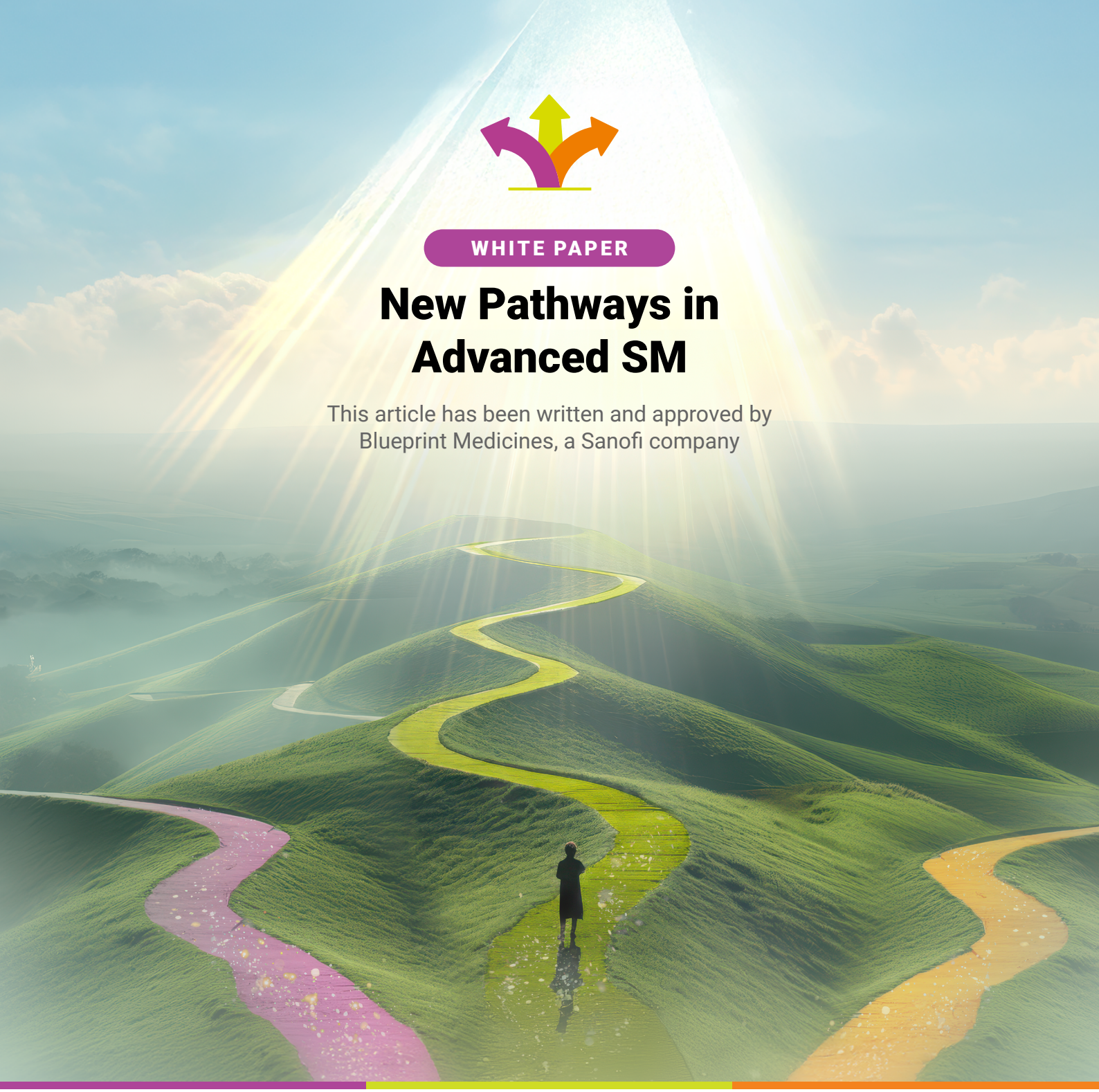

WHITE PAPER

New Pathways in Advanced SM

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Within the last two decades, systemic mastocytosis (SM) has undergone major reclassification, with Advanced SM emerging as a distinct form, as reflected in the 2022 iterations of the 5th edition World Health Organization (WHO) and International Consensus Criteria (ICC) classifications. Advanced SM is rare but clinically significant, with prognosis and disease trajectory differing markedly from indolent forms of SM.

