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# Recognizing and Managing Systemic Mastocytosis: The Dermatologist's Role in Early Diagnosis, Treatment, and Collaborative Care

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# Disclosures

**David E. Sloane, MD, EdM** has nothing to disclose in relation to this activity

# Learning Objectives

- Evaluate current guidelines to identify both cutaneous and systemic features of SM, and facilitate timely diagnosis and referral for systemic evaluation

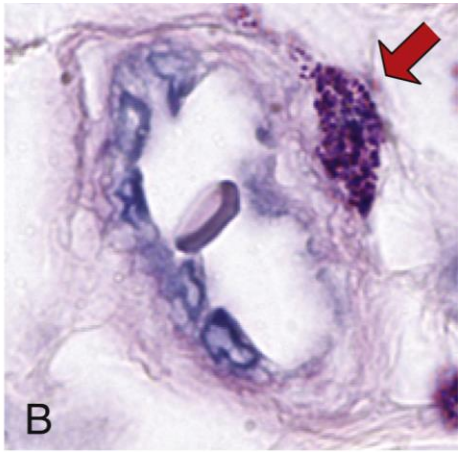
- Assess the mechanism of action, efficacy, and safety data of newer and emerging targeted therapies for SM

- Apply multidisciplinary management strategies for patients with SM to ensure coordinated, comprehensive, and person-centered care

**SM = systemic mastocytosis.**

# The Spectrum of Mast Cell-Mediated Disease

# Mast Cells




- Mast cell basic biology
  - Bone marrow-derived
  - Connective tissue vs mucosal
- Preformed stored granule mediators
  - Vasoactive mediators (eg, histamine)
  - Tryptase
- De novo synthesized arachidonic acid metabolites
  - Cysteinyl leukotrienes (eg, $LTC_4$)
  - Prostaglandins (eg, $PGD_2$)
- Cytokines (eg, TNF-$\alpha$, IL-1, IL-6)

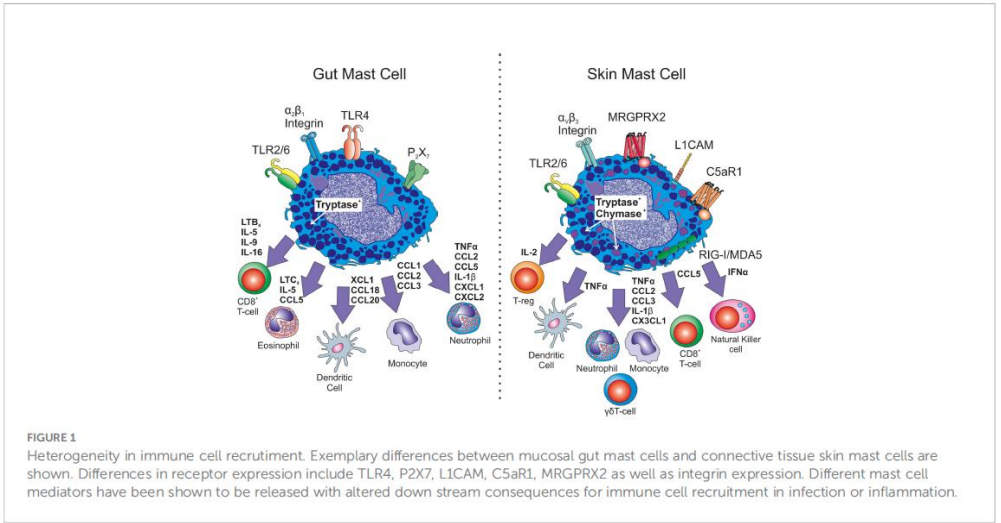



FIGURE 1
Heterogeneity in immune cell recruitment. Exemplary differences between mucosal gut mast cells and connective tissue skin mast cells are shown. Differences in receptor expression include TLR4, P2X7, L1CAM, C5aR1, MRGPRX2 as well as integrin expression. Different mast cell mediators have been shown to be released with altered down stream consequences for immune cell recruitment in infection or inflammation.

**TNF = tumor necrosis factor; IL = interleukin.**

**West PW, Bulfone-Paus S. *Front Immunol*. 2022;13:932090. Abbas AK, et al. *Cellular and Molecular Immunology*. 10th ed. Elsevier; 2021.**

# Mast Cell Physiologic Functions

- Sentinel cells of innate immunity

detect pathogens

- Incite, expedite, and manage or sculpt inflammation
  - Vasodilation
  - Chemoattraction
  - Diapedesis

(probably more…
…a lot more)

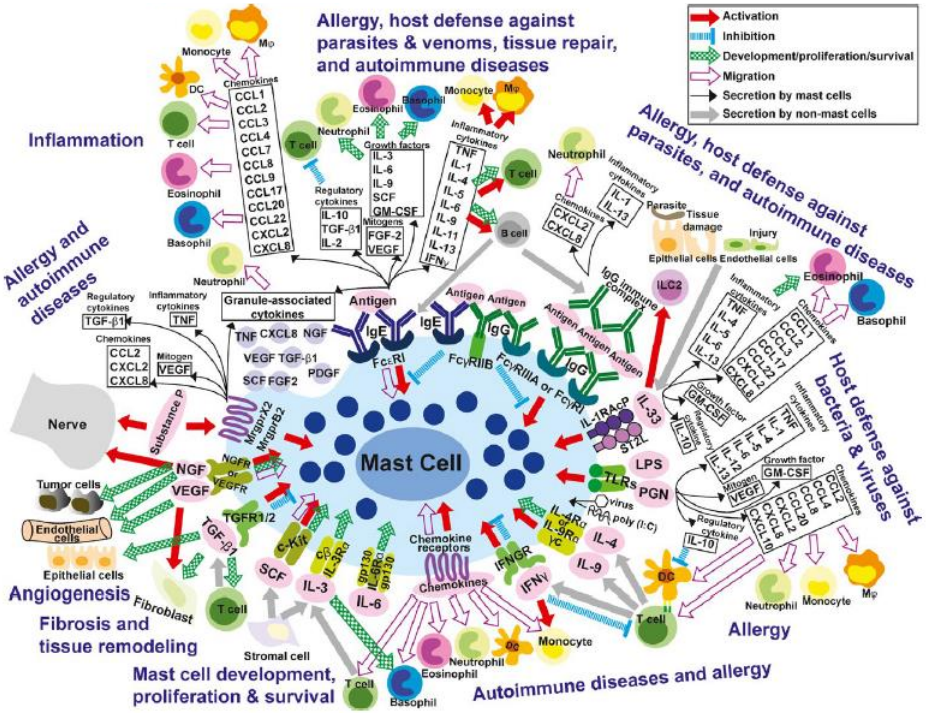
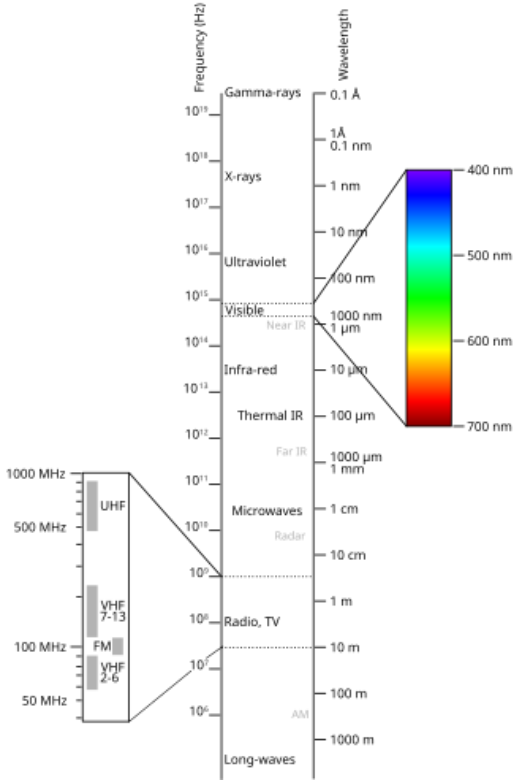



