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): September 13, 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** **(Address of principal executive offices)**	**19805** **(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 September 13, 2024, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing the first interim clinical data from its Phase 1 open-label, dose-escalation trial of PRT3789, a novel, highly-selective SMARCA2 degrader. The press release was issued simultaneously with the previously announced oral presentation of an abstract regarding such data at the European Society of Medical Oncology (ESMO) Congress 2024. A copy of the press release is attached as Exhibit 99.1 to this report. Additionally, the Company hosted an investor webcast on September 13, 2024 at 12:00 p.m. EST. A copy of the presentation materials from the investor webcast is attached as Exhibit 99.2 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 99.3 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	Webcast presentation
99.3	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: September 13, 2024

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

Exhibit 99.1

Prelude Therapeutics' SMARCA2 Degrader PRT3789 Demonstrated Promising Initial Clinical Activity and Safety Profile in Phase 1 Trial

- *Encouraging signs of anti-tumor activity including objective responses observed in patients with SMARCA4-mutated non-small cell lung cancer (NSCLC) and esophageal cancer in early PRT3789 monotherapy dose escalation*

- *At doses studied to date, PRT3789 was generally well-tolerated with no dose-limiting toxicities or study drug-related serious adverse events*

- *Company to host investor conference call and webcast on Friday, September 13, 2024 at 12:00 PM EST*

WILMINGTON, Del., Sep. 13, 2024 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today announced the first interim clinical data from its ongoing Phase 1 open-label, dose-escalation trial of PRT3789, a first-in-class SMARCA2 degrader, highly selective for SMARCA2 and designed to treat cancer patients with a SMARCA4 mutation. The data were presented at the European Society for Medical Oncology (ESMO) Congress 2024 in Barcelona, Spain.

The study investigators reported that, as of the August 5, 2024 data cutoff date (the Cutoff Date), 65 patients were safety evaluable, enrolled and treated. This included 46 efficacy evaluable patients (with a post-baseline scan) with any tumor type harboring any SMARCA4 mutation.

As reported today by the study investigators, PRT3789 was generally well-tolerated through 8 dosing cohorts. Dose escalation continues, now in the 9th dosing cohort. The majority of adverse events reported by investigators have been mild to moderate. A maximum tolerated dose has not yet been identified.

Overall, of the 26 advanced, heavily pre-treated NSCLC or esophageal patients evaluable for efficacy, 7 had tumor shrinkage. RECIST confirmed partial responses (PRs) were observed in 3 patients. Additional patients demonstrated clinical benefit as measured by prolonged stable disease (SD) including one patient on treatment for more than 1 year.

"For cancer patients harboring a SMARCA4 mutation, the disease is particularly aggressive and prognosis with current standard of care is quite poor," stated Robin Guo, M.D., Memorial Sloan Kettering Cancer Center. "The observation of durable stable disease and tumor regressions in Phase I monotherapy dose escalation, coupled with a tolerable emerging safety profile, is

encouraging. This is what we hope to see with a first-in-class new therapy for a novel target in patients with a high unmet need."

"We are encouraged by the early clinical activity and emerging safety profile observed to date with PRT3789," stated Jane Huang, M.D., President and Chief Medical Officer of Prelude. "These data represent initial proof of concept that selective SMARCA2 degradation can yield antitumor activity in certain SMARCA4 mutated cancers."

Continued Dr. Huang, "Monotherapy dose escalation continues, now at cohort 9 (500mg once weekly) with backfill cohorts continuing to enroll enriched for NSCLC and esophageal cancer patients with Class 1 mutations. We intend to confirm the biologically active dose for PRT3789 as monotherapy by year-end and continue to advance monotherapy and docetaxel combination studies in parallel to best position PRT3789 as a new treatment option for patients suffering from this aggressive type of cancer."

PRT3789 Interim Phase 1 Results
PRT3789 is currently being evaluated in an ongoing dose-escalation Phase 1 trial in patients with solid tumors harboring any SMARCA4 mutation refractory to standard of care and generally multiple lines of therapy in most patients. As of the Cutoff Date, 65 patients with advanced cancer have been treated at eight dose levels (24 mg QW, 48 mg QW, 80 mg QW, 120 mg QW, 160 mg QW, 212 mg QW, 283 mg QW, 376 mg QW). The median age of these patients is 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 in the 65 patients treated as of the Cutoff Date. Adverse events are reported regardless of attribution to study drug. Adverse events of any grade observed to date consisted of nausea (24.5%), decreased appetite (18.5%), fatigue (18.5%), abdominal pain (16.9%), anemia (16.9%) and constipation (15.4%). 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 observed was more prolonged than PK half-life, reaching trough inhibition of 70-75% at higher doses. Increasing doses demonstrated a deeper and more prolonged PD effect. Evaluation of the AUC of PD (SMARCA2 and SMARCA4) demonstrated a dose dependent decrease of SMARCA2 but not SMARCA4, demonstrating the high selectivity of PRT3789.

Analysis of Initial Clinical Activity
As of the Cutoff Date, there were 46 efficacy evaluable patients with a post-baseline scan across all tumor types with any SMARCA4 mutation. Of the 26 advanced, heavily pre-treated NSCLC or esophageal patients who were evaluable for efficacy, 7 had tumor shrinkage. RECIST confirmed partial responses (PRs) were observed in 3 patients (2 esophageal, 1 NSCLC). 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. One patient remains on study having been treated for more than 1 year. Of the 20 patients with tumor types other than NSCLC and esophageal cancer, none demonstrated tumor shrinkage at dose levels studied to date.

Conference Call and Webcast Information
Prelude Therapeutics management team will host a conference call, live webcast with slides and a Q&A on Friday, September 13, 2024 at 12:00 PM ET. A live webcast of the presentation will be available at Events & Presentations - Prelude Therapeutics (preludetx.com) A replay of the webcast will be available shortly after the conclusion of the call at Events & Presentations - Prelude Therapeutics (preludetx.com) and archived on the Company's website for 60 days following the call.

Interim Phase 1 data selected for Plenary Session at upcoming EORTC-NCI-AACR Symposium
Interim Phase 1 data for PRT3789 was also selected for a Plenary Session oral presentation at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics. The presentation titled, *"First Clinical Results from a Phase 1 Trial of PRT3789, a First-in-Class SMARCA2 Degrader, in Patients with Advanced Solid Tumors with a SMARCA4 Mutation*," will be presented by Timothy Yap, M.D. from University of Texas MD Anderson Cancer Center. The presentation is scheduled for October 24, 2024 at 10:00 AM CEST (4:00 AM EST) as part of the Proffered Papers: Advancing Patient Care Through Novel Clinical Trials session.

About PRT3789 – A first-in-class, highly selective, intravenous SMARCA2 degrader

PRT3789 is a first-in-class SMARCA2 degrader, highly selective for SMARCA2 and designed to treat patients with a SMARCA4 mutation. Cancer patients whose tumors have SMARCA4 mutations have a poor prognosis and as a result, this is an area of high unmet medical need.

PRT3789 is in Phase 1 clinical development in biomarker selected SMARCA4 mutant patients. Enrollment remains on track, and the Company expects to conclude monotherapy dose escalation in 2024 and identify a recommended Phase 2 dose. In addition, enrollment of patients into back-fill cohorts enriched for NSCLC and SMARCA4 loss-of-function mutations is ongoing, as is enrollment of the docetaxel combination cohort.

Objectives for this first Phase 1 clinical trial are to establish the safety and tolerability profile of PRT3789 as both monotherapy and in combination with docetaxel, evaluate activity, pharmacokinetics and pharmacodynamics and determine a dose and potential indications for advancement into registrational clinical trial(s).

Prelude launched an educational video series focused on the science of SMARCA biology, the discovery of first-in-class, highly selective SMARCA2 degraders and the unmet medical need for patients with SMARCA4 mutated cancer. This series can be found on the Company's website under Highly Selective SMARCA2 Degraders - Prelude Therapeutics (preludetx.com).

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.

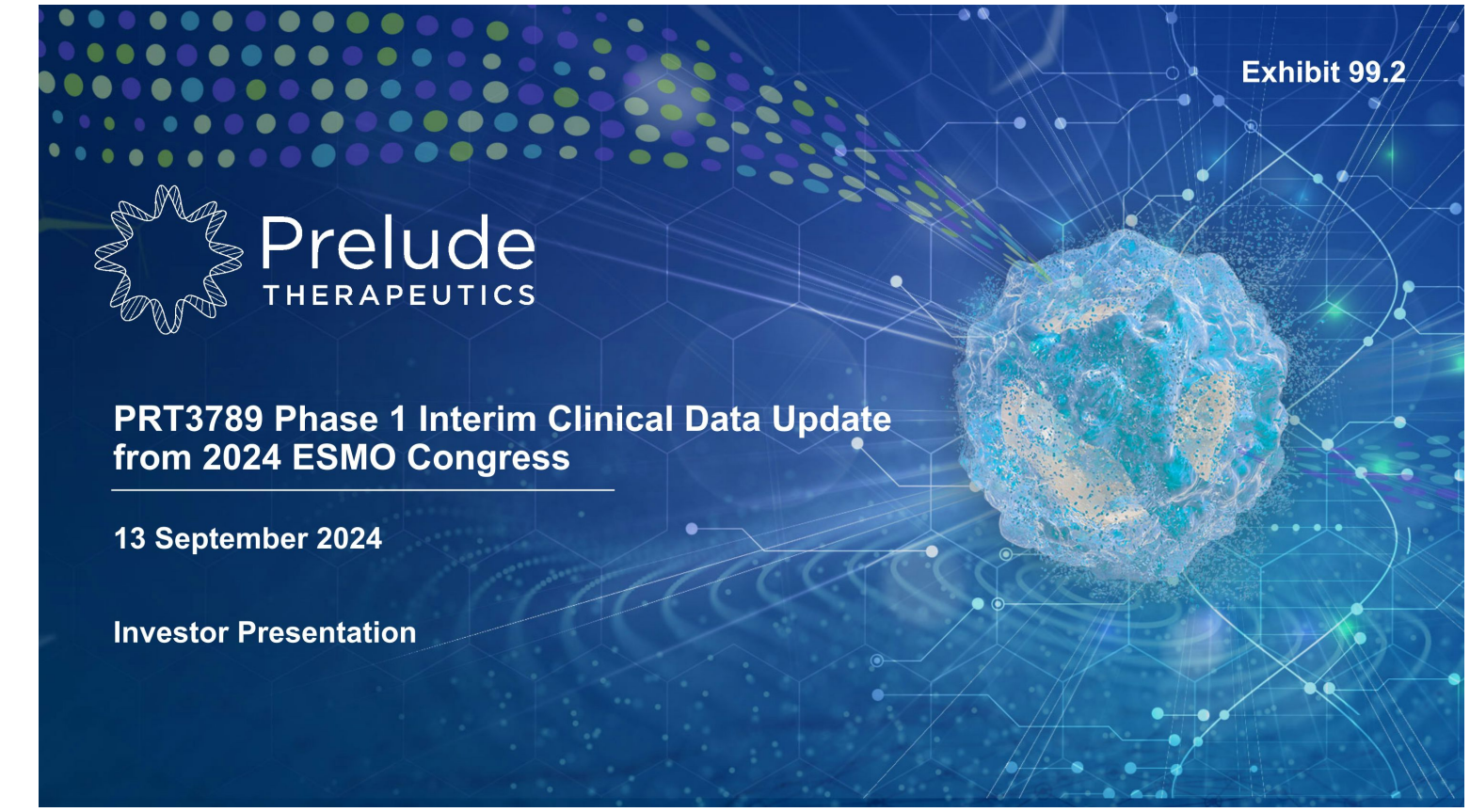
Cautionary Note Regarding Forward-Looking Statements

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 the expected timeline for concluding the monotherapy dose escalation and identifying the biologically active dose, and expected ongoing work on and development of PRT3789. 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
Prelude Therapeutics Incorporated
484.639.7235
rdoody@preludetx.com

Exhibit 99.2



Prelude THERAPEUTICS

PRT3789 Phase 1 Interim Clinical Data Update from 2024 ESMO Congress

13 September 2024

Investor Presentation

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, including product candidates that are the subjects of the Company’s collaborations and partnerships, 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 and our Quarterly Reports on Form 10-Q.

