

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): August 14, 2025

Prelude Therapeutics Incorporated
(Exact Name of Registrant as Specified in its Charter)

Delaware (State or other jurisdiction of incorporation or organization)	001-39527 (Commission File Number)	81-1384762 (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 2.02 Results of Operations and Financial Condition.

On August 14, 2025, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing its financial results for the three months ended June 30, 2025. A copy of the press release is attached as Exhibit 99.1 to this Current Report on Form 8-K.

Item 7.01 Regulation FD Disclosure.

The Company has prepared investor presentation materials with information about the Company, which it intends to use as part of investor presentations. A copy of the investor presentation materials to be used by management for presentations is attached as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated herein by reference.

The information in this Current Report on Form 8-K and in Exhibits 99.1 and 99.2 attached hereto is being furnished, but shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (“Exchange Act”), and is not incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press release issued by Prelude Therapeutics Incorporated regarding its financial results for the three months ended June 30, 2025, dated August 14, 2025.
99.2	Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PRELUDE THERAPEUTICS INCORPORATED

Date: August 14, 2025

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



Prelude Therapeutics Reports Second Quarter 2025 Financial Results and Provides Corporate Update

PRT7732, once daily oral SMARCA2 degrader, currently enrolling at the seventh dosing cohort (125 mg); Company to provide an update with preliminary clinical data, including PK/PD, safety and initial clinical activity by year end 2025

Phase 1 study of PRT3789, a once weekly IV SMARCA2 degrader, has been completed; Company to provide final data by year end 2025

Prelude is advancing a development candidate for its oral KAT6A degrader program and remains on track to file an IND in the first half of 2026

Current cash runway into the second quarter of 2026 with \$77.3 million in cash, cash equivalents, restricted cash and marketable securities as of June 30, 2025

WILMINGTON, Del., Aug. 14, 2025 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a clinical-stage precision oncology company, today reported its financial results for second quarter ended June 30, 2025, and provided an update on its clinical development pipeline and other corporate developments.

“From the discovery of first-in-class highly selective SMARCA2 degraders through Phase 1 studies in biomarker selected population of patients, Prelude demonstrated exemplary execution of our SMARCA2 program to deliver a potentially novel treatment option for patients with aggressive cancers harboring SMARCA4 deletion,” stated Kris Vaddi, Ph.D., Chief Executive Officer of Prelude. “This past quarter, we completed our Phase 1 dose escalation of PRT3789 (IV), both as monotherapy and in combination with docetaxel. With the knowledge and experience gained through PRT3789 clinical development, we were able to expeditiously advance our oral program, PRT7732, which began in the fourth quarter of 2024. I am pleased with the progress made to date with PRT7732, which is currently enrolling our seventh dose cohort of 125 mg.”

Vaddi continued, “We’ve decided to pause further development of PRT3789, and focus solely on PRT7732 as our go-forward strategy for our SMARCA2 Program. While PRT3789 demonstrated initial proof of concept for the mechanism, a number of considerations – including the potential need for higher target coverage throughout the dosing interval, and capital needs to continue to advance both agents – contributed to this decision. The clinical profile observed to date with PRT7732 including oral once daily dosing, safety and tolerability, oral exposures, and >90%

target degradation positions us well to explore the potential for this mechanism in SMARCA4 deleted cancers and determine the path forward for continued development by year end.”

Continued Vaddi, “We’ve made significant progress across our core research and development organization, while employing disciplined capital management through resource allocation and headcount management throughout the Company. Notably, we’ve continued to advance our KAT6A degrader program, on track for IND filing in the first half of 2026, presented preclinical data on mCALR-targeted ADCs and continued progress with our partner AbCellera related to precision ADCs.”

Clinical Program Updates and Upcoming Milestones

SMARCA2 Degradation Development Program

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

PRT3789 is designed to treat patients with a SMARCA4 mutation. Patients with SMARCA4-mutated cancer, a particularly aggressive form of the disease, have a very poor clinical prognosis. Approximately 10% of all non-small cell lung cancers and 5% of all cancers broadly, harbor a SMARCA4 mutation. In NSCLC, these patients tend to have poor response to standard of care chemoimmunotherapy and are largely ineligible for other targeted therapies. We believe that this represents an area of high unmet medical need.

PRT3789 has completed Phase 1 clinical development in patients with biomarker selected SMARCA4-mutated cancers. The Company anticipates providing updated data from the Phase 1 study by year-end 2025. Based on the totality of the data and available resources, the Company would only advance the program in the context of a partnership and will be focusing internal resources solely on PRT7732.

PRT7732 – A potent, highly selective and orally bioavailable SMARCA2 degrader

PRT7732 is a highly selective and orally bioavailable SMARCA2 degrader with a distinct chemical composition to PRT3789. In the fourth quarter of 2024, the Company initiated and enrolled the first patients in a phase 1 multi-dose escalation trial of PRT7732 (NCT06560645) in biomarker selected SMARCA4 mutated cancers. Enrollment continues to advance rapidly, and the Company is currently enrolling patients in the seventh dose escalation cohort (125 mg once daily). The Company expects to provide an initial first-in-human data update including PK/PD, safety and an initial look at clinical activity at biologically relevant doses by year end 2025.

Highly selective KAT6A oral degrader program

KAT6 is an emerging and recently validated target in the treatment of ER+ breast cancer and other malignancies. Prelude discovered and is developing the industry’s first – based on currently published patents and literature – highly potent, selective and orally bioavailable KAT6A selective degraders. The Company is now advancing a development candidate and remains on track to file an IND in the first half of 2026. Prelude believes that selectively degrading KAT6A has the potential for improved efficacy, tolerability and combinability with other agents relative to non-selective inhibitors of KAT6A/B. The Company recently presented preclinical data validating this hypothesis at the AACR Annual Meeting 2025. The presentation can be found at Publications - Prelude Therapeutics.

Precision ADCs with SMARCA2/4 dual degrader payload

Prelude is developing potent SMARCA2/4 dual degraders that robustly inhibit cancer cell growth and induce cell death across multiple cancer types as payloads for precision ADCs. The Company presented the first preclinical data from its precision ADC platform at the 36th EORTC-NCI-AACR Symposium in October. These data demonstrated that SMARCA2/4 degrader antibody conjugates have potential for significantly better *in vivo* efficacy and tolerability when compared to traditional cytotoxic ADCs when tested head-to-head in xenograft models. The presentation can be found at Publications - Prelude Therapeutics.

Mutated Calreticulin (mCALR)

Mutant CALR is a neoantigen presented on the cell surface of malignant myeloid cells but not normal cells and is found in approximately 25-35% of patients with myelofibrosis (MF) and essential thrombocythemia (ET). Recently, a mCALR-targeted monoclonal antibody demonstrated robust clinical activity in high-risk ET patients. Prelude is seeking to further optimize this modality by developing mCALR-targeted precision ADCs using the Company's proprietary degrader payloads. The Company presented the first preclinical data from this discovery effort at the European Hematology Association 2025 Congress in June. The presentation can be found at Publications - Prelude Therapeutics.

