Mutant Calreticulin–Specific Monoclonal Antibody, INCA033989, Is Well Tolerated and Achieves Robust Spleen, Anemia, and Molecular Responses in Patients With Myelofibrosis

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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]
  - Approximately 70% of mut*CALR* are classified as Type 1[4]
- Patients with mut*CALR* have distinct clinical and biological features and have inferior responses to current therapies, with lower spleen and symptom responses, and higher rates of anemia reported with ruxolitinib treatment[5,6]
- Current MF treatments are not mutant targeted and have limited efficacy in reducing mut*CALR* variant allele frequency (VAF)[7]
- Janus kinase inhibitor (JAKi) therapies treat clinical features of disease with limited impact on stem and progenitor cells that initiate and sustain disease[8]

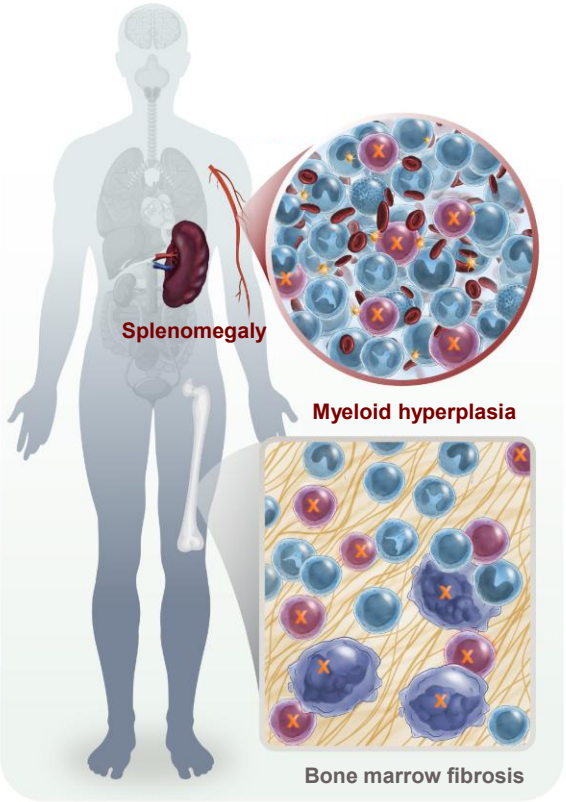
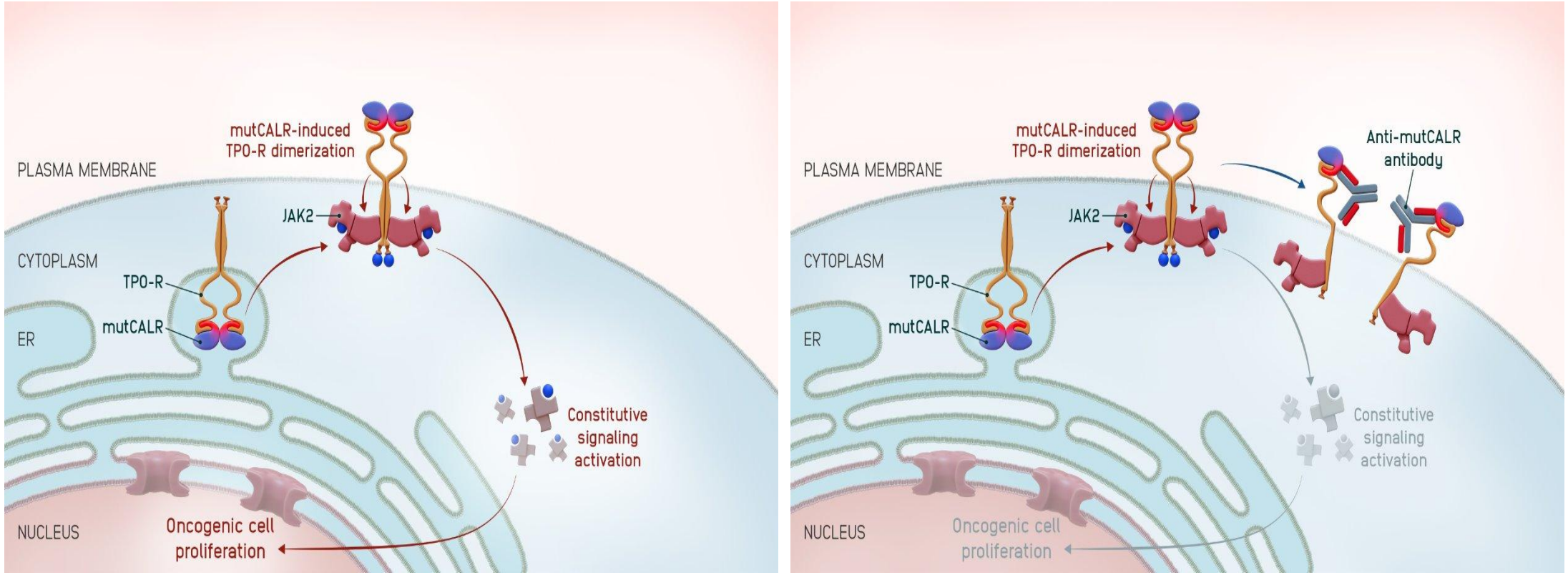


Illustration by DrawImpacts.

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. Palandri F, et al. *Ann Hematol.* 2025;104:241-251. 6. Rampal RK, et al. *Nat Med.* 2025;31:1531-1538. 7. Tefferi A. *Am J Hematol.* 2023;98:801-821. 8. Loscocco GG, Vannucchi AM. *Int J Hematol.* 2022;115:626-644.

INCA033989 Is a mutCALR-Targeted Therapy for Patients With MF and Essential Thrombocythemia (ET)

- Unique mechanism of action vs other therapies
  - Novel, fully human, high-affinity, Fc-silenced, IgG1 monoclonal antibody selectively targets mutCALR in complex with TPO-R to inhibit oncogenic signaling and cell proliferation[1]



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

ER, endoplasmic reticulum; Fc, fragment crystallizable; IgG, IgG, immunoglobulin; JAK2, Janus kinase 2; MF, myelofibrosis; mutCALR, mutations of calreticulin; TPO-R, thrombopoietin receptor (myeloproliferative leukemia protein).