Prelude THERAPEUTICS

Opening Remarks

Kris Vaddi, Ph.D., CEO
Prelude Therapeutics Incorporated

Prelude THERAPEUTICS

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

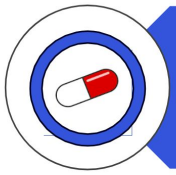
Strive for first- or best-in-class and anchor to patient unmet need

Select the best modality to precisely target oncogenic mechanisms

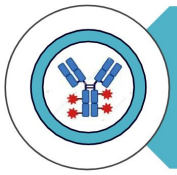
Draw on decades of experience and proven leadership to drive innovation

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

PRT3789 Overview and Phase 1 Interim Data

Dr. Jane Huang, President & Chief Medical Officer
Prelude Therapeutics Incorporated

A Phase 1 Trial of PRT3789, a First-in-Class SMARCA2 Degrader in Patients with Advanced Solid Tumors With a SMARCA4 Mutation

Guo, R. et. al., ESMO Congress, 13 Sept 2024

Expert Perspective on SMARCA4-*mutated* Cancer

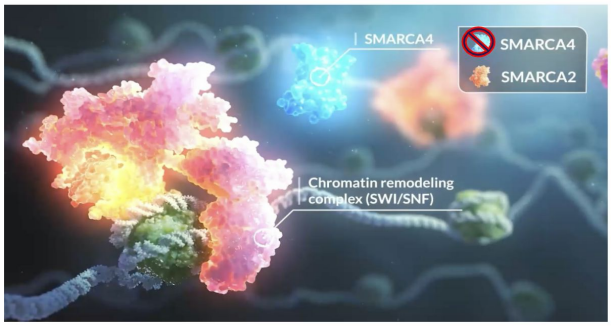
Dr. Timothy Yap, University of Texas MD Anderson Cancer Center

Investigator on PRT3789-01:

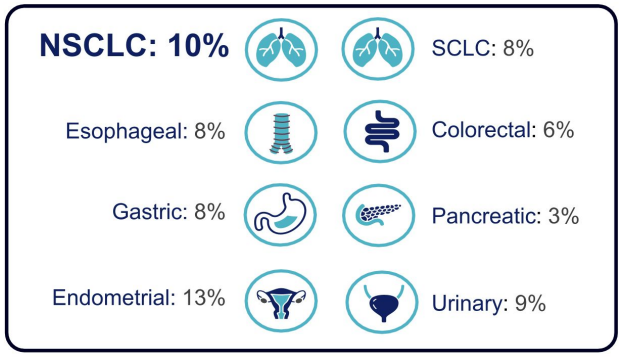
A Phase 1 Trial of PRT3789, a First-in-Class SMARCA2 Degrader in Patients with Advanced Solid Tumors With a SMARCA4 Mutation

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

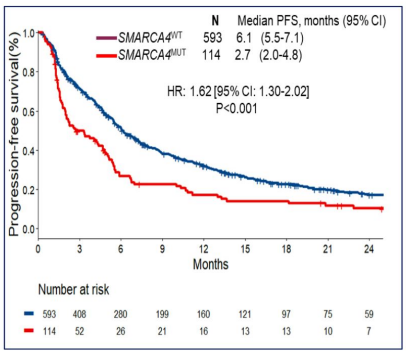
Selectively degrading SMARCA2 induces "synthetic lethality" in SMARCA4-*deficient* cancers

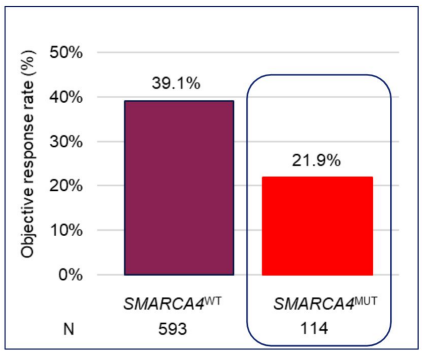
Patients with SMARCA4 mutations are not typically eligible for other targeted therapies

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





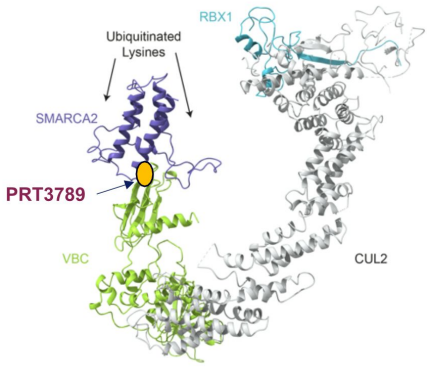
Median progression free survival for <u>first-line</u> SMARCA4-mutated NSCLC treated with chemoimmunotherapy is 2.7 months and response rates approximately 22%

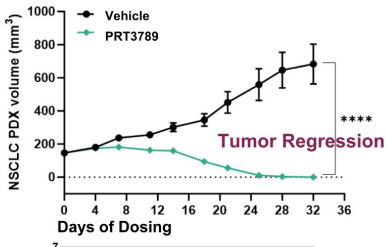
There is even greater unmet need in <u>second-line and beyond</u>

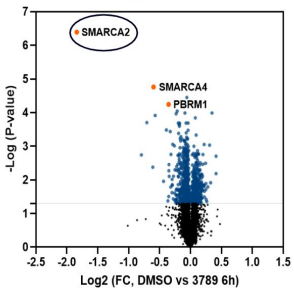
Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193.

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







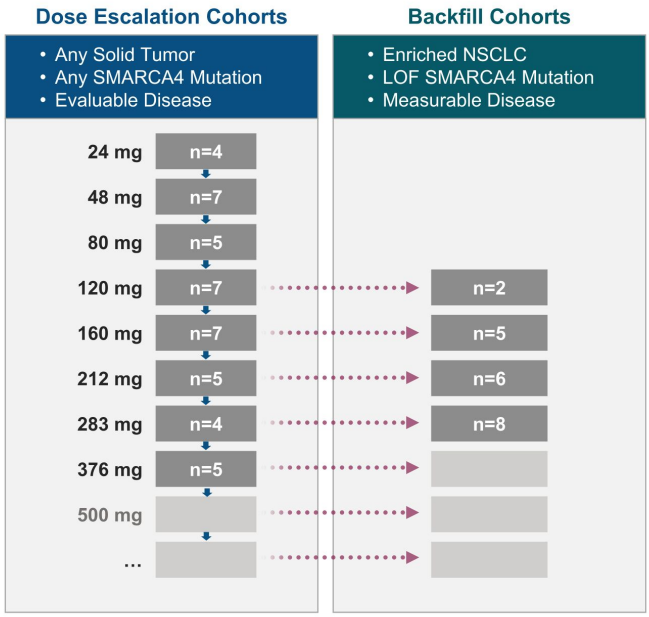
Hulse et al. *Cancer Res*. (2022); 82 (12_Suppl) :3263.
AACR 2022: https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

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

PRT3789-01: Study Schema and Enrollment



Phase 1 dose escalation study enrolled patients who had evaluable disease, any solid tumors, and any type of SMARCA4 mutation

All patients received PRT3789 intravenously once weekly

Patients treated in escalating doses from 24 to 376 mg and backfill cohort patients who had SMARCA4 (Class 1) loss of function mutations

LOF, loss of function; NSCLC, non-small cell lung cancer

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

PRT3789-01: Demographics and Disease Characteristics

Characteristics	Patients (N=65)
Age (years)	
Median	62.0
Sex, n (%)	
Male	36 (55.4)
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	34 (52.3)
Pancreatic cancer	6 (9.2)
Breast cancer	4 (6.2)
Cholangiocarcinoma	2 (3.1)
Colorectal cancer	2 (3.1)
Esophageal cancer	2 (3.1)
Ovarian 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)

IHC, immunohistochemistry; VUS, variant of uncertain significance.

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

65 patients were safety evaluable

Primary tumor type was NSCLC (n = 34) patients along with a range of other solid tumors

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

PRT3789-01: Patient Disposition

	24 mg (n=4)	48 mg (n=7)	80 mg (n=5)	120 mg (n=9)	160 mg (n=12)	212 mg (n=11)	283 mg (n=12)	376 mg (n=5)	Total (N=65)
Treated, n (%)	4 (100)	7 (100)	5 (100)	9 (100)	12 (100)	11 (100)	12 (100)	5 (100)	65 (100)
On treatment	0	1 (14.3)	0	0	0	2 (18.2)	7 (58.3)	4 (80.0)	14 (21.5)
Off treatment	4 (100)	6 (85.7)	5 (100)	9 (100)	12 (100)	9 (81.8)	5 (41.7)	1 (20.0)	51 (78.5)
Reason for treatment discontinuation, n (%)									
Adverse event	0	0	0	0	1 (8.3)	0	0	0	1 (1.5)
Physician decision	0	0	0	1 (11.1)	0	0	0	0	1 (1.5)
Disease progression	4 (100)	6 (85.7)	5 (100)	8 (88.9)	11 (91.7)	8 (72.7)	5 (41.7)	1 (20.0)	48 (73.8)
Withdrawal of consent	0	0	0	0	0	1 (9.1)	0	0	1 (1.5)
Duration of treatment (weeks)									
Median	7.5	5.9	3.1	6.0	3.9	6.0	2.4	4.1	5.0
Min, Max	6.0, 9.7	1.0, 54.6	1.0, 16.0	2.0, 30.0	1.0, 18.0	0.1, 23.1	0.1, 16.0	1.0, 6.0	0.1, 54.6

As of the data cutoff, 21.5% patients remained on treatment

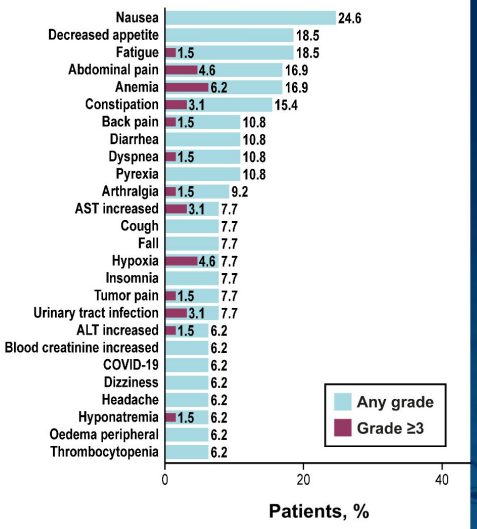
Only one patient discontinued treatment due to an adverse event, considered unrelated to study drug

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

PRT3789-01: Summary of Adverse Events

Adverse events, n (%)	Patients (N=65)
Any adverse event	58 (89.2)
Treatment related	37 (56.9)
Grade ≥3 adverse event	33 (50.8)
Treatment related	3 (4.6)
Serious adverse event	19 (29.2)
Treatment related	0
Adverse event leading to	
Dose hold	18 (27.7)
Dose reduction	0
Treatment discontinuation	2 (3.1)
Death	0
Any dose-limiting toxicity	0



65 patients were safety evaluable

PRT3789 was generally well tolerated; no drug related SAEs or dose limiting toxicities to date

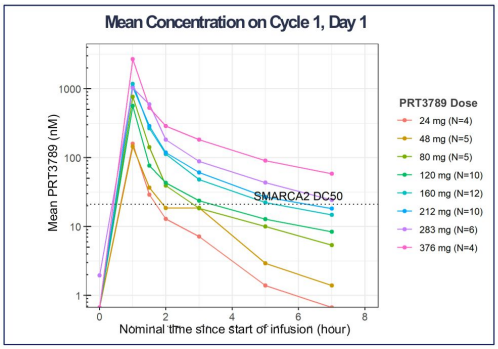
Of all adverse events, nausea, decreased appetite and fatigue had the highest incidence

Patients receiving at least one dose of PRT3789
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

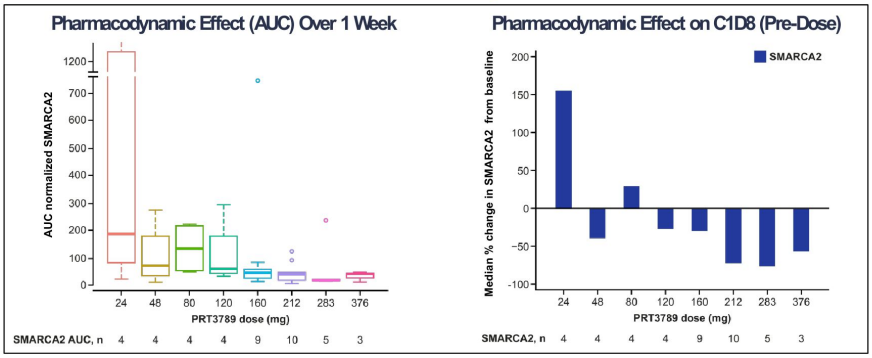
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

PRT3789-01: Phase 1 Interim PK/PD Findings



- Preliminary PK data are available from 24mg to 376mg
- General trend of increases in exposure (C_{max}, AUC) with dose were seen
- Mean concentrations were above SMARCA2 plasma DC_{50} (21 nM) for approximately 8 hours at 376 mg
- Mean half-life was 4.7 hours at the 376 mg dose level
- No accumulation seen with repeat dose administration; consistent with the half-life and once-weekly administration



AUC, area under the curve; C_{max}, maximum concentration; DC_{50}, half-maximal degradation concentration; PK, pharmacokinetics. C1D8, cycle1 day 8.

