GERON

Patologia di Riferimento: MIELOFIBROSI. Relapsed / refractory to JAK inhibitor treatment

Contatti: PI: Marco De Gobbi marco.degobbi@unito.it SI: Federico Itri f.itri@sanluigi.piemonte.it SC: Tatiana Deambrosi tatianadeambrosi@icloud.com

Criteri di inclusione:

1. ≥18 years of age.
2. Diagnosis of PMF according to the revised WHO criteria (Section 18.2); or PET-MF or PPV-MF according to the IWG-MRT criteria (Section 18.3) confirmed by local pathology report.
3. Dynamic International Prognostic Scoring System intermediate-2 or high-risk MF (Section 18.4).
4. Relapsed / refractory to JAK inhibitor treatment as defined in either inclusion 4.1, 4.2 or 4.3 and not eligible for ASCT at screening:

4.1: Treatment with JAK inhibitor for ≥ 6 months duration, including at least 2 months at an optimal dose as assessed by the investigator for that participant and at least ONE of the following:

a) no decrease in spleen volume (< 10% by MRI or CT) from the start of treatment with JAK inhibitor.

b) no decrease in spleen size (< 30% by palpation or length by imaging) from start of treatment with JAK inhibitor

c) no decrease in symptoms (< 20% by MFSAF or myeloproliferative neoplasm SAF) from start of treatment with JAK inhibitor.

d) a score of at least 15 on TSS assessed using the MFSAF v4.0 (adapted as the MF Symptom Recall Form, Section 18.6) during screening.

4.2: Treatment with JAK inhibitor for ≥ 3 months duration with maximal doses for that participant (e.g., 20-25 mg twice daily ruxolitinib) without a spleen or symptom response as defined in inclusion criterion 4.1 (a, b, or c) and would not benefit from remaining on treatment for 6 months.

4.3: Following maximum tolerated doses of JAK inhibitor therapy for ≥3 months duration, having documented relapsed disease defined as either:

• Increase in spleen volume **from time of best response** by 25% measured by MRI or CT, or
• Increase in spleen size by palpation, CT, or ultrasound
o For splenomegaly of 5-10 cm at the start of JAK inhibitor treatment, at least 100% increase in palpable spleen size **from time of best response**;
o For splenomegaly of > 10 cm at the start of JAK inhibitor treatment, at least 50% increase in palpable spleen size **from time of best response**; **AND** not a candidate for further JAK inhibitor at screening per investigator.

5. Measurable splenomegaly demonstrated by a palpable spleen measuring ≥ 5 cm below the left costal margin or a spleen volume ≥ 450 cm3 by MRI or CT.
6. Active symptoms of MF on the MFSAF v4.0 (adapted as the MF Symptom Recall Form, Section 18.6) demonstrated by a symptom score of at least 5 points (on a 0 to 10 scale) on at least 1 of the symptoms or a score of 3 or greater on at least 2 of the following symptoms: fatigue, night sweats, itchiness, abdominal discomfort, pain under ribs on left side, early satiety, and bone pain.
7. Hematology laboratory test values within the following limits:
• absolute neutrophil count (ANC) ≥ 1.5 x 109/L independent of growth factor support, AND
• platelets ≥ 75 x 109/L independent of platelet transfusion support.
8. Biochemical laboratory test values must be within the following limits:
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of

normal (ULN);
• Alkaline phosphatase (ALP) ≤ 5 x ULN;

Criteri di esclusione:

Any potential participant who meets any of the following criteria will be excluded from participating in the study:
1. Peripheral blood blast count of ≥ 10% or bone marrow blast count of ≥ 10%.
2. Known allergies, hypersensitivity, or intolerance to imetelstat or its excipients (refer to the current IB).
3. Prior treatment with imetelstat.
4. Any chemotherapy or MF directed therapy, including investigational drug regardless of class or mechanism of action, immunomodulatory or immunosuppressive therapy, corticosteroids > 30 mg/day prednisone or equivalent, and JAK inhibitor treatment ≤ 14 days prior to randomization.
5. Persistent unresolved toxicity from prior treatment, i.e., has not returned to Grade ≤ 1 or pre-treatment baseline.
6. Diagnosis or treatment for malignancy other than MF except:
• Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before randomization.
• Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
• Adequately treated cervical carcinoma in situ without evidence of disease.
7. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
8. Known history of human immunodeficiency virus or any uncontrolled active systemic infection requiring IV antibiotics.
9. Active systemic hepatitis infection requiring treatment (carriers of hepatitis virus are permitted to enter the study), or any known acute or chronic liver disease requiring treatment unless related to underlying hepatosplenomegaly due to MF.
10. Major surgery within 28 days prior to randomization.
11. Female participants who are pregnant or are currently breastfeeding or planning to become pregnant while enrolled in this study or within 30 days after the end of dosing.
12. Male participants who plan to father a child while enrolled in this study or within 90 days after the end of dosing.
13. Any life-threatening illness (e.g., COVID-19), medical condition, or organ system dysfunction which, in the investigator’s opinion, could compromise the participant’s safety, interfere with the imetelstat metabolism, or put the study outcomes at undue risk; if participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., compromise the well- being) or that could prevent, limit, or confound the protocol-specified assessments.