

Mutant Calreticulin–Specific Monoclonal Antibody, INCA033989, Is Well Tolerated and Achieves Rapid and Sustained Hematologic and Molecular Responses in Patients With Essential Thrombocythemia

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Introduction

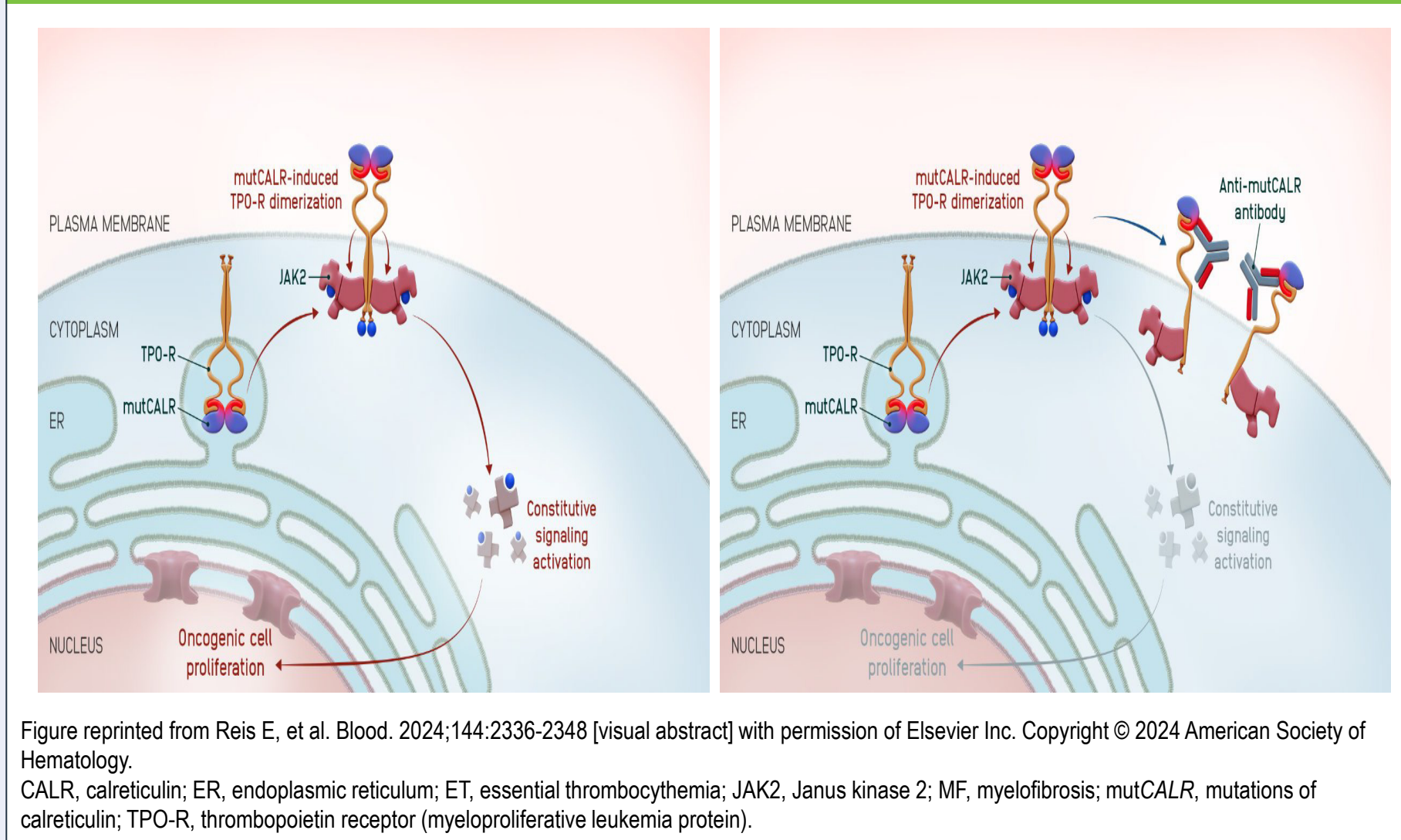
Calreticulin Mutations Are Frequent in Essential Thrombocythemia With No Mutant-Specific Treatment Available

- Essential thrombocythemia (ET) is characterized by megakaryocyte hyperplasia and clustering, thrombocytosis, and an increased risk of thrombosis, hemorrhage, and transformation to myelofibrosis (MF)^{1,2}
- Mutations of calreticulin (mutCALR) in exon 9 are found in 25-30% of patients with ET³⁻⁵
- ET with mutCALR is associated with diagnosis at a younger age and higher risk of transformation to MF compared with JAK2V617F^{6,7}
- Current treatments are broadly myelosuppressive, not mutant targeted, and have limited efficacy in reducing mutCALR allele frequency^{8,9}

