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Highlights from Phase 1 Clinical Program Evaluating INCA033989, mutCALR antibody, in Myelofibrosis

American Society of Hematology 2025 Annual Meeting

December 7, 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 generally and INCA033989 specifically, including the expansion of the addressable treatment population across all MPNs; planned next steps for INCA033989, including the initiation of pivotal registration studies in the near future and the development of a subcutaneous formulation; and expectations regarding additional planned development for INCA033989, including study initiations, data readouts and discussions with regulators.

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; timing of clinical trials, including initiation and completion; 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 September 30, 2025. Incyte disclaims any intent or obligation to update these forward-looking statements.

Opening Remarks

Pablo Cagnoni, MD
Head of Research & Development

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Today's agenda

01	Welcome & opening remarks	**Pablo Cagnoni, MD** Head of Research & Development
02	Myelofibrosis: Disease overview, treatment goals & current care paradigm	**Claire Harrison, MD, FRCP** Guy's and St Thomas' Hospital
03	Preliminary efficacy & safety results from two Phase 1 dose escalation trials evaluating INCA033989 in patients with myelofibrosis	**John Mascarenhas, MD** Icahn School of Medicine at Mount Sinai
04	Molecular characterization of patients with myelofibrosis & essential thrombocythemia treated with INCA033989	**Bethan Psaila, MD, PhD** University of Oxford
05	Next steps	**Steven Stein, MD** EVP, Chief Medical Officer
06	Q&A	**Incyte Team**

Featured expert speakers

Claire Harrison, MD, FRCP
Deputy Chief Medical Officer at Guy's and St. Thomas' Hospital

Professor of Medicine at Guy's and St. Thomas' Hospital

John Mascarenhas, MD
Director of the Center of Excellence for Blood Cancers and Myeloid Disorders

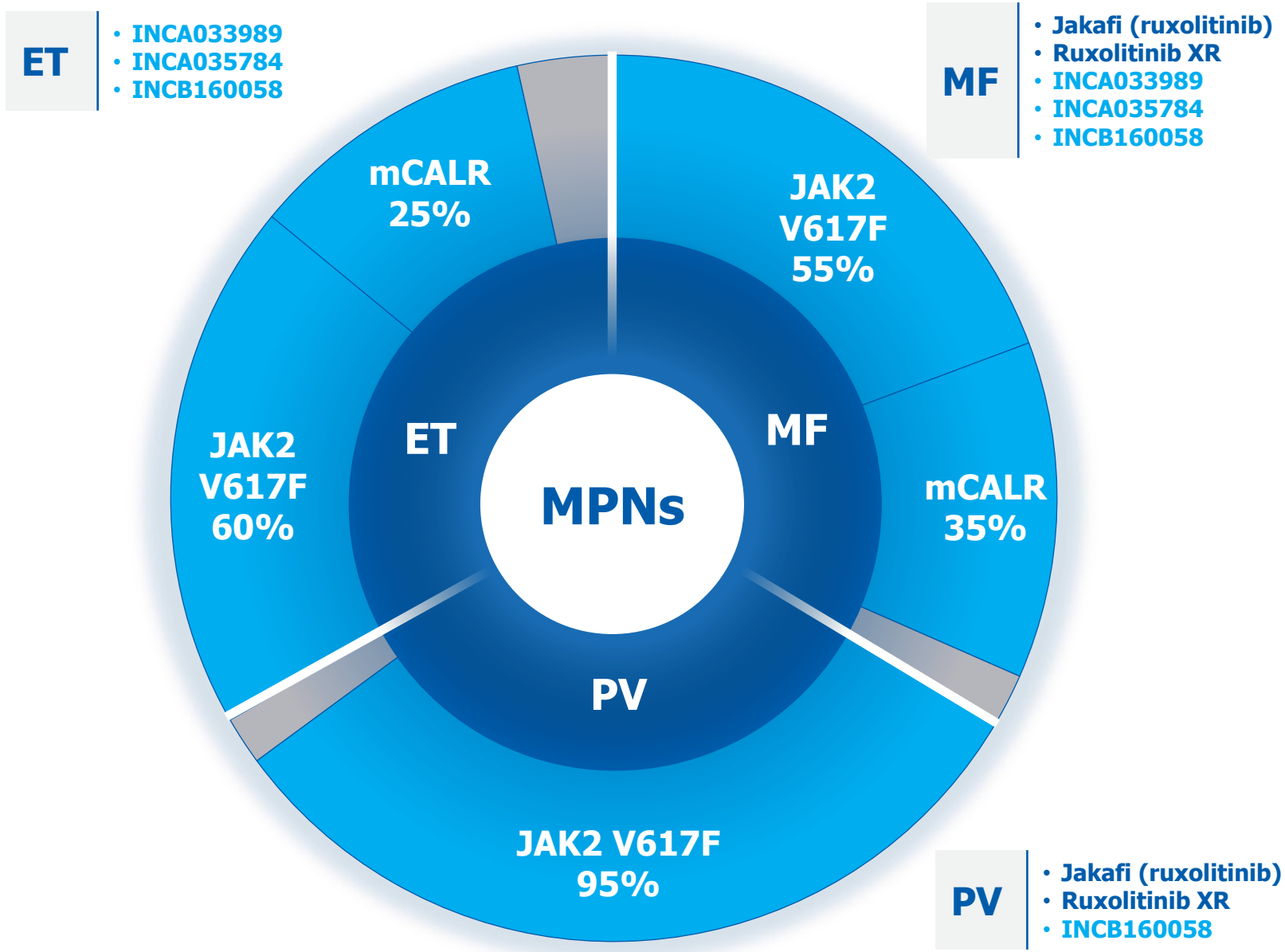
Professor of Medicine at the Icahn School of Medicine at Mount Sinai

Bethan Psaila, MD, PhD
Associate Member of the Oxford Branch of the Ludwig Institute for Cancer Research

Professor in Haematology at the University of Oxford

Delivering solutions across the MPN spectrum

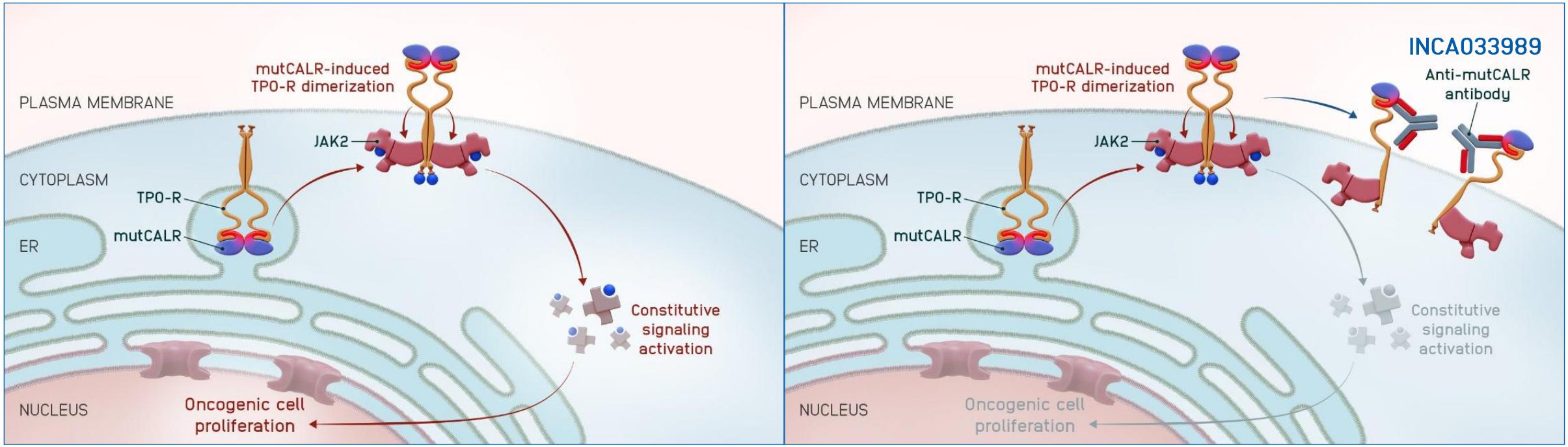
- Expanding addressable treatment population across all MPNs through **symptomatic** and **targeted** therapies
- Pipeline potential to address **85%+** of people living with MPNs



ET, essential thrombocythemia; JAK, Janus kinase; mCALR, mutations of calreticulin; MF, myelofibrosis; MPL, myeloproliferative leukemia; PV, polycythemia vera.

INCA033989: Novel mutant CALR targeted therapy

Monoclonal antibody that selectively targets mutCALR in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells[1]



[1]Reis, et al. *Blood*. 2024;22:2336-2348.

Figure reprinted from Reis E, et al. *Blood*. 2024;144:2336-2348 with permission of Elsevier Inc. Copyright © 2024 American Society of Hematology.

Abbreviations: CALR, calreticulin; MPL, myeloproliferative leukemia protein; mutCALR, mutations of calreticulin; TPO-R, thrombopoietin receptor (MPL).

Proof-of-concept trials capture broad treatment paradigm and anchor future development

ET 989 monotherapy	**MF** 989 monotherapy	**MF** 989 + ruxolitinib	**MF** 989 vs 989 + ruxolitinib
High-risk patients resistant or intolerant to prior cytoreductive therapy ***Breakthrough Therapy Designation (Type 1)****	Patients previously treated with JAK inhibitor who are resistant, refractory, or intolerant to treatment or intermediate to high-risk patients who are ineligible for JAK inhibitor treatment	Intermediate to high-risk patients who exhibiting a suboptimal response to ruxolitinib (≥12 weeks of ruxolitinib treatment)	Intermediate to high-risk treatment-naïve patients

*U.S. FDA granted INCA033989 Breakthrough Therapy Designation in December 2025
989, INCA033989; ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis

Key oral presentations highlights novel mCALR antibody for the treatment of CALR-mutated MPNs

ET 989 monotherapy	**MF** 989 monotherapy	**MF** 989 + ruxolitinib	**MF & ET** Translational
#1024 Safety and efficacy of INCA033989, a novel first in class mutant calreticulin-specific monoclonal antibody, in patients with essential thrombocythemia	**#484** Safety and efficacy of the mutant calreticulin-specific monoclonal antibody INCA033989 as monotherapy or in combination with ruxolitinib in patients with myelofibrosis: preliminary results from dose escalation of two global phase 1 studies		**#71** Molecular characterization of patients with myeloproliferative neoplasms treated with INCA033989 demonstrates selective targeting of CALR mutant hematopoietic cells

989, INCA033989; ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis

Myelofibrosis: Disease overview, treatment goals and current care paradigm

Claire Harrison, MD
Guy's and St Thomas' Hospital

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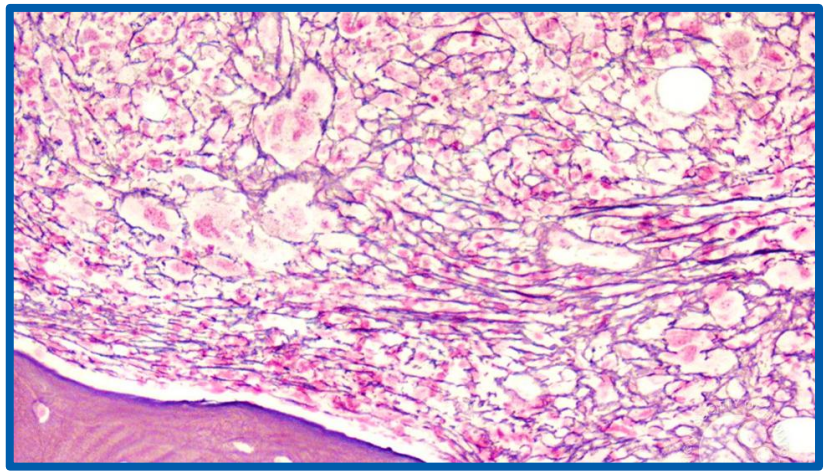
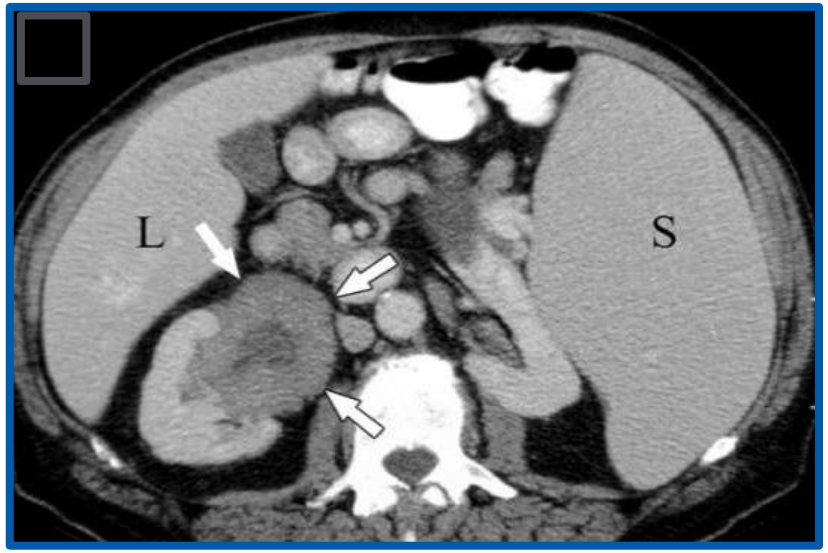
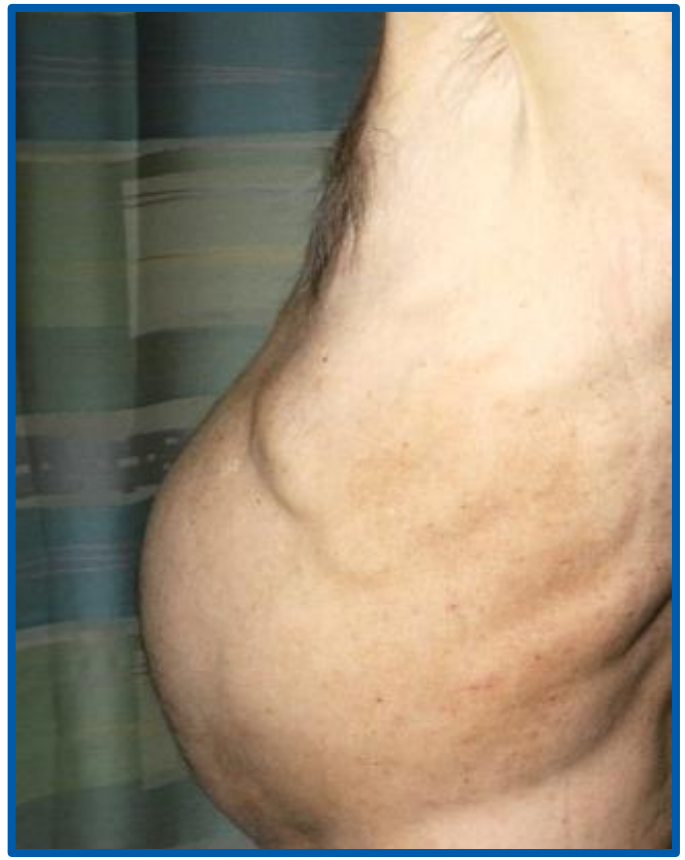
Myelofibrosis overview







◀ Contrast-enhanced CT scan of the upper abdomen showing massive splenomegaly (S), the liver (L), and a renal pelvic mass (arrows) suggesting extramedullary hematopoiesis

Disease characteristics:

- Clonal disorder
- Bone marrow fibrosis
- Splenomegaly & extramedullary hematopoiesis[1,2,a,b]
- Abnormal blood counts:
  - Anemia
  - Thrombocytosis
  - Thrombocytopenia

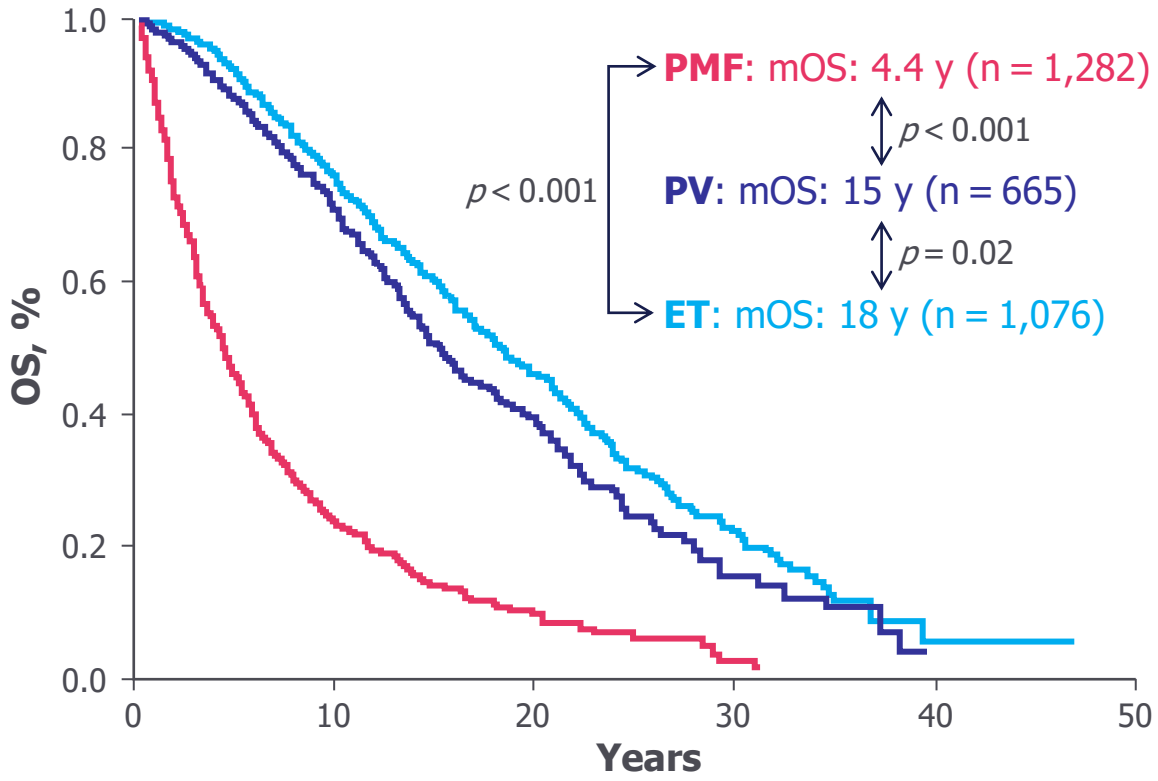
Constitutional symptoms:

- Most common reported symptoms[3,a]
  - Fatigue
  - Early satiety
  - Inactivity
  - Abdominal pain
- MF-related symptoms have been shown to reduce QOL in up to 42% of patients[3]

[a]Figure adapted from Choi H, et al. *Radiology*. 2004;231:52-56. Permission to use granted by RSNA.
[b]Photograph courtesy of Srdan Verstovsek, MD, PhD. MD Anderson Cancer Center. Houston, TX.
[1]Georgiades CS, et al. *AJR Am J Roentgenol*. 2002;179:1239-1243. [2]Choi H, et al. *Radiology*. 2004;231:52-56.
[3]Randhawa J, et al. *J Hematol Oncol*. 2012;5:43. [4]Mesa RA, et al. *Cancer*. 2006;107:361-370.
Abbreviations: CT, computed tomography; PMF, primary myelofibrosis; QOL, quality of life.

