An Updated Analysis on Safety and Efficacy of Avapritinib in Patients With Advanced Systemic Mastocytosis From the EXPLORER Clinical Study: Long-term Efficacy and Safety

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Background

- Advanced systemic mastocytosis (AdvSM) is a rare myeloid neoplasm driven by *KIT* D816V mutations in approximately 95% of patients[1,2]
- AdvSM includes three subtypes: aggressive SM (ASM), mast cell leukemia (MCL), and SM with an associated hematologic neoplasm (SM-AHN; most common)[3,4]
- All subtypes of AdvSM are associated with poor quality of life and prognosis, and an estimated median survival from diagnosis ranging from 2 months for MCL to 2 years for SM-AHN and 3.4 years for ASM[5,6]
- Avapritinib, an oral, highly potent and selective inhibitor of KIT D816V, is approved in the USA for treatment of adult patients with AdvSM, and in the EU after ≥1 prior systemic therapy[7,8]
  - Avapritinib is not recommended for the treatment of patients with AdvSM with platelet counts of <50×10⁹/L
- The aim of the multi-center, international, phase 1 EXPLORER (NCT02561988) study was to determine maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety, and tolerability[9]
- In the previously presented analyses of EXPLORER, patients showed rapid and deep responses to avapritinib treatment regardless of prior therapy, AdvSM subtype, or presence of high-risk mutations[9]
  - Median time to partial remission or better was 2 months (range, 2–27)
  - An overall response rate per modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (ORR per mIWG-MRT-ECNM) of 75%, including 36% with complete response with full or partial hematologic recovery
  - ≥50% reduction from baseline in objective disease burden measures in most patients: bone marrow mast cell (BM MC) burden (92%), *KIT* D816V variant allele frequency (VAF; 80%), and serum tryptase (99%)
  - ≥35% reduction from baseline in spleen volume in 82% of patients
- Here we present long-term analyses of efficacy and safety from the EXPLORER study

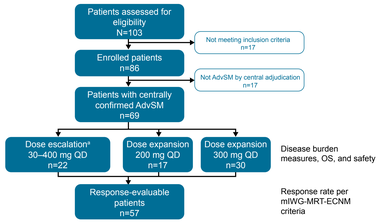
Methods

- Analyses included patients aged ≥18 years with centrally confirmed AdvSM who initiated avapritinib 30–400 mg once daily
- Primary endpoints were MTD, RP2D, safety, and tolerability
- Secondary endpoints included
  - ORR per mIWG-MRT-ECNM response criteria defined as complete remission with full (CR) or partial (CRh) recovery of peripheral blood counts, partial remission, or clinical improvement
  - Duration of response (DOR)
  - Changes in objective disease burden measures: BM MC burden, serum tryptase, *KIT* D816V VAF, and spleen volume
- Progression-free survival (PFS) and overall survival (OS) were evaluated as exploratory endpoints

Results

- As of April 5, 2022, with a median follow-up of 45 months, 69 patients with AdvSM were enrolled in EXPLORER
- The ORR per mIWG-MRT-ECNM criteria improved to 77% (n=57) from 75% (n=53) since previous analyses (data cutoff: May 27, 2020)[9]
  - There were 4 additional complete responses
- Median OS was not reached (NR) in all AdvSM, ASM, and MCL, and was 46.9 months (95% CI 29.6–NE) in SM-AHN
- Median duration of response (DOR) for all responders was not reached (NR)
- Median PFS (95% CI) in response-evaluable patients was 49 months (31–NE)

Summary of patient enrollment in the EXPLORER trial



[a]Patients in the dose escalation group received 30 mg (n=3), 60 mg (n=4), 100 mg (n=1), 130 mg (n=1), 200 mg (n=3), 300 mg (n=4), or 400 mg (n=6).
AdvSM, advanced systemic mastocytosis; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis; OS, overall survival; QD, once-daily.

Baseline characteristics for patients with advanced systemic mastocytosis

	AdvSM (n=69)
Age, median years (range)	67 (34–83)
Male, n (%)	41 (59)
ECOG PS, n (%)	
0–1	48 (70)
2–3	21 (30)
SM subtype, n (%)	
ASM	8 (12)
SM-AHN	48 (70)
MCL	13 (19)
At least one prior systemic therapy, n (%)	41 (59)
Prior midostaurin, n (%)	23 (33)
KIT D816V positive per central assay, n (%)	64 (93)
KIT D816V VAF in BM, median % (range)	14 (0–81)
SRSF2/ASXL1/RUNX1 positive, n (%)	36 (52)
Median BM MC burden, % (range)	40 (5–95)
Median serum tryptase, ng/mL (range)	173 (12–1414)
Median spleen volume, mL (range)	994 (149–2300)