Two Ongoing Phase 1 Studies Evaluating INCA033989 in Patients With MF and ET

Dose Escalation

MF
- ≥18 years of age with a diagnosis of primary or post-ET MF
- Presence of mut*CALR* exon 9
- Spleen volume imaging ≥450 mL or palpable splenomegaly of ≥5 cm
- Monotherapy
  - Intolerant, resistant after ≥12 weeks,* or ineligible for JAKi treatment
- Combination therapy
  - Prior ruxolitinib treatment for ≥12 weeks with a suboptimal response

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 weeks 12 and 24
- Anemia response[1]
- Symptom improvement based on the MPN-SAF TSS
- Changes in allele burden of mut*CALR*

Dose Expansion

- MF (monotherapy)
- MF (INCA033989 + ruxolitinib)
- JAKi-naive MF (randomly assigned to monotherapy or INCA033989 + ruxolitinib)
- ET

- **INCA033989-101** (NCT05936359; outside the US) and **INCA033989-102** (NCT06034002; US only) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA033989 in patients harboring a *CALR* exon-9 mutation with high-risk ET or MF (as monotherapy or in combination with ruxolitinib)
- INCA033989 was administered intravenously every 2 weeks (24-3500 mg, monotherapy; 70-2500 mg, combination therapy)
  - The dose expansion phase evaluated doses of 250 mg and 2000 mg

*A JAKi washout was not required. 1. Tefferi A. *Blood*. 2024;144:1813-1820.
CALR, calreticulin; CT, computed tomography; ET, essential thrombocythemia; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mut*CALR*, mutations of calreticulin; SVR25, spleen volume reduction ≥25%; SVR35, spleen volume reduction ≥35%; TSS, total symptom score.

Demographics and Disease Characteristics

Variable	Monotherapy (N=83)		Combination (N=21)
	JAKi R/R/I (N=62)	JAKi Ineligible* (N=21)	
Median age (range), years	60 (38.0, 81.0)	64 (34.0, 82.0)	61 (38, 82)
Female, n (%)	23 (37.1)	6 (28.6)	5 (23.8)
Median time from initial diagnosis (range), years	6.6 (0.1, 26.2)	3.5 (0, 15.6)	3.2 (0.4, 16)
DIPSS risk status, n (%)			
Low risk	5 (8.1)	3 (14.3)	0
INT-1 risk	26 (41.9)	7 (33.3)	8 (38.1)
INT-2 risk	29 (46.8)	11 (52.4)	10 (47.6)
High risk	2 (3.2)	0	3 (14.3)
CALR exon 9 mutation type, n (%)			
Type 1	37 (59.7)	11 (52.4)	13 (61.9)
Non-Type 1	25 (40.3)	10 (47.6)	8 (38.1)
Median duration of INCA033989 exposure (range), days	233 (1, 889)	345 (17, 815)	335.0 (137, 593)
Median baseline ruxolitinib daily dose (range), mg	N/A	N/A	40 (10, 50)

Variable	Monotherapy (N=83)		Combination (N=21)
	JAKi R/R/I (N=62)	JAKi Ineligible (N=21)	
Median platelets (range), G/L	281 (41, 1845)	345 (55, 1267)	221 (76, 506)
Median leukocytes (range), G/L	6.5 (1.5, 59.4)	7.0 (3.5, 13.2)	10.7 (2.4, 85)
Median hemoglobin (range), g/L	99 (60, 156)	101 (70, 147)	94 (72, 126)
Median MPN-SAF TSS (range)	29 (0, 69)	17 (3, 51)	17 (3, 56)
Median spleen volume (range), mL	1396 (226, 5060)	1225 (450, 3970)	2376 (848, 5338)
Median *CALR* VAF (range)†	37 (30, 73)	36 (24, 53)	39 (30, 85)
INCA033989 dose level, n (%)			
24-200 mg	12 (19.4)	5 (23.8)	3 (14.3)
250 mg	15 (24.2)	4 (19.0)	5 (23.8)
400 mg	3 (4.8)	1 (4.8)	N/A
750 mg	10 (16.1)	3 (14.3)	5 (23.8)
1500 mg	5 (8.1)	4 (19.0)	5 (23.8)
2000 mg	9 (14.5)	4 (19.0)	N/A
2500 mg	5 (8.1)	0	3 (14.3)
3500 mg	3 (4.8)	0	N/A

Data cutoff: March 6, 2026.

*JAKi naïve and ineligible for JAKi treatment per investigator. †Measured centrally in peripheral blood by next-generation sequencing. *CALR*, calreticulin; DIPSS, Dynamic International Prognostic Scoring System; G/L, 10^9/L; g/L, grams/L, 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.

INCA033989 Monotherapy Is Well Tolerated in Patients With MF

Summary of Treatment-Emergent Adverse Events (TEAEs)

TEAE, n (%)	N=83
Any TEAE	76 (91.6)
Treatment related	48 (57.8)
Grade ≥3	22 (26.5)
Serious	7 (8.4)*
Fatal	0
Discontinuation due to TEAEs	2 (2.4)†
Dose reduction due to TEAEs	2 (2.4)‡
Infusion interruption due to TEAEs	5 (6.0)
Dose delay due to TEAEs	17 (20.5)

Most Common TEAEs (≥15% of Patients)

