

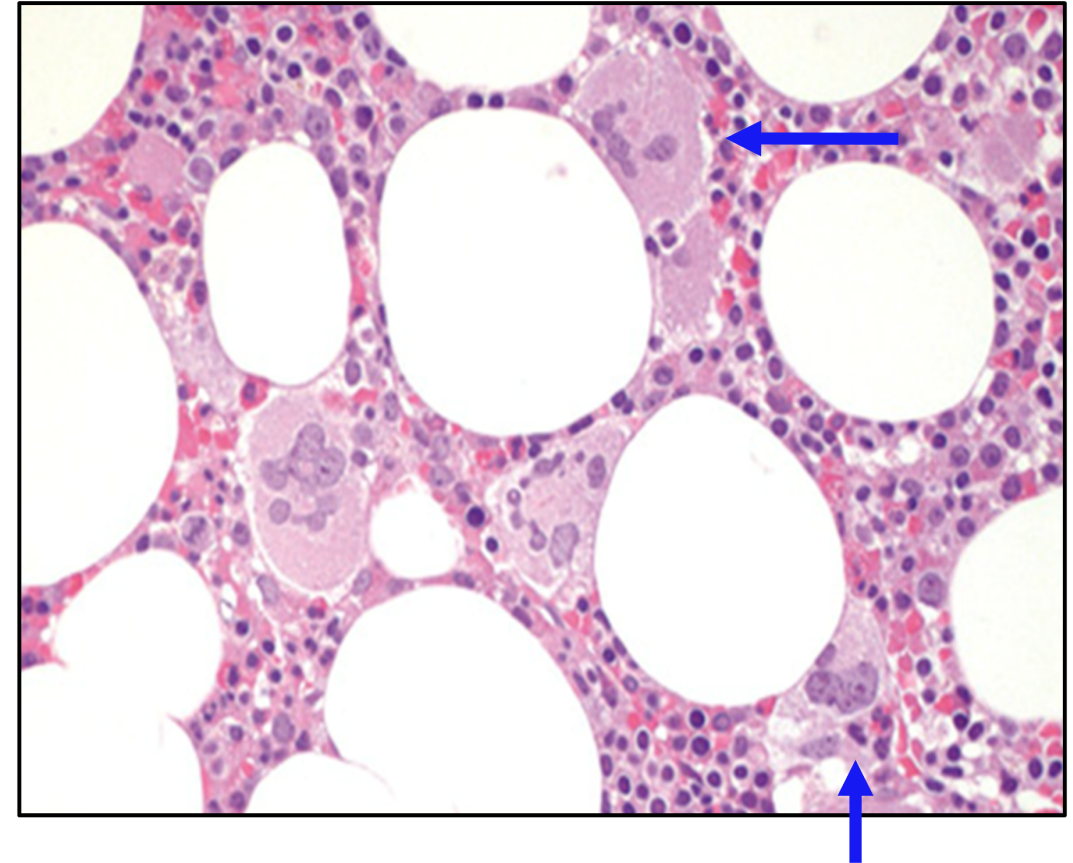
Safety and Efficacy of INCA033989, a Novel First in Class Mutant Calreticulin–Specific Monoclonal Antibody, in Patients With Essential Thrombocythemia

Vikas Gupta,¹ John Mascarenhas,² Haris Ali,³ David M. Ross,⁴ Abdulraheem Yacoub,⁵ Tania Jain,⁶ Lynette Chee,⁷ Aaron Gerds,⁸ Jean-Jacques Kiladjian,⁹ Ruben Mesa,¹⁰ William Shomali,¹¹ Makoto Yoshimitsu,¹² Rosa Ayala Diaz,¹³ Joan How,¹⁴ Steffen Koschmieder,¹⁵ Caroline McNamara,¹⁶ Yosuke Nakaya,¹⁷ Francesca Palandri,¹⁸ Francesco Passamonti,¹⁹ Andrew Perkins,²⁰ Bethan Psaila,²¹ Raajit Rampal,²² Natasha Szuber,²³ Frank Stegelmann,²⁴ Alessandro Maria Vannucchi,²⁵ Hiroki Yamaguchi,²⁶ Jason Gotlib,¹¹ Jyoti Nangalia,²⁷ Chenwei Tian,²⁸ Betty Lamothe,²⁸ Erin Crowgey,²⁸ Tatiana Zinger,²⁸ Evan Braunstein,²⁸ Claire Harrison²⁹

¹Princess Margaret Cancer Centre, Toronto, ON, Canada; ²Icahn School of Medicine at Mount Sinai, New York, NY, USA; ³City of Hope Medical Center, Duarte, CA, USA; ⁴Royal Adelaide Hospital, Adelaide, SA, Australia; ⁵The University of Kansas Cancer Center, Kansas City, KS, USA; ⁶Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; ⁷Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, Melbourne, VIC, Australia; ⁸Cleveland Clinic, Cleveland, OH, USA; ⁹Saint-Louis Hospital, Paris Cité University, INSERM, Paris, France; ¹⁰Wake Forest University Baptist Medical Center, Winston-Salem, NC, USA; ¹¹Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; ¹²Kagoshima University Hospital, Kagoshima, Japan; ¹³12 de Octubre University Hospital, Madrid, Spain; ¹⁴Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA, USA; ¹⁵RWTH Aachen University, Faculty of Medicine, and Center for Integrated Oncology (CIO-ABCD), Aachen, Germany; ¹⁶Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; ¹⁷Department of Hematology, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan; ¹⁸IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ¹⁹Fondazione IRCCS Ca Ganda Ospedale Maggiore, Milan, Italy; ²⁰The Alfred Hospital, Melbourne, VIC, Australia; ²¹University of Oxford, Oxford, UK; ²²Memorial Sloan Kettering Cancer Center, New York, NY, USA; ²³Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; ²⁴Universitätsklinikum Ulm, Ulm, Germany; ²⁵Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; ²⁶Nippon Medical School Hospital, Tokyo, Japan; ²⁷The Sanger Institute, Cambridge, UK; ²⁸Incyte Corporation, Wilmington, DE, USA; ²⁹Guy's and St Thomas' NHS Foundation Trust, London, UK

