Avapritinib as first-line therapy in patients with advanced systemic mastocytosis: Efficacy and safety from the PATHFINDER clinical study

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Disclosures

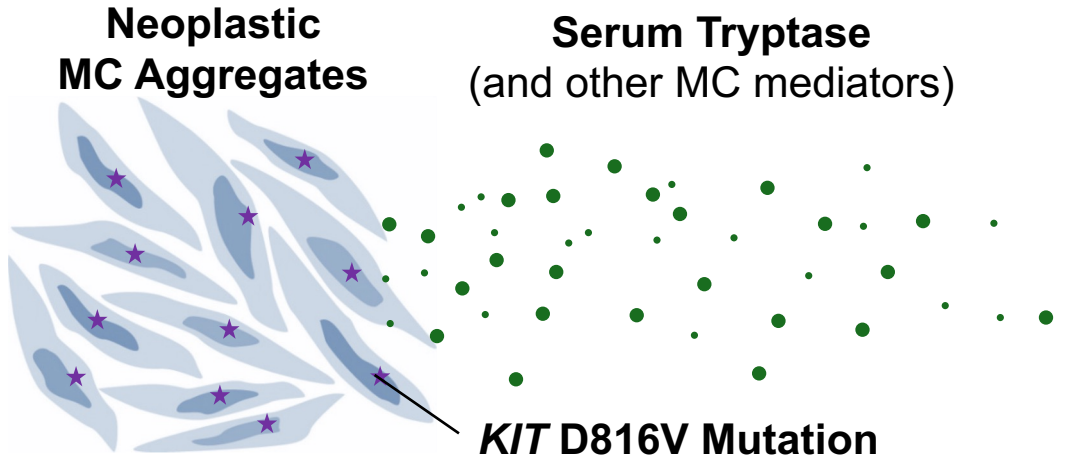
AYVAKIT® (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

AYVAKYT® (avapritinib) is approved by the European Medicines Agency (EMA) as monotherapy for the treatment of adult patients with ASM, SM-AHN, or MCL, after at least one systemic therapy.

Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of $<50\times10^9$/L.

Advanced systemic mastocytosis is a rare myeloid neoplasm driven by the *KIT* D816V mutation in approximately 95% of cases[1,2]

- AdvSM includes three subtypes: ASM, SM-AHN, and MCL,[3,4] all with high disease burden and limited treatment options[3–5]
  - SM-AHN is the most prevalent (~70%), subtypes include CMML, MDS/MPN-U, MDS and CEL
- Proliferation of malignant mast cells can result in life-threatening organ damage due to infiltration by mast cells[6]
- Symptoms are often severe, debilitating and complicated by mast cell mediator release[6]



Organ Damage (C-findings)

- Cytopenias
- Liver dysfunction
- Ascites, pleural effusions
- Splenomegaly with hypersplenism
- Malabsorption with weight loss
- Large osteolytic lesions

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; MC, mast cell; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN-U, myeloproliferative neoplasms unclassifiable; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

1. Ungerstedt J et al. Cancers. 2022;14:3942. 2. Garcia-Montero A et al. Blood. 2006;108:2366-2372. 3. Gotlib J et al. Blood. 2013;121:2392–2401;
4. Jennings S et al. Immunol Allergy Clin N Am. 2018;38:505–525; 5. Midostaurin for treating advanced mastocytosis. NICE Technology appraisal guidance. https://www.nice.org.uk/guidance/ta728/chapter/1-Recommendations. Accessed February 17, 2022. 6. Pardanani A. Am J Hematol. 2019;94:363–377;

Avapritinib in advanced systemic mastocytosis

- Avapritinib is an oral, highly potent, and selective inhibitor of KIT D816V, approved in the USA and the EU based on results from the phase 1 EXPLORER study and interim results from phase 2 PATHFINDER (NCT03580655) study[1–4]
- Response rate[a] regardless of prior therapy was 75% in both studies[1,2]
- Rapid and durable responses across all AdvSM subtypes and regardless of prior therapy
- Avapritinib showed significantly better survival benefit vs best available therapy (including midostaurin and cladribine) in a retrospective real-world analysis[5]

[a]Response rate includes complete remission, complete remission with partial hematologic recovery, partial remission, and clinical improvement.

1. DeAngelo D et al. *Nature Medicine.* 2021;27:2183–2191; 2. Gotlib J et al. *Nature Medicine.* 2021;27:2192–2199; 3. Ayvakit (avapritinib) [package insert].Cambridge, MA: Blueprint Medicines Corporation; 2021; 4. Ayvakyt (avapritinib) Summary of Product Characteristics. Cambridge, MA; Blueprint Medicines Corporation; 2022. 5. Reiter A et al. Leukemia. 2022;36:2108-2120.

