Prelude THERAPEUTICS

Corporate Presentation

November 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	Initial Proof of Concept Data 2nd Half 2027
JAK2V617F Mutant Selective JH2 Inhibitors	VF+ Myeloproliferative Neoplasms (MPNs) (MF, PV, ET)	PRT12396			Incyte [1]	INCY Option Expiration First Half 2027 Phase 1 Early Data 2027
mCALR Precision DACs	CALR-mutated MPNs (ET, MF)				Prelude wholly owned	Preclinical Data ASH 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

Treatment Duration [1,5]

Early-Stage

- **Low Risk** (aromatase inhibitors) — *5+ years*
- **High Risk** (AI or ET +/- CDK4/6i) — *5+ years*

Advanced / Metastatic

- **1L** — *9-36+ mo.*
- **2L** — *6-12+ mo.*
- **3L+** — *3-9+ mo.*

Combinations are now SoC (ET + CDK4/6 +/- mutation-targeted Tx)

Chemotherapy, ADCs, clinical trial

Suboptimal Treatments → **Disease Progression** → **Acquired Mutations** → **Worsening Outcomes**

~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

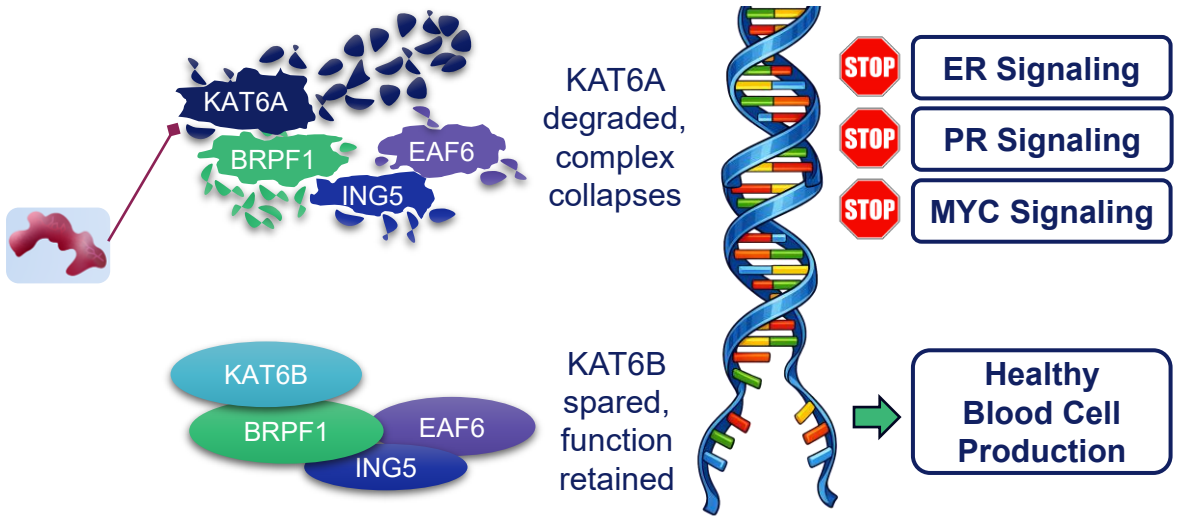
→ **Unclear path to first-line treatment settings**

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

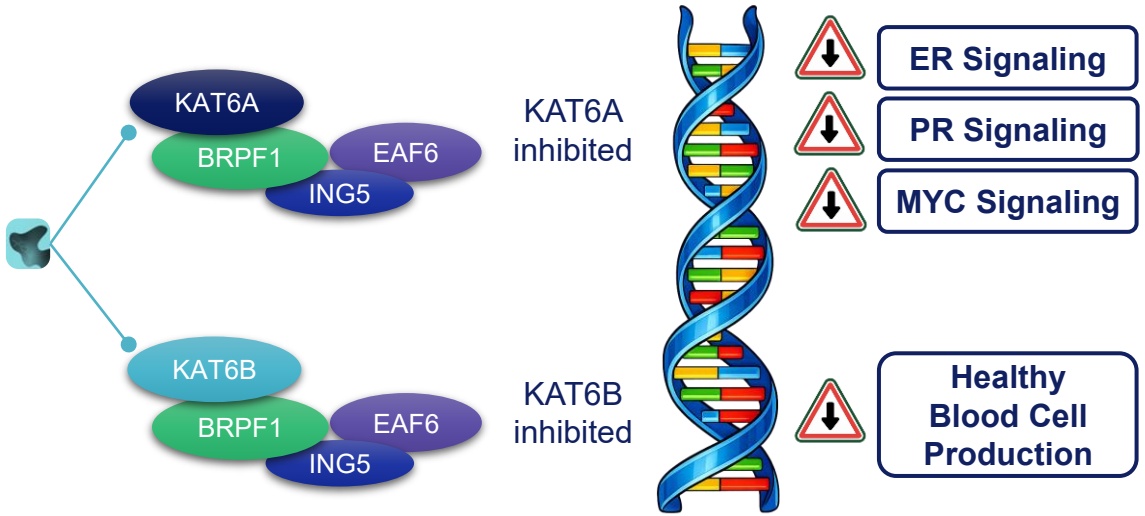
1. P LoRusso, *et al.*, Dose optimization of PF-07248144, a first-in-class KAT6 inhibitor, in patients (pts) with ER+/HER2− metastatic breast cancer (mBC): Results from phase 1 study to support the recommended phase 3 dose (RP3D) ASCO 2025 Annual Meeting, J *Clin Oncol* **43**, 1020 (2025) ; 2. 78% of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

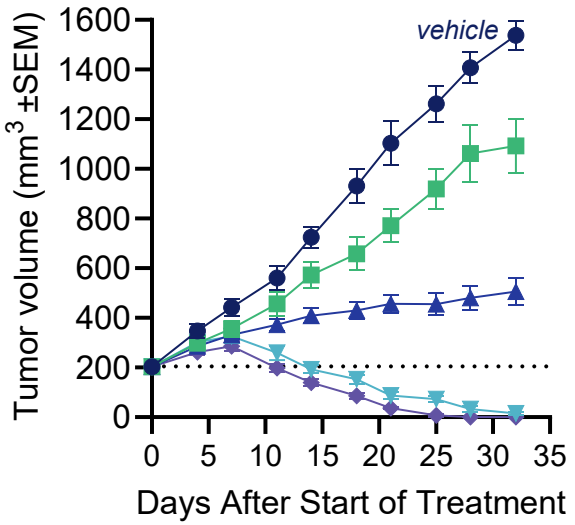
POTENT
Sub-nanomolar degrader (0.3 nM DC50)

