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MPN Data Highlights from EHA 2025

June 15, 2025

Forward Looking Statements

Except for the historical information set forth herein, the matters set forth in this release contain predictions, estimates and other forward-looking statements, including any discussion of the following: the potential presented by Incyte's portfolio, including the disease modifying potential and the potential path to a cure for patients with MPNs offered by INCA033989; planned next steps for INCA033989, including initiating a registration study in 2026, accelerating the development of INCA033989 in EF and MF (both as a single agent and in combination with ruxolitinib), developing a co-diagnostic, presenting data in patients with MF in 2025 and developing a sub-cutaneous formulation; additional planned development regarding Incyte's mutCALR mAB, mutCALR x CD3 bispecific and JAK2-V617F inhibitor and the potential presented by each; and the possibility for 2025 to be a year of defining catalysts for Incyte in terms of launches, study initiations, data readouts and regulatory approvals.

These forward-looking statements are based on Incyte's current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials and the ability to enroll subjects in accordance with planned schedules; determinations made by the FDA, EMA and other regulatory agencies; Incyte's dependence on its relationships with and changes in the plans of its collaboration partners; the efficacy or safety of Incyte's products and the products of Incyte's collaboration partners; the acceptance of Incyte's products and the products of Incyte's collaboration partners in the marketplace; market competition; unexpected variations in the demand for Incyte's products and the products of Incyte's collaboration partners; the effects of announced or unexpected price regulation or limitations on reimbursement or coverage for Incyte's products and the products of Incyte's collaboration partners; sales, marketing, manufacturing and distribution requirements, including Incyte's and its collaboration partners' ability to successfully commercialize and build commercial infrastructure for newly approved products and any additional products that become approved; greater than expected expenses, including expenses relating to litigation or strategic activities; variations in foreign currency exchange rates; and other risks detailed in Incyte's reports filed with the Securities and Exchange Commission, including its annual report on form 10-K and its quarterly report for form 10-Q for the quarter ended March 31, 2025. Incyte disclaims any intent or obligation to update these forward-looking statements.

Welcome

Hervé Hoppenot, Chief Executive Officer

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Opening Remarks

Pablo Cagnoni, President and Head of Research & Development

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Agenda

Introduction	**Pablo Cagnoni, MD** Head of Research & Development
Essential Thrombocythemia Disease Overview	**Claire Harrison, MD, FRCP** Guy's and St Thomas' Hospital
Biology of mutCALR in MPNs	**Jyoti Nangalia, MD, PhD** Cambridge Stem Cell Institute
Mechanism of mutCALR Antibody: INCA033989	**Patrick Mayes, PhD** Group Vice President, Biology
Phase 1 Data from a Novel, First-in-Class, Mutant Calreticulin-Specific Monoclonal Antibody in Patients with Essential Thrombocythemia (ET)	**John Mascarenhas, MD** Icahn School of Medicine at Mount Sinai
Closing Remarks	**Pablo Cagnoni, MD** Head of Research & Development
Available for Q&A	**Incyte Team**

Claire Harrison, MD, FRCP

Claire Harrison is a professor of myeloproliferative neoplasms (MPN) and Deputy Chief Medical Officer at Guy's and St Thomas' Hospital in London.

Claire cofounded MPN Voice over 20 years ago and is a Trustee of Blood Cancer UK. She sits on several European Hematology Association (EHA) boards and is Deputy Editor in Chief of HemaSphere.

Jyoti Nangalia, MD, PhD

Jyoti Nangalia discovered *CALR* mutations in patients with myeloproliferative neoplasms (MPN) in 2013.

She has continued to make landmark scientific contributions. She has integrated genomics and clinical factors to provide personalized predictions of disease outcome in MPN (Predict:Blood). Her team identified that the genetic drivers of MPN are acquired many decades before clinical diagnosis, and can even occur *in utero.* Her team has also led the molecular analysis of clinical trials.

Jyoti is a Group Leader at the Sanger Institute and Cambridge Stem Cell Institute. Her group studies somatic mutation patterns, methylation changes and clonal selection over life, and how these alter during ageing and cancer. She is also a practicing Consultant Haematologist at Cambridge University Hospitals NHS Foundation Trust.

John Mascarenhas, MD

John Mascarenhas is Professor of Medicine at the Icahn School of Medicine at Mount Sinai, Director of the Center of Excellence for Blood Cancers and Myeloid Disorders, and a member of The Tisch Cancer Institute. He directs the Adult Leukemia Program and leads clinical investigation within the Myeloproliferative Disorders Program.

John is Principal Investigator (PI) of the clinical trials project within the National Cancer Institute-sponsored Myeloproliferative Neoplasms Research Consortium. He has served as PI or Study Chair of multiple investigator-initiated and industry-sponsored early- and late-phase clinical trials evaluating innovative approaches to the treatment of MPNs and AML. Additionally, he is Chair of the Leukemia Disease Management Team, Co-Chair of the Hematologic Malignancy Disease Focus Group, and a full member of the Tisch Cancer Institute Protocol and Review Monitoring Committee.

Essential Thrombocythemia Disease Overview

Claire Harrison, MD, FRCP

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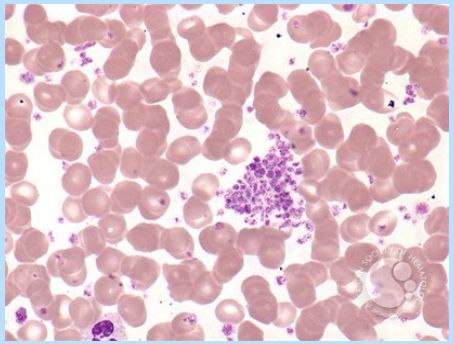
Essential Thrombocythemia is a Clonal Disease

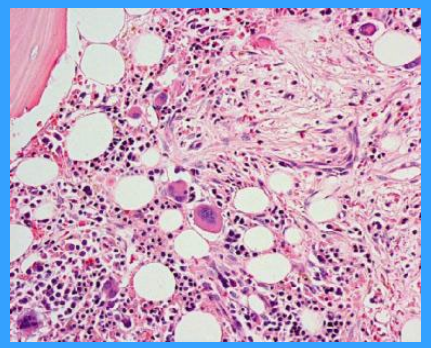
CALR mutations account for 25% of cases

Essential Thrombocythemia (ET)

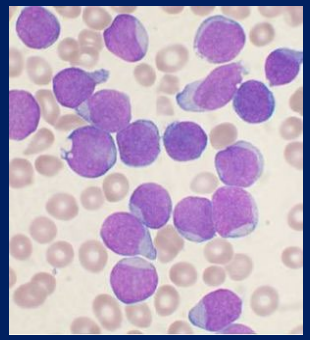


Polycythemia Vera (PV)

Primary/Secondary Myelofibrosis



Post MPN-AML



Natural History of ET

Incidence:

~ 1 per 100,000

Bimodal distribution:

- Younger individuals*
- Median age ~67 years

Main Clinical Presentation

- Thrombosis/hemorrhage
- Impact on quality of life

Progression

(10-year risk)

Myelofibrosis: 5-10%

Acute leukemia: 3%

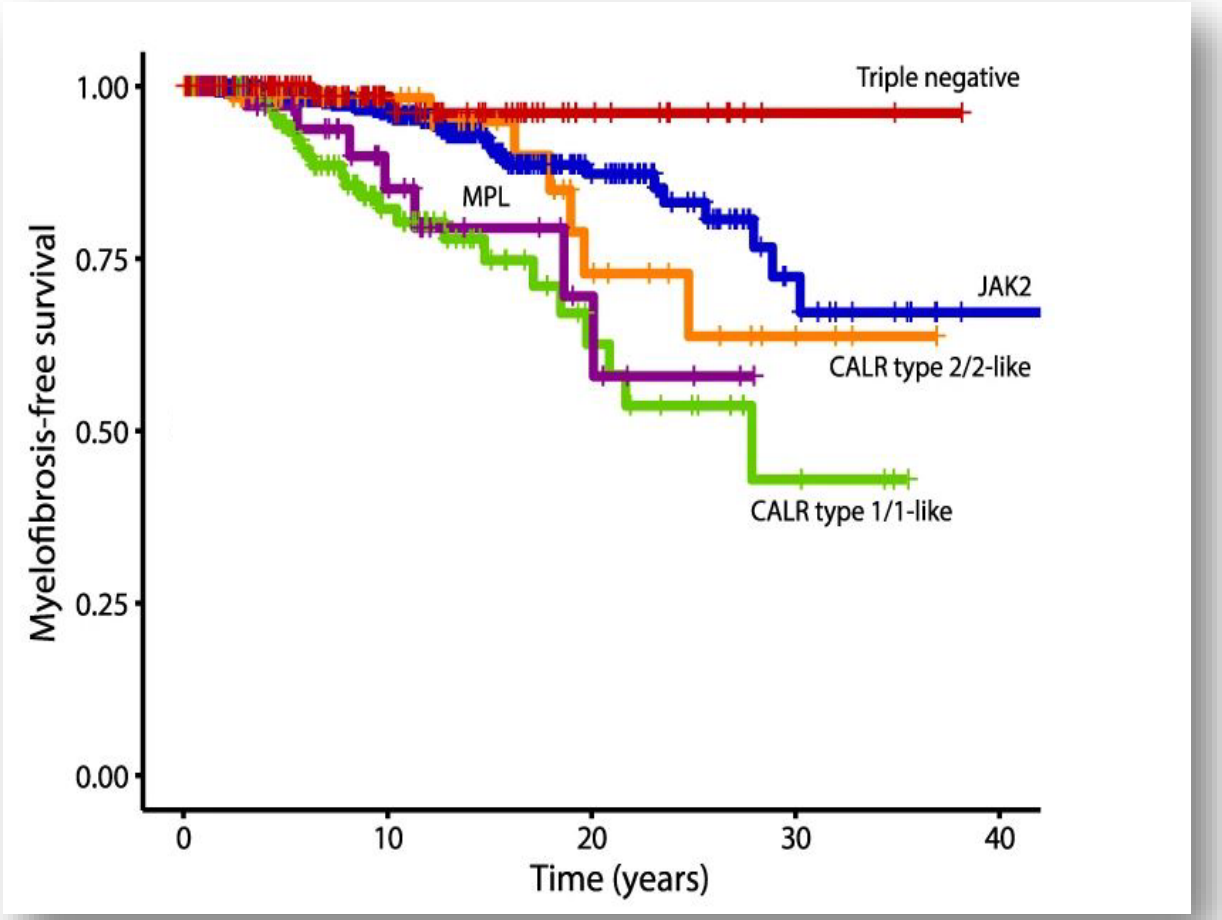
Median overall survival of 20 years

* Predominantly in women

mutCALR ET: A Distinct Clinical Subtype

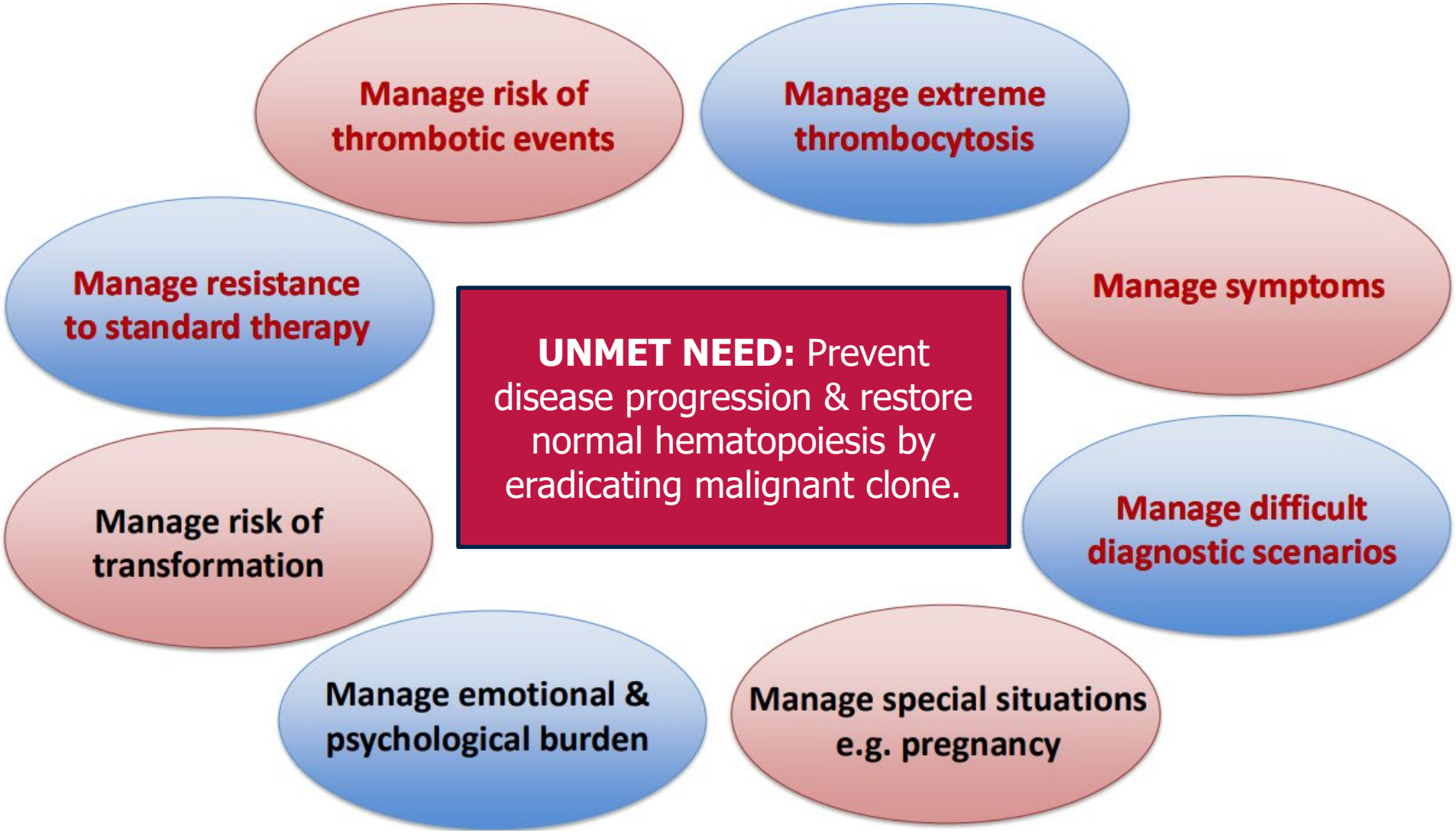
Younger, higher risk of MF transformation, VAF and platelet count

- **Younger** at diagnosis[1]
  (53 yrs vs 61 yrs for JAK2)
- Higher risk of **MF transformation**[1]
  (17% for mutCALR vs 7.5% for JAK2)
- **Higher VAF**[2]
  (median ~30% vs ~19% JAK2)
  - Higher baseline VAF -> higher risk of disease progression and poorer outcomes[5,6]
- **Higher platelets**[1]
  (median 897 vs 690 for JAK2)
- **Platelets ≥ 1000 x 10^9/ L**[1]
  (38% vs 14% for JAK2)
- More **likely to bleed with aspirin**[3]
- **Poorer response to cytoreductive therapies**[4]



1.Tefferi et al, JAMA 2025 Feb 25;333(8):701-714 2. Rumi et al, Blood 2014, 123(10):1544–1551 3. Ratnam et al, Blood Adv (2024) 8 (23): 6043–6054. 4. Campbell et al Lancet 2005, 366 (9501): 1945-1953 5. Cavalloni et al, Oncotarget. 2017 May 16;8(20):33416-33421 6. Gugliemelli et al, Blood 2024 Mar 28;143(13):1310-1314

Key Clinical Challenges Remain:



Current Treatments Aimed at Reducing Disease Associated Risks but Do Not Impact the Natural History

High Risk
>60 years
OR Thrombosis
OR Hemorrhage

- Low dose aspirin* (75–100mg/d)[1]
- AND Hydroxyurea[1-2] *or* Interferon†
- OR Anagrelide

These treatments attempt to:
- Control blood counts
- Reduce thrombosis and haemorrhage
- Reduce some symptoms

No evidence that they modify the disease

*anticoagulants in case of venous thrombosis; † off-label; could be considered for younger patients

