A Phase 1 Study of Avapritinib in Combination with Decitabine in Patients with Systemic Mastocytosis with an Associated Hematologic Neoplasm

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INTRODUCTION

- Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) is the most common form of Advanced SM (AdvSM)
- SM is commonly driven by an oncogenic driver mutation in *KIT*.
- KIT inhibition, particularly with avapritinib, has significantly altered the treatment paradigm for SM-AHN.
- Still, patients with SM-AHN experience disease progression.
- Often, disease progression occurs in the AHN component of the disease.
- Combination therapy may be needed to provide comprehensive disease control.

AIM

- We aim to assess the safety of combined decitabine (oral or IV) and avapritinib in patients with SM-AHN.

STUDY DESIGN

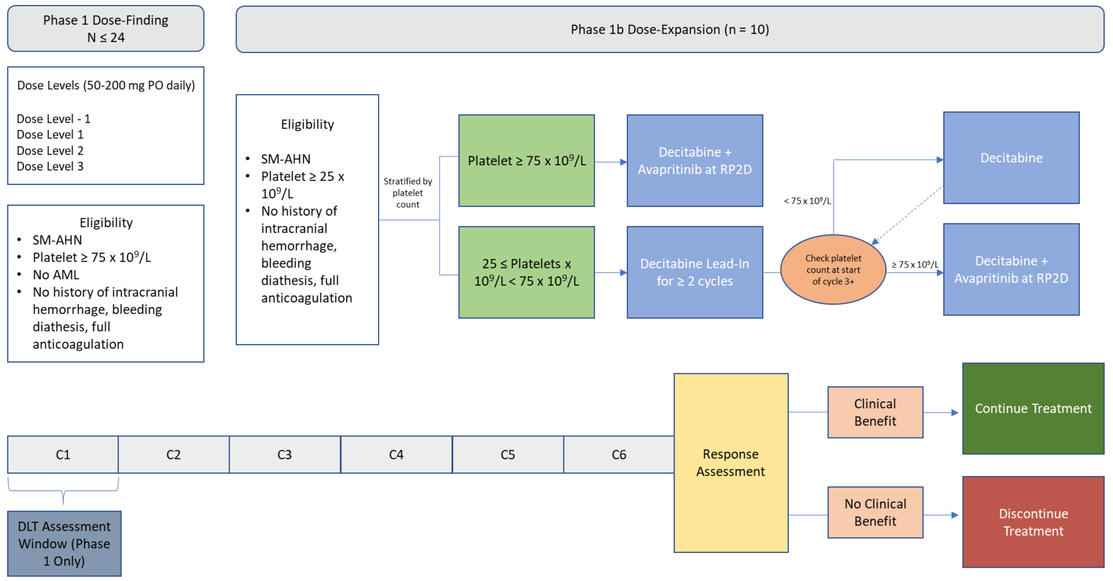
Key Inclusion Criteria

- Patients with a diagnosis of SM-AHN by WHO 2022 criteria.
- AHN must meet criteria for MDS, CMML, MDS/MPN with neutrophilia, MDS/MPN with *SF3B1* mutation and thrombocytosis, or MDS/MPN-NOS.
  - MDS can be intermediate, high-, or very-high risk by IPSS-R OR
  - Low- or very low-risk by IPSS-R and intolerant/refractory to ESA or have serum EPO > 200 U/L.
- Baseline platelet count of ≥ 75 x 10^9/L for dose-finding
  - ≥ 25 x 10^9/L for dose-expansion.

Key Exclusion Criteria

- Diagnosis of AML.
- History of intracranial hemorrhage or significant risk for intracranial hemorrhage.
- Prior progression of SM while on avapritinib
- Prior progression of AHN while on decitabine

STUDY SCHEMA



OBJECTIVES

Primary Objective

- Establish the recommended phase 2 dose of avapritinib in combination with decitabine based upon dose-limiting toxicity, overall safety, and clinical activity.

Secondary Objectives

- Assess the efficacy of combined avapritinib and decitabine in patients with SM-AHN
- Describe the toxicity profile of combined avapritinib and decitabine in patients with SM-AHN.

DOSE FINDING

- N ≤ 24
- Bayesian adaptive design.
- Avapritinib doses will be evaluated from 50 to 200 mg PO daily.
- Decitabine will be dosed at a standard dose of 20 mg/m^2/day IV on days 1-5 of 28 day cycles
- Decitabine/cedazuridine will be dosed at 35/100 mg/day PO day 1-5 of 28 day cycles
- Strict parameters regarding treatment-emergent thrombocytopenia requiring treatment hold, platelet support, and dose modification when/if platelet count drops below 50 x 10^9/L.

DOSE EXPANSION

- Patients with platelet ≥ 75 x 10^9/L will receive combination therapy.
- Patients with baseline platelet count ≥ 25 x 10^9/L and < 75 x 10^9/L will receive lead-in dosing with decitabine or decitabine/cedazuridine.
  - Conditional addition of avapritinib if platelet count ≥ 75 x 10^9/L on day 1 of cycle 3+.

PLANNED CORRELATIVE STUDIES

- Single-cell multi-omics utilizing scDNA-seq and immunophenotyping to assess impact of combined decitabine and avapritinib on a molecular complex disease state.

CONTACT INFORMATION

Funding support for this study provided by Blueprint Medicines.

Please contact Andrew Kuykendall at Andrew.Kuykendall@moffitt.org for any additional information.

STUDY STATUS

- This study is registered (NCT06327685) and currently open to accrual.