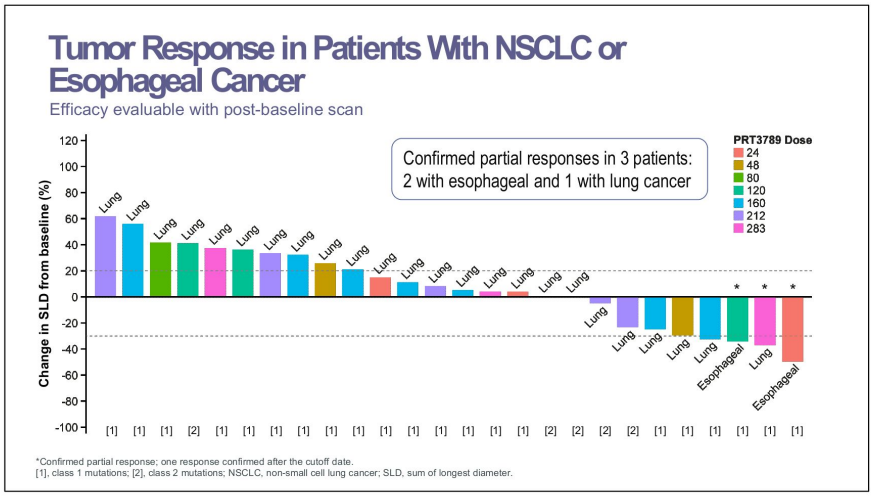
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

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

Increasing doses showed deeper and more prolonged SMARCA2 degradation in the peripheral blood monocytes (PBMCs) of patients

PRT3789 showed selective SMARCA2 degradation with minimal observed effect on SMARCA4 levels

PRT3789-01: Phase 1 Interim Clinical Activity



- Positive correlation observed between tumor shrinkage and a higher level of sustained SMARCA2 degradation
- Enrollment is now into dose cohort 9 (500 mg QW)

Of the 26 NSCLC or esophageal patients with at least one post baseline scan who were evaluable for efficacy, 7 had tumor shrinkage

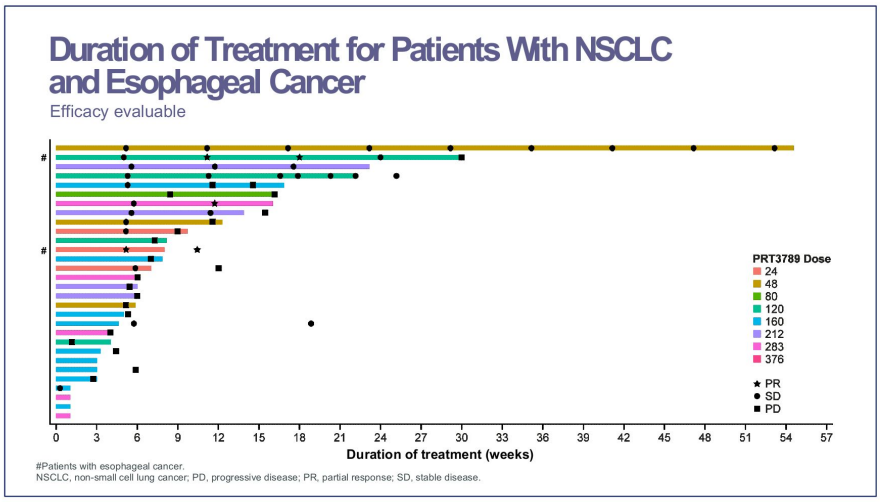
RECIST confirmed partial responses (PRs) were observed in 3 patients (2 esophageal, 1 NSCLC)

Tumor shrinkage was observed in patients with both Class 1 and Class 2 SMARCA4 mutations

Tumor shrinkage defined as 5% or greater decrease in sum of longest diameters of target lesions

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

PRT3789-01: Phase 1 Interim Clinical Activity



The median progression free survival for <u>first-line</u> SMARCA4-*mutated* NSCLC treated with chemo-immunotherapy is 2.7 months[1]

In this heavily pretreated patient population of SMARCA4-*mutated* patients, some have demonstrated clinical benefit as measured by prolonged stable disease (SD) and confirmed responses

One patient remains on study having been on treatment for more than 1 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. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193.

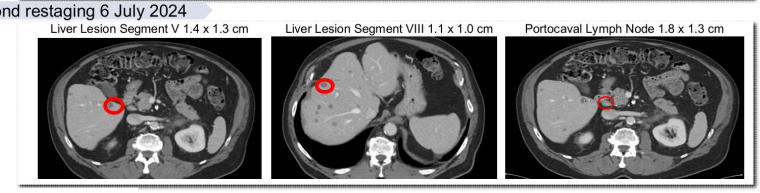
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

PRT3789-01: Patient Case Study

72-Year-Old Man With Metastatic, Poorly Differentiated Carcinoma of the Lung With Squamous Differentiation; Prior Therapy Included Carbo/Paclitaxel and Carbo/Docetaxel/Pembrolizumab

Baseline 11 April 2024

Second restaging 6 July 2024



Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

The patient images depicted here are representative of a "classical" patient with SMARCA4 mutations: poorly differentiated, aggressive disease

This patient experienced a confirmed PR, with tumor shrinkage in liver lesions and lymph nodes

This patient was treated at 283 mg and is ongoing on the trial

PRT3789-01: Key Takeaways

Summary and Conclusions

- PRT3789, a first-in-class, selective SMARCA2 degrader is being developed to treat SMARCA4-deficient cancer
- At doses studied, PRT3789 is generally well tolerated, with no dose-limiting toxicities or study drug-related serious adverse events reported to date
- Pharmacokinetic analysis shows increases in exposure (C_{max}, AUC) with dose
- Pharmacodynamic effect is more prolonged than pharmacokinetic half-life; increasing doses show deeper and more prolonged pharmacodynamic effect
- Encouraging signs of anti-tumor activity are seen in patients with NSCLC or esophageal cancer
- RP2D not reached, dose escalation and backfill enrollment ongoing
- Combinations of PRT3789 + docetaxel and PRT3789 + pembrolizumab will also be tested

AUC, area under the curve; C_{max}, maximum concentration; NSCLC, non-small cell lung cancer.

These data represent initial proof of concept that selective SMARCA2 degradation can yield anti-tumor activity in certain SMARCA4-*mutated* cancers

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

What's Next for PRT3789?

'3789 Monotherapy Dose Confirmation

- Currently enrolling patients in dose escalation cohort 9 (500 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 to be presented at plenary session of Triple Meeting, October 24th, 2024

'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 on track to initiate in 2H 2024
- Subject of recent clinical collaboration agreement with Merck
- Goal is to assess safety and clinical activity in combination

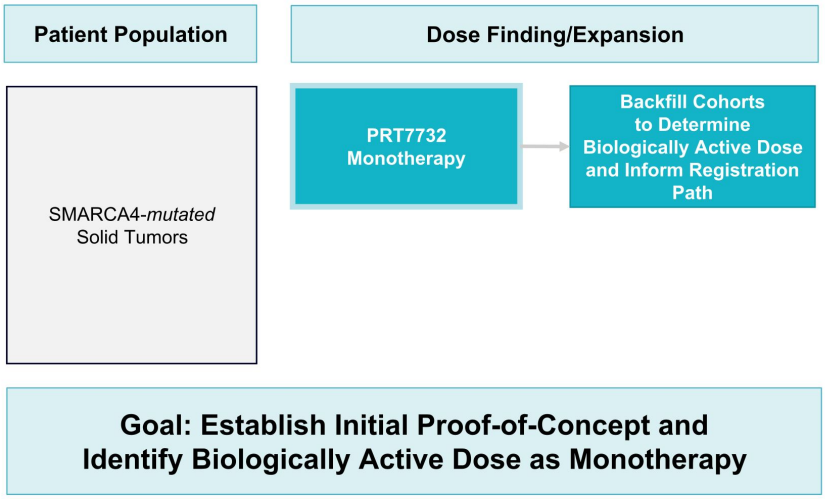
'3789 Program Priorities:

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

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; DLT = dose limiting toxicity; NSCLC – non-small cell lung cancer; 2L = second-line

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

Preclinical 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 Identify 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 supporting once-daily projected human dose

Closing Remarks

Kris Vaddi, Ph.D., CEO
Prelude Therapeutics Incorporated

Open for Questions

Kris Vaddi, PhD
Chief Executive Officer

Jane Huang M.D.
President and Chief Medical Officer

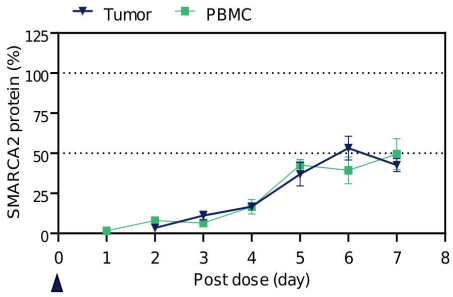
Peggy Scherle, PhD
Chief Scientific Officer

Sean Brusky, MBA
Chief Business Officer

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

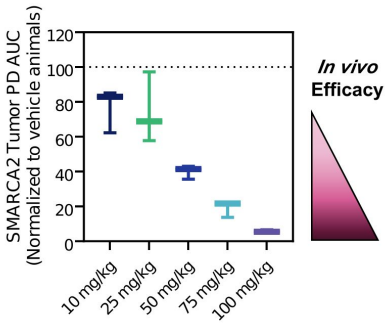
PD Correlates with Efficacy in Preclinical Models

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 exposure

PD AUC/Efficacy Correlation



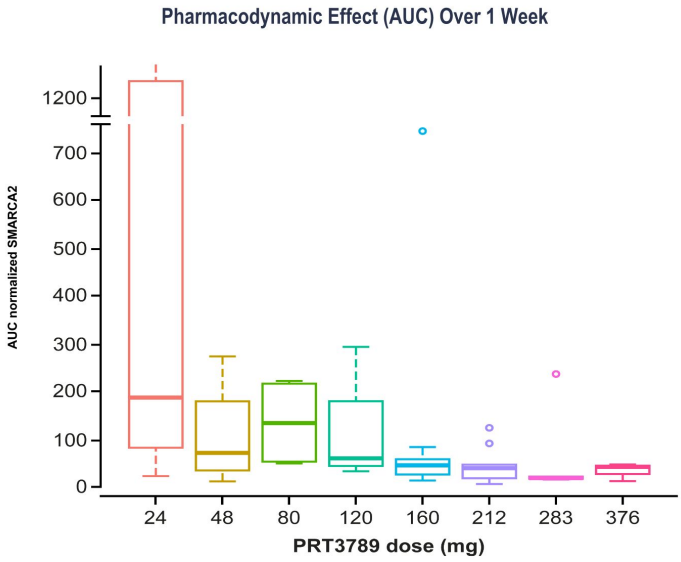
50 mg/kg = 243 mg human dose equivalent
75 mg/kg = 365 mg human dose equivalent
100 mg/kg = 487 mg human dose equivalent

Correlation observed between peripheral blood monocyte (PBMC) and tumor SMARCA2 degradation levels at efficacious doses

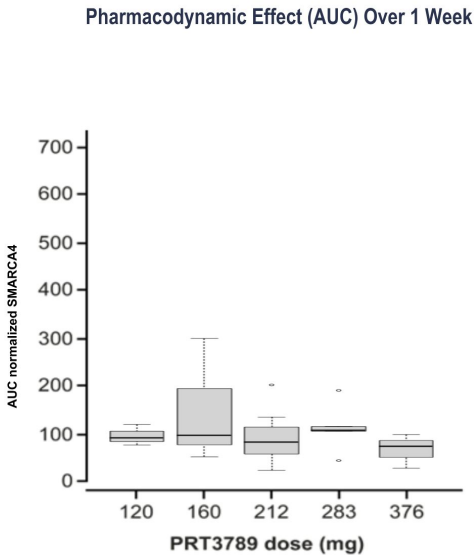
Increasing doses result in increased reduction in SMARCA2 PD AUC in tumors and were associated with higher efficacy

AUC, area under curve
Source: Wang et al. ENA 2023; Data on file

Dose Dependent Degradation of SMARCA2, but not SMARCA4



SMARCA2 AUC, n	4	4	4	4	9	10	5	3



SMARCA4 AUC, n	3	8	10	5	3

Exhibit 99.3

Corporate Presentation

September 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)
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**

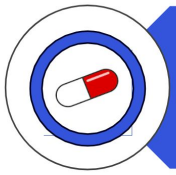
Prelude's Precision Medicine Pipeline & Discovery Engine

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)		**Expand SMARCA Portfolio to Address Cancers Without SMARCA4 Mutations**
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)		**First Program to be Presented at Medical Conference in Q4 2024**

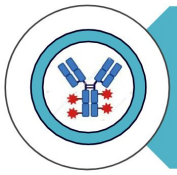
* Precision ADCs are the focus of our strategic collaboration with AbCellera