CALR Mutations Are Frequent in Essential Thrombocythemia With No Mutant-Specific Treatment Available

- Essential thrombocythemia (ET) is characterized by megakaryocyte hyperplasia and clustering, thrombocytosis, and an increased risk of thrombosis, hemorrhage, and transformation to myelofibrosis (MF)¹
- Mutations of calreticulin (mutCALR) in exon 9 are found in ~25-30% of patients with ET^{2,3}
- ET with mutCALR is associated with diagnosis at a younger age and earlier transformation to MF compared with *JAK2V617F*^{4,5}
- Current treatments are broadly myelosuppressive, not mutant targeted, and have limited efficacy in reducing mutCALR allele frequency^{6,7}



Bone marrow biopsy of patient with ET displaying megakaryocyte hyperplasia and clustering (arrows)

1. Brière JB. *Orphanet J Rare Dis*. 2001;2:3. 2. Guglielmelli P, et al. *Blood*. 2024;143:1310-1314. 3. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390. 4. Campbell PJ, et al. *Lancet*. 2005;366:1945-1953. 5. Loscocco GG, et al. *Blood Cancer J*. 2024;14:10. 6. Knudsen TA, et al. *Blood Adv*. 2022;6:2107-2119. 7. Yacoub A, et al. *Clin Lymphoma Myeloma Leuk*. 2021;21:461-469. CALR, calreticulin.

INCA033989 is a mutCALR-Targeted Therapy for Patients With ET and MF

- INCA033989 has a unique mechanism of action compared with other available therapies
 - INCA033989 is a novel, fully human, high-affinity, Fc-silenced, immunoglobulin G1 monoclonal antibody that selectively targets mutCALR in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells¹

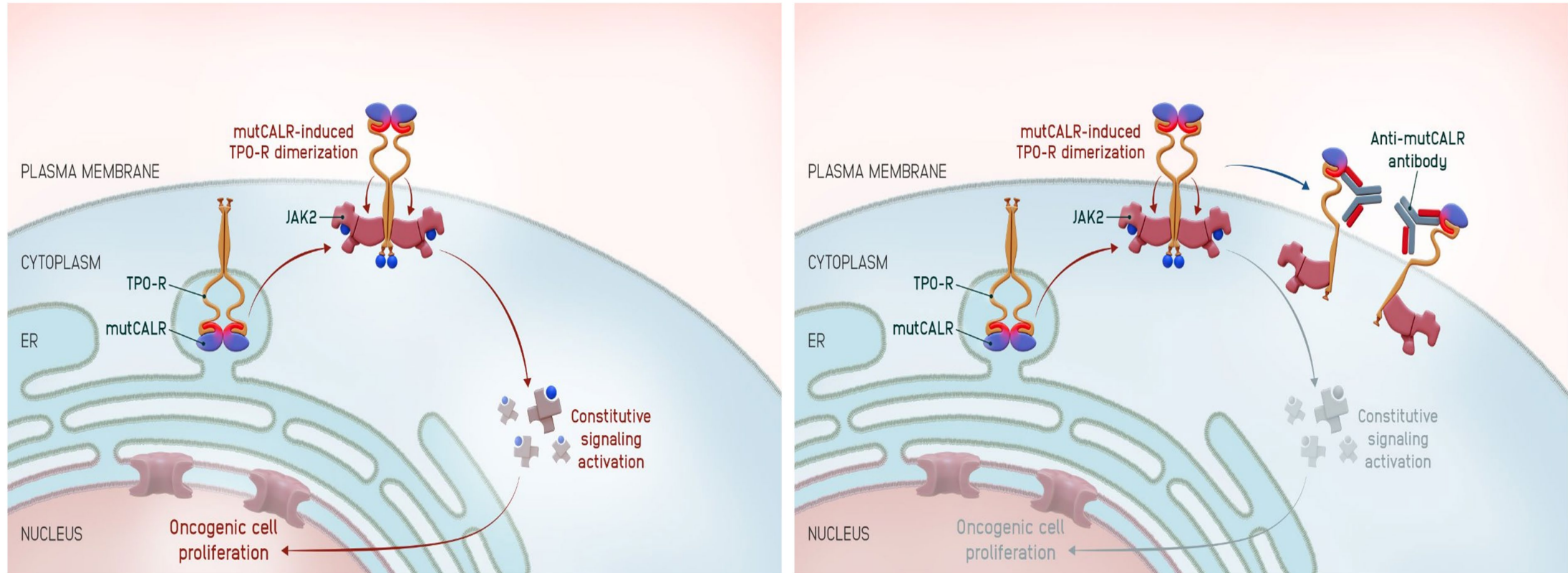


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1. Reis ES, et al. *Blood*. 2024;22:2336-2348.

CALR, calreticulin; ER, endoplasmic reticulum; ET, essential thrombocythemia; 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 ET and MF

Study Design

Dose Escalation

ET

- Diagnosis of ET (2022 WHO criteria)
- Presence of mutCALR exon 9
- High risk, defined as: ≥ 60 years of age *or* history of thrombosis *or* history of major bleeding *or* extreme thrombocytosis
- Documented resistance/intolerance to ≥ 1 line of prior cytoreductive therapy
- Platelet count $> 450 \times 10^9/L$
- Concomitant therapy with anagrelide or hydroxyurea permitted

MF (Monotherapy)

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

MF (INCA033989 + Ruxolitinib)

- Prior ruxolitinib treatment for ≥ 12 weeks with a suboptimal response

Primary Endpoints

- Dose-limiting toxicities
- Treatment-emergent adverse events

Secondary Endpoints

- Response using ELN response criteria¹
- Symptom improvement (MPN-SAF TSS)
- Changes in allele burden of mutCALR
- Pharmacokinetic parameters

Dose Expansion

ET

MF (monotherapy)

MF (INCA033989 + ruxolitinib)

Treatment-naïve MF (randomly assigned to monotherapy or INCA033989 + ruxolitinib)

- **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 (range 24-2500 mg)

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

CALR, calreticulin; ELN, European LeukemiaNet; ET, essential thrombocythemia; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mutCALR, mutations of calreticulin; TSS, total symptom score; WHO, World Health Organization.