ORAL
Convenient once-daily oral dosing [1]

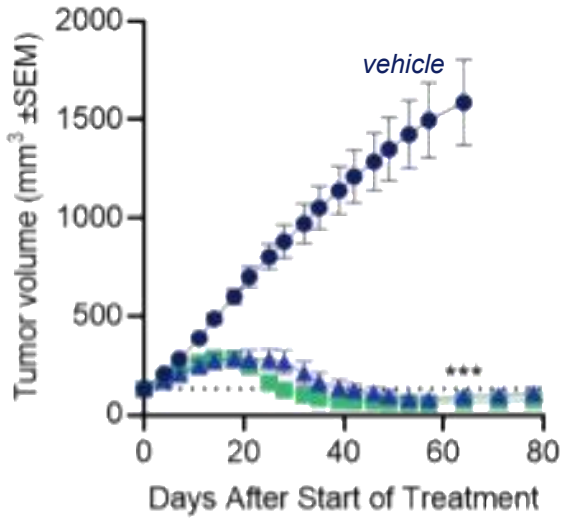
COMBINABLE
Demonstrated synergy with ET, CDK4/6i & PI3Kαi at well-tolerated doses [1]

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

KAT6A Amplified (ZR-75-1)[2]



KAT6A Non-amplified (T-47-D)[3]



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

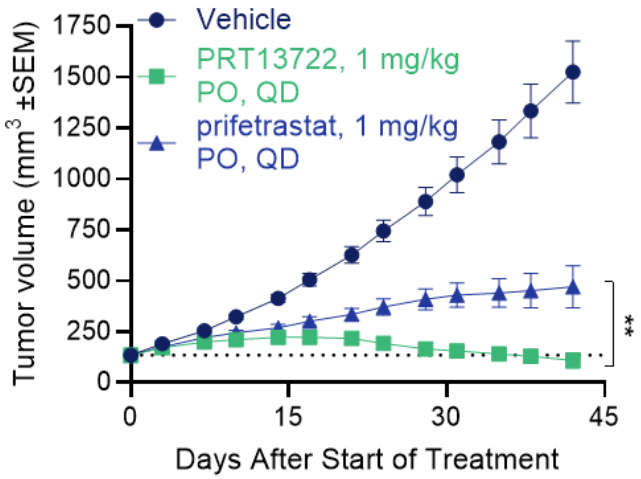
Prelude AACR 2026 poster presentation (access here); 1. Once-daily dosing projected based on preclinical PK and modeling; combinability based on preclinical data; 2. Mice harboring ZR-75-1 xenografts were treated with PRT13722; effects on tumor growth are shown; 3. Mice harboring T47-D xenografts were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

Prelude THERAPEUTICS

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

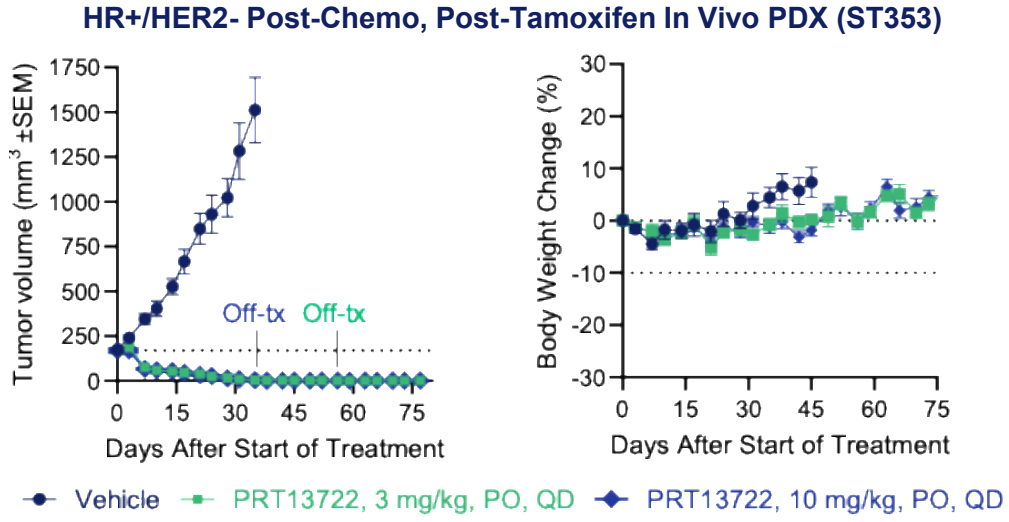
Class	Treatment	% Tumors Regressed^
Monotherapy	prifetrastat, 1 mg/kg	0%
	PRT13722, 1 mg/kg	**50%**
	PRT13722*, 3 mg/kg	75%
+ ET	**prifetrastat, 1 mg/kg + fulvestrant**	**13%**
	PRT13722, 1 mg/kg + fulvestrant	88%

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

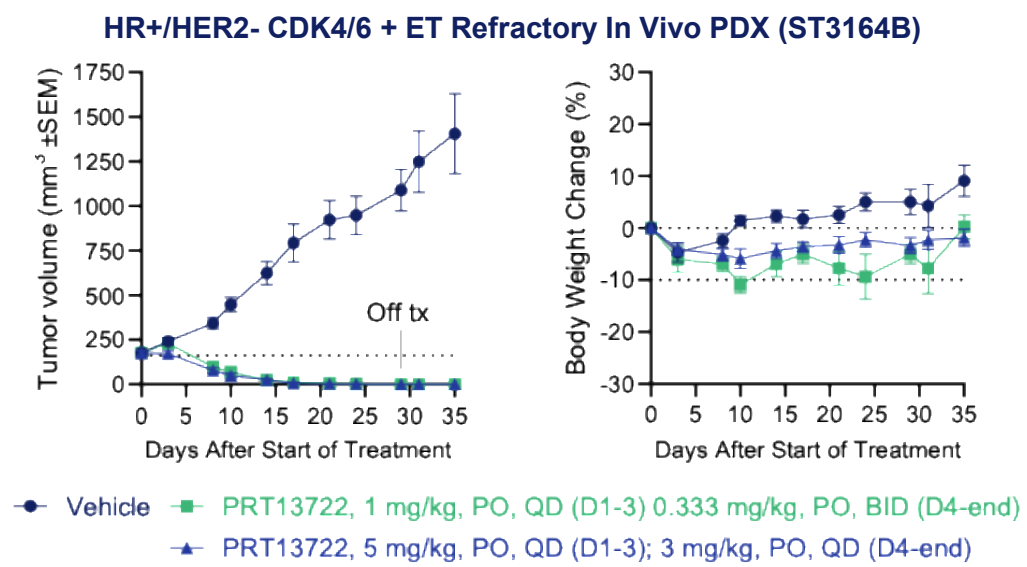
Prelude AACR 2026 poster presentation (access here); mice harboring T47-D xenografts were treated with PRT13722 or a racemic mixture of PRT13722*; effects on tumor growth shown. # TGI, Tumor Growth Inhibition (n = 8 or 16 mice per study); ^ % of T47-D tumors that regressed below baseline on Day 31/32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

