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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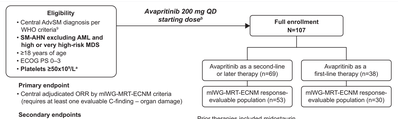
Background

- 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]
- Avapritinib is approved in the USA for adult patients with indolent systemic mastocytosis and AdvSM, 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 survival benefit *versus* the best available therapy (including midostaurin and cladribine) in patients with AdvSM[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, myelodysplasia syndrome; 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]	21 (30)	11 (29)	32 (30)
MDS/MPN[b]	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[c], median percent (range)	20 (0–47)	6 (0–45)	16 (0–47)
S/A/R mutation per central assay[d], 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 (150–2897)	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]There were 33 patients with CMML: 26 were CMML-0, 6 were CMML-1, and one was MCL-CMML-1. Diagnoses based on WHO 2016 classification guidelines. [b]There were 12 patients with MDS, two patients with MPN, and 15 patients with MDS/MPN-U. [c]Assessed by ddPCR in both peripheral blood and bone marrow (majority were in peripheral blood). [d]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/MPN-U, myelodysplastic syndrome/myeloproliferative neoplasm-unclassifiable; MPN, myeloproliferative neoplasms; NGS, next-generation sequencing; S/A/R, SRSF2, ASXL, and/or RUNX1.

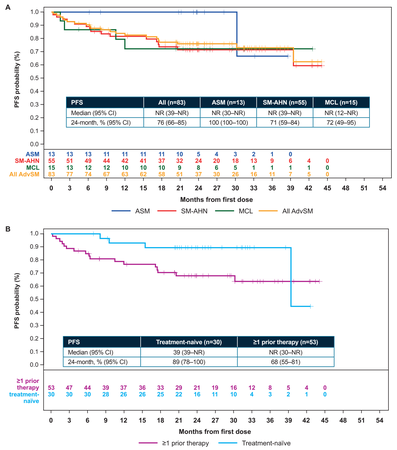
Table 2. Efficacy in response-evaluable patients (mIWG-MRT-ENCM criteria)

	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) 71–99	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 (n=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)	86 (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; Hgb, hemoglobin; 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 naïve 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**)

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



- 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**)
- 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

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

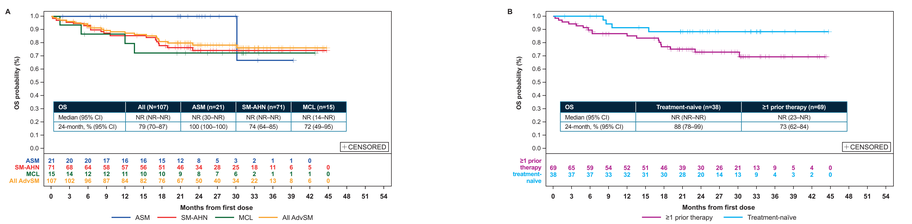


Figure 4. Reductions in objective measures of disease burden: (A) BM mast cells (B) serum tryptase level, (C) *KIT* D816V VAF, and (D) spleen volume

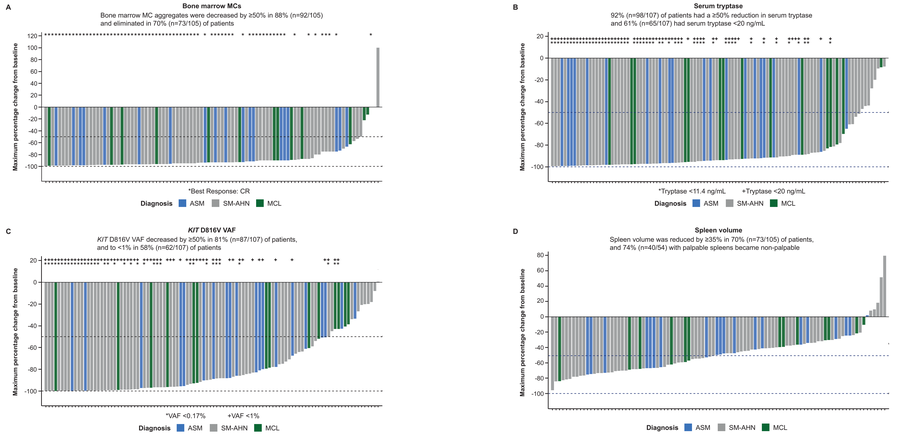
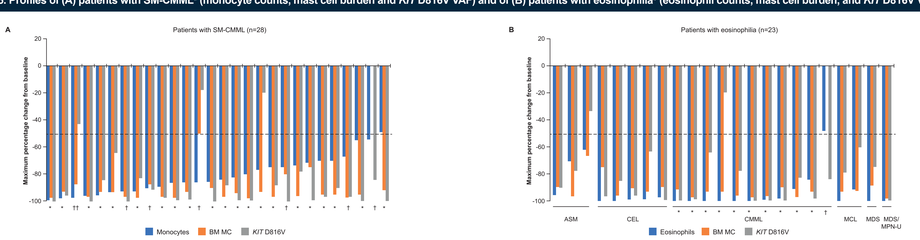


Figure 5. Profiles of (A) patients with SM-CMML[a] (monocyte counts, mast cell burden and *KIT* D816V VAF) and of (B) patients with eosinophilia[b] (eosinophil counts, mast cell burden, and *KIT* D816V VAF)



[a]Only patients with baseline and post-baseline assessments (n=28/33) were included in the figure. [b]Eosinophilia was defined by an eosinophil count >0.5 at baseline. Patients with subtype: other (n=2) were not included in the figure. [a]Patients with CMML-0. [b]Patients with CMML-1. [c]Patient with MCL-CMML-1.

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.

- Consistent with the well characterized safety and tolerability profile, there were no new safety concerns across all patients (N=107; **Table 3**)
- 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 with earlier reports[5]
  - 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 and 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

References

1. Evans EK et al. *Sci Transl Med*. 2017;9(414):eaao1690; 2. Gotlib J et al. *Blood*. 2013;121:2392–2401; 3. Shomali W, Gotlib J. *Int J Mol Sci*. 2021;22:2983; 4. DeAngelo D et al. *Nat Med*. 2021;27:2183–2191; 5. Gotlib J et al. *Nat Med*. 2021;27:2192–2199; 6. AYVAKIT® (avapritinib) [package insert]. May 2023. Blueprint Medicines Corporation; 7. AYVAKYT® (avapritinib) Summary of Product Characteristics. 2023. Blueprint Medicines Corporation; 8. Reiter A et al. *Leukemia*. 2022;36:2108–2120; 9. Horny HP et al. Mastocytosis. In: Sverdlow SH, eds. *World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2016.

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