Demographics and Disease Characteristics

Variable	Total (N=55)
Median age (range), years	61 (23, 87)
≥65, n (%)	23 (41.8)
Female, n (%)	35 (63.6)
Median time from initial diagnosis (range), years	7.0 (0.3, 27.9)
CALR exon 9 mutation type, n (%)	
Type 1	28 (50.9)
Type 2	18 (32.7)
Other	9 (16.4)
Prior systemic anticoagulant therapy, n (%)	11 (20.0)
Prior aspirin therapy, n (%)	34 (61.8)
Prior cytoreductive therapy,* n (%)	
Hydroxyurea	49 (89.1)
Anagrelide†	18 (32.7)
Interferons‡	18 (32.7)
Other§	7 (12.7)

Variable	Total (N=55)
Mean CALR VAF,¶ % (SD)	33 (9.5)
Median platelets (range), GI/L	931.0 (447.0, 2017.0)
Median leukocytes (range), GI/L	7.0 (3.1, 13.8)
Median hemoglobin (range), g/dL	12.5 (8.4, 17.1)
Median MPN-SAF TSS (range)	14.0 (0, 52.0)
Median spleen volume** (range), mL	316.0 (126.0, 866.0)
INCA033989 dose level, n (%)	
24 mg	3 (5.5)
50 mg	3 (5.5)
70 mg	3 (5.5)
100 mg	3 (5.5)
200 mg	5 (9.1)
250 mg	8 (14.5)
400 mg	5 (9.1)
750 mg	9 (16.4)
1500 mg	9 (16.4)
2500 mg	7 (12.7)

Data cutoff: September 25, 2025.
*Categories not mutually exclusive. †Anagrelide (n=14), anagrelide hydrochloride (n=4). ‡Categories not mutually exclusive: interferon(s) (n=6), interferon alpha (n=1), peginterferon alpha-2a (n=10), peginterferon-alpha (n=1), peginterferon (n=1), ropeginterferon alpha-2B-NJFT (n=1). §Categories not mutually exclusive: bomedemstat (n=1), pelabresib (n=1), busulfan (n=2), ruxolitinib (n=5). ¶Measured centrally in peripheral blood by next-generation sequencing (n=54). ||n=53. **n=52.
CALR, calreticulin; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; SD, standard deviation; TSS, total symptom score; VAF, variant allele frequency.

INCA033989 Monotherapy is Well Tolerated

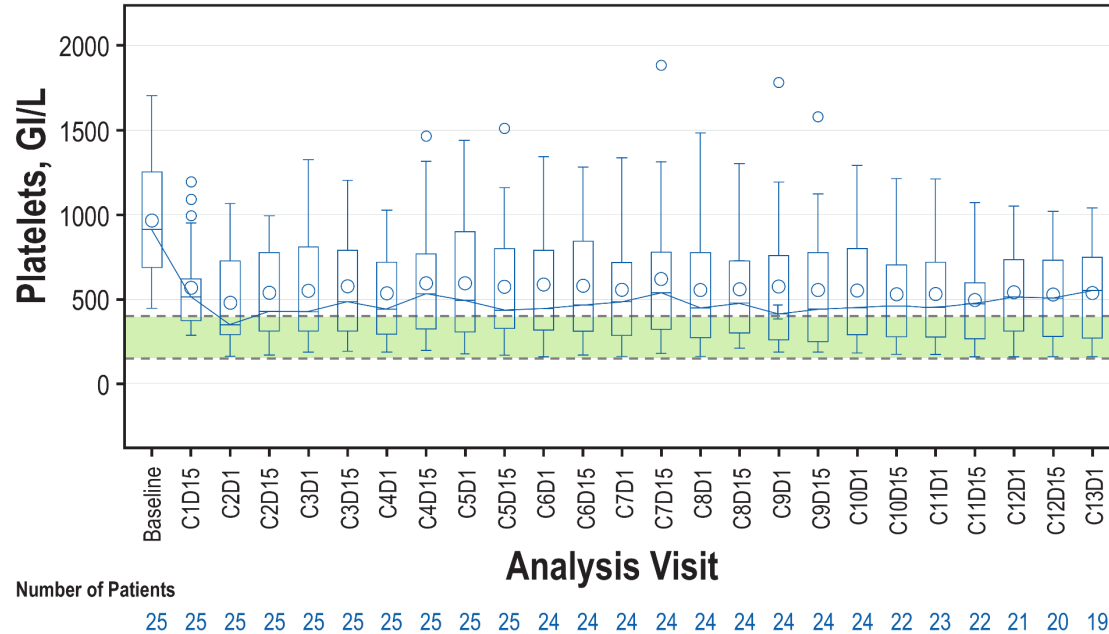
Summary of TEAEs		Most common TEAEs (≥15% of patients)		Most common grade ≥3 TEAEs (>1 patient)	
TEAE, n (%)	Total (N=55)	TEAE, n (%)	Total (N=55)	TEAE, n (%)	Total (N=55)
Any TEAE	53 (96.4)	Fatigue	17 (30.9)	Neutropenia	4 (7.3)
Treatment-related	36 (65.5)	Headache	15 (27.3)	Amylase increased	2 (3.6)
Grade ≥3*	14 (25.5)	URTI	15 (27.3)	Anemia	2 (3.6)
Serious†	3 (5.5)	Anemia	11 (20.0)	Lipase increased	2 (3.6)
Fatal	0	Diarrhea	10 (18.2)		
Discontinuation due to TEAEs	1 (1.8)	Pruritus	10 (18.2)		
Dose reduction due to TEAEs	1 (1.8)	Arthralgia	9 (16.4)		
Infusion interruption due to TEAEs	1 (1.8)	Dizziness	9 (16.4)		
Dose delay due to TEAEs	15 (27.3)	Lipase increase	9 (16.4)		
Dose-limiting toxicity	0	Nausea	9 (16.4)		

- Overall, 51 (93%) patients are still receiving treatment, and 4 patients discontinued treatment‡
- No dose-limiting toxicities were observed; maximum tolerated dose was not reached
- Grade ≥3 anemia and/or neutropenia TEAEs occurred in 5 patients (all received hydroxyurea prior or during the event), no grade ≥3 thrombocytopenia TEAEs were observed
- Lipase increases resolved in all 9 patients, were transient, and were not associated with dose

