Disease-Modifying Effects of Avapritinib in Patients With Advanced Systemic Mastocytosis: Improvements in Bone Density

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Background

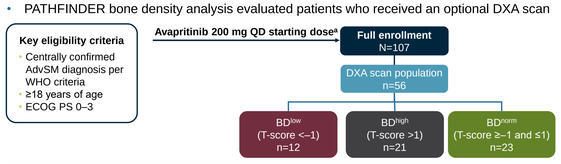
- Systemic mastocytosis (SM) is a rare, clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases[1,2]
- SM is a spectrum of disease including indolent SM (ISM) and advanced SM (AdvSM)
  - AdvSM subgroups include aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL)[3,4]
- Bone disease is among the most frequent comorbidities in SM[5]
- Prevalence of low (osteopenia, osteoporosis) and high (osteosclerosis) bone density (BD) in AdvSM and ISM generally ranges between ~30% (ISM) and ~50% (AdvSM), likely underdiagnosed due to a lack of awareness[5-12]
  - Low BD is predominantly associated with ISM, and high BD is associated with AdvSM[9]
  - In a study of 61 patients with SM, increased BD was detected in 75% of patients with AdvSM and was associated with a worse prognosis[9]
- Avapritinib, a highly selective KIT D816V inhibitor, has been approved for treatment of adult patients with ISM and AdvSM[13,14]
  - Avapritinib demonstrated deep and sustained effects after >3 years of follow-up regardless of AdvSM subtype or prior therapy, including:
    - High overall response rate (73%), including 87% in treatment-naïve patients[15]
    - Complete remission/complete remission with partial hematologic recovery in 29% of all patients and 43% in treatment-naïve patients[15]
  - In PATHFINDER, median overall survival was not reached after >3 years of follow up, and in a study comparing avapritinib with best available therapy in patients with AdvSM, the avapritinib cohort had significantly longer survival[15,16]
- Here, we report the effect of avapritinib on BD in AdvSM from a subset of patients enrolled in the PATHFINDER (NCT03580655) study

Methods

- PATHFINDER is an international, multicenter, open-label, single-arm, phase 2 study designed to assess the efficacy and safety of avapritinib in adult patients with centrally confirmed AdvSM (**Figure 1**)
- Dual-energy X-ray absorptiometry (DXA) scans measuring T-scores (DXA scan evaluable population) were performed at screening and approximately every 12 months during avapritinib treatment, according to local procedures at study centers
  - Patients were grouped according to baseline lumbar T-score, the parameter with the most consistent serial measurements:
    - Low BD (BD^{low}) T-score <–1
    - High BD (BD^{high}) T-score >1
    - Normal BD (BD^{norm}) T-score ≥–1 and ≤1
- Changes in T-scores were evaluated using paired *t*-tests comparing baseline and follow-up measurements to assess bone density improvement and stability; timing of last evaluation varied by patient
- Myelofibrosis and osteosclerosis scores were evaluated at baseline and at weeks 8, 24, and 40

Figure 1: PATHFINDER study design

- PATHFINDER bone density analysis evaluated patients who received an optional DXA scan



Data cut-off date: September 15, 2023.
[a]Two patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD.
[b]Assessments included BMMC aggregates, cellularity, myelofibrosis, and osteosclerosis.
AdvSM, advanced systemic mastocytosis; BD, bone density; BM, bone marrow; BMMC, bone marrow mast cells; DXA, dual-energy X-ray absorptiometry; ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; WHO, World Health Organization.

Results

- Serial DXA scans were available in 56/107 (52%) enrolled patients at baseline and at ≥2 follow-up visits (median visits: 3; range 2–6)
  - Median time from baseline to last DXA scan was 22.0 months (range, 3.7–55.0 months)
  - At baseline, low BD was observed in 12/56 (21%) patients and high BD in 21/56 (38%) patients
- Baseline demographic parameters and disease characteristics in patients with serial DXA scans were similar to the overall study population (**Table 1**)
  - No significant differences in baseline characteristics were observed across the 3 BD groups (all P values >0.1)
- 4 patients in the BD^{low} group had medical history of relevant bone fractures before entering the study, and 1 of those experienced an additional fracture on study