1. Barbui T, et al. *JCO* 2011;29:761–70 2. Vannucchi AM, et al. *Ann Oncol* 2015;26(Suppl. 5):v85–99

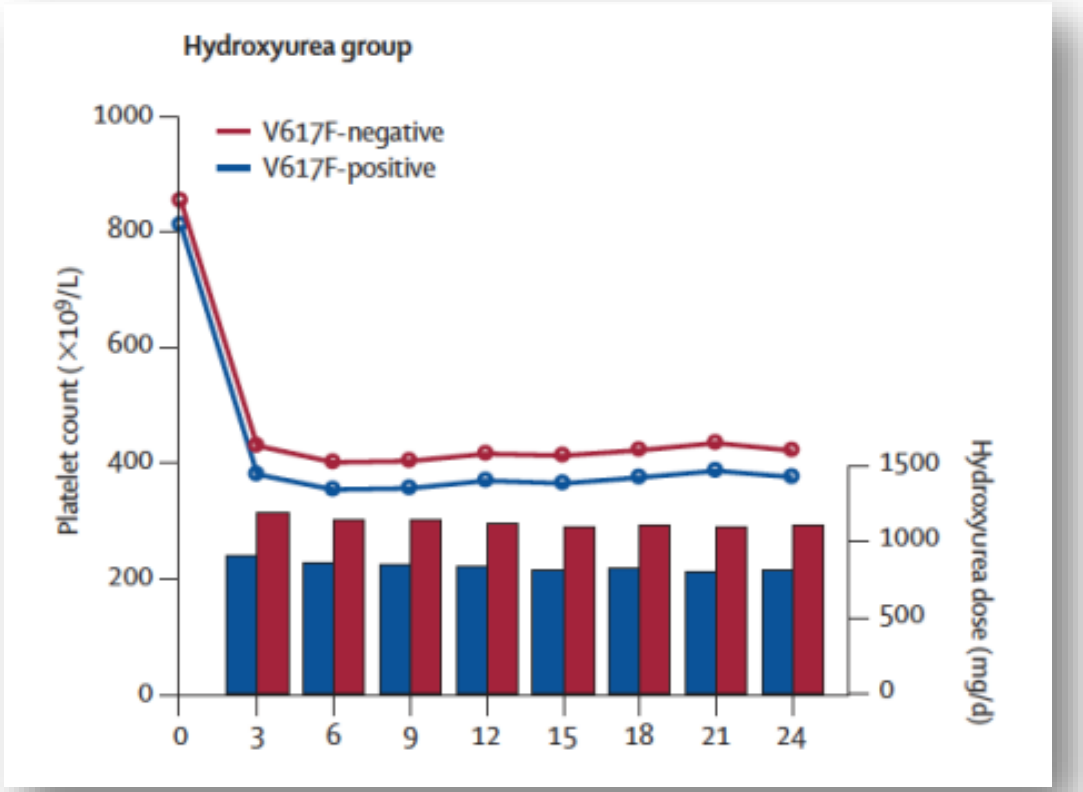
JAKV617 Negative ET Patients Show Inferior Response to Cytoreduction

Hematological responses are:

- **Less frequent**
- **Take longer to achieve**
- **Less durable**

Higher rates of hydroxyurea **resistance/intolerance**

Higher doses of hydroxyurea needed



1. Campbell et al, Lancet 2005

Unmet Need Still Remains in ET…

Resistance and Intolerance to available treatments [1,2]

- HU: 20-30% of patients are resistant to treatment
- Interferon: 20-30% of patients discontinue due to tolerability issues

No impact on long term disease outcomes and associated therapeutic risks

- HU & Anagrelide may increase risk of transformation (myelofibrosis, leukaemia) [3]
- Anagrelide associated with VAF increases (median +40%) [4]

Limited innovation: HU, interferon or anagrelide available for >20 years

- These treatments are all problematic

No current treatment offers a cure, evidence of disease modification or consistent change in key pathological features such as mutation burden or **VAF or resolution of bone marrow changes…**

1. Hernandez Boluda et al Br J Haematol. 2011 Jan;152(1):81-8 2. Barbui et al Ann Hematol 2024 Feb;103(2):437-442 3. Birgegard et al Leuk Res. 2018 Nov;74:105-109 4. Zi Yun Ng Blood (2024) 144 (Supplement 1): 485

The Challenging ET Journey of a Young mutCALR Patient

Available treatments do not impact natural course of the disease

Presentation at Diagnosis

- **17-year-old female, coincidental thrombocytosis**
- Wbc 8 $x10^9$/L; Hb 123g/l; Platelets 1204 $x10^9$/L
- No splenomegaly
- **Bone marrow biopsy** "consistent with **ET**"
- Molecular workup was negative for JAK2 V617F, MPL exon10

Therapeutic Options considered

- Knee injury required surgery… **Anagrelide** prescribed to manage surgery… **stopped after 6 weeks**
- **Anagrelide:** believed to be safe but subsequent limited use due to **risks of bleeding, transformation to myelofibrosis and less efficacy in preventing thrombosis** (PT-1 study)

"Blood cancer diagnosis with significant long-term risk and no curative treatment options except bone marrow transplant (if develops myelofibrosis)"

The Challenging ET Journey of a Young mutCALR Patient

Available treatments do not impact natural course of the disease

Long-Term Disease Evolution

- **Wants to get pregnant**, but **elevated platelets** (1670 x 109/L)…
- Treated with **interferon alpha (to reduce risk of miscarriage)**
- Got pregnant but has a **miscarriage**
- **Poor experience with interferon** – flu-like symptoms, worsened fatigue, refuses to take the treatment
- **Found to be CALR positive**…
- 20 years after ET diagnosis: **post ET myelofibrosis**

Key Take aways

- **Uncontrolled and progressive disease**
- **Complications & intolerance to available therapeutic options**
- **Still young but shortened life expectancy**

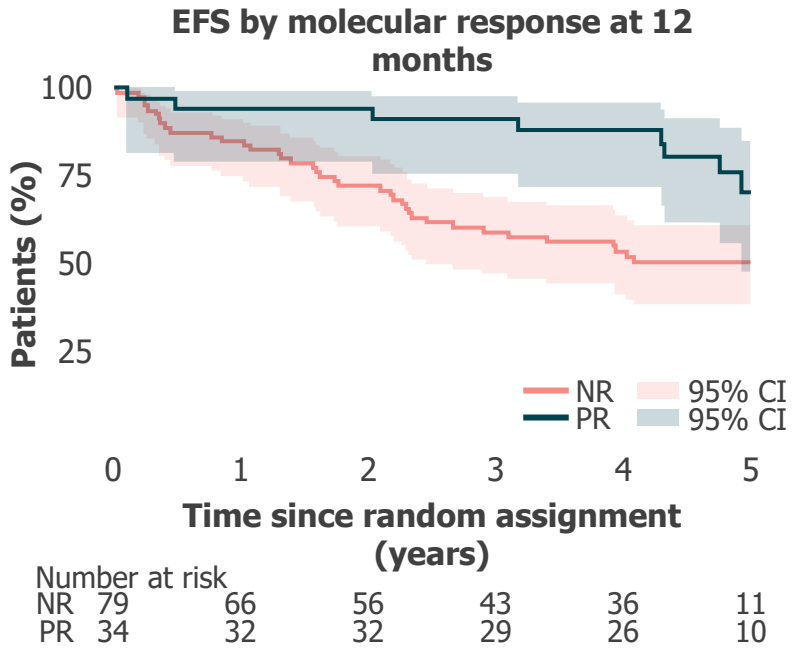
Need therapies with disease modifying potential!

Molecular Response Matters in MPNs

VAF reductions (molecular response) are associated with improved outcomes: EFS, PFS, OS

- In MAJIC-PV[1], a **MR** (50% reduction in *JAK2*V617F VAF) at 1 year **correlated with superior EFS**
- Patients with **durable MR** at last time point had significant **improvements in EFS, PFS, and OS**, regardless of treatment
- Similar results reported in other studies[2]

	Any treatment MR			
	Whole trial	**No response**	**50% reduction**	**p value**
	(n = 127)	**(n = 74)**	**(n=53)**	
Thromboembolic event	38 (30%)	28 (38%)	10 (19%)	0.02
Hemorrhagic event	28 (22%)	23 (31%)	5 (9%)	0.004
PFS	35 (28%)	29 (39%)	6 (11%)	0.001
EFS	53 (42%)	40 (54%)	13 (25%)	0.001
OS	22 (17%)	18 (24%)	4 (8%)	0.01



MR, molecular response; NR, non-response; OS, overall survival; PR, partial response; PFS, progression-free survival; EFS, event-free survival
1. Harrison CN, et al. J Clin Oncol. 2023;41:3534-44 2. Guglielmelli et al. Am J Hematol 2024 Aug;99(8):1550-1559

Conclusions

- CALR mutated ET has **distinct phenotypic presentation** with onset at younger age, poor response to cytoreductive therapy and earlier transformation to MF and secondary AML
- **Current therapies** are poorly tolerated, frequently ineffective and **do not offer disease modification** and **do not target abnormal clone** or underlying mechanism of disease
- There is **unmet need for disease modifying therapies**
- Emerging evidence indicates that **reduction of the clone in MPNs** (MAJIC PV study) is **associated with improvement in clinical outcomes** including survival
  - Conversely increases in mutCALR VAF occur with Anagrelide, a treatment that has been associated with Myelofibrosis transformation

Biology of mutCALR in MPNs

Jyoti Nangalia, MD, PhD

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CALR Mutation Discovery to Phase 1 Clinical Trial in <10 yrs

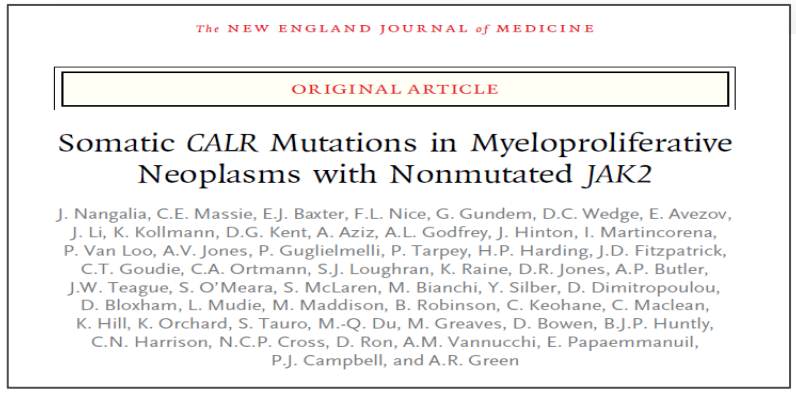
2013
DISCOVERY OF mutCALR

2023
PHASE 1 MONOCLONAL ANTIBODY INCA033989

LESS THAN 10 YEARS

1st

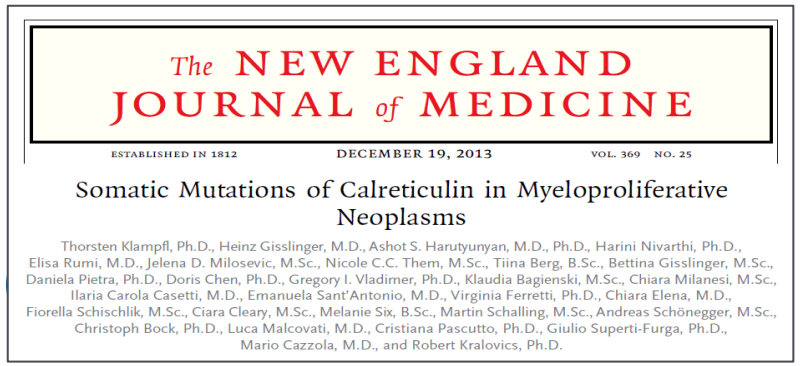
- **First mutCALR oncogene-targeted therapy**
- **Developed for patients with MPNs**


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Somatic *CALR* Mutations in Myeloproliferative Neoplasms with Nonmutated *JAK2*

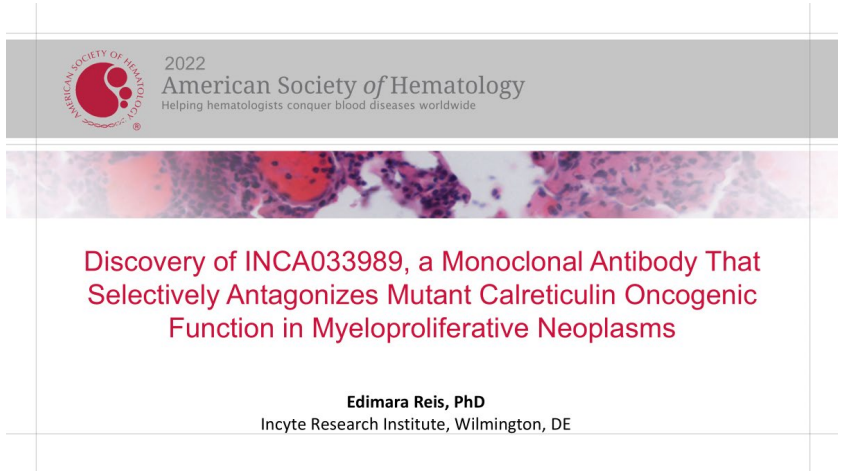
J. Nangalia, C.E. Massie, E.J. Baxter, F.L. Nice, G. Gundem, D.C. Wedge, E. Avezov, J. Li, K. Kollmann, D.G. Kent, A. Aziz, A.L. Godfrey, J. Hinton, I. Martincorena, P. Van Loo, A.V. Jones, P. Guglielmelli, P. Tarpey, H.P. Harding, J.D. Fitzpatrick, C.T. Goudie, C.A. Ortmann, S.J. Loughran, K. Raine, D.R. Jones, A.P. Butler, J.W. Teague, S. O'Meara, S. McLaren, M. Bianchi, Y. Silber, D. Dimitropoulou, D. Bloxham, L. Mudie, M. Maddison, B. Robinson, C. Keohane, C. Maclean, K. Hill, K. Orchard, S. Tauro, M.-Q. Du, M. Greaves, D. Bowen, B.J.P. Huntly, C.N. Harrison, N.C.P. Cross, D. Ron, A.M. Vannucchi, E. Papaemmanuil, P.J. Campbell, and A.R. Green


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 19, 2013 VOL. 369 NO. 25

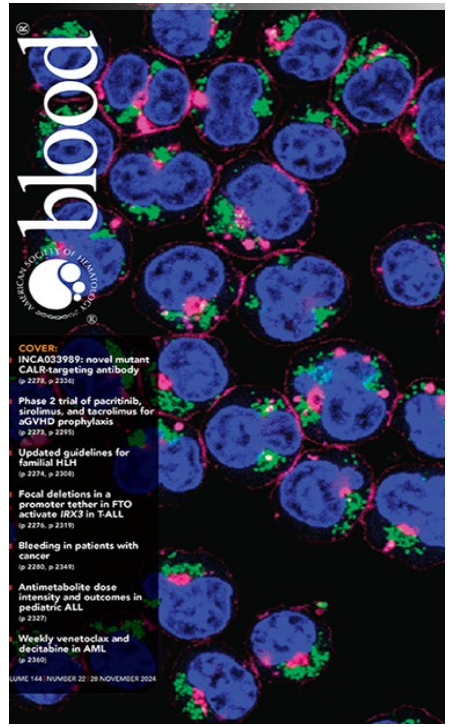
Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms

Thorsten Klampfl, Ph.D., Heinz Gisslinger, M.D., Ashot S. Harutyunyan, M.D., Ph.D., Harini Nivarthi, Ph.D., Elisa Rumi, M.D., Jelena D. Milosevic, M.Sc., Nicole C.C. Them, M.Sc., Tiina Berg, B.Sc., Bettina Gisslinger, M.Sc., Daniela Pietra, Ph.D., Doris Chen, Ph.D., Gregory I. Vladimer, Ph.D., Klaudia Bagienski, M.Sc., Chiara Milanesi, M.Sc., Ilaria Carola Casetti, M.D., Emanuela Sant'Antonio, M.D., Virginia Ferretti, Ph.D., Chiara Elena, M.D., Fiorella Schischlik, M.Sc., Ciara Cleary, M.Sc., Melanie Six, B.Sc., Martin Schalling, M.Sc., Andreas Schönegger, M.Sc., Christoph Bock, Ph.D., Luca Malcovati, M.D., Cristiana Pascutto, Ph.D., Giulio Superti-Furga, Ph.D., Mario Cazzola, M.D., and Robert Kralovics, Ph.D.

