MPN-556

Mutant Calreticulin-Specific Monoclonal Antibody, INCA033989, Produces Clonal Molecular Responses That Correlate With Clinical Responses in Patients With Myelofibrosis

Presented at the
Society of Hematologic Oncology (SOHO) Annual Meeting
Houston, TX, USA • September 9-12, 2026
Originally presented at EHA 2026

John Mascarenhas,[1] Jyoti Nangalia,[2] Claire Harrison,[3] Jason Gotlib,[4] Chenwei Tian,[5] Betty Lamothe,[5] Tatiana Zinger,[5] Erin Crowgey,[5] Evan Braunstein,[5] Steffen Koschmieder[6]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Wellcome Sanger Institute, Hinxton, UK; [3]Guy's and St Thomas' NHS Foundation Trust, London, UK; [4]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; [5]Incyte Corporation, Wilmington, DE, USA; [6]RWTH Aachen University, Faculty of Medicine, and Center for Integrated Oncology (CIO-ABCD), Aachen, Germany.

Introduction

- Approximately 25-35% of patients with essential thrombocythemia (ET) and myelofibrosis (MF) harbor a calreticulin (*CALR*) mutation (mut*CALR*)[1]
- All mutations result in aberrant expression of mutCALR on the cell surface
- INCA033989 is a first-in-class, novel, fully human, Fc-silenced, immunoglobulin G1 (IgG1) monoclonal antibody that selectively targets mutCALR with high affinity when in complex with TPO-R, to inhibit oncogenic signaling and proliferation of cells[2]
- INCA033989-101 (NCT05936359) and -102 (NCT06034002) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA033989 as monotherapy or in combination with ruxolitinib in patients with previously treated ET or MF harboring a *CALR* mutation
- Analyses of clinical and molecular responses in MF patients with high molecular risk (HMR) mutations are presented

Figure 1. INCA033989 Mechanism of Action

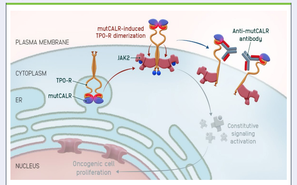


Figure reprinted from Reis E, et al. *Blood*. 2024;144:2336-2348 [visual abstract] with permission from Elsevier Inc. Copyright © 2024 American Society of Hematology.
ER, endoplasmic reticulum; JAK2, Janus kinase 2; TPO-R, thrombopoietin receptor.

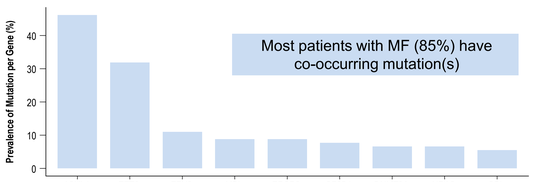
Results

Table 1. Baseline Characteristics

	Total (N=91)	HMR* (n=46)	No HMR (n=45)
Age			
Years, median (range)	61.0 (34.0, 82.0)	61.5 (41.0, 77.0)	60.0 (34.0, 82.0)
18 to <65 years, n (%)	59 (64.8)	30 (65.2)	29 (64.4)
≥65 years, n (%)	32 (35.2)	16 (34.8)	16 (35.6)
Sex, n (%)			
Male	64 (70.3)	34 (73.9)	30 (66.7)
Female	27 (29.7)	12 (26.1)	15 (33.3)
Time from initial diagnosis, years, median (range)	5.56 (0.02, 25.4)	6.52 (0.39, 25.4)	4.88 (0.02, 17.9)
Spleen volume, mL, median (range)	1495 (226, 5338)	2014.5 (343, 5338)	1179.0 (226, 2880)
Hemoglobin, g/L, median (range)	98 (60, 147)	96.0 (70, 137)	100.0 (60,147)
Platelets, G/L, median (range)	287 (41, 1290)	235 (42, 1290)	355 (41, 1267)
Leukocytes, G/L, median (range)	7.0 (1.5, 85.0)	7.85 (2.4, 85.0)	6.70 (1.5, 21.1)
DIPSS risk level, n (%)			
High risk level (5 or 6 prognostic points)	3 (3.3)	1 (2.2)	2 (4.4)
Intermediate risk level 2 (3 or 4 prognostic points)	48 (52.7)	27 (58.7)	21 (46.7)
Intermediate risk level 1 (1 or 2 prognostic points)	33 (36.3)	17 (37.0)	16 (35.6)
Low risk level (0 prognostic points)	7 (7.7)	1 (2.2)	6 (13.3)
Treatment cohort, n (%)			
INCA033989 monotherapy	71 (78.0)	30 (65.2)	41 (91.1)
INCA033989 + ruxolitinib	20 (22.0)	16 (34.8)	4 (8.9)
mut*CALR* type, n (%)			
Type 1	54 (59.3)	26 (56.5)	28 (62.2)
Non-Type 1	37 (40.7)	20 (43.5)	17 (37.8)
Multiple MPN driver mutation, n (%)	6 (6.6)	4 (8.7)	2 (4.4)
>1 *CALR* exon 9 mutation	4 (4.4)	3 (6.5)	1 (2.2)
MPL p.W515 mutation	2 (2.2)	1 (2.2)	1 (2.2)
mut*CALR* VAF†, mean	43	43	43

