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REVIEW

Advances in the Management of Mediator-Related Symptoms in Non-Advanced Systemic Mastocytosis

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Abstract: Systemic mastocytosis (SM) is a rarely occurring clonal mast-cell disorder defined by aberrant mast-cell accumulation and episodic or chronic mediator release, giving rise to a broad range of manifestations from pruritus and flushing to gastrointestinal symptoms and anaphylaxis. In non-advanced SM, mediator-related symptoms are the major source of morbidity and substantially impair quality of life. Traditional symptom-directed therapies—including antihistamines, leukotriene modifiers, and mast-cell stabilizers—remain the foundation of care, but a subset of patients experience persistent, refractory symptoms. Advances in mast-cell biology have expanded therapeutic options for these patients, including selective KIT inhibitors, mast-cell–modulating small molecules, inhibitory-receptor agonists, epithelial-derived cytokine blockade, and agents targeting IgE-dependent and IgE-independent activation pathways. Key gaps remain, including the absence of validated biomarkers that distinguish activation from mast-cell burden, limited long-term safety data, and uncertainty around optimal dosing strategies. This review summarizes current understanding of mediator-driven disease in non-advanced SM and highlights targeted, mechanism-based therapies for refractory symptoms.

Keywords: non-advanced systemic mastocytosis, mast cell activation, targeted therapy, tyrosine kinase inhibitors, Bruton tyrosine kinase inhibitors (BTKIs), siglecs

Introduction

Systemic mastocytosis (SM) is a rare clonal mast cell disorder most often associated with activating KIT mutations, notably the KIT D816V variant. Such mutations promote mast cell accumulation, survival, and altered functional behaviour across multiple organ systems, including bone marrow, skin, gastrointestinal tract, and lymph nodes.[1–4] SM comprises a spectrum spanning indolent to advanced subtypes, the latter characterized by organ damage. However, the majority of patients are diagnosed with non-advanced categories such as bone marrow mastocytosis (BMM), indolent systemic mastocytosis (ISM), and smoldering systemic mastocytosis (SSM), all of which are characterized by the absence of organ dysfunction. Across multiple cohorts, approximately 85–90% of patients with SM present with non-advanced disease, underscoring the predominance of these subtypes in clinical practice.[5,6]

Non-advanced SM is a chronic clonal mast cell disorder in which patients often experience clinically significant symptoms driven by mast-cell-derived mediators, including histamine, tryptase, prostaglandins, and leukotrienes—which produce a wide array of symptoms affecting multiple organ systems. Typical manifestations include cutaneous signs (flushing, pruritus), gastrointestinal symptoms, neurocognitive issues, musculoskeletal pain, and bone fragility leading to osteoporotic fractures, as well as episodes of severe or recurrent anaphylaxis.[1,7]

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Recent progress in understanding mast-cell biology and the mechanisms underlying mast-cell activation has prompted a reevaluation of therapeutic approaches. Traditional symptom directed therapies remain the cornerstone of care, but emerging targeted agents and biologics offer new opportunities for patients with refractory symptoms.[8–10]

In this article, we summarize current concepts in the biology and clinical expression of mediator-driven disease in non-advanced SM and outline recent therapeutic developments. By integrating mechanistic insights with practical therapeutic strategies, the goal is to support clinicians in optimizing care for this complex and often misunderstood condition.

Overview of Non-Advanced Systemic Mastocytosis

Classification and Disease Spectrum

The World Health Organization (WHO) classifies mastocytosis into cutaneous mastocytosis (CM), SM, and the rare entity mast cell sarcoma.[2,3] SM includes multiple subcategories, such as BMM, which is considered a non-advanced form featuring low mast-cell burden and bone-marrow involvement in the absence of cutaneous disease. Additional non-advanced variants include ISM and SSM.[2,3] Advanced forms comprise aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).[2,3] ISM represents the most frequently encountered subtype and is typically associated with preserved organ function without evidence of C-findings and favorable long-term survival.[2,6]

Diagnostic Criteria

SM is diagnosed (Table 1) by applying a combination of major and minor criteria, typically one major plus one minor, or alternatively three minor criteria when the major feature is absent.[1–3] The major diagnostic feature consists of multifocal clusters of MCs—defined as aggregates of at least 15 cells—in bone marrow or another extracutaneous site. Minor criteria include: (1) over 25% atypical or spindle-shaped mast cell morphology; (2) aberrant mast cell immunophenotype (CD30, CD25, and/or CD2 expression); (3) detection of a KIT activating mutation including D816V; (4) elevated basal serum tryptase (≥20 ng/mL).[2,3] Baseline serum tryptase is a useful but imperfect marker; elevations may also occur in hereditary alpha tryptasemia (HαT), which can confound diagnosis.[11] Updated criteria are summarized in Table 1.

Pathophysiology of Mediator Release

In non-advanced SM, clinical symptoms arise predominantly from mast cell activation and mediator release rather than tissue infiltration or organ damage.[12] Activating mutations—most commonly KIT D816V—drive constitutive signalling through the KIT receptor tyrosine kinase, promoting mast cell proliferation, survival, and accumulation in tissues. KIT D816V-mutated MCs display ligand independent KIT phosphorylation and enhanced downstream signalling, leading to increased proliferation and survival.[13] Patients with KIT D816V-positive clonal mast-cell disease have an increased risk of severe anaphylaxis with hymenoptera venom representing the most potent and well-defined trigger, although a substantial proportion of reactions occur without an identifiable stimulus.[14] Complementary in vivo provocation studies

Table 1 Diagnostic Criteria of SM According to WHO

Major Criterion	Multifocal dense infiltrates of mast cells (≥ 15 mast cells in aggregates) in sections of bone marrow and/or other extracutaneous organ(s)
Minor Criteria	1. > 25% of all MCs are atypical cells type I or type II on bone marrow smears or are spindle-shaped in mast cells infiltrates detected in sections of bone marrow or other extracutaneous organs
	2. KIT-activating point mutations at codon 816 or in other critical regions of KIT in bone marrow or other extracutaneous organs
	3. Expression of CD2 and/or CD25 and/or CD30 on mast cells in bone marrow, blood or another extracutaneous organs
	4. Baseline serum tryptase concentration ≥ 20 ng/mL; when HαT is also present, the tryptase level should be adjusted[11]

nevertheless show that mast-cell reactivity in SM is not uniformly heightened across different challenge modalities, supporting the view that KIT-driven abnormalities do not translate into a globally lowered activation threshold.[15] Although, it is reported that[16] KIT D816V-mutated mast cells exhibit intrinsic abnormalities—including altered granularity, size, and histamine content— these features do not necessarily translate into a globally lowered activation threshold.

Mast cell activation can occur through multiple pathways.[17] IgE-dependent activation via the high-affinity IgE receptor (FcεRI) remains a central mechanism, particularly in patients with concomitant atopy or venom allergy.[17,18] However, IgE-independent pathways are also important and include activation by complement components (C3a, C5a), stimulation of the MRGPRX2 receptor, and engagement by neuropeptides like substance P.[19] Additional triggers include cytokines, toll-like receptor ligands, physical stimuli (heat, cold, friction), as well as infections, alcohol, and emotional or physiological stress.