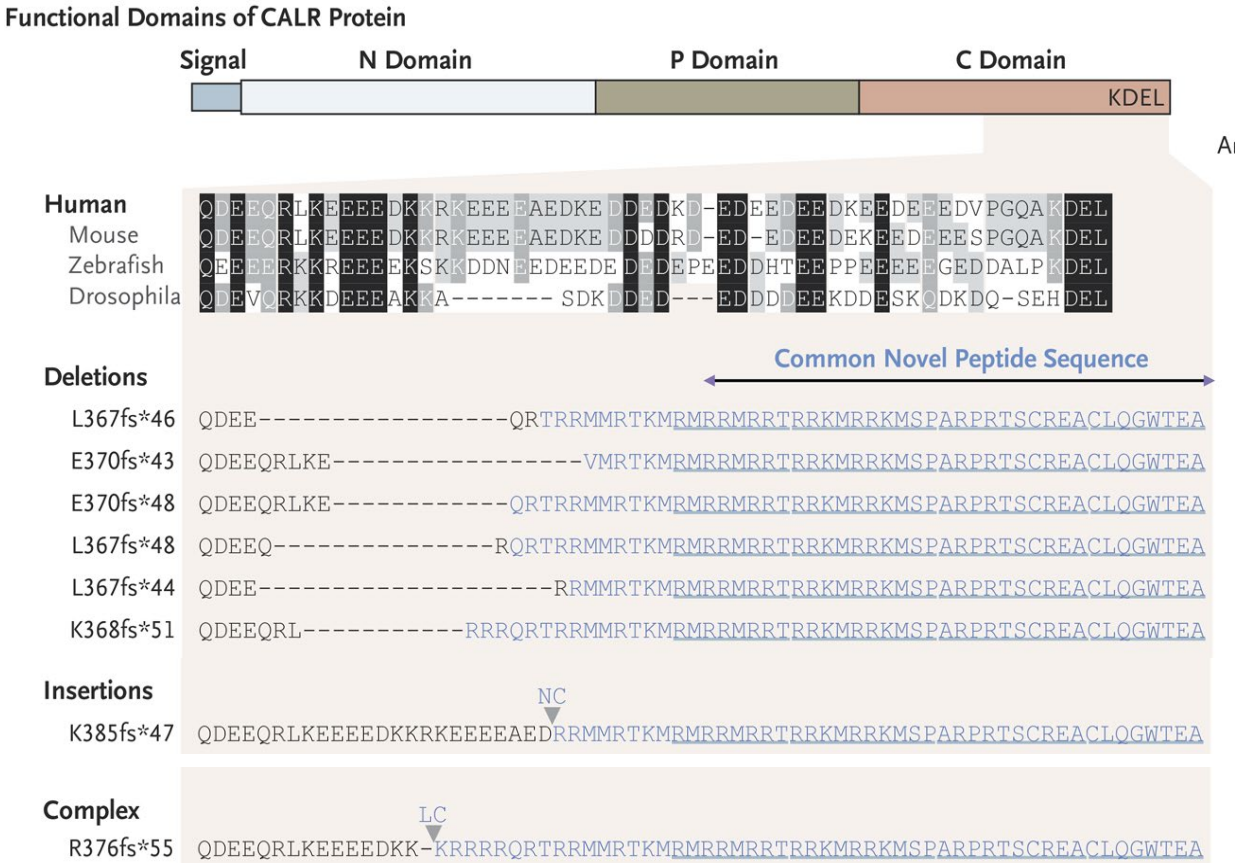

2022 American Society of Hematology
Helping hematologists conquer blood diseases worldwide

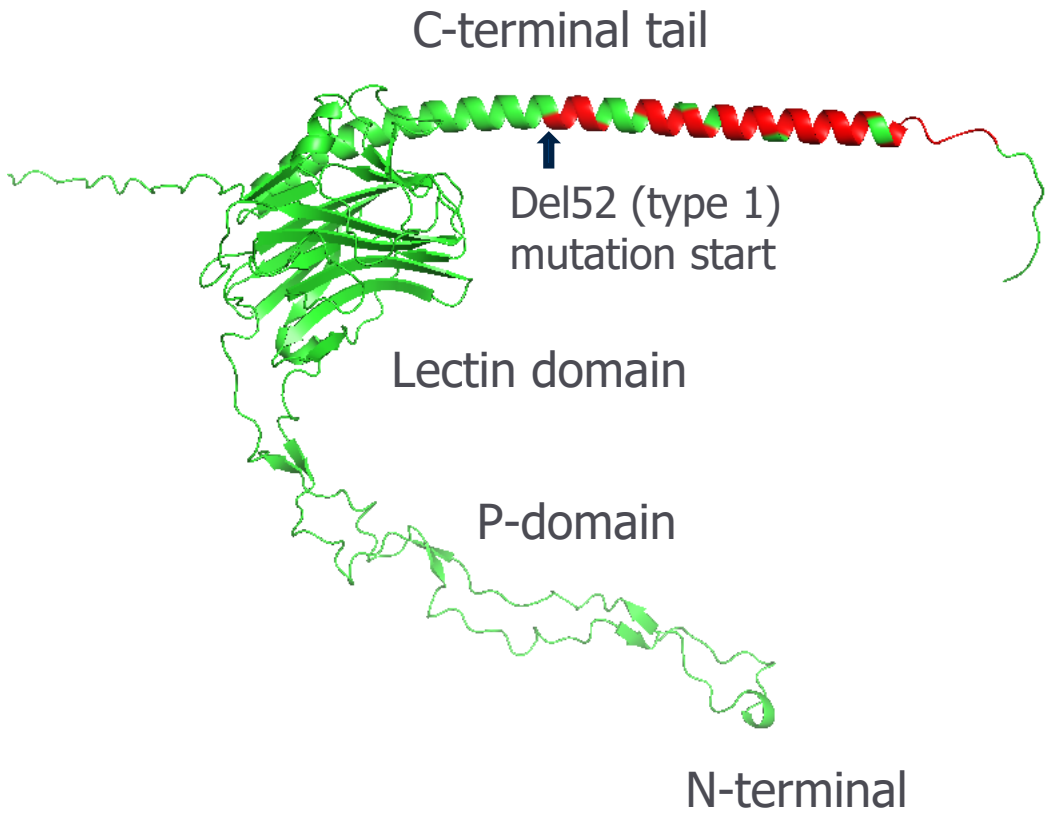
Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms

Edimara Reis, PhD
Incyte Research Institute, Wilmington, DE



CALR Mutations Result in a Novel C-terminus

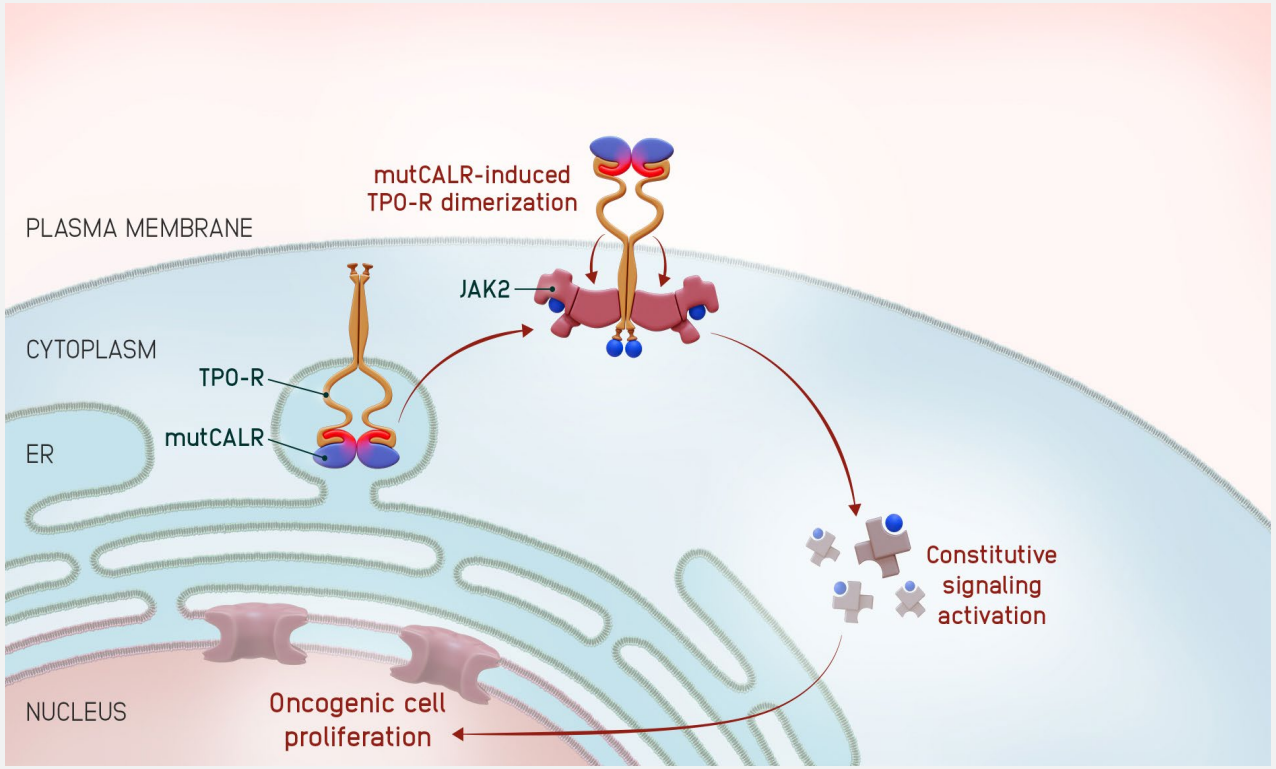




1. Nangalia *et al* NEJM 2013; PMID:24325359

Mutant CALR Mechanism of Action in MPNs

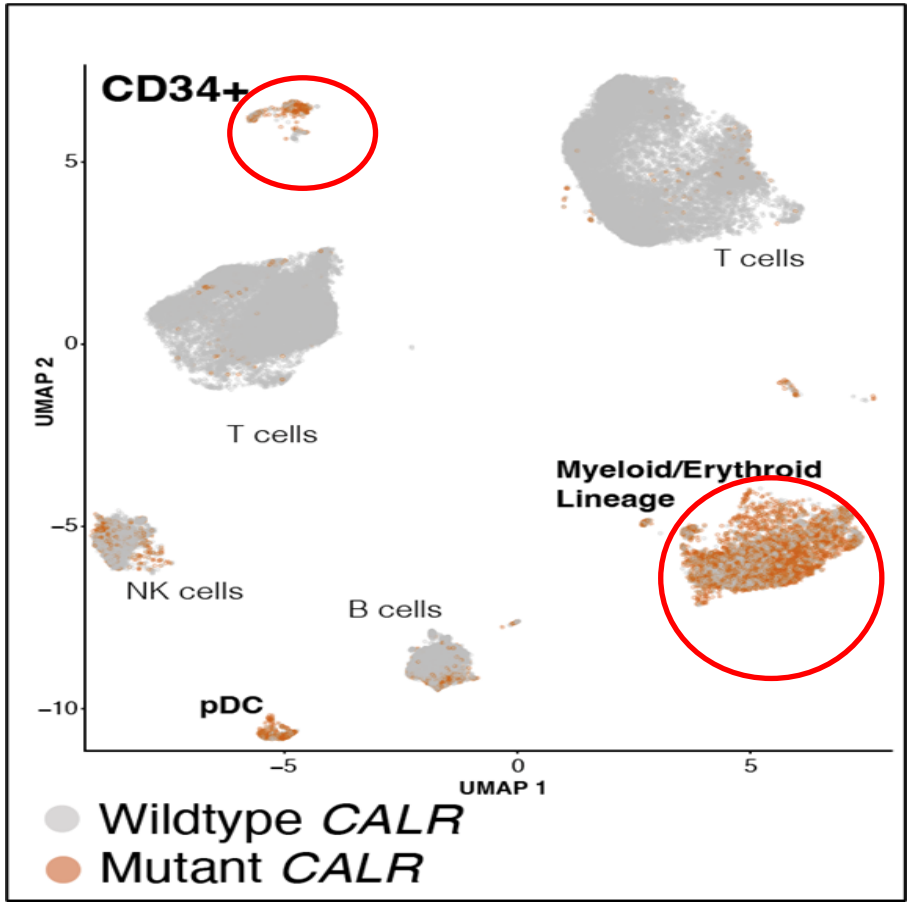
mutCALR binding to TPOR drives constitutive JAK/STAT signaling activation & oncogenic cell proliferation



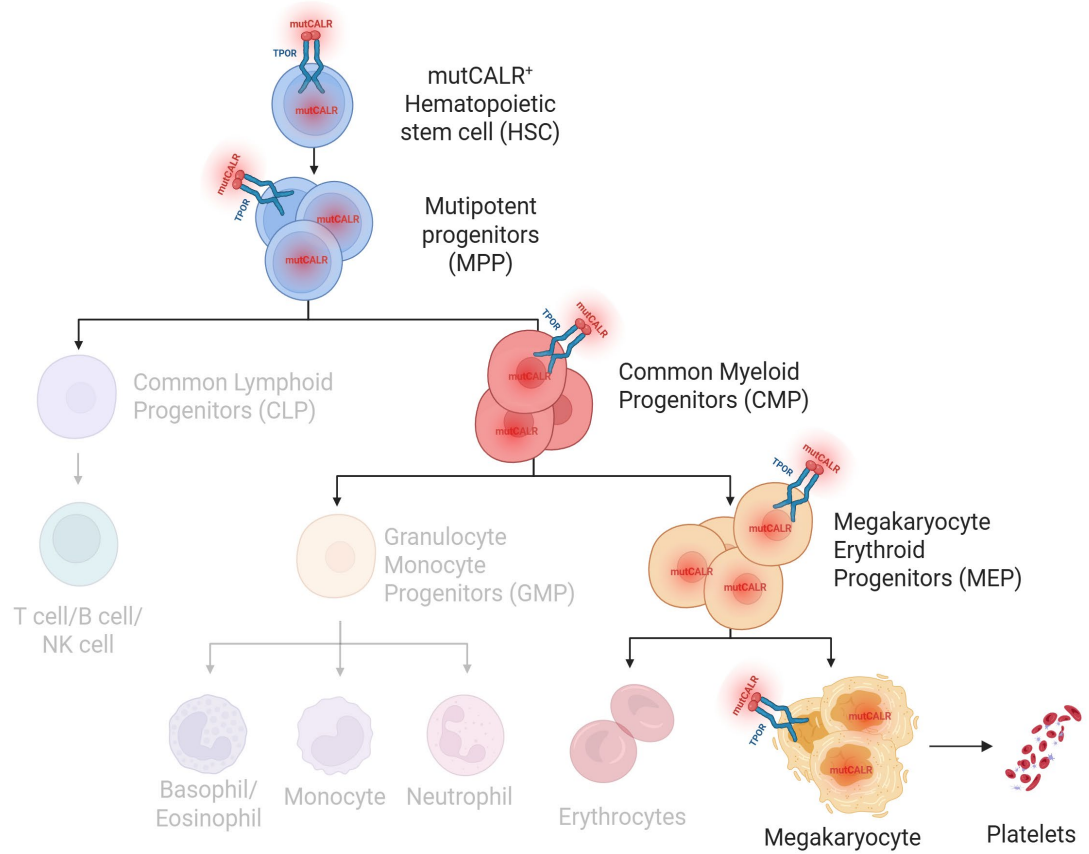
- Wild-type Calreticulin (CALR) is an intracellular protein involved in cellular homeostasis
- Mutant forms of CALR are translocated to the cell surface membrane in complex with TPOR
- mutCALR binding to TPOR results in constitutive JAK/STAT signaling and oncogenic function in MPNs

Adapted from Reis, E. et al, Blood 2024

Mutant CALR is Oncogenic Only in Cells Co-Expressing TPOR

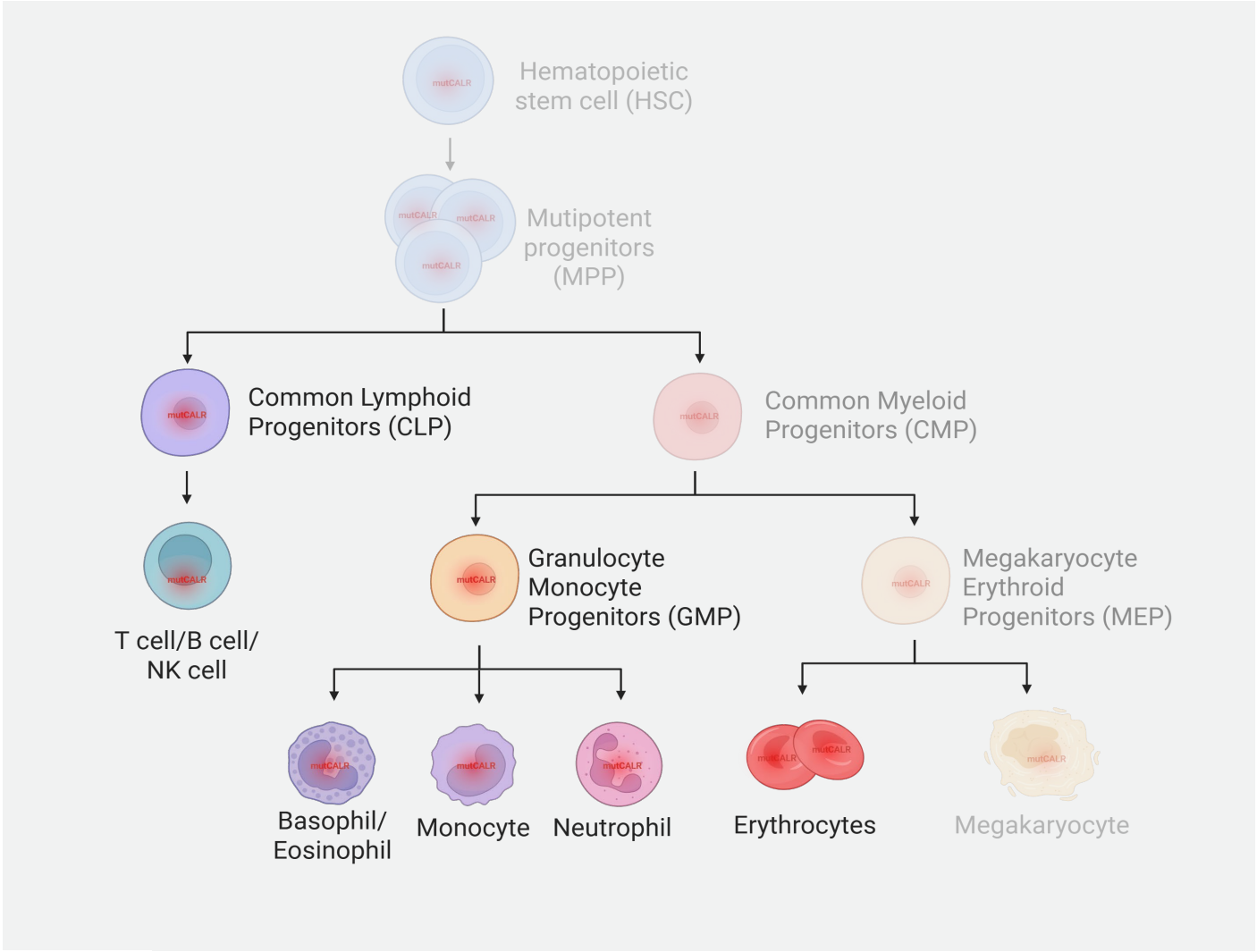


mutCALR cells co-expressing TPOR (<1% in PBMC and <5% in Bone Marrow)



TPOR-positive: Enriched in CD34+ stem and progenitor cells and myeloid/erythroid/megakaryocyte lineages

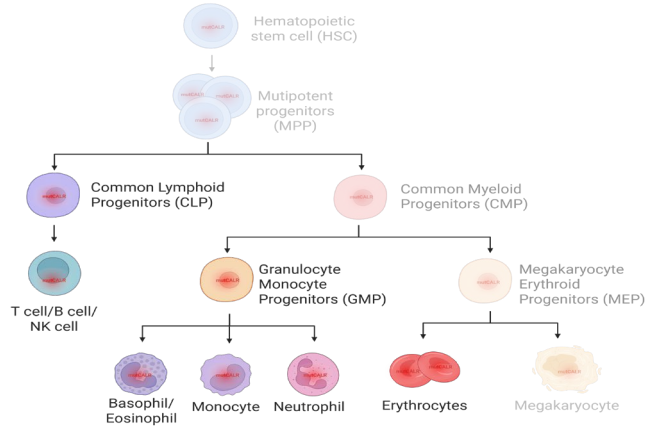
CALR Mutation is Present but Silent in TPOR Negative Cells



