Efficacy of Avapritinib in Patients With Advanced Systemic Mastocytosis: Hematologic and Bone Marrow Responses From the Phase 2 Open-Label, Single-Arm, PATHFINDER Study

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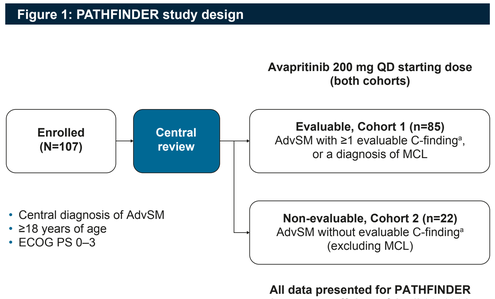
Introduction

- Systemic mastocytosis (SM) is a myeloid neoplasm driven by the *KIT* D816V mutation in ~95% of cases, resulting in mast cell (MC) hyperactivation and accumulation in various organs[1–3]
- Diagnosis of SM includes[3–7]:
  - Evaluation of MC aggregates in bone marrow (BM) and extracutaneous organs
  - Atypical MC morphology
  - Expression of CD25 with or without CD2 on MCs
  - Detection of the *KIT* D816V mutation
  - Serum tryptase level of >20 ng/ml (if no associated myeloid neoplasm is present)
- In addition, expression of CD30 is observed on neoplastic MCs in patients with SM[8]
- Patients with advanced systemic mastocytosis (AdvSM), including mast cell leukemia (MCL), SM with an associated hematologic neoplasm (SM-AHN), and aggressive SM (ASM), have traditionally had a poor prognosis[9]
- Avapritinib, a highly potent and selective KIT D816V inhibitor, is now approved by the FDA for the treatment of adults with AdvSM, and by the EMA as monotherapy for the treatment of adults with ASM, SM-AHN or MCL, after at least one systemic therapy, based on the results from the phase 1 open-label, single-arm dose escalation EXPLORER (NCT02561988) study and phase 2 open-label, single-arm PATHFINDER (NCT03580655) study[10,11]
- In EXPLORER (cut-off date May 27, 2020) and PATHFINDER (cut-off date June 23, 2020) overall response rates (ORR; defined as complete remission + complete remission with partial hematologic recovery + partial remission + clinical improvement) per modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MNRT-ECNM) criteria were 75% in both studies[12–14]
  - In both studies, improvements in BM MC burden and patient symptoms were observed[12–14]
  - Responses were observed across subtypes, including SM-AHN, the most frequent subtype[12–14]
  - In PATHFINDER, reductions ≥50% in absolute eosinophil counts were observed in 88% of patients with baseline elevated eosinophils, and reductions of ≥50% in absolute monocyte counts were observed in 80% of patients with systemic mastocytosis with associated chronic myelomonocytic leukemia as associated hematologic neoplasm (SM-AHN CMML)[13,14]
- Here we report on the effect of avapritinib on MC burden, morphology, and immunohistochemistry in BM, BM cellularity and fibrosis, as well as changes in selected hematologic parameters in patients with AdvSM enrolled in the PATHFINDER study (cut-off date of April 20, 2021)

Study design

Figure 1: PATHFINDER study design



[a]Per modified IWG-MRT-ECNM criteria, response assessment requires ≥1 evaluable C-finding at baseline. MCL without an evaluable C-finding may be assessed for response based on disease burden alone (Gotlib et al. *Blood*. 2013;21:2393–2401).
AdvSM, advanced systemic mastocytosis; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MCL, mast cell leukemia; QD, once daily.

Methods

- Peripheral blood smears, bone marrow biopsies (BMBs), bone marrow aspirates (BMAs) and complete blood counts were obtained at screening and after approximately 8, 24, and 40 weeks
- Evaluations of morphology were performed using standard Wright-Giemsa and H&E staining, while immunohistochemistry was performed on formalin-fixed EDTA-decalcified BM sections using standard techniques for tryptase, CD117, CD25, and CD30. Staining was also performed to detect reticulin and collagen fibrosis
- Changes in BM cellularity, myelofibrosis (MF) score, collagen fibrosis grade, and osteosclerosis grade were also assessed
  - Bone marrow fibrosis grading was performed using the European Consensus grading system (MF 0–3)[15]; a separate grading was conducted for collagen fibrosis and osteosclerosis (Grade 0–3)[16]

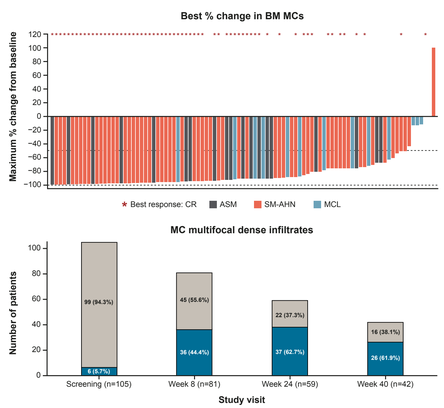
Results

Table 1. Baseline characteristics (N=107)

