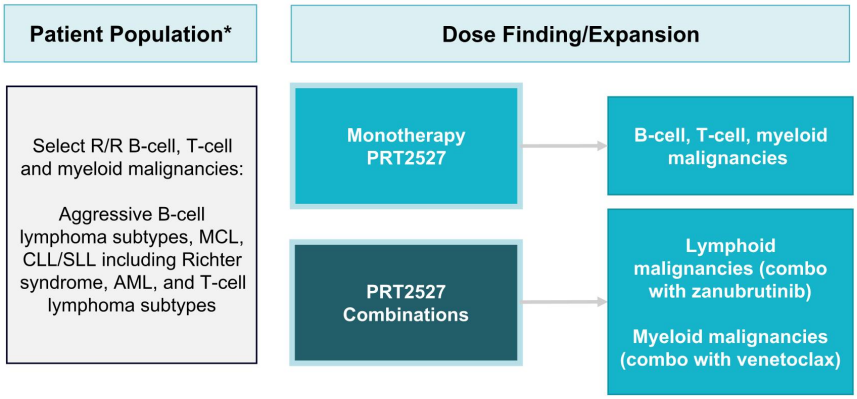
Precision ADCs have the potential to expand the therapeutic reach of SMARCA2/4 degraders to patients without SMARCA4 mutations

Highly Selective CDK9 Inhibitor

PRT2527



Phase 1 Trial of PRT2527 in Hematologic Malignancies is Underway



Goal: Establish Initial PoC and Identify Mono and/or Combination Recommended Doses for Expansion

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

ClinicalTrials.gov Identifier: NCT05159518

What to Expect in Q4 2024

Initial safety and tolerability data for monotherapy dose escalation cohorts in hematologic malignancies

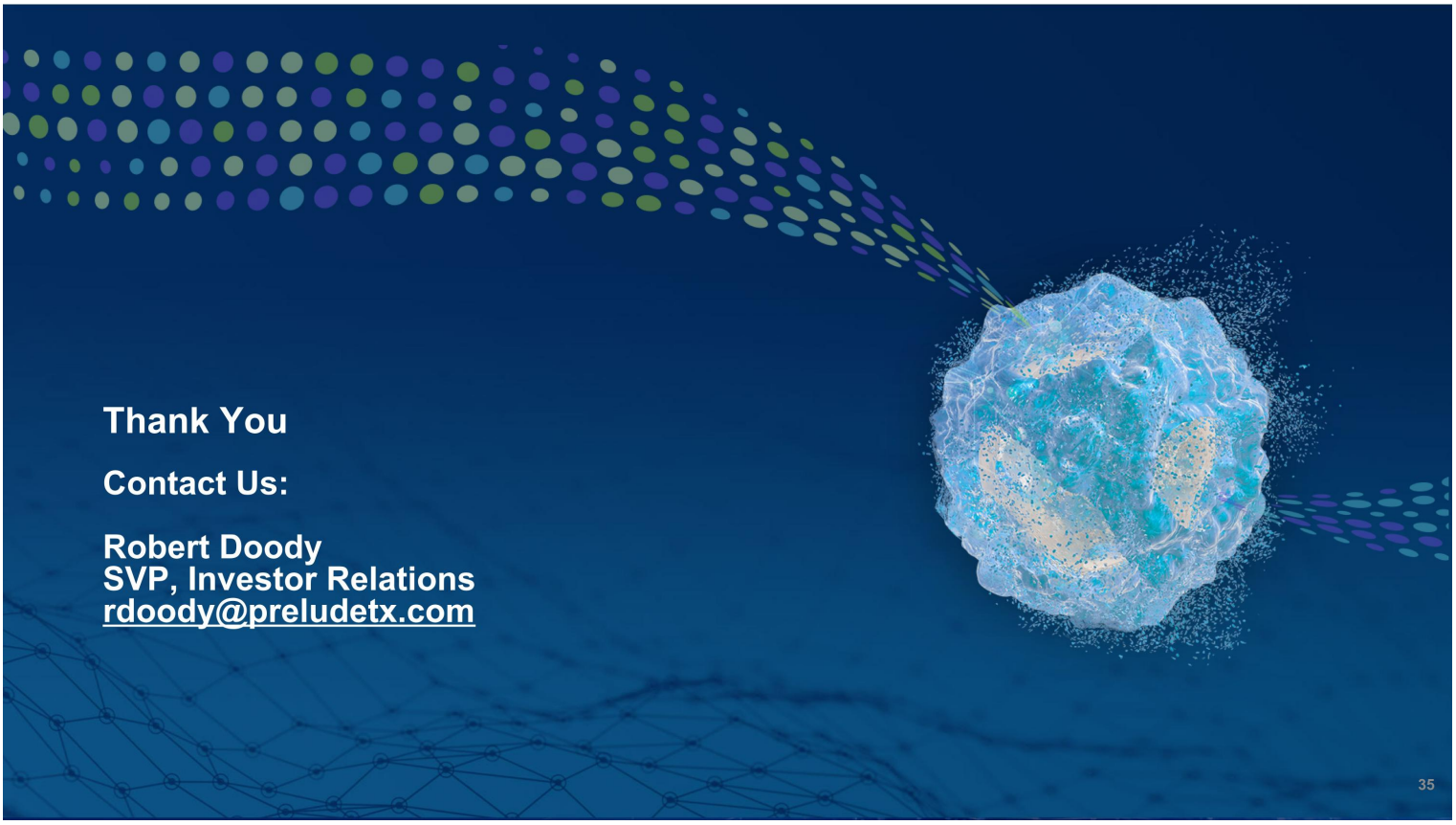
Initial assessment of clinical activity in B-cell malignancies as monotherapy

Initial clinical data with zanubrutinib from combination cohort

Continued Execution Across Strategic Priorities

PROGRAM	EXPECTED DELIVERABLE	MILESTONE
Lead IV SMARCA2 Degrader PRT3789	• **Report interim Phase 1 clinical results in 2H 2024 (ESMO & ENA)** • Initiate Phase 2 trial in combination with pembrolizumab • Complete monotherapy escalation and fully enroll backfill cohorts	• *Complete* • *Complete* • YE 2024
Oral SMARCA2 Degrader PRT7732	• Investigational New Drug (IND) authorization from FDA • Initiate Phase 1 in patients with SMARCA4 mutations • **Report interim Phase 1 clinical results**	• *Complete* • *Complete* • **2025**
Selective CDK9 Inhibitor PRT2527	• Initiate zanubrutinib combination study • Initiate myeloid cohort in the existing phase 1 study • Complete monotherapy dose escalation in B-cell malignancies • **Report interim phase 1 clinical results in 2024**	• *Complete* • *Complete* • 2H 2024 • **Q4 2024**
Discovery Engine Precision ADCs & Other	• Advance next first-in-class, novel small molecule discovery candidate • Advance first SMARCA2/4 Precision ADC in partnership with AbCellera • Advance second Precision ADC program in partnership with AbCellera	• 2024 • 2025 • 2025

Cash, Cash Equivalents of $179.8 Million as of 6/30/2024


Thank You
Contact Us:
Robert Doody
SVP, Investor Relations
rdoody@preludetx.com
35

APPENDIX

- **Highly Selective SMARCA2 Degrader Program**
  - Discovery Effort & Oral Degrader Program (PRT7732)
  - Preclinical Rationale for Combinations (**2024 EORTC-NCI-AACR Symposium Update**)
  - Current Treatment Paradigm & Testing Landscape
- **Precision ADCs**
  - **First Preclinical Proof-of-Concept Data Presented at 2024 EORTC-NCI-AACR Symposium**
  - Overview of Prelude's Precision ADC Program and Next Steps
- **CDK9 Program for Hematologic Malignancies (PRT2527)**
  - Background, Unmet Need and Scientific Rationale
  - Early Clinical Safety and PK/PD Data from Phase I Study in Solid Tumors
  - Interim Phase I Update Planned for Major Medical Meeting in Q4 2024

BOLD = New data included in Appendix with this update

Prelude THERAPEUTICS

When it Comes to Targeting SMARCA2, Degraders Offer Distinct Advantages

	Inhibitors	Degraders
Potency	☑	☑
High Selectivity	X	☑
Extended PD	X	☑
Oral Bioavailability	☑	☑

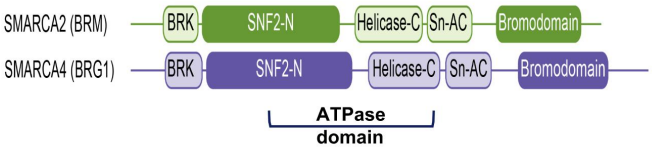
Early attempts at achieving both potency and selectivity with inhibitor approaches had challenges

