KARTA BADANIA
NAZWA BADANIA: A Phase 2, Randomized, Open-label, Study of Momelotinib in Participants with Anemia due to Low-risk Myelodysplastic Syndrome
NUMER PROTOKOŁU: **MIDAS 223584**
WSKAZANIE- D47.1 - Przewlekła choroba mieloproliferacyjna D46.9 - Zespół mielodysplastyczny, nieokreślony

Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria

apply.

1. Age ≥18 years OR of legal age of consent in the jurisdiction in which the study is taking place, at the time of signing the ICF.

2. Documented diagnosis of MDS according to the World Health Organization classifications [Arber, 2016] with an IPSS-R classification of very low, low, or intermediate risk disease, with an overall risk score ≤3.5 [Greenberg, 2012].

3. Received ESA, luspatercept and/or other therapies approved by health authorities and available for the treatment of LR-MDS-related anemia that is relapsed/refractory or intolerant to the most recent therapy prior to screening.

• Relapsed/Refractory to most recent prior treatment: documentation of loss of erythroid (E) response or never achieved hematologic improvement (HI-E) response as defined by the IWG 2018 criteria [Platzbecker, 2019]. If the most recent prior treatment is ESA or Luspatercept, below are the minimum exposure requirements:

i. ESA: received epoetin alfa (≥40,000 units/weekly for a minimum of 8 doses or equivalent) OR darbepoetin alfa (≥500 micrograms Q3W for a minimum of 4 doses or equivalent).

ii. Luspatercept: received ≥1 mg/kg Q3W for a minimum of 6 doses at the optimal dose per local/standard practice

• Intolerant to prior treatment: documentation of reasons for discontinuation of due to intolerance or adverse event.

4. Red blood cell transfusion dependence, defined as requiring an average of ≥4 units of pRBC transfused over an 8-week period during the 16 weeks preceding randomization. Documentation of a participant's transfusion policy during this 16-week period is required.

5. A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

a. Is a woman of non-childbearing potential (WONCBP) (as defined in Section 10.4),

OR

b. Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency (as described in Section 10.4) 28 days prior to and during the study intervention period and for at least 1 week after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

A WOCBP must have a negative highly sensitive pregnancy test (serum as required by local regulations) within 24 hours before the first dose of study intervention. Additional requirements for pregnancy testing during and after the study intervention are located in Section 8.3.5. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

6. Is capable of giving signed informed consent as described in Section 10.1, including compliance with the requirements and restrictions listed in the ICF and in this protocol.

7. Eastern Cooperative Oncology Group performance status ≤2 (see Section 10.7)

8. Adequate organ function as defined in Table 8.

Table 8 Definitions of adequate organ function

System	Laboratory Value
Hematologic	
ANC[a]	≥750/μL (≥0.75 × 10^9/L)
Platelets[b]	≥50 000/μL (≥50 × 10^9/L)
Hepatic	
ALT and AST	≤3.0 × ULN OR ≤5.0 × ULN if related to iron chelator therapy that was started within prior 60 days
Total bilirubin	≤1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin ≤35% Participants with Gilbert's syndrome can be included with a total bilirubin value >1.5x ULN, provided direct bilirubin is ≤1.5x ULN and participant otherwise meets entry criteria
Renal	
eGFR calculated by CKD-EPI	≥30 mL/min

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; L = liter; min = minute; mL = milliliters; ULN = upper limit of normal.

a. Without requirement for growth factor support within 28 days of randomization except for febrile neutropenia then requirement is within 14 days of randomization.

b. Without requirement for platelet transfusion within 14 days of randomization.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply.