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

- INCA033989 has a unique mechanism of action (Figure 1)
 - INCA033989 is a novel, first-in-class, fully human, Fc-silenced, immunoglobulin G1 monoclonal antibody that selectively targets mutCALR with high affinity, when in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells¹⁰

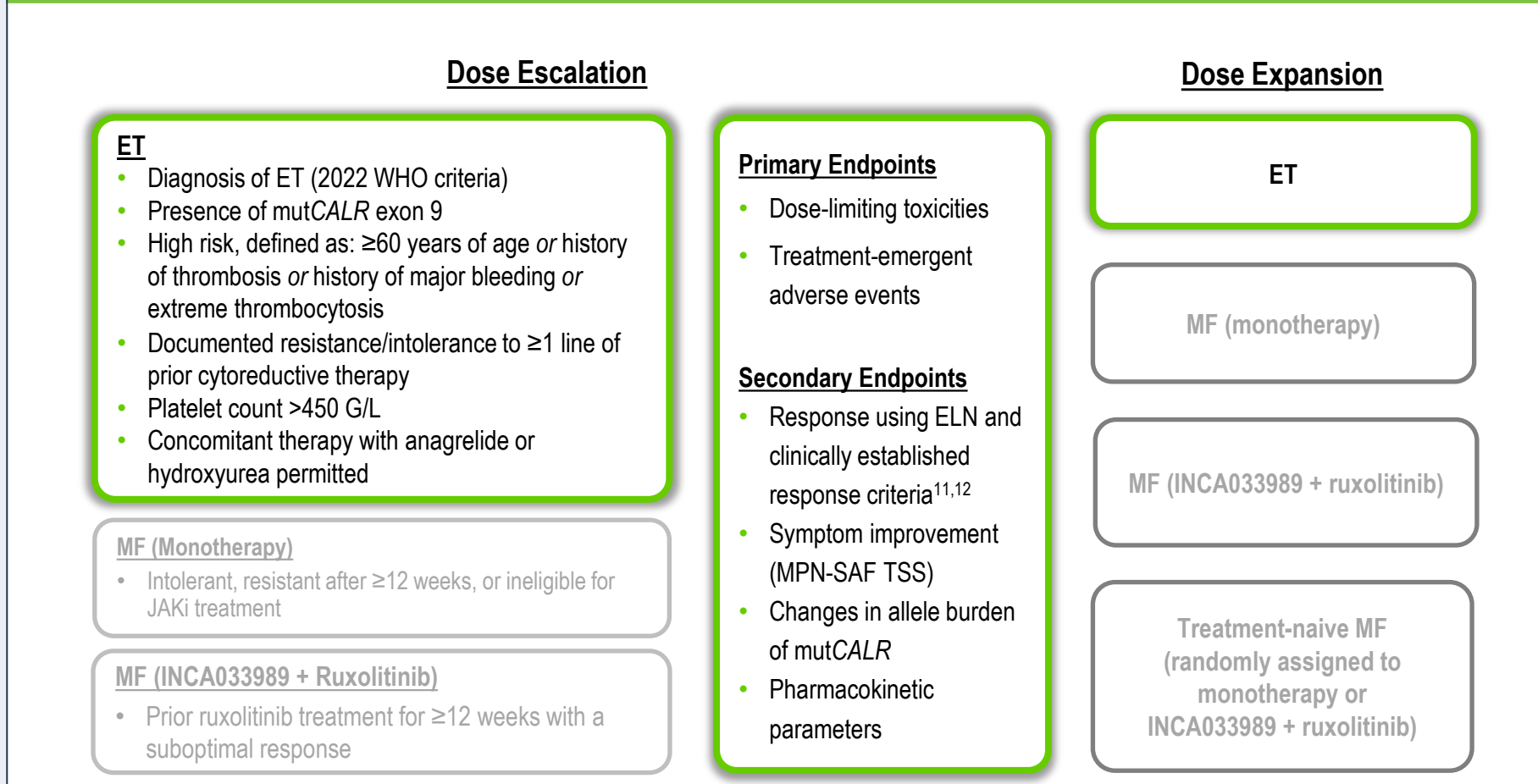
Figure 1. INCA033989 Mechanism of Action



Methods

- 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), alternative frequencies were tested (Q4W, other; Figure 2)

Figure 2. Study Design



ELN, European LeukemiaNet; ET, essential thrombocythemia; JAK1, Janus kinase inhibitor; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mutCALR, mutations of calreticulin; TSS, total symptom score; WHO, World Health Organization.