Inhibitors do not degrade the target and need to be dosed at levels that retain IC_{90} coverage continuously

Degraders demonstrate sustained PD effect as it takes 48-72h for SMARCA2 to resynthesize

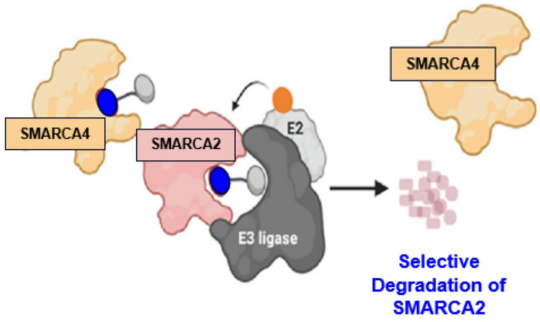
Selectively Targeting SMARCA2 Has Been a Significant Challenge for Industry

Selective SMARCA2 Inhibition is an Unmet Medicinal Chemistry Challenge



- **Bromodomain Binders**
  - Non-selective and inactive in SMARCA4 mutated cancer cells[1]
- **ATPase Inhibitors**
  - Inhibitors show low selectivity for SMARCA2 in cell proliferation assays (<10 fold[2] and ~33 fold[3])

Prelude's Targeted Protein Degradation (TPD) Approach

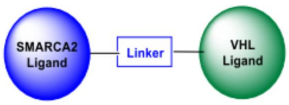


- **SMARCA2 Selective Degradation** is possible through differences in ternary complexes and subsequent ubiquitination of unique lysine residues

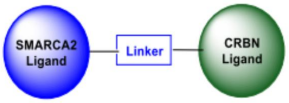
[1] Vangamudi et al, Cancer Res. **2015** (Pfizer); Taylor et al, J. Med. Chem **2022** (Genentech) [2] Papillon et al, J. Med. Chem **2018** (Novartis) [3] AACR **2024** (Foghorn/Lilly)

Prelude Scientists Solved the SMARCA2 Selectivity Enigma

Parallel VHL- and CRBN-based SMARCA2 Degrader Programs



PRT3789
(IV or SC formulation)



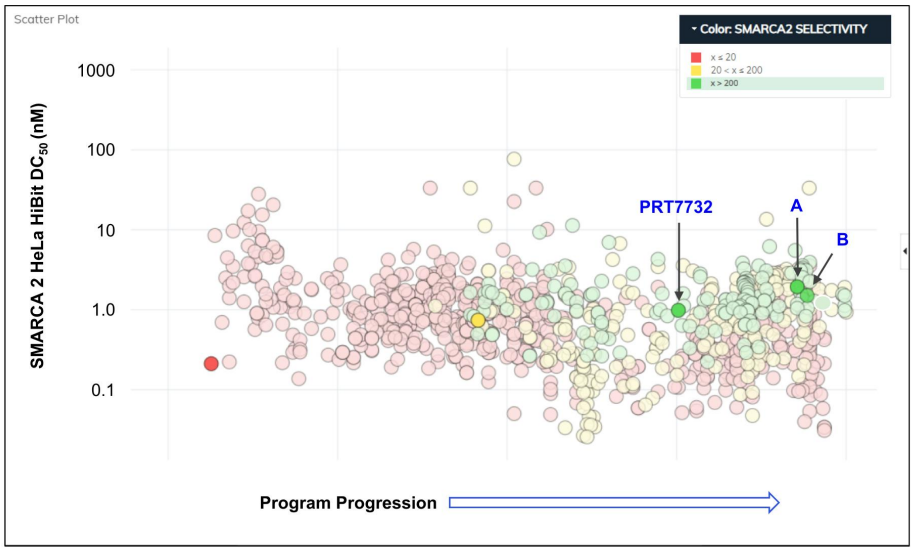
PRT7732
(Oral Candidate)

- **IV or SC Candidate** - **VHL-TPD**s provided an expedited path to potential clinical development with QW dosing
- **Oral Candidate** - **CRBN-TPD**s provided oral candidates, but required extensive lead optimization with balancing of potency, selectivity and oral PK properties

Our lead IV and oral clinical candidates both have sub-nanomolar degradation potencies and very high selectivity (>1000 fold) for SMARCA2 over SMARCA4

Our SMARCA2 Oral Degrader Program Progressed Rapidly and Systematically

SMARCA2 HiBit DC_{50} & SMARCA4 Selectivity



Note: Inactive & weakly potent compounds removed for clarity

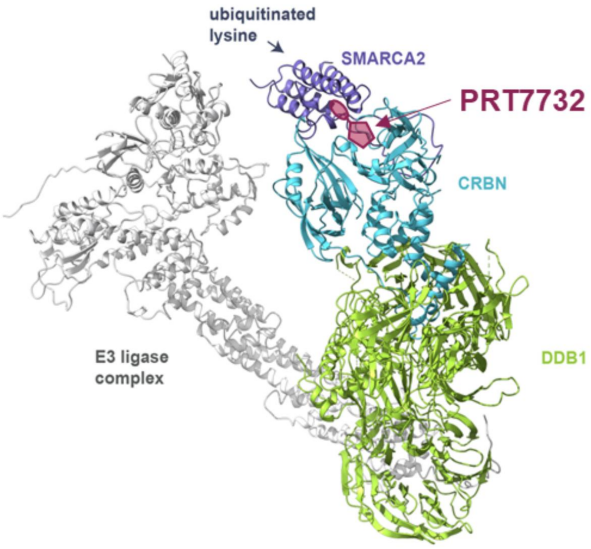
Solving for potency, selectivity and oral bioavailability was a challenge

PRT7732: Lead Oral Candidate with >3000-fold Selectivity

A and B: Two additional structurally distinct oral back-up candidates

PRT7732: Our Lead Oral SMARCA2 Degrader

Tertiary Complex of SMARCA2/ PRT7732/CRBN-DDB1 E3 Ligase



Shvartsbart, K. Ito et al., AACR Poster, April 2024. (http://www.preludetx.com/science/publications)

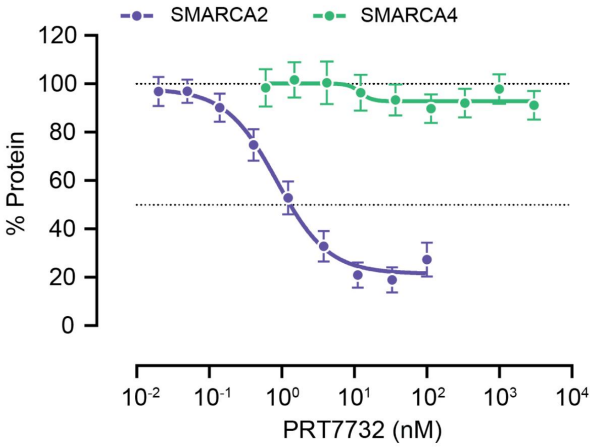
PRT7732 binds to the SMARCA2 bromodomain and CRBN/DDB1 E3 ligase complex

PRT7732 has been shown to catalyze the polyubiquitination of unique lysine residues expressed only in SMARCA2 and not SMARCA4

Unique conformational bias promotes selective ubiquitination and degradation of SMARCA2

PRT7732 is Highly Potent and Orally Bioavailable With Near-Absolute Selectivity for SMARCA2

Preclinical Assay	PRT7732
SMARCA2 Degradation (nM)	0.98
Selectivity: Degradation (SMARCA4 / SMARCA2)	>3000 fold
Selectivity: Cell Proliferation (SMARCA4 / SMARCA2)	>1000 fold*



* Based on highest concentration tested

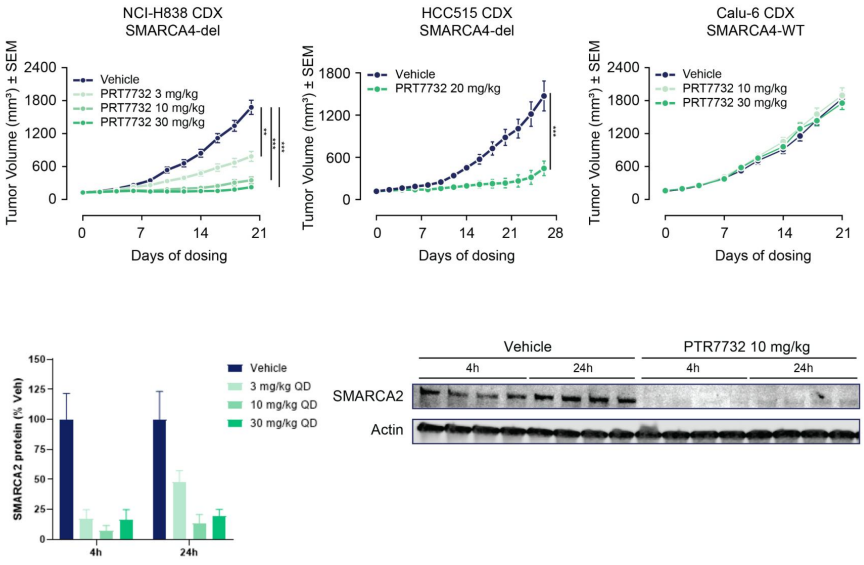
Shvartsbart, K. Ito et al., AACR Poster, April 2024. (http://www.preludetx.com/science/publications)