	N=83			
TEAE,¶¶ n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3§
Thrombocytopenia	25 (30.1)	15 (18.1)	5 (6.0)	5 (6.0)¶
Anemia	24 (28.9)	10 (12.0)	8 (9.6)	6 (7.2)¶
Arthralgia	21 (25.3)	11 (13.3)	10 (12.0)	0
Fatigue	17 (20.5)	10 (12.0)	7 (8.4)	0
Headache	17 (20.5)	13 (15.7)	4 (4.8)	0
Neutropenia	17 (20.5)	3 (3.6)	9 (10.8)	5 (6.0)¶
Cough	14 (16.9)	11 (13.3)	3 (3.6)	0
Diarrhea	13 (15.7)	12 (14.5)	1 (1.2)	0
Leukopenia	13 (15.7)	2 (2.4)	6 (7.2)	5 (6.0)¶
Nausea	13 (15.7)	11 (13.3)	2 (2.4)	0
Pruritus	13 (15.7)	12 (14.5)	1 (1.2)	0

- Overall, 84% (n=70) patients were still receiving treatment and 16% (n=13) discontinued‖
- No dose-limiting toxicities were observed, and a maximum tolerated dose was not reached
- Most frequent grade ≥3 TEAEs were cytopenias, usually occurring in patients with pre-existing cytopenias
- No dose relationship with TEAEs was observed

*9 SAEs occurred in 7 patients, 1 event for each of the following: abdominal pain (70 mg); tendonitis (70 mg); basal cell carcinoma (100 mg); lung adenocarcinoma (250 mg); mantle cell lymphoma (400 mg); small intestinal obstruction (400 mg); infection (1500 mg); arthritis (1500 mg); pneumonia (2500 mg). All serious TEAEs were considered unrelated to INCA033989, except tendonitis. †Mantle cell lymphoma (n=1, 400mg); neutropenia (n=1, 750 mg). ‡AST increase (n=1) and thrombocytopenia (n=1). §Other grade ≥3 TEAEs that occurred in >1 patient: hypertension (n=3); abdominal pain (n=2); ¶Thrombocytopenia grade 3 (n=3) and grade 4 (n=2); anemia grade 3 (n=6); neutropenia grade 3 (n=2) and grade 4 (n=3); leukopenia grade 3 (n=3) and grade 4 (n=2). ‖Adverse event (n=3); lack of efficacy (n=3); physician decision (n=3); progressive disease (n=3); withdrawal by patient (n=1). ¶¶Patients were counted once under the highest grade.
n, number of individual patients.

INCA033989 Is Well Tolerated in Combination With Ruxolitinib in Patients With MF

Summary of TEAEs

TEAE, n (%)	N=21
Any TEAE	21 (100.0)
Treatment-related*	14 (66.7)
Grade ≥3	14 (66.7)
Serious	6 (28.6)†
Fatal	0
Discontinuation of INCA033989 due to TEAEs	3 (14.3)‡
Dose reduction of INCA033989 due to TEAEs	2 (9.5)
Infusion interruption due to TEAEs	1 (4.8)
Dose delay of INCA033989 due to TEAEs	9 (42.9)

Most Common TEAEs (≥15% of Patients)

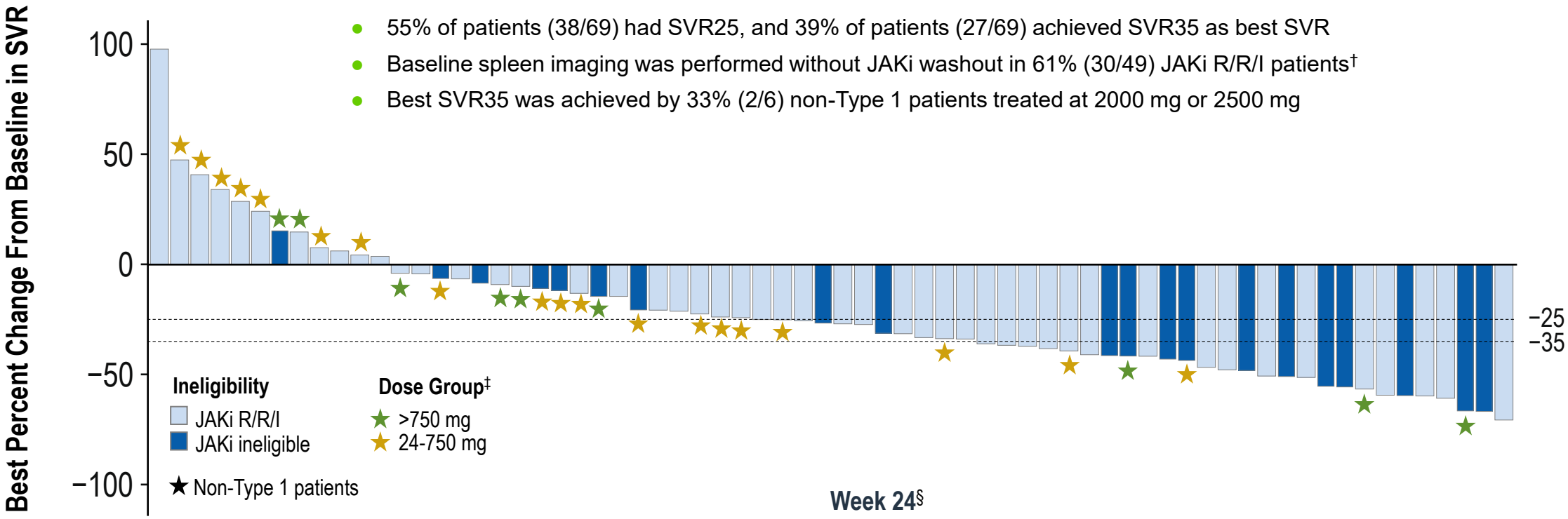
	N=21			
TEAE,¶¶ n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3§
Thrombocytopenia	9 (42.9)	4 (19.0)	3 (14.3)	2 (9.5)¶
Anemia	8 (38.1)	0	1 (4.8)	7 (33.3)¶
Diarrhea	5 (23.8)	4 (19.0)	1 (4.8)	0
Fatigue	5 (23.8)	4 (19.0)	1 (4.8)	0
ALT increase	4 (19.0)	2 (9.5)	1 (4.8)	1 (4.8)¶
AST increase	4 (19.0)	3 (14.3)	1 (4.8)	0