Results

Table 1. Demographics and Disease Characteristics

Variable	Total (N=114)
Age, years, median (range)	62 (23, 89)
≥65, n (%)	48 (42.1)
Female, n (%)	69 (60.5)
Time from initial diagnosis, years, median (range)	6.9 (0.3, 27.9)
CALR exon 9 mutation type, n (%)	
Type 1	50 (43.9)
Non-Type 1	64 (56.1)
Median CALR VAF,* % (range)	34 (10, 75)
Median platelets (range), G/L	913 (444, 3152)
Receiving anticoagulant therapy at baseline, n (%)	17 (14.9)
Receiving aspirin at baseline, n (%)	69 (60.5)
Prior cytoreductive therapy†, n (%)	
Hydroxycarbamide	100 (87.7)
Anagrelide	36 (31.6)
Interferons	35 (30.7)
Other‡	12 (10.5)

Data cutoff: March 6, 2026.
*Measured centrally in peripheral blood by NGS (n=107). †Categories not mutually exclusive. ‡bomedenstat (n=2), pelabresb (n=1), busulfan (n=2), ruxolitinib (n=9). CALR, calreticulin; VAF, variant allele frequency.

INCA033989 Monotherapy Is Well Tolerated

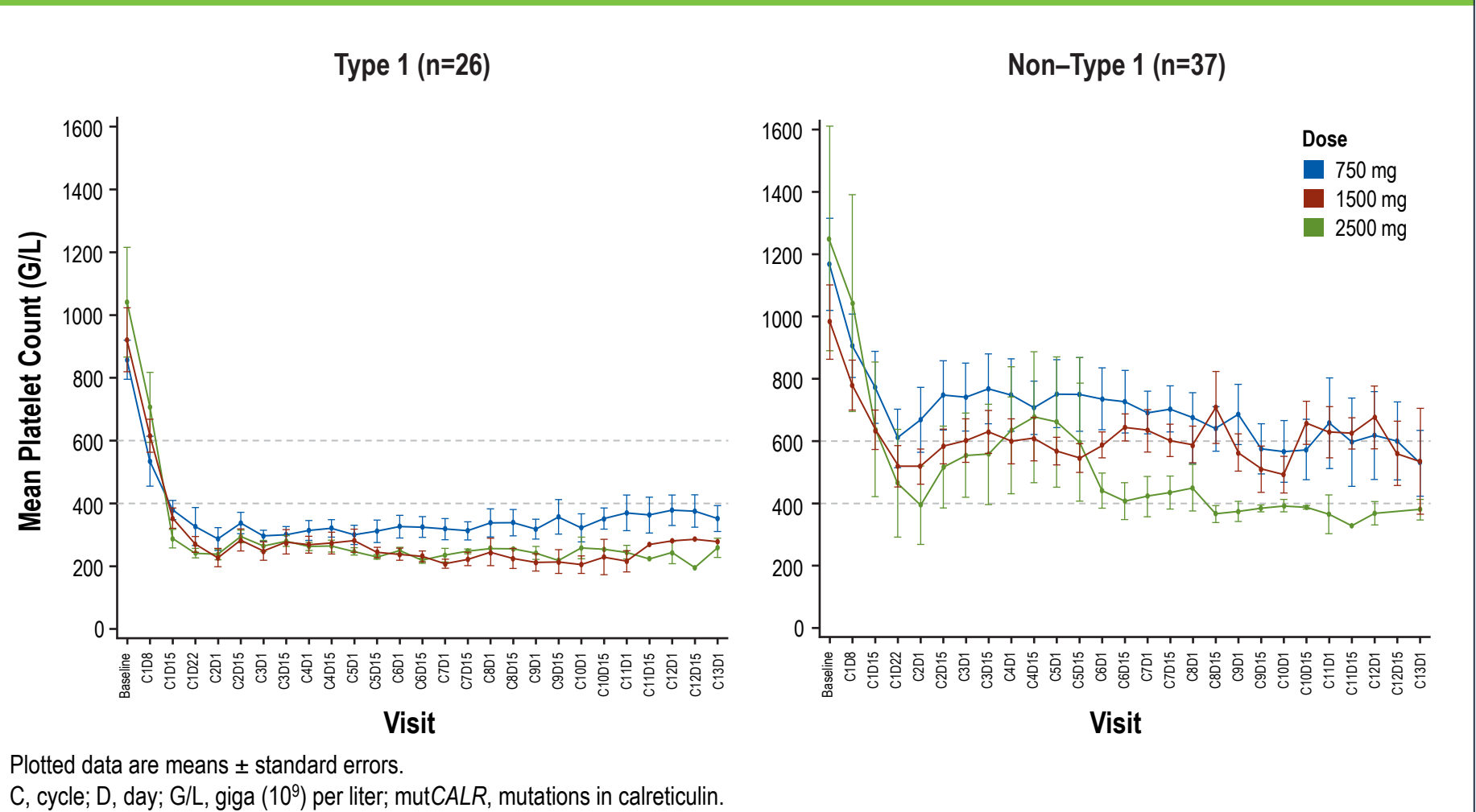
- 95% of patients (108/114) remain on treatment; only 5% (6/114) patients discontinued treatment
- The median (range) duration of INCA033989 exposure was 8.1 months (0.59, 27.0)
- Grade ≥3 cytopenia treatment-emergent adverse events (TEAEs) occurred in 6% (7/114) patients; no grade ≥3 thrombocytopenia TEAEs were observed (Table 2)
- Lipase or amylase elevations were transient, with no associated clinical sequelae

