NMP XPORT-MF-034

A PHASE 1/3 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SELINEXOR, A SELECTIVE INHIBITOR OF NUCLEAR EXPORT, IN COMBINATION WITH RUXOLITINIB IN TREATMENT-NAÏVE PATIENTS WITH MYELOFIBROSIS

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https://clinicaltrials.gov/study/NCT04562389

Study population:

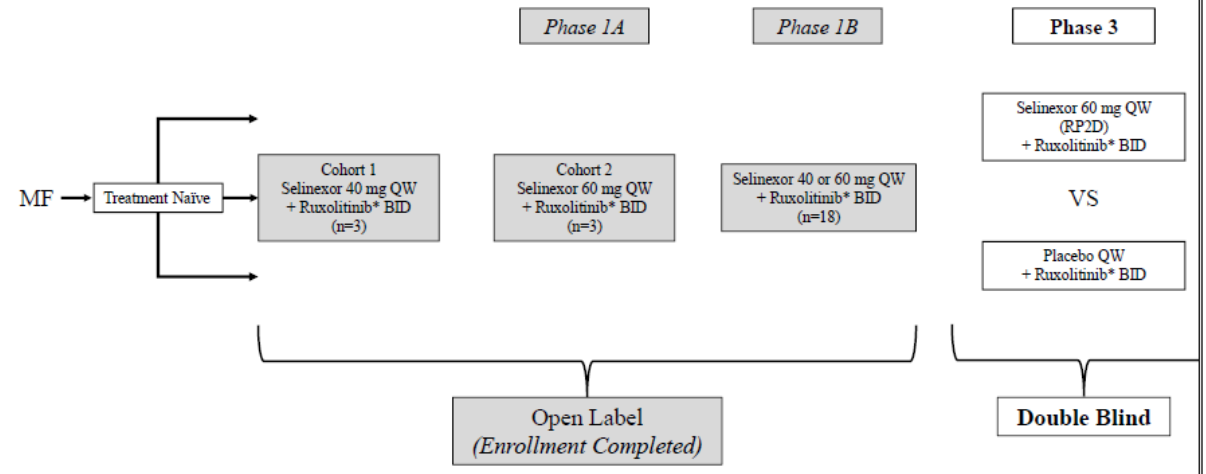
Phase 3: Approximately 300 to 450 treatment-naïve patients with MF will be enrolled for the primary analysis.

Study Treatment:

In the Phase 1 part of the study, the RP2D of selinexor was established as 60 mg QW in combination with ruxolitinib dosing (per local product label).
In Phase 3 of the study, selinexor at dose of 60 mg QW or matching placebo, will be administered to the patients in combination with ruxolitinib (per local product label).

Schéma de traitement :

Figure 1: Study XPORT-MF-034 Overview



BID=twice daily; QW=once weekly; MF=myelofibrosis.
*Ruxolitinib dose is based on the patient's baseline platelet count (per local product label):

- >200 × 10^9/L: 20 mg BID
- 100 to 200 × 10^9/L: 15 mg BID

Rate of visits: 1 cycle = 28D.
In Phase 3 of the study, selinexor at dose of 60 mg QW or matching placebo, will be administered to the patients in combination with ruxolitinib (per local product label).

