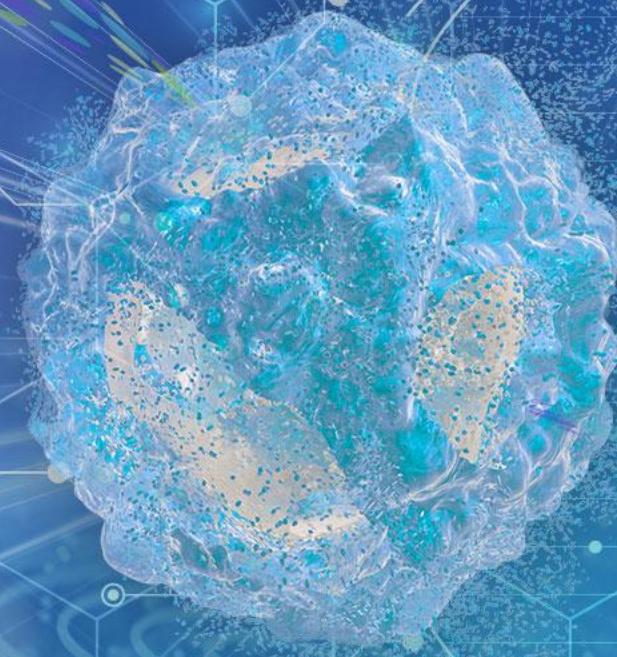
Prelude
THERAPEUTICS

Corporate Presentation

March 2026



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 Therapeutic 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,” ‘‘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).

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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, 2024.

Prelude THERAPEUTICS

Prelude THERAPEUTICS

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

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

Select the best modality to precisely target oncogenic mechanisms

Draw on decades of experience and proven leadership to drive innovation

Experienced Leadership Team With Proven Track Records

Kris Vaddi, PhD

Chief Executive Officer

Jakafi (ruxolitinib tablets) · olumiant (baricitinib tablets) 2 mg · TABRECTA (capmatinib) tablets · VELCADE (bortezomib)

Peggy Scherle, PhD

Chief Scientific Officer

Jakafi (ruxolitinib tablets) · olumiant (baricitinib tablets) 2 mg · TABRECTA (capmatinib) tablets · Pemazyre (pemigatinib tablets)

Andrew Combs, PhD

Chief Chemistry Officer

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

Sean Brusky, MBA

Chief Business & Strategy Officer

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

Bryant Lim, J.D.

Chief Financial Officer, Chief Legal Officer, Secretary

MERCK · ViroPharma Incorporated · Incyte · idera

Dr. Victor Sandor, former CMO at Array BioPharma and current member of our Board of Directors, is serving as a senior medical advisor, providing strategic and operational leadership for our clinical development programs

Prelude THERAPEUTICS

Prelude's Pipeline & Discovery Engine

PROGRAM	POTENTIAL INDICATIONS	DISCOVERY/ LEAD OPT.	IND-ENABLING	PHASE 1	PROGRAM INTEREST	MILESTONES
JAK2V617F Mutant Selective JH2 Inhibitors	VF+ myeloproliferative neoplasms (MPNs) (MF, PV, ET)		PRT12396		Incyte[1]	Phase 1 initiation anticipated in 2Q 2026
KAT6A Selective Degraders	ER+ breast cancer, other malignancies		PRT13722		Prelude wholly owned	IND filing mid-2026
mCALR DAC	CALR-mutated MPNs (ET, MF)				Prelude wholly owned	Oral abstract presented at ASH 2025
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; ER+, estrogen 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)

Our Investment Thesis Centers on Advancing Two Programs – Both Representing Highly Differentiated Approaches to Clinically Validated Targets

JAK2V617F

Mutant Selective Inhibitors

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

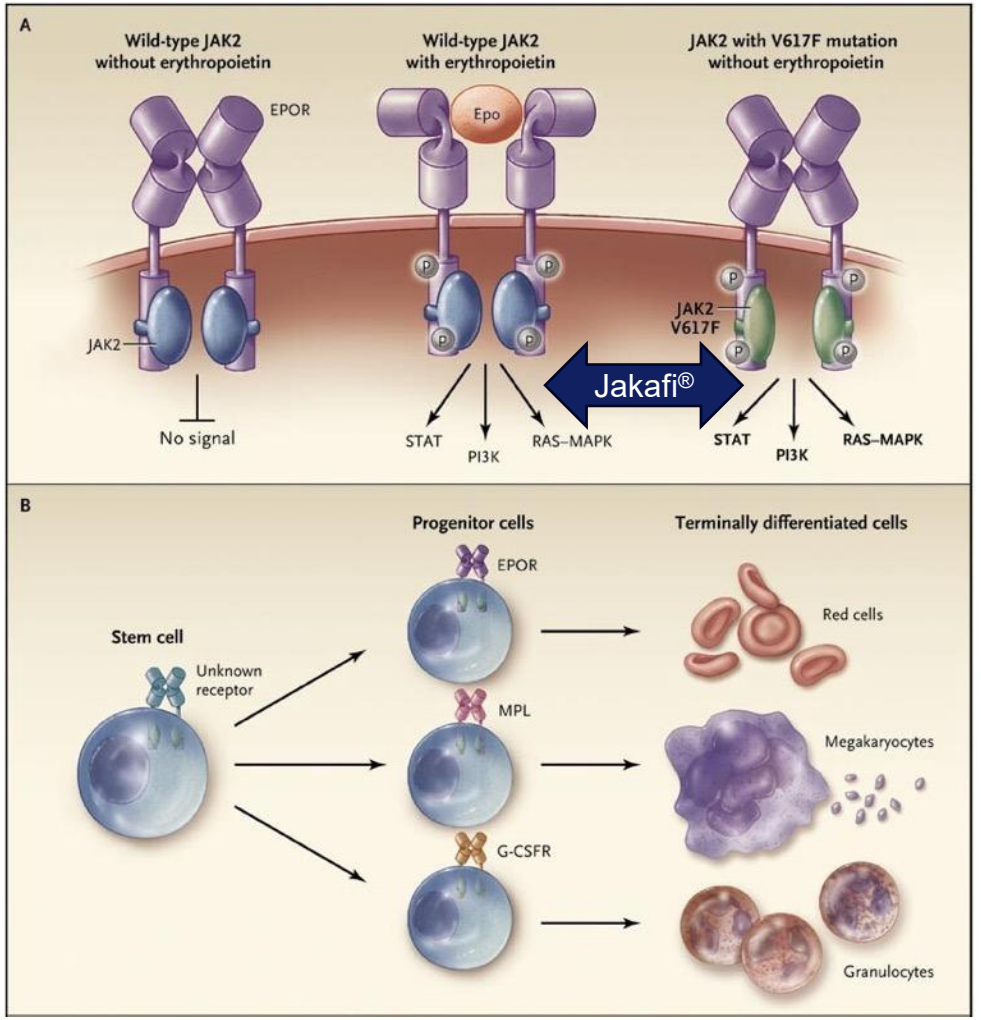
KAT6A

Highly Selective Oral Degraders

First-in-class KAT6A degraders, with absolute selectivity over KAT6B – a differentiated modality and selectivity profile with potential to become a backbone therapy in the treatment of ER+ breast cancer