Sub-nanomolar SMARCA2 degradation potency

Near-absolute cellular selectivity for SMARCA2 vs SMARCA4 (>3000 fold) in HiBit cell lines and >1000-fold in cell proliferation assays

Good oral bioavailability observed across species supporting once-daily projected human dose

PRT7732 Has Significant Anti-Tumor Activity in SMARCA4-Deficient Cancer Xenograft Models



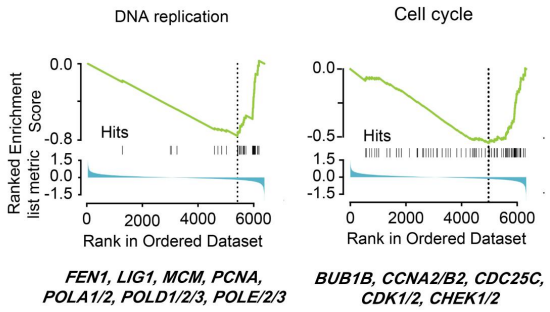
Shvartsbart, K. Ito et al., AACR Poster, April 2024. (http://www.preludetx.com/science/publications)

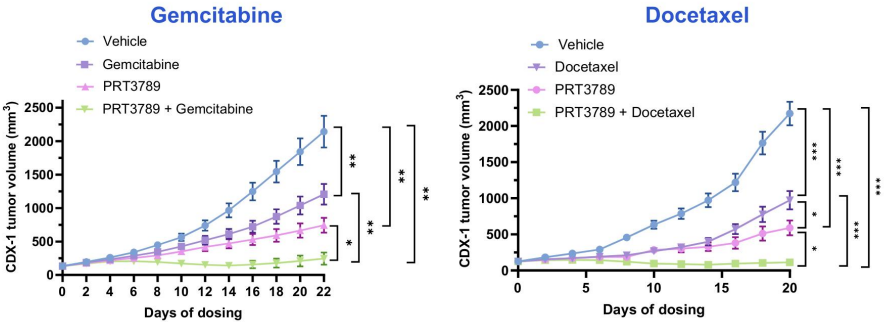
Daily oral administration of PRT7732 demonstrates anti-tumor activity in SMARCA4-deficient but not SMARCA4 wild type tumors

PRT7732 rapidly decreases SMARCA2 protein levels in tumor xenograft models at low doses

Preclinical data supported advancing PRT7732 to Phase I with once-daily dosing

PRT3789 Demonstrates Potential for Synergy with Chemotherapy and Apoptosis-Inducing Agents





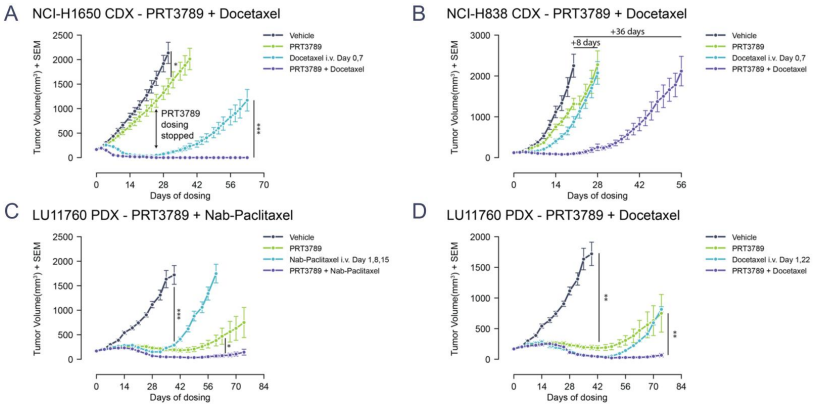
AACR 2022, 2023 Posters (http://www.preludetx.com/science/publications)

Several oncogenic gene sets regulated by PRT3789

Supports combination strategies with both cytotoxic and apoptosis-inducing agents (*e.g.,* RAS)

***In vivo* CDX models show strong tumor regression in combination with gemcitabine or docetaxel**

PRT3789 + Taxanes Induce Durable Regressions in SMARCA4-*mutated* NSCLC CDX & PDX Models



Intravenous (i.v.) or subcutaneous (s.c.) administration of PRT3789 in combination with docetaxel or nab-paclitaxel (Abraxane®) induced tumor regression and extended tumor growth delay (TGD) in the NCI-H1650 CDX model **(A)**; NCI-H838 CDX model **(B)**; and a NSCLC PDX tumor model **(C-D)** in mice at well-tolerated doses. *P<0.05 **P<0.01 ***P<0.001, versus vehicle (two-tailed Mann-Whitney test).

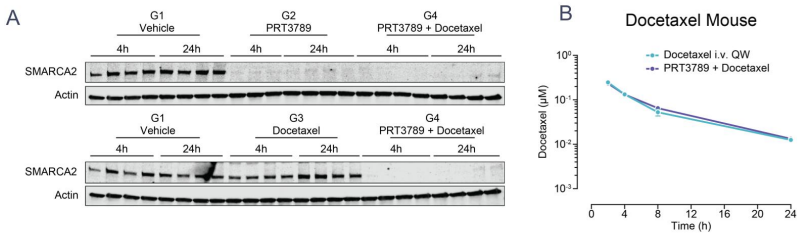
Hulse M., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

2024 Triple Meeting Update

PRT3789 enhances chemotherapy efficacy as shown in NSCLC models with SMARCA4 mutations, including both cell line-derived and patient-derived xenografts

PRT3789 significantly improved the efficacy of standard-of-care taxane chemotherapy agents (docetaxel or nab-paclitaxel)

Preclinical PK/PD Data Shows No Adverse Drug-Drug Interaction Between PRT3789 and Taxanes



(A) Tumor PD (SMARCA2 protein) was analyzed in samples from NCI-H838 efficacy studies by Western blot. PRT3789 treatment resulted in complete degradation of SMARCA2 protein in PRT3789 monotherapy (G2) and PRT3789 + docetaxel combination groups (G4). In contrast, taxanes did not interfere with the SMARCA2 degradation induced by PRT3789 *in vivo* as demonstrated by docetaxel monotherapy group (G3) and PRT3789 + docetaxel combination groups (G4). PK analysis of mouse plasma revealed no adverse drug-drug interactions (DDI) between PRT3789 and docetaxel. **(B)** Exposure of docetaxel was not affected by combination with PRT3789 .

Hulse M., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

2024 Triple Meeting Update

PRT3789 treatment results in complete degradation of SMARCA2 protein as both monotherapy and in combination with docetaxel

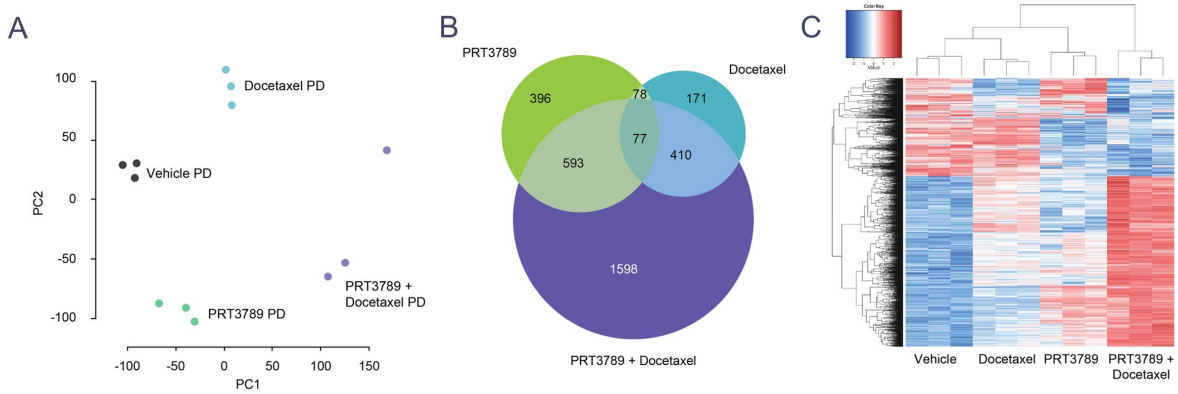
Taxanes do not interfere with the SMARCA2 degradation induced by PRT3789 *in vivo*

