Identification of Clonal Mast Cell Disease in Patients With Anaphylaxis or Evidence of Systemic Mast Cell Activation: A *Post Hoc* Analysis From PROSPECTOR

Poster Number 301

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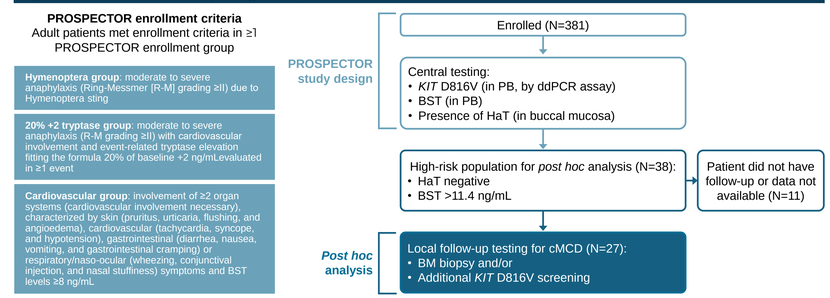
Background

- Clonal mast cell disease (cMCD) is defined by clonal expansion of aberrant mast cells and includes systemic mastocytosis (SM), monoclonal mast cell activation syndrome (MMAS), and cutaneous mastocytosis[1,2]
  - cMCD is predominately caused by the gain-of-function mutation *KIT* D816V in mast cells, which drives ~95% of cases of SM in adults[1,3]
  - Historically, prevalence of SM has been estimated at 1 in 10,000 although a recent study suggests that it could affect up to 1 in 5,000 people[4–7]
- Diagnostic delays have been observed for patients with cMCD due to the disease's nonspecific and variable symptoms; diagnostic workup includes measuring basal serum tryptase (BST) and testing bone marrow (BM) cells for the *KIT* D816V mutation[1,2,8]
- Elevated BST can be indicative of cMCD, although patients with hereditary α-tryptasemia (HaT; a genetic condition defined by increased copy numbers of the *TPSAB1* gene, which encodes the α- and β-tryptase enzymes) can also have high BST values[2,9]
  - Testing for the *KIT* D816V mutation has been limited by relatively low-sensitivity next-generation sequencing tools[10]
- Recently developed highly sensitive assays such as droplet digital polymerase chain reaction (ddPCR) have been shown to detect *KIT* D816V in samples of patients' peripheral blood (PB) with greater sensitivity than next-generation sequencing[10,11]
  - These assays allow screening of *KIT* D816V to be performed in a wider population and may help identify patients who should undergo a full workup for a cMCD diagnosis[10,11]
- The PROSPECTOR study reported the prevalence of *KIT* D816V in patients with anaphylaxis or suspected systemic mast cell activation to be 1 in 25 as evaluated by ddPCR in PB[12]
- However, cMCD may go undetected via PB testing in some patients, as mast cells mostly reside in BM and are not typically present in large quantities in PB[10]
  - A recent study reported that 85% of patients with indolent systemic mastocytosis had *KIT* D816V detected in PB by ddPCR (limit of detection, 0.03%), and an additional 10% had mutations detected in PB by ultrasensitive duplex sequencing[13]
- The National Institutes of Health BST CALCULATER predicts abnormal levels of BST based on patients' *TPSAB1* genotype; patients without HaT and with BST >11.4 ng/mL have abnormally elevated BST levels per the BST CALCULATER and may be at high risk of having cMCD[14]
- This *post hoc* analysis of the PROSPECTOR study reports the cMCD diagnosis and *KIT* D816V status of patients with BST >11.4 ng/mL, without HaT, and who underwent follow-up assessment

