Avapritinib Treatment of Patients with Advanced Systemic Mastocytosis: 4-Year Safety, Effect on Bone and First-Line Efficacy Results of the PATHFINDER Clinical Study

Poster Number MPN - 1037

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Introduction

- Advanced systemic mastocytosis (AdvSM) is a clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases[1–7]
- AdvSM includes aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL)[1–5]
- AdvSM is associated with life-threatening organ damage and reduced survival[1–5]
- Bone disease is prevalent in AdvSM—predominantly high bone density (BD) (~75% of cases) and osteosclerosis (~50% of cases)—and is associated with dysregulated bone turnover markers[8,9]
- Avapritinib is a highly potent and selective KIT D816V inhibitor approved in the US for adult patients with AdvSM and in Europe for adults with AdvSM after ≥1 prior systemic therapy[10,11]
- Here we report final analyses from the completed PATHFINDER study (NCT03580655) of avapritinib in AdvSM and the potential impact of avapritinib on bone disease

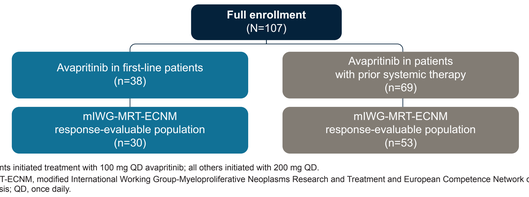
Methods

- PATHFINDER was an international, multicenter, open-label, single-arm, phase 2 study designed to assess the efficacy and safety of avapritinib in adult patients with a centrally confirmed AdvSM diagnosis
- Eligible patients were aged ≥18 years with a centrally confirmed AdvSM diagnosis per World Health Organization criteria, an Eastern Cooperative Oncology Group performance status score of 0–3, and a platelet count ≥50×10^9/L
- The primary endpoint was centrally adjudicated overall response rate (ORR) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis criteria
- Secondary endpoints included biomarkers of objective disease burden measures (bone marrow mast cells [BM MCs], serum tryptase, *KIT* D816V variant allele fraction [VAF], and spleen volume), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety
- Exploratory endpoints comprised BD and levels of bone turnover markers:
  - Procollagen type 1 N-terminal propeptide (PINP) – a biomarker of osteoblast activity/bone formation[12]
  - Tartrate-resistant acid phosphatase 5b (TRAcP-5b) – a biomarker associated with osteoclast activity/bone resorption[13,14]

Results

- In total, 107 patients received avapritinib (n=38 as first-line therapy) (**Figure 1; Table 1**)

Figure 1. Patient disposition



[a]Two patients initiated treatment with 100 mg QD avapritinib; all others initiated with 200 mg QD.
mIWG MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; QD, once daily.

Table 1. Patient baseline characteristics

	Overall population[a] (N=107)	First-line patients (n=38)
Age, years, median (range)	**68 (31–88)**	68 (39–88)
Female, n (%)	**45 (42)**	18 (47)
ECOG PS, n (%)		
2–3[b]	**28 (26)**	7 (18)
AdvSM subtype per central assessment, n (%)		
ASM	**21 (20)**	7 (18)
SM-AHN[c]	**71 (66)**	28 (74)
MCL (including four MCL-AHN)[d]	**15 (14)**	3 (8)
BM MC burden, median percentage (range)	**40 (1–95)**	35 (3–90)
Serum tryptase level, median ng/mL (range)	**262 (24–1600)**	178 (37–1336)
***KIT* D816V mutation by central assay, n (%)**	**103 (96)**	36 (95)
***KIT* D816V VAF,[e] median percent (range)**	**16 (0–47)**	6 (0–45)
***SRSF2/ASXL1/RUNX1 (S/A/R)* mutation per central assay,[f] n (%)**	**48 (45)**	23 (61)
Number of prior antineoplastic therapy, median (range)	**1 (0–6)**	0
1 prior antineoplastic therapy, n (%)	**42 (39)**	–
≥2 prior antineoplastic therapies, n (%)	**27 (25)**	–

