Diagnostic Evolution in Systemic Mastocytosis: Clinical Impact of WHO 2022 Criteria on Smoldering Systemic Mastocytosis Identification in PIONEER

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Introduction

- Systemic mastocytosis (SM) is a hematologic neoplasm driven by the *KIT* D816V mutation, which results in abnormal activation and proliferation of mast cells (MCs)[1,2]
- While the underlying cause of SM, the *KIT* D816V mutation, is homogenously found in nearly all patients with the diagnosis, the clinical presentation of SM is heterogenous and exists along a spectrum. SM includes[3–5]:
  - **Advanced SM subtypes:**
    - Aggressive SM, SM with an associated hematological neoplasm, and MC leukemia
    - Involves severe organ damage and associated with a decreased life expectancy
  - **Non-advanced SM subtypes:**
    - Bone marrow mastocytosis, indolent SM (ISM), and smoldering SM (SSM)
    - Distinguished by the lack of C-findings (end organ damage), with the number of concurrent B-findings (burden of disease) further informing subtype diagnosis (**Figure 1**)
    - ISM is the most common form of SM, with a low MC burden and a near normal life expectancy
    - SSM is associated with a higher MC burden, but no organ damage and has a higher risk of progressing to a more advanced subtype

Figure 1. Systemic mastocytosis is categorized into subtypes according to specific WHO criteria[4,5]

Disease subtype	ISM	SSM	AdvSM
Frequency	~80%[2,6,7]	~5%[8]	~15%[2,6,7]
Diagnosis	≤1 B-finding	≥2 B-findings	≥1 C-finding
Disease features	Driven by the *KIT* D816V mutation in ~95% of cases[3,8,9]		

Debilitating symptoms[3,10–12]

Low-to-moderate MC burden	High MC burden	Highest MC burden
	Neurological (memory/cognitive difficulties); Cardiovascular (anaphylaxis, syncope, dizziness); Skin (flushing, itching); GI (diarrhea, abdominal pain, nausea and vomiting); Bone (osteoporosis); Organomegaly	Cytopenia; Cardiovascular (anaphylaxis, syncope, dizziness); GI malabsorption/ weight loss; Organ damage; Bone (fractures)

AdvSM, advanced systemic mastocytosis; GI, gastrointestinal; HαT, hereditary α-tryptasemia; ISM, indolent systemic mastocytosis; MC, mast cell; SSM, smoldering systemic mastocytosis; WHO, World Health Organization.

- The definition of B-findings has evolved with the advancement of disease understanding and technology to better classify patients across the spectrum of non-advanced SM subtypes
  - Droplet digital PCR – Detects and quantifies *KIT* D816V variant allele frequency (VAF) with a higher sensitivity than next-generation sequencing (NGS)[13–15]
  - NGS – Detects low-level co-occurring mutations[13,14]
- In 2022, the World Health Organization (WHO) updated the definition for B-findings, including broadening the definition of MC burden[4,5] (**Table 1**)

Table 1. The evolving definition of B-findings: WHO 2016[16] *versus* WHO 2022[4,5]

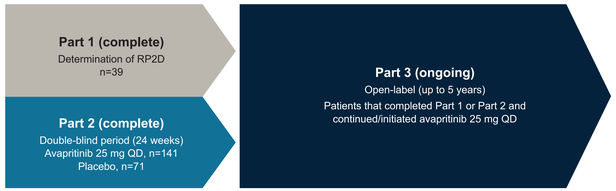
	WHO 2016[16]	WHO 2022[4,5]
MC burden	>30% BM MC **AND** Serum tryptase level >200 ng/mL	≥30% BM MC **AND/OR** Serum tryptase level ≥200 ng/mL (Adjusted for HαT) **AND/OR** *KIT* D816V VAF ≥10% in BM or PB
Pathologic precursors to AHN	Signs of dysplasia or myeloproliferation	
Organomegaly	Hepatomegaly, splenomegaly, or lymphadenopathy without functional impairment	

HαT is a genetic trait that leads to elevated serum tryptase, present in 9–18% of patients with SM[17–19]

AHN, associated hematologic neoplasm; BM, bone marrow; PB, peripheral blood; VAF, variant allele frequency.

- PIONEER (NCT03731260) is a randomized placebo-controlled clinical trial that led to the approval of avapritinib, an oral KIT D816V-selective inhibitor, for the treatment of ISM[20–22] (**Figure 2**)
  - Patients with ISM were enrolled according to WHO 2016 classification, while individuals meeting criteria for SSM were excluded

Figure 2. Study design



QD, once-daily; RP2D, recommended Part 2 dose.

