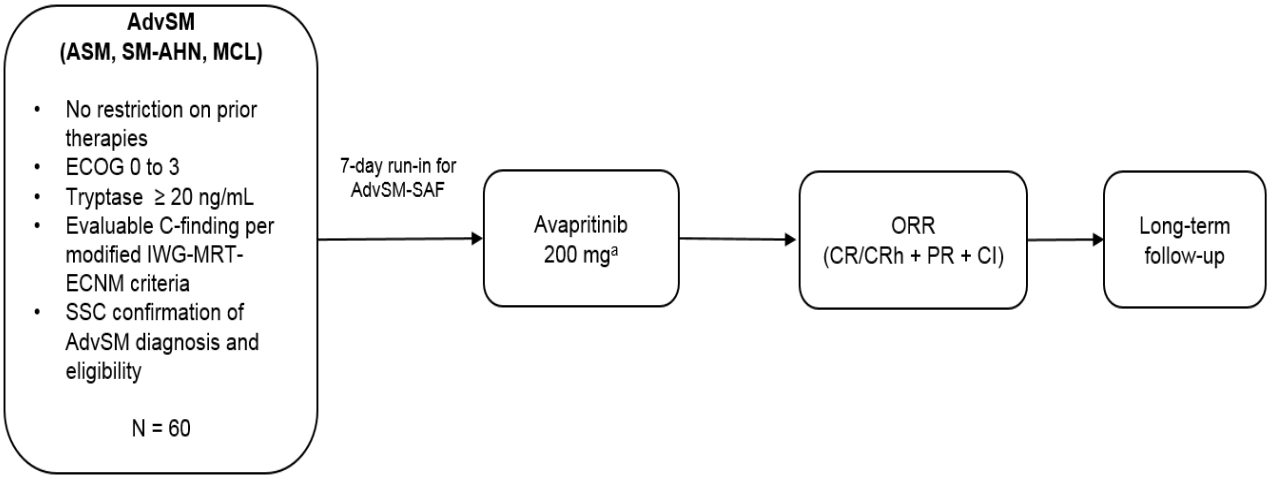
SAMENVATTING BLUPRINT 285-2202

TITEL: An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis

INDICATIE : Advanced Systemic Mastocytosis

SCHEMA:



INCLUSIE CRITERIA

1. Patients who are ≥ 18 years of age.
2. Patients must have 1 of the following diagnoses as confirmed by WHO diagnostic criteria (Appendix 4, Appendix 5, and Appendix 6). Before enrollment, the SSC must confirm the diagnosis of AdvSM (based on Central Pathology Laboratory assessment of BM).

o ASM.

o SM-AHN.

▪ The AHN must be myeloid, with the following exceptions that are excluded:

• AML.

• Myelodysplastic syndrome that is very high- or high-risk, as defined by the International Prognostic Scoring System for Myelodysplastic Syndromes (Greenberg et al, 2012).

• A myeloid AHN with ≥ 10% BM or PB blasts.

• Philadelphia chromosome-positive malignancies.

▪ Incidental indolent, low-grade lymphoid AHNs (eg, chronic lymphocytic leukemia) not requiring treatment are eligible.

o MCL.

3. Patients with SM-AHN should have received prior treatment for the AHN component of disease if, in the opinion of the Investigator, such therapy was appropriate.

4. Patient must have BM biopsy available to be shipped to the Central Pathology Laboratory ≥ 21 days before initiation of study treatment (C1D1).

5. Patient must have at least 1 of the following measurable C-findings, per modified IWG-MRT-ECNM criteria, attributed to SM (Appendix 6) and evaluable for response assessment unless diagnosis is MCL, which does not require a C-finding. Laboratory abnormality C-findings should not be assessed until the required time period from last cytoreductive therapy has been met.

o Cytopenias:

▪ ANC < 1.0 × 109/L or

▪ Hemoglobin < 10 g/dL or

▪ Platelet count < 75 × 109/L.

