Avapritinib in Patients With Advanced Systemic Mastocytosis (AdvSM): Efficacy and Safety Analysis From the Phase 2 PATHFINDER Study With 3-year Follow-up

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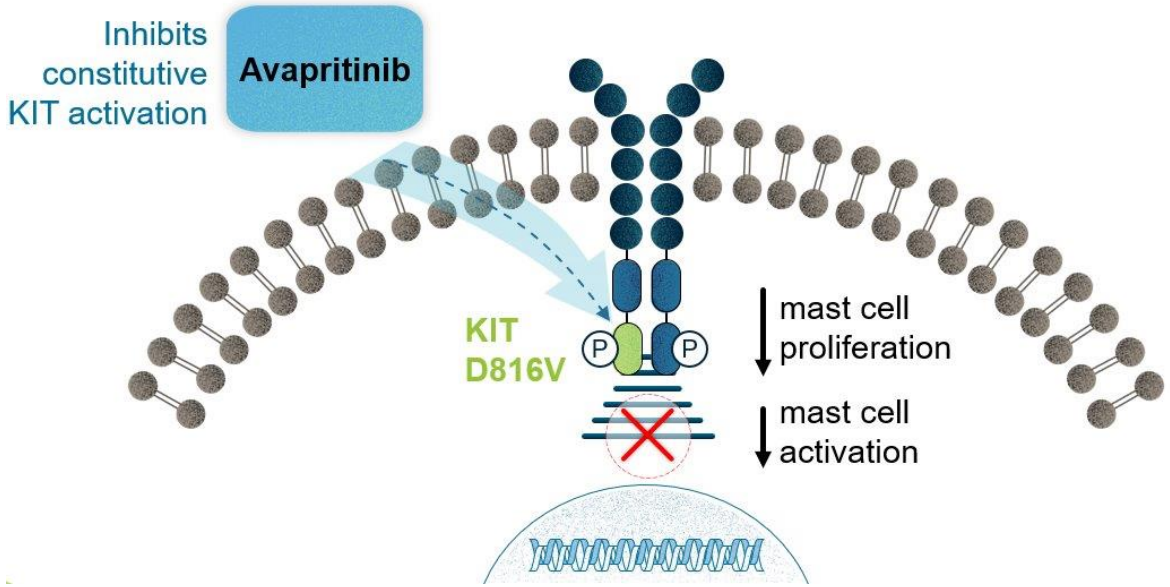
AdvSM is a clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases

- Advanced systemic mastocytosis (AdvSM) encompasses aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL)[1–5]
- AdvSM is characterized by the proliferation and infiltration of neoplastic mast cells (MCs) and variably, hematologic neoplasms in various organs that can result in life-threatening organ damage and reduced survival[6,7]
- Hyperactivation and MC mediator release often lead to severe and debilitating symptoms associated with functional impairment and reduced quality of life[6,7]
- Patients with AdvSM have a poor prognosis
  - Reported median overall survival (OS) of 3.4–6.2 years in ASM, 2.0–2.9 years in SM-AHN, and 0.2–1.9 years in MCL[8–10]

1. Kristensen T et al. *Am J Hematol*. 2014;89:493–498; 2. Rossignol J et al. *F1000 Faculty Rev-1961*. 2019;8; 3. Shomali W et al. *Hematology Am Soc Hematol Educ Program*. 2018;2018:127–36; 4. Ungerstedt J et al. *Cancers (Basel).* 2022;14:3942; 5. Garcia-Montero AC et al. *Blood*. 2006;108:2366–2372; 6. Pardanani A. *Am J Hematol*. 2023;98:1097–1116; 7. Valent P et al. *Int J Mol Sci*. 2019;20:2976. 8. Lim K-H et al. *Blood.* 2009;113:5727–5736. 9. Sperr WR et al. *Lancet Haematol.* 2019;6:e638–649. 10. Kennedy VE et al. *Blood Adv.* 2023;7:1713–1724.