	All doses (N=107)
Median age, years (range)	68 (31–88)
Male, n (%)	62 (57.9)
Female, n (%)	45 (42.1)
ECOG PS n (%)	
0	22 (20.6)
1	58 (54.2)
2	19 (17.8)
AdvSM subtype per central assessment, n (%)	
ASM	21 (19.6)
SM-AHN	71 (66.4)
MCL	15 (14.0)
KIT D816V VAF positive in blood, median % (range)	15.8 (0–47.5)
KIT D816V mutation positive, n (%)	103 (96.3)
SRSF2/*ASXL1*/*RUNX1* mutation positive, n (%)	48 (44.9)
Any prior anti-neoplastic therapy, n (%)	
Midostaurin	58 (54.2)
Cladribine	12 (11.2)
BM biopsy MC burden, median % (range)	40 (1–95)
Serum tryptase level, median ng/mL (range)	262 (23.8–1600.0)
Spleen volume, median mL (range)	839.4 (44.2–2897.1)

AdvSM, advanced systemic mastocytosis; BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MC, mast cell; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematologic neoplasm, VAF, variant allele fraction.

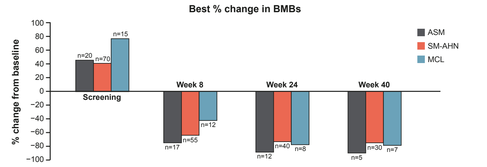
Figure 2. Reduction of BM MC burden observed in >95% of patients with avapritinib (N=107)



AdvSM, advanced systemic mastocytosis; BM, bone marrow; CR, complete remission; MC, mast cell.

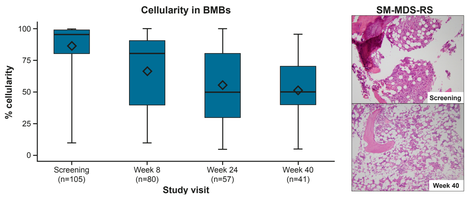
- Reductions of ≥50% from baseline in BM MCs were observed in 83.8% (88/105) of patients, and 60.0% (63/105) of patients had elimination of BM MC aggregates

Figure 3. Reduction in mean percentage of MCs in BMBs by AdvSM subtypes over time



AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BM, bone marrow; BMBs, bone marrow biopsies; MC, mast cell; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

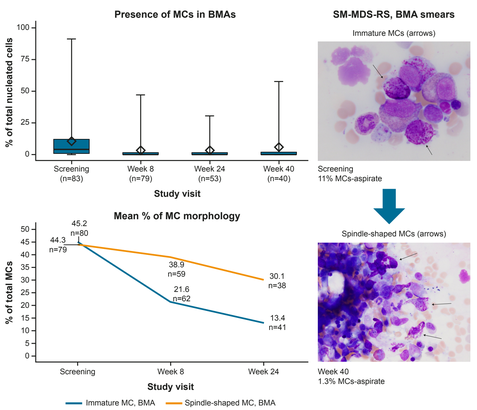
Figure 4. Cellularity in BMBs decreased with avapritinib by Weeks 8 and 24



BMBs, bone marrow biopsies; SM-MDS-RS, systemic mastocytosis-myelodysplastic syndrome-with ring sideroblasts. 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 max and min values.

- Cellularity in BMBs decreased from a mean of 85.4% at screening to 66.1% at Week 8 and 55.3% by Week 24

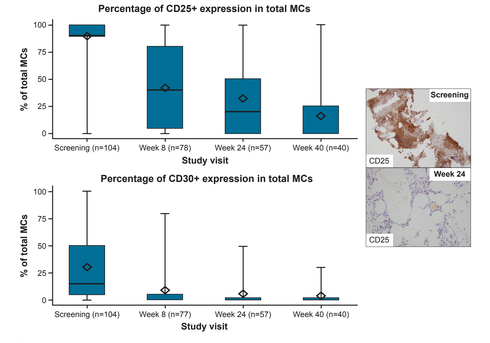
Figure 5: Avapritinib decreased MCs and atypical morphology (immature and spindle shaped MCs) in BMAs by Week 8



BMAs, bone marrow aspirates; MC, mast cell, SM-MDS-RS, systemic mastocytosis-myelodysplastic syndrome-with ring sideroblast. Data shown in box and whisker plots explained in Figure 4.