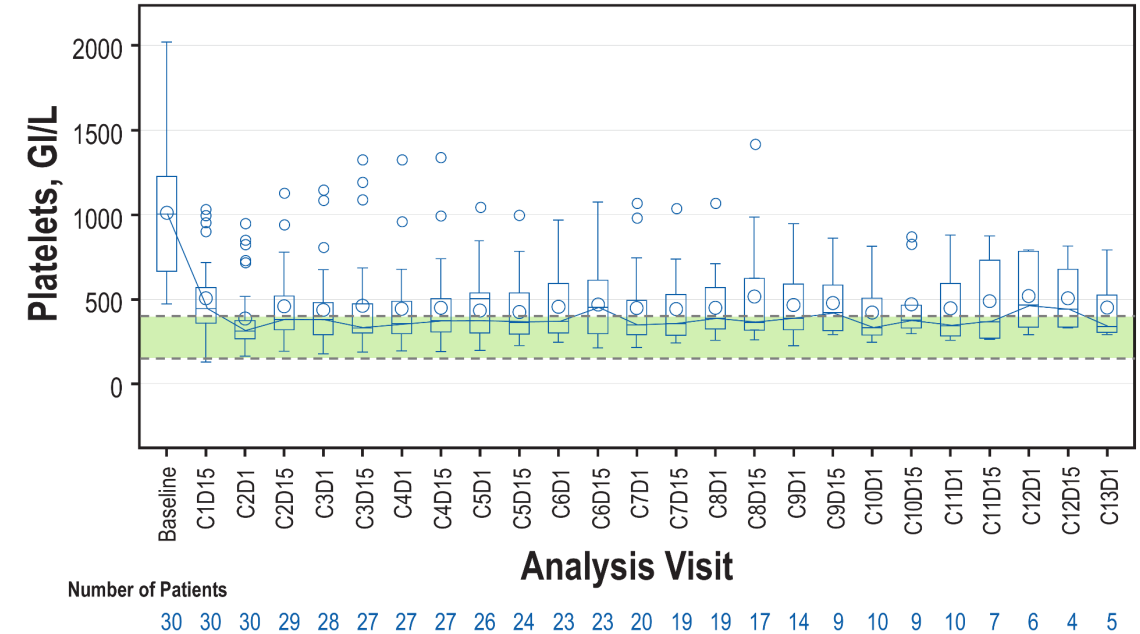
*1 grade 4 TEAE was observed (transient neutropenia related to concomitant hydroxyurea). †Visceral venous thrombosis (n=1; 24 mg; considered related to INCA033989) followed by melena (after anticoagulant initiation; considered unrelated to INCA033989) and treatment discontinuation; diverticulitis (n=1; 400 mg; considered unrelated to INCA033989); polymyalgia rheumatica (n=1; 1500 mg; considered unrelated to INCA033989). ‡Adverse event (visceral venous thrombosis; n=1), lack of efficacy (n=1), pregnancy (n=1), and patient withdrawal (n=1).
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Rapid and Durable Platelet Normalization With Optimal Response at Higher Doses of INCA033989

Platelet Counts (24-250 mg* Q2W; n=25)



Platelet Counts (400-2500 mg* Q2W; n=30)



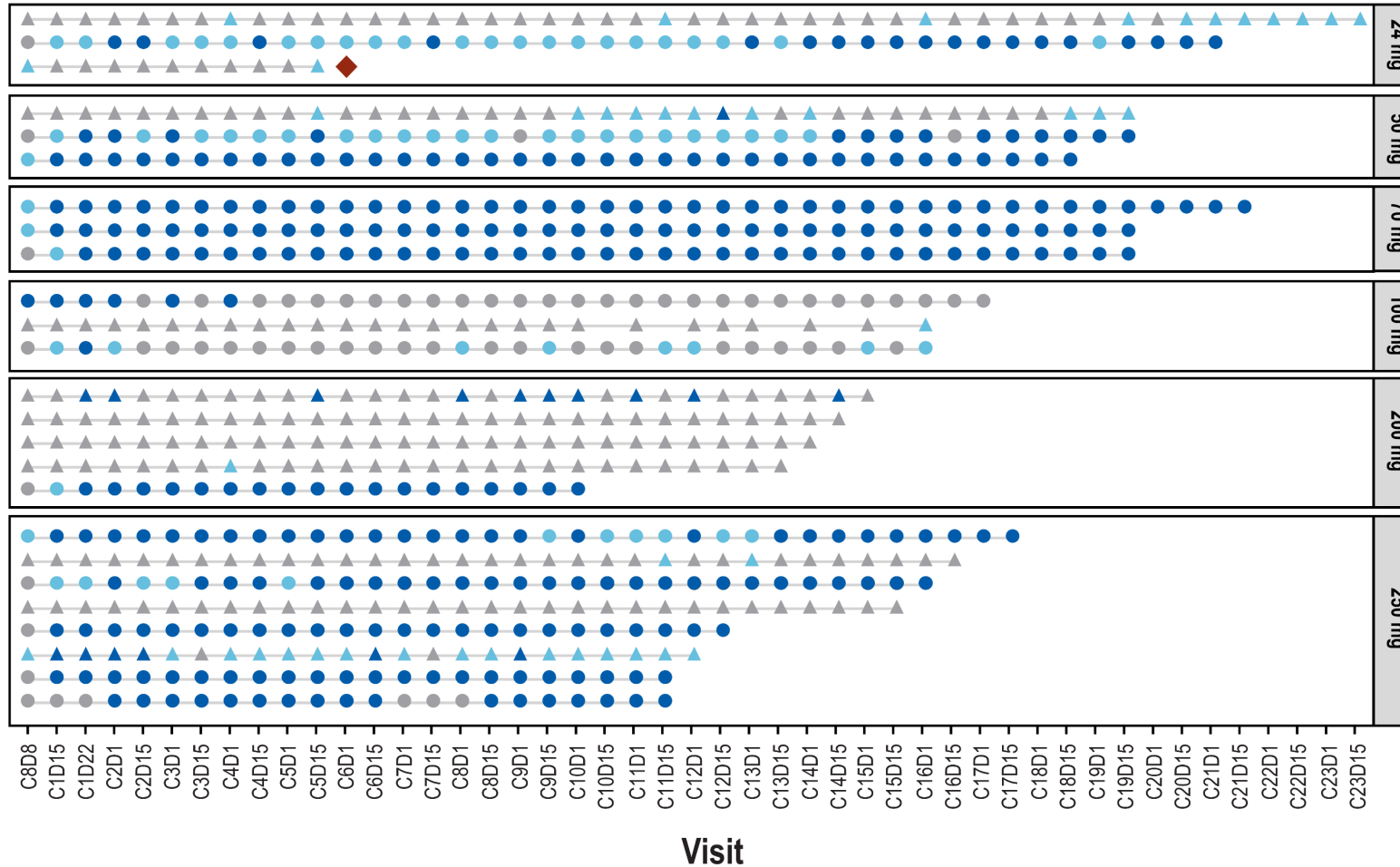
- Median (range) duration of exposure was 45.0 (4.0, 94.1) weeks
- Of the 34 patients who enrolled with concomitant cytoreductive therapy (hydroxyurea [n=27] or anagrelide [n=7]), most (71%) discontinued and remained on study
 - Median (range) time to discontinuation of cytoreductive therapy (hydroxyurea and anagrelide) was 23.0 (1.0-322.0) days

