

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

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Introduction

- Approximately 25-35% of patients with essential thrombocythemia (ET) and myelofibrosis (MF) harbor a calreticulin (*CALR*) mutation (*mutCALR*)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 cells²
- 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

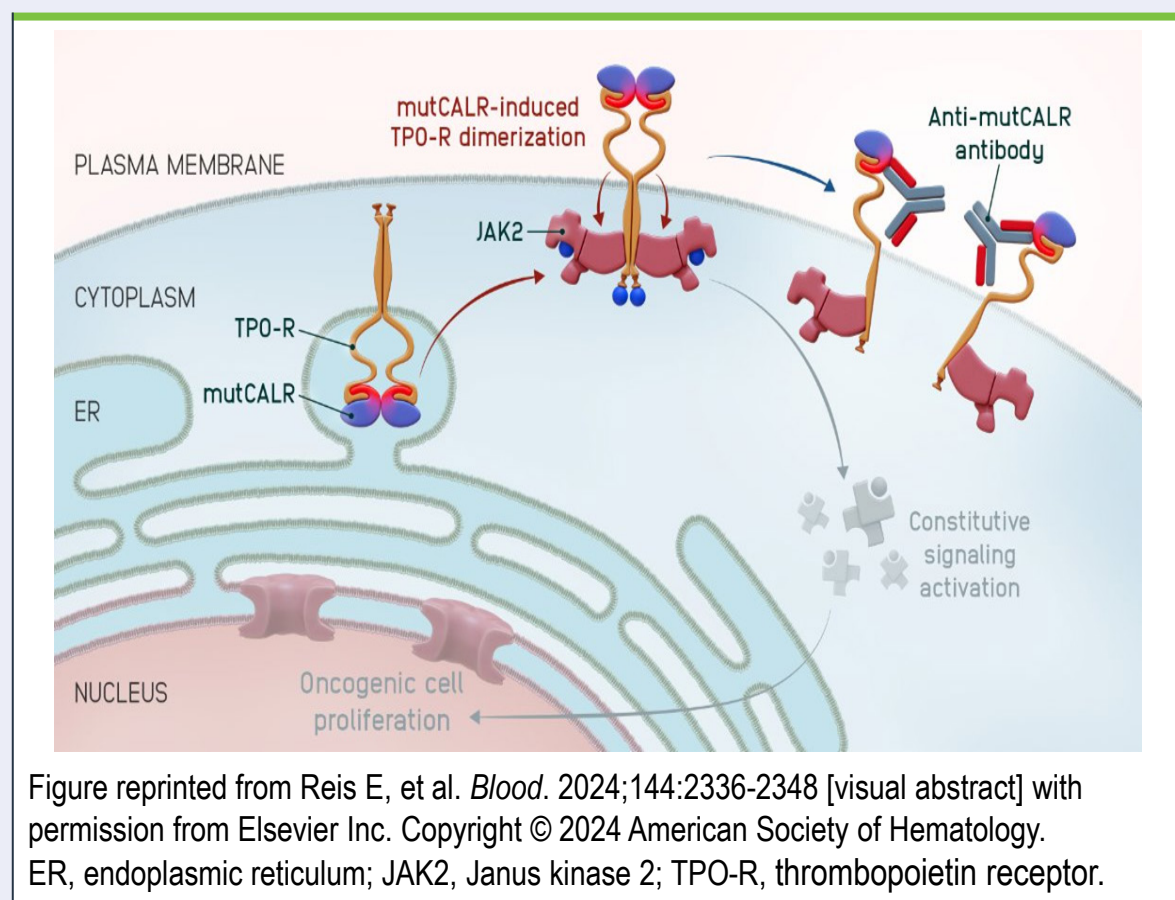


Figure reprinted from Reis E, et al. *Blood*. 2024;144:2336-2348 [visual abstract] with permission from Elsevier Inc. Copyright © 2024 American Society of Hematology. ER, endoplasmic reticulum; JAK2, Janus kinase 2; TPO-R, thrombopoietin receptor.

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)
mutCALR 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 (%)			
>1 <i>CALR</i> exon 9 mutation	4 (4.4)	3 (6.5)	1 (2.2)
<i>MPL</i> p.W515 mutation	2 (2.2)	1 (2.2)	1 (2.2)
mutCALR VAF[†], mean	43	43	43

Genomic data presented is from patients with baseline measured centrally in peripheral blood by NGS (targeted panel n=37 genes). *Defined as high molecular risk (HMR) per MPSS70 (*ASXL1*, *SRSF2*, *IDH1*, *IDH2*, *EZH2*). †kmer-corrected VAF for *CALR* exon 9 frameshift mutations. DIPSS, Dynamic International Prognostic Scoring System; G/L, giga (10⁹) per liter; MPN, myeloproliferative neoplasm; VAF, variant allele frequency.