**Image source: https://static0.gamerantimages.com/wordpress/wp-content/uploads/2022/01/Aragorn-At-Council.jpg.**
**Mukai K, et al. *Immunol Rev*. 2018;282(1):121-150.**

# A Spectrum of Mast Cell-Mediated Diseases




- Acute urticaria
- Acute angioedema
- Allergic conjunctivitis and rhinitis
- Chronic urticaria
- Chronic angioedema
- Allergic asthma
- Food allergy (>OAS)
- Cutaneous mastocytosis
- Systemic mastocytosis
  - Indolent
  - Aggressive
- Mast cell leukemia
- Mast cell sarcoma

Clonal

**OAS = oral allergy syndrome; MCAS = mast cell activation syndrome.**
**Image source: https://en.wikipedia.org/wiki/File:Electromagnetic-Spectrum.svg.**

# Overview of Mastocytosis

# Disease Pathogenesis: Role of MCs

- A clonal proliferation of mast cells
- Activating mutations in the KIT gene
  – c-KIT D816V mutation in the majority of patients, but other mutations in c-KIT have been discovered

- Proliferation and accumulation of clonal MCs in various tissues
  – Bone marrow
  – **Skin**
  – GI tract
  – Liver
  – Spleen

**MCs = mast cells; GI = gastrointestinal.**

# Biopsies:
# MPCM and MCL

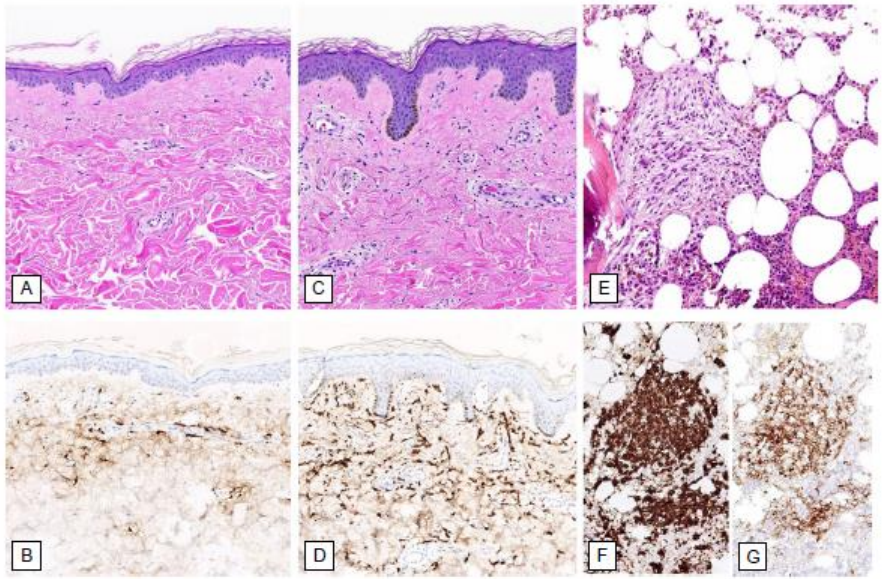
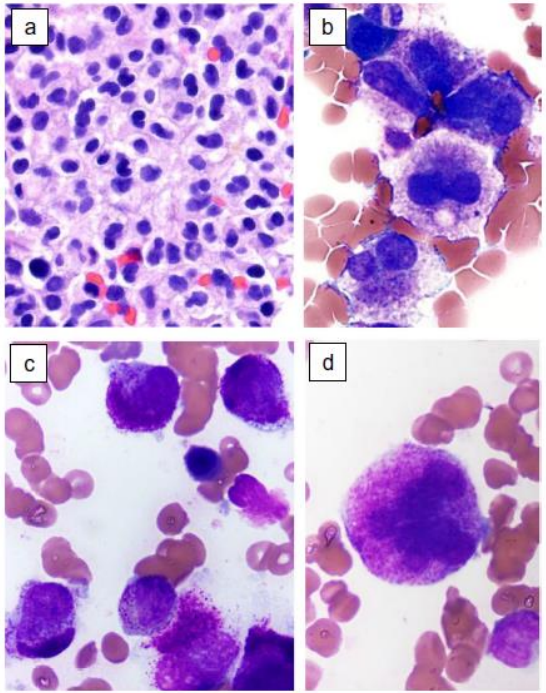



Fig. 3 Skin and bone marrow biopsies of a 54-year-old male presenting with brown–red lenticular macules throughout the trunk and upper legs, consistent with the clinical diagnosis maculopapular cutaneous mastocytosis (MPCM). A non-lesional (control) and a lesional skin biopsy were taken from the abdomen. Compared to the control skin biopsy (**A** HE, **B** tryptase), the lesional skin biopsy (**C** HE, **D** tryptase) shows a subtle increase in mast cells in the reticular dermis and an increase in basal cell pigmentation of the epidermis, conforming the diagnosis MPCM. The subsequent bone marrow biopsy (**E**–**G**) shows multifocal dense infiltrates composed of spindled mast cells (**E** HE), positive for CD117 and CD25 (**F** CD117/c-KIT, **G** CD25), consistent with an underlying indolent systemic mastocytosis

