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 10, 2026

Prelude Therapeutics Incorporated

(Exact Name of Registrant as Specified in its Charter)

Delaware	**001-39527**	**81-1384762**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

175 Innovation Boulevard **Wilmington, Delaware**	**19805**
(Address of principal executive offices)	**(Zip Code)**

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

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

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

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

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

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

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

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

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

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

Emerging growth company ☐

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

Item 7.01 Regulation FD Disclosure

On September 10, 2026, Prelude Therapeutics Incorporated (the "Company") issued a press release announcing that the U.S. Food and Drug Administration cleared the Company to proceed with a Phase 1 study under its Investigational New Drug Application for PRT13722, a KAT6A degrader, being developed for the treatment of patients with HR+ breast cancer. A copy of the press release is filed as Exhibit 99.1 to this Current Report on Form 8-K.

The Company has also 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 dated September 10, 2026
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: September 10, 2026

By: /s/ *Bryant Lim*
Bryant Lim
Chief Financial Officer and Chief Legal Officer

Exhibit 99.1

Prelude Therapeutics Receives FDA Clearance of Investigational New Drug (IND) Application for PRT13722, Its First-in-Class Oral KAT6A Selective Degrader

Phase 1 study of PRT13722 in patients with HR+ breast cancer anticipated to begin enrolling patients in the fourth quarter of 2026.

WILMINGTON, Del., Sep. 10, 2026 (GLOBE NEWSWIRE) – Prelude Therapeutics Incorporated (Nasdaq: PRLD), a precision oncology company, today announced that the U.S. Food and Drug Administration (FDA) cleared the Company to proceed with a Phase 1 study under its Investigational New Drug Application (IND) for PRT13722, an oral KAT6A selective degrader being developed for the treatment of patients with HR+/HER2- breast cancer. The Company expects to begin enrolling patients in the fourth quarter of 2026.

"Recent clinical data validated KAT6 as a targetable mechanism in the treatment of HR+/HER2- breast cancer, including those with actionable mutations," stated Charles Morris, MBChB, MRCP, Chief Medical Officer of Prelude. "Dual KAT6A/B inhibitors, however, demonstrated overlapping toxicities with current backbone therapies may limit the utility in earlier lines of treatment. Our approach of selectively degrading KAT6A has the potential to address this challenge by maximizing the therapeutic window with enhanced efficacy and improved hematological safety, as supported by our preclinical data. We look forward to advancing PRT13722 into the clinic with the ultimate goal of providing a new therapeutic option for patients with HR+/HER2- breast cancer."

The Phase 1 study is a first-in-human, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and antitumor activity of PRT13722 as monotherapy and in combination with endocrine and targeted therapies in adults with locally advanced or metastatic HR-positive, HER2-negative breast cancer.

Highly selective KAT6A oral degrader program
KAT6 is an emerging and clinically validated target in the treatment of ER+ breast cancer. Prelude discovered and is developing first-in-class, highly potent, highly selective and orally bioavailable KAT6A degraders. Prelude believes that selectively degrading KAT6A and sparing KAT6B has the potential for improved efficacy, tolerability and combinability with other agents relative to dual inhibitors of KAT6A/B.

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 features highly selective KAT6A

degraders and JAK2V617F mutant selective inhibitors -- new approaches to clinically validated targets with transformative potential for patients. We are leveraging our expertise in targeted protein degradation to create and develop next generation degrader antibody conjugates (DACs) with novel payloads. 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, the expected timeline for clinical trial results for Prelude's product candidates, and the sufficiency of Prelude's cash runway. 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, 2025, 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

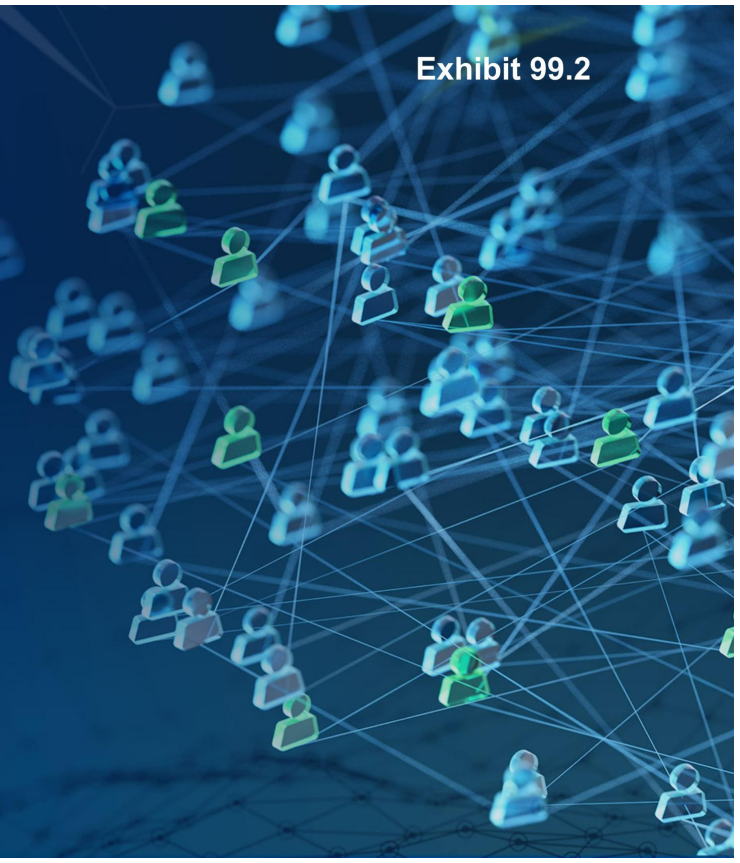
Exhibit 99.2

Prelude THERAPEUTICS

Corporate Presentation

September 2026

Patient focused.
Science driven.
Precision oncology.



Forward Looking Statements & Disclaimers

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 and milestones, the potential safety, efficacy, benefits and addressable market for Prelude Therapeutics Incorporated's (the "Company") product candidates.

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,’’ “aim,” “associated,” ‘‘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).

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, 2025.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to product growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

This presentation concerns drugs that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (the "FDA"). They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

Prelude THERAPEUTICS

Patients Living with Cancer Deserve Better Therapies

Our mission is to deliver practice-changing cancer medicines

Target first, modality flexible approach to cancer drug discovery focused on validated biologic pathways

Fully resourced to deliver key data catalysts across multiple programs over the next 12-24 months

Experienced management team with a track record of clinical and commercial success

Prelude THERAPEUTICS

Experienced Leadership Team With Proven Track Record

Kris Vaddi, PhD

Chief Executive Officer

Charles Morris, MD

Chief Medical Officer

Peggy Scherle, PhD

Chief Scientific Officer

Andrew Combs, PhD

Chief Chemistry Officer

Sean Brusky, MBA

Chief Business & Strategy Officer

Bryant Lim, J.D.