Dotted lines indicate upper (400 G/L) and lower limit (150 G/L) 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.

*Starting dose.

C, cycle; D, day; Q2W, every 2 weeks.

Rapid and Durable Hematologic Responses With INCA033989 Monotherapy (Doses 24-250 mg)

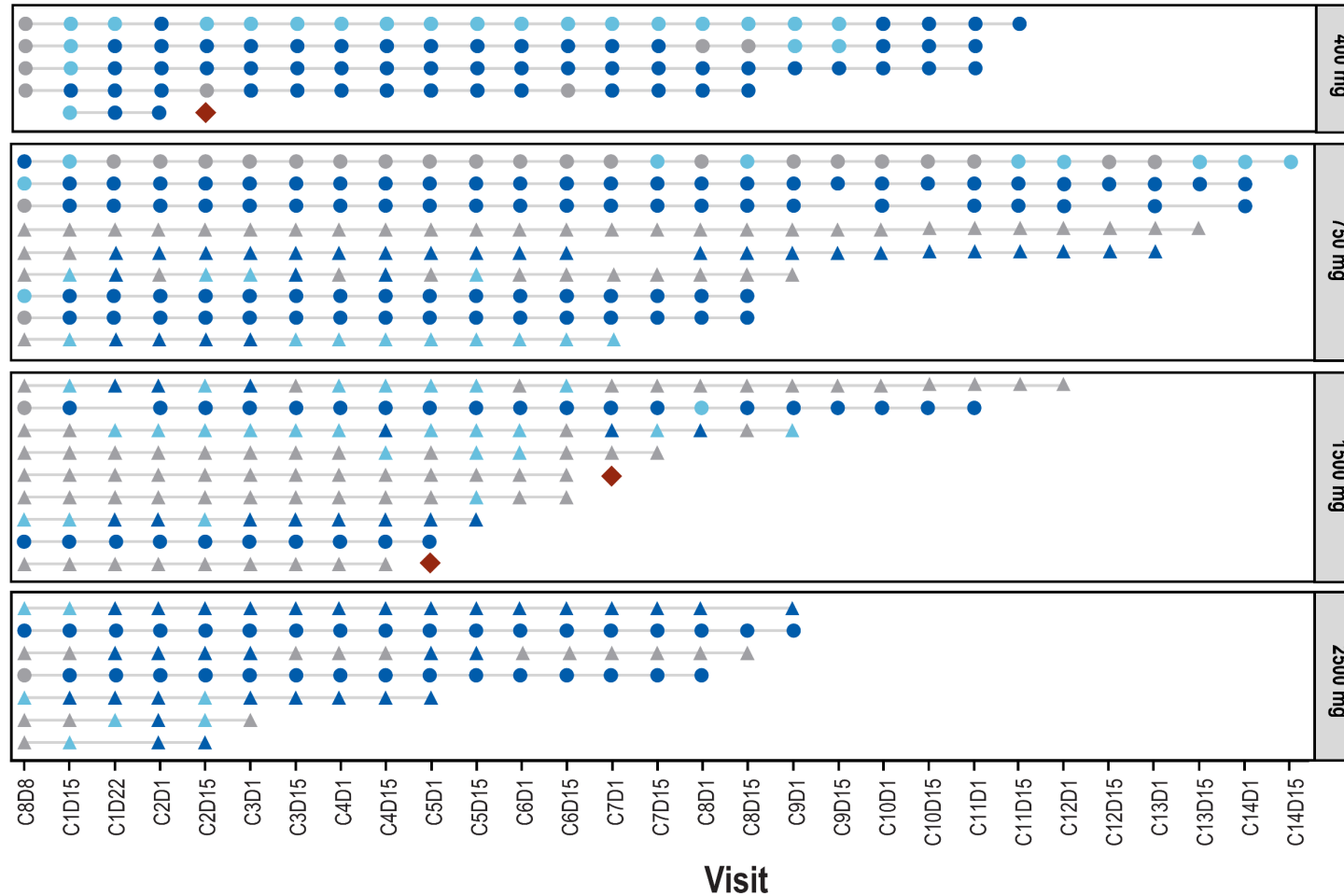


- 25 patients with starting dose 24-250 mg
 - **HR: 22 (88.0%)**
 - **CHR*: 17 (68.0%)**
 - Durable[†] (12 weeks) HR: 14 (56.0%)
 - Durable CHR: 11 (44.0%)

*CHR defined as platelet count $\leq 400 \times 10^9/L$ and leukocytes $< 10 \times 10^9/L$, partial hematologic response (PHR) defined as platelet count $\leq 600 \times 10^9/L$ and leukocytes $< 10 \times 10^9/L$ (baseline platelet count $> 600 \times 10^9/L$). [†]Durable response defined as maintaining for ≥ 12 weeks.

C, cycle; CHR, complete hematologic response; D, day; HR, hematologic response; NR, no response; PHR, partial hematologic response.

