Avapritinib Durably Improves Cutaneous Involvement of Indolent Systemic Mastocytosis in Patients Treated in the PIONEER Study

Poster Number 147

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Introduction

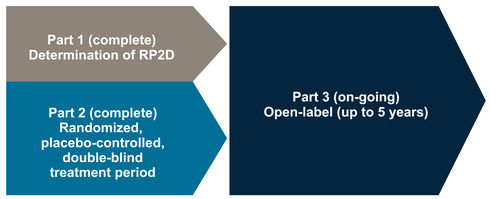
- Indolent systemic mastocytosis (ISM), the most common form of systemic mastocytosis, is a chronic clonal mast cell disease, and is primarily driven by the *KIT* D816V mutation in ~95% of cases[1-4]
- Patients with ISM may experience lifelong debilitating symptoms due to the accumulation and hyperactivation of aberrant mast cells (MCs) in various organs, including the skin[4,5]
- Skin manifestations include brown maculopapular skin lesions, pruritus, and wheals. Darier's sign is a hallmark of these skin lesions, and is related to the release of histamine and other mediators from MCs[6,7]
- Skin lesions also impact patients' self-image and can lead to social isolation and sleep disturbance, all contributing to a considerable decrease in quality of life (QoL)[8-10]
- Symptom-directed therapies are often insufficient at controlling skin manifestations and do not target the pathogenic driver of disease[11]
- Avapritinib, an oral, highly selective, potent inhibitor of D816V-mutated KIT, is the only therapy currently approved in the USA and Europe to treat adults with ISM[12,13]
- In the randomized, placebo-controlled Part 2 of PIONEER, avapritinib demonstrated improvements in skin manifestations compared with placebo at 24 weeks[14] (**Figure 1**)
  - Patients with skin involvement who were treated with avapritinib reported statistically significant reductions in the overall skin domain and in each of the individual mastocytosis-related cutaneous symptoms including spots, itching, and flushing compared with those who received placebo
  - Avapritinib reduced lesion surface area in the most affected skin region *versus* placebo (median –50% vs 0%, respectively). Additionally, the majority of patients treated with avapritinib experienced lightening of skin lesion color, whereas no change was observed among those receiving placebo
- Here, we report the impact of longer-term treatment in patients with ISM who started with avapritinib 25 mg once daily (QD) on skin symptoms, skin lesion area, and skin lesion color in the PIONEER study

Methods

- Patients with moderate to severe ISM symptoms who completed the randomized dose-finding (Part 1), or randomized, double-blind, placebo-controlled (Part 2) portions of PIONEER rolled over to the open-label, long-term extension (Part 3) with up to 5-year follow-up (**Figure 1**)

Figure 1. Study design

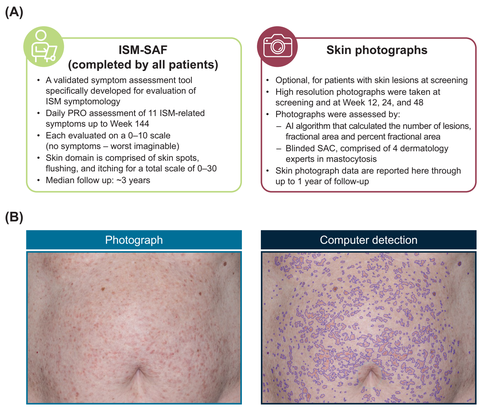
Overall, 226 patients initiated avapritinib 25mg QD across Parts 1, 2, and 3[a]



[a]n=226, includes patients from Part 1 and Part 2 who started and continued avapritinib 25 mg QD in Part 3 or Part 2 patients who crossed over from placebo to avapritinib 25 mg QD in Part 3.
QD, once daily; RP2D, recommended part 2 dose.

- Symptoms were assessed using the ISM Symptom Assessment Form (ISM-SAF; ©2018 Blueprint Medicines Corporation), and patients had the option of undergoing standardized clinical skin photography for assessment by the expert skin assessment committee and algorithm (**Figure 2A** and **2B**)
- Here, we present data at a cut-off of September 20, 2024

Figure 2. Comprehensive assessment of skin changes from baseline (A) and AI algorithm assessment of skin changes (B)



AI, artificial intelligence; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; PRO, patient-reported outcome; SAC, skin assessment committee.

