

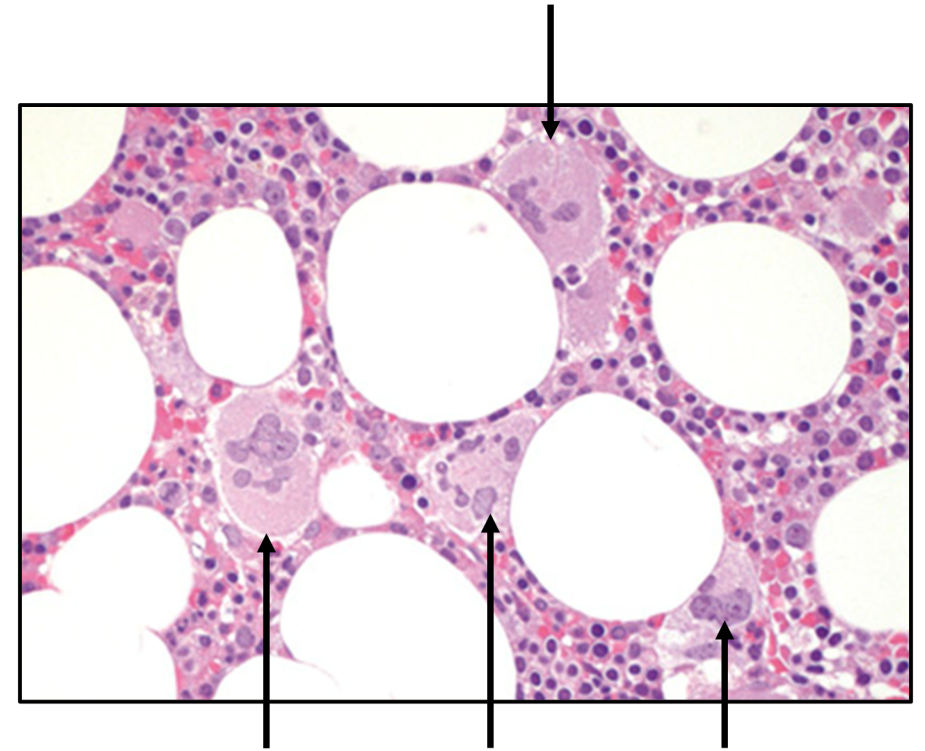
# INCA33989 Is a Novel, First-in-Class, Mutant Calreticulin-Specific Monoclonal Antibody That Demonstrates Safety and Efficacy in Patients With Essential Thrombocythemia (ET)

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# CALR Mutations Are Frequent in Essential Thrombocythemia

- Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) characterized by megakaryocyte hyperplasia, thrombocytosis, vasomotor symptoms, and increased risk for thrombosis, hemorrhage, and transformation to myelofibrosis (MF) or acute myeloid leukemia (AML)<sup>1</sup>
- Mutations of calreticulin (mutCALR) in exon 9 are found in ~25% of patients with ET<sup>2,3,4</sup>
  - 54% type 1 (52-bp deletions)
  - 36% type 2 (5-bp insertions)
  - 10% other
- ET with mutCALR is associated with lower rates of response to treatment and higher risk of transformation to MF compared with JAK2V617F<sup>5,6</sup>
- Current treatments aim to control blood counts, prevent vascular complications, and improve symptoms, but are limited by toxicity and/or poor activity and are not targeted to driver mutations<sup>7</sup>



Bone marrow biopsy of patient with ET displaying hyperlobated classical ET megakaryocytes (arrows)

1. Briere. *Orphanet J Rare Dis*. 2001;2:3. 2. Guglielmelli, et al. *Blood*. 2024;143:1310-1314. 3. Klampfl et al. *N Engl J Med*. 2013;369:2379-2390. 4. Nangalia, et al. *N Engl J Med*. 2013;369:2391-2405. 5. Campbell, et al. *Lancet*. 2005;366:1945-1953. 6. Loscocco, et al. *Blood Cancer J*. 2024;14:10; 7. Yacoub et al. *Clin. Lymphoma Myeloma Leuk*. 2021;21:461-469.



# INCA33989 Is a Mutant-Specific Targeted Therapy for Patients With *CALR* Mutations

- INCA33989 has a unique mechanism of action compared with other available therapies
  - INCA33989 is a high-affinity, fully human IgG1 monoclonal antibody that selectively targets mutCALR in complex with TPO-R (MPL) to inhibit cell signaling and proliferation<sup>1</sup>