Table 1: Baseline demographic and disease characteristics

	All AdvSM (N=107)	Serial DXA scans available (n=56)	BD^{low} (n=12)	BD^{high} (n=21)	BD^{norm} (n=23)
Age, mean, (SD)	65 (11)	69 (8)	68 (9)	69 (9)	68 (7)
Female, n (%)	45 (42)	27 (48)	6 (50)	9 (43)	12 (52)
Postmenopausal, n (%)	41 (91)	25 (93)	6 (100)	7 (78)	12 (100)
AdvSM subtype, n (%)					
ASM	21 (20)	9 (16)	2 (17)	1 (5)	6 (26)
MCL	15 (14)	6 (11)	1 (8)	3 (14)	2 (9)
SM-AHN	71 (66)	41 (73)	9 (75)	17 (81)	15 (65)
BMMC burden					
Mean % (SD)	46.8 (26.5)	47.5 (25.8)	36.4 (25.2)	46.7 (27.8)	53.5 (23.4)
Median % (range)	40.0 (1.0–95.0)	50.0 (10.0–95.0)	20.0 (10.0–75.0)	40.0 (10.0–95.0)	50.0 (10.0–90.0)
Basal serum tryptase, mean ng/mL (SD)	331.5 (291.9)	286.6 (253.5)	277.7 (316.7)	275.2 (310.7)	301.7 (149.4)
KIT D816V VAF in peripheral blood, mean % (SD)	18.6 (16.4)	20.8 (16.4)	19.1 (18.8)	20.6 (18.1)	21.8 (13.9)

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; BD, bone density; BD^{high}, T-score >1; BD^{low}, T-score <–1; BD^{norm}, T-score ≥–1 and ≤1; BMMC, bone marrow mast cells; DXA, dual-energy X-ray absorptiometry; MC, mast cell; MCL, mast cell leukemia; SD, standard deviation; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; VAF, variant allele frequency.

- No substantial differences in avapritinib mean dose per day across bone density populations
- Duration of avapritinib treatment was similar across BD populations (**Table 2**)

Table 2: Treatment history: DXA scan evaluable population

	Serial DXA scans available (n=56)	BD^{low} (n=12)	BD^{high} (n=21)	BD^{norm} (n=23)
Concomitant medications, n (%)				
Bisphosphonates[a,b]	4 (7)	2 (17)	1 (5)	1 (4)
Calcium/vitamin D[b]	26 (46)	5 (42)	6 (29)	15 (65)
Corticosteroids[c]	33 (59)	4 (33)	12 (57)	17 (74)
Avapritinib treatment duration				
Mean months (SD)	27.1 (8.6)	23.4 (8.8)	29.7 (9.0)	26.7 (7.6)
Median months (range)	25.8 (6.0–44.1)	21.5 (6.0–39.9)	28.1 (15.2–44.1)	25.3 (7.4–36.8)

Median follow-up was 25.8 months.
[a]Alendronate (n=3) or zoledronate (n=1).
[b]Four patients received both bisphosphonate and calcium/vitamin D.
[c]Corticosteroids were primarily oral (57%), topical (20%), or intravenous (20%) in the DXA scan evaluable population. Systemic corticosteroids included, but were not limited to dexamethasone, methylprednisolone, prednisolone, and prednisone.
BD, bone density; BD^{high}, T-score >1; BD^{low}, T-score <–1; BD^{norm}, T-score ≥–1 and ≤1; DXA, dual-energy X-ray absorptiometry; SD, standard deviation.

- Histopathology assessments of myelofibrosis revealed a shift to lower scores and improvement in all 3 BD cohorts (**Table 3**)
- Osteosclerosis histopathology assessments revealed improvement in patients with high osteosclerosis scores (**Table 3**)

Table 3: Myelofibrosis and osteosclerosis scores in the DXA scan evaluable population

	Serial DXA scans available (N=56)		BD^{low} (n=12)		BD^{high} (n=21)		BD^{norm} (n=23)	
	Baseline	Last visit	Baseline	Last visit	Baseline	Last visit	Baseline	Last visit
Myelofibrosis score, n (%)[a]								
0 or 1	27 (50)	36 (86)	6 (55)	9 (90)	10 (48)	16 (84)	11 (50)	11 (85)
2 or 3	27 (50)	6 (14)	5 (45)	1 (10)	11 (52)	3 (16)	11 (50)	2 (15)
Missing[b]	2	14	1	2	0	2	1	10
Osteosclerosis score, n (%)[c]								
0 or 1	30 (64)	30 (88)	8 (80)	8 (100)	9 (60)	8 (73)	13 (59)	14 (93)
2 or 3	17 (36)	4 (12)	2 (20)	0	6 (40)	3 (27)	9 (41)	1 (7)
Missing[b,d]	9	22	2	4	6	10	1	8

[a]0: scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow; 1: loose network of reticulin with many intersections, especially in perivascular areas; 2: Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen and/or focal osteosclerosis; 3: diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers mostly consistent with collagen, usually associated with osteosclerosis.[17]
[b]Missing values are not included in percentage calculations.
[c]0: no osteosclerosis (normal bone); 1: mild osteosclerosis (mildly thickened bone); 2: moderate osteosclerosis (moderately thickened bone); 3: severe osteosclerosis (markedly thickened bone).[17]
[d]Missing indicates biopsy samples that were not evaluable for osteosclerosis.
BD, bone density; BD^{high}, T-score >1; BD^{low}, T-score <–1; BD^{norm}, T-score ≥–1 and ≤1; DXA, dual-energy X-ray absorptiometry.