PK analysis of mouse plasma reveals no adverse drug-drug interactions (DDIs) between PRT3789 and docetaxel

Exposure of docetaxel is not affected by combination with PRT3789

PRT3789 and Docetaxel Regulate Distinct Pathways Involved in Tumor Cell Growth and Apoptosis

2024 Triple Meeting Update

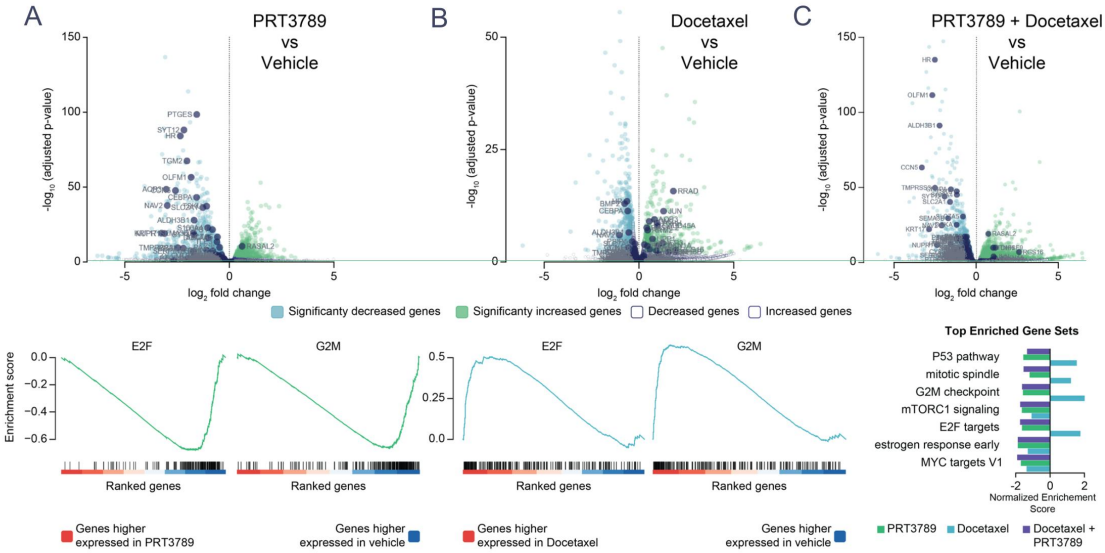


RNA-sequencing was conducted on SMARCA4-mutated NCI-H838 tumor tissues treated with PRT3789 and/or docetaxel for one week. **(A)** Principal components analysis (PCA)[6] was calculated by applying the prcomp() R function to counts per million (CPM)-normalized values for all 43,236 targets in the experiment. **(B)** Overlap genes analysis-differential genes were defined as genes with an adjusted p-value of less than or equal to 0.05, and a fold change greater than 1.5 or less than 0.5. **(C)** Clustering analysis- features were filtered using an adjusted p-value ≤ 0.01 and $\log_2$ fold change threshold of 1. Heatmap shows counts per million (CPM)-normalized, $\log_2$-transformed, and zscore-transformed values. Analysis performed using Pluto (https://pluto.bio).

Hulse M., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

PRT3789 Counteracts Docetaxel-Induced Cell Cycle Activation, Resulting in Enhanced Efficacy of the Combination

2024 Triple Meeting Update



Differential expression analysis was performed comparing the groups: **(A)** PRT3789 vs Vehicle, **(B)** docetaxel vs Vehicle, **(C)** PRT3789+ docetaxel vs Vehicle. Differential expression analysis was performed with the DESeq2 R package[6] and Log_2 fold change was calculated for the above comparisons. Volcano plots showing the log_2 fold change of each gene on the x-axis and the -log_{10}(adjusted p-value) on the y-axis.

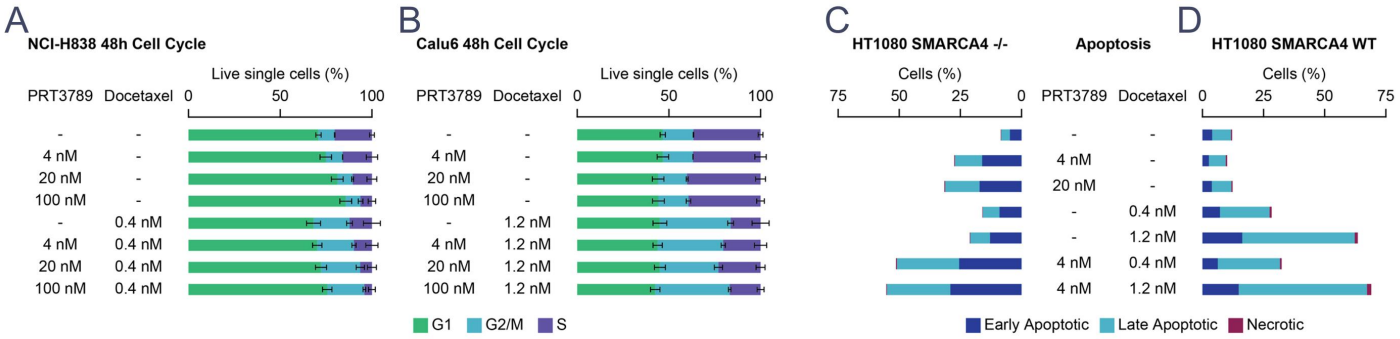
The sign(log_2 fold change) * -log_{10}(p-value) from the above differential expression comparisons was used to rank genes. Hallmarks gene set collection from the Molecular Signatures Database (MSigDB)[7,8] was curated using the msigdbr R package[9].

Analysis performed using Pluto (https://pluto.bio).

Hulse M., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

PRT3789 and Docetaxel Combination Induces a Dual G1 and G2/M Arrest and Enhances Apoptosis in SMARCA4-*deleted* Cells

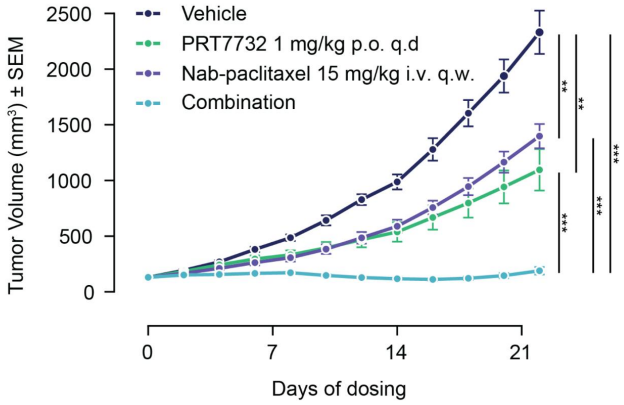
2024 Triple Meeting Update



Cell cycle analysis was performed using the Invitrogen™ Click-iT™ EdU Pacific Blue™ Flow Cytometry Assay Kit on the SMARCA4-del NSCLC cell line NCI-H838 **(A)** and the SMARCA4-WT NSCLC cell line Calu-6 **(B)** following 48 hr PRT3789 and/or docetaxel for treatment. The isogenic SMARCA4 KO **(C)** and SMARCA4 WT **(D)** HT1080 cell lines were dosed with PRT3789 and/or docetaxel for 48 hrs. The Pacific Blue™ Annexin V/SYTOX™ AADvanced™ Apoptosis Kit was used to determine the apoptotic cell population. Early apoptotic cells were defined as SYTOX-/annexin V+. Late apoptotic cells were defined as SYTOX+/annexin V+.