Second Quarter 2025 Financial Results**Cash, Cash Equivalents, Restricted Cash and Marketable Securities:**

Cash, cash equivalents, restricted cash and marketable securities as of June 30, 2025 were \$77.3 million. The Company anticipates that its existing cash, cash equivalents, restricted cash and marketable securities will fund Prelude's operations into the second quarter of 2026.

Research and Development (R&D) Expenses:

For the second quarter of 2025, R&D expense decreased to \$25.8 million from \$29.5 million for the prior year period. Included in the R&D expense for the three months ended June 30, 2025 was \$2.2 million of non-cash expense related to stock-based compensation, including employee stock options, compared to \$3.4 million for the three months ended June 30, 2024. Research and development expenses decreased primarily due to a decrease in expense related to our SMARCA2 clinical trials. Research and development expenses may fluctuate from period to period depending upon the stage of certain projects and the level of preclinical and clinical trial-related activities.

General and Administrative (G&A) Expenses:

For the second quarter of 2025, G&A expenses decreased to \$6.4 million from \$7.7 million for the prior year period. Included in general and administrative expenses for the three months ended June 30, 2025, was \$1.6 million of non-cash expense related to stock-based compensation, including employee stock options, compared to \$2.7 million for the three months ended June 30, 2024. The decrease in general and administrative expenses was primarily due to a decrease in stock-based compensation due to lower valuation on more recent grants due to the decrease in our stock price.

Net Loss:

For the three months ended June 30, 2025, net loss was \$31.2 million, or \$0.41 per share compared to \$34.7 million, or \$0.46 per share, for the prior year period. Included in the net loss for the three months ended June 30, 2025, was \$3.8 million of non-cash expenses related to the impact of expensing share-based payments, including employee stock options, as compared to \$6.1 million for the same period in 2024.

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 SMARCA2 and KAT6A degraders, and ongoing research into other precision oncology targets. 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. Our corporate presentation can be found at Events & Presentations - Prelude Therapeutics. 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, the expected timeline for clinical trial results for Prelude's product candidates, and the sufficiency of Prelude's cash runway into the second quarter of 2026. 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.

PRELUDE THERAPEUTICS INCORPORATED

STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(UNAUDITED)

(in thousands, except share and per share data)	Three Months Ended June 30,	
	2025	2024
Operating expenses		
Research and development	25,784	29,509
General and administrative	6,410	7,655
Total operating expenses	32,194	37,164
Loss from operations	(32,194)	(37,164)
Other income, net	963	2,424
Net loss	<u>\$ (31,231)</u>	<u>\$ (34,740)</u>
Per share information:		
Net loss per share of common stock, basic and diluted	<u>\$ (0.41)</u>	<u>\$ (0.46)</u>
Weighted average common shares outstanding, basic and diluted	<u>75,993,941</u>	<u>75,762,152</u>
Comprehensive loss:		
Net loss	\$ (31,231)	\$ (34,740)
Unrealized loss on marketable securities, net of tax	(13)	(55)
Comprehensive loss	<u>\$ (31,244)</u>	<u>\$ (34,795)</u>

PRELUDE THERAPEUTICS INCORPORATED

BALANCE SHEETS

(in thousands, except share data)		June 30, 2025	December 31, 2024
Assets		(unaudited)	
Current assets:			
Cash and cash equivalents	\$	25,752	\$ 12,474
Marketable securities		47,464	121,140
Prepaid expenses and other current assets		3,660	2,281
Total current assets		76,876	135,895
Restricted cash		4,044	4,044
Property and equipment, net		5,956	6,767
Operating lease right-of-use asset		27,932	28,699
Other assets		110	110
Total assets	\$	114,918	\$ 175,515
Liabilities and stockholders' equity			
Current liabilities:			
Accounts payable	\$	4,962	\$ 7,732
Accrued expenses and other current liabilities		13,235	15,209
Operating lease liability		2,711	2,492
Finance lease liability		—	208
Total current liabilities		20,908	25,641
Other liabilities		2,966	3,090
Operating lease liability		15,206	15,325
Total liabilities		39,080	44,056
Commitments			
Stockholders' equity:			
Voting common stock, \$0.0001 par value: 487,149,741 shares authorized; 43,744,066 and 42,298,859 shares issued and outstanding at June 30, 2025 and December 31, 2024, respectively		4	4
Non-voting common stock, \$0.0001 par value: 112,850,259 and 12,850,259 shares authorized at June 30, 2025 and December 31, 2024, respectively; 12,850,259 shares issued and outstanding at both June 30, 2025 and December 31, 2024		1	1
Additional paid-in capital		722,713	714,982
Accumulated other comprehensive (loss) income		(1)	35
Accumulated deficit		(646,879)	(583,563)
Total stockholders' equity		75,838	131,459
Total liabilities and stockholders' equity	\$	114,918	\$ 175,515

Investor Contact:

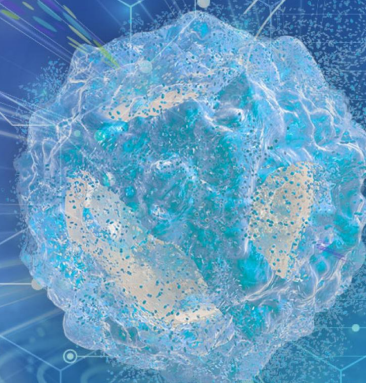
Robert A. Doody, Jr.
Senior Vice President, Investor Relations
Prelude Therapeutics Incorporated
484.639.7235
rdoody@preludetx.com



Prelude
THERAPEUTICS

Corporate Presentation

August 2025



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.





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



Strive for first-in-class science focused on areas of highest 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



Jane Huang M.D.
President and Chief Medical Officer



Peggy Scherle, PhD
Chief Scientific Officer



Andrew Combs, PhD
Chief Chemistry Officer



Sean Brusky, MBA
Chief Business Officer



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



Prelude’s Precision Medicine Pipeline & Discovery Engine

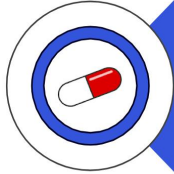
PROGRAM		POTENTIAL INDICATIONS	DISCOVERY/ PRECLINICAL	PHASE 1	PHASE 2/3	UPCOMING MILESTONES
Clinical	Oral SMARCA2 Degrader	SMARCA4-mutated NSCLC & other cancers				First Interim Phase 1 Data YE 2025
	Oral KAT6A Degrader	ER+ breast cancer & other solid tumors				Lead DC Advancing IND Filing 1H 2026
Preclinical	Precision ADCs Novel Degrader Payloads	Multiple				Program Updates Anticipated in 2H 2025*
	New Discovery Programs	Hard-to-treat cancers, “Undruggable” targets, High unmet need		Established track record of delivering a first-or best-in-class new program into the clinic every 12-18 months		Additional Pipeline Updates Anticipated in 2H 2025
	Prelude Discovered Programs Available for Partnering • PRT3789: Highly selective SMARCA2 degrader (Ph1, IV) • PRT2527: Highly selective CDK9 inhibitor (Ph 1, IV) • PRT3645: Brain-penetrant CDK4-biased inhibitor (Ph 1, oral) • Additional discovery and preclinical stage programs and IP					Full Global Rights Available

* Advancing up to 5 Precision ADC Programs in collaboration with AbCellera [Press Release](#)