- Overall, 76% (n=16) patients were still receiving treatment and 24% (n=5) discontinued treatment‖
- No dose-limiting toxicities were observed; the maximum tolerated dose was not reached

*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); gastroenteritis, *Escherichia coli* (n=1; 70 mg). ‡Anemia (n=1; 250 mg); diffuse large B-cell lymphoma (n=1; 70 mg); thrombocytopenia (n=1; 1500 mg). §Other grade ≥3 TEAEs: neutropenia (n=2), abscess limb, acute myocardial infarction, basal cell carcinoma, diffuse large B-cell lymphoma, gastroenteritis (*Escherichia coli*), lymphopenia, obstructive sleep apnea syndrome, and stomatitis (each n=1). ¶Thrombocytopenia, grade 3 and 4 (n=1 each); anemia, grade 3 (n=6) and 4 (n=1); ALT increase, grade 3 (n=1). ‖Adverse event (n=3); physician decision (n=2). ¶¶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.

Rapid and Robust Spleen Volume Reductions Observed in Patients With MF

Best spleen response with monotherapy (n=68)*

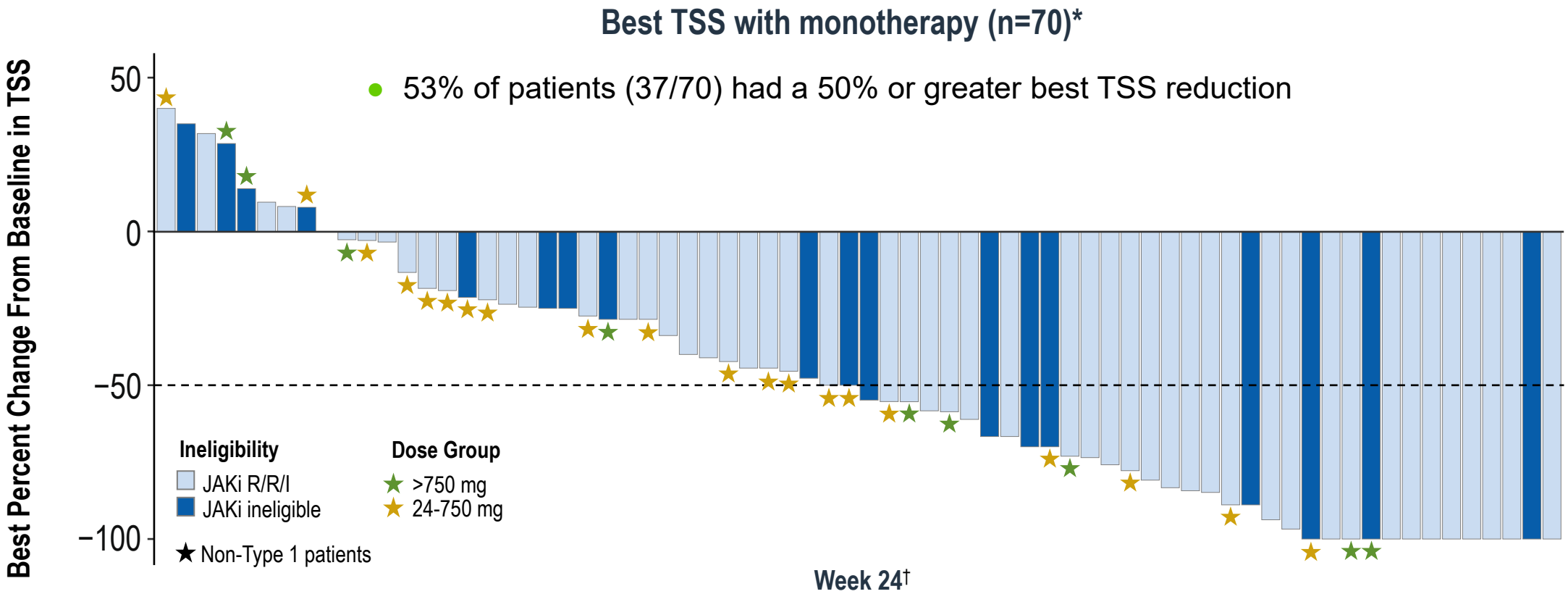


Week 24§

Variable, % (n/N)	Monotherapy							Combination
	JAKi Ineligible			JAKi R/R/I			Total	Total
	All Types	Type 1	Non-Type 1	All Types	Type 1	Non-Type 1		
SVR25	53 (9/17)	70 (7/10)	29 (2/7)	33 (15/45)	54 (14/26)	5 (1/19)	39 (24/62)	55 (11/20)
SVR35	47 (8/17)	60 (6/10)	29 (2/7)	20 (9/45)	31 (8/26)	5 (1/19)	27 (17/62)	30 (6/20)

*n=15 patients are excluded due to lack of postbaseline assessment, 14 remain on treatment, and 1 discontinued and was considered a nonresponder. †Washout defined as baseline spleen assessed >7 days after last JAKi dose. ‡Dose group reflects starting dose. §Patients who discontinued prior to week 24 are considered as nonresponders. MF, myelofibrosis; R/R/I, relapsed/refractory/intolerant; SVR25, spleen volume reduction of ≥25%; SVR35, spleen volume reduction of ≥35%.