Alongside clinical features, advances in molecular diagnostics — most notably the identification of the KIT *D816V and additional high-risk mutations — have deepened our understanding of disease biology. Yet, despite these developments, investigating Advanced SM remains complex.*

In this article, we explore the diagnostic challenge of Advanced SM, the role of multidisciplinary care in defining patient-centred treatment objectives, and the recent therapeutic advances that are reshaping outcomes for this rare disease.

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Contents

Introduction

Mastocytosis is a clonal proliferation of abnormal mast cells (MC) accumulating in skin, bone marrow and extracutaneous organs.[1,2] It is broadly classified into SM, cutaneous mastocytosis (CM) and MC sarcoma.[1] CM is characterised by MC infiltration limited to the skin, whereas SM is characterised by MC infiltration in one or more extracutaneous organs.[3] SM itself is divided into two main forms: non-advanced SM and Advanced SM. The six subtypes of SM include bone marrow mastocytosis (BMM), indolent SM (ISM), smouldering SM (SSM), aggressive SM (ASM), SM with an associated haematological neoplasm (SM-AHN) and MC leukaemia (MCL).[1]

The prevalence of SM in Europe is estimated to be between 1 in 7,700 and 1 in 10,400,[4] with Advanced SM representing approximately 20% of cases.[5] MC infiltration can occur in multiple organs — including the skin, bone marrow, liver, spleen, gastrointestinal tract and peripheral blood. While SM affects each individual differently, it can present with debilitating symptoms ranging from skin lesions, abdominal pain and fatigue that impair quality of life, to profound psychological burden and, in its more advanced forms, organ dysfunction that shortens lifespan.[3,6]

The current diagnostic standards for SM are defined by recent WHO and ICC guidelines, which both require a combination of major (multifocal dense infiltrates of MCs) and minor criteria (atypical MC morphology, *KIT* mutation, CD2/25/30 expression and elevated serum tryptase) (Figure 1). The WHO guidelines require one major plus one minor criterion or three minor criteria, while the ICC allows a diagnosis of SM with the major criterion alone.[1,2,7]

Advanced SM comprises three subtypes: ASM, SM-AHN (termed "SM-AMN" by the ICC to reflect myeloid associations) and MCL.[1,2] ASM is defined by the presence of at least one "C-finding" (which may not be present in SM-AHN or MCL), indicating end-organ damage, such as cytopenias, hepatomegaly with impaired liver function, osteolytic bone lesions and/or pathological fractures, splenomegaly with hypersplenism, or malabsorption related to gastrointestinal involvement. SM-AHN is diagnosed when criteria for both SM and an associated haematologic neoplasm are met. MCL is a rare but highly aggressive form, defined by ≥20% MCs in bone marrow aspirates or peripheral blood.[7]

Major criterion
Multifocal, dense mast cell aggregates (≥15 mast cells) in BM biopsy and/or other extracutaneous organ – cells should be **CD117 or tryptase positive**
Minor criteria
>25% of all mast cells from extracutaneous biopsy sample (e.g. BM, liver) are **spindle-shaped** in dense and diffuse mast cell infiltrates, or are **atypical** cells on BM smears
Activating *KIT* point mutation at codon 816 or other critical regions in BM, blood or other extracutaneous organ
Mast cells in BM, blood or other extracutaneous organ(s) aberrantly express one or more of the following antigens: **CD2, CD25, CD30**
Persistently elevated serum tryptase level (>20 ng/mL) (if there is an associated myeloid neoplasm, this parameter is not valid, and in known HαT, the tryptase level should be adjusted)

Figure 1. WHO diagnostic criteria for SM.[1,7]

BM=bone marrow; HαT=hereditary alpha tryptasemia; SM=systemic mastocytosis; WHO=World Health Organization.

