Responses to Avapritinib in Patients With Advanced Systemic Mastocytosis: Histopathologic Analyses From EXPLORER and PATHFINDER Clinical Studies

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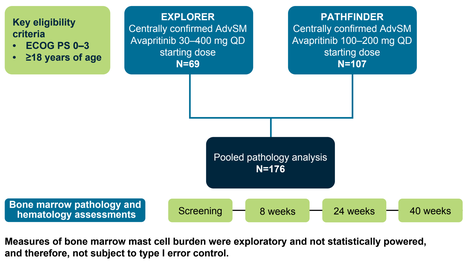
Introduction

- Systemic mastocytosis (SM) is a mast cell (MC) neoplasm driven by *KIT* D816V mutation in ~95% of cases, characterized by the accumulation of neoplastic MC in various organs[1,2]
- Advanced systemic mastocytosis (AdvSM) includes three subtypes: mast cell leukemia (MCL), SM with an associated hematologic neoplasm (SM-AHN), and aggressive SM (ASM), and all subtypes typically have a poor prognosis[3]
- Diagnosis of SM includes[4–8]:
  - Evaluation of MC aggregates in bone marrow 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[9]
- Avapritinib, is an oral, highly potent, and selective inhibitor of *KIT* D816V approved in the United States for the treatment of adults with AdvSM and in Europe as a monotherapy for the treatment of adult patients with ASM, SM-AHN, or MCL, after at least one systemic therapy
- Approvals were based on efficacy and safety outcomes 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 both EXPLORER (cut-off date May 27, 2020) and PATHFINDER (cut-off date June 23, 2020), avapritinib demonstrated a 75% overall response rate (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[12–14]
  - Improvements in bone marrow (BM) MC burden, and patient symptoms were recorded in both studies[12–14]
  - Responses were observed across the three subtypes of AdvSM including SM-AHN, the most frequent and most heterogenous subtype[12–14]
  - In PATHFINDER, reductions ≥50% in absolute eosinophil counts were observed in 88% (14/16) of patients with baseline elevated eosinophils, and reductions of ≥50% in absolute monocyte counts were observed in 80% (16/20) of patients with systemic mastocytosis with associated chronic myelomonocytic leukemia as associated hematologic neoplasm (SM-AHN CMML)[13,14]
- Here we describe a comprehensive pooled evaluation of the effect of avapritinib on BM pathology including 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 EXPLORER and PATHFINDER studies

Study design

Figure 1: Study design



Measures of bone marrow mast cell burden were exploratory and not statistically powered, and therefore, not subject to type I error control.

AdvSM, advanced SM; ECOG PS, Eastern Cooperative Oncology Group Performance Status; QD, once daily.

Methods

- Bone marrow biopsies (BMBs), bone marrow aspirates (BMAs), peripheral blood smears, and complete blood counts were collected at screening and after 8, 24, and 40 weeks
- Evaluations of morphology were conducted 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
- Bone marrow fibrosis grading was performed using the European Consensus grading system (MF 0–3)[15]; separate grading was conducted for osteosclerosis (Grade 0–3)[16]
- Changes in BM cellularity, fibrosis and osteosclerosis grade were assessed

Results

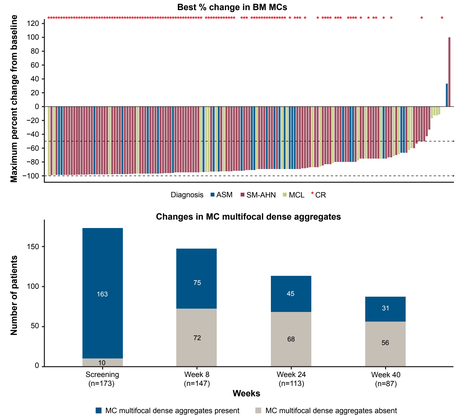
Table 1. Baseline characteristics (N=176)

	All doses (N=176)
Median age, years (range)	68 (31–88)
Female, n (%)	73 (41.5)
ECOG PS n (%)	
0	36 (20.5)
1	92 (52.3)
2	33 (18.8)
3	15 (18.5)
AdvSM subtype per central assessment, n (%)	
ASM	29 (16.5)
SM-AHN	119 (67.6)
MCL	28 (15.9)
KIT D816V VAF in blood[a], median % (range)	14.8 (0.0–80.1)
KIT Exon 17 mutation positive, n (%)	167 (94.9)
SRSF2/ASXL1/RUNX1 mutation positive, n (%)	84 (47.7)
Any prior anti-neoplastic therapy, n (%)	110 (62.5)
Midostaurin	81 (46.0)
Cladribine	22 (12.5)
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)	839.39 (44.2–2897.3)

[a]Assessed by central D816V digital droplet PCR assay.
ASM, aggressive systemic mastocytosis; BM, bone marrow; MC, mast cell; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with associated hematologic neoplasm, VAF, variant allele fraction.