Among classic MPNs, MF is associated with the shortest median survival and highest risk of transformation

Comparison of survival in patients with MPNs[1]



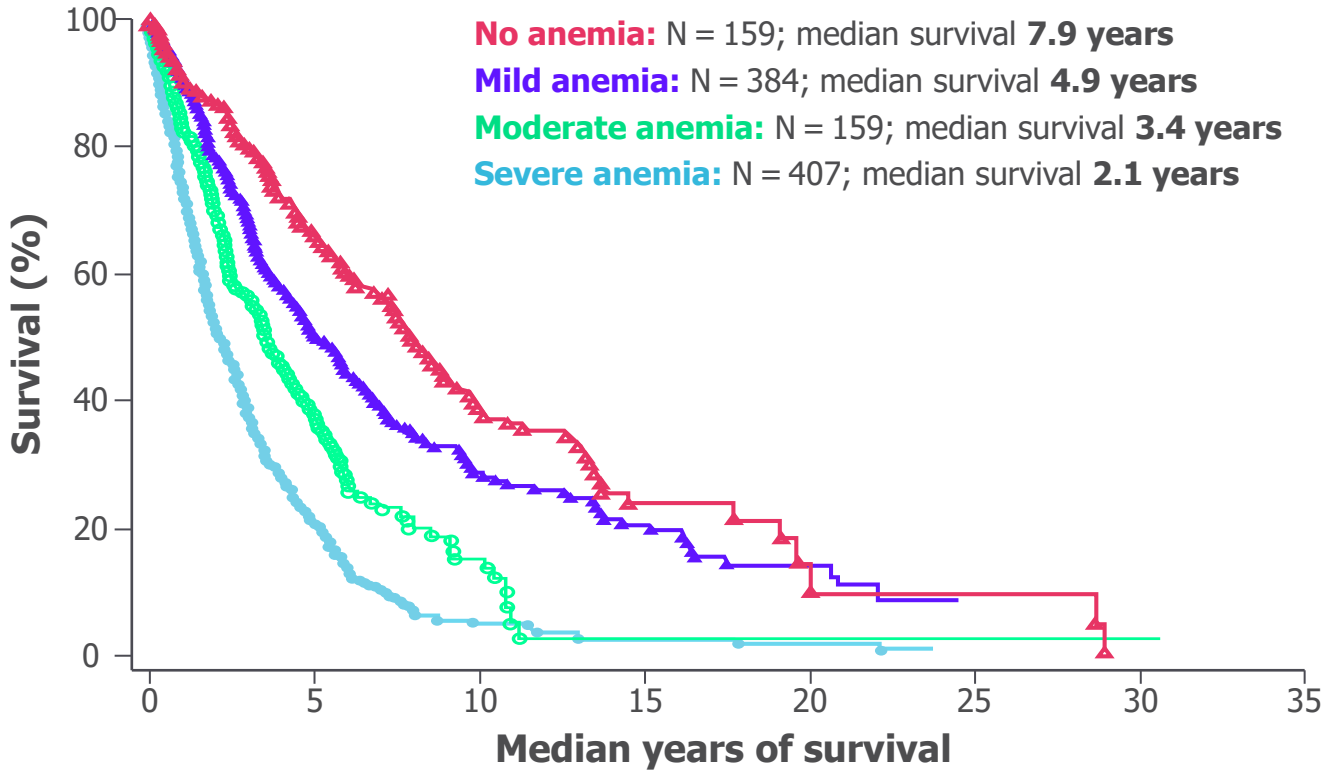
MPN	Median Survival (All Patients)	Risk of Transformation (Per 10 years)
PMF	**4.4 years**	**8 – 23%[2]**
PV	15 years	5 – 15%[3]
ET	18 years	1.4%[4]

1. Modified from Szuber N, et al. *Mayo Clin* Proc. 2019;94:599-610. 2. Mesa RA, et al. Blood. 2005;105:973-977. 3. Finazzi G, et al. Blood. 2005;105:2664-2670. 4. Wolanskyj AP, et al. Mayo Clin Proc. 2006;81:159-166.
ET, essential thrombocythemia; MPN, myeloproliferative neoplasm; mOS, median overall survival; OS, overall survival; PMF, primary myelofibrosis; PV, polycythemia vera.

Anemia in MF is a key predictor of poor prognosis

- **35%** of patients with MF are **anemic at diagnosis**[1]
- **Significantly reduced overall survival** compared to those without anemia*[1]
  - More than **double the risk of death** compared to non-anemic patients
- Anemia in MF leads to fatigue, weakness, reduced exercise tolerance, and **impaired quality of life**
- Anemia **exacerbates other MF symptoms**, such as dyspnea and palpitations, and can limit the ability to tolerate certain therapies
- **Improving anemia** has been shown to be associated with **improved survival**[3]

Survival stratified by degree of anemia[2]



*Hemoglobin <10 g/dL

1. Guglielmelli P, Vannucchi AM. Leuk Res. 2013;37:1429-1431. 2. Nicolosi M, et al. Leukemia 2018;32;1254–18. 3. Palandri F et al., EHA 2025.

Management goals in MF[1,2]

Reduce splenomegaly

Reducing splenomegaly may decrease associated morbidities and improve QOL[3,4]

Alleviate anemia

Anemia is the most common laboratory abnormality and is a negative prognostic factor[6]

Improve symptoms

81% of patients reported that their MF-related symptoms reduced their QOL[5,a]

Improve survival

Despite current therapies, median overall survival is only 4 – 5 years[7]

[a]Based on an analysis of the MPN Landmark survey, a web-based survey that included 65 multiple-choice questions with an estimated completion time of 20-25 minutes. Questions evaluating emotional impact and burden of disease were evaluated on a scale that ranged from 1 (not at all) to 5 (a great deal).

[1]Tefferi A, Vainchenker W. *J Clin Oncol*. 2011;29:573-582. [2]Tefferi A. *Am J Hematol*. 2016;91:1262-1271. [3]Randhawa J, et al. *J Hematol Oncol*. 2012;5:43.[4]Mesa RA, et al. *Cancer*. 2006;107:361-370. [5]Mesa R, et al. *BMC Cancer*. 2016;16:167. [6]Guglielmelli P, Vannucchi AM. *Leuk Res*. 2013;37:1429-1431. [7]Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610.

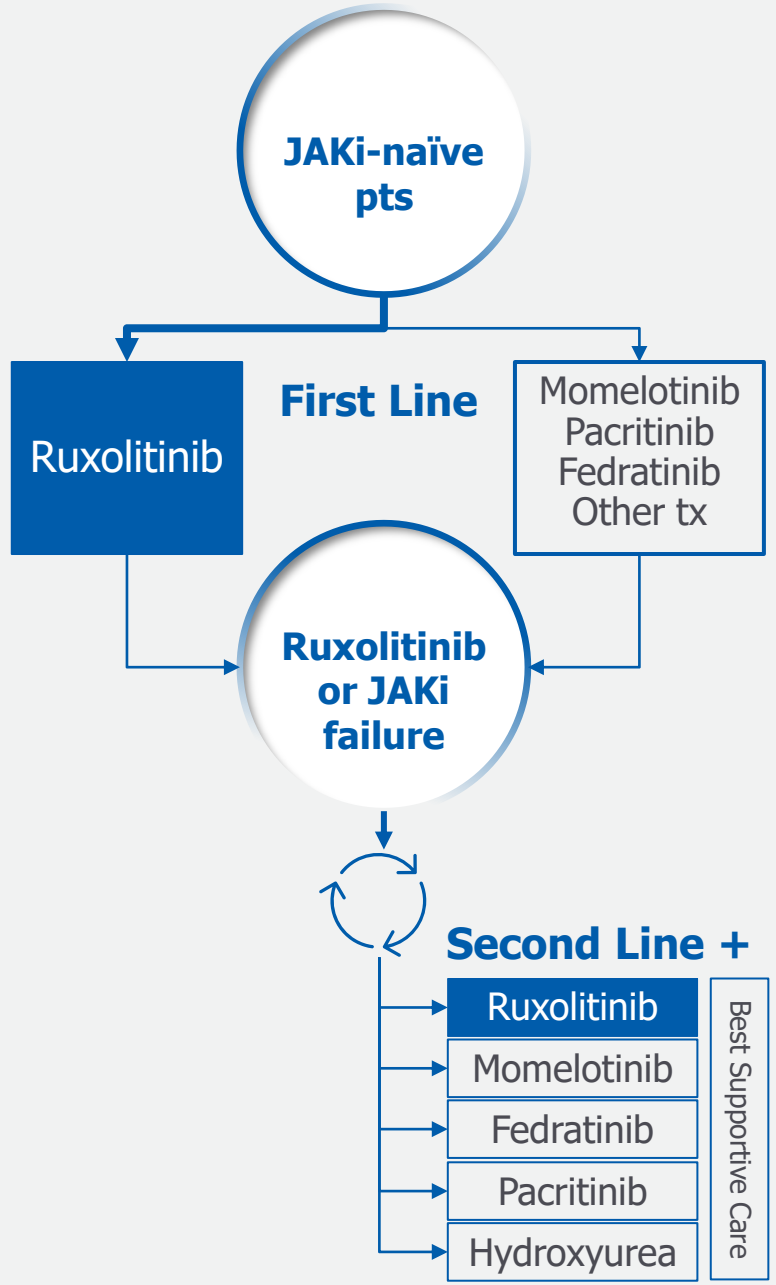
Persistent unmet need for disease-modifying therapies

First Line

- **Jakafi** (ruxolitinib) is the **standard of care** in 1L MF
- Despite all current therapies, **median overall survival is only 4 – 5 years**

Second Line +

- **Post-JAK outcomes are poor**
- **Median survival** following ruxolitinib discontinuation is **14 months**



[1]Passamonti F et al., *Crit Rev Oncol Hematol* 2022; 180: 103862. [2]Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610.
Abbreviations: JAKi, janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; tx, therapy.

Conclusion

- **Myelofibrosis** (MF) is a **clonal**, **progressive myeloproliferative neoplasm** characterized by:
  - Bone marrow fibrosis
  - Extramedullary hematopoiesis with splenomegaly
  - Cytopenias
  - Constitutional symptoms
- Each hallmark of MF contributes to disease burden and prognosis, collectively leading to **impaired quality of life and shortened survival**
- Goals of MF management remain only partially met
- Current treatments improve spleen size, symptoms and survival (ruxolitinib) but patients ultimately progress:
  - **Median overall survival of 4 – 5 years**
- **Unmet need remains** for innovative approaches **targeting underlying molecular drivers**

Preliminary efficacy and safety results from two Phase 1 dose escalation trials evaluating INCA033989 in patients with myelofibrosis

John Mascarenhas, MD
Icahn School of Medicine at Mount Sinai

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CALR mutations are frequent in myelofibrosis with no mutant-specific treatment available

- **Myelofibrosis** (MF) is a myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis, anemia, splenomegaly, debilitating symptoms, morbidity, and mortality[1]
- Mutations in exon 9 of calreticulin (mut*CALR*) are found in **~25-35%** of patients with MF[2,3]
- **Higher *CALR* variant allele frequency** (VAF) in MF has been associated with **more advanced disease**, including anemia and elevated peripheral blasts[4]
- Current treatments in MF are **not mutant targeted** and have limited efficacy in reducing mut*CALR* VAF[5]

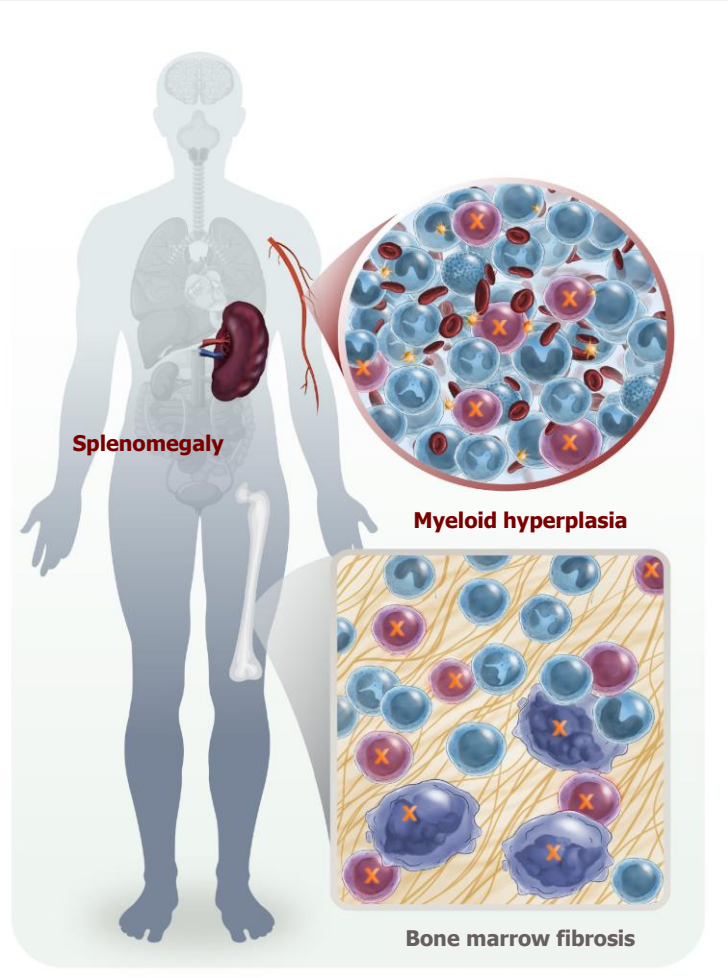


Illustration by DrawImpacts.

1. Arber DA, et al. *Blood.* 2016;127:2391-2405. 2. Klampfl T, et al. *N Engl J Med.* 2013;369:2379-2390. 3. Nangalia J, et al. *N Engl J Med.* 2013;369:2391-2405. 4. Guglielmelli P, et al. *Blood Cancer J.* 2023;13:21.
5. Tefferi A. *Am J Hematol.* 2023;98:801-821..

Phase 1 program evaluating INCA033989 in patients with a CALR mutation

MF
- ≥18 years of age with a diagnosis of primary or post-ET MF
- Presence of mutCALR exon 9
- Spleen volume imaging ≥ 450 mL or palpable splenomegaly of ≥5 cm

Intolerant, resistant after ≥12 weeks, or ineligible for JAKi treatment

Prior ruxolitinib treatment for ≥12 weeks with a suboptimal response

Intermediate to high-risk treatment-naïve patients

ET
- High risk; documented resistance/intolerance to ≥1 line of prior cytoreductive therapy

Primary Endpoints
- Dose-limiting toxicities
- Treatment-emergent adverse events

Secondary Endpoints
- SVR25 and SVR35 at week 24*
- Anemia response[1]
- Symptom improvement based on the MPN-SAF TSS
- Changes in allele burden of mut*CALR*

- **INCA033989-101** (NCT05936359; outside the US) and **INCA033989-102** (NCT06034002; US only) are Phase 1 open-label studies evaluating INCA033989 in patients with high-risk ET or MF (as monotherapy or in combination with ruxolitinib)
- Administered intravenously every 2 weeks (24-2500mg)

1. Tefferi A. Blood. 2024;144(17):1813-1820.
*A spleen response requires confirmation by MRI or CT showing ≥25% or ≥35% spleen volume reduction.
CALR, calreticulin; CT, computed tomography; ET, essential thrombocythemia; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; MRI, magnetic resonance imaging; mut*CALR*, mutations of calreticulin; RDE, recommended dose for expansion; TSS, total symptom score.

Demographics and disease characteristics (monotherapy)

Variable	INCA033989 (N=52)
Median age (range), years	59.5 (34, 76)
Female, n (%)	17 (32.7)
Median time from initial diagnosis (range), years	7.4 (0, 25.3)
DIPSS risk status, n (%)	
Low risk	6 (11.5)
INT-1 risk	21 (40.4)
INT-2 risk	25 (48.1)
High risk	0
CALR exon 9 mutation type, n (%)	
Type 1	30 (57.7)
Type 2	11 (21.2)
Other	11 (21.2)
Median *CALR* VAF (range),* %	36 (24, 53)
No prior JAKi therapy, n (%)	10 (19.2)

Variable	INCA033989 (N=52)
Median platelets (range), GI/L	316.5 (41, 1290)
Median leukocytes (range), GI/L	6.1 (1.5, 27.2)
Median hemoglobin (range), g/dL	10.0 (7.0, 14.3)
Median MPN-SAF TSS (range)	21 (0, 65)
Median spleen volume (range), mL	1372 (226, 5060)
INCA033989 dose level, n (%)	
24 mg	3 (5.8)
50 mg	3 (5.8)
70 mg	3 (5.8)
100 mg	3 (5.8)
200 mg	5 (5.8)
250 mg	4 (7.7)
400 mg	4 (7.7)
750 mg	13 (25.0)
1500 mg	9 (17.3)
2500 mg	5 (5.8)

Data cutoff: September 25, 2025.
*Measured centrally in peripheral blood by next-generation sequencing (INCA033989 monotherapy).
CALR, calreticulin; DIPSS, Dynamic International Prognostic Scoring System; INT, intermediate; JAKi, Janus kinase inhibitor; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; TSS, total symptom score; VAF, variant allele frequency.

