

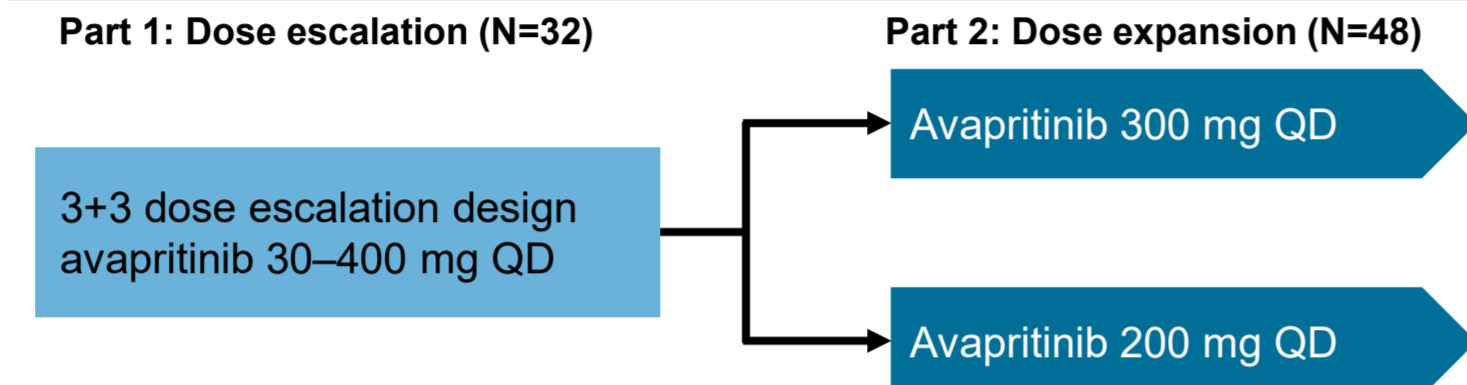
Avapritinib Induces Responses in Patients with Advanced Systemic Mastocytosis (AdvSM), Regardless of Prior Midostaurin Therapy

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Background and methods

- Systemic mastocytosis (SM) is a clonal mast cell (MC) neoplasm driven by the *KIT* D816V mutation characterised by severe skin, gastrointestinal and systemic MC mediator symptoms^{1,2}
- In addition to MC activation symptoms, patients with AdvSM have poor overall survival (OS), with median OS \leq 3.5 years, due to organ damage and/or severe pathologic features³⁻⁵
- AdvSM comprises three subtypes: aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL)⁴
- Midostaurin, a multikinase inhibitor, is approved for AdvSM; however, few patients achieve complete remissions, and patients commonly experience gastrointestinal adverse events (e.g. vomiting and nausea), which contribute to high rates of discontinuation^{5,6}
- Avapritinib is a selective and potent inhibitor of KIT D816V⁷
- EXPLORER (NCT02561988, Figure 1) is an ongoing phase 1 study designed to determine the recommended phase 2 dose (RP2D), safety and preliminary efficacy of avapritinib in patients with AdvSM and relapsed/refractory myeloid malignancies
- Cut-off date for presented data:** 30 August 2019

Figure 1: EXPLORER study design



Key entry criteria

- AdvSM (ASM, SM-AHN, or MCL) or R/R myeloid malignancy per local assessment
- Age \geq 18 years, ECOG PS 0-3, platelets \geq 50 x 10⁹/L

Study objectives

- Primary: RP2D and safety
- Secondary: antineoplastic activity, pharmacokinetics, changes in serum tryptase and blood/bone marrow *KIT* D816V mutant allele fraction, and patient-reported outcomes

ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; R/R, relapsed/refractory.