Advanced SM is associated with poor prognosis and outcomes,[5,8] with a median overall survival of 2 to 41 months, mainly due to the abnormal infiltration of MCs into multiple organs (Figure 2).[8]

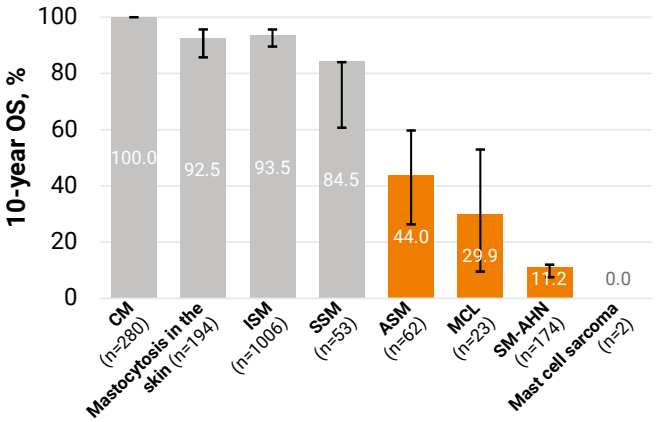
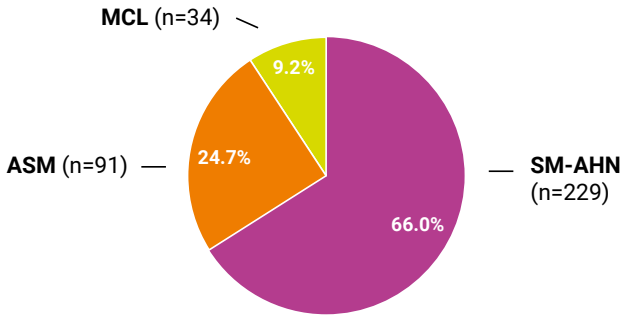


Figure 2. 10-year OS in WHO subgroups of mastocytosis. Data based on study of 1,794 patients in the ECNM registry.[5] Error bars show 95% CI.

ASM=aggressive SM; CI=confidence interval; CM=cutaneous mastocytosis; ECNM=European Competence Network on Mastocytosis; ISM=indolent SM; MCL=mast cell leukaemia; OS=overall survival; SM-AHN=SM with an associated haematological neoplasm; SSM=smouldering SM; WHO=World Health Organization.

Notably, SM-AHN is the most common subtype of Advanced SM, accounting for up to 70% cases.[9] These patients present unique diagnostic challenges, owing to the coexistence of two clonal haematologic neoplasms within the bone marrow niche. Advanced SM predominantly

presents with associated haematological neoplasms of myeloid origin (also known as AMN), with chronic myelomonocytic leukaemia (CMML), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN) and MDS/MPN being most common (Figure 3).[10,11] Interestingly, SM is identified in up to 3% of patients with CMML,[12] and SM-CMML is associated with a worse survival than CMML alone.[13]



	Examples	Prevalence among SM-AHN†,10
SM with an associated myeloid neoplasm	SM-CMML	30%
	SM-MPN	25%
	SM-MDS	20%
	SM-MDS/MPN	10%
	SM-AML‡	8%
	SM-CEL	5%
SM with an associated lymphoid neoplasm	SM-NHL	3%
	SM-MM	2%
	SM-CLL	2%
	SM-ALL	<1%

Figure 3. Distribution of Advanced SM subtypes* and delineation of AHN types in patients with SM-AHN.[9,10]

*Data based on ECNM patient cohort. Only patients with Advanced SM are shown here (N=354).[9] †Estimated prevalence among all reported cases of SM-AHN, based on published data (PubMed).[10] ‡Cases reported to have AML at first presentation. The prevalence of SM-AML is much higher (estimate: 30–40%) when the follow-up cases are also counted. In fact, many patients with myeloid-type AHN progress to SM-AML during follow-up.[10]

ALL=acute lymphoblastic leukaemia; AML=acute myeloid leukaemia; ASM=aggressive SM; BMM=bone marrow mastocytosis; CEL=chronic eosinophilic leukaemia; CLL=chronic lymphocytic leukaemia; CMML=chronic myelomonocytic leukaemia; ECNM=European Competence Network on Mastocytosis; MCL=mast cell leukaemia; MDS=myelodysplastic syndrome; MM=multiple myeloma; MPN=myeloproliferative neoplasm; NHL=non-Hodgkin lymphoma; SM=systemic mastocytosis; SM-AHN=SM with an associated haematological neoplasm.