Robust Symptom Improvement Observed in a Majority of Patients With MF

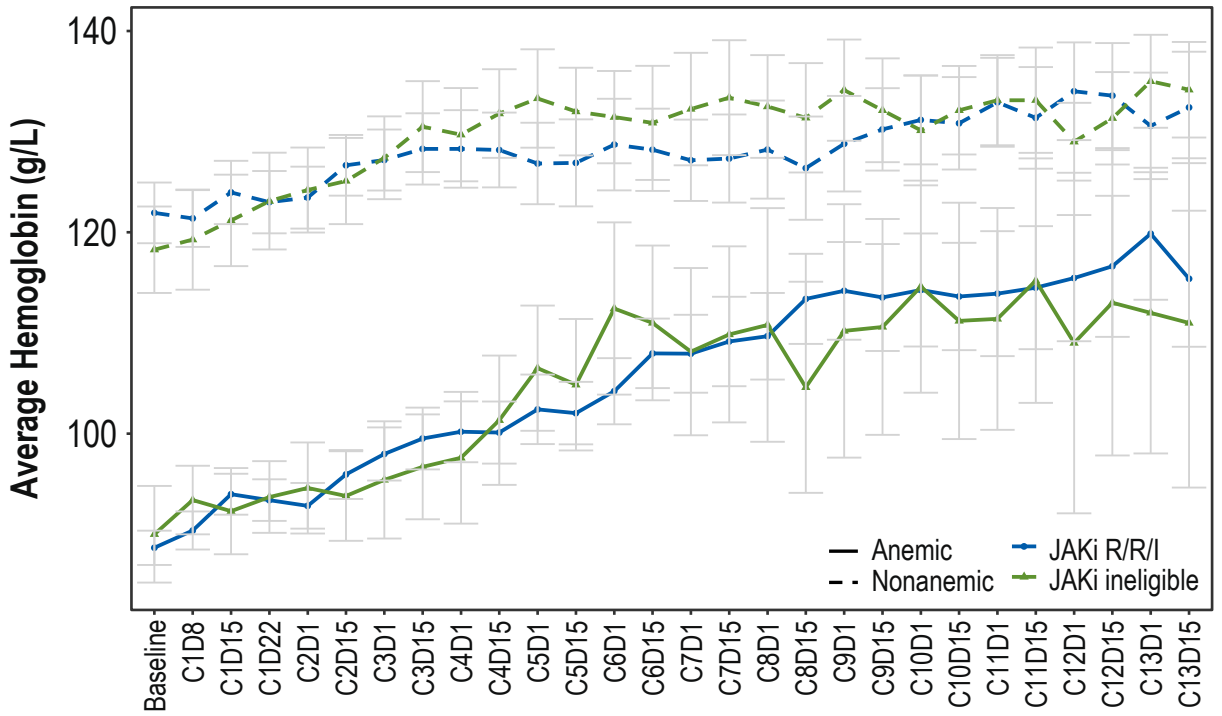


Variable, % (n/N)	Monotherapy							Combination
	JAKi Ineligible			JAKi R/R/I				
	All Types	Type 1	Non-Type 1	All Types	Type 1	Non-Type 1	Total	Total
TSS50	29 (4/14)	33 (3/9)	20 (1/5)	33 (14/42)	44 (10/23)	21 (4/19)	32 (18/56‡)	31 (5/16)

*n=13 patients excluded: 11 due to lack of postbaseline assessment (patients remain on treatment), 1 due to missing baseline assessment, and 1 due to baseline TSS value of 0. †Patients who discontinued prior to week 24 are considered as nonresponders. ‡5 patients are excluded due to missing baseline or week 24 assessments, 1 patient excluded due to baseline TSS value of 0. Postbaseline assessments performed every 12 weeks. MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; R/R/I, relapsed/refractory/intolerant; TSS, total symptom score; TSS50, ≥50% reduction in MPN-SAF TSS.

Rapid and Durable Anemia Improvements Observed in Most Patients With MF

Mean Hemoglobin by Anemic Status* (Monotherapy; n=83)



Best Anemia Response in Evaluable† Monotherapy Patients

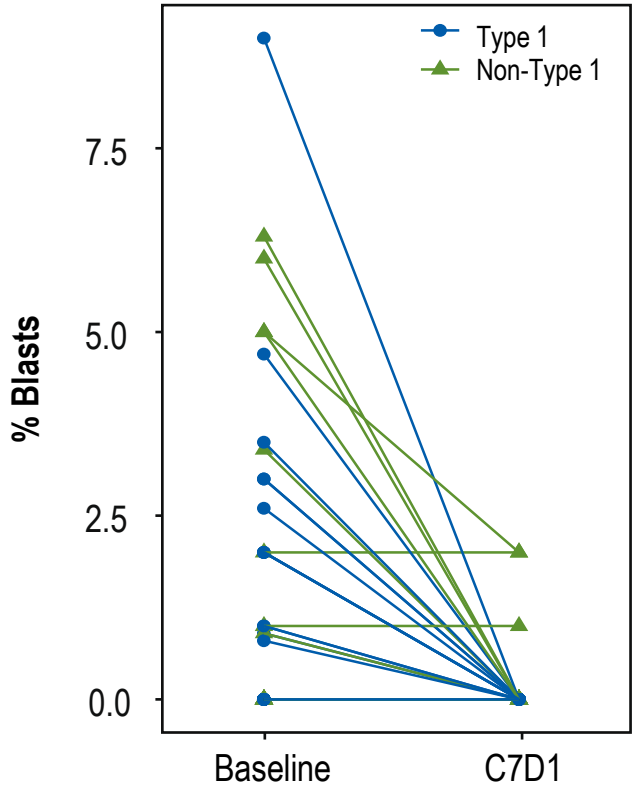
Variable, n (%)	Non-anemic (n=29)	TDA (n=6)	Non-TDA (n=34)	Total‡ (n=69)
Anemia response*	18 (62.1)	4 (66.7)	20 (58.8)	42 (60.9)
Major	15 (51.7)	3 (50.0)	18 (52.9)	36 (52.2)
Minor	3 (10.3)	1 (16.7)	2 (5.9)	6 (8.7)
Stable	11 (37.9)	1 (16.7)	11 (32.4)	23 (33.3)
Progressive	0 (0)	1 (16.7)	1 (2.9)	2 (2.9)

- Anemia response occurred in 60% (24/40) of evaluable† anemic patients; most patients achieved a major response
- Improvement in anemia was observed in 63% (31/49) JAKi R/R/I patients and 55% (11/20) JAKi ineligible patients
- Anemia response occurred in 35% (6/17) of evaluable anemic patients in combination with ruxolitinib

