RESPONSES TO AVAPRITINIB IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS: HISTOPATHOLOGIC ANALYSES FROM THE EXPLORER AND PATHFINDER CLINICAL STUDIES

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Disclosure

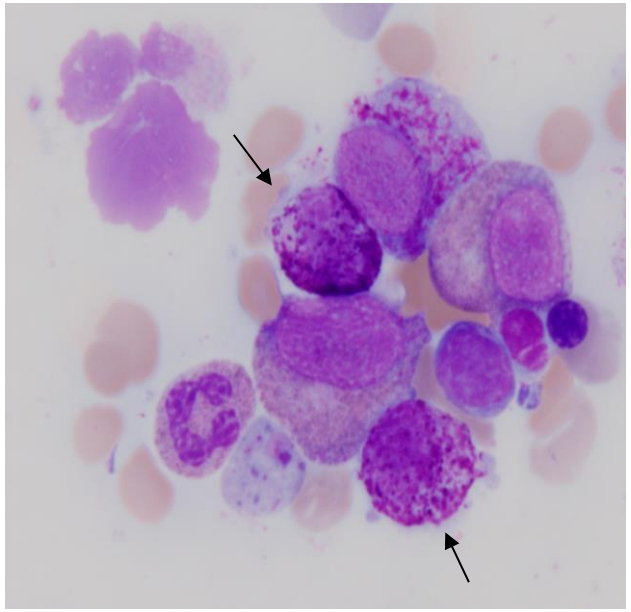
Conflict of Interest

- Dr George has received consulting fees and is a study steering committee member for Blueprint Medicines Corporation, BMS/Celgene, Cogent Biosciences, and Incyte

Background

- Systemic mastocytosis (SM) is a hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases[1–4]
- In advanced SM (AdvSM), the *KIT* mutation is associated with neoplastic mast cell (MC) proliferation and accumulation which can cause life-threatening organ damage and debilitating symptoms[5–7]
- Patients with AdvSM have historically had a poor prognosis[4,8]
- Avapritinib is a potent, oral, selective *KIT* D816V inhibitor approved in the USA and Europe for adults with AdvSM based on phase 1 open-label, single-arm EXPLORER (NCT02561988) study and the interim phase 2 open-label, single-arm PATHFINDER (NCT03580655) study. Avapritinib is not recommended for patients with platelet counts <50x10^9/L[9,10]

Immature MCs (arrows)



AdvSM, advanced systemic mastocytosis; MC, mast cell; SM, systemic mastocytosis.

1. Cohen S et al. *Br J Haematol.* 2014;166:521–528; 2. Ungerstedt J et al. *Cancers (Basel).* 2022;14:3942; 3. Kristensen T et al. *Am J Hematol.* 2014;89:493–498; 4. Pardanani A. *Am J Hematol.* 2023;98:1097–1116; 5. Rossignol J et al. *F1000Research.* 2019;8:1961; 6. Mesa RA et al. *Cancer.* 2022;128:3691–3699; 7. Jennings S et al. *J Allergy Clin Immunol Pract.* 2014;2:70–76; 8. Valent P et al. *Blood.* 2017;129:1420–1427; 9. Ayvakyt (avapritinib) Summary of Product Characteristics. Cambridge, MA; Blueprint Medicines Corporation; 2023; 10. Ayvakit (avapritinib) Prescribing Information. Cambridge, MA: Blueprint Medicines Corporation; 2023

EXPLORER and PATHFINDER trials

- In long-term analyses of almost 4 years in the EXPLORER study,[1] and 3 years of follow-up in the PATHFINDER study,[2] patients treated with avapritinib achieved sustained high response rates, marked reductions in objective measures of disease burden (serum tryptase level, *KIT* D816V variant allele fraction, and BM MC), and a favorable benefit-risk profile
- In addition to high response rates, avapritinib treatment was associated with normalization of bone marrow histopathologic and hematologic parameters[3]
- Here we present an extended analysis of BM MC burden, morphology, immunophenotype, BM fibrosis, and hematology in patients with AdvSM who received avapritinib

BM, bone marrow.

1. DeAngelo DR et al. Presented at ASH 2022. Poster #1710; 2. Gotlib J et al. Presented at EHA 2024. Abstract #S224; 3. George T et al. Presented at EHA 2022. Poster #P1027

