Avapritinib in patients with advanced systemic mastocytosis (AdvSM): Efficacy and safety analyses from the phase 2 PATHFINDER study with 2-year follow-up

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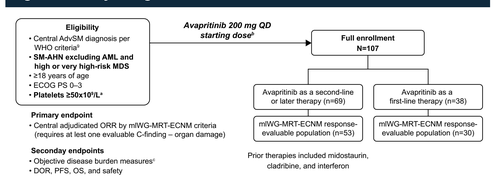
Background

- Advanced systemic mastocytosis (AdvSM), a rare, heterogeneous myeloid neoplasm driven by the *KIT* D816V mutation in ~95% of cases, is characterized by hyperactivation and accumulation of mast cells which often leads to severe and debilitating symptoms, life-threatening organ damage, and poor prognosis[1,2]
- AdvSM includes three subtypes: ASM, SM-AHN, and MCL[2]; SM-AHN is the most prevalent subtype (70%)[3]
- Avapritinib, a highly potent and selective KIT D816V inhibitor, demonstrated rapid, deep, and durable responses in patients with AdvSM in the phase 1 EXPLORER (NCT02561988) study and in an interim analysis of the phase 2 PATHFINDER (NCT03580655) study[4,5]
  - The overall response rate (ORR) by mIWG-MRT-ECNM criteria regardless of prior therapy or disease subtype was 75% in both studies[5]
- Data from these studies led to the approval of avapritinib in the USA for adult patients with AdvSM regardless of prior therapy and in Europe for adult patients with AdvSM after ≥1 prior systemic therapy. In patients with a platelet count <50×10⁹/L, avapritinib is not recommended[6,7]
  - In a recent retrospective comparative study with real-world data, avapritinib treatment showed significant survival benefit versus the best available therapy (including midostaurin and cladribine)[8]
- Here, we report on the efficacy and safety of avapritinib in the full AdvSM patient population enrolled in the PATHFINDER study with >2 years of follow-up

Methods

- PATHFINDER, an international, multicenter, open-label, single-arm, phase 2 registrational trial assessed the efficacy and safety of avapritinib in adult patients with a centrally confirmed diagnosis of AdvSM (**Figure 1**)

Figure 1. Study design



[a]Implemented in 2019 to reduce risk of intracranial bleeding. [b]Two patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD. [c]Disease burden measures include BM MCs, serum tryptase, *KIT* D816V VAF, and spleen volume. No type 1 error control for these endpoints.

AdvSM, advanced systemic mastocytosis; AML, acute myeloid leukemia; BM, bone marrow; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; MDS, myelodysplastic syndromes; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; VAF, variant allele fraction; WHO, World Health Organization

Results

- As of September 9, 2022, 107 patients with AdvSM initiated avapritinib 200 mg (n=105) or 100 mg (n=2) once daily (QD)
  - 36% (n=38/107) were treatment-naïve, and 64% (n=69/107) had received ≥1 prior systemic therapy (**Table 1**)
  - Most patients had SM-AHN (n=71); AHN subtypes include MDS, MPN, MDS/ MPN such as CMML or MDS/ MPN-U, and CEL
- Median (range) daily dose was 112 (29–240) mg across all patients (n=107)

Table 1. Baseline patient demographics and characteristics

	Patients with ≥1 prior therapy (n=69)	Treatment-naïve patients (n=38)	All AdvSM (N=107)
Age, median years (range)	68 (31–86)	68 (39–88)	68 (31–88)
Female, n (%)	27 (39)	18 (47)	45 (42)
ECOG performance status, n (%)			
0–1	48 (70)	31 (82)	79 (74)
2–3	21 (30)	7 (18)	28 (26)
AdvSM subtype per central assessment, n (%)			
ASM	14 (20)	7 (18)	21 (20)
SM-AHN	43 (62)	28 (74)	71 (66)
CMML[a]	22 (32)	11 (29)	33 (31)
MDS/MPN-U	16 (23)	13 (34)	29 (27)
CEL	3 (4)	3 (8)	6 (6)
Other	3 (4)	1 (3)	4 (4)
MCL	12 (17)	3 (8)	15 (14)
KIT D816V mutation by central assay, n (%)	67 (97)	36 (95)	103 (96)
KIT D816V VAF[b], median percent (range)	20 (0–47)	6 (0–45)	16 (0–47)
SRSF2/A/R mutation per central assay[c], n (%)	25 (36)	23 (61)	48 (45)
BM mast cell burden, median percentage (range)	50 (1–95)	35 (3–90)	40 (1–95)
Serum tryptase level, median ng/mL (range)	312 (24–1600)	178 (37–1336)	262 (24–1600)
Spleen volume, median mL (range)	830 (44–2652)	863 (149–2897)	839 (44–2897)
One prior systemic therapy, n (%)	42 (61)	0	42 (39)
Prior antineoplastic therapy, n (%)			
Midostaurin	58 (84)	0	58 (54)
Cladribine	12 (17)	0	12 (11)
Imatinib	5 (7)	0	5 (5)
Interferon	10 (14)	0	10 (9)