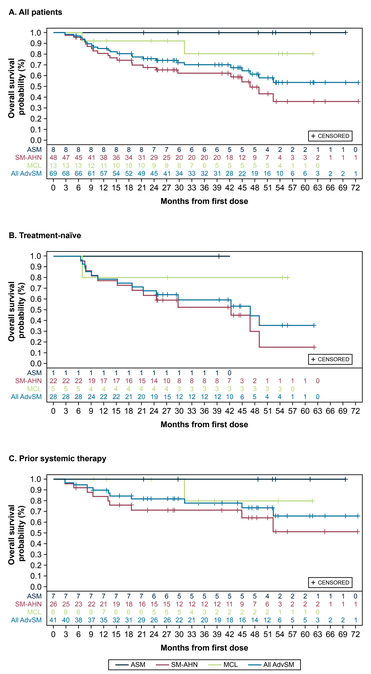
ASM, aggressive systemic mastocytosis; BM MC, bone marrow mast cell; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

Summary of efficacy for patients with advanced systemic mastocytosis and by subtype

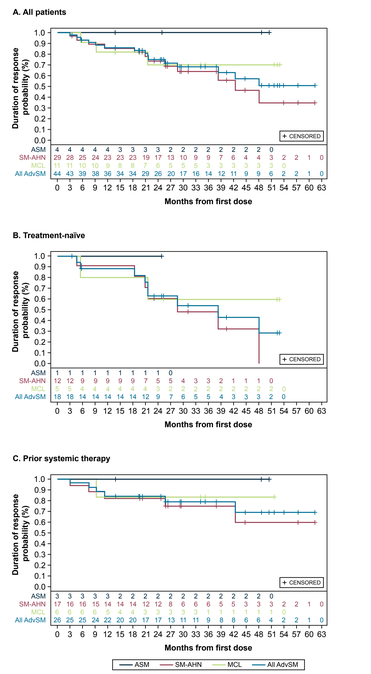
Outcome, n (%)	All patients[a] (n=57)	ASM (n=4)	SM-AHN (n=40)	MCL (n=13)	Treament-naïve (n=22)	≥1 prior systemic therapy (n=35)
ORR,[b] n (%) [95% CI]	44 (77) [64–87]	4 (100) [40–100]	29 (73) [56–85]	11 (85) [55–98]	18 (82) [60–95]	26 (74) [57–88]
CR	12 (21)	2 (50)	6 (15)	4 (31)	5 (23)	7 (20)
CRh	11 (19)	1 (25)	9 (23)	1 (8)	6 (27)	5 (14)
PR	19 (33)	1 (25)	14 (35)	4 (31)	6 (27)	13 (37)
CI	2 (4)	0	0	2 (15)	1 (5)	1 (3)
SD	12 (21)	0	10 (25)	2 (15)	4 (18)	8 (23)
PD	0	0	0	0	0	0
NE	1 (2)	0	1 (3)	0	0	1 (3)

[a]57 patients with a confirmed diagnosis of AdvSM, and ORR evaluable per mIWG-MRT-ECNM criteria at baseline.
[b]CR + CRh + PR + CI
95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; NE, not evaluable for response; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

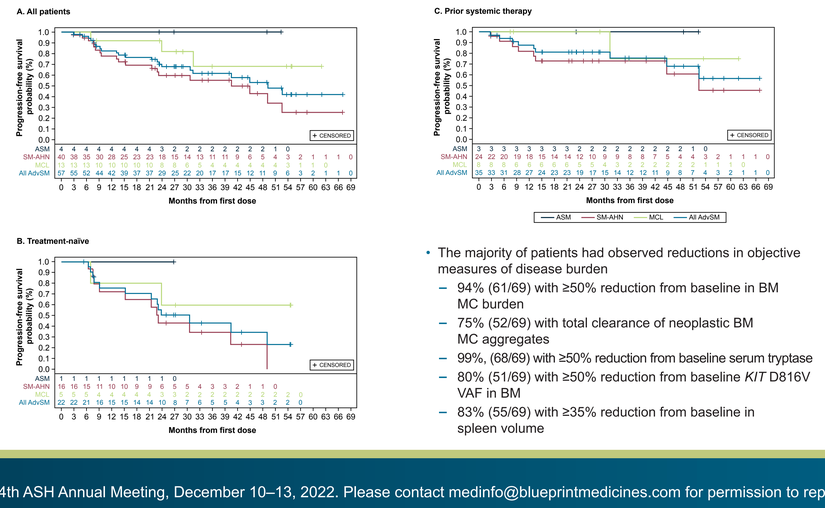
Kaplan-Meier OS curves in patients overall and by subtype (A), in treatment-naïve patients (B), and in patients with ≥1 prior systemic therapy (C)



Kaplan-Meier DOR curves in patients overall and by subtype (A), in treatment-naïve patients (B), and in patients with ≥1 prior systemic therapy (C)

