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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

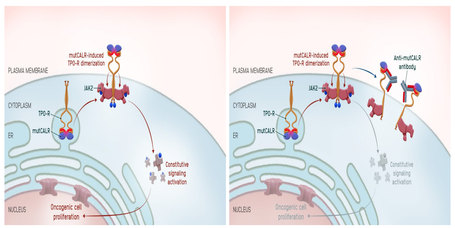
Calreticulin Mutations Are Frequent in Essential Thrombocythemia With No Mutant-Specific Treatment Available

- 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



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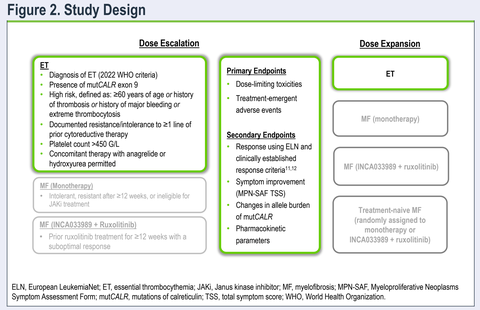
CALR, calreticulin; ER, endoplasmic reticulum; ET, essential thrombocythemia; JAK2, Janus kinase 2; MF, myelofibrosis; mut*CALR*, mutations of calreticulin; TPO-R, thrombopoietin receptor (myeloproliferative leukemia protein).

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

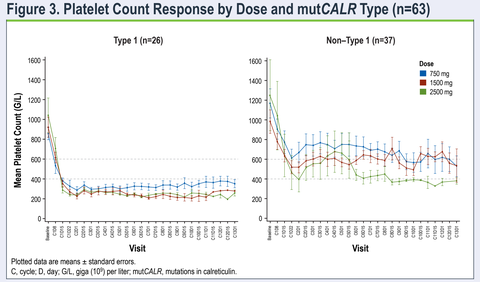
- 95% of patients (108/114) remain on treatment; only 5% (6/114) patients discontinued treatment
- The median (range) duration of INCA033989 exposure was 8.1 months (0.59, 27.0)
- Grade ≥3 cytopenia treatment-emergent adverse events (TEAEs) occurred in 6% (7/114) patients; no grade ≥3 thrombocytopenia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

Table 2. Safety Outcomes

Overall TEAE Summary		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)	Lipase increased	4 (3.5)
Grade ≥3*	22 (19.3)	Lipase increased	21 (18.4)	Hypertension	3 (2.6)
Serious†	5 (4.4)	Constipation	18 (15.8)	Leukopenia	3 (2.6)
Fatal	0 (0)	Diarrhea	18 (15.8)	Amylase increased	2 (1.8)
Discontinuation due to TEAEs	1 (0.9)	Anemia	17 (14.9)	Anemia	2 (1.8)
Dose reduction due to TEAEs	2 (1.8)	Nausea	17 (14.9)		
Infusion interruption due to TEAEs	6 (5.3)	URTI	17 (14.9)		
Dose delay due to TEAEs	25 (21.9)	Dizziness	16 (14.0)		
Dose-limiting toxicity	0 (0)	Arthralgia	14 (12.3)		
		Pruritus	14 (12.3)		
		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

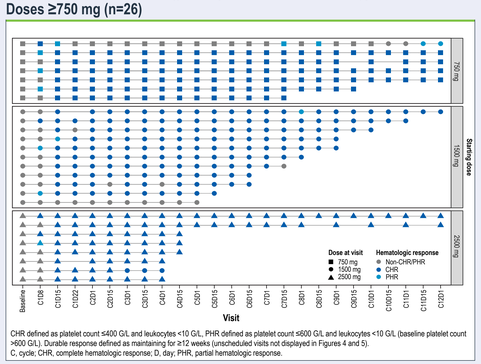
Figure 3. Platelet Count Response by Dose and mut*CALR* Type (n=63)