Figure 2. Most Frequent Co-Occurring Mutations

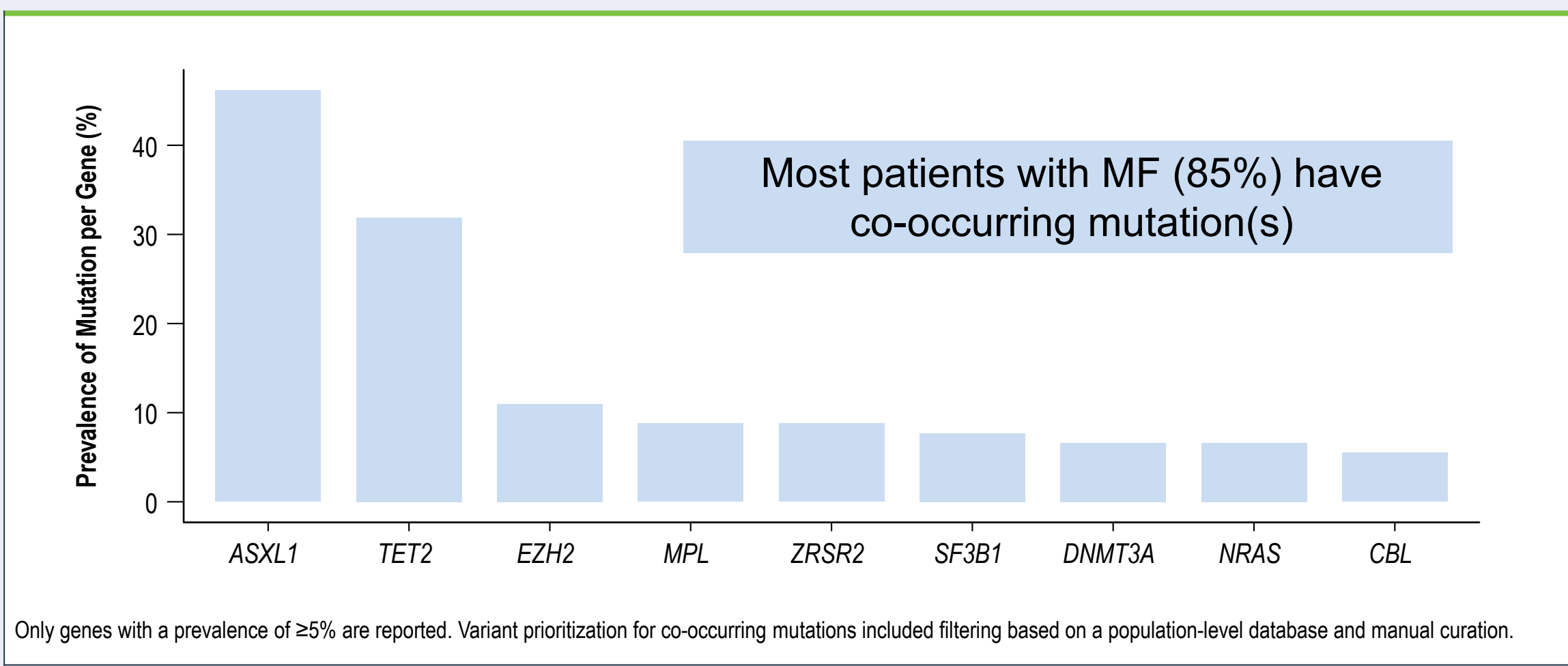
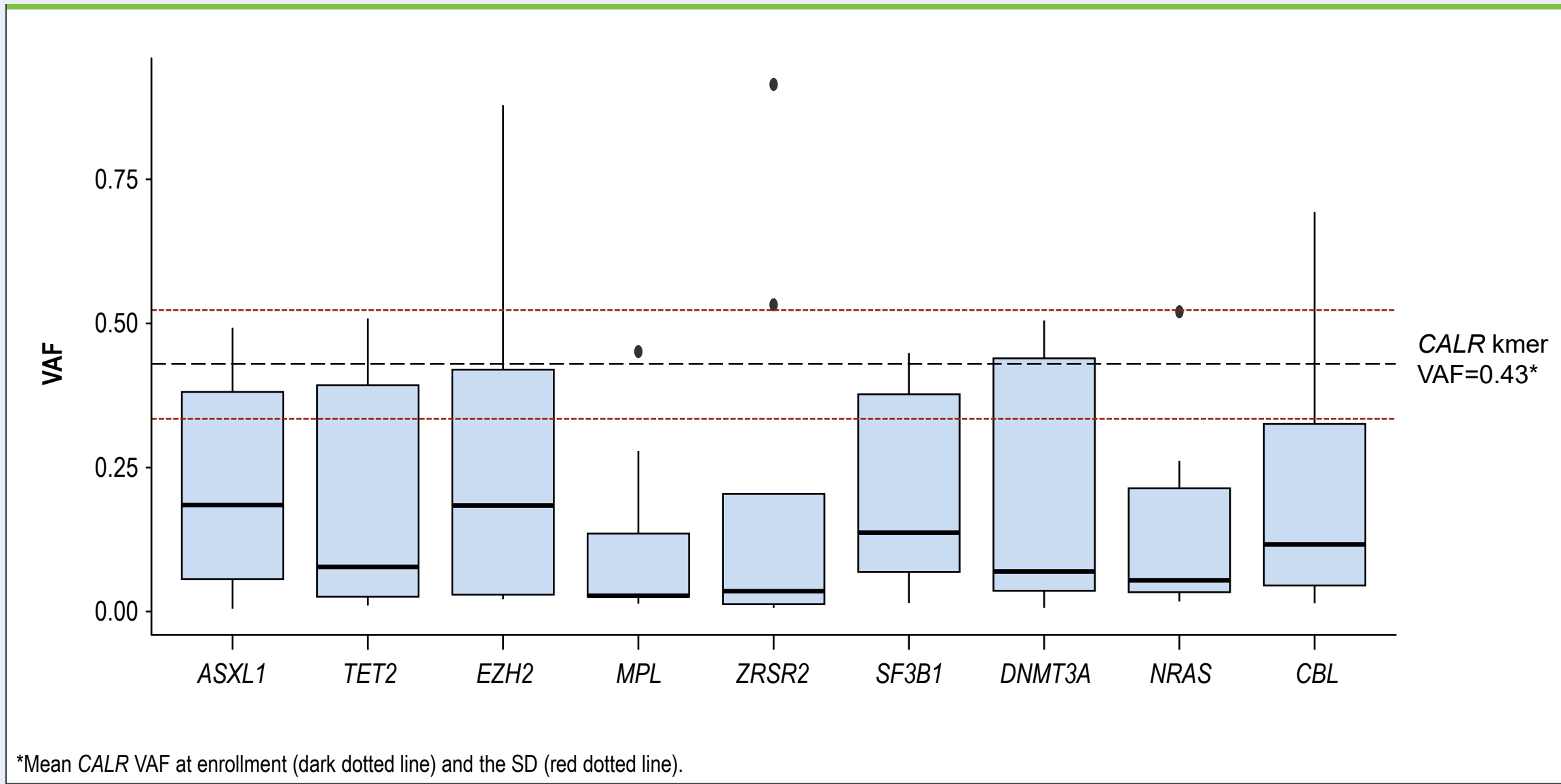