[a]Of the 33 patients with CMML, 20 were CMML-0, 10 were CMML-1 and three were other (essential thrombocythemia, MDS-SLD, and MDS-ED-1). Diagnoses based on WHO 2016 classification guidelines. [b]Assessed by ddPCR in both peripheral blood and bone marrow (majority were in peripheral blood). [c]Assessed by NGS.

ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; ddPCR, droplet digital polymerase chain reaction; MCL, mast cell leukemia; MDS, myelodysplastic syndromes; MDS-ES-1, myelodysplastic syndrome with excess blasts 1; MDS/MPN-U, myelodysplastic syndrome/myeloproliferative neoplasm-unclassifiable; MDS-SLD, myelodysplastic syndrome with single lineage dysplasia; MPN, myeloproliferative neoplasms; NGS, next-generation sequencing; SI/AR, SRSF2, ASXL, and/or RUNX1.

Table 2. Efficacy in response-evaluable patients (mIWG-MRT-ENCM criteria)

		AdvSM subtype			Treatment-naïve		After ≥1 prior therapy	
	All (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)	All (n=30)	SM-AHN (n=22)	All (n=53)	SM-AHN (n=33)
ORR[a] 95% CI	73 (n=61) 63–83	77 (n=10) 46–95	75 (n=41) 61–85	67 (n=10) 38–88	90 (n=27) 74–98	91 (n=20) 71–99	64 (n=34) 50–77	64 (n=21) 45–80
CR/CRh[b]	27 (n=22)	15 (n=2)	31 (n=17)	20 (n=3)	40 (n=12)	50 (n=11)	19 (10)	18 (n=6)
PR[c]	42 (n=35)	62 (n=8)	36 (n=20)	47 (n=7)	50 (n=15)	41 (n=9)	38 (n=20)	33 (n=11)
CI	5 (n=4)	0	7 (n=4)	0	0	0	8 (n=4)	12 (n=4)
SD	17 (n=14)	23 (n=3)	15 (n=8)	20 (n=3)	10 (n=3)	9 (n=2)	21 (n=11)	18 (n=6)
PD[d]	2 (n=2)	0	2 (n=1)	7 (n=1)	0	0	4 (n=2)	3 (n=1)
NE	7 (n=6)	0	9 (n=5)	7 (n=1)	0	0	11 (n=6)	15 (n=5)
Median TTR (range), months	2.3 (0.3–15)	2.1 (0.3–15)	2.1 (0.5–12)	7.3 (1.7–12.2)	3.7 (0.3–15.0)	3.1 (0.5–12.2)	2.0 (0.5–14.6)	1.9 (0.5–8.2)
Median time to CR+CRh (range), months	9.1 (1.8–26)	2.8 (1.8–3.7)	9 (1.8–26)	20 (9.3–26)	7.5 (2.0–25.8)	6.1 (2.0–25.8)	12.1 (1.8–15.0)	12.1 (1.8–26.0)
Median DOR[e] (95% CI)	NR (37–NR)	NR (27–NR)	NR (37–NR)	NR (NR–NR)	NR (37–NR)	37 (37–NR)	NR (NR–NR)	NR (NR–NR)
24-month DOR[e], % (95% CI)	89 (81–97)	89 (68–100)	87 (76–98)	100 (100–100)	92 (81–100)	89 (74–100)	87 (75–99)	85 (69–100)

[a]CR + CRh + PR + CI. [b]CRh requires full resolution of all evaluable C-findings, elimination of BM mast cell aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10⁹/L with normal differential, platelet count >50×10⁹/L, and Hgb level >8.0 g/dL). [c]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both BM MCs and serum tryptase. [d]Two patients had PD as best response. [e]The denominator is based on patients with overall response.

95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; NE, not evaluable; NR, not reached; PR, partial response; PD, progressive disease; SD, stable disease; TTR, time to response.

