Advanced Systemic Mastocytosis (SM) Brochure

This resource for haematologists provides an overview of Advanced SM, including key symptoms and diagnostic testing

blueprint MEDICINES
a sanofi company

Advanced SM is a rare clonal mast cell neoplasm[1]

Systemic mastocytosis is a rare disorder characterised by abnormal proliferation of mast cells,[1] driven by the *KIT* D816V mutation in ~95% of cases.[2,3] It is divided into two main forms: non-advanced SM and Advanced SM.[4]

~1 in 10,000

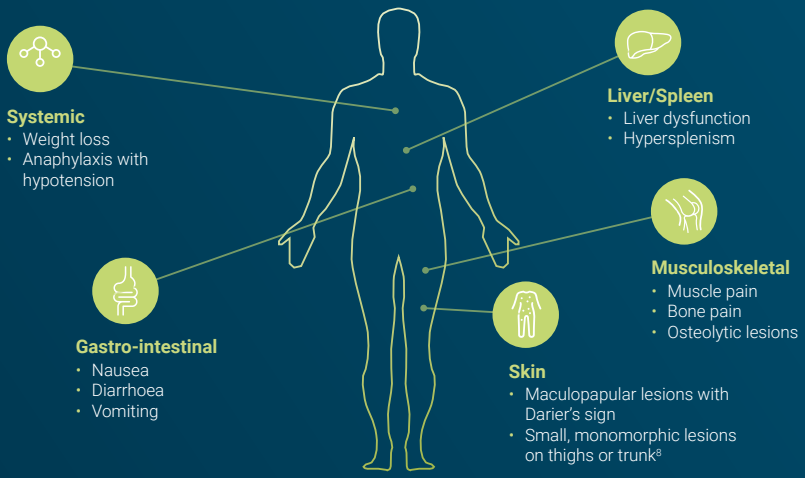
people have SM[3]

Advanced SM has three different subtypes[4]

- **Aggressive systemic mastocytosis (ASM)**
- **Systemic mastocytosis with an associated haematological neoplasm (SM-AHN)**
- **Mast cell leukaemia (MCL)**

Identifying Advanced SM in your practice

Patients with Advanced SM can experience debilitating mast cell mediator symptoms that impair quality of life and cause organ damage.[5–7]



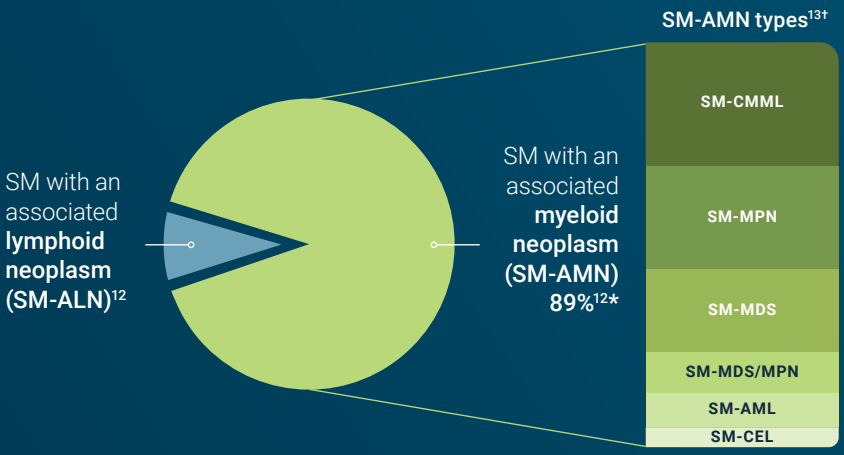
Advanced SM is associated with a poor prognosis and decreased overall survival[9]

Historical median overall survival for patients with Advanced SM[9]

Data based on the ECNM registry of patients diagnosed with mastocytosis between 1978 and 2017. Only patients with Advanced SM are shown here (N=259).[9]

Advanced SM may be missed in patients with concurrent myeloid neoplasms[10]

Approximately two-thirds of patients with Advanced SM present with an associated haematological neoplasm,[11] primarily of myeloid origin[12]



*Data based on a retrospective study at the Mayo Clinic. Only patients with SM-AHN are reported (N=138).[12]

†Estimated prevalence among all reported cases of SM-AHN, based on published data (PubMed) reported in the Valent 2024 study.[13]

AML=acute myeloid leukaemia; CEL=chronic eosinophilic leukaemia; CMML=chronic myelomonocytic leukaemia; ECNM=European Competence Network of Mastocytosis; MDS=myelodysplastic syndrome; MDS/MPN=myelodysplastic syndrome/myeloproliferative neoplasm; MPN=myeloproliferative neoplasm.

