PROSPECTOR: A Global, Prospective Study to Determine the Prevalence of the *KIT* D816V Mutation in Peripheral Blood From Patients With Evidence of Systemic Mast Cell Activation

Poster Number 161

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Background

- Mast cell activation syndromes (MCAS) are a frequently underdiagnosed group of disorders characterized by systemic mast cell (MC) activation which can be caused by IgE-mediated and non-IgE-mediated triggers[1–3]
- Patients may experience debilitating symptoms associated with abnormal mast cell mediator release involving 2 or more organ systems (**Table 1**)[1,2,4]
- MCAS can be classified as clonal or non-clonal based on the presence or absence of the *KIT* D816V mutation and/or aberrant CD25 expression on MCs[2,5]
- SM is a rare clonal MC disease primarily driven by the *KIT* D816V mutation in approximately 95% of cases[6,7]
- Importantly, *KIT* D816V in bone marrow (BM) MCs can be detected in early stages of SM[5], however, the invasive nature of BM sampling required for diagnosis per World Health Organization (WHO)[8] criteria and limited molecular assay sensitivity can be barriers for diagnosis[7]
- The Spanish Network on Mastocytosis (Red Española de Mastocitosis [REMA]) developed a scoring system, that is not dependent on BM biopsies, for predicting MC clonality in patients presenting with MCAS symptoms[9,10]
- Further, high sensitivity real-time qPCR assays, such as allele-specific oligonucleotides-PCR[6] or droplet digital PCR[11], are now available to detect the presence of *KIT* D816V more reliably in peripheral blood (PB)[12]
- Testing for increased *TPSAB1* gene copy number as an indicator of hereditary alpha-tryptasemia (HaT), which causes elevated serum tryptase, may also aid in the diagnosis of SM[13]
- Despite these efforts, the prevalence of clonal mast cell disease with evidence of systemic MCA is still unknown and warrants further investigation

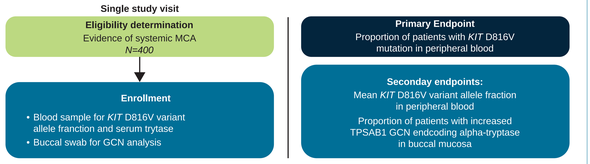
Table 1. Summary of symptoms related to systemic mast cell activation

Organ system	Symptoms
Skin	Pruritus, urticaria, angioedema, and flushing
Gastrointestinal	Nausea, vomiting, diarrhea, and abdominal cramping
Cardiovascular	Hypotensive syncope or near syncope, and tachycardia
Respiratory/naso-ocular	Wheezing, conjunctival injection, and nasal congestion
Neurological	Difficulty concentrating, fatigue, headaches
Musculoskeletal	Bone pain, muscle pain, osteopenia

Study design and objectives

- PROSPECTOR (NCT04811365) is a global, multi-center screening study determining the prevalence of *KIT* D816V mutation in PB in patients with evidence of systemic MCA (**Figure 1**)
- The key eligibility criteria and key study endpoints are shown in **Table 2** and **Table 3**, respectively

Figure 1. PROSPECTOR study design



GCN, gene copy number; MCA, mast cell activation; TPSAB1, tryptase Alpha/Beta 1.

Table 2. Key eligibility criteria

Inclusion criteria

- Aged ≥18 years
- Evidence of systemic mast cell activation, based on meeting ≥1 of 3 criteria:
  - Involvement of ≥2 organ systems (cardiovascular involvement necessary) and serum basal tryptase ≥8 ng/mL
  - Severe anaphylaxis from hymenoptera sting
  - Severe anaphylaxis with cardiovascular involvement and event-related tryptase elevation fitting the formula 20% of baseline plus 2 ng/mL in ≥1 event

Exclusion criteria

- Patients with known diagnoses of mastocytosis, including:
  - Mastocytosis in the skin
  - Indolent systemic mastocytosis
  - Smoldering systemic mastocytosis
  - Systemic mastocytosis with associated hematologic neoplasm
  - Aggressive systemic mastocytosis
  - Mast cell leukemia
  - Mast cell sarcoma

Table 3. Key study endpoints

Primary endpoint	Secondary endpoints
• The prevalence of *KIT* D816V mutation in PB by droplet digital PCR defined as the proportion of patients with evidence of systemic MCA and the *KIT* D816V mutation in PB	• *KIT* D816V variant allele fraction in PB • The prevalence of HaT defined as the proportion of patients with an increased *TPSAB1* gene copy number encoding alpha-tryptase on a single allele in buccal mucosa • The relationship between *KIT* D816V in PB and REMA score, other MCA clinical parameters or HaT diagnosis

Enrollment and status

- Enrollment in PROSPECTOR is ongoing with 24 planned centers participating in the United States, the United Kingdom, and Europe (**Figure 2**)
- As of August 15, 2022, there were 105 patients enrolled and evaluated for *KIT* D816V mutation (**Table 4**) in PB using droplet digital PCR
  - 3/105 patients (2.9%) had detectable *KIT* D816V mutation
  - 15/105 patients (14.3%) had tryptase levels ≥20 ng/mL and 23.8% (25/105) of patients had an increased number of the alpha tryptase gene

