Effective Control of Advanced Systemic Mastocytosis with Avapritinib: Mutational Analysis from the EXPLORER Clinical Study

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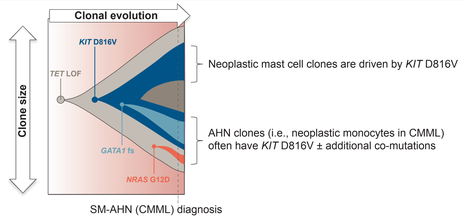
Introduction

- Advanced systemic mastocytosis (AdvSM) is a myeloid neoplasm driven by *KIT* D816V in ~95% of cases[1]
- Patients have complex genomics with multiple clones and co-mutations[1]
- ~60–70% of patients have a distinct, associated hematological neoplasm (SM-AHN)[2] (**Figure 1**)

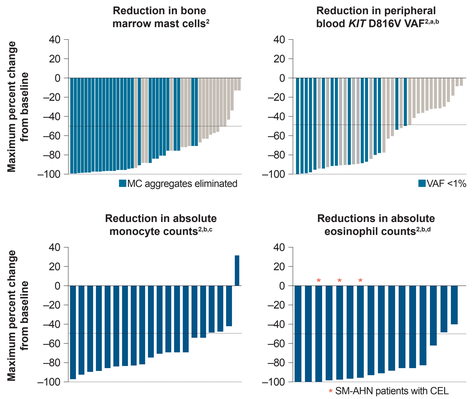
Figure 1: AdvSM is heterogenous in nature



AHN, associated hematological neoplasm; CMML, chronic myelomonocytic leukemia; SM, systemic mastocytosis.

- Patients with SM-AHN have poor outcomes, with only a 49% two-year survival rate following treatment with midostaurin[3]
- Disease progression and mortality may occur due to the SM, AHN, or both[4]
- Avapritinib, a selective KIT D816V inhibitor, improved measures of disease burden[5,6] (**Figure 2**)

Figure 2: Avapritinib improves measures of disease burden



[a]Patients with SM-AHN. [b]Ad hoc analysis. [c]Patients with SM-CMML. [d]Patients with baseline eosinophilia and SM-CEL.ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematological recovery; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; MC, mast cell; MCL, mast cell leukemia; PR, partial remission; *SIAIR, SRSF2/ASXL1/RUNX1*; SM, systemic mastocytosis; SM-CEL, systemic mastocytosis with chronic eosinophilic leukemia; VAF, variant allele fraction.

- Avapritinib induced deep SM responses, including in patients with SM-AHN[5,6]
  - 75% response rate by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria, including 100% in aggressive systemic mastocytosis (ASM), 76% in SM-AHN and 69% in mast cell leukemia (MCL)[5]
  - Responses regardless of prior therapy or high-risk *SRSF2*/*ASXL1*/*RUNX1* (*SIAIR*) co-mutations and is generally well tolerated[5]
  - Activity observed in mast cell (MC) and non-MC lineages, including reductions in the *KIT* D816V variant allele fraction (VAF)[5,6]
  - Patients with SM-AHN had a 67% two-year survival on avapritinib with 38 months median duration of response[5]
- EXPLORER (NCT02561988) is a phase 1 dose escalation study of avapritinib in 86 patients with local diagnosis of AdvSM, of which 69 were centrally confirmed[5]
- Avapritinib 30–400 mg was studied with expansion cohorts at 200 mg and 300 mg once daily (QD)

Methods

- Patients enrolled in EXPLORER with centrally confirmed diagnoses of AdvSM were included in these analyses. Peripheral blood and bone marrow (BM) samples were collected at baseline, during treatment, and at clinical progression, as determined by the local investigator, for biomarker analyses and assessment of disease response to treatment
- Serial samples from baseline, on study, and at end-of-treatment (when available) were evaluated centrally by droplet digital polymerase chain reaction assay for detection of *KIT* D816V
- Central next-generation sequencing (TruSight™ Myeloid Panel) of *KIT* and other genes mutated in myeloid malignancies was performed at baseline and on study (in a subset of patients with/without clinical progression)
- Mutation-adjusted risk score (MARS) was used for evaluation of progression-free survival (PFS) and overall survival (OS)[7]