Results

Table 1: Baseline characteristics

Characteristic	mIWG evaluable (n=48)	All patients (N=80)
Median age (range), years	66 (34-83)	64 (34-83)
Male, n (%)	28 (58)	42 (53)
ECOG PS, n (%)		
0-1	32 (67)	59 (74)
2-3	16 (33)	21 (26)
Any prior anti-neoplastic therapy, n (%)	30 (63)	51 (64)
Midostaurin	15 (31)	24 (30)
Cladribine	7 (15)	13 (16)
SM subtype by central assessment, n (%)		
AdvSM	48 (100)	62 (78)
ASM	3 (6)	7 (9)
SM-AHN	35 (73)	44 (55)
MCL	10 (21)	11 (14)
Other*	0	18 (23)
<i>KIT</i> mutation by central assays, n (%)		
D816V positive by ddPCR	46 (96)	73 (91)
D816Y positive by NGS	2 (4)	2 (3)
Negative for D816 mutation	0	5 (6)
<i>SRSF2/ASXL1/RUNX1</i> positive, n (%)	26 (54)	36 (45)
Median BM MC burden (range), %	50 (5-95)	30 (5-95)
Median serum tryptase (range), ng/mL	178 (21-765)	158 (12-1414)
Median <i>KIT</i> D816V allele burden (range), %	17 (0-81)	10 (0-81)
Median spleen volume (range), mL	1175 (258-2300)	827 (130-2300)

*Fourteen patients with indolent SM, two with smoldering SM and one with chronic myelomonocytic leukemia; one patient's diagnosis was pending central adjudication. BM, bone marrow; ddPCR, droplet digital polymerase chain reaction; mIWG evaluable, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis evaluable; NGS, next-generation sequencing.

Table 2: Best ORR (mIWG-MRT-ECNM)

- High overall response rate (ORR) was achieved across all AdvSM subtypes with responses (confirmed) in both midostaurin-naïve and midostaurin-treated patients
- Reasons for discontinuing midostaurin therapy included disease progression/relapse (33%), adverse events (33%), inadequate response (17%), and unknown/other (17%)

Best response	All evaluable (n=48)	By AdvSM subtype			By prior therapy	
		ASM (n=3)	SM-AHN (n=35)	MCL (n=10)	Prior mido Yes (n=15)	No (n=33)
ORR, % (95% CIs)	77 (63-88)	100	77	70	60	85
CR+CRh, n (%)	13 (27)	2 (67)	9 (26)	2 (20)	0	13 (39)
CR, n (%)	4 (8)	0	2 (6)	2 (20)	0	4 (12)
CRh, n (%)	9 (19)	2 (67)	7 (20)	0	0	9 (27)
PR, n (%)	20 (42)	1 (33)	16 (46)	3 (30)	8 (53)	12 (36)
CI, n (%)	4 (8)	0	2 (6)	2 (20)	1 (7)	3 (9)
SD, n (%)	10 (21)	0	7 (20)	3 (30)	5 (33)	5 (15)
PD, n (%)	0	0	0	0	0	0
NE, n (%)	1 (2)	0	1 (3)	0	1 (7)	0

CI, clinical improvement; CIs, confidence intervals; CR, complete remission; CRh, complete remission with partial hematologic recovery; Mido, midostaurin; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease.

Figure 2: Patient-reported outcomes

- Patients in Part 2 participated in patient-reported outcome collection with the AdvSM-Symptom Assessment Form (SAF)
- The severity of eight symptoms was queried daily and summed as a Total Symptom Score (TSS; range: 0-80)
- Mean TSS at baseline was 18.7 points (n=33)