IV SMARCA2 Degradar (PRT3789)

- Proof-of-concept established in Phase I dose escalation
- Confirmed responses in NSCLC and EC/GC as monotherapy
- Pausing development and transitioning resources to PRT7732

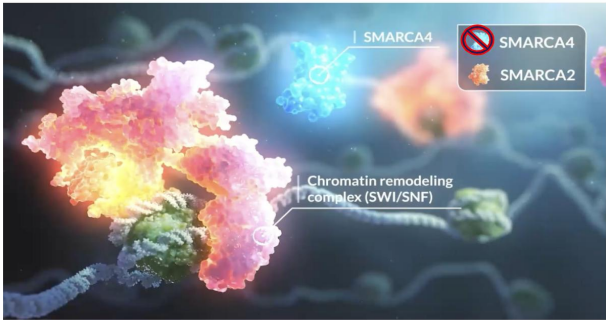


Oral SMARCA2 Degradar (PRT7732)

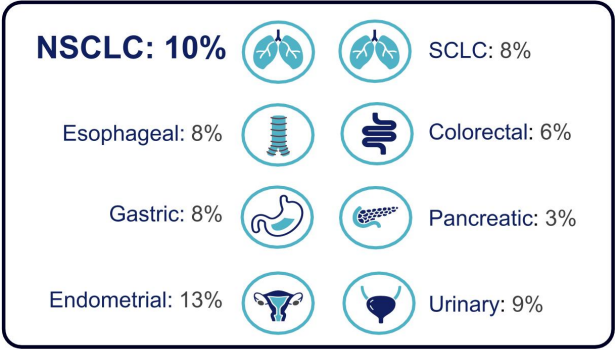
- Distinct new chemical entity with PK supporting once-daily dosing
- Daily dosing enables 'around the clock' target engagement
- Phase I underway – now enrolling at dose level 7 (125mg)

Targeting SMARCA4-deficient Cancers 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



¹Dagogo-Jack et al. Journal of Thoracic Oncology. 2020 Foundation Medicine dataset
²Fernando et al. Nature Communications 2020

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

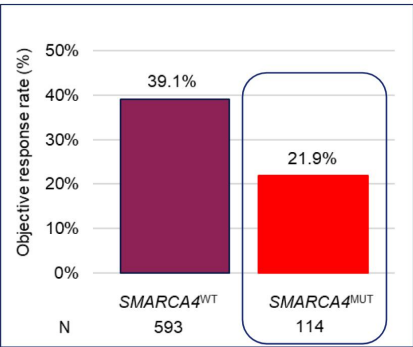
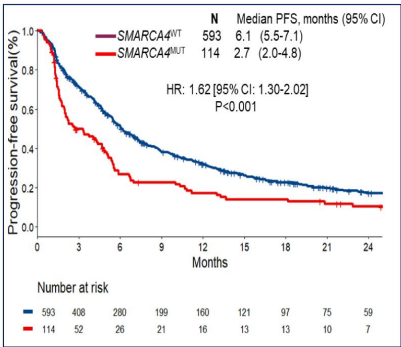
Selectively degrading SMARCA2 induces "synthetic lethality" in SMARCA4-deficient cancers

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



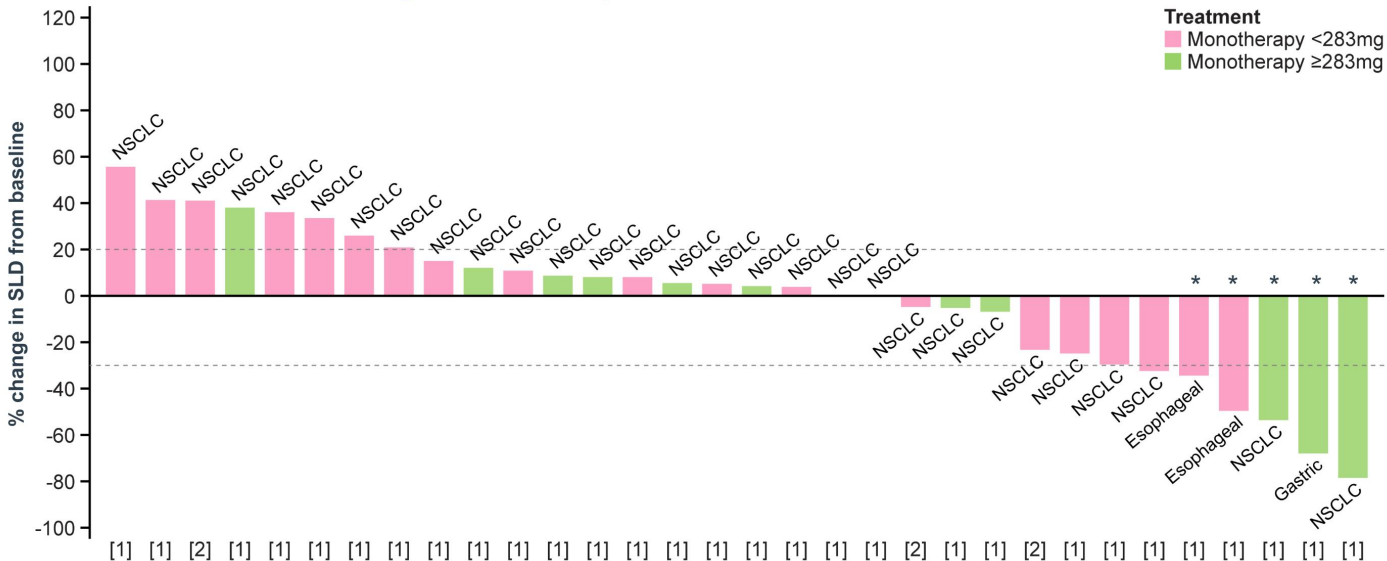
Median progression free survival for first-line SMARCA4-mutated NSCLC treated with chemoimmunotherapy is 2.7 months and response rates approximately 22%

The prognosis for patients with relapsed/refractory SMARCA4-mutated NSCLC is likely even worse

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.

Initial Proof-of-Concept Observed With PRT3789 Monotherapy: Change in Tumor Burden in Patients With NSCLC or Upper GI Cancer

Efficacy Evaluable Population With Post-Baseline Scan



Data cutoff: 30 November 2024 and patients enrolled by 31 August 2024.
GI, gastrointestinal; NSCLC, non-small cell lung cancer; SLD, sum of longest diameter.

