

Efficacy and Safety of ≤200 mg Avapritinib in Patients With Advanced Systemic Mastocytosis: Pooled Results From Phase 1 EXPLORER and Interim Phase 2 PATHFINDER Studies

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Background

- Systemic mastocytosis (SM) is a rare hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases and is often characterized by skin, gastrointestinal, and systemic mast cell (MC) mediated symptoms^{1,2}
- Organ damage and severe pathologic features in patients with advanced SM (AdvSM) result in poor survival outcomes; MC hyperactivation also leads to severe mediator symptoms and poor quality of life³
- AdvSM comprises three subtypes: aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL)⁴
- Avapritinib is approved in the USA for the treatment of adult patients with AdvSM at a recommended dose of 200 mg once daily (QD),⁵ based on results from the EXPLORER and PATHFINDER studies
 - Avapritinib is not recommended for the treatment of patients with AdvSM with platelet counts less than 50×10⁹/L⁵
- EXPLORER (NCT02561988) is an open-label, phase 1 study with expansion that established the phase 2 recommended dose and evaluated the safety and efficacy of avapritinib 30–400 mg QD in patients with AdvSM or other relapsed/refractory myeloid malignancies⁶
- PATHFINDER (NCT03580655) is an ongoing, open-label, single-arm, phase 2 study evaluating the efficacy and safety of avapritinib 200 mg QD in patients with AdvSM⁷
- Here we report on pooled analyses of patients with centrally confirmed AdvSM enrolled in the EXPLORER and PATHFINDER studies treated with avapritinib at starting doses up to 200 mg QD

Results

With the data cut-off date of May 27, 2020 for EXPLORER and June 23, 2020 for PATHFINDER, demographics and baseline characteristics are shown for three AdvSM populations:

- Overall safety population:** 131 patients who initiated avapritinib at 30–400 mg QD
 - 69 patients in EXPLORER, 62 patients in PATHFINDER
- 200 mg starting dose population:** 80 patients who initiated avapritinib at 200 mg QD
- Overall response rate (ORR)-evaluable population:** 53 patients who were response-evaluable per modified (m) International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) response criteria and initiated at avapritinib doses ≤200 mg QD

Patient demographics and baseline characteristics

Characteristic	ORR-evaluable (n=53)	200 mg starting dose population (n=80)	Overall safety population (N=131)
Median age, years (range)	67 (37–85)	69 (31–88)	68 (31–88)
Male, n (%)	31 (58)	46 (58)	75 (57)
ECOG PS, n (%)			
0–1	36 (68)	55 (69)	91 (69)
2–3	17 (32)	25 (31)	40 (31)
ASM, n (%)	2 (4)	9 (11)	17 (13)
SM-AHN, n (%)	40 (75)	55 (69)	91 (69)
CEL	4 (8)	4 (5)	5 (4)
CMML	18 (34)	27 (34)	45 (34)
MDS	5 (9)	4 (5)	9 (7)
MDS/MPN-U	10 (19)	13 (16)	25 (19)
MPN	1 (2)	2 (3)	2 (2)
Other	2 (4)	5 (6)	5 (4)
MCL, n (%)	11 (21)	16 (20)	23 (18)
Prior antineoplastic therapy, n (%)	35 (66)	52 (65)	83 (63)
Prior midostaurin, n (%)	25 (47)	42 (53)	57 (44)
<i>KIT</i> D816V positive, n (%)	50 (94)	75 (94)	123 (94)
<i>SRSF2/ASXL1/RUNX1</i> positive, n (%)	26 (49)	36 (45)	62 (47)
Median BM MC burden, % (range)	50 (5–95)	50 (1–95)	40 (1–95)
Median serum tryptase, ng/mL (range)	256 (24–1600)	256 (20–1600)	215 (12–1600)

ASM, aggressive systemic mastocytosis; BM, bone marrow; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MC, mast cell; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN-U, unclassifiable myeloproliferative neoplasm; ORR, overall response rate; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