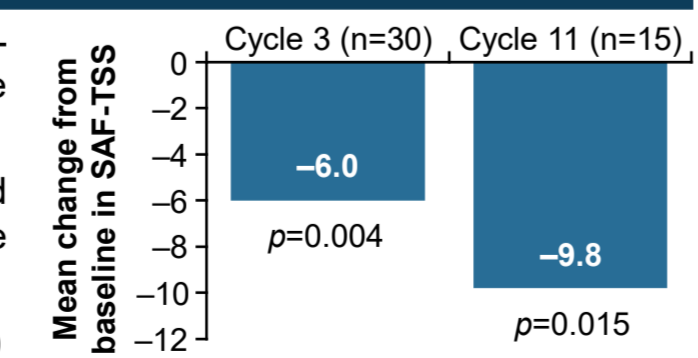


Figure 3: Change in measures of MC burden

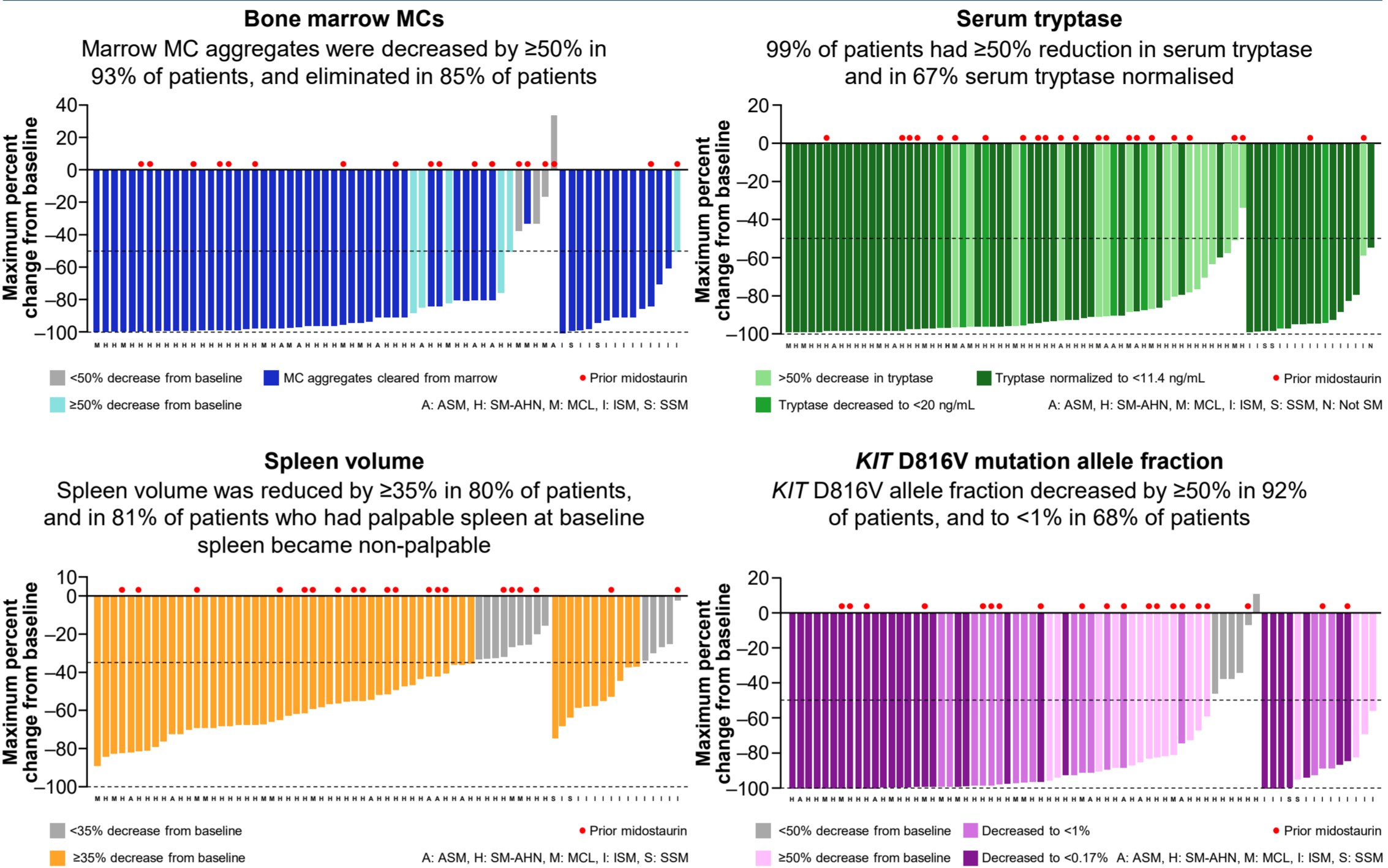


Figure 4: Responses over time

- Median time to initial confirmed response was \sim 2 cycles
- Responses deepen over time into complete responses
- 3-year duration of response was 63% (95% CI, 39-88%)