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

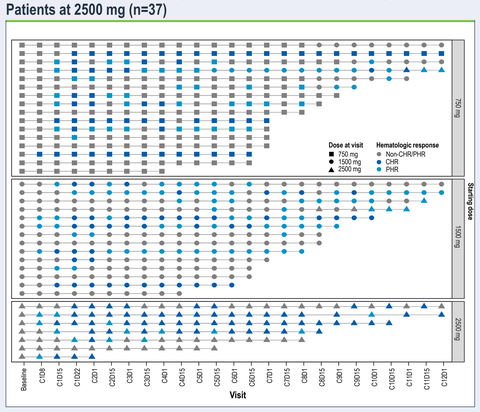
INCA033989 Monotherapy Produces Rapid and Durable Hematologic Responses

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



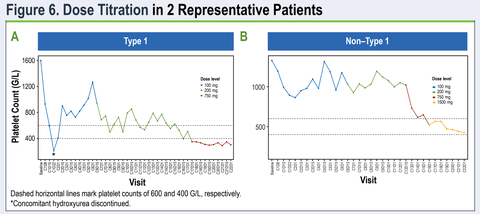
CHR defined as platelet count ≤400 G/L and leukocytes <10 G/L. PHR defined as platelet count ≤600 G/L and leukocytes <10 G/L (baseline platelet count >600 G/L). Durable response defined as maintaining for ≥12 weeks (unscheduled visits not displayed in Figures 4 and 5).
C, cycle; CHR, complete hematologic 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)**

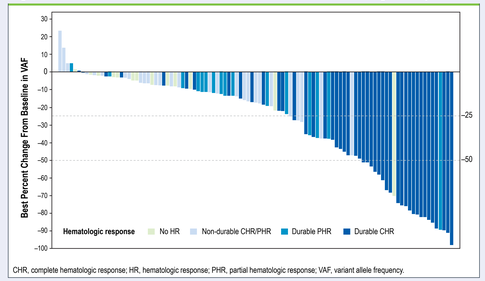
Figure 6. Dose Titration in 2 Representative Patients



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

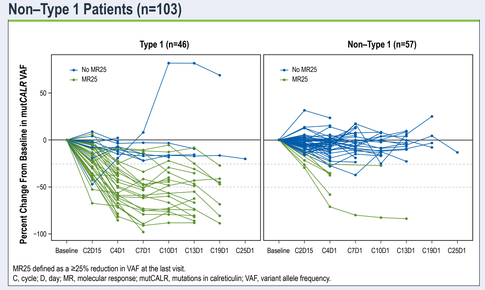
Figure 7. Correlation of mut*CALR* VAF and Durable Hematologic Response



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

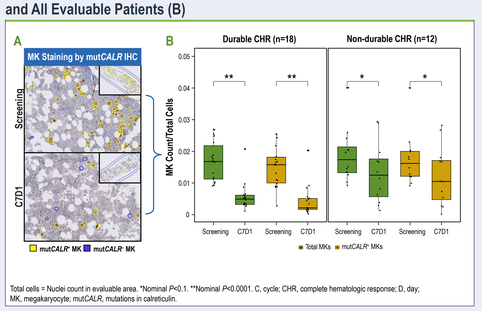
- A ≥25% VAF reduction correlated with durable CHR (nominal *P*<0.0001, n=103; **Figure 7**)
- Among 45 patients who achieved durable CHR and had ≥1 postbaseline VAF assessment, 73% (33/45) achieved a ≥25% reduction in VAF

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



MR25 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.

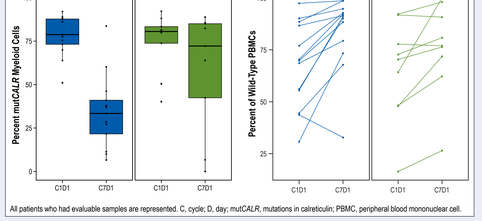
Figure 9. Bone Marrow Megakaryocyte Analysis in Representative Patient (A) and All Evaluable Patients (B)



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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EXCALIBUR-ET2