Finding Advanced SM: Investigations and Complexities in Testing

Mastocytosis has a heterogeneous clinical presentation, ranging from asymptomatic disease to highly aggressive courses with multisystem involvement. MC mediator-related symptoms are common across all types of SM. In Advanced SM, however, organopathy due to MC infiltration, including ascites, osteoporosis, liver dysfunction, weight loss, cytopenias and hypersplenism, is particularly prominent.[3]

Patients with Advanced SM can experience a prolonged delay to diagnosis, with a median of three years between symptom onset and confirmation, largely due to multiple specialist referrals before recognition of the disease.[14] Advanced SM may come to clinical attention in different ways and is often suspected on the basis of common presenting symptoms, including skin symptoms, fatigue, diarrhoea, nausea and allergic reactions, which are not typically found in other haematological malignancies (Figure 4). Referral routes vary, but the most frequent are from general practitioners (33%), immunologists (28%), dermatologists (11%) and oncologists (11%), before eventual evaluation by a haematologist.[15]

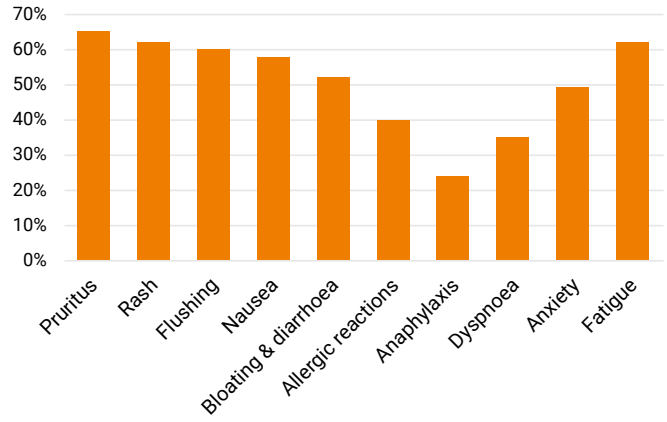


Figure 4. Common symptoms of Advanced SM at presentation. Data from a cross-section study of 55 patients with Advanced SM in the USA.[15]

SM=systemic mastocytosis.

Investigation begins with detailed clinical and physical examination.[16] Findings such as skin lesions, elevated serum tryptase and organomegaly should raise suspicion for SM and prompt a full diagnostic work-up based on WHO criteria.[7,16] Serum tryptase test is recommended as an initial screening step upon suspicion.[16] *KIT* D816V is present in ~95% of patients with SM, hence a positive *KIT* D816V mutation significantly increases the likelihood of disease.[17,18] As only a small fraction of circulating *KIT* mutations may be detectable in peripheral blood, highly sensitive assays are essential. High-sensitivity polymerase chain reaction (PCR) methods, such as digital droplet PCR (ddPCR), are preferred, as next-generation sequencing (NGS) lacks sufficient

sensitivity to reliably identify low variant allele frequencies (VAF).[16,19] In one ISM study (N=39), ddPCR detected *KIT* D816V mutations in 95% of peripheral blood samples, whereas NGS identified the mutation in only 28% of cases. Notably, eight patients had a VAF of <0.1%, which is below the detection limit of NGS, highlighting the importance of ddPCR for capturing clinically relevant low-level mutations.[19] A bone marrow biopsy is important to confirm or exclude a diagnosis when there is a high index of suspicion.[16] These approaches reflect established UK diagnostic pathways and current National Institute for Health and Care Excellence (NICE) guidance, providing the foundation for evidence-based treatment decisions.[20] Radiological investigations, such as dual-energy X-ray absorptiometry (DEXA) scans or computed tomography (CT) imaging, are also useful to support the diagnosis.[21]

Establishing a diagnosis of SM, and distinguishing its subtype, is not always straightforward. A stepwise algorithmic approach is recommended, described in Figure 5. Once SM is confirmed, the two important questions are: (1) whether an additional haematologic non-MC-lineage neoplasm is present; and (2) whether the patient has end-organ damage consistent with C-findings. Differentiation between ASM and MCL then requires examination of bone marrow and peripheral blood smears.[7]