1. Prior treatment with the following at any time:

a. JAK1/2 inhibitors

b. ACVR1 inhibitors

c. ACTRIIb receptor ligand trap other than luspatercept

d. Hypomethylating agents or other disease modifying agents (i.e., IMiDs) and immunosuppressive therapy for MDS

Note: Exception to this exclusion is if ≤1 week of treatment received; provided last dose was ≥8 weeks from randomization

2. Use of the following treatments within the noted time periods referenced from date of randomization:

a. ESA within 4 weeks, or 8 weeks for long-acting ESA

b. Growth factors (i.e., G-CSF, GM-CSF) within 4 weeks

c. Luspatercept within 8 weeks

d. Imetelstat within 8 weeks

e. Investigational agents within 4 weeks or 5 half-lives, whichever is longer

f. Corticosteroids for treatment of the underlying disease within 28 days. Supportive care use of steroids for non-MDS indications may be used provided participant is on a stable dose equivalent to ≤10 mg prednisone per day

g. Other active anti-MDS therapy not otherwise listed within 28 days or 5 half-lives whichever is longer

h. Potent cytochrome P450 3A4 (CYP3A4) inducers, except for rifampin and rifampicin, within 14 days prior to the first dose of momelotinib

i. Has received a live vaccine within 30 days

3. Prior allogeneic or autologous stem cell transplant

4. Has had any major surgery within 28 days prior to randomization

5. Ongoing adverse reaction(s) from prior therapy that have not recovered to ≤Grade 1 or to the baseline status preceding prior therapy, except if the investigator, with the agreement of the sponsor, considers to be not clinically relevant for the tolerability of study intervention in the current clinical study.

6. MDS associated with del 5q cytogenetic abnormality

7. Secondary MDS (i.e., MDS that is known to have arisen as the result of chemical injury, treatment with chemotherapy, and/or radiation for other diseases).

8. Known history of diagnosis of acute myeloid leukemia.

9. Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, gastrointestinal bleeding, or thalassemia.

10. Diagnosis of invasive malignancy or history of invasive malignancy other than the disease under study within the last 5 years, except as noted below:

a. History of an invasive malignancy for which the participant was definitively treated, and in which the participant has been disease free for at least 2 years, and which, in the opinion of the principal investigator and medical monitor, is not expected to affect the evaluation of the effects of the study intervention on the currently targeted disease under study

b. Curatively treated basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, and/or in situ breast cancer may be enrolled

c. Incidental histologic finding of prostate cancer (T1a or T1b using the TNM clinical staging system)

11. Uncontrolled intercurrent illness including, but not limited to:

a. Active uncontrolled infection (participants receiving outpatient antibacterial and/or antiviral treatments for infection that is under control or as infection prophylaxis may be included in the trial); or

b. Significant active or chronic bleeding event ≥Grade 2 per CTCAE v5.0 within 4 weeks prior randomization

c. Uncontrolled acute and chronic liver disease (e.g., Child-Pugh score ≥10) OR has current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. NOTE: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) is acceptable if participant otherwise meets entry criteria

12. Any of the following conditions within 6 months prior to randomization:

a. Unstable angina pectoris

b. Symptomatic congestive heart failure

c. Uncontrolled cardiac arrhythmia

13. QTc interval >480 msec (corrected using Fridericia formula).

14. Psychiatric illness, social situation, or any other condition that would limit

compliance with trial requirements or may interfere with the interpretation of study results, as judged by investigator or sponsor.

15. Presence of peripheral neuropathy ≥Grade 2 per CTCAE v5.0.

16. Known positive status for HIV.

17. Hepatitis A, B, or C status as defined below:

a. Chronic active or acute viral hepatitis A.

b. Active Hepatitis B infection indicated by the presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to the first dose of study intervention.

c. Positive hepatitis C antibody test result at screening or within 3 months before the first dose of study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained.

18. Has any clinically significant gastrointestinal conditions or abnormalities that may alter absorption, e.g., uncontrolled nausea, vomiting, malabsorption syndrome or major resection of the stomach and/or bowels.

19. Is unable to swallow and/or retain oral medications

20. Known contraindication or hypersensitivity to momelotinib and its metabolites, or any of their excipients.

Lifestyle considerations

Lifestyle restrictions are not applicable

KARTA BADANIA
NAZWA BADANIA: A Phase 1/2, Dose-finding Study Investigating the Safety and Efficacy of Pirtobrutinib in Adults with Immune Thrombocytopenia
NUMER PROTOKOŁU: **J2N-MC-JZNZ**
WSKAZANIE- D69.3 - Samoistna plamica małopłytkowa