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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 (mut*CALR*) in exon 9 are found in 25-30% of patients with ET[3-5]
- ET with mut*CALR* is associated with diagnosis at a younger age and higher risk of transformation to MF compared with *JAK2*V617F[6,7]
- Current treatments are broadly myelosuppressive, not mutant targeted, and have limited efficacy in reducing mut*CALR* 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 cells[10]

Figure 1. INCA033989 Mechanism of Action

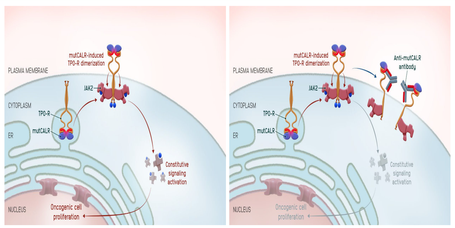
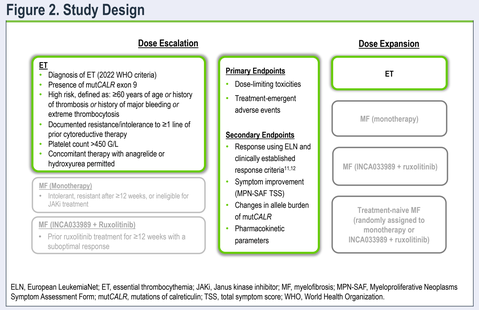


Figure reprinted from Reis E, et al. Blood. 2024;144:2336-2348 [visual abstract] with permission of Elsevier Inc. Copyright © 2024 American Society of Hematology.
CALR, calreticulin; ER, endoplasmic reticulum; ET, essential thrombocythemia; JAK2, Janus kinase 2; MF, myelofibrosis; mut*CALR*, mutations of calreticulin; TPO-R, thrombopoietin receptor (myeloproliferative leukemia protein).

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; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mut*CALR*, 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. ‡bomedemstat (n=2), pelabresib (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

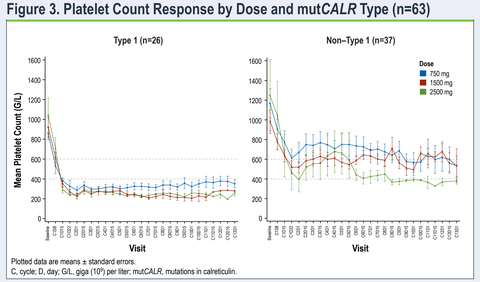
Overall TEAE Summary	Total (N=114)
Any TEAE	104 (91.2)
Treatment-related	70 (61.4)
Grade ≥3*	22 (19.3)
Serious†	5 (4.4)
Fatal	0 (0)
Discontinuation due to TEAEs	1 (0.9)
Dose reduction due to TEAEs	2 (1.8)
Infusion interruption due to TEAEs	6 (5.3)
Dose delay due to TEAEs	25 (21.9)
Dose-limiting toxicity	0 (0)

Most Common TEAEs (≥10% of Patients)	Total (N=114)
Fatigue	29 (25.4)
Headache	24 (21.1)
Lipase increased	21 (18.4)
Constipation	18 (15.8)
Diarrhea	18 (15.8)
Anemia	17 (14.9)
Nausea	17 (14.9)
URTI	17 (14.9)
Dizziness	16 (14.0)
Arthralgia	14 (12.3)
Pruritus	14 (12.3)
Amylase increased	13 (11.4)

Most Common Grade ≥3 TEAEs (≥2 Patients)	Total (N=114)
Neutropenia	5 (4.4)
Lipase increased	4 (3.5)
Hypertension	3 (2.6)
Leukopenia	3 (2.6)
Amylase increased	2 (1.8)
Anemia	2 (1.8)

*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.

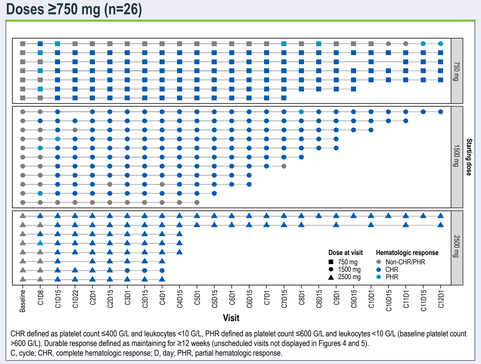
Figure 3. Platelet Count Response by Dose and mut*CALR* Type (n=63)



Plotted data are means ± standard errors.
C, cycle; D, day; G/L, giga (10^9) per liter; mut*CALR*, mutations in calreticulin.