Chief Financial Officer, Chief Legal Officer, Secretary

Advancing Multiple Differentiated Programs for Clinically Validated Targets

	POTENTIAL INDICATIONS	DISCOVERY	IND-ENABLING	PHASE 1	PROGRAM INTEREST	ANTICIPATED MILESTONES
KAT6A Selective Degraders	HR+ breast cancer, other malignancies		PRT13722		Prelude wholly owned	Phase 1 start 4Q 2026
JAK2V617F Mutant Selective JH2 Inhibitors	VF+ Myeloproliferative Neoplasms (MPNs) (MF, PV, ET)		PRT12396		Incyte [1]	Phase 1 Early Data 2027
mCALR Precision DACs	CALR-mutated MPNs (ET, MF)				Prelude wholly owned	Program Update by YE 2026
Degrader Payloads for DACs	Broad utility across multiple indications		*Proprietary degrader payloads available for licensing to partners developing next generation DACs*		AbCellera [2] . . .	Additional Partnerships

JAK2, janus kinase 2; JH2, JAK2 homology domain 2 (pseudokinase regulatory domain); VF+, V617F mutated; MPNs, myeloproliferative neoplasms; MF, myelofibrosis; PV, polycythemia vera; ET, essential thrombocythemia; HR+, hormone receptor positive; DAC, degrader antibody conjugate; mCALR, mutated calreticulin
1 - Exclusive option agreement with Incyte (Nov. 2025); 2 - DAC Discovery Collaboration with AbCellera (Nov. 2023, amended and expanded 2H 2025)

Three Key Programs With Data Catalysts Over the Next 12-24 Months

KAT6A (PRT13722)
Highly Selective Oral Degrader

First-in-class KAT6A degrader with >1000x selectivity over KAT6B – a differentiated modality and profile with potential to become a new backbone therapy in the treatment of HR+ breast cancer

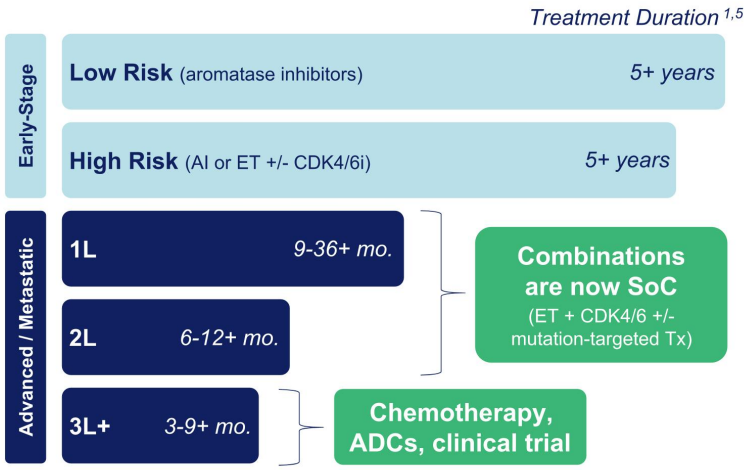
JAK2V617F (PRT12396)
Mutant Selective Inhibitor

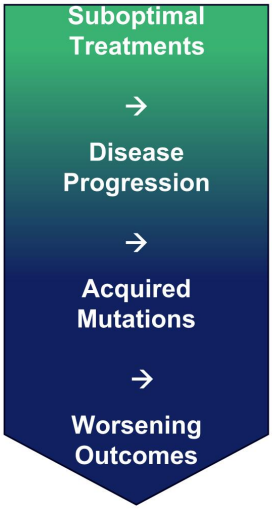
Potentially transformative JAK2V617F allosteric JH2 inhibitor designed to reduce mutant allele burden and modify the course of disease progression in patients with myeloproliferative neoplasms (MPNs)

mCALR Precision DAC
Next Generation Precision DAC

First-in-class mutated calreticulin (mCALR) DAC (Degrader Antibody Conjugate) that is equipotent on CALR Type 1 & 2 mutations and >100x more potent compared to clinical-stage CALR antibodies for patients with MPNs

Patients With HR+/HER2- Breast Cancer Need Better Therapies





~1/3
of early-stage patients ultimately recur or progress to metastatic disease [1]

>50%
of advanced stage patients experience disease progression or death within 2 years on current SoC [2-4]

Well-tolerated treatments are needed that span mutational subtypes, combinations, and lines of care

1. SEER Cancer Stats: Breast Cancer Subtypes, Global Data (EU5 only); NCCN Guidelines V5.2025 (accessed March 2026); Risk stratification varies based on guidelines and staging tools used; 2. Khatpe AS, et al., Cancers 2021. 3. Reinert T, et al., Ther Adv Med Oncol 2015. 4. Brufsky A, et al., Clin Breast Cancer 2019. 5. Prelude estimates based on clinical trial data and package inserts. 1L: 1st line; 2L: 2nd line; 3L: 3rd line SoC: Standard of Care; AI: aromatase inhibitors, ET: endocrine therapy (AI, SERM, SERD, etc.)

Prelude THERAPEUTICS

Pfizer Validated KAT6 as a Target, but Showed the Limits of Dual A/B Inhibition

Initial clinical profile of prifetrastat established in Phase 1/2 trial [1]:

- ✓ **Limited clinical activity as monotherapy** (5mg): **11.4% ORR**; **3.3 mo mPFS**
- ✓ **Initial ORR/PFS in combo with fulvestrant** (5mg, 500mg FUL): **37.2% ORR**; **10.3 mo mPFS**

… with notable limitations [1,2]:

Neutropenia (Gr 3/4)
46%
Dysgeusia (Gr 1/2)
84%
Dose Reductions
56%

→ **Dose intensity limits efficacy**

Combination with current backbone therapies, especially CDK4/6 inhibitors, will be challenging

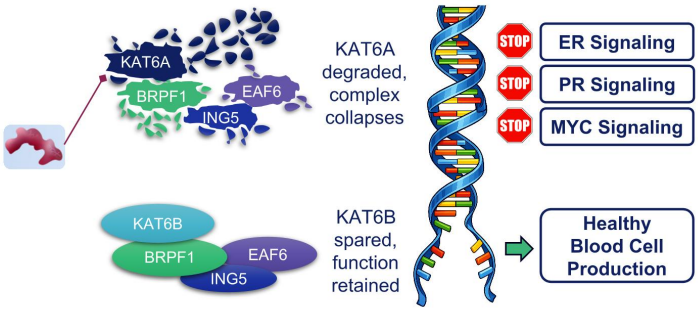
→ **Unclear path to first-line treatment settings**

Initial validation has opened a crowded fast-follower field, but nearly all other players are pursuing dual KAT6A/B inhibitors and are likely to face similar limitations