989 monotherapy is well tolerated in patients with MF

Summary of TEAEs

TEAE, n (%)	INCA033989 (N=52)
Any TEAE	50 (96.2)
Treatment-related	30 (57.7)
Grade ≥3	16 (30.8)
Serious	5 (9.6)*
Fatal	0
Discontinuation due to TEAEs	2 (3.8)†
Dose reduction due to TEAEs	2 (3.8)‡
Infusion interruption due to TEAEs	3 (5.8)
Dose delay due to TEAEs	12 (23.1)
Dose-limiting toxicity	0

- **86.5%** patients were still receiving treatment‖
- **No dose-limiting toxicities** were observed; the maximum tolerated dose was not reached (dose range 24-2500 mg)
- 11 patients experienced increased AST; 9 of 11 resolved (2 Grade 1 ongoing) at the time of data cut off
  - Roughly half (45%, n=5) had Grade 1 AST elevations at baseline
  - One (50mg) Grade 3 AST elevation; resolved within 6 days with dose reduction; patient subsequently increased to 1500mg and remains on treatment
  - No dose delays or discontinuations due to AST elevations
- No association of TEAEs with dose was observed

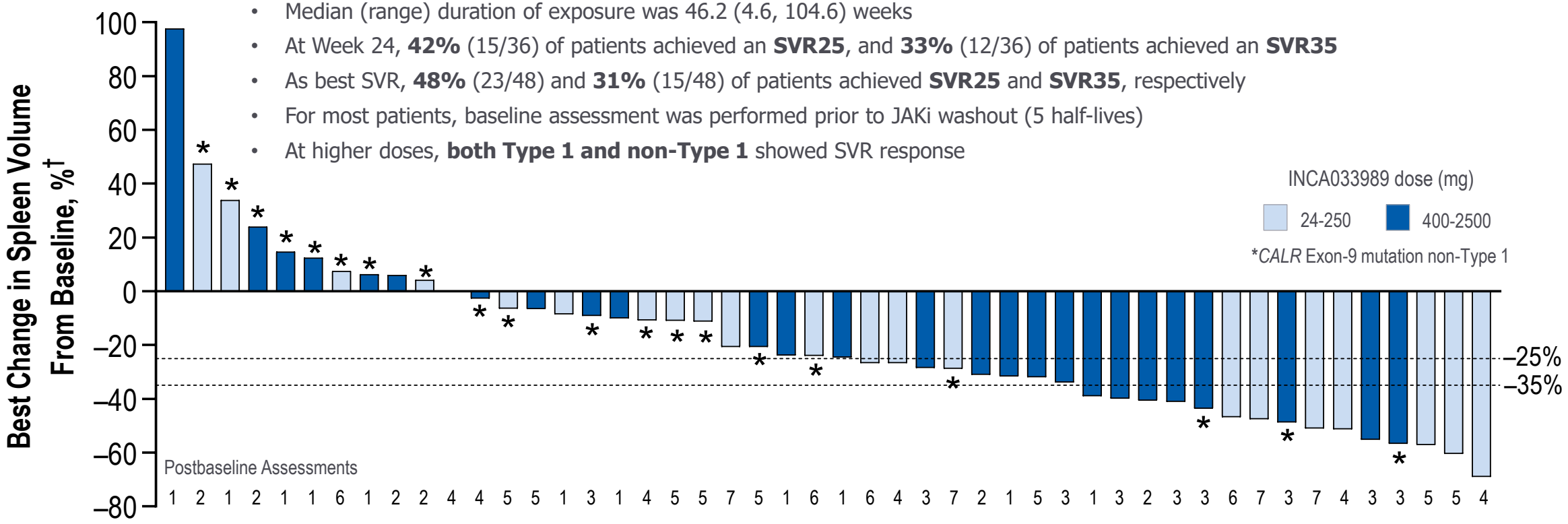
Most Common TEAEs (≥15%)

	Any Grade	Grade 1	Grade 2	Grade ≥3§
Anemia	16 (30.8)	7 (13.5)	5 (9.6)	4 (7.7)
Fatigue	14 (26.9)	9 (17.3)	5 (9.6)	0
Thrombocytopenia	13 (25.0)	7 (13.5)	2 (3.8)	4 (7.7)¶
Arthralgia	11 (21.2)	6 (11.5)	5 (9.6)	0
AST increased	11 (21.2)	8 (15.4)	2 (3.8)	1 (1.9)
Cough	11 (21.2)	9 (17.3)	2 (3.8)	0
Diarrhea	11 (21.2)	10 (19.2)	1 (1.9)	0
Headache	11 (21.2)	7 (13.5)	4 (7.7)	0
Leukopenia	11 (21.2)	1 (1.9)	6 (11.5)	4 (7.7)¶
Nausea	11 (21.2)	9 (17.3)	2 (3.8)	0
Pruritus	11 (21.2)	10 (19.2)	1 (1.9)	0
Hyperglycemia	10 (19.2)	6 (11.5)	3 (5.8)	1 (1.9)
Neutropenia	10 (19.2)	0	5 (9.6)	5 (9.6)¶
Nasal congestion	8 (15.4)	6 (11.5)	2 (3.8)	0
Pain in extremity	8 (15.4)	7 (13.5)	1 (1.9)	0

*Abdominal pain and tendonitis (70 mg); MBL (progressed to MCL) and small intestinal obstruction (n=1; 400 mg); arthritis (n=1; 1500 mg); basal cell carcinoma (n=1; 100 mg); and pyrexia (n=1; 1500 mg). All serious TEAEs were considered unrelated to INCA033989, except tendonitis.
†MBL (progressed to MCL; n=1; 400 mg) and neutropenia (n=1; 750 mg). ‡AST increase (n=1) and thrombocytopenia (n=1). §Other grade ≥3 TEAEs: abdominal pain (n=2), dental caries, hypertension, joint effusion, lipase increased, MBL (progressed to MCL), edema peripheral, small intestinal obstruction, tendonitis, and viral upper respiratory tract infection (each n=1). ¶Grade 4 (n=2). ‖Adverse event (n=2); lack of efficacy (n=2); physician decision (n=1); progressive disease (n=2).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MBL, monoclonal B-cell lymphocytosis; MCL, mantle cell lymphoma; n, number of individual patients.

Clinically meaningful reductions in spleen volume observed

- Median (range) duration of exposure was 46.2 (4.6, 104.6) weeks
- At Week 24, **42%** (15/36) of patients achieved an **SVR25**, and **33%** (12/36) of patients achieved an **SVR35**
- As best SVR, **48%** (23/48) and **31%** (15/48) of patients achieved **SVR25** and **SVR35**, respectively
- For most patients, baseline assessment was performed prior to JAKi washout (5 half-lives)
- At higher doses, **both Type 1 and non-Type 1** showed SVR response



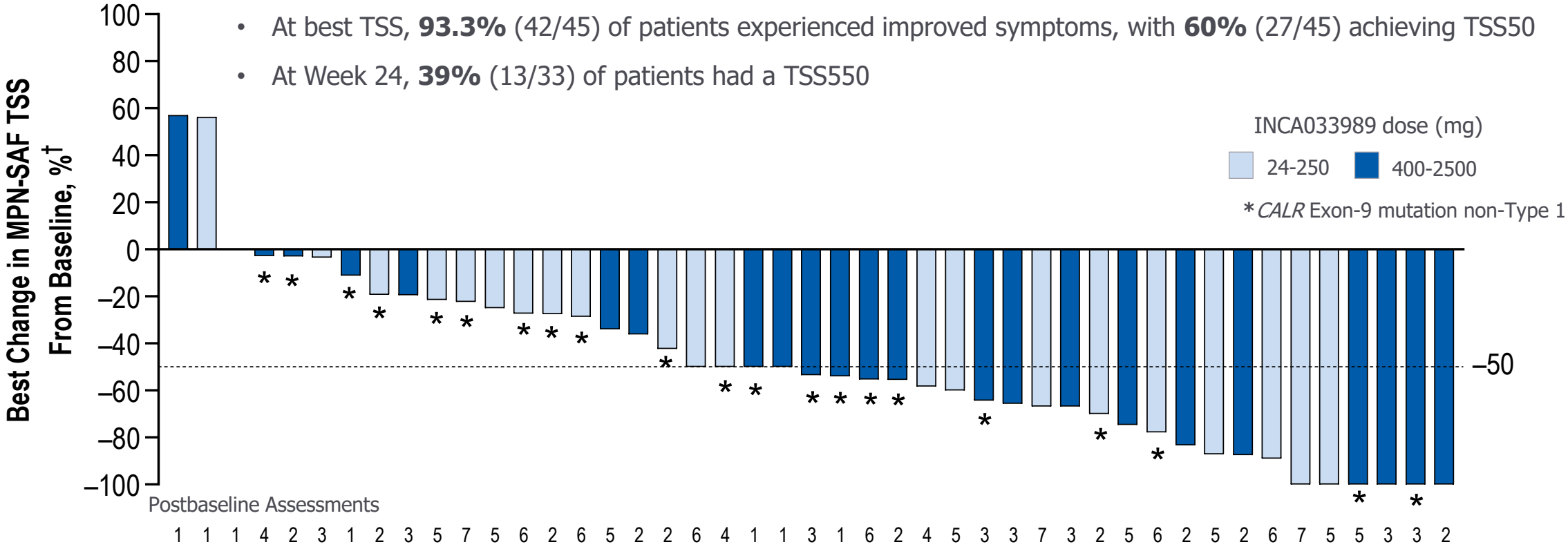
SVR at Week 24 (N=36)

	Total	No Prior JAKi	R/R or Intolerant to JAKi‡
SVR25, % (n/N)	**41.7% (15/36)**	71.4% (5/7)	34.5% (10/29)
SVR35, % (n/N)	**33.3% (12/36)**	57.1% (4/7)	27.6% (8/29)

†N=48; 4 patients excluded due to lack of postbaseline assessments but remain on study. Postbaseline assessments performed every 12 weeks. ‡ R/R or intolerant to JAKi, including 7 patients with incomplete data (6 of 7 known prior JAKi treatment ≥12 weeks).
JAKi, Janus kinase inhibitor; R/R, relapsed/refractory; SVR25, spleen volume reduction ≥25%; SVR35, spleen volume reduction ≥35%.

Symptom benefit observed in vast majority of treated patients

- At best TSS, **93.3%** (42/45) of patients experienced improved symptoms, with **60%** (27/45) achieving TSS50
- At Week 24, **39%** (13/33) of patients had a TSS550



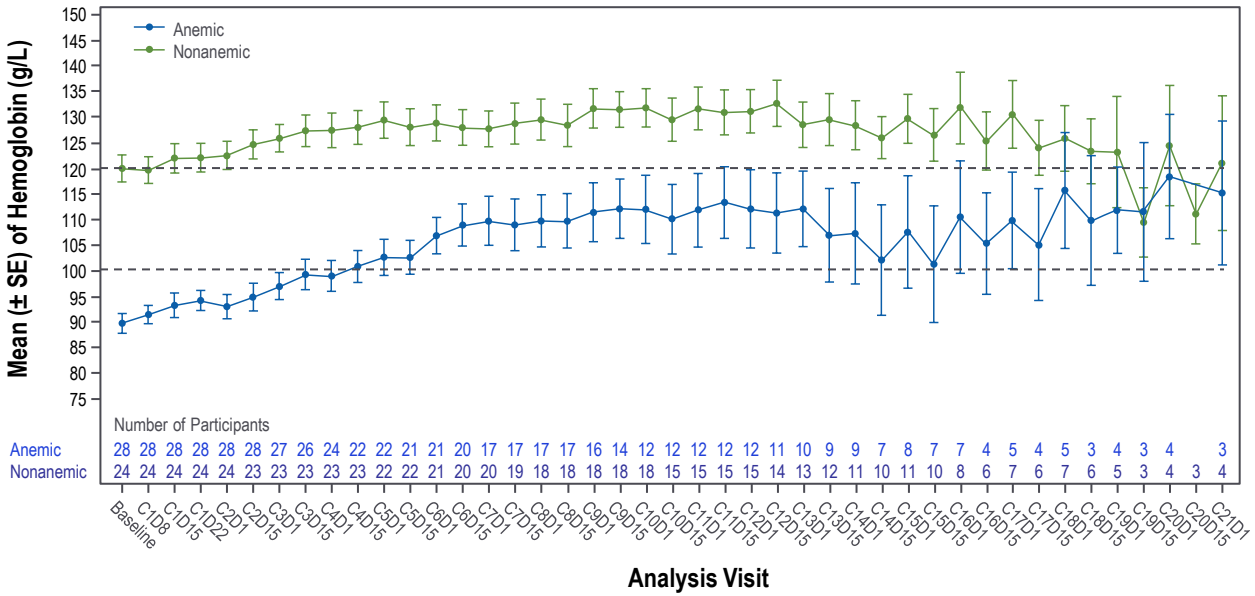
TSS50 at Week 24 (N=33)

	Total	No Prior JAKi‡	R/R or Intolerant to JAKi§
TSS50, % (n/N)	**39.4% (13/33)**	60.0% (3/5)	35.7% (10/28)

†N=45; 7 patients excluded due to lack of postbaseline assessment. Postbaseline assessments performed every 12 weeks. § R/R or intolerant to JAKi, including 7 patients with incomplete data (6 of 7 known prior JAKi treatment ≥12 weeks).
JAKi, Janus kinase inhibitor; MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; R/R, relapsed/refractory; TSS, total symptom score; TSS50, ≥50% reduction in MPN-SAF TSS.

Robust anemia improvements observed with 989 monotherapy

Mean Hemoglobin During Study by Anemic Status*



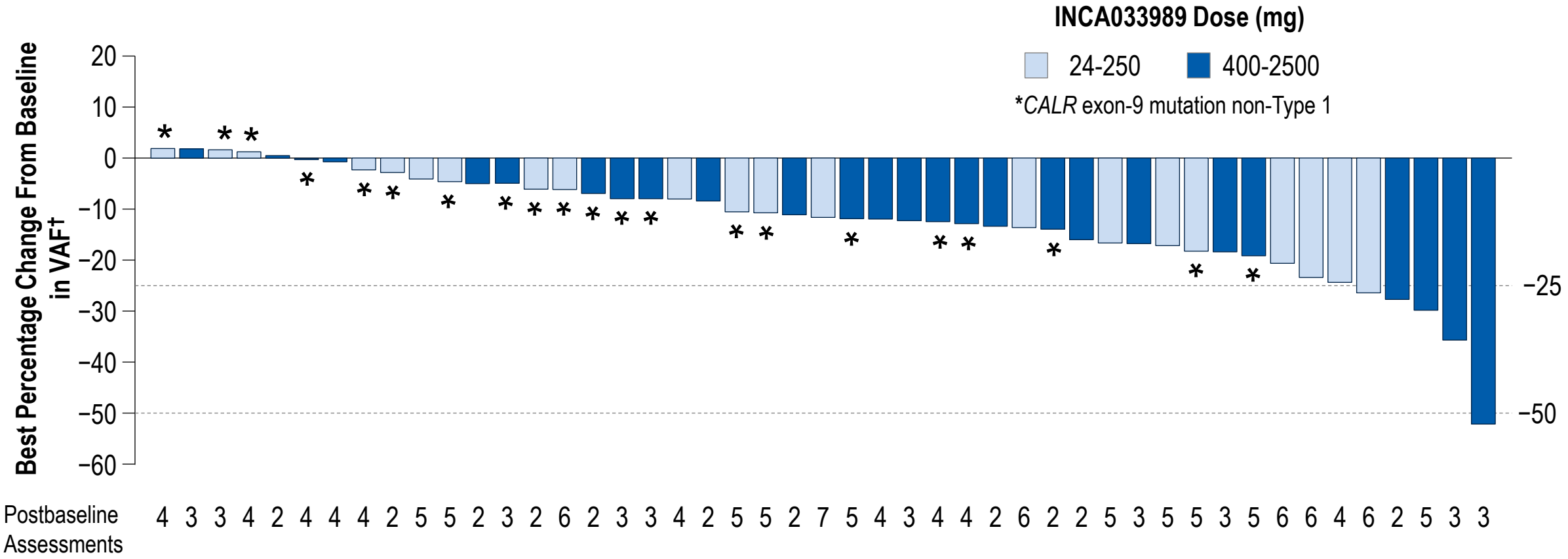
Best Anemia Response in Evaluable Patients

Variable	Total (N=25)	TDA (N=5)	Non-TDA (N=20)
Best anemia response, n (%)			
Major response	10 (40.0)	1 (20.0)	9 (45.0)
Minor response	4 (16.0)	2 (40.0)	2 (10.0)
Stable anemia	8 (32.0)	1 (20.0)	7 (35.0)
Progressive anemia	2 (8.0)	1 (20.0)	1 (5.0)
Missing†	1 (4.0)	0	1 (5.0)

- At baseline, median (range) hemoglobin among patients with anemia was 92 (70, 108) g/L
- **Anemia response occurred in 56%** of evaluable‡ anemic patients, with most (40%) achieving a **major response**
- **Hemoglobin remained stable** in patients who were non-anemic at baseline

*Criteria for baseline anemia and response based on Tefferi A. *Blood.* 2024;114:1813. Major anemia response for patients with TDA: no transfusions for 12 weeks and rolling 12-week average hemoglobin increase of ≥1.5 g/dL from pretreatment baseline. Major anemia response for patients with non-TDA: rolling 12-week average hemoglobin increase of ≥1.5 g/dL from pretreatment baseline (also requires no transfusions). Dotted lines indicate anemia threshold (100 g/L) and lower limit of normal (120 g/L). †Patient who terminated treatment before 12 weeks. ‡3/28 anemic patients were not evaluable for response due to missing data at 12 weeks.
TDA, transfusion-dependent anemia.

