Effect of Avapritinib on Skin Lesions in Patients With Advanced Systemic Mastocytosis Using a Novel, Artificial Intelligence-Based Technology

Poster Number 2030

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Introduction

- Systemic mastocytosis (SM), a clonal hematologic neoplasm, is driven by the *KIT* D816V mutation in ~95% of cases, and has been estimated to affect up to 1 in 5,000 people[1–8]
- Advanced SM (AdvSM) includes aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL)[9]
- Avapritinib, an oral, potent, selective inhibitor of KIT D816V, is approved in the United States regardless of prior therapy and in the European Union after ≥1 prior therapy for adults with AdvSM[10,11] based on results from the phase 1 EXPLORER (NCT02561988) and phase 2 PATHFINDER (NCT03580655) clinical studies[12,13]
- Approximately 50% of patients with AdvSM exhibit monomorphic, maculopapular skin lesions typical for mastocytosis may be associated with pruritus and adversely impact quality of life[14–16]
- We assessed the effects of avapritinib treatment on skin lesions in patients with AdvSM

Methods

- In PATHFINDER, 105 of 107 enrolled patients initiated avapritinib at a starting dose of 200 mg once daily in cycles of 28 days
- Patient-reported symptoms in skin were captured using the validated 10-item (0 = "none" and 10 = "worst imaginable") AdvSM-Symptom Assessment Form (AdvSM-SAF[17]), which assesses symptoms specific to AdvSM over a recall period of 24 hours. Overall skin domain scores (sum of individual scores for itching, flushing, and spots; range: 0–30) were generated based on average scores for each 7 days. Mean change in AdvSM-SAF score was assessed using one-sided t-tests
- Overall response rate (ORR) was assessed per the Modified International Working Group-Myeloproliferative Neoplasm Research and Treatment-European Competence Network on Mastocytosis (mIWG-MRT-ECNM)[18] criteria by central adjudication
- The objective disease burden was evaluated by: 1) bone marrow mast cell (BM MC) percentage using standard histopathologic evaluation of formalin-fixed, paraffin-embedded bone marrow biopsies; 2) serum tryptase level measurements were performed by ImmunoCAP™ Tryptase kit (ThermoFisher Scientific); 3) *KIT* D816V VAF by droplet digital polymerase chain reaction assay (limit of detection = 0.02%; and 4) spleen volume as evaluated locally by standard MRI imaging
- Changes in skin findings over time were evaluated by standardized photography and analysis of images by artificial intelligence (AI)[19]
  - Skin images of 4 views (front torso, back torso, front thigh, and back thigh) were captured by photography at 5 timepoints: Screening, Week 8, Week 24, Week 40, and Week 64
  - Four computer vision AI algorithms were developed at Canfield Scientific, creating target area of interest (AOI) metrics: area of the AOI, area of detected mastocytosis skin lesions, percent of AOI with detected mastocytosis skin lesions (fractional area), and detected lesion count
  - A Skin Assessment Committee composed of 4 independent dermatologists evaluated images for the appropriate computer algorithms in a blinded setting

Results

- Of 107 patients enrolled in PATHFINDER as of the September 2022 data cut, 34 (32% of patients; median [range] age: 67 [37–85] years; 71% male), including 18 with SM-AHN, 10 with MCL, and 6 with ASM, had baseline and ≥1 evaluable post-baseline skin assessments (**Table 1**)

Table 1. Baseline characteristics of patients with skin assessments and all patients from the PATHFINDER study

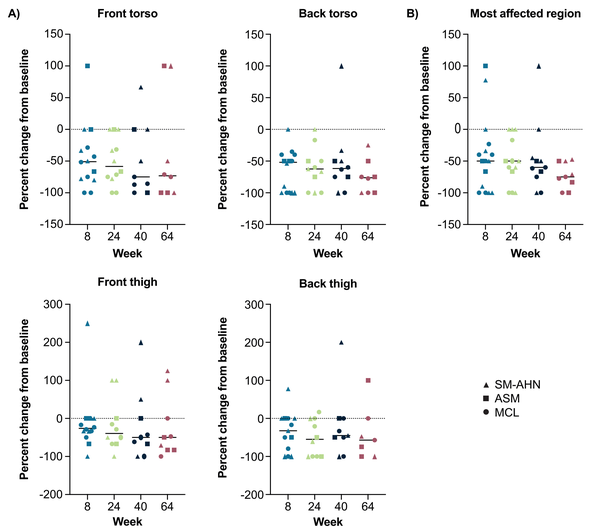
Baseline characteristics	Patients with skin assessments (n=34)	All patients (N=107)
Median age, years (range)	67 (37–85)	68 (31–88)
Female, n (%)	10 (29)	45 (42)
Ethnicity, n (%)		
White	29 (85)	91 (85)
Other	5 (15)	16 (15)
ECOG PS, n (%)		
0–1	23 (68)	79 (74)
2–3	11 (32)	28 (26)
AdvSM subtype, n (%)		
ASM	6 (18)	21 (20)
SM-AHN	18 (53)	71 (66)
MCL	10 (29)	15 (14)
Prior therapy, n (%)	22 (65)	42 (39)
Midostaurin	18 (82)	58 (54)
Cladribine	5 (23)	12 (11)
Interferon	3 (14)	10 (9)
***KIT* D816V mutation status by central ddPCR, n (%)**	32 (94)	103 (96)
Median *KIT* D816V variant allele fraction, % (range)	25 (0–44)	16 (0–47)
***SRSF2/ASXL1/RUNX1* mutation as per central assay, n (%)**	11 (32)	48 (45)
Median bone marrow biopsy mast cell burden, % (range)	70 (10–95)	40 (1–95)
Median serum tryptase level, ng/mL (range)	334 (77–1600)	262 (24–1600)
Median spleen volume, mL (range)	896 (231–2897)	839 (44–2897)