Table 2. Safety Outcomes

Overall TEAE Summary		Most Common TEAEs (≥10% of Patients)		Most Common Grade ≥3 TEAEs (≥2 Patients)	
TEAE, n (%)	Total (N=114)	TEAE, n (%)	Total (N=114)	TEAE, n (%)	Total (N=114)
Any TEAE	104 (91.2)	Fatigue	29 (25.4)	Neutropenia	5 (4.4)
Treatment-related	70 (61.4)	Headache	24 (21.1)		
Grade ≥3*	22 (19.3)	Lipase increased	21 (18.4)	Lipase increased	4 (3.5)
Serious†	5 (4.4)	Constipation	18 (15.8)	Hypertension	3 (2.6)
Fatal	0 (0)	Diarrhea	18 (15.8)	Leukopenia	3 (2.6)
Discontinuation due to TEAEs	1 (0.9)	Anemia	17 (14.9)		
Dose reduction due to TEAEs	2 (1.8)	Nausea	17 (14.9)	Amylase increased	2 (1.8)
Infusion interruption due to TEAEs	6 (5.3)	URT†	17 (14.9)	Anemia	2 (1.8)
		Dizziness	16 (14.0)		
		Arthralgia	14 (12.3)		
Dose delay due to TEAEs	25 (21.9)	Pruritus	14 (12.3)		
Dose-limiting toxicity	0 (0)	Amylase increased	13 (11.4)		

*One grade 4 TEAE was observed (transient neutropenia related to concomitant hydroxyurea). †The following serious adverse events were considered unrelated to INCA033989: acute sinusitis (n=1, 750 mg); basal cell carcinoma (n=1, 2500 mg Q2W); diverticulitis (n=1, 400 mg); polymyalgia rheumatica (n=1, 1500 mg); proctitis (n=1, 1500 mg); urinary tract infection (n=1, 1500 mg). One event, visceral venous thrombosis (n=1, 24 mg) followed by melena (after anticoagulant initiation) and treatment discontinuation, was related to INCA033989. ‡Adverse event (visceral venous thrombosis; n=1), lack of efficacy (n=2), pregnancy (n=1), and patient withdrawal (n=2). Q2W, every 2 weeks; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

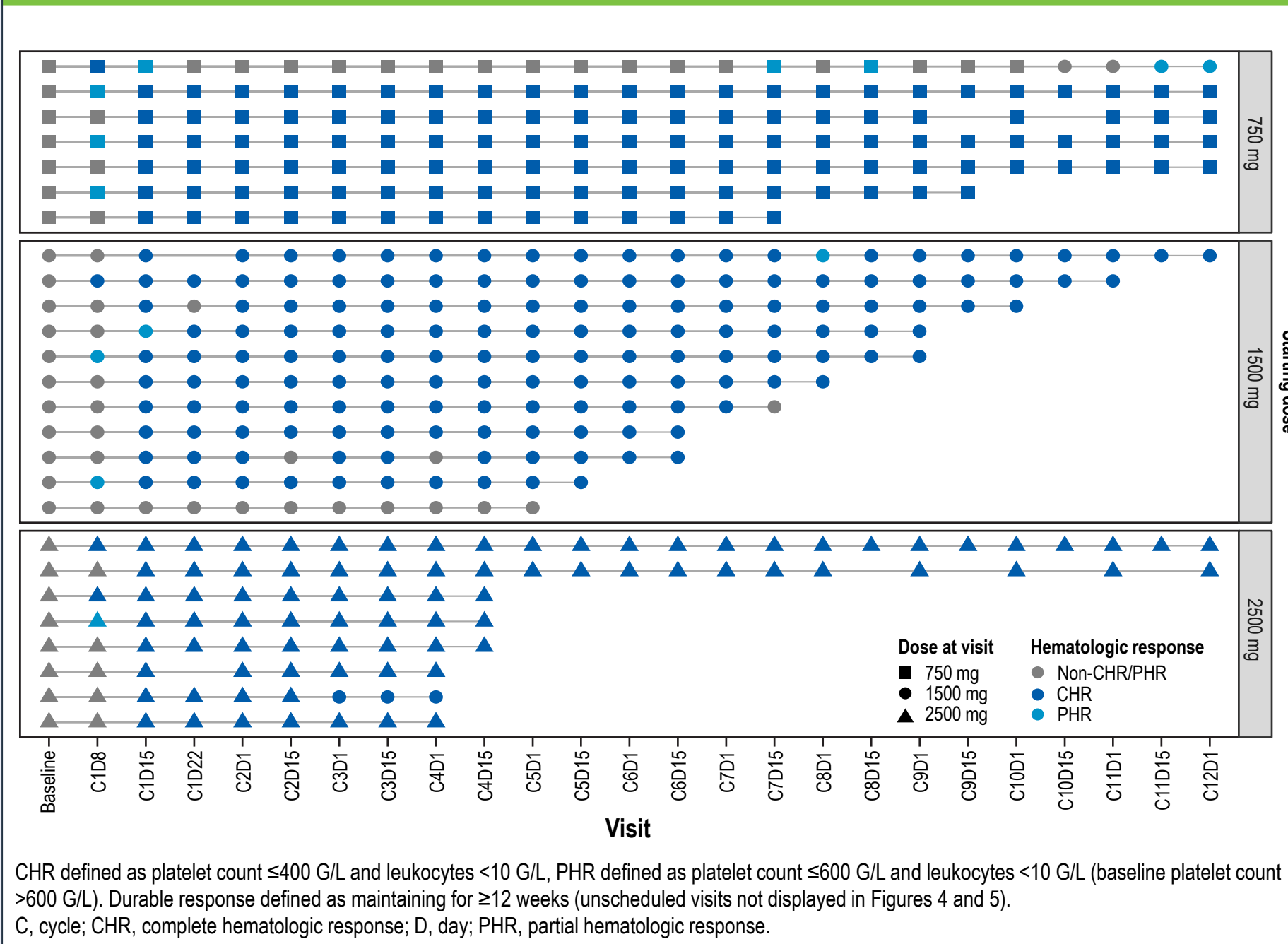
Figure 3. Platelet Count Response by Dose and mutCALR Type (n=63)