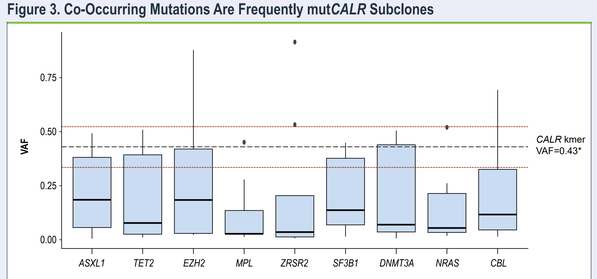
Genomic data presented are from patients with baseline measured centrally in peripheral blood by NGS (targeted panel n=37 genes). *Defined as high molecular risk (HMR) per MIPSS70 (*ASXL1, SRSF2, IDH1, IDH2, EZH2*). †kmer-corrected VAF for CALR exon 9 frameshift mutations.
DIPSS, Dynamic International Prognostic Scoring System; G/L, giga (10^9) per liter; MPN, myeloproliferative neoplasm; VAF, variant allele frequency.

Figure 2. Most Frequent Co-Occurring Mutations



Only genes with a prevalence of ≥5% are reported. Variant prioritization for co-occurring mutations included filtering based on a population-level database and manual curation.

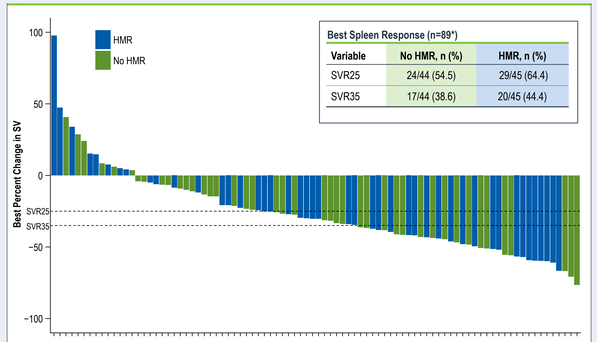
Figure 3. Co-Occurring Mutations Are Frequently mut*CALR* Subclones



*Mean *CALR* VAF at enrollment (dark dotted line) and the SD (red dotted line).

- For each patient, a comparison between mut*CALR* VAF and the concurrent somatic mutation was analyzed
- For most (67%) of the genes analyzed, a majority of patients (≥75%) demonstrate a subclonal pattern

Figure 4. Spleen Responses in Patients With or Without HMR

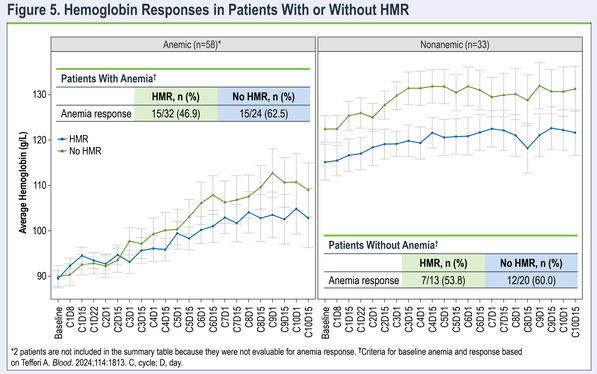


Best Spleen Response (n=89*)		
Variable	**No HMR, n (%)**	**HMR, n (%)**
SVR25	24/44 (54.5)	29/45 (64.4)
SVR35	17/44 (38.6)	20/45 (44.4)