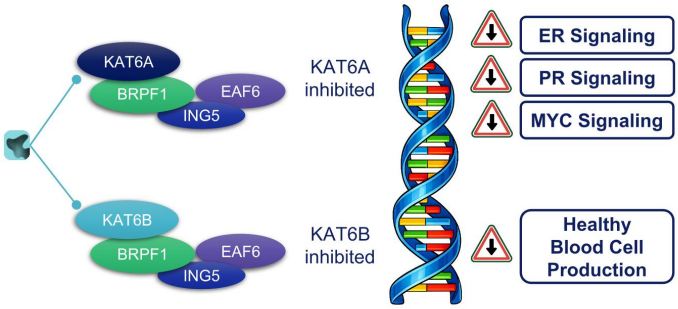
1. P LoRusso, *et al*., Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients (pts) with ER+/HER2− metastatic breast cancer (mBC): Results from phase 1 study to support the recommended phase 3 dose (RP3D) ASCO 2025 Annual Meeting, J *Clin Oncol* **43**, 1020 (2025) ; 2. 78% of dose reductions were attributable to neutropenia (44% of patients required dose reductions due to neutropenia), R Layman, *et. al*., J Clin Oncol 44, 2026 (suppl 16; abstr 1068)

KAT6A Degradation May Be a Better Approach than KAT6A/B Dual Inhibition

KAT6A Degrader



KAT6A/B Inhibitor



A KAT6A selective degrader has potential to drive deeper biologic suppression of key oncogenic drivers and a better therapeutic index in HR+ breast cancer

Prelude AACR 2026 poster presentation (access here); Pfizer reference - Sharma S, et al., Discovery of a highly potent, selective, orally bioavailable inhibitor of KAT6A/B histone acetyltransferases with efficacy against KAT6A-high ER+ breast cancer. Cell Chemical Biology. 2023; 30(10):1191-1210.e20.

PRT13722: Our First-in-Class KAT6A Selective Degrader Candidate

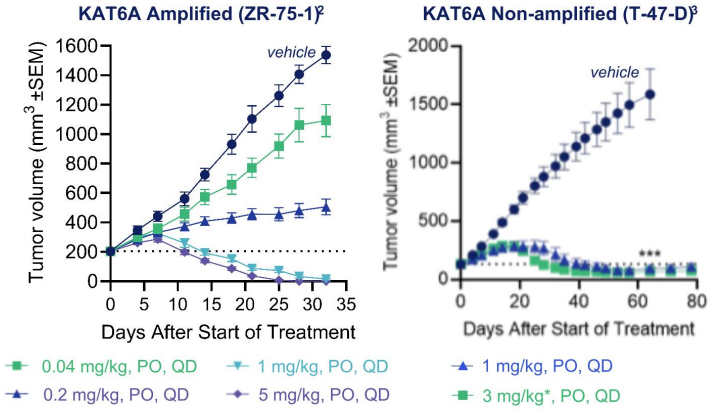
SELECTIVE
>1,000X selectivity for KAT6A over KAT6B

POTENT
Sub-nanomolar degrader (0.3 nM DC50)

ORAL
Convenient once-daily oral dosing [1]

COMBINABLE
Demonstrated synergy with ET, CDK4/6i & PI3Kαi at well-tolerated doses [1]

Complete tumor regressions as monotherapy
across multiple preclinical HR+ breast cancer models



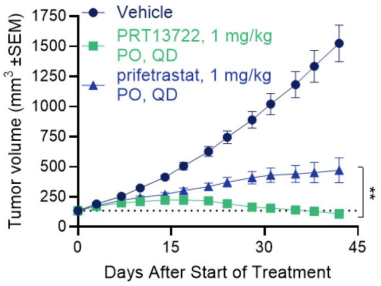
Engineered to be a potential part of backbone therapy for the treatment of HR+ breast cancer

Prelude AACR 2026 poster presentation (access here); 1. Once-daily dosing projected based on preclinical PK and modeling; combinability based on preclinical data; 2. Mice harboring ZR-75-1 xenografts were treated with PRT13722; effects on tumor growth are shown; 3. Mice harboring T47-D xenografts were treated with PRT13722 or a racemic mixture of PRT13722*; well-tolerated with no observed body weight loss in animals in either model.

PRT13722 Monotherapy Demonstrates Better Efficacy Head-to-Head Versus Prifetrastat in Preclinical Studies

Better Efficacy Head-to-Head vs. Prifetrastat

HR+/HER2-, *PIK3CA* H1047R (T47-D)



Treatment	Day 28 TGI#	Plasma C_{ave} (μM)
prifetrastat, 1 mg/kg, QD	**59%**	**5.50**
PRT13722*, 0.3 mg/kg, QD	**67%**	**0.09**
PRT13722, 1 mg/kg, QD	89%	0.35
PRT13722*, 3 mg/kg, QD	101%	1.32

>50-fold

Lower exposure (AUC) required for comparable efficacy to prifetrastat

Better Efficacy as Monotherapy vs. Prifetrastat + Fulvestrant in Combination

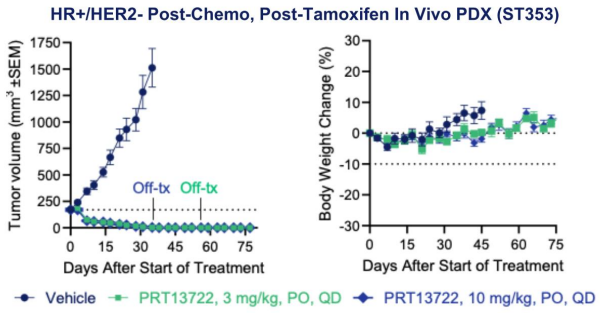
Class	Treatment	% Tumors Regressed^
Monotherapy	prifetrastat, 1 mg/kg	0%
	PRT13722, 1 mg/kg	**50%**
	PRT13722*, 3 mg/kg	75%
+ ET	**prifetrastat, 1 mg/kg + fulvestrant**	**13%**
	PRT13722, 1 mg/kg + fulvestrant	88%

Fulvestrant (25 mg/kg, SC, QW+LD)

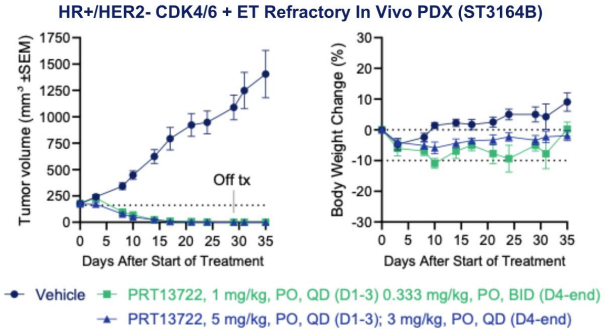
Prelude AACR 2026 poster presentation (access here); mice harboring T47-D xenografts were treated with PRT13722 or a racemic mixture of PRT13722*; effects on tumor growth shown. # TGI, Tumor Growth Inhibition (n = 8 or 16 mice per study); ^ % of T47-D tumors that regressed below baseline on Day 31/32 of studies. ** <0.01 p-value t-test