Developing an Industry Leading Portfolio of SMARCA-Targeted Precision Medicines

Lead SMARCA2 Degrader (PRT3789)



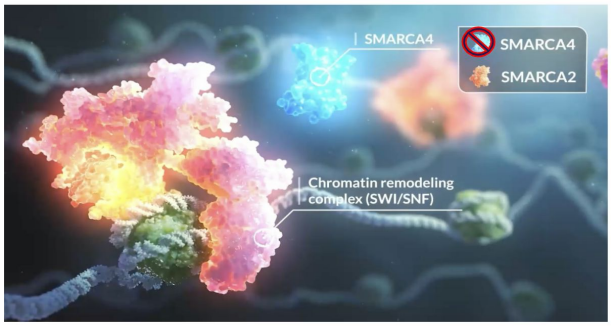
Oral SMARCA2 Degrader (PRT7732)



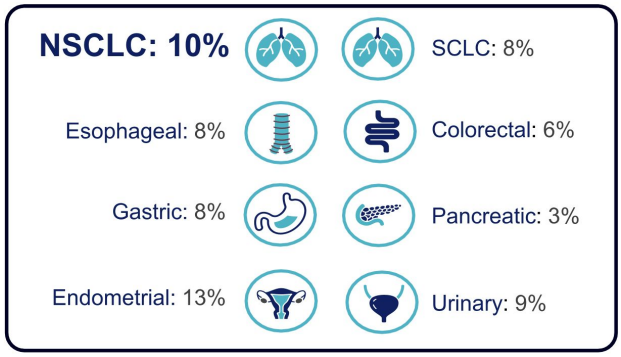
Precision ADCs with SMARCA2/4 Degrader Payload

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

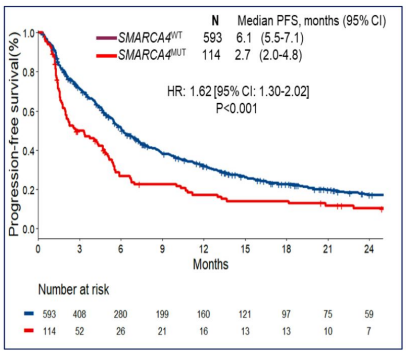
Selectively degrading SMARCA2 induces "synthetic lethality" in SMARCA4-*deficient* cancers

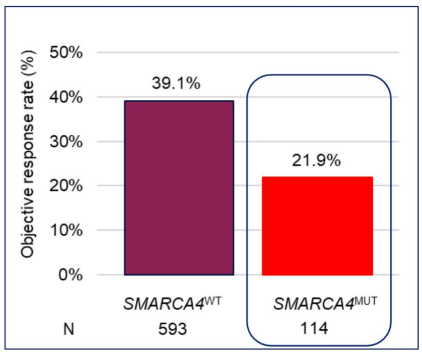
Patients with SMARCA4 mutations are not typically eligible for other targeted therapies

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





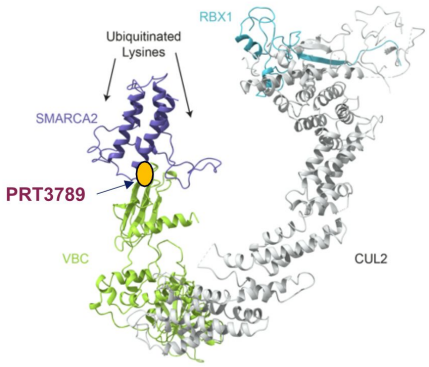
Median progression free survival for <u>first-line</u> SMARCA4-mutated NSCLC treated with chemoimmunotherapy is 2.7 months and response rates approximately 22%

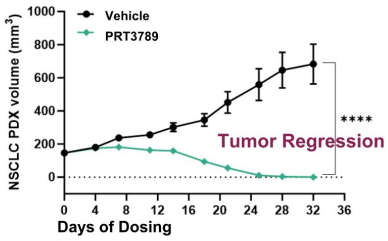
There is even greater unmet need in <u>second-line and beyond</u>

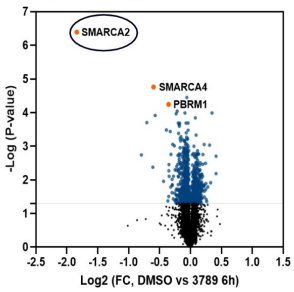
Alessi JV, et al. Clinicopathologic and genomic factors impacting efficacy of first-line chemoimmunotherapy in advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2023 Feb 10:S1556-0864(23)00121-1. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193.

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







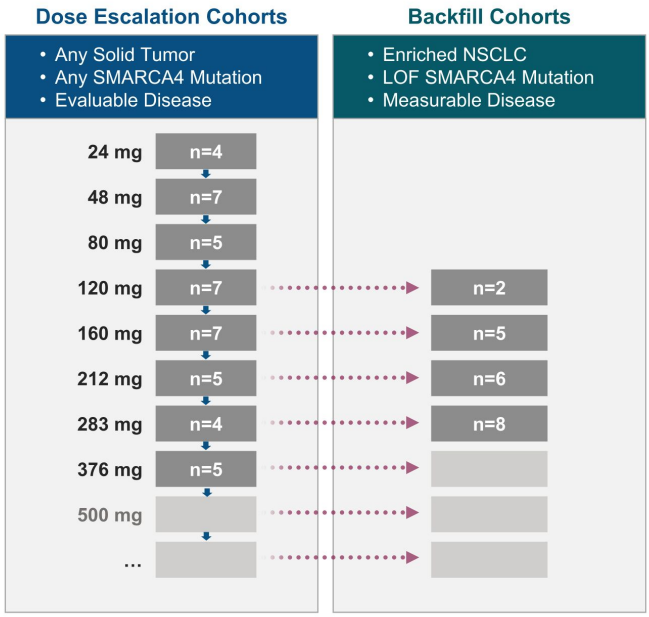
Hulse et al. *Cancer Res*. (2022); 82 (12_Suppl) :3263.
AACR 2022: https://preludetx.com/wp-content/uploads/2022/05/Prelude_AACR_Hulse-SMARCA2-FINAL-21Mar2022.pdf

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

PRT3789-01: Study Schema and Enrollment



Phase 1 dose escalation study enrolled patients who had evaluable disease, any solid tumors, and any type of SMARCA4 mutation

All patients received PRT3789 intravenously once weekly

Patients treated in escalating doses from 24 to 376 mg and backfill cohort patients who had SMARCA4 (Class 1) loss of function mutations

LOF, loss of function; NSCLC, non-small cell lung cancer

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

PRT3789-01: Demographics and Disease Characteristics

Characteristics	Patients (N=65)
Age (years)	
Median	62.0
Sex, n (%)	
Male	36 (55.4)
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	34 (52.3)
Pancreatic cancer	6 (9.2)
Breast cancer	4 (6.2)
Cholangiocarcinoma	2 (3.1)
Colorectal cancer	2 (3.1)
Esophageal cancer	2 (3.1)
Ovarian 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)

IHC, immunohistochemistry; VUS, variant of uncertain significance.

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

65 patients were safety evaluable

Primary tumor type was NSCLC (n = 34) patients along with a range of other solid tumors

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

PRT3789-01: Patient Disposition

	24 mg (n=4)	48 mg (n=7)	80 mg (n=5)	120 mg (n=9)	160 mg (n=12)	212 mg (n=11)	283 mg (n=12)	376 mg (n=5)	Total (N=65)
Treated, n (%)	4 (100)	7 (100)	5 (100)	9 (100)	12 (100)	11 (100)	12 (100)	5 (100)	65 (100)
On treatment	0	1 (14.3)	0	0	0	2 (18.2)	7 (58.3)	4 (80.0)	14 (21.5)
Off treatment	4 (100)	6 (85.7)	5 (100)	9 (100)	12 (100)	9 (81.8)	5 (41.7)	1 (20.0)	51 (78.5)
Reason for treatment discontinuation, n (%)									
Adverse event	0	0	0	0	1 (8.3)	0	0	0	1 (1.5)
Physician decision	0	0	0	1 (11.1)	0	0	0	0	1 (1.5)
Disease progression	4 (100)	6 (85.7)	5 (100)	8 (88.9)	11 (91.7)	8 (72.7)	5 (41.7)	1 (20.0)	48 (73.8)
Withdrawal of consent	0	0	0	0	0	1 (9.1)	0	0	1 (1.5)
Duration of treatment (weeks)									
Median	7.5	5.9	3.1	6.0	3.9	6.0	2.4	4.1	5.0
Min, Max	6.0, 9.7	1.0, 54.6	1.0, 16.0	2.0, 30.0	1.0, 18.0	0.1, 23.1	0.1, 16.0	1.0, 6.0	0.1, 54.6

As of the data cutoff, 21.5% patients remained on treatment

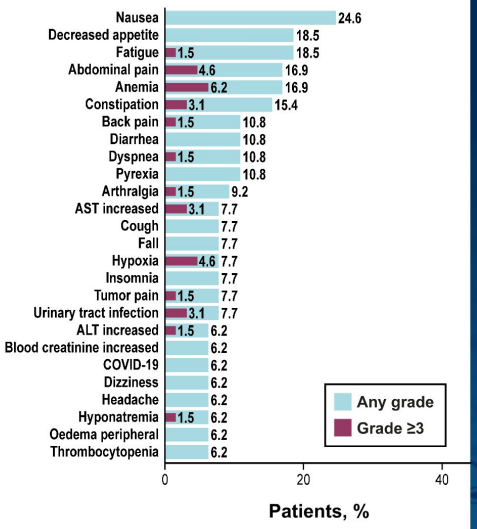
Only one patient discontinued treatment due to an adverse event, considered unrelated to study drug

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

PRT3789-01: Summary of Adverse Events

Adverse events, n (%)	Patients (N=65)
Any adverse event	58 (89.2)
Treatment related	37 (56.9)
Grade ≥3 adverse event	33 (50.8)
Treatment related	3 (4.6)
Serious adverse event	19 (29.2)
Treatment related	0
Adverse event leading to	
Dose hold	18 (27.7)
Dose reduction	0
Treatment discontinuation	2 (3.1)
Death	0
Any dose-limiting toxicity	0



65 patients were safety evaluable

PRT3789 was generally well tolerated; no drug related SAEs or dose limiting toxicities to date

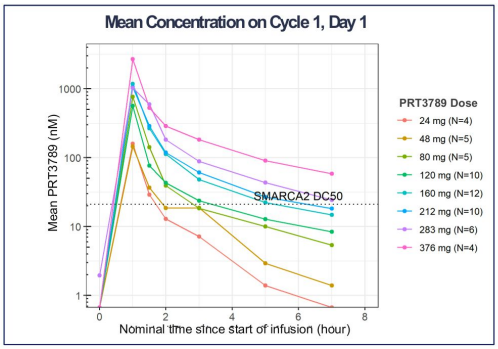
Of all adverse events of any grade, nausea, decreased appetite and fatigue had the highest incidence

Patients receiving at least one dose of PRT3789
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

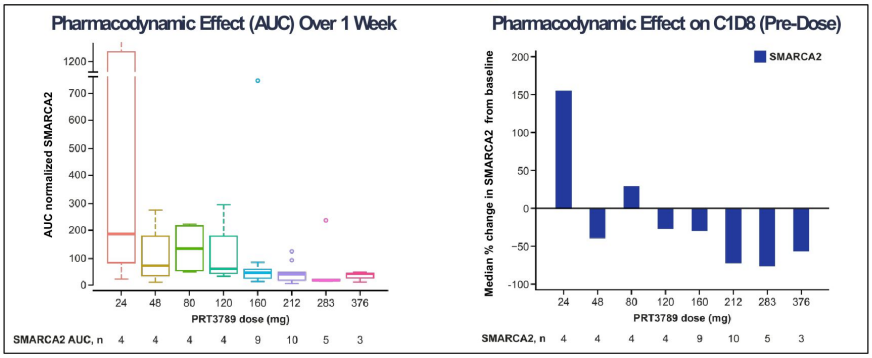
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

Data cutoff: 05 August 2024

PRT3789-01: Phase 1 Interim PK/PD Findings



- Preliminary PK data are available from 24mg to 376mg
- General trend of increases in exposure (C_{max}, AUC) with dose were seen
- Mean concentrations were above SMARCA2 plasma DC_{50} (21 nM) for approximately 8 hours at 376 mg
- Mean half-life was 4.7 hours at the 376 mg dose level
- No accumulation was seen with repeat dose administration; consistent with the half-life and once-weekly administration



AUC, area under the curve; C_{max}, maximum concentration; DC_{50}, half-maximal degradation concentration; PK, pharmacokinetics. C1D8, cycle1 day 8.