Fig. 1 Mast cell leukemia. Bone marrow biopsy (**a**; HE) showing a sheet-like compact proliferation of atypical mast cells. Aspirate smears (**b**, **c**, and **d**; Wright-Giemsa stain) displaying atypical immature mast cells, consisting of promastocytes (**b**), metachromatic blasts (**c**), and a multilobated promastocyte (**d**)




**MPCM = maculopapular cutaneous mastocytosis; MCL = mast cell leukemia.**
**Leguit RJ, et al. *Virchows Arch*. 2023;482(1):99-112.**

# World Health Organization Classification and Diagnosis of Mastocytosis: Update 2023 and Future Perspectives

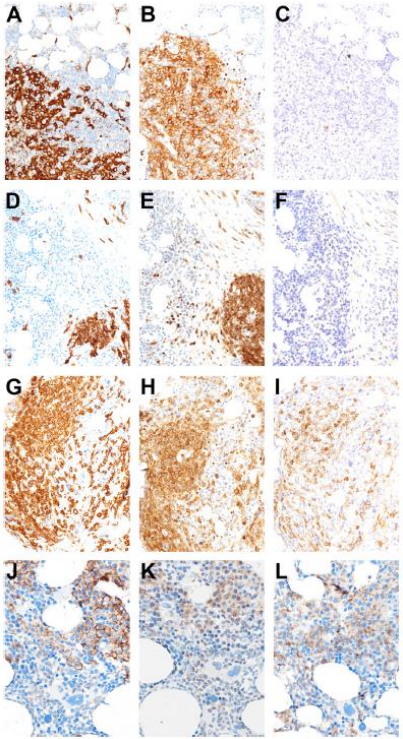



**Fig. 1.** Typical immunohistochemical findings in various subtypes of systemic mastocytosis (SM). (*A–C*) a compact MC infiltrate in the bone marrow of a patient with indolent SM (ISM) stained with antibodies against KIT (CD117) (*A*), CD25 (*B*), and CD30 (*C*). (*D–F*), in another patient with ISM, mast cells not only expressed CD117 (*D*) and CD25 (*E*), but did also express some CD30 (*F*). *G–I*, in a case of SM-AHN (ASM-MDS/MPN), besides expression of CD117 (*G*) and CD25 (*H*), most mast cells were also found to strongly display CD30 (*I*). *J–L*, in a patients with SM with well-differentiated morphology (SMWD) (*J*), mast cells typically express KIT (CD117) (*J*) but lack CD25 (*K*). However, aberrant expression of CD30 (*L*) confirms the neoplastic nature of mast cells and thus the diagnosis of SM.

**Valent P, et al. *Immunol Allergy Clin North Am*. 2023;43(4):627-649.**

# Mastocytosis Subtypes and Prevalence

- Cutaneous mastocytosis (CM)
  - Maculopapular CM (previously urticaria pigmentosa)
  - Diffuse CM
  - Mastocytoma of the skin
- Systemic mastocytosis (SM)
  - Non-advanced
    - Indolent (ISM, 46-88% if you include BMM and SSM)
    - Bone marrow (BMM)
    - Smoldering (SSM)
  - Advanced
    - Aggressive (4-13%)
    - With associated myeloid neoplasm (7.7-40%)
    - Mast cell leukemia (≤1%)
- Mast cell sarcoma (MCS)

**Bergstrom A, et al. *Acta Oncol*. 2024;63:44-50. Jorgensen MP, et al. *Eur J Epidemiol*. 2025;40(1):43-53.**

# Disease Burden and QoL Impact: TouchStone SM Survey 2022

**TABLE 2.** Systemic Mastocytosis Symptoms From the Indolent Systemic Mastocytosis Symptom Assessment Form, $n = 56$

| Symptom queried | Mean ± SD severity score, 0–10 scale[a] | 95% CI |
|---|---|---|
| Bone pain | 4.05 ± 2.89 | 3.28–4.83 |
| Abdominal pain | 5.18 ± 3.10 | 4.35–6.01 |
| Nausea | 4.27 ± 3.31 | 3.38–5.15 |
| Spots on skin | 3.77 ± 3.27 | 2.89–4.64 |
| Itching | 4.43 ± 3.06 | 3.61–5.25 |
| Flushing | 5.07 ± 3.26 | 4.20–5.95 |
| Fatigue | 6.75 ± 2.91 | 5.97–7.53 |
| Dizziness | 4.11 ± 2.91 | 3.33–4.89 |
| Brain fog | 5.32 ± 3.32 | 4.43–6.21 |
| Headache | 4.75 ± 3.57 | 3.79–5.71 |
| Diarrhea | 4.96 ± 3.06 | 4.15–5.78 |
| Total symptom score | 52.66 ± 21.28 | 47.09–58.23 |

Abbreviations: CI, confidence interval; SD, standard deviation.
[a]Severity for each symptom queried is reported on a scale from 0 (no symptoms) to 10 (worst imaginable symptoms).

**QoL = quality of life.**
**Mesa RA, et al. *Cancer*. 2022;128(20):3691-3699.**

# Disease Burden and QoL Impact: TouchStone SM Survey 2022

**TABLE 4.** Work Impairment as a Result of Systemic Mastocytosis Stratified by ≥2 Injectable Epinephrine Uses and Severe Pain, $n = 56$

| | No./total no. (%) | | |
|---|---|---|---|
| Work impairment[a] | Patients overall | Injectable epinephrine use ≥2 times in 1 year | Severe pain in prior 4 weeks |
| Reduced hours at work | 30 (54) | 5/30 (17) | 16/30 (53) |
| Voluntarily quit job | 15 (27) | 4/15 (27) | 13/15 (87) |
| Taken early retirement | 4 (7) | 1/4 (25) | 4/4 (100) |
| Gone on medical disability | 18 (32) | 4/18 (22) | 12/18 (67) |
| Been terminated from job | 9 (16) | 3/9 (33) | 6/9 (67) |
| No impact of disease on work | 15 (27) | 1/15 (7) | 3/15 (20) |

[a]Respondents reported impairment over a typical 7-day period before the COVID-19 pandemic.