Suspecting Advanced SM: A combination of diagnostic tests is required due to its heterogeneity[14]

Serum tryptase

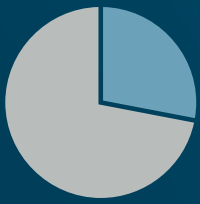
Serum tryptase testing is recommended as an initial step in evaluating SM upon suspicion.[14]

High-sensitivity *KIT* D816V testing

High-sensitivity PCR methods such as droplet digital polymerase chain reaction (ddPCR; ~0.01% sensitivity) are recommended for detecting *KIT* D816V in peripheral blood.[14]

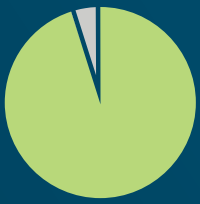
Next-generation sequencing (NGS) assays have low sensitivity and are insufficient for reliably detecting *KIT* D816V:

*In a study of ISM patients (n=39)[15]**



28% detection of *KIT* 2816V with NGS

Statistical analysis was not performed



95% detection of *KIT* 2816V with ddPCR

**Although this study was conducted in ISM, similar principles apply — ddPCR offers superior sensitivity for* KIT *D816V detection across the SM spectrum.*

Bone marrow biopsy

A bone marrow examination is recommended for patients with clear signs of SM:[14]

- *Typical skin lesions*
- *Spontaneous anaphylaxis*
- *Persistently elevated tryptase levels*
- *REMA score† ≥2*
- *KIT-activating mutation*
- *Splenomegaly*
- *Unexplained osteoporosis*
- *Blood cell count abnormalities*

†The REMA scoring system assigns points as follows: male (+1) or female (–1); basal serum tryptase <15 ng/mL (–1) or >25 ng/mL (+2); presence (–1) or absence (+1) of urticaria/pruritus/angioedema; and presence of presyncope or syncope (+3). It is a predictive model for clonal mast cell disorders, with a score 2 indicating high risk.

ISM=indolent systemic mastocytosis; PCR=polymerase chain reaction; REMA=Red Española de Mastocitosis (Spanish Network on Mastocytosis).

Diagnosing Advanced SM

WHO DIAGNOSTIC CRITERIA FOR SM[4]

1 major and ≥1 minor criterion, or ≥3 minor criteria

Major Criterion

Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)

Minor Criteria

≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates in sections of bone marrow or other extracutaneous organs

KIT-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT* in bone marrow or another extracutaneous organ

Mast cells in bone marrow, blood or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30

Baseline serum tryptase concentration >20 ng/mL. In the case of a known HαT, the tryptase level should be adjusted

HαT=hereditary alpha-tryptasemia; WHO=World Health Organization.

Advanced SM is associated with a poor prognosis and decreased overall survival due to organ damage[9]

Advanced SM predominantly presents with an associated haematological neoplasm (SM-AHN), most commonly of myeloid origin.[10] The presence of persistent non-chemotherapy-specific symptoms or unexplained organopathy due to mast cell infiltration in AHNs should prompt further investigation for SM.[10,14]

For more information on SM-AHN, download the ***SM-AHN leaflet***

References:

1. Zhang X, *et al. Diagn Pathol.* 2023;18:17.
2. Garcia-Montero AC, *et al. Blood.* 2006;108(7):2366–2372.
3. Ungerstedt J. *Cancers.* 2022;14(16):3942.
4. Valent P, *et al. Hemasphere.* 2021.5(11):e646.
5. Jennings S, *et al. Immunol Allergy Clin N Am.* 2018;38(3):505–525.
6. Pardanani A. *Am J Hematol.* 2023;98(7):1097–1116.
7. Gülen T, *et al. J Intern Med.* 2016;279(3):211–228.
8. Hartmann K, *et al. J Allergy Clin Immunol.* 2016;137(1):35–45.
9. Sperr WR, *et al. Lancet Haematol.* 2019;6(12):e638–e649.
10. Schwaab J, *et al. J Allergy Clin Immunol Pract.* 2020;8(9):3121–3127.e1.
11. Valent P, *et al. J Allergy Clin Immunol Pract.* 2019;7(1):81–87.
12. Pardanani A, *et al. Blood.* 2009;114(18):3769–3772.
13. Valent P, *et al. J Allergy Clin Immunol Pract.* 2024;12(12):3250–3260.e5.
14. Valent P, *et al. J Allergy Clin Immunol Pract.* 2022;10(8):1999–2012.e6.
15. George TI, *et al. Blood.* 2020;136(Suppl 1):7.

blueprint MEDICINES
a sanofi company

UKBP-PRNON-25.008, date of preparation 11/25