Hulse M., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

PRT7732 Also Shows High Potential for Synergy With Other Common Anti-Cancer Agents

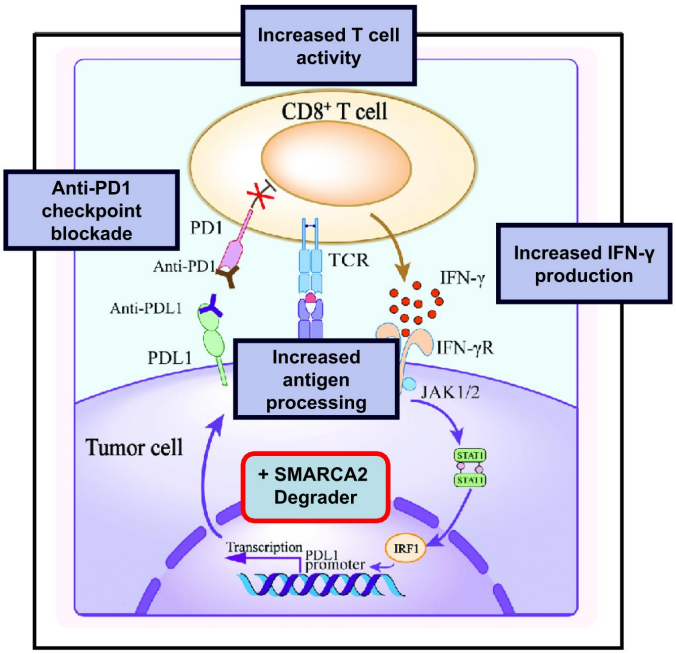


Shvartsbart, K. Ito et al., AACR Poster, April 2024. (http://www.preludetx.com/science/publications)

Oral daily administration of PRT7732 in combination with nab-paclitaxel induces tumor regressions in murine tumor xenograft models

SMARCA2 Degraders May Also Help to Potentiate PD1/PDL1 Immunotherapy

"Turning Cold Tumors Hot?"



In SMARCA4-*deficient* cancer cell lines, SMARCA2 degradation…

Induces presentation of unique MHC-I peptide

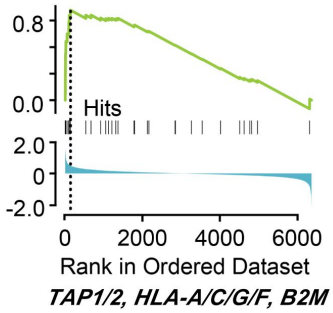
Upregulates antigen processing and presentation machinery

Increases cytokine production

Promotes T-cell activity and accelerates tumor cell killing

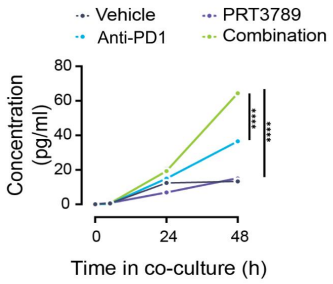
Preclinical Data for PRT3789 Support Rationale for Anti-PD1 Combination

PRT3789 Upregulates Genes for Antigen Processing and Presentation

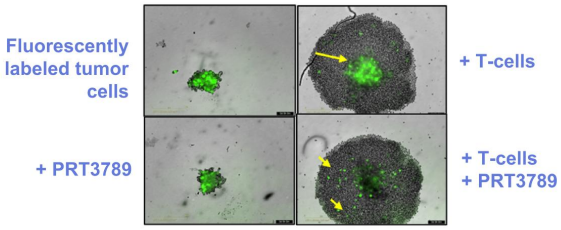


TAP1/2, HLA-A/C/G/F, B2M

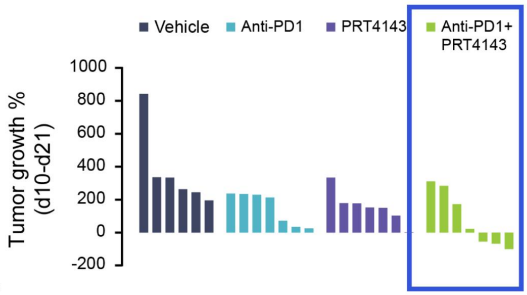
PRT3789 Increases IFN-g Levels in Combination with anti-PD1 *In Vitro*



PRT3789 Promotes T-cell mediated Tumor Cell Killing *In Vitro*

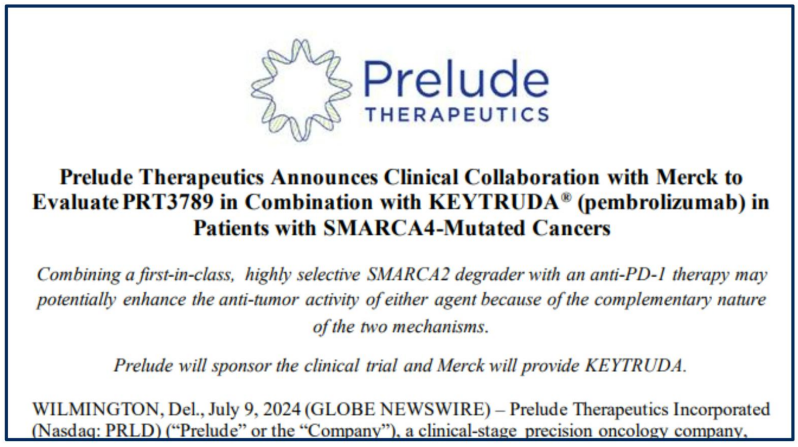


SMARCA2 Degrader + Anti-PD1 Demonstrates Tumor Regression *In Vivo*



ENA 2023 Poster (http://www.preludetx.com/science/publications); Data on file

Prelude Has Initiated a Phase 2 Combination Study of PRT3789 + Pembrolizumab



Prelude Therapeutics Announces Clinical Collaboration with Merck to Evaluate PRT3789 in Combination with KEYTRUDA® (pembrolizumab) in Patients with SMARCA4-Mutated Cancers

Combining a first-in-class, highly selective SMARCA2 degrader with an anti-PD-1 therapy may potentially enhance the anti-tumor activity of either agent because of the complementary nature of the two mechanisms.

Prelude will sponsor the clinical trial and Merck will provide KEYTRUDA.

WILMINGTON, Del., July 9, 2024 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD) ("Prelude" or the "Company"), a clinical-stage precision oncology company,

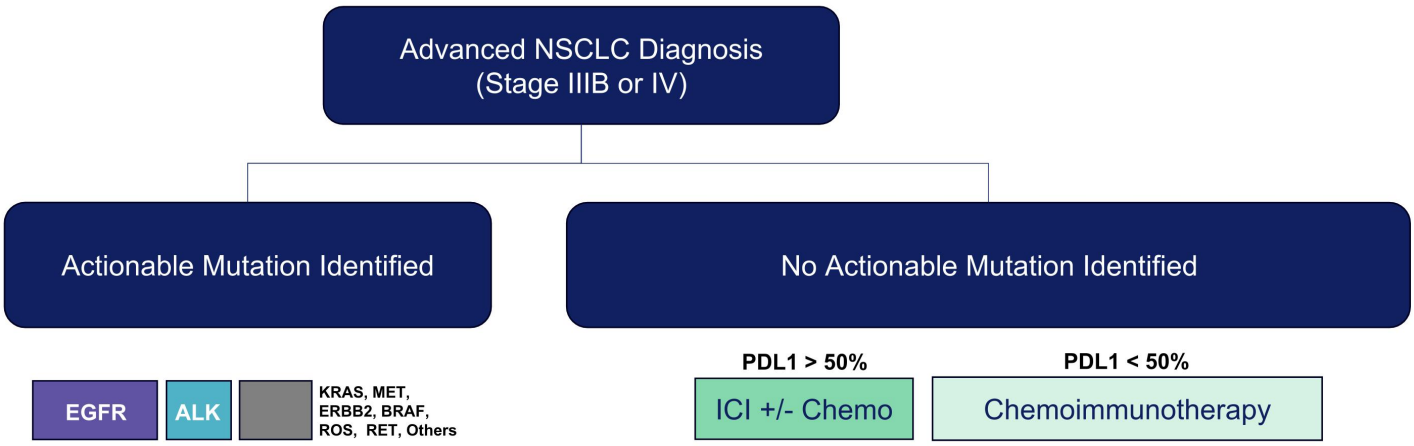
Preclinical evidence provides rationale for enhanced efficacy with PRT3789 and anti-PD1 therapy combination

PRT3789 upregulates genes encoding antigen processing and presentation machinery

Trial will explore safety and anti-tumor activity of the combination

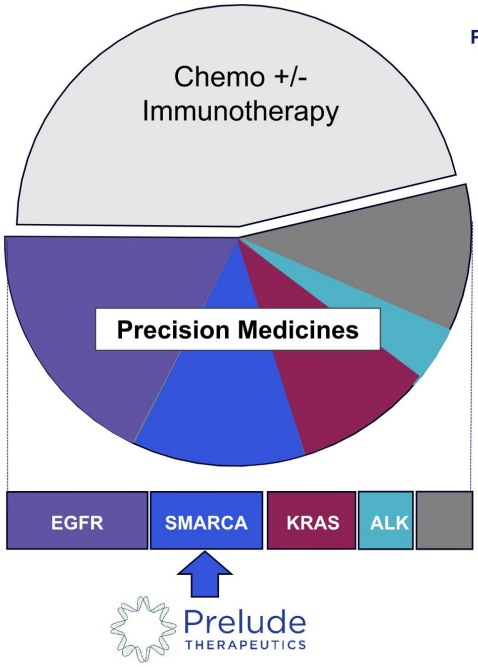
KEYTRUDA® is a registered trademark of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Majority of Advanced NSCLC Patients Are Treated with Chemoimmunotherapy