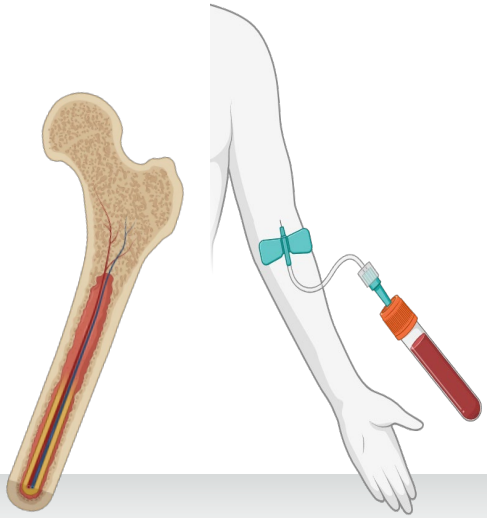
- Mutant CALR **TPOR-negative** cells represent the **majority of mutCALR expressing blood cells** in MPNs

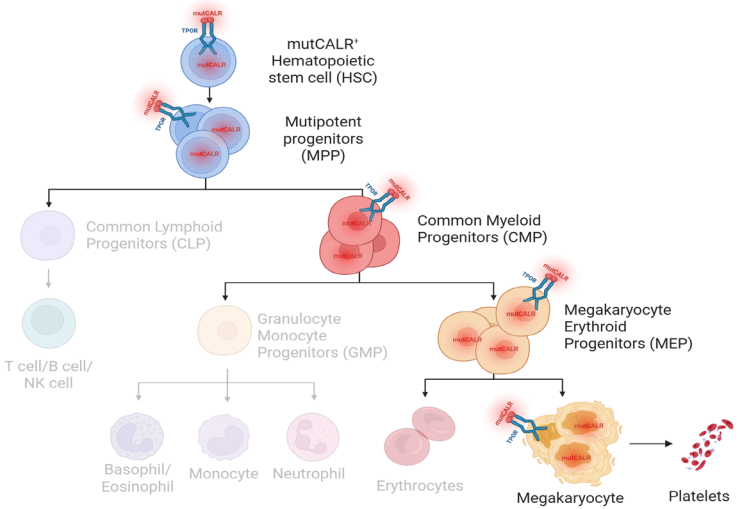
- Mutant CALR **TPOR-negative** cells are **eliminated according to their natural half life** (some long-lived)

Monitoring for Disease Modification in ET*



mutant CALR cells that don't express TPOR





mutant CALR cells that co-express TPOR

Lagging Clinical Indicators

- **VAF reduction in whole blood** by Next-Gen DNA sequencing mutCALR VAF
- **Reduction of TPOR-negative mutCALR VAF** by single cell DNAseq analysis

Early Clinical indicators

- **Reduction of platelets** in blood
- **Reduction of megakaryocyte** hyperplasia in bone marrow by IHC
- **Reduction of TPOR-positive mutCALR VAF** by single cell DNAseq analysis

* For a therapeutic agent targeting mutCALR/TPOR complex

Conclusions

- MPNs are blood cancers that arise after the acquisition of a driver mutation in stem/progenitor cells
- **Mutations in the CALR** protein leads to **constitutive activation of JAK/STAT signaling** and uncontrolled proliferation of myeloid cells and their progenitors
- A small fraction of blood cells which co-express TPOR are dependent upon mutCALR for survival and function
- **mutCALR clones not expressing TPOR** will survive according to their natural half-lives
- Time of MPN diagnosis is related to cancer growth rate. **Eliminating mutant cells will restore normal hematopoiesis and reduce allele burden over time**
- VAF reductions may push back the disease natural history by years or decades

Mechanism of mutCALR Antibody: INCA033989

Patrick Mayes, PhD, Group Vice President, Biology

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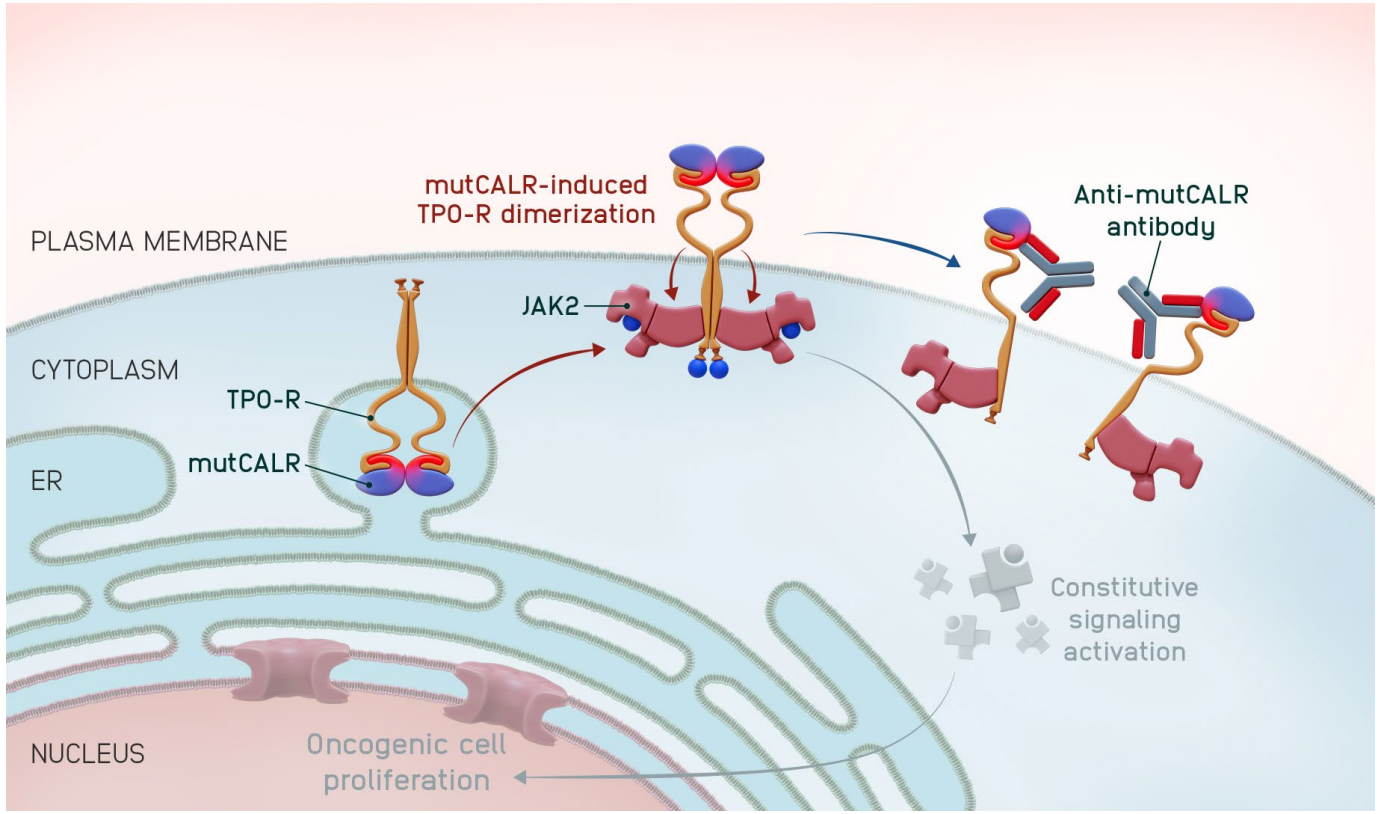
INCA033989: A First-In-Class Antagonist Antibody Inhibiting mutCALR



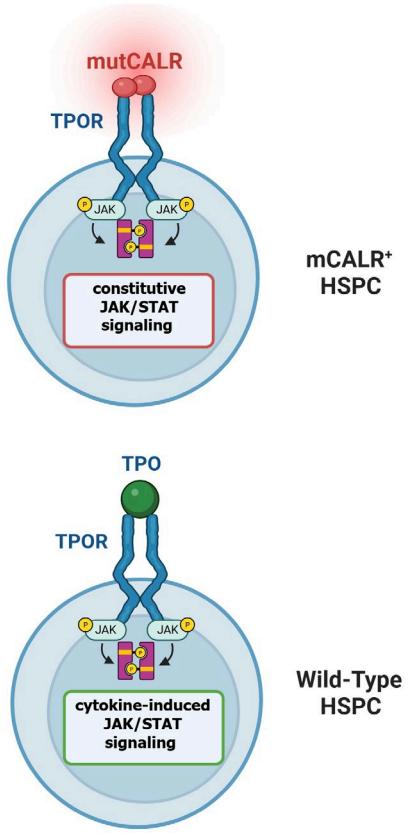
INCA033989 Properties

- ✓ Fully human, Fc-silent IgG1
- ✓ Selective, high-affinity binding to mutCALR (Type 1 and 2)
- ✓ Potent inhibition of constitutive JAK/STAT signaling induced by mutCALR
- ✓ No effect on normal TPO/TPOR signaling

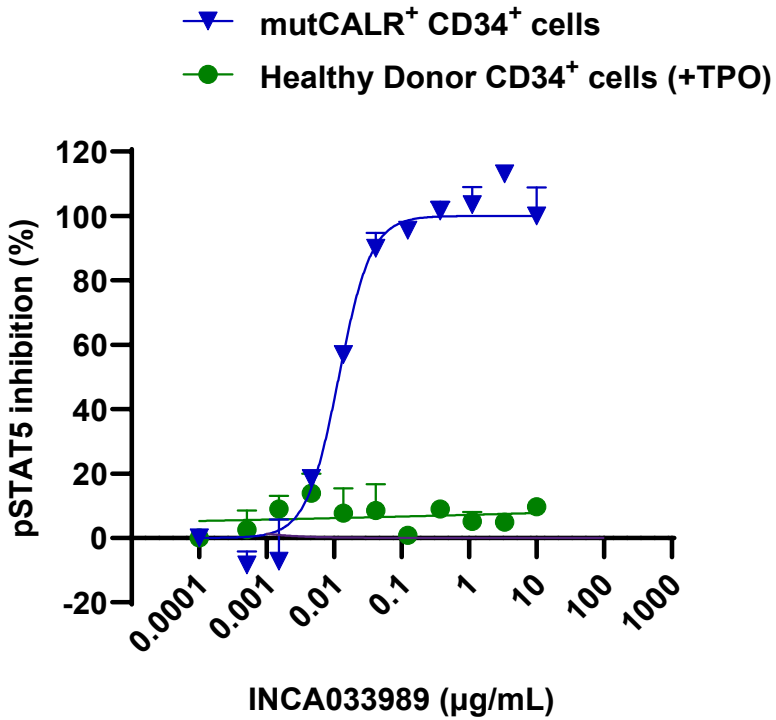
Adapted from Reis, E. et al, Blood 2024

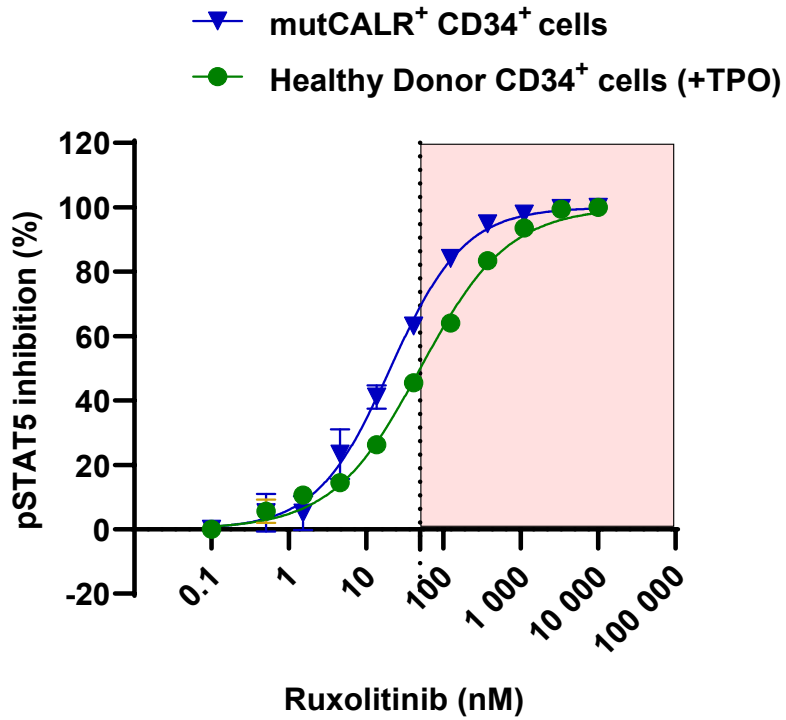
INCA033989 Selectively Inhibits Constitutive JAK/STAT Signaling Induced by mutCALR

CD34⁺ Hematopoietic Stem and Progenitor Cell (HSPC)



- INCA033989 selectively inhibits constitutive JAK/STAT signaling in mutCALR⁺ HSPCs
- Spares cytokine-induced JAK/STAT signaling in wild-type HSPCs
- Unlike JAK inhibitors which inhibit JAK/STAT signaling equally in mutCALR⁺ and WT HSPCs



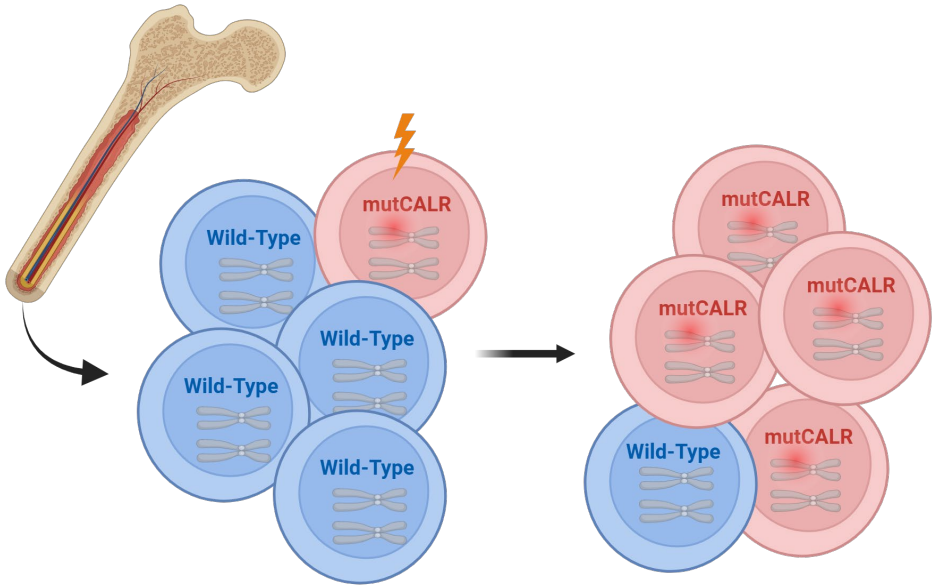


Shaded area indicates concentrations too toxic to dose clinically

1. Adapted from Reis, E. et al, Blood 2024 2. Shi, J.G. et al, Journal of Clin. Pharm., 2011

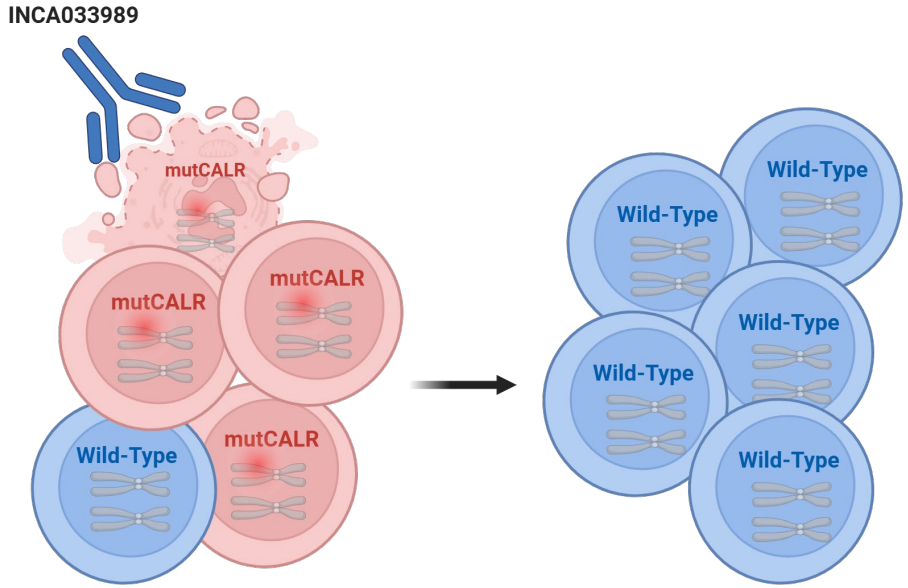
Disease Modifying Potential of INCA033989 in MPN

Mutant CALR (mutCALR) gives stem cells a clonal advantage over wild-type



- Mean mutCALR^{+} VAF of 30-40% in ET[1,2]
- Reservoir of wild-type HSPCs exists

