Changes in mast cell numbers and phenotype in patients with indolent systemic mastocytosis treated with avapritinib

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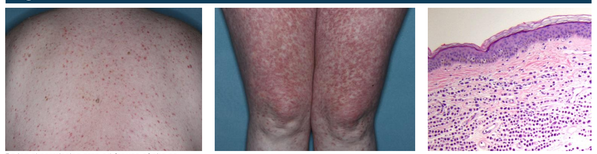
Background

- Systemic mastocytosis (SM) is a mast cell (MC) neoplasm driven by the *KIT* D816V mutation in approximately 95% of cases. The *KIT* D816V mutation is the underlying driver of MC hyperactivation and accumulation throughout various organs, leading to debilitating skin, gastrointestinal, neurocognitive, and systemic symptoms[1,2]
- In indolent systemic mastocytosis (ISM), a variant of non-advanced SM, cutaneous involvement is frequent and is associated with pruritus, flushing, and pigmented skin lesions (**Figure 1**) which can severely impact quality of life[1,2]
- Diagnosis of SM includes abnormal surface expression of CD25 with or without CD2 on neoplastic bone marrow (BM) MCs per minor WHO criterion;[3] detection of the *KIT* D816V mutation in peripheral blood or BM with a highly sensitive assay is recommended[4–7]
- Increased expression of the CD30 tumor necrosis factor receptor family antigen has also been observed in BM MCs[8] and in skin lesions of patients with ISM[9]
- No approved therapies effectively reduce the burden of disease in ISM, including skin lesions[2,3] and there are limited data regarding the immunophenotype of MCs in the skin of patients with ISM[10]
- A highly potent and selective investigational inhibitor of KIT D816V, avapritinib, has been shown to improve skin lesions in patients with ISM as compared with placebo in data from the PIONEER study[11]
- Here, we describe the effect of avapritinib on the number and immunophenotype of MCs in BM and skin biopsies from lesional tissue (LT) and non-lesional tissue (NLT) in 39 patients with ISM from Part 1 (dose escalation) of the placebo-controlled phase 2 PIONEER (NCT03731260) study

Figure 1: Cutaneous involvement in ISM



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Methods

Biopsy preparation

- A Wright stain was performed on air-dried, unstained BM aspirate smears obtained at Screening
- BM core biopsies were fixed in 10% neutral buffered formalin, transported in 70% ethanol, and decalcified in ethylenediaminetetraacetic acid before standard processing
- Skin biopsies from LT and NLT were obtained at Screening and end of Week 12. Skin biopsies were fixed in 10% neutral buffered formalin, transported in 70% ethanol, and underwent standard processing

Immunohistochemistry (IHC)

- IHC was performed on formalin-fixed sections using the Ventana Benchmark assay or the Leica Bond III autostainer with the following antibodies: CD3 (Clone LN10, skin only), CD25 (Clone 4C9), CD30 (Clone Ber-H2), CD34 (Clone QBend/10), CD117 (Clone EP10), and tryptase (Clone AA1)

Examination of BM samples and skin biopsies

- Examination of BM samples was performed by a hematopathologist; enumeration of MCs on BM aspirate smears was based on total nucleated cells
- Enumeration of MCs on biopsy sections was estimated by immunohistochemical stains and based on total BM cellularity; percentage of cells staining for CD25, CD30, CD117, and tryptase were calculated based on total number of MCs
- Examination of skin biopsies was performed by 3 pathologists; MCs were identified by immunohistochemical stains and counted per mm^2
- Based on data cut-off date of December 4, 2020