* Confirmed partial response: [1], class 1 mutation: [2], class 2 mutation: [3]

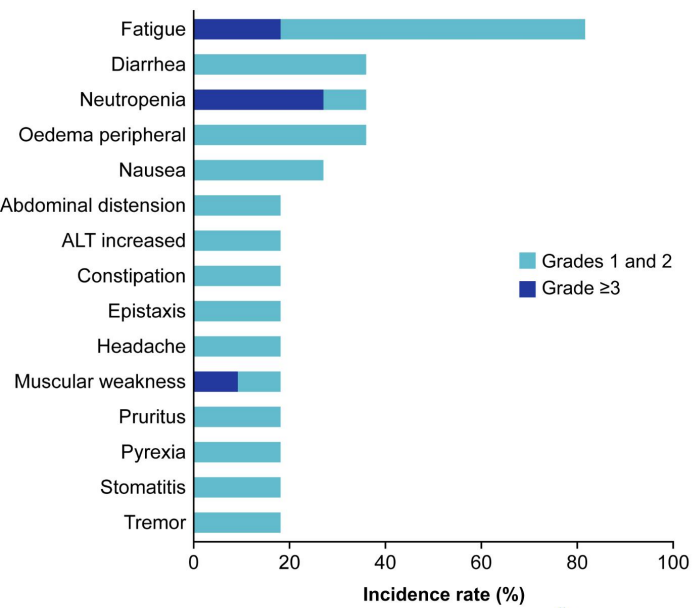
Yap, T. *et al.*, JSMO Annual Meeting, Kobe Japan, March 8th 2025 (Abstract 101356)

Phase 1 Study Also Demonstrated That a SMARCA2 Selective Degradator (PRT3789) Can Be Safely Combined with Docetaxel

Summary of Adverse Events

Adverse Events, n (%)	PRT3789 + Docetaxel (N=11)
Any adverse event	11 (100.0)
PRT3789 treatment related	7 (63.6)
Docetaxel treatment related	11 (100.0)
Grade ≥3 adverse event	8 (72.7)
Serious adverse event	4 (36.4)
PRT3789 treatment related	0
Docetaxel treatment related	1 (9.1)
Adverse event leading to	
PRT3789 dose hold	8 (72.7)
PRT3789 treatment related	2 (18.2)
Docetaxel dose hold	8 (72.7)
Dose reduction ^a	1 (9.1)
Treatment discontinuation	0
Death	0
Any dose-limiting toxicity	2 (18.2)

Most Frequent Adverse Events



Data cutoff: 30 November 2024 and patients enrolled by 24 September 2024.
ALT, alanine aminotransferase. ^a Patient had both docetaxel dose hold and dose reduction.
Yap, T. *et al.*, JSMO Annual Meeting, Kobe Japan, March 8th 2025 (Abstract 101356)

A Highly Selective Oral SMARCA2 Degradator Offers Distinct Advantages Over Inhibitor Approaches

	Inhibitors	Degraders
Potency	✓	✓
High Selectivity	✗	✓
Extended PD	✗	✓
Disruption of the SWI/SNF Complex	✗	✓
Oral Bioavailability	✓	✓

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

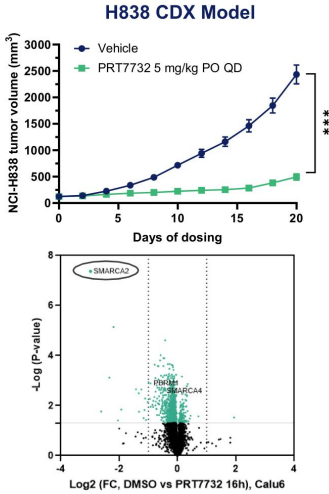
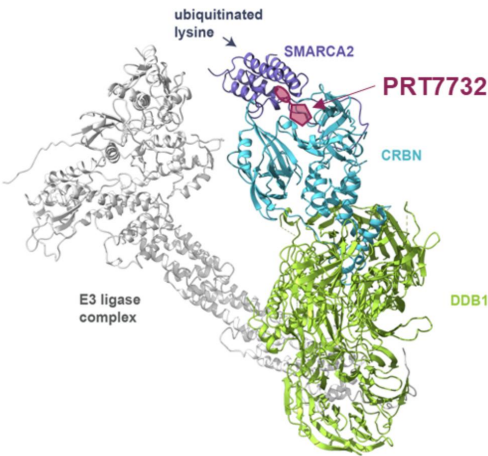
Inhibitors do not degrade the target and need to be dosed at levels that retain IC₉₀ coverage continuously

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

Prelude’s oral SMARCA2 degrader offers potential for once-daily (QD) dosing at low dose levels and convenience advantages for patients

PRT7732 is 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

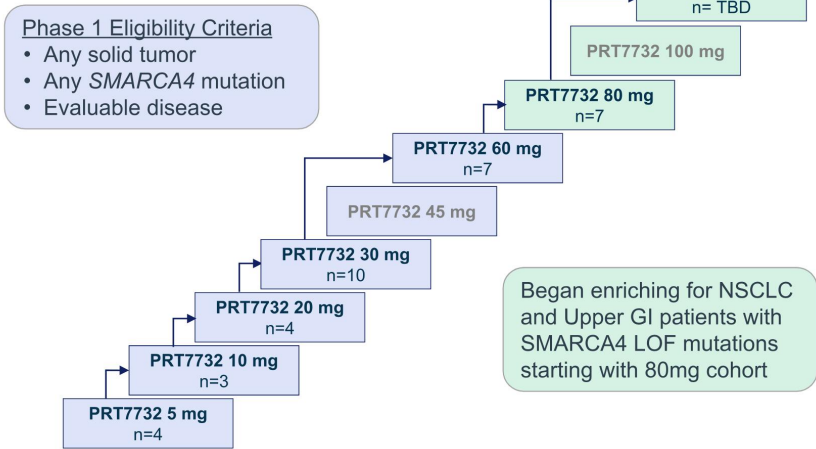
Near-absolute cellular selectivity for SMARCA2 vs SMARCA4 (>3000 fold) in HiBit cell lines and >1000-fold in cell proliferation assays and selective across the proteome

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

PRT7732-01: Phase I Trial is Underway and Enrollment has Progressed Rapidly

Monotherapy Dose-Escalation Cohorts

- PRT7732 is dosed orally, once daily
- Dose escalation ongoing at 125 mg



ClinicalTrials.gov Identifier: [NCT06560645](#)
Confidential

Now enrolling patients in dose cohort 7 (125 mg QD)

No DLTs observed to date
No Gr3+ related AEs, all other Gr3+ unrelated AEs associated with progression occurring contemporaneously

First interim data update on safety, PK, PD and initial clinical activity anticipated in 2H 2025

Small Molecules

Oral KAT6A Selective Degradator

First-in-class program with potential to advance the standard of care in ER+ breast cancer and other solid tumors

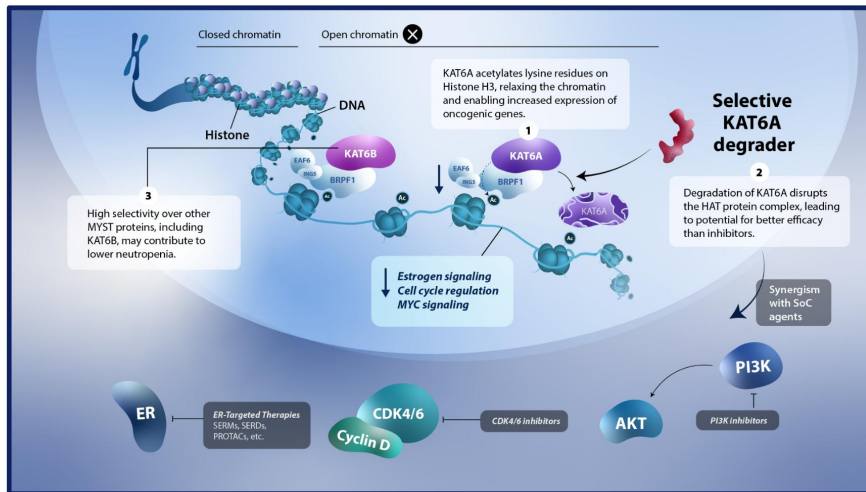
Precision ADCs

Prelude's Precision ADC Platform

Jointly advancing first novel degrader antibody conjugate ("DAC") from our AbCellera collaboration* as we expand our library of highly optimized, ultra potent degrader payloads for Precision ADCs (available for partnering)