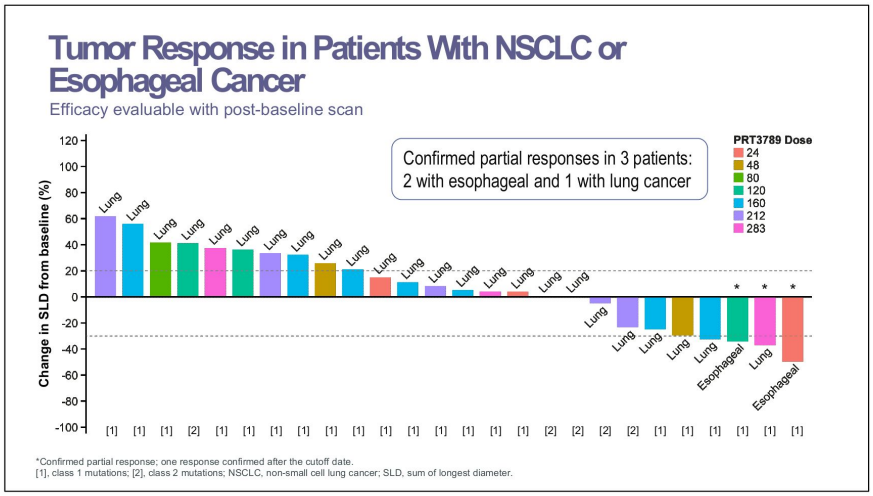
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

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

Increasing doses show deeper and more prolonged SMARCA2 degradation in the peripheral blood monocytes (PBMCs) of patients

PRT3789 showed selective SMARCA2 degradation with minimal observed effect on SMARCA4 levels

PRT3789-01: Phase 1 Interim Clinical Activity



- Positive correlation observed between tumor shrinkage and a higher level of sustained SMARCA2 degradation
- Enrollment is now into dose cohort 9 (500 mg QW)

Of the 26 NSCLC or esophageal patients with at least one post baseline scan who were evaluable for efficacy, 7 had tumor shrinkage

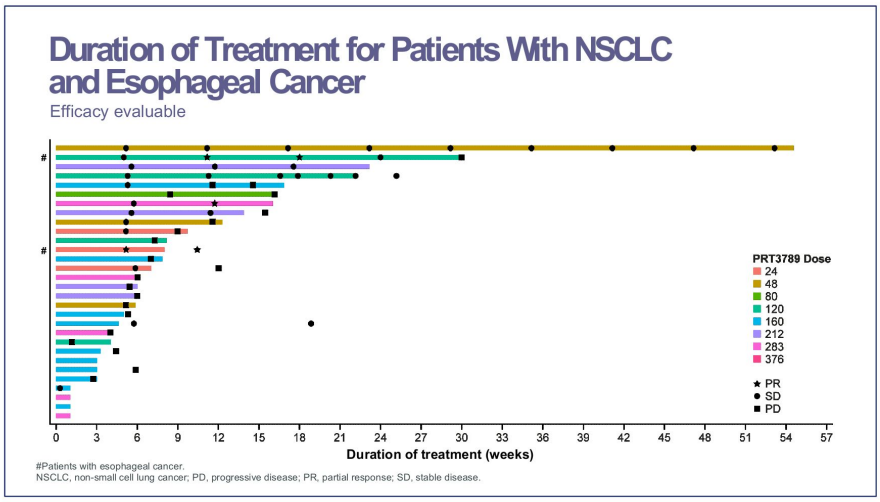
RECIST confirmed partial responses (PRs) were observed in 3 patients (2 esophageal, 1 NSCLC)

Tumor shrinkage was observed in patients with both Class 1 and Class 2 SMARCA4 mutations

Tumor shrinkage defined as 5% or greater decrease in sum of longest diameters of target lesions

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

PRT3789-01: Phase 1 Interim Clinical Activity



The median progression free survival for <u>first-line</u> SMARCA4-*mutated* NSCLC treated with chemo-immunotherapy is 2.7 months[1]

In this heavily pretreated patient population of SMARCA4-*mutated* patients, some have demonstrated clinical benefit as measured by prolonged stable disease (SD) and confirmed responses

One patient remains on study having been on treatment for more than 1 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. doi: 10.1016/j.jtho.2023.01.091. PMID: 36775193.

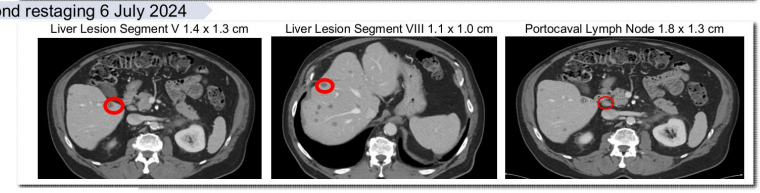
Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

PRT3789-01: Patient Case Study

72-Year-Old Man With Metastatic, Poorly Differentiated Carcinoma of the Lung With Squamous Differentiation; Prior Therapy Included Carbo/Paclitaxel and Carbo/Docetaxel/Pembrolizumab

Baseline 11 April 2024

Second restaging 6 July 2024



Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

The patient images depicted here are representative of a "classical" patient with SMARCA4 mutations: poorly differentiated, aggressive disease

This patient experienced a confirmed PR, with tumor shrinkage in liver lesions and lymph nodes

This patient was treated at 283 mg and is ongoing on the trial

PRT3789-01: Key Takeaways

Summary and Conclusions

- PRT3789, a first-in-class, selective SMARCA2 degrader is being developed to treat SMARCA4-deficient cancer
- At doses studied, PRT3789 is generally well tolerated, with no dose-limiting toxicities or study drug-related serious adverse events reported to date
- Pharmacokinetic analysis shows increases in exposure (C_{max}, AUC) with dose
- Pharmacodynamic effect is more prolonged than pharmacokinetic half-life; increasing doses show deeper and more prolonged pharmacodynamic effect
- Encouraging signs of anti-tumor activity are seen in patients with NSCLC or esophageal cancer
- RP2D not reached, dose escalation and backfill enrollment ongoing
- Combinations of PRT3789 + docetaxel and PRT3789 + pembrolizumab will also be tested

AUC, area under the curve; C_{max}, maximum concentration; NSCLC, non-small cell lung cancer.

These data represent initial proof of concept that selective SMARCA2 degradation can yield anti-tumor activity in certain SMARCA4-*mutated* cancers

Guo, R. *et al.*, ESMO Congress, 13 Sept 2024

What's Next for PRT3789?

'3789 Monotherapy Dose Confirmation

- Currently enrolling patients in dose escalation cohort 9 (500 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 to be presented at plenary session of Triple Meeting, October 24th, 2024

'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 on track to initiate in 2H 2024
- Subject of recent clinical collaboration agreement with Merck
- Goal is to assess safety and clinical activity in combination

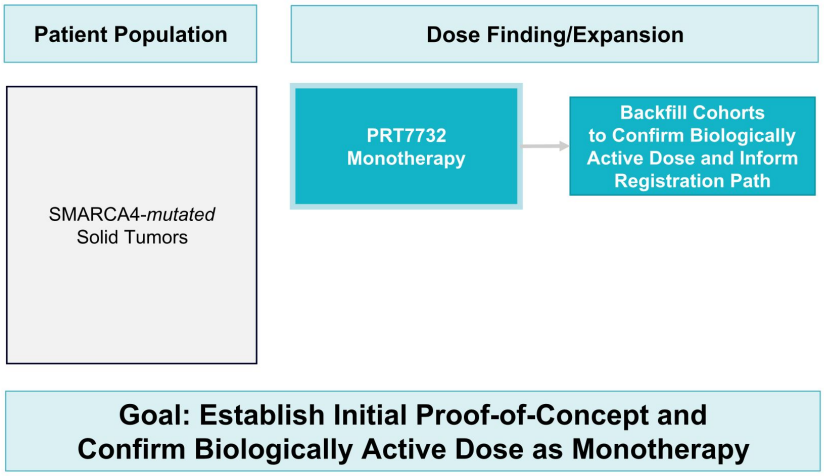
'3789 Program Priorities:

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

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; DLT = dose limiting toxicity; NSCLC – non-small cell lung cancer; 2L = second-line

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

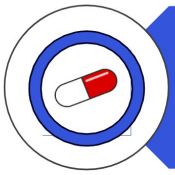
Sub-nanomolar SMARCA2 degradation potency in cell lines

Very high selectivity for SMARCA2 over SMARCA4

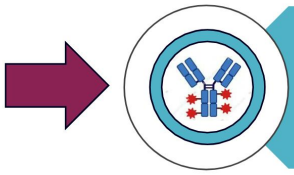
Good oral bioavailability observed across species supports projected once-daily human dose

Expanding Our Portfolio of SMARCA-Targeted Precision Medicines

Lead SMARCA2 Degrader (PRT3789)



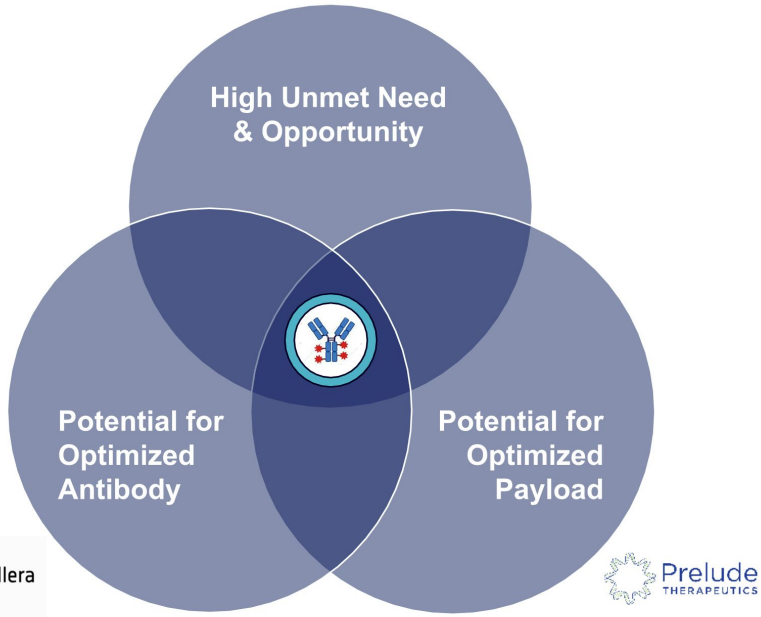
Oral SMARCA2 Degrader (PRT7732)



Precision ADCs with SMARCA2/4 Degrader Payload

- Cancers with dysregulated SMARCA pathway
- 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 exploration remain undisclosed at this time

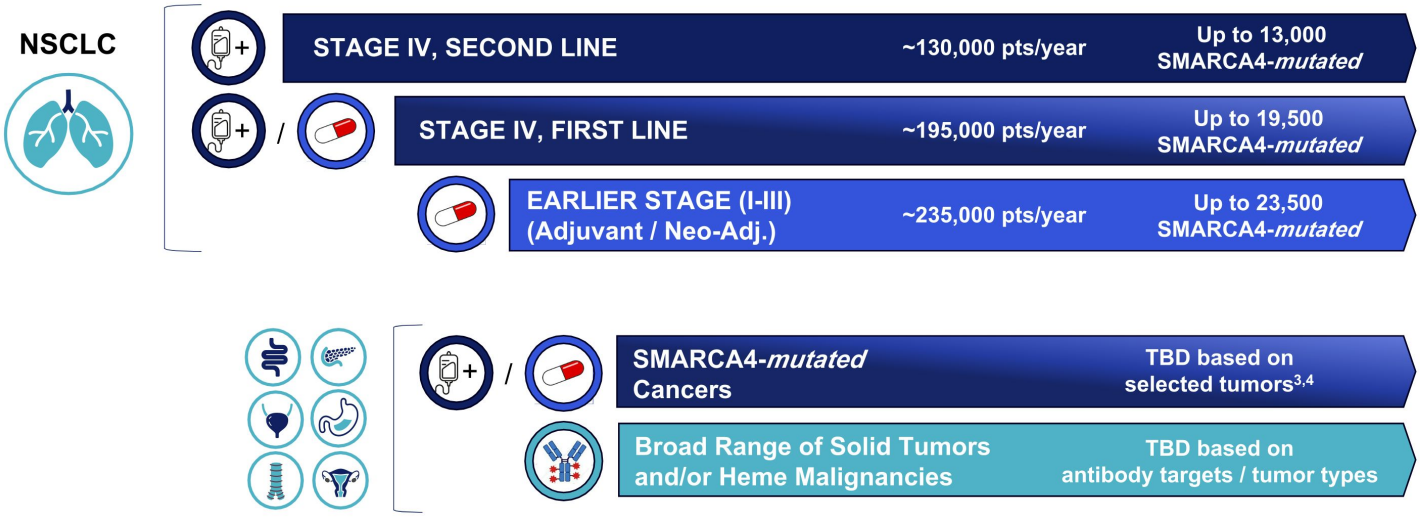
Initial program will link an optimized Prelude SMARCA2/4 dual degrader as a "Precision Payload" to an optimized AbCellera antibody*

Prelude's SMARCA2/4 dual degraders have shown picomolar potency on par with cytotoxics (MMAE) but with potential for a differentiated safety profile

Expands the reach of SMARCA degrader technology to cancers without SMARCA4 mutations

Prelude's SMARCA Portfolio Strategy Addresses a Significant Unmet Need

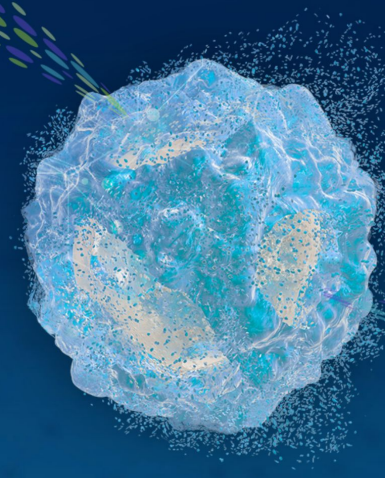
Potential Addressable Patient Populations US and EU5 [1-5]



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 NSCLC Report 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.