NOTE: Cytopenias attributable to prior cytoreductive therapy or causes other than SM may not be used as C-findings.

o Symptomatic ascites or pleural effusion requiring medical intervention such as:

▪ Use of diuretics (Grade 2) or

▪ ≥ 2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over the 12 weeks before C1D-8 and 1 of the procedures is performed during the 6 weeks before C1D-8.

o ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × upper limit of normal [ULN]), aspartate aminotransferase (AST; > 3.0 × ULN), alanine aminotransferase (ALT; > 3.0 × ULN), or alkaline phosphatase (> 2.5 × ULN) with 1 of the following present:

▪ Ascites or

▪ Clinically relevant portal hypertension or

▪ Liver MC infiltration that is biopsy-proven or

▪ No other identified cause of abnormal liver function.

o ≥ Grade 2 hypoalbuminemia (< 3.0 g/dL).

o A spleen that is palpable ≥ 5 cm below the left costal margin.

o Transfusion-dependent anemia defined as:

▪ Transfusion of ≥ 6 units packed red blood cells (PRBCs) in the 12 weeks before C1D-8 and

▪ Most recent transfusion occurring during the 4 weeks before C1D-8 and

▪ Transfusion administered for hemoglobin ≤ 8.5 g/dL and

▪ Reason for transfusion is not bleeding, hemolysis, or therapy-related.

o Transfusion-dependent thrombocytopenia, defined as:

▪ Transfusion of ≥ 6 units of apheresed platelets (or ≥ 6 pools of random donor or buffy coat platelets) during the 12 weeks before C1D-8 and

▪ ≥ 2 units transfused during the 4 weeks before C1D-8 and

▪ Transfusions administered for platelet count < 20×10^9/L.

o > 10% weight loss that is medically documented over the 24 weeks (± 12 weeks) before C1D-8.

6. Patient must have a serum tryptase ≥ 20 ng/mL.

7. Patients with cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance.

8. Patient must have symptom management optimized with nonantineoplastic therapies (ie, BSC; eg, H1 and H2 blockers). Dose must be stable for ≥ 14 days C1D-8.

9. If the patient is receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent and dose must be stable for ≥ 14 days before C1D-8.

10. Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 3.

11. Patient must give written informed consent.

EXCLUSIE CRITERIA

1. Patient has received prior treatment with avapritinib.

2. Patient has received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab vedotin) less than 28 days before obtaining screening BM biopsy for this study.

3. Patient has received prior radiotherapy within 14 days before the screening BM biopsy, unless given to palliate specific sites of disease (eg, bone lesion).

4. Patient received any hematopoietic growth factor within 14 days of screening BM biopsy.

5. Patient requires therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4 (Appendix 12).

6. Patient has had a major surgical procedure within 14 days of the first dose of study drug. Surgical procedures such as central venous catheter placement, BM biopsy, and feeding tube placement are considered minor surgical procedures.

7. Patient is a candidate for allogeneic hematopoietic stem cell transplantation for treatment of SM, in the opinion of the Investigator.

8. Patient has eosinophilia and known positivity for the *FIP1L1-PGDFRA* fusion, unless the patient has demonstrated relapse or PD on prior imatinib therapy. Patients with eosinophilia (> 1.5 × 10_9/L), who do not have a detectable *KIT* D816 mutation, should be tested for a *PDGFRA* fusion mutation by fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR).

9. Patient has history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. The following are exempt from the 3-year limit: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.

10. Patient meets any of the following laboratory criteria: o AST or ALT > 3.0 × ULN; no restriction if due to suspected liver infiltration by MCs.

o Bilirubin > 1.5 × ULN; no restriction if due to suspected liver infiltration by MCs or Gilbert's disease.

o Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 or creatinine clearance calculated by Cockcroft-Gault equation < 40 mL/min.

11. Patient has a QT interval corrected using Fridericia's formula (QTcF) > 450 msec.

12. Patient has a history of a seizure disorder (eg, epilepsy) or requirement for antiseizure medication.

13. Patient has a history of a cerebrovascular accident or transient ischemic attacks within 1 year before the first dose of study drug.

14. Patient has a known risk or recent history (within the preceding 1 year) of intracranial bleeding (eg, brain aneurysm).

15. Patient has a primary brain malignancy or metastases to the brain.

16. Patient has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months; clinically significant, uncontrolled arrhythmias; or uncontrolled hypertension.

17. Patient is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures and study restrictions.

18. Female patients who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 30 days after the last dose of study drug. Men who are unwilling, if not surgically sterile, to abstain from sexual intercourse or employ highly effective contraception during the study drug administration period and for at least 90 days after the last dose of study drug.

19. Female patients who are pregnant, as documented by a serum beta human chorionic gonadotropin (β-hCG) pregnancy test consistent with pregnancy obtained within 15 days before the first dose of study drug. Women with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written approval of the Sponsor after pregnancy has been excluded. Women of nonchildbearing potential (ie, women who are postmenopausal or have undergone hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) do not require a serum β-hCG pregnancy test.

20. Women who are breast feeding.
21. Patient has a prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the opinion of the Investigator, could affect the safety of the patient, alter the absorption, distribution, metabolism, or excretion of the study drug, or impair the assessment of study results.