* First Precision ADC Program discovered and advanced in collaboration with AbCellera ([Press Release](#))

Prelude is Advancing the Industry's First* Oral KAT6A Selective Degraders



There is a high unmet need for novel modalities to treat advanced breast cancer & other solid tumors

Pfizer's KAT6A/B inhibitor has demonstrated early clinical PoC in ER+ breast cancer in combination with fulvestrant, albeit with potential for dose limiting neutropenia¹

Selectively degrading KAT6A has potential to yield improved efficacy, tolerability and combinability over inhibitor approaches²

* Based on publicly disclosed information and published patents available as of July 2025

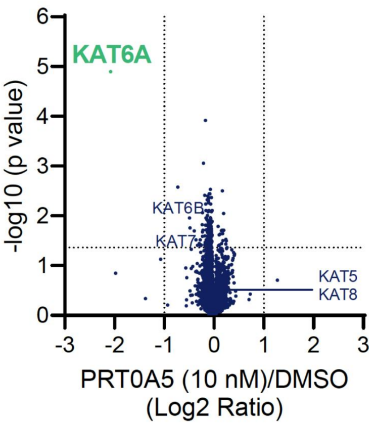
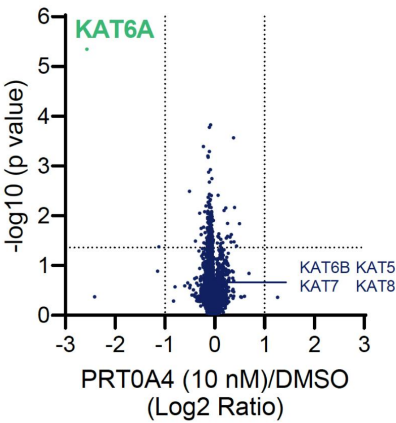
1- T. Mukohara et. al., "PF-07248144, a first-in-class KAT6 inhibitor, in patients with HR+ HER2- metastatic breast cancer: Updated results from phase 1 dose expansion study". SABCS 2024

2 - J. Carter et. al., Discovery of first-in-class potent and selective oral degraders of KAT6A that demonstrate anti-cancer activity in pre-clinical models, AACR2025; Abstract #1649 (<http://www.preludetx.com/science/publications>)

Prelude’s Early KAT6A Degraders Demonstrated Picomolar Potency and Excellent Selectivity Globally and Against KAT Family Members, Including KAT6B & KAT7

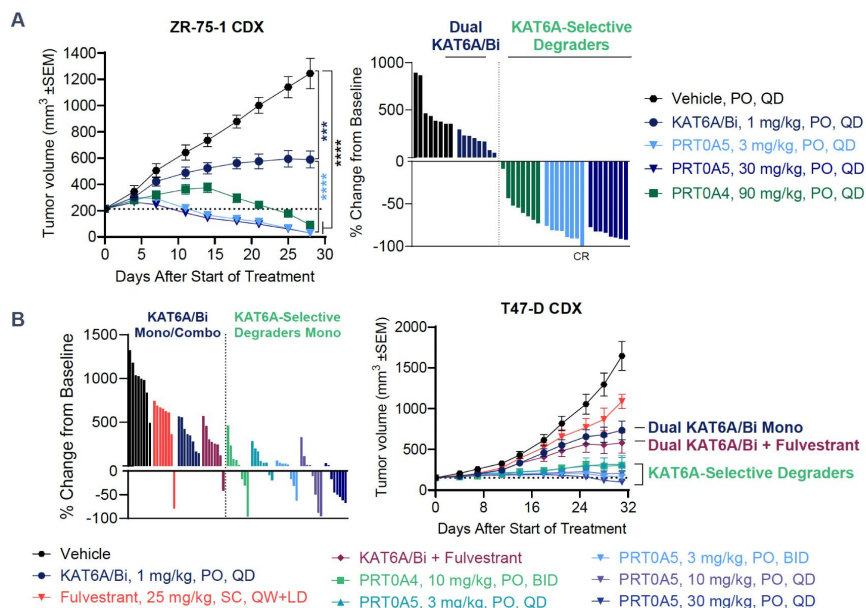
Assay	KAT6A/Bi	PRT0A1	PRT0A2	PRT0A3	Early PoC Leads	
					PRT0A4	PRT0A5
HeLa KAT6A HiBiT nM DC ₅₀	NA	19.7	2.8	1.7	0.8	0.2
T47-D CTG nM Rel EC ₅₀ (E _{MAX})	0.5 (43%)	8.9 (77%)	1.4 (90%)	1.3 (85%)	1.0 (80%)	0.1 (85%)

Note: KAT6A degradation potency at 24 h using a HeLa KAT6A HiBiT model and corresponding anti-proliferative activity in T47-D cell proliferation assays (CTG) are shown.



Note: Global proteomics profile of PRT0A4 and PRT0A5, early leads selected for proof-of-concept studies, in ZR-75-1 cells treated at 10 nM for 6 h are shown. Excellent selectivity against other MYST family proteins are highlighted.

Prelude's Early KAT6A Degraders Demonstrated Superior Monotherapy Efficacy to a KAT6A/B Dual Inhibitor When Studied Head-to-Head In Vivo



- KAT6A degraders demonstrate superior efficacy to a KAT6A/B dual inhibitor at clinically relevant doses
- Deep regressions and complete response observed with a 3 mg/kg oral dose of PRT05A that was well-tolerated
- Deep regressions also achieved with highly selective KAT6A degrader (PRT04A); dose response in progress

Key Takeaways:

Degraders show potential for better monotherapy efficacy than inhibitors

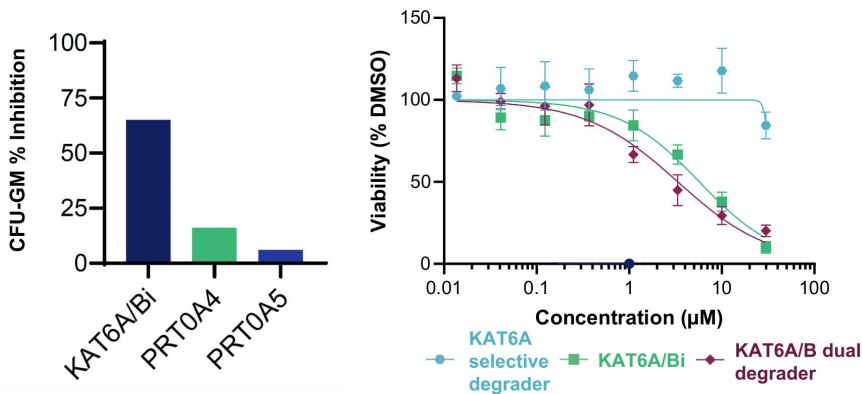
Inhibition or degradation of KAT6B or KAT7 may not be necessary for efficacy

Figure 7. (A) Oral KAT6A-selective degraders safely achieved deep and complete tumor regressions at low oral doses in an orthotopic ZR-75-1 xenograft model, superior to a dual KAT6A/B inhibitor. (B) Oral KAT6A-selective degraders induced significant tumor growth inhibition and tumor regressions in T47-D xenografts as a monotherapy, outperforming combination of a KAT6A/Bi with Fulvestrant. *** $P < 0.0005$, **** $P < 0.0001$.