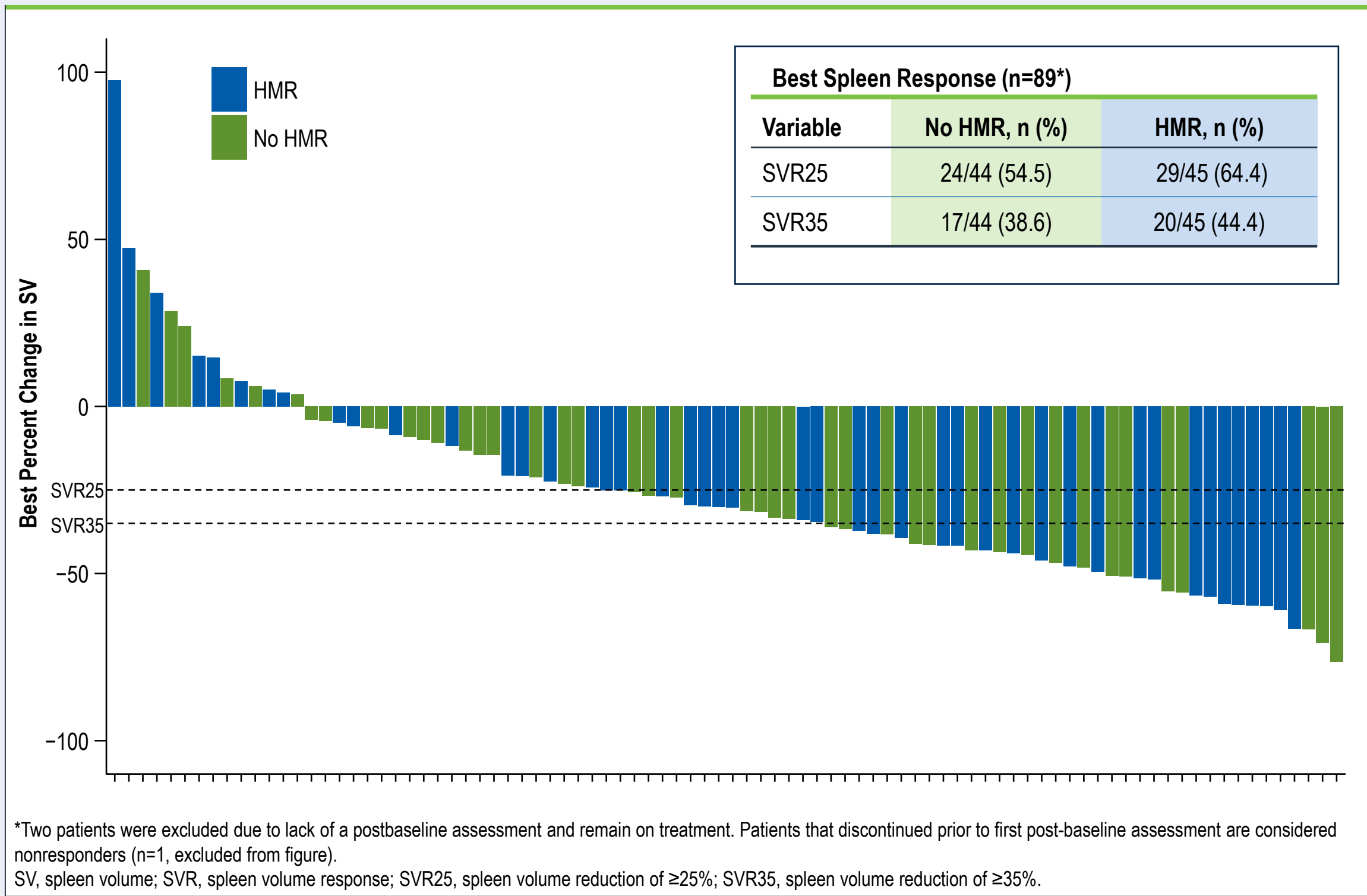
Figure 3. Co-Occurring Mutations Are Frequently *mutCALR* Subclones