Most patients experienced VAF reduction with monotherapy



- A **reduction in mut*CALR* VAF** from baseline occurred in **89.4%** (42/47) of patients with ≥1 postbaseline VAF measurement
  - 5/47 (10.6%) achieved ≥25% best reduction in VAF

*N=47. 5 patients were excluded due to lack of postbaseline assessment. Postbaseline assessments performed C2D15, C4D1, and every 3 cycles thereafter.
C, cycle; D, day; MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; mut*CALR*, mutations of calreticulin; TSS, total symptom score; VAF, variant allele frequency.

Demographics and disease characteristics (combination)

Variable	INCA033989 + Ruxolitinib (N=20)
Median age (range), years	61.0 (38, 82)
Female, n (%)	4 (20.0)
Median time from initial diagnosis (range), years	3.1 (0.4, 16.4)
DIPSS risk status, n (%)	
Low risk	0
INT-1 risk	8 (40.0)
INT-2 risk	9 (45.0)
High risk	3 (15.0)
CALR exon 9 mutation type, n (%)	
Type 1	12 (60.0)
Type 2	7 (35.0)
Other	1 (5.0)
Median *CALR* VAF (range),* %	39 (30, 85)
Mean baseline ruxolitinib daily dose (range), mg	33.5 (10, 50)

Variable	INCA033989 + Ruxolitinib (N=20)
Median platelets (range), GI/L	229.5 (76, 506)
Median leukocytes (range), GI/L	10.6 (2.4, 85.0)
Median hemoglobin (range), g/dL	9.4 (7.2, 12.6)
Median MPN-SAF TSS (range)	15.5 (3, 56)
Median spleen volume (range), mL	2351 (848, 5338)
INCA033989 dose level, n (%)	
24 mg	N/A
50 mg	N/A
70 mg	3 (15.0)
100 mg	N/A
200 mg	N/A
250 mg	5 (25.0)
400 mg	N/A
750 mg	5 (25.0)
1500 mg	4 (20.0)
2500 mg	3 (15.0)

Data cutoff: September 25, 2025.
*Measured centrally in peripheral blood by next-generation sequencing (INCA033989 + ruxolitinib, n=18).
CALR, calreticulin; DIPSS, Dynamic International Prognostic Scoring System; INT, intermediate; JAKi, Janus kinase inhibitor; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; N/A, not applicable; TSS, total symptom score; VAF, variant allele frequency.

989 is well tolerated in combination with ruxolitinib in patients with MF

Summary of TEAEs

TEAE, n (%)	INCA033989 N=20
Any TEAE	20 (100.0)
Treatment-related*	13 (65.0)
Grade ≥3	11 (55.0)
Serious	5 (25.0)†
Fatal	0
Discontinuation* due to TEAEs	2 (10.0)‡
Dose reduction* due to TEAEs	1 (5.0)
Infusion interruption* due to TEAEs	1 (5.0)
Dose delay* due to TEAEs	8 (40.0)
Dose-limiting toxicity	0

Most Common TEAEs (≥15%)

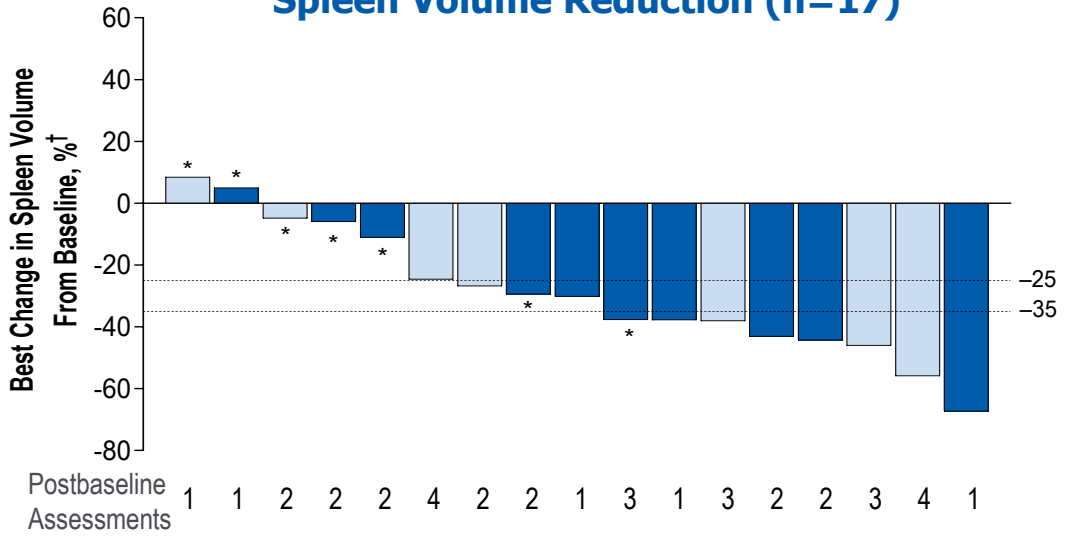
TEAE,¶¶ n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3§
Anemia	9 (45.0)	2 (10.0)	1 (5.0)	6 (30.0)¶
Thrombocytopenia	7 (35.0)	3 (15.0)	2 (10.0)	2 (10.0)
ALT increased	4 (20.0)	2 (10.0)	2 (10.0)	0
Diarrhea	4 (20.0)	4 (20.0)	0	0
Fatigue	4 (20.0)	4 (20.0)	0	0
AST increased	3 (15.0)	2 (10.0)	1 (5.0)	0
Cough	3 (15.0)	1 (5.0)	2 (10.0)	0

- Overall, **85%** (n=17) patients were **still receiving treatment** and 15% (n=3) discontinued treatment at the time of data cutoff‖
- **No dose-limiting toxicities** were observed; the maximum tolerated dose was not reached (dose range 70-2500 mg)
- Four patients experienced increased AST and/or ALT; all events were Grade 1 or 2; 2 (Grade 1) events ongoing at the time of data cut

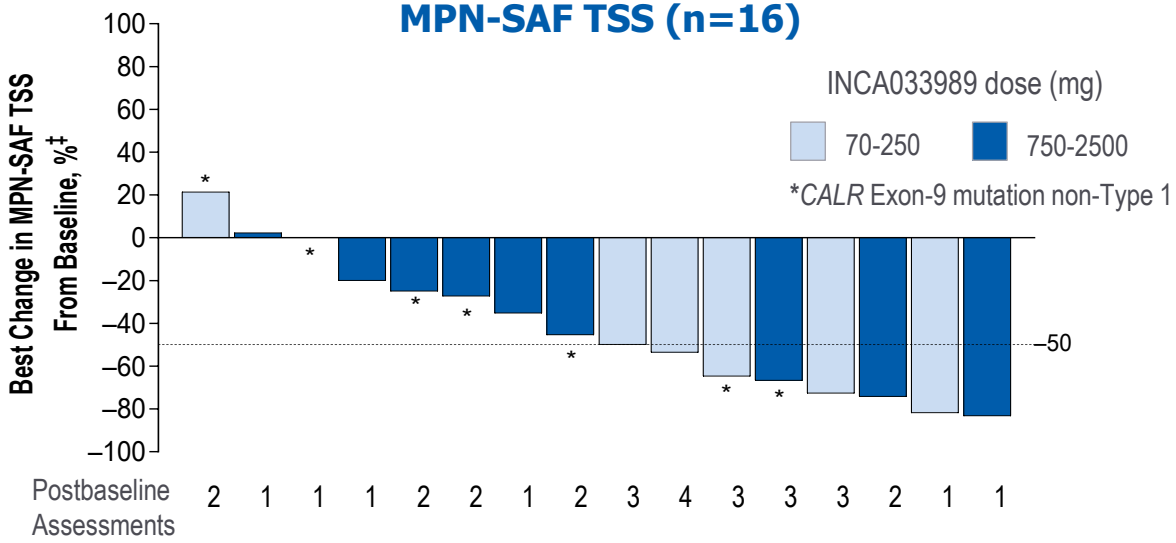
*Related to INCA033989. †Acute myocardial infarction (n=1; 750 mg); anemia (n=1; 1500 mg); basal cell carcinoma (n=1; 250 mg); diffuse large B-cell lymphoma (n=1; 70 mg); stomatitis (n=1; 750 mg). ‡Anemia (n=1; 250 mg); diffuse large B-cell lymphoma (n=1; 70 mg). §Other grade ≥3 TEAEs: neutropenia (n=2), abscess limb, acute myocardial infarction, diffuse large B-cell lymphoma, obstructive sleep apnea syndrome, and stomatitis (each n=1). ¶Grade 4 (n=1). ‖Adverse event (n=2); physician decision (n=1). ¶¶Patients were counted once under the highest grade.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; MF, myelofibrosis; n, number of individual patients; TEAE, treatment-emergent adverse event.

Most patients experienced spleen volume reductions and symptom improvements with 989 + ruxolitinib

Spleen Volume Reduction (n=17)

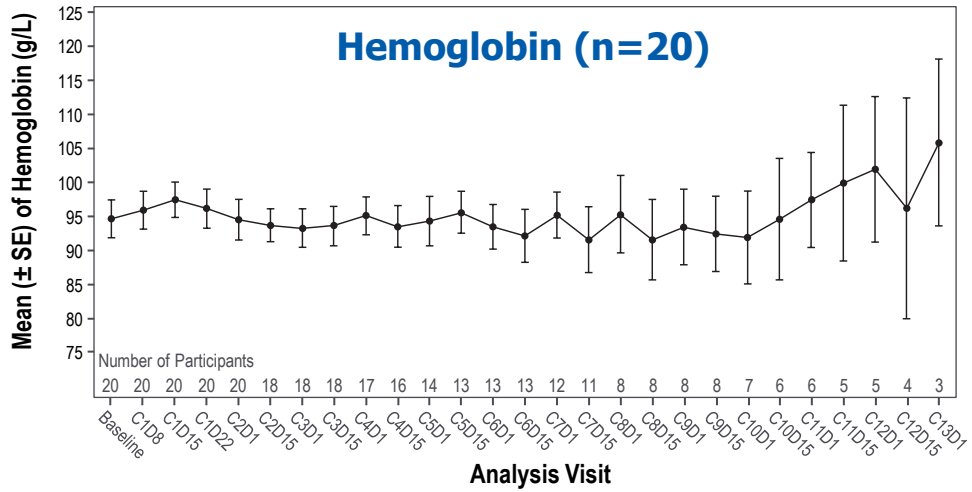


MPN-SAF TSS (n=16)



- As best SVR, **65%** (11/17) achieved an **SVR25**, and **47%** (8/17) of patients achieved an **SVR35**
- At Week 24, **50%** (6/12) and **25%** (3/12) had an **SVR25** and **SVR35**, respectively
- **81%** (13/16) of patients experienced symptom improvement, with **33%** (3/9)§ achieving **TSS50** at week 24
- Among 14 evaluable patients,¶ **86%** had **stable anemia** during the study (TDA, n=1; non-TDA, n=11); 1 patient (non-TDA) had a major anemia response[1]

Hemoglobin (n=20)



1. Tefferi A. *Blood*. 2024;114:1813.

†N=17; 3 patients excluded due to lack of postbaseline assessment but remain on study. ‡N=16; 4 patients excluded due to lack of baseline or postbaseline assessment but remain on study. §Patients with available percentage change in MPN-SAF TSS at week 24 compared with baseline. ¶4 patients were excluded as they were not anemic at baseline or had not been treated for 12 weeks.

C, cycle; D, day; MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; SE, standard error; SVR25, spleen volume reduction ≥25%; SVR35, spleen volume reduction ≥35%; TDA, transfusion-dependent anemia; TSS, total symptom score; TSS50, ≥50% reduction in MPN-SAF TSS.

Conclusions

- INCA033989 was **well tolerated**, both as monotherapy and in combination with ruxolitinib, in patients with MF who were resistant/intolerant to prior JAKi therapy or ineligible for JAKi treatment
  - **No dose-limiting toxicities** were observed, and a maximum tolerated dose was not reached
  - **87%** of patients remain on INCA033989 monotherapy and **85%** of patients remain on INCA033989 + ruxolitinib
- Rapid and **robust spleen and anemia responses,** as well as **symptom improvements**, occurred in both cohorts despite advanced disease and limited follow-up
- At higher doses, reductions in spleen volume, improvement in symptoms, and anemia response seen among both **Type 1 and non-Type 1 patients**
- **mutCALR VAF reduction** was observed in the majority of patients
- These data demonstrate a **clear and robust proof of concept** in MF that will enable pivotal registration studies in the near future

JAKi, Janus kinase inhibitor; MF, myelofibrosis; MK, megakaryocytes; mutCALR, mutations of calreticulin; VAF, variant allele frequency.

Molecular characterization of patients with myelofibrosis and essential thrombocythemia treated with INCA033989

Bethan Psaila, MD, PhD
University of Oxford

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Myeloproliferative Neoplasms are clonal disorders and *CALR* mutations are frequent in ET and MF

- **25%-35% of patients with ET and MF have a *CALR*** mutation[1]
  - **mut*CALR* Type-1** is the **most common** mutation (50-70%)[1,2]

- **All mutations result in aberrant expression of mutCALR* on the cell surface in complex with TPO receptors (TPO-R)**[3-7]
  - Activates the JAK/STAT pathway

- **INCA033989 is a first-in-class antagonist antibody inhibiting mutCALR**
  - INCA033989 is a novel, fully human, high-affinity, Fc-silenced, IgG1 monoclonal antibody that selectively targets mutCALR in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells[8]

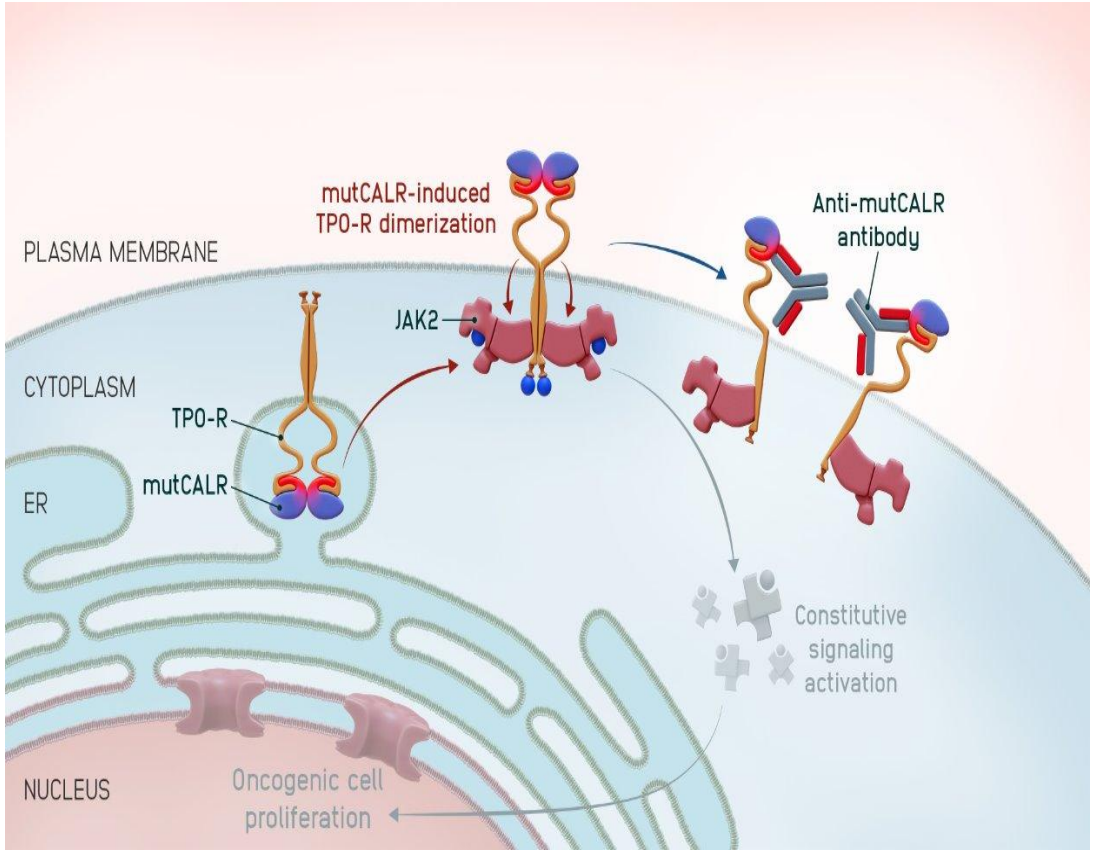


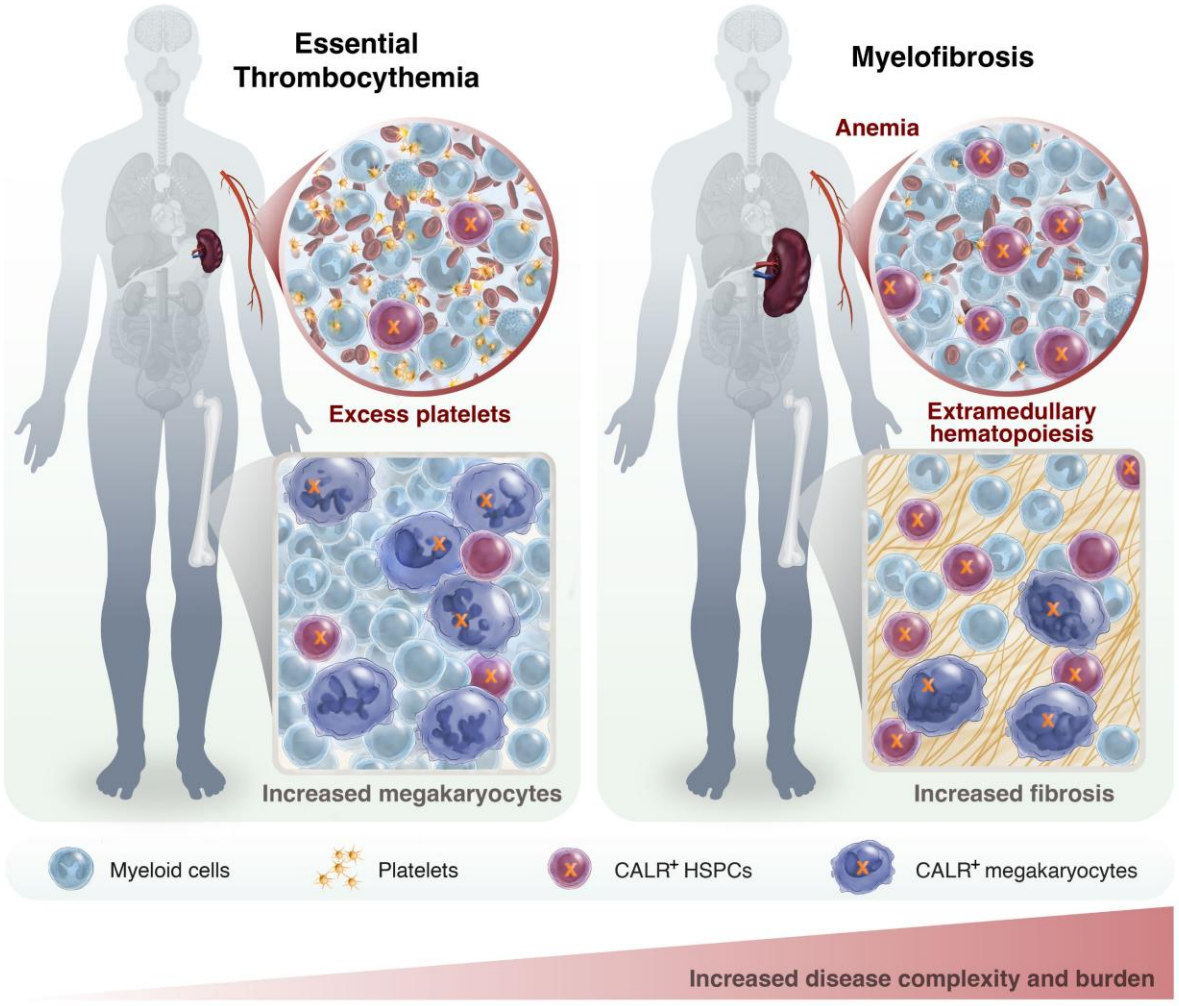
Figure reprinted from Reis E, et al. *Blood*. 2024;144:2336-2348 [visual abstract] with permission from Elsevier Inc. Copyright © 2024 American Society of Hematology.