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[a]Patients with AdvSM initiated avapritinib 200 mg (n=105) or 100 mg (n=2) QD.
[b]Remaining patients were ECOG PS 0–1.
[c]SM-AHN subtypes included CMML (29%), MDS (11%), MPN (3%), MDS/MPN-U (14%), CEL (6%), and other (4%).
[d]Of the patients with subtype MCL (n=15), four were MCL AHN.
[e]Assessed by ddPCR in both peripheral blood (majority) and BM with a limit of detection of 0.02%.
[f]Assessed by NGS.
AdvSM, advanced systemic mastocytosis; ASXL1, Additional Sex Combs-Like 1; BM, bone marrow; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; ddPCR, digital droplet polymerase chain reaction; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with an associated hematologic neoplasm; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; MDS/MPN-U, myelodysplastic syndrome/myeloproliferative neoplasm unclassifiable; NGS, next-generation sequencing; RUNX1, Runt-related Transcription Factor 1; S/A/R, SRSF2/ASXL1/RUNX1; SM-AHN, SM with an associated hematological neoplasm; SRSF2, Serine and Arginine Rich Splicing Factor 2; QD, once daily; VAF, variant allele fraction.

Results continued

Efficacy

- Avapritinib demonstrated a high response rate across AdvSM subtypes (**Table 2**) and was associated with rapid, robust, and sustained responses with ~4 years median follow-up (**Table 3**)
- Durable reductions were observed in all biomarkers of disease burden, regardless of prior treatment (**Figure 2**)
  - Clearance of BM MC aggregates was seen in 74% of all patients and 84% of first-line patients (**Figure 2A**)
  - A reduction in serum tryptase to <20 ng/ml was observed in 65% of all patients and 79% of first-line patients (**Figure 2B**)
  - A total of 64% of all patients and 68% of first-line patients had post baseline KIT D816V VAF of <1% (**Figure 2C**)
  - In patients with baseline palpable spleens, clinical resolution was observed in 78% overall and 72% of first-line patients (**Figure 2D**)

Table 2. Response rate with avapritinib across AdvSM subtypes

	Overall response-evaluable population				First-line response-evaluable population			
	All (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)	All (n=30)	ASM (n=5)	SM-AHN (n=22)	MCL (n=3)
ORR,[a] n (%) 95% CI	61 (73) 63–83	10 (77) 46–95	41 (75) 61–85	10 (67) 38–88	26 (87) 69–96	4 (80) 28–100	19 (86) 65–97	3 (100) 29–100
Best response[b]								
CR or CRh[c]	25 (30)	4 (31)	18 (33)	3 (20)	13 (43)	1 (20)	11 (50)	1 (33)
CR	14 (17)	1 (8)	10 (18)	3 (20)	8 (27)	1 (20)	6 (27)	1 (33)
CRh	11 (13)	3 (23)	8 (15)	0	5 (17)	0	5 (23)	0
PR[d]	32 (39)	6 (46)	19 (35)	7 (47)	13 (43)	3 (60)	8 (36)	2 (67)
CI	4 (5)	0	4 (7)	0	0	0	0	0
SD	13 (16)	3 (23)	7 (13)	3 (20)	3 (10)	1 (20)	2 (9)	0
PD	2 (2)	0	1 (2)	1 (7)	0	0	0	0
NE	7 (8)	0	6 (11)	1 (7)	1 (3)	0	1 (5)	0

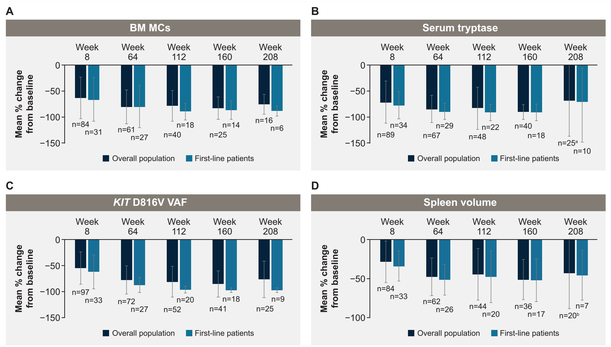
Final database lock: March 13, 2025.
[a]ORR evaluable per mIWG-MRT-ECNM criteria at baseline.
[b]Best confirmed response per mIWG-MRT-ECNM criteria. CR+CRh+PR+CI.
[c]CRh requires full resolution of all evaluable C-findings, elimination of BM MC aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10^9/L with normal differential, platelet count >50×10^9/L, and hemoglobin level >8.0 g/dL).
[d]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both BM MCs and serum tryptase.
95% CI, 95% confidence interval; ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3. TTR, DOR, and PFS with avapritinib across AdvSM subtypes