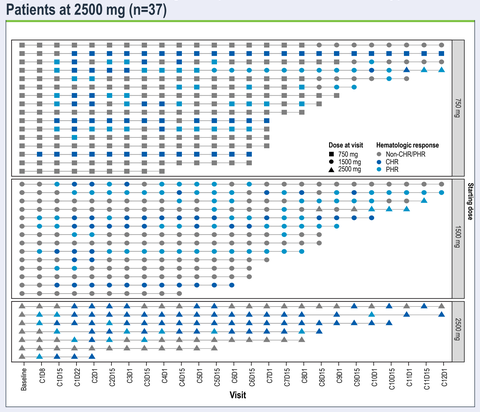
INCA033989 Monotherapy Produces Rapid and Durable Hematologic Responses

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



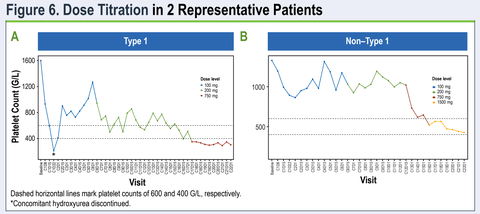
CHR defined as platelet count ≤400 G/L and leukocytes <10 G/L. PHR defined as platelet count ≤600 G/L and leukocytes <10 G/L (baseline platelet count >600 G/L). Durable response defined as maintaining for ≥12 weeks (unscheduled visits not displayed in Figures 4 and 5).
C, cycle; CHR, complete hematologic 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 mut*CALR* achieved a durable CHR at 750 mg and above; 50% of patients (3/6) with non–Type 1 mut*CALR* 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)**

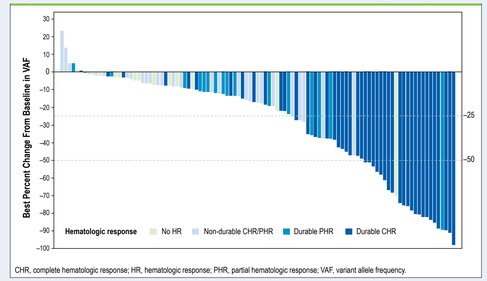
Figure 6. Dose Titration in 2 Representative Patients



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

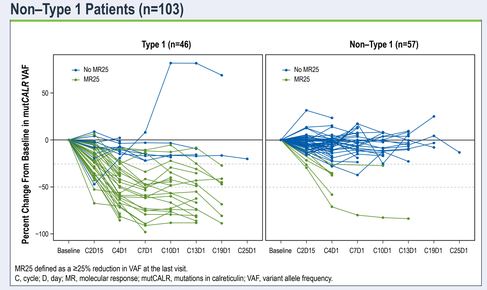
Figure 7. Correlation of mut*CALR* VAF and Durable Hematologic Response



CHR, complete hematologic response; HR, hematologic response; PHR, partial hematologic response; VAF, variant allele frequency.

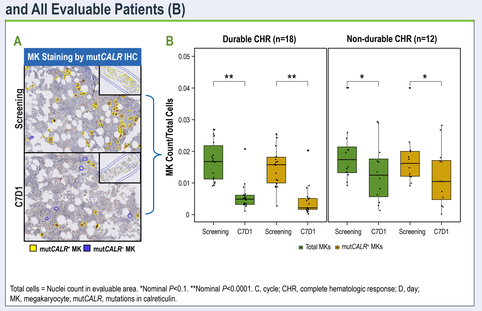
- A ≥25% VAF reduction correlated with durable CHR (nominal *P*<0.0001, n=103; **Figure 7**)
- Among 45 patients who achieved durable CHR and had ≥1 postbaseline VAF assessment, 73% (33/45) achieved a ≥25% reduction in VAF

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



MR2S defined as a ≥25% reduction in VAF at the last visit.
C, cycle; D, day; MR, molecular response; mut*CALR*, mutations in calreticulin; VAF, variant allele frequency.

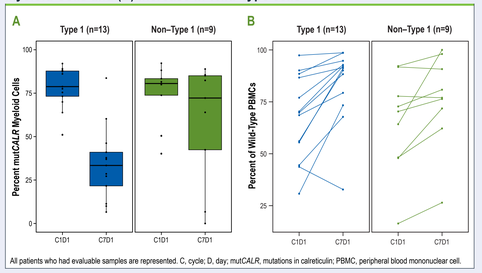
Figure 9. Bone Marrow Megakaryocyte Analysis in Representative Patient (A) and All Evaluable Patients (B)



Total cells = Nuclei count in evaluable area. *Nominal *P*<0.1. **Nominal *P*<0.0001. C, cycle; CHR, complete hematologic response; D, day; MK, megakaryocyte; mut*CALR*, mutations in calreticulin.

- IHC analysis of bone marrow showed reduction in total megakaryocytes and mut*CALR*$^+$ megakaryocytes from baseline to cycle 7, day 1 in patients both with and without durable CHR

Figure 10. mut*CALR* Molecular Response Is Driven by (A) Loss of mut*CALR* Myeloid Cells and (B) Increase in Wild-Type cells



All patients who had evaluable samples are represented. C, cycle; D, day; mut*CALR*, mutations in calreticulin; PBMC, peripheral blood mononuclear cell.

- The fraction of mut*CALR* myeloid cells in PBMCs was reduced with INCA033989 monotherapy
- Most patients with Type 1 or non–Type 1 mut*CALR* had increased percentages of wild-type PBMCs over time

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 mut*CALR* at ≥750 mg (CHR, 81%; 21/26), and in non–Type 1 mut*CALR* 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 mut*CALR***
- **Treatment with INCA033989 reduced mut*CALR* megakaryocytes in the bone marrow and mut*CALR* 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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