Avapritinib is a highly potent and selective KIT D816V inhibitor

- Avapritinib is approved for adult patients with AdvSM or indolent systemic mastocytosis (ISM)
  - AdvSM approval was based on the phase 1 EXPLORER and phase 2 PATHFINDER studies[a,1–4]
  - ISM approval was based on outcomes of the phase 2 PIONEER trial[b,1,2,5]



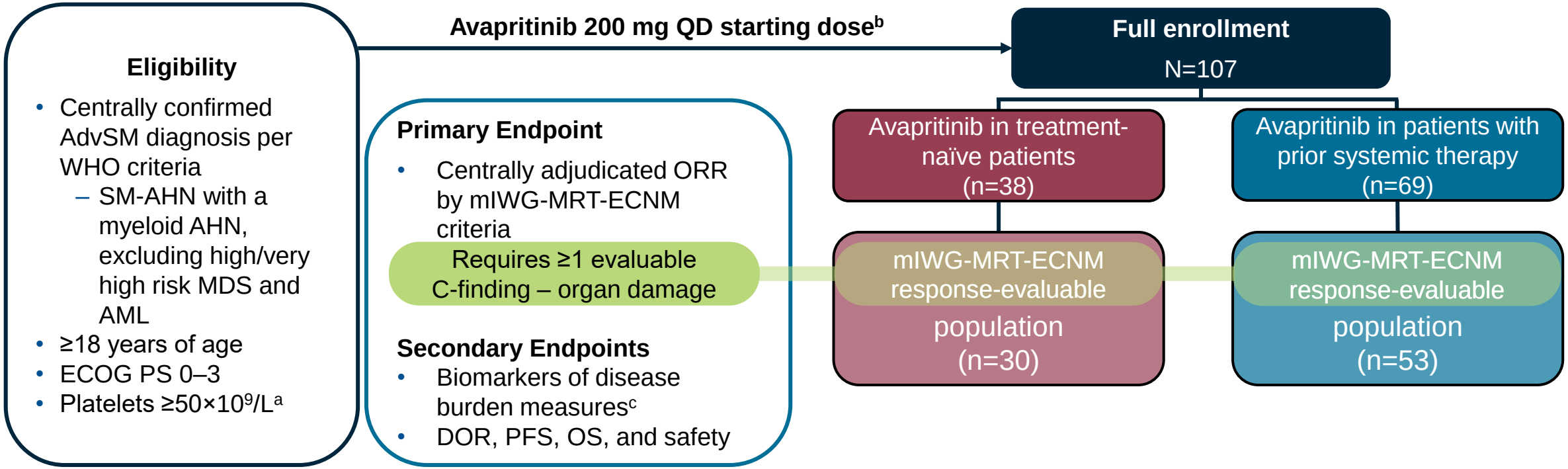
Potently and selectively inhibits the autophosphorylation of KIT D816V, with an IC_{50} of 0.27 nanomolar in selective cellular assays[6]

[a]Avapritinib is approved in the USA for adult patients with AdvSM irrespective of prior therapy and in Europe for adult patients with AdvSM after ≥1 systemic therapy. [b]Avapritinib is approved in the USA for adult patients with ISM and in Europe for adult patients with ISM with moderate to severe symptoms inadequately controlled on symptomatic treatment.
IC_{50}, half-maximal inhibitory concentration.

1. Ayvakit (avapritinib) [package insert]. May 2023. Blueprint Medicines Corporation; 2. Ayvakyt (avapritinib) Prescribing Information. 2024. Blueprint Medicines Corporation; 3. DeAngelo DJ et al. *Nat Med*. 2021;27:2183–2191; 4. Gotlib J et al. *Nat Med*. 2021;27:2192–2199. 5. Gotlib J et al. *NEJM Evid.* 2023;2:EVIDoa2200339. 6. Evans EK et al. *Sci. Transl. Med* 2017;9:eaao1690.

PATHFINDER: 3-year efficacy and safety

- 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 a centrally confirmed AdvSM



Data cut-off date: September 15, 2023. [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]Biomarkers of disease burden measures include BM MCs, serum tryptase, *KIT* D816V variant allele fraction (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 syndrome; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR, objective response rate; OS, overall survival; PFS, progression free survival; QD, once daily; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; WHO, World Health Organization.

Patient baseline characteristics

	All AdvSM[a] (N=107)	Treatment-naïve patients (n=38)	Patients with prior systemic therapy (n=69)
Age, median years (range)	**68 (31–88)**	68 (39–88)	68 (31–86)
Female, n (%)	**45 (42)**	18 (47)	27 (39)
ECOG performance status, n (%)			
2–3[b]	**28 (26)**	7 (18)	21 (30)
AdvSM subtype per central assessment, n (%)			
ASM	**21 (20)**	7 (18)	14 (20)
SM-AHN[c]	**71 (66)**	28 (74)	43 (62)
MCL (including 4 MCL-AHN)[d]	**15 (14)**	3 (8)	12 (17)
BM MC burden, median percentage (range)	**40 (1–95)**	35 (3–90)	50 (1–95)
Serum tryptase level, median ng/mL (range)	**262 (24–1600)**	178 (37–1336)	312 (24–1600)
***KIT* D816V mutation by central assay, n (%)**	**103 (96)**	36 (95)	67 (97)
***KIT* D816V VAF,[e] median percent (range)**	**16 (0–47)**	6 (0–45)	20 (0–47)
***S/A/R* mutation per central assay,[f] n (%)**	**48 (45)**	23 (61)	25 (36)
Number of prior antineoplastic therapy, median (range)	**1 (0–6)**	0	1 (0–6)
1 prior antineoplastic therapy, n (%)	**42 (39)**	–	42 (61)
≥2 prior antineoplastic therapies, n (%)	**27 (25)**	–	27 (39)

