NMP - CPI 0610-04

Étude de phase III, randomisée, en double aveugle, avec comparateur actif, portant sur l'association CPI-0610 + ruxolitinib vs placebo + ruxolitinib chez des patients atteints de MF et naïfs de traitement par un JAKi

Investigateur principal : Jean-Jacques KILADJIAN

https://clinicaltrials.gov/ct2/show/NCT04603495

Population cible : Les patients éligibles sont des adultes qui ont un diagnostic confirmé de MF (MFP ou MF-PPV ou MF-PTE) conformément aux critères 2016 de l'Organisation mondiale de la santé (OMS), n'ont jamais reçu d'inhibiteur de JAK pour le traitement d'un néoplasme myéloprolifératif et sont de catégorie de risque DIPSS Intermédiaire-1 ou plus.

Traitement à l'étude : CPI-0610

Schéma de traitement : CPI-0610 + ruxolitinib ou placebo + ruxolitinib

- Le traitement en double aveugle (CPI-0610 ou placebo correspondant) sera administré une fois par jour (1x/j) pendant 14 jours consécutifs, suivis d'une pause de 7 jours, ce qui est considéré comme un cycle de traitement (1 cycle = 21 jours).
- Le ruxolitinib sera administré deux fois par jour (2x/j) pendant les 21 jours de chaque cycle.

Rythme des visites : 1 cycle = 21 jours

- Premier cycle : J1, J14
- Puis chaque J1 des cycles suivants

Critères d'inclusion	O	N
1. ≥ 18 years of age at the time of signing the informed consent		
2. Have a confirmed diagnosis of MF (PMF or PPV-MF or PET-MF) in accordance with the 2016 WHO criteria		
3. Require therapy for MF in the opinion of the Investigator and are eligible for treatment with ruxolitinib		
4. Have DIPSS risk category Intermediate-1 or higher		
5. Have spleen volume of ≥ 450 cm3 by MRI or CT scan (either local or central read)		
6. Have completed the MFSAF v4.0 at least 5 of 7 days prior to randomization		
7. Have at least 2 symptoms with an average score ≥ 3 over the 7-day period prior to randomization or an average total score of ≥ 10 over the 7-day period prior to randomization using the MFSAF v4.0		
8. Have acceptable laboratory assessments obtained within 28 days prior to the first dose of study medication: • ANC ≥ 1 × 109/L in the absence of growth factors or transfusions for the previous 4 weeks • Platelet count ≥ 100 × 109/L in the absence of growth factors or transfusions for the previous 4 weeks • Peripheral blood blast count < 5%		

• AST and ALT ≤ 2.5 × ULN (≤ 5 × if the elevation can be ascribed to liver involvement; e.g., presence of hepatomegaly) • Serum direct bilirubin < 2.0 × ULN • Calculated or measured CrCl of ≥ 45 mL/min		
9. ECOG performance status of ≤ 2		
10. Life expectancy > 24 weeks per Investigator assessment		
11. Have fully recovered from major surgery, intervention, and from the residual Grade 1 toxicity from prior MF-specific therapy (grade 1 peripheral neuropathy and alopecia are allowed)		
12. Male and female patients with reproductive potential and partners of patients must agree to use highly effective contraceptive methods (i.e., condoms or sexual abstinence if the preferred and usual lifestyle of the patient for males and oral, intravaginal, transdermal inhibitors of ovulation that contain estrogen and progesterone; oral, injectable or implantable inhibitors of ovulation that contain progesterone; IUD; IUS; bilateral tubal occlusion; vasectomized partner; sexual abstinence if the preferred and usual lifestyle of the patient for females) while on study therapy and for 3 months after the last dose of study drug for male patients and male partners of female patients, and for 6 months after the last dose of study drug for female patients and female partners of male patients. NOTE: Male patients should be informed of the risk of testicular toxicity and provided with adequate advice regarding sperm preservation.		
13. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol		

Critères d'exclusion	**O**	**N**
1. Had splenic irradiation within 6 months of starting study drug		
2. Had prior splenectomy		
3. Are a candidate for, and willing to undergo allogeneic HSCT, and, in the opinion of the Investigator, the benefit of proceeding to an allogeneic HSCT prior to treatment with a JAK2 inhibitor outweighs its risks		
4. Have current known active or chronic infection with HIV, hepatitis B, or hepatitis C. Screening of patients with serologic testing for these viruses is not required. However, patients who have a past history of viral hepatitis or in whom there is a current suspicion of viral hepatitis should have serologic testing for hepatitis B and hepatitis C performed to determine whether there is any current evidence for ongoing infection with these viruses. Patients considered to be at risk for HIV infection should have HIV		

testing performed.		
5. Have an active infection. Patients will not be eligible for enrollment until recovery to ≤ Grade 1 for at least 2 weeks prior to the first dose of study drug.		
6. Have impaired gastrointestinal function or gastrointestinal disease, including active IBD, that could significantly alter the absorption of study drug, including any unresolved nausea, vomiting, or diarrhea > Grade 1		
7. Have known hypersensitivity to the investigational agent or ruxolitinib, or its metabolites or formulation excipients		
8. Have a history of progressive multifocal leukoencephalopathy		
9. Have impaired cardiac function or clinically significant cardiac diseases, including any of the following: • Acute myocardial infarction or unstable angina pectoris ≤ 6 months prior to starting study drug • QTcF > 500 msec on the screening ECG • New York Heart Association Class III or IV congestive heart failure • Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded) Note that patients with a history of coronary artery disease and revascularization are not excluded.		
10. Have ongoing uncontrolled hypertension (resting systolic blood pressure >160 mmHg and resting diastolic blood pressure >100 mmHg) despite maximal treatment with at least 2 anti-hypertensive agents		
11. Have ongoing uncontrolled blood glucose increase (HbA1c ≥9%) despite maximal treatment with oral and/or injectable anti-hyperglycemic agents		
12. Have a history of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to randomization, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 3 years		
13. Have any other concurrent severe and/or uncontrolled concomitant medical condition that in the opinion of the Investigator could compromise participation in the study or analysis of study data. This includes but is not limited to clinically significant pulmonary disease or neurological disorders.		
14. Had prior treatment with any JAKi or BET inhibitor for treatment of a		

myeloproliferative neoplasm		
15. Had systemic anti-cancer treatment other than hydroxyurea and anagrelide less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug. NOTE: Hydroxyurea and anagrelide are permitted up to 24 hours prior to start of study drug.		
16. Had any investigational agent (whether as cancer treatment or not) less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug		
17. Had hematopoietic growth factor (granulocyte growth factor, erythropoiesis stimulating agent, thrombopoietin mimetic) or androgenic steroids less than 4 weeks before the first dose of study drug		
18. Had a strong CYP3A4 inhibitor or inducer within 2 weeks prior to the first dose of study drug, including St. John's wort. Initiation of treatment or concomitant use of a strong CYP3A4 inhibitor or inducer during study treatment is prohibited.		
19. Require systemic corticosteroids of ≥10 mg QD prednisolone or equivalent 4 weeks before the first dose of study drug. Patients who received topical, nasal, intra-articular, or inhaled corticosteroids are eligible.		
20. Women who are lactating or pregnant females as documented by a serum β-hCG pregnancy test consistent with pregnancy, obtained within 72 hours prior to the first dose of study drug. Female patients with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Sponsor's Medical Monitor, after pregnancy has been excluded. Female patients of non-child bearing potential (post-menopausal for more than 1 year; bilateral tubal ligation; hysterectomy) do not require a serum pregnancy test.		
21. Are unwilling or unable to comply with this study protocol or study requirements.		