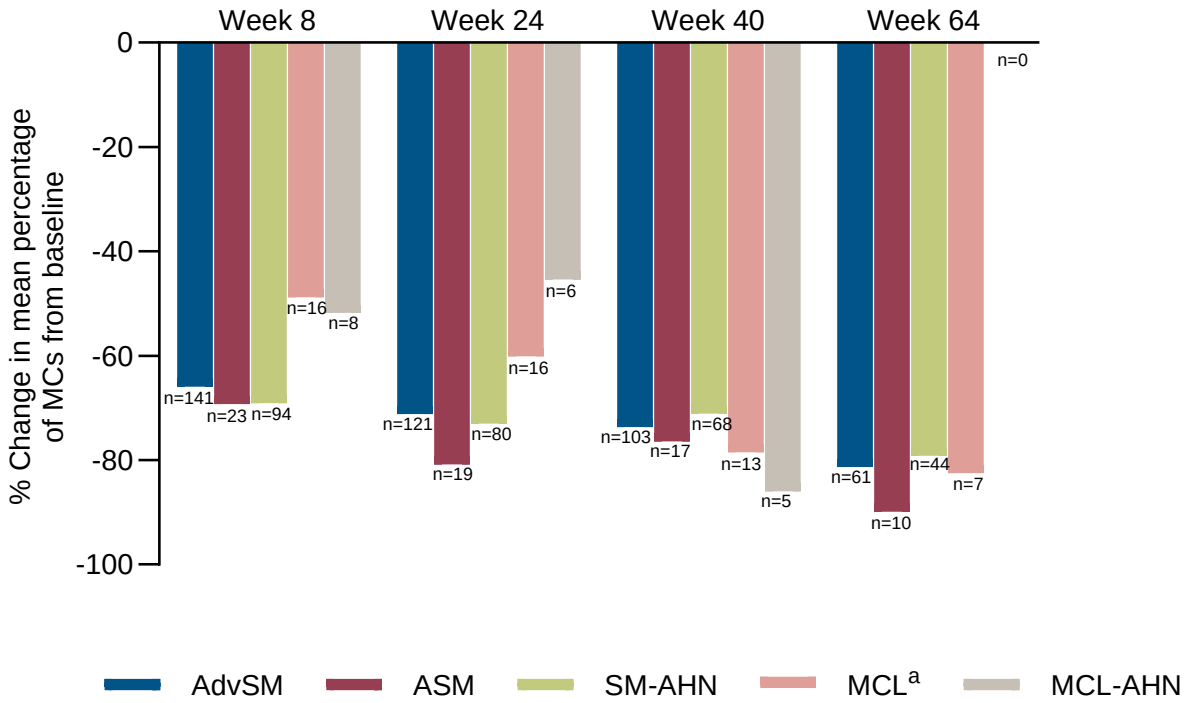
Baseline characteristics

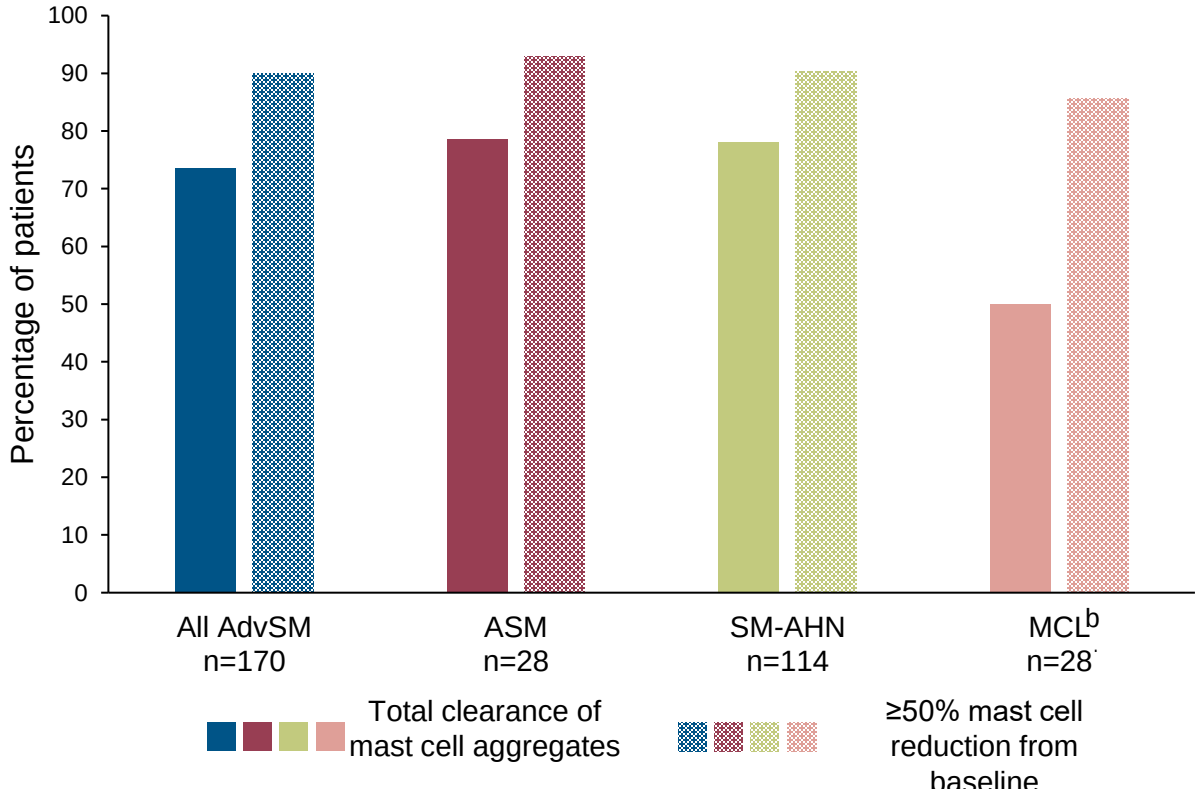
Baseline characteristics	All doses (N = 176)
Age, years, median (range)	68 (31-88)
Female, n (%)	73 (41)
ECOG PS, n (%)	
0	36 (21)
1	92 (52)
2	33 (19)
3	15 (9)
AdvSM subtype per central assessment, n (%)	
ASM	29 (16)
SM-AHN	119 (68)
MCL	19 (11)
MCL-AHN	9 (5)
***KIT* D816V VAF in blood,[a] %, median (range)**	14.8 (ND-80.1)
***KIT* exon 17 mutation positive, n (%)**	167 (95)
***SRSF2*/*ASXL1*/*RUNX1* mutation positive, n (%)**	84 (48)
Any prior anti-neoplastic therapy, n (%)	110 (63)
Midostaurin	81 (74)
Cladribine	22 (20)
BM biopsy MC burden, %, median (range)	40 (1-95)
Serum tryptase level, ng/ml, median (range)	216 (12.4-1600)
Spleen volume, ml, median (range)	875.8 (44.2-2897.1)

[a]Assessed by central D816V digital droplet PCR assay.
ASM, aggressive systemic mastocytosis; BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with an associated hematologic neoplasm; ND, not detected; PCR, polymerase chain reaction; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SSM, aggressive systemic mastocytosis; VAF, variant allele fraction.