Data cut-off date: September 15, 2023. [a]Patients with AdvSM initiated avapritinib 200 mg (n=105) or 100 mg (n=2) QD. [b]Remaining patients are ECOG performance status 0–1. [c]SM-AHN subtypes included CMML (30%), MDS (11%), MPN (2%), MDS/MPN-U (14%), CEL (6%), and other (4%). [d]Of the patients with subtype MCL (n=15), 4 were MCL-AHN. [e]Assessed by ddPCR in both peripheral blood and BM (majority were in peripheral blood); limit of detection 0.02%. [f]Assessed by NGS.

ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; ddPCR, digital droplet polymerase chain reaction; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with an associated hematologic neoplasm; MDS/MPN-U, myelodysplastic syndrome/ myeloproliferative neoplasm-unclassifiable; NGS, next-generation sequencing.

Avapritinib demonstrated a high response rate across subtypes and regardless of prior treatment

	All[a] (n=83)	AdvSM subtype			Treatment-naïve (n=30)	Patients with ≥1 prior systemic therapy (n=53)
		ASM (n=13)	SM-AHN (n=55)	MCL (n=15)		
ORR,[b] n (%) **95% CI**	**61 (73)** **63–83**	10 (77) 46–95	41 (75) 61–85	10 (67) 38–88	26 (87) 69–96	35 (66) 52–79
Best response						
CR or CRh[c]	**24 (29)**	3 (23)	18 (33)	3 (20)	13 (43)	11 (21)
CR	**13 (16)**	1 (8)	9 (16)	3 (20)	7 (23)	6 (11)
CRh	**11 (13)**	2 (15)	9 (16)	0	6 (20)	5 (9)
PR[d]	**33 (40)**	7 (54)	19 (35)	7 (47)	13 (43)	20 (38)
CI	**4 (5)**	0	4 (7)	0	0	4 (8)
SD	**13 (16)**	3 (23)	7 (13)	3 (20)	3 (10)	10 (19)
PD	**2 (2)**	0	1 (2)	1 (7)	0	2 (4)
NE	**7 (8)**	0	6 (11)	1 (7)	1 (3)	6 (11)
Patients with best *KIT* D816V VAF response <1%, n (%)[e]	55 (67)	8 (62)	38 (70)	9 (60)	27 (90)	28 (54)

Data cut-off date: September 15, 2023. Median follow-up of 38 months. [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 mast cell 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 bone marrow mast cells and serum tryptase. [e]82 of 83 patients had baseline and post baseline VAF measurements; 1 patient (SM-AHN with prior systemic treatment) had no post baseline VAF measurement.