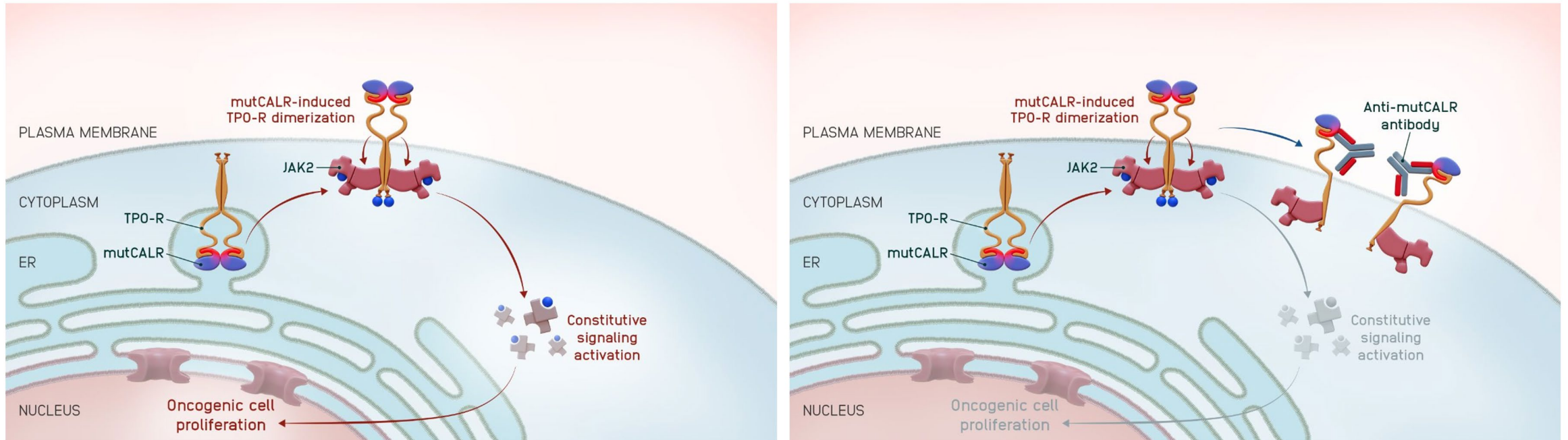


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1. Reis, et al. *Blood*. 2024;22:2336-2348.

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

# Study Design: INCA33989-101 and INCA33989-102

## Dose Escalation

### ET

- Diagnosis of ET (2022 WHO criteria)
- Presence of mutCALR exon 9
- High risk, defined as: age  $\geq 60$  years or history of thrombosis or history of major bleeding without any clearly documented alternative explanation or extreme thrombocytosis
- Documented resistance/intolerance to  $\geq 1$  line of prior cytoreductive therapy
- Platelet count  $>450 \times 10^9/L$
- Concomitant therapy with anagrelide or hydroxyurea permitted

### MF (Monotherapy)

- Relapsed/refractory

### MF (INCA33989 + ruxolitinib)

- Ruxolitinib  $\geq 12$  weeks, 8 weeks with stable dose; suboptimal responder

### Primary Endpoints

- Dose-limiting toxicities
- Treatment-emergent adverse events

### Secondary Endpoints

- Response using European LeukemiaNet response criteria<sup>1</sup>
- Symptom improvement based on the MPN-SAF TSS
- Changes in allele burden of mutCALR
- Pharmacokinetic parameters

## Dose Expansion

### ET

(n=15; RDE)

### MF (monotherapy)

(n=15; RDE)

### MF (INCA33989 + ruxolitinib)

(n=15; RDE)

↓  
After positive  
benefit/risk confirmed

Treatment-naïve MF (randomly  
assigned to monotherapy or  
INCA33989 + ruxolitinib)

