(S217) EFFICACY AND SAFETY OF BEZUCLASTINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS: PRIMARY RESULTS FROM THE APEX STUDY

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background

Advanced systemic mastocytosis (AdvSM) is a rare clonal myeloid neoplasm associated with significant disease burden and comprises aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Bezuclastinib is an oral, selective type I tyrosine kinase inhibitor (TKI) with potent activity against *KIT* p.D816V, the driving mutation in ~95% of SM cases. Part 2 of the Apex study evaluated the efficacy and safety of bezuclastinib in patients with AdvSM.

Methods

Apex is an ongoing, phase 2, open-label, registrational study evaluating bezuclastinib in patients with AdvSM. Based on tolerability, clinical activity, and pharmacokinetic data from the dose confirmation portion of the study, 150 mg daily dose of bezuclastinib was selected as the Part 2 dose. The primary endpoint was overall response rate (ORR) per modified International Working Group (mIWG)-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (MRT-ECNM) response criteria. Key secondary endpoints included ORR per pure pathologic response (PPR) criteria and safety.

Results

Bezuclastinib 150 mg was administered in 81 patients (intention-to-treat [ITT] population) with AdvSM, including 57 patients with SM-AHN, 11 with ASM, and 13 with MCL and MCL-AHN. Sixty eight patients were evaluable for response assessment per mIWG-MRT-ECNM criteria. In the ITT population, median age (range) was 70 (43-87) years; 23 (28%) patients were female; 28 patients (35%; avapritinib, 7%; midostaurin, 30%) received prior KIT-targeted TKI therapy. Median (range) baseline bone marrow (BM) mast cell (MC) burden, serum tryptase, and whole blood *KIT* p.D816V variant allele frequency (VAF) were 35% (3-95), 191 ng/mL (23.3-1987), and 6.7% (0.0-91.4), respectively.
At the time of the primary analysis, September 19, 2025, ORR was 57% in evaluable patients per mIWG-MRT-ECNM criteria (complete response [CR/CRh], 13%; partial response [PR], 35%; clinical improvement, 9%) and 80% in the ITT population per PPR criteria (CR/CRh, 57%; PR, 24%). In evaluable patients, median time to response was 2.0 months. At the time of data cut, duration of response was not yet mature; median duration of treatment was 9.4 months. In the ITT population, bezuclastinib reduced MC burden, serum tryptase, and *KIT* p.D816V VAF by ≥50% in 89%, 89%, and 91% of patients, respectively.
Overall, treatment-related adverse events (TRAEs) occurred in 93% of patients, with a low incidence of drug-related serious AEs (6%). The most frequent TRAEs (total/grade ≥3) were hair color change (31%/0%), neutropenia (30%/24%), altered taste (28%/0%), thrombocytopenia (25%/14%), and alanine/aspartate aminotransferase increased (21%/1%). Dose reductions due to TRAEs occurred in 14.8% of patients and were mainly due to hematologic events; no other AEs led to dose reduction in >1 patient. There were no discontinuations due to TRAEs. No treatment-related deaths occurred.

Summary/Conclusion

Bezuclastinib demonstrated high response rates, led to deep reductions in objective markers of MC burden, and was well-tolerated, with infrequent dose reductions and no discontinuations due to TRAEs. Positive results from Apex support bezuclastinib as a potential treatment for patients with AdvSM.