HARBOR: An Ongoing Phase 2/3 Study of Elenestinib in Patients With Indolent Systemic Mastocytosis

Poster Number 533

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Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast-cell (MC) disease primarily driven by D816V-mutant *KIT* in ~95% of cases[1–3]
- Historically, the prevalence of systemic mastocytosis (SM) has been estimated at 1 in 10,000 people,[4–6] although a recent study suggests that it could affect up to 1 in 5,000 people[7]
- ISM is characterized by the accumulation and hyperactivation of aberrant MCs in bone marrow, skin, the gastrointestinal tract, and other organs[8]
- Patients with ISM often experience long-term debilitating symptoms related to release of MC mediators that impact quality of life[9–12]
- Consequences for patients with ISM include:
  - Anaphylaxis, which may occur in up to 50% of patients[13]
  - Bone disease, such as osteopenia and osteoporosis, affecting up to ~40% of patients[14]
  - Mastocytosis-typical skin lesions that may be experienced as disfiguring[10,15]
- Approximately 5% of patients with ISM show disease progression to severe forms of SM associated with poor overall survival[16]
- Elenestinib is a next-generation, potent and highly selective KIT D816V inhibitor with limited central nervous system penetration
- The Phase 2/3 HARBOR trial (NCT04910685) is an ongoing, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of elenestinib plus symptom-directed therapy (SDT) in patients with ISM and smoldering SM (SSM)
- The safety, tolerability, and efficacy in Part 1 of HARBOR demonstrated a benefit/risk profile that supports the Part 2 and Part 3 design[17]
- This study will further evaluate the impact of KIT D816V inhibition on symptom improvement, anaphylaxis rates, bone density loss, and disease burden markers such as *KIT* D816V variant allele fraction, serum tryptase, and bone marrow MCs in patients with ISM and SSM

Key eligibility criteria for enrolling cohorts

Inclusion criteria

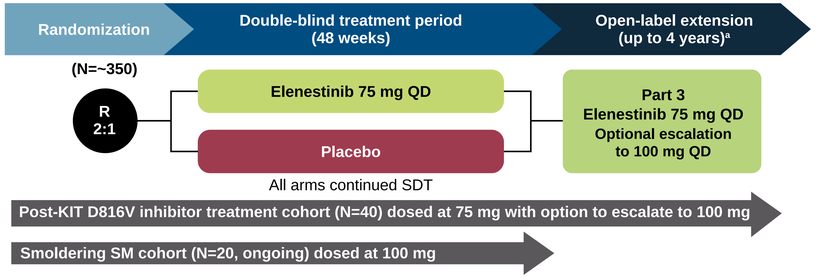
- ≥18 years of age
- Eastern Cooperative Oncology Group performance status is 0–2
- Moderate to severe symptoms based on the ISM-SAF mean TSS (Part 2, Post–KIT D816V inhibitor cohort)
- Centrally confirmed diagnosis of ISM (Part 2, Post–KIT D816V inhibitor cohort) or SSM (SSM cohort) confirmed by central review of B- and C-findings according to WHO diagnostic criteria[a,18] and failure to achieve adequate symptom control for ≥1 baseline symptoms (Part 2 only)[b]
- SDT for ISM symptom management[c] must be stable for ≥14 days prior to starting screening procedures (Part 2)

Exclusion criteria

- Patient has been diagnosed with another SM subclassification, including an associated hematologic neoplasm, or C-findings attributable to SM[d]
- Patient has received the following therapy prior to first dose of the study drug:
  - Radiotherapy or psoralen and ultraviolet A (PUVA) therapy <14 days before beginning the screening assessments
  - Any hematopoietic growth factor <14 days before beginning the screening assessments
- Patient is currently receiving an investigational agent in another interventional study
- Patient has a history of a primary malignancy that has been diagnosed or required therapy within 3 years prior to the study[e]
- TEAEs from previous KIT inhibitors must be resolved to Grade ≤1 prior to the first dose of elenestinib (Post–KIT D816V inhibitor cohort)

[a]An archival biopsy may be used if completed within the past 12 months. [b]Using ≥2 of the following symptomatic therapies: H1 blockers, H2 blockers, proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, omalizumab. [c]No new medications ≥14 days before beginning the 14-day eligibility screening period. [d]World Health Organization SM subclassification (cutaneous SM only, SM with associated hematological neoplasm of non-MC lineage, aggressive SM, MC leukemia, MC sarcoma). [e]The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.
ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form (©2018, Blueprint Medicines Corporation); MC, mast cell; SDT, symptom-directed therapy; SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis; TEAE, treatment-emergent adverse event; TSS, total symptom score; WHO, World Health Organization.