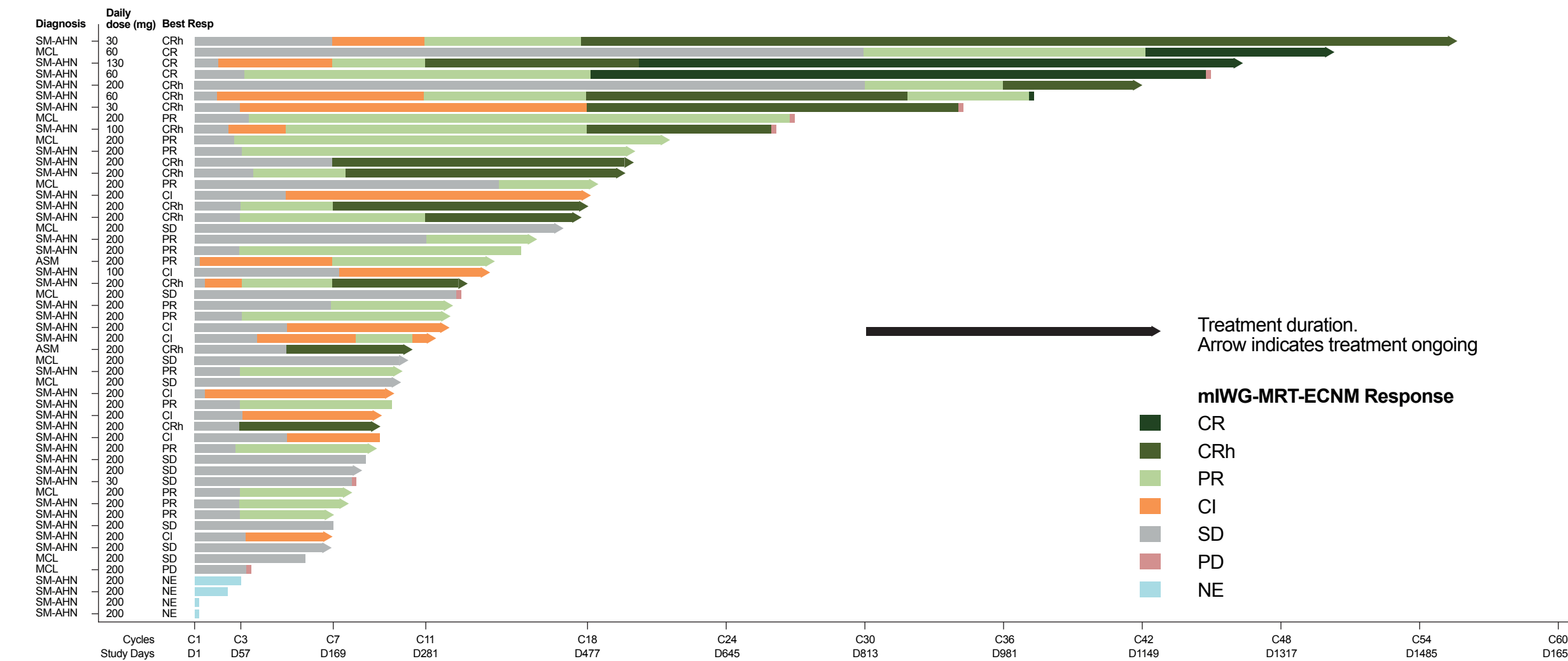
ORR and estimated PFS by mIWG-MRT-ECNM response criteria

	All ORR-evaluable (n=53)	ASM (n=2)	SM-AHN (n=40)	MCL (n=11)	Prior antineoplastic Tx		Prior midostaurin		S/A/R mutation positive	
					Yes (n=35)	No (n=18)	Yes (n=25)	No (n=28)	Yes (n=26)	No (n=27)
ORR (CR+CRh+PR+CI), n (%)	38 (72)	2 (100)	31 (78)	5 (45)	24 (69)	14 (78)	17 (68)	21 (75)	18 (69)	20 (74)
CR or CRh, n (%)	15 (28)	1 (50)	13 (33)	1 (9)	8 (23)	7 (39)	5 (20)	10 (36)	8 (31)	7 (26)
CRh, n (%)	12 (23)	1 (50)	11 (28)	0	6 (17)	6 (33)	4 (16)	8 (29)	7 (27)	5 (19)
PR, n (%)	15 (28)	1 (50)	10 (25)	4 (36)	9 (26)	6 (33)	6 (24)	9 (32)	5 (19)	10 (37)
CI, n (%)	8 (15)	0	8 (20)	0	7 (20)	1 (6)	6 (24)	2 (7)	5 (19)	3 (11)
SD, n (%)	10 (19)	0	5 (13)	5 (45)	6 (17)	4 (22)	4 (16)	6 (21)	4 (15)	6 (22)
PD, n (%)	1 (2)	0	0	1 (9)	1 (3)	0	0	1 (4)	0	1 (4)
NE, n (%)	4 (8)	0	4 (10)	0	4 (11)	0	4 (16)	0	4 (15)	0
Estimated median PFS, months (95% CI)	40.3 (23.0–NE)	NE (NE–NE)	40.3 (23.0–NE)	23.8 (10.5–NE)	NE (NE–NE)	30.5 (23.0–40.3)	NE (NE–NE)	40.3 (23.0–NE)	23.8 (10.5–NE)	40.3 (30.5–NE)

ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete response; CRh, CR with partial hematologic recovery; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL, mast cell leukemia; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial remission; S/A/R, *SRSF2/ASXL1/RUNX1*; SD, stable disease; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; Tx, therapy.