Rapid and Durable Hematologic Responses With INCA033989 Monotherapy (Doses 400-2500 mg)



- 30 patients with starting dose of 400-2500 mg
 - HR: 27 (90.0%)
 - CHR*: 25 (83.3%)
- Of 28 evaluable patients[†]
 - Durable[‡] HR: 18 (64.3%)
 - Durable CHR: 13 (46.4%)
- Median (range) time to onset of durable CHR for 24-2500 mg dose levels was 15 (8, 379) days

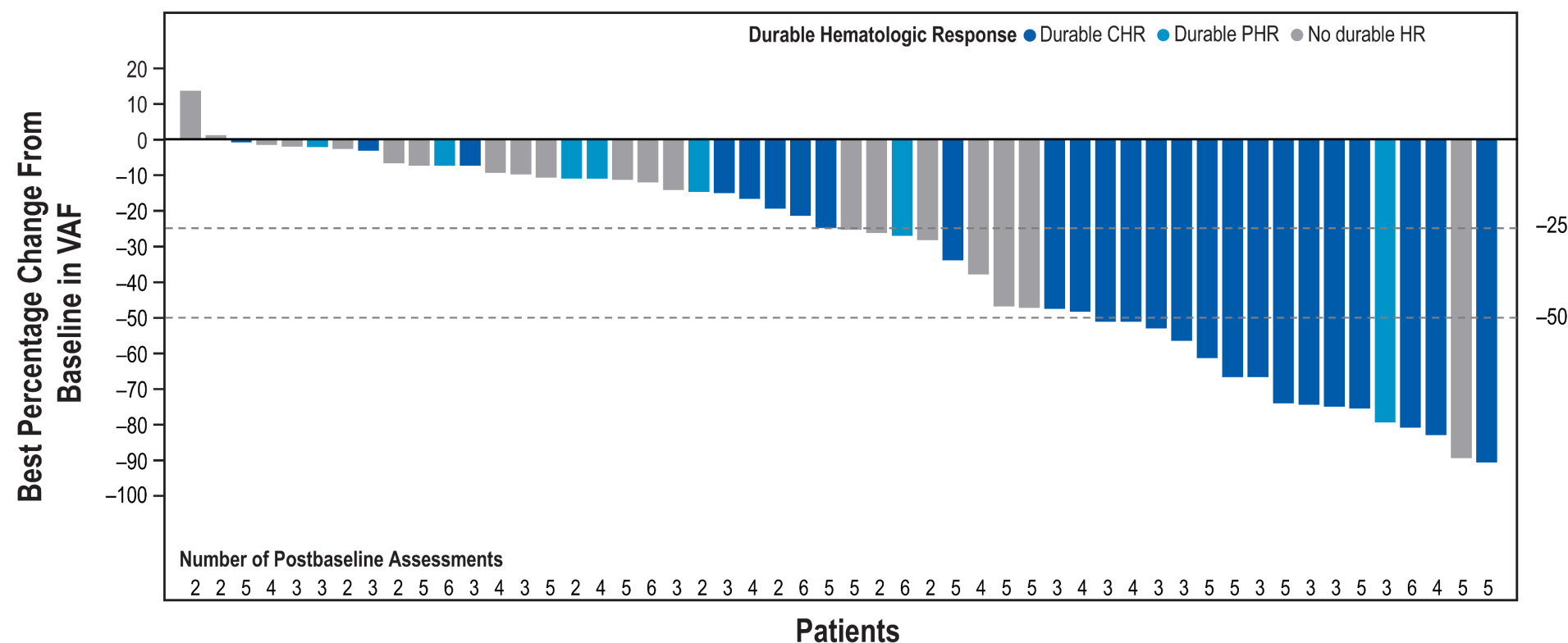


*CHR defined as platelet count $\leq 400 \times 10^9/L$ and leukocytes $< 10 \times 10^9/L$, PHR defined as platelet count $\leq 600 \times 10^9/L$ and leukocytes $< 10 \times 10^9/L$ (baseline platelet count $> 600 \times 10^9/L$). [†]Patients with ≥ 12 weeks of INCA033989 treatment or early termination. [‡]Durable response defined as maintaining for ≥ 12 weeks.

C, cycle; CHR, complete hematologic response; D, day; HR, hematologic response; NR, no response; PHR, partial hematologic response.

