An Analysis of Clonal Dynamics in Patients With Indolent Systemic Mastocytosis Treated With Avapritinib in the PIONEER Study

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Introduction

- Systemic mastocytosis (SM) is a clonal mast cell disease driven by the *KIT* D816V mutation in ~95% of cases[1,2]
- The prevalence of SM has been estimated at up to 1 in 5,000 people[3–6]
- Historically, most patients have relied on symptom-directed best supportive care (BSC) medications which do not treat the underlying driver of indolent SM (ISM). However, emerging targeted therapies offer the potential to not only alleviate symptoms but also modify the course of the disease
- Avapritinib, an oral, potent, selective inhibitor of *KIT* D816V, improves overall survival in advanced SM (AdvSM), reduces disease-related symptoms and improves quality of life (QOL) in ISM, leading to its approval for treatment in both subtypes[7,8]
- In AdvSM, avapritinib therapy leads to the rapid and durable suppression of the *KIT* D816V mutation and is not associated with the development of on-target resistant *KIT* mutations[9]
- In the randomized, double-blind, three-part PIONEER (NCT03731260) trial, patients with ISM treated with avapritinib showed rapid, durable, and clinically meaningful improvements in symptoms and QoL with over 3 years of follow-up. Avapritinib had a well-tolerated safety profile that was similar to the randomized placebo-controlled portion.[10–12] (Please see Poster #2024)
- Here, we performed centralized droplet digital polymerase chain reaction (ddPCR) and next-generation sequencing (NGS) on peripheral blood (PB) samples from patients with ISM both at time of trial enrollment and after treatment with avapritinib in the PIONEER study
- For the first time, this analysis provides an understanding of the dynamics of both *KIT* and non-*KIT* clonal mutations in the peripheral blood of patients with ISM receiving a selective *KIT* D816V inhibitor

Methods

- Adults with centrally confirmed ISM and uncontrolled moderate-to-severe symptoms who completed the randomized dose-finding (Part 1), or randomized, double-blind, placebo-controlled (Part 2) portions of PIONEER rolled over to the open-label, long-term extension (Part 3) with up to 5-years follow-up
- All patients received avapritinib therapy + BSC in Part 3
- Centralized ddPCR testing for *KIT* D816V variant allele frequency (VAF) in the PB was performed at baseline and while on study using the ICON plc., Cambridge, MA, USA, CLIA-validated assay with a limit of detection (LOD) of 0.022%
  - 245 patients at baseline and 154 patients who received avapritinib for 48 weeks were tested for *KIT* D816V VAF by ddPCR
- Additional testing for mutations in 54-myeloid-malignancy-related genes (including *KIT* exons 2, 8–11, 13, and 17) was performed on banked PB samples from baseline and while on study using the Illumina® TruSight Myeloid NGS panel
- In this analysis, we report on non-*KIT* Tier-1 mutations, which are known to be pathogenic
  - At baseline, 245 patients were tested for mutations by NGS
  - Following 24 weeks of avapritinib treatment, 120 patients received NGS testing
  - Following ≥48 weeks of avapritinib, 128 patients received NGS testing, of which 18 patients were tested at 48 weeks, 49 patients were tested at 48-96 weeks, 48 patients were tested at 96–144 weeks, and 13 patients were tested at >144 weeks

Results

Baseline demographics: All patients with NGS testing

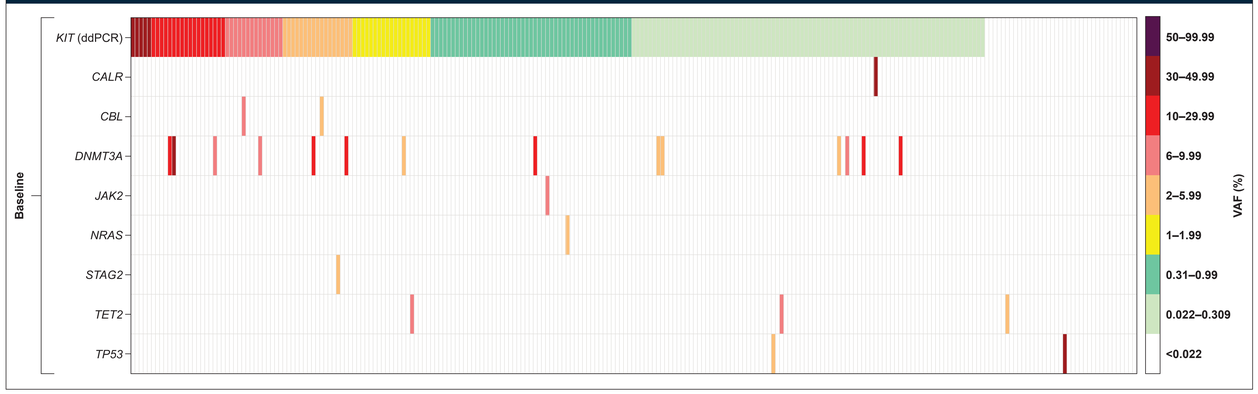
- As of February 21, 2025, a total of 245 patients with ISM received avapritinib treatment across Parts 1, 2, and/or 3 of the study and had ddPCR for *KIT* D816V
- Demographics of these patients are shown in **Table 1**
- The median (range) *KIT* D816V VAF at baseline across all patients was 0.34% (undetectable–41.29%, **Figure 1**)