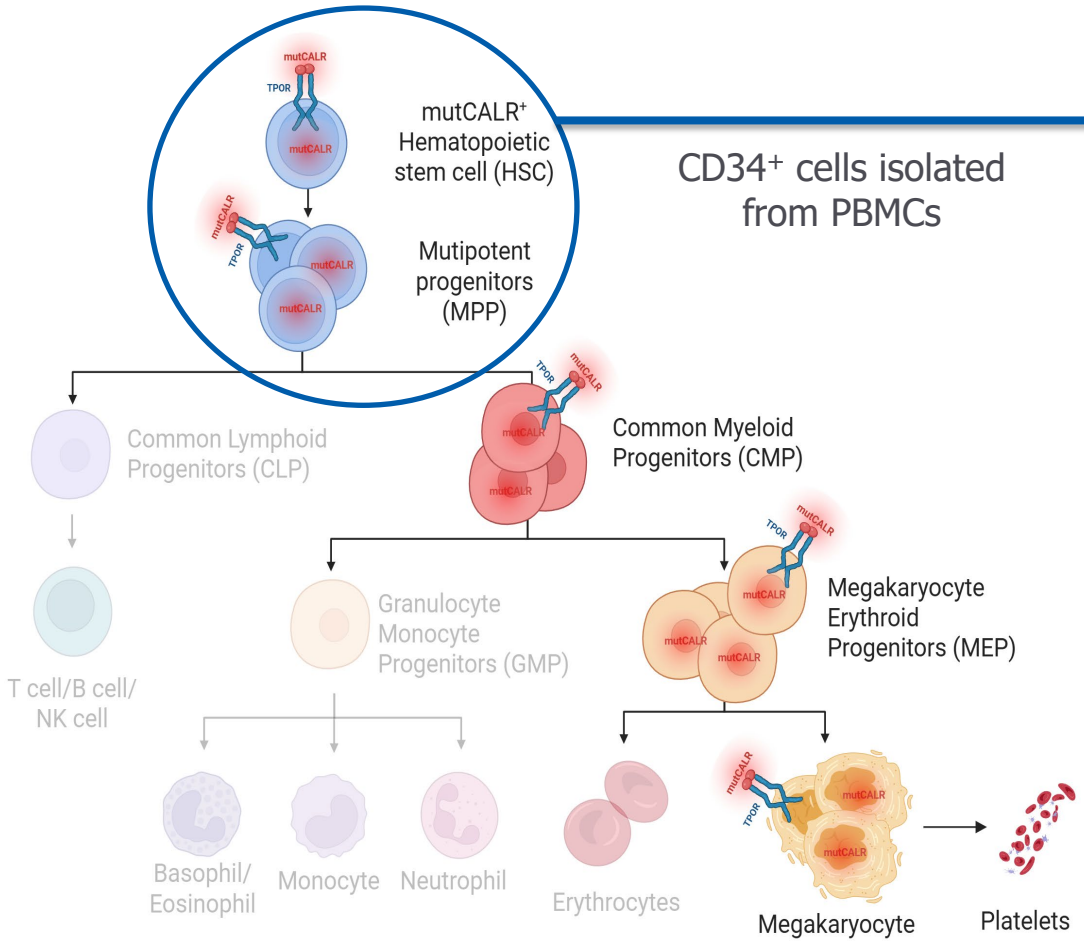
INCA033989 Inhibits mutCALR^{+} stem cells while sparing wild-type

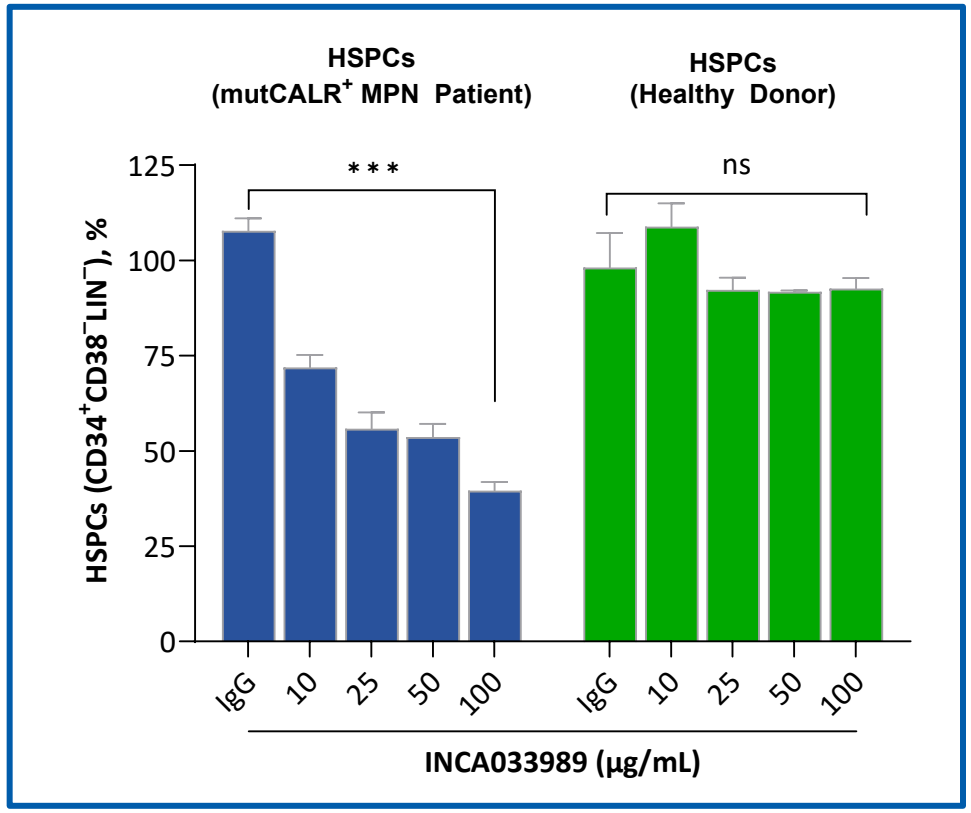


- Targeted elimination of mutCALR^{+} HSPC clones and expansion of wild-type
- Decrease in mutCALR^{+} VAF over time

1. Guglielmelli P et. al, Blood 2024 2. Rumi et al, Blood 2014

Selective Inhibition of Stem and Progenitor Cells from mutCALR⁺ MPN Patient

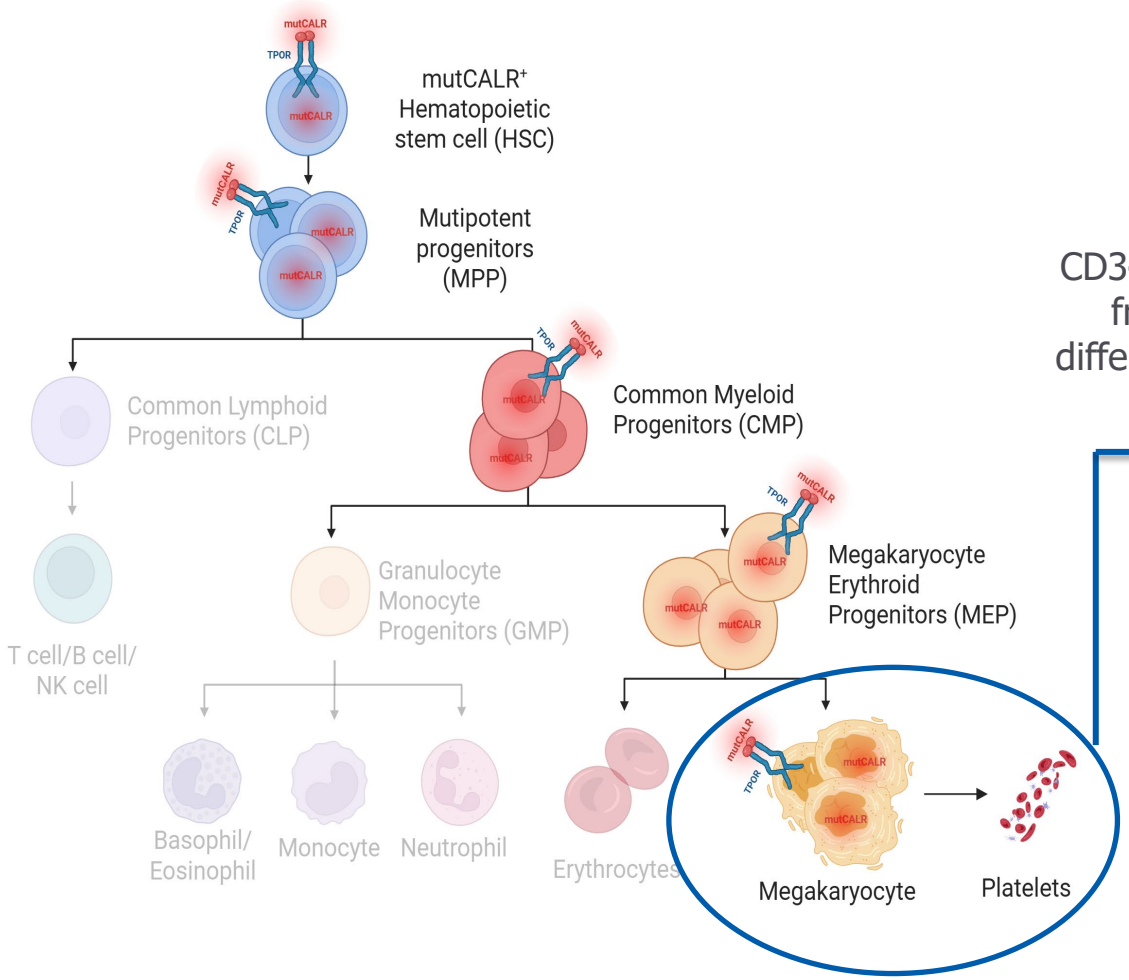




- Potent inhibition of mutCALR⁺ HSPCs
- No activity in wild-type HSPCs

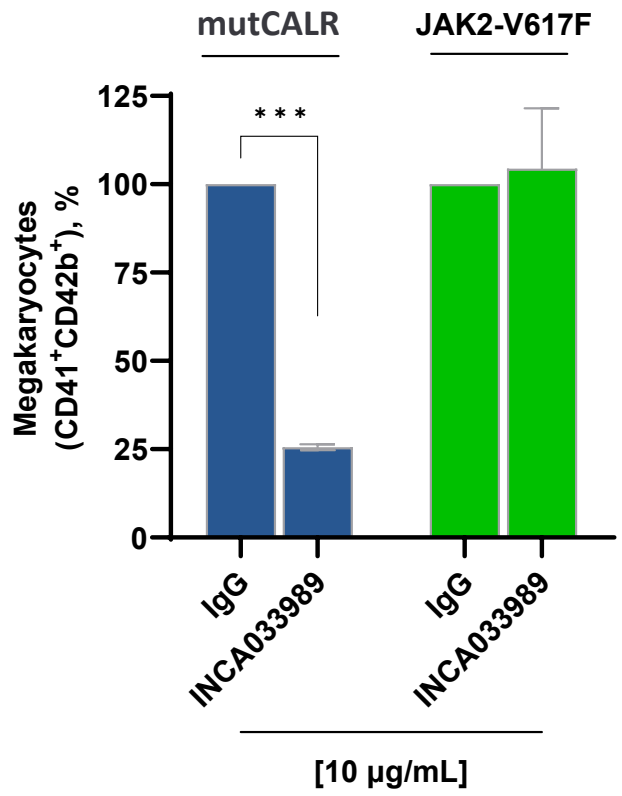
Adapted from Reis, E. et al, Blood 2024

Selective Inhibition of mutCALR⁺ Megakaryocytes



CD34⁺ Cells Isolated from MPN and differentiated to MgK ex vivo

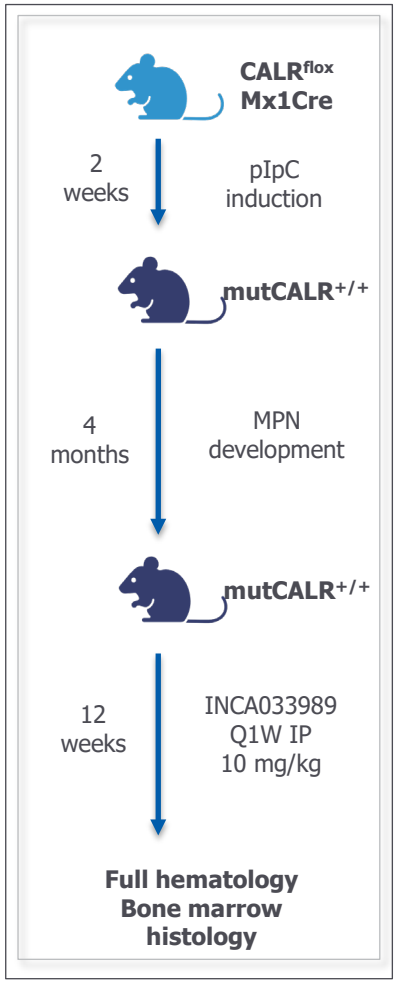
INCA033989 Selectively Inhibits mutCALR⁺ Megakaryocyte Maturation



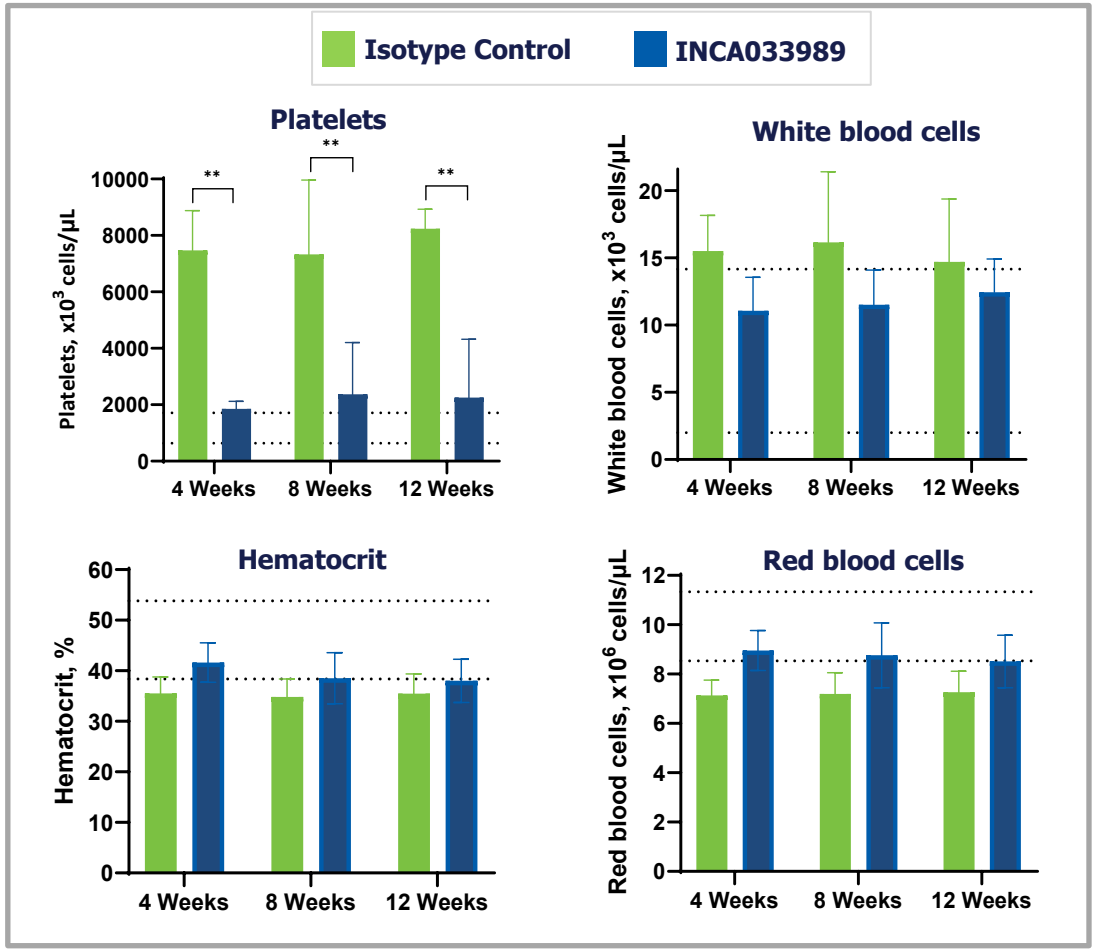
Adapted from Reis, E. et al, Blood 2024

Significant Activity of INCA033989

In a mutCALR knock-in mouse model of MPN

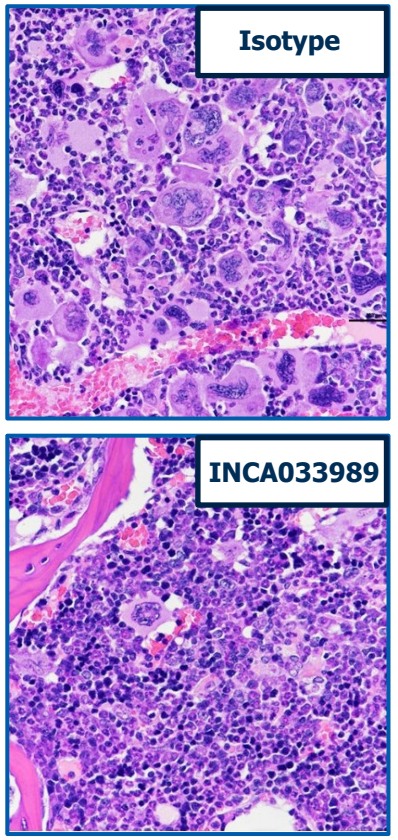


Normalization of Blood Parameters



Dotted lines represent normal range of C57BL/6 Mice (Charles River)