JAK2V617F is the Primary Driver Mutation Leading to Activated JAK-STAT Signaling, Uncontrolled Proliferation, and Disease Progression in MPNs

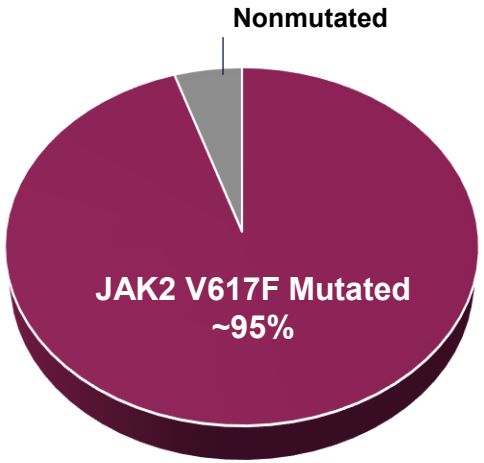
- The JAK-STAT pathway mediates growth factor signaling, most notably:
  - Thrombopoietin receptor for platelet production
  - Erythropoietin receptor for red blood cell production
- The JAK2V617F mutation leads to growth factor-independent hyperactivation of JAK-STAT pathway and uncontrolled myeloid and erythroid proliferation
- Inhibition of wildtype JAK2 causes anemia and thrombocytopenia and current JAK inhibitors, like ruxolitinib (Jakafi®), while effective, equally inhibit both WT and V617F-mutated (VF+) JAK2
- JAK2 JH2 inhibitors that selectively target VF+ progenitor cells have potential to reduce mutant allele burden, modify disease progression, and transform treatment outcomes for MPN patients



Campbell P.J. and Green A.R. N Engl J Med 2006;355:2452-2466

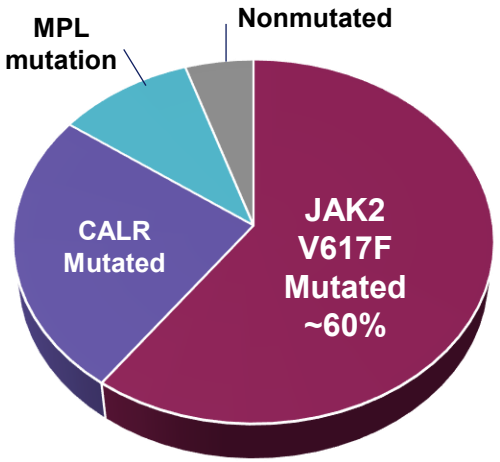
Jakafi® is a registered trademark of Incyte Corporation

A JAK2V617F Mutant Selective Inhibitor Could Become a Disease Modifying Option for the Majority of MPN Patients and Represents an Expansive Opportunity



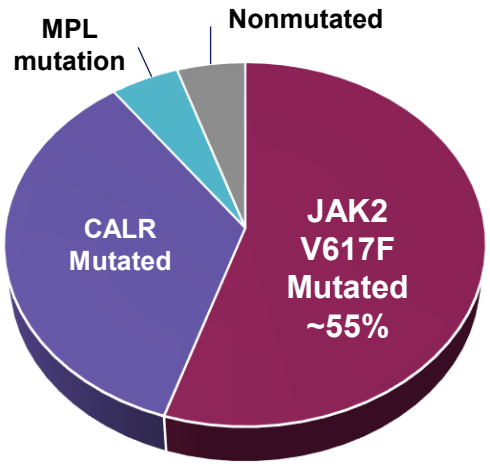
Polycythemia Vera (PV)

~142,000



Essential Thrombocythemia (ET)

~78,500



Primary Myelofibrosis (PMF)