Table 1. Baseline demographics

	All patients with NGS testing N=245	Patients with non-*KIT* Tier-1 mutations N=25	Patients without non-*KIT* Tier-1 mutations N=220
Age, median (range)	51.0 (18–79)	53.0 (39–76)	50.5 (18–79)
Female, n (%)	179 (73)	21 (84)	158 (72)
Serum tryptase, median (range)	39.8 (3.6–590.4)	41.1 (6.7–161.0)	39.7 (3.6–590.4)
***KIT* D816V VAF, median (range)**	0.34 (0–41.29)	0.54 (0–25.17)	0.29 (0–41.29)
% BM MC, median (range)	7.0 (1.0–60.0)	5.0 (1–50)	7.0 (1.0–60.0)
ISM-SAF TSS, mean (SD)	48.6 (19.6)[a]	52.9 (19.1)	48.1 (19.7)[b]

BM, bone marrow; ISM-SAF, indolent systemic mastocytosis-symptom assessment form; MC, mast cell; SD, standard deviation; TSS, total symptom score.
[a]n=243. [b]n=218.

Figure 1. Individual Baseline non-*KIT* Tier-1 Mutations and *KIT* D816V (ddPCR) in PIONEER



Each column represents a patient. VAF, variant allele frequency.

KIT mutational analysis following avapritinib treatment

- Out of 154 patients who had detectable *KIT* D816V VAF in PB at baseline and who had *KIT* D816V VAF testing at 48 weeks of avapritinib treatment:
  - 151 (98%) patients experienced a decrease in *KIT* D816V VAF (median [range] VAF 0.13% [undetectable–33.01%])
  - 102 (66%) experienced a ≥50% decrease in *KIT* D816V VAF
  - 20 (13%) reached a *KIT* D816V VAF below 0.022%, the LOD
- Of the 120 patients who received NGS testing at 24 weeks and 128 patients who received NGS testing at ≥48 weeks, no new on-treatment *KIT* mutations were detected by NGS in any patients

Baseline characteristics: Patients with or without non-KIT Tier 1 mutations

- At baseline, 25/245 (10%) patients had one additional non-*KIT* Tier-1 (i.e., known pathogenic) mutation (**Figure 1**)
- Demographics of patients with or without non-*KIT* Tier-1 mutations were generally similar (**Table 1**)
- The median (range) age of patients with non-*KIT* Tier-1 mutations was 53.0 (39–76) years old versus 50.5 (18–79) years old in patients without non-*KIT* Tier-1 mutations (*P*-value: 0.049)
  - Other than age, there were no significant differences in baseline characteristics between patients with or without non-*KIT* Tier-1 mutations
  - Notably, median *KIT* D816V VAF in patients with non-*KIT* Tier-1 mutation(s) was higher than median *KIT* D816V VAF in patients without non-*KIT* Tier-1 mutation(s), although this difference was not significant (P-value: 0.31)
- None of the 25 patients with non-*KIT* Tier-1 mutations had hereditary alpha-tryptasemia