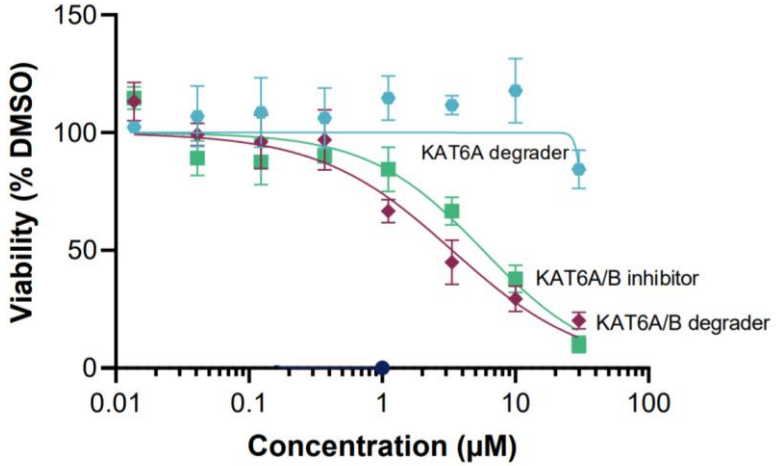
SELECTIVITY
>1,000X selective for KAT6A over KAT6B

IMPACT
KAT6B spared in the bone marrow

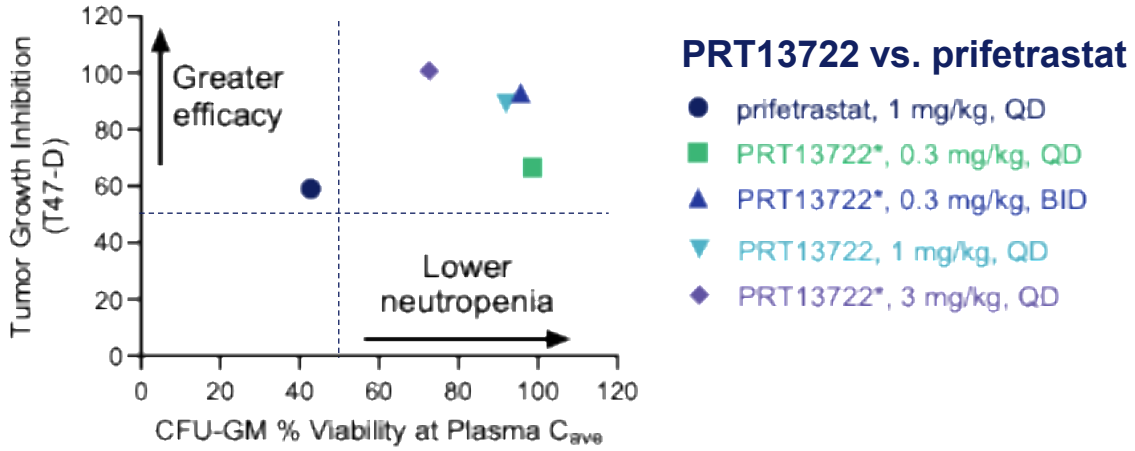
RESULT
Limited effects on neutrophils in preclinical models

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

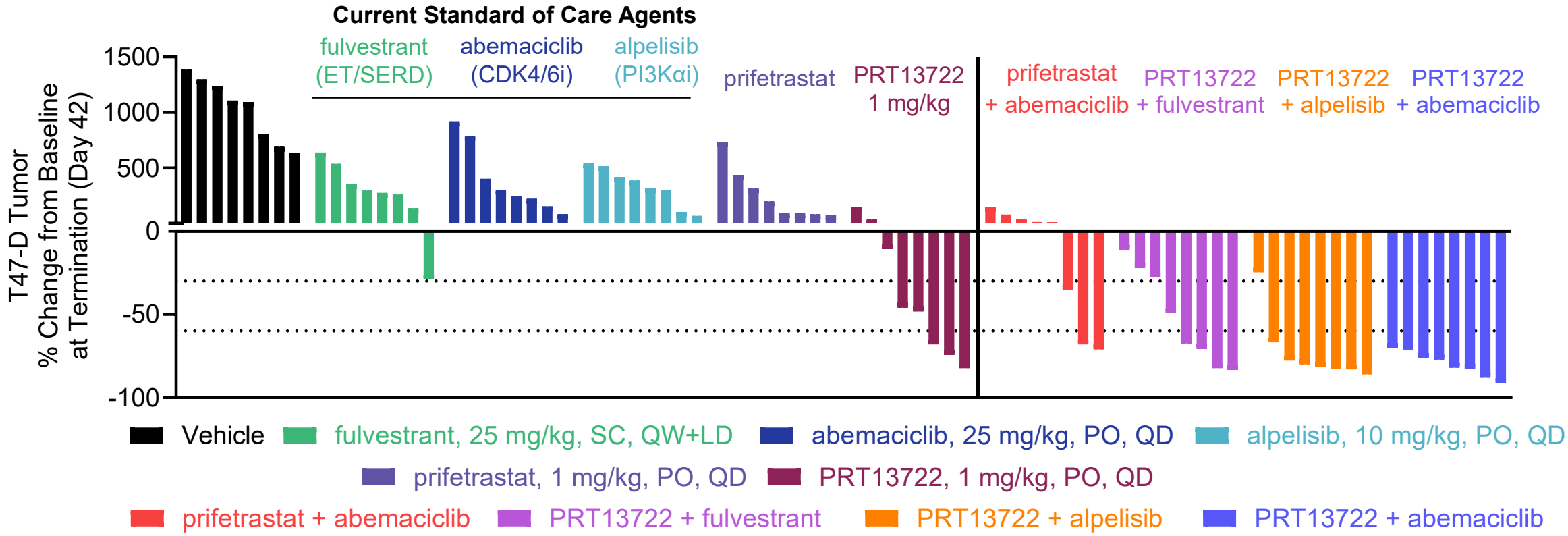
Prelude Data on File; CFU-GM, Colony-Forming Unit-Granulocyte/Macrophage, myeloid progenitor cells found in bone marrow; LD, low dose; HD, high dose; CD, clinical dose
*Study conducted with PRT13722 or a racemic mixture of PRT13722; Prelude AACR 2026 poster presentation (access here)