Plotted data are means ± standard errors.
C, cycle; D, day; G/L, giga (10⁹) per liter; mutCALR, mutations in calreticulin.

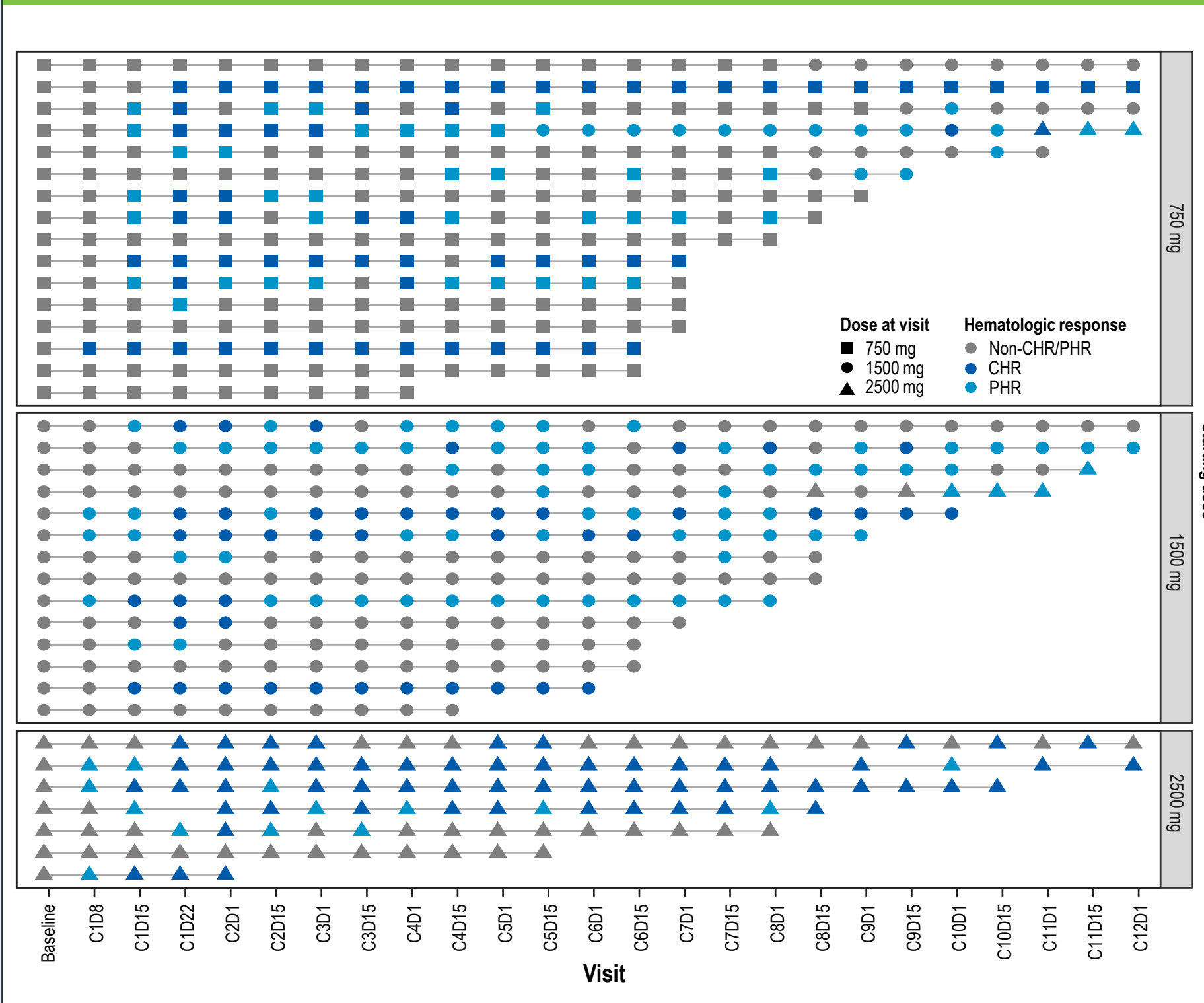
INCA033989 Monotherapy Produces Rapid and Durable Hematologic Responses

