World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:16, No:07, 2022

MANIFEST-2, a Global, Phase 3, Randomized, Double-Blind, Active-Control Study of Pelabresib (CPI-0610) and Ruxolitinib vs. Placebo and Ruxolitinib in JAK Inhibitor-Naïve Myelofibrosis Patients

Authors : Claire Harrison, Raajit K. Rampal, Vikas Gupta, Srdan Verstovsek, Moshe Talpaz, Jean-Jacques Kiladjian, Ruben Mesa, Andrew Kuykendall, Alessandro Vannucchi, Francesca Palandri, Sebastian Grosicki, Timothy Devos, Eric Jourdan, Marielle J. Wondergem, Haifa Kathrin Al-Ali, Veronika Buxhofer-Ausch, Alberto Alvarez-Larrán, Sanjay Akhani, Rafael Muñoz-Carerras, Yury Sheykin, Gozde Colak, Morgan Harris, John Mascarenhas

Abstract : Myelofibrosis (MF) is characterized by bone marrow fibrosis, anemia, splenomegaly and constitutional symptoms. Progressive bone marrow fibrosis results from aberrant megakaryopoeisis and expression of proinflammatory cytokines, both of which are heavily influenced by bromodomain and extraterminal domain (BET)-mediated gene regulation and lead to myeloproliferation and cytopenias. Pelabresib (CPI-0610) is an oral small-molecule investigational inhibitor of BET protein bromodomains currently being developed for the treatment of patients with MF. It is designed to downregulate BET target genes and modify nuclear factor kappa B (NF-κB) signaling. MANIFEST-2 was initiated based on data from Arm 3 of the ongoing Phase 2 MANIFEST study (NCT02158858), which is evaluating the combination of pelabresib and ruxolitinib in Janus kinase inhibitor (JAKi) treatment-naïve patients with MF. Primary endpoint analyses showed splenic and symptom responses in 68% and 56% of 84 enrolled patients, respectively. MANIFEST-2 (NCT04603495) is a global, Phase 3, randomized, double-blind, active-control study of pelabresib and ruxolitinib versus placebo and ruxolitinib in JAKi treatment-naïve patients with primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF. The aim of this study is to evaluate the efficacy and safety of pelabresib in combination with ruxolitinib. Here we report updates from a recent protocol amendment. The MANIFEST-2 study schema is shown in Figure 1. Key eligibility criteria include a Dynamic International Prognostic Scoring System (DIPSS) score of Intermediate-1 or higher, platelet count ≥100 × 10^9/L, spleen volume ≥450 cc by computerized tomography or magnetic resonance imaging, ≥2 symptoms with an average score ≥3 or a Total Symptom Score (TSS) of ≥10 using the Myelofibrosis Symptom Assessment Form v4.0, peripheral blast count <5% and Eastern Cooperative Oncology Group performance status ≤2. Patient randomization will be stratified by DIPSS risk category (Intermediate-1 vs Intermediate-2 vs High), platelet count (>200 × 10^9/L vs 100–200 × 10^9/L) and spleen volume (≥1800 cm^3 vs <1800 cm^3). Double-blind treatment (pelabresib or matching placebo) will be administered once daily for 14 consecutive days, followed by a 7 day break, which is considered one cycle of treatment. Ruxolitinib will be administered twice daily for all 21 days of the cycle. The primary endpoint is SVR35 response (≥35% reduction in spleen volume from baseline) at Week 24, and the key secondary endpoint is TSS50 response (≥50% reduction in TSS from baseline) at Week 24. Other secondary endpoints include safety, pharmacokinetics, changes in bone marrow fibrosis, duration of SVR35 response, duration of TSS50 response, progression-free survival, overall survival, conversion from transfusion dependence to independence and rate of red blood cell transfusion for the first 24 weeks. Study recruitment is ongoing; 400 patients (200 per arm) from North America, Europe, Asia and Australia will be enrolled. The study opened for enrollment in November 2020. MANIFEST-2 was initiated based on data from the ongoing Phase 2 MANIFEST study with the aim of assessing the efficacy and safety of pelabresib and ruxolitinib in JAKi treatment-naïve patients with MF. MANIFEST-2 is currently open for enrollment.

Keywords : CPI-0610, JAKi treatment-naïve, MANIFEST-2, myelofibrosis, pelabresib
Conference Title : ICHO 2022 : International Conference on Hematology and Oncology
Conference Location : Rome, Italy
Conference Dates : July 21-22, 2022