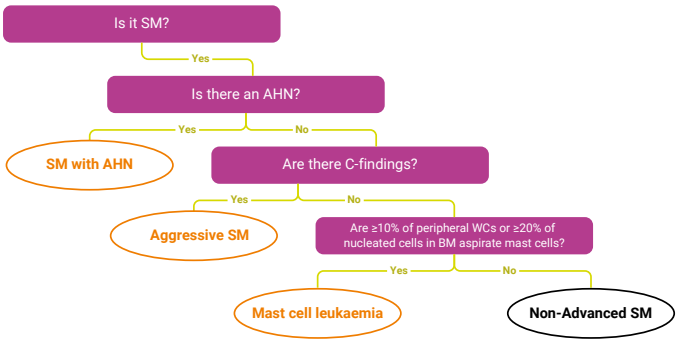


Figure 5. Diagnostic algorithm for patients referred with possible Advanced SM.[7]

AHN=associated haematological neoplasm; BM=bone marrow; SM=systemic mastocytosis; WC=white blood cells.

These AHNs are more common in clinical practice and may lead to overlooking the diagnosis of coexisting SM[22]. The presence of persistent non-chemotherapy-specific constitutional symptoms or unexplained organopathy due to MC infiltration in AHNs should prompt further investigation for SM.[16] Sheets of neoplastic AHN cells (e.g. AML and CMML) may also obscure the presence of SM within SM-AHN. As such, routine analyses, including tryptase or CD117 (KIT) staining of bone marrow biopsy slides, serum tryptase testing, and/or *KIT* D816V mutation analysis, are recommended to screen for hidden SM in myeloid neoplasms.[22,23] The reverse situation is equally important: evidence of monocytosis, eosinophilia, splenomegaly, elevated lactate dehydrogenase or high *KIT* VAF in peripheral blood, or additional somatic mutations, are clues that can help uncover a coexisting neoplasm in patients diagnosed with SM.[24]

Advanced SM is a multimutated disease with somatic mutations beyond *KIT* D816V.[25] SM-specific histopathological and molecular parameters are critical for risk stratification and prognostication in Advanced SM. In particular, mutational profiling using myeloid NGS panels, though not appropriate for diagnosis, provides valuable prognostic information.[26,27] The presence and number of mutations in the so-called *S/A/R* gene set (*SRSF2, ASXL1, RUNX1*) are associated with poorer overall survival, making it an important tool in patient management.[26] Furthermore, ddPCR is valuable not only for detecting *KIT* D816V mutations that may be missed by NGS, but also for determining VAFs to assess disease burden and monitor treatment effectiveness.[27]

Taken together, these complexities mean that the diagnosis of Advanced SM rarely rests on a single investigation. Instead, it requires coordinated interpretation of clinical, molecular and pathological findings — underscoring the need for a multidisciplinary approach to patient care.

Challenges and Multidisciplinary Approaches in Advanced SM

The management of Advanced SM presents considerable challenges owing to the heterogeneity of the disease. Treatment objectives are rarely uniform; instead, they are shaped by a complex interplay of disease biology, clinical presentation and patient-specific considerations. Several factors influence these objectives. Clinical features such as subtype, tempo of progression, organ involvement and transplant eligibility must be weighed alongside patient presentation, including mediator-driven symptoms, degree of organ damage, comorbidities and overall burden of disease. Underlying biology, including age, organomegaly and cytopenias, laboratory markers such as tryptase, alkaline phosphatase, and β2-microglobulin, as well as cytogenetic and molecular abnormalities, all contribute important prognostic information.[28,29]

This complexity is most evident in SM-AHN, the

most common subtype of Advanced SM. Here, aggressiveness varies widely — ranging from indolent to aggressive forms in the SM component, and from low-risk MDS to highly aggressive AML in the AHN component. Treatment decisions must therefore account for MC burden, presence of C-findings, *KIT* D816V lineage involvement, the type and severity of AHN, and the contribution of additional somatic mutations (Figure 6).[28]

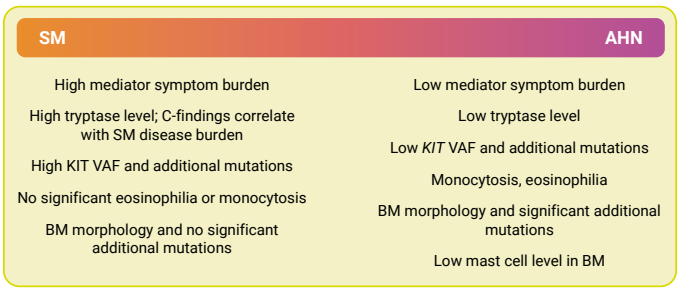


Figure 6. Factors that guide treatment priorities in SM-AHN.[28]

AHN=associated haematological neoplasm; BM=bone marrow; SM=systemic mastocytosis; VAF=variant allele frequency.