*2 patients were excluded due to lack of a postbaseline assessment and remain on treatment. Patients that discontinued prior to first postbaseline assessment are considered nonresponders (n=1, excluded from figure).
SV, spleen volume; SVR, spleen volume response; SVR25, spleen volume reduction of ≥25%; SVR35, spleen volume reduction of ≥35%.

- No difference in spleen response was observed between patients with vs without HMR (nominal Fisher's *P* value >0.05)

Figure 5. Hemoglobin Responses in Patients With or Without HMR



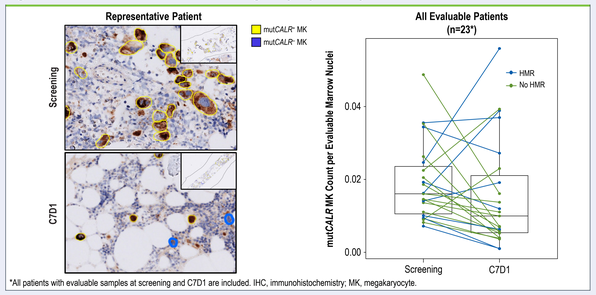
Patients With Anemia†		
	HMR, n (%)	**No HMR, n (%)**
Anemia response	15/32 (46.9)	15/24 (62.5)

Patients Without Anemia†		
	HMR, n (%)	**No HMR, n (%)**
Anemia response	7/13 (53.8)	12/20 (60.0)

*2 patients are not included in the summary table because they were not evaluable for anemia response. †Criteria for baseline anemia and response based on Tefferi A. *Blood*. 2024;114:1813. C, cycle; D, day.

- Anemic and nonanemic patients show improvements in hemoglobin levels with INCA033989 treatment
- In anemic patients, hemoglobin increased over time in both HMR (*P*<0.05) and no HMR groups (*P*<0.001)

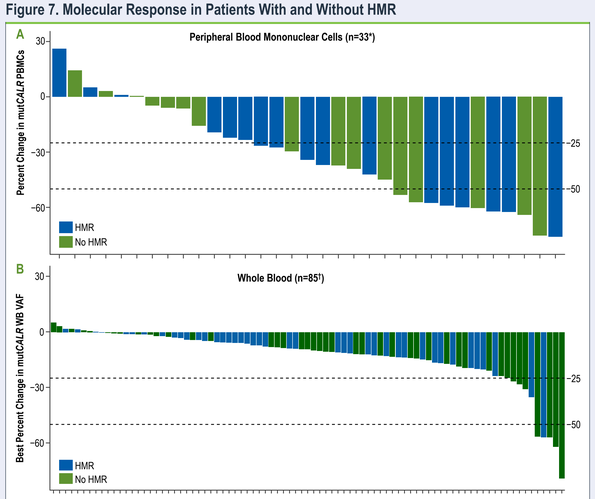
Figure 6. Bone Marrow mut*CALR* IHC Megakaryocyte Analysis



*All patients with evaluable samples at screening and C7D1 are included. IHC, immunohistochemistry; MK, megakaryocyte.

- 56% (5/9) and 86% (12/14) had a reduction in mut*CALR* MK in patients with and without HMR, respectively

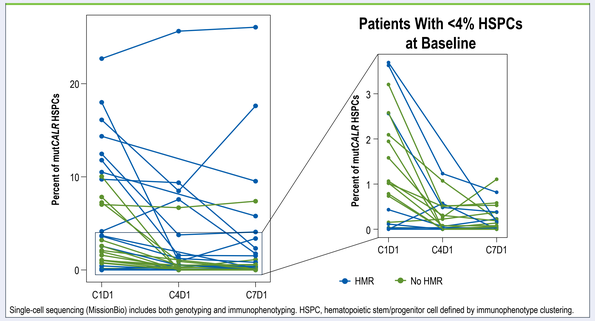
Figure 7. Molecular Response in Patients With and Without HMR



*Total number of patients with evaluable PBMCs. †Total number of patients evaluable for WB VAF. Patients with >1 mut*CALR* were not included in this analysis.
PBMC, peripheral blood mononuclear cell; WB, whole blood.