J. Carter et. al., Discovery of first-in-class potent and selective oral degraders of KAT6A that demonstrate anti-cancer activity in pre-clinical models, AACR2025; Abstract #1649

CFU-GM Assay Data Demonstrate Potential Benefit of KAT6A Selective Degradation in Reducing Bone Marrow Toxicity and Lowering Neutropenia Risk

In Vitro CFU-GM Assay and Dose Response



Normal donor bone marrow was treated with 30 μM KAT6A/Bi, PRT0A4, or PRT0A5 for two weeks to assess their effect on human myeloid progenitor proliferation using colony forming cell assays. Percent inhibition in the CFU-GM myeloid assay is shown, in which KAT6A-selective degraders demonstrate reduced activity. KAT6A/B dual degrader tool compound used as control.

- In vitro CFU-GM assays are used as a pre-clinical indicators of high-grade neutropenia
- KAT6A/B inhibitors demonstrate inhibition of CFU-GM colonies at concentrations being tested in the clinic
- Prelude's KAT6A selective degraders show limited to no activity in CFU-GM assays

Key Takeaways:

- KAT6A selective degraders show potential for:**
- **Lower bone marrow toxicity vs. KAT6A/B dual inhibitors**
 - **Lower risk of neutropenia**

Improved Tolerability and Lower Neutropenia Risk Confer Potential for Improved Combinability with Other Commonly Used Agents in Breast Cancer

Early studies demonstrate potential for mechanistic synergy with CDK4/6 and PI3K inhibitors

KAT6A Degradator + PI3K Inhibitor

PRT02A	0.4	55.3967	45.3002	35.6505	22.0604	9.97141	8.78306
	0.1	62.5447	54.4139	37.5268	22.0783	10.8024	8.47034
	0.025	69.9607	62.0086	40.9221	22.9986	9.65868	8.09507
	0.00625	83.3631	73.8027	54.7713	32.4339	12.6162	9.22981
	0.00156	95.9614	81.6655	69.8713	47.3553	16.6816	10.2395
	0	100	107.398	90.6898	63.7956	40.6808	15.654
	Dosing	0	0.00391	0.01563	0.0625	0.25	1
	PI3K008 (uM)						

Average ZIP = 13.9, % viability shown

KAT6A Degradator + CDK4/6 Inhibitor

PRT02A	0.4	59.4142	47.8847	46.304	32.5244	20.1767	19.9535
	0.1	65.272	52.1618	53.0916	32.9149	17.9265	20.7717
	0.025	65.7369	55.695	54.0214	37.6569	20.3533	21.2087
	0.00625	83.9609	69.3631	60.623	41.655	22.9475	23.8959
	0.00156	95.2115	86.0995	81.1715	68.7122	34.1237	30.2743
	0	100	104.51	97.9079	85.8205	45.1883	36.9131
	Dosing	0	0.00391	0.01563	0.0625	0.25	1
	Palbociclib(uM)						

Average ZIP = 12.5, % viability shown

- One of Prelude's early KAT6A degraders (PRT02A) was tested with both CDK4/6 inhibitor (palbociclib) and a mutant-selective PI3Ka inhibitor tool compound (PI3K008) in T47-D cells *in vitro*
- Both combinations were synergistic based on ZIP scores
- Additional *in vivo* combinations are planned to confirm findings with advanced lead candidates

KAT6A Selective Degradar Program Summary & Next Steps

Selective KAT6A degraders have the potential for better monotherapy efficacy, improved tolerability (neutropenia) and combinability, and synergy with other approved agents

- Now Advancing a First-in-Class Oral KAT6A Selective Degradar Development Candidate
 - Highly potent (picomolar) and highly selective for KAT6A
 - Excellent oral bioavailability across species
 - Complete regressions observed with *in vivo* efficacy models as monotherapy at low doses
 - No activity in CFU-GM assay (model of bone marrow toxicity)
- Studies in Progress
 - Additional profiling, including *in vivo* PK/PD and efficacy studies
 - Dose range finding toxicology studies
- On Track for IND Filing in 1H 2026

Milestones Achieved

Picomolar Potency

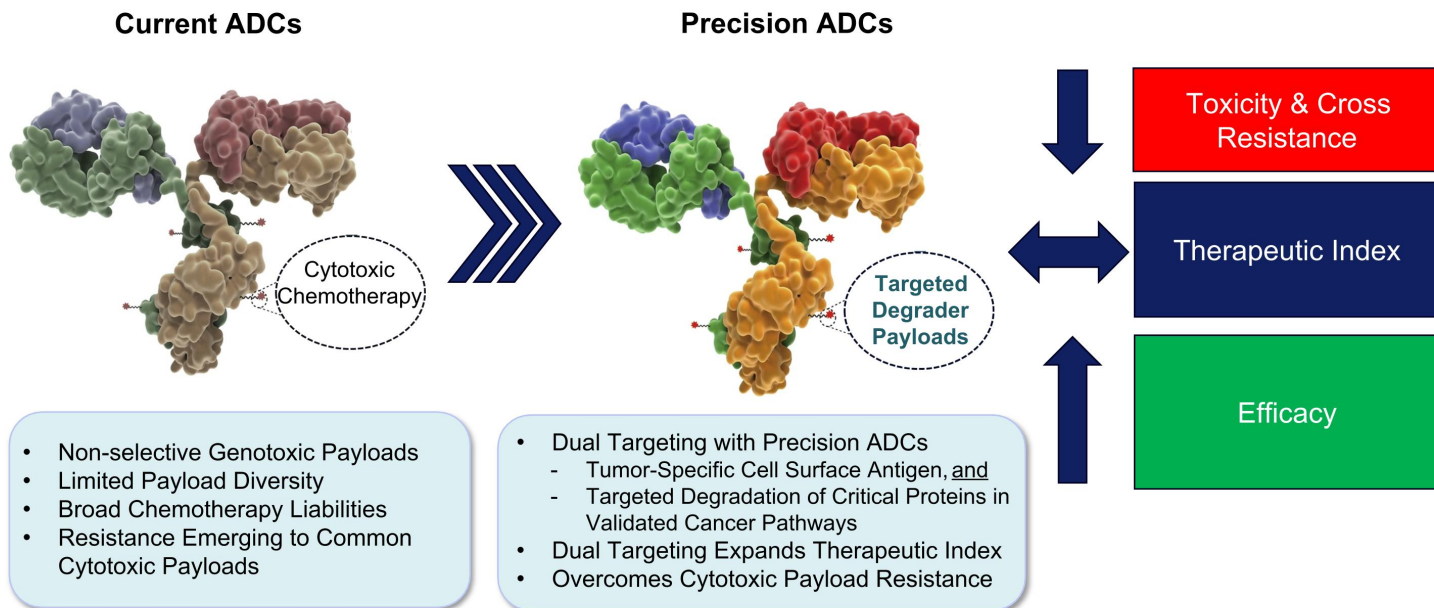
Excellent Oral PK

In Vivo Efficacy – Regressions as Monotherapy at Low Oral Doses

Evidence Supporting Potential for Synergy with Other Modalities

Evidence for Improved Safety Profile (BM Tox)