PRT13722 Completely Eradicates Tumors in Treatment Refractory PDX Models: *100% Complete Response Rate as Monotherapy*

Post- Chemo, Tamoxifen



Post- CDK4/6 + ET



100%
of test animals achieved complete and durable responses across two PDX studies

Responses persisted following treatment cessation in treatment refractory models

Minimal observed body weight changes in either study

Prelude AACR 2026 poster presentation (access here); Prelude Data On File; Off-tx indicates treatment cessation

PRT13722 Lowers Bone-Marrow Toxicity Potential by Sparing KAT6B

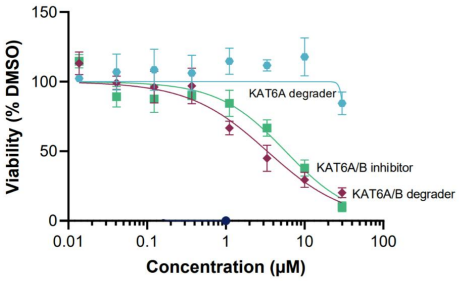
SELECTIVITY
>1,000X selective for KAT6A over KAT6B

IMPACT
KAT6B spared in the bone marrow

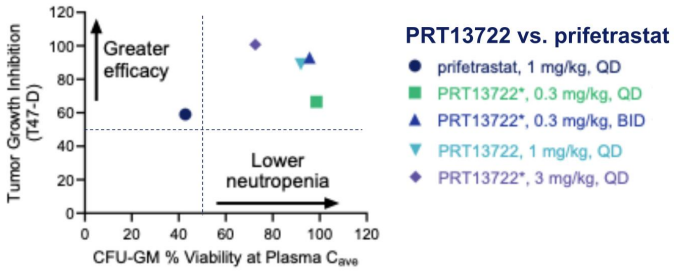
RESULT
Limited effects on neutrophils in preclinical models

OUTCOMES
Maintain higher dose intensity and ability to combine with CDK4/6i's

Ex Vivo Dose Response of CFU-GM



Plot of *In Vivo* Efficacy vs. Impact on CFU-GM Viability



Selectivity may enable improved combinability with standard-of-care therapies

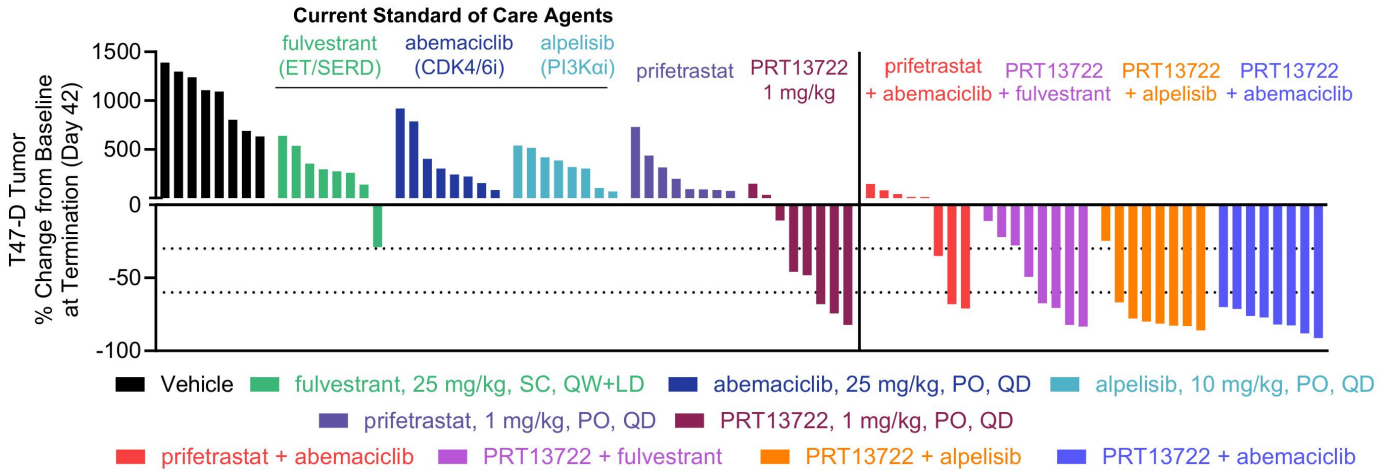
Prelude Data on File; CFU-GM, Colony-Forming Unit-Granulocyte/Macrophage, myeloid progenitor cells found in bone marrow; LD, low dose; HD, high dose; CD, clinical dose
*Study conducted with PRT13722 or a racemic mixture of PRT13722; Prelude AACR 2026 poster presentation (access here)

PRT13722 Shows Synergistic Potential in Combo with Current SoC Agents

ENDOCRINE THERAPY
fulvestrant & oral SERDs
✓ Synergistic

CDK4/6 INHIBITORS
ribociclib, abemaciclib
✓ Synergistic

PI3Kα INHIBITORS
alpelisib, inavolisib
✓ Synergistic



Prelude AACR 2026 poster presentation (access here)

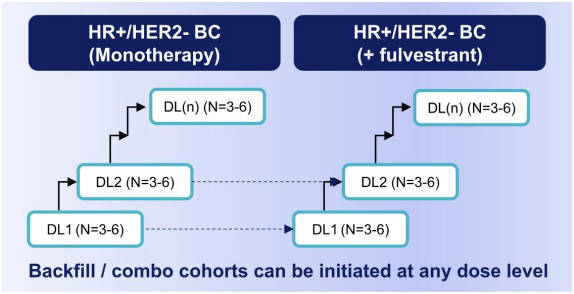
Robust Phase 1 Designed to Show PRT13722 is in a Class of Its Own

1 Demonstrate Differentiated Safety Profile

2 Profile Monotherapy & Combination Efficacy

3 Inform the Registration Path

Phase 1 Dose Escalation



Backfill / combo cohorts can be initiated at any dose level

Mono & Combo Expansion Cohorts

Mono, fulvestrant combo, fulvestrant/CDK4/6 combo and oral SERD combo

Key Data Readouts in 2027/2028

- ORR as mono and combo, durability of response
- Molecular response and ctDNA profiling
- Safety, tolerability and dose intensity as mono and in combo with first-line agents