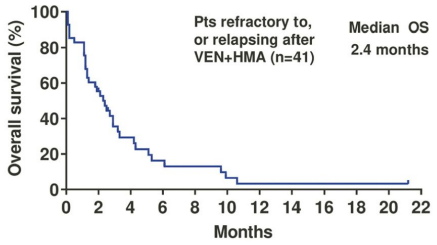
Highly Selective CDK9 Inhibitor

PRT2527

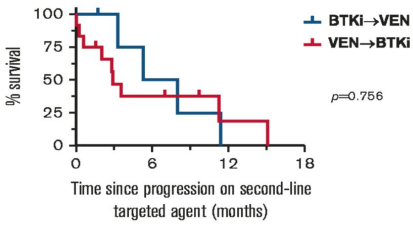


Patients with Hematologic Malignancies Refractory to Current Treatments Experience Poor Outcomes

(1) AML



(2) CLL

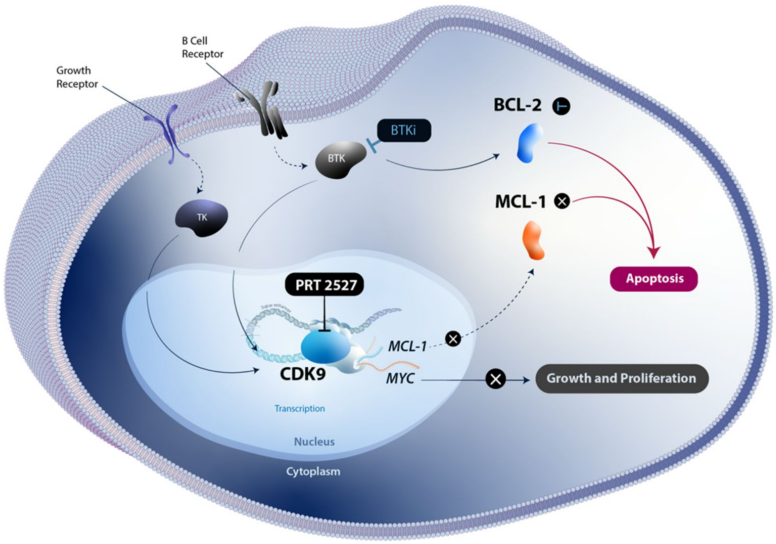


Source:
1) Maiti A et al. Haematologica 2021. https://doi.org/10.3324/haematol.2020.252569
2) Lew TE et al. Blood Advances 2021. https://doi.org/10.1182/bloodadvances.2021005083

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

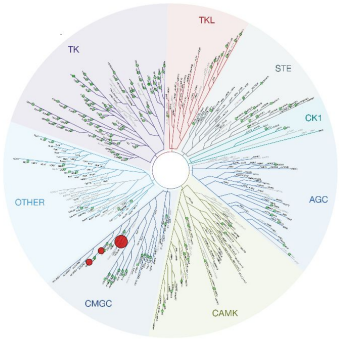
PRT2527 is a Potent, Highly Selective CDK9 Inhibitor That Depletes MCL-1 and MYC

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

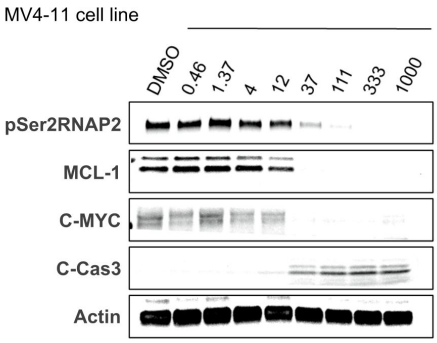
10 -100x >100x

Highly Selective in Kinome



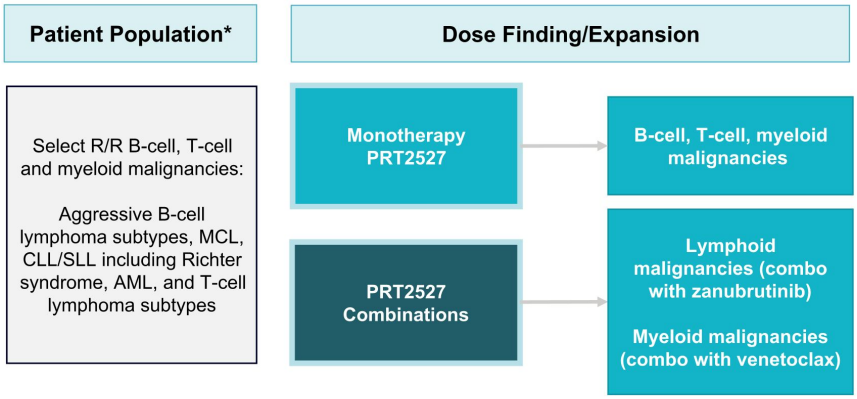
PRT2527
177 Assays tested
3 Interactions Mapped
S-Score(35) = 0.02

PRT2527 Treatment Depletes MCL-1 and MYC Proteins



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

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: NCT05665530

What to Expect in Q4 2024

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

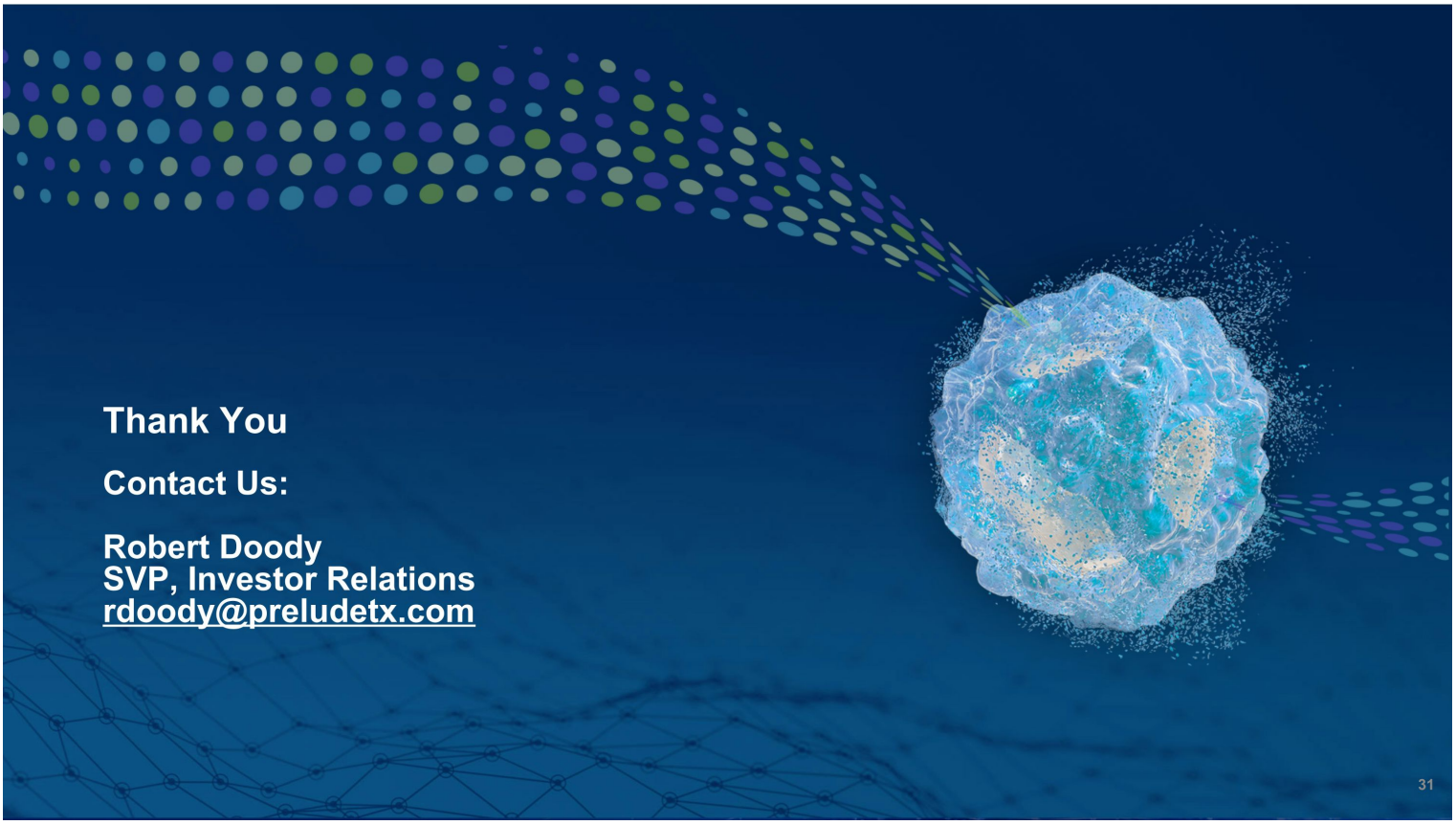
Initial assessment of clinical activity in B-cell malignancies as monotherapy

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)** • Complete monotherapy escalation and fully enroll backfill cohorts • Initiate Phase 2 trial in combination with pembrolizumab	• *Complete* • YE 2024 • Q4 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
31

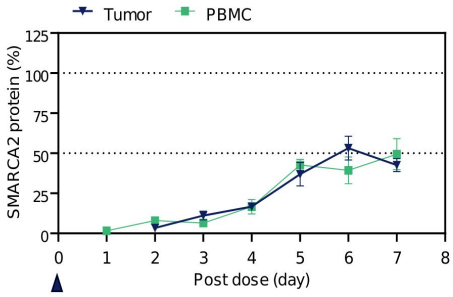
APPENDIX

- Highly Selective SMARCA2 Degrader Program
  - Additional PK/PD Data on PRT3789
  - Discovery Effort & Oral Degrader Program
  - Preclinical Rationale for Combinations
  - Current Treatment Paradigm & Testing Landscape
- Precision ADCs
- CDK9

Prelude THERAPEUTICS

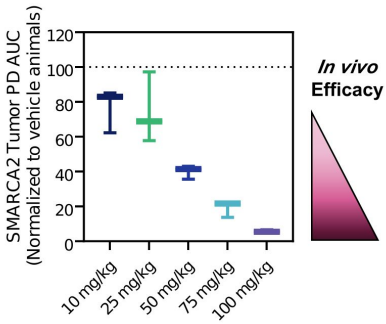
PD Correlates with Efficacy in Preclinical Models

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

Correlation observed between peripheral blood monocyte (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
Source: Wang et al. ENA 2023; Data on file

When it Comes to Targeting SMARCA2, Degraders Offer Distinct Advantages

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

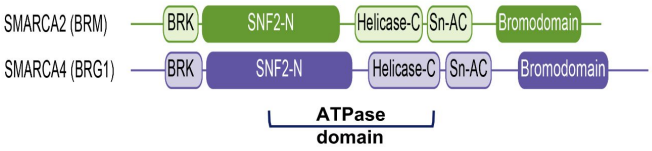
Early attempts at achieving both potency and selectivity with inhibitor approaches had challenges

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

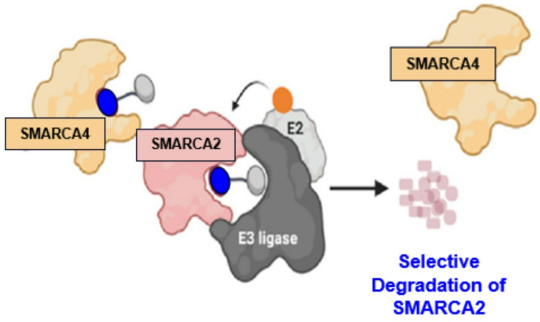
Selectively Targeting SMARCA2 Has Been a Significant Challenge for Industry