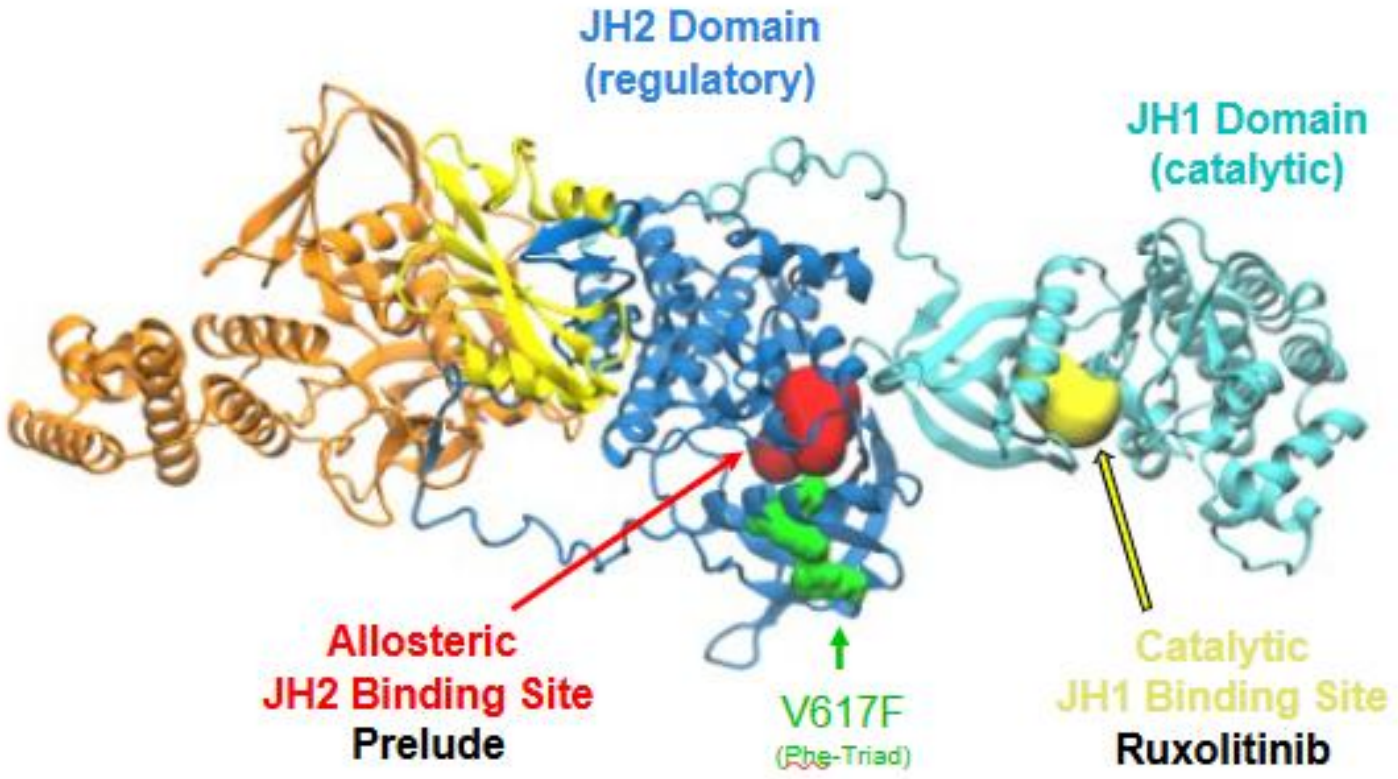
~8,000

Est. # of U.S. Patients with JAK2V617F Mutation
~228,500

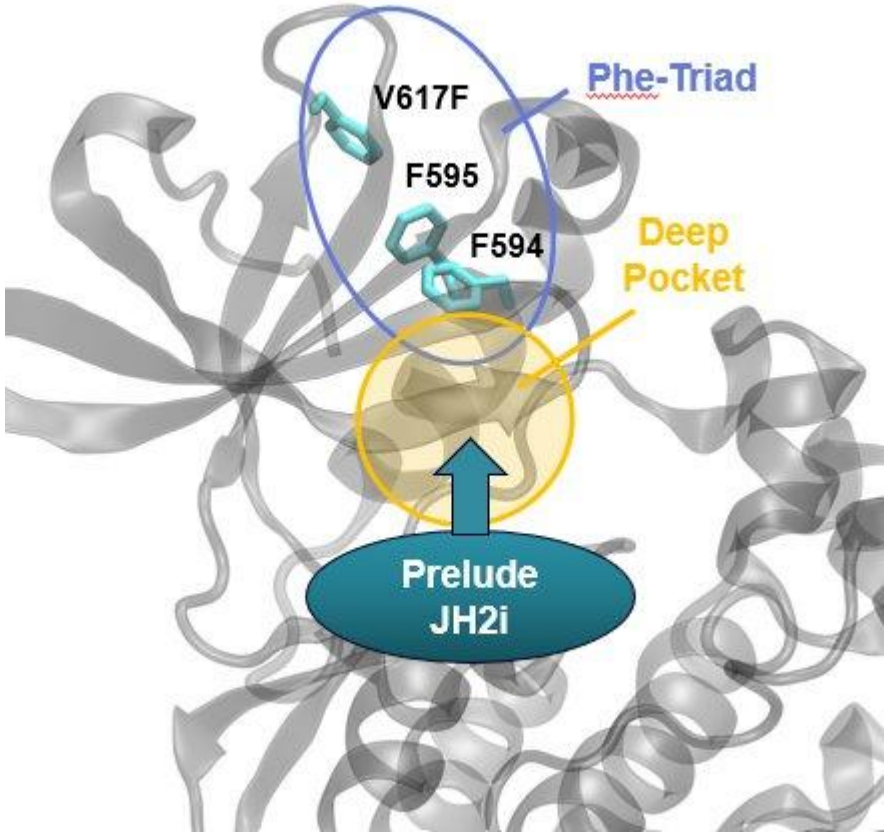
Sources: NCI SEER Database (accessed Dec 2024), Leukemia & Lymphoma Society Facts & Figures; F. Passamonte et.al., "Clinical Significance of JAK2 V617F Mutant Allele Burden"; Haematologica 2009 Jan;94(1):7–10

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 Catalytic Domain



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



JAK2V617F Mutant Selective Inhibitors Are Highly Differentiated From 1st Generation JAK Inhibitors in a Large and Growing Market

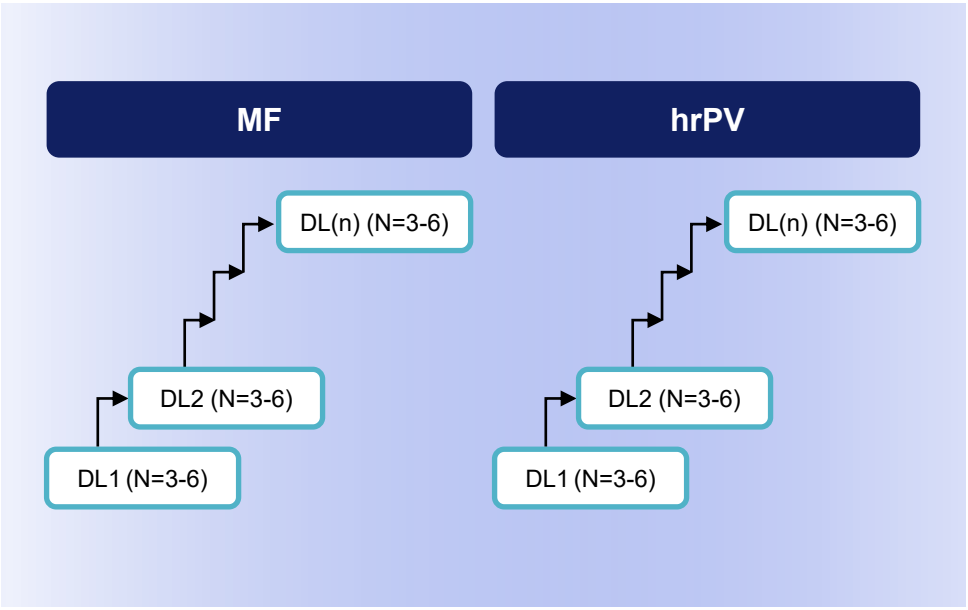
- Global sales of ruxolitinib (Jakafi® /Jakavi®) alone grew to over $4.5B in 2024[1,2]
  - Continuing strong sales growth for ruxolitinib in PV
- First generation JAK inhibitors have delivered transformative efficacy for MF patients
  - Highly effective at reducing symptoms and spleen size
  - However, toxicities from wild-type activity limit ability to reach maximal efficacy
- Ruxolitinib is the only JAK inhibitor approved in PV (2L only) and none are approved in ET
- Prelude's JAK2V617F mutant selective inhibitors demonstrate:
  - Potent and selective reduction in JAK2V617F cells *in vitro* compared to WT cells
  - Improved efficacy, reduced toxicity, and rapid reduction of mutant alleles *in vivo*
  - Potential for transformative efficacy and disease modification in PV, ET and MF

First Public Disclosure of Preclinical Data on Prelude's JAK2V617F Program Presented at ASH 2025

1 - Incyte Pharmaceuticals (Q4 2024 Financial Results and Corporate Update Presentation, February 10, 2025); Jakafi is a registered trademark of Incyte
2 - Novartis Pharmaceuticals (Full Year 2024 Product Sales, Accessed August 2025; Jakavi is a registered trademark of Novartis

JAK2V617F Program[1]: Phase 1 Study Design (Illustrative)

Phase 1a Dose Escalation



Expansion Cohorts

Expansion in hrPV & MF 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	2029

Phase 1
(MF & hrPV)

First Look at Spleen/Symptoms/CHR
Mutant Allele Burden

Phase 1 Expansion Cohorts

1 - Subject to exclusive option agreement with Incyte (announced November 2025)
MPNs, myeloproliferative neoplasms; MF, myelofibrosis; hrPV, high risk polycythemia vera; CHR, complete hematologic response; DL, dose level

Option Agreement With Incyte Provides Significant Capital to Further Advance Our JAK2V617F and KAT6A Programs

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)

Our Investment Thesis Centers on Advancing Two Programs – Both Representing Highly Differentiated Approaches to Clinically Validated Targets