2026	2027	2028

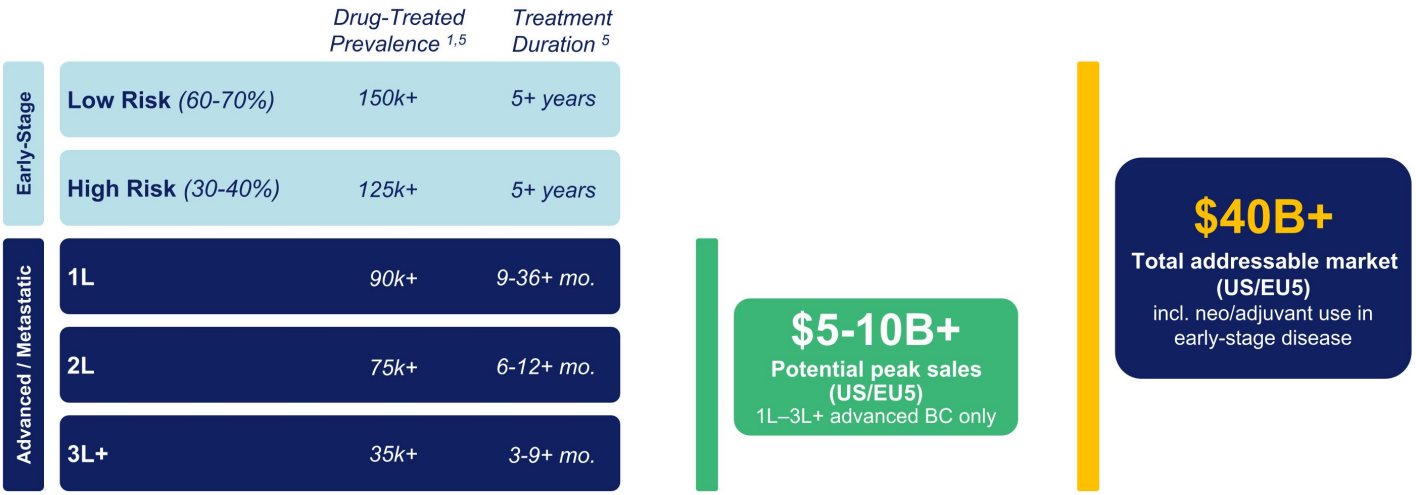
IND cleared

Ph 1 start 4Q 2026

Phase 1 Dose Escalation - *Monotherapy and Combinations*

Trial schema is illustrative.

A New Backbone Therapy for HR+ BC Could Address a $40B+ Total Market



HR+/HER2- is the most common subtype of the most common cancer in women

1. SEER Cancer Stats: Breast Cancer Subtypes, analyst estimates (EU5 only); NCCN Guidelines V5.2025 (accessed: March 2026); Risk stratification varies based on guidelines and staging tools used; 2. Khatpe AS, et al., Cancers 2021. 3. Reinert T, et al. Ther Adv Med Oncol 2015. 4. Brufsky A, et al., Clin Breast Cancer 2019. 5. Prelude estimates based on clinical trial data and package inserts. 1L: 1st line; 2L: 2nd line; 3L: 3rd line

Prelude's First-in-Class KAT6A Selective Degrader Program Summary

- Prelude is advancing a highly selective oral KAT6A degrader (PRT13722) with potential to become a new backbone therapy in the treatment of HR+ breast cancer
- PRT13722 has potential to achieve more robust efficacy relative to KAT6A/B inhibitors as monotherapy or in combination with commonly used agents in breast cancer
- PRT13722 was well-tolerated in preclinical studies, supporting potential to differentiate based on overall safety and combinability with standard of care agents across lines of therapy
- Initial Phase 1 designed to demonstrate early proof-of-concept on differentiated profile as both monotherapy and in combination with current standard-of care agents
- IND application clearance received; Phase 1 study of PRT13722 in patients with HR+/HER2- breast cancer anticipated to being enrolling in the fourth quarter.

Three Key Programs With Data Catalysts Over the Next 12-24 Months

KAT6A (PRT13722)
Highly Selective Oral Degrader

First-in-class KAT6A degrader with >1000x selectivity over KAT6B – a differentiated modality and profile with potential to become a new backbone therapy in the treatment of HR+ breast cancer

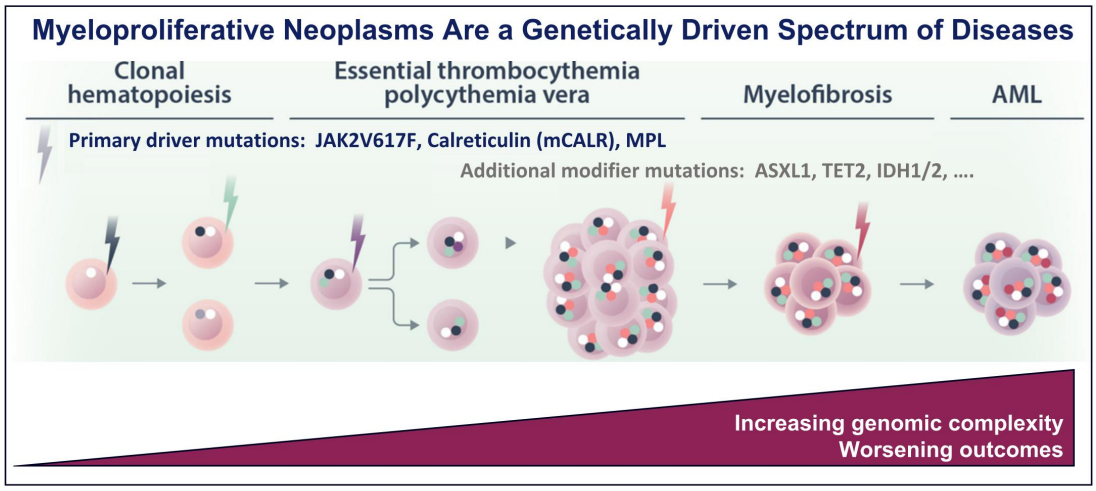
JAK2V617F (PRT12396)
Mutant Selective Inhibitor

Potentially transformative JAK2V617F allosteric JH2 inhibitor designed to reduce mutant allele burden and modify the course of disease progression in patients with myeloproliferative neoplasms (MPNs)

mCALR Precision DAC
Next Generation Precision DAC

First-in-class mutated calreticulin (mCALR) DAC (Degrader Antibody Conjugate) that is equipotent on CALR Type 1 & 2 mutations and >100x more potent compared to clinical-stage CALR antibodies for patients with MPNs

Biomarker-Directed Therapy is the New Frontier in the Treatment of MPNs



JAK2V617F
is the primary driver mutation in MPNs

V617F mutation leads to constitutive JAK-STAT signaling, uncontrolled proliferation, and potentially to disease progression (ET/PV → MF → AML)

A JAK2V617F mutant selective inhibitor has disease modifying potential

DL Paz et al. Genetic basis and molecular profiling in myeloproliferative neoplasms. *Blood* (2023) 141 (16): 1909–1921. F. Passamonte et.al., Clinical Significance of JAK2 V617F mutant allele burden; Haematologica 2009 Jan;94(1):7–10; MPNs, myeloproliferative neoplasms; MF, myelofibrosis; PV, polycythemia vera; ET, essential thrombocythemia