*mutCALR: CALR exon 9 frameshift mutations. †NCT05936359 (outside the US). ‡NCT06034002 (US only).

1. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390; 2. Cabagnols et al. *Blood*. 2014;124:1823. 3. Chachoua I, et al. *Blood*. 2016;127:1325-1335; 4. Elf S, et al. *Cancer Discov*. 2016;6:367-381; 5. Elf S, et al. *Blood*. 2018;131:782-786; 6. Papadopoulos N, et al. *Nat Commun*. 2023;14:1881; 7. Pecquet C et al. *Blood*. 2019;133:2669-2681; 7. Reis, et al. *Blood*. 2024;22:2336-2348.

ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasms.

ET and MF share common oncogenic drivers but differ in pathophysiology, genomic complexity, and disease burden



INCA033989-101/102 Studies
Higher *CALR* VAF in MF vs ET at enrollment*

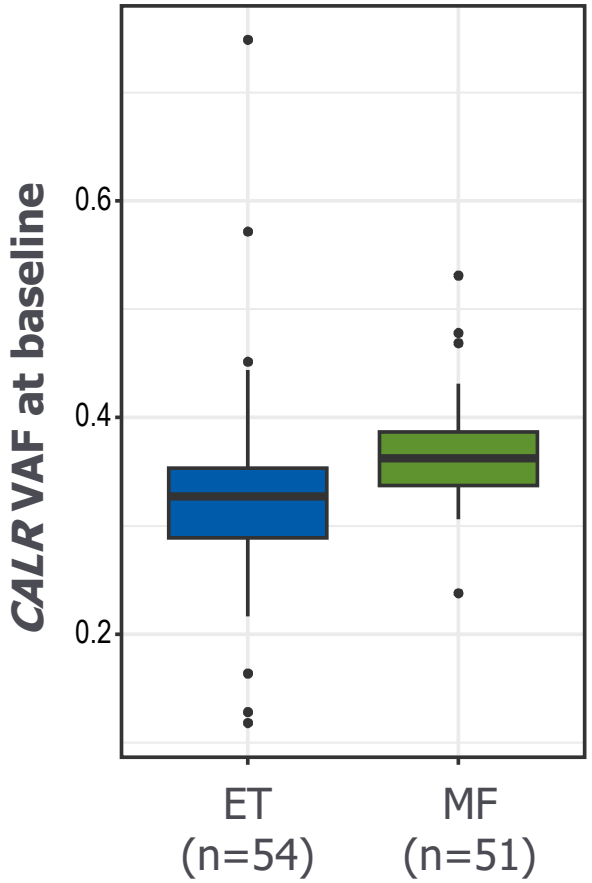
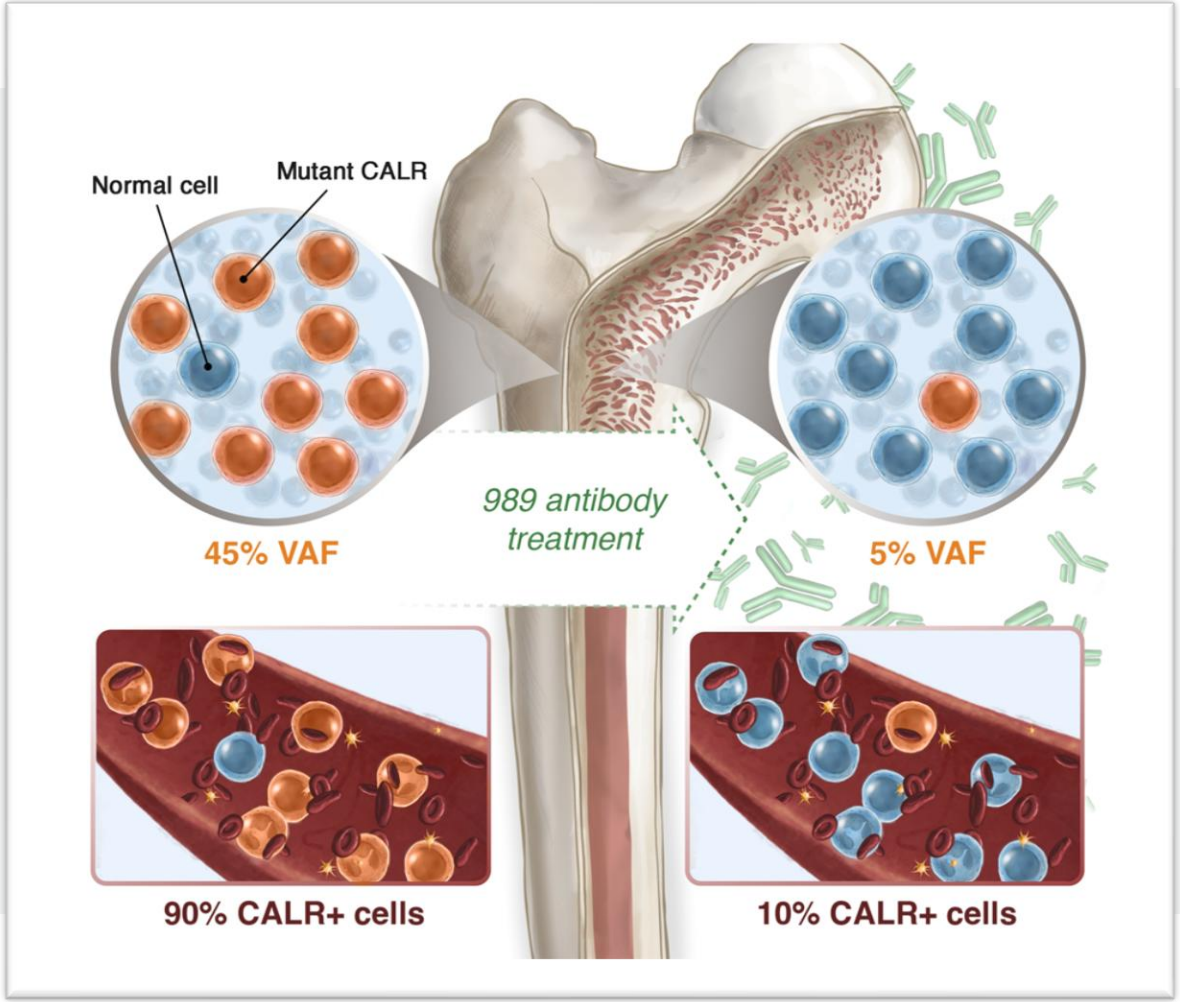


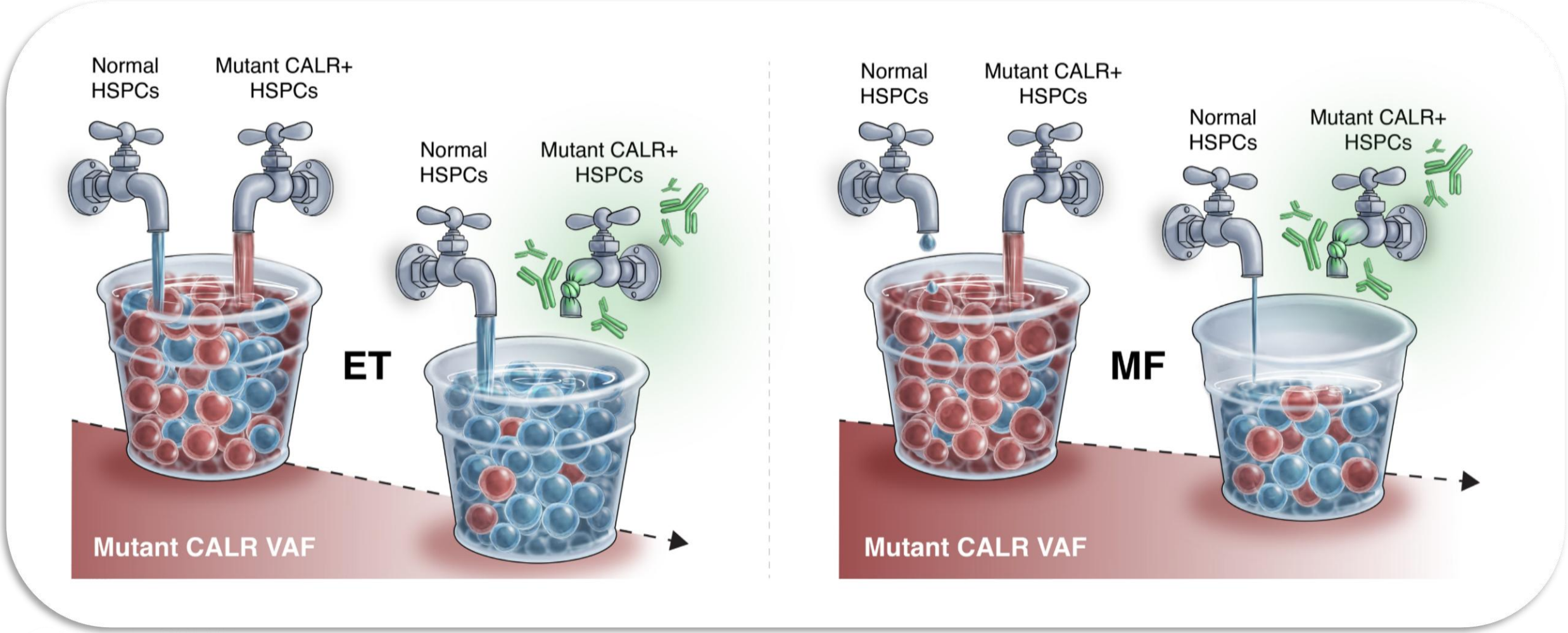
Illustration by DrawImpacts.
*Genomic data presented are from all ET and MF monotherapy patients with peripheral blood samples at screening measured by next-generation sequencing.
CALR, calreticulin; ET, essential thrombocythemia; MF, myelofibrosis; VAF, variant allele frequency.

CALR mutant patients are nearly all heterozygous – relating VAF to mutCALR positive cells

- **High burden** of CALR mutant cells in many MPN patients
  - 45% VAF relates to 90% of all hematopoietic cells being mutCALR positive
- Even **small mutCALR VAF reductions matter**
  - 5% reduction in VAF = 10% reduction in CALR+ (mutant) cells



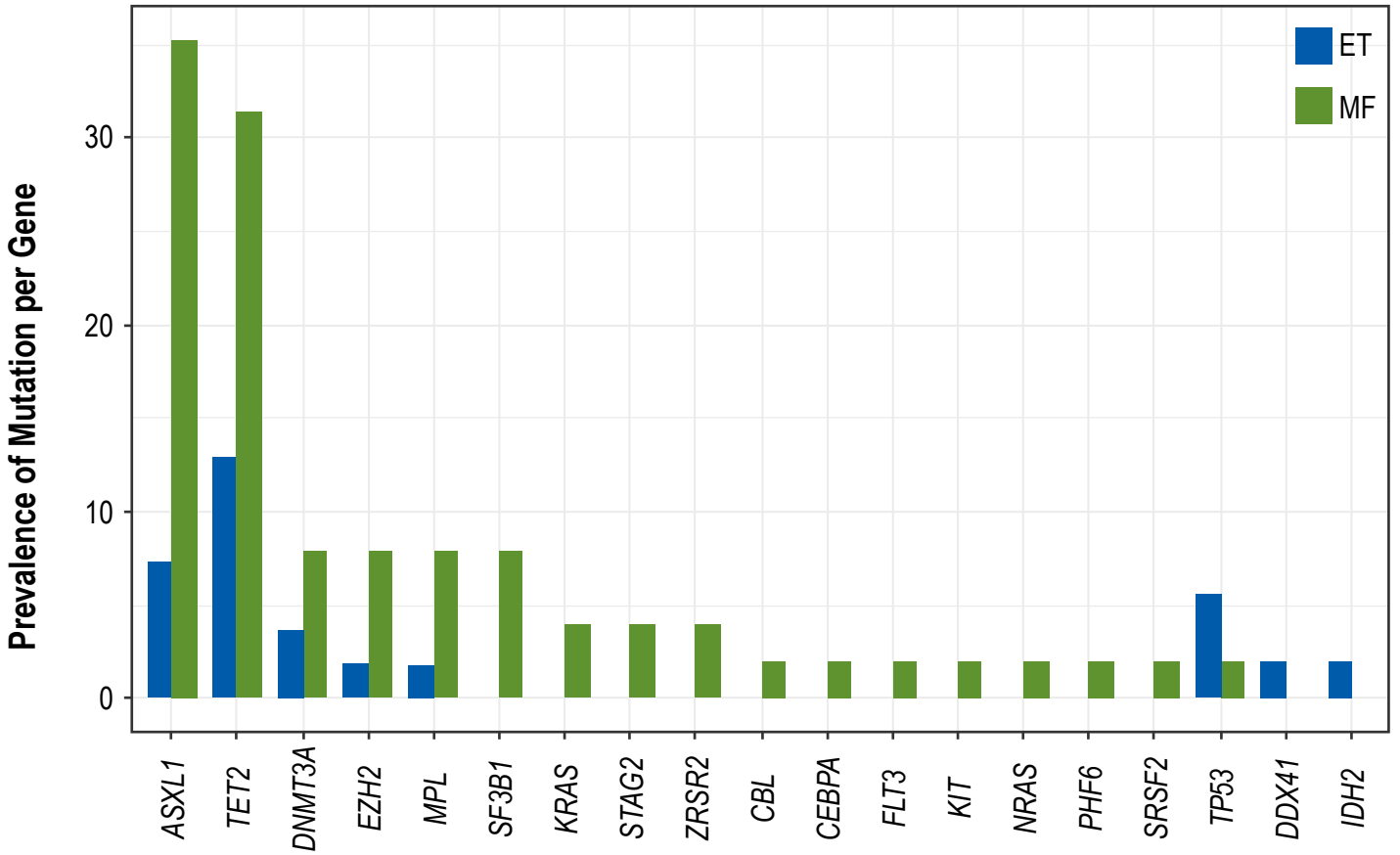
Whole blood VAF is expected to reduce slower in MF vs ET



Patients with MF have greater clonal complexity at baseline compared with ET

- **Co-occurring mutations correlate with disease severity and progression** in patients with ET and MF[1,2]
- Most patients with **MF** had a co-occurring mutation (**76.5%**), compared with **32%** of patients with **ET** (37 gene panel*)