JAK2V617F

Mutant Selective Inhibitors

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

KAT6A

Highly Selective Oral Degraders

First-in-class KAT6A degraders, with absolute selectivity over KAT6B – a differentiated modality and selectivity profile with potential to become a backbone therapy in the treatment of ER+ breast cancer

Prelude's Oral KAT6A Selective Degrader Program

- KAT6 is an emerging, clinically-validated target in ER+ breast cancer
  - A KAT6A/B dual inhibitor (PF-07248144, prifetrestat) has initiated a pivotal phase 2/3 trial in combination with fulvestrant, after progression on a CDK4/6 inhibitor[1]
  - Limited monotherapy activity, but compelling efficacy in combo with fulvestrant in post-CDK4/6 inhibitor setting in a broad (unselected) population of ER+ BC[1]
  - Clinically relevant safety observations including grade 3/4 neutropenia and dysgeusia are challenging and may limit dosing to maximal benefit in combination with SoC treatments (*e.g.,* CDK4/6 inhibitors)[1]
- Prelude's KAT6A selective degrader program aims to differentiate based on:
  - Efficacy as monotherapy or in combination
  - Potential for lower risk of hematological toxicity and neutropenia
  - Improved combinability and synergy with other agents (*e.g.,* oral SERDs, AIs, CDK4/6s, PI3Kαs)
- Prelude's lead (PRT13722) is in IND-enabling studies and on track for IND filing in mid-2026

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)

KAT6 Landscape is Evolving, But Most Others Are Pursuing Inhibitor Approaches

Company	Asset	Program Status	KAT(X) Inhibitor
Pfizer	PF-07248144 (prifetrastat)	Ph2/3	KAT6A/B Inhibitor
Olema, Aurigene	OP-3136	Ph1	KAT6A/B Inhibitor
Menarini, Insilico	MEN2312	Ph1	KAT6A/B Inhibitor
BeOne	BG-75202	Ph1	KAT6A/B Inhibitor
Pfizer	PF-08032562	Ph1	KAT6A/B/7 Inhibitor
Ideaya	IDE251	IND	KAT6A/B/7 Inhibitor
Others	Multiple	Research / Preclinical	KAT6A/B Inhibitors
Prelude	**PRT13722**	**IND-enabling**	**KAT6A Degrader**

- Pfizer Clinical Candidate PF-07248144 (prifetrastat)
  - Clinical PoC in combination with fulvestrant for ER+ BC
  - Advancing to Ph2/3 registrational trial
- Olema, Menarini and BeOne
  - Starting Ph1 with chemotypes very similar to Pfizer
  - All are KAT6A/B dual inhibitors
- Ideaya, Pfizer
  - KAT6A/B and KAT7 cross-selective inhibitors
  - KAT7 inhibition may play a role beyond ER+ BC
- Others
  - Multiple research-stage programs globally

Prelude is the first KAT6A selective degrader* poised to enter the clinic in 2026

* Based on recent patent and literature search (as of March 1, 2026)

Selective KAT6A Degradation Represents a Differentiated Approach Versus KAT6A/B/(7) Inhibition With Significantly Broader Commercial Potential

	2L/3L+ r/r ER+/HER2- mBC	1L ER+/HER2- mBC	Early-stage ER+ BC (adjuvant, neo-adjuvant)
Current SoC[1]	• Fulvestrant + CDK4/6i • Targeted therapies • Chemotherapy	• Aromatase Inhibitors + CDK4/6 inhibitors • Future: Oral SERDs, next gen CDK2/4/6s, targeted therapies, ADCs, others	• Endocrine therapy / AIs • Future: Oral SERDs, others
KAT6A/B/(7) Inhibitors	Pfizer, BeOne, Olema, Ideaya, Menarini, Others	• Limited monotherapy efficacy reported to date with KAT6A/B inhibitors • KAT6B-mediated neutropenia may limit combinability with SoC agents used in the frontline setting (e.g., CDK4/6s, PI3Kαs, etc.)	
KAT6A Selective Degrader	Prelude THERAPEUTICS	• First-in-class opportunity: Only KAT6 degrader approaching clinical development • Potential for best-in-class monotherapy and combination efficacy • KAT6A selectivity may contribute to lower neutropenia and improve combinability	

$42B total market by 2033 [2]

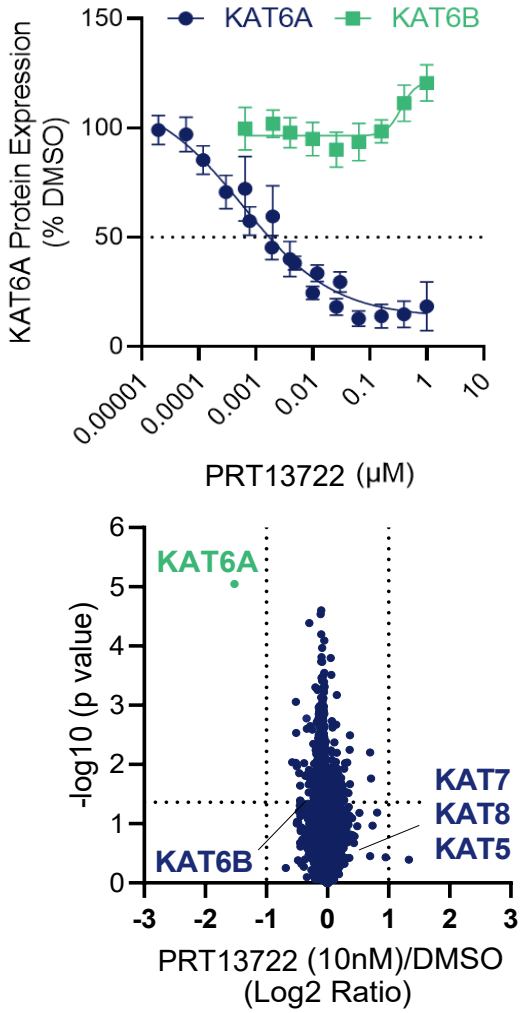
1 - NCCN Treatment Guidelines for Invasive Metastatic and Early Stage Breast Cancer (v5.2025)
2 - Vision Research Reports; "Estrogen Receptor Positive Breast Cancer Treatment Market Forecast 2024-2033. ER+ BC Treatment Market Size | Companies