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)

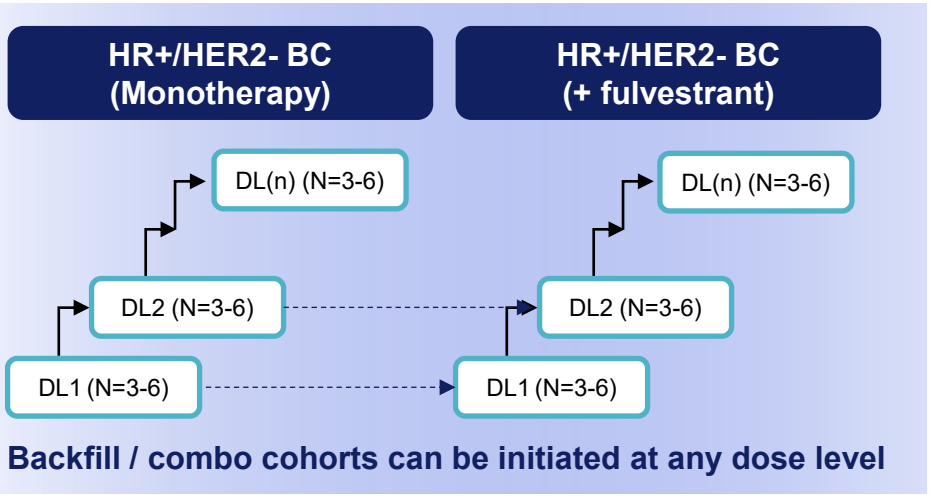
Robust Phase 1 Designed to Show PRT13722 is in a Class of Its Own

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 started 4Q 2026

Phase 1 Dose Escalation - *Monotherapy and Combinations*

Trial schema is illustrative.

Clinical Trial Collaboration and Supply Agreement with Lilly Now in Effect

Prelude Announces Clinical Trial Collaboration and Supply Agreement with Lilly to Evaluate KAT6A Selective Degrader PRT13722 in Combination with Verzenio® and Inluriyo® in Patients with HR+/HER2- Breast Cancer

Combination cohorts are part of Prelude's Phase 1 trial evaluating PRT13722 in patients with HR+/HER2- breast cancer, on track to initiate enrollment in the fourth quarter of 2026

The collaboration is underpinned by pre-clinical data that demonstrate monotherapy efficacy for PRT13722 and synergy with both CDK4/6 inhibitors and endocrine therapies across multiple HR+ breast cancer models

Prelude maintains full global development and commercial rights to PRT13722 as a wholly owned program.

Phase 1 supply
of abemaciclib (CDK4/6 inhibitor) and imlunestrant (oral SERD)

CDK4/6 combo
enables evaluation with agent used in frontline treatment of HR+/HER2- mBC

Oral SERD combo
enables evaluation with oral endocrine therapy

See press release: https://investors.preludetx.com/news-releases/

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

		Drug-Treated Prevalence [1,5]	*Treatment Duration [5]*
Early-Stage	**Low Risk** *(60-70%)*	*150k+*	*5+ years*
Early-Stage	**High Risk** *(30-40%)*	*125k+*	*5+ years*
Advanced / Metastatic	**1L**	*90k+*	*9-36+ mo.*
Advanced / Metastatic	**2L**	*75k+*	*6-12+ mo.*
Advanced / Metastatic	**3L+**	*35k+*	*3-9+ mo.*

$5-10B+
Potential peak sales (US/EU5)
1L–3L+ advanced BC only

$40B+
Total addressable market (US/EU5)
incl. neo/adjuvant use in early-stage disease

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; enrollment of Phase 1 study of PRT13722 in patients with HR+/HER2- breast cancer is underway; initial proof of concept data anticipated in 2nd half of 2027.

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)

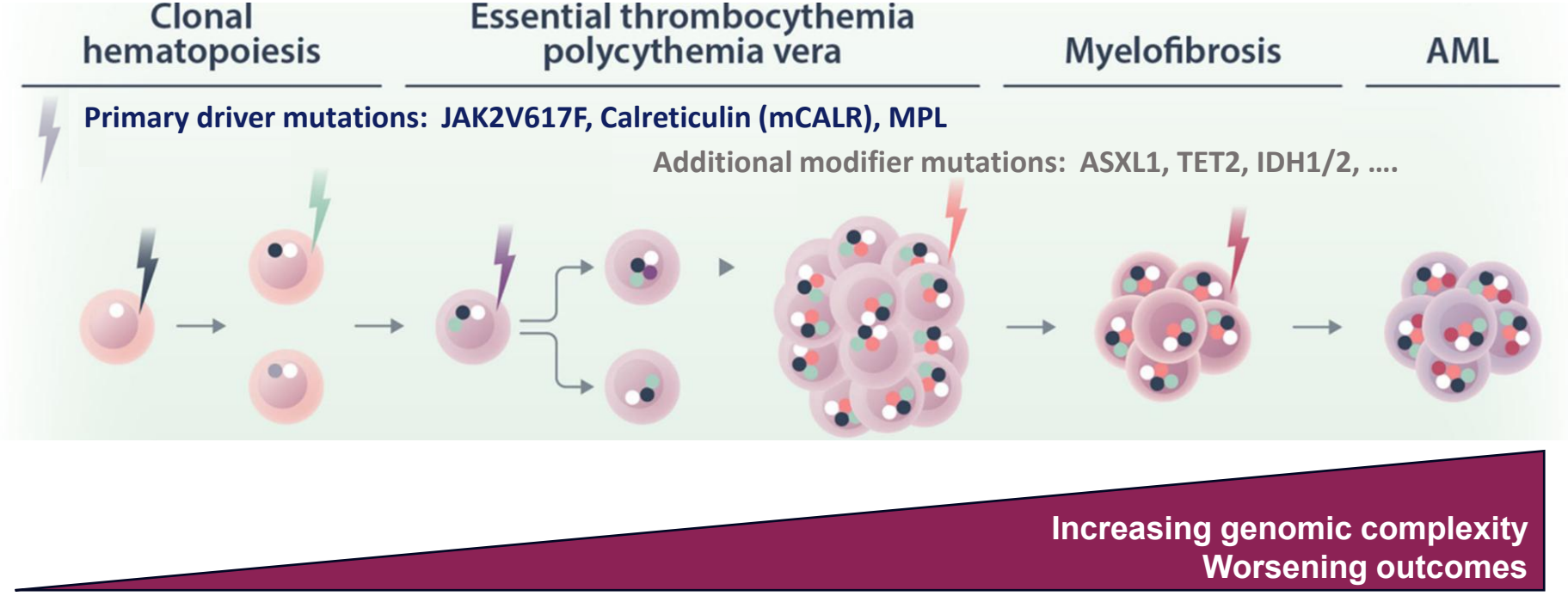
mCALR Precision DAC

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

Myeloproliferative Neoplasms Are a Genetically Driven Spectrum of Diseases



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

Prelude THERAPEUTICS

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)