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

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

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



# Demographics and Disease Characteristics

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

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

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

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

# Safety: No Dose Limiting Toxicities Were Observed

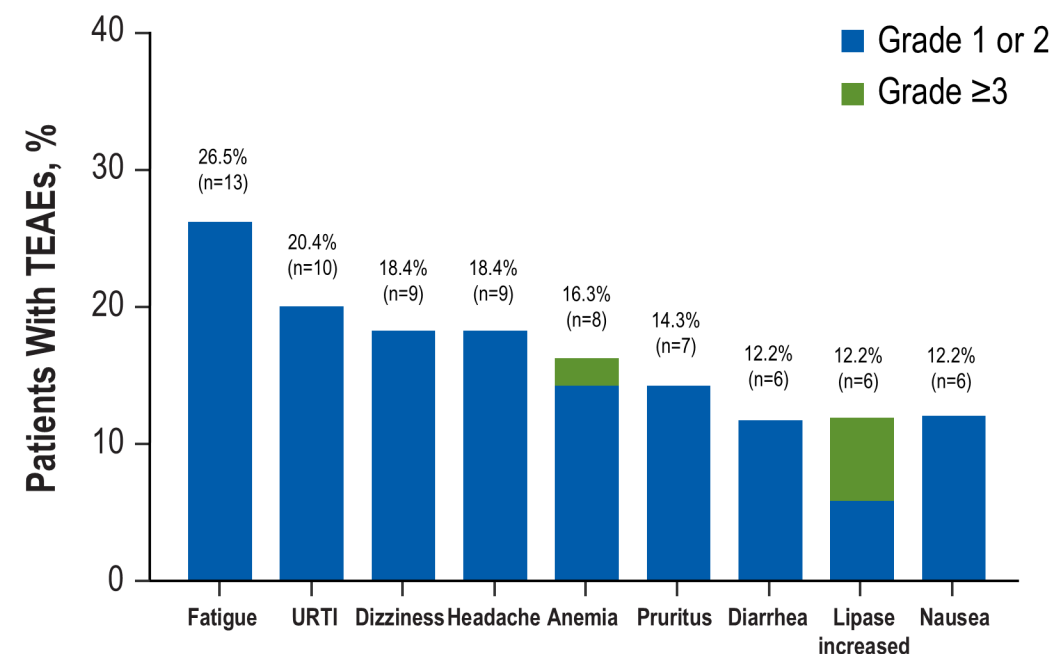
## Summary of TEAEs

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

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

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

## Most Common TEAEs

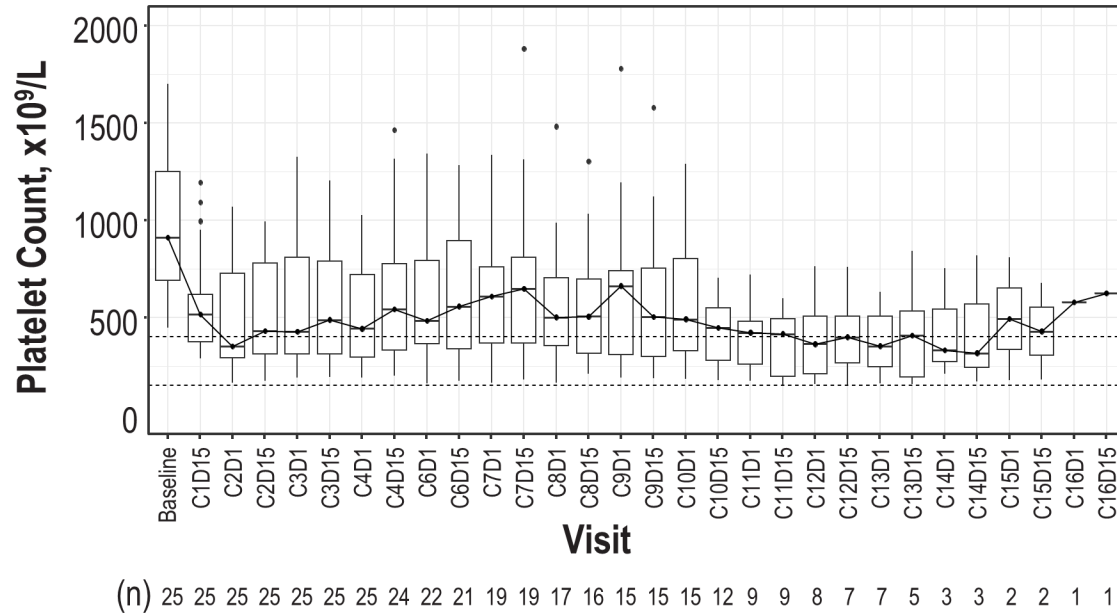


- The majority of TEAEs were grade 1-2
- Most frequent grade  $\geq 3$  TEAE was transient, asymptomatic lipase increase (6.1%)
  - All resolved without clinical sequelae
  - No correlation to dose or onset post treatment