- PIONEER includes one of the largest, most well-characterized populations of patients with ISM and provides an opportunity to gain deeper insights into the clinical and biological heterogeneity of ISM
- The evaluation of baseline characteristics enabled us to explore the differences between the WHO 2016 and WHO 2022 criteria, and how these criteria impact the subtype diagnosis in PIONEER

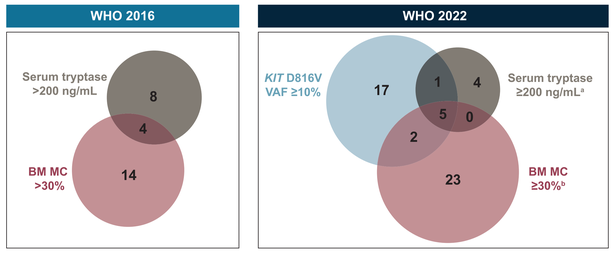
Methods

- Baseline characteristics of all patients with ISM (N=250) enrolled into PIONEER were evaluated in this analysis
- At the time of study enrollment, the following measurements were collected: serum tryptase level, bone marrow (BM) MC burden, HαT status, *KIT* D816V VAF (and other somatic mutations) in the peripheral blood, and liver and spleen size by palpation
- Baseline symptoms were measured using the total symptom score (TSS) from the ISM-Symptom Assessment Form[a] a validated symptom assessment tool[23–25]
- NGS testing for mutations in 54 genes was performed using the Illumina TruSight Myeloid Sequencing Panel
  - Patients with ISM who harbor Tier 1 (i.e., known pathogenic) mutations such as *DNMT3A, TET2, CBL,* and *TP53* are considered to be at a higher risk of disease progression[26]
- Histopathology was assessed via a central review by expert hematopathologists
- A retrospective analysis assessed B-finding distribution at baseline using WHO 2016 and WHO 2022 criteria

Results

- The number of patients from PIONEER with the MC burden B-finding substantially increased with the revised WHO 2022 criteria (**Figure 3**)
  - **WHO 2016**
    - Four of 250 patients (2%) met the high MC burden B-finding (BM MC >30% and serum tryptase >200 ng/mL)
  - **WHO 2022**
    - Fifty-two of 250 patients (20%) met the revised high MC burden B-finding (BM MC ≥30% and/or serum tryptase ≥200 ng/mL and/or *KIT* D816V VAF ≥10%)
    - There was limited overlap between patients with *KIT* D816V VAF ≥10%, serum tryptase ≥200 ng/mL, or BM MC ≥30%

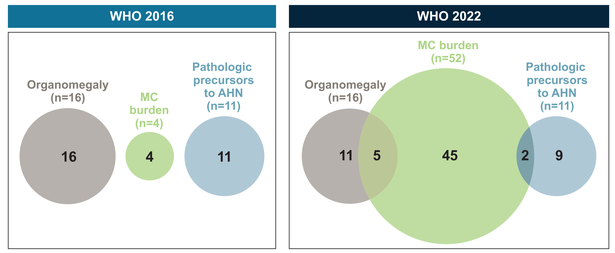
Figure 3. MC burden B-finding by WHO criteria



[a]Of the 12 patients with tryptase >200 ng/mL per WHO 2016 criteria, 3 had HαT-adjusted tryptase of <200 ng/mL per the WHO 2022 criterion; 1 additional patient not included per the WHO 2016 criterion had tryptase equal to 200 ng/mL, so was included per the WHO 2022 criterion. Overall, the exclusion of 3 patients and addition of 1 patient resulted in 2 fewer patients meeting the WHO 2022 *vs* WHO 2016 serum tryptase threshold.

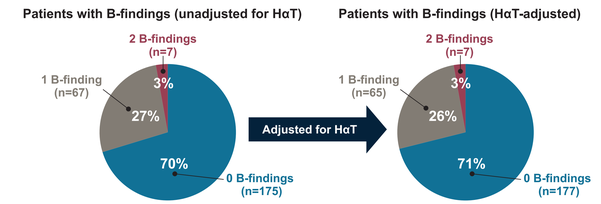
[b]Of the 30 patients with BM MC ≥30% per the WHO 2022 criterion, 12 had BM MC of 30%, so were not considered as above the 30% threshold (i.e., >30%) per the WHO 2016 criterion.

