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Titolo:	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
Patologia:	primary MF [PMF], post-polycythemia vera [PV] MF, post-essential thrombocytopenia [ET] MF
Tipo di Studio:	Randomized, Double-blind
Fase:	3
Principali criteri di inclusione:	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 (as per protocol definition and within 28 days prior to the first dose of ruxolitinib monotherapy): a. Hematologic: i. Absolute neutrophil count (ANC) ≥ 1.5 × 109/L in the absence of myeloid growth factors during the prior 28 days. ii. Platelet count ≥ 100 × 109/L. iii. White blood cell count ≤ 50 × 109/L. b. Hepatic: i. Total serum bilirubin within normal limits. If total bilirubin is > upper limit of normal (ULN), patients are eligible if direct bilirubin is ≤ 2 × ULN and total bilirubin is ≤ 3 × ULN. ii. Aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) ≤ 2.5 × ULN. c. Renal: estimated creatinine clearance ≥ 30 mL/min by the Cockcroft Gault equation. 8. Female patients of childbearing potential and their male partners, or male patients who have female partners of childbearing potential must both use a highly effective contraception method during the study. In addition, after the last dose of study drug, female patients must continue to use a highly effective method of contraception for one month and one week, and male patients must continue to use a highly effective method of contraception for three months and one week. A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming post-menopausal unless permanently sterile

Principali criteri di esclusione:	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. Patients 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 patient 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. Patients 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. 9. Women who are pregnant or breastfeeding. 10. History of solid organ transplant. 11. Infection with human immunodeficiency virus (HIV). 12. Active hepatitis B or hepatitis C infection 13. Active serious viral, mycobacterial, parasitic, fungal, and bacterial infections, including acute hepatitis A, herpes zoster, and progressive multifocal leukoencephalopathy (PML). Active serious infections must be resolved before enrollment. Patients with acute infections requiring systemic antibiotic use should delay enrollment until the course of antibiotic therapy has been completed. 14. Patients with uncontrolled intercurrent illness including but not limited to; clinically significant cardiac disease (New York Heart Association Class III or IV); symptomatic congestive heart failure; unstable angina pectoris; ventricular arrhythmia; or patients with psychiatric illness/social situations that would limit compliance with study requirements; or patients who have been committed to an institution by judicial or administrative authority. 15. Active or chronic bleeding within 28 days prior to the first dose of ruxolitinib monotherapy. 16. Patients with active fever (temperature higher than 38.2°C [100.8°F]) within 14 days prior to the first dose of ruxolitinib monotherapy. 17. Other malignancy within the last three years, other than curatively treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated non-metastatic prostate cancer with normal prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial/non-invasive transitional cell bladder carcinoma.

	18. Grade 2 or higher QTc prolongation (> 480 milliseconds per NCI-CTCAE criteria, version 5.0). 19. History of difficulty swallowing, gastric or small bowel surgery with history of malabsorption or other chronic gastrointestinal disease conditions that may hamper compliance and / or absorption of the study treatment. 20. History of severe hypersensitivity reaction to any component of navtemadlin or ruxolitinib, any of their excipients, or to required prophylaxis. 21. History of stroke, reversible ischemic neurological defect, or transient ischemic attack within six months prior to first dose of ruxolitinib monotherapy. 22. Patients with indwelling surgical drains (eg, peritoneal, CNS, or pleural). 23. Patients with symptomatic ascites or requiring paracentesis. 24. Patients with any open wound or ulcer.
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