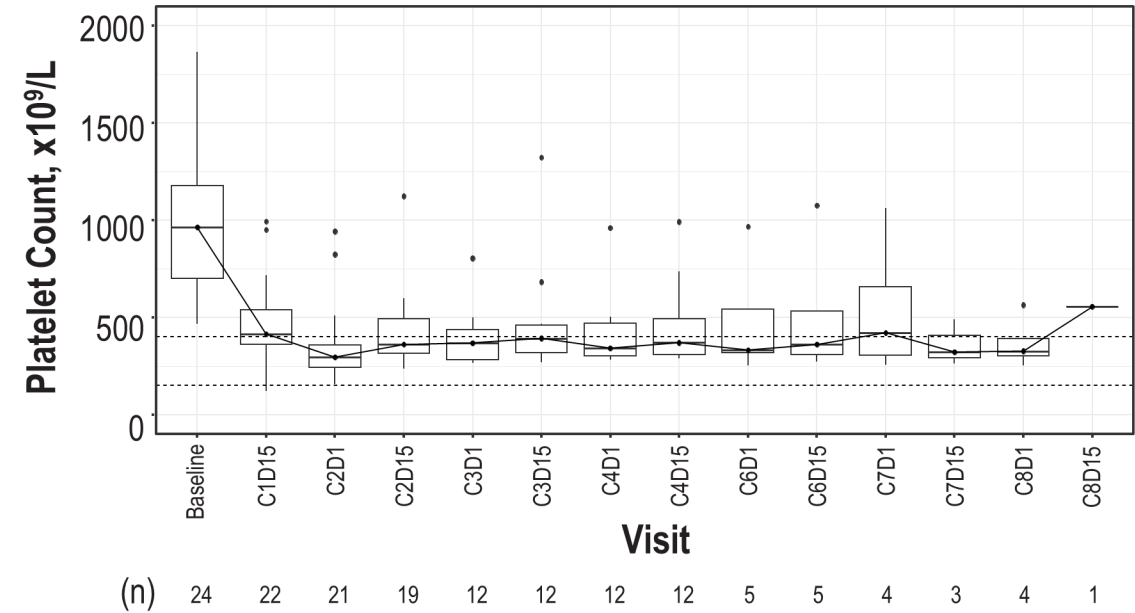


# Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

Doses 24-250 mg\*



Doses 400-2500 mg†



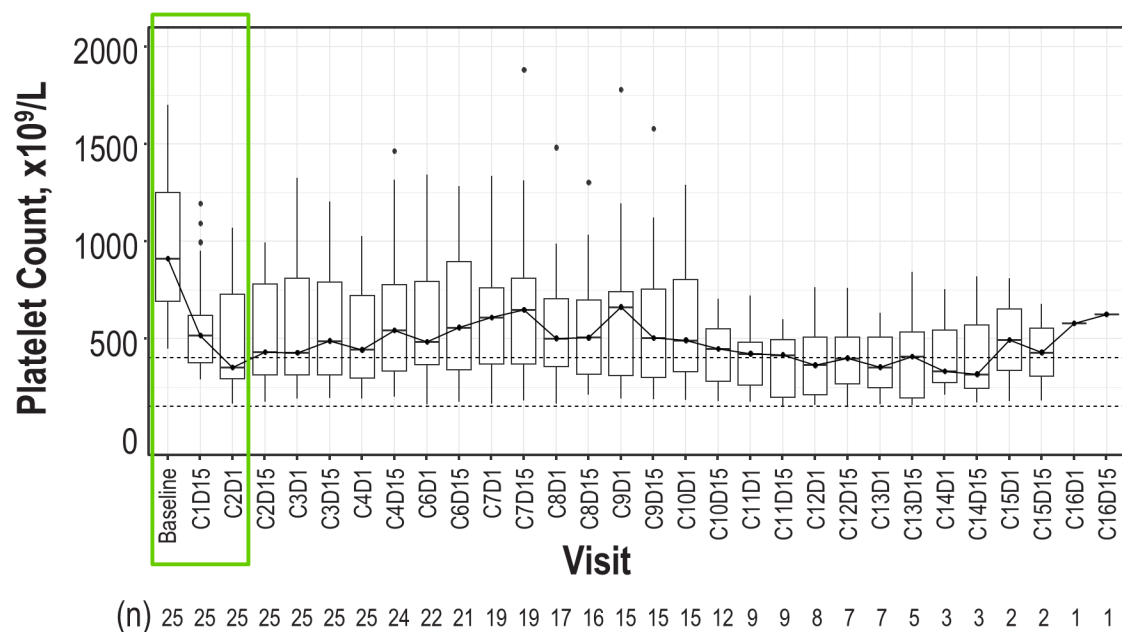
- Of the 31 patients that enrolled with concomitant cytoreductive therapy (hydroxyurea or anagrelide), 20 (65%) discontinued it and remained on study
- Thrombocytopenia was not observed in any patient
- Doses of  $\geq 400$  mg produced higher frequency of platelet count normalization

Dotted lines indicate upper and lower limit of normal. Boxes denote the first and third quartiles, lines represent the median. Number of patients with available data at each visit is noted below the x axis.

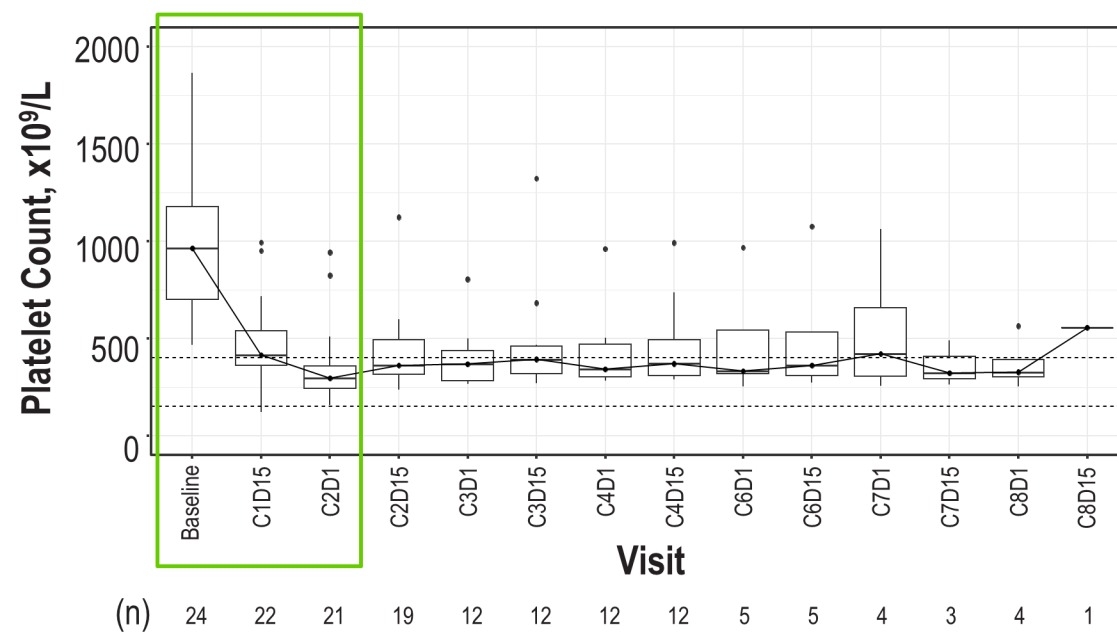
\*24 mg (n=3), 50 mg (n=3), 70 mg (n=3), 100 mg (n=3), 200 mg (n=5), 250 mg (n=8). †400 mg (n=5), 750 mg (n=9), 1500 mg (n=6), 2500 mg (n=4). C, cycle; D, day.

# Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

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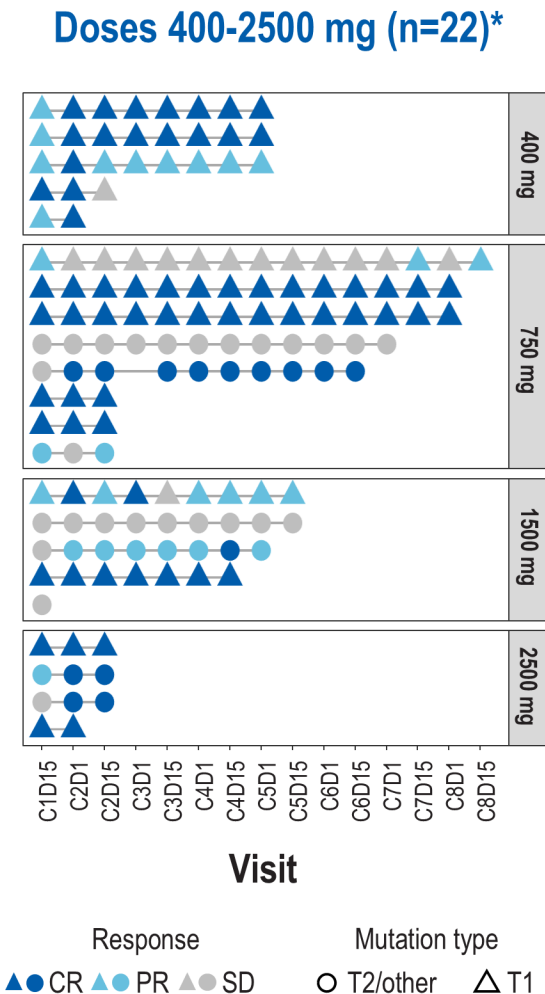
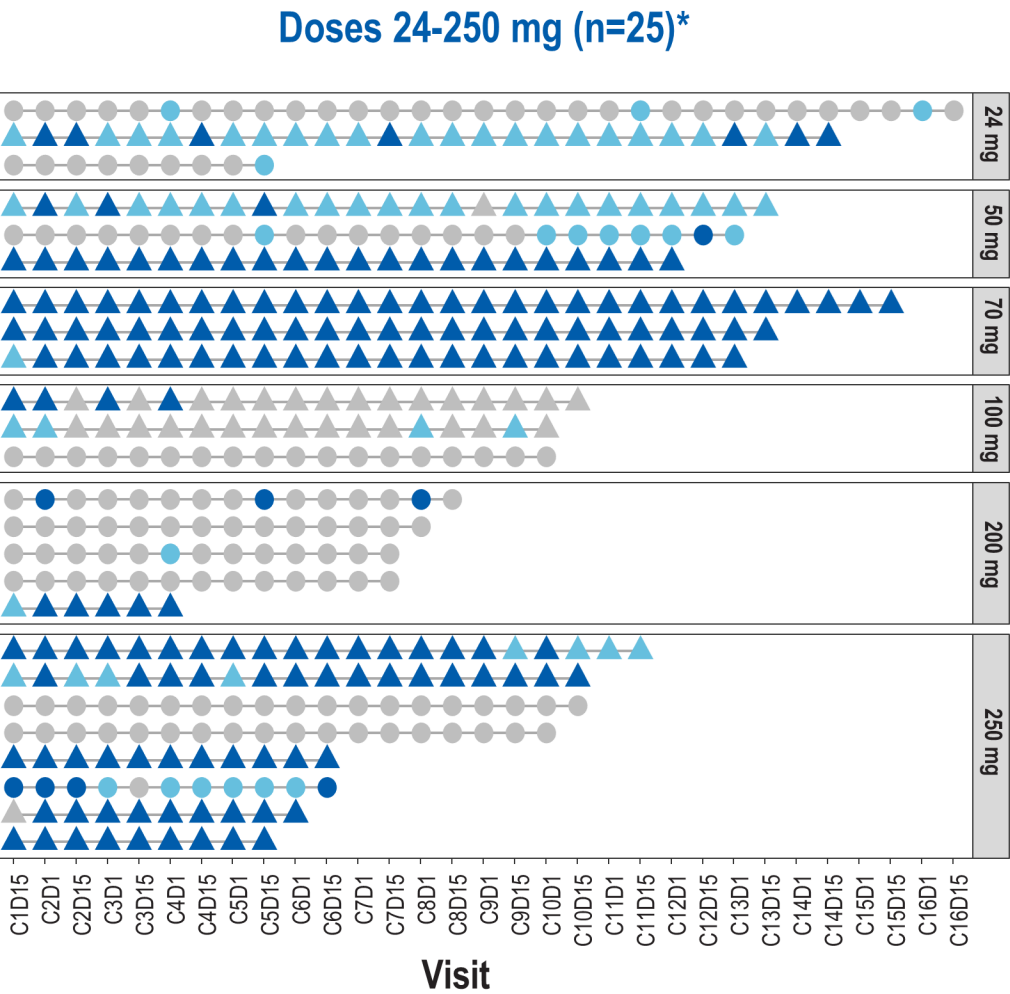
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# Hematologic Responses Are Achieved Early and Are Sustained