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; ddPCR, droplet digital polymerase chain reaction; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

Results

- There were 16 patients with available analyses at Week 8, 13 patients at Week 24, 11 patients at Week 40, and 9 patients at Week 64, for skin image evaluation by the AI algorithms; color assessments were completed in 15, 11, 10, and 9 patients at those time points
- Median reduction from baseline at Week 64 in fractional area affected by skin lesions for the front torso, back torso, front thigh, and back thigh was 73%, 76%, 50%, and 57%, respectively (**Figures 1** and **2** [**case example**])
  - Median reduction at Week 64 in the most affected area was 75%. Reductions were rapid and durable; improvements in the most affected area reached 50% at Week 8 and were maintained through Week 64
- Change in skin lesion color of the front torso (8/9), back torso (9/9), front thigh (6/8), and back thigh (4/7) by Week 64 was adjudicated to be "lighter" or "a lot lighter" (**Figures 3** and **2** [**case example**])
- The most affected body part was adjudicated as "lighter" or "a lot lighter" in 13 of 15 (87%) patients by Week 8 and sustained in 8 of 9 (89%) patients thereafter until Week 64

Figure 1. Reduction of skin lesion area by AOI from baseline to Week 64 (A), and reduction of skin lesion area in the most affected area from baseline to Week 64 (B).



AOI, area of interest.

- Mean (standard deviation; number of patients) AdvSM-SAF skin domain score at baseline was 9.6 (6.8; 31) and significantly decreased to 4.8 (3.7; 32) at Week 8, 4.7 (3.4; 31) at Week 24, 4.0 (2.9; 34) at Week 40, and 3.4 (2.9; 32) at Week 64 (all P<0.001) (**Figure 4**)
- Of the 34 patients with skin assessments, 30 patients were response-evaluable with ORR (95% confidence interval) of 73% (54–88)
- In this skin assessment patient population and as of the data cut (~2 years of treatment), a majority of patients experienced reductions in objective disease burden (**Table 2**)
  - Normalization of objective disease burden measures, including total clearance of bone marrow mast cells aggregates in the bone marrow, undetectable *KIT* D816V VAF, and serum tryptase <20 ng/mL was reported in 62%, 29%, and 50% of patients, respectively

Figure 3. Improvements in skin lesion color by AOI from baseline to Week 64 (A), and improvement of skin lesion color in most affected area (B).

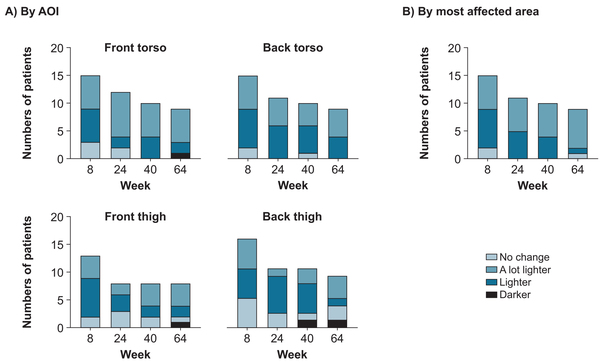
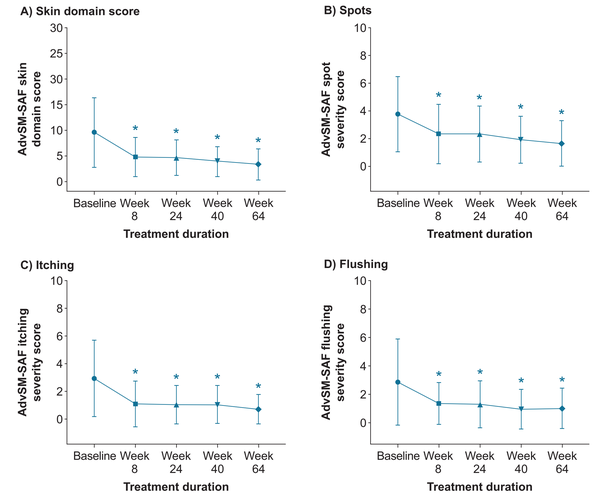