- Regardless of disease subtype or prior therapy avapritinib treatment resulted in a high response rate with deep and durable responses (**Table 2**)
- In mIWG-MRT-ECNM response-evaluable patients (n=83), ORR (95% confidence interval [CI]) was 73% (63–83)
  - CR or CRh was achieved by 27% of patients
- In treatment naive mIWG-MRT-ECNM response-evaluable patients (n=27/30), ORR was 90% (74–98), with 40% of these patients achieving CR or CRh (**Table 2**)
- Median progression-free survival (PFS) was not reached regardless of subtype or in previously treated patients (**Figure 2A** and **Figure 2B**)
  - Median PFS (95% CI) was 39 months (39–NR) in treatment-naïve patients (**Figure 2B**)
- Median overall survival (OS; n=107), with a median follow-up of 26 months, was not reached regardless of subtype or prior therapy (**Figure 3A** and **Figure 3B**)

Figure 2. Progression–free survival (A) by disease subtype and (B) by treatment history

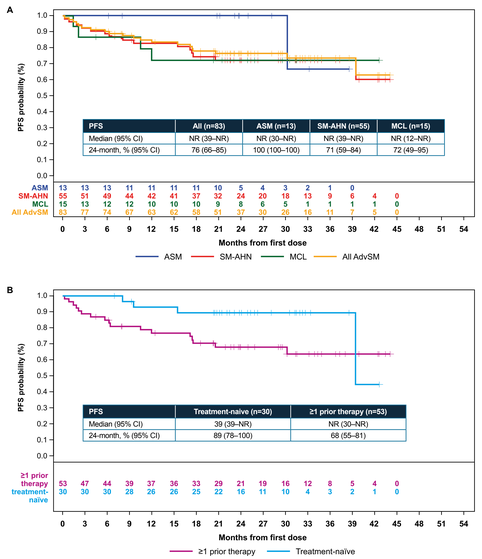


Figure 3. Overall survival (A) by disease subtype and (B) by treatment history

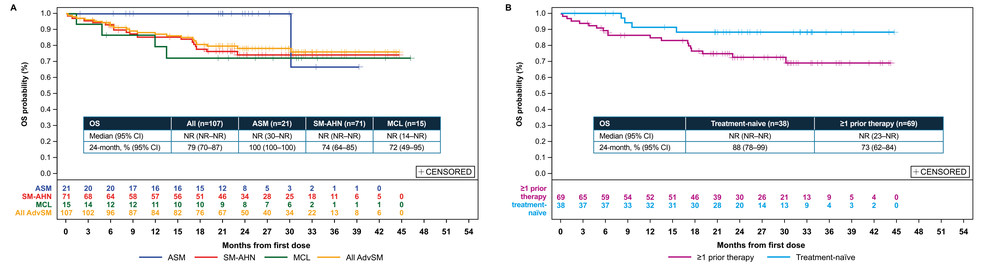


Figure 4. Reductions in objective measures of disease burden: (A) BM mast cells (B) serum tryptase level, (C) *KIT* D816V VAF, and (D) spleen volume

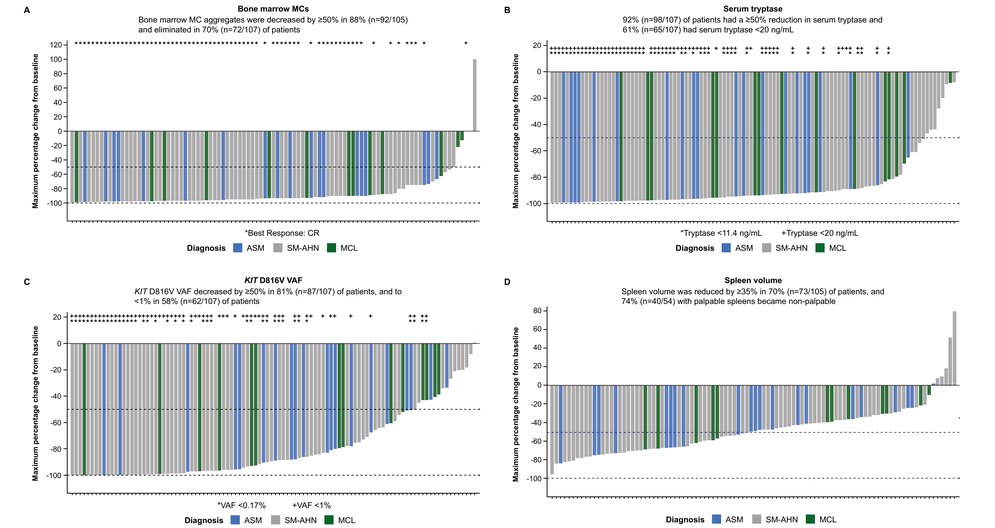
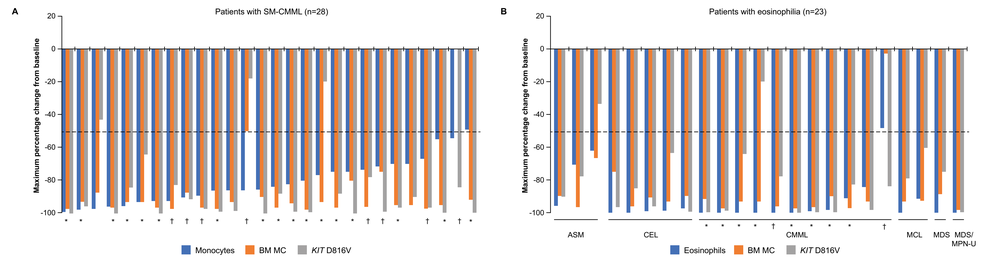