Current JAK Inhibitors Do Not Selectively Target JAK2V617F+ Mutant Clones

	Ruxolitinib[1]	Fedratinib[2]	Pacritinib[3]	Momelotinib[4]
Targets	JAK1, JAK2	JAK2, JAK1 (weak), FLT3	JAK2, FLT3, IRAK1, ACVR1	JAK1, JAK2, ACVR1
Indicated use	Intermediate or high-risk MF, 2L+ PV	Intermediate-2 or high-risk MF	Intermediate or high-risk MF w/ platelet count <50x10^9/L	Intermediate or high-risk MF with anemia
Key liabilities, labeled risks	Thrombocytopenia, anemia, infection, weight gain	GI toxicity, Wenicke encephalopathy	Hemorrhage, CV events, GI toxicity	Anemia, thrombocytopenia

No JAK inhibitors are currently approved in first-line PV or ET

DLTs (cytopenias) with JAK inhibitors limit dose intensity and ability to achieve molecular response

Ruxolitinib takes >5 years to achieve meaningful mutant allele burden reduction[5]

Current JAK inhibitors provide spleen and symptom benefits in MF with limited impact on disease course

Molecular response is associated with improved patient outcomes and event-free survival (EFS).[6] JAK2V617F mutant selective inhibitors have greater potential to deliver molecular responses.

1-4. Package Inserts; 5. Guglielmelli et al. *Blood* (2022) 140: 1788–1789. 6. Harrison et al. J.Clin Oncol. 2023; 41(19);3544

A JAK2V617F Mutant Selective Inhibitor Has Broad Potential in the Treatment of Myeloproliferative Neoplasms (MPNs)

JAK2V617F Mutation Prevalence in MPNs

Polycythemia Vera (PV) ~150,000 U.S. patients	**~95% mutated → ~142,000**
Essential Thrombocythemia (ET) ~140,000 U.S. patients	**~60% mutated → ~84,000**
Myelofibrosis (MF) ~20,000 U.S. patients	**~55%* mutated → ~12,000**

~310,000
patients in the U.S. living with a MPN (20,000+ newly diagnosed each year)

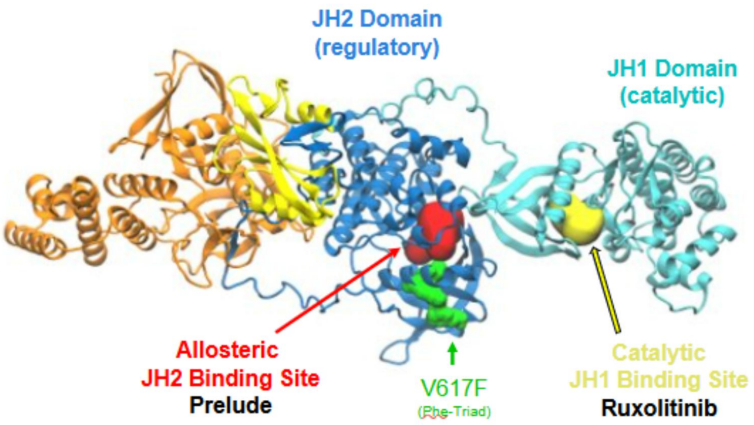
~238,000
patients with JAK2V617F-driven MPNs in the U.S. alone

JAK2V617F is the dominant driver mutation across all three main MPN subtypes

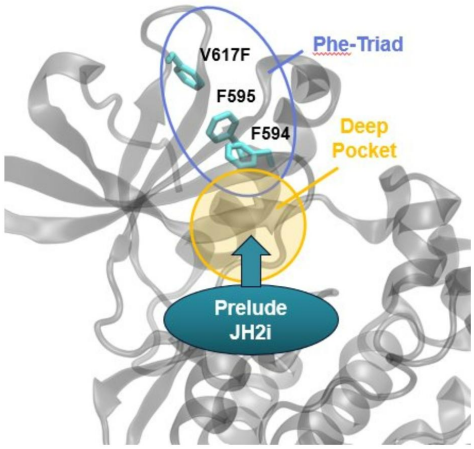
Source: NCI SEER Database (accessed June 2026), Blood Cancer United (LLS) Facts & Figures.
* Prevalence of V617F mutation in Primary Myelofibrosis (PMF); prevalence in post-PV/ET MF is 85-95%+.

Prelude Scientists Recently Discovered the First Known JAK2 Inhibitors that Bind in the JAK2 JH2 "Deep Pocket" Where the V617F Mutation Resides

Allosteric JH2 Regulatory Domain vs. JH1 Catalytic Domain



Prelude JAK2 JH2 Inhibitors Bind into the "Deep Pocket" Adjacent to V617F Mutation



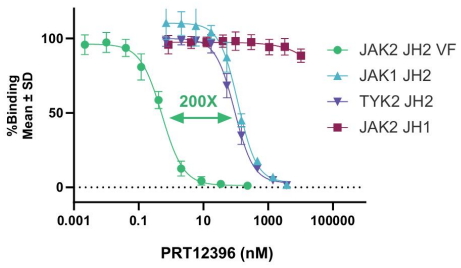
Prelude Data on File

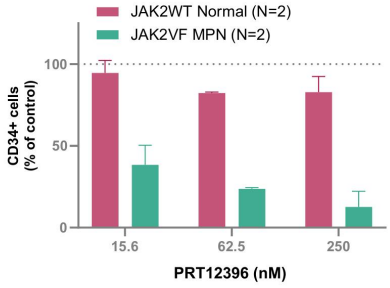
PRT12396: Our Lead JAK2V617F Mutant Selective JH2 Inhibitor

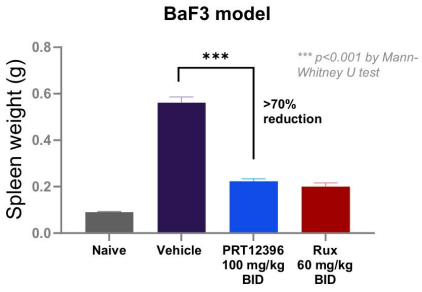
>200-fold
selectivity over JAK1 and TYK2, plus clean profile in KinomeSCAN™ panel of >450 kinases

Minimal
impact on JAK2 wild-type (WT) cells at doses demonstrating anti-proliferative effects in JAK2VF+ MPN cells

>70%
reduction in splenomegaly and normalization of pathogenic cytokines in vivo







PRT12396 has potential for improved efficacy, tolerability and disease modification in JAK2V617F+ MPNs

Prelude ASH Annual Meeting 2025 oral presentation (access here)

PRT12396: Designed to Overcome the Limitations of Current JAK Inhibitors

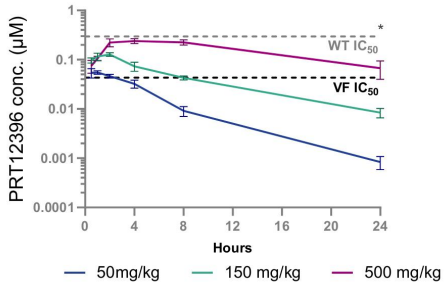
SELECTIVITY
Plasma exposures at efficacious doses remain below JAK2 WT IC50