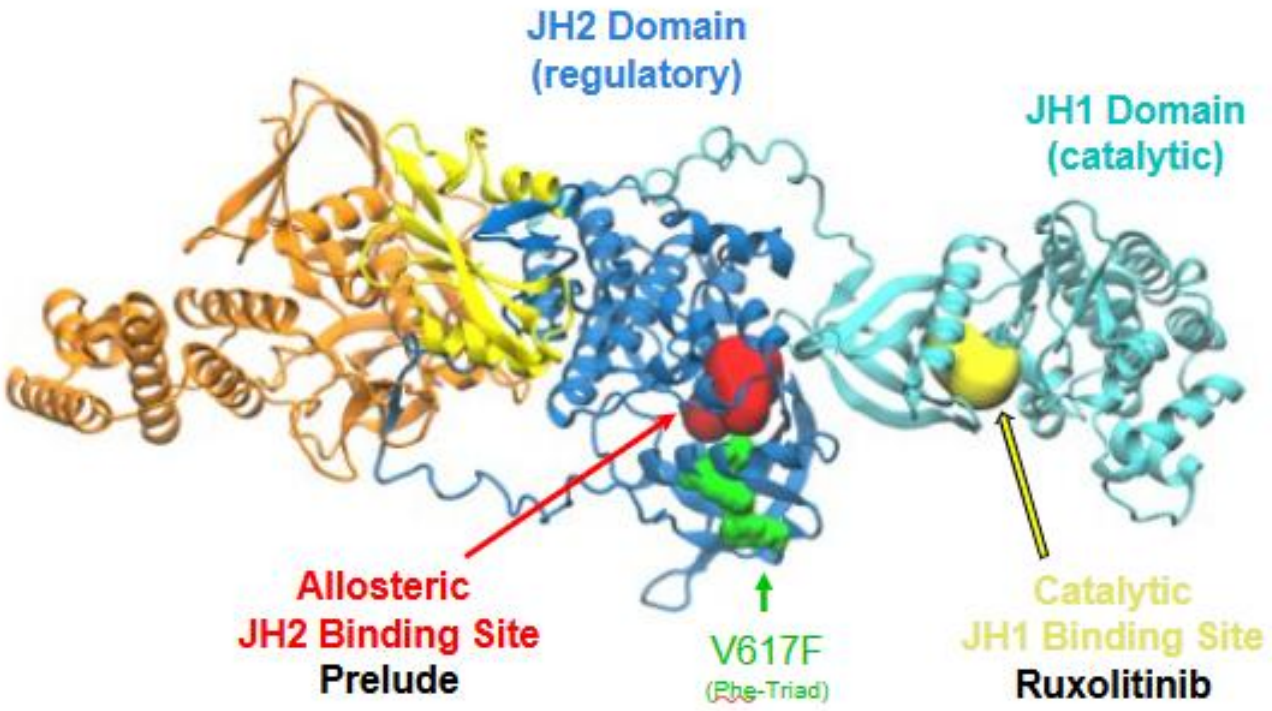
~238,000
patients with JAK2V617F-driven MPNs in the U.S. alone

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

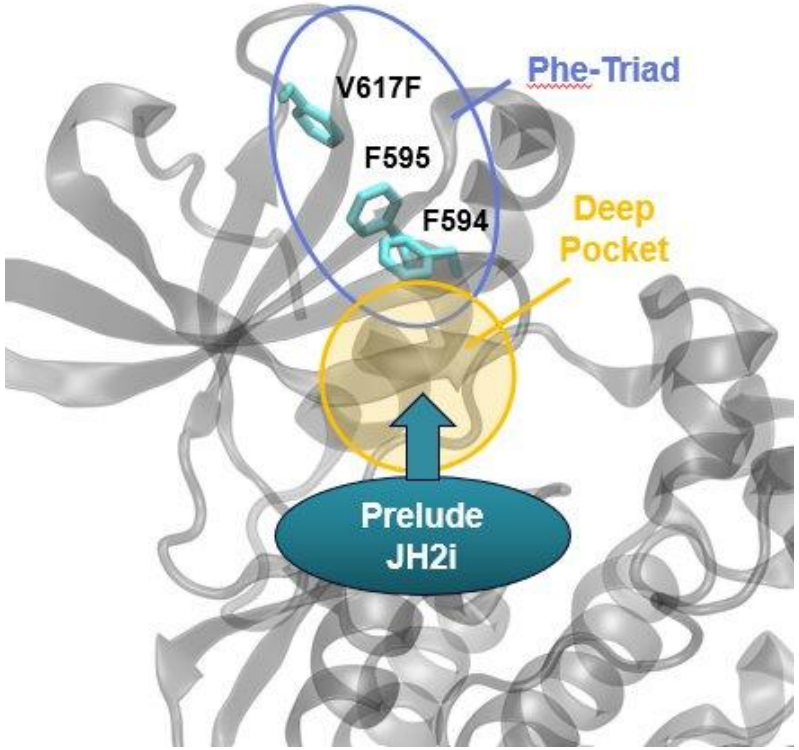
Source: NCI SEER Database (accessed June 2026), Blood Cancer United (LLS) Facts & Figures.
* Prevalence of V617F mutation in Primary Myelofibrosis (PMF); prevalence in post-PV/ET MF is 85-95%+.