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

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

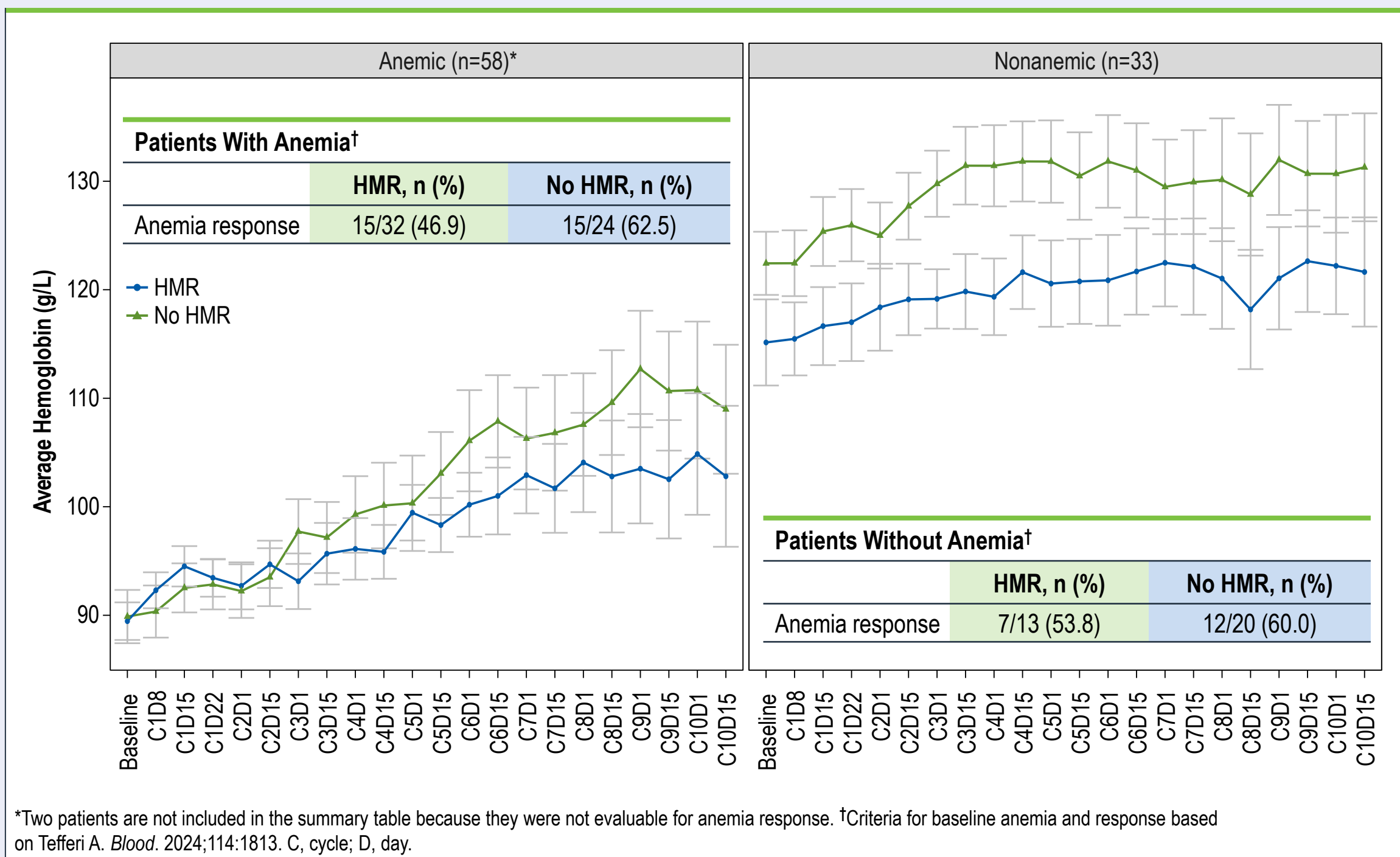
Figure 4. Spleen Responses in Patients With or Without HMR