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

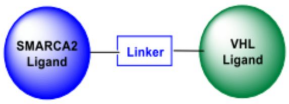


- **SMARCA2 Selective Degradation** is possible through differences in ternary complexes and subsequent ubiquitination of unique lysine residues

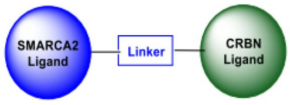
[1] Vangamudi et al, Cancer Res. **2015** (Pfizer); Taylor et al J. Med. Chem **2022** (Genentech)
[2] Papillon et al, J. Med. Chem **2018** (Novartis) [3] AACR **2024** (Foghorn/Lilly)

Prelude Scientists Solved the SMARCA2 Selectivity Enigma

Parallel VHL- and CRBN-based SMARCA2 Degrader Programs



PRT3789
(IV or SC formulation)



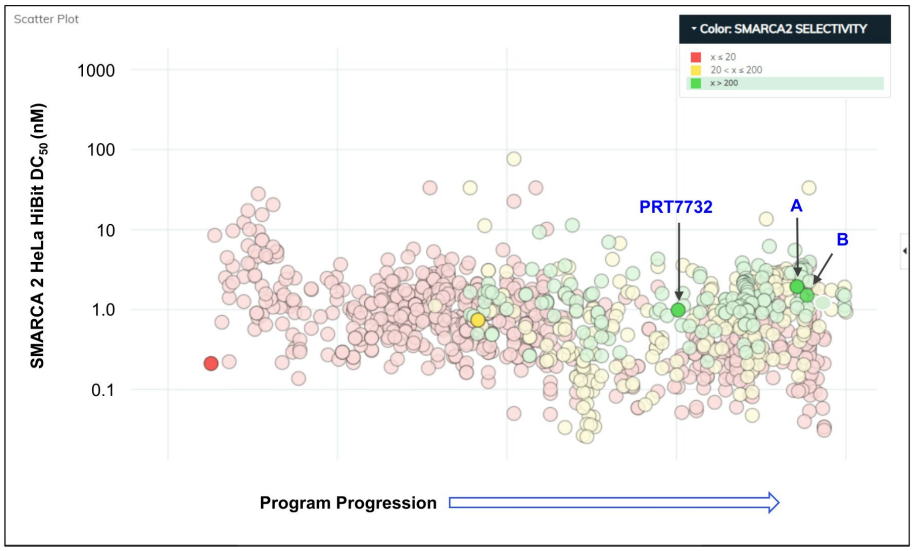
PRT7732
(Oral Candidate)

- **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



*Inactive & weakly potent compounds removed for clarity

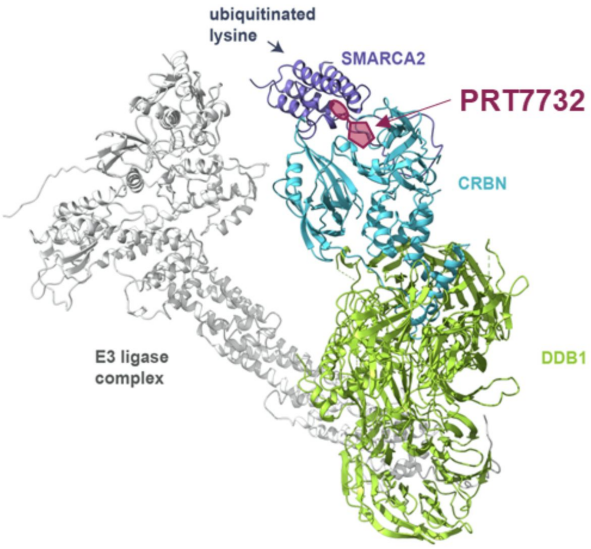
Solving for potency, selectivity and oral bioavailability was a challenge

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



Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

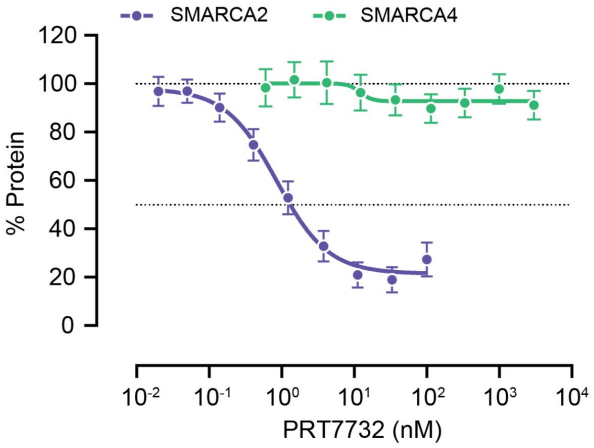
PRT7732 binds to the SMARCA2 bromodomain and CRBN/DDB1 E3 ligase complex

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*



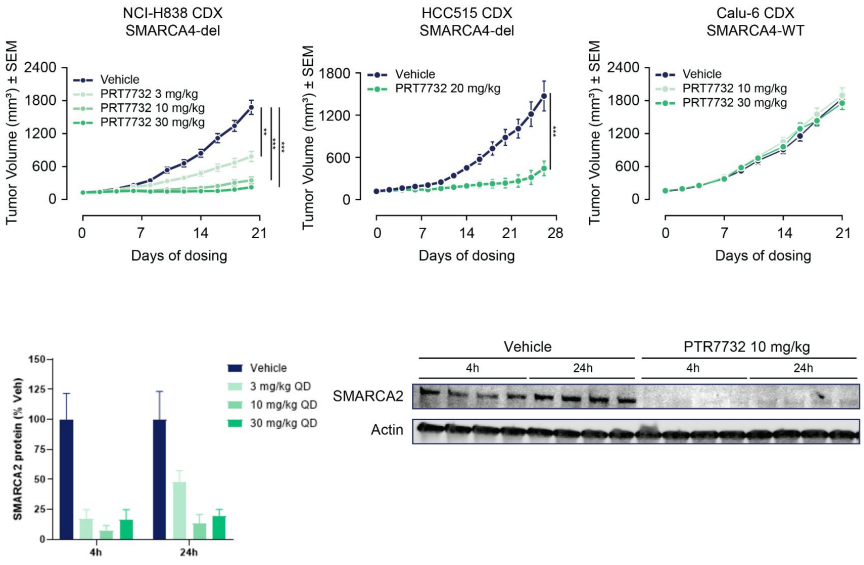
* Based on highest concentration tested
Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

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



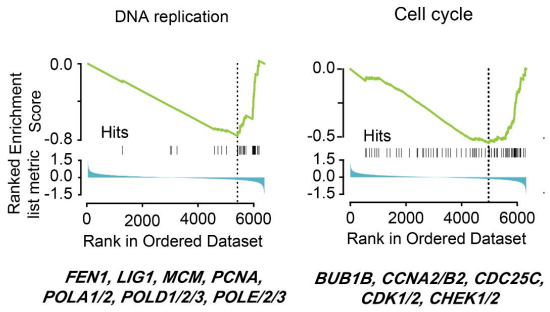
Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

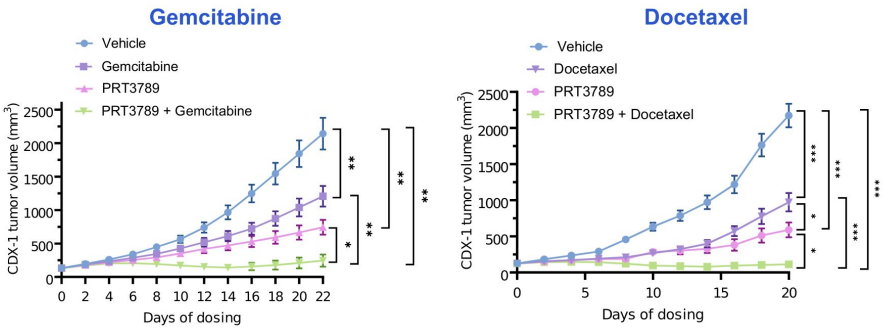
Daily oral administration of PRT7732 demonstrates anti-tumor activity in SMARCA4-deficient but not SMARCA4 wild type tumors

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





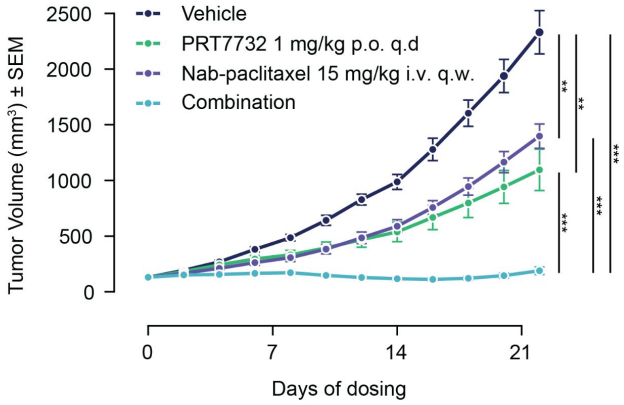
AACR 2022, 2023

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**

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

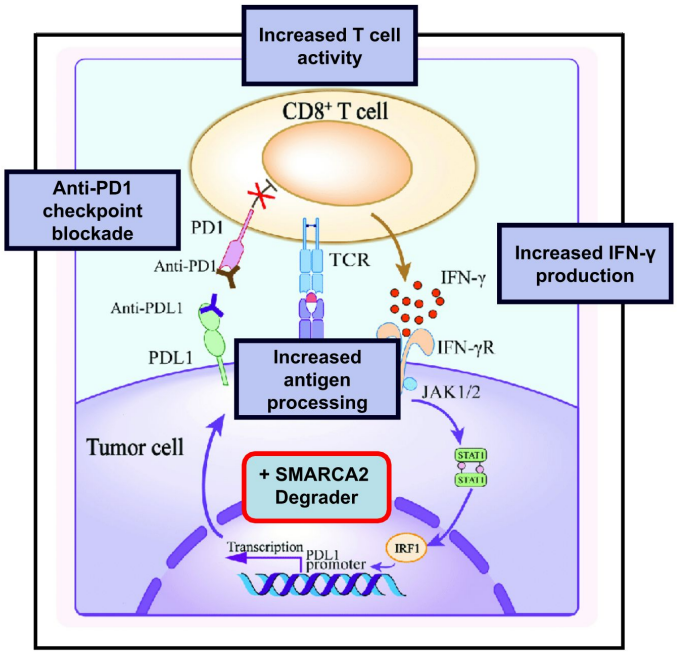


Source: Shvartsbart, K. Ito et al., AACR Poster, April 2024. Available here: Preclinical Characterization Of PRT7732: A Highly Potent, Selective, And Orally Bioavailable Targeted Protein Degrader Of SMARCA2

Oral daily administration of PRT7732 1 mg/kg in combination with nab-paclitaxel (Abraxane®) induces tumor regression in the NCI-H838 tumor model in mice

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

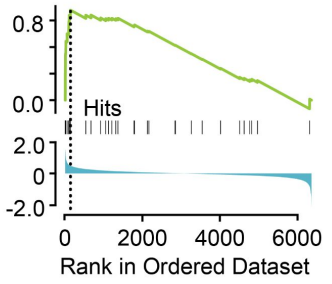
Upregulates antigen processing and presentation machinery

Increases cytokine production

Promotes T-cell activity and accelerates tumor cell killing

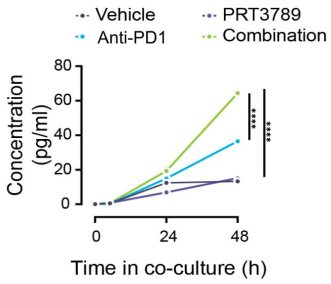
Preclinical Data for PRT3789 Support Rationale for Anti-PD1 Combination

PRT3789 Upregulates Genes for Antigen Processing and Presentation

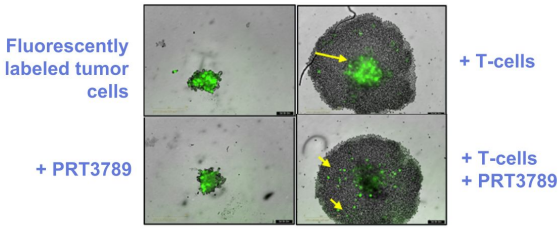


TAP1/2, HLA-A/C/G/F, B2M

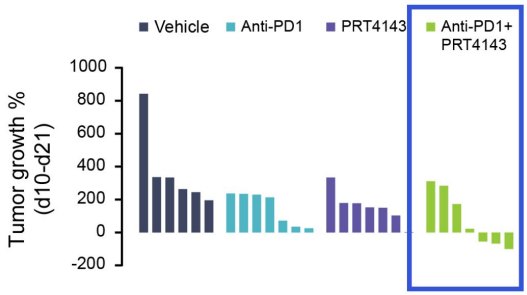
PRT3789 Increases IFN-g Levels in Combination with anti-PD1 *In Vitro*



