Interpreting Baseline Serum Tryptase During Screening for Clonal Mast Cell Disease in the Presence or Absence of Hereditary Alpha-Tryptasemia

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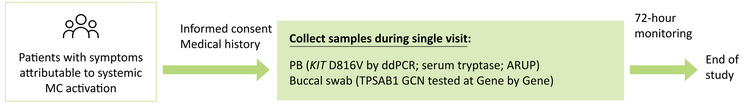
Background

- Clonal mast cell diseases (cMCDs) are primarily driven by the *KIT* D816V mutation[1–4]
  - Around 95% of patients with systemic mastocytosis (SM), the most common cMCD subtype, carry this mutation
- The PROSPECTOR trial (NCT04811365) demonstrated a meaningful *KIT* D816V prevalence in patients with anaphylaxis or symptoms of systemic mast cell (MC) activation[5]
- Basal serum tryptase (BST) ≥20.0 ng/mL is one of the criteria used to diagnose SM[6,7]
- However, SM can also occur in patients with BST <20.0 ng/mL and tryptase gating at ≥20.0 ng/mL may delay diagnosis[5]
  - BST ≥8.0 ng/mL may suggest hereditary alpha-tryptasemia (HaT), a genetic trait that causes elevated BST[8,9]
- We evaluated the real-world utility and reliability of BST in predicting cMCD in patients with anaphylaxis with unknown HaT status

Methods

- PROSPECTOR was a multicenter, prospective, screening study that evaluated the prevalence of *KIT* D816V mutation in peripheral blood (PB) by central laboratory testing using droplet digital PCR (limit of detection = 0.03%) in 381 patients with anaphylaxis or systemic MC activation[5] (**Figure 1**)
- A subset of patients underwent additional cMCD evaluation through further *KIT* D816V screening and/or bone marrow (BM) biopsy. This comprised:
  - *Post hoc* local follow-up
  - Additional single-site evaluation at the Institute of Mastocytosis Studies of Castilla-La Mancha (CLMast)
- This *post hoc* analysis included patients who received additional evaluation or were *KIT* D816V-positive in central testing
- The distribution of patients diagnosed with cMCD in this analysis was assessed across BST strata
- A BST-HaT model evaluated whether BST predicts cMCD based on HaT status
- Analyses compared 2 groups within this subset: HaT carriers included (in) vs HaT carriers excluded (ex)

Figure 1. PROSPECTOR study design[5]



Primary endpoint: proportion of patients with the *KIT* D816V mutation

Key eligibility

- Age ≥18 years
- Evidence of system MC activation by one of the following:
  1) **Cardiovascular group**: involvement of cardiovascular and ≥1 other organ system and BST levels ≥8 ng/mL
  2) **Hymenoptera group**: moderate-to-severe anaphylaxis due to hymenoptera sting
  3) **20% + 2 tryptase group**: moderate-to-severe anaphylaxis with cardiovascular involvement and increased tryptase of 20% + 2 ng/mL
- No prior history of SM or myeloid neoplasm

Additional endpoints

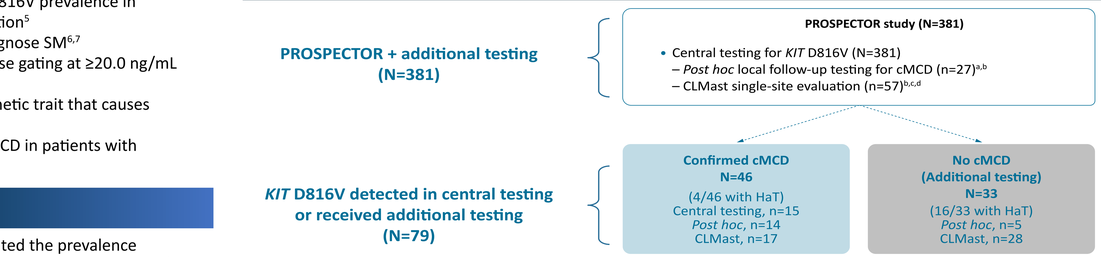
- Mean *KIT* D816V VAF in PB
- Proportion of patients with HaT

AE, adverse event; ARUP, Associated Regional and University Pathologists; BST, basal serum tryptase; ddPCR, droplet digital polymerase chain reaction; GCN, gene copy number; HaT, hereditary alpha-tryptasemia; MC, mast cell; PB, peripheral blood; SM, systemic mastocytosis; VAF, variant allele frequency.

Results

- Of the 381 PROSPECTOR patients, 79 (21%) had either *KIT* D816V detected in central testing or received additional evaluation, meeting the criteria for this analysis (**Figure 2, Table 1**)

Figure 2. Results from PROSPECTOR and additional testing populations



[a]Patients were HaT-negative with basal serum tryptase >11.4 ng/mL. Individual sites contacted for additional laboratory findings, BM biopsy, diagnosis. [b]Overlap of 8 patients occurred across the 2 additional testing populations and were only counted once in this analysis. [c]One patient who failed screening for PROSPECTOR due to prior diagnosis of SM was excluded from this analysis. [d]The following additional testing was performed: *KIT* D816V testing in PB by ASO-qPCR; BM characterization (n=40) *KIT* D816V testing by ASO-qPCR in whole BM, or by ASO-qPCR or PNA-PCR in BM MCs.
ASO-qPCR, allele-specific oligonucleotide quantitative polymerase chain reaction; BM, bone marrow; CLMast, Institute of Mastocytosis Studies of Castilla-La Mancha; cMCD, clonal mast cell disease; ddPCR, droplet digital polymerase chain reaction; HaT, hereditary alpha-tryptasemia; PB, peripheral blood; PNA-PCR, peptide nucleic acid polymerase chain reaction; REMA, Red Española de Mastocitosis; SM, systemic mastocytosis.