Avapritinib as first-line therapy in patients from PATHFINDER

Eligibility

- Central AdvSM diagnosis per WHO criteria[1]
  - **SM-AHN excluding AML and high or very high-risk MDS**
- ≥18 years of age
- ECOG PS 0–3
- **Platelets ≥50×10⁹/L[a]**

Avapritinib 200 mg QD starting dose[b]

Full enrolment

N=107

Avapritinib as second line or later therapy (n=69)

mIWG-MRT-ECNM response-evaluable population (n=49)

Prior therapies included midostaurin, cladribine, and interferon

Avapritinib as first-line therapy (n=38)

mIWG-MRT-ECNM response-evaluable population (n=25)

Current analysis

Primary Endpoint

- Central adjudicated ORR by mIWG-MRT-ECNM criteria (requires at least one evaluable C-finding - organ damage)

Secondary Endpoints

- Objective disease burden measures[c]
- DOR, PFS, OS, and safety

[a]Implemented in 2019 to reduce risk of intracranial bleeding. [b]2 patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD. [c]Disease burden measures include bone marrow MCs, serum tryptase, *KIT* D816V variant allele fraction, and spleen volume. No type 1 error control for these endpoints.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; 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; WHO, World Health Organization.

1. Horny HP et al. Mastocytosis. In: Sverdlow SH et al. World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2016.

Baseline characteristics

Characteristic	First-line population	
	All 200 mg QD (N=38)	mIWG-evaluable 200 mg QD (N=25)
Median age, years (range)	68 (39–88)	68 (54–88)
Male, n (%)	20 (53)	12 (48)
ECOG PS, n (%)		
0–1	32 (84)	20 (80)
2–3	6 (16)	5 (20)
Disease type		
ASM, n (%)	7 (18)	4 (16)
SM-AHN, n (%)	28 (74)	19 (76)
CMML, n (%)	11 (39)	9 (47)
MDS/MPN-U, n (%)	7 (25)	4 (21)
MDS, n (%)	6 (21)	3 (16)
CEL, n (%)	3 (11)	2 (11)
CMML-HE, n (%)	1 (4)	1 (5)
MCL, n (%)	3 (8)	2 (8)
Median BM myeloblasts, % (range)	2 (1–7)	2 (1–7)
Median BM MC burden, % (range)	35 (3–90)	40 (10–90)
Median serum tryptase, ng/mL (range)	178 (37.3–1336)	171 (37.3–1336)
Molecular data		
KIT D816V positive, n (%)	36 (94.7)	25 (100)
KIT D816V VAF in peripheral blood, median % (range)	5.5[b] (0–45)	9.9[a] (0–45)
SRSF2/ASXL1/RUNX1 positive, n (%)	23 (60.5)	17 (68)
Median spleen volume mL (range)	863 (149.8–2897.1)	808 (149.8–1511.8)

Majority of patients had SM-AHN

[a]Only patients with positive values were included in this analysis, n=24. [b]Only patients with positive values were included in this analysis, n=37.
BM, bone marrow; CMML-HE, chronic myelomonocytic leukemia with hypereosinophilia; VAF, variant allele fraction.

High ORR across subtypes including patients with SM-AHN

Outcome, % (n)	All[a] (n=25)	ASM (n=4)	SM-AHN (n=19)	MCL (n=2)
ORR,[b]	**84 (n=21)**	**75 (n=3)**	**95 (n=18)**	–
CR or CRh	32 (n=8)	25 (n=1)	37 (n=7)	–
Complete Remission	8 (n=2)	–	11 (n=2)	–
CR with Partial Hematologic Recovery[c]	24 (n=6)	25 (n=1)	26 (n=5)	–
Partial Remission[d]	48 (n=12)	50 (n=2)	53 (n=10)	–
Clinical Improvement	4 (n=1)	–	5 (n=1)	–
Stable Disease	16 (n=4)	25 (n=1)	5 (n=1)	100 (n=2)
Progressive Disease	–	–	–	–
Not Evaluable	–	–	–	–
Median time to response (range), months	2.0 (0.3–12.2)	1.9 (0.3–2.1)	2.2 (0.5–12.2)	–
Median time to CR/CRh (range), months	5.8 (2.0–12.2)	2.1 (2.1–.2.1)	6.1 (2.0–12.2)	–
Median duration of response (95% CI), months	NR	NR	NR	NE