Avapritinib reduced the mean percentage of mast cells

Mean percentage of MCs in BMBs by AdvSM subtype and change in number of patients with MC aggregates over time

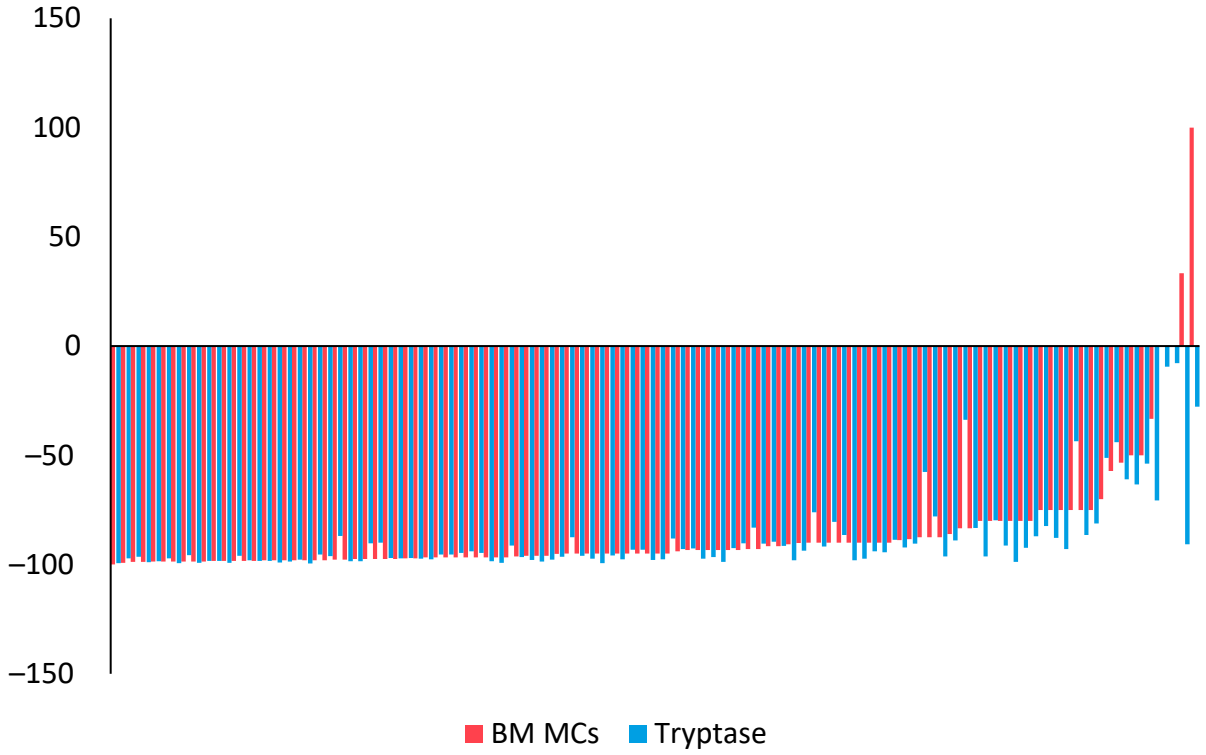




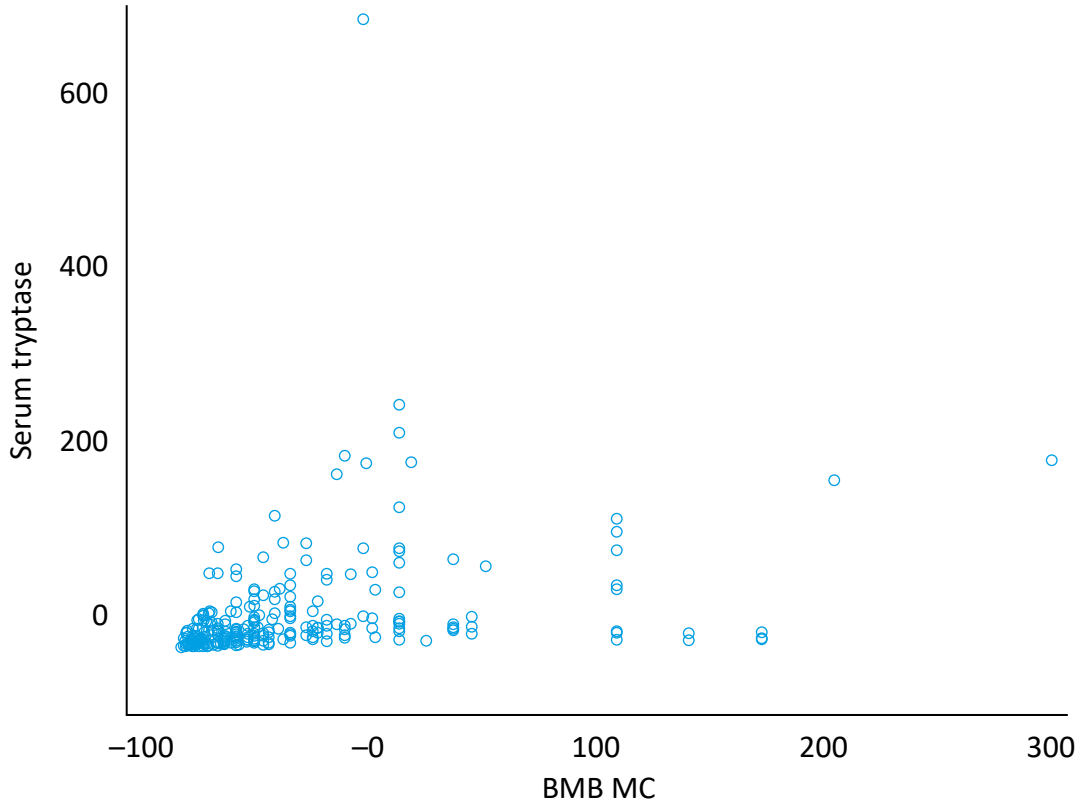
[a]Excluding patients with MCL-AHN; [b]Including patients with MCL-AHN.
BMB, bone marrow biopsy.