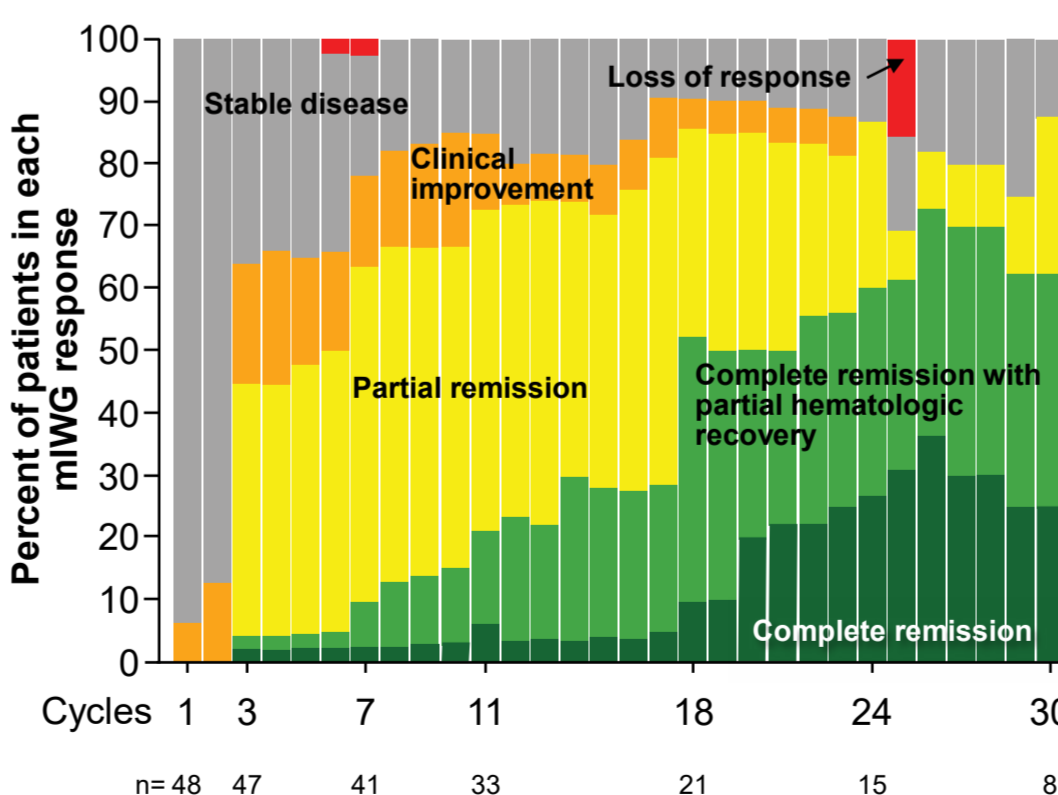


Figure 5: Overall survival

- Median OS at 24 months was not reached for any subtype
- OS profile was not significantly different between patients who received prior midostaurin and those who did not