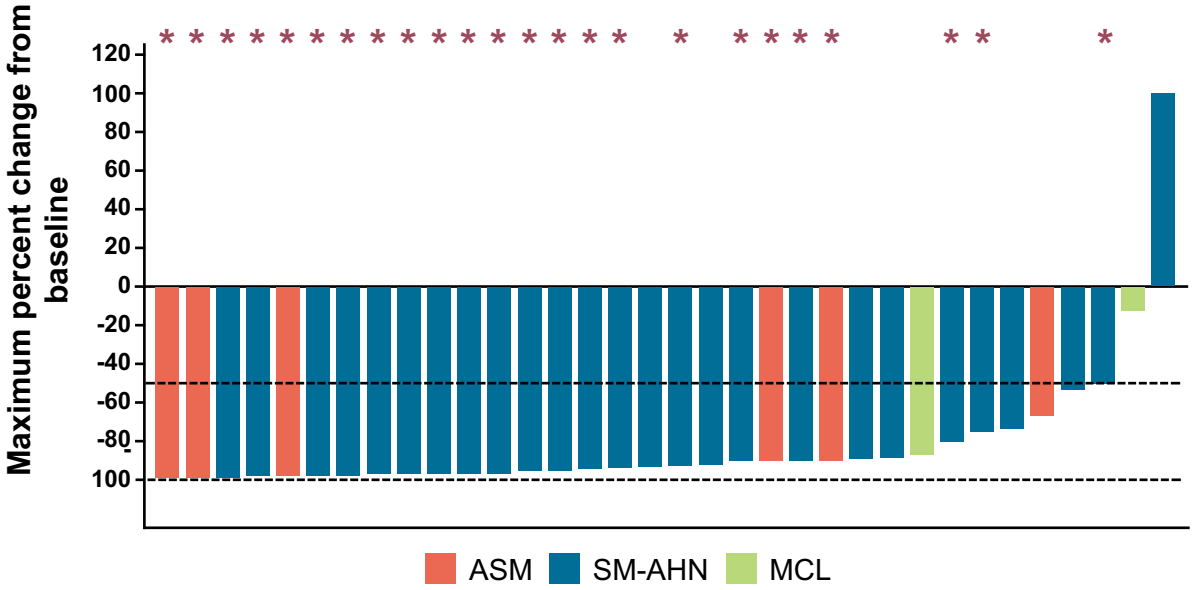
- **32% of patients in the ORR-evaluable population experienced complete remission (CR or CRh)**

Data cut off: April 20, 2021. [a]25 treatment-naïve patients with a confirmed diagnosis of AdvSM, and ORR evaluable per mIWG-MRT-ECNM criteria at baseline. [b]ORR includes CR, CRh, PR and 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 Hgb 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. CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

Profound reduction in disease burden observed across subtypes

Bone marrow MCs[a]

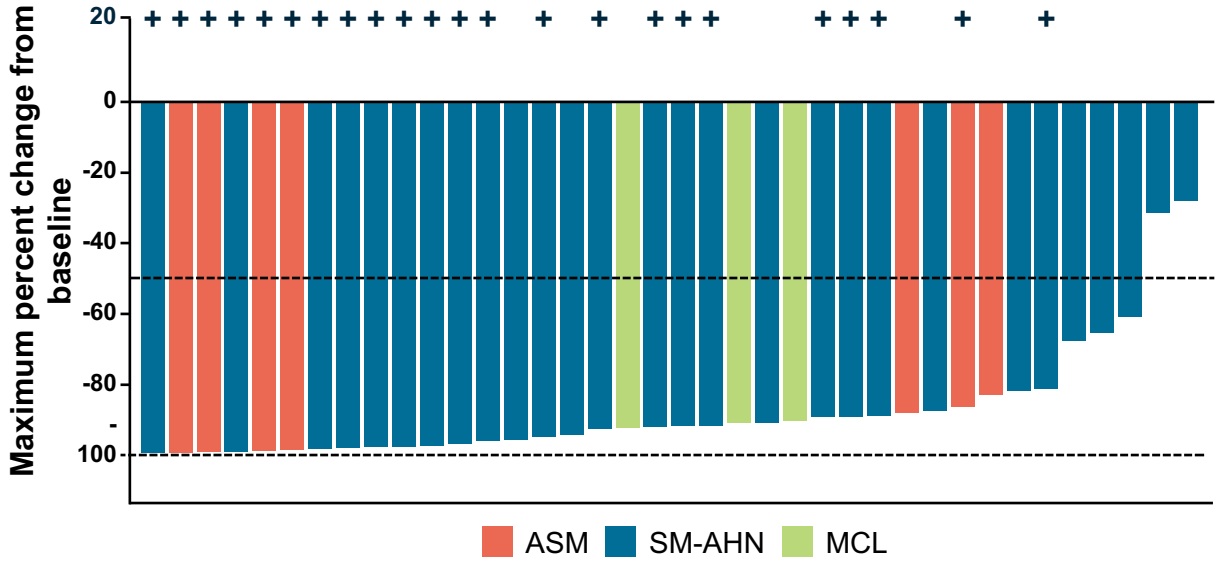
- **Bone marrow MCs decreased by ≥50% in 84% of patients (32/38),** including 25 of 28 patients with SM-AHN
- **MC aggregates total clearance in 63% of patients (24/38)**, including 19 of 28 patients with SM-AHN



* Best response: CR

Serum tryptase[a]

- **Serum tryptase level decreased by ≥50% in 95% of patients (36/38),** including 26 of 28 patients with SM-AHN
- **60% of patients (22/37) had CR (decrease to <20 ng/mL) in serum tryptase,** including 18 of 28 patients with SM-AHN