PRT13722: Our Lead KAT6A Selective Degrader Development Candidate

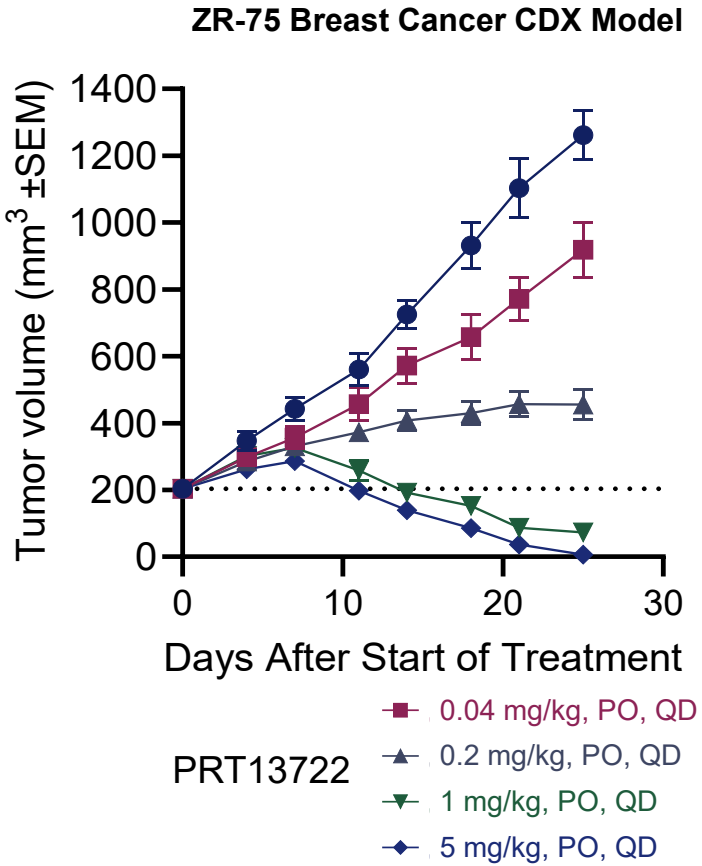
PRT13722: Highly Potent KAT6A Degrader in Preclinical Models

- Absolute kinetic selectivity for KAT6A over KAT6B (>1000-fold)
- Global proteomics demonstrates highly selective KAT6A degradation
- Excellent oral PK across species
- Compelling *in vivo* efficacy as monotherapy in multiple models
- Reduced effect on neutrophils in preclinical models
- Non-GLP DRF studies complete
- IND-enabling studies underway

Absolute Degradation Selectivity (KAT6A vs KAT6B)



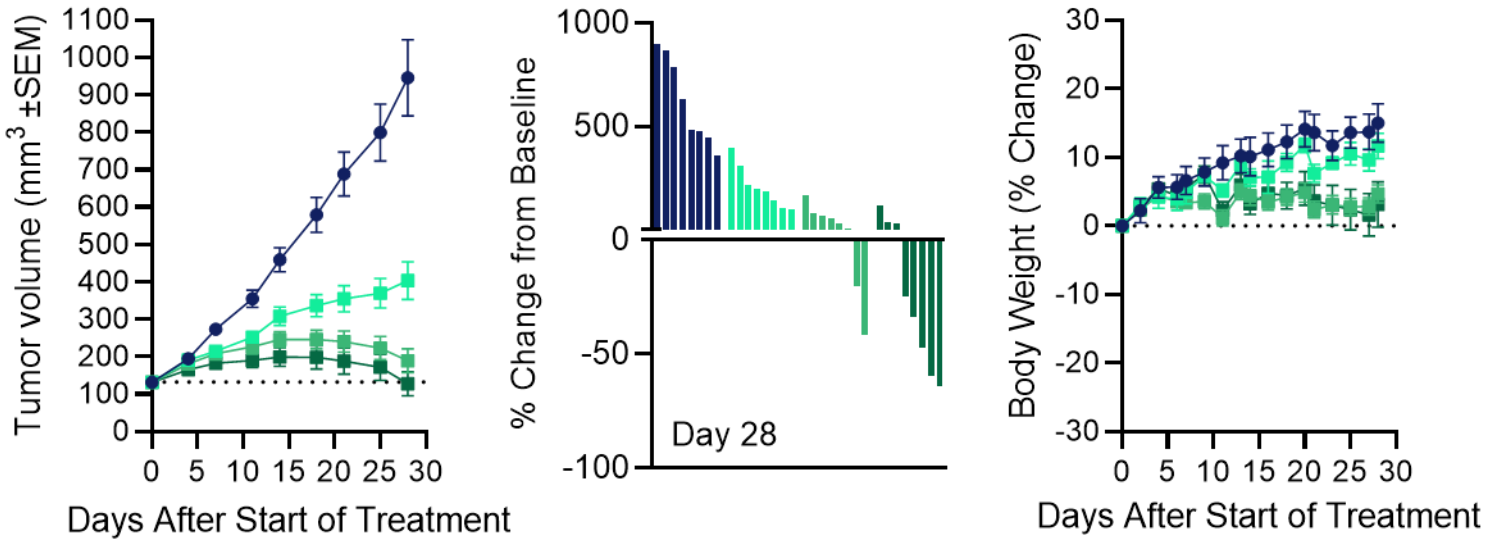
Compelling *In Vivo* Efficacy (Complete Regressions)



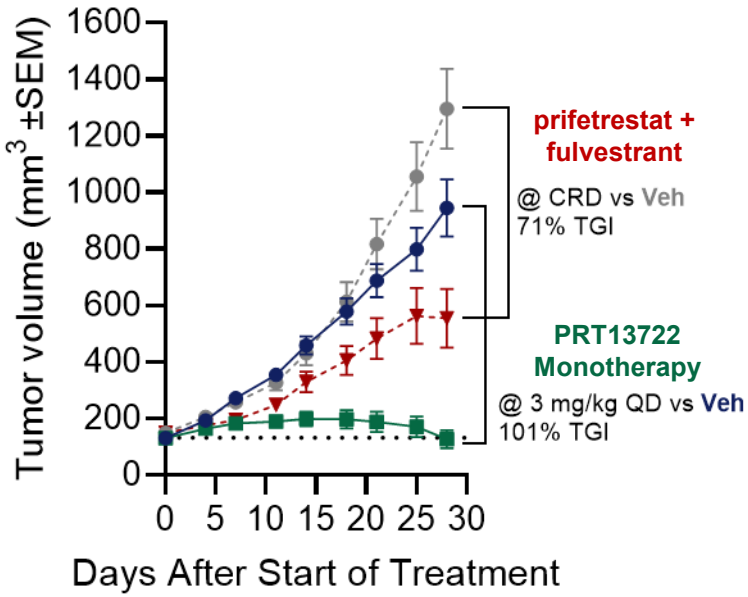
Prelude Data on File

PRT13722 Monotherapy Drives Tumor Regressions in the Challenging T47-D Breast Cancer Model with Improved Efficacy Over Prifetrestat + Fulvestrant

Tumor Regressions Observed at Low Doses



Significant TGI as Monotherapy vs. prifetrestat + fulvestrant

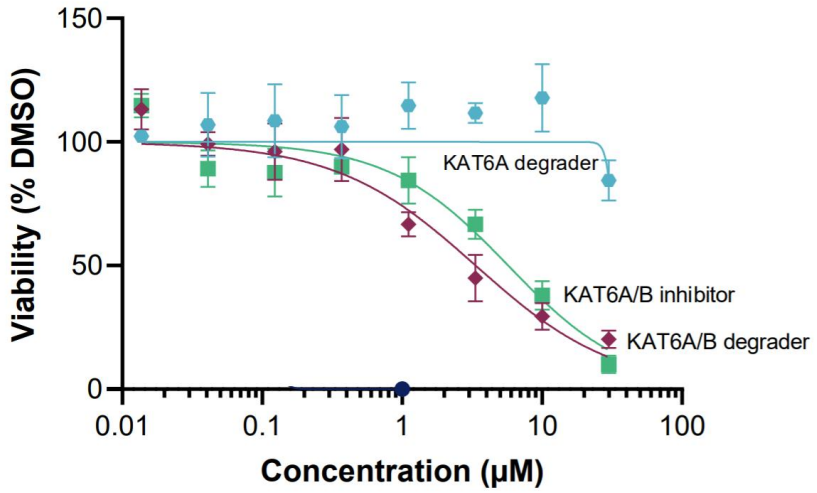


- PRT13722 demonstrates dose-dependent efficacy, driving tumor regressions at low oral doses in preclinical models
- Well-tolerated with no observed body weight loss in preclinical models