Critères d'inclusion	O	N
1. A diagnosis of primary MF, post-essential thrombocythemia (ET), or postpolycythemia vera (PV) MF according to the 2016 World Health Organization (WHO) classification of MPN, confirmed by the most recent local pathology report.		
2. Measurable splenomegaly during the screening period as demonstrated by spleen volume of ≥450 cm3 by MRI or CT scan (results from MRI or CT imaging performed within 28 days prior to screening are acceptable).		
3. Patients with DIPSS risk category of intermediate-1, or intermediate-2, or high-risk.		
4. Patients ≥18 years of age.		
5. ECOG performance status ≤2		
6. Platelet count ≥100 × 109/L without platelet transfusion.		
7. Absolute neutrophil count (ANC) ≥1.0 × 109/L without need for growth factors within 7 days prior to C1D1.		
8. Adequate liver function as defined by the following: aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit normal (ULN) and serum total bilirubin ≤2 × ULN.		
9. Calculated creatinine clearance (CrCl) >15 mL/min based on the Cockcroft and Gault formula.		
10. Patients with active hepatitis B virus (HBV) are eligible if antiviral therapy for hepatitis B has been given for >8 weeks and the viral load is <100 IU/mL.		
11. Patients with history of hepatitis C virus (HCV) are eligible if they have received adequate curative anti-HCV treatment and HCV viral load is below the limit of quantification.		
12. Patients with history of human immunodeficiency virus (HIV) are eligible if they have CD4+ T-cell counts ≥350 cells/µL, negative viral load, and no history of acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections in the last year and should be on established antiretroviral therapy (ART) for at least 4 weeks.		

13. Female patients of childbearing potential must have a negative serum pregnancy test at screening and within 3 days prior to first dose on C1D1 and agree to use highly effective methods of contraception throughout the selinexor treatment period and for 90 days following the last dose of selinexor treatment. A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.		
14. Male patients who are sexually active must use a barrier method in addition to highly effective methods of contraception throughout the study treatment period and for 90 days following the last dose of selinexor treatment. Male patients must agree not to donate sperm during the study treatment period and for at least 90 days after the last dose of selinexor treatment. Patients must sign written informed consent in accordance with federal, local, and institutional guidelines.		
15. Active symptoms of MF as determined by presence of at least 2 symptoms with a score ≥3 or total score of ≥10 at screening using the MFSAF v4.0.		
16. Patient currently not eligible for stem cell transplantation.		
17. Patients must provide bone marrow biopsy samples (samples obtained up to 3 months prior to C1D1 are permitted) at screening and during the study.		
18. Life expectancy of greater than 6 months in the opinion of the Investigator.		
19. Patients with no other concomitant malignancies or history of another malignancy within 2 years prior to C1D1 except for adequately treated early-stage basal cell or squamous cell carcinoma of skin, adequately treated carcinoma in situ of breast or cervix or organ confined prostate cancer, or PV or ET.		
20. Subjects must be able to voluntarily provide informed consent per all relevant rules and institutional policies before any study procedures are performed. No incapacitated subjects will be recruited for participation. Where the subject cannot sign the ICF due to a physical disability, an impartial witness will be appointed.		

Critères d'exclusion	**O**	**N**
1. More than 10% blasts in peripheral blood or bone marrow (accelerated or blast phase).		
2. Previous treatment with JAK inhibitors for MF.		

3. Previous treatment with selinexor or other XPO1 inhibitors.		
4. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of selinexor (e.g., vomiting or diarrhea CTCAE v5.0 Grade 2 or higher), Grade 3 or higher hyponatremia, Grade 3 or higher fatigue, or Grade 2 or higher ocular toxicity.		
5. Received strong cytochrome P450 3A (CYP3A) inhibitors ≤7 days prior to selinexor dosing OR strong CYP3A inducers ≤14 days prior to selinexor dosing (Phase 1 patients only)		
6. Major surgery <28 days prior to C1D1.		
7. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 7 days prior to C1D1; however, prophylactic use of these agents is acceptable (including parenteral).		
8. Any life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could compromise the patient's safety, prevent the patient from giving informed consent, or being compliant with the study procedures, or confound the ability to interpret study results.		
9. Female patients who are pregnant or lactating.		
10. Prior splenectomy, or splenic radiation within 6 months prior to C1D1.		
11. Unable or unwilling to undergo CT scan or MRI per protocol.		
12. Patients with contraindications or known hypersensitivity to selinexor or ruxolitinib or excipients.		
13. History of pulmonary hypertension.		
14. History of myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG), cerebrovascular accident (stroke or transient ischemic attack [TIA]), ventricular arrhythmias, congestive heart failure New York Heart Association (NYHA) class >2 within 6 months of C1D1.		
15. Patients unable to tolerate 2 forms of antiemetics prior to each dose for at least 2 cycles.		