Upon activation, mast cells release a broad array of mediators that contribute to distinct symptom clusters. Preformed mediators, such as histamine, tryptase, chymase, and heparin, are stored in cytoplasmic granules and released immediately, producing acute symptoms including flushing, pruritus, hypotension, and anaphylaxis.[20] Lipid mediators, including prostaglandin D_2 (PGD_2) and leukotrienes (LTC_4, LTD_4, LTE_4), are synthesized de novo and contribute to prolonged vasodilation, bronchoconstriction, gastrointestinal hypermotility, and systemic symptoms such as fatigue.[20] Cytokines and chemokines (eg, TNF-α, IL-6) may drive chronic inflammation, bone remodelling abnormalities, and neurocognitive complaints.[20] Figure 1 illustrates a range of mediators and their potential influence on the development of different symptoms.

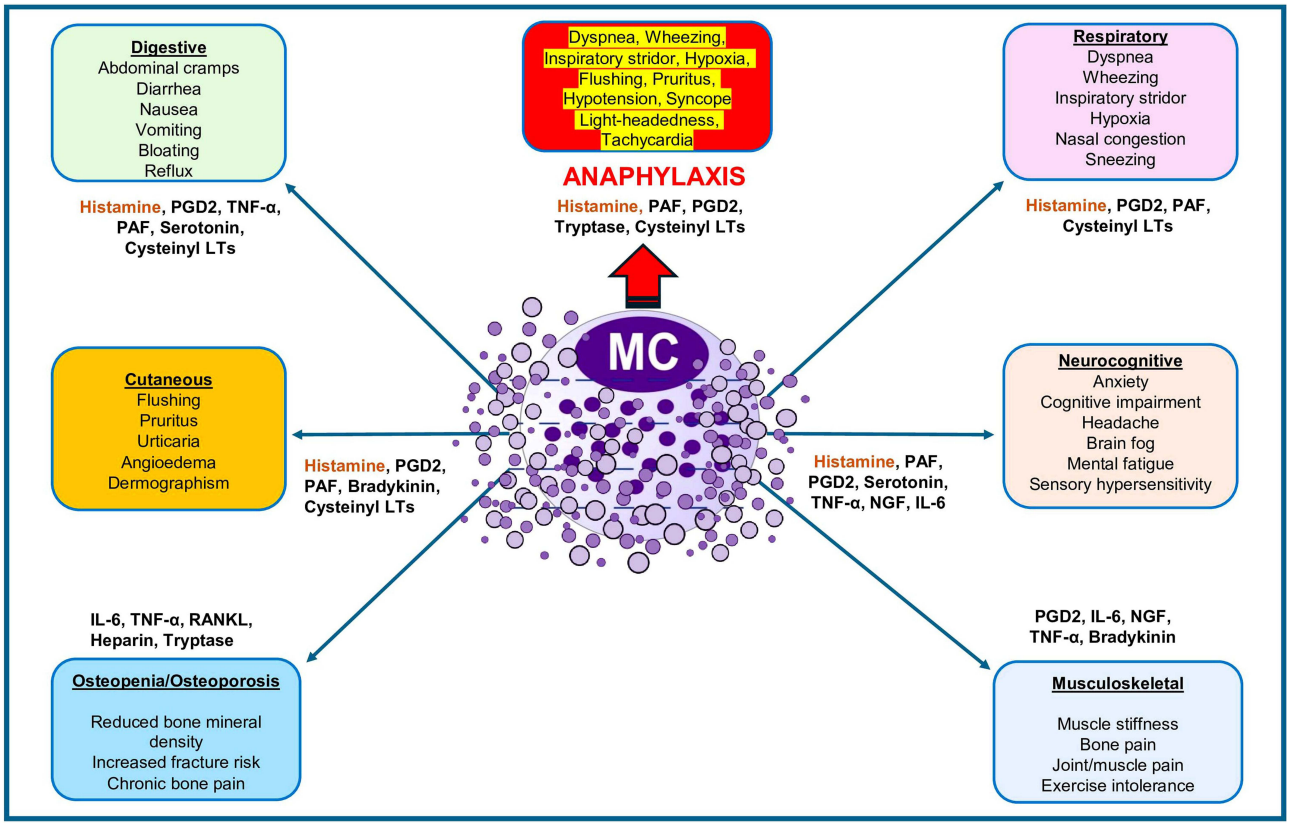

Figure 1 Mast-cell-derived mediators and their links to symptom domains and key comorbidities. The figure illustrates how major categories of mast-cell mediators—including preformed granule mediators, lipid mediators, cytokines, and additional bioactive factors—contribute to multisystem clinical effects. Arrows indicate conceptual relationships between mediator classes and five principal symptom domains (cutaneous, digestive, respiratory, neurocognitive, and musculoskeletal). The diagram also highlights two clinically relevant comorbidities associated with acute or chronic mast-cell activation: anaphylaxis and osteopenia/osteoporosis.
Abbreviations: PGD2, Prostaglandin D2; LT, Leukotriene; PAF, Platelet-Activating Factor; TNF-α, Tumor Necrosis Factor-alpha; NGF, Nerve Growth Factor; RANKL, Receptor Activator of Nuclear Factor-κB Ligand.

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The combined effect of these mediators results in the heterogeneous, multisystem symptom profile characteristic of non-advanced SM. Variability in mediator patterns, mast cell burden, genetic background (including atopy, hereditary alpha-tryptasemia), and individual trigger sensitivity contributes to the wide clinical spectrum observed among patients.

General Principles of Management

Although non-advanced SM, especially BMM and ISM, does not typically shorten survival, mediator-related symptoms can be debilitating. Effective management requires a comprehensive, individualized approach that requires a combination of trigger avoidance, patient education, and pharmacologic therapy.[8–10] Recent therapeutic advances—including biologics and targeted inhibitors—have expanded treatment options for patients with persistent or severe symptoms.

The management of mediator-related symptoms in mastocytosis is multifaceted and overall includes a stepwise approach.

Trigger Avoidance and Lifestyle Modifications

Symptom management in mastocytosis often begins with identifying and avoiding relevant triggers. However, patients vary widely in their sensitivity to specific stimuli, and general advice to avoid all theoretically reported mast-cell-activating factors are not helpful. A personalized, symptom-focused approach is therefore preferred.[8,9] Allergy assessment can help clarify individual provoking factors, including selected foods, medications, or environmental exposures that may elicit mast-cell activation. Routine exclusion of histamine-containing foods[21] or universal avoidance of medications such as NSAIDs is generally unwarranted.[22,23] When specific triggers are clearly established for an individual patient, the primary preventive strategy is strict avoidance of those agents or circumstances likely to precipitate symptoms.

Anti-Mediator Therapy

As no randomized studies have evaluated maintenance treatments in mastocytosis, therapy is generally introduced in a stepwise manner and tailored to the patient's predominant symptom profile[8,9] (Table 2). First-line management typically begins with H1-antihistamines.[8,9] Doses can be individualized and increased up to four times the standard recommendation, similar to chronic urticaria practice.[24] Non-sedating agents are preferred initially, although a sedating H1-antihistamine may be added when nocturnal symptoms such as pruritus predominate.[8,9] When gastrointestinal symptoms are prominent, H2-antihistamines can be introduced early, and proton-pump inhibitors may be added for additional symptom relief (Table 2).