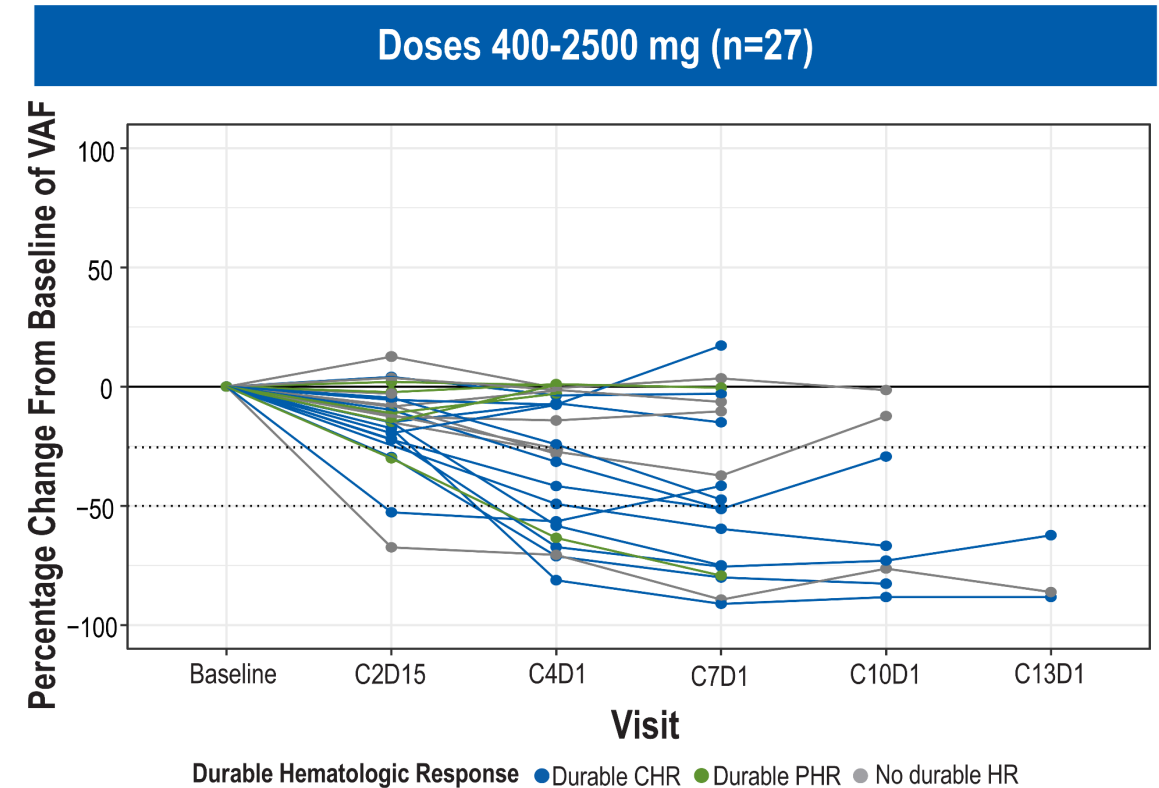
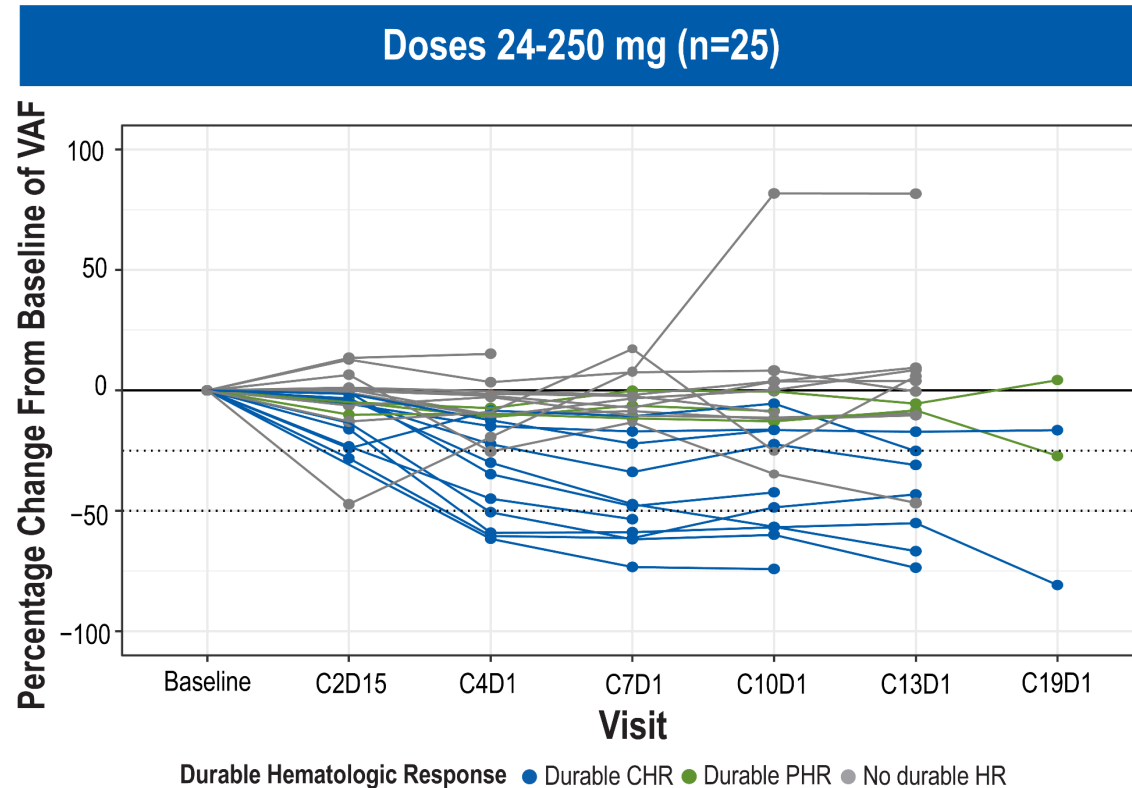
Frequent Molecular Responses Correlate With Hematologic Responses With INCA033989 Monotherapy

- A reduction in mutCALR VAF from baseline occurred in 50/52* (96.2%) patients with ≥1 postbaseline VAF measurement
 - Best reduction in VAF ≥25%: 27/52 (52%)
 - Best reduction in VAF ≥50%: 16/52 (31%)