Note: Simplified schematic based on current ESMO and NCCN Clinical Practice Guidelines and current clinical experience; could include combination treatments with bevacizumab, pemetrexed, nab-paclitaxel and others

SMARCA2 Degraders Have Potential to Expand Precision Medicine Access for NSCLC Patients



Percent of Total Advanced NSCLC Patients Treated (FUTURE STATE)

ILLUSTRATIVE

Potentially more patients than ALK, MET, BRAF, ROS and RET combined [1]

Reinforces need for comprehensive genomic profiling

SMARCA4 mutations already included on most commonly used commercial NGS testing panels

More patients tested = More patients eligible

[1] Based on mutational prevalence; Source for current relative patient share: Datamonitor 2023 Lung Cancer Report

APPENDIX

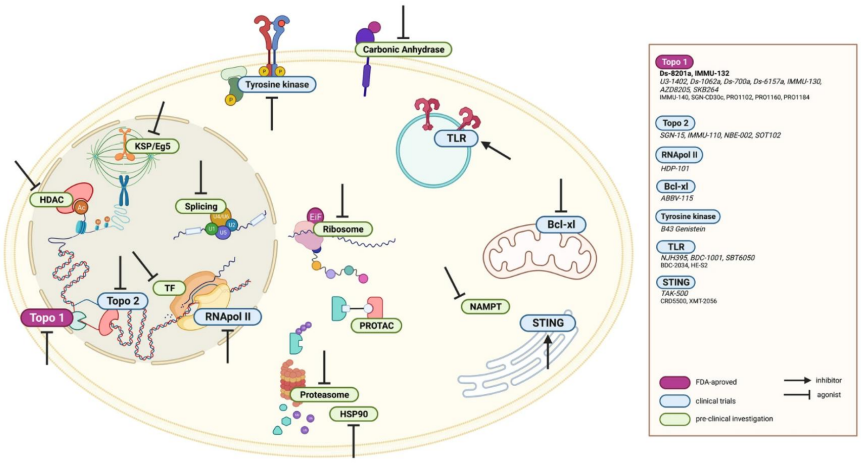
- **Highly Selective SMARCA2 Degrader Program**
  - Discovery Effort & Oral Degrader Program (PRT7732)
  - Preclinical Rationale for Combinations (**2024 EORTC-NCI-AACR Symposium Update**)
  - Current Treatment Paradigm & Testing Landscape
- **Precision ADCs**
  - **First Preclinical Proof-of-Concept Data Presented at 2024 EORTC-NCI-AACR Symposium**
  - Overview of Prelude's Precision ADC Program and Next Steps
- **CDK9 Program for Hematologic Malignancies (PRT2527)**
  - Background, Unmet Need and Scientific Rationale
  - Early Clinical Safety and PK/PD Data from Phase I Study in Solid Tumors
  - Interim Phase I Update Planned for Major Medical Meeting in Q4 2024

BOLD = New data included in Appendix with this update

Prelude THERAPEUTICS

Need for Payload Diversification is an Emerging Theme for Next Generation ADCs in the Clinic

From: Payload diversification: a key step in the development of antibody–drug conjugates



Schematic representation of the ADC payload's target landscape beyond microtubules and DNA-intercalating agents. Notations: FDA-approved ADCs, *ADCs in clinical trials*

Approved ADCs possess payloads with similar mechanisms of action to conventional chemotherapy such as Monomethyl Auristatin E (MMAE)

Novel payloads may allow targeting of previously intractable biological pathways (e.g., SMARCA2/4)

Novel payloads may open the ADC modality to other cancers that do not currently benefit from targeted therapies

Prelude's Precision ADCs are Designed to Improve the Therapeutic Index Over Traditional ADCs

	ADC	Precision ADC
Potency	☑	☑
Antibody Selectivity	☑	☑
Payload Selectivity	☒	☑
PD Marker for Payload	☒	☑
Therapeutic Index	☒	☑

Payload Selectivity
Highly potent and cell line selective targeted protein degrader

X

Antibody Selectivity
Highly selectively antibody that targets cancers that are sensitive to our payload

=

Precision ADC
Potential for enhanced potency and selectivity of antibody and payload to improve both efficacy and therapeutic index

Together, Prelude and AbCellera are Creating Novel, First-in-Class Precision ADCs

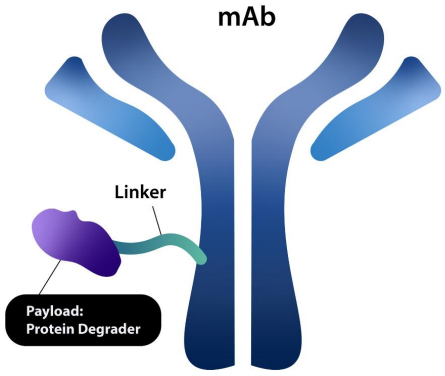
Prelude THERAPEUTICS

Expertise in chemistry and biology of targeted protein degradation and clinical development capabilities

+

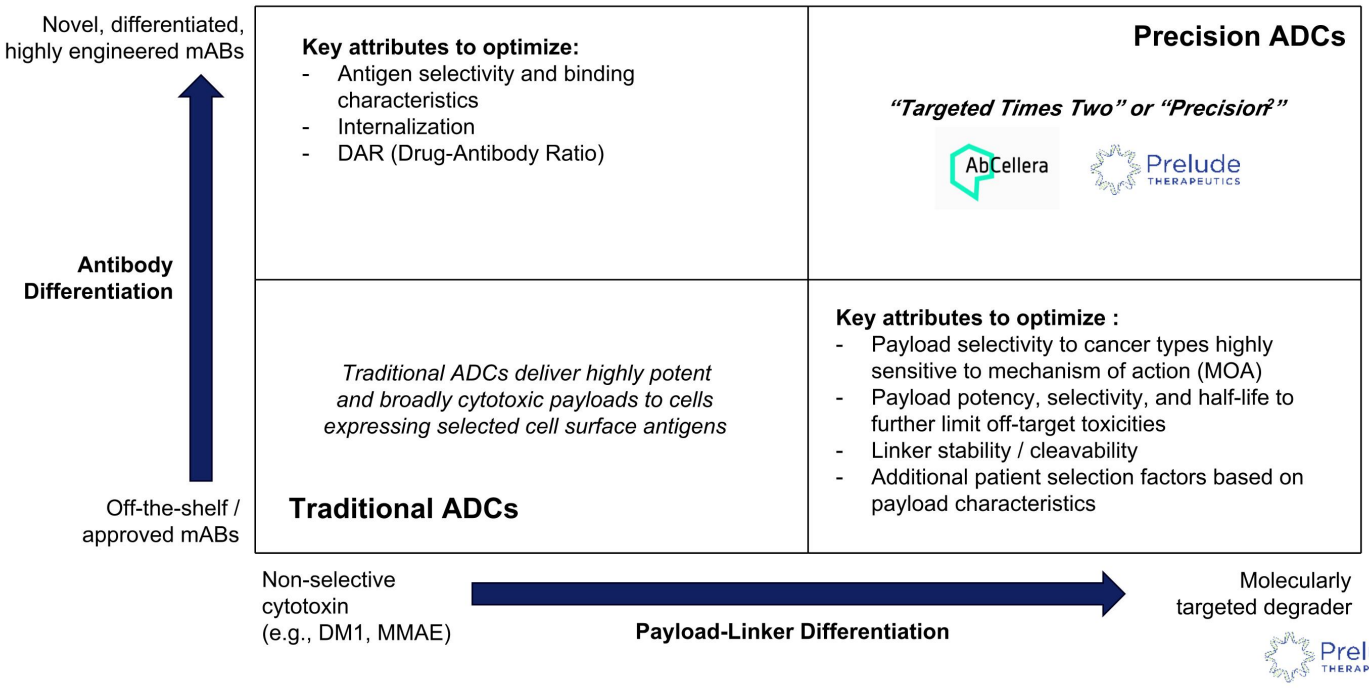
AbCellera

Expertise in antibody discovery, engineering and manufacturing capabilities



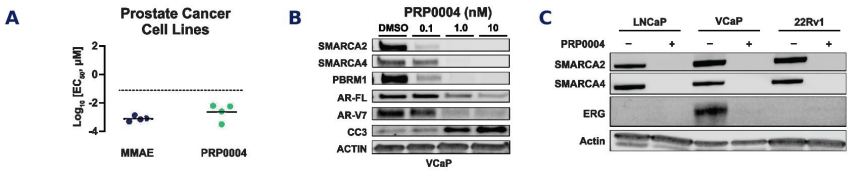
- Multi-year global collaboration to jointly discover, develop and commercialize novel Precision ADCs for up to five programs
- AbCellera will lead manufacturing activities
- Prelude will lead clinical development and global commercialization (AbCellera co-promote option)

Framework for Precision ADC Differentiation



Prelude THERAPEUTICS

SMARCA2/4 Degrader Payload (PRP0004) Induces Apoptosis and Regulates the Expression of Key Oncoprotein Drivers in Prostate Cancer Cells



(A) EC_{50} of human prostate cancer cell lines treated with PRP0004 or MMAE for 7-days (CellTiter-Glo® assay). (B) Western blot showing the expression of SMARCA2/4, AR-FL, AR-V7, and cleaved-caspase 3 (CC3) in VCaP cells treated with PRP0004 for 3 days. (C) Western blot showing the expression of ERG following treatment with PRP0004 in cells that express a *TMPRSS2-ERG* fusion.