Figure 4. Durable Hematologic Response Is Observed in Type 1 Patients at Doses ≥750 mg (n=26)



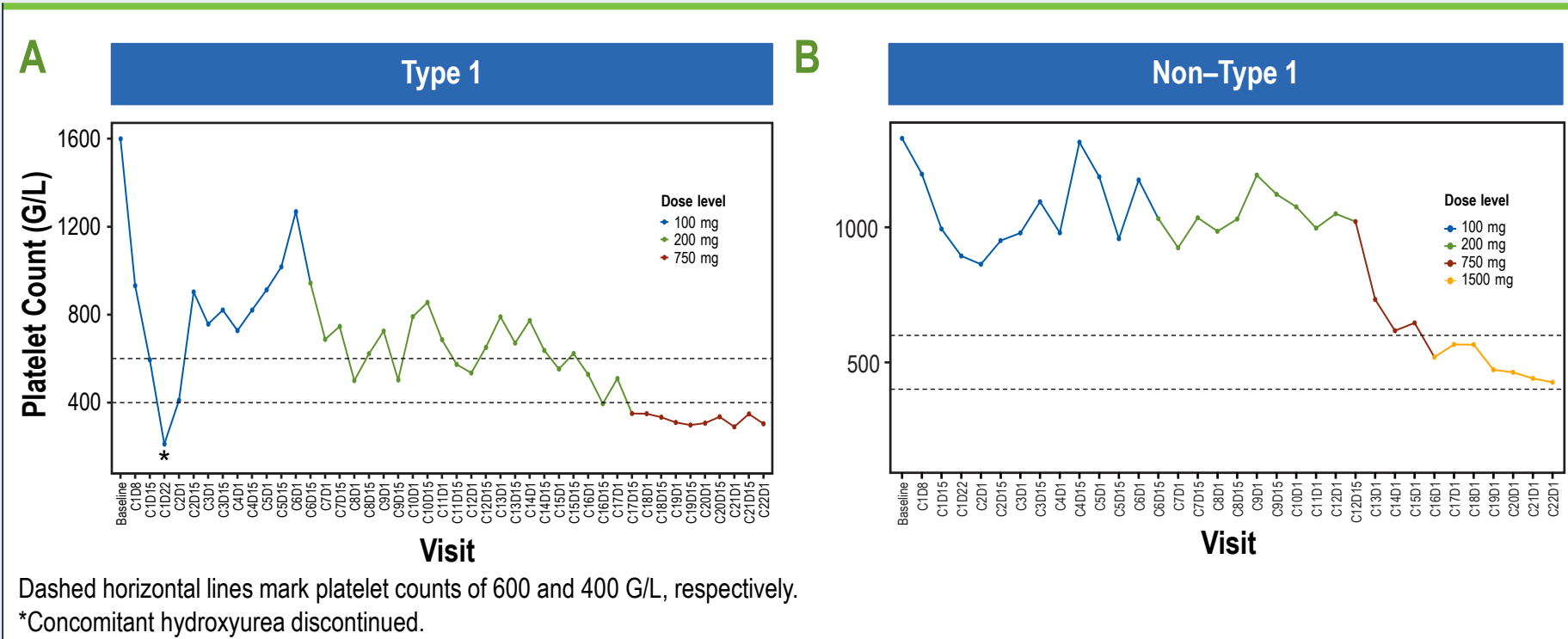
CHR defined as platelet count <400 G/L and leukocytes <10 G/L. PHR defined as platelet count <500 G/L and leukocytes <10 G/L (baseline platelet count >500 G/L). Durable response defined as maintaining for ≥12 weeks (unscheduled visits not displayed in Figures 4 and 5). C, cycle; CHR, complete hematologic response; D, day; PHR, partial hematologic response.