Management of SM-AHN should be highly individualised. It is recommended that treatment prioritisation should follow the factors outlined in Figure 6, with recognition that therapeutic needs and objectives may shift over the disease course.[28]

Other key challenges and questions remain. What is the best way to risk stratify individual patients in such a genetically and clinically diverse population? How should mutational profiling guide treatment selection and ongoing response monitoring? What is the optimal sequencing of KIT- and AHN-directed therapies, particularly given the limitations of KIT inhibition in genetically complex disease and the risk of progression to AML in a subset of patients? Finally, what role should allogeneic haematopoietic cell transplantation (allo-HCT) play?

Prognostic scoring systems such as the International Prognostic Scoring System for Mastocytosis (IPSM), the Mayo Alliance Prognostic System (MAPS) and the Mutation-Adjusted Risk Score (MARS) can help address some of these questions by supporting risk stratification and informing treatment planning. Several such systems are available and, although there is currently no UK guideline specifying which to apply, they share common key risk factors (Table 1).[5,26,30]

	IPSM	MARS	MAPS
Age >60 years	✓	✓	✓
Low haemoglobin	≤11 g/dL	<10 g/dL	Below sex-adjusted normal
Low PLT	<100 × 10^9/L	<100 × 10^9/L	<150 × 10^9/L
Leucocytosis	>16 × 10^9/L		
Increased serum levels	Baseline serum tryptase		ALP
Mutational profile		Additional somatic mutations (*SRSF2, ASXL1, RUNX1*)	
Skin involvement	✓		

Table 1. Multiparameter prognostic scoring systems.[5,26,30]

ALP=alkaline phosphatase; IPSM=International Prognostic Scoring System for Mastocytosis; MAPS=Mayo Alliance Prognostic System; MARS=Mutation-Adjusted Risk Score; PLT=platelet.

Treatment options, including targeted therapies and conventional approaches, offer the potential to address some of these challenges and help individualise management strategies. The advent of tyrosine kinase inhibitors (TKIs) such as avapritinib and midostaurin has changed the treatment paradigm for Advanced SM in the UK over the last decade. Other treatment options include cytoreductive therapy, with allo-HCT offering a potentially curative option for selected high-risk cases.[20,31]

Current Advances in the Management of Advanced SM

In the UK, an individualised and multidisciplinary approach is recommended for the management of Advanced SM. Treatment options range from observation alone (supplemented by preventive measures to avoid known triggers of MC degranulation and the use of epinephrine to prevent anaphylaxis) to symptom-directed therapies, such as management of pruritus or diarrhoea, and cytoreductive therapy for MC debulking in refractory disease. Historically, cytoreductive agents including interferon-α2b, hydroxyurea and cladribine were employed in Advanced SM.[20,31,32]

Recent advances with potent TKIs have demonstrated marked improvements in MC burden, reversion of organ damage and potential for molecular remission of *KIT* D816V.[31] In the UK, NICE recommends avapritinib and midostaurin as treatment options for eligible adults with Advanced SM.[33,34] Avapritinib is the only targeted therapy specifically against *KIT* D816V and was approved

in the UK in 2024 for first-line treatment of adult patients with Advanced SM.[35] Interim results from the ongoing phase 2 PATHFINDER trial of avapritinib 200 mg daily showed an overall response rate (ORR) of 75% and a rate of complete response (CR) or CR with partial hematologic recovery (CRh) of 19% among 32 response-evaluable patients using the modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria. Reductions of ≥50% in bone marrow MC burden and elimination of bone marrow MC aggregates were observed in 88% and 60% of patients, respectively.[36] The latest three-year follow-up data also demonstrated high response rates across subtypes, irrespective of prior therapy, with an ORR and CR/CRh rate of 73% and 29%, respectively. The safety profile was favourable, with adverse events managed primarily through dose modifications.[37]