Results

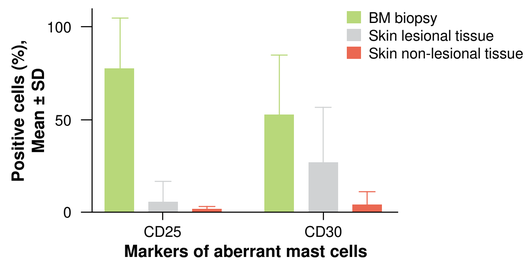
- Screening BM biopsies had a mean (standard deviation [SD]) of 15.7% (15.5%) MCs, of which 74.2% (23.6%) were spindled
- BM aspirates had a mean (SD) of 2.8% (3.1%) MCs, of which 4.3% (1.7%) were immature
- Mean (SD) number of MCs/mm^2 was 639.5 (854.2) in skin LT and 115.9 (87.9) in skin NLT
- BM biopsies had higher mean rates of CD25+ and CD30+ MCs (77.6% CD25+/52.8% CD30+) compared with skin LT (5.9% CD25+/26.9% CD30+) and NLT (1.8% CD25+/4.3% CD30+)

Table 1: Patient demographics and clinical characteristics

Patient demographics		All doses (n=39)	
Age (years), median (range)		51 (21–75)	
Female, n (%)		30 (77)	
ECOG PS, n (%)			
0		12 (31)	
1		19 (49)	
2		8 (21)	
MC burden		**All doses (n=39)**	
Central diagnosis of ISM, n (%)		39 (100)	
Tryptase (central) ng/mL, mean (SD)		84 (101)	
<11.4 ng/mL, n (%)		3 (8)	
11.4–20 ng/mL, n (%)		6 (15)	
>20 ng/mL, n (%)		30 (77)	
***KIT* D816V mutation**	**Local[a]**	**Central NGS[b]**	**Central ddPCR[c]**
Detected, n (%)	31 (80)	11 (28)	37 (95)
Median VAF, % (range)	–	11 (1.9–32)	0.36 (0.02–30.22)
SM therapy		**All doses (n=39)**	
Prior cytoreductive therapy, n (%)		6 (15)	
Midostaurin, imatinib, dasatinib, masitinib		5 (13)	
Interferon-alfa		1 (3)	
Baseline supportive care medications, median (range)		4 (2–9)	
H1 blockers, n (%)		37 (95)	
H2 blockers, n (%)		30 (77)	
Leukotriene receptor antagonists, n (%)		23 (59)	
Proton pump inhibitors, n (%)		18 (46)	
Cromolyn sodium, n (%)		12 (31)	
Corticosteroids, n (%)		6 (15)	
Omalizumab, n (%)		9 (23)	
Patient disposition		**All doses (n=39)**	
Weeks on study, median (range)		18 (1–36)	
Still on study, n (%)		37 (95)	
Discontinued study, n (%)		2 (5)	
Patient decision, n		1	
Protocol non-compliance, n		1	

Based on data cut-off date of December 27, 2019. [a]Local quantitative and qualitative *KIT* testing of BM, various methods and sensitivities. [b]NGS targeted myeloid panel (central) in BM samples at Screening, algorithmic calling sensitivity to 1.0% VAF. [c]ddPCR in blood (central), sensitivity to 0.02% VAF; detected: positive at Screening or C1D1; median VAF and range at C1D1 in those with any detection.
BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; C1D1, Cycle 1 Day 1; ddPCR, digital droplet polymerase chain reaction; ISM, indolent systemic mastocytosis; MC, mast cell; NGS, next generation sequencing; SD, standard deviation; VAF, variant allele fraction.

Figure 2: Bone marrow biopsies had higher rates of CD25+ and CD30+ mast cells than skin lesional tissue and non-lesional tissue