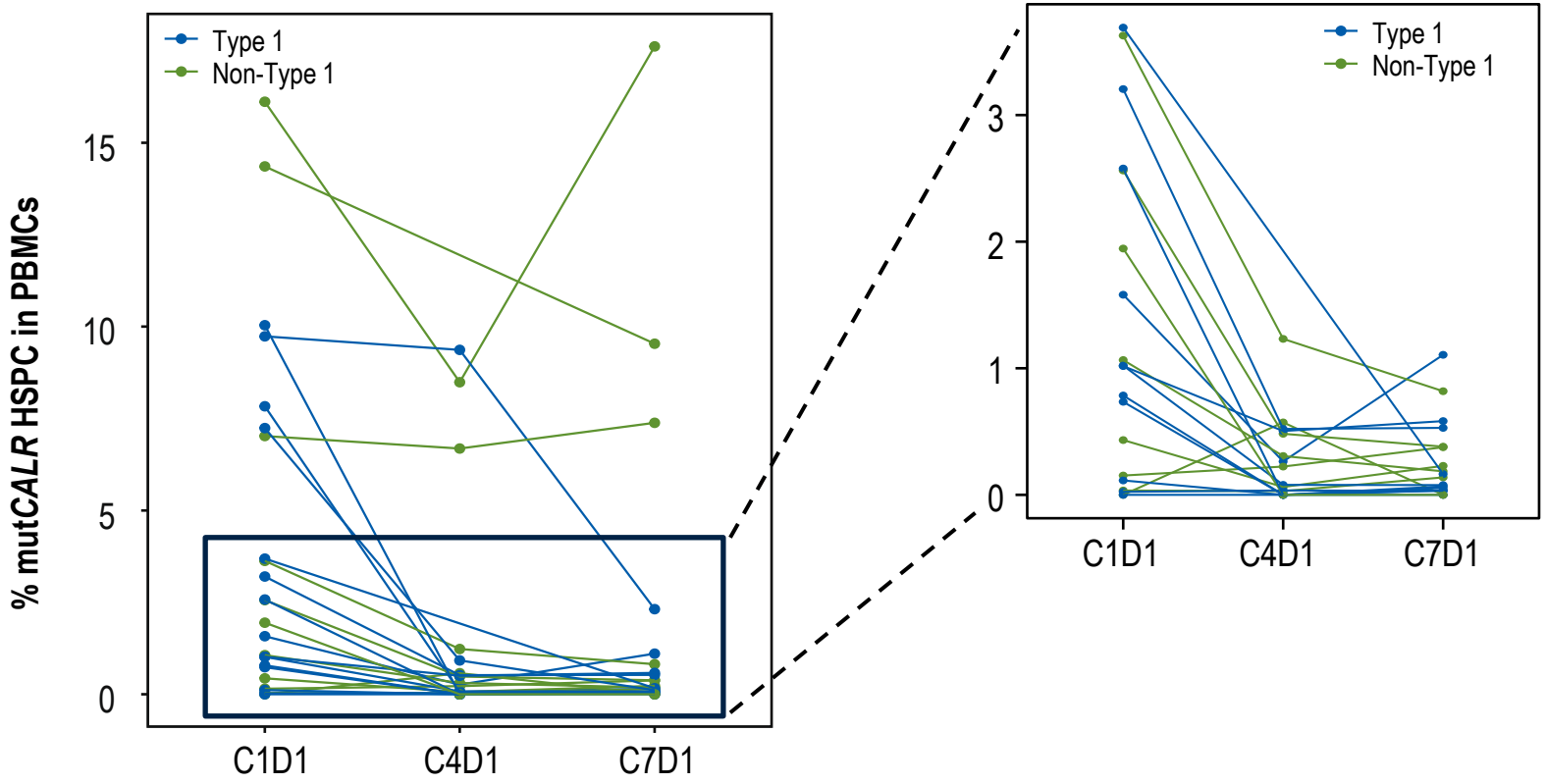
1 cycle = 2 doses (~28 days). *Criteria for baseline anemia and response based on Tefferi A. *Blood*. 2024;114:1813. †14 patients excluded due to <12 weeks exposure and remain on treatment. ‡2 anemic/non-TDA patients had missing data due to discontinuing from treatment with less than 12 weeks of exposure to INCA033989 and are considered nonresponders. R/R/I, relapsed/refractory/intolerant; TDA, transfusion-dependent anemia.

Reduction in Blasts and Progenitor Cells Observed Across All Mutation Types

Peripheral Blast* Reductions Observed in Type 1 and Non-Type 1 Patients (n=50†)

