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Title of Presentation	Evaluation of Bone Formation Marker Changes in Summit, a Trial Assessing Bezuclastinib in Adults with Non-Advanced Systemic Mastocytosis: An Exploratory Analysis
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Abstract of Presentation	Background: Mast cells play a critical role in bone turnover, metabolism, and homeostasis. In patients with nonadvanced systemic mastocytosis (NonAdvSM), mast cell dysregulation may contribute to skeletal complications such as osteolysis, osteopenia, and osteoporosis, often leading to an increased risk of fragility fractures. The KIT c.2447 C>T (p.D816V) mutation is found in most patients with SM. Bezuclastinib, an oral, potent type 1 tyrosine kinase inhibitor with selective activity against KIT p.D816V, is being investigated in the Summit trial. Here, we report the effect of bezuclastinib on bone formation markers. Methods: Summit (NCT05186753) is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial in patients with NonAdvSM who have inadequate symptom control despite best supportive care. Bone formation markers, including Serum type I N-terminal propeptide of type 1 procollagen (P1NP) and osteocalcin were evaluated. Results: At baseline, 27 patients had a history of osteopenia, while 37 patients had documented osteoporosis. Additionally, 26 patients had previously received treatment with bone-modifying agents, including denosumab (n=7) and

	bisphosphonates (n=19). Following 24 weeks of treatment with bezuclastinib, bone formation markers P1NP and osteocalcin were increased compared to baseline. In contrast, patients in the placebo group exhibited minimal changes in these markers. These findings suggest that bezuclastinib may stimulate osteoblast activity, potentially through mast cell modulation, thereby promoting bone formation. Conclusions: Bezuclastinib appears to have a favorable impact on bone remodeling, with early stimulation of bone formation. These findings support its potential role in managing bone health in systemic mastocytosis, where bone turnover is often disrupted.