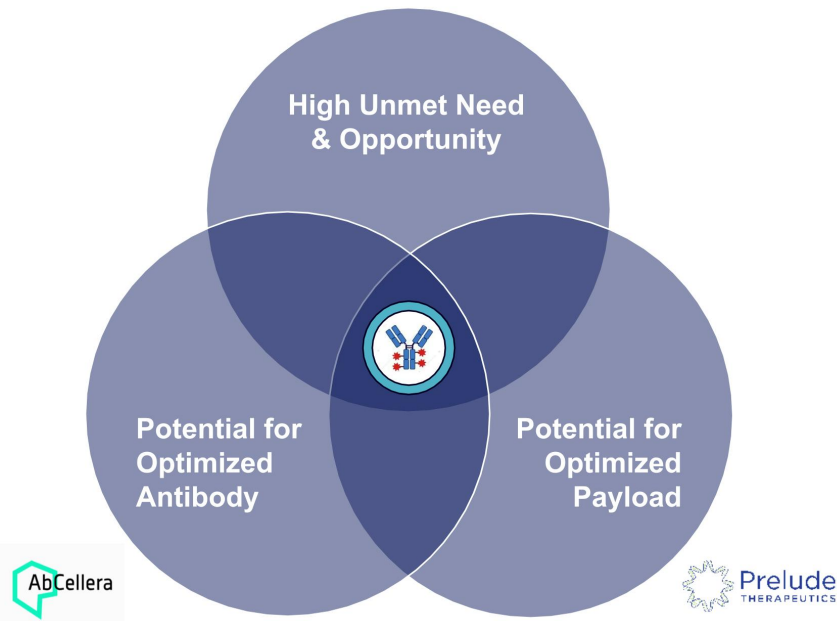
Precision ADCs (or “DACs”) Represent the Next Generation of ADCs



DACs, Degradable Antibody Conjugates

Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* 7, 93 (2022).

Prelude Established a Strategic Partnership with AbCellera in 2023 to Enable First Precision ADCs



Prelude-AbCellera Precision ADC Collaboration Announced in 4Q 2023 ([Press Release](#))
1 - Carter J., et al., 2024 EORTC-NCI-AACR Symposium Poster (<http://www.preludetx.com/science/publications>)

Initial proof-of-concept demonstrated with a novel, highly potent SMARCA2/4 dual degrader as a “Precision Payload” conjugated to multiple antibodies ¹

Prelude’s SMARCA degraders have been optimized to deliver picomolar potency with potential for increased efficacy, selectivity and an improved therapeutic index

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Prelude's Degradable Payloads: Engineered to Improve Efficacy, Tolerability and Developability Compared to Traditional Cytotoxic Payloads

Payload	Rationale	Precision ADC Properties		
		Efficacy	Tolerability	Developability
Exceptional Potency (pM)	Allows low DAR; Low aggregation	+		+
Permeable	Enable localized bystander effect	+		
or Non-Permeable	Limit off-target toxicity from payload diffusion		+	
Highly stable E3 Ligase binder	Long $t_{1/2}$ in vivo; Stable drug substance	+		+
Prodrug	Lower risk of cleavage in plasma		+	+
High Clearance	Rapid clearance in plasma		+	
Non-Genotoxic	Indications beyond cancer		+	

Prelude's Degradable Payloads Have the Potential to Deliver Precision ADCs with an Improved Efficacy and Therapeutic Index

Extensive Optimization Provided a Broad Library of Both VHL- and CRBN-based SMARCA2/4 Dual Degradar Payloads for Testing

	1 st Gen Payload	2 nd Gen Payload	3 rd Gen Payload	4 th Gen Payload
Potency & selectivity assays	PRP0004	PRP0005	PRP0006	PRP0007
E3 Ligase	VHL	VHL	CRBN	CRBN
HeLa HiBit SM2 DC ₅₀ (nM) (D _{max})	0.37 (97%)	0.26 (95%)	0.04 (97%)	0.031 (99%)
HeLa HiBit SM4 DC ₅₀ (nM) (D _{max})	2.7 (96%)	1.2 (97%)	0.09 (97%)	0.029 (99%)
Fold Selectivity SM4/SM2	7	5	2	1
Prostate (LNCaP) prolif EC ₅₀ (nM)	0.21 (96%)	0.082 (95%)	0.074 (93%)	0.049 (94%)
Myeloid (KO52) prolif EC ₅₀ (nM)	3.1 (93%)	1.2 (97%)	0.9 (95%)	<0.1 (98%)
DMPK				
hLM CLint mL/min/kg	High	High	High	High
Plasma stability (7 d)	High	High	Low	High

Prelude Data on File

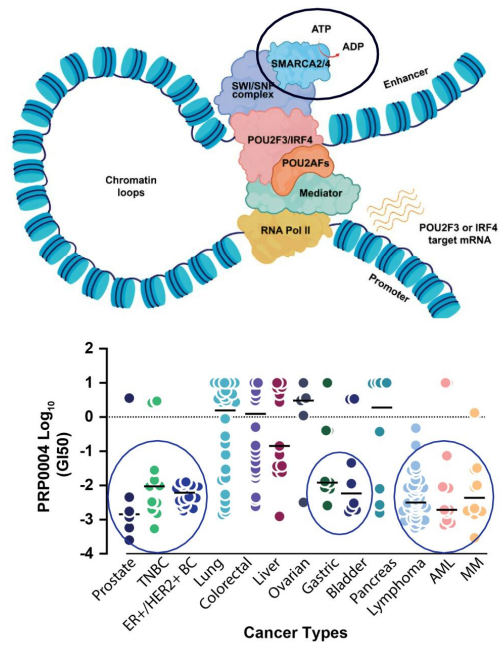
Prelude designed and optimized a series of SMARCA degrader payloads aided by extensive SAR from our IV and Oral SMARCA2 selective degrader programs

Picomolar potencies in HiBit, Western and Proliferation assays were essential for delivering highly potent Precision ADCs

High clearance was built into these payloads to limit systemic exposure that would lead to diminished therapeutic index

These optimized SMARCA degrader payloads are wholly owned by Prelude

Prostate and Myeloid Cancer Cell Lines are Among The Cancer Types Most Highly Sensitive to Prelude’s SMARCA Degraders