- In all 3 BD cohorts, BM cellularity and proportion of patients with BMMC aggregates decreased from first to last BM pathology assessment (**Table 4**)

Table 4: Cellularity and BMMC aggregates in the DXA scan evaluable population

	Serial DXA scans available (N=56)		BD^{low} (n=12)		BD^{high} (n=21)		BD^{norm} (n=23)	
	Baseline	Last visit	Baseline	Last visit	Baseline	Last visit	Baseline	Last visit
Cellularity, mean % (SD)[a]	89 (14)	54 (25)	88 (13)	58 (23)	91 (13)	55 (24)	89 (15)	52 (27)
Presence of BMMC aggregates, n (%)	51 (98)[b]	14 (25)	11[c] (100)	5 (42)	18[d] (95)	3 (14)	22[c] (100)	6 (26)

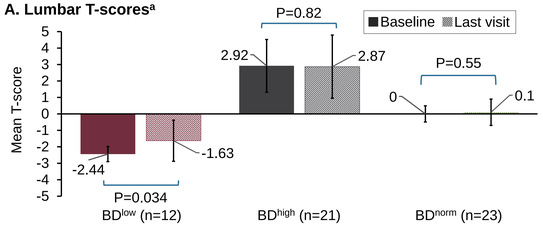
[a]1 observation missing for this parameter (n=55).
[b]4 observations missing for this parameter; missing values not included in percentage calculation.
[c]1 observation missing for this parameter; missing value not included in percentage calculation.
[d]2 observations missing for this parameter; missing values not included in percentage calculation.
BD, bone density; BD^{high}, T-score >1; BD^{low}, T-score <–1; BD^{norm}, T-score ≥–1 and ≤1; BMMC, bone marrow mast cell; DXA, dual-energy X-ray absorptiometry; SD, standard deviation.

- Patients in the BD^{low} group had significantly improved T-scores from baseline to last visit (**Figure 2A**)
  - In this group, a large majority of patients had lumbar T-scores that improved or remained stable (**Figure 2B**)
  - The mean time to best improvement in T-score in the BD^{low} group was 11.5 months (first DXA measurement)
  - In 5/12 patients in the BD^{low} group with osteoporosis (T-score, ≤–2.5), T-scores improved in 4 patients and remained stable in 1 patient
- In the BD^{high} and BD^{norm} groups, mean lumbar T-score did not change significantly (**Figure 2A**)
  - In these groups, most patients' lumbar T-scores improved or remained stable (**Figure 2B**)

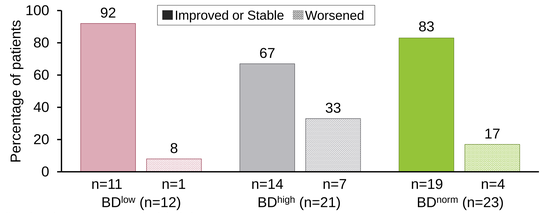
Figure 2: T-score changes during avapritinib treatment

- Avapritinib significantly improved low BD and stabilized normal and high BD T-scores in the DXA scan evaluable population; 58% of patients in the BD^{low} group improved from baseline to last visit

A. Lumbar T-scores[a]



B. Change in patient lumbar T-scores from baseline to last visit[b]



[a]Error bars in A represent standard deviation.
[b]Improved defined as change in T-score ≥0.5 toward normal range; stable defined as change in T-score <0.5; worsened defined as change in T-score ≥0.5 away from normal range.
BD, bone density; BD^{high}, T-score >1; BD^{low}, T-score <–1; BD^{norm}, T-score ≥–1 and ≤1.

Conclusions

- With >3 years of follow-up, treatment with avapritinib demonstrated significant and sustained disease-modifying effects based on lumbar T-scores:
  - Improved myelofibrosis and osteosclerosis seen in the evaluable population
  - Improvement of low bone density in patients in the BD^{low} group
  - Stable bone density in patients in the BD^{norm} and BD^{high} groups
- Treatment with avapritinib, a potent KIT D816V inhibitor, is associated with dynamic changes in bone density
- These results are relevant to other SM subtypes, particularly ISM where osteopenia and osteoporosis are highly prevalent
- Future studies are warranted to evaluate the potential for avapritinib to improve bone health in patients with SM

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