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



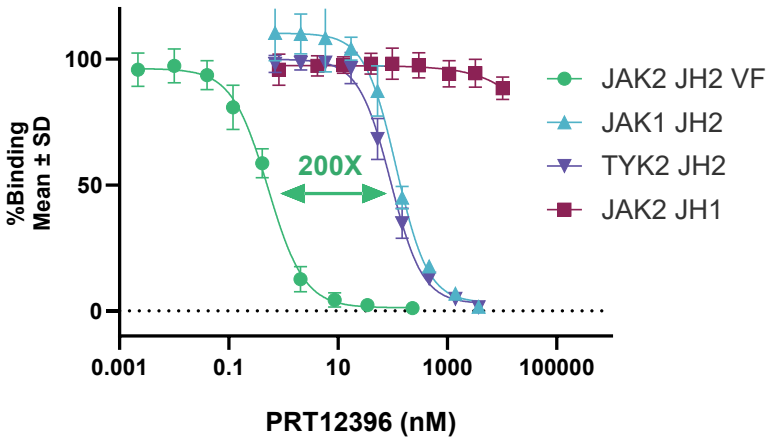
Prelude Data on File

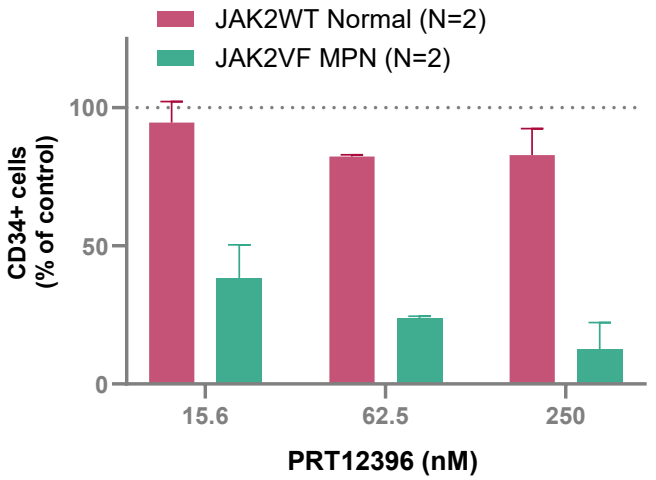
PRT12396: Our Lead JAK2V617F Mutant Selective JH2 Inhibitor

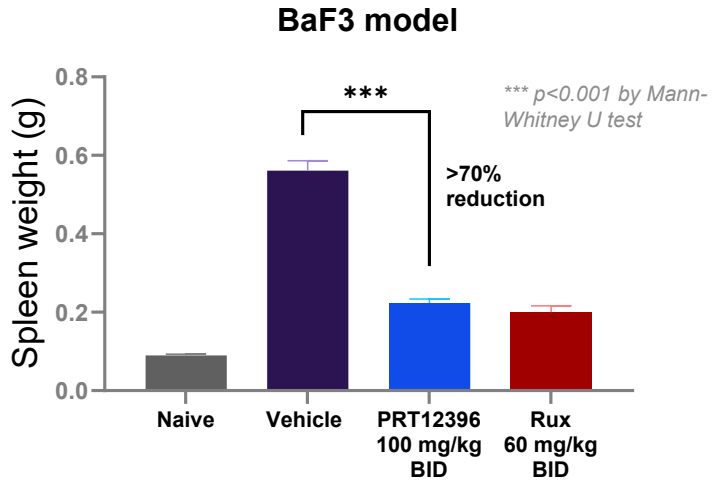
>200-fold
selectivity over JAK1 and TYK2, plus clean profile in KinomeSCAN™ panel of >450 kinases

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

PRT12396: Designed to Overcome the Limitations of Current JAK Inhibitors

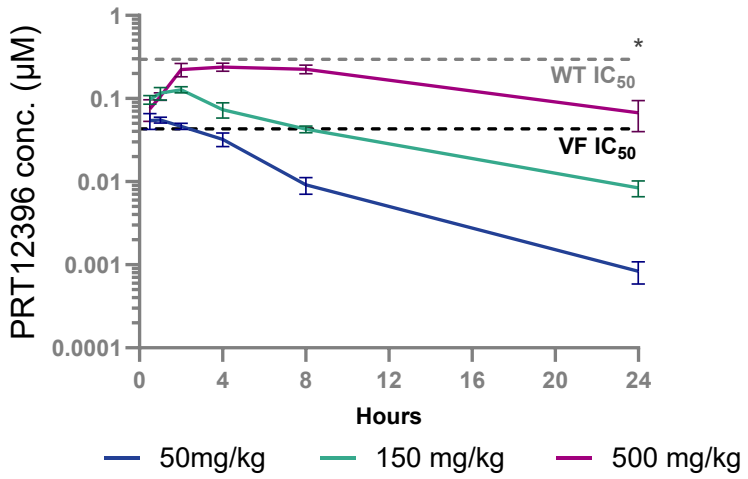
SELECTIVITY
Plasma exposures at efficacious doses remain below JAK2 WT IC50

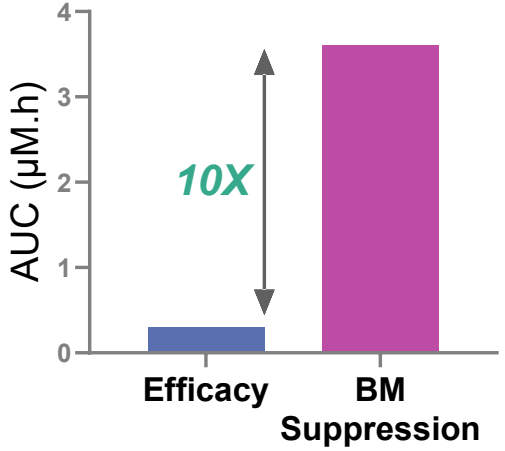
IMPACT
Efficacy AUC is 10-fold lower than toxicity AUC in vivo

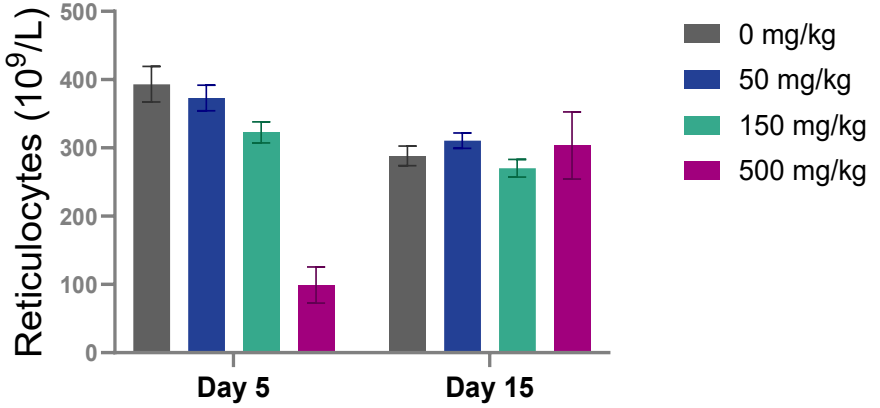
RESULT
Limited effects on reticulocytes at efficacious doses

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)