For persistent gastrointestinal symptoms, cromolyn sodium, a mast-cell-stabilizing agent, may be introduced as a second-step option, even though its exact mechanism of action is not fully elucidated. Antileukotrienes can be used when cutaneous symptoms persist, and some patients report improvement in gastrointestinal or asthma-like symptoms as well, though responses vary. In selected patients who tolerate them, NSAIDs or aspirin may ameliorate flushing,[25] whereas individuals who do not tolerate these agents may experience paradoxical worsening of symptoms. The benefit of aspirin in refractory flushing is linked to its ability to suppress mast-cell-derived PGD_2,[25] analogous to its effect in preventing niacin-induced PGD_2-mediated flushing.[26] Ketotifen, which combines H1-receptor blockade with mast-cell-stabilizing activity, is another option for cutaneous symptoms[27] and may also help with neuropsychiatric or gastrointestinal features,[28] although its advantage over other antihistamines is uncertain.

For individuals whose symptoms do not improve with earlier measures, additional interventions may be considered. Systemic glucocorticoids can be used when symptoms clearly reflect mast-cell activation.[8,9] If benefit is observed, tapering should proceed slowly over months, and some patients may require low-dose maintenance. Nonetheless, long-term glucocorticoid therapy is limited by the risk of exacerbating osteoporosis, a recognized complication in SM. Bone involvement—including osteopenia, osteoporosis, compression fractures, and back pain—is considerably more common in ISM than in the general population.[29,30] As such, vitamin D and calcium supplementation and the use of bisphosphonates are recommended for SM patients with osteoporosis.[31] In refractory cases, treatment with a receptor activator of nuclear factor kappa B ligand (RANKL) inhibitor may help mitigate bone loss.[32,33] Additionally, because SM may be

Table 2 Traditional Symptom Focused Pharmacologic Management in Mastocytosis

Drug/Class	General Purpose	Symptom Domains Most Affected	Additional Notes
H1-antihistamines (non-sedating or sedating)	First-line anti-mediator therapy	Pruritus, flushing, urticaria, general mediator symptoms	Doses may be adjusted up to four-fold; sedating agents sometimes added for nocturnal symptoms.
H2-antihistamines	Adjunctive therapy	Gastrointestinal symptoms	Often combined with H1 blockers when GI symptoms dominate.
Proton-pump inhibitors	Acid suppression	Reflux, dyspepsia, upper GI discomfort	Used when H2 blockers alone are insufficient.
Cromolyn sodium	Mast-cell stabilizer	GI symptoms, systemic mediator symptoms	Mechanism and receptor target not fully defined; used when GI symptoms persist.
Leukotriene receptor antagonists (eg, montelukast)	Anti-leukotriene therapy	Flushing, pruritus, cutaneous symptoms; sometimes GI or asthma-like symptoms	Responses vary among individuals.
NSAIDs/Aspirin	Symptom reduction in selected cases	Flushing, prostaglandin-mediated symptoms	Aspirin may help refractory flushing by inhibiting PGD_2 pathways; used only when tolerated.
Ketotifen	H1-blockade + mast-cell stabilization	Cutaneous symptoms; may help neuropsychiatric or GI symptoms	Unclear whether superior to other antihistamines.
Systemic glucocorticoids	Third-line option for refractory symptoms	Severe mediator-related symptoms	Used when symptoms clearly reflect mast-cell activation; tapered gradually if effective.
Vitamin-D and calcium	Bone health support	Osteopenia/osteoporosis	Recommended due to increased bone involvement in ISM.
Bisphosphonates	Bone-density preservation	Osteoporosis, fracture risk	Used when bone involvement is significant.
RANKL inhibitors	Alternative bone-targeted therapy	Refractory osteoporosis	Considered when bisphosphonates are insufficient.
SSRIs	Management of neuropsychiatric manifestations	Anxiety, depression, cognitive complaints	Used when these symptoms impair quality of life.

associated with neuropsychiatric manifestations—such as anxiety, depression, or cognitive complaints— selective serotonin reuptake inhibitors (SSRIs) can be considered when these symptoms impair quality of life.[34]

Management of Anaphylaxis

Anaphylaxis is a significant potential complication in SM. Episodes may occur without an identifiable trigger and are often more severe than in the general population.[35] Epinephrine remains the cornerstone of acute management.[36] Its distinct efficacy has been demonstrated in reports describing patients with SM who failed to respond to conventional vasopressor therapy such as dopamine but improved rapidly following epinephrine administration.[37] These observations underscore the unique pathophysiology of mast cell-driven anaphylaxis in SM, in which massive mediator release can lead to profound hypotension and rapid clinical deterioration.

For these reasons, intramuscular epinephrine remains the treatment of choice. Early intramuscular administration is essential, as timely treatment has been shown to prevent progression to more severe manifestations.[38] All mastocytosis patients with a history of anaphylaxis or MCAS should carry multiple epinephrine auto injectors.[12,14] Additionally, an effective plan for managing anaphylaxis extends beyond acute treatment and relies heavily on preparation and patient education. Individuals at risk should be confident in using an epinephrine auto injector, with regular training to ensure they can recognize symptoms quickly and administer the medication without hesitation.

Preventive strategies are also important for patients with recurrent episodes. A particularly relevant context is hymenoptera venom allergy, which represents one of the most frequent and severe triggers of anaphylaxis in SM. In patients with confirmed venom allergy, life-long venom immunotherapy (VIT) is recommended.[39] Another concern is recurrent, unexplained anaphylactic episodes. Omalizumab, a humanized anti-IgE monoclonal antibody, has been

reported to reduce recurrent anaphylactic symptoms in individuals who do not respond adequately to conventional anti mediator therapies.[40–43] Additionally, because adverse reactions during VIT dose escalation are more common in this population, omalizumab has been successfully used as a co-treatment specifically during the up-dosing phase to facilitate VIT, thereby improving its safety and tolerability in this high-risk group.[39,44]

Management in Special Conditions

Certain clinical situations in SM require additional therapeutic considerations beyond standard anti-mediator therapy. These scenarios may involve comorbid conditions, specific risk factors, or circumstances in which mast-cell activation risk is increased.

Perioperative Management

Perioperative management in mastocytosis requires individualized planning because surgical procedures, anesthesia, and perioperative stress can provoke mast cell activation. A coordinated discussion among the patient, allergist, anesthesiologist, and surgeon helps review personal risk factors and anticipate potential triggers.[9] Decisions regarding premedication and other preventive strategies are made strictly on a case-by-case basis. Whenever feasible, procedures should be performed in a hospital with access to emergency and intensive care resources to ensure optimal safety. Radiocontrast studies warrant the same individualized assessment to reduce the likelihood of mediator-related reactions.

Pregnancy

Most patients with non-advanced SM complete pregnancy without major complications, although mediator-related symptoms may fluctuate during gestation due to hormonal and immune changes.[45] Flushing, pruritus, and gastrointestinal discomfort can occur, but severe reactions remain uncommon. Delivery planning should anticipate potential mast-cell activation triggers and ensure immediate access to emergency medications, ideally within a coordinated team that includes obstetricians, anesthesiologists, and allergists.[45] Antihistamines with established safety profiles can generally be continued, while other treatments require individualized assessment. The guiding principle in managing pregnancy in mastocytosis is to maintain symptom control with the lowest effective medication dose, as uncontrolled mast-cell mediator release poses greater potential risk to the fetus than most standard therapies.[45]

Vaccinations

Vaccinations are generally safe in SM, although local or systemic reactions may be more frequent. Premedication with antihistamines may be considered in patients with a history of vaccine-related reactions.[46,47] Standard vaccination schedules should be maintained unless contraindications exist.[46]

Novel Approaches to Mediator-Directed Therapy in Non-Advanced Systemic Mastocytosis