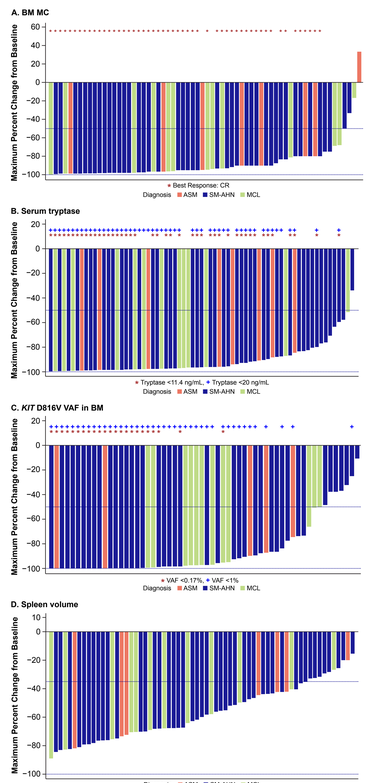


Kaplan-Meier PFS curves in patients overall and by subtype (A), in treatment-naïve patients (B), and in patients with ≥1 prior systemic therapy (C)



- The majority of patients had observed reductions in objective measures of disease burden
  - 94% (61/69) with ≥50% reduction from baseline in BM MC burden
  - 75% (52/69) with total clearance of neoplastic BM MC aggregates
  - 99%, (68/69) with ≥50% reduction from baseline serum tryptase
  - 80% (51/69) with ≥50% reduction from baseline *KIT* D816V VAF in BM
  - 83% (55/69) with ≥35% reduction from baseline in spleen volume

Changes in objective measures of disease burden from baseline for BM MC (A), serum tryptase (B), *KIT* D816V VAF in BM (C), and spleen volume (D)



Safety

- The most frequent (≥30%) treatment-related adverse events (TRAEs; any grade) were periorbital edema, anemia, thrombocytopenia, nausea, and peripheral edema
  - Grade ≥3 TRAEs were observed in 74% of patients
- Nine patients experienced intracranial bleeding (ICB) events
  - Starting doses in patients who experienced ICBs were 200 mg QD (n=2), 300 mg QD (n=6), and 400 mg QD (n=1)
  - Eight events were associated with pre-existing severe thrombocytopenia
  - There have been no additional ICBs since previously published analyses[9]
- Cognitive effects[a] were experienced by 44% of patients, mostly Grade 1 and 2, and 3% were Grade 3 with no events Grade 4 or 5
  - As anticipated, events were more frequent at at the 300-mg starting dose (19/34) compared to to the 200-mg starting dose (4/20)

[a]Pooled cognitive effects were defined by 17 AE preferred terms (memory impairment, cognitive disorder, confusional state, amnesia somnolence, encephalopathy, agitation, delirium, dementia, disorientation, hallucination, mental status changes, psychotic disorder, mental impairment, mood altered, personality change, and speech disorder) while previously published analyses of cognitive effects were defined by four AE preferred terms (memory impairment, cognitive disorder, confusional state, and encephalopathy).[9]

TRAEs in ≥10% of patients

TRAEs in ≥10% of patients, n (%)	Any grade (n=69)	Grade ≥3 (n=69)
Hematologic events, n (%)		
Anemia	29 (42)	17 (25)
Thrombocytopenia	25 (36)	18 (26)
Neutropenia	12 (17)	10 (14)
Non-hematologic events, n (%)		
Periorbital edema	44 (64)	1 (1)
Nausea	23 (33)	2 (3)
Peripheral edema	23 (33)	0 (0)
Diarrhea	17 (25)	1 (1)
Fatigue	15 (22)	3 (4)
Vomiting	15 (22)	1 (1)
Hair color changes	15 (22)	1 (1)
Memory impairment	14 (20)	0 (0)
Blood bilirubin increase	9 (13)	2 (3)
Lacrimation increased	9 (13)	1 (1)
Alopecia	8 (12)	0 (0)
Ascites	8 (12)	2 (3)
Cognitive disorder	8 (12)	1 (1)
Dysgeusia	8 (12)	0 (0)
Dry mouth	7 (10)	0 (0)
Epistaxis	7 (10)	0 (0)
Headache	7 (10)	0 (0)
Pleural effusion	7 (10)	0 (0)

Data cutoff: April 5, 2022.
TRAE, treatment-related adverse events.

- 73% of patients had dose reduction and 83% had dose interruptions
  - Dose reductions occurred in 30/34 of patients at at the 300-mg starting dose and 13/20 of patients at at the 200-mg starting dose
  - Dose interruptions occurred in 26/34 of patients at the 300-mg starting dose and 18/20 of patients at the 200-mg starting dose
- 20% of patients discontinued treatment due to AEs of any cause (10% due to TRAEs)
  - These occurred in 9/34 of patients at the 300-mg starting dose and 3/20 of patients at the 200-mg starting dose

Conclusions

- ORR per mIWG-MRT-ECNM response criteria was 77% in all patients with AdvSM and 82% in treatment-naive patients
- At a median follow-up of 45 months, survival benefit across subtypes and regardless of prior therapy was ongoing with median OS not reached, and median PFS of 49 months (95% CI, 31–NE)
- Among all patients treated with avapritinib, rapid (median time to PR or better, 2 months [range, 2–27]) and durable responses (median DOR not reached) were observed. Dose modification did not impact clinical efficacy
- Based on the safety, pharmacokinetics, and efficacy profile of avapritinib, a starting dose of 200 mg QD was recommended

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Disclosures

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