386 A Phase 2 Study of the LSD1 Inhibitor Img-7289 (bomedemstat) for the Treatment of Essential Thrombocythemia (ET)

Authors: Francesca Palandri, Nicola Vianelli, David M Ross, Tara Cochrane, Steven W Lane, Stephen R Larsen, Aaron T. Gerds, Anna B. Halpern, Jake Shortt, James M. Rossetti, Kristen M. Pettit, Amber Jones, Jennifer Peppe, Georges Natsoulis, Willis Navarro, Wan-Jen Hong, William S. Stevenson, Claire N. Harrison, Moshe Talpaz, Hugh Young Rienhoff Jr.

Abstract:

Many patients with ET are resistant to or intolerant of current standards of care (SOC) - hydroxyurea (HU), interferon, anagrelide - underscoring the need for novel therapies with distinct modes of action that reduce the risk of thrombosis, improve the patient's experience and favorably alter the natural history. Lysine-specific demethylase-1 (LSD1) is an enzyme critical for the self-renewal potential of malignant cells and hematopoietic differentiation, e.g., LSD1 licenses progenitors to mature into megakaryocytes, a cell central to ET pathogenesis. Bomedemstat is an orally active LSD1 inhibitor that reduced peripheral cell counts, splenomegaly, inflammatory cytokines, mutant cell burdens and improved survival in mouse models of MPNs (Kleppe et al. 2015; Jutzi et al. 2018). IMG-7289-CTP-201 is a global, open-label, Phase 2b study of bomedemstat taken once daily for 24+ weeks in patients with ET who are resistant to or intolerant of at least one SOC treatment (NCT04254978).

Key eligibility criteria include patients who require cytoreduction, a platelet count >450 x 109/L, hemoglobin ≥10 g/dL and absolute neutrophil count ≥0.5 x 109/L. Key objectives are safety and response, defined as platelets ≤400 x 109/L without new thromboembolism or disease progression. Exploratory endpoints include durability of response, reduction in WBCs, changes in mutant allele frequencies (MAF), and symptom improvement. All patients start at a dose of 0.6 mg/kg/d that is titrated to a target platelet count of 200-400 x 109/L.

At data cut-off (15July'21), 30 patients have enrolled. Baseline median age was 68 (42-84) years with 33% males; 77% were resistant to or intolerant of HU, 10% to anagrelide, 7% to interferon, and 3% each to busulfan and ruxolitinib. The Day 1 (washout up to 28 days) mean platelet, WBC and hemoglobin values were 876 x 109/L (457-2220), 9.7 x 109/L (4.4-30.6), and 13.0 g/dL (9.4-16.5) respectively. Among all patients, median MPN10 total symptom score (TSS) at baseline was 16 (0-74); TSS >10 was observed in 63% (19/30); median 30 (11-74). Genotyping by sequencing at screening (N=32) revealed mutations in JAK2 (50%) and CALR (44%) with a wide distribution of MAFs (1-85%). All patients were wild-type at the MPL locus, two patients were "triple-negatives" and five patients had copy number neutral loss of heterozygosity. Non-driver mutations were present in 31% (10/32) including EZH2, ASXL1, SF3B1 and TP53.

Median time on study is 16 weeks (0-41). Platelet count was reduced in 92% (24/26) of patients treated for more than 6 weeks with 81% (21/26) achieving a platelet count of ≤400 x 109/L. Of the 9/30 (30%) patients with a Day 1 WBC count ≥10 x 109/L, 89% (8/9) had a WBC count <10 x 109/L while on treatment (see graphs). All patients maintained a stable hemoglobin (see graph). In patients with baseline TSS >10 (19/30), at Week 12, 77% (10/13) had decreased scores and 46% (6/13) demonstrated >10-point improvement. Of patients resequenced (261 genes) at Week 24 (N=6), mutant allele frequencies were stable and no new mutations were detected. Enrollment is on-going; additional clinical and genetic data will be presented.

The most common (reported by >15% of patients) treatment-emergent AEs deemed related were dysgeusia (40%), fatigue, thrombocytopenia (without bleeding), constipation, and diarrhea (each 17%). Six AEs ≥Grade 3 were reported in 5 patients, with 2 (dysgeusia and constipation) deemed related to bomedemstat by the Investigator. Two unrelated SAEs were reported: a lung infection and a pulmonary embolus. Four patients discontinued treatment, three due to AEs (nausea, dysgeusia x 2) and one withdrew consent on Day 1. Similar to an ongoing MF study of bomedemstat (NCT03136185), there have been no safety signals, DLTs, or deaths related to drug. At the time of data cut-off, 87% (26/30) of patients remain on study.

To date, in a majority of patients who were resistant or intolerant to at least one standard of care, bomedemstat has shown to be well-tolerated, reduce platelets, improve symptoms, and moderate WBC counts while maintaining hemoglobin. For those patients treated for at least 6 weeks, 81% achieved a complete peripheral blood count remission without evidence of disease progression. The mutation burden remained stable despite high molecular risk mutations.