Carter J., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

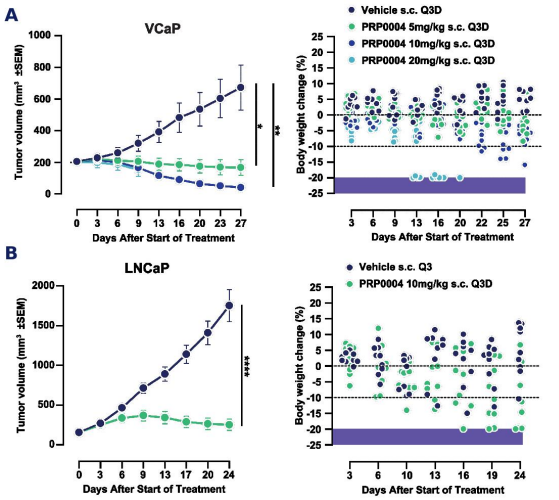
Triple Meeting Update

Prostate cancer was amongst the most sensitive cell lines to SMARCA2/4 degradation rationalizing the use of PSMA-targeting antibodies for further proof-of-concept studies

SMARCA2/4 degradation downregulates the expression of several key oncoprotein drivers in prostate cancer cell lines

Selective induction of apoptosis in prostate cancer cell lines with a novel payload could lead to an improved therapeutic index

SMARCA2/4 Degrader Payload (PRP0004) Administered On Its Own Induces Tumor Regressions in Prostate Cancer Models, But With a Narrow Therapeutic Index



(A) Payload PRP0004 administered s.c. Q3D demonstrated dose-dependent tumor growth inhibition in the human prostate cancer VCaP CDX model. At higher doses, PRP0004 induced tumor regressions but caused time and dose-dependent body weight loss and mouse deaths. *P<0.05 **P<0.01 versus vehicle (T-test) (B) Payload PRP0004 administered s.c. Q3D induced significant tumor growth inhibition in the human prostate cancer LNCaP CDX model, while leading to delayed body weight loss and mouse death. ****P<0.0001 versus vehicle (T-test).

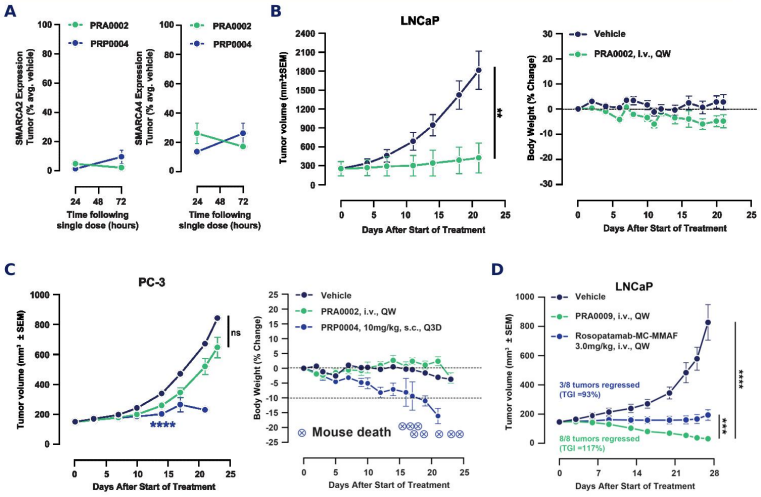
Carter J., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

Triple Meeting Update

On its own, payload PRP0004 demonstrated dose-dependent tumor growth inhibition in human prostate cancer CDX models

However, as anticipated, at higher doses, PRP0004 induced tumor regressions but was limited by a narrow therapeutic index

Anti-PSMA SMARCA2/4 DACs Demonstrate Robust and Significant Antigen-Selective Tumor Growth Inhibition



(A) SMARCA2/4 protein expression was analyzed in DAC PRA0002 and payload PRP0004-treated LNCaP tumors at the indicated time points following a single dose. Graphs are quantitation of western blots. (B) Weekly i.v. administration of PRA0002 was well-tolerated and demonstrated significant tumor growth inhibition (89%) of PSMA+ LNCaP tumors. (C) Weekly i.v. administration of PRA0002 did not induce significant tumor growth inhibition in PSMA- PC3 tumors, in comparison to PRP0004 which was efficacious, but caused mouse body weight loss and death (D) Weekly i.v. administration of PRA0009 demonstrated tumor regression and significantly better efficacy compared to a PSMA cytotoxic ADC (Rosopatamab-MC-MMAF, DAR2) in LNCaP tumors.

Carter J., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

2024 Triple Meeting Update

Anti-PSMA SMARCA2/4 DACs were well tolerated and demonstrated robust target engagement and antigen-dependent efficacy in xenograft models

These data highlight the potential of utilizing a SMARCA2/4 degrader payload to achieve maximal target degradation in tumors while sparing healthy tissues

Precision ADCs have the potential to expand the therapeutic reach of SMARCA2/4 degraders to patients without SMARCA4 mutations

Overview of Prelude's Precision ADC Program and Next Steps

- Degrader Antibody Conjugates (DACs) represent a new frontier in advancing the scientific and clinical potential of antibody drug conjugates (ADCs)
- Prelude is developing DACs with potent SMARCA2/4 dual degraders as payloads on tumor specific antibodies to achieve maximal target degradation in tumors and spare healthy tissues
  - SMARCA2 and SMARCA4 are the core catalytic subunits of SWI/SNF complexes and play a key role in controlling chromatin remodeling and gene expression
  - Targeting SWI/SNF complexes with targeted protein degraders demonstrates robust anti-tumor activity
  - Because either SMARCA2 or SMARCA4 is necessary for normal cellular functions, maximal suppression of both SMARCA2/4 proteins simultaneously is unlikely to be tolerated
  - Prelude's SMARCA2/4 dual degraders have shown picomolar potency with potential for increased efficacy, selectivity and a broader therapeutic index leading to a differentiated safety profile
- Preclinical proof-of-concept has now been presented with novel, highly potent SMARCA2/4 dual degraders conjugated as a "Precision Payloads" to multiple antibodies (PSMA, CEACAM5, TROP-2, C-MET, CD33)
- DACs expand the reach of SMARCA degrader technology to cancers without SMARCA4 mutations
- Work is underway to advance first-in-class DAC development candidates from the program and expand our portfolio of novel degrader payloads

Carter J., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (http://www.preludetx.com/science/publications)

APPENDIX

- **Highly Selective SMARCA2 Degrader Program**
  - Discovery Effort & Oral Degrader Program (PRT7732)
  - Preclinical Rationale for Combinations (**2024 EORTC-NCI-AACR Symposium Update**)
  - Current Treatment Paradigm & Testing Landscape

- **Precision ADCs**
  - **First Preclinical Proof-of-Concept Data Presented at 2024 EORTC-NCI-AACR Symposium**
  - Overview of Prelude's Precision ADC Program and Next Steps

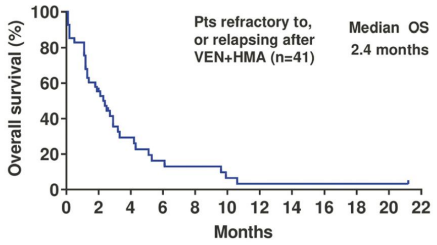
- **CDK9 Program for Hematologic Malignancies (PRT2527)**
  - Background, Unmet Need and Scientific Rationale
  - Early Clinical Safety and PK/PD Data from Phase I Study in Solid Tumors
  - Interim Phase I Update Planned for Major Medical Meeting in Q4 2024