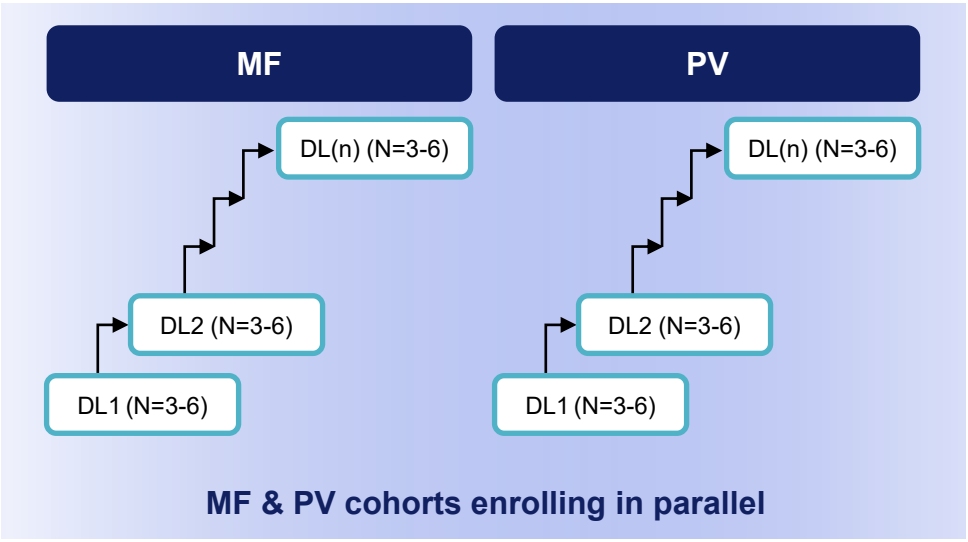
PRT12396: Phase 1 Study Now Enrolling MF and PV Cohorts in Parallel

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

Time-Bound Option Agreement With Incyte In Effect Into 1H 2027

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)

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

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**

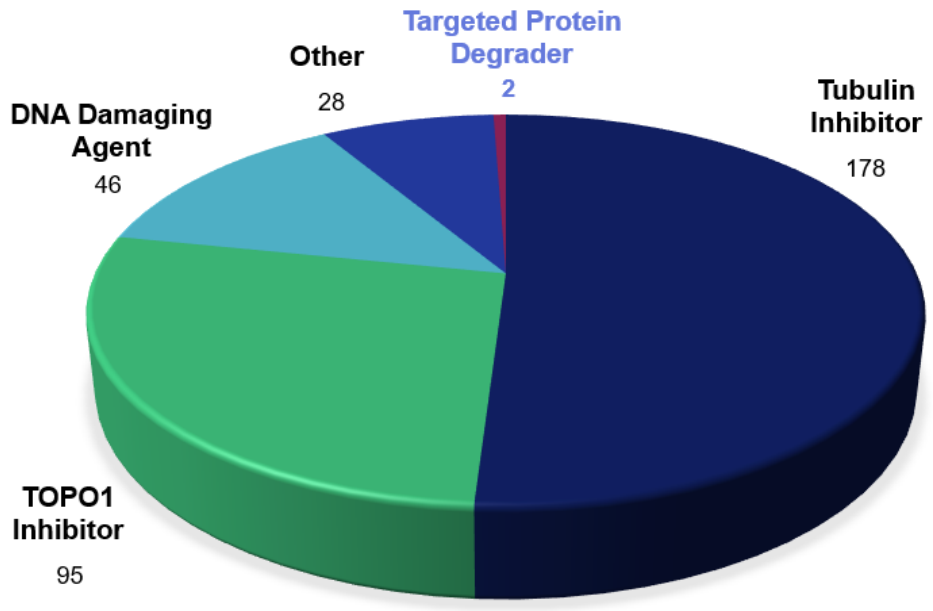
→ **Additional therapies needed to fully maximize the CALR opportunity for patients**

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*

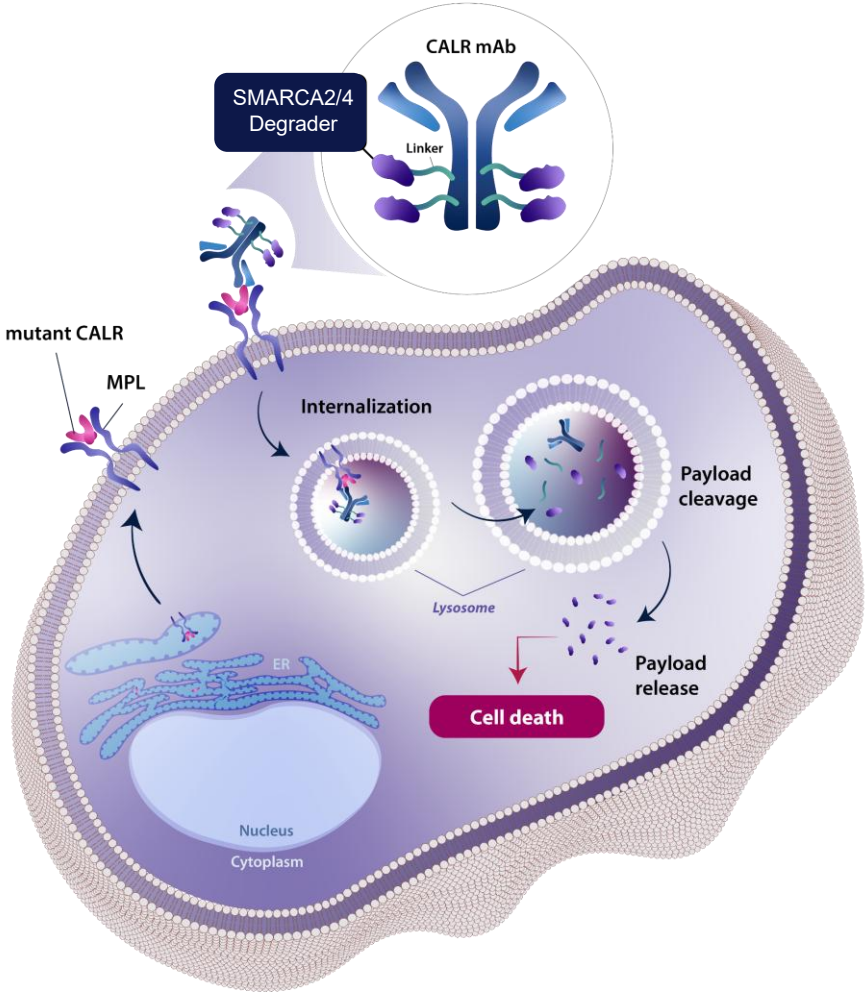


Property	Traditional ADC	Precision DAC
Potency	✓	✓
Antibody Selectivity	✓	✓
Payload Selectivity	X	✓
PD Marker - Payload	X	✓
Non-Genotoxic	X	✓

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]