*Two patients were excluded due to lack of a postbaseline assessment and remain on treatment. Patients that discontinued prior to first post-baseline 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)

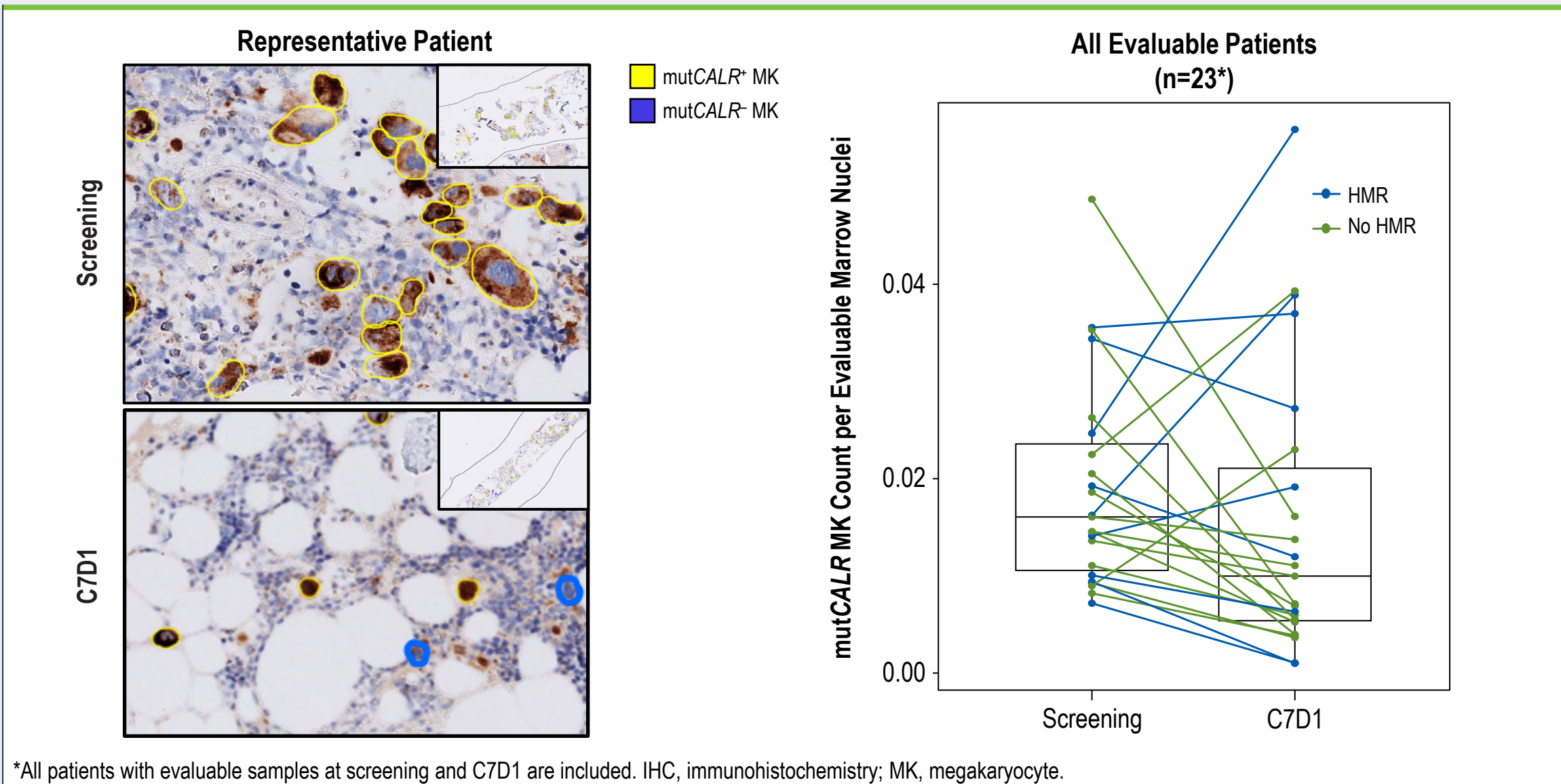
Figure 5. Hemoglobin Responses in Patients With or Without HMR