- CR+CRh+PR rate in the ORR-evaluable population (n=53) was 57%**

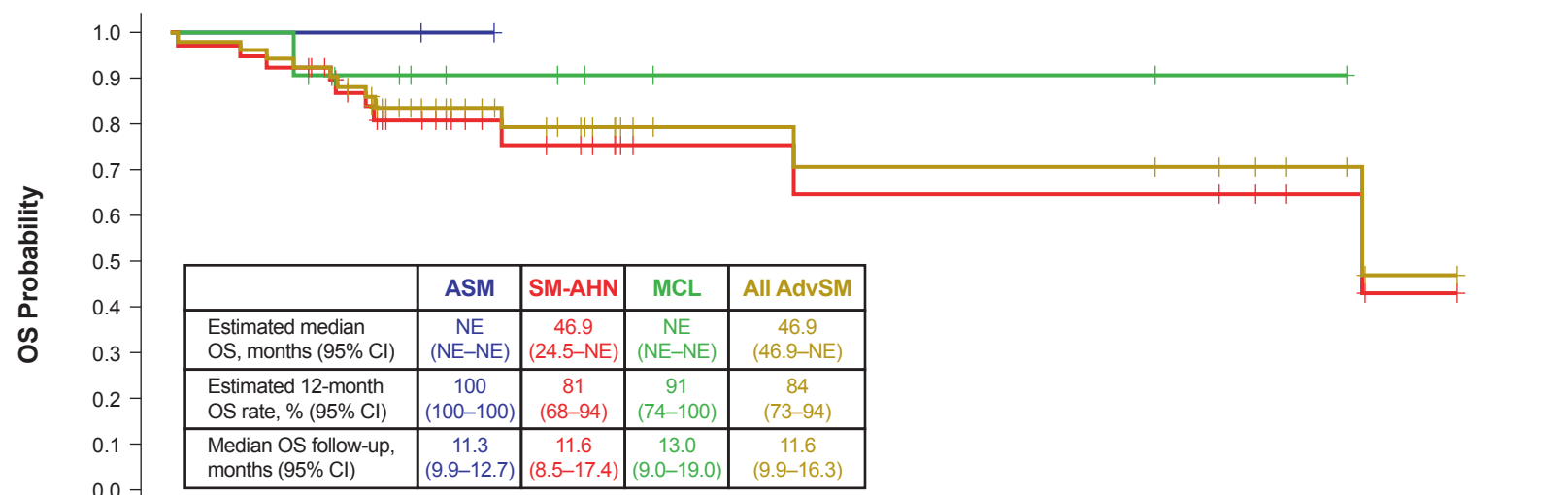
Deepening responses per mIWG-MRT-ECNM criteria over time (ORR-evaluable population)



ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete response; CRh, complete response with partial hematologic recovery; KM, Kaplan–Meier; MCL, mast cell leukemia; 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; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

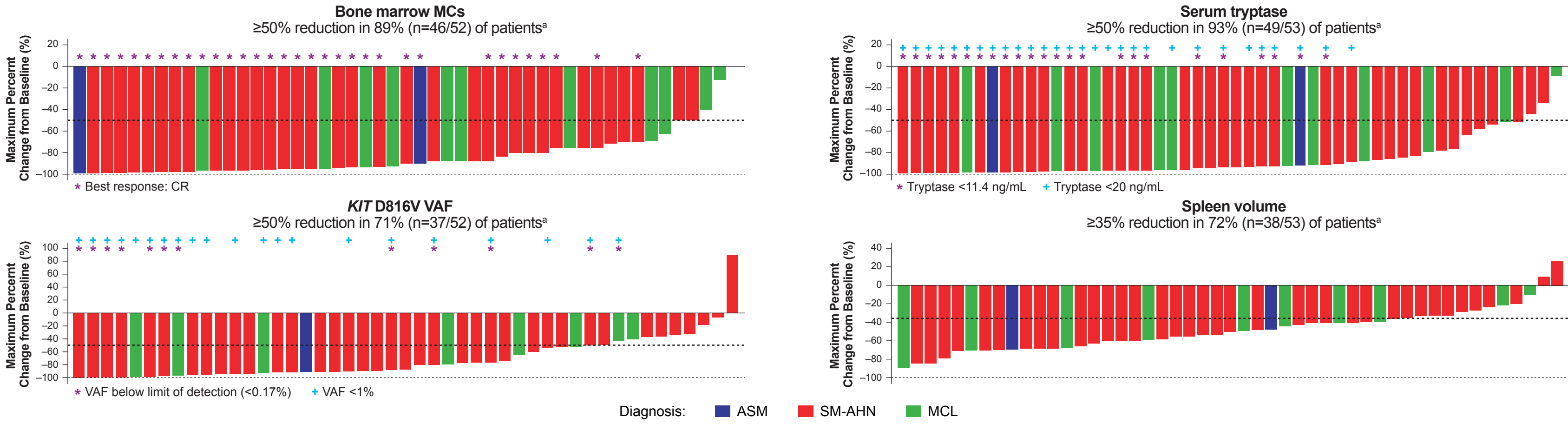
Estimates of OS and correlation with response (ORR-evaluable population)

