Abstract: PB2225

Title: A RANDOMIZED OPEN-LABEL, PHASE 3 STUDY OF IMETELSTAT VS BEST AVAILABLE THERAPY IN INTERMEDIATE-2 OR HIGH-RISK MYELOFIBROSIS RELAPSED/REFRACTORY TO JAK INHIBITOR (IMPACTMF)

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Session Title: Myeloproliferative neoplasms - Clinical

Background:

Janus kinase (JAK) inhibitors, ruxolitinib (JAK1/2), fedratinib (JAK2/FLT3), and pacritinib (JAK2/IRAK1), are the only approved treatment options for myelofibrosis (MF). For patients who discontinue treatment with ruxolitinib, the median overall survival (OS) is dismal at 11 to 16 months. There remains a great unmet need for patients whose MF has relapsed or is nonresponsive and have discontinued treatment with a JAK inhibitor (JAKi). Imetelstat is a 13-mer lipid-conjugated oligonucleotide that specifically targets the RNA template of human telomerase and is a potent, first-in-class direct and competitive inhibitor of telomerase activity. Imetelstat has shown meaningful clinical improvement in symptom response and OS in IMbark, a phase 2 study in patients with intermediate-2 (Int-2) or high-risk (HR) MF who have relapsed after or are refractory to JAKis. In IMbark, imetelstat demonstrated improvement in bone marrow fibrosis, longer OS, and disease-modifying activity by targeting malignant clones. The improvement in OS for patients treated with imetelstat was further supported by analyses of patients in IMbark with closely matched real-world data.

Aims:

Compelling OS results from IMbark and an acceptable safety profile led to initiation of a phase 3 study in patients with relapsed/refractory MF, with OS as the primary endpoint.

Methods:

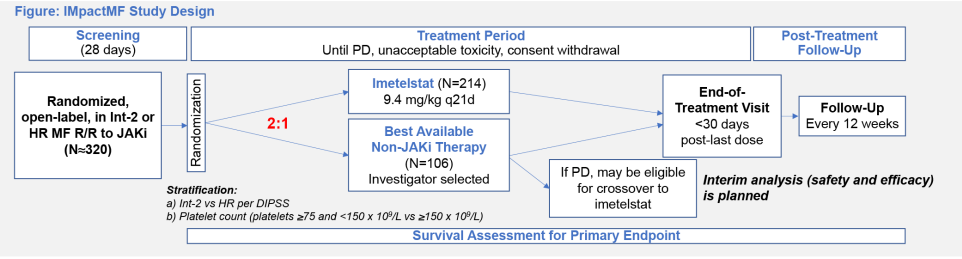
IMpactMF (MYF3001, NCT04576156) is an open label, randomized, multicenter phase 3 study of imetelstat vs best available therapy (BAT) in ≈320 adult patients with Int-2 or HR MF whose disease is relapsed/refractory to a JAKi, who are not candidates for further JAKi treatment, and who are not eligible for allogeneic stem cell transplantation. Eligible patients will have an Eastern Cooperative Oncology Group Performance Status score of 0–2 and peripheral blood and marrow blast counts <10%. Patients cannot have clinically significant cardiovascular disease, active systemic hepatitis infection, or chronic liver disease unrelated to underlying MF. Patients will be randomized 2:1 to receive imetelstat IV 9.4 mg/kg every 21 days or investigator-selected BAT that may include hydroxyurea, thalidomide, interferon, danazol, hypomethylating agents, chemotherapy, or other non-JAKi-containing therapy as appropriate. Patients will be stratified based on Int-2 vs HR per Dynamic International Prognostic Scoring System and platelet count at study entry (platelets ≥75 and <150 × 10^9/L vs ≥150 × 10^9/L). Patients who meet progressive disease criteria and discontinue BAT may be eligible to crossover to imetelstat if they exhibit a ≥25% increase in spleen volume from pretreatment baseline at any time during the study or a palpable increase in splenomegaly following 6 months of BAT.

Results:

The primary endpoint is OS; an interim analysis is planned when ≈35% of patients enrolled have died. Secondary endpoints include symptom and spleen response rates at Week 24, progression-free survival, clinical response assessments per modified 2013 International Working Group – Myeloproliferative Neoplasms Research and Treatment criteria, time to and duration of response, reduction in degree of bone marrow fibrosis, safety, pharmacokinetics, and patient-reported outcomes. Exploratory endpoints include biomarkers and mutation analyses (Figure).

Summary/Conclusion:

Approximately 180 sites are planned across North and South America, Europe, the Middle East, Australia, and Asia. The study is currently open for enrollment.



DIPSS, Dynamic International Prognostic Scoring System; HR, high risk; Int-2, intermediate-2; JAKi, Janus kinase inhibitor; MF, myelofibrosis; PD, progressive disease; q21d, every 21 days; R/R, relapsed/refractory.

Keywords: Myelofibrosis, Telomerase activity, Therapy, Janus Kinase inhibitor