Normalization of Bone Marrow Megakaryopoeisis



Adapted from Reis, E. et al, Blood 2024

Conclusions

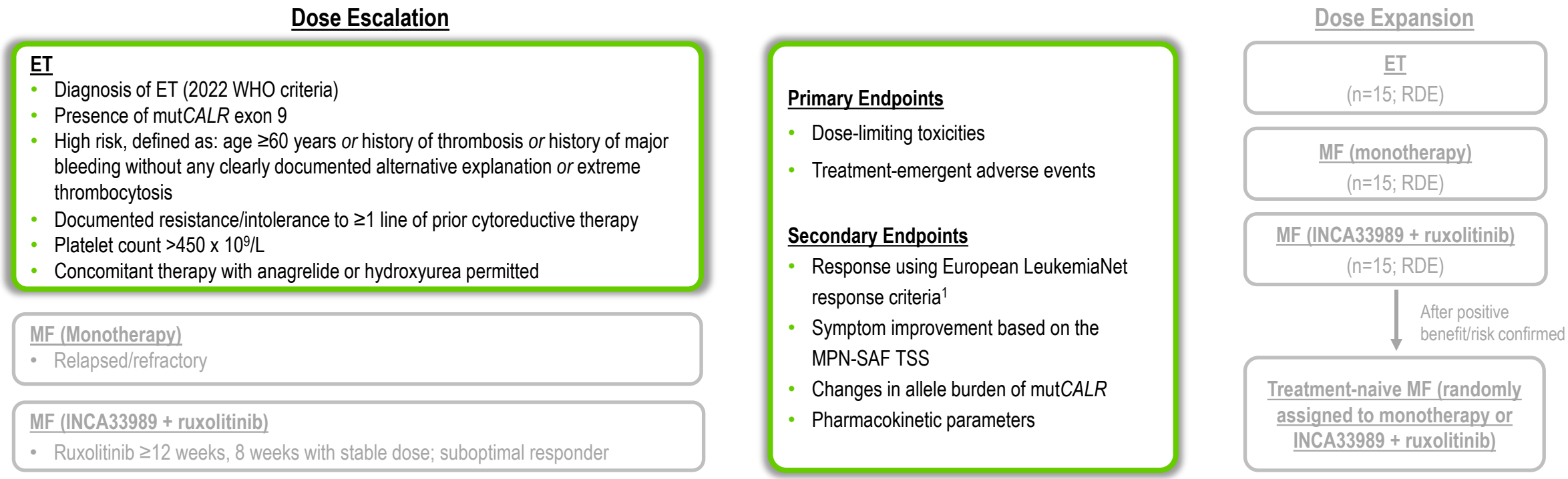
- INCA033989 is a **high affinity** mutant CALR **selective monoclonal antibody**
- INCA033989 selectively **inhibits constitutive JAK/STAT signaling** induced by mutCALR while sparing cytokine-induced JAK/STAT signaling
- INCA033989 directly **inhibits mutCALR^{+} CD34^{+} HSPCs and megakaryocytes, without affecting** non-mutated, **healthy cells** allowing for disease modifying activity of this agent
- In a mutCALR conditional knock-in mouse model of established MPN, INCA033989 **treatment led to platelet normalization, reversal of anemia and elimination of megakaryocyte hyperplasia** in the **bone marrow**
- Overall, the preclinical safety and pharmacology profile of INCA033989 makes it a promising candidate for clinical testing in mutCALR-positive MPN patients

INCA33989 Is a Novel, First-in-Class, Mutant Calreticulin-Specific Monoclonal Antibody That Demonstrates Safety and Efficacy in Patients With Essential Thrombocythemia (ET)

John Mascarenhas, MD

Incyte | SOLVE ON.

Study Design: INCA33989-101 and INCA33989-102



- **INCA33989-101** (NCT05936359; outside the US) and **INCA33989-102** (NCT06034002; US only) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA33989 in patients harboring a *CALR* exon-9 mutation with high-risk ET or MF (as monotherapy or in combination with ruxolitinib)
- INCA33989 is administered intravenously every 2 weeks

1. Barosi et al. *Blood*. 2013;23:4778-4781.

CALR, calreticulin; ET, essential thrombocythemia; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mut*CALR*, mutations of calreticulin; RDE, recommended dose for expansion; TSS, total symptom score.

Demographics and Disease Characteristics

- 49 patients were enrolled at doses ranging from 24 mg to 2500 mg

Variable	Total (N=49)
Median age, years (range)	60 (23, 82)
≥65, n (%)	20 (40.8)
Female, n (%)	29 (59.2)
Race, n (%)	
White	35 (71.4)
Asian	5 (10.2)
Black/African American	3 (6.1)
Other*	6 (12.2)
Median BMI, kg/m^2 (range)	23.6 (18.7, 44.7)
Median time from diagnosis, years (range)	7.0 (0.3, 27.9)
CALR exon 9 mutation type, n (%)	
Type 1	28 (57.1)
Type 2/other	21 (42.9)

Variable	Total (N=49)
Prior systemic anticoagulant therapy, n (%)	10 (20.4)
Prior aspirin therapy, n (%)	28 (57.1)
Prior cytoreductive therapy†, n (%)	
Hydroxyurea	38 (77.6)
Anagrelide	12 (24.5)
Interferon‡	7 (14.3)
Median *CALR* VAF§, % (range)	32.5 (12.8, 51.0)
Median platelets, GI/L (range)	931.0 (447.0, 2017.0)
Median leukocytes, GI/L (range)	7.1 (3.1, 13.8)
Median hemoglobin, g/L (range)	125.0 (84.0, 171.0)
Median MPN-SAF TSS (range)	14.0 (0, 49)
Median spleen volume, mL (range)	301.5 (70.0, 866.0)

*Other includes not reported, other, missing. †Categories not mutually exclusive. ‡Peginterferon alpha-2a (n=6), unspecified (n=1). §Measured centrally in peripheral blood by next generation sequencing.
BMI, body mass index; CALR, calreticulin; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; TSS, total symptom score; VAF, variant allele frequency.

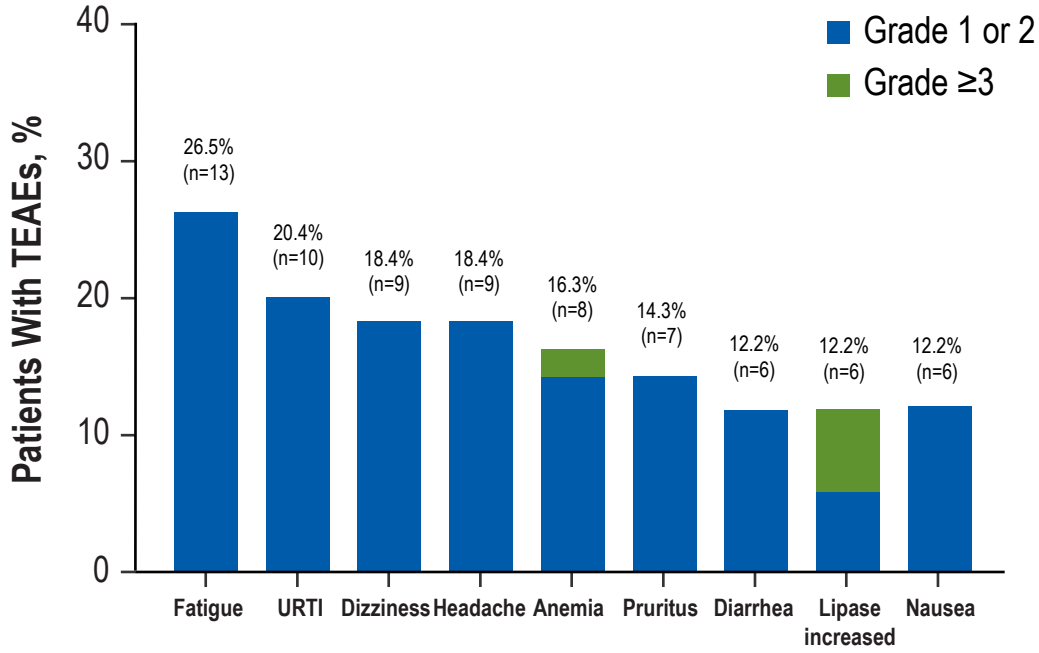
Safety: No Dose Limiting Toxicities Were Observed

Summary of TEAEs

TEAE, n (%)	Total (N=49)
Any TEAE	42 (85.7)
Treatment-related	30 (61.2)
Grade ≥3*	13 (26.5)
Serious	3 (6.1)
Discontinuation due to TEAEs	1 (2.0)
Dose reduction due to TEAEs	1 (2.0)
Infusion interruption due to TEAEs	0
Dose-limiting toxicity	0

- A maximum tolerated dose was not reached
- Only 1 patient discontinued due to a treatment-emergent adverse event (TEAE)
- Serious TEAEs:
  - Asymptomatic lipase increase (n=1; 24 mg)
  - Visceral venous thrombosis† (n=1; 24 mg)
  - Diverticulitis (n=1; 400 mg)

Most Common TEAEs

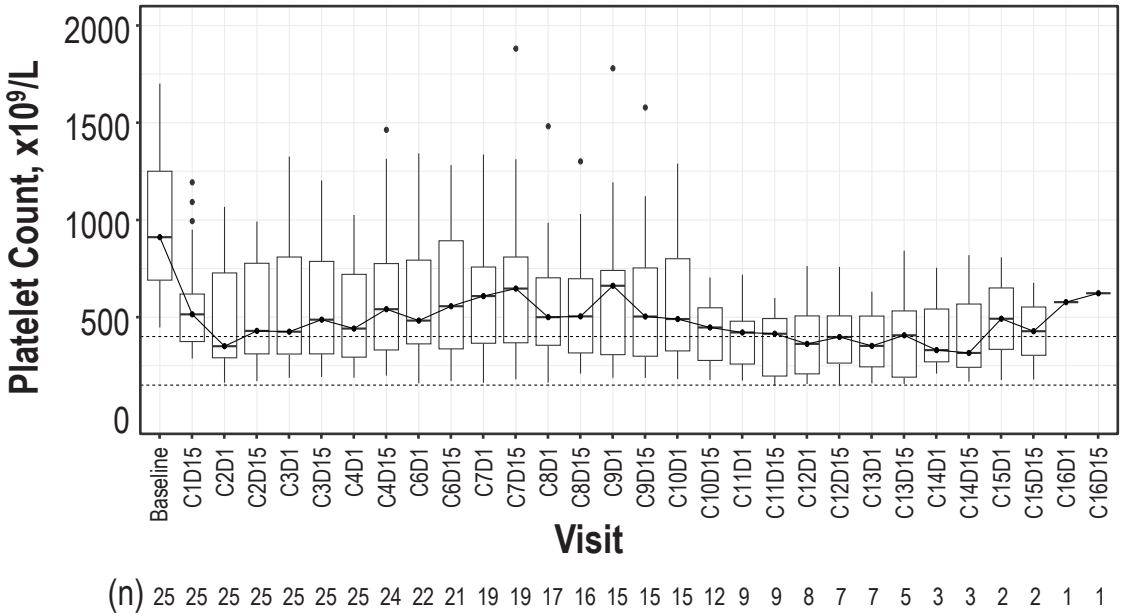


- The majority of TEAEs were grade 1-2
- Most frequent grade ≥3 TEAE was transient, asymptomatic lipase increase (6.1%)
  - All resolved without clinical sequelae
  - No correlation to dose or onset post treatment

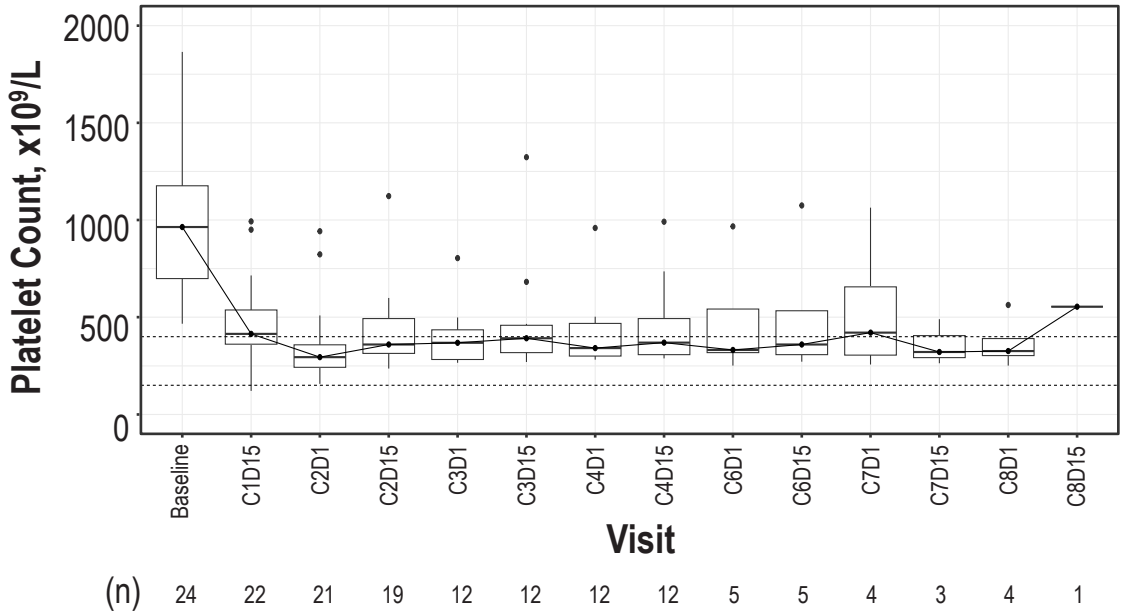
*One grade 4 TEAE was observed (transient neutropenia related to concomitant hydroxyurea). †Followed by melena (after anticoagulant initiation) and treatment discontinuation.
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

Doses 24-250 mg*



Doses 400-2500 mg†



- Of the 31 patients that enrolled with concomitant cytoreductive therapy (hydroxyurea or anagrelide), 20 (65%) discontinued it and remained on study
- Thrombocytopenia was not observed in any patient
- Doses of ≥400 mg produced higher frequency of platelet count normalization

Dotted lines indicate upper and lower limit of normal. Boxes denote the first and third quartiles, lines represent the median. Number of patients with available data at each visit is noted below the x axis.
*24 mg (n=3), 50 mg (n=3), 70 mg (n=3), 100 mg (n=3), 200 mg (n=5), 250 mg (n=8). †400 mg (n=5), 750 mg (n=9), 1500 mg (n=6), 2500 mg (n=4). C, cycle; D, day.

Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

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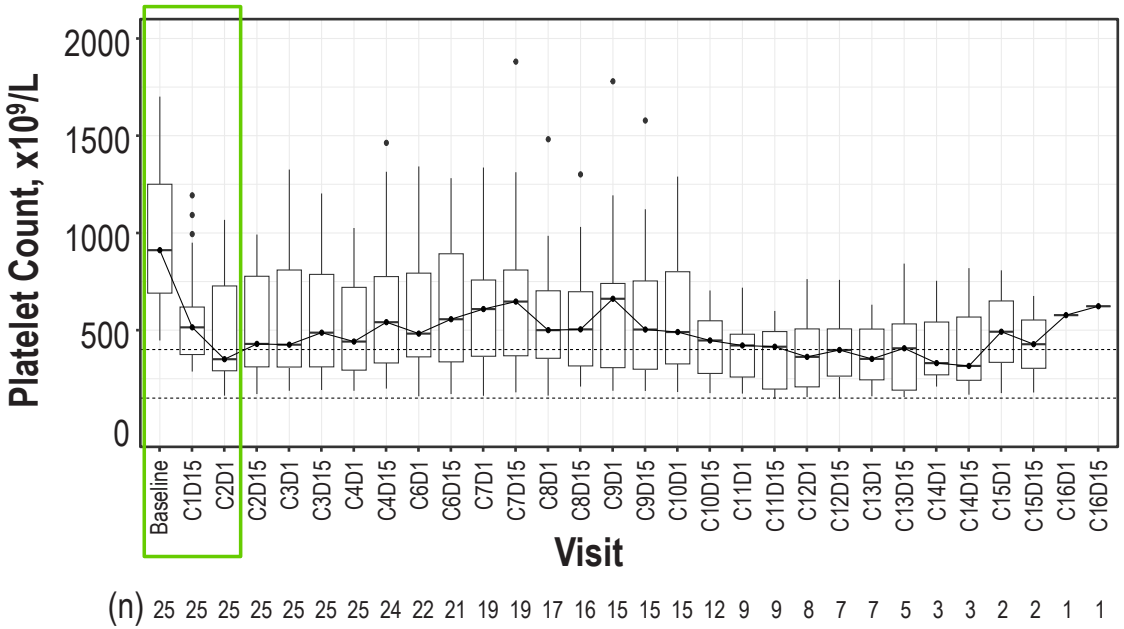

