KRT-232-115

A Phase 3, Randomized, Double-blind, Add-on Study Evaluating the Safety and Efficacy of Navtemadlin Plus Ruxolitinib vs Placebo Plus Ruxolitinib in Patients with Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib

Contatti: Monia Marchetti, monia.marchetti@uniupo.it

Trattamento: Navtemadlin, Ruxolitinib

Sindromi MIELOPROLIFERATIVE CRONICHE target: Myelofibrosis

Principali Criteri Inclusione:

Ruxolitinib Run-in Period

1. Adults ≥ 18 years of age able to provide informed consent.

2. Confirmed diagnosis of PMF, post-PV MF, or post-ET MF, as assessed by the treating physician according to the World Health Organization (WHO) criteria.

3. IPSS risk category of Intermediate-1, Intermediate-2, or High.

4. Spleen measuring ≥ 450 cm3 by MRI or CT scan (central review).

5. MF symptoms as defined by a baseline TSS of ≥ 10. Baseline TSS will be calculated as a 7-day average per MFSAF v4.0.

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

7. Adequate hematological, hepatic, and renal organ function

Randomized Period

1. PMF, post-PV MF, or post-ET MF that is *TP53*WT as assessed by central testing.
2. Treatment with ruxolitinib monotherapy for ≥ 18 weeks but < 25 weeks and on a stable dose of ruxolitinib in the 8 consecutive weeks prior to study treatment.
3. Suboptimal response to standard of care ruxolitinib monotherapy, defined as SVR of > 0% but < 35% and TSS reduction of > 0% but < 50%, assessed from the start of the run-in period baseline to the end of the run-in period

Principali Criteri Esclusione:

Ruxolitinib Run-in Period

1.Participation in another interventional clinical trial within four weeks prior to the first dose of ruxolitinib monotherapy (participation in observational studies is permitted).

2. Prior therapy with any JAK inhibitor.

3. Prior therapy with BCL-XL, BET, MDM2, PI3K, PIM, or XPO1 inhibitors; prior p53-directed therapy. Subjects must have discontinued all drugs (including hydroxyurea) used to treat underlying MF ≥ 28 days prior to first dose of ruxolitinib monotherapy. Erythroid growth factors, danazol (or equivalent androgen), or prednisone (or equivalent corticosteroid) are permitted if the subject is on a stable dose for at least two months prior to starting ruxolitinib.

4. Prior splenectomy.

5. Splenic irradiation within three months prior to the first dose of ruxolitinib monotherapy.

6. Non-spleen-directed radiation therapy for MF or major surgery or planned major surgery within 28 days prior to the first dose of ruxolitinib monotherapy.

7. Prior allogeneic stem-cell transplantation or eligible for allogeneic stem cell transplantation. Subjects who are eligible for stem cell transplant but refuse transplant are not excluded.

8. Peripheral blood or bone marrow blast count ≥ 10% at any time within 28 days prior to the first dose of ruxolitinib monotherapy

Randomized Period

1. White blood cell count that meets both of the following criteria:

a. Increases by two-fold (ie, doubles) or more during therapy with ruxolitinib monotherapy (comparing baseline prior to the run-in period vs pre-randomization) and

b. Exceeds 50 × 109/L at pre-randomization.

2. Active treatment with BCL-XL, BET, MDM2, PI3K, PIM, or XPO1 inhibitors, or p53-directed therapy.