Results

- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg QD + best supportive care (BSC)
- Baseline characteristics were comparable in n=79 patients with paired skin photographs and the pooled avapritinib 25 mg QD population at Week 24 (**Table 1**)

Table 1. Baseline patient demographics and characteristics

Patient demographics	Patients with paired skin photographs (n=79)	Avapritinib 25 mg QD (n=226)
Age (years), median (range)	50 (22–77)	49.8 (18–79)
Female, n (%)	58 (73)	166 (73)
TSS baseline, mean (SD)[a]	49.1 (19.2)	48.1 (19.5)
Most severe symptom score, mean (SD)	7.7 (1.8)	7.5 (1.9)
Mast cell burden		
Median serum tryptase (central), ng/mL (range)	37.6 (3.6–248.8)	39.2 (3.6–590.4)
Median bone marrow biopsy mast cells (central), % (range)	10 (1–40)	7 (1–60)
Median *KIT* D816V VAF in peripheral blood, % (range)[b]	0.48 (Undetectable–29.18)	0.39 (Undetectable–41.29)
Systemic mastocytosis therapy		
Prior cytoreductive therapy, n (%)[c]	13 (16)	29 (13)
Prior TKI therapy, n (%)	8 (10)	17 (8)
Number of BSC treatments, median (range)[d]	3 (0–10)	3 (0–10)

[a]Eligibility for enrollment was based on TSS ≥28 at screening; patients may have a score <28 at baseline.
[b]The limit of detection was 0.02%. [c]Cytoreductive therapies included dasatinib, imatinib, masitinib, nilotinib, midostaurin, brentuximab vedotin, cladribine, hydroxyurea, rapamycin, and interferon α. Includes treatments received by patients at baseline; patients may have received BSC treatments previously discontinued at the time of enrollment/baseline. [d]All patients had at least two BSC treatments prior to or at screening.
BSC, best supportive care; TSS, total symptom score; SD, standard deviation; TKI, tyrosine kinase inhibitor; VAF, variant allele fraction.

- Improvements in the ISM-SAF continued at Week 48 in patients who started with avapritinib 25 mg QD, the mean (standard deviation [SD]) change from baseline in the skin symptom domain was −6.9 (7.1) at Week 48 (1 year) and −2.5 (2.5), –2.5 (2.8), –2.0 (2.7) for spot severity, itching, and flushing, respectively (**Figure 3**)
  - These improvements were sustained, and at Week 144 (3 years), the mean (SD) change in skin symptom domain was –8.1 (7.9)

Results (continued)

Figure 3. ISM-SAF skin symptoms in patients treated with avapritinib 25 mg QD

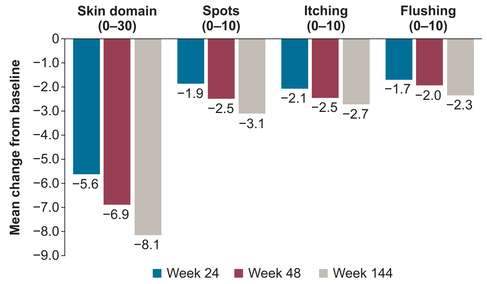


Figure 4. Change in skin lesion fractional area estimate from start of avapritinib determined by a computer-generated algorithm

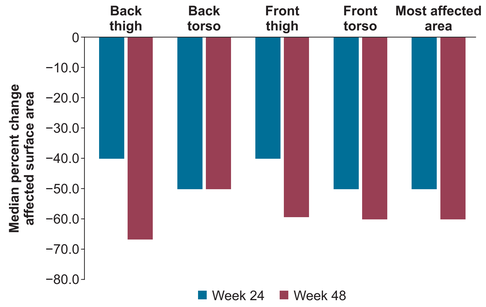
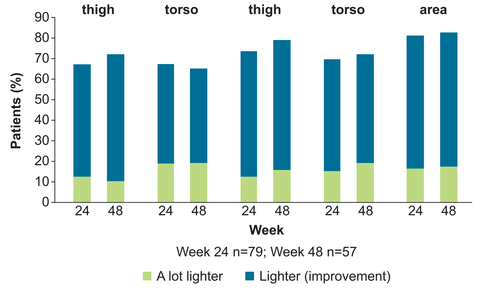