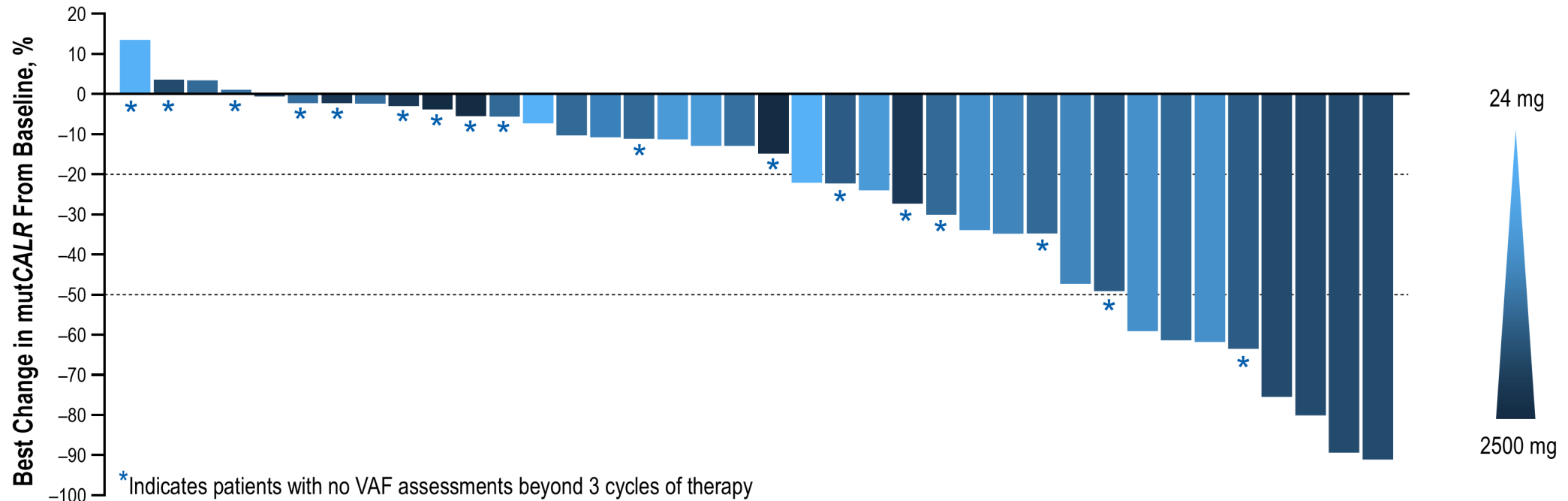
Dose, mg	Best Overall Response				
	N	CR	PR	SD	OR
24-250	25	17 (68%)	3 (12%)	5 (20%)	20 (80%)
400-2500	22	18 (82%)	1 (5%)	3 (14%)	19 (86%)

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

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

# Molecular Responses Are Rapid and Frequent

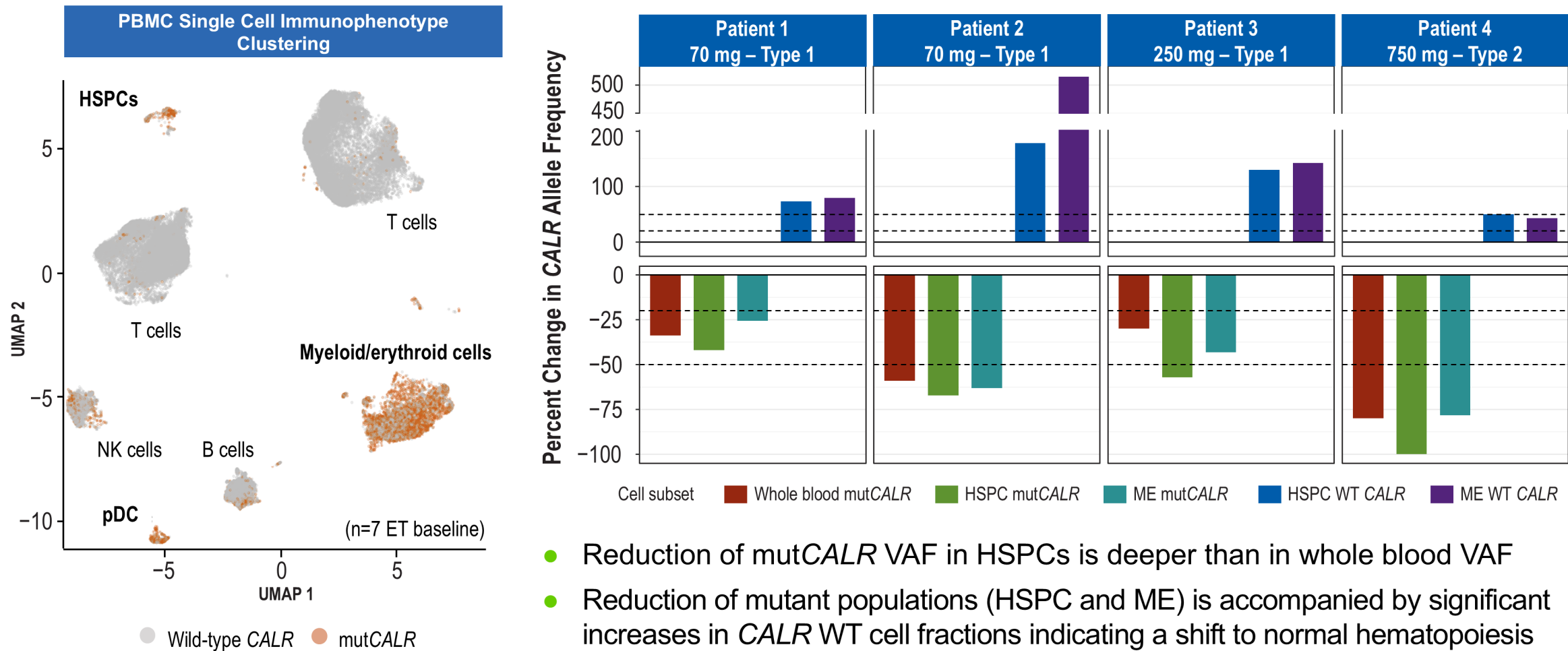
- A reduction in mutCALR VAF from baseline occurred in 34/38 (89%) evaluable patients
  - 18/38 (47%) achieved >20% best reduction in VAF
  - 8/38 (21%) achieved >50% best reduction in VAF
- A reduction of  $\geq 20\%$  VAF occurred within 6 cycles of therapy for all 18 responders
- All 18 molecular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