\+ Tryptase <20 ng/mL

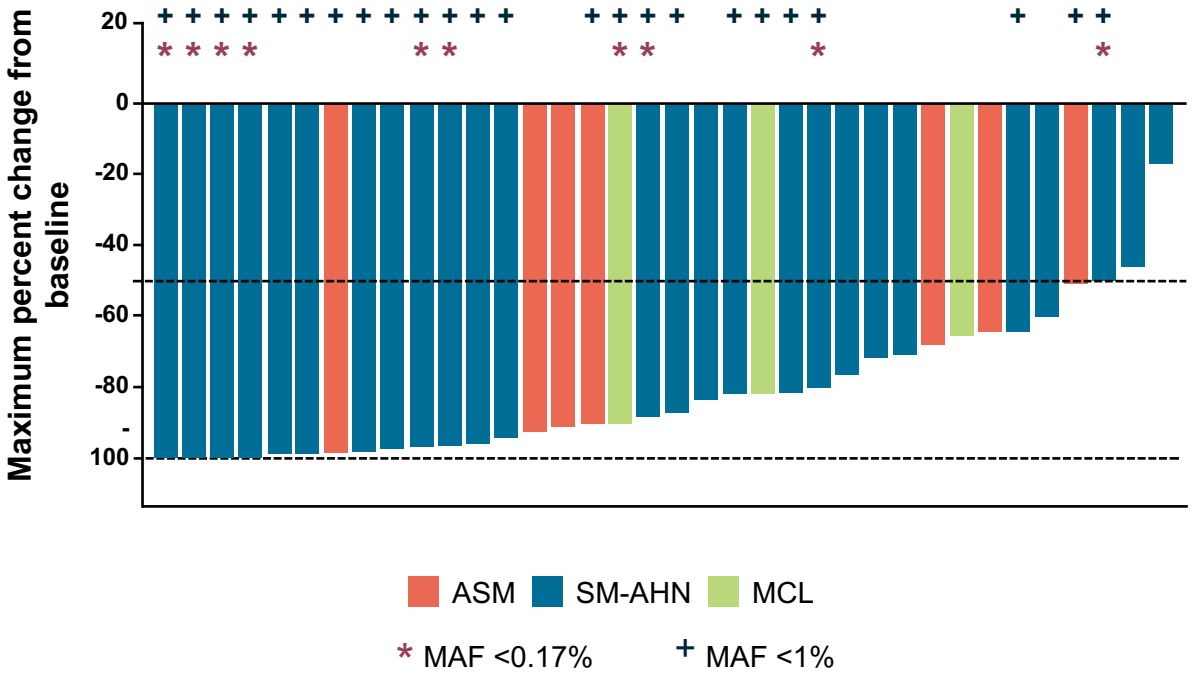
Data cut off: April 20, 2021.

[a]Only patients with post-baseline measurements were included in both waterfall plots. There was no type I error control.

Profound reduction in disease burden observed across subtypes

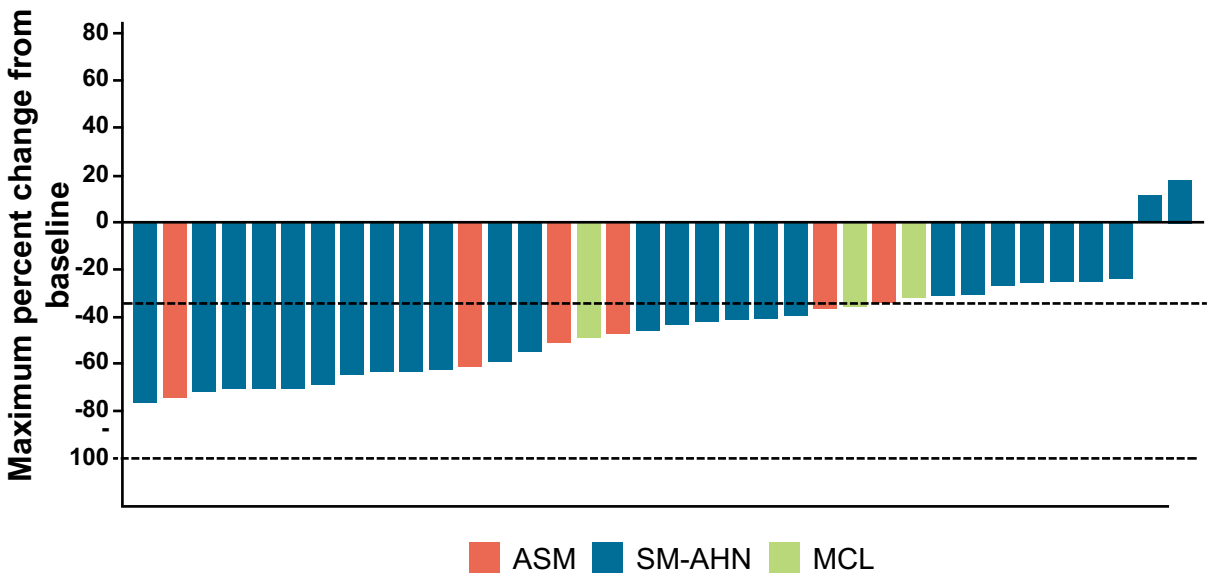
KIT D816V variant allele fraction in peripheral blood[a]

- ***KIT* D816V VAF[b] decreased by ≥50% in 89% of patients (34/38)**, including 24 of 28 patients with SM-AHN
- ***KIT* D816V VAF[b] decreased below 1% in 63% of patients (24/38)**, including 19 of 28 patients with SM-AHN



Spleen volume[a]

- **Spleen volume decreased by ≥35% in 66% of patients (25/38),** including 18 of 28 patients with SM-AHN
- **61% (n=11/18) of patients whose spleen was palpable at baseline became non-palpable during treatment,** including 10 of 28 patients with SM-AHN



Data cut off: April 20, 2021.