Although traditional anti-mediator therapies remain the backbone of symptom management in non-advanced SM, there are still some refractory cases. Recent advances in mast cell biology have expanded the therapeutic landscape (Figure 2). These newer strategies aim not only to block downstream mediators but also to modulate mast cell activation thresholds, stabilize MCs, or interrupt upstream signalling pathways (Table 3). As understanding of KIT driven signalling and mast cell-immune interactions has deepened, several promising therapeutic classes have emerged.[48,49]

Biologic Therapies Targeting Mast-Cell Activation Pathways

Omalizumab

Omalizumab, a monoclonal antibody targeting free IgE, lowers circulating IgE levels and thereby reduces engagement of FcεRI on MCs and basophils. In SM, its use has been associated with fewer anaphylactic episodes and improvement in mediator-related symptoms such as flushing, pruritus, and gastrointestinal complaints, particularly in patients who also exhibit atopic features.[43] Observational data and case series further describe reduced symptom burden and decreased need for emergency interventions, with benefits most apparent in individuals with elevated IgE or MCAS-like presentations.[50,51]

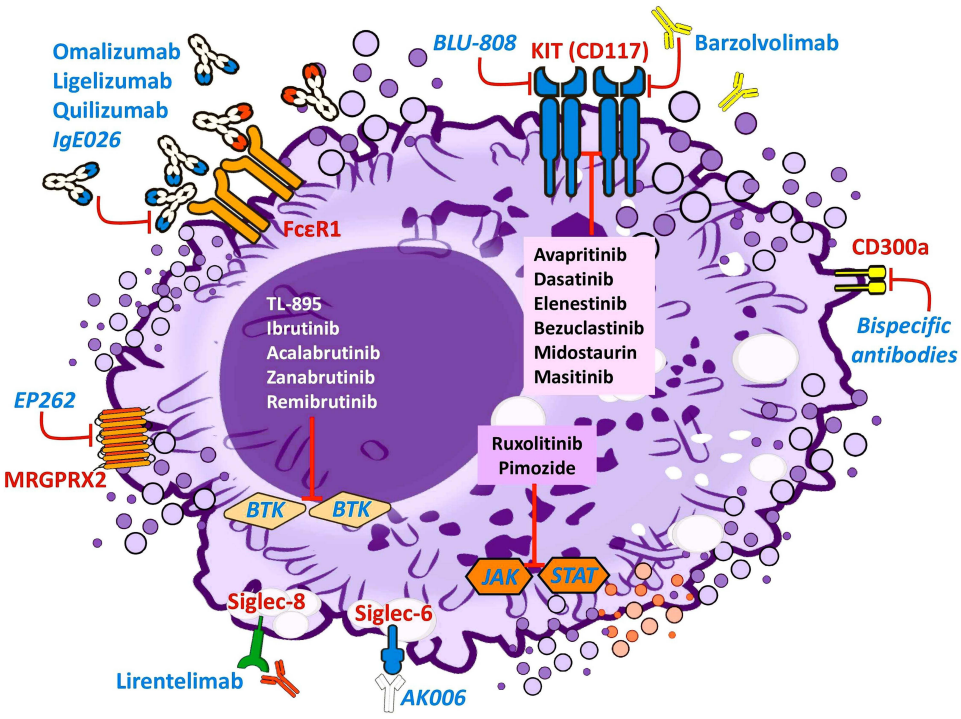

Figure 2 Therapeutic landscape of mechanism-based treatments for non-advanced systemic mastocytosis. This figure illustrates key mechanistic pathways targeted by selected approved, investigational, and conceptual agents relevant to mast-cell activation and survival in non-advanced SM. Shown are representative molecules acting on the IgE-FcεRI axis (omalizumab, ligelizumab, quilizumab, IgE-026), KIT/CD117 signalling (avapritinib, bezuclastinib, elenestinib, midostaurin, dasatinib, masitinib, BLU-808, barzolvolimab), BTK-dependent pathways (ibrutinib, acalabrutinib, zanubrutinib, remibrutinib, TL-895), inhibitory receptor-directed agents including Siglec-8, Siglec-6, and CD300a-directed monospecific and bispecific antibodies, MRGPRX2-mediated activation (EP262), and JAK/STAT signalling (ruxolitinib, pimozide). The agents depicted represent a subset of those discussed in the manuscript and are intended to complement Table 3 by providing a visual overview of mechanistic classes rather than a comprehensive list of all therapies.

Abbreviations: BTK, Bruton tyrosine kinase; FcεRI, high-affinity receptor for IgE; JAK/STAT, Janus kinase/signal transducers, and activators of transcription; MC, mast cell; MRGPRX2, Mas-related G-protein-coupled receptor member X2; NSAIDs, non-steroidal anti-inflammatory drugs; Siglec, sialic-acid-binding immunoglobulin-like lectins.

Clinical experience also includes reports of improvement in both cutaneous and systemic manifestations in children with diffuse CM and in adults with maculopapular CM.[40] In ISM, approximately 40% of patients in one series achieved complete control of mediator-related symptoms—cutaneous, gastrointestinal, or anaphylactic episodes—although two small placebo-controlled trials did not confirm statistically significant efficacy.[41,52] Partial benefit has also been described for neuropsychiatric symptoms—including anxiety, mood disturbances, sleep issues, fatigue, and cognitive complaints—

Table 3 Mechanisms of Action Across Approved, Investigational, and Conceptual Agents in Non-Advanced Systemic Mastocytosis

Therapeutic Class	Agent	Type	Primary Mechanism	Approval/Evidence Status	Role in Non-Adv SM
Biologic therapies targeting mast-cell activation pathways	Omalizumab	Monoclonal antibody	Binds free IgE → down-regulates FcεRI	Approved (allergy); off-label in SM	Reduces mediator symptoms; anaphylaxis prevention
	Dupilumab	Monoclonal antibody	IL-4Rα blockade → inhibits IL-4/IL-13 signaling	Approved (atopic disease, asthma); off-label in SM	Helpful in SM with atopic overlap
KIT-targeting mast-cell-depleting biologics	Barzolvolimab (CDX-0159)	Monoclonal antibody	Extracellular KIT blockade → mast-cell depletion	Investigational (clinical trials)	Emerging biologic; upstream mast-cell suppression

(*Continued*)

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Table 3 (Continued).