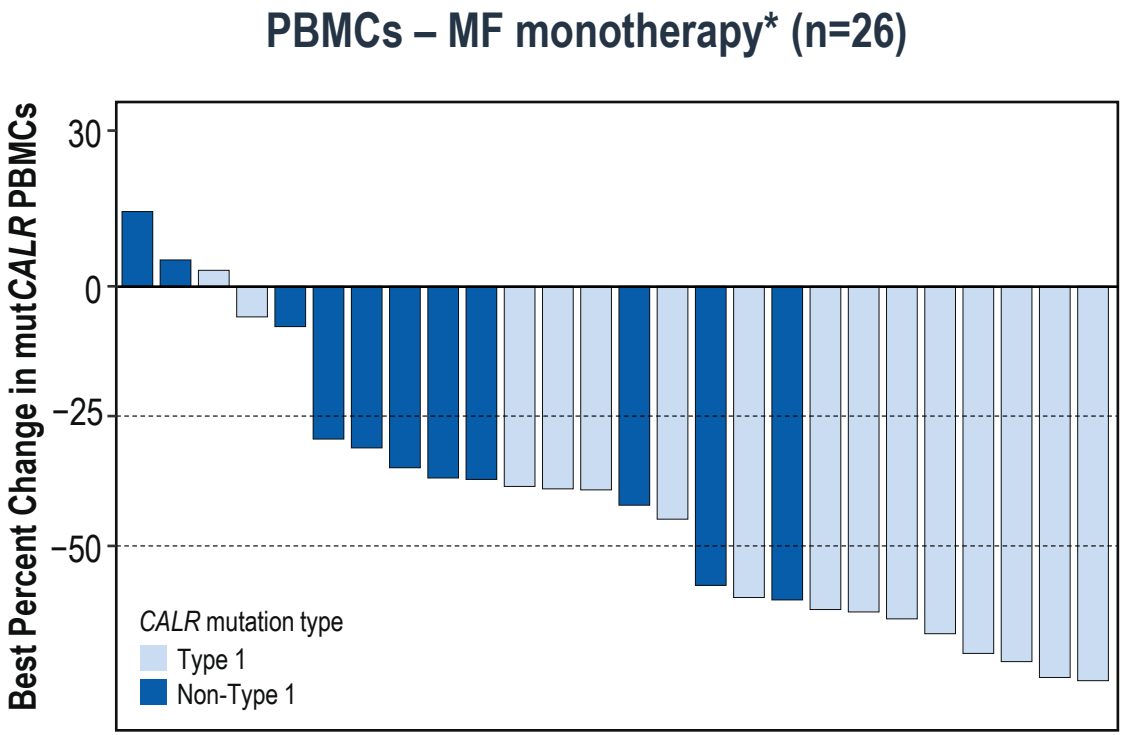


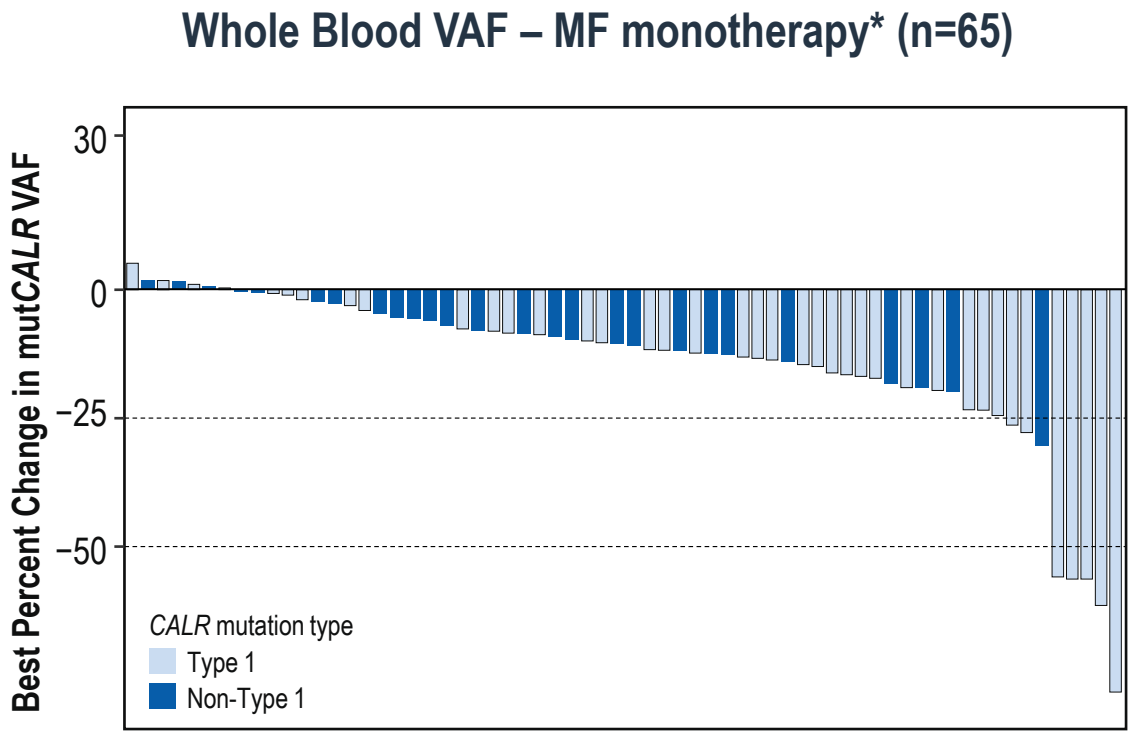
Peripheral HSPC‡ Reductions Observed in Type 1 and Non-Type 1 Patients (n=26§)



*Percent blasts from local or central peripheral blood analysis. †Only MF monotherapy patients with baseline and C7D1 assessments are represented. ‡HSPC data are based on single cell sequencing data using clustering based on immunophenotype. §All MF monotherapy patients with at least 1 postbaseline assessment are represented. C, cycle; D, day; HSPC, hematopoietic stem and progenitor cell; mutCALR, mutations of calreticulin; PBMC, peripheral blood mononuclear cell.

Reduction in mut*CALR* PBMCs and Peripheral VAF Observed Across All Mutation Types



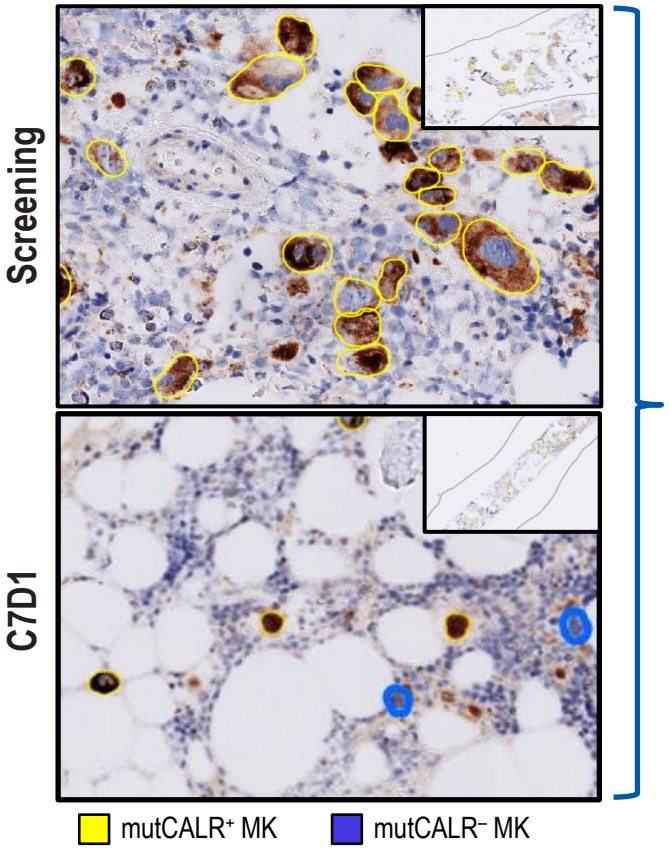


- 81% of patients (21/26) had a 25% reduction in mut*CALR* PBMCs, of whom 62% (13/21) had Type 1 and 38% (8/21) had non-Type 1 mut*CALR*
- 89% of patients (35/39 Type 1; 23/26 non-Type 1) had reduction in whole blood mut*CALR* VAF; 12.3% of patients reached MR25 as best molecular response