- The mean percentage of total MCs in BMAs decreased from 10.5% at screening to 2.5% by Week 8
- Of 7 patients with circulating MCs at screening and post-screening sample measurements (6 with SM-AHN diagnoses and 1 with MCL), all 7 had no detectable MCs by Week 8

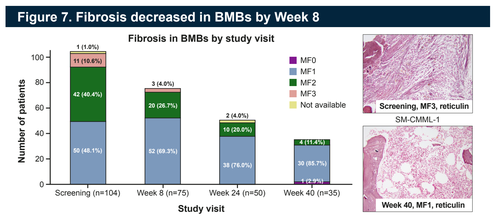
Figure 6. Reduction in the proportion of CD25+ and CD30+ MCs by Week 8



BMBs, bone marrow biopsies; MC, mast cell. Data shown in box and whisker plots explained in Figure 4.

- The proportion of CD25+ in BMBs decreased from a mean of 90.0% at screening to 41.5% by Week 8 and 32.3% by Week 24
- The proportion of CD30+ in BMBs decreased from a mean of 30.6% at screening to 8.6% by Week 8

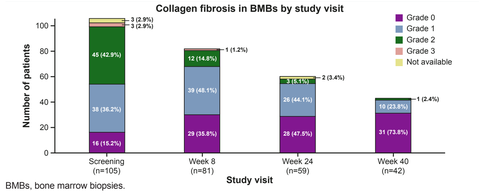
Figure 7. Fibrosis decreased in BMBs by Week 8



BMBs, bone marrow biopsies; MF, myelofibrosis; SM-CMML, systemic mastocytosis-chronic myelomonocytic leukemia.

- Fibrosis was present in BMBs in 99.0% (103/104) of patients at screening, 92.6% (75/81) of patients at Week 8, and in 82.8% (48/58) of patients at Week 24
- Fibrosis was reduced during avapritinib treatment in those patients presenting with increased fibrosis at screening

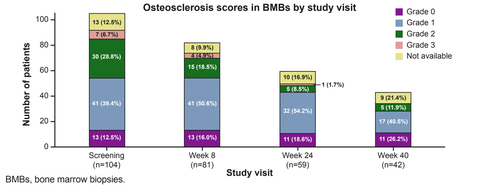
Figure 8. Collagen fibrosis in BMBs decreased by Week 8 and 24



BMBs, bone marrow biopsies.

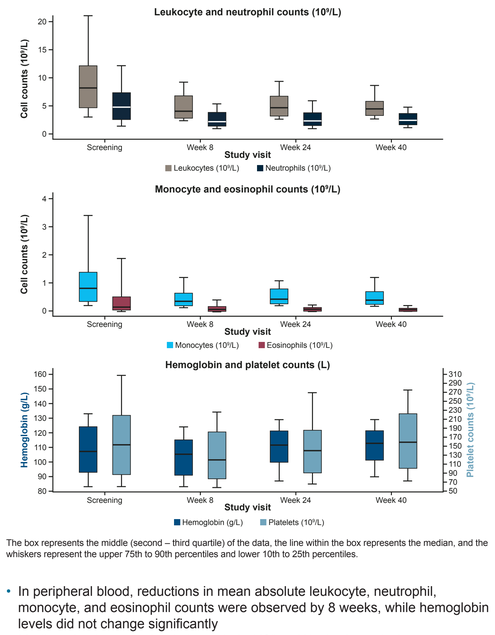
- Collagen fibrosis was reduced during avapritinib treatment in those patients presenting with increased fibrosis at screening

Figure 9. No significant changes in osteosclerosis scores were observed



BMBs, bone marrow biopsies.

Figure 10. Changes in selected hematologic parameters in peripheral blood at screening, Weeks 8 and 24 (N=107)



The box represents the middle (second – third quartile) of the data, the line within the box represents the median, and the whiskers represent the upper 75th to 90th percentiles and lower 10th to 25th percentiles.

- In peripheral blood, reductions in mean absolute leukocyte, neutrophil, monocyte, and eosinophil counts were observed by 8 weeks, while hemoglobin levels did not change significantly
- Median platelets remained above 140x10⁹/L at Weeks 24 and 40

Discussion

- The current findings, along with the previously reported high response rate with avapritinib,[12–14] support the clinical efficacy and provide proof of mechanistic concept for this highly selective and potent KIT D816V inhibitor
- High response rate was accompanied by a normalization of BM cellularity, as well as a decrease in fibrosis and marked improvement in hematologic parameters
- Avapritinib demonstrated rapid (Week 8) and sustained (Week 24) reductions in neoplastic MC burden characterized by a reduction of the total MC burden in BMBs and BMAs with return to a normal morphologic appearance and normal immunophenotype
- These improvements in disease histopathology, along with known deep molecular remission of *KIT* D816V, support the ability of avapritinib to improve AdvSM disease natural history

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