Therapeutic Class	Agent	Type	Primary Mechanism	Approval/Evidence Status	Role in Non-Adv SM
Cytoreductive therapies	Interferon-α	Immuno-modulator	Reduces mast-cell burden	Historical use; refractory-only	Refractory cases; tolerability limits
	Cladribine (2-CdA)	Purine analog	Mast-cell apoptosis	Approved for AdvSM; refractory-only in Non-AdvSM	Rapid cytoreduction; immuno-suppressive
Selective KIT D816V inhibitors	Avapritinib	Small- molecule TKI	Selective KIT D816V inhibition, also WT and other mutant forms	Approved for ISM	Approved therapy
	Bezuclastinib	Small- molecule TKI	Selective KIT D816V inhibition	Investigational (clinical trials)	Early-phase biomarker reductions
	Elenestinib	Small- molecule TKI	Selective KIT D816V inhibition	Investigational (clinical trials)	Emerging; strong biomarker reductions
Multikinase TKIs	Midostaurin	Multikinase TKI	KIT/SRC inhibition	Approved for AdvSM	Symptom improvement
	Dasatinib	Multikinase TKI	SRC-family + KIT inhibition	Not recommended (historical investigational use)	Investigational only
Mast-cell-modulating small molecules	Masitinib	Multikinase TKI	KIT-WT/LYN/BTK inhibition	Approved in some regions (non-SM indications)	Improves mediator symptoms
	BLU-808	Selective small-molecule TKI	Selective KIT-WT inhibition	Investigational (preclinical/ early clinical)	Emerging WT-KIT modulator
	BTK inhibitors	Small- molecule inhibitors	IgE-mediated activation blockade	Investigational (minimal SM data)	Minimal SM data
	SYK inhibitors	Small- molecule inhibitors	FcεRI-proximal signaling inhibition	Investigational (no SM trials)	No SM trials
	PI3K inhibitors	Small- molecule inhibitors	Degranulation/cytokine reduction	Investigational (no SM trials)	No SM trials
	LYN-pathway modulators	Small- molecule inhibitors	Dual-role LYN signaling modulation	Preclinical	Preclinical only
JAK/STAT inhibitors	Ruxolitinib	JAK1/2 inhibitor	Cytokine- driven activation reduction	Approved (other diseases); no SM trials	No SM trials
Inhibitory receptor agonists (Siglecs)	Lirentelimab (Siglec-8 mAb)	Monoclonal antibody	Inhibits MC activation; eosinophil apoptosis	Investigational (positive EoGID trials)	Positive EoGID trials
	Siglec-6 agonists	Monoclonal antibodies	Potent mast-cell inhibition	Preclinical / early development	Early development
CD300a- targeting antibodies	Monoclonal / bispecific antibodies	Antibodies linking KIT/IgE to CD300a	ITIM- mediated mast-cell inhibition; bispecific KIT/IgE suppression	Preclinical; conceptual KIT-independent inhibitory strategy	Preclinical only
MRGPRX2 antagonists	Small-molecule antagonists	GPCR inhibitors	Blocks non-IgE MC activation	Preclinical	Preclinical efficacy
Epithelial- derived cytokine blockade	TSLP inhibitors (eg, tezepelumab)	Monoclonal antibody	Epithelial immune-modulation affecting MC pathways	Approved (asthma); no SM trials	No SM trials

in a substantial proportion of the 29 ISM patients within a cohort of 55 individuals with mast-cell disorders.[53] Omalizumab has further been used to support VIT by decreasing acute reactions during dose escalation and enabling successful continuation of treatment.[44,54]

Beyond omalizumab, several next-generation anti-IgE biologics—including ligelizumab, quilizumab, and IgE-026—have been developed to enhance IgE pathway suppression. However, these agents remain investigational, have no clinical data in SM, and their relevance is currently mechanistic rather than therapeutic.

Dupilumab

Dupilumab binds to the IL-4 receptor-α chain, thereby blocking activation of IL-4 and IL-13 signaling pathways that drive type 2 inflammation. Although not approved specifically for mastocytosis, it is being explored for its potential to modulate mast cell-associated symptoms in patients with prominent atopic or eosinophilic comorbidities. Dupilumab is currently being investigated as a symptom-directed therapy in non-advanced SM. An ongoing European trial (EudraCT 2023-509,111-89-00) is evaluating dupilumab in combination with fexofenadine in indolent SM with cutaneous involvement, focusing on reductions in pruritus and other mediator-related symptoms. A separate Phase III study is also underway in patients with indolent SM and skin involvement, although no public registry number is yet available. Together, these studies aim to clarify whether IL-4/IL-13 blockade can provide clinically meaningful symptom relief in non-advanced SM.

Cytoreductive Therapies: Interferon-Alpha and Cladribine

Although cytoreductive agents are primarily used in advanced SM, they may be considered in highly refractory cases of non-advanced SM with severe, debilitating symptoms despite maximal mediator directed therapy. Interferon-alpha (IFN-α) 2b and cladribine were the most used MC cytoreductive agents and generally provided temporary and incomplete MC reduction.

Interferon-Alpha

Interferon-α has both immunomodulatory and antiproliferative properties and was one of the earliest cytoreductive agents used in SM, preceding the availability of modern TKIs. Although its use has diminished with the introduction of more targeted therapies, it remains an option for patients who cannot receive cladribine or selective TKIs, or for situations in which a slower, stepwise reduction of mast-cell burden is preferred. IFN-α can alleviate mediator-related symptoms and is considered relatively safe in pregnancy; however, its therapeutic effect develops gradually, and treatment is often limited by adverse effects such as flu-like symptoms.[55,56] Pegylated formulations may be somewhat better tolerated, yet fatigue, mood changes, and cytopenias continue to restrict long-term use.

Cladribine (2-CdA)

Cladribine is a purine-analog cytoreductive agent capable of inducing apoptosis in both dividing and resting MCs. It has long served as an established treatment in advanced SM—particularly in ASM and SM-AHN—where it can produce meaningful reductions in mast-cell burden.[57,58] In non-advanced SM, cladribine should be reserved for the most refractory cases only, given its toxicity profile and the availability of safer mediator-directed therapies. In selected patients with non-advanced SM who experience severe mediator-related symptoms, high mast-cell load, or cytopenias unresponsive to standard therapy, cladribine may also be considered. Reports have described resolution of recurrent anaphylaxis during treatment.[59] Compared with interferon-α, cladribine generally induces cytoreduction more rapidly, but its use is limited by myelosuppressive and immunosuppressive effects, necessitating antibiotic prophylaxis in many patients.[57,60]

Targeted KIT Inhibition in Non-Advanced SM

Although not yet standard for all non-advanced SM patients, this approach is increasingly considered for non-advanced SM patients whose symptoms remain burdensome despite conventional therapy.

KIT-Blocking Monoclonal Antibody (Mast-Cell-Depleting Therapy)

Barzolvolimab

Barzolvolimab (CDX 0159) is a humanized monoclonal antibody directed against the extracellular domain of KIT, effectively blocking stem cell factor-mediated signalling and inducing profound depletion of tissue MCs.[61] Early clinical

studies in mast cell-driven disorders such as chronic spontaneous urticaria and chronic inducible urticarias have demonstrated rapid and sustained suppression of mast cell activity, accompanied by marked improvements in symptom burden (NCT05368285; NCT05405660). Although formal trials in SM are still lacking, the mechanism of action is directly relevant to mast cell survival and activation, and the degree of mast cell depletion observed in human tissue suggests potential applicability to SM and related mast cell activation disorders.

Early studies have identified several mechanism-related adverse events, including transient neutropenia, hair and skin depigmentation due to KIT inhibition in melanocytes, and potential effects on fertility and spermatogenesis. These reflect the broader consequences of targeting wild-type KIT in non-mast-cell tissues and will require careful evaluation as Barzolvolimab advances into later-phase trials.

Selective KIT D816V Inhibitors

Selective KIT D816V inhibitors represent a central therapeutic option in this setting, offering targeted suppression of the mutant mast-cell clone for patients with debilitating symptoms refractory to conventional anti-mediator therapy.