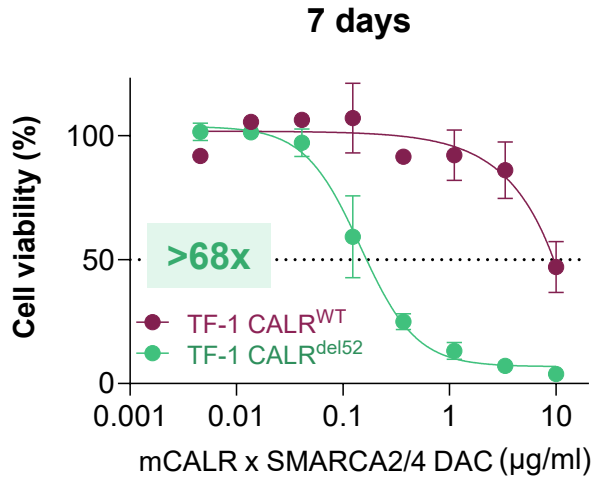
Prelude's mCALR x SMARCA2/4 DACs could represent a best-in-category approach with disease modifying potential

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);

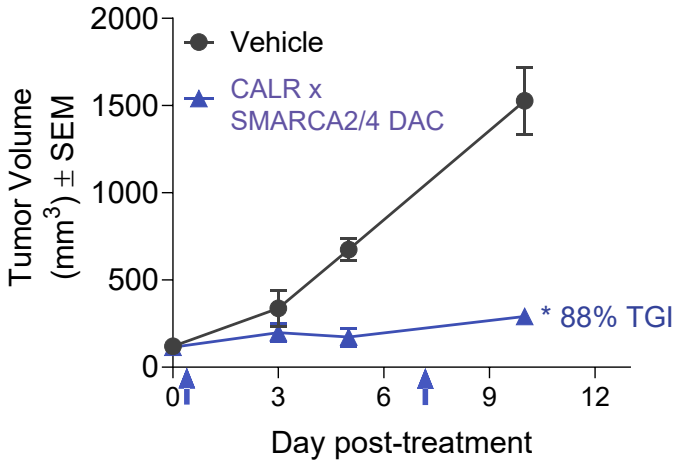
Prelude is Advancing mCALR DACs Equipotent for Type 1 & 2 Mutations

On Track to Nominate Development Candidate by YE 2026

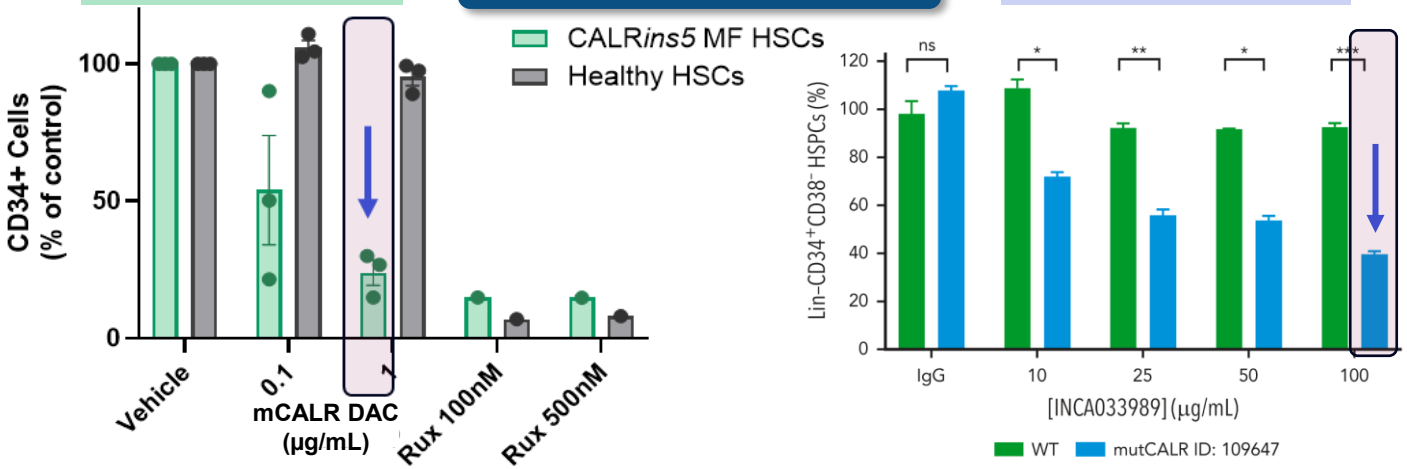
Selective Cytotoxicity *in vitro*



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

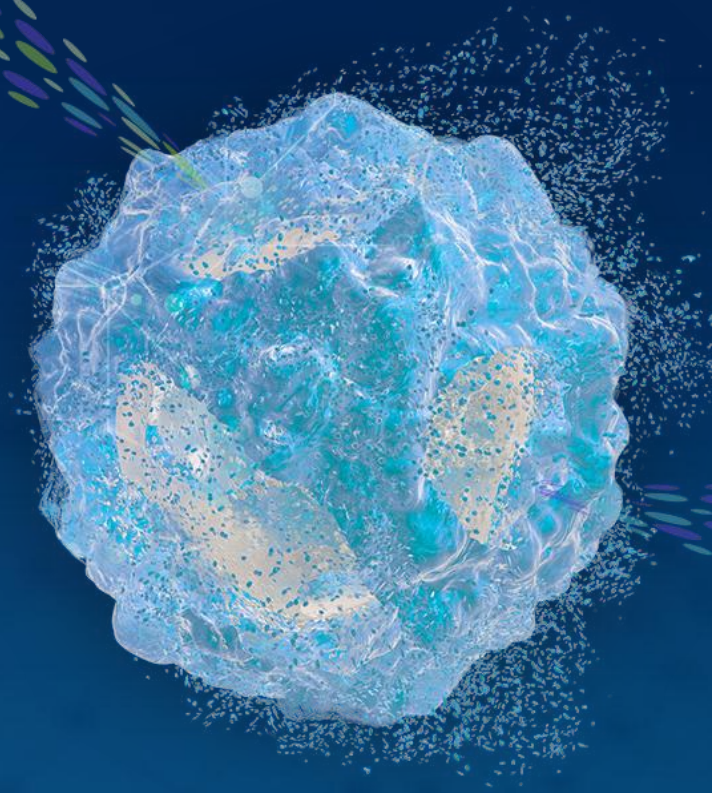
Potential for low volume subcutaneous administration

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) in the clinic with potential to demonstrate differentiated efficacy and safety over KAT6A/B inhibitors; initial POC data anticipated 2nd Half 2027
- 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

Contact Us:

Robert Doody
SVP, Investor Relations
rdoody@preludetx.com