Mast cell percentage in BM biopsies correlated with serum tryptase in AdvSM

Percentage change in BM MCs and serum tryptase in response to avapritinib



Relative change (%) from baseline of MC percentage in BMB vs relative change (%) from baseline tryptase in PB

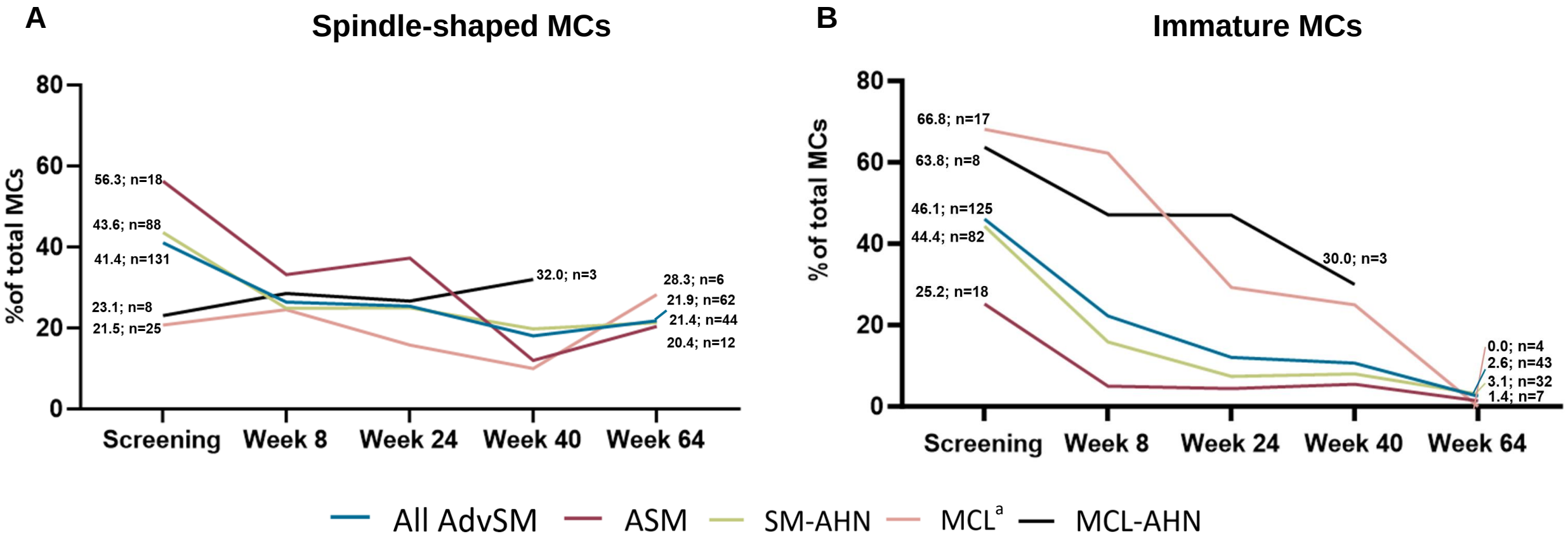


BM, bone marrow; BMB, bone marrow biopsy; MC, mast cells; PB, peripheral blood.

Spearman correlation coefficient
r=0.76
P<0.0001

Avapritinib reduced the fraction of mast cells with atypical morphology

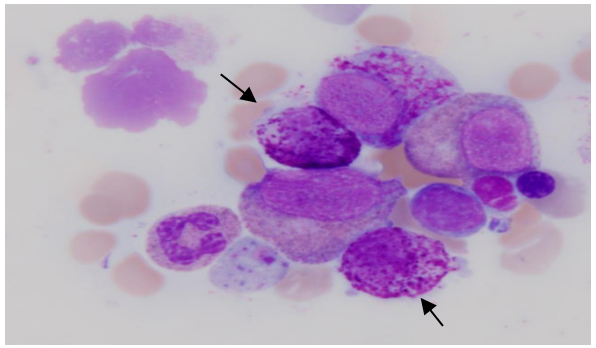
Atypical morphology (spindle-shaped [A] and immature [B] MCs) in BMAs in all subtypes of AdvSM



[a]Excluding patients with MCL-AHN.
BMA, bone marrow aspirate.

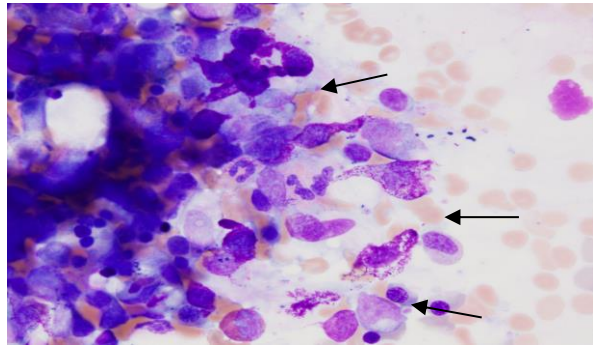
Avapritinib reduced the fraction of mast cells with atypical morphology

SM-MDS-RS, BMA smears
Immature MCs (arrows)