Avapritinib

Avapritinib is a highly selective inhibitor targeting KIT D816V and has become a central therapeutic option for symptomatic indolent SM. Early clinical experience suggested that even low doses might alleviate severe mediator-related manifestations, including recurrent anaphylaxis in SM-AHN.[62] The pivotal randomized PIONEER trial (NCT03731260) later demonstrated clear efficacy in a larger ISM population: at week 24, avapritinib produced a greater reduction in Total Symptom Score (mean change −15.6 vs. −9.2 with placebo), along with pronounced improvements in key laboratory and bone-marrow measures.[63] In line with these biological effects, more than half of treated patients achieved ≥50% reductions in baseline serum tryptase, and substantial decreases were observed in KIT D816V allele burden and bone-marrow mast-cell infiltration.[63] These clinical and laboratory responses translated into better quality-of-life measures, and nearly one-quarter of patients were able to decrease their need for best supportive care therapies.[63] Separate analyses focusing on cutaneous involvement also showed improvements in clinician-rated skin lesions and patient-reported skin symptoms.[64] In non-advanced SM, avapritinib is generally well tolerated, with side effects such as periorbital and peripheral edema, dizziness, fatigue, headache, nausea, or diarrhea, and flushing; cognitive symptoms can occur but are typically low-grade, and clinically significant thrombocytopenia—common in advanced SM—is exceptionally rare in patients with ISM.[63]

Emerging Selective KIT Inhibitors

Two next-generation KIT D816V-selective agents have shown promising early results:

Bezuclastinib evaluated in the SUMMIT trial, has shown promising activity, including reductions in bone marrow mast cell infiltration, normalization of serum tryptase (<20 ng/mL), and substantial decreases in KIT D816V allele burden (≥50%), alongside improvements in symptom scores and quality of life (49% vs 21% placebo).[65]

Elenestinib is another selective KIT D816V inhibitor that has shown promising activity in indolent SM. In the Phase 2/3 HARBOR study, elenestinib produced dose-dependent improvements in symptom burden alongside substantial reductions in mast-cell parameters, including a −57.9% decrease in bone-marrow mast-cell burden, a −68.4% reduction in baseline serum tryptase, and a −77% median decline in KIT D816V variant allele fraction at the 100 mg dose level.[66] The treatment was generally well tolerated, with no serious adverse events attributed to therapy, supporting its potential role as a selective and effective option for patients with symptomatic ISM.[66]

Compared with avapritinib, elenestinib exhibits a more restricted kinase-inhibition profile with minimal off-target activity and lower predicted CNS penetration, features that may account for its favorable tolerability in early studies. This enhanced selectivity distinguishes elenestinib within the class of KIT D816V inhibitors and supports its potential as an alternative option for patients who require mutation-selective therapy but may be sensitive to the broader kinase effects associated with first-generation agents.

Broader KIT-Targeting Multikinase TKIs

Midostaurin

Midostaurin is an oral multikinase inhibitor with activity against KIT D816V and several other kinases. Its broader kinase profile contributes to more off-target effects and gastrointestinal toxicity.[67,68] In advanced SM, midostaurin improves mediator-related symptoms and quality of life.[68,69] Although it is not approved for non-advanced SM, several small prospective and retrospective studies have evaluated its use in ISM. These studies report reductions in mediator-related symptoms, decreases in baseline serum tryptase, and improvements in disease-specific quality of life at doses ranging from 50 to 200 mg daily.[70,71] However, gastrointestinal adverse effects frequently require dose reductions or discontinuation, limiting its utility in routine management of non-advanced SM.[70,71]

Dasatinib

Dasatinib is a multikinase inhibitor with activity against several targets, including wild-type and mutant KIT isoforms such as KIT D816V.[72,73] Although not approved for SM, it has been explored in both indolent and advanced disease. Small case series and phase 2 experiences have reported symptomatic improvement in selected patients—including reductions in rash, diarrhea, or bone pain—but data remain limited and heterogeneous, and no large, controlled studies have been completed in this population.[73,74] Given the limited efficacy observed and lack of robust data, dasatinib is not pursued further in SM and should be regarded as a historical, non-routine option rather than an active therapeutic candidate.

Mast-Cell-Modulating Small-Molecule Kinase Inhibitors

These agents are small-molecule kinase inhibitors that modulate mast-cell activation rather than deplete KIT D816V-mutated clones, positioning them as adjunctive therapies for refractory mediator-driven symptoms. They act through inhibition of wild-type KIT or other proximal signalling kinases, and their clinical benefit is reflected in improvements in mediator-related manifestations rather than in changes to clonal mast-cell burden.

Mast-Cell-Modulating TKIs with Wild Type KIT Activity (Non-D816V Selective)

Masitinib

Masitinib is an oral multikinase TKI targeting KIT (predominantly wild-type), LYN, and BTK, thereby leading to attenuation of mast-cell activation. Its activity against KIT D816V is limited relative to selective KIT D816V inhibitors.[75] Clinical studies have demonstrated improvements in mediator-related symptoms in non-advanced SM, including a randomized placebo-controlled Phase 3 trial in severely symptomatic ISM/SSM.[76] Masitinib is already used in some regions for severe symptomatic disease (NCT00814073; NCT04333108). It can be considered in severely symptomatic, refractory non-advanced SM after optimized anti-mediator therapy—and pragmatically after biologics (eg, omalizumab) and before or after KIT-directed therapy depending on patient phenotype and access.

It should also be noted that, although previously evaluated in a phase 3 trial, masitinib is not part of ongoing SM-specific drug-development programs, but it remains available in some regions for symptomatic treatment of severely affected patients.

BLU 808

BLU-808 is a next-generation, highly selective small-molecule inhibitor of wild-type KIT designed to suppress mast-cell activation in disorders where SCF-dependent KIT WT signaling drives mast-cell survival and mediator release. Unlike D816V-selective TKIs, BLU-808 does not target the mutant KIT receptor and therefore functions as a mast-cell activation modulator rather than a cytoreductive agent. Preclinical data demonstrate potent inhibition of KIT WT phosphorylation and downstream degranulation pathways, positioning BLU-808 mechanistically alongside masitinib within the class of WT KIT-active TKIs.[77] Although clinical studies in SM have not yet been conducted, its pharmacologic profile suggests potential relevance for mast-cell activation disorders characterized by intact KIT signaling and possibly for patients with WT-KIT disease rather than those harboring KIT D816V. Clinical evaluation is ongoing (NCT06931405).

Non-KIT TKIs That Inhibit MC-Activation Signalling

Bruton Tyrosine Kinase (BTK) Inhibitors

Bruton tyrosine kinase (BTK) is a key mediator of FcεRI-dependent mast-cell and basophil activation, and short-term BTK inhibition can markedly suppress IgE-driven reactivity. In a humanized mouse model, two oral doses of acalabrutinib completely prevented moderate IgE-mediated anaphylaxis.[78] Early human studies in food allergy similarly show that transient BTK blockade can blunt reactivity during controlled challenges.[79–81]

A Phase 2 trial of the oral BTK inhibitor TL-895 in indolent SM is ongoing (NCT04655118), although no results have yet been reported. Clinical data for other BTK inhibitors in SM remain very limited. A phase 2 single-arm study of ibrutinib in advanced SM (NCT02415608) was terminated early due to slow enrollment (≈4 participants), preventing meaningful assessment of efficacy. Thus, ibrutinib, acalabrutinib, and zanubrutinib should not be considered therapeutic options in SM and their relevance is mechanistic rather than clinical.[82,83]

Next-generation, highly selective BTK inhibitors—remibrutinib and fenebrutinib—demonstrate potent, rapid, and reversible suppression of IgE-mediated mast-cell activation in trials for chronic spontaneous urticaria, allergic asthma, and food allergy.[84,85] However, no published studies or case reports exist in SM, and these agents likewise have no therapeutic role in SM at present.

