INCB57643-103

Patologia di Riferimento: MIELOFIBROSI - JAK naive, sub optimal response, R/R MF
TROMBOCITEMIA ESSENZIALE - R/R/I linee precedenti - Fase 1

Contatti: PI: Marco De Gobbi marco.degobbi@unito.it SI: Federico Itri f.itri@sanluigi.piemonte.it
SC: Tatiana Deambrosi tatianadeambrosi@icloud.com

Criteri di inclusione:

1. Ability to comprehend and willingness to sign a written ICF for the study.
2. Age 18 years and older at the time of signing the informed consent.
3. Part 1: Participants with relapsed or refractory MF, MDS, MDS/MPN, or ET who have received at least 1 prior line of therapy; are either refractory, relapsed, or intolerant to the last therapy; and there is no available therapy that would provide clinical benefit in the opinion of the investigator.
a. MF
− Primary MF or secondary MF (post–PV MF and post ET MF) that is histologically or cytologically confirmed, according to WHO 2016 criteria with measurable disease and risk category of intermediate-2 or high according to DIPSS.
− Measurable disease is defined:
o For dose escalation as having a palpable spleen of ≥ 5 cm below the left subcostal margin on physical examination at the screening visit. o For dose expansion as having a palpable spleen at least 5 cm below the left subcostal margin on physical examination during screening or spleen volume ≥ 450 cm3 on imaging assessed during screening and active symptoms of MF at the screening visit as demonstrated by the presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Score.
− Must have received a JAK inhibitor(s), such as ruxolitinib (except for participants being enrolled in Cohorts C, H, and I).
b. MDS
− Very low-, low-, intermediate-, or high-risk MDS as per the IPSS-R criteria (Greenberg et al 2012) and according to the WHO 2016 criteria (Arber et al 2016).
− Exception: MDS with excess blasts will be excluded according to the WHO 2016 criteria (Arber et al 2016).
c. MDS/MPN
− Low-, intermediate-, or high-risk chronic myelomonocytic leukemia, atypical chronic myeloid leukemia, MDS/MPN with ring sideroblasts and thrombocytosis, and MDS/MPN unclassifiable as per the WHO 2016 criteria (Arber et al 2016).
− Exception: Participants presenting with juvenile myelomonocytic leukemia will be excluded.
d. ET
− Confirmed diagnosis of ET as per the WHO 2016 criteria.
− Participants should have disease refractory to hydroxyurea, are intolerant to hydroxyurea or for whom treatment with hydroxyurea is contraindicated as determined by the treating physician **OR** participants who have refused treatment with hydroxyurea due to side effects. The treating physician must concur that discontinuation of hydroxyurea is in the best interest of the participant.
− Peripheral blood blast count < 1% at screening hematology assessment.
4. Part 2: Combination with ruxolitinib
a. Primary MF or secondary MFs (post–PV MF and post–ET MF), histologically or cytologically confirmed according to WHO 2016 criteria (Arber et al 2016) with measurable

disease, either currently receiving ruxolitinib with suboptimal response or JAKi-naive.
− Measurable disease is defined as having a palpable spleen of at least 5 cm below the left subcostal margin on physical examination during screening or spleen volume ≥ 450 cm3 on imaging assessed during screening and active symptoms of MF at the screening visit as demonstrated by the presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Score (see Appendix I).
− Suboptimal response is defined as currently being treated with ruxolitinib monotherapy at a stable dose for ≥ 8 weeks immediately preceding the first dose of study treatment. One dose reduction due to toxicities within 8 weeks prior to Study Day 1 is permitted. Acceptable ruxolitinib doses are 5 mg BID to 25 mg BID; QD dose administration is not allowed. Participants must have measurable disease as defined above.
− JAKi-naive is defined as those participants that have no prior use of any JAK inhibitor, including ruxolitinib.
b. Part 2 dose escalation: Risk category of intermediate-2 or high according to DIPSS (Passamonti et al 2010).
c. Part 2 dose expansion: Risk category of intermediate-1, intermediate-2, or high.
d. Part 2 dose expansion Cohorts D and E participants with chronic MF are defined as participants with bone marrow myeloblast percentage < 5% (not applicable if dry tap or blast count deemed not reliable by the investigator) and blast count in peripheral blood < 1% at screening and who are currently receiving ruxolitinib and having a suboptimal response. Note: Study treatment should be delayed if peripheral blood blast count at baseline is > 3%; treatment should only be started with medical monitor approval.
e. Part 2 dose expansion Cohorts F and G participants with accelerated-phase MF (refer to the RDE[s] as defined in Section 4.1.3) are defined as having either a bone marrow myeloblast percentage ≥ 5% to < 20% or a myeloblast percentage ≥ 10% in peripheral blood on 2 occasions at least 2 weeks apart, AND are currently receiving ruxolitinib and have a suboptimal response.
f. Part 2 dose expansion Cohorts H and I participants with JAKi-naive MF are eligible to receive ruxolitinib, with peripheral blood blast count of < 10% at the screening hematology assessment.
5. Removed during Protocol Amendment 3.
6. Must not be a candidate for potentially curative therapy, including hematopoietic stem-cell transplantation. Participants who are ineligible for transplant due to inadequate disease control or in the opinion of the investigator are eligible.
7. ECOG performance status 0 to 2.
8. Life expectancy ≥ 24 weeks.
9. Willingness to undergo a pretreatment bone marrow biopsy and/or aspirate at screening/baseline, or archival sample obtained since completion of most recent therapy. If a biopsy is not possible or contraindicated, or the tissue requirement cannot be satisfied, this requirement may be waived with approval from the medical monitor.
10. Willingness to avoid pregnancy or fathering children based on the following criteria:
a. Men must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 90 days after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
b. Women of childbearing potential must have a negative serum pregnancy test at screening and before the first dose on Day 1 and must agree to take appropriate precautions to avoid pregnancy

(with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
c. Women of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea without any other medical reasons such as treatment with anticancer agents) are eligible.