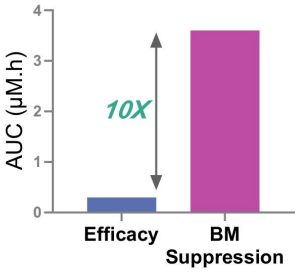
IMPACT
Efficacy AUC is 10-fold lower than toxicity AUC in vivo

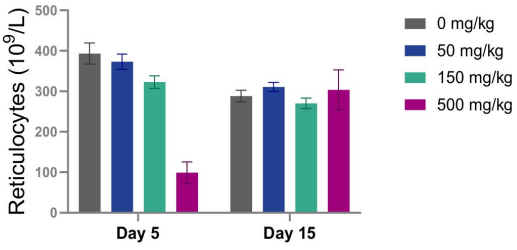
RESULT
Limited effects on reticulocytes at efficacious doses

OUTCOMES
Potential for improved efficacy and tolerability

No evidence of wild-type JAK2 inhibition in 2-week rat toxicology study at doses providing efficacious exposures







Reticulocyte inhibition only at high dose, with full recovery by day 15

Potential for efficacious exposures at well-tolerated doses could enable PRT12396 to maintain dose intensity over an extended duration of therapy

* Dotted lines represent proliferation IC_{50} values from SET2 (VF) and UT-7 (WT) 7-day proliferation assay
Prelude ASH Annual Meeting 2025 oral presentation (access here)

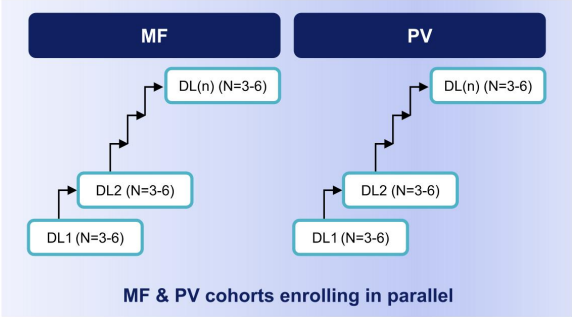
PRT12396: Phase 1 Study Now Enrolling MF and PV Cohorts in Parallel

1 Demonstrate Differentiated Safety Profile

2 Profile Efficacy in MF & PV incl. Molecular Response

3 Inform the Registration Path

Phase 1 Dose Escalation



Expansion Cohorts

Expansion in MF & PV at Dose

OBJECTIVE

- CHR rate, durability (24 week) and molecular response rate (allele burden reduction)
- Spleen and symptom benefit
- Data generation in preparation for first registrational trial(s)

2026	2027	2028
★	Phase 1 (enrolling MF & PV cohorts in parallel)	Phase 1 Expansion Cohorts

Trial schema is illustrative. MPNs, myeloproliferative neoplasms; MF, myelofibrosis; PV, high risk polycythemia vera; CHR, complete hematologic response; DL, dose level

Option Agreement With Incyte Provides Significant Capital to Advance Pipeline

Prelude Therapeutics Announces Exclusive Option Agreement with Incyte to Advance Mutant Selective JAK2V617F JH2 Inhibitors

Incyte secures an exclusive option to acquire Prelude's mutant selective JAK2V617F JH2 inhibitor program

Mutant selective JAK2V617F JH2 inhibitors have disease-modifying potential in treating patients living with myeloproliferative neoplasms (MPNs)

Prelude to receive a $35 million upfront payment and $25 million strategic equity investment at closing, $100 million if Incyte were to exercise the option to acquire the program, and up to $775 million in additional potential milestones plus royalties on net sales

Prelude will continue to develop all JAK2V617F program assets during the option period; if optioned, Incyte would lead development and commercialization globally

Exclusive option agreement with Incyte (announced November 2025)

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Next Generation Precision DAC

First-in-class mutated calreticulin (mCALR) DAC (Degrader Antibody Conjugate) that is equipotent on CALR Type 1 & 2 mutations and >100x more potent compared to clinical-stage CALR antibodies for patients with MPNs

Mutated Calreticulin (mCALR) Represents a Promising Target for a Next Generation Degrader Antibody Conjugate (DAC)

CALR Mutation Prevalence in MPNs

Essential Thrombocythemia (ET)
~140,000 prevalent U.S. patients
~25% mutated → ~35,000

Myelofibrosis (MF)
~20,000 prevalent U.S. patients
~35% mutated → ~7,000

~45-55%
Type I mutations (e.g., 52-bp deletion)

~30-40%
Type II mutations (e.g., 5-bp insertion)

~42,000
patients with mCALR-driven ET or MF in the U.S. alone

Mutant CALR is a neoantigen presented on the surface of malignant cells but not normal cells

CALR mutations drive constitutive JAK/STAT signaling and uncontrolled proliferation of myeloid cells leading to increased risk of disease progression

mCALR is emerging as a validated target in MPNs for biomarker-directed therapy

Sources: NCI SEER Database (accessed June 2026), Blood Cancer United (LLS) Facts & Figures; J.How et. al., Mutant calreticulin in myeloproliferative neoplasms, *Blood* (2019) 134 (25): 2242–2248; Tefferi A, et al. Type 1 versus Type 2 calreticulin mutations in essential thrombocythemia: a collaborative study of 1027 patients. Am J Hematol. 2014 Aug;89(8):E121-4. doi: 10.1002/ajh.23743. Epub 2014 May 16. PMID: 24753125.

INCA989 Validated mCALR as a Target, Albeit with Notable Limitations

Initial clinical profile of INCA'989 established in Phase 1/2 trial [1]:

- ✓ **83%** of patients achieved **complete hematological response (CHR)** at doses ≥ 400mg IV, with **47%** durable CHR ≥12 weeks
- ✓ **52%** and **31%** of patients achieved >25% and >50% best **mCALR variant allele frequency (VAF) reduction**, respectively
- ✓ **Generally well-tolerated** with **93%** of patients remaining on treatment at time of analysis

… with notable limitations [1-3]:

Go Forward Ph 3 Dose (ET)
750mg - 2500mg
Q2W IV (escalation)

Activity in Non-Type 1 Mutants
Limited molecular responses

→ **Patient convenience, efficacy in non-Type 1 mutants, and improved VAF reduction remain significant areas of unmet need**

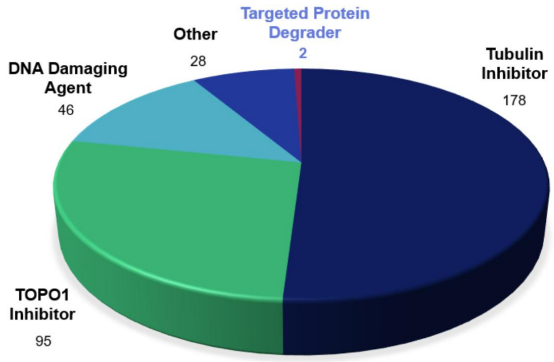
→ **Additional therapies needed to fully maximize the CALR opportunity for patients**

New treatments are needed that are equipotent against all CALR mutations and deliver disease modifying activity at lower, well-tolerated doses.