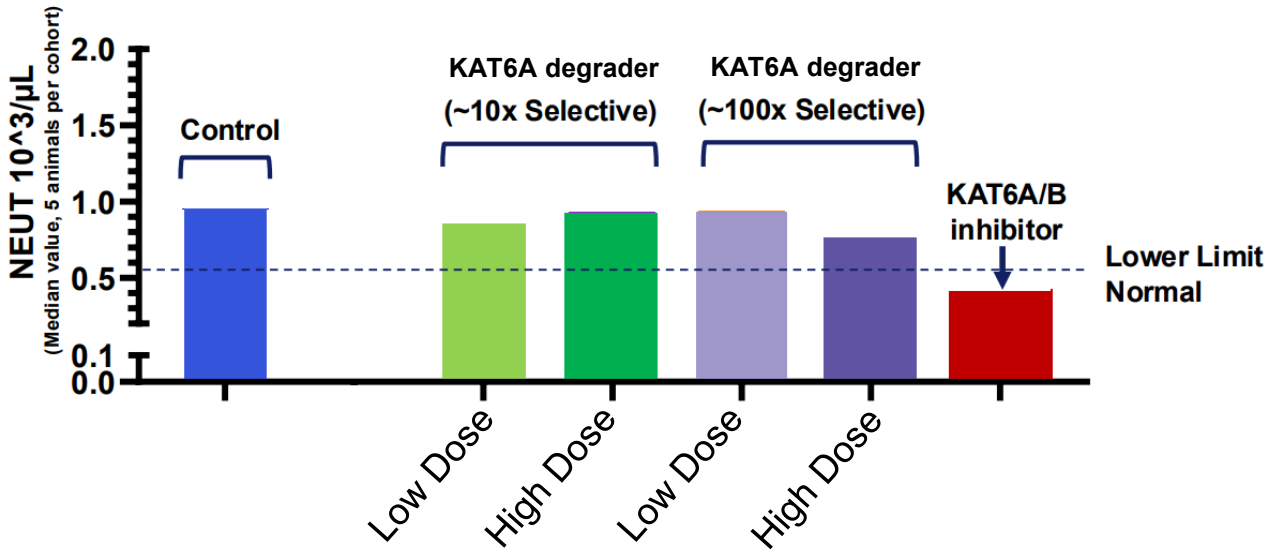
TGI, tumor growth inhibition; PO, orally administered; QD, once daily; BID, twice daily; CRD, clinically relevant dose; Veh, vehicle
Prelude Data on File

KAT6A Selective Degraders Show Potential for Lower Bone Marrow Toxicity in Preclinical Models Compared to KAT6A/B Dual Inhibitors

Dose Response of CFU-GM



Neutrophils Day 5



Ex vivo and *in vivo* studies with early KAT6A selective degrader tool compounds showed limited effects on neutrophils in contrast to dual KAT6A/B inhibitors or degraders; in non-GLP toxicology studies, PRT13722 was well tolerated with no dose dependent impact on neutrophils observed [1]

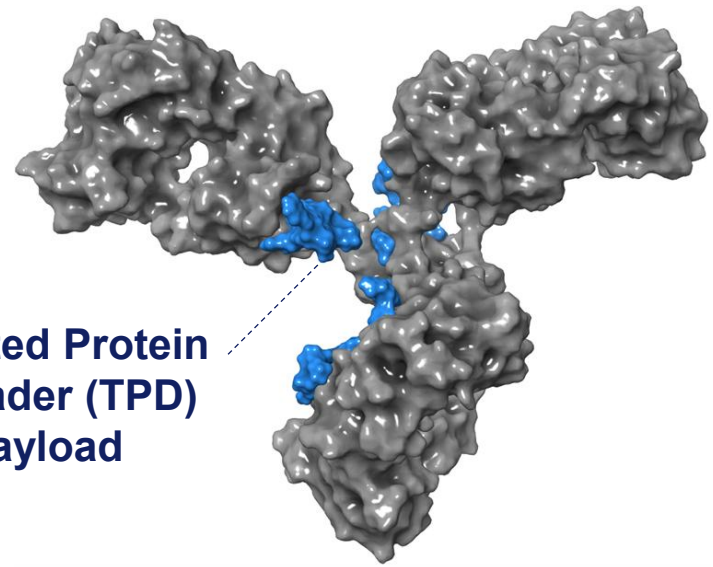
1 - Impact on neutrophils and other hematologic safety parameters to be further assessed as part of on-going 28 day toxicology studies with PRT13722
Prelude Data on File

KAT6A Selective Degrader Program Summary

- Prelude is advancing a first-in-class, highly selective KAT6A degrader (PRT13722) with broad potential to become a new backbone therapy in the treatment of ER+ breast cancer
- PRT13722 has potential to achieve best-in-class efficacy relative to dual KAT6A/B inhibitors
- PRT13722 has completed dosing in non-GLP toxicology studies and was well tolerated, supporting potential to differentiate further based on overall safety and broad combinability with other agents
- On track for IND filing in mid-2026 with phase 1 start expected in 2H 2026

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

Model of Precision DAC
(DAR 4 example)



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

- **Precision DACs enable improved selectivity in two ways**
  - ✓ **Antibodies** target tumor-specific cell surface antigens sparing healthy cells, and
  - ✓ **Targeted Protein Degraders** address critical proteins in validated biological pathways
- **Potential to deliver both improved efficacy and improved tolerability**