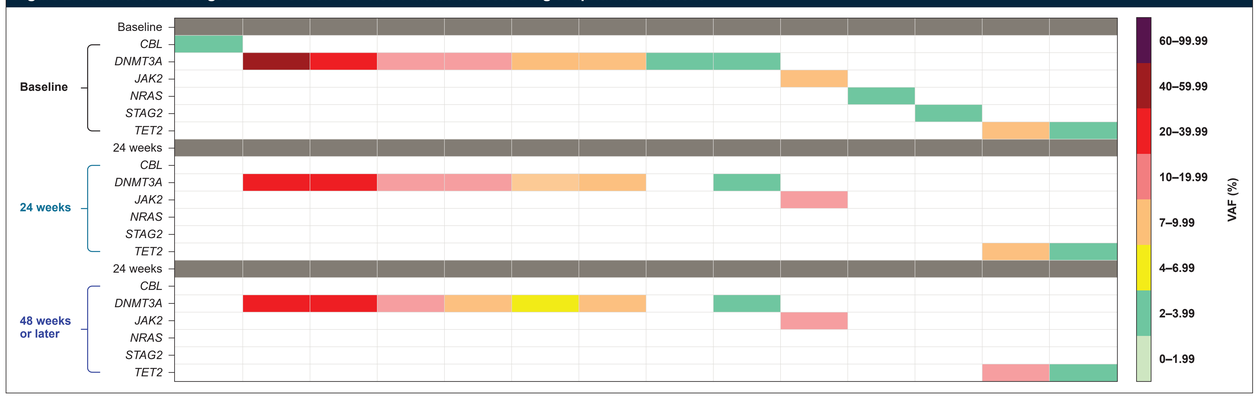
Baseline non-KIT Tier 1 mutations

- The presence of a non-*KIT* Tier 1 mutation could signify a precursor to an associated hematologic neoplasm (AHN), though in some cases it could still represent unrelated clonal hematopoiesis of indeterminate potential (CHIP)
- Tier-1 mutations in non-*KIT* genes occurring in more than 1 patient included *DNMT3A* (n=14, median VAF 9.4%), *TET2* (n=3, median VAF 8.5%), *CBL* (n=2), and *TP53* (n=2) (**Table 2**)
  - Median *KIT* D816V VAF in patients with non-*KIT* Tier-1 *DNMT3A* mutations was higher than median *KIT* D816V VAF in patients without non-*KIT* Tier-1 *DNMT3A* mutations, although this difference was not significant (P-value: 0.53)
  - In patients with non-*KIT* Tier-1 *DNMT3A* mutations, the median (range) age was 57 (39–76) years old

Non-KIT Tier 1 mutational analysis following avapritinib treatment

- Following 24 weeks (n=241) of avapritinib treatment, the fraction of patients with detectable non-*KIT* Tier-1 mutations in the PB had decreased to 6% (n=15) and following ≥48 weeks (n=234) of avapritinib treatment, this fraction had decreased further to 4% (n=10)
  - After ≥48 weeks of avapritinib therapy, no patient had the emergence of a new non-*KIT* Tier-1 mutation that was not detected in baseline testing
- 14 out of 25 patients with non-*KIT* Tier-1 mutations at baseline had a paired sample tested at 24 weeks and at/after 48 weeks (**Figure 2**)
  - Furthermore, comparing paired samples taken both at baseline and after ≥48 weeks of avapritinib therapy, 57% (n=8/14) of patients had a reduction in the VAF of the non-*KIT* Tier-1 mutations, including 4 patients with undetectable clonal frequencies for such mutations
  - Mutations in the *DNMT3A* gene were most frequently reduced or eliminated; *DNMT3A* mutations are common in SM, particularly in AdvSM, and are associated with poor prognosis[13]

Figure 2. Patient-level changes in VAF of non-*KIT* Tier-1 mutations following avapritinib treatment



Each column represents a patient.

Table 2: Non-*KIT* genes with Tier 1 mutations in ISM patients

Non-*KIT* gene with mutations at baseline (Tier-1 only)	Number of patients with genes with non-*KIT* Tier-1 mutations at baseline	Median (range) VAF (%)	Median (range) *KIT* D816V VAF (%)
DNMT3A	14	9.4 (2.4–45.3)	0.84 (0.04–25.17)
TET2	3	8.5 (2.5–9.7)	0.08 (0.01–0.97)
CBL	2	NA	NA
TP53	2	NA	NA
CALR	1	NA	NA
JAK2	1	NA	NA
NRAS	1	NA	NA
STAG2	1	NA	NA

NA, not applicable.

Conclusions

- Longer-term avapritinib therapy is associated with favorable clonal dynamics in patients with ISM
- After more than 48 weeks of therapy, there was no emergence of drug-resistant mutations in *KIT*, nor the appearance of additional pathogenic mutations in other genes commonly implicated in hematologic malignancies
- These data suggest that prolonged treatment with avapritinib in ISM does not promote the emergence of new known pathogenic mutations
  - These findings are in line with TruSight Myeloid NGS data in patients with AdvSM from the EXPLORER/PATHFINDER studies demonstrating no new on-target resistant *KIT* mutations emerged with avapritinib treatment[14]
- Understanding whether treatment can modify rates of progression to SM with associated hematological neoplasms would require larger prospective studies and longer follow-up
- These data suggest that avapritinib treatment in ISM does not promote the emergence of clonal hematopoiesis and, in some cases, is associated with regression of abnormal clones. These findings warrant longitudinal follow-up
- Further evaluation of how changes in the VAF of non-*KIT* mutations correlate with changes in the VAF of *KIT* mutations may reflect whether the mutations arise within a single clone or separate clones

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Conflicts of interest/disclosures

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