**TABLE 5.** Patients Reporting Systemic Mastocytosis-Related Physician Office Visits Over 1 Year

| | No./total no. (%) | | | | |
|---|---|---|---|---|---|
| No. of patient-reported visits | Primary care | Allergy/immunology | Gastroenterology | Dermatology | Hematology/oncology |
| 0 | 11/55 (20) | 13/56 (23) | 24/55 (44) | 30/55 (55) | 28/54 (52) |
| ≥1 | 44/55 (80) | 43/56 (77) | 31/55 (56) | 25/55 (45) | 26/54 (48) |
| ≥3 | 28/55 (51) | 25/56 (45) | 13/55 (24) | 4/55 (7) | 17/54 (31) |
| ≥6 | 13/55 (24) | 12/56 (21) | 6/55 (11) | 1/55 (2) | 6/54 (11) |
| ≥12 | 6/55 (11) | 7/56 (13) | 3/55 (5) | 0/55 (0) | 4/54 (7) |

**Mesa RA, et al. *Cancer*. 2022;128(20):3691-3699.**

# Disease Burden and QoL Impact: TouchStone SM Survey 2022

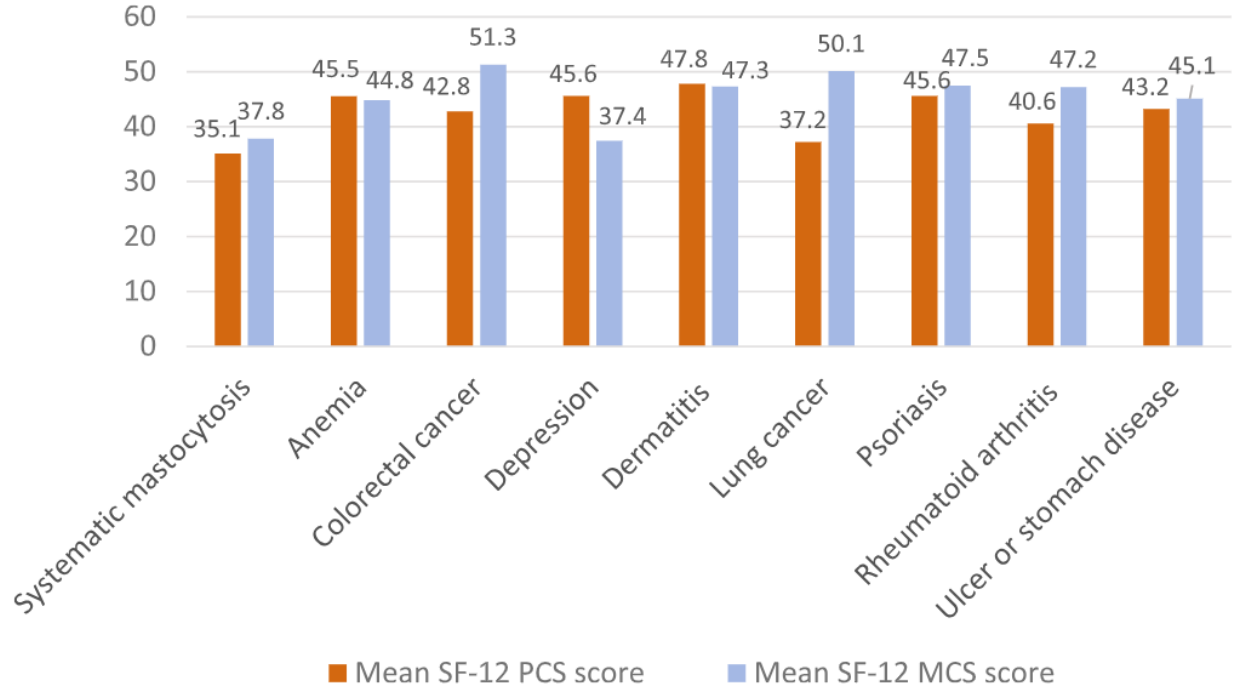



**Figure 1.** SF-12 mean mental component score and physical component score for patients in the TouchStone SM Patient Survey compared with values for other conditions[28,29] MCS indicates mental component score; PCS, physical component score; SF-12, 12-item Short-Form Health Survey; SM, systemic mastocytosis.