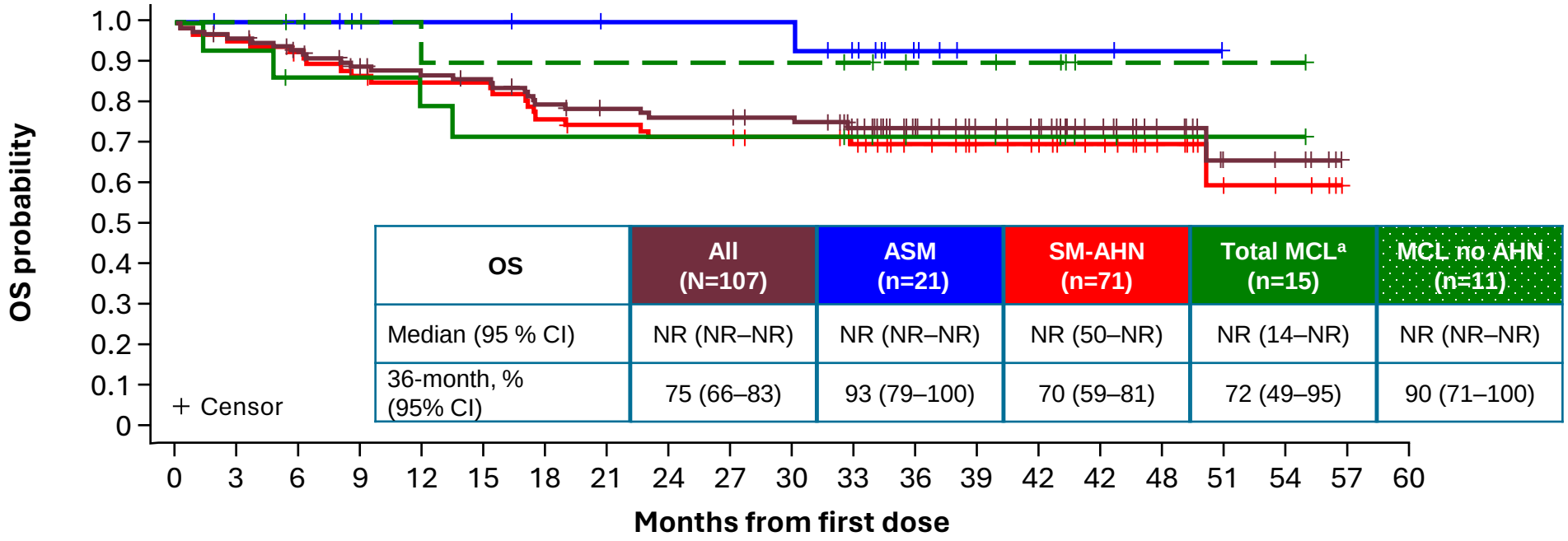
95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; mCR, morphologic complete remission; mCRh, morphologic complete remission with partial recovery of peripheral blood counts; mPR, morphologic partial remission; NR, not reached; PR, partial response; PD, progressive disease; SD, stable disease.

Avapritinib demonstrated durable sustained responses with no SM progressions

- **Median follow-up was 38 months**
- **Median (range) time to response (TTR) was 2.3 (0.3–20.3) months**
  - TTR for MCL was 7.3 (1.7–12.2) months
- **Median duration of response (DOR) and progression-free survival (PFS) were not reached**
- **Rate of disease progression was 14% (15/107[a]) in patients with AdvSM receiving avapritinib**
  - AHN progressions occurred in 11 patients
  - Non-mast cell progressions of undetermined cause occurred in 4 patients

Data cut-off date: September 15, 2023. [a]Following abstract submission, 3 patients originally classified as having PD were re-adjudicated per central review to not PD.