Table 2. Percentage of patients achieving reductions of objective measures of disease burden at 2 years of follow-up

	Patients with skin assessments (n=34)	All patients (N=107)
≥50% reduction in serum tryptase, n (%)	28 (82)	98 (92)
≥50% reduction in *KIT* D816V VAF, n (%)	24 (71)	87 (82)
≥50% reduction in bone marrow mast cell burden, n (%)	28 (82)	92 (88)[a]
≥35% reduction in spleen volume, n (%)	21 (62)	73 (70)[a]

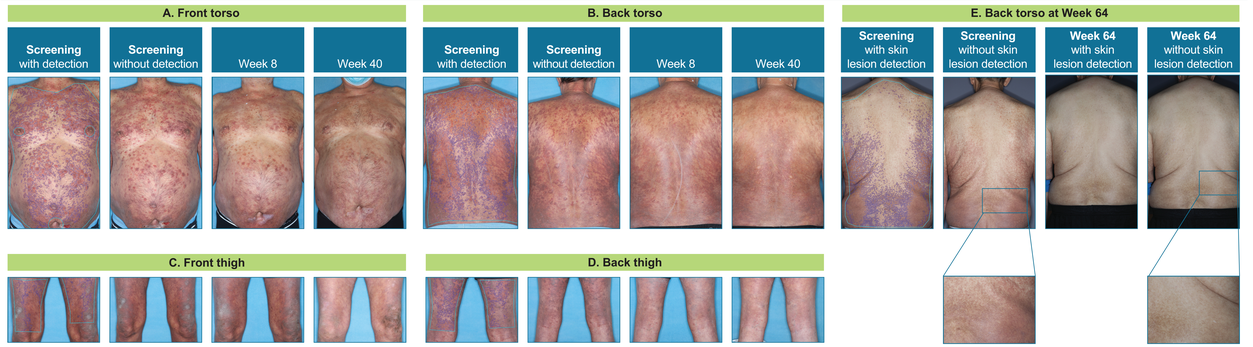
[a]N=105.
VAF, variant allele fraction.

Figure 4. Reduction in AdvSM-SAF skin domain (A), spots (B), itching (C), and flushing (D) severity scores



The skin domain score of the AdvSM-SAF consists of itching, flushing, and spot individual symptom scores. *P<0.05.
AdvSM-SAF, AdvSM-Symptom Assessment Form.

Figure 2. Reductions of skin lesion area and improvement in color in the front (A) and back (B) torso, and front (C) and back (D) thighs maintained through Week 40, and back torso (E) maintained through Week 64



Conclusions

- Avapritinib treatment resulted in rapid reductions in affected skin lesion area and improvement in skin lesion color in the majority of patients analyzed
- Skin assessment was based on a novel AI method which is a new and unique technique for qualitative and quantitative evaluation of disease-specific skin lesions including objective evaluation of responses to treatment
- Avapritinib treatment also significantly decreased mean AdvSM overall skin domain severity score from baseline through Week 64
- Furthermore, this group of patients experienced rapid and durable improvements in objective disease burden measures, as also described earlier for patients treated with avapritinib,[13] such as serum tryptase, *KIT* D816V VAF, and BM MC burden and response to treatment by mIWG-MRT-ECNM criteria
- Novel, objective analyses by AI of changes in skin lesions over time, combined with patient-reported symptom data, reinforce the durable and clinically meaningful impact of avapritinib on the cutaneous manifestations of AdvSM

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Acknowledgements

Writing and editorial support under the direction of the authors was provided Frank Golder, BVSc, PhD, CMPP, and Travis Taylor, BA, both of Prime (Knutsford, United Kingdom). Writing and editorial support provided by Prime was funded by Blueprint Medicines Corporation.

Conflicts of interest/disclosures

Dr Radia has been a clinical advisory board/study steering group member (EXPLORER/PATHFINDER) for Blueprint Medicines Corporation, a study steering committee member for Cogent Biosciences, and involved in educational events and advisory boards for Novartis. She has also received author fees for Medscape cases. For all author disclosures, please contact medinfo@blueprintmedicines.com.

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Presented at the 67th American Society of Hematology Annual Meeting & Exposition, December 6–9, 2025, Orlando, FL, USA.