[a]There was no type I error control.

[b]*KIT* D816V VAF measured in peripheral blood using a ddPCR assay with detection limit of 0.17%, consistent with prior presentations on AdvSM.

ddPCR, droplet digital polymerase chain reaction.

High ORR across subtypes including patients with SM-AHN

Outcome, % (n)	All[a] (n=25)	ASM (n=4)	SM-AHN (n=19)	MCL (n=2)
ORR,[b]	84 (n=21)	75 (n=3)	**95 (n=18)**	–
CR or CRh	32 (n=8)	25 (n=1)	37 (n=7)	–
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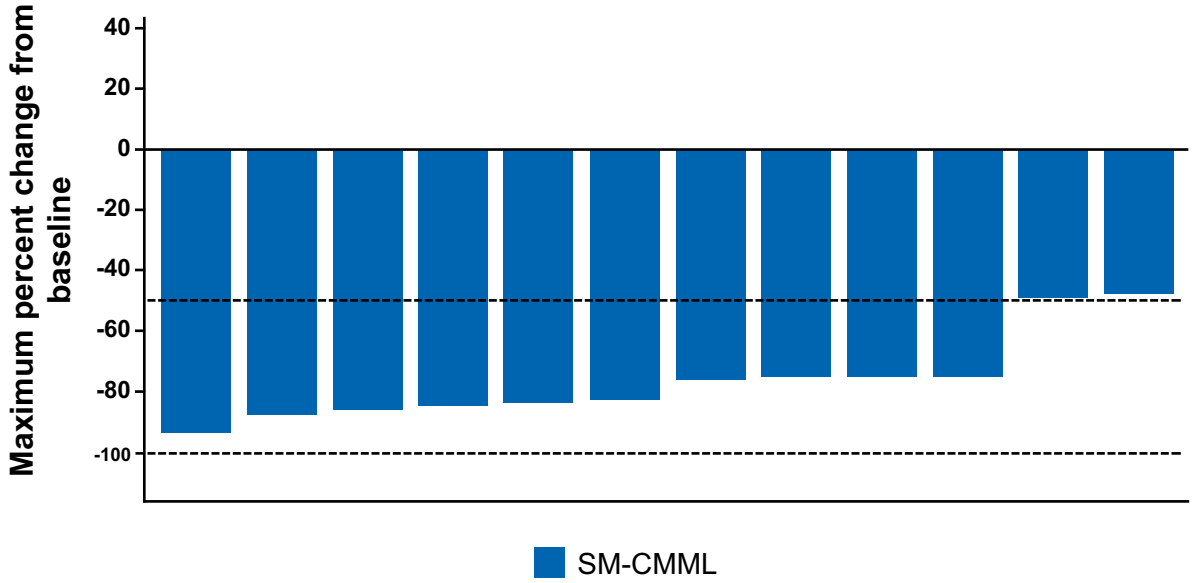
Stable Disease	16 (n=4)	25 (n=1)	5 (n=1)	100 (n=2)
Progressive Disease	–	–	–	–
Not Evaluable	–	–	–	–
Median time to response (range), months	2.0 (0.3–12.2)	1.9 (0.3–2.1)	2.2 (0.5–12.2)	–
Median time to CR/CRh (range), months	5.8 (2.0–12.2)	2.1 (2.1–.2.1)	6.1 (2.0–12.2)	–
Median duration of response (95% CI), months	NR	NR	NR	NE

Data cut off: April 20, 2021. [a]25 treatment-naïve patients with a confirmed diagnosis of AdvSM, and ORR evaluable per mIWG-MRT-ECNM criteria at baseline. [b]ORR includes CR, CRh, PR and 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 Hgb 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. CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