**Mesa RA, et al. *Cancer*. 2022;128(20):3691-3699.**

# Psychological Impact

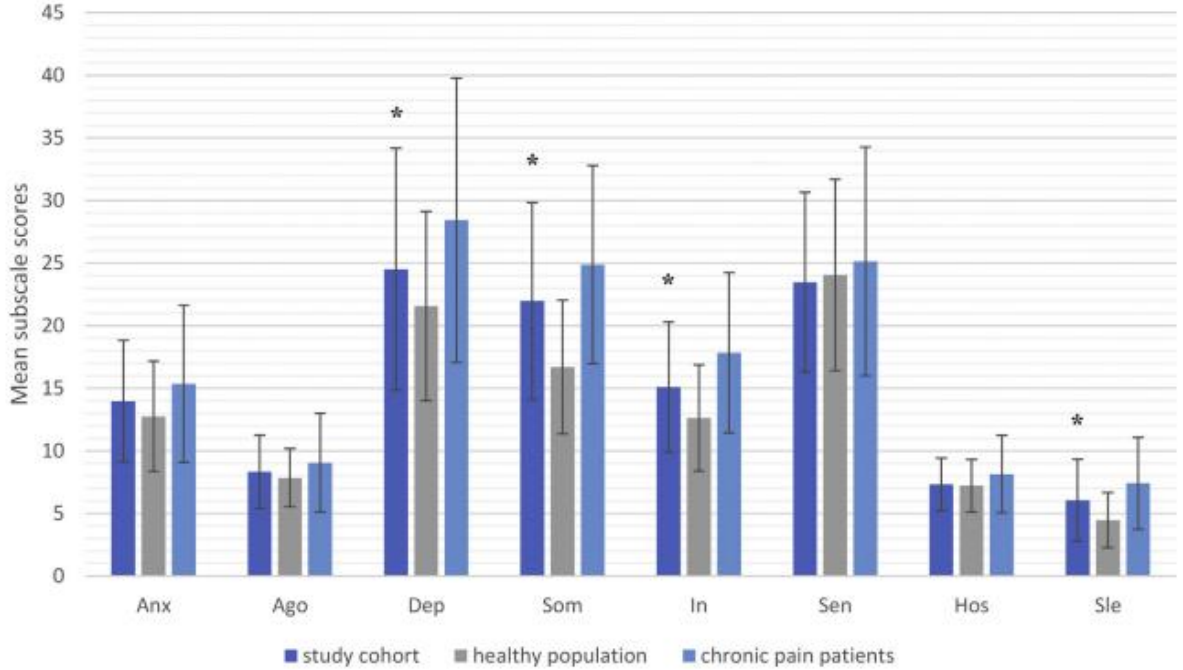



**Figure 1.** Mean 90-item Symptom Checklist (SCL-90) subscale scores of the study cohort compared with SCL-90 normal scores of healthy persons and patients with chronic pain. A higher score means more symptoms. Ago, agoraphobic symptoms; Anx, anxiety; Dep, depression; Hos, hostility; In, inadequacy of thinking and acting; Sen, interpersonal sensitivity; Sle, sleeping problems; Som, somatization. *$P < .05$ for comparison of the subscale value of the study population vs the healthy group ($t$ test).

**Vermeiren MR, et al. *Ann Allergy Asthma Immun*. 2020;124(4):373-378.e2.**

# Psychological Impact

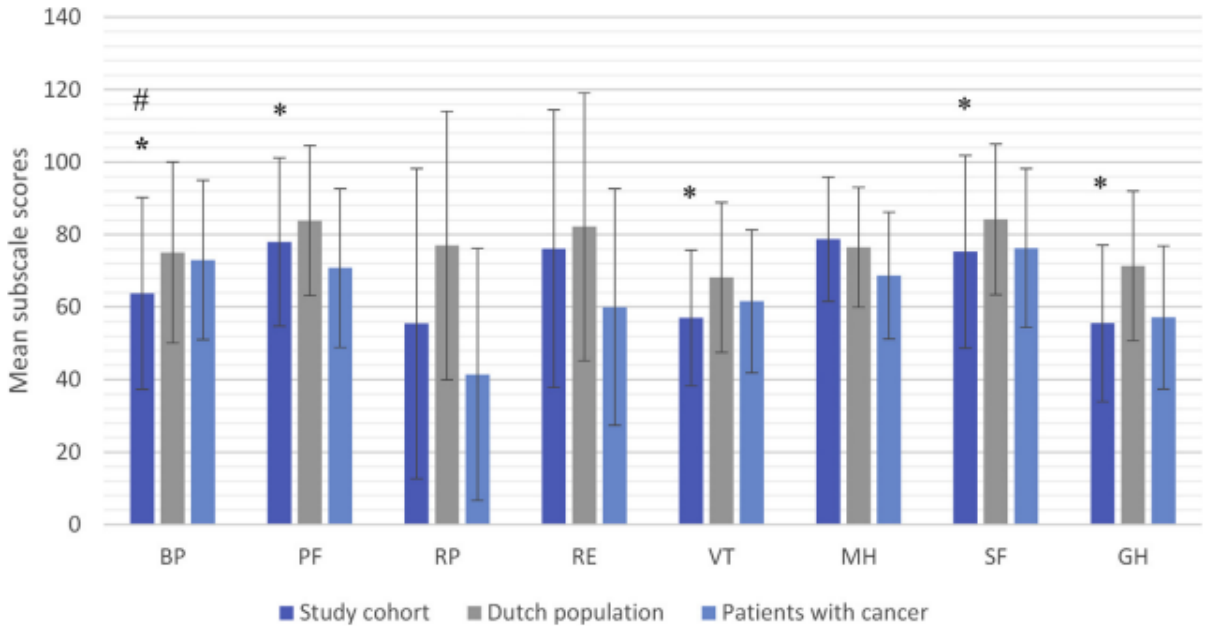



**Figure 2.** Mean 36-item Short-Form Health Survey (SF-36) subscale values of the study cohort compared with SF-36 normal scores of the Dutch population and patients with cancer. A lower score means lower quality of life on that area. BP, bodily pain; GH, general health perception; MH, mental health; PF, physical functioning; RE, emotional role functioning; RP, physical role functioning; SF, social role functioning; VT, vitality. $^{*}P < .05$ for comparison of the subscale value of the study population vs the healthy group ($t$ test) $^{\#}P < .05$ for significantly worst subscale score for the study population vs the group of patients with cancer ($t$ test).

**Vermeiren MR, et al. *Ann Allergy Asthma Immun*. 2020;124(4):373-378.e2.**

# Key Learning Points

- Mastocytosis is a *clonal* mast cell disease
- Many of the symptoms make sense given the release from mast cells of their classic mediators like histamine, leukotrienes, prostaglandins, and cytokines
- Symptoms may have a significant impact on patients, and in the extreme, may be life-threatening (eg, anaphylaxis)
- Psychological symptoms are prominent

# SM Classification and Diagnostic Criteria

# Benefits of Early Diagnosis

- Control of symptoms should improve QoL, function, mental health

- Preparation for surgery, pregnancy, childbirth, vaccinations to limit acute reactions

# Cutaneous and Systemic Features

**Cutaneous**

- Maculopapular CM: Papules and small red to brown plaques, (+) Darier's sign
- Diffuse CM: Widespread erythroderma with some islands of spared uninvolved skin
- Often telangiectasias (recall histamine is a vasoactive mediator)
- Episodic flushing, urticaria, angioedema

**Systemic**

- Cardiovascular (episodic tachycardia, hypo-/hypertension, [pre]syncope)
- Respiratory (largely asthma; [+] wheezing, cough, chest tightness, dyspnea)
- GI (nausea, vomiting, bloating, cramping, abd pain, diarrhea)
- Neuro (waxing and waning "brain fog," episodic delirium, rarely seizures)
- Osteopenia, osteoporosis

**When to refer for additional workup**

- If a patient with cutaneous symptoms has any systemic symptoms, check a serum tryptase and, if elevated, refer to allergy or hematology/oncology