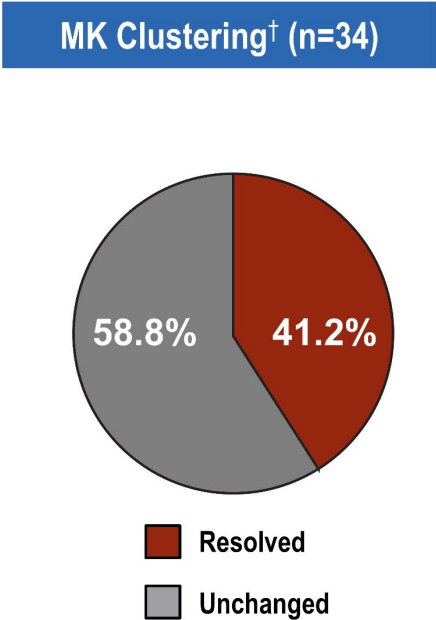
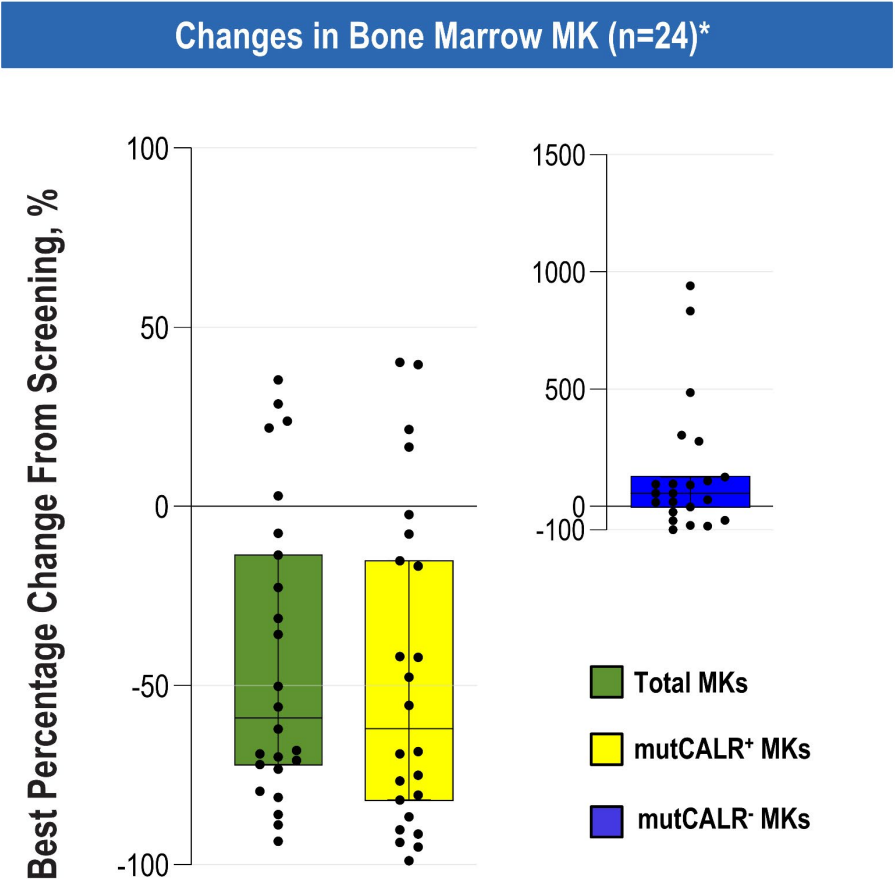
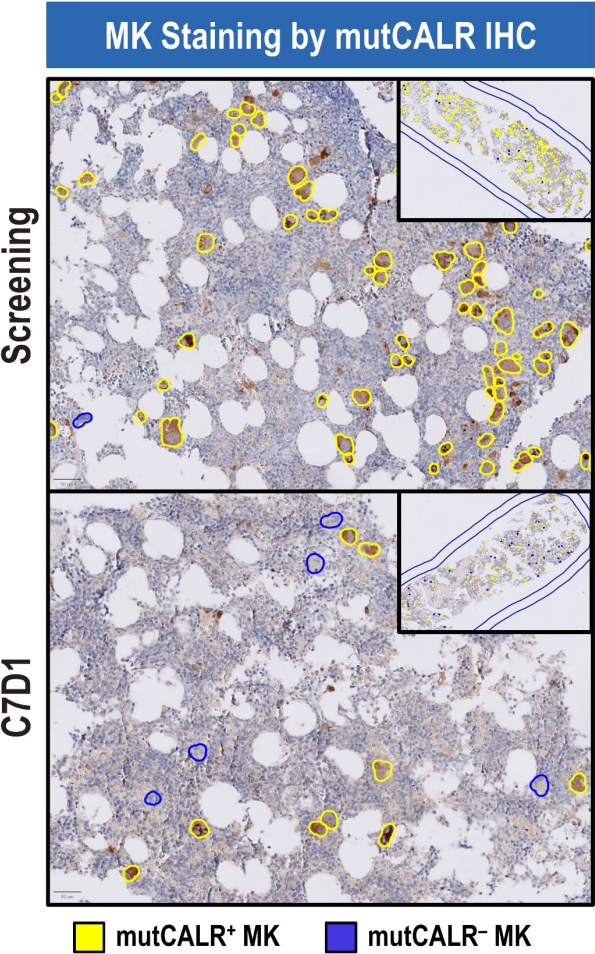
*3 patients were excluded due to lack of postbaseline assessment. Postbaseline assessments performed C2D15, C4D1, and every 3 cycles thereafter. CHR defined as platelet count $\leq 400 \times 10^9/L$ and leukocytes $< 10 \times 10^9/L$, PHR defined as platelet count $\leq 600 \times 10^9/L$ and leukocytes $< 10 \times 10^9/L$ (baseline platelet count $> 600 \times 10^9/L$). Durable response defined as maintaining for ≥ 12 weeks. C, cycle; CHR, complete hematologic response; D, day; HR, hematologic response; mutCALR, mutations in calreticulin; PHR, partial hematologic response; VAF, variant allele frequency.

Molecular Responses Are Rapid, Durable, and Improve at Higher Doses of INCA033989



- Reduction in mutCALR VAF was observed within 3-6 months and was maintained over time in most patients
- More consistent reduction in mutCALR VAF was observed at higher doses

Reduction in mutCALR⁺ Megakaryocytes (MK) Marks Improvement in Bone Marrow Hematopoiesis



*1 patient with 0 mutCALR⁻ MK at screening is not shown. Bone marrow mutCALR IHC quantitative assessment of mutCALR⁺ and mutCALR⁻ MK were conducted for patients with available samples at screening and at timepoints on-treatment (primarily 3 or 6 cycles). [†]MK clustering was centrally assessed for patients with available samples at screening and C7D1. "Resolved": present at screening and absent at C7D1; "Unchanged": present at screening and present at C7D1. C, cycle; CHR, complete hematologic response; D, day; IHC, immunohistochemistry; mutCALR, mutations in calreticulin; PHR, partial hematologic response.

Conclusions

- INCA033989 monotherapy is well tolerated in patients with ET who are resistant/intolerant to prior cytoreductive therapy
 - No dose-limiting toxicities were observed, and a maximum tolerated dose was not reached
 - 93% of patients remain on treatment
- Rapid and durable normalization of platelets was observed
 - Trend towards improved responses at higher doses
 - Most patients achieved a CHR
- Molecular responses were frequent, rapid, durable and correlated with hematologic responses
- Exploratory analysis indicated improvement of MK hyperplasia, and recovery of normal hematopoiesis supports the disease-modifying potential of INCA033989
- Dose expansion is ongoing, and a phase 3 study is planned for initiation in 2026
 - Development of a subcutaneous formulation is ongoing

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