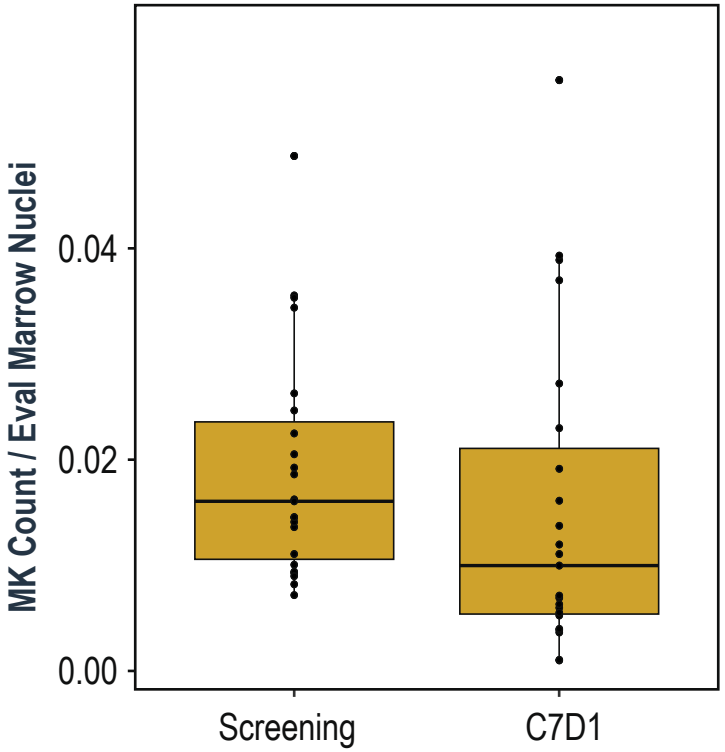
*MF monotherapy patients with at least 1 postbaseline assessment are represented. PBMC data was generated using single-cell sequencing (MissionBio). WB VAF data was generated by using targeted next-generation sequencing.
MR25, molecular response of 25% reduction mut*CALR* VAF; mut*CALR*, mutations of calreticulin; PBMC, peripheral blood mononuclear cell; VAF, variant allele frequency; WB, whole blood.

Rapid Improvement in Bone Marrow Pathology and Restoration of Hematopoiesis Suggest Potential Disease Modification With Monotherapy

Representative mutCALR IHC*

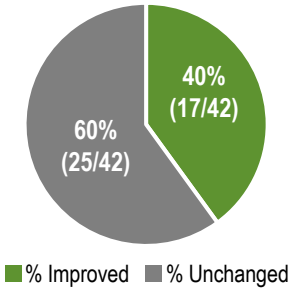


mutCALR MK Quantitative Analysis†

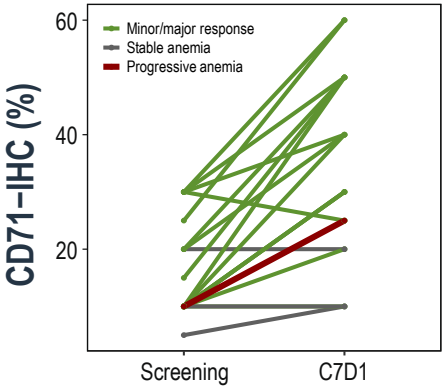


Fibrosis Grade‡

Change by C7D1



CD71§



*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). †n=23.
‡Fibrosis grade was centrally assessed for all patients with available screening and C7D1 samples. "Improved": decreased by ≥1 grade; "Unchanged": stable. §CD71 IHC was centrally assessed by a single pathologist; data includes all patients with baseline anemia and available CD71 IHC for screening and C7D1 (n=20). C, cycle; D, day; IHC, immunohistochemistry; MF, myelofibrosis; MK, megakaryocytes; mut*CALR*, mutations of calreticulin.

Conclusions

- INCA033989 administered as monotherapy or in combination with ruxolitinib continues to show a favorable safety profile in patients with MF who are relapsed/resistant/intolerant to, or ineligible for, JAKi therapy or had a suboptimal response to ruxolitinib
- No dose-limiting toxicities were observed, and the maximum tolerated dose was not reached
  - Overall, 84% of patients remain on INCA033989 monotherapy and 76% of patients remain on INCA033989 + ruxolitinib
- Rapid and robust spleen, symptom, and anemia responses were observed
- mut*CALR* VAF reduction was observed along with improvements in bone marrow pathology and restoration of hematopoiesis in a majority of patients
- These data support the disease modification potential of INCA033989 and the initiation of a phase 3 program in patients with MF

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

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- Additional INCA033989 presentations:
  - Clinical safety, tolerability, and efficacy in the ET cohort will be presented by Dr. John Mascarenhas on **Friday, June 12, 6:45 pm to 7:45 pm CEST (#PS1983)**
  - Analyses of clinical and molecular responses in MF patients with high molecular risk mutations will be presented by Dr. Jyoti Nangalia on **Saturday, June 13, 6:45 pm to 7:45 pm CEST (#PF884)**
- These data support the planned initiation of a phase 3 program (NCT07623200; EXCALIBUR-ET2)

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