Figure 2. Countries with active enrollment sites

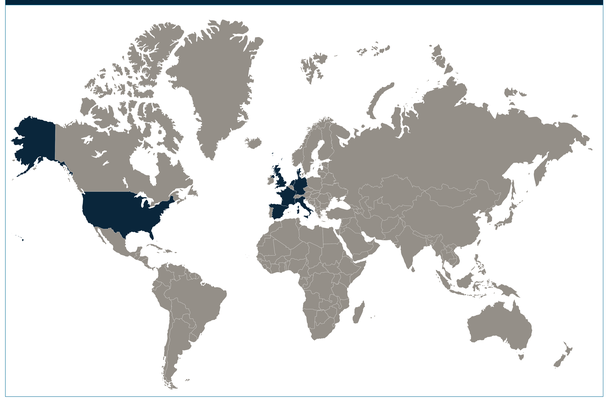


Table 4. Preliminary baseline demographics

Characteristic	N=105		
Age, mean (range)	55.7 (19–86)		
Gender, n (%)			
Female	59 (56.2)		
Male	46 (43.8)		
Ethnicity, n (%)			
Hispanic or Latino	2 (1.9)		
Not Hispanic or Latino	64 (61.0)		
Not reported	36 (34.3)		
Unknown	3 (2.9)		
KIT D816V positive, n (%)	3 (2.9)[a]		
Increased alpha-tryptase	25 (23.8)		
Serum tryptase (ng/mL), n (%)	All patients	*KIT* D816V positive	Increased alpha-tryptase
0–<8	42 (40.0)	1 (1.0)	0 (0)
8–<20	44 (41.9)	2 (1.9)	16 (15.2)
≥20	15 (14.3)	0 (0)	8 (7.6)
Unknown	4 (3.8)	0 (0)	1 (1.0)
REMA score, mean (range)	-1.3 (-4–7)		
Inclusion criteria, n (%)			
Involvement of ≥2 organ systems (cardiovascular involvement necessary) and serum basal tryptase ≥8 ng/mL	45 (42.9)		
Severe anaphylaxis from hymenoptera sting	44 (41.9)		
Severe anaphylaxis with cardiovascular involvement and event-related tryptase elevation fitting the formula 20% of baseline plus 2 ng/mL in ≥1 event	16 (15.2)		

[a]The number of *KIT* D816V positive patients was initially reported to be 7 (6.7%) but subsequently was amended to 3 (2.9%).

Summary

- The PROSPECTOR screening trial aims to determine the prevalence of clonal mast cell disease with evidence of systemic MCA, and by association, better define the epidemiology of the disease
- Of patients enrolled thus far, the proportion assessed as being *KIT* D816V positive was low (3/105 [2.9%]) while 25 (23.8%) patients had HaT, as confirmed by the detection of increased copies of the alpha-tryptase gene
- Despite the high sensitivity of droplet digital PCR, the detection of low *KIT* D816V VAF levels (<0.03%) in PB can be problematic; enrichments strategies and/or higher sensitive assays may be required to more accurately detect the *KIT* D816V mutation in patients with clonal mast cell disorders
- For more information, visit

https://clinicaltrials.gov/ct2/show/NCT04811365

- To learn more about our clinical trials, visit blueprintclinicaltrials.com or contact us in the USA at medinfo@blueprintmedicines.com or 1-888-BLU-PRNT (1-888-258-7768), and in Europe at medinfoeurope@blueprintmedicines.com or +31 85 064 4001

References

1. Jackson CW et al. *Int J Mol Sci*. 2021;22(20). 2. Akin C et al. *J Allergy Clin Immunol*. 2010;126(6):1099–1104 e1094. 3. González-de-Olano D et al. *Front Immunol*. 2017;8:792. 4. Pardanani A. *Am J Hematol*. 2021;96(4):508–525. 5. Valent P et al. *Int Arch Allergy Immunol*. 2012;157(3):215–225. 6. Garcia-Montero AC et al. *Blood*. 2006;108:2366–2372. 7. Kristensen T et al. *J Mol Diagn*. 2011;13:180–188. 8. Valent P et al. *Blood*. 2017:16;129(11):1420–1427. 9. Alvarez-Twose I et al. J Allergy Clin Immunol. 2010;125(6):1269–1278.e2. 10. Alvarez-Twose I et al. *Int Arch Allergy Immunol*. 2012;157(3):275–280. 11. Greiner G et al. *Clin Chem*. 2018;64(3):547–555. 12. Kristensen T et al. *Eur J Haematol*. 2016;96(4):381–388. 13. Lyons JJ et al. *J Allergy Clin Immunol*. 2021;147(2):622–632.

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