Figure 1. Study design



[a]Up to a total of 5 years treatment between Parts 2 and 3.
QD, once daily; R, randomized.

Study endpoints

Primary

Randomized Part 2
- Mean change in ISM-SAF TSS from baseline[a]

Open-label Part 3
- Long-term safety and tolerability by determining AEs, SAEs, and lab parameters
- Mean change in ISM-SAF TSS

Secondary

Randomized Part 2 (key secondary endpoints)[a]
- Proportion of patients achieving:
  - Normalization of tryptase
  - Undetectable or ≥50% reduction in *KIT* D816V VAF
  - Symptom control as measured by TSS
- Change in bone mineral density
- Change in annualized rate of anaphylaxis
- Change in quality of life

Randomized Part 2 and open-label Part 3 (secondary endpoints)
- Change in measures of disease burden: serum tryptase, *KIT* D816V VAF, BM MCs, urinary MC biomarkers
- Bone health assessed through DXA scans, x-rays for fracture surveillance, and bone turnover biomarkers

Post–KIT D816V inhibitor cohort
- Change in ISM-SAF TSS
- Safety and tolerability determined by AEs, SAEs, and lab parameters
- Change in measures of disease burden including serum tryptase and *KIT* D816V VAF

SSM cohort
- Change in ISM-SAF TSS
- Change in measures of disease burden, including serum tryptase, *KIT* D816V VAF, and the proportion of patients achieving PPR
- Safety and tolerability determined by AEs, SAEs, and lab parameters in patients with SSM

[a]Compared to placebo. Measured after 48 weeks of treatment.
AE, adverse event; BM, bone marrow; PPR, pure pathologic response; SAE, serious adverse event; VAF, variant allele fraction.

Study objectives and design

- In HARBOR Part 2, approximately 350 patients will be randomized 2:1 to elenestinib 75 mg once daily (QD) or placebo for 48 weeks (**Figure 1**)
  - All arms will include the use of SDT
- After completing Part 2, patients will have the option to roll over to Part 3 and receive open-label active therapy, with the option to dose escalate to 100 mg QD, for up to 5 years overall
- An additional open-label cohort of up to 40 patients with previously approved selective KIT D816V-targeted treatment will be included to evaluate efficacy and safety of 75 mg elenestinib in this population, with the option to escalate to 100 mg
- Disease response and safety of 100 mg QD elenestinib in patients with SSM will be evaluated in an open-label cohort of 20 patients
- The change in the frequency of anaphylaxis episodes will be assessed in this study
- The change in bone mineral density will be evaluated in patients with baseline osteopenia or osteoporosis after 48 weeks of treatment
  - Approximately 50% of patients are expected to have osteopenia or osteoporosis at screening
  - DXA scans will be taken throughout the double-blind and open-label parts of the study
  - Vertebral fractures among patients with a history of fractures or low bone density will be studied

Summary

- HARBOR Part 2 has been optimized to include:
  - Endpoints that evaluate disease modification including anaphylaxis frequency, bone health, and symptom control as these will address issues that critically impact the overall health of the patients
  - Timing of endpoints that reflect the chronic nature of disease
- HARBOR Part 3 will prospectively evaluate multiple doses, providing dosing flexibility
- HARBOR Part 2 has initiated and will be expanded internationally

To learn more about our clinical trials, visit blueprintclinicaltrials.com or contact us in the USA at **medinfo@blueprintmedicines.com** or 1-888-BLU-PRNT (1-888-258-7768), and in Europe at **medinfoeurope@blueprintmedicines.com** or +31 85 064 4001

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Conflicts of interest/disclosures

Dr Castells has served as a consultant for Blueprint Medicines Corporation and is a PI on several clinical trials for Blueprint Medicines Corporation.
She has received author fees from the Editorial Board for Annals of Allergy, Asthma & Immunology. For all author disclosures, please contact medinfo@blueprintmedicines.com.