(PF885) THE EFFECT OF BEZUCLASTINIB ON THE PATHOBIOLOGY OF ADVANCED SYSTEMIC MASTOCYTOSIS: RESULTS FROM THE PIVOTAL APEX TRIAL

Topic: 16. Myeloproliferative neoplasms - Clinical

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Background

Systemic mastocytosis (SM) is characterized by abnormal mast cell (MC) accumulation, driven by the gain-of-function *KIT* p.D816V mutation in ~95% of patients. Advanced SM (AdvSM) is a life-threatening form that includes aggressive SM, SM with associated hematologic neoplasm, and mast cell leukemia. Pathological and molecular markers of disease burden, such as bone marrow (BM) MC burden and characterization, serum tryptase, and *KIT* p.D816V variant allele frequency (VAF), are used to determine AdvSM subtype and disease severity, monitor disease modification, and predict prognosis and survival.
Bezuclastinib is an investigational, oral, potent, selective tyrosine kinase inhibitor (TKI) with activity against KIT D816V. Primary results from the Apex trial of bezuclastinib demonstrated favorable efficacy and safety in AdvSM. Herein we report the effect of bezuclastinib on pathological markers of SM from the pivotal portion of Apex.

Methods

Apex (NCT04996875) is a Phase 2, open-label, multipart trial evaluating bezuclastinib in AdvSM. The pivotal Part 2 portion evaluated bezuclastinib at the selected dose of 150 mg once daily in adults with and without measurable C-findings. Primary endpoint was overall response rate (ORR) per mIWG-MRT-ECNM criteria, reported separately. Secondary endpoints included ORR per pure pathologic response (PPR) criteria and reductions in disease markers.
BM biopsy and aspirate, serum tryptase, and *KIT* p.D816V VAF were collected and tested centrally at baseline, every three 28-day cycles for the first 12 months, and then every six cycles. MC burden and aggregation, immunophenotype, and morphology were assessed; immunohistochemical staining was performed on BM sections.

Results

In Part 2, 81 patients with AdvSM received bezuclastinib: median age (range), 70 (43-87) years; 28% female; 93% with MC aggregates at baseline. Median (range) baseline BM MC burden was 35% (3-95), serum tryptase was 191 ng/mL (23.3-1987.0), and *KIT* p.816V VAF in blood was 6.7% (0-91.4).

As of the September 19, 2025 primary analysis, ORR was 80.2% per PPR criteria (median treatment duration 9.4 months). Of patients with pertinent baseline and ≥1 postbaseline BM assessments, 76% had clearance of MC aggregates, 69% had serum tryptase reduction to <20 ng/mL, and 28% had undetectable *KIT* p.D816V VAF, each representing a key threshold to assess treatment response in SM.

At Cycle 3, bezuclastinib treatment led to reductions in BM MCs, CD25 and CD30 expression, and spindle-shaped MCs; early Cycle 3 reductions observed in these markers continued to deepen at Cycle 6 (Table 1). Mean percentage reduction in BM MCs in biopsy was 79% at Cycle 6.

Table 1: Reductions in BM Disease Markers Following Bezuclastinib Treatment

Marker	Baseline	Bezuclastinib Cycle 3 Day 1	Bezuclastinib Cycle 6 Day 1
		Mean [N]	
BM MCs (biopsy), %	**41** [81]	**19** [74]	**8** [61]
BM MCs (aspirate), %	**9** [67]	**5** [46]	**2** [32]
CD25 Expression, %	**88** [81]	**53** [75]	**31** [60]
CD30 Expression, %	**25** [80]	**10** [75]	**2** [60]
Spindle-Shaped MCs (biopsy), %	**59** [77]	**34** [71]	**30** [57]
Spindle-Shaped MCs (aspirate), %	**60** [43]	**36** [24]	**40** [17]

Summary/Conclusion

In patients with AdvSM from Apex, bezuclastinib demonstrated high response rates and significant changes in BM MC burden, aggregation, immunophenotype, and morphology, as well as in serum tryptase and *KIT* p.D816V VAF. Substantial reductions in objective markers of disease burden, to the extent of normalization/elimination in many cases, signifies modification of underlying AdvSM pathobiology with bezuclastinib treatment.