Midostaurin, a multikinase inhibitor targeting kinase-domain *KIT* mutants, was approved in the UK for adult patients with Advanced SM in 2021,[38] demonstrating overall response rates of 60% per modified Valent and Cheson criteria, and 28% per International Working Group (IWG) criteria.[39,40] (*Note:* mIWG-MRT-ECNM criteria are stricter than modified Valent/Cheson, requiring deeper, more durable responses across organ damage and blood counts.[41])

Beyond approved therapies, a number of investigational TKIs have also shown promising efficacy.[31,42]

Despite these advances, important challenges exist. Most TKI studies predominantly included patients with SM-AHN (~70%) and excluded those with significant AHN-driven disease.[36,39] Disease progression in Advanced SM is often driven by the AHN component;[37,43] for example, in PATHFINDER, 14% of patients progressed, primarily in the AHN component.[37] The role of KIT inhibitors within broader treatment strategies is not yet fully defined, and sequencing decisions are often influenced by safety considerations.[29]

Decisions regarding allo-HCT in transplant-eligible patients are guided by the European Society for Blood and Marrow Transplantation (EBMT) Practice Harmonisation and Guidelines framework, but several complexities remain. These include the rare and heterogeneous nature of Advanced SM, variable responses to TKI therapy, limited contemporary allo-HCT outcome data, and the need for expertise in managing MC mediator symptoms and risk of allergic phenomena. There is currently no consensus on how KIT-directed therapies fit into transplant algorithms.[44]

The current treatment pathway for Advanced SM in the UK, in line with the NICE guidance, is summarised in Figure 7.[20,31,32] While conventional treatment goals have focused on symptom improvement, reduction of MC burden and prolongation of progression-free and overall survival, these objectives are now evolving to encompass molecular remission, treatment-free remission, combination therapy for both KIT and AHN components, prevention of AHN progression and AML, and strategic use of KIT inhibitors in the peri-transplant setting in the TKI era.[45]

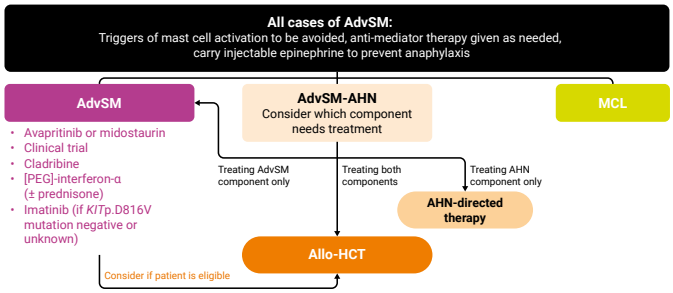


Figure 7. Treatment algorithm for Advanced SM.[31,32]

AdvSM=Advanced SM; AHN=associated haematological neoplasm; HCT=haematopoietic cell transplantation; MCL=mast cell leukaemia; PEG=pegylated; SM=systemic mastocytosis.

Future Outlook

Advanced SM research is increasingly focused on improving long-term outcomes and refining treatment goals. Real-world evidence will help confirm trial findings, while long-term durability remains important as up to 20% of patients progress, often in the AHN component.[31] Optimising KIT inhibitor use around transplantation, integrating molecular remission (e.g. *KIT* VAF) into treatment objectives, and harmonising response criteria across Valent, Cheson and mIWG-MRT-ECNM frameworks are key priorities.[29,31,45] In addition, molecular monitoring for patients with AHN may allow proactive management of disease progression and optimisation of therapy.[31]

Conclusion

The landscape of SM has evolved remarkably over the past decade. Advances in disease classification, prognostic stratification and routine molecular testing have enhanced our understanding and identification of both indolent and aggressive

disease subsets. In particular, for patients with Advanced SM, the introduction of targeted TKIs has been exciting.

Despite these advances, optimal management requires careful clinical judgement and a nuanced approach, particularly in patients with coexisting AHN. A multidisciplinary approach is essential to ensure accurate diagnosis, guide treatment prioritisation, and tailor therapy to both disease components.

By combining accurate diagnosis, individualised treatment plans and a multidisciplinary collaboration both within the general community and haematology, clinicians can meaningfully improve outcomes and continue to push the boundaries of what is possible for patients with this rare and heterogeneous disease.

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