Table 1. Baseline demographics and clinical characteristics

Parameters	PROSPECTOR *post hoc* + CLMast			
	Any HaT status (n=79)		Excluding HaT (n=59)	
	cMCD (n=46)	No cMCD (n=33)	cMCD (n=42)	No cMCD (n=17)
Age, years				
Mean (SD)	54.2 (12.0)	56.1 (15.4)	53.8 (12.4)	50.7 (12.1)
Median (range)	56.5 (27, 75)	53.0 (28, 86)	56.0 (27, 75)	50.0 (28, 78)
Female, n (%)	17 (37)	18 (55)	14 (33)	8 (47)
Race, n (%)				
Black or African American	1 (2)	0	1 (2)	0
White	14 (30)	3 (9)	14 (33)	3 (18)
Other	0	1 (3)	0	1 (6)
Unknown	5 (11)	4 (12)	5 (12)	3 (18)
Not reported	26 (57)	25 (76)	22 (52)	10 (59)
Distribution by inclusion criteria, n (%)				
Cardiovascular group	20 (43)	18 (55)	16 (38)	6 (35)
Hymenoptera group	29 (63)	15 (45)	29 (69)	12 (71)
20% + 2 tryptase group	14 (30)	5 (15)	12 (29)	2 (12)
BST level, ng/mL, n (%)				
0.0 – <8.0	10 (22)	9 (27)	10 (24)	9 (53)
8.0 – <11.4	7 (15)	3 (9)	7 (17)	3 (18)
11.4 – <15.0	12 (26)	4 (12)	11 (26)	1 (6)
15.0 – <20.0	8 (17)	11 (33)	8 (19)	4 (24)
≥20.0	9 (20)	6 (18)	6 (14)	0
***KIT* D816V status, n (%)**				
Detected	38 (83)	0	34 (81)	0
Undetected	8 (17)[a]	33 (100)	8 (19)	17 (100)

[a]Of 8 patients with undetected *KIT* D816V, 2 had PB *KIT* D816V VAF >0–<0.03% and 6 had CD25+ mast cells by flow cytometry; 7 patients underwent bone marrow biopsy.
BST, basal serum tryptase; CLMast, Institute of Mastocytosis Studies of Castilla-La Mancha; cMCD, clonal mast cell disease; HaT, hereditary alpha-tryptasemia; PB, peripheral blood; SD, standard deviation; VAF, variant allele frequency.

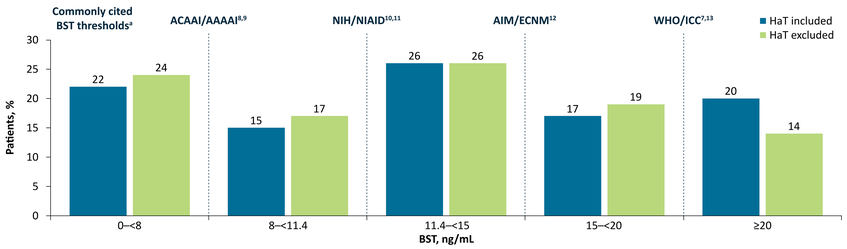
Table 2. Serum tryptase from central laboratory (ng/mL)

	N	Median (range)
HaT carriers included (in)		
No cMCD	33	15.6 (2.6, 45.1)
Confirmed cMCD	46	12.8 (3.4, 200.0)
HaT carriers excluded (ex)		
No cMCD	17	7.8 (2.6, 19.2)
Confirmed cMCD	42	12.7 (3.4, 200.0)

cMCD, clonal mast cell disease; HaT, hereditary alpha-tryptasemia.

- Median BST was similar in cMCD patients regardless of HaT inclusion (12.8 ng/mL [in] vs 12.7 ng/mL [ex]; **Table 2**)
- HaT drove high BST in patients without confirmed cMCD (15.6 ng/mL [in] vs 7.8 ng/mL [ex])
- A BST-HaT carrier status model revealed that BST was not predictive of cMCD in either HaT-negative or HaT-mixed groups (odds ratio 0.999 [95% Wald CI 0.870–1.148]; p=0.18)
- In **Figure 3**, a BST threshold of ≥20.0 ng/mL captured:
  - 20% (9/46) of cMCD patients when HaT was included
  - 14% (6/42) of cMCD patients when HaT was excluded

Figure 3. Distribution of PROSPECTOR *post hoc* + CLMast patients with cMCD across BST strata



[a]Thresholds used for screening recommendation (ACAAI/AAAAI), definition of normal levels (NIH/NIAID; AIM/ECNM), or diagnosis (WHO/ICC).
AAAAI, American Academy of Allergy, Asthma, and Immunology; ACAAI, American College of Allergy, Asthma, and Immunology; AIM, American Initiative in Mast Cell Diseases; BST, basal serum tryptase; cMCD, clonal mast cell disease; ECNM, European Competence Network on Mastocytosis; HaT, hereditary alpha-tryptasemia; ICC, International Consensus Classification; NIAID, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health; WHO, World Health Organization.

Conclusions

- **cMCD was identified in 12.1% (46/381) of PROSPECTOR patients overall and was observed across all BST strata, with values as low as 3.4 ng/mL**
- **The majority of patients (80%) with underlying cMCD identified in PROSPECTOR had a BST <20 ng/mL, including 22% with BST <8 ng/mL**
- **Restricting further work-up for cMCD to patients based on a single BST value or threshold could miss and delay diagnosis, particularly in anaphylaxis populations**
- **cMCD is frequent in patients with anaphylaxis and can sometimes only be detected after careful clinical assessment (e.g. anaphylaxis severity) and testing to determine *KIT* mutation status**

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