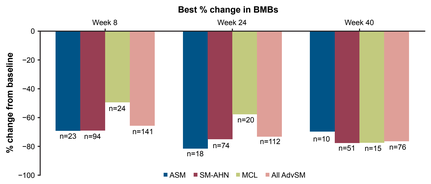
- Almost all patients had reductions in mast cell burden with avapritinib (**Figure 2**)
- The proportion of patients with multifocal dense aggregates of MCs in BMBs decreased from 94.2% at screening to 51.0% by Week 8 and 35%.6 by Week 40

Figure 2. Reduction in mean percentage of MCs in BMBs by AdvSM subtype (N=176)



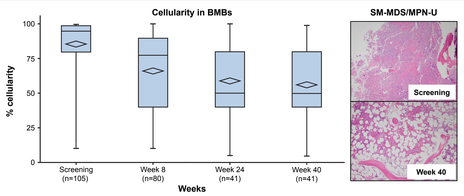
BMB, bone marrow biopsy; CR, complete remission.

Figure 3. Reduction in mean percentage of MCs in BMBs by AdvSM subtypes (N=176)



- Cellularity in BMBs decreased from a mean of 85.8% at screening to 56.0% by Week 40 (**Figure 4**)

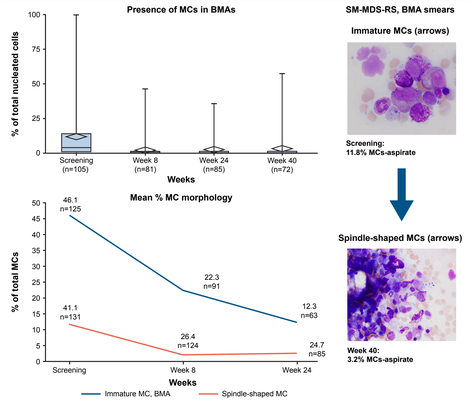
Figure 4. Reduction of abnormal cellularity in BMBs with avapritinib



SM-MDS/MPN-U, systemic mastocytosis with an unclassifiable myelodysplastic/myeloproliferative neoplasm.
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.

- The mean percentage of total MCs in BMAs decreased from 11.8% at screening to 2.1% by Week 8 and was maintained at this level at later timepoints (**Figure 5**)
- Marked reductions in immature MCs and spindle-shapred MCs were also noted by Week 8 and later timepoints
- Of nine patients with circulating MCs at screening and post-screening sample measurements (six with SM-AHN diagnosis and three with MCL), 8 had no detectable MCs by Week eight

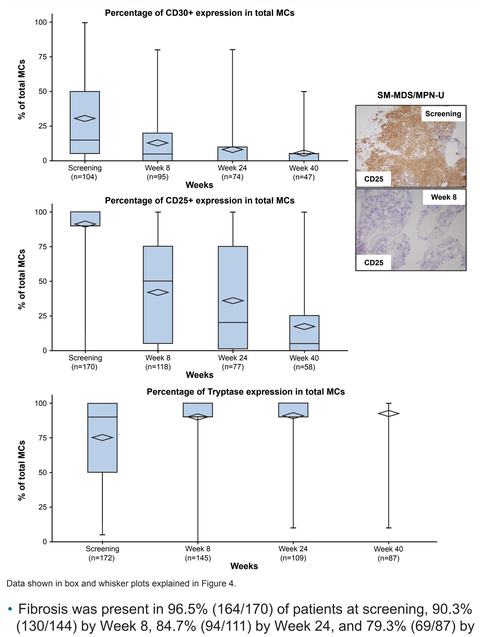
Figure 5. Reduction of MCs and atypical morphology (immature and spindle shaped MCs) in BMAs with avapritinib



BMA, bone marrow aspirate.
Data shown in box and whisker plots explained in Figure 4.