Methods

- PROSPECTOR (NCT04811365) was a multicenter, prospective screening study that enrolled 381 patients with anaphylaxis or symptoms consistent with systemic mast cell activation involving ≥2 organ systems (**Figure 1**)
- *KIT* D816V mutation in PB, BST levels, and presence of HaT were centrally evaluated (**Figure 1**)
- This post hoc analysis sought additional information from investigators for patients with elevated BST and no HaT, including (**Figure 1**): BM biopsy, *KIT* D816V retesting, and confirmed diagnoses of cMCD (either SM or MMAS)
- Within the PROSPECTOR population, 38 of 381 patients (10%) had BST >11.4 ng/mL and no HaT (**Figure 1**)
  - Of these 38 patients, 27 had local follow-up for cMCD diagnosis
  - Of the 11 patients with BST >11.4 ng/mL, no HaT, and no local follow-up, 3 had *KIT* D816V detected in PB in the PROSPECTOR study

Figure 1: PROSPECTOR study design and *post hoc* evaluation



BM, bone marrow; BST, basal serum tryptase; cMCD, clonal mast cell disease; ddPCR, droplet digital polymerase chain reaction; HaT, hereditary α-tryptasemia; PB, peripheral blood.

Results

Table 1: Demographics, clinical characteristics, and prevalence of *KIT* D816V

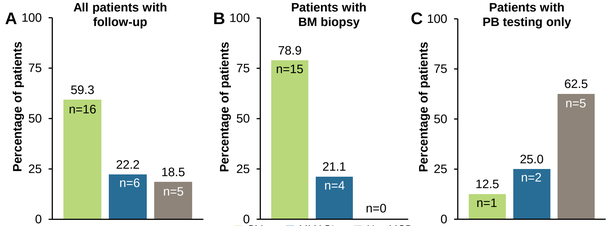
- Patients in PROSPECTOR and the subset of patients with BST >11.4 ng/mL, no HaT, and follow-up had similar age and history of anaphylaxis (**Table 1**)
- A total of 3.9% (15 of 381) of patients enrolled in PROSPECTOR and 29.6% (8 of 27) of patients with BST >11.4 ng/mL, no HaT, and follow-up had the *KIT* D816V mutation detected in centrally analyzed PB samples (**Table 1**)
  - The prevalence of detectable *KIT* D816V in the evaluable cohort was 4.1% (15 of 369) (**Table 1**)
  - Of the patients with detectable *KIT* D816V in PROSPECTOR's central test, 66.7% (10 of 15) were female

Parameters	All enrolled patients (N=381)	Patients with BST >11.4 ng/mL, no HaT, and follow-up (N=27)
Age, years		
Mean (SD)	53.7 (14.85)	53.9 (14.85)
Median (min, max)	56 (18, 92)	57 (27, 78)
Sex, n (%)		
Female	227 (59.6)	11 (40.7)
Male	154 (40.4)	16 (59.3)
Race, n (%)		
Asian	1 (<1)	0
Black or African American	2 (<1)	0
White	295 (77.4)	13 (48.1)
Other	19 (5.0)	2 (7.4)
Not reported	64 (16.8)	12 (44.4)
History of anaphylaxis, n (%)		
Yes	334 (87.7)	24 (88.9)
No	47 (12.3)	3 (11.1)
***KIT* D816V mutation, n (%)**		
Detected	15 (3.9)	8 (29.6)
Not detected	354 (92.9)	18 (66.7)
Unknown[a]	12 (3.1)	1 (3.7)

[a]Among the 381 enrolled patients, 12 had blood samples that were not evaluable for *KIT* D816V testing by ddPCR by the central laboratory, for the following reasons: sample was not collected (n=2), sample was not received by the central laboratory (n=2), sample reached the central laboratory past stability (n=6), and unknown reasons (n=2).
SD, standard deviation.

Figure 2: Prevalence of cMCD in patients with BST >11.4 ng/mL, no HaT, and follow-up

- Of 27 patients, 22 (81%) had a confirmed diagnosis of cMCD (**Figure 2A**)
- The prevalence of cMCD (SM or MMAS) in patients with BM biopsy was 100% (**Figure 2B**)
- In contrast, the prevalence of cMCD in patients who had additional *KIT* D816V testing in PB only was 37.5% (**Figure 2C**)



[a]Two patients classified with MMAS had confirmed clonality (detected *KIT* D816V) but incomplete assessment for SM.
MMAS, monoclonal mast cell activation syndrome; SM, systemic mastocytosis.