Criteri di esclusione:

1. Prior receipt of a BET inhibitor. Note: For Part 1 monotherapy dose escalation, prior receipt of a BET inhibitor is allowed, as long as it is not within 5 half-lives of the compound and/or the participant has not experienced BET inhibitor–related AE(s) resulting in dose discontinuation.
2. Receipt of anticancer medications or investigational drugs within the following interval before the first dose of study treatment:
a. < 5 half-lives or 14 days, whichever is longer, for any investigational agent.
b. < 28 days for any antibodies or biological therapies.
c. < 5 half-lives for all other nonbiologic anticancer medications, which is ≤ 14 days for ruxolitinib (for Part 1 participants only).
d. < 6 weeks for mitomycin-C or nitrosourea.
e. Hydroxyurea: Use during the 8 weeks prior to C1D1 for participants in Part 2 Cohorts D, E, F, and G and within 3 weeks prior to C1D1 for participants in Part 2 Cohorts H and I.
Note: Use of hydroxyurea is allowed during the screening period up to 72 hours before the first dose of study treatment for participants in Part 1.
f. For Part 2 JAKi-naive (Cohorts H and I), prior use of a JAK inhibitor (including ruxolitinib) and no use of experimental drug therapy for MF or any other standard drug (except hydroxyurea) used for MF or another indication within 3 months of starting study drug. Note: For participants in Part 2 Cohorts D, E, F, and G, ruxolitinib will continue at the participants' current, ongoing doses. No ruxolitinib washout is needed.
3. Participants with laboratory values at screening defined in Table 23.
4. Concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, investigational therapy, tumor embolization) other than the therapies being tested in this study or with exception to the following:
a. Low-dose corticosteroids (prednisone or the equivalent ≤ 10 mg per day) may be administered. Use of inhaled or topical steroids and prophylactic corticosteroids for radiographic procedures is permitted.
b. Hydroxyurea: Not allowed during the study treatment period.
5. Participants who have received allogeneic hematopoietic stem cell transplantation within 6 months of enrollment (unless approved by the medical monitor), or have active graft-versus-host disease, or have received immunosuppressive therapy following allogeneic transplant within 2 weeks of the first dose of study treatment.
6. Unless approved by the medical monitor, may not have received autologous hematopoietic stem-cell transplant within 3 months before the first dose of study treatment.
7. Has any unresolved toxicity ≥ Grade 2 from previous anticancer therapy, except for stable chronic toxicities (≤ Grade 2) not expected to resolve, such as stable Grade 2 peripheral neuropathy.8. Radiotherapy within the 2 weeks before the first dose of study treatment. Palliative radiation treatment performed less than 2 weeks before treatment initiation may be considered with medical monitor approval. Participants may not have splenic irradiation within 6 months of the first

dose of study treatment.
9. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer/intraepithelial carcinoma of the cervix, papillary thyroid and follicular thyroid cancers that have undergone potentially curative therapy. Participants with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
10. Significant concurrent, uncontrolled medical condition, including but not limited to the following:
a. GI
− Significant GI disorder, including but not limited to the following AEs ≥ Grade 2: large esophageal varices, GI hemorrhage, ulcer (any site except oral), or diarrhea/colitis.
− History of clinically significant GI bleeding, perforation, or fistula.
b. Cardiovascular
− History of or current clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction, New York Heart Association Class III or IV clinically significant congestive heart failure, ischemic heart disease, uncontrolled hypertension, or serious cardiac arrhythmias.
− History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful. A screening QTcF interval > 470 ms is excluded. For participants with an intraventricular conduction delay (QRS interval ≥ 120 ms), the JTc interval may be used in place of the QTc with sponsor approval. Participants with left bundle branch block are excluded.
• Ejection fraction < 55% (all participants are required to have an MUGA/ECHO during screening and/or baseline assessment in order to meet this criterion).
11. Active bacterial, fungal, parasitic, or viral infection that requires therapy. Participants with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
12. Active HBV or HCV infection or at risk for HBV reactivation. Participants will be eligible if immune due to hepatitis B vaccination, HBV or HCV infection cleared, or chronically infected (see Section 8.3.6.2). For Japan and China, when HBsAg is negative AND HBcAb and/or HBsAb is positive, HBV DNA should be measured. When HBV DNA is negative (ie, < 20 IU/mL; or < 1.3 LogIU/mL), the participant could be enrolled in the study with close monitoring of HBV activities (Drafting Committee for Hepatitis Management Guidelines 2020).
13. Known HIV infection.
14. Current use of prohibited medication as described in Section 6.7.2.
15. Use of any potent CYP3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of study treatment.
16. Known hypersensitivity or severe reaction to INCB057643 or excipients of INCB057643 (refer to the IB).
17. Inability or unlikeliness of the participant to comply with the dose schedule and study evaluations, in the opinion of the investigator.
18. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
19. Women who are pregnant or breastfeeding. Note: If a woman withholds breastfeeding during the treatment and until ≥ 30 days of the last administration, she can be enrolled
into the study.

20. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.
21. Inability of the participant (or parent, guardian, or legally authorized representative) to comprehend the ICF or unwillingness to sign the ICF.
22. History of bleeding disorder or at a high risk of bleeding (eg, chronic liver disease, prior GI bleed).