*Two patients are not included in the summary table because they were not evaluable for anemia response. †Criteria for baseline anemia and response based on Telfer 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)

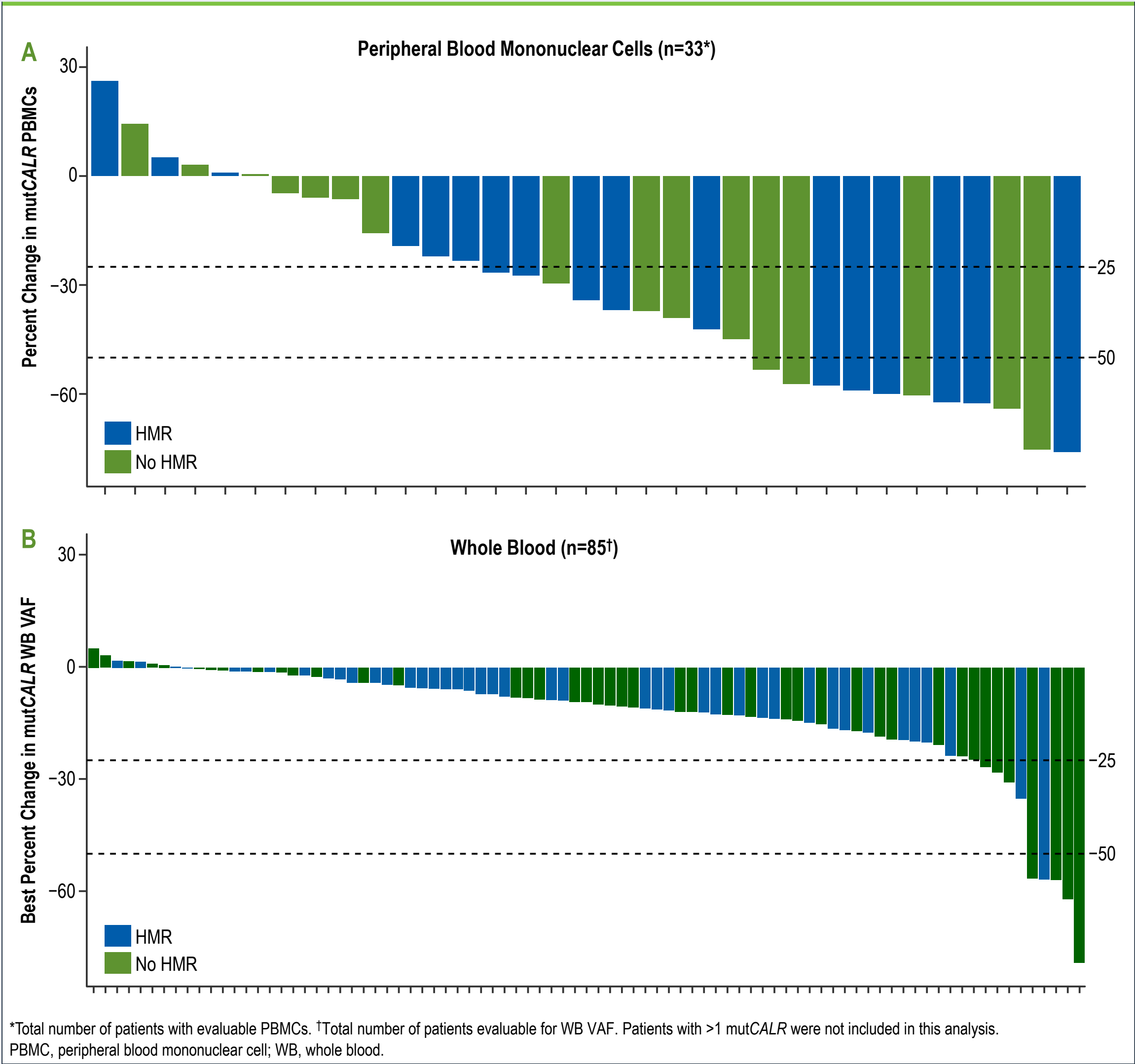
Figure 6. Bone Marrow *mutCALR* IHC Megakaryocyte Analysis



