AOU Città della Salute e della Scienza di Torino – PO Molinette

Titolo:	a phase 2 study to evaluate the efficacy and safety of selinexor monotherapy in subjects with jak inhibitor-naïve myelofibrosis and moderate thrombocytopenia
Patologia:	mielofibrosi
Tipo di Studio:	Multicentrico, open-label
Fase:	2
Principali criteri di inclusione:	A diagnosis of MF or post-ET or post-PV MF according to the 2016 World Health Organization (WHO) classification of MPN in Appendix 2 (Barbui 2018), confirmed by the most recent local pathology report. 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 C1D1 are acceptable). Patients with DIPSS risk category of intermediate-1 with symptoms, or intermediate-2, or high□risk. Patients ≥18 years of age. ECOG Performance Status ≤2, see Appendix 3 (Oken 1982). Platelet count of ≥50 × 109 /L without platelet transfusion within 7 days prior to the first dose of selinexor. Absolute neutrophil count ≥1.0 × 109 /L without need for growth factors within 7 days prior to the first dose of selinexor. Adequate liver function as defined by the following: aspartate transaminase and alanine transaminase ≤2.5 × upper limit normal (ULN) and serum total bilirubin ≤3× ULN. Calculated creatinine clearance (CrCl) >15 mL/min based on the Cockcroft and Gault formula. Patients with active hepatitis B virus (HBV) are eligible if antiviral therapy for HBV has been given for >8 weeks and the viral load is <100 IU/mL. 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.

	Patients with history of human immunodeficiency virus (HIV) are eligible if they have cluster of differentiation 4 (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. . 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 and other IMPs. They must agree to refrain from egg donation from first dose until at least 90 days following the last dose of any treatment. As noted in the SmPC for EMEND® (aprepitant), the efficacy of hormonal contraceptives may be reduced during and for 28 days after the administration of EMEND. Therefore, patients using EMEND for anti-emetic prophylaxis must use an effective alternate non-hormonal contraceptives such as condoms and spermicides during treatment with EMEND, and for 2 months following the last dose of EMEND. A woman is considered of childbearing potential (ie, fertile) following menarche and until becoming postmenopausal 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. 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 and other IMPs. As noted in the SmPC for EMEND (aprepitant), the efficacy of hormonal contraceptives may be reduced during and for 28 days after the administration of EMEND. Therefore, patients using EMEND for anti-emetic prophylaxis must use an effective alternate non-hormonal contraceptives such as condoms and spermicides during treatment with EMEND, and for 2 months following the last dose of EMEND. 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. Active symptoms of MF as determined by presence of at least 2 symptoms with an average score ≥5 or an average total score of ≥12 at screening (at least 5 of 7 consecutive

	days immediately preceding C1D1) using the MFSAF v4.0. Patients must provide bone marrow biopsy samples (samples obtained up to 3 months prior to C1D1 are permitted) at screening and during the study. Life expectancy of greater than 6 months in the opinion of the Investigator. 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. Patients currently not eligible for stem cell transplantation. Patients must be willing to complete the MFSAF v4.0 daily during the study for evaluating the symptom response (ie, TSS50). Patients must be able to voluntarily provide informed consent per all relevant rules and institutional policies before any study procedures are performed. No incapacitated patients will be recruited for participation
Principali criteri di esclusione:	More than 10% blasts in peripheral blood or bone marrow (accelerated or blast phase). Previous treatment with JAK inhibitors for MF. Previous treatment with selinexor or other XPO1 inhibitors. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of selinexor (eg, vomiting or diarrhea Common Terminology Criteria for Adverse Events [CTCAE] v5.0 Grade 2 or higher), and uncontrolled or currently progressing ocular toxicities. Major surgery <28 days prior to C1D1. Uncontrolled (ie, 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). 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. Female patients who are pregnant or lactating. Prior splenectomy, splenic radiation, or splenic embolization within 6 months prior to C1D1. Unable or unwilling to undergo CT scan, MRI, or bone marrow biopsy per protocol. Patients with contraindications or known hypersensitivity to selinexor or excipients.

	History of myocardial infarction, unstable angina, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, cerebrovascular accident, transient ischemic attack (TIA), ventricular arrhythmias, or congestive heart failure class >2 per New York Heart Association within 6 months of C1D1. Patients unable to tolerate 2 forms of anti-emetics prior to each dose for the first 2 cycles
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