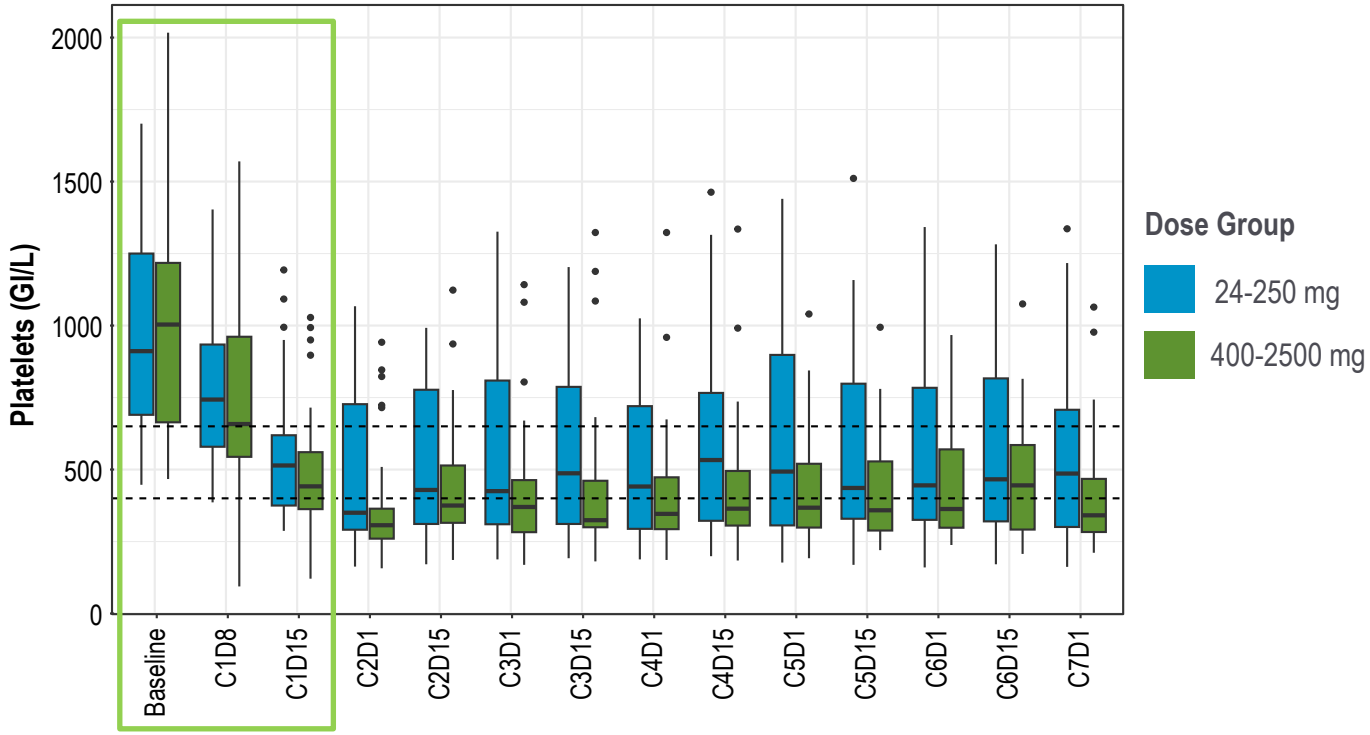
Prevalence of Co-occurring Mutations in Patients with ET and MF



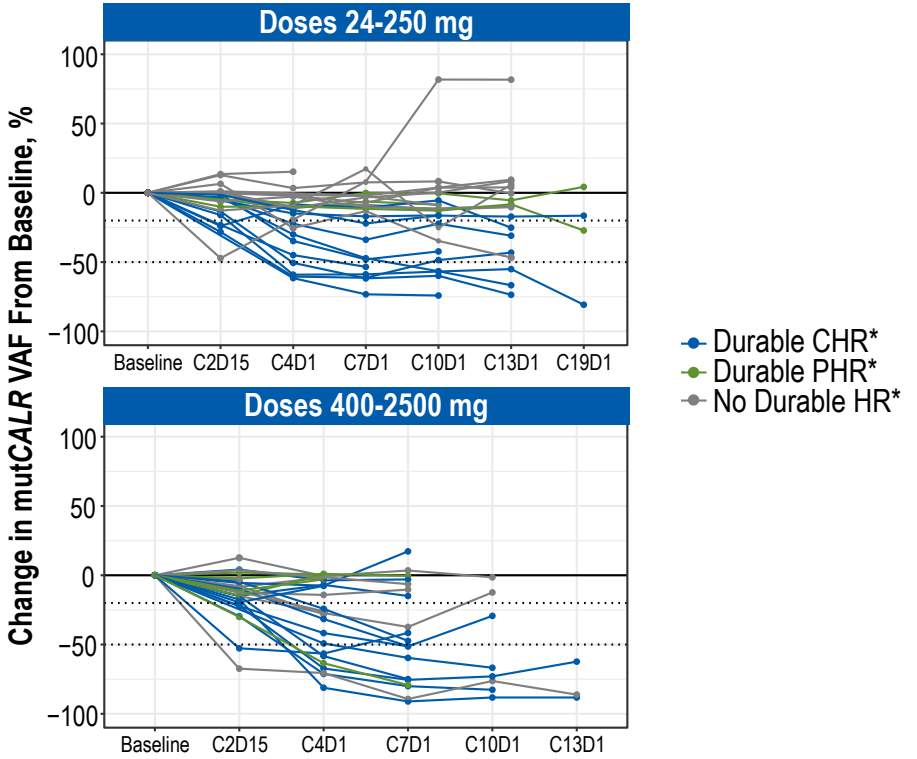
1. Mawalkar R, et al. *Blood.* 2024;144(Supplement 1):3173; 2. Tefferi A, et al. *Blood Adv.* 2016;1:21-30.
*ArcherDx™ library preparation followed by sequencing on the Illumina™ platform.
ET, essential thrombocythemia; MF, myelofibrosis.

Patients with ET treated with 989 achieve rapid and durable platelet normalization with correlated VAF reductions

Durable Platelet Reduction (n=55)



mut*CALR* VAF Reduction (n=52†)



- Deeper and more consistent responses are observed with higher doses of INCA033989

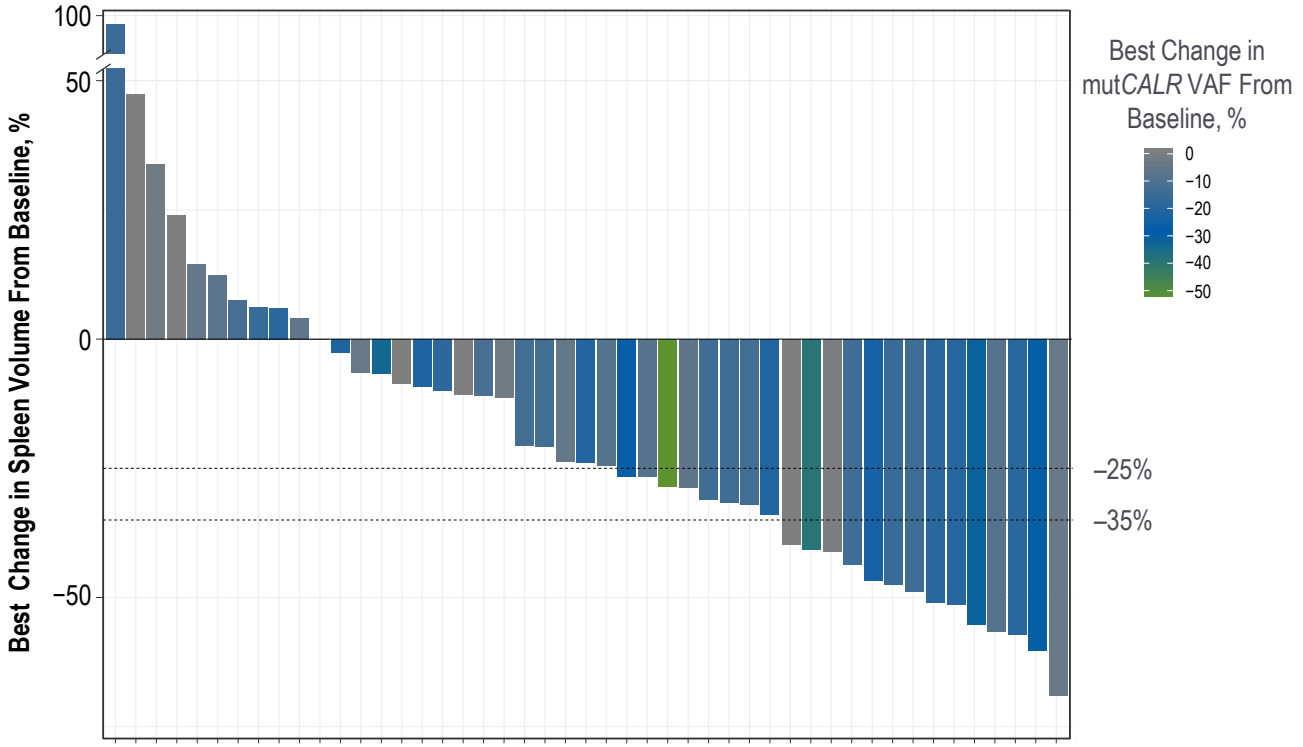
*CHR defined as platelet count ≤400x10^9/L and leukocytes <10x10^9/L, PHR defined as platelet count ≤600x10^9/L and leukocytes <10x10^9/L (baseline platelet count >600x10^9/L). Durable response defined as maintaining for at least 12 weeks.

†3 patients were excluded due to lack of postbaseline VAF assessment.

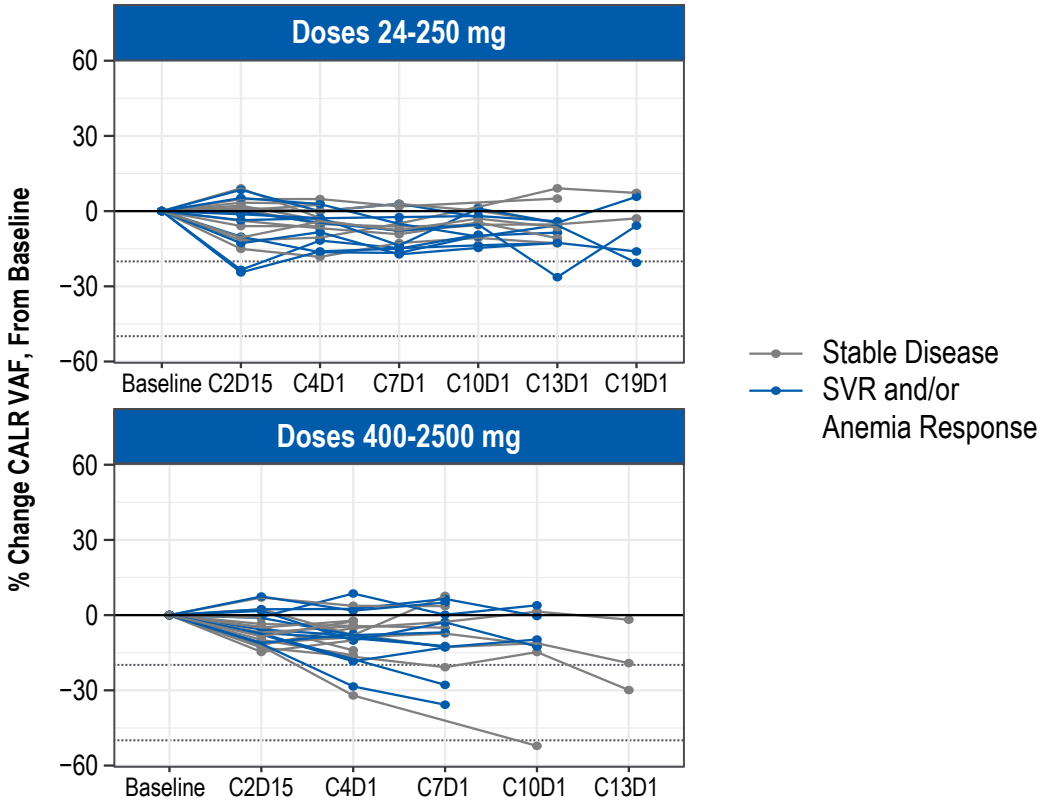
CHR, complete hematologic response; ET, essential thrombocythemia; HR, hematologic response; PHR, partial hematologic response; VAF, variant allele frequency.

Patients with MF treated with 989 achieve rapid spleen reductions with deeper VAF reductions at higher doses

Spleen Volume Reduction vs Molecular Response*



Percentage Change in mut*CALR* VAF From Baseline*



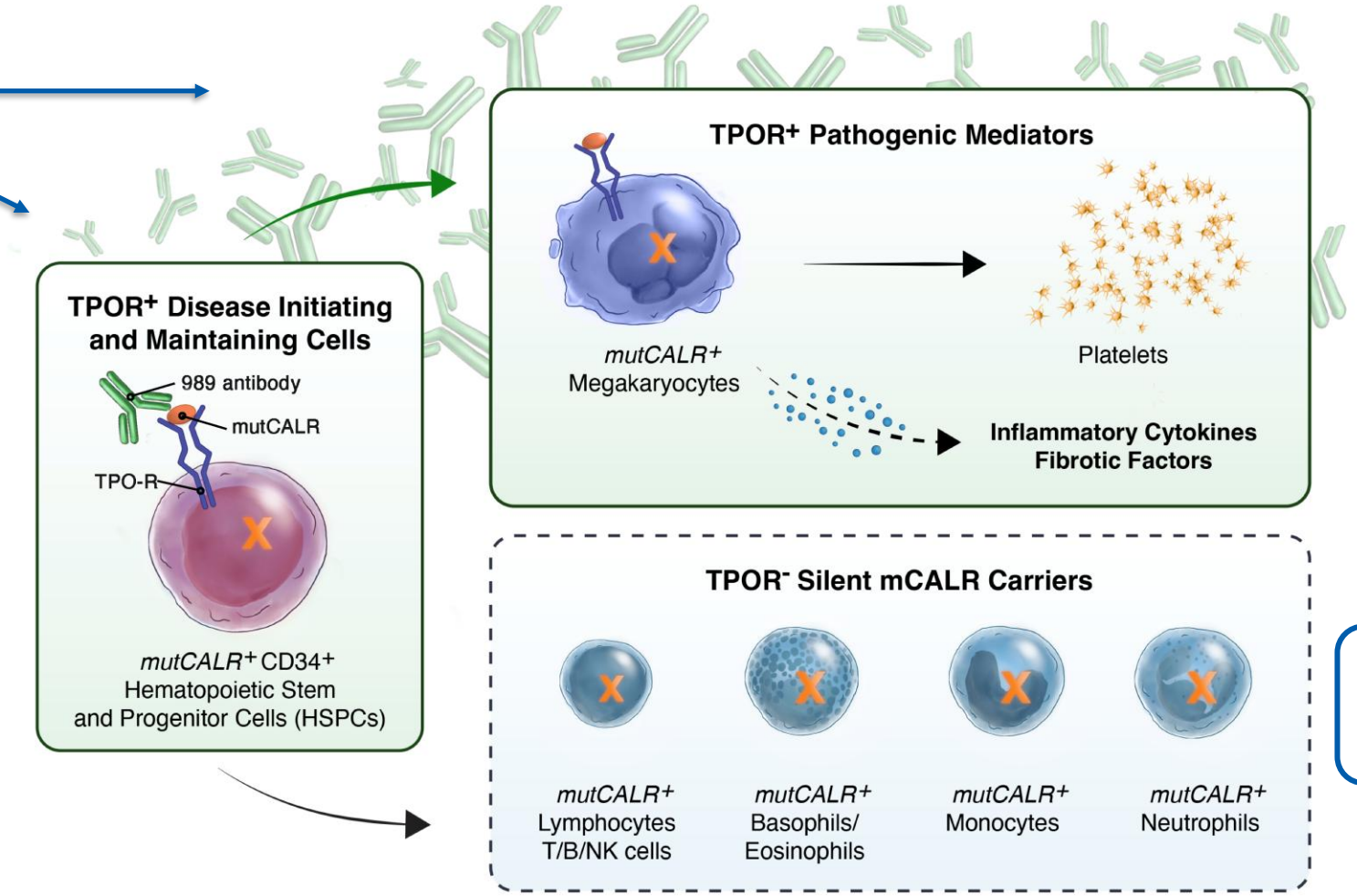
- For all patients with MF with SV measurement (n=48), 23 (47.9%) patients had SVR25, and 15 (31.3%) patients had SVR35
- For patients with ≥1 postbaseline VAF measurement (n=47), 42/47 (89.4%) had a reduction in mut*CALR* VAF
- Deeper reductions in VAF were observed with higher doses and SVR responses

*Data include only monotherapy MF patients with both a spleen volume and post-treatment VAF measurements (n=47).
SVR25, spleen volume reduction ≥25%; SVR35, spleen volume reduction ≥35%; VAF, variant allele frequency.

989 targets disease-initiating and -maintaining cells including hematopoietic stem/progenitor cells (HSPCs) and megakaryocytes

Direct targets of INCA033989

mut*CALR* CD34+ HSPCs give rise to terminally differentiated mature blood cells



Major contributors of mut*CALR* VAF in whole blood

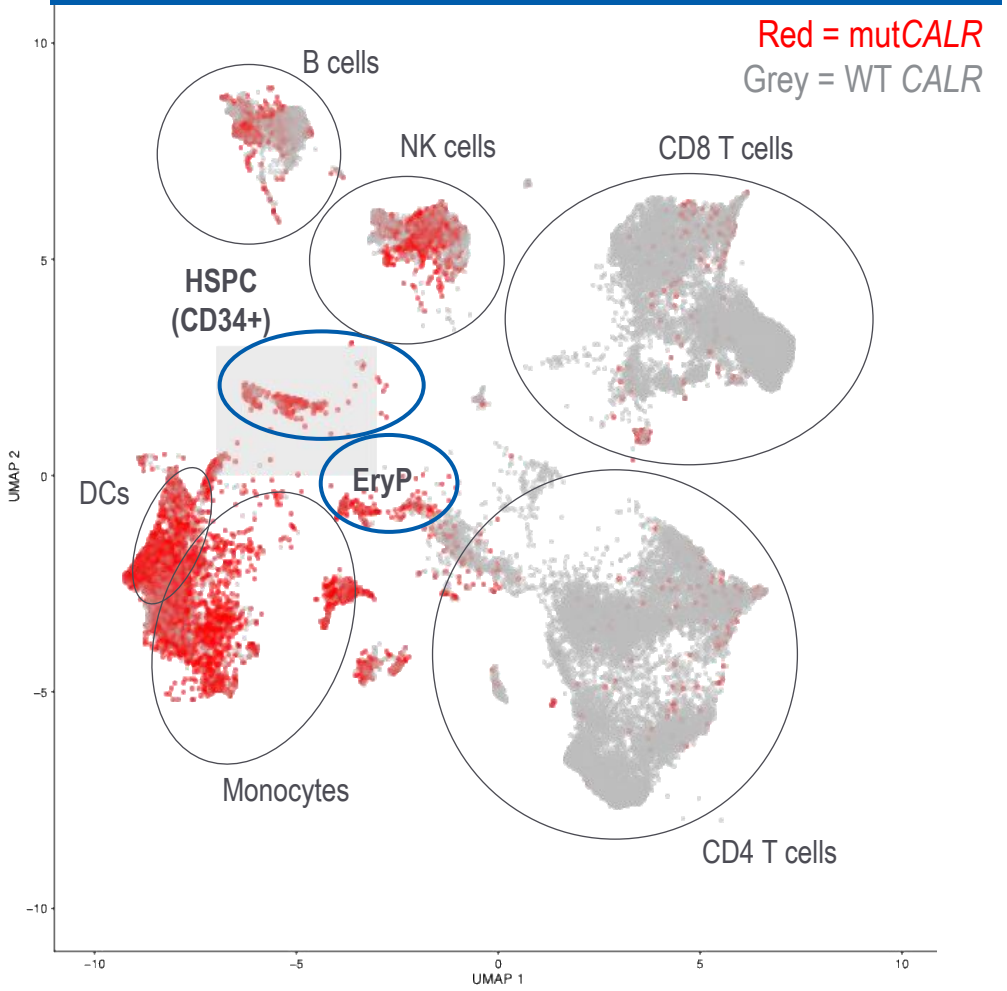
Illustration by DrawImpacts.

