(PS1983) MUTANT CALRETICULIN–SPECIFIC MONOCLONAL ANTIBODY, INCA033989, IS WELL TOLERATED AND ACHIEVES RAPID AND SUSTAINED HEMATOLOGIC AND MOLECULAR RESPONSES IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA (ET)

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background

ET is a myeloproliferative neoplasm characterized by megakaryocytic hyperplasia and clustering, thrombocytosis, and elevated risk of thrombosis, hemorrhage, and transformation to myelofibrosis (MF). About 25% of patients (pts) with ET harbor calreticulin mutations (mut*CALR*). INCA033989 is a novel, fully human, Fc-silenced, IgG1 monoclonal antibody that selectively targets mut*CALR* in complex with thrombopoietin receptor and inhibits oncogenic signaling and cell proliferation. INCA033989-101 (NCT05936359) and -102 (NCT06034002) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA033989 in pts with ET or MF.

Aims

To evaluate safety and efficacy of INCA033989 in pts with ET and mut*CALR*.

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Methods

Pts enrolled had ET with mut*CALR*; high risk disease (age ≥60 y; history of thrombosis, major bleeding, or extreme thrombocytosis); resistance/intolerance to ≥1 prior line of cytoreductive treatment (tx); and a platelet count (PLT) >450 G/L. The primary endpoint was safety and tolerability. Efficacy was evaluated by hematologic response: PLT ≤400 G/L (complete hematologic response [CHR]) or ≤600 G/L (partial hematologic response [PHR]); a leukocyte count of <10 G/L. Reduction in mut*CALR* variant allele frequency (VAF) was also evaluated.

Results

As of Jan 5, 2026, 110 pts were enrolled as part of dose escalation (24-2500 mg) and dose expansion; no DLTs were observed; MTD was not reached. The median (range) age was 61.5 y (23, 89); 60% of pts were female. The most frequent prior cytoreductive tx were hydroxycarbamide (84%), anagrelide (31%), and interferons (32%). Fifty-one (46%), 40 (36%), and 19 pts (17%) had Type 1, Type 2, and other mut*CALR*, respectively. Baseline median (Q1, Q3) PLT was 913 G/L (657, 1214); median (Q1, Q3) mut*CALR* VAF was 33% (28, 37).

INCA033989 was well tolerated with 106/110 pts (96.4%) continuing tx. The median (range) exposure was 28 weeks (4, 109). Tx-emergent adverse events (TEAEs) occurred in 94 pts (85%); most frequently (≥20%) fatigue (24%) and headache (20%). In 84% of pts, all TEAEs were grade 1-2 and most resolved during tx; 18 pts (16%) had grade ≥3 TEAEs. 7 serious AEs were reported in 3 pts (all grade 3; max duration, 12 days); 1 event (venous thrombosis, 24 mg) led to discontinuation, 1 event (diverticulitis, 400mg) led to dose reduction (pt remained on study and later dose escalated). Infusion reactions were rare (6%), with interruptions occurring in only 5 pts (5%).

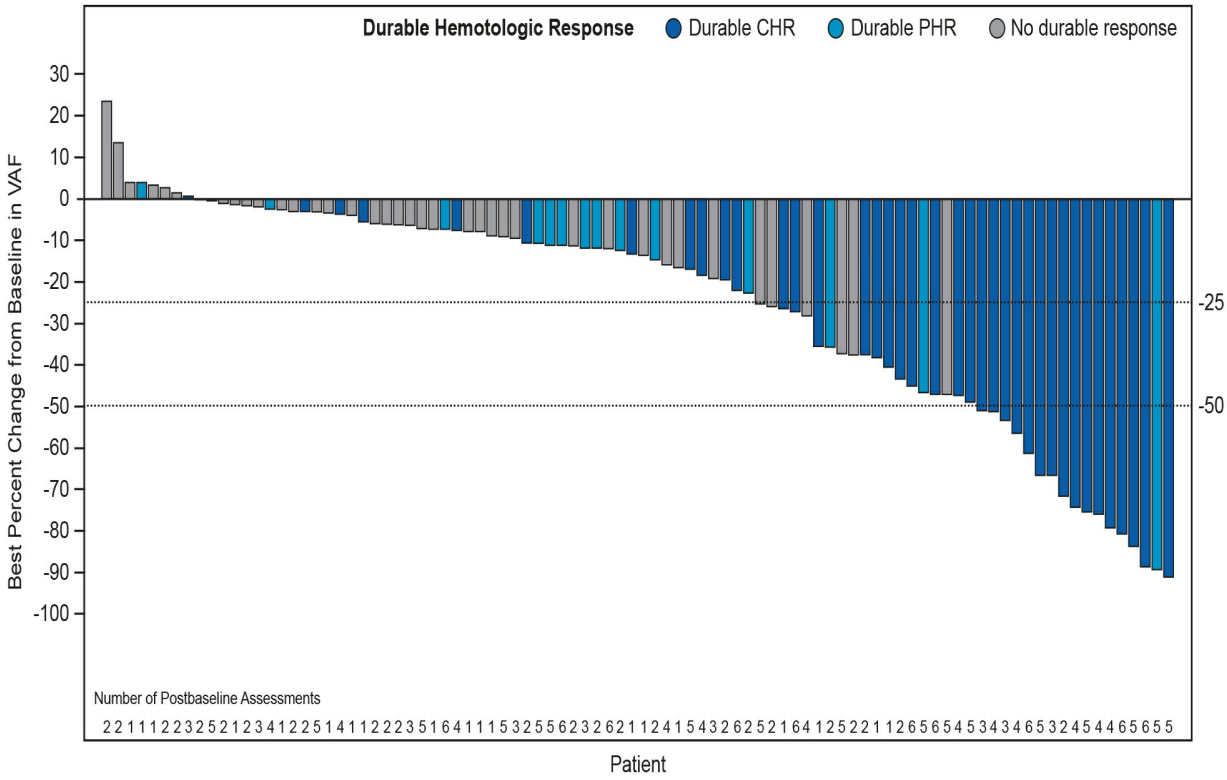
Across all doses, 75 (68%) pts had a CHR and 93 (85%) had a CHR/PHR, with a median (range) duration of CHR/PHR of 15 (0.14, 95) weeks. The median (range) time to onset of durable (≥12 weeks) CHR was 2.1 (1.1, 64) weeks. At C7D1 (~24 weeks), doses of ≥750 mg resulted in 100% of Type 1 and 47% of non-Type 1 pts having PLT <600 G/L, and 92% of Type 1 and 33% of non-Type 1 pts having PLT <400 G/L. A ≥25% VAF reduction correlated with durable CHR (nominal $P<0.0001$); among 38 pts who achieved durable CHR and have ≥1 post-baseline VAF assessment, 71% (27/38) achieved a ≥25% reduction in VAF (**Figure**). Histopathology analysis of bone marrow showed reduction in megakaryocyte cell clustering from baseline to C7D1, correlating with a ≥25% reduction in VAF (nominal $P=0.02$).

Summary/Conclusion

INCA033989 continues to demonstrate favorable safety and efficacy in pts with ET and resistance/intolerance to prior cytoreductive tx. Most pts had a rapid, durable CHR that correlated with a reduction in mut*CALR* VAF. These data support the planned initiation of phase 3 trials in pts with ET.

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Figure. In Patients with ET Treated with INCA033989, Greater Improvement in VAF from Baseline is Associated with Durable Hematologic Response



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

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