**Theoharides TC, et al. *N Engl J Med*. 2015;373(2):163-172.**

# Classification Systems:
# WHO (2022) and ICC (2024)

**WHO = World Health Organization; ICC = International Consensus Classification.**

# World Health Organization Classification and Diagnosis of Mastocytosis: Update 2023 and Future Perspectives

**Table 1**
**World Health Organization classification of mastocytosis**

| Variant<br>Subvariant | Abbreviation |
|---|---|
| Cutaneous mastocytosis | CM |
| Maculopapular CM | MPCM |
| (Urticaria pigmentosa)[a] | UP[a] |
| Diffuse CM | DCM |
| Mastocytoma of skin | - |
| Systemic mastocytosis[b] | SM |
| Bone marrow mastocytosis | BMM |
| Indolent SM | ISM |
| Smoldering SM | SSM |
| SM with and associated hematologic neoplasm | SM-AHN |
| Aggressive SM | ASM |
| Mast cell leukemia | MCL |
| Mast cell sarcoma | MCS |
| Extracutaneous mastocytoma[c] | - |

[a] The term *urticaria pigmentosa* (UP) is still in use and is still regarded standard, but should be replaced by the term MPCM.
[b] In a few patients with SM, mast cells are rather mature and well granulated. In these cases, a well-differentiated subtype of SM ($SM_{WD}$) can be diagnosed. This $SM_{WD}$ type may be found in any WHO variant of SM.
[c] Extracutaneous mastocytoma is a very rare nonmalignant disease variant that has mostly been reported in lung tissue. Based on its rarity this variant is not listed in the current classifications of mastocytosis.[35,37,38]

**Valent P, et al. *Immunol Allergy Clin North Am*. 2023;43(4):627-649.**

# World Health Organization Classification and Diagnosis of Mastocytosis: Update 2023 and Future Perspectives

**Table 2**
**Classification and typical features (criteria) of cutaneous mastocytosis and cutaneous involvement in SM**

| Variant and Subvariants | Abbreviation | Features/Criteria |
|---|---|---|
| A. Maculopapular cutaneous mastocytosis | MPCM | Positive Darier sign[a]<br>Typical pigmented skin lesions<br>Positive histology[b]<br>*KIT* mutation in lesional skin |
| (1) Monomorphic variant | MPCM-m | Monomorphic skin lesions[c]<br>Criteria for SM not fulfilled[d] |
| (2) Polymorphic variant | MPCM-p | Polymorphic skin lesions[c]<br>Criteria for SM not fulfilled[d] |
| B. Diffuse cutaneous mastocytosis | DCM | Positive Darier sign[a]<br>Diffuse involvement of the entire skin<br>Positive histology[b]<br>Criteria for SM not fulfilled[d] |
| C. Cutaneous mastocytoma | - | Positive Darier sign[a]<br>Positive histology[b] |
| (1) Isolated mastocytoma | | 1 single lesion |
| (2) Multilocalized mastocytomas | | 2 or 3 lesions<br>Criteria for SM not fulfilled[d] |
| D. Cutaneous involvement in SM[e] | | Criteria for SM fulfilled |

**Valent P, et al. *Immunol Allergy Clin North Am*. 2023;43(4):627-649.**

# World Health Organization Classification and Diagnosis of Mastocytosis: Update 2023 and Future Perspectives

**Table 3**
**Major and minor diagnostic criteria of systemic mastocytosis (SM)**

| | |
|---|---|
| Major criterion | Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organs |
| Minor criteria | 1. >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 detected in sections of BM or other extracutaneous organs[a] |
| | 2. KIT-activating *KIT* point mutations at codon 816 or in other critical regions of *KIT*[b] in bone marrow or another extracutaneous organ |
| | 3. Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2, CD25, and/or CD30[c] |
| | 4. Baseline serum tryptase concentration >20 ng/mL (in the case of an unrelated myeloid neoplasm, an elevated tryptase level does not count as an SM criterion; in the case of a known hereditary HαT, the tryptase level should be adjusted[d]). |
| | If at least 1 major and 2 minor *or* 3 minor criteria are fulfilled → the diagnosis is SM |

**Valent P, et al. *Immunol Allergy Clin North Am*. 2023;43(4):627-649.**

# WHO B-Findings and C-Findings

**Table 5**
**Proposed refined B-findings and C-findings**

| B-findings | C-findings (SM-induced Organ Damage) |
|---|---|
| *High MC burden*: | |
| Infiltration grade (MC) in BM ≥ 30% in histology (IHC) and/or serum tryptase level ≥200 ng/mL[a] and/or *KIT* D816V VAF ≥10% in BM or PB leukocytes | |
| *Signs of myeloproliferation and/or myelodysplasia*[b]: | *Cytopenia* |
| Hypercellular BM with loss of fat cells and prominent myelopoiesis ± left shift and eosinophilia ± leukocytosis and eosinophilia and/or | ANC < $1 \times 10^9$/L |
| discrete signs of myelodysplasia (<10% neutrophils, erythrocytes, and megakaryocytes) | Hb < 10 g/dL |
| *Organomegaly*: | PLT < $100 \times 10^9$/L |
| Palpable hepatomegaly without ascites or other signs of organ damage or/and | (1 or more found) |
| palpable splenomegaly without hypersplenism and without weight loss or/and lymphadenopathy | *Hepatopathy*: |
| Palpable or visceral LN enlargement found in ULS or CT (>2 cm) | Ascites and elevated liver enzymes[c] ± hepatomegaly or cirrhotic liver ± portal hypertension |
| | *Spleen*: |
| | Palpable splenomegaly with hypersplenism ± weight loss ± hypoalbuminemia |
| | *GI tract*: |
| | Malabsorption with hypoalbuminemia ± weight loss |
| | *Bone*: |
| | Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain |

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# WHO B-Findings and C-Findings

**Box 1**
**Role of B-findings and C-findings in the definition of bone marrow mastocytosis (BMM), indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), and aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL)**

| Number of B-findings | Number of C-findings | Potential Diagnosis[a] |
|---|---|---|
| 0 | 0 | BMM or ISM |
| 1 | 0 | ISM |
| 2–3 | 0 | SSM |
| 0–3 | 1 or more[b] | ASM or MCL[a] |

[a]In patients with 1 or more C-findings, the final diagnosis may be ASM, but may also be (A)SM-AHN or MCL.[b]Depending on the organ systems involved, patients with ASM or MCL may exhibit multiple C-findings.