CALR, calreticulin; HSPCs, hematopoietic stem/progenitor cells; MK, megakaryocytes; mut*CALR*, mutations of calreticulin; VAF, variant allele frequency; WB, whole blood.

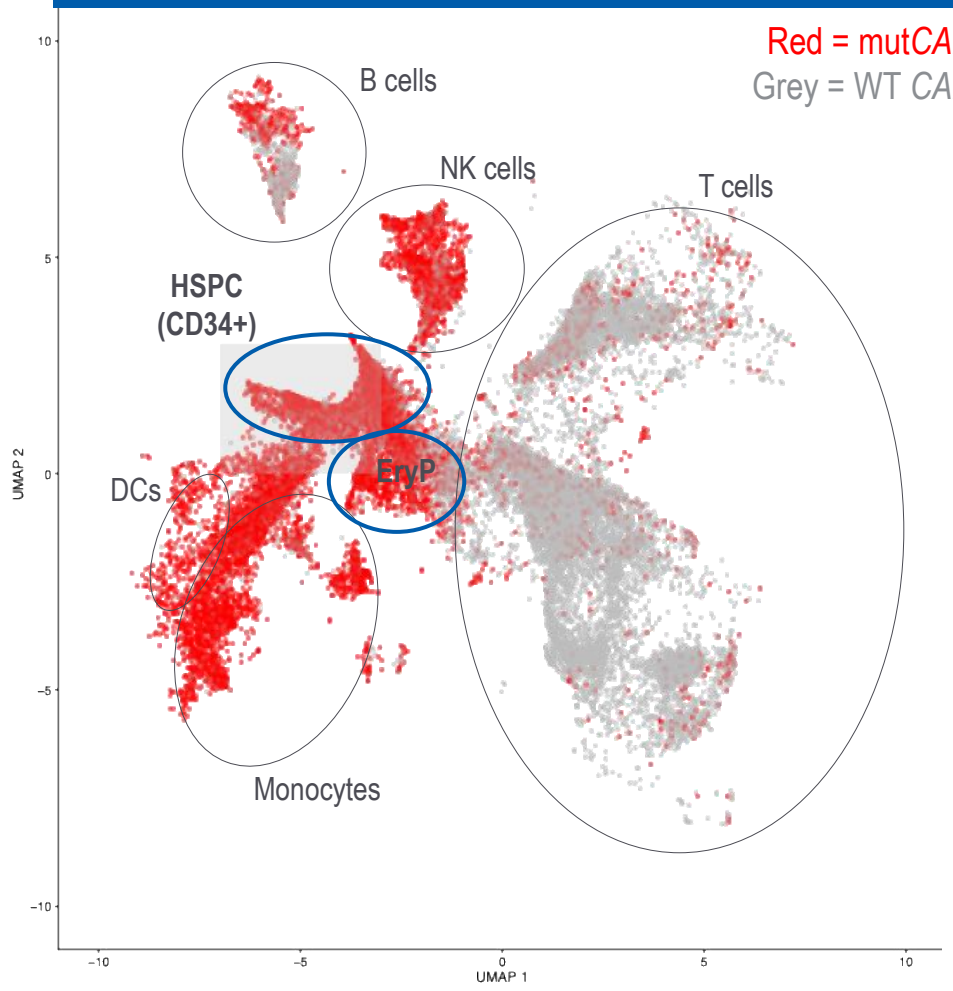
Single-cell immunophenotyping and genotyping demonstrates differential complexity of mut*CALR*+ cells in PBMCs from patients with ET & MF

- mut*CALR* PBMCs ranged from 9%-45% at baseline in patients with ET
- mut*CALR* PBMCs ranged from 28%-62% at baseline in patients with MF
- Circulating HSPCs ($CD34^+$) and progenitor cells were prominently detected in patients with MF

Patients with ET (n=7)



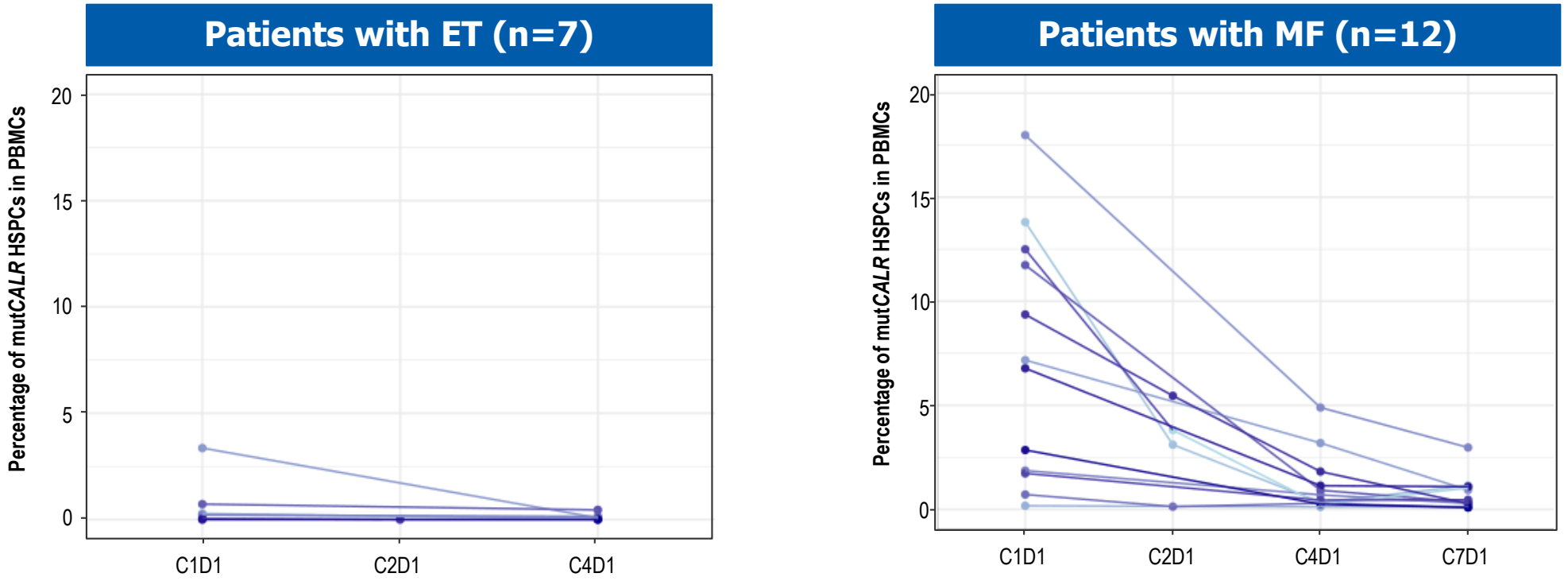
Patients with MF (n=12)



Single-cell DNA sequencing: Presented scDNAseq data are from available dose escalation patient samples: ET (n=7, 70-750mg), MF (n=12, 50-1500mg). Cells were clustered and visualized using a UMAP based on cell surface expression of 46 proteins. *CALR*, calreticulin; EryP, Erythroid Progenitor Cells (CD71); HSPCs, hematopoietic stem/progenitor cells (CD34-high); mut*CALR*, mutations in calreticulin; NK, natural killer; PBMC, peripheral blood mononuclear cells; UMAP, uniform manifold approximation and projection.

989 treatment significantly eliminates disease-initiating and -maintaining CD34+ HSPCs in PBMCs from patients with ET or MF

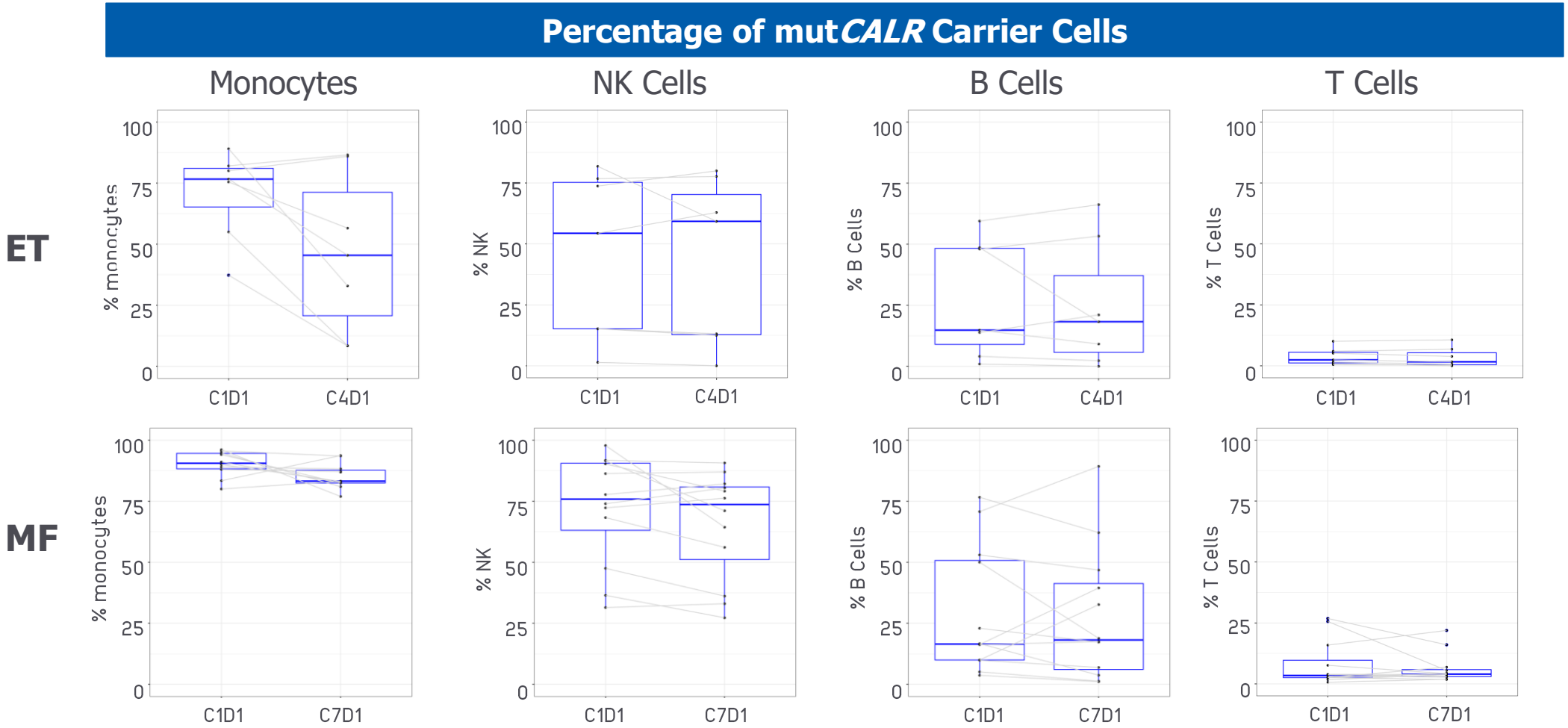
Single-cell Data: mut*CALR* HSPCs (CD34^{+})



- High levels of **mut*CALR* HSPCs** (CD34^{+}) are **decreased** with INCA033989 treatment in patients with MF
  - Lower levels of mut*CALR* HSPCs in PBMCs from patients with ET are also decreased

Single-cell DNA sequencing (MissionBioTM): Presented scDNAseq data is from available dose escalation patient samples: ET (n=7, 70-750mg), MF (n=12, 50-1500mg).
C, cycle; *CALR*, calreticulin; D, day; ET, essential thrombocythemia; HSPC, hematopoietic stem and progenitor cells; MF, myelofibrosis; PBMC, peripheral blood mononuclear cells.

Single-cell analyses of MF and ET samples indicate minimal reduction in mut*CALR*$^{+}$ TPO-R^{-} cells at early time points

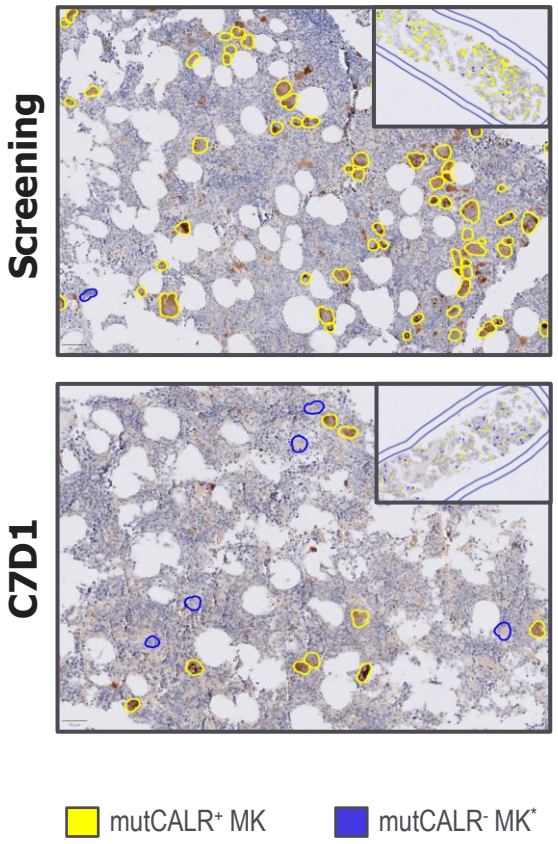


- The percentage of mut*CALR*$^{+}$ lymphocytes are relatively unchanged
- Among mut*CALR* carrier cells, the percentage of mut*CALR*$^{+}$ monocytes are consistently but modestly decreased

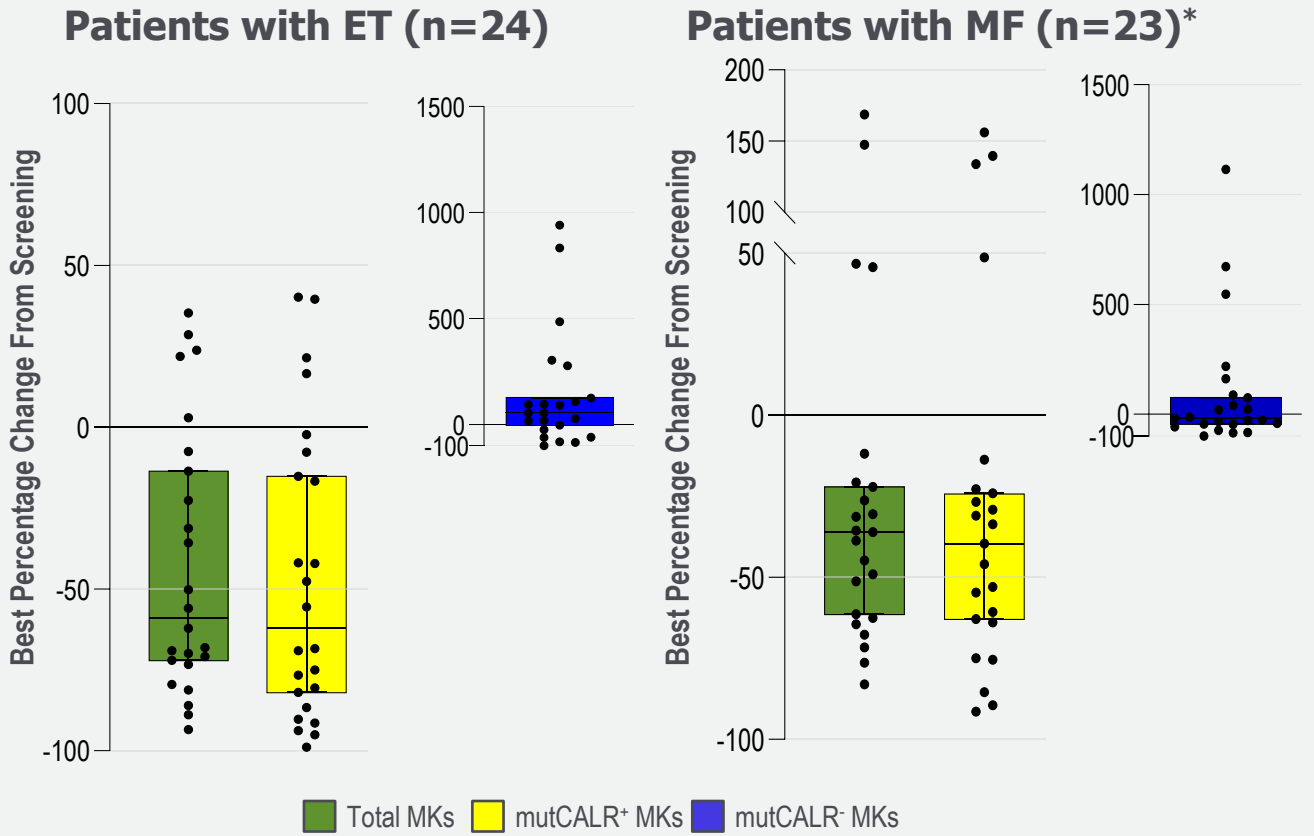
Single-cell DNA sequencing: Presented scDNAseq data is from available dose escalation patient samples: ET (N=7, 70-750mg), MF (n=12, 50-1500mg).
CALR, calreticulin; ET, essential thrombocythemia; MF, myelofibrosis; NK, natural killer.