Figure 5. Durable Hematologic Response Is Observed in Non-Type 1 Patients at 2500 mg (n=37)



- Across all doses, 70% of patients (80/114) had a complete hematologic response (CHR) and 87% (99/114) had a CHR or partial hematologic response (PHR)
- The median (range) duration of CHR/PHR was 23 (0.14, 107) weeks
- The median (range) time to onset of durable (≥12 weeks) CHR was 2.1 (1.1, 68) weeks
- 81% of patients (21/26) with Type 1 mutCALR achieved a durable CHR at 750 mg and above; 50% of patients (3/6) with non-Type 1 mutCALR achieved a durable CHR/PHR at 2500 mg (Figures 4-5)
- Dose titration resulted in hematologic response in patients initially treated at lower doses (Figure 6)

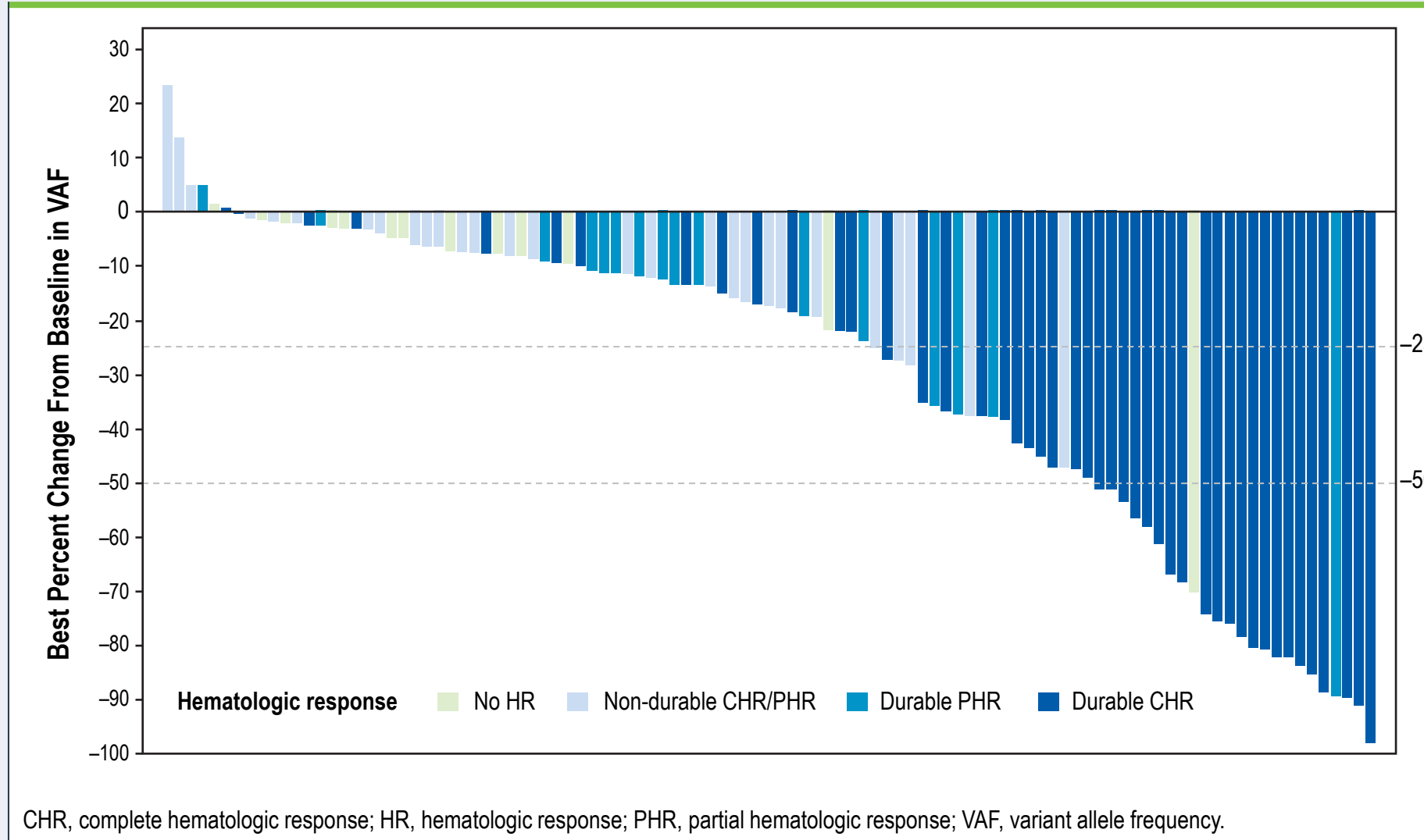
Figure 6. Dose Titration in 2 Representative Patients



Dashed horizontal lines mark platelet counts of 600 and 400 G/L, respectively.
*Concomitant hydroxyurea discontinued.