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# ICC Diagnostic Criteria

**Table 1** Systemic mastocytosis: diagnostic criteria

Major criterion

- Multifocal dense infiltrates of tryptase- and/or CD117-positive mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)[a]

In the absence of the major criterion, at least three of the following four minor criteria must be present

- In bone marrow biopsy or in section of other extracutaneous organs, > 25% of mast cells are spindle shaped or have an atypical immature morphology[b]
- Mast cells in bone marrow, peripheral blood, or other extracutaneous organs express CD25, CD2, and/or CD30, in addition to mast cell markers
- *KIT* D816V mutation or other activating *KIT* mutation detected in bone marrow, peripheral blood, or other extracutaneous organs[a/c]
- Elevated serum tryptase level, persistently > 20 ng/mL. In cases of SM-AMN, an elevated tryptase does not count as a SM minor criterion

[a]In the absence of a *KIT* mutation particularly in cases with eosinophilia, the presence of tyrosine kinase gene fusions associated with myeloid/lymphoid neoplasm with eosinophilia and kinase gene fusion (M/LN-eo) must be excluded

[b]Round-cell well-differentiated morphology can occur in a small subset of cases. In these cases, the mast cells are often negative for CD25 and CD2 but positive for CD30

[c]To avoid "false negative" results, use of a high sensitivity PCR assay for detection of *KIT* D816V mutation is recommended. If negative, exclusion of *KIT* mutation variants is strongly recommended in suspected SM

**Leguit RJ, et al. *Virchows Arch*. 2023;482(1):99-112.**

# ICC B-Findings and C-Findings

**Table 2** B-findings

- High mast cell burden, > 30% of infiltration of bone marrow cellularity by mast cell aggregates (assessed on bone marrow biopsy) and serum total tryptase > 200 ng/mL
- Cytopenia (not meeting criteria for C-findings) or -cytosis. Reactive causes are excluded, and criteria for other myeloid neoplasms are not met
- Palpable hepatomegaly without impairment of liver function, or palpable splenomegaly without features of hypersplenism including thrombocytopenia, and/or lymphadenopathy (> 1 cm size) on palpation or imaging

**Table 3** C-findings

- BM dysfunction caused by neoplastic MC infiltration, manifested by ≥ 1 cytopenia: absolute neutrophil count < $1.0 \times 10^9$/L, hemoglobin level < 10 g/dL, and/or platelet count < $100 \times 10^9$/L
- Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension
- Skeletal involvement, with large osteolytic lesions with or without pathologic fractures[a]
- Palpable splenomegaly with hypersplenism
- Malabsorption with weight loss due to gastrointestinal tract MC infiltrates

[a]Pathological fractures caused by osteoporosis do not qualify as a C-finding

**Leguit RJ, et al. *Virchows Arch*. 2023;482(1):99-112.**

# Harmonized International Guidelines

**TABLE I.** Proposed harmonized classification of mastocytosis (H-2024) and comparison to the EU/US Consensus Group Proposal, WHO Classification, and ICC Group Proposal

| | Classification proposed by | | | |
|---|---|---|---|---|
| **Variants and subvariants (abbreviations)** | **EU/US 2021** | **WHO 2021** | **ICC 2021** | **H-2024*** |
| Cutaneous mastocytosis (CM) | CM | CM | CM | CM |
| Nonadvanced systemic mastocytosis (non-AdvSM) | | | | |
| Bone marrow mastocytosis (BMM) | BMM | BMM | —† | BMM |
| Indolent SM (ISM) | ISM | ISM | ISM (BMM)† | ISM |
| Smoldering SM (SSM) | SSM | SSM | SSM | SSM |
| Advanced SM (AdvSM) | | | | |
| Aggressive SM (ASM) | ASM | ASM | ASM | ASM |
| SM with an associated hematologic (myeloid or lymphoid) neoplasm (SM-AHN) | SM-AHN | SM-AHN | SM-AMN | SM-AHN: SM-AMN SM-ALN |
| Mast cell leukemia (MCL) | MCL | MCL | MCL | MCL |
| Mast cell sarcoma (MCS) | MCS | MCS | MCS | MCS |
| Extracutaneous mastocytoma (ECM)‡ | — | — | — | ECM |

*EU*, Europe; *US*, United States of America.
*H-2024: Harmonized classification proposed in 2024 (in this article).
†In the ICC proposal, BMM is regarded a (provisional) subvariant of ISM.
‡Although several cases have been reported in the literature (most in the lungs), ECM is regarded a provisional category of mastocytosis. However, the etiology and clonality of MCs in ECM remain to be determined.

**Valent P, et al. *J Allergy Clin Immunol Pract*. 2024;12(12):3250-3260.e5.**

# Harmonized International Guidelines

With regard to SM, our harmonization proposal includes both BMM and SSM as separate SM variants (Table I). BMM is regarded as a unique variant of SM, based on a much better prognosis regarding survival and a worse prognosis regarding the frequency of anaphylaxis and severe mediator-related events compared with patients with ISM or SSM (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[21] With regard to BMM, however, it is important to state that sometimes skin lesions are overlooked at first presentation. Therefore, it is of great importance to recommend a detailed inspection of the skin before concluding that the patient is suffering from BMM. Our harmonization panel also proposes that SM be divided into non-AdvSM, encompassing BMM, ISM, and SSM, and AdvSM, including ASM, SM-AHN, and MCL (Table I).[14-17] This delineation has also been proposed by the WHO and the ICC.[18,42-44] Details of harmonizing diagnostic criteria in sub-variants of non-AdvSM and AdvSM are provided below.

Valent P, et al. *J Allergy Clin Immunol Pract.* 2024;12(12):3250-3260.e5.

# Harmonized International Guidelines

**TABLE II.** Proposed harmonized classification of CM and comparison to the EU/US Consensus Group Proposal, WHO Classification, and ICC Group Proposal

| | Classification proposed by | | | |
|---|---|---|---|---|
| **Variants and subvariants of CM (abbreviations)** | **EU/US 2021** | **WHO 2021** | **ICC 2021** | **H-2024** |
| Cutaneous mastocytosis (CM) | CM | CM | CM | CM |
| Maculopapular CM (MPCM) | MPCM | MPCM | MPCM | MPCM |
| Monomorphic MPCM (MPCM-m)* | MPCM-m | MPCM-m | — | MPCM-m |
| Polymporphic MPCM (MPCM-p)* | MPCM-p | MPCM-p | — | MPCM-p |
| Diffuse CM (DCM) | DCM | DCM | DCM | DCM |
| Cutaneous mastocytoma (CUTM) | + | + | — | CUTM† |
| Isolated (cutaneous) mastocytoma | + | + | — | CUTM1† |
| Multilocalized (cutaneous) mastocytoma | + | + | — | CUTM2/3† |

EU, Europe; US, United States of America.