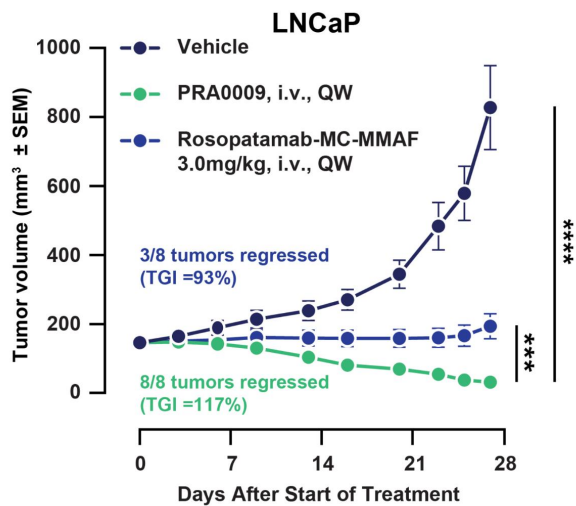
Carter J., *et al.*, 2024 EORTC-NCI-AACR Symposium Poster (<http://www.preludetx.com/science/publications>)

Prelude tested multiple highly potent and selective SMARCA2/4 dual degraders across a range of cell lines

SMARCA degraders robustly inhibit cancer growth and induce cell death across cancer cell lines tested

Prostate and myeloid cancer cell lines are among the cancer types most consistently sensitive to SMARCA degrader payloads

Early Anti-PSMA SMARCA DACs Demonstrated Tumor Regressions and Significantly Better Efficacy Compared to Traditional Anti-PSMA Cytotoxic ADC



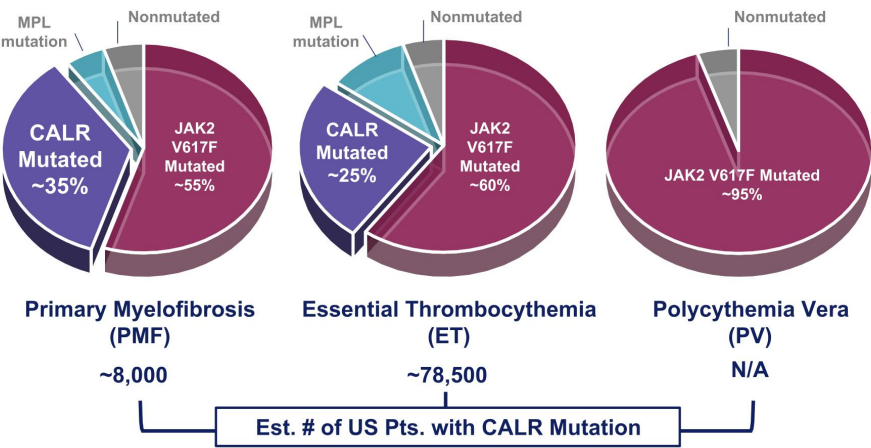
Carter J., et al., 2024 EORTC-NCI-AACR Symposium Poster (<http://www.preludetx.com/science/publications>)

Anti-PSMA SMARCA DACs using Prelude's 1st gen payloads demonstrated robust efficacy in vivo and were well-tolerated

Anti-PSMA SMARCA DACs enable maximal target degradation in tumors while sparing healthy tissues

Prelude is advancing a range of novel Precision ADCs leveraging our SMARCA degrader payloads

Mutated Calreticulin (mCALR) Represents a Promising ADC Target and Pathway to Potential Molecular Remission in Both MF and ET



CALR mutations are predominant driver mutations in MPNs, associated with poor clinical prognosis and disease progression

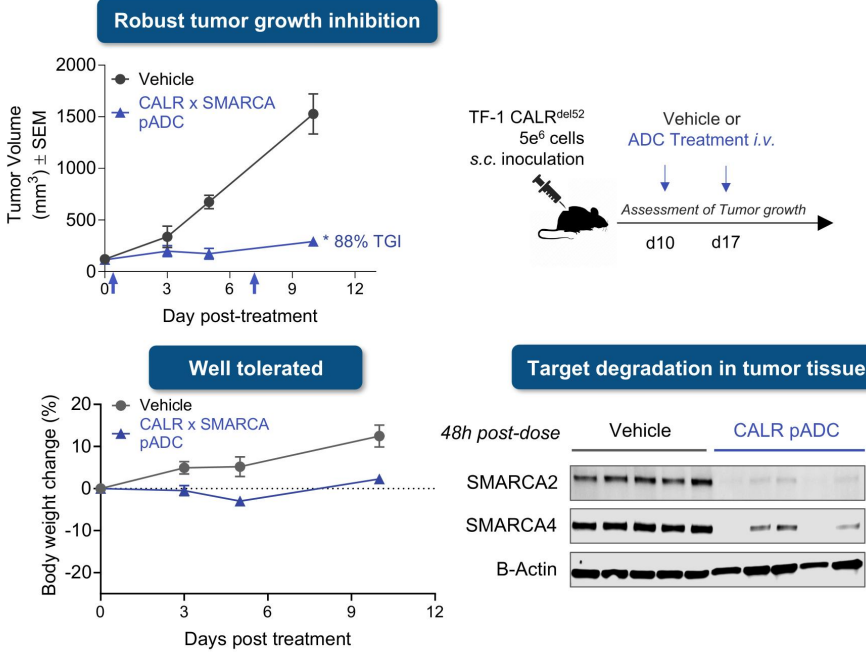
Mutant CALR is a neoantigen presented on the cell surface of malignant cells but not normal cells and is found in 25-35% of patients with Myelofibrosis (MF) and ET

SMARCA degraders are highly active in CALR mutated MPN cell lines and can be used as novel payloads for mCALR-targeted Precision ADCs

A mCALR-targeted Precision ADC, delivering Prelude's degrader payloads to disease-initiating clones has the potential to be a first-in-class, disease modifying therapy

Source: NCI SEER Database (accessed Dec 2024), Leukemia & Lymphoma Society Facts & Figures

CALR x SMARCA pADCs Demonstrate Robust Anti-Tumor Activity In Vivo and Are Well-Tolerated



CALR x SMARCA pADCs drive robust tumor growth inhibition in a TF-1 CALR^{del52} subcutaneous xenograft model highlighting their potent *in vivo* anti-tumor activity

CALR x SMARCA pADCs efficiently degrade SMARCA2/4 in tumor tissue confirming effective payload delivery and on-target engagement

Repeat dosing of CALR x SMARCA pADCs is well tolerated, with no signs of systemic toxicity, underscoring potential for a favorable therapeutic index

Fultang N., et al., EHA2025 Oral Abstract, 12 June 25; Discovery Of First-in-class Precision ADCs Targeting Mutant Calreticulin For The Treatment Of MPNs. ([Link](#))

Our Focus is Continued Execution Across Strategic Priorities

PROGRAM	EXPECTED DELIVERABLE	MILESTONE BY
SMARCA2 Degradar Program PRT3789 PRT7732	- Report Phase 1 data - Report first Phase 1 interim data (Safety, PK/PD, Clinical Activity)	- YE2025 - YE2025
Discovery Engine KAT6A & Precision ADCs	- IND filing for lead KAT6A degrader development candidate(s) - Advance first Precision ADC candidate in partnership w/ AbCellera	1H 2026 2H 2025

Cash, cash equivalents, restricted cash and marketable securities of \$77.3 Million as of 6/30/2025

Thank You

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