Screening: 11.8% MCs-aspirate

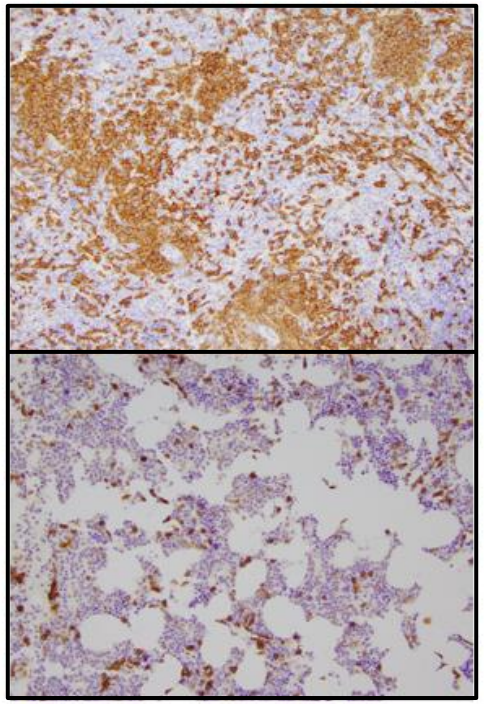
Spindle-shaped MCs (arrows)



Week 40: 3.2% MCs-aspirate

MCs in BMBs in patients with AdvSM

MC aggregates



CD117/KIT (Screening)

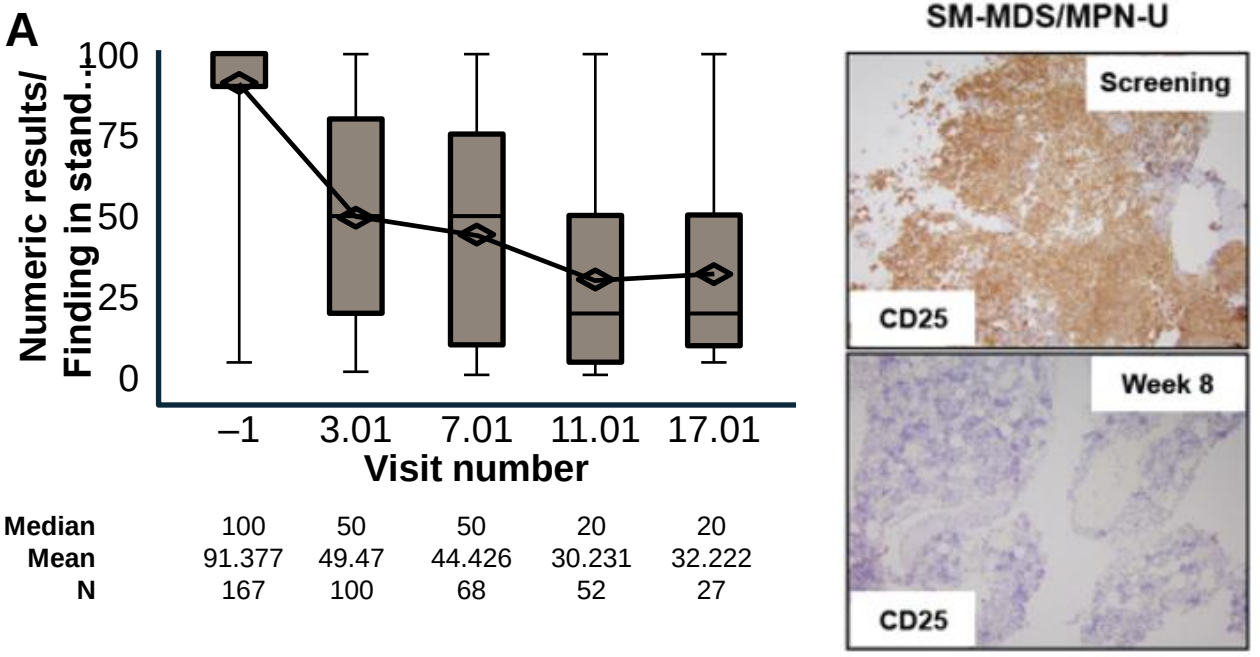
CD117/KIT (Week 64)

- CD117 expression level on MCs did not change while atypical MC number reduced by avapritinib treatment

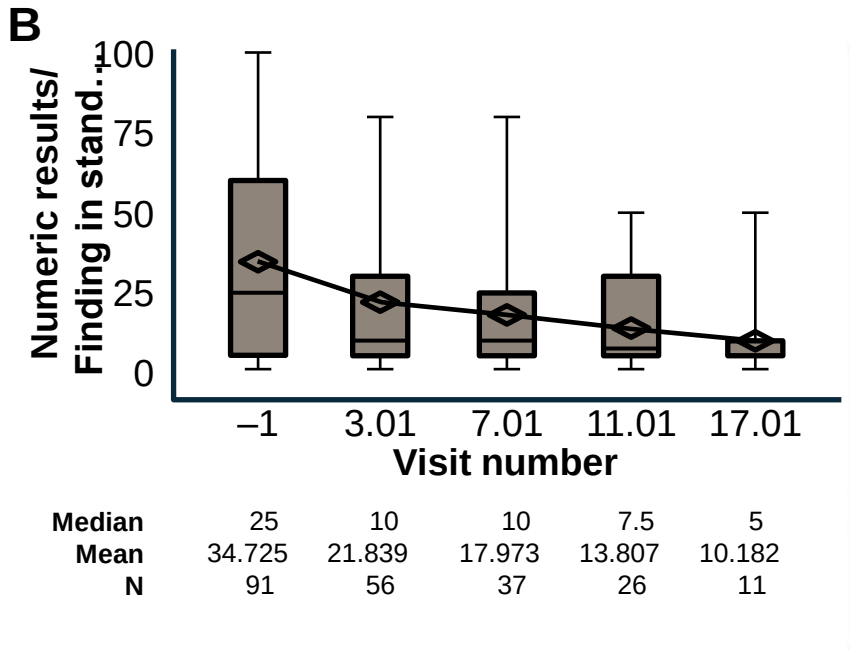
BMA, bone marrow aspirate; BMB, bone marrow biopsy; MC, mast cells SM-MDS-RS, systemic mastocytosis myelodysplastic syndrome with ring sideroblasts.