- 65% (11/17) and 56% (9/16) had a ≥25% reduction in mut*CALR* PBMCs in patients with and without HMR, respectively
- 93% (39/42) and 88% (38/43) had a reduction in mut*CALR* WB VAF in patients with and without HMR, respectively

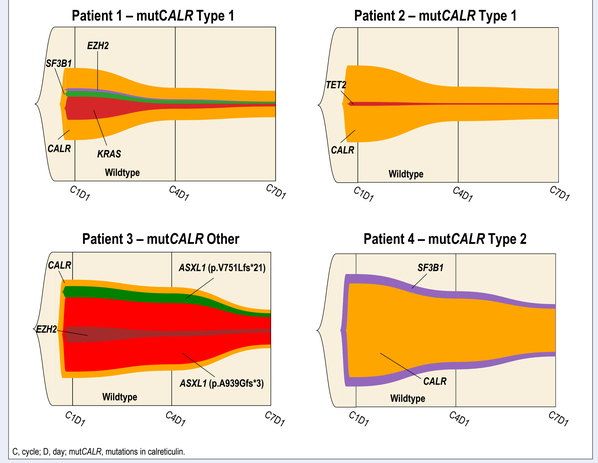
Figure 8. Evaluation of mut*CALR* HSPCs in Patients With or Without HMR



Single-cell sequencing (MissionBio) includes both genotyping and immunophenotyping. HSPC, hematopoietic stem/progenitor cell defined by immunophenotype clustering.

- Reductions in circulating mut*CALR* hematopoietic stem/progenitor cells (HSPCs) were observed with INCA033989 treatment, demonstrating a targeted effect on disease-initiating cells
- Reductions were noted in patients regardless of baseline percent mut*CALR* HSPCs

Figure 9. Clonal Response in Representative Patients



C, cycle; D, day; mut*CALR*, mutations in calreticulin.

- In 3 representative patients, the presence of non-driver subclones did not prevent molecular response of the mut*CALR* clone
- A molecular response was also observed in a fourth patient with mut*CALR* present as a subclone of SF3B1

Conclusions

- **A majority of patients with MF (85%) had co-occurring somatic mutations**
  - **Non-driver somatic mutations were frequently subclones of mut*CALR***
- **Clinical efficacy was observed in patients with and without HMR following treatment with INCA033989**
  - **Spleen and anemia responses were observed in the presence of HMR mutations**
  - **Molecular responses were observed in the presence of HMR mutations**
  - **Reductions in mut*CALR* HSPCs and MKs were observed in a majority of patients, regardless of the presence of HMR mutations**
- **Subclonal complexity within the mut*CALR* clone did not impact molecular response in most evaluable patients**
- **Overall, these findings demonstrate that INCA033989 reduces disease-initiating mut*CALR* clones, including subclones harboring HMR mutations**
- **A phase 3 program of INCA033989 is being initiated (NCT07623000; EXCALIBUR-ET2)**

Disclosures

Dr. Mascarenhas: Consulting fees: *AbbVie, Bristol Myers Squibb, Disc, Geron, GlaxoSmithKline, Incyte, Italfarmaco Spa, Kartos, Karyopharm, Keros, Merck, MorphoSys, Novartis, PharmaEssentia, Roche, Sobi, and Sumitomo.* Research funding: *Bristol Myers Squibb, Disc, Geron, Incyte, Italfarmaco, Kartos, Karyopharm, Novartis, and PharmaEssentia.*

Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study. This study was sponsored by Incyte Corporation (Wilmington, DE, USA) Medical writing assistance was provided by Sandra J. Page, PhD, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, and funded by Incyte Corporation. These data were originally presented at EHA 2026.

References

1. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390.
2. Reis ES, et al. *Blood*. 2024;22:2336-2348.

EXCALIBUR-ET2