Figure 5. Skin lesion color change



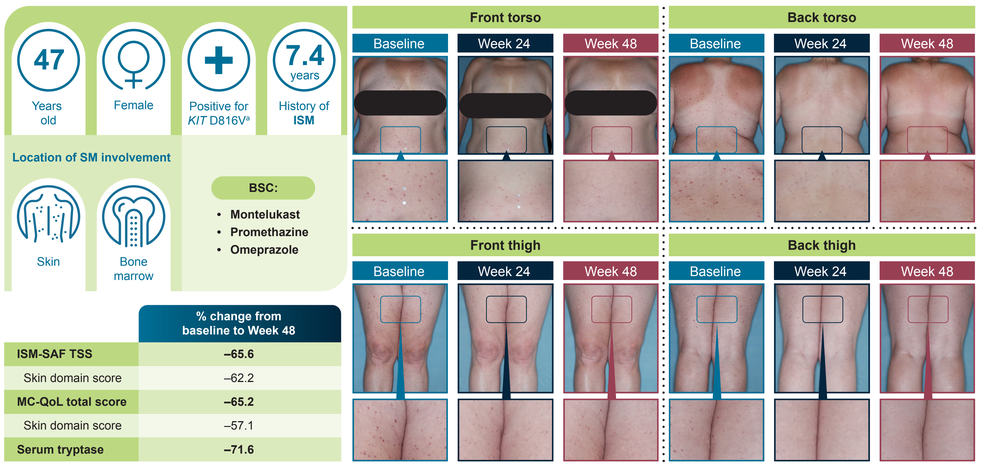
- The surface area of skin lesions was reduced at Week 24 in avapritinib-treated patients and was sustained at Week 48 (1 year) (**Figure 4**)
- Patients with paired photographs showed a median percent reduction in lesion surface area in the most affected skin region of –60% at Week 48
- As assessed by a blinded skin assessment committee, the majority of patients had an improvement in skin lesion color at Week 24 while treated with avapritinib and was sustained at Week 48 (1 year) (**Figure 5**)
- The safety profile of avapritinib was similar to placebo in the randomized, blinded part of the trial, and remained favorable in the longer-term open-label extension part of the trial, with a median follow-up of 3 years (**Table 2**)
- The most frequently reported adverse events associated with avapritinib were edema events, with the majority being Grade 1
- Grade ≥3 treatment-related adverse events (TRAEs) remained low and consistent with the randomized portion of the study
- Treatment discontinuations due to TRAEs remained limited occurring in seven patients (3%)

Table 2. Safety profile of avapritinib

	Part 2[a]		Parts 1, 2, 3 combined[b]
	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	All patients who initiated avapritinib 25 mg QD + BSC (N=226)
Median length of follow-up (months)[c]	**5.6**	**5.6**	**35.3**
Any AEs, n (%)	**128 (91)**	**66 (93)**	**224 (99)**
Any TRAEs, n (%)	77 (55)	32 (45)	168 (74)
Grade ≥3 AEs	**30 (21)**	**15 (21)**	**103 (46)[d]**
Grade ≥3 TRAEs	3 (2)	2 (3)	14 (6)
Serious AEs	**7 (5)**	**8 (11)**	**45 (20)**
Serious TRAEs	0 (0)	0 (0)	3 (1)[e]
TRAEs leading to discontinuation	**2 (1)**	**1 (1)**	**7 (3)**
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	29 (13)
Periorbital edema	9 (6)	2 (3)	22 (10)
Headache	11 (8)	7 (10)	21 (9)
Nausea	9 (6)	6 (8)	18 (8)
Fatigue	6 (4)	2 (3)	16 (7)
Diarrhea	4 (3)	2 (3)	14 (6)
Alopecia	5 (4)	3 (4)	13 (6)
Dizziness	4 (3)	5 (7)	11 (5)

[a]Data cut: June 23, 2022. [b]Data cut: September 20, 2024. [c]Reflects median length of follow-up during the indicated study period. [d]One death (Grade 5 AE) occurred during the study and was unrelated to treatment; the patient had a medical history of anaphylaxis and atrial fibrillation, and the event was assessed as due to anaphylaxis in the context of atrial fibrillation. [e]Serious TRAEs included peripheral edema (1), gastric hemorrhage (1), and transient loss of vision (1). None of these events led to discontinuation.
AEs, adverse events; TRAEs, treatment-related adverse events.

Case study



	% change from baseline to Week 48
ISM-SAF TSS	**–65.6**
Skin domain score	–62.2
MC-QoL total score	**–65.2**
Skin domain score	–57.1
Serum tryptase	**–71.6**

[a]*KIT* point mutation at codon 816 in the BM or another extracutaneous organ.

Conclusions

- These results support previous analyses in which avapritinib demonstrated statistically significant and clinically meaningful improvements *versus* placebo (both with BSC) in symptoms, as measured with the TSS
  - Of the patients with skin involvement, those treated with avapritinib 25 mg QD experienced marked reductions in skin symptoms, skin color, and surface area of skin lesions
- We show that these improvements were persistent with a longer-term follow-up
  - Symptom improvements continued to be durable for up to 3 years
- Improvements in skin lesion size and color were also detected in clinical photographs for up to 1 year, corresponding to the predefined duration of photographic follow-up
- Avapritinib was generally well tolerated with no new safety concerns observed, with a median follow-up of 3 years
- Avapritinib achieved sustained and durable improvements in the skin manifestations of ISM while maintaining a long-term favorable benefit-risk profile in patients with ISM. These data highlight the ability of avapritinib to achieve long-term disease modification

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Conflicts of interest / Disclosures

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