Results

- Baseline characteristics are summarized in **Table 1**

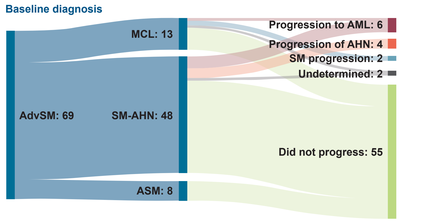
Table 1: Baseline characteristics

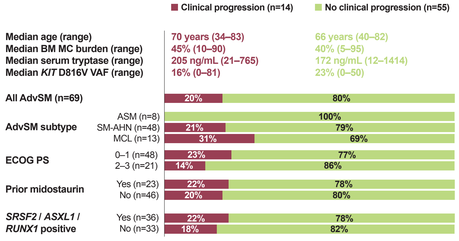
Characteristic	All AdvSM (n=69)
Median age, years (range) / Male, n (%)	67 (34–83) / 41 (59)
ECOG PS 0–1 / 2–3, n (%)	48 (70) / 21 (30)
Prior anti-neoplastic therapy, n (%)	41 (59)
Midostaurin	23 (33)
Cladribine	10 (14)
***KIT* D816V or Y positive, n (%)[a]**	65 (94)
Any myeloid co-mutation, n (%)	64 (93)
***SRSF2* / *ASXL1* / *RUNX1* positive, n (%)**	36 (52)
1 / 2 / 3 genes mutated	22 (32) / 11 (16) / 3 (4)
Median BM MC burden, % (range)	40 (5–95)
Median serum tryptase, ng/mL (range)	173 (12–1414)
Median *KIT* D816V VAF, % (range)	17 (0–81)

[a]Assessed by central D816V ddPCR assay and Trusight Myeloid Panel (for D816Y). VAF (%) assessed using validated ddPCR by central assay with limit of detection of 0.17%. BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; VAF, variant allele fraction.

- Only 14 (20%) patients had clinical progression on treatment (**Figure 3**)
  - 10 (21%) patients with SM-AHN, 4 (31%) with MCL, and 0 with ASM had clinical progression
- Median duration of treatment was 9.5 months
- The majority were AHN or acute myeloid leukemia progressions in patients with baseline AHN

Figure 3: Limited clinical progression on treatment



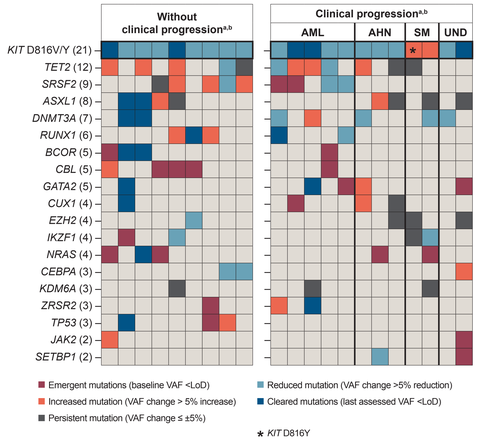


Data cut-off: May 27, 2020 (median follow-up of 23 months). [a]As determined by investigator; a subset with AML met the mIWG-MRT-ECNM criteria definition for progressive disease.AML, acute myeloid leukemia; mIWG-MRT-ECNM, (modified) International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; QD, once-daily.

- Only 2 patients, both with MCL, had a SM progression
- Characteristics of patients who did or did not have clinical progression are summarized in **Figure 3**
- Majority of patients had deep responses in BM MC burden (**Figure 4A**), serum tryptase (**Figure 4B**), and in BM *KIT* D816V VAF (**Figure 4C**) at last assessment regardless of progression.

