BACKGROUND

• Patients with systemic mastocytosis (SM) can suffer from severe mast cell (MC) mediator reactions, caused by MC mediator production and hyperactivity due to the KIT D816V mutation.
• Symptoms may include skin lesions, pruritus, diarrhea, anaphylaxis, bronchospasm, and bone pain, which can be severely debilitating and have a profoundly negative impact on quality of life.
• Polypharmacy with multiple symptomatic treatments (e.g., antihistamines, ketotifen, omalizumab, cromolyn sodium, leukotriene inhibitors, and cyclosporine) was seen in 60% of patients with SM, with varying degrees of efficacy.
• Patients with advanced SM (ASM) and mastocytosis (SM-MM) have a single dose of Avapritinib (100 mg) in M1:1 ratio for the best supportive care (BSC) followed by rollover to the recommended phase 2 dose (RP2D) in phase 2/3 trials.

METHODS

• PIONEER is a multicenter, randomized, double-blind, placebo-controlled, phase 2 study of patients with SM or ASM whose symptoms are not adequately controlled by best supportive care (BSC).
• The primary endpoint is the change in the ISM-Symptom Assessment Form (ISM-SAF) in patients at 12 weeks.
• The ISM-SAF was determined based on a change in Total Symptom Score (TSS) from the SM Symptom Assessment Form (SM-SAF) and change in serum tryptase, safety, and pharmacokinetics (PK) at each dose level (100 mg, 50 mg, or placebo) compared to baseline. Patients were then stratified into 11 symptomatic and inactive domains for a change of symptomatic status from baseline to week 12 (symptom reduction or increase).
• The primary endpoint of part 2 of the study is the change in ISM-SAF TSS from baseline to week 12.
• Patients with toxic liver injury (i.e., >50% decrease from baseline by 1 month; every patient at 11+ months).

RESULTS

• 105 patients were randomized, of which 100 were considered evaluable for the change in TSS from baseline to week 12 (Figure 3).
• Every SM and ASM patient had >50% serum tryptase reduction by 1 month; every patient at 11+ months.

CONCLUSIONS

• All baseline SM patients had median of 2 supportive care medications, with the most severe patient reported symptoms being fatigue, brain fog, flushing and cutaneous symptoms.
• Patients treated with avapritinib at doses of 25 mg, 50 mg and 100 mg QD showed rapid decreases in MC burden, in measures of mast cell burden, by May 6.
• Avapritinib was generally well-tolerated in patients with SM.
• No patient discontinued treatment with avapritinib due to an AE.
• Most common AEs of all grades (avapritinib/placebo) were nausea (30%/21%), headache (23%/15%), and diarrhea (20%/17%) for SM-MM occurred in avapritinib-treated patients.
• In placebo-treated patients, 22% had an SAE with mastocytosis flare being predominant.
• Additional pending data from part 1 of the PIONEER study, including the change in TSS on the SM-SAF, will inform selection of the RP2D.
• The registration-enabling part 2 of the PIONEER study is anticipated to initiate patient screening in the first half of 2020.

More information on our SM trials at www.blueprintclinicaltrials.com/sm/