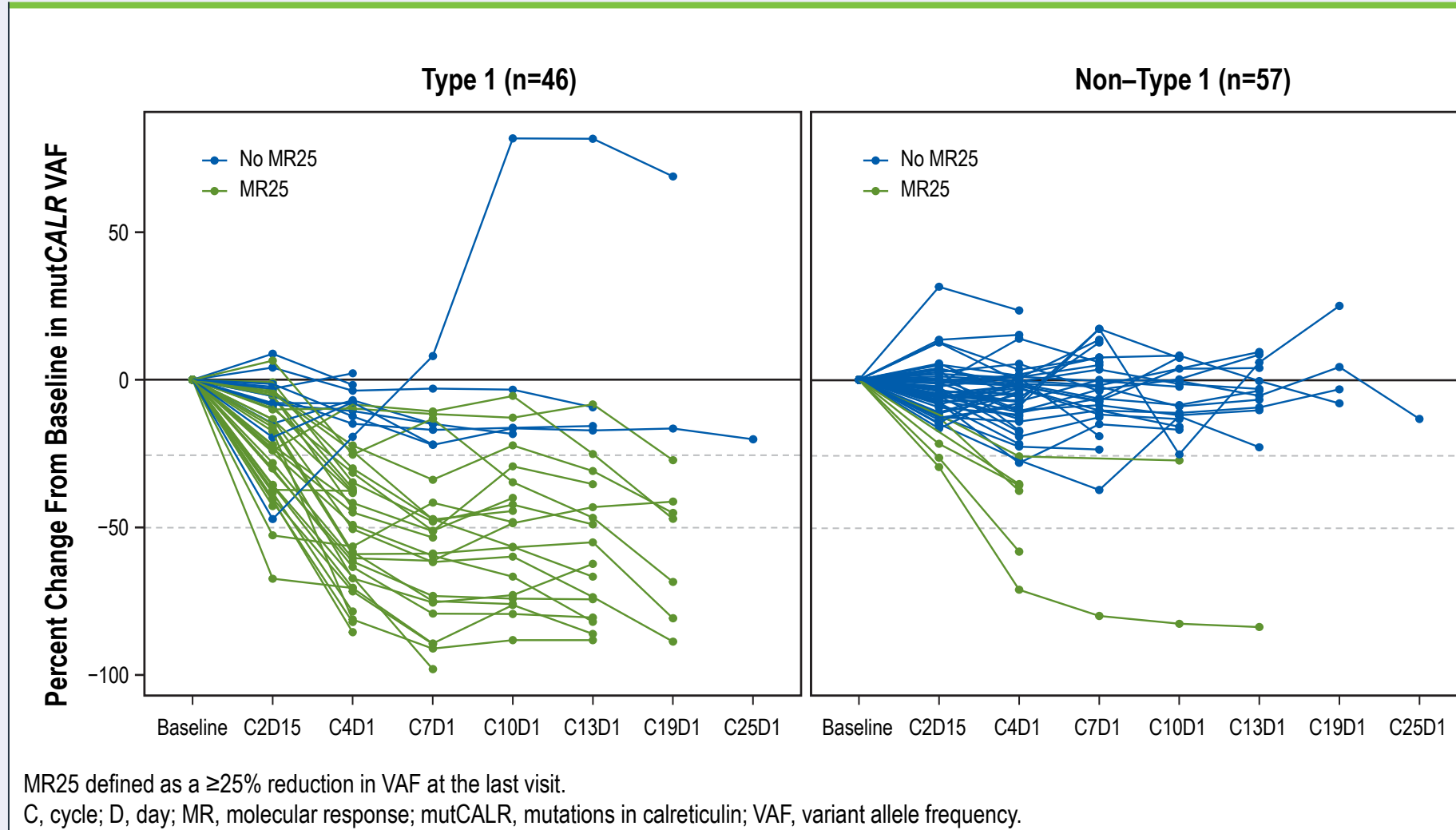
Molecular Response Is Durable and Correlates With Hematologic Response

Figure 7. Correlation of mutCALR VAF and Durable Hematologic Response



- A ≥25% VAF reduction correlated with durable CHR (nominal P<0.0001, n=103; Figure 7)
- Among 45 patients who achieved durable CHR and had ≥1 postbaseline VAF assessment, 73% (33/45) achieved a ≥25% reduction in VAF

Figure 8. Molecular Responses Are Durable and Observed in Type 1 and Non-Type 1 Patients (n=103)



Conclusions

- INCA033989 continues to demonstrate a favorable safety profile in patients with ET and resistance/intolerance to prior cytoreductive therapy**
 - Overall, 95% (108/114) of patients remain on treatment
 - No grade ≥3 thrombocytopenia was observed, with a majority of cytopenias occurring in the presence of concurrent hydroxyurea
- INCA033989 produces rapid and durable responses**
 - Across all doses, 70% (80/114) patients had a CHR and 87% (99/114) had a CHR/PHR
 - Durable hematologic response was seen in most patients with Type 1 mutCALR at ≥750 mg (CHR, 81%; 21/26), and in non-Type 1 mutCALR at 2500 mg (CHR/PHR, 50%; 3/6)
 - A ≥25% VAF reduction correlated with durable CHR
 - Dose titration resulted in hematologic response in patients initially treated at lower doses
- Durable molecular response is observed in both Type 1 and non-Type 1 mutCALR**
- Treatment with INCA033989 reduced mutCALR megakaryocytes in the bone marrow and mutCALR myeloid cell fractions**
- These data support the planned initiation of a phase 3 program in patients with ET (NCT07623200; EXCALIBUR-ET2)**

Disclosures

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

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