In rare, highly selected cases where compassionate-use BTK inhibition is considered for refractory mediator-driven episodes (eg, recurrent anaphylaxis) in non-advanced SM, clinicians may draw on allergy-trial experience and use short, pulsed courses within a structured protocol. Such use is exceptional, and potential benefits must be weighed against known BTK-inhibitor risks—bleeding, atrial fibrillation, infections—and current guidance continues to prioritize established SM therapies.[82,83]

Other Small Molecule Mast Cell Signalling Inhibitors

Beyond BTK, several other proximal signalling nodes—including SYK, PI3K, and LYN—are being explored for their ability to modulate mast cell activation, although clinical translation in SM remains limited. These kinases regulate early events in FcεRI- and GPCR-driven degranulation and the generation of lipid and cytokine mediators in human mast cells.[86,87] Proof of mechanism for SYK and PI3K inhibition is well established in ex vivo human mast cell systems and in early clinical studies across allergic diseases.

SYK Inhibitors

SYK is a proximal kinase immediately downstream of FcεRI and is essential for early mast cell activation.[86,87] Although SYK inhibition has been explored extensively in hematologic diseases—most notably with fostamatinib[88]—clinical data in SM are lacking, and no trials in non-advanced SM have demonstrated symptom benefit.

PI3K Inhibitors

PI3K-δ/γ signalling contributes to mast-cell degranulation and cytokine production.[89] In a randomized, crossover Phase 1 study[90] in allergic rhinitis, the PI3K-δ inhibitor idelalisib improved symptom scores and reduced basophil activation during controlled allergen-chamber exposure—supporting its anti-allergic potential—but SM-specific trials are absent.

LYN Pathway Targeting

LYN kinase plays a dual role in FcεRI signalling, initiating activation while also providing negative feedback.[91] Preclinical studies of LYN-modulating agents such as KIRA6 demonstrate suppression of mast-cell-dependent allergic responses.[92] However, no translational work in SM exists, and the bidirectional biology of LYN complicates therapeutic targeting, limiting current clinical relevance.

Emerging Non-KIT Targeted Immunomodulatory Therapies

Beyond kinase inhibition, several emerging strategies target immune regulatory pathways or inhibitory receptors to attenuate mast cell activation and the broader inflammatory milieu. These approaches—including JAK/STAT blockade,

engagement of inhibitory Siglecs (Siglec 8/6), antagonism of the non-IgE GPCR MRGPRX2, and modulation of the epithelial alarmin axis (TSLP, IL 33, IL 25)—are mechanistically distinct from KIT directed agents and small-molecule TKIs. They are best considered non-KIT immunomodulators with growing translational support in mast cell-driven disease biology, particularly from early studies in allergic inflammation, anaphylaxis models, and mast cell activation disorders.[93]

JAK/STAT Pathway Inhibition

Janus kinase–STAT signaling integrates cytokine cues such as IL-3, IL-5, and GM-CSF, which potentiate mast-cell and basophil activation through STAT5 and related downstream nodes. In vitro and ex vivo studies demonstrate that the JAK1/2 inhibitor ruxolitinib suppresses IgE- and IL-3-driven mediator release from human basophils and inhibits degranulation and cytokine production from human MCs, reducing histamine, leukotrienes, and pro-inflammatory cytokines.[94,95] These findings support a class-level immunomodulatory effect on mast-cell activation, although disease--specific trials in non-advanced SM are lacking. A single published case report also described symptomatic improvement and enhanced quality of life in a patient with aggressive SM treated with ruxolitinib, suggesting potential adjunctive benefit in selected individuals.[96] However, disease-specific trials in non-advanced SM remain absent.

Experimental STAT5-targeting compounds (eg, pimozide) have shown suppression of mast-cell activation in pre-clinical systems, but their pharmacologic liabilities and lack of clinical development limit their relevance to mechanistic insight rather than therapeutic application.

From a clinical-practice standpoint, any off-label exploration of JAK inhibitors must balance potential symptom control against known risks—including cytopenias, infections, and taper-related considerations derived from hematologic indications—underscoring their adjunctive rather than disease-modifying role in SM at present.[97]

Siglec 8/6 Pathway Targeting

Stimulation of Siglec receptors results in downregulation of mast-cell activation, with potential effects on the surrounding inflammatory environment.[98] Despite this strong mechanistic rationale, no clinical trials in systemic mastocytosis have been completed, and their role in SM remains investigational pending disease-specific evaluation.

Siglec-8 functions as an inhibitory surface receptor and is expressed with high selectivity on human mast cells and eosinophils. Ligation induces apoptosis in eosinophils and inhibits mast-cell activation through suppression of FcεRI- and GPCR-mediated degranulation, without depleting mast cells themselves.[99,100] A humanized anti-Siglec-8 monoclonal antibody, lirentelimab (AK002), has demonstrated clinical proof-of-concept in eosinophilic gastritis and duodenitis: in a randomized, placebo-controlled phase 2 trial, lirentelimab reduced tissue eosinophils and mast cells and improved gastrointestinal symptoms, supporting the translational relevance of Siglec-8 engagement in mast-cell/eosinophil-driven disease.[101] An open-label Phase I study in indolent SM has explored feasibility and symptomatic impact in refractory patients, although results remain preliminary and non-comparative.[102] These findings position Siglec-8 targeting as a checkpoint-like immunomodulatory strategy rather than a clonally cytoreductive approach. However, the first-generation anti-Siglec-8 antibody lirentelimab (AK002) failed to meet primary endpoints in two Phase 3 trials in eosinophilic gastrointestinal diseases, leading to discontinuation of its development program in this form. These outcomes highlight uncertainties regarding the translational potential of Siglec-8 targeting and underscore the need for further refinement of this pathway, including next-generation agents such as AK006.

Siglec-6, another mast-cell-selective inhibitory receptor, is emerging as a therapeutic target with overlapping yet distinct signaling interactions compared with Siglec-8. Agonistic anti-Siglec-6 antibodies suppress mast-cell activation and, with chronic dosing in preclinical systems, can reduce mast-cell numbers; in vivo, single-dose administration prevented anaphylaxis in humanized mouse models.[103] Proteomic and functional analyses indicate that Siglec-6 organizes large inhibitory complexes linking to FcεRI, KIT, IL-33, and IL-4 receptor pathways, suggesting the potential to dampen both IgE-dependent and non-IgE triggers.[104,105] Additional work has characterized Siglec-6 expression and regulation on human mast cells and basophils, further supporting its relevance as a therapeutic target.[106] Although still preclinical, these data justify clinical exploration of Siglec-6 agonists and engineered formats (eg, bispecifics antibody–

drug conjugates) as non-KIT immunomodulators for mast-cell-driven disease, including SM phenotypes dominated by activation symptoms.

Collectively, Siglec-8 (and more speculatively Siglec-6) represents a mechanistically distinct, non-KIT immunomodulatory axis with growing support from allergic and eosinophil/mast-cell-associated disease biology. Beyond early exploratory work, no controlled or disease-focused clinical studies have evaluated Siglec-directed therapies in SM.

CD300a-targeting Strategies

CD300a is an inhibitory immunoreceptor expressed on human mast cells, basophils, eosinophils, and myeloid cells. Through its ITIM motifs, CD300a recruits SHP-1/2 phosphatases upon engagement with phosphatidylserine, leading to suppression of FcεRI-mediated activation and attenuation of downstream mediator release.[107] Antibody-mediated CD300a engagement can inhibit IgE-dependent mast-cell activation and abrogate allergic responses in vivo.[108] A bispecific antibody linking KIT to CD300a has further demonstrated suppression of both normal and malignant KIT signaling, highlighting the potential relevance of CD300a engagement in mast-cell neoplasms.[109] Although no CD300a-directed therapies have entered clinical testing, these preclinical findings position CD300a as a conceptually attractive, KIT-independent inhibitory pathway. To date, no studies have evaluated CD300a targeting in SM, and its therapeutic potential remains exploratory.