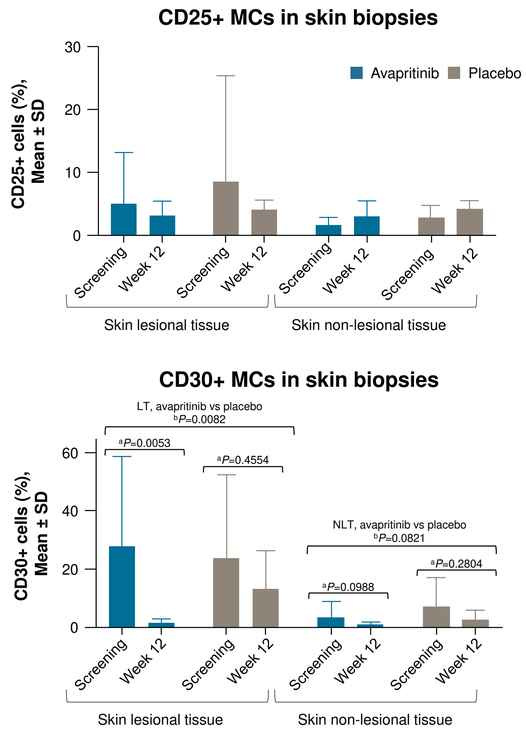
- In contrast to BM MCs, the proportion of CD30+ MCs in skin LT at Screening exceeded that of CD25+ MCs

Table 2: Avapritinib reduced mast cell burden in skin lesional tissue biopsies by Week 12

	Skin lesional tissue				Skin non-lesional tissue			
	Avapritinib		Placebo		Avapritinib		Placebo	
	Scr (n=25)	W12 (n=17)	Scr (n=8)	W12 (n=7)	Scr (n=25)	W12 (n=21)	Scr (n=8)	W12 (n=7)
MCs/mm^2, mean (SD)	702.8 (961.0)	233.9 (216.5)	441.8 (331.8)	547.7 (477.7)	115.2 (98.3)	103.5 (42.3)	118.4 (47.2)	177.1 (75.7)

Scr, Screening; W12, Week 12.

Figure 3: Avapritinib reduced CD25+ and CD30+ mast cells in skin lesional tissue by Week 12

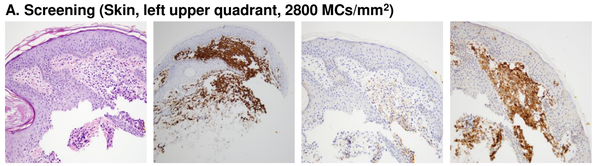


[a]Paired sample *t*-test. [b]Fisher's exact test.

- At Week 12, avapritinib produced significant reductions in the proportion of CD30+ MCs in skin LT compared with placebo (P=0.0082) and non-significant reductions in CD30+ MCs in skin NLT (P=0.0821)

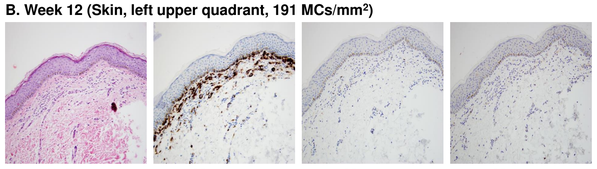
Figure 4: Avapritinib reduced CD25+ and CD30+ mast cells at Week 12 (B) compared with Screening (A) in skin lesional tissue biopsy stains

A. Screening (Skin, left upper quadrant, 2800 MCs/mm^2)



H&E, 25× | CD117, 12.5× 100% positive | CD25, 25× 10% positive | CD30, 25× 90% positive

B. Week 12 (Skin, left upper quadrant, 191 MCs/mm^2)



H&E, 20× | CD117, 20× 100% positive Note perivascular pattern | CD25, 20× 2% positive | CD30, 20× 1% positive

H&E, hematoxylin and eosin.

- Avapritinib markedly decreased the total number of MCs and the CD25+ and CD30+ MC fraction in skin LT by Week 12 of treatment

Conclusions

- We previously showed that avapritinib could reduce signs, symptoms, and MC burden in patients with ISM[11]
- Our data confirm the results of previous studies showing that aberrant MCs are present in skin in both LT and NLT
- The MC immunophenotype in skin LT differs from that of aberrant BM MCs, with a greater percentage of BM MCs expressing CD30 and CD25
- Avapritinib significantly reduced total MC burden as well as abnormal CD30+ MCs in skin lesions from patients with ISM
- CD30 may be a superior biomarker of aberrant MCs in skin in patients with ISM compared with CD25

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Disclosures

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