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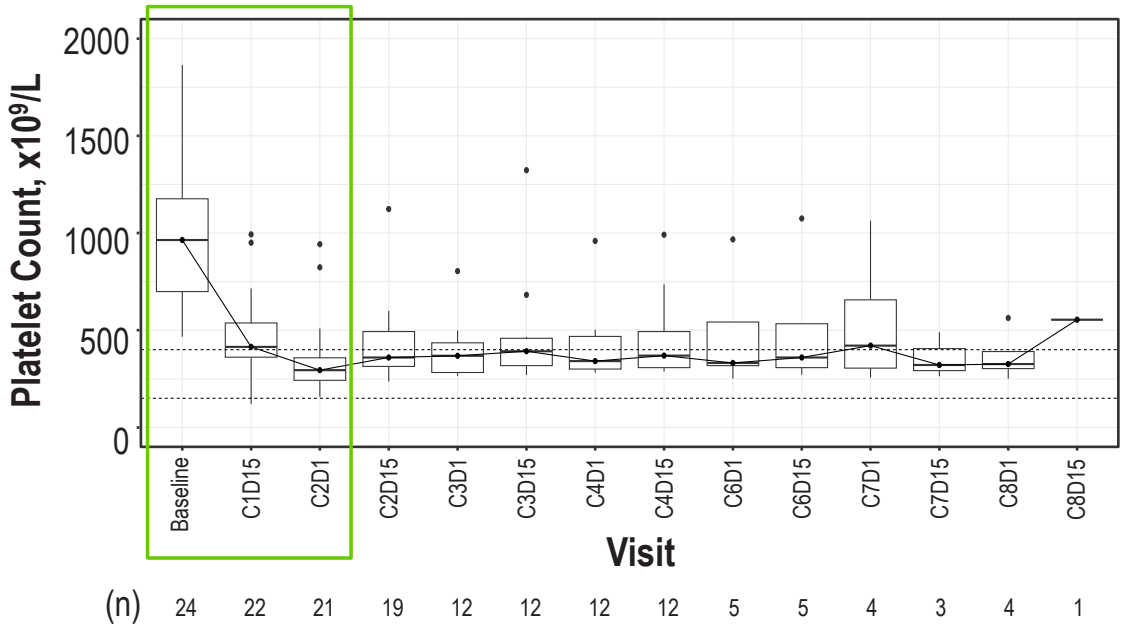

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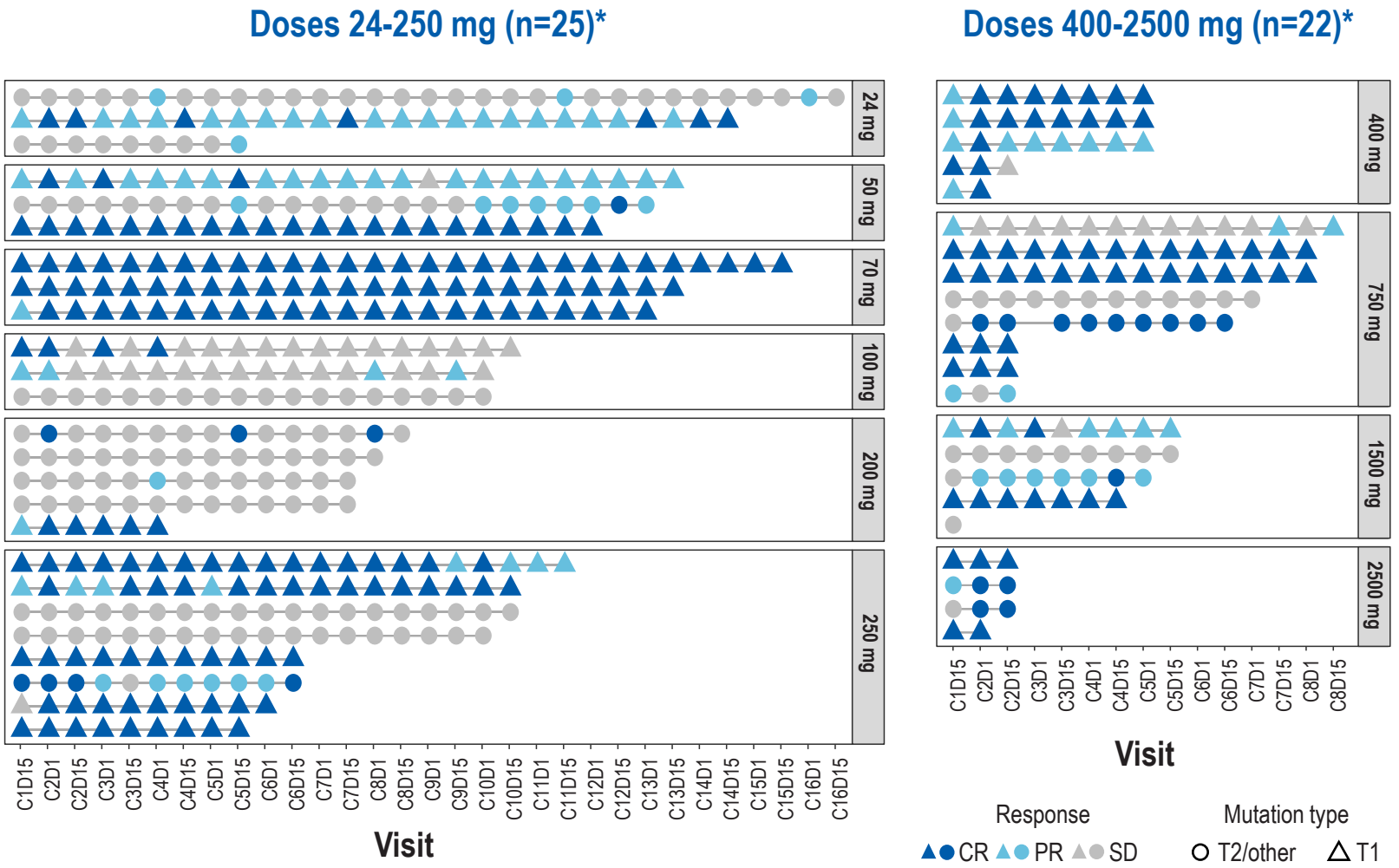
Hematologic Responses Are Achieved Early and Are Sustained



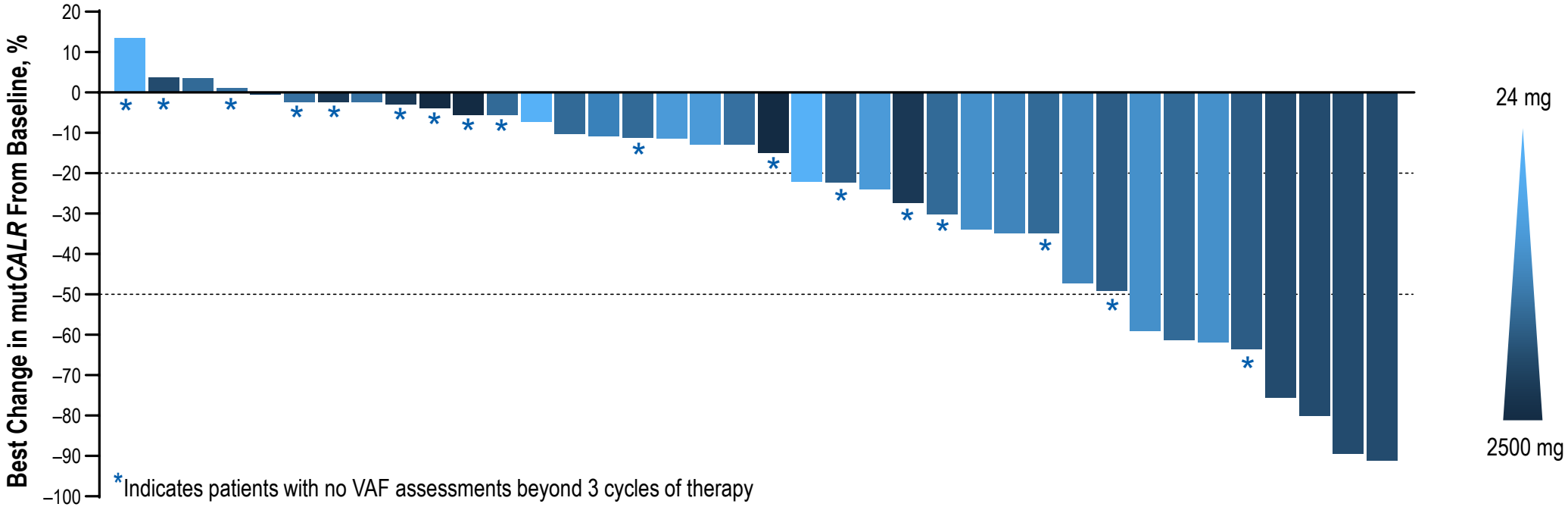
Dose, mg	Best Overall Response				
	N	CR	PR	SD	OR
24-250	25	17 (68%)	3 (12%)	5 (20%)	20 (80%)
400-2500	**22**	**18 (82%)**	**1 (5%)**	**3 (14%)**	**19 (86%)**

- 86% of patients that received ≥400 mg had a response
- Mean (STD) duration of exposure was 26.0 (17.3) weeks
- Only 1 patient discontinued treatment, all others are ongoing

*47 evaluable patients who have reached C1D15 are presented. Complete response was defined as achievement of platelet count <400x10^9/L and leukocytes <10x10^9/L, partial response was defined as achievement of platelet count <600x10^9/L and leukocytes <10x10^9/L (baseline platelet count >600x10^9/L). 1 cycle = 28 days or 2 doses. C, cycle; CR, complete response; D, day; OR, overall response; PR, partial response; SD, stable disease; STD, standard deviation.

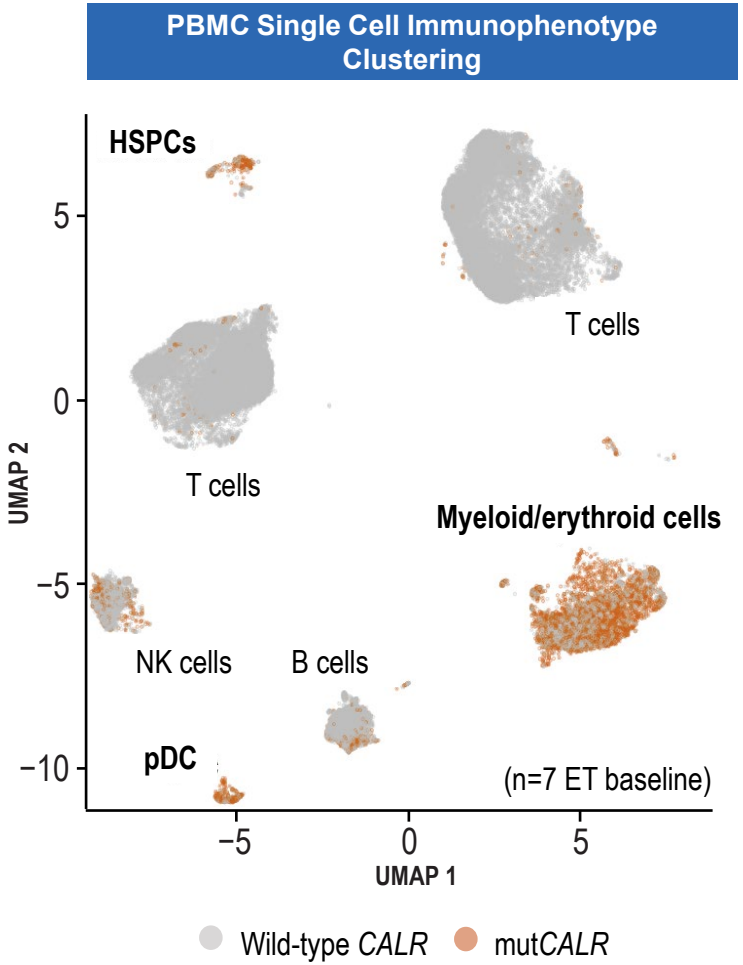
Molecular Responses Are Rapid and Frequent

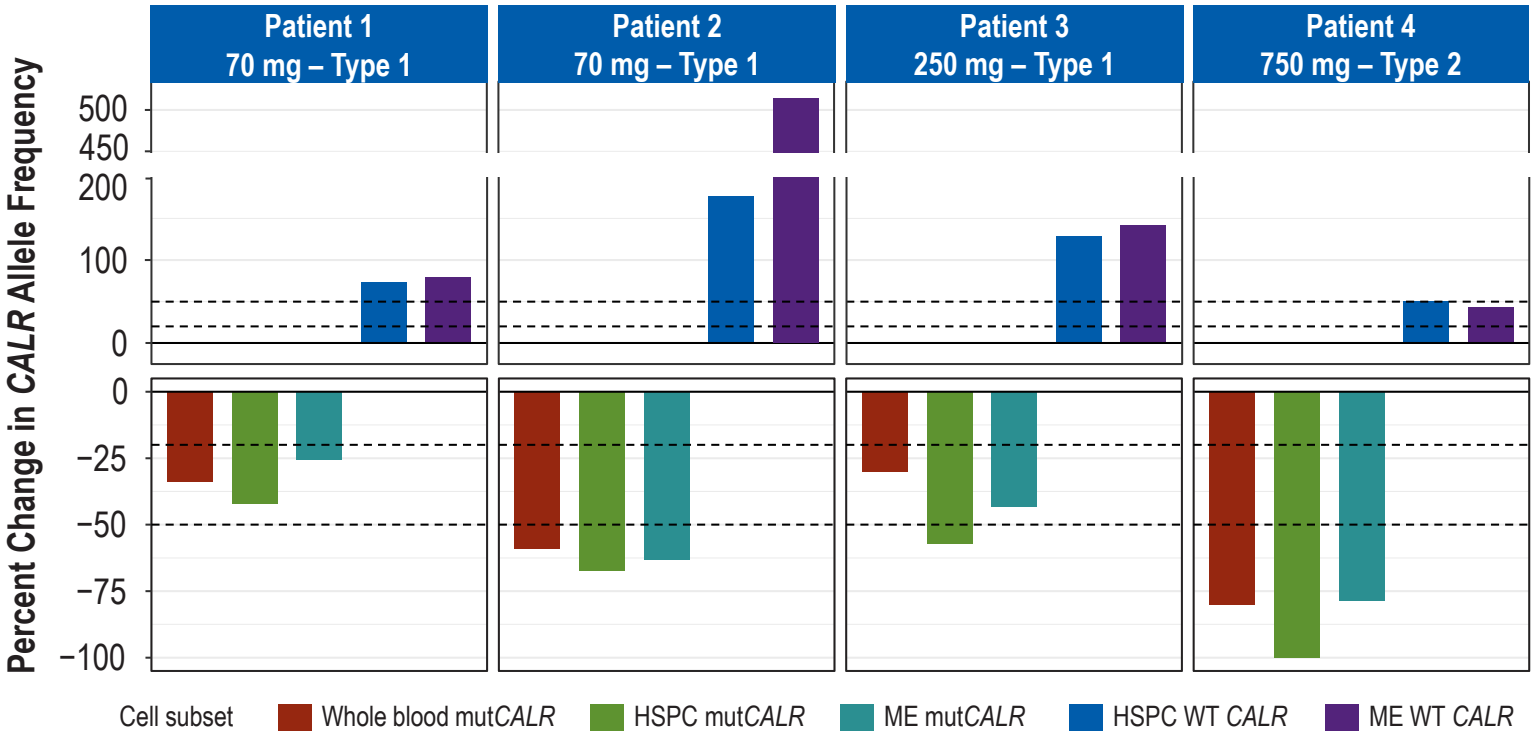
- A reduction in mut*CALR* VAF from baseline occurred in 34/38 (89%) evaluable patients
  - 18/38 (47%) achieved >20% best reduction in VAF
  - 8/38 (21%) achieved >50% best reduction in VAF
- A reduction of ≥20% VAF occurred within 6 cycles of therapy for all 18 responders
- All 18 molecular responders achieved a hematological response of CR or PR



Dotted lines represent 20% and 50% VAF thresholds. 1 cycle = 28 days or 2 doses. CR, complete response; mut*CALR*, mutations in calreticulin; PR, partial response; VAF, variant allele frequency.