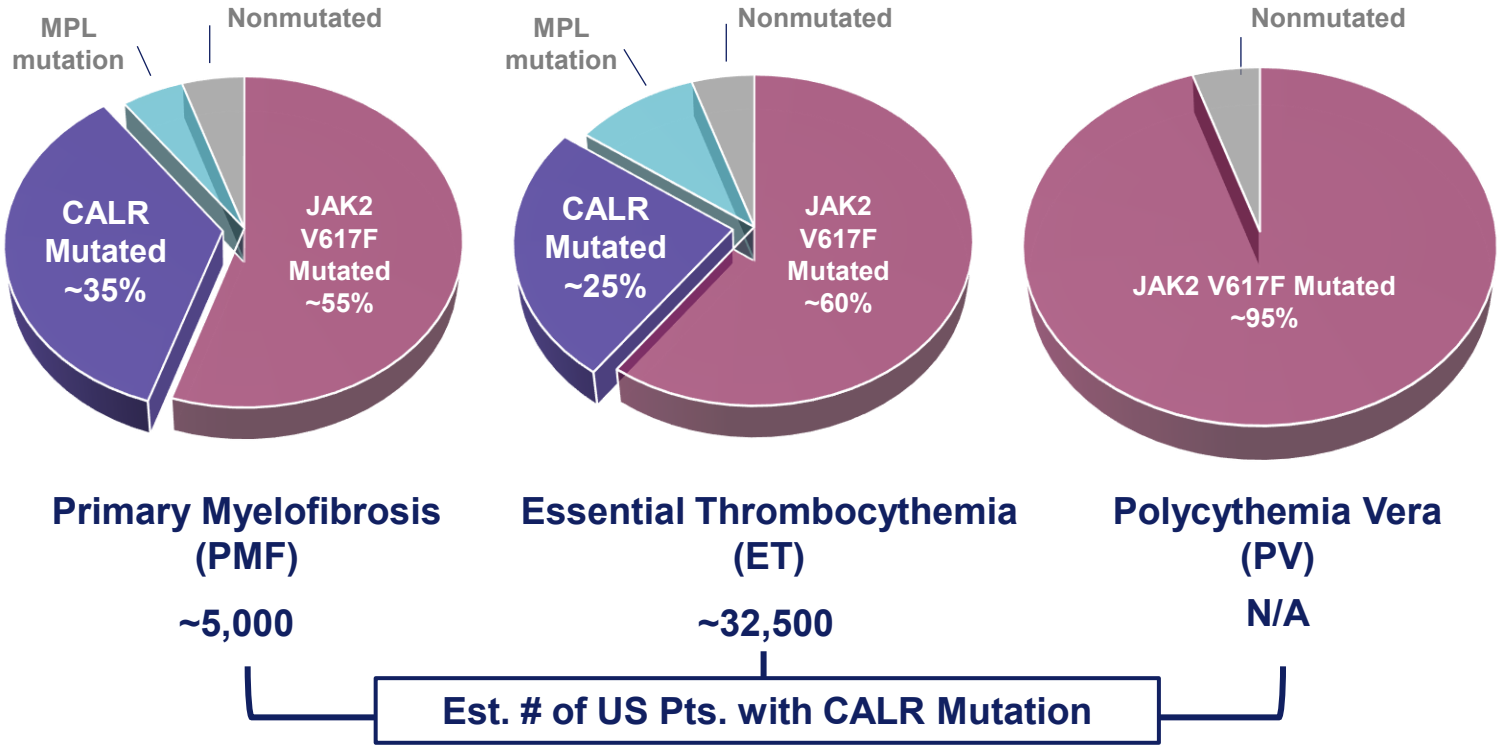
For a review of ADCs, see Fu, Z., Li, S., Han, S. *et al. Sig Transduct Target Ther* **7**, 93 (2022).

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

Payload	Rationale	DAC Properties			Prelude Degrader Payload-Linkers
		Efficacy	Tolerability	Developability	
Exceptional Potency (pM)	Allows low DAR; Catalytic effect	+		+	**SMARCA2/4 Dual Degraders (VHL- and CRBN- based)** **CDK9 Degraders**
Permeable or Non-Permeable	Enable localized bystander effect 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 Degrader Payloads Have the Potential to Deliver Novel DACs with Improved Efficacy and Therapeutic Index

Mutated Calreticulin (mCALR) Represents a Promising Target for Next Generation DACs



Primary Myelofibrosis (PMF)	Essential Thrombocythemia (ET)	Polycythemia Vera (PV)
~5,000	~32,500	N/A

Est. # of US Pts. with CALR Mutation

mCALR is emerging as a clinically validated target in MPNs with disease modifying potential

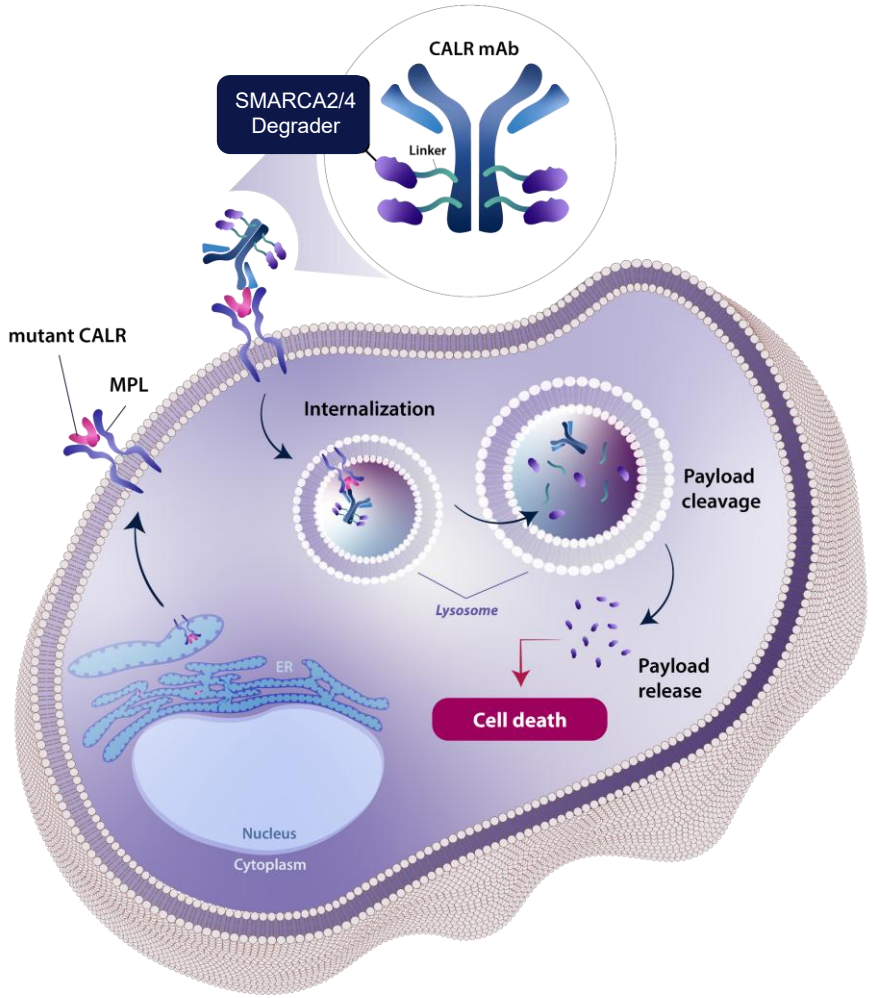
Sources: NCI SEER Database (accessed Dec 2024), Leukemia & Lymphoma Society Facts & Figures; J.How et. al., Mutant calreticulin in myeloproliferative neoplasms, *Blood* (2019) 134 (25): 2242–2248