Avapritinib reduced the proportion of CD25+ and CD30+ mast cells

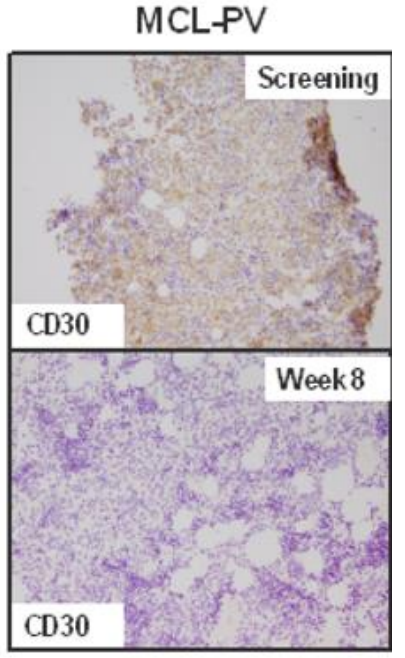
The proportion of CD25+ (A) CD30+ (B) MCs in BMBs in patients with AdvSM



	–1	3.01	7.01	11.01	17.01
Median	100	50	50	20	20
Mean	91.377	49.47	44.426	30.231	32.222
N	167	100	68	52	27



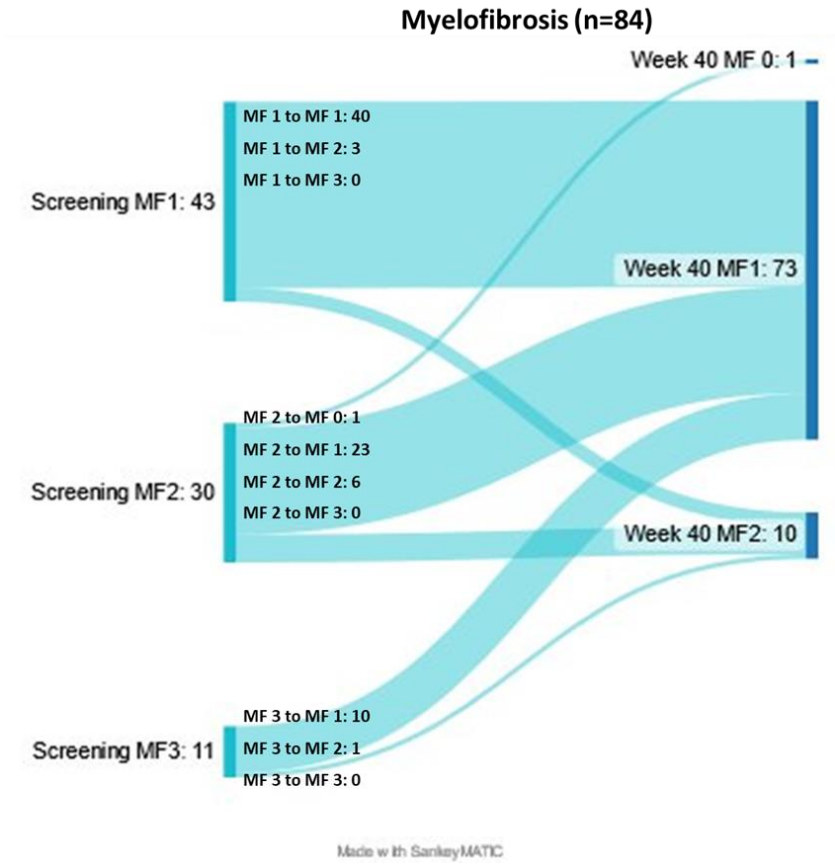
	–1	3.01	7.01	11.01	17.01
Median	25	10	10	7.5	5
Mean	34.725	21.839	17.973	13.807	10.182
N	91	56	37	26	11

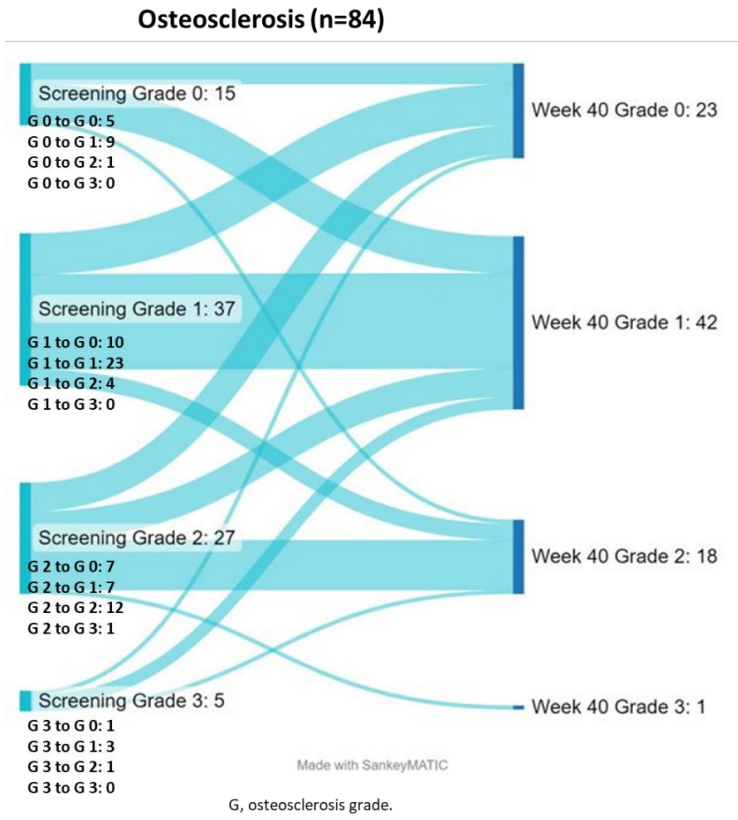


The box represents the middle (second and third quartile) of the data, the line within the box represents the median, the diamond represents the mean, and the end of the whiskers represents the maximum and minimum values.
MCL-PV, mast cell leukemia-polycythemia vera; SM-MDS/MPN-U, systemic mastocytosis with an unclassifiable myelodysplastic/myeloproliferative neoplasm.