Treatment with 989 rapidly decreases mutCALR⁺ megakaryocytes in bone marrow samples from patients with ET and MF

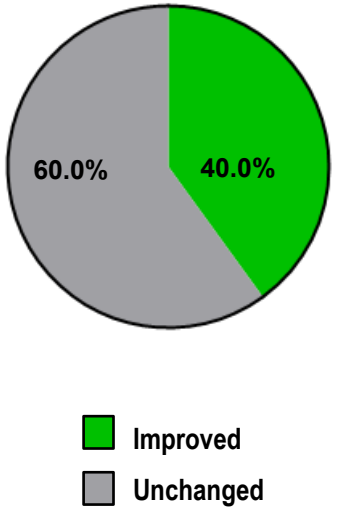
MK Staining by mutCALR-IHC (ET)



Best Percent Change from Screening in Total, mutCALR⁺, and mutCALR⁻ MKs



Fibrosis Grade† (n=30)



- Reductions in total and mutCALR⁺ MKs is accompanied by an increase in wild-type (mutCALR⁻) MKs

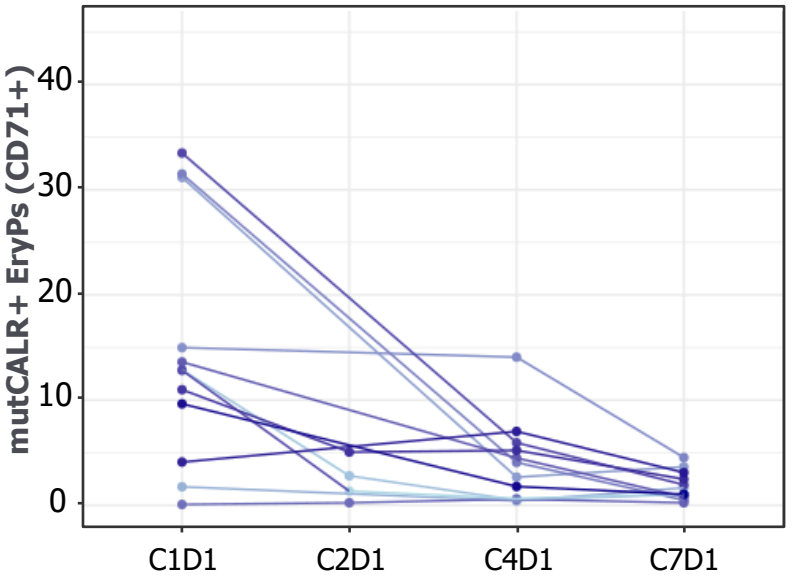
*1 patient with 0 mut*CALR*⁻ MK at screening is not shown. Bone Marrow mutCALR IHC quantitative assessment of mutCALR+ and mutCALR- MK were conducted by pathologist at screening and at timepoints on-treatment (primarily 3 or 6 cycles). †Fibrosis grade was centrally assessed for all patients with available screening and C7D1 samples. "Improved": decreased by ≥1 grade; "Unchanged": stable.
ET, essential thrombocythemia; IHC, Immunohistochemistry; MF, myelofibrosis; MK, megakaryocytes; SVR35, spleen volume reduction ≥ 35%.

989 normalizes erythropoiesis in patients with MF and is associated with anemia response

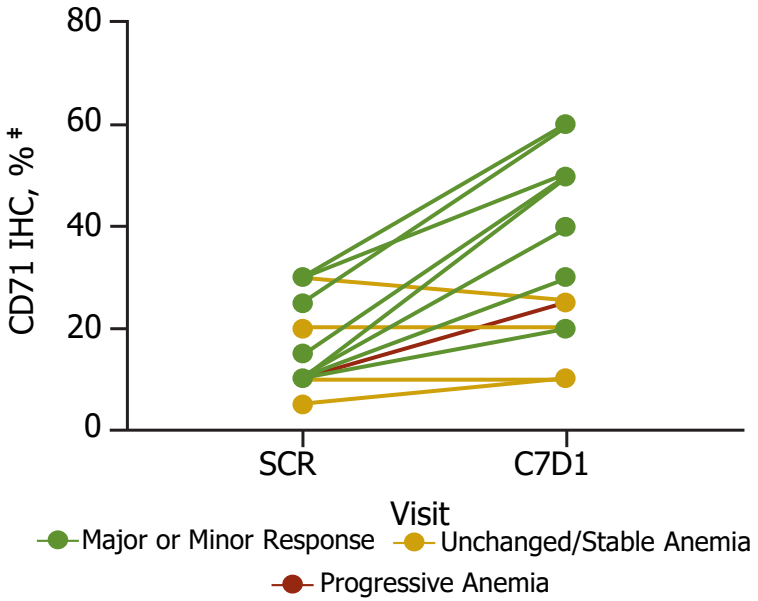
Anemia Response* in Evaluable Patients (MF)

Variable	TDA (n=5)	Non-TDA (n=20)	Total (n=25)
Best Anemia Response, n (%)			
Major Response	1 (20)	9 (45)	10 (40)
Minor Response	2 (40)	2 (10)	4 (16)
Stable Anemia	1 (20)	7 (35)	8 (32)
Progressive Anemia	1 (20)	1 (5)	2 (8)
Missing†	0 (0)	1 (5)	1 (4)

Atypical Circulating mutCALR⁺ EryPs (MF)



EryPs in BM of Anemic Patients With (MF)

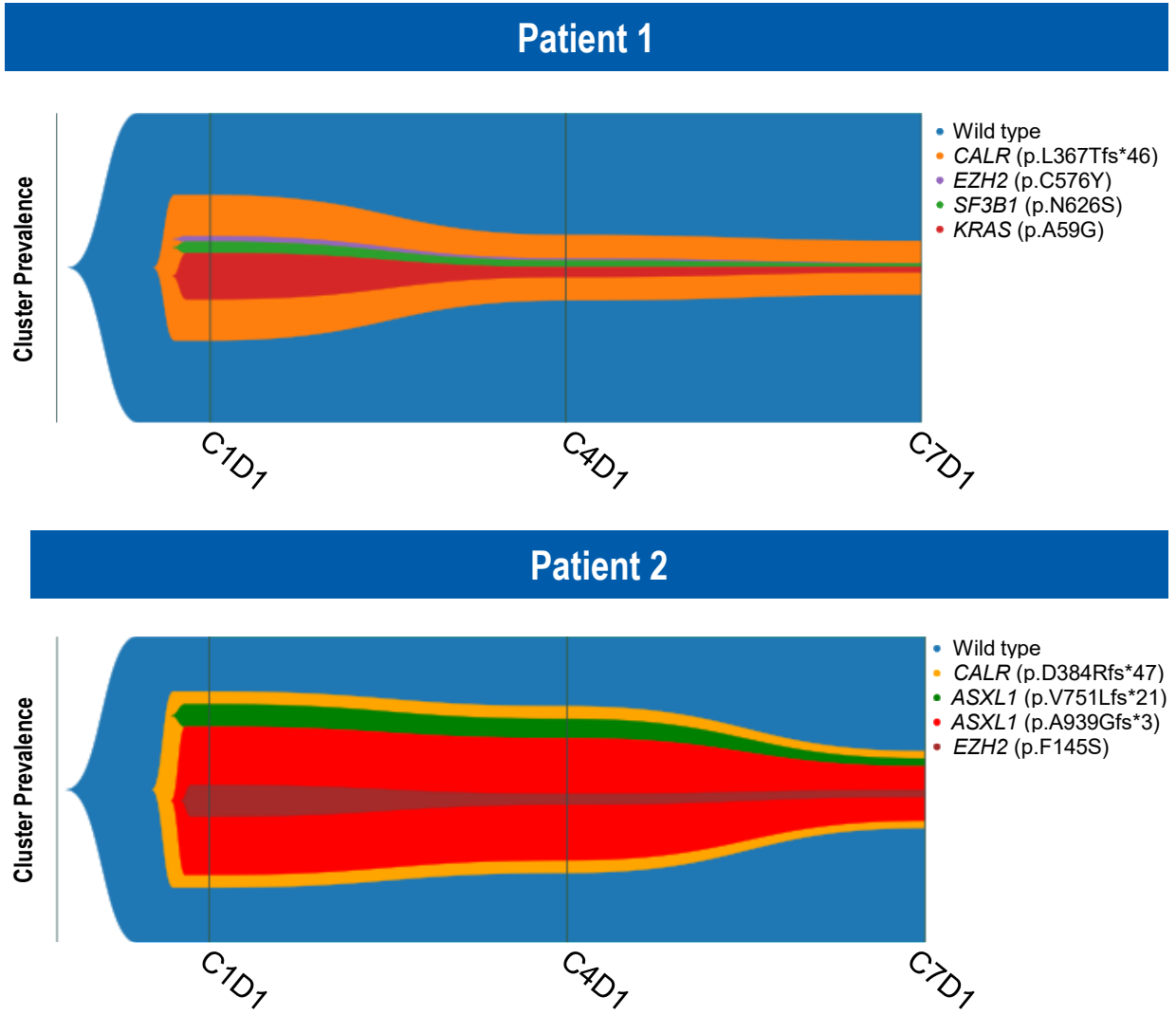


- Elevated levels of atypical circulating erythroid progenitor cells (EryPs) (CD71⁺) associated with extramedullary hematopoiesis were decreased in patients with MF with INCA033989 treatment
- EryPs (CD71 immunohistochemistry [IHC]) in bone marrow increased in anemic patients with MF, correlating with hemoglobin increase and clinical anemia response

Single-cell DNA sequencing: Presented scDNAseq data is from available dose escalation patient samples: MF (n=12, 50-1500mg).
*Criteria for baseline anemia and response based on Tefferi A. *Blood.* 2024;114:1813. Major anemia response for patients with TDA: no transfusions for 12 weeks and rolling 12-week average hemoglobin increase of ≥1.5 g/dL from pretreatment baseline. Major anemia response for patients with non-TDA: rolling 12-week average hemoglobin increase of ≥1.5 g/dL from pretreatment baseline (also requires no transfusions). †Patient terminated treatment before 12 weeks. ‡CD71 IHC was centrally assessed by a single pathologist; data include all patients with baseline anemia and available CD71 IHC for screening and C7D1 (n=14). BM, bone marrow; EryPs, erythroid progenitor cells; IHC, Immunohistochemistry; MF, myelofibrosis; mutCALR, mutations in calreticulin; SCR, screening; TDA, transfusion-dependent anemia.

Reductions in mut*CALR* clones in PBMCs are evident, regardless of the presence of co-occurring mutations in patients with MF

- **76.5%** (39/51) of patients with MF had a co-occurring mutation (mean [range], 2.6 [1-4])
- **40.5%** (15/37*) of patients with a co-occurring mutation had SVR and/or anemia response
- 2 patients with MF (analyzed with single-cell sequencing) with high clonal complexity are displayed on the right and demonstrate reductions in all clones with mut*CALR*, independent of co-occurring mutations



*2 patients with co-occurring mutations at baseline do not have response data.
CALR, calreticulin; MF, myelofibrosis; mut*CALR*, mutations in calreticulin, PBMC, peripheral blood mononuclear cells; SVR35, spleen volume reduction ≥35%.

Conclusions

- INCA033989 results in **rapid normalization of platelet counts** in ET, and splenomegaly, **symptoms** and **anemia responses** in MF
- **Clinical responses** are **associated** with rapid **reductions in mut*CALR* clone burden**
  - Demonstrating speed and depth of molecular response
  - Highlighting VAF as a relevant, measurable endpoint
- **Clonal responses** in MF are also observed in patients who have **co-occurring high-risk mutations**, including those associated with increased risk of progression to AML
- **Improvements in bone marrow** are demonstrated by decreases in mut*CALR* megakaryocytes and increases in erythroid progenitor cells and are associated with anemia response
- Support the **potential of INCA033989 to modify the disease** of patients with mut*CALR* MPNs

Next Steps

Steven Stein, MD
Executive Vice President, Chief Medical Officer

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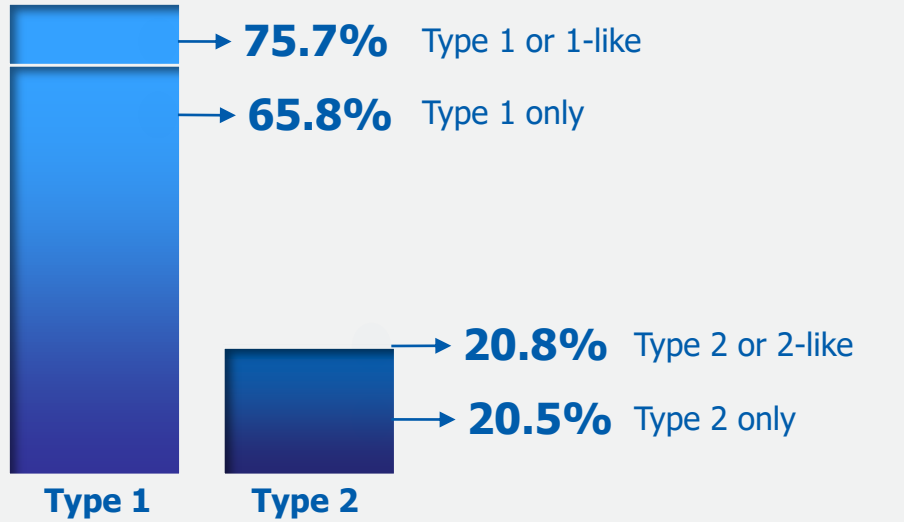
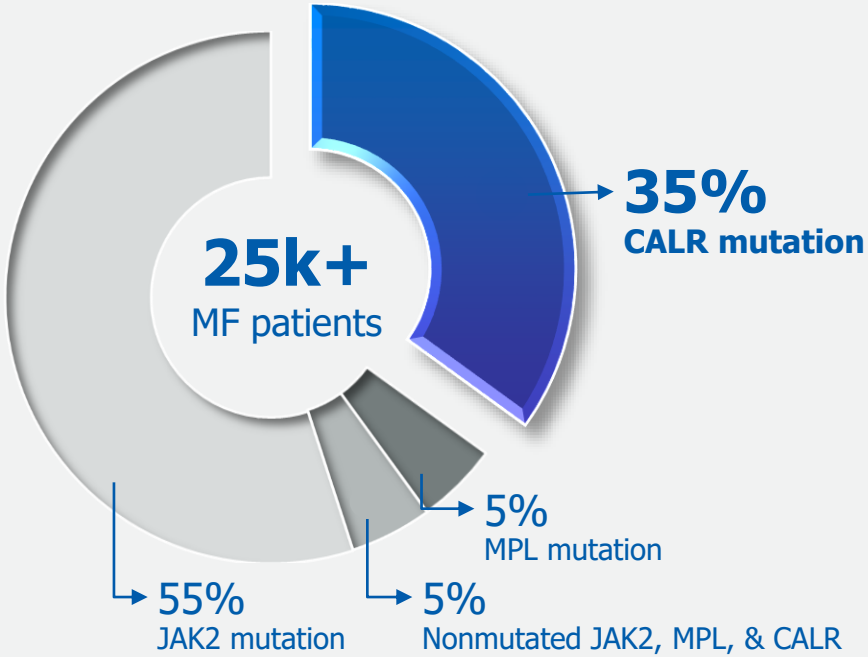
Mutation landscape defines clear opportunities for targeted development in myelofibrosis

- ~25k people living with myelofibrosis in the U.S.
- CALR is the **second most common mutation** in MF patients, occurring in **35% of patients**
- Goals of MF management remain **only partially met today**, with only 1/3 of patients respond to current JAK inhibitors
- Need remains for innovative **approaches targeting underlying molecular drivers**
- **76% of mutCALR patients are Type 1 or Type 1-like**[1]

CALR Mutation Type in MF Patients





CALR, calreticulin; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein
1. Incyte data on file

Data support differentiated, disease modifying opportunity in MF patients with CALR mutation

- '989 was generally **well-tolerated**, with **85%+ of patients remaining on therapy** in both cohorts
  - No DLTs; MTD not reached
- Rapid and **robust reductions** in spleen volume in monotherapy and combination therapy cohorts
  - At Week 24, 42% and 33% of patients achieved an SVR25 and SVR35, respectively (monotherapy)
- **Improvements in symptoms** seen in majority of patients across monotherapy (93%) and combination (81%) cohorts
  - At Week 24, 39% (monotherapy) and 33% (combination) of patients achieved TSS50
- **Robust improvements in anemia; 56%** of evaluable patients achieved an anemia response
- At higher doses, reductions in spleen volume, improvement in symptoms, and anemia response seen among both **Type 1 and non-Type 1 patients**
- **Improvements in bone marrow** are demonstrated by **decreases in mut*CALR* megakaryocytes and increases in erythroid progenitor cells** and are associated with anemia response
  - Support the **potential for disease-modifying activity** of '989 in patients with a CALR mutation

DLT, dose-limiting toxicity; MF, myelofibrosis; MTD, maximum tolerated dose;

Early evidence across populations anchors the path to pivotal development

ET (2L)

- ✓ **Breakthrough Therapy Designation**

Planned Phase 3 trial initiation in mid-2026*

- 989 IV Q2W vs. BAT

MF (2L)

- ✓ Phase 1 dose expansion ongoing (mono, combo)
- ✓ **Finalizing dose** selection

Planned Phase 3 trial initiation in 2H26†

- 989 IV Q2W vs. BAT

MF (1L)

- ✓ Phase 1 **dose expansion ongoing** (989 vs. 989 +ruxolitinib)

Preliminary Phase 1 results anticipated 2H26¶

- Data to inform 1L pivotal trial design

SubQ (ET, MF)

- ✓ Agreement with Enable signed for development of **EnFuse® device**

Phase 1 trial initiation in ET & MF early-2026

- Data to enable bridging strategy in ET & MF

*Planned evaluation of INCA033989 in mutCALR ET patients who are resistant/intolerant to prior cytoreductive therapy, pending alignment with regulators in early-2026; †Planned evaluation of INCA033989 in mutCALR MF patients who are r/r to JAK treatment, pending alignment with regulators in mid-2026 ¶ Intermediate to high-risk treatment-naïve
BAT, best available therapy; ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis

Q&A

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