Reduction of mut*CALR*$^{+}$ HSPCs and Myeloid/Erythroid Cells in Clinical Responders

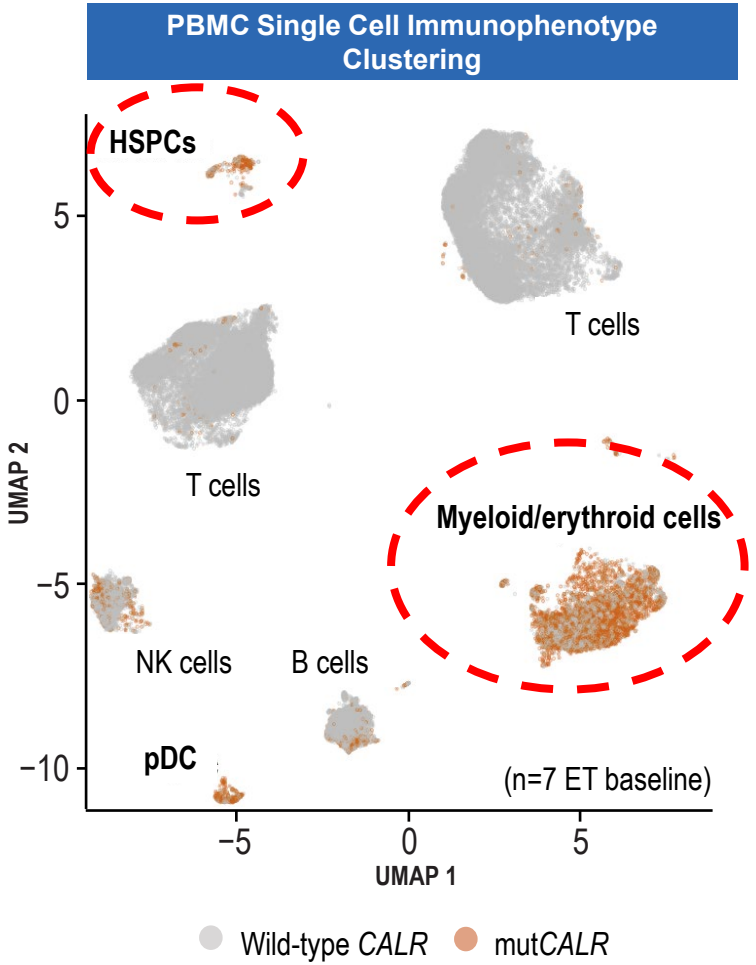


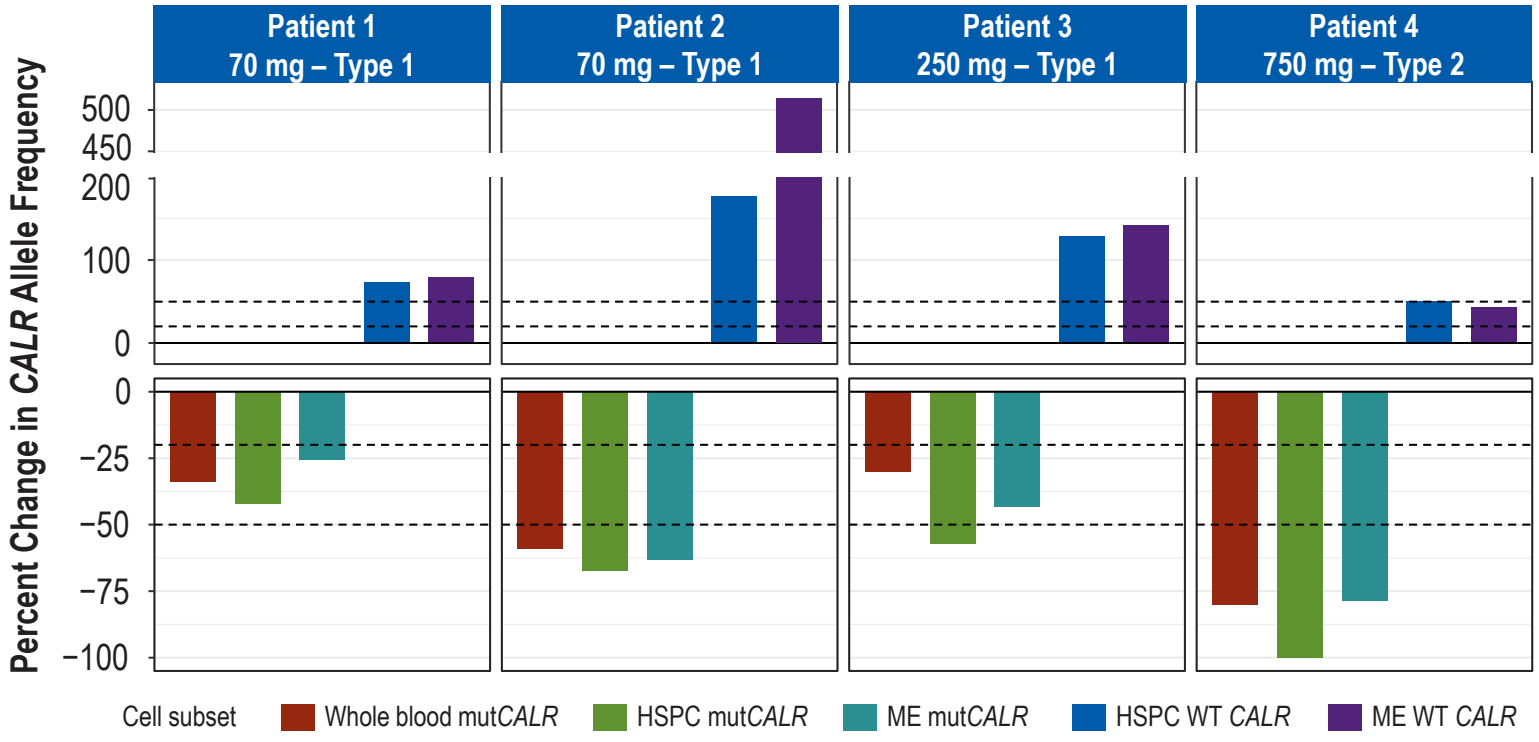


- Reduction of mut*CALR* VAF in HSPCs is deeper than in whole blood VAF
- Reduction of mutant populations (HSPC and ME) is accompanied by significant increases in *CALR* WT cell fractions indicating a shift to normal hematopoiesis

Single-cell sequencing (Tapestri™) conducted on PBMCs collected at C1D1 and C4D1. Cells were clustered and visualized using a UMAP based on cell surface expression of 46 proteins.
CALR, calreticulin; ET, essential thrombocythemia; HSPCs, hematopoietic stem/progenitor cells; ME, myeloid/erythroid; mut*CALR*, mutations in calreticulin; NK, natural killer; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cells; scDNA, single-cell deoxyribonucleic acid; UMAP, Uniform Manifold Approximation and Projection; WT, wild-type; VAF, variant allele frequency.

Reduction of mut*CALR*$^{+}$ HSPCs and Myeloid/Erythroid Cells in Clinical Responders





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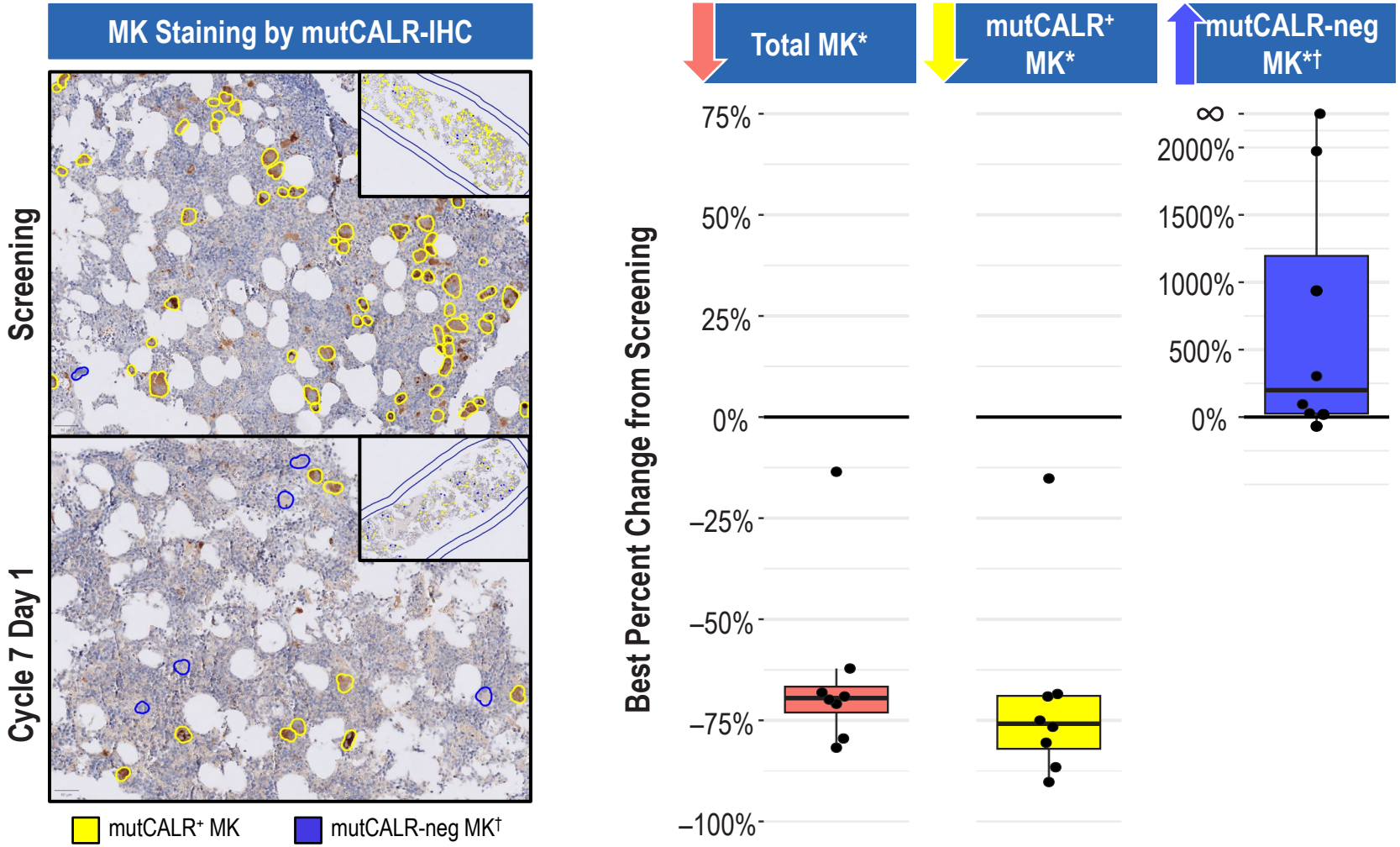
Reduction in mutCALR⁺ Megakaryocytes in the Bone Marrow of Clinical Responders



In 8 patients with hematologic response after 6 cycles of treatment:

- Total number of megakaryocytes (MK) decreased
- Fraction of mutCALR⁺ MKs decreased
- Fraction of mutCALR negative MKs increased

*Best % change in total, mutCALR⁺, or mutCALR-neg MKs in hematologic responders with available data (n=8), dose range 24 mg-250 mg. †Undetectable mutCALR protein by IHC. Bone marrow biopsies stained for mutCALR using mutant-specific IHC. MKs quantified by semi-automated pathology scoring. CALR, calreticulin; IHC, immunohistochemistry; MK, megakaryocytes; mutCALR, mutations in calreticulin.

Conclusions

- In 2 separate phase 1 dose-escalation studies, INCA33989 monotherapy was well tolerated in patients with ET who were resistant/intolerant to prior cytoreductive therapy
  - No dose-limiting toxicities were observed at any dose, and a maximum tolerated dose was not reached
  - 98% of patients remain on treatment at data cutoff (median duration of exposure: 22.6 weeks [range, 0.6-69.2])
- Rapid and sustained hematologic responses were observed in the majority of patients, with a trend toward improved responses at higher doses
- A reduction in peripheral blood mut*CALR* VAF was observed in nearly all patients and correlated with hematologic responses
- Biomarker analysis supports a reduction in mut*CALR* stem/progenitor cells and megakaryocytes in patients achieving a hematologic response
- These findings support the potential of INCA33989, a mutation-specific targeted therapy, to provide durable hematologic responses and modify the disease of patients with mut*CALR* ET

ET, essential thrombocythemia; mut*CALR*, mutations in calreticulin; VAF, variant allele frequency.

Closing Remarks

Pablo Cagnoni, President and Head of Research & Development

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Summary

1. **INCA033989 was well tolerated** with only 1/49 patients discontinuing therapy
2. INCA033989 led to **rapid and sustained normalization of platelets in patients with previously treated ET**
3. **Rapid and sustained reductions in VAF** were observed in most patients, despite the short follow up, and they correlated with hematologic responses
4. **Reduction in mutCALR+ megakaryocytes** in the bone marrow as well as **reduction in mutCALR+ CD34+ cells** in peripheral blood demonstrated the **disease modifying potential** of INCA033989 and offer a **potential path to a cure**

Next Steps for ‘989 Development

Pivotal Trial

Initiate registrational trial in ET by early 2026

MF Data

Present data in patients with MF in 2025

Combo

Accelerate development in MF as single agent and with ruxolitinib

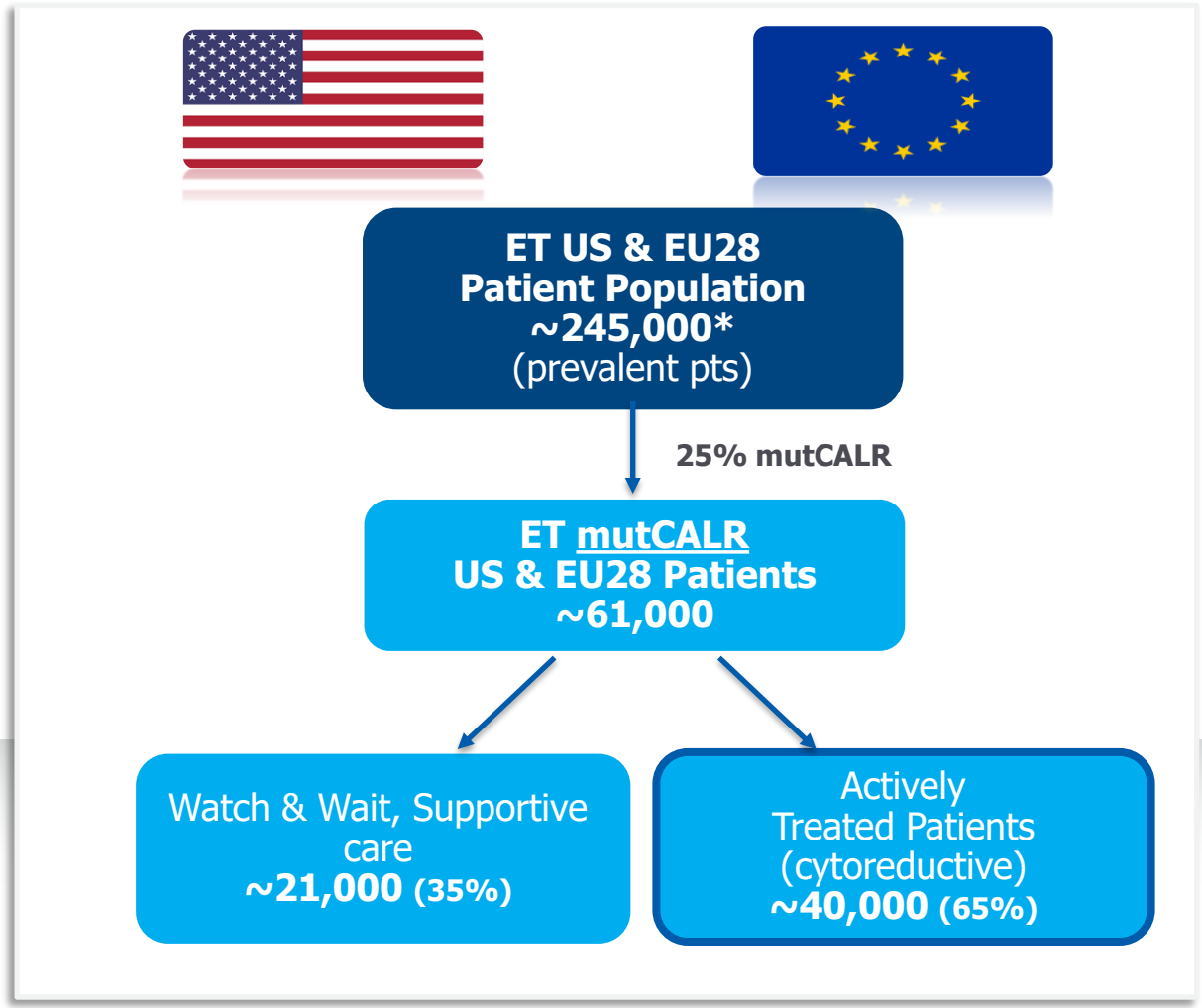
Co-Diagnostic

Collaboration established to develop co-diagnostic

Sub-Q Formulation

Subcutaneous formulation in development

Essential Thrombocythemia: Large Addressable Patient Population

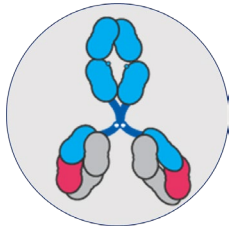


For reference:

There were ~28,000 patients treated with Jakafi in all indications in the US in 2024

* Epi Source: DRG- Prevalence 2026

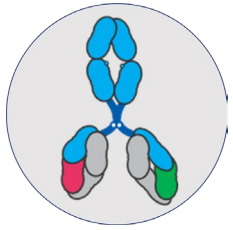
Incyte in MPNs: Continued Innovation as a Path to a Cure



mutCALR mAb

- First-in-Class mutCALR targeted therapy
- Potential optimal balance of efficacy & tolerability
- No competitor mAbs in development

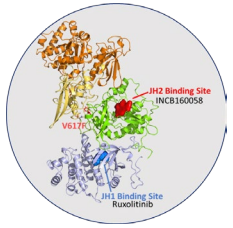
POC in ET demonstrated; Development in MF ongoing



mutCALR x CD3 bispecific

- Distinct cell killing MoA
- Equipotent activity towards all CALR mutation types (Type 1, Type 2 and Other)
- Distinct binding epitope versus mutCALR mAb, no competition for binding

Ph1 Ongoing



JAK2-V617F Inhibitor

- First-in-class, mutation selective JAK2-V617F inhibitor
- Binds pseudokinase domain (JH2), restoring kinase auto-inhibition, prevents cytokine independent signaling.
- Spares cytokine-dependent JAK/STAT signaling

Ph1 Ongoing

2025: A Year of Defining Catalysts

		H1'25		H2'25
Derm / IAI	Ruxolitinib Cream	✓ P3 data (PN)	✓ P3 HS Study Initiation	Peds AD approval
	Povorcitinib	✓ P3 data (HS)	✓ P2 data (CSU)	P2 data (asthma)
	anti-CD122			P1 data
MPN / GVHD	Axatilimab	✓ Q1 launch		
	BETi	Pivotal Study Initiation		
	mutCALR	✓ P1 PoC data (ET)		P1 PoC data (MF)
	JAK2V617Fi	P1 MF PoC data		
	Ruxolitinib XR	✓ Bioequivalence data		
Oncology	Retifanlimab			✓ SCAC approval
	Tafasitamab			FL approval
	Tafasitamab			P3 data (1L DLBCL)
	CDK2i			Pivotal Studies Initiation
	KRASG12D			P1 PoC data
	TGFßR2×PD-1			P1 PoC data

MPN= myeloproliferative neoplasms; GVHD= graft-versus-host disease; IAI= inflammation and autoimmunity; SCAC= squamous cell anal carcinoma; FL= follicular lymphoma; PoC= proof-of-concept; MF= myelofibrosis; DLBCL= diffuse large B-cell lymphoma; AD= atopic dermatitis; PN= prurigo nodularis; HS= hidradenitis suppurativa; CSU= chronic spontaneous urticaria

Q&A

Incyte

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