Definition of symbols: +, mentioned in the classification without listing subvariants in a table; —, not mentioned and not listed in the classification.

*Although the monomorphic form of childhood-onset MPCM (MPCM-m) may persist into adulthood in many cases, the polymorphic form (MPCM-p) often resolves around puberty.

†Based on the number of lesions, CUTM is divided into isolated CUTM = CUTM1 (1 lesion) and CUTM with 2 or 3 lesions (CUTM2/3).

**Valent P, et al. *J Allergy Clin Immunol Pract*. 2024;12(12):3250-3260.e5.**

# Harmonized International Guidelines

**TABLE III.** Proposal for a harmonized definition of SM-AHN variants

| Variant | Definition of variant |
|---|---|
| SM-AMN | SM criteria by WHO and/or ICC are fulfilled |
| | WHO or ICC criteria for an AMN-type disease are fulfilled |
| | Confirming observation*: The SM cells and the AMN cells express the same somatic lesion(s) |
| SM-ALN | SM criteria by WHO and/or ICC are fulfilled |
| | WHO or ICC criteria for an ALN-type disease are fulfilled |
| | Confirming observation*: The SM cells and the ALN cells express the same somatic lesion(s) |

*ALN*, Associated lymphoid neoplasm; *AMN*, associated myeloid neoplasm.
*Although not mandatory, demonstration of identical somatic lesions confirms the common origin of the SM and AHN (AMN or ALN) components of the disease.

**TABLE V.** Harmonized minor diagnostic criteria for SM

1. More than 25% of all MCs are atypical MC type I or atypical MC type II in BM smears or are spindle-shaped in MC infiltrates in BM sections or in histologic studies in other extracutaneous organ(s)*
2. KIT-activating point mutation(s) at codon 816 or in other critical regions of the *KIT* gene† found in BM cells or in other extracutaneous organ(s)
3. MCs in the BM, blood, or another extracutaneous organ display 1 or more of the following aberrant markers: CD2 and/or CD25 and/or CD30‡
4. BST concentration ≥20 ng/mL. In the case of an AMN, an elevated BST (≥20 ng/mL) does not count as a minor SM criterion. When HαT is diagnosed, the BST level should be adjusted§

*An abnormal MC morphology counts in both the compact and diffuse (or mixed compact plus diffuse) MC infiltrates. However, the spindle shape is not an SM criterion when MCs are lining vascular cells, fat cells, nerve cells, or endosteal-lining cells. In the BM smear, an atypical morphology of MCs does not count as an SM criterion when MCs are located in or adjacent to BM particles.
†Any type of KIT-activating *KIT* mutation qualifies as a minor SM criterion.
‡Expression of CD2, CD25, and CD30 can be documented by flow cytometry or by immunohistochemistry (usually in BM biopsy sections). The identity of MCs should be confirmed by applying antibodies against KIT and CD34: independent of the pathology and differentiation stage, MCs are always $KIT^{+}/CD34^{-}$ cells.
§Although the optimal way of adjusting for HαT remains under debate, we recommend dividing the BST by 1 plus the extra copy numbers of the TPSAB1 gene coding for alpha tryptase.

**Valent P, et al. *J Allergy Clin Immunol Pract.* 2024;12(12):3250-3260.e5.**

# Diagnostic Criteria and Risk Stratification

- C-KIT mutations
- Clinical relevance of B- and C-findings
- The International Prognostic Scoring System for Mastocytosis (IPSM)
- Mutation-Adjusted Risk Score (MARS)
- Global Prognostic Score (GPS)
- Mayo Alliance Prognostic System (MAPS)

# C-KIT Mutations

- The most common c-KIT mutation by far is the D816V mutation, but the frequency of this mutation differs depending on the subtype of mastocytosis
  - Of all patients with SM, 80% have D816V
  - Of adults with ISM or ASM, 93% have D816V
  - <1% of patients have another D816 mutation
  - <3% of patients have a non-816 mutation in c-KIT
  - 5-10% of patients may have no c-KIT mutation at all (AKA wild-type c-KIT)

- But in MCL, only 46-68% of patients have KIT D816V

- And in MCS, only 7% of patients have KIT D816V, while 21% have other KIT mutations

**Leguit RJ, et al. *Virchows Arch*. 2023;482(1):99-112.**

# Clinical Relevance of B- and C-Findings

**Prognostically**

- Having ISM with 0-1 “B”s and 0 “C”s is associated with a normal lifespan
- Having SSM with ≥2 “B”s and 0 “C”s is associated with a shorter lifespan, but not as severe as…
  - Having ASM, implying any “C”s (≥1), in which lifespan is ≈3.5-5.8 years

**Workup, Monitoring, and Treatment**

- ISM/SSM (no or limited B-findings, no C-findings)
  - Observation or clinical trial for asymptomatic patients
  - Symptom-directed therapy for mast cell mediator symptoms
  - Annual surveillance with assessment of symptom burden
  - No indication for cytoreductive therapy
- ASM (≥1 C-finding)
  - Cytoreductive therapy is indicated to reverse organ dysfunction

**Leguit RJ, et al. *Virchows Arch*. 2023;482(1):99-112.**

# The International Prognostic Scoring System for Mastocytosis (IPSM)

| | Patients (n) | Risk population | Risk of patients with non-advanced mastocytosis | | | | Risk of patients with advanced systemic mastocytosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | | | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Male sex | 1641 | .. | 2·01 (1·14–3·55) | 0·016 | 1·47 (0·67–3·14) | 0·35 | 1·74 (1·20–2·54) | 0·004 | 1·12 (0·67–1·86) | 0·48 |
| Age (years) | 1641 | ≥60 | 1·11 (1·08–1·14) | <0·0001 | 10·75 (5·68–20·32) | <0·0001 | 1·04 (1·03–1·06) | <0·0001 | 2·14 (1·42–3·22) | <0·0001 |
| Tryptase (ng/mL) | 1530 | ≥125 | 3·01 (1·59–5·70) | <0·0001 | 1·61 (0·72–3·72) | 0·24 | 1·66 (1·18–2·35) | 0·0004 | 1·81 (1·20–2·75) | 0·005 |
| Leukocytes (×10⁹ per L) | 1543 | ≥16 | 2·08 (0·26–16·65) | 0·491 | .. | .. | 1·94 (1·20–3·14) | 0·007 | 1