Figure 5. Profiles of (A) patients with SM-CMML (monocyte counts, mast cell burden and *KIT* D816V VAF) and of (B) patients with eosinophilia[a] (eosinophil counts, mast cell burden, and *KIT* D816V VAF)



[a]Eosinophilia was defined by an eosinophil count >0.5 at baseline. Patients with subtype: other (n=2) were not included in the figure. *Patients with CMML-0. †Patients with CMML-1, while those with no symbols (in the CMML subtype) were other.

- Patients with CMML and post-baseline measurements showed marked decreases in absolute monocyte counts with avapritinib regardless of prior therapy (**Figure 5A**)
- In addition, the vast majority of patients assessed with CMML and eosinophilia at baseline showed marked reductions in objective measures of disease burden (**Figure 5A and B**)
- Patients with baseline eosinophilia and post-baseline measurements showed notable decreases in absolute eosinophil counts regardless of prior therapy (**Figure 5B**)
  - Eleven (48%) patients had complete clearance of eosinophils

Table 3. Treatment-related adverse events

TRAEs	All patients (n=107)	
	Any grade	Grade ≥3
Hematological AEs in ≥15%, n (%)		
Thrombocytopenia	42 (39)	19 (18)
Anemia	31 (29)	14 (13)
Neutropenia	20 (19)	18 (17)
Non-hematological AEs in ≥15%, n (%)		
Periorbital edema	42 (39)	6 (6)
Peripheral edema	41 (38)	2 (2)
Eyelid edema	18 (17)	0
Cognitive disorder	17 (16)	3 (3)
Dysgeusia	17 (16)	0
Face edema	16 (15)	0

AE, adverse events; TRAE, treatment-related adverse events.

- Well characterized safety and tolerability profile from 107 patients with most adverse events of Grade 1–2 (**Table 3**), with no new safety concerns
- Treatment-related cognitive effects occurred in 24% of patients, which were mostly Grade 1–2 and managed with dose modification
- Intracranial bleeds (ICB) occurred in 3.7%; all patients discontinued treatment and events were resolved
  - All patients with ICB (n=4) had confounders including hypertension, use of antithrombotic treatment, or head trauma
- Dose reductions, interruptions, and discontinuations due to treatment-related adverse events occurred in 80 (75%), 68 (64%), and 11 (10%) patients, respectively
- There were no treatment-related deaths

Conclusions

- After more than 2 years of follow-up of the PATHFINDER study, patients treated with avapritinib were shown to achieve:
  - Sustained high response rate and low rate of progression, accompanied by marked reductions in objective measures of disease burden (BM mast cells, serum tryptase, and *KIT* D816V VAF), suggesting a substantial disease modification effect
  - Deepening and durable responses over time; CR/CRh rates (27% of all response-evaluable patients) were higher compared to earlier reports[10]
  - Continued good prognosis, with median OS not reached
- Notably, the vast majority of patients with CMML and eosinophilia showed marked reduction in monocyte and eosinophil counts, respectively, in addition to reductions of markers of mast cell burden
- Avapritinib has a well characterized safety profile with a favorable benefit-risk profile
  - Adverse events were effectively managed with dose reductions/interruptions with sustained efficacy
- With long-term follow-up, patients with AdvSM regardless of prior therapy or disease subtype continued to experience deep and durable responses and clinically meaningful benefit with avapritinib treatment

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