Median overall survival was not reached regardless of AdvSM subtype

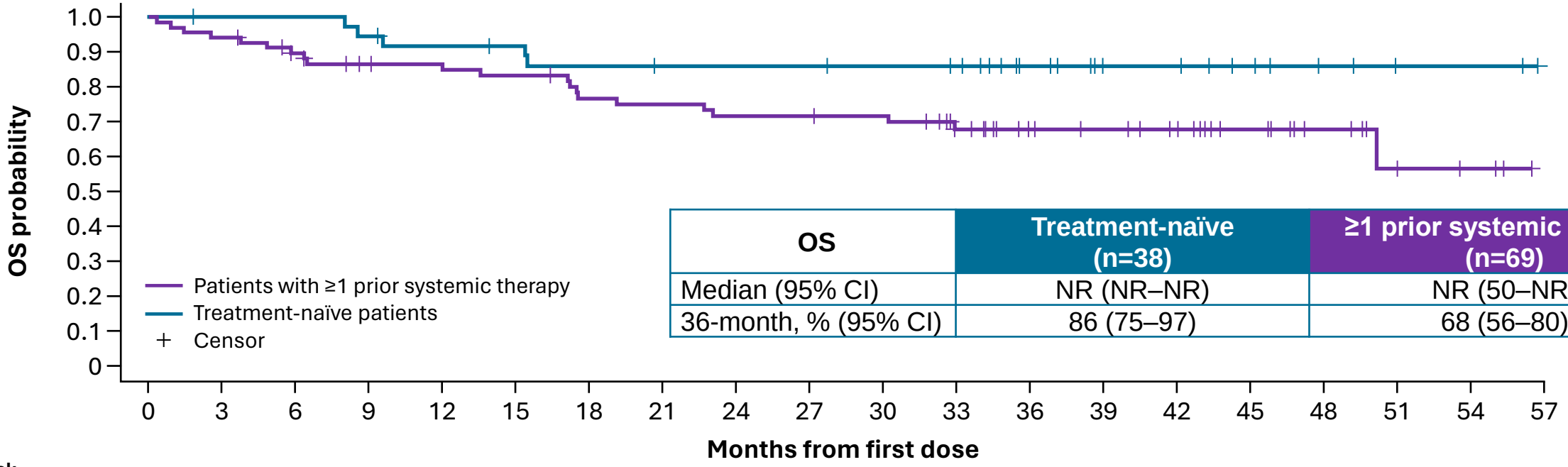


OS	All (N=107)	ASM (n=21)	SM-AHN (n=71)	Total MCL[a] (n=15)	MCL no AHN (n=11)
Median (95 % CI)	NR (NR–NR)	NR (NR–NR)	NR (50–NR)	NR (14–NR)	NR (NR–NR)
36-month, % (95% CI)	75 (66–83)	93 (79–100)	70 (59–81)	72 (49–95)	90 (71–100)

At risk																				
All AdvSM	107	102	96	89	85	83	76	73	71	71	69	61	46	35	32	22	13	6	5	0
ASM	21	20	20	17	16	16	15	14	14	14	14	11	6	3	3	2	1	0		
SM-AHN	71	68	64	60	58	57	51	49	47	47	45	41	33	25	23	18	11	5	4	0
Total MCL[a]	15	14	12	12	11	10	10	10	10	10	10	9	7	7	6	2	1	1	1	0
MCL no AHN	11	11	10	10	9	9	9	9	9	9	9	8	6	6	5	1	1	1	1	0

Data cut-off date: September 15, 2023. Median (range) follow-up was 38 months (95% CI; 35.5–42.0). [a]Includes subset with no AHN (n=11) and subset with AHN (n=4). Per WHO classification, the diagnostic criteria for subtyping MCL includes BM aspirate smears ≥20% (regardless of the presence of AHN).

Median overall survival was not reached regardless of treatment history



OS	Treatment-naïve (n=38)	≥1 prior systemic therapy (n=69)
Median (95% CI)	NR (NR–NR)	NR (50–NR)
36-month, % (95% CI)	86 (75–97)	68 (56–80)

At risk

Treatment-naïve	38	37	37	35	33	32	30	29	29	29	28	27	20	12	12	8	4	2	2	0
≥1 prior systemic therapy	69	65	59	54	52	51	46	44	42	42	41	34	26	23	20	14	9	4	3	0

Data cut-off date: September 15, 2023. Median (range) follow-up was 38 months (95% CI; 35.5–42.0).

Continued favorable safety profile after more than 3 years of follow-up with avapritinib

Long term safety and tolerability are well characterized and consistent with prior reports[1]:

- AEs were generally managed with dose modifications
  - Dose reductions, interruptions, and discontinuations due to TRAEs occurred in 76%, 63%, and 13% of patients, respectively
- Treatment-related cognitive effects remained similar to previous reports[1] and were mostly Grade 1–2
- No additional intracranial bleeding events since prior data cut-off in September 2022 (n=4 [3.7% of patients])[1]
- No treatment-related deaths occurred

Most common TRAEs (≥15%), n (%)	Safety population (N=107)	
	Any grade	Grade 3/4
Hematological AEs		
Thrombocytopenia[a]	43 (40)	19 (18)
Anemia[a]	34 (32)	14 (13)
Neutropenia[a]	20 (19)	18 (17)
Non-hematological AEs		
Periorbital edema	44 (41)	6 (6)
Peripheral edema	41 (38)	2 (2)
Cognitive disorder	18 (17)	3 (3)
Eyelid edema[a]	18 (17)	0 (0)
Hair color changes	18 (17)	0 (0)
Face edema	17 (16)	0 (0)

Data cutoff date: September 15, 2023. [a]Grouped term. AE, adverse event; TRAE, treatment-related adverse event

1. Gotlib et al. Presented at EHA 2023. Poster #P1023

Avapritinib continued to demonstrate a favorable benefit-risk profile after more than 3 years of follow-up

- **Avapritinib demonstrated deep and sustained effects regardless of AdvSM subtype or prior therapy including:**
  - High ORR (73%), including 87% in a treatment-naïve setting, by centrally-adjudicated mIWG-MRT-ECNM criteria
  - CR/CRh in 29% of all patients and 43% in treatment-naïve patients
  - Low rate of progression with no MC progressions
  - Median DOR and PFS were not reached
- **Median OS was not reached with OS of 75% at 36 months**
  - Data in treatment-naïve patients suggest better outcomes with earlier treatment
- **Avapritinib maintained a well characterized safety profile with no new safety concerns observed**
  - AEs were effectively managed with dose reductions/interruptions with sustained efficacy

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- We also thank the investigators and clinical trial teams who participated in the study

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