Figure 3: Distribution of BST levels by HaT status in PROSPECTOR patients (N=381)

- Patients enrolled in PROSPECTOR had BST levels spanning a wide range (**Figure 3**)
  - A total of 146/381 (38%) patients had BST <8 ng/mL and no HaT
  - There were 27 patients with BST >11.4 ng/mL, no HaT, and follow-up

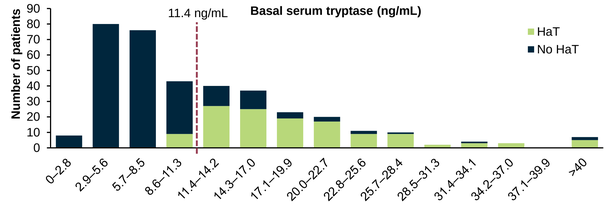
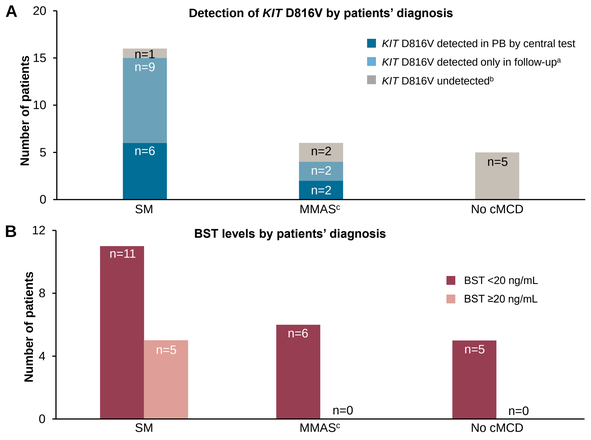


Figure 4: *KIT* D816V status and BST levels in patients with BST >11.4 ng/mL and no HaT

- Local follow-up of patients with BST >11.4 ng/mL and no HaT identified an additional 14 patients with cMCD; when combined with PROSPECTOR's detection of *KIT* D816V in PB, this increased the prevalence of cMCD from 4% to 8% of the enrolled population
  - A total of 11 patients with cMCD were negative for *KIT* D816V in the PROSPECTOR study and positive for *KIT* D816V in the follow-up analysis (**Figure 4A**)
    - Of the 11 patients, 7 had *KIT* D816V detected in PB in local testing, with variant allele fraction ranging from 0.01 to 0.05
  - Three patients were negative for *KIT* D816V in both the PROSPECTOR study and the follow-up analysis
- Of the 22 patients diagnosed with cMCD, 17 (77%) had BST <20 ng/mL (**Figure 4B**)



[a]Local testing includes tests for *KIT* D816V done both in PB and in BM biopsy tissue.
[b]N without detected *KIT* D816V includes patients with *KIT* D816V test results reported as inconclusive or not applicable.
[c]Two patients classified with MMAS had confirmed clonality (detected *KIT* D816V) but incomplete assessment for SM.

Conclusions

- The PROSPECTOR study demonstrated that *KIT* D816V is highly enriched in patients with anaphylaxis or symptoms consistent with systemic mast cell activation and that cMCD may be more prevalent, up to 8% (29 of 381) of patients, than previously recognized in this population
- Elevated BST levels in the absence of HaT may help identify patients with cMCD who initially had no *KIT* D816V detected in PB and who require a full assessment of cMCD via BM biopsy
  - cMCD was diagnosed in 100% (19 of 19) of patients with elevated BST who were negative for HaT and had a BM biopsy
- Upon local evaluation, the majority of patients in this sub-analysis were determined to have SM versus MMAS
- These findings highlight the need for even more sensitive blood-based assays for *KIT* D816V and support recent evidence that SM may be more prevalent than previously thought[4]

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Disclosures
Dr Hartmann reports acting as a consultant/speaker for ALK-Abelló, Allergopharma, Almirall, BioCryst, Blueprint Medicines Corporation, Cogent, Galderma, KalVista, Leo, Menarini, Novartis, Pfizer, Sanofi, Takeda, and Thermo Fisher. For all authors disclosures, please contact medinfo@blueprintmedicines.com.

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