1. Mascarenhas 2025 (ASH); ClinicalTrials.gov/NCT07623200 (A Phase 3 Study of INCA033989 Versus Best Available Therapy in Participants With Essential Thrombocythemia)
2. Incyte investor presentations; 3. High volume on-body injection (OBI) device in development, along with recently announced collaboration to explore subcutaneous dosing enabled by Halozyme ENHANZE® technology.

Degrader Antibody Conjugates (DACs) Represent the Next Generation of ADCs

Targeted Protein Degraders (TPDs) are an Emerging Payload Class for ADCs in the Clinic*

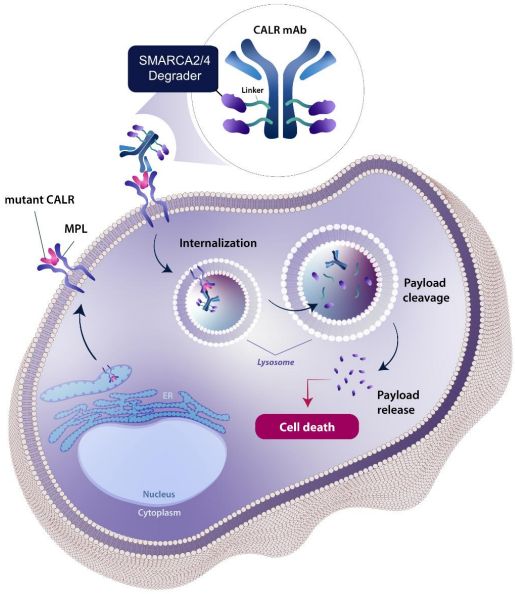


Property	Traditional ADC	Precision DAC
Potency	✓	✓
Antibody Selectivity	✓	✓
Payload Selectivity	X	✓
PD Marker - Payload	X	✓
Non-Genotoxic	X	✓

DACs have potential to deliver both improved efficacy and tolerability over traditional ADCs

For a review of next generation ADC payloads, see Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* **7**, 93 (2022).
* Morris, J. Beacon ADC by HansonWade. "Analyzing the ADC Boom: Landscape Review." World ADC (San Diego). November 2024. Denotes Payload MOA for clinical stage assets currently in development at time of analysis.

mCALR-Targeted DACs Offer a Differentiated Approach to Eradicating CALR Mutant Clones



Naked antibodies bind to the target impacting signaling and proliferation, but do not have the selective mutant cell killing potential of a DAC

SMARCA2/4 degraders are highly active in mCALR MPN cell lines and can be used as highly potent payloads for mCALR-targeted DACs[1]

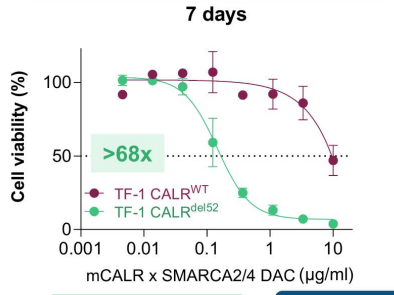
Prelude's mCALR x SMARCA2/4 DACs could represent a best-in-category approach with disease modifying potential

1. Prelude Data on File; 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. (access here);

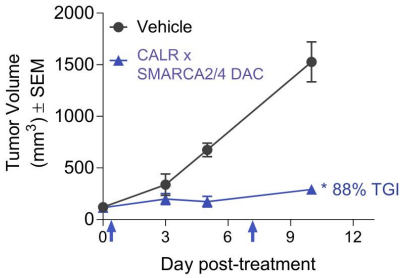
Prelude is Advancing mCALR DACs Equipotent for Type 1 & 2 Mutations

On Track to Nominate Development Candidate by YE 2026

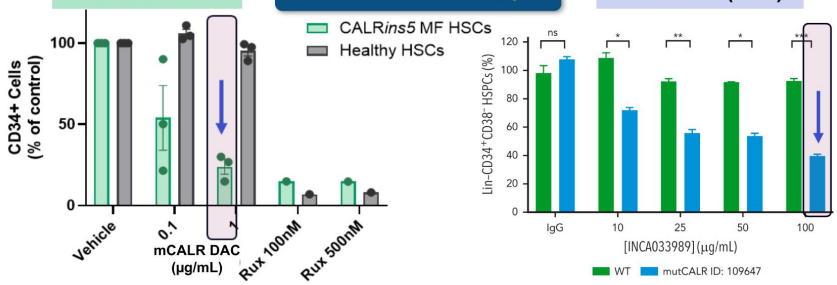
Selective Cytotoxicity *in vitro*



Robust Tumor Growth Inhibition *in vivo*



Prelude DACs ← **~100x Better Potency** → **Naked Ab ('989)**



Selective cytotoxicity and robust tumor growth inhibition at well-tolerated doses *in vivo*

100X

Better potency than INCA989 at low, well tolerated doses

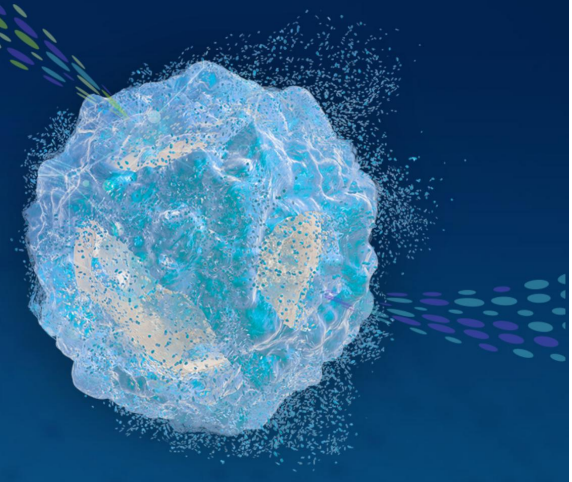
Potential for low volume subcutaneous administration

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. (access here); Reis, et al. Blood. 2024;144(22):2336

Executive Summary

- First-in-class KAT6A selective degrader (PRT13722) on track to enter the clinic in the fourth quarter with potential to demonstrate differentiated efficacy and safety over KAT6A/B inhibitors
- JAK2V617F mutant selective inhibitor (PRT12396) IND cleared and Phase 1 study enrollment underway with potential Incyte option exercise decision by 1H 2027 [1]
- Novel mCALR precision DAC program advancing to DC nomination by YE 2026 with potential to deliver improved disease modifying efficacy over mCALR-targeted antibodies
- Continued investment in foundational discovery engine poised to deliver future pipeline of potential practice-changing cancer medicines in areas of high unmet need
- Current cash runway expected into second quarter of 2028

1 - Subject of exclusive option agreement with Incyte (announced November 2025)



Thank You

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rdoody@preludetx.com