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

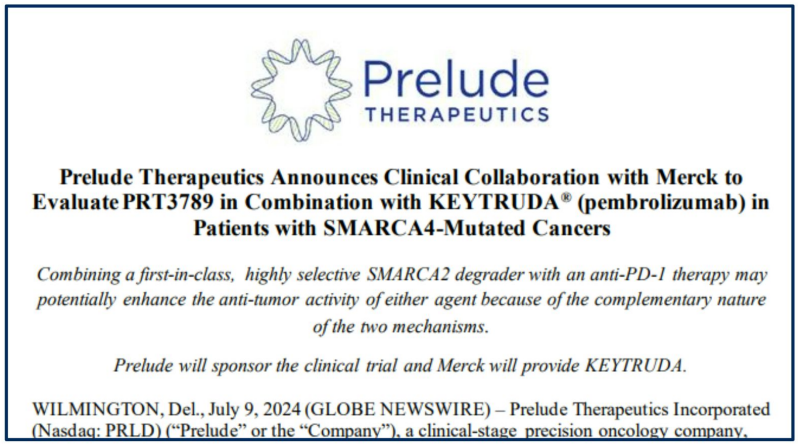


SMARCA2 Degrader + Anti-PD1 Demonstrates Tumor Regression *In Vivo*



ENA 2023; data on file

Prelude to Initiate Phase 2 Combination Study of PRT3789 + Pembrolizumab in Q4 2024



Prelude THERAPEUTICS

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,

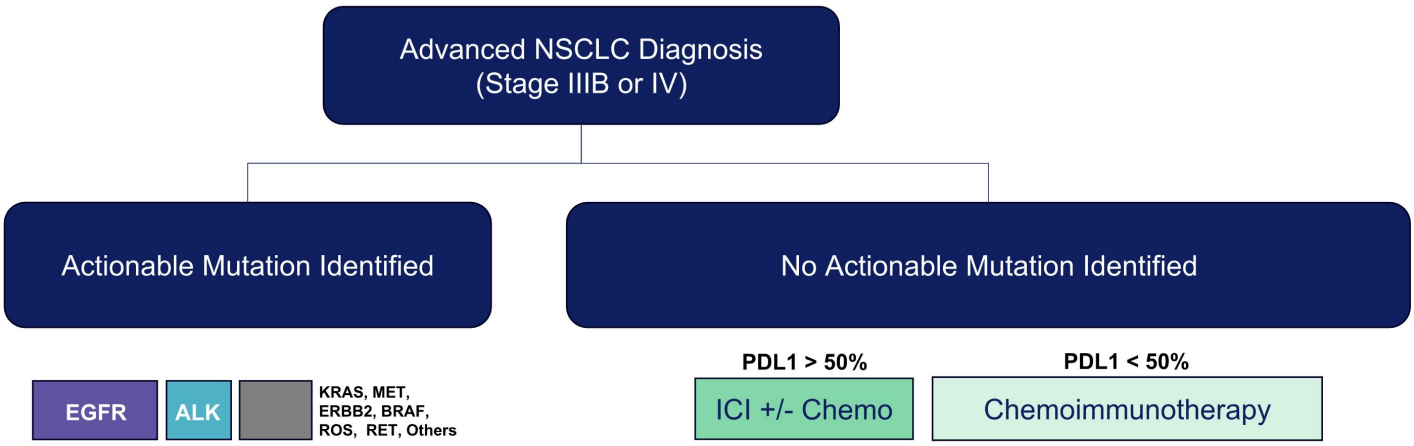
KEYTRUDA® is a registered trademark of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Preclinical rationale supportive of enhanced efficacy with PRT3789 and anti-PD1 therapy combination

PRT3789 upregulates genes encoding antigen processing and presentation machinery

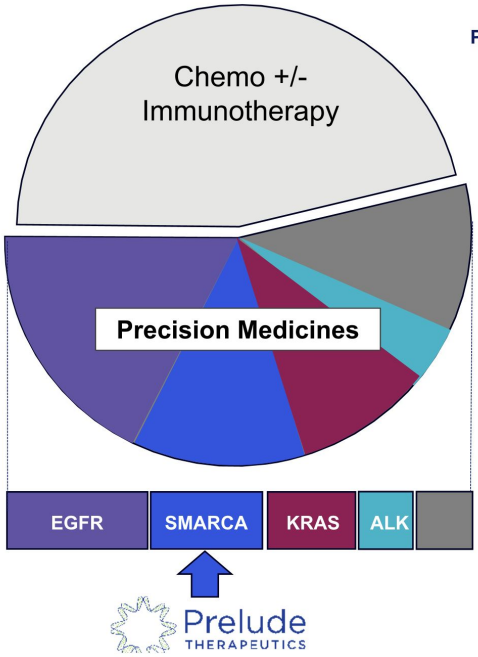
Trial will explore safety and anti-tumor activity of the combination

Majority of Advanced NSCLC Patients Currently 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

SMARCA has the Potential to Significantly Expand Precision Medicine for Even More NSCLC Patients



Percent of Total Advanced NSCLC Patients Treated (FUTURE STATE)

ILLUSTRATIVE

MET, ERBB2, BRAF, ROS, RET, Others

Prelude THERAPEUTICS

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

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

APPENDIX

- Highly Selective SMARCA2 Degrader Program
  - Additional PK/PD Data on PRT3789
  - Discovery Effort & PRT7732 Preclinical Data
  - Preclinical Rationale for Combinations
  - Current Treatment Paradigm & Testing Landscape
- Precision ADCs
- CDK9

Prelude THERAPEUTICS

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

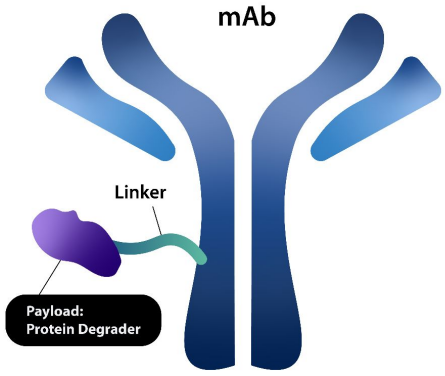
Prelude THERAPEUTICS

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

+

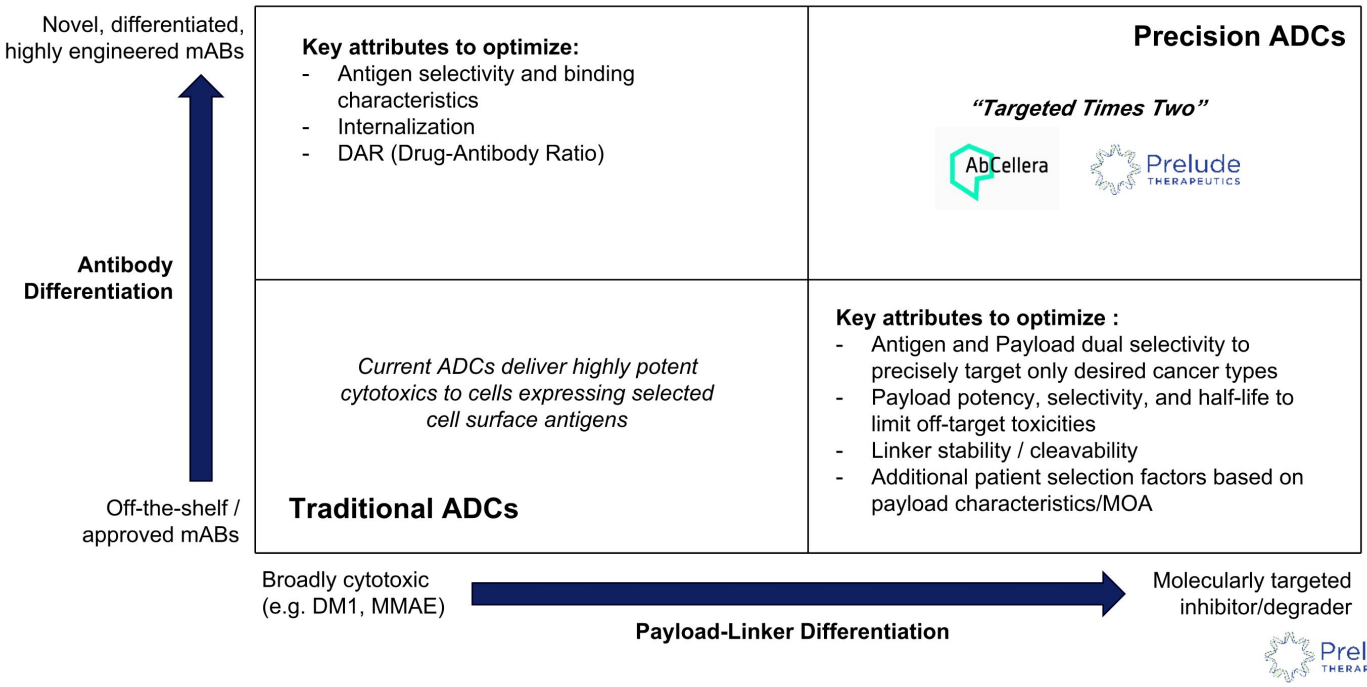
AbCellera

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

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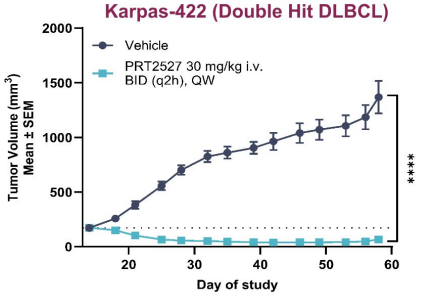
Prelude THERAPEUTICS

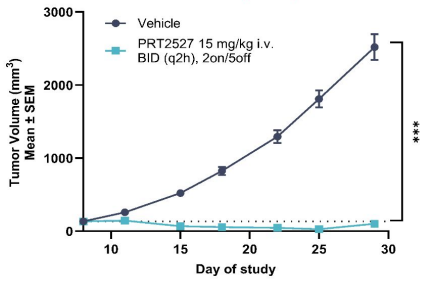
PRT2527 is Highly Efficacious In Vivo in Models of Hematologic Malignancies

Monotherapy

Karpas-422 (Double Hit DLBCL)

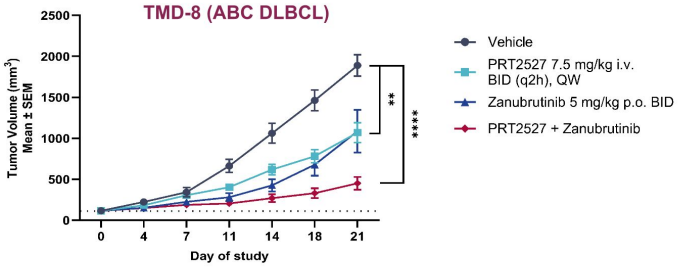


MV4-11 (AML)

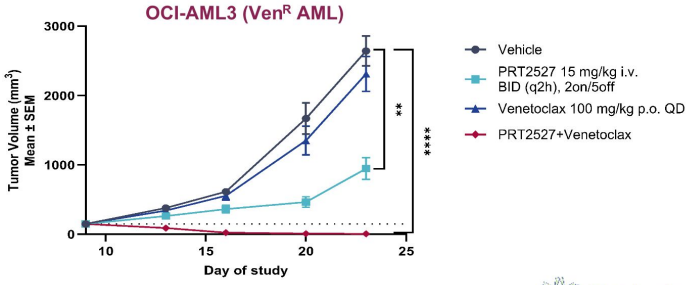


Combination

TMD-8 (ABC DLBCL)



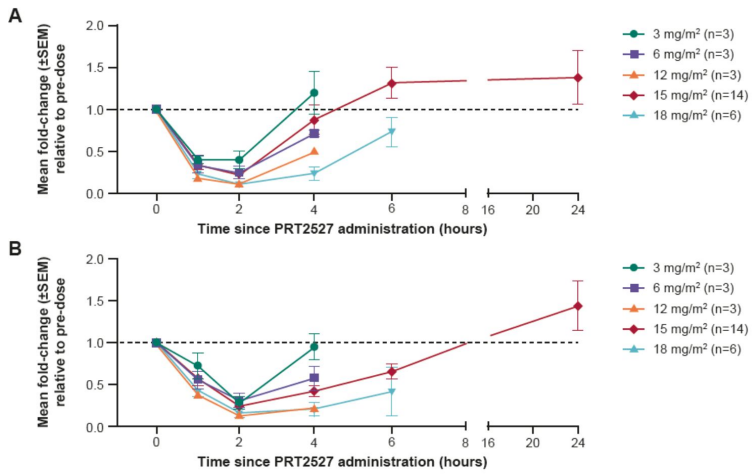
OCI-AML3 (Ven^{R} AML)



Presented at ASH 2022; https://preludetx.com/wp-content/uploads/2023/03/ASH-2022_PRT2527-Presentation.pdf; 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

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)