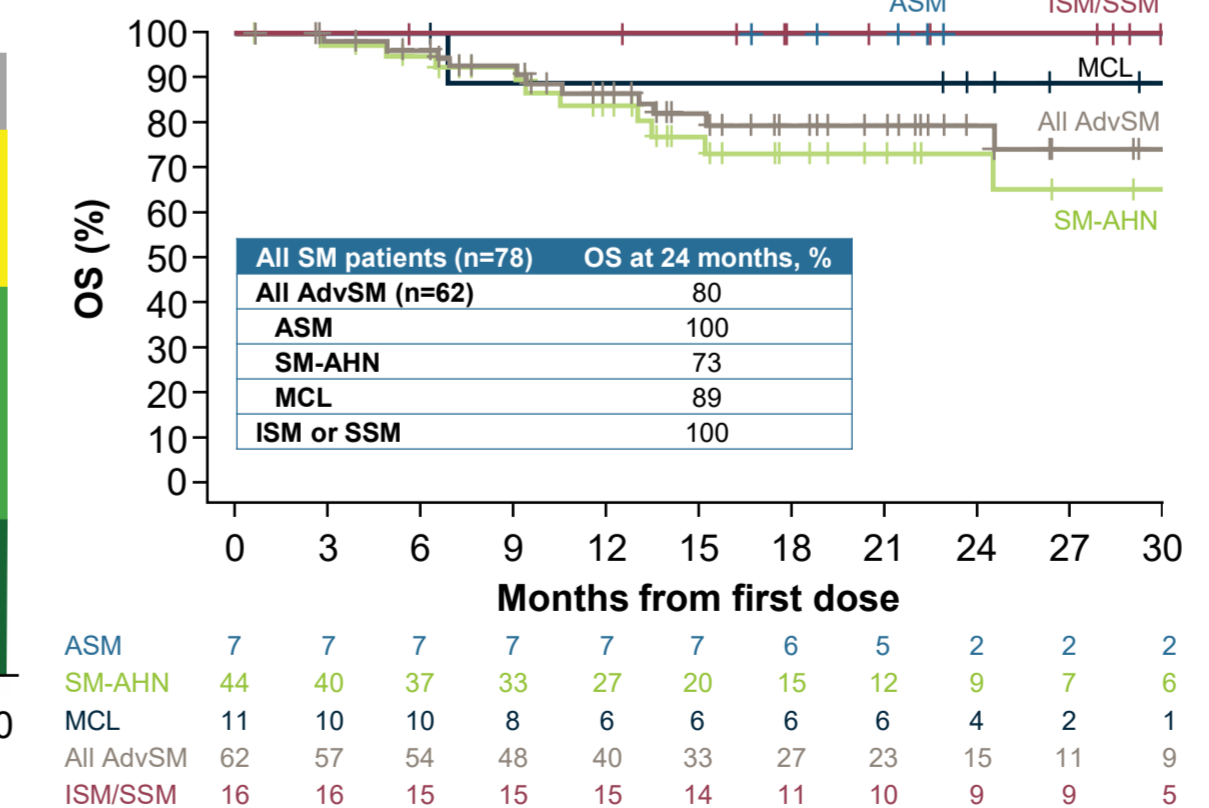


Table 3: Adverse events (AEs, N=80)

Event	All grades	Grade \geq 3
Non-hematologic AEs in \geq20% of patients, n (%)		
Periorbital oedema	57 (71)	3 (4)
Diarrhoea	33 (41)	1 (1)
Fatigue	32 (40)	7 (9)
Peripheral oedema	32 (40)	0
Nausea	31 (39)	3 (4)
Vomiting	27 (34)	3 (4)
Cognitive effect*	27 (34)	3 (4)
Hair colour change	22 (28)	1 (1)
Arthralgia	20 (25)	1 (1)
Abdominal pain	17 (21)	1 (1)
Constipation	17 (21)	1 (1)
Dizziness	16 (20)	1 (1)
Hematologic AEs in \geq10% of patients, n (%)		
Anaemia	44 (55)	23 (29)
Thrombocytopenia	31 (39)	21 (26)
Neutropenia	11 (14)	10 (13)

*Cognitive effects include the following AE terms: cognitive disorder, confusional state and memory impairment.

- Most of AEs were Grade 1 and 2; 15% (12/80) of patients discontinued treatment due to clinical progression and 8% (6/80) due to treatment-related AEs
- Non-traumatic intracranial bleeding (ICB) occurred in 8% (6/80) of patients, 4 were asymptomatic; an additional patient experienced ICB event, which was considered related to a severe fall
- Among patients with platelets $<$ 50,000/ μ L at baseline, 44% (4/9) had an ICB event, while in patients with platelets \geq 50,000/ μ L at baseline, 3% (2/71) had a non-traumatic ICB event, both asymptomatic and associated with treatment-emergent severe thrombocytopenia ($<$ 50,000/ μ L)
- Severe thrombocytopenia now managed by strict dose interruption/reduction and platelet support

Conclusions

- Avapritinib induced rapid, deep and durable reductions in measures of MC burden, which were associated with significant reduction in disease-related symptoms regardless of prior midostaurin exposure or AdvSM subtype
- The starting dose of avapritinib in patients with AdvSM is 200 mg QD
- In patients with platelets \geq 50,000/ μ L, ICB events were uncommon
- The phase 2 PATHFINDER trial is currently enrolling patients with AdvSM to further characterize the safety and efficacy of avapritinib

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