Reduction in circulating monocytes and eosinophils observed

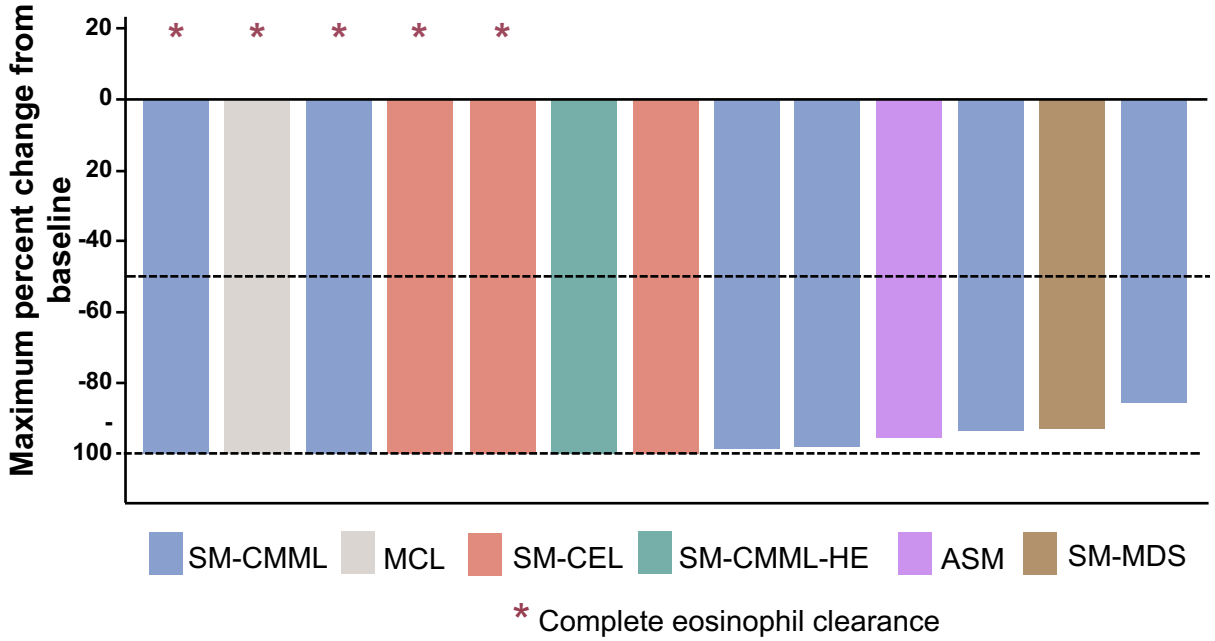
Monocytes in peripheral blood[a] (patients with SM-CMML)

- All 12 patients with CMML and post-baseline measurements showed decreases in monocyte counts with avapritinib



Eosinophils in peripheral blood[a]

- All 13 patients with baseline eosinophilia and post-baseline measurements showed decreases in eosinophil counts
- Five (38%) patients including 4 with SM-AHN had complete clearance of eosinophils



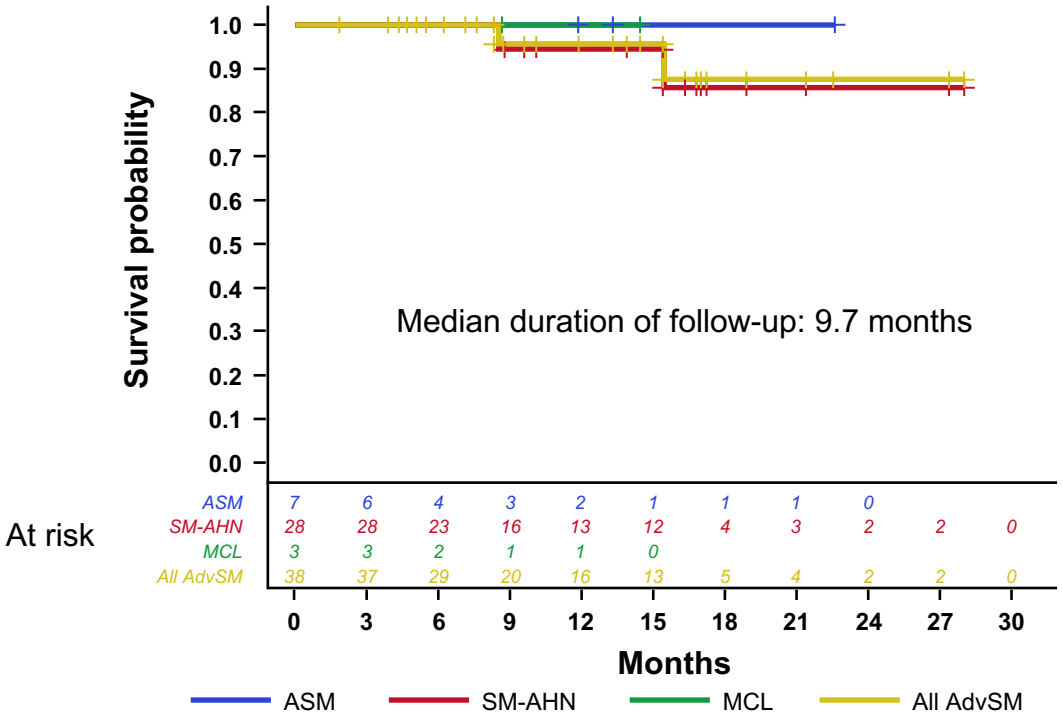
Bone marrow blasts

- Bone marrow blasts were reduced in 44% of patients with measurements (15/34), including 11 of 26 patients with SM-AHN