Figure 4. B-finding distribution by WHO criteria



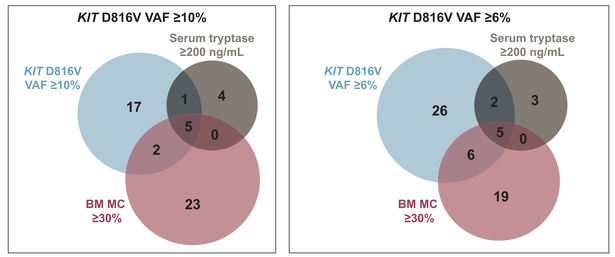
- Using WHO 2022 criteria, 7 patients had ≥2 B-findings (i.e., SSM) based on their baseline characteristics in PIONEER compared with no patients using WHO 2016 criteria (**Figure 4**)
  - Baseline ISM-SAF TSS, tryptase, VAF, and BM MC were higher in patients with SSM compared to patients with ISM; age and sex were similar.

Figure 5. The impact of adjusting basal serum tryptase in patients with HαT



- In PIONEER, 28 out of 249 patients (11%) were HαT+ (**Figure 5**)
  - Adjusting for serum tryptase in HαT+ patients had a minimal impact on the number of patients with 1 B-finding and no change in the number of patients with ≥2 B-findings (i.e., SSM)

Figure 6. Distribution of patients in PIONEER according to *KIT* D816V VAF



- *KIT* D816V VAF is an indirect assessment of multilineage involvement; a *KIT* D816V VAF threshold ≥6% is highly specific for multilineage involvement of the *KIT* mutation, and may be prognostic[27]
- Lowering the *KIT* D816V VAF threshold from 10% (as per WHO 2022 criteria) to 6% increased the number of patients with high MC burden from 52 to 61 patients but did not change the number of patients with ≥2 B-findings (SSM) (**Figure 6**)

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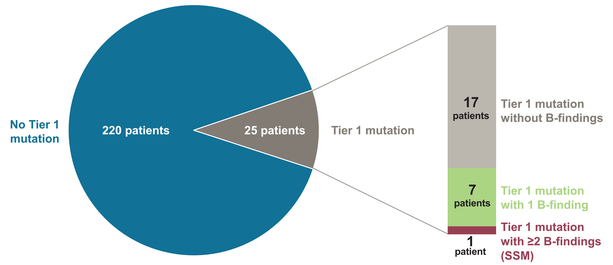
Conflicts of interest/disclosures

Dr George has received consulting fees and is a study steering committee member for Blueprint Medicines Corporation, BMS/Celgene, Cogent Biosciences, and Incyte.

Figure 7. Analysis of Tier 1 mutations in patients in PIONEER



- In total, 25 patients in PIONEER harbored non-*KIT* pathogenic mutations (**Figure 7**)
- Only 1/25 (4%) patients who had a non-*KIT* mutation met the WHO 2022 criteria for SSM
- Seven patients with 1 B-finding were found to have a Tier 1 mutation, which may signify a precursor to an associated hematologic neoplasm, though in some cases it could still represent unrelated clonal hematopoiesis of indeterminate potential
- Incorporation of patients with Tier 1 mutations into the classification of myeloproliferation and/or myelodysplasia B-finding would increase the number of patients meeting the criterion of ≥2 B-findings from 7 to 14

Conclusions

- According to WHO 2022 criteria, 7 patients enrolled in PIONEER would be considered as having SSM, none of whom had an SSM diagnosis per WHO 2016 criteria at the time of enrollment
- Considerably more patients in PIONEER met the MC burden B-finding using WHO 2022 criteria *versus* WHO 2016 criteria (52 patients *vs* 4 patients)
- Accounting for HαT did not significantly change the number of patients with B-findings or SSM
- *KIT* D816V VAF ≥10% is a specific surrogate for multilineage involvement, but the VAF threshold that best correlates with prognostic risk has yet to be determined and needs to be further explored[28]
  - Lowering the *KIT* D816V VAF threshold to ≥6% would expand the proportion of patients meeting the high MC burden B-finding associated with a higher prognostic risk
  - *KIT* D816V VAF is a disease burden finding distinct from serum tryptase and BM MC[29]
- Patients with ISM and concurrent non-*KIT* mutations represent a unique subset, largely uncaptured by current B-finding definitions
  - If Tier 1 mutations were included in the myeloproliferation and/or myelodysplasia B-finding, the number of patients in PIONEER with ≥2 B-findings would double (from 7 patients to 14 patients)
- These findings highlight the heterogeneity of ISM and novel insights from clinical trials may serve to improve future SM classification and management

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