	Overall response-evaluable population				First-line response-evaluable population			
	All (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)	All (n=30)	ASM (n=5)	SM-AHN (n=22)	MCL (n=3)
Median TTR, months (range)	2.3 (0.3–20.3)	2.1 (0.3–15.0)	2.1 (0.5–20.3)	7.3 (1.7–12.2)	3.1 (0.3–15.0)	1.8 (0.3–15.0)	2.4 (0.5–12.2)	9.2 (9.2–9.3)
Median DOR, months (95% CI)	57.8 (46.1–NE)	NR (26.5–NE)	54.5 (42.6–NE)	NR (NE–NE)	NR (37.1–NE)	NR (NE–NE)	NR (31.2–NE)	NR (29.0–NE)
Median PFS,[a] months (95% CI)	51.3 (38.7–NE)	NR (NE–NE)	45.1 (31.4–61.6)	NR (12.0–NE)	NR (39.4–NE)	NR (NE–NE)	48.1 (25.4–NE)	NR (38.2–NE)

Final database lock: March 13, 2025. DOR, TTR, and PFS were assessed in the response-evaluable population.
[a]PFS was defined as the time from first dose to the time of initial documentation of progressive disease or death due to any cause, whichever occurred first.
DOR, duration of response; NR, not reached; PFS, progression-free survival; TTR, time to response.

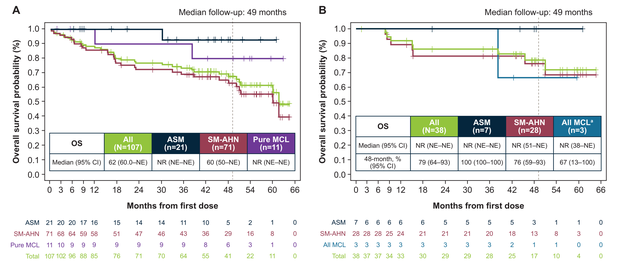
Figure 2. Effect of avapritinib on (A) BM MCs, (B) serum tryptase, (C) *KIT* D816V VAF, and (D) spleen volume in the overall population and first-line patients



Final database lock: March 13, 2025. Error bars = ±SD.
[a]SD = 85.5.
[b]SD = 45.5.
SD, standard deviation.

- OS was >5 years in the overall population and was not reached in first-line patients with ~4 years median follow-up (**Figure 3**)
  - Median (95% confidence interval [CI]) OS in four patients with MCL with an associated hematologic neoplasm (MCL-AHN) was 9.2 months (1.4–not reached); all four patients had been treated with prior therapy
  - All cases of MCL in first-line patients were pure MCL (none with MCL-AHN)

Figure 3. Overall survival with avapritinib in (A) the overall population and (B) first-line patients



Final database lock: March 13, 2025.
OS, overall survival.

Safety

- Avapritinib demonstrated a continued favorable benefit-risk profile after ~4 years of treatment (**Table 4**)
- Long-term safety and tolerability are well characterized and were consistent with prior reports[15,16]
- No intracranial bleeding events were observed after the September 2022 data cut-off (four patients [3.7%] overall in the study)[15]
  - All four patients had confounding factors, such as medical history of hypertension (n=3), use of antithrombotic treatment (n=3), or head trauma around the time the bleeding occurred (n=1), and three out of the four patients experienced severe thrombocytopenia over the course of the study
  - No events were fatal
- Adverse events (AEs) were generally managed with dose modifications, allowing patients to continue to receive treatment
  - In total, 19% of patients discontinued treatment due to treatment-related adverse events (TRAEs), with a median daily dose (range) of 106 mg (27–240 mg)
- Liver transaminase elevation TRAEs were low (8%), and all were Grade 1–2
- One treatment-related death occurred; the patient, an 80-year-old male with a history of kidney disease, died due to acute kidney injury following administration of antibiotics

Table 4. Safety profile of avapritinib

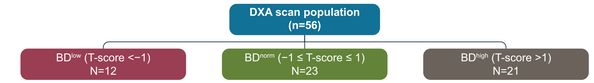
Most common TRAEs (≥15%), n (%) Median duration 32.7 months (0.2–63.5)	Safety population (N=107)	
	Any grade	Grade ≥3
Hematological AEs		
Thrombocytopenia[a]	55 (51)	31 (29)
Anemia[a]	35 (33)	17 (16)
Neutropenia[a]	30 (28)	27 (25)
Non-hematologic AEs		
Periorbital edema[a]	59 (55)	6 (6)
Peripheral edema[a]	42 (39)	2 (2)
Face edema[a]	23 (21)	0
Cognitive disorder	19 (18)	5 (5)
Hair color changes	18 (17)	0
Diarrhea	16 (15)	1 (<1)

Final database lock: March 13, 2025.
[a]Pooled term.
AE, adverse event; TRAE, treatment-related adverse event.