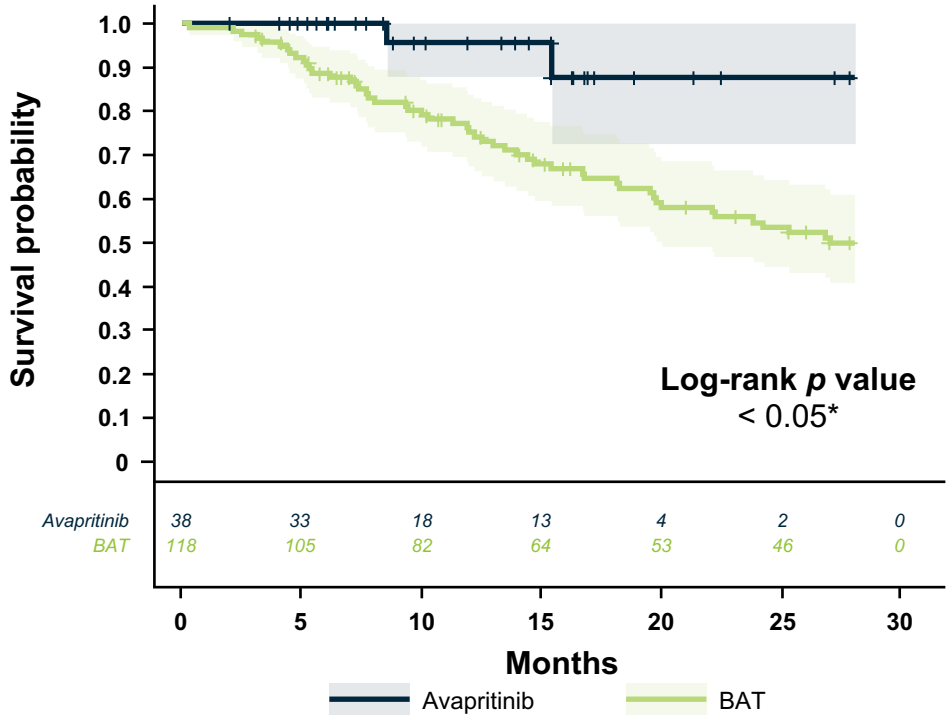
[a]There was no type I error control. Data was not statistically powered for these analyses.
SM-CEL, systemic mastocytosis with chronic eosinophilic leukemia; SM-CMML, systemic mastocytosis with associated hematologic neoplasm of chronic myelomonocytic leukemia; SM-CMML-HE, systemic mastocytosis with associated hematologic neoplasm of chronic myelomonocytic leukemia with hypereosinophilia; SM-MDS, systemic mastocytosis with myelodysplastic syndrome

Overall survival in PATHFINDER and vs real-world data

OS by disease subtypes



OS with avapritinib vs real-world best available therapy[a]



Estimated OS rate (95% CI)	All (n=38)	ASM (n=7)	SM-AHN (n=28)	MCL (n=3)
12 months	95.7 (87.3–100)	100 (100–100)	94.4 (83.9–100)	100 (100–100)
24 months	87.7 (70.9–100)	-	85.9 (67.2–100)	-

[a]Data for best available therapy from retrospective real-world patient chart review, methodology described previously; shading represents 95% confidence interval.[1] BAT, best available therapy.

1. Reiter A et al. Leukemia. 2022;36:2108-2120.

Avapritinib was generally well tolerated with a favorable benefit-risk profile

TRAEs in ≥10% of patients, n (%)	Any grade	Grade ≥3
Hematologic events, n (%)		
Thrombocytopenia	17 (44.7)	8 (21.1)
Anemia	10 (26.3)	5 (13.2)
Neutropenia	7 (18.4)	6 (15.8)
Neutrophil count decreased	6 (15.8)	5 (13.2)
Non-hematologic events, n (%)		
Periorbital edema	20 (52.6)	2 (5.3)
Edema peripheral	14 (36.8)	1 (2.6)
Dysgeusia	7 (18.4)	0
Fatigue	6 (15.8)	1 (2.6)
Nausea	5 (13.2)	0
Face edema	5 (13.2)	0
Eyelid edema	5 (13.2)	0
Hair color changes	5 (13.2)	0
Edema	4 (10.5)	0
Alopecia	4 (10.5)	0
Cognitive disorder	4 (10.5)	0

AE, adverse event; TRAE, treatment related adverse event.