- Of patients with baseline and post-baseline assessments, 88% had a ≥50% reduction in *KIT* D816V VAF, with *KIT* D816V becoming undetectable (limit of detection <0.17%) in peripheral blood in 24 of 56 (43%) after a median of 15.4 months (**Figure 5**)

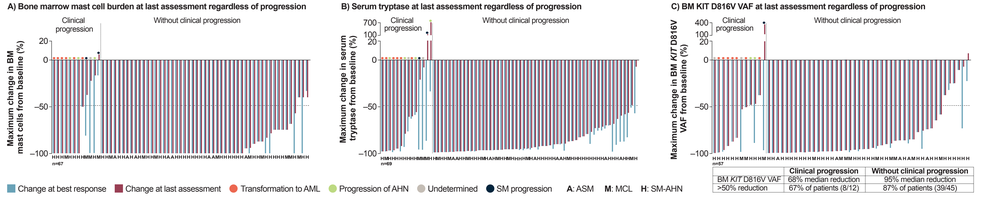
Figure 5: Complex pattern of co-mutation evolves regardless of outcome



[a]Only a random subset of non-progressing patients had serial mutational profiling; 12 of 14 patients who progressed had serial profiling. [b]Other mutations found in single patients were *KRAS, SF3B1, U2AF1, ATRX, BCORL1, SMC3, NPM1, CDKN2A, STAG2, IDH1, IDH2,* and *MYD88*. LoD, limit of detection; UND, undetermined.

- 83% (10 of 12) of progressions were not associated with increased *KIT* D816V/Y VAF
- 2 (17%) patients with baseline MCL had SM progressions with increased *KIT* D816V/Y VAF, but no additional mutations in *KIT* were identified
- No clear pattern of increasing or decreasing VAF was observed for most mutations
- MARS predicted both PFS (*P*=0.0126) and OS (*P*=0.0015), with a MARS ≥2 being associated with higher risk (**Figure 6**)

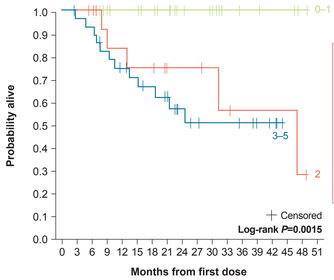
Figure 4: Avapritinib induces deep responses in majority of patients



No statistical analysis conducted

	Clinical progression	Without clinical progression
BM *KIT* D816V VAF >50% reduction	68% median reduction 67% of patients (8/12)	95% median reduction 87% of patients (39/45)

Figure 6: Overall survival is more favorable in patients with a low baseline Mutation-Adjusted Risk Score (MARS)



MARS[7] is a validated, WHO-independent prognostic score based on 5 parameters:
1) >60 years of age
2) Anemia (Hgb <10 g/dL)
3) Thrombocytopenia (Platelets <100×10⁹/L)
4) 1 *SIAIR* mutation
5) ≥2 *SIAIR* mutations

MARS category																					
0–1	25	25	25	22	19	19	17	15	12	11	9	5	4	4	3	3	1	0			
2	15	15	14	11	10	9	9	5	5	5	4	3	2	2	2	2	1	0			
3–5	29	27	26	22	19	17	15	12	9	7	6	6	5	3	2	0					

Hgb, hemoglobin; WHO, World Health Organization.

Conclusions

- Avapritinib showed profound and durable reductions in objective disease burden in patients with AdvSM, in both the SM and AHN components
- With a median follow-up of 23 months, only 20% of patients have progressed on treatment, driven in most cases by *KIT* D816V-negative AHN clones
- Overall survival was more favorable in patients with lower baseline MARS scores
- In most patients who progressed, *KIT* D816V remained suppressed, suggesting a rationale for the addition of AHN-directed therapies
- These data highlight the potential value of single-cell sequencing of SM and AHN components of AdvSM

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Disclosures

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