MRGPRX2 Pathway Antagonists

MRGPRX2 is a non-IgE G-protein-coupled receptor expressed on human skin MCs that mediates rapid, non-IgE-dependent degranulation in response to multiple drugs, neuropeptides, and cationic secretagogues.[110] In certain contexts, MRGPRX2 activation can act additively with FcεRI signaling, amplifying mast-cell reactivity.[111] Recent translational programs have identified potent, selective, orally bioavailable MRGPRX2 antagonists capable of inhibiting substance-P-induced degranulation in freshly isolated human skin mast cells, blocking histamine release in ex vivo human skin, and suppressing vascular permeability and scratching responses in human MRGPRX2 knock-in models.[112,113]

Complementary work has demonstrated that pharmacological blockade of MRGPRX2 can attenuate mast-cell-driven inflammation in skin-relevant systems and supports the receptor's pathogenic role in drug-induced hypersensitivity and chronic urticaria endotypes.[114]

These findings, together with expanding clinical and pathophysiological analyses, support MRGPRX2 blockade as a first-in-class immunomodulatory strategy for conditions characterized by prominent non-IgE mast-cell activation (eg, specific chronic-urticaria endotypes, drug-induced hypersensitivity). Although clinical development is still early, MRGPRX2 antagonism may ultimately serve as an adjunctive approach in SM patients with difficult-to-control, trigger-linked flares where non-IgE pathways contribute to symptom burden.

Epithelial Alarmin Axis

The epithelial alarmins TSLP, IL 33, and IL 25 are upstream cytokines released by barrier tissues in response to allergens, microbes, pollutants, and mechanical stress. These mediators prime mast cells, enhance FcεRI-dependent activation, and amplify cytokine and lipid mediator production, thereby shaping both acute and chronic mast cell-driven inflammation. In human mast cells, IL-33 and TSLP can potentiate degranulation, increase survival, and augment responsiveness to IgE dependent and non-IgE stimuli, while IL-25 contributes to type-2 cytokine amplification through ILC2 and Th2 circuits.[115]

Therapeutic targeting of this axis has advanced through biologics such as anti-TSLP (tezepelumab) and anti- IL-33/anti ST2 antibodies, which reduce type 2 inflammation and mast cell-relevant endpoints in asthma and other epithelial driven diseases. In the CASCADE mechanistic trial, tezepelumab reduced airway eosinophils, mast cells, and other inflammatory cells and improved airway hyperresponsiveness.[116] Subsequent clinical and translational work has reinforced the concept of epithelial driven asthma endotypes that respond particularly well to TSLP blockade.[117,118] Although IL-33/TSLP targeted therapies have not been studied in SM, these findings illustrate how non-KIT

immunomodulatory strategies can reshape mast cell-driven disease biology when mast cell activation is embedded within a broader epithelial/type-2 inflammatory network.

Clinical Considerations in Non-Advanced SM

In non-advanced SM, the primary therapeutic goal remains control of mediator-related symptoms and reduction of anaphylaxis risk, while cytoreductive strategies are reserved for advanced disease or exceptional non-advanced cases. Within this framework, non-KIT immunomodulators are best positioned as adjunctive therapies after guideline-based anti-mediator treatment, biologics such as anti-IgE when appropriate, and selective KIT inhibition for D816V driven symptomatology. However, emerging KIT-targeted therapies carry mechanism-specific adverse events that may limit their use in non-advanced SM. In this context, mast cell silencing may offer symptom control with less toxicity than mast cell-eliminating strategies. By contrast, mast cell elimination remains reserved for advanced disease or rare refractory cases, given its higher risk profile.

Clinical management also relies on regular follow-up, which is essential for understanding how the condition evolves over time and for ensuring that symptoms remain well controlled. These visits typically involve reviewing symptom patterns, adjusting medications, monitoring serum tryptase as an indicator of mast cell burden, and remaining alert for any signs of disease progression. Because non-advanced SM can present with a wide range of manifestations, care is usually coordinated by clinicians experienced in mast cell disorders. This most often includes allergists/immunologists, with hematology consultation when clinically indicated.

Research Gaps and Future Directions

Despite the rapid expansion of mast cell-targeted therapeutics, clinical trials specifically designed for SM—particularly for non-KIT immunomodulators—remain limited. A major challenge is the absence of validated endpoints that can reliably distinguish mast cell activation from mast cell burden. Current symptom composite scores and available biomarkers only partially capture these dimensions, and integrating them into a unified framework remains an unmet need. Rational dosing strategies also require clarification: some agents may ultimately be best suited to short, pulsed regimens that transiently suppress activation, as suggested by BTK-based anti-activation paradigms, whereas others—such as inhibitory receptor agonists—may require continuous exposure to maintain effect. Long-term safety warrants careful evaluation, especially because many patients with non-advanced SM are not cytopenic and may require therapy for extended periods. The broader biomarker gap—specifically, the difficulty of differentiating changes in mast cell numbers from changes in activation state—continues to limit precise patient selection and response assessment.

In parallel, the lack of validated patient-reported outcome measures (PROMs) remains a barrier to progress. Existing tools do not fully capture the fluctuating, multisystem symptom burden characteristic of SM or reliably quantify patient-perceived disease control. Developing disease-specific PROMs aligned with biologic endpoints would strengthen clinical trial design and support more patient-centered evaluation of therapeutic benefit. Two additional outcome domains remain insufficiently evaluated in clinical trials. First, the impact of emerging therapies on osteoporosis—a major contributor to morbidity in non-advanced SM—has not been systematically assessed, despite the biological plausibility that reducing mast-cell-mediated inflammation could influence bone remodeling. Second, the effect of these agents on anaphylaxis risk remains largely unknown, as current studies are not powered or designed to capture changes in severe, episodic events. Addressing both domains will be essential for defining the full clinical relevance of future therapies.

Across mast cell-driven diseases, the therapeutic pipeline continues to expand, encompassing nonspecific immunosuppressants, mast cell stabilizers, mast cell-depleting TKIs, antagonists of IgE-dependent and IgE-independent activation pathways, and agonists of inhibitory receptors. As TKIs such as avapritinib, bezuclastinib, and elenestinib move into earlier disease stages, safety considerations—including teratogenicity and the consequences of prolonged mast cell depletion—will require sustained long-term study to ensure that therapeutic benefit is balanced against risk.

Conclusion

The therapeutic landscape for non-advanced SM is shifting toward a more mechanism-based approach, balancing symptom-directed immunomodulation with selective KIT targeted therapy when clonal mast cell burden contributes to

disease expression. These advances highlight the growing ability to target mast cell activation, mast cell burden, or both, depending on patient phenotype. Important gaps remain: validated biomarkers that distinguish activation from clonal load are still lacking, long-term safety data are limited, and optimal dosing strategies for agents with fundamentally different mechanisms are not well defined. As mutation selective KIT inhibitors move into earlier disease stages and novel pathways—such as inhibitory receptor agonists and KIT WT-directed agents—enter clinical development, careful phenotyping, and rigorous trial design will be essential. Continued progress will depend on integrating mechanistic insights with clinically meaningful endpoints to enable more precise, durable, and individualized treatment strategies for patients with non-advanced SM.

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