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

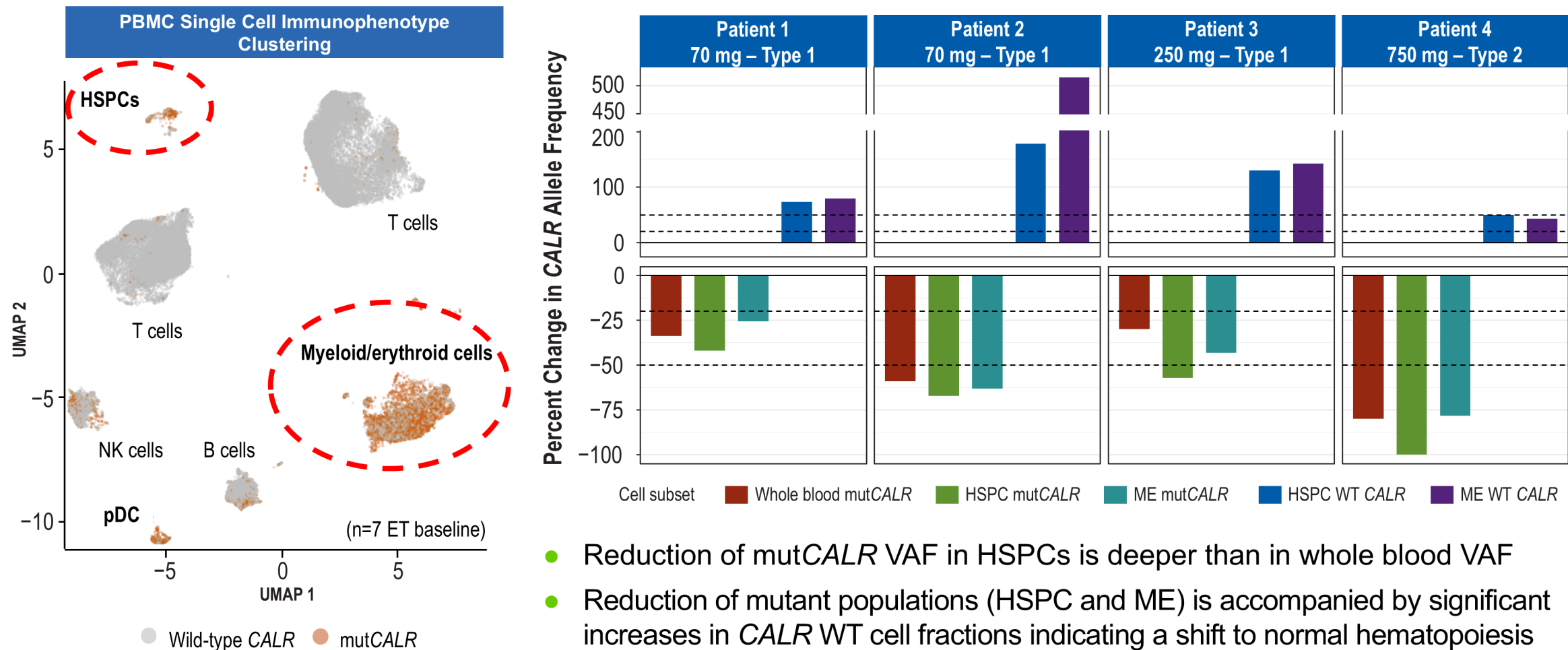


# Reduction of mutCALR<sup>+</sup> HSPCs and Myeloid/Erythroid Cells in Clinical Responders



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

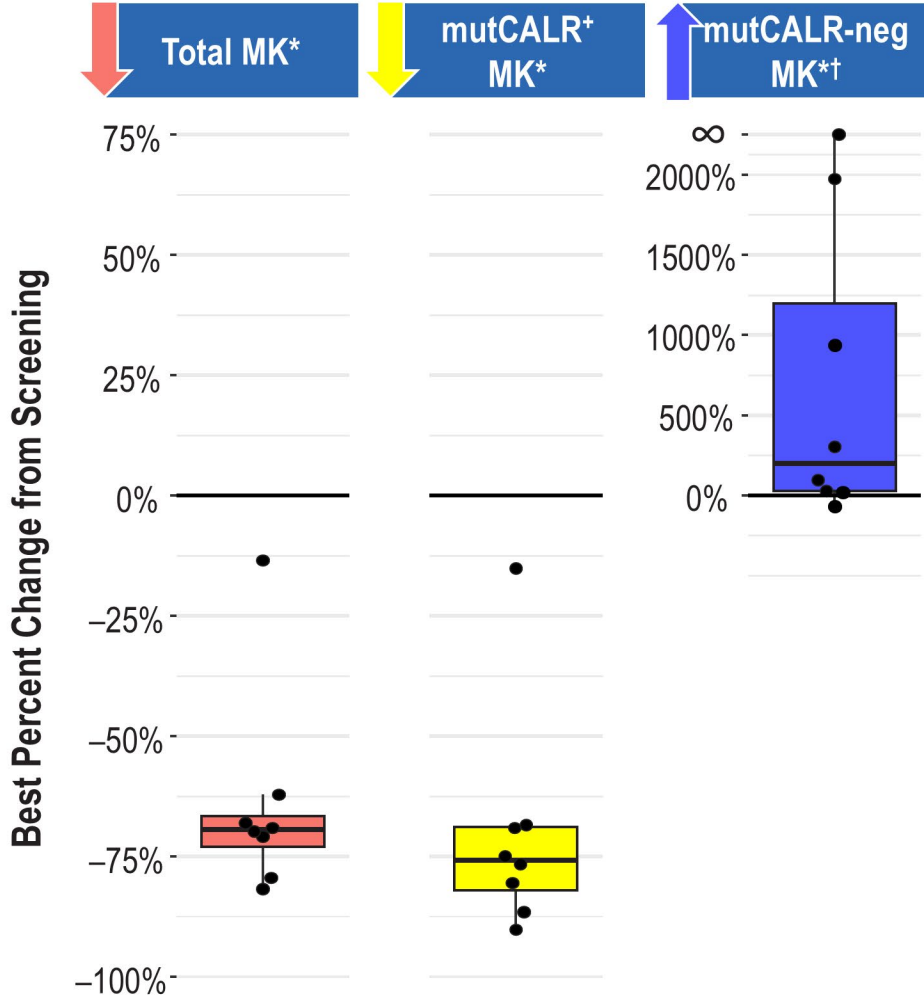
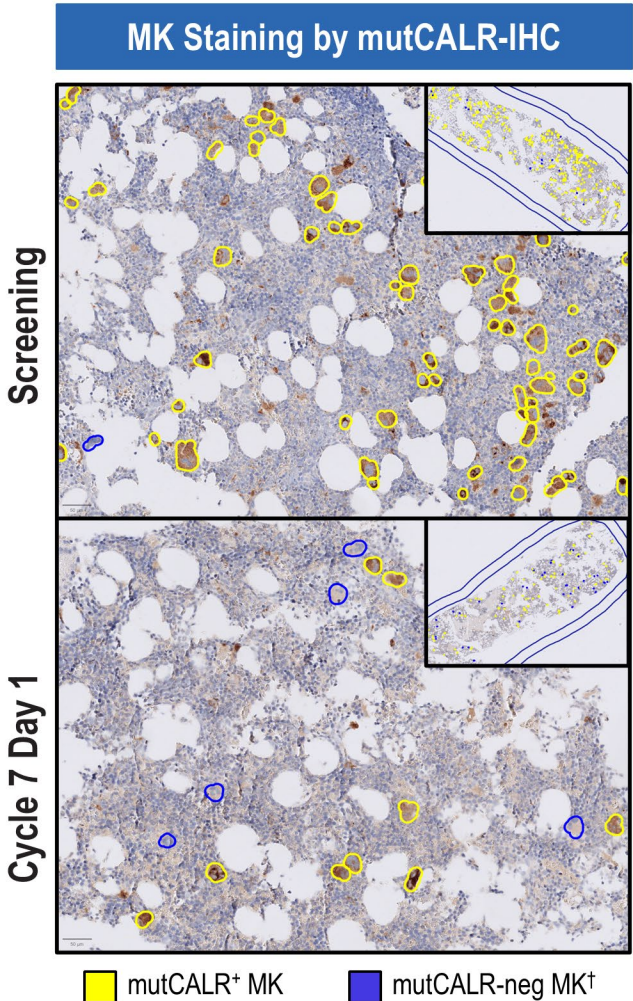
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# Reduction in mutCALR<sup>+</sup> Megakaryocytes in the Bone Marrow of Clinical Responders



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

- Total number of megakaryocytes (MK) decreased
- Fraction of mutCALR<sup>+</sup> MKs decreased
- Fraction of mutCALR negative MKs increased

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

# Conclusions

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

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# Disclosures

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