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

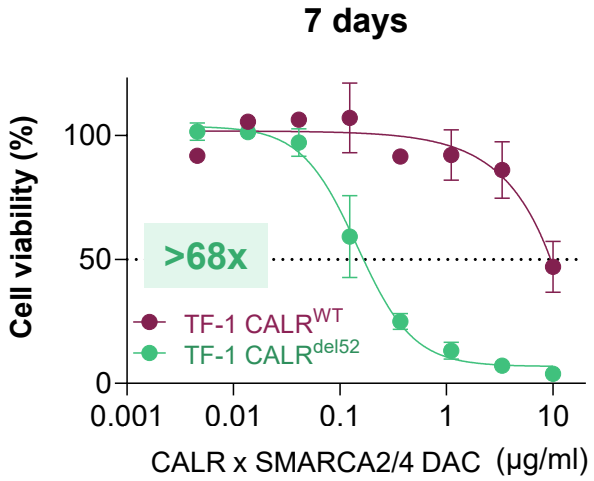
SMARCA2/4 and CDK9 degraders are both highly active in CALR mutated MPN cell lines and can be used as payloads for mCALR-targeted DACs

mCALR-targeted DACs, delivering Prelude's degrader payloads to disease-initiating clones have the potential to be first-in-class, disease modifying therapies

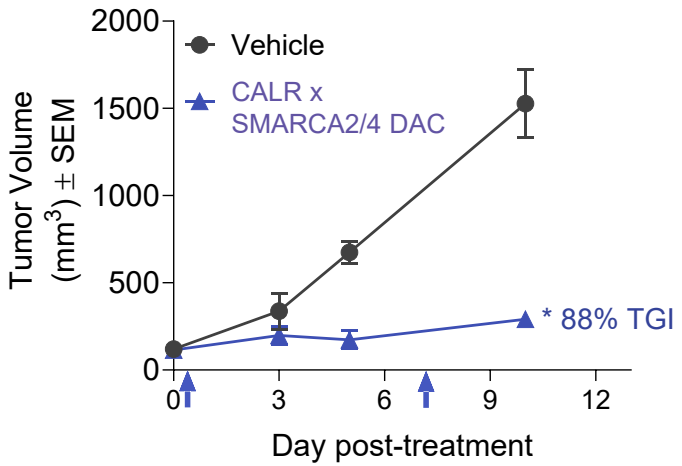
CALR x SMARCA2/4 DACs Demonstrate Robust and Selective Tumor Growth Inhibition and Improved Potency vs. Antibody Alone in CALR Mutant Cells



Selective Cytotoxicity *in vitro*

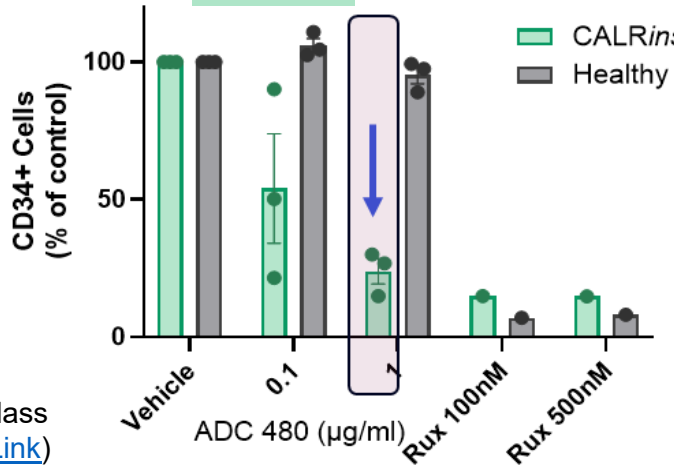


Robust Tumor Growth Inhibition *in vivo*

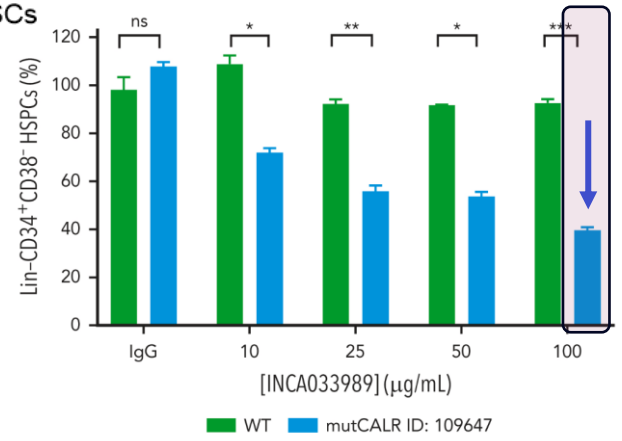


100x Better Potency

DAC



Naked Ab



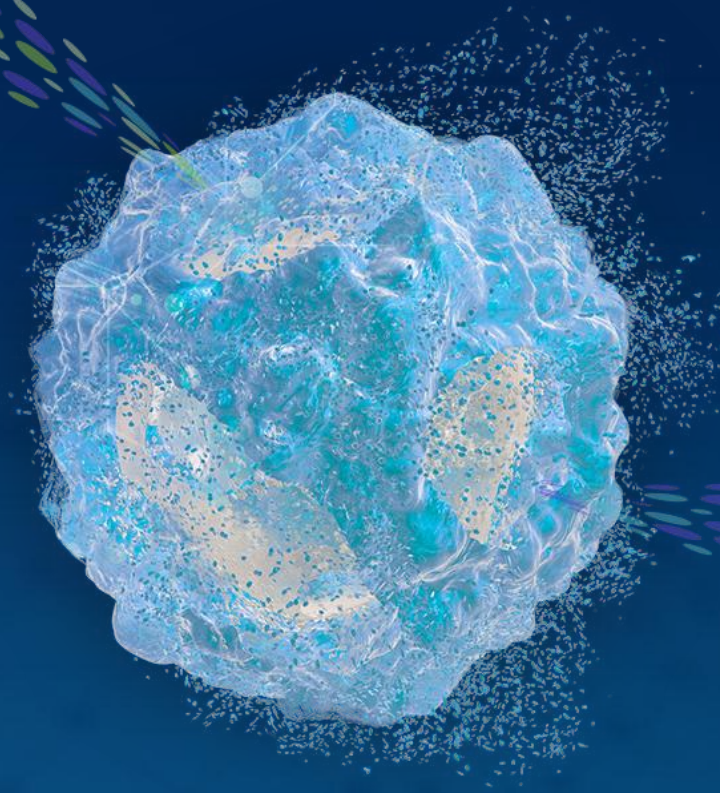
Fultang N., *et al.*, EHA2025 Oral Abstract, 12 June 25; Discovery Of First-in-class Precision ADCs Targeting Mutant Calreticulin For The Treatment Of MPNs. (Link)

1 - Abstract now available: ASH Annual Meeting & Exposition - Hematology.org

Executive Summary

- Lead JAK2V617F mutant selective inhibitor (PRT12396) IND accepted and on track for Phase 1 study initiation in 2Q 2026[1]
- First-in-class KAT6A selective degrader (PRT13722) on track to enter the clinic in 2026 with clear path to differentiation in ER+ breast cancer market
- Novel approaches to clinically-validated targets (e.g., mCALR) poised to deliver differentiated pipeline candidates beyond JAK2 and KAT6
- Current cash runway expected into second quarter of 2027 with $106 million in cash, cash equivalents, restricted cash and marketable securities as of December 31, 2025

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



Thank You

Contact Us:

Robert Doody
SVP, Investor Relations
rdoody@preludetx.com