Abstract: P1055

Title: SYMPTOM-FOCUSED RESULTS FROM SUMMIT PART 1: AN ONGOING, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 CLINICAL TRIAL OF BEZUCLASTINIB IN ADULT PATIENTS WITH NONADVANCED SYSTEMIC MASTOCYTOSIS

Abstract Type: Poster Presentation

Topic: Myeloproliferative neoplasms - Clinical

Background:

Systemic mastocytosis (SM) is a rare disease characterized by neoplastic mast cell infiltration of cutaneous and extracutaneous tissues and encompasses a spectrum of subtypes that can range from non-advanced to advanced disease. Nonadvanced SM (NonAdvSM) is often associated with debilitating symptoms which may significantly reduce health-related quality of life (HRQoL). In up to 95% of patients, SM is driven by the somatic KIT D816V mutation. Bezuclastinib is an oral, potent, and selective type 1 tyrosine kinase inhibitor with highly selective activity against KIT D816V and minimal brain penetration in preclinical studies. Initial results from the Summit trial (NCT05186753) demonstrated that bezuclastinib was associated with an encouraging safety and tolerability profile with the majority of adverse events being of low grade and reversible. Bezuclastinib was also associated with encouraging clinical activity, with demonstrated reductions in markers of disease burden including serum tryptase, bone marrow mast cell burden, and KIT D816V variant allele fraction (VAF). Bezuclastinib also improved patient-reported outcome measures (PROMs) (Modena et al. J Allergy Clin Immunol (AAAAI) 2024. Poster 694). Data from Part 1 led to selection of bezuclastinib 100mg QD which demonstrated a significant reduction in the novel disease-specific mastocytosis symptom severity daily diary (MS2D2) total symptom severity (TSS) compared to placebo at Week 12 (-23.78 vs. -9.03; p=0.0003) with no dose reductions.

Aims:

Part 1 of the Summit trial was designed to determine the recommended dose of bezuclastinib based on a composite of safety, PK, and PD data and to explore the effects of bezuclastinib on the signs and symptoms of NonAdvSM.

Methods:

Summit is a multi-center, Phase 2, randomized, double-blind, placebo-controlled clinical trial of bezuclastinib in patients with NonAdvSM who have moderate to severe disease despite treatment with best supportive care (BSC). PROMs, including the MS2D2, mastocytosis activity score (MAS), and the mastocytosis quality of life (MC-QoL) measure, are being used to assess treatment impact on symptoms and HRQoL. Skin photography is performed at baseline and week 12 for quantitative assessment of skin lesions. Patient entry and exit interviews are conducted for qualitative understanding of patient symptoms.

Results:

Summit Part 1 enrolled 54 patients; 51 patients had ISM and 3 patients had SSM. In Part 1, a majority of patients were women (67%) and the mean age was 53 years. Patients utilized a median (range) of 3 (2 to 9) BSC medications, with 89% using H1 blockers, 83% using H2 blockers, 41% using leukotriene receptor antagonists, and 7% using omalizumab.

At baseline, patients had a median (range) serum tryptase of 44 (9 to 592) ng/mL and 82% of patients had a serum tryptase ≥20 ng/mL. 80% of patients were KIT D816V positive and median (range) KIT D816V VAF in whole blood was 0.14% (0 to 32%). Median (range) percent bone marrow mast cell burden was 15% (1 to 80%). At baseline, most patients reported severe disease symptoms that resulted in a moderate impact to their QoL as indicated by the median MAS score of 39 (range 21-78) and median MC-QoL score of 52 (range 28-

91), respectively. At baseline, within the MS2D2 TSS, median (range) of 47 (23 – 92), the most severe symptoms for patients included “covered with spots” and “feeling of tiredness”. In patients who had skin photography analyzed at baseline and after 12 weeks of treatment (n=18), bezuclastinib resulted in a mean change in lesion fractional area of -55% vs +3% for placebo.

Summary/Conclusion:

The patients enrolled in Part 1 of the Summit trial are generally representative of the population of patients with moderately to severely symptomatic NonAdvSM based on number of BSC medications, symptom severity, and disease impact on HRQoL. Bezuclastinib demonstrated an encouraging safety and tolerability profile. After 12 weeks of treatment, PROMs were improved compared to placebo, and skin lesions were markedly reduced in patients receiving bezuclastinib. Further evaluation of skin and other specific symptoms experienced by patients with NonAdvSM at baseline and after bezuclastinib treatment will be presented.

Keywords: Clinical trial, Mast cell disease, Mastocytosis, Systemic mastocytosis