Bone density and bone turnover markers

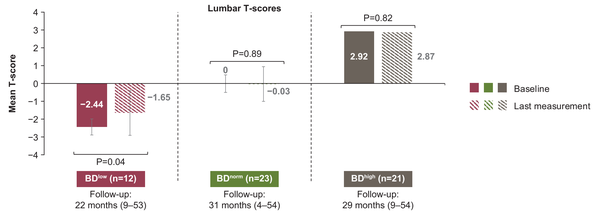
- Serial dual-energy X-ray absorptiometry (DXA) scans were optional, and were available in 52% of enrolled patients at baseline and at ≥2 follow-up visits
- Baseline demographic parameters and markers of mast cell (MC) disease burden in patients with serial DXA scans were not significantly different from those without serial DXA scans
- Patients were categorized as having low BD (BD^{low}), normal BD (BD^{norm}), or high BD (BD^{high})
- BD^{low} and BD^{high} were observed in 21% and 38% of patients, respectively (**Figure 4**)
- BD significantly improved in the BD^{low} group (**Figure 5**)
  - Mean lumbar T-scores significantly improved in the BD^{low} group and did not worsen in the BD^{high} and BD^{norm} groups
  - 11/12 patients in the BD^{low} group had T-scores that either improved (n=7) or remained stable (n=4)
  - The mean time to best improvement in T-score for the BD^{low} group was 11.5 months, which corresponded with the first post-baseline DXA assessment
- The bone turnover markers, PINP and TRAcP-5b (analyzed in 47 patients), normalized following treatment with avapritinib (**Figure 6**)

Figure 4. Baseline BD groups in patients evaluated by DXA scans



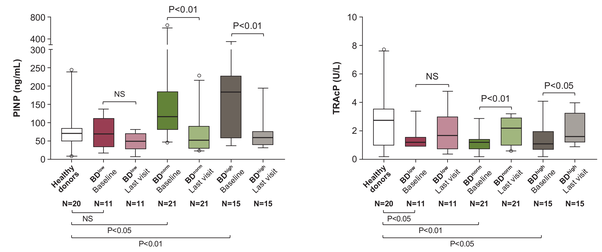
BD, bone density; BD^{high}, high BD; BD^{low}, low BD; BD^{norm}, normal BD; DXA, dual-energy X-ray absorptiometry.

Figure 5. Changes in BD with avapritinib



Error bars represent SD.

Figure 6. Changes in (A) PINP and (B) TRAcP-5b with avapritinib



Final database lock: March 13, 2025.
NS, not significant; PINP, procollagen type 1 N-terminal propeptide; TRAcP-5b, tartrate-resistant acid phosphatase 5b.

Conclusions

- Avapritinib was well tolerated, with robust and durable efficacy, favorable survival, and disease modification after median ~4 years follow-up
- OS in first-line patients suggests better outcomes with earlier treatment with avapritinib
- Survival outcomes were favorable, especially considering the reduced survival that has been reported in patients with SM-AHN[5]
- Avapritinib demonstrated deep and sustained effects regardless of AdvSM subtype or prior therapy, including favorable ORR, complete remission (CR)/complete remission with partial hematologic recovery (CRh), DOR, and PFS
- There was a consistent reduction in disease burden, regardless of prior treatment
- Avapritinib maintained a well-characterized safety profile with no new safety concerns observed after several years of treatment
- Avapritinib may improve low BD T-scores and normalize bone turnover markers

Acknowledgements

Medical writing support was provided by Alice Singleton, MSc, and editorial support was provided by Travis Taylor, BA, of the Prime Group of Companies (Knutsford, UK) and funded by Blueprint Medicines Corporation, a wholly-owned subsidiary of Sanofi. The sponsor reviewed and provided feedback on the poster. However, the authors had full editorial control and provided final approval of all content.

We thank the patients and their families for making the PATHFINDER study possible. We also thank the investigators and clinical trial teams who participated in the study.

Conflicts of interest/disclosures

Dr Reiter has received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from AbbVie, AOP, Blueprint Medicines Corporation, a wholly-owned subsidiary of Sanofi, BMS, Cogent, GSK, Incyte, and Novartis. Full disclosures for all authors are available upon request at medinfo@blueprintmedicines.com.

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Presented at the 14th Annual Meeting of the Society of Hematologic Oncology, September 9–12, 2026, Houston, TX, USA.