*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 *mutCALR* MK in patients with and without HMR, respectively

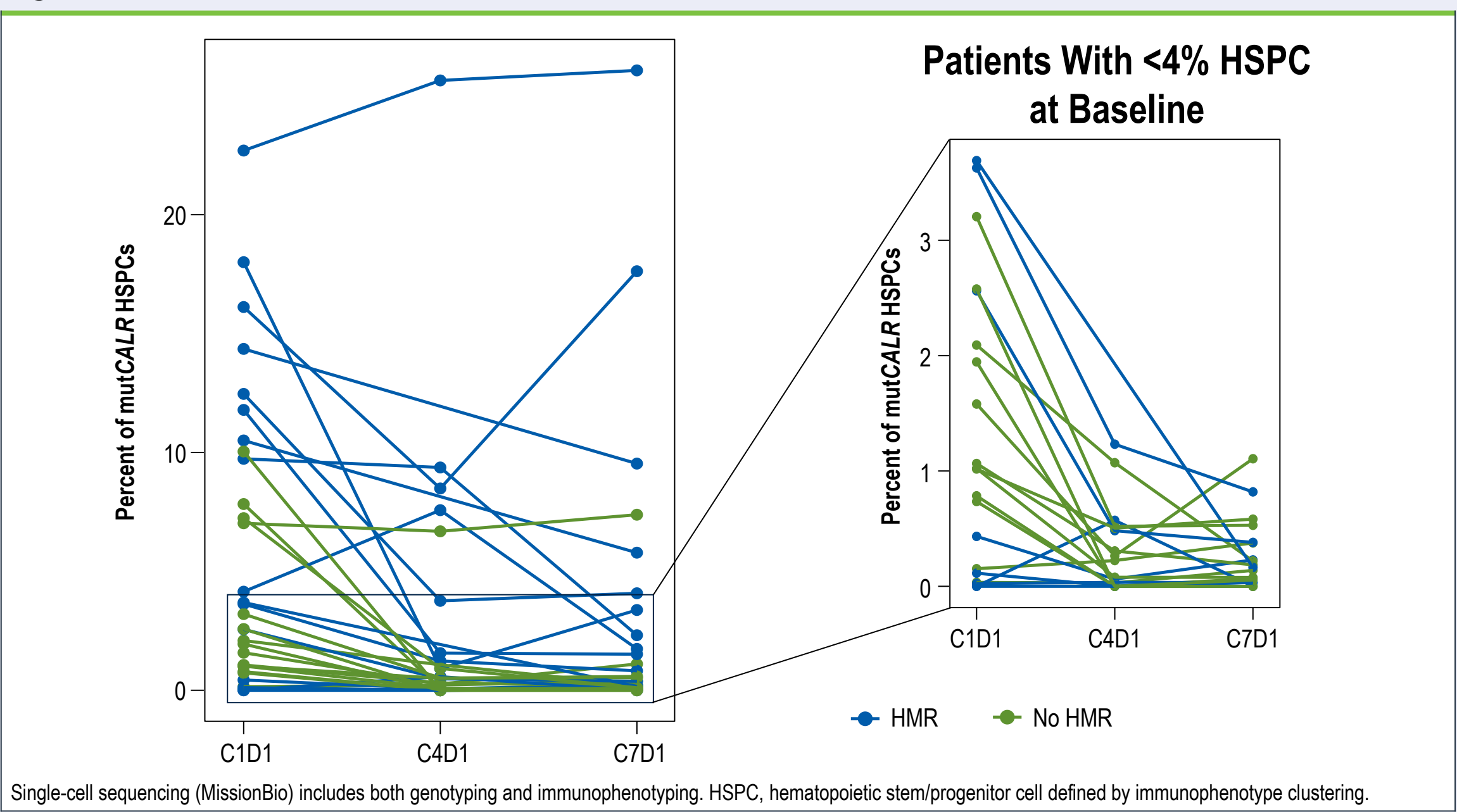
Figure 7. Molecular Response in Patients With and Without HMR