Avapritinib reduced myelofibrosis and osteosclerosis

Myelofibrosis and osteosclerosis scores in BMBs

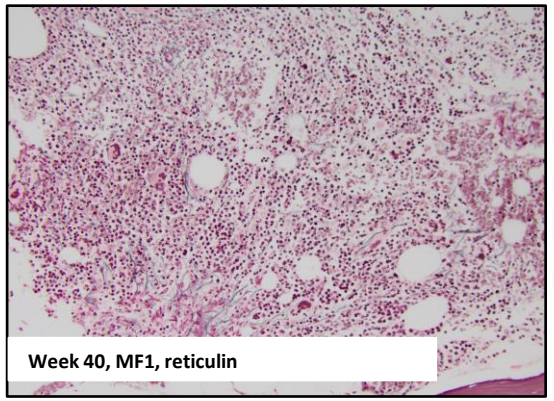




G, osteosclerosis grade.

Screening, MF2, reticulin

SM-CMML-1

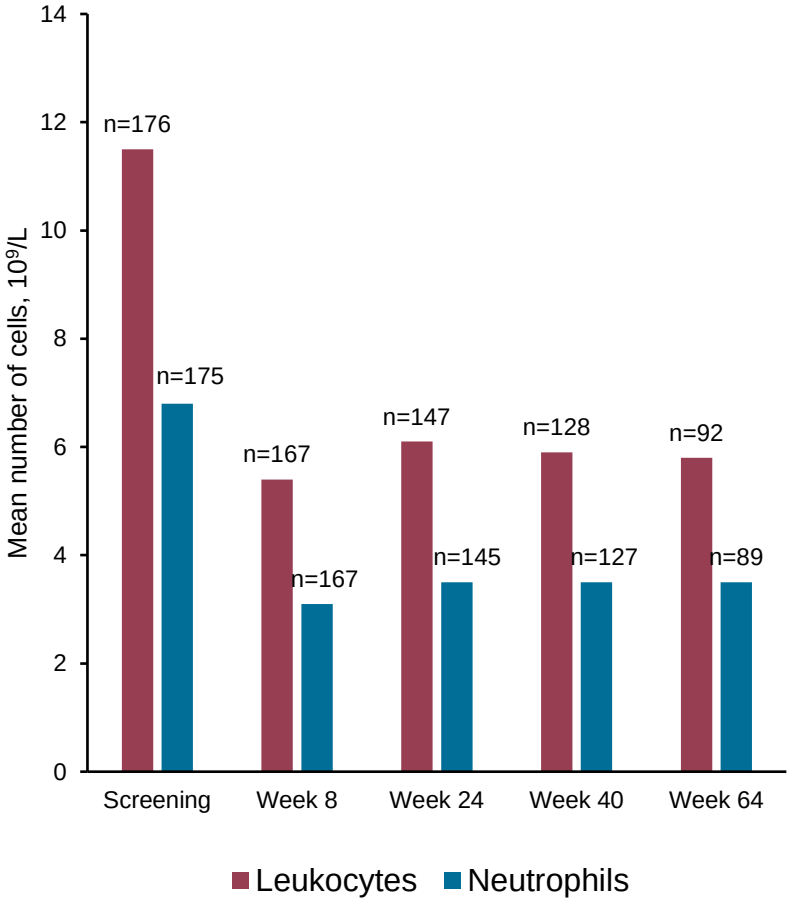


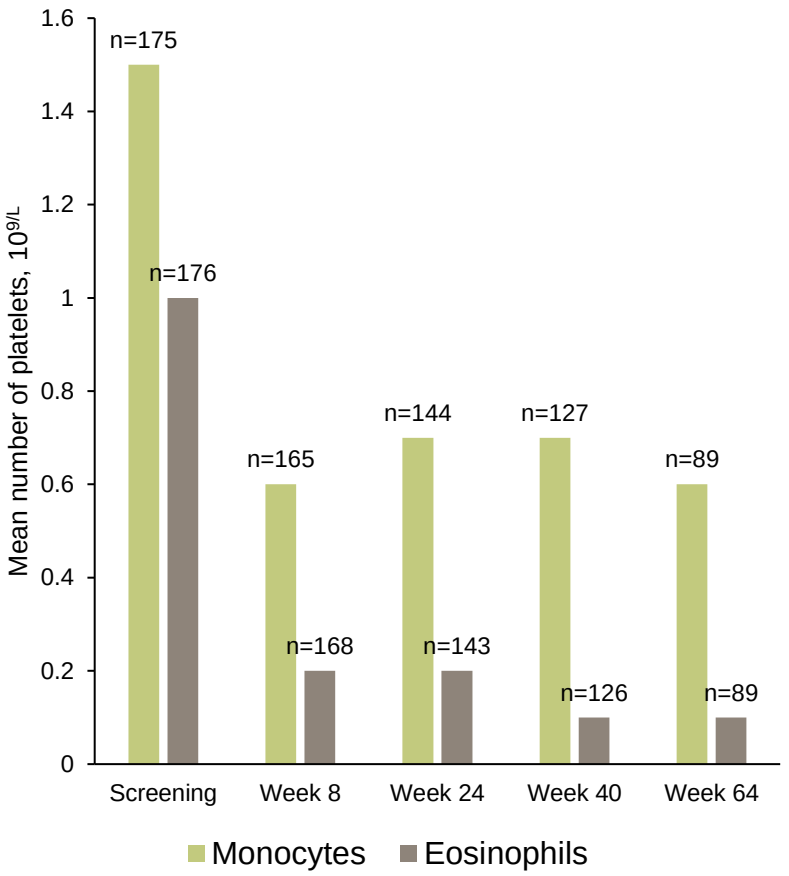
Week 40, MF1, reticulin

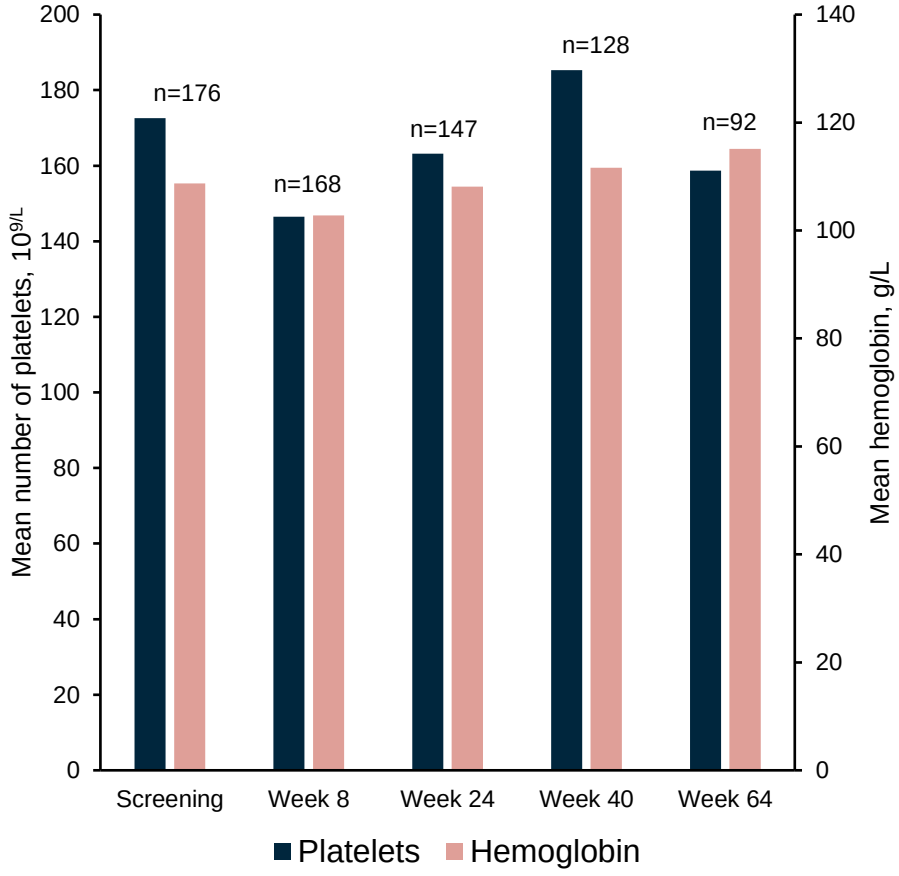
MF, myelofibrosis grade.

Hematologic parameters

Absolute values of hematological parameters over time



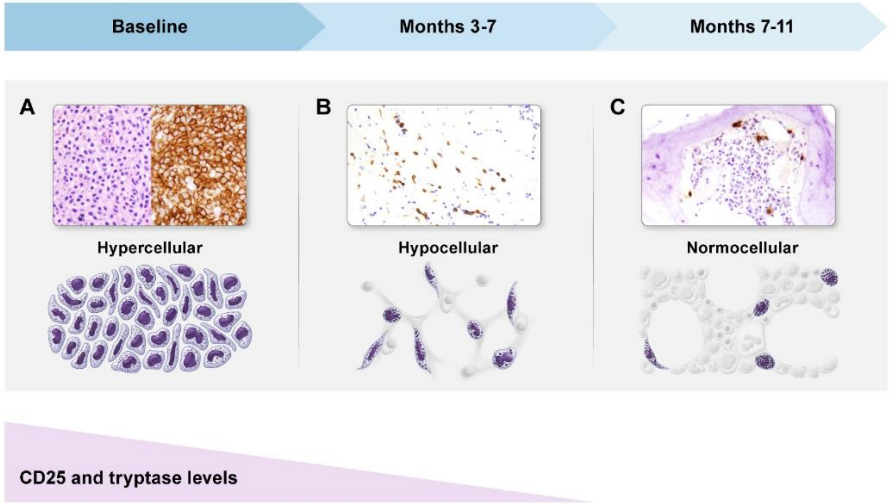




Eight out of 9 patients with peripheral blood MCs samples had no peripheral blood MCs at Week 8.

Conclusions

- In both PATHFINDER and EXPLORER, avapritinib treatment was associated with high response rates and improvements in objective disease measures and disease symptoms.[1,2] Here, we show these were accompanied by a normalization of histopathologic disease-related parameters and improvements in hematologic measures
- Avapritinib showed rapid (Week 8), marked, and sustained (Week 64) reductions in neoplastic BM MCs, return to normal MC phenotype and morphology, and decreased circulating MCs, accompanied by normalized BM cellularity and improved fibrosis
- Improvements at Week 64 in hematological parameters including reduced neutrophils, leukocytes, monocytes, eosinophils, white blood cells, and maintenance of hemoglobin and platelets were observed in response to avapritinib treatment



1. Gotlib J et al. *Nat Med.* 2021;27:2192–2199; 2. DeAngelo DJ et al. *Nat Med.* 2021;27:2183–2191