- The proportion of CD25+ in BMBs decreased from a mean of 91.0% at screening to 41.9% by Week 8, 35.8% by Week 24, and 17.1% by Week 40 (**Figure 6**)
- The proportion of CD30+ in BMBs decreased from a mean of 30.6% at screening to 12.9% by Week 8, 8.4% by Week 24, and 5.7% by Week 40
- The proportion of tryptase expression in BMBs increased from a mean of 72.1% at screening to 90.0% by Week 8, 90.7% by Week 24, and 92.7% by Week 40

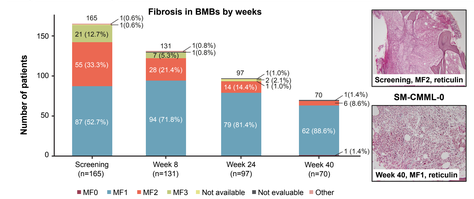
Figure 6. Reduction in the proportion of CD25+ and CD30+ MCs



Data shown in box and whisker plots explained in Figure 4.

- Fibrosis was present in 96.5% (164/170) of patients at screening, 90.3% (130/144) by Week 8, 84.7% (94/111) by Week 24, and 79.3% (69/87) by Week 40 (**Figure 7**)
- Fibrosis grade was reduced during avapritinib treatment in those patients presenting with increased fibrosis (**Figure 7**)

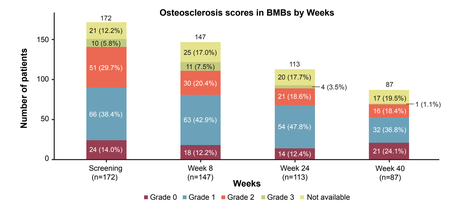
Figure 7. Changes in Fibrosis in BMBs



SM-CMML, systemic mastocytosis-chronic myelomonocytic leukemia; MF, myelofibrosis grade.

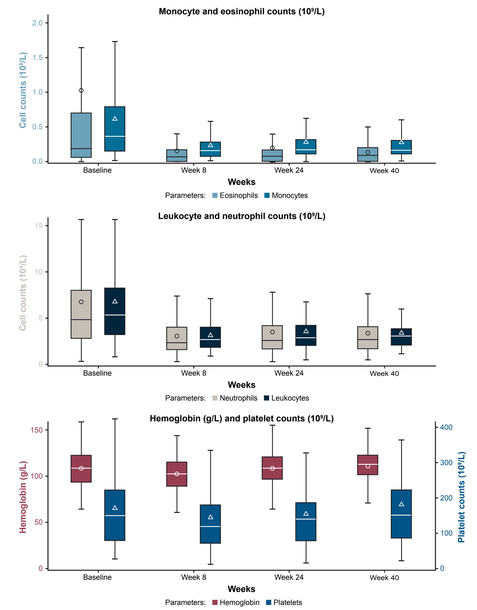
- Osteosclerosis (grade) was slightly reduced only during avapritinib treatment in those patients presenting with Grade3 by Week 40 (**Figure 8**)

Figure 8. Changes in osteosclerosis score in BMBs



- In peripheral blood, absolute reductions in mean leukocyte, neutrophil, eosinophil, and monocyte counts were observed by 8 weeks, while hemoglobin levels did not change markedly (**Figure 9**)
- Median platelets remained above 115x10⁹/L at Week 8, and ≥140x10⁹/L at Weeks 24 and 40

Figure 9. Changes in selected hematologic parameters in peripheral blood (N=176)



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.

Discussion

- Findings from this study, together with previously reported response rates in patients with AdvSM treated with avapritinib,[12–14] support the clinical efficacy and provide mechanistic proof of concept for this highly selective and potent *KIT* D816V inhibitor
- The high response rate was accompanied by a normalization of BM cellularity and histopathologic disease-related parameters, reduction in overall fibrosis and grade of fibrosis, and marked improvement in hematologic parameters
- Patients treated with avapritinib were observed to have rapid (Week 8) and marked (Week 24) reductions in BM cellularity, neoplastic BM MC burden characterized by a reduction of the total MC burden in BMBs, BMAs, and MC aggregates with a return to a normal morphologic appearance and immunophenotype and reduction in fibrosis. This was accompanied by a decrease in circulating MCs

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