1. Gotlib J et al. *Nat Med.* 2021;27:2192–2199.

In 38 patients who initiated 200 mg QD without prior antineoplastic treatment, the safety profile was similar to what was previously reported for avapritinib[1] :

- The most common TRAEs included periorbital edema, thrombocytopenia, and edema peripheral
- AEs were generally managed with dose modifications
  - TRAEs leading to dose reduction and interruption occurred in 74% (28/38) and 66% (25/38) of patients
- One intracranial bleeding event was reported in a patient who previously experienced head trauma
- Four (11%) patients discontinued treatment due to TRAEs
- No treatment-related deaths

Avapritinib demonstrates efficacy and tolerability as first-line treatment for patients with AdvSM

- **High response rate to avapritinib in previously untreated patients with AdvSM across subtypes**
  - 84% ORR (mIWG-MRT-ECNM criteria) including 32% CR/CRh (resolution of organ damage)
  - 95% ORR in patients with SM-AHN
- **Marked reductions in objective measures of disease burden**
  - ≥50% in BM MCs, serum tryptase, and *KIT* D816V VAF
  - Reductions in monocyte and eosinophil count observed in all patients with CMML and eosinophilia
- **Median OS not reached across subtypes**
  - 86% OS rate at 24 months in patients with SM-AHN
  - First-line avapritinib significantly improved OS vs real-world best available therapy[a]
- **Favorable benefit-risk as first-line treatment for patients with AdvSM**
  - Avapritinib was generally well-tolerated; AEs were managed with dose reductions/interruptions

[a]Data for best available therapy from retrospective real-world patient chart review

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BACKUP SLIDES

Backup: Evaluable C-findings per mIWG-MRT-ECNM criteria

- One or more evaluable C-finding required to be considered response-evaluable

Non-hematologic C-findings	
Ascites or pleural effusions	• Symptomatic ascites or pleural effusion requiring medical intervention such as: – Use of diuretics (Grade 2) or – ≥2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over 12 weeks before study entry with one procedure performed during the 6 weeks before study start
Liver function abnormalities	• Grade ≥2 abnormalities in direct bilirubin (>1.5 × ULN), AST (>3.0 × ULN), ALT (>3.0 × ULN) or AP (>2.5 × ULN) in the presence of: – Ascites and/or – Clinically relevant portal hypertension, and/or – Liver mast cell infiltration that is biopsy-proven, or – No other unidentified causes of abnormal liver function
Hypoalbuminemia	• Grade ≥2 hypalbuminaemia (<3.0 g/dL)
Marked splenomegaly	• Spleen palpable ≥5 cm below left costal margin

Haematologic C-findings	
Neutropenia	• Grade ≥3 absolute neutrophil counts (<1.0 x 10^9/L)
Anemia (transfusion-independent)	• Grade ≥2 hemoglobin (<10 g/dL)
Anemia (transfusion-dependent)	• Transfusion of ≥6 units packed red blood cells in the 12 weeks before start of treatment and • Most recent transfusion occurring during the preceding 4 weeks and • Transfusions administered for hemoglobin ≤8.5 g/dL, and • Reason for transfusions is not bleeding, hemolysis, or therapy-related
Thrombocytopenia (transfusion-independent)	• Grade ≥2 thrombocytopenia (<75 x 10^9/L)
Thrombocytopenia (transfusion-dependent)	• Transfusion of ≥6 units of apheresed platelets (or ≥6 pools of random donor or buffy coat) during the 12 weeks preceding treatment and • ≥2 units transfused during the preceding 4 weeks, and • Transfusions administered for platelet count <20 × 10^9/L

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Backup: mIWG-MRT-ECNM Response Criteria

Response	Criteria for Response
CR	Requires all four of the following criteria, and response duration must be ≥12 weeks: • No presence of compact neoplastic MC aggregates in the BM or other biopsied extracutaneous organ • Serum tryptase level <20 ng/mL • Peripheral blood count remission defined as: – ANC ≥1 × 10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* – Platelet count ≥100 × 10^9/L *and* – Hgb level ≥11 g/dL • Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (C-findings)
CRh	Requires all criteria for CR be met and response duration must be ≥12 weeks; however, patient may have residual cytopenias. The following minimum recovery of peripheral blood counts is required: • ANC >0.5 × 10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* • Platelet count >50 × 10^9/L *and* • Hgb level >8.0 g/dL
PR	Requires all three of the following criteria, and response duration must be ≥12 weeks, in the absence of CR/CRh and PD: • Reduction by ≥50% in neoplastic MCs in the BM and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage • Reduction of serum tryptase level by ≥50% • Resolution of one or more biopsy-proven or suspected SM-related organ damage (C-findings)

Response	Criteria for Response	
CI	• Response duration must be ≥12 weeks • Requires one or more of the non-hematologic and/or hematologic response criteria to be fulfilled in the absence of CR, CRh, PR, or PD	
SD	Not meeting criteria for CR/CRh, PR, CI, or PD	
PD	Requires ≥1 element from the criteria below; duration must be ≥4 weeks:	
	Baseline	**Post Baseline**
	Any Grade 2 non-hematologic organ damage	• Worsening by 1 grade *and* • Minimum 100% increase (doubling) of laboratory abnormality
	Grade ≥2 albumin	• Worsening by 1 grade *and* • Decrease by ≥0.5 g/dL
	Grade ≥3 non-hematologic organ damage	Minimum 100% increase (doubling) of laboratory abnormality
	Grade ≥2 transfusion-independent anemia or thrombocytopenia	New transfusion dependence for an 8-week period of ≥4 units of PRBCs or platelets

ANC, absolute neutrophil count; Hgb, hemoglobin; PBRCs, packed red blood cells.