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

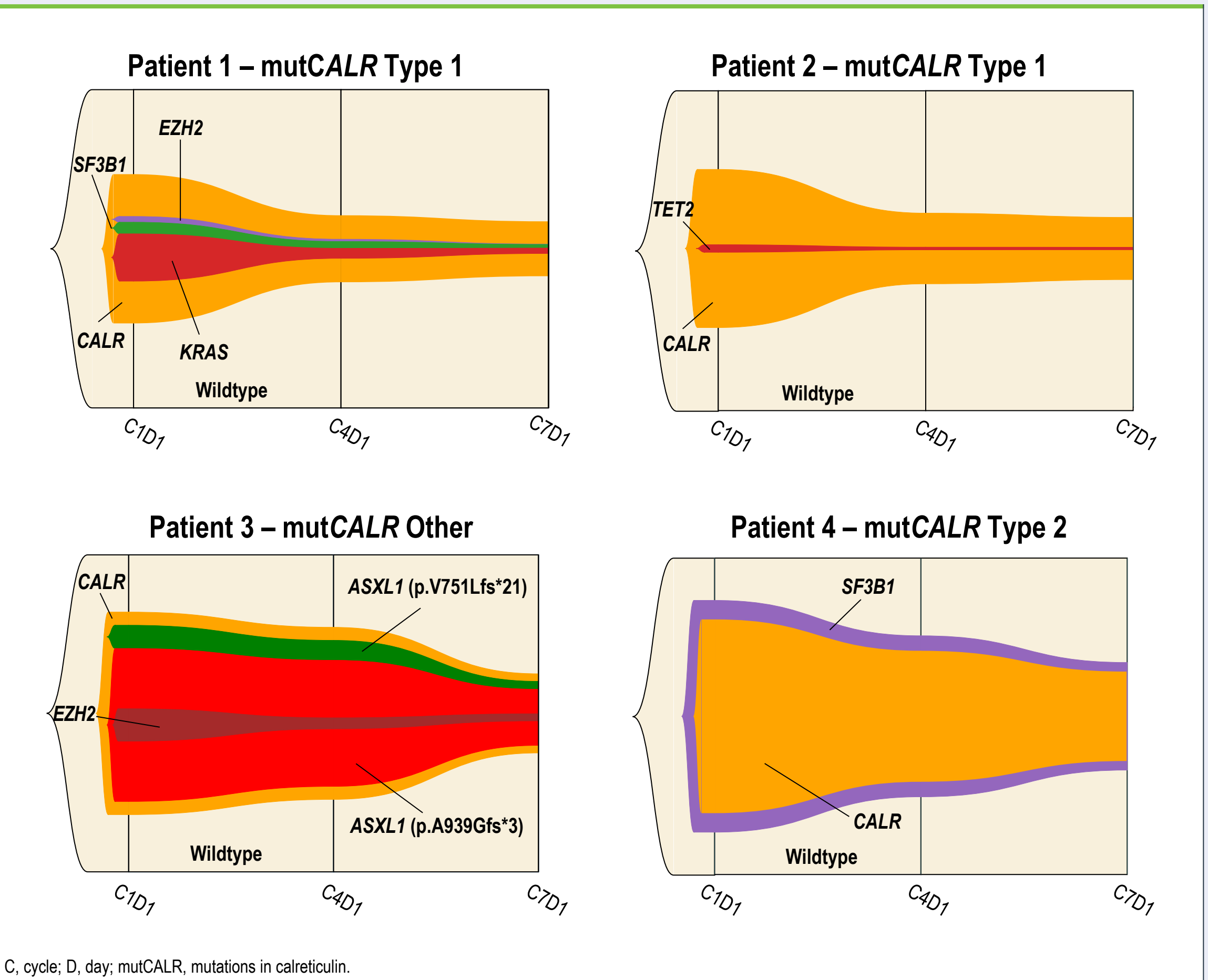
- 65% (11/17) and 56% (9/16) had a ≥25% reduction in *mutCALR* PBMCs in patients with and without HMR, respectively
- 93% (39/42) and 88% (38/43) had a reduction in *mutCALR* WB VAF in patients with and without HMR, respectively

Figure 8. Evaluation of *mutCALR* HSPC in Patients With or Without HMR



- Reductions in circulating *mutCALR* HSPC were observed with INCA033989 treatment, demonstrating a targeted effect on disease-initiating cells
- Reductions were noted in patients regardless of baseline percent *mutCALR* HSPCs

Figure 9. Clonal Response in Representative Patients



C, cycle; D, day; *mutCALR*, mutations in calreticulin.

- In 3 representative patients, the presence of non-driver subclones did not prevent molecular response of the *mutCALR* clone
- A molecular response was also observed in a fourth patient with *mutCALR* 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 *mutCALR*
- 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 *mutCALR* HSPCs and MKs were observed in a majority of patients, regardless of the presence of HMR mutations
- Subclonal complexity within the *mutCALR* clone did not impact molecular response in most evaluable patients
- Overall, these findings demonstrate that INCA033989 reduces disease-initiating *mutCALR* clones, including subclones harboring HMR mutations
- A phase 3 program of INCA033989 is being initiated (NCT07623200; EXCALIBUR-ET2)

Disclosures

Dr. Nangalia: Advisory board/consultancy – Bioskyrb, Incyte, Merck/MSD, Calytrix Bio.

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References

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



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