KM curves of overall survival by AdvSM subtype



AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, clinical improvement; CRh, complete response with partial hematologic recovery; KM, Kaplan–Meier; MCL, mast cell leukemia; NE, not evaluable; ORR, overall response rate; OS, overall survival; PR, partial response; SD, stable disease; SM-AHN, systemic mastocytosis with associated hematologic neoplasm.

Reductions in biomarkers of disease burden (ORR-evaluable population)



*Calculation includes patients without post baseline assessments, who were excluded from the waterfall plot. CR, complete response; MC, mast cell; ORR, overall response rate; VAF, variant allele fraction.

Adverse events (AEs)

AEs in ≥10% of patients,* n (%)	200 mg starting dose population (n=80)		Overall safety population (N=131)	
	All grades	Grade ≥3	All grades	Grade ≥3
Edema ^b	63 (79)	4 (5)	106 (81)	5 (4)
Thrombocytopenia	28 (35)	12 (15)	53 (40)	30 (23)
Anemia	26 (33)	16 (20)	58 (44)	35 (27)
Diarrhea	22 (28)	1 (1)	44 (34)	1 (<1)
Nausea	19 (24)	1 (1)	40 (31)	4 (3)
Fatigue/Asthenia ^b	18 (23)	3 (4)	37 (28)	9 (7)
Vomiting	14 (18)	2 (3)	33 (25)	4 (3)
Neutropenia	13 (16)	12 (15)	22 (17)	21 (16)
Headache	12 (15)	0	17 (13)	1 (<1)
Cognitive effects ^b	11 (14)	1 (1)	33 (25)	3 (2)
Abdominal pain ^b	11 (14)	1 (1)	27 (21)	1 (<1)
Taste effects ^b	10 (13)	0	21 (16)	0
Dizziness	10 (13)	0	19 (15)	1 (<1)
Platelet count decreased	10 (13)	7 (9)	13 (10)	9 (7)
Constipation	9 (11)	0	20 (15)	1 (<1)
Epistaxis	9 (11)	0	18 (14)	0
Arthralgia	8 (10)	1 (1)	23 (18)	2 (2)

*List of AEs limited to those with ≥10% incidence (all grades) in the 200 mg starting dose population (n=80).

^bGrouped terms.

- Median follow-up was 7.9 months (95% CI, 6.8–9.0) in the 200 mg starting dose population (n=80) and 12.7 months (95% CI, 9.6–17.5) in the overall safety population (N=131)

In the 200 mg starting dose population (n=80):

- Three patients (4%) had subdural hematomas. Serious AEs of a hemorrhagic nature included hemorrhagic diathesis, duodenal ulcer, hemorrhagic shock, hemorrhage, and gastrointestinal (GI), bronchial, intra-abdominal, and lower GI hemorrhages (1 [1%] patient each)
- 60% of patients had dose interruptions, 68% of patients had dose reductions, and 10% of patients permanently discontinued due to AEs (5% due to treatment-related events)
- There were 2 (3%) AE-related deaths but neither were treatment related
- Median time to first dose reduction due to AEs was 6.9 weeks
- Median dose strength at 6 months in the AdvSM population was 100 mg
- At 2 months after treatment initiation, the number of patients per prescribed dose (QD) was: 1 (1%) at 25 mg, 1 (1%) at 50 mg, 30 (41%) at 100 mg, and 41 (56%) at 200 mg
 - Seven patients (10%) discontinued or had insufficient time on treatment

Conclusions

- Treatment with avapritinib at starting doses ≤200 mg QD in patients with AdvSM resulted in rapid (1.9 month median TTR), durable (38.3 months median DOR), and deepening responses
- Avapritinib resulted in reductions in bone marrow MC burden, serum tryptase, *KIT* D816V variant allele fraction, and spleen volume in patients with AdvSM
- While many patients dose reduced, avapritinib was well tolerated, with only 10% of patients discontinuing treatment due to AEs (5% due to treatment-related AEs)

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