BOLD = New data included in Appendix with this update

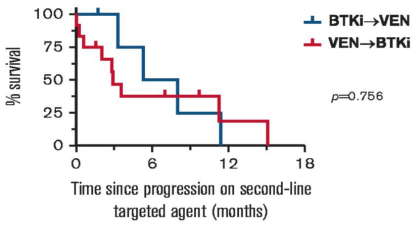
Prelude THERAPEUTICS

Patients with Hematologic Malignancies Refractory to Current Treatments Experience Poor Outcomes

(1) AML



(2) CLL

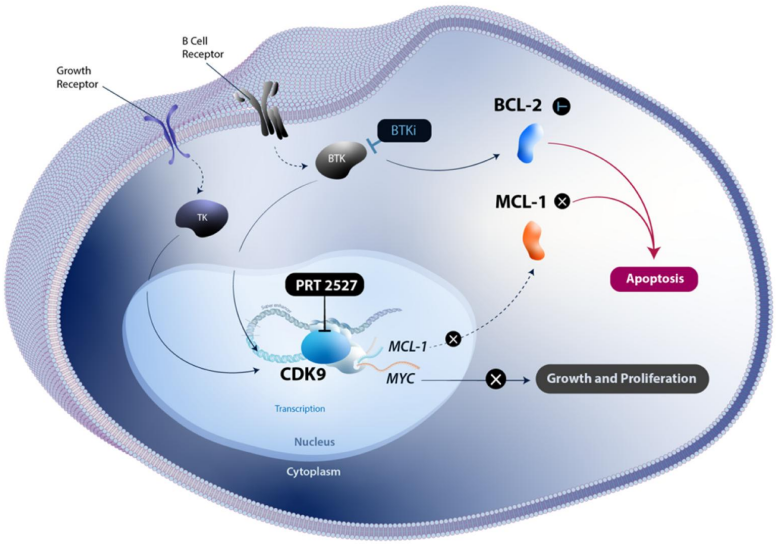


Source:
1) Maiti A et al. Haematologica 2021. https://doi.org/10.3324/haematol.2020.252569
2) Lew TE et al. Blood Advances 2021. https://doi.org/10.1182/bloodadvances.2021005083

After SoC (venetoclax + HMA), AML patients ineligible for intensive therapy have very poor outcomes (mOS of 2.4 months)

Double class (BTKi and BCL2i) resistant CLL is another population with high unmet need (mOS of 3-5 months)

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



CDK9 is the primary transcriptional regulator of a major oncogene MYC and an apoptosis inducer MCL-1

Dysregulated pathways involving MYC and MCL-1 drive pathogenesis and resistance in hematologic cancers including lymphoid and myeloid cancers

Prior CDK9i therapies have shown significant GI toxicity, likely driven by poor selectivity across the kinome

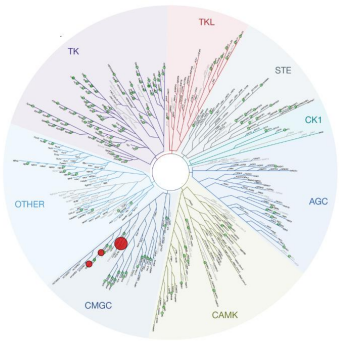
PRT2527 is a Potent, Highly Selective CDK9 Inhibitor That Depletes MCL-1 and MYC

Highly Isoform Selective CDK9 Inhibitor

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

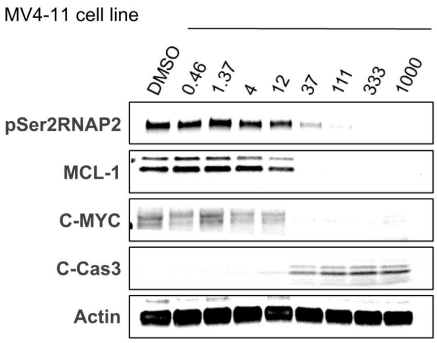
10 -100x >100x

Highly Selective in Kinome



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

PRT2527 Treatment Depletes MCL-1 and MYC Proteins

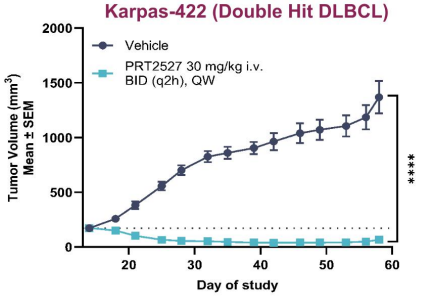


*Internal data; biochemical assay at 1 mM ATP, H929 CTG proliferation assay
ASH 2022 Presentation (https://www.preludetx.com/science/publications)

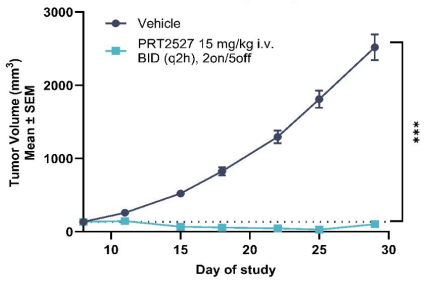
PRT2527 is Highly Efficacious In Vivo in Models of Hematologic Malignancies

Monotherapy

Karpas-422 (Double Hit DLBCL)

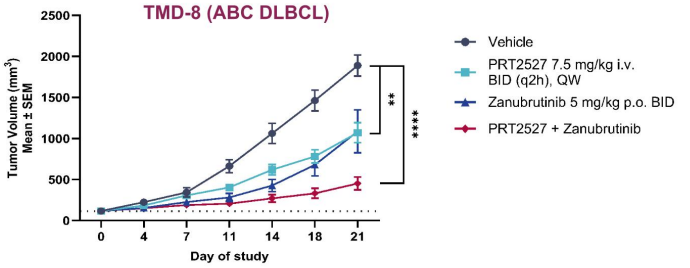


MV4-11 (AML)

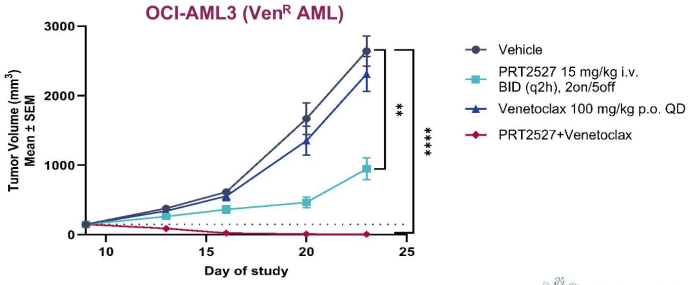


Combination

TMD-8 (ABC DLBCL)



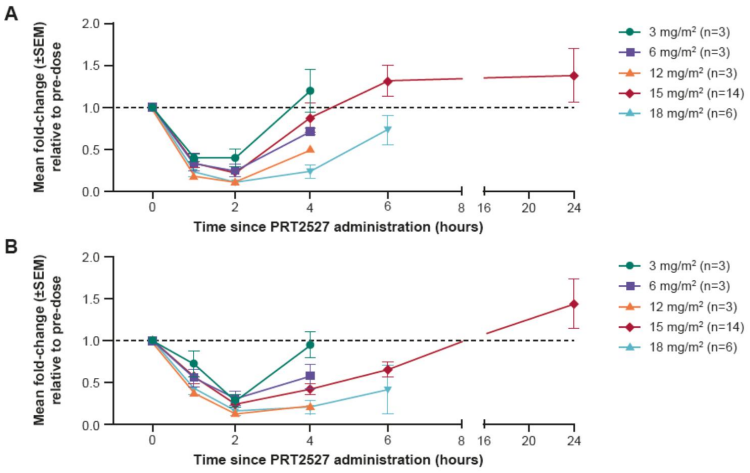
OCI-AML3 (Ven^{R} AML)



ASH 2022 Presentation (https://www.preludetx.com/science/publications); Data on file

Initial Phase 1 Study of PRT2527 in Solid Tumors Evaluated Both Safety and PK/PD Properties

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



Note: The dotted line represents pre-dose baseline levels.

Source: Patel, MR et al., AACR-NCI-EORTC 2023, Poster C164 (http://www.preludetx.com/science/publications)

ClinicalTrials.gov Identifier: NCT05159518

Favorable tolerability with manageable neutropenia and absence of significant gastrointestinal events or hepatotoxicity

Dose-dependent downregulation of CDK9 transcriptional targets – MYC and MCL-1 mRNA expression in PBMCs isolated from treated patients

12 mg/m² QW dosing and higher showed optimal target inhibition

Overall safety profile observed in this study supported further development of PRT2527 in hematologic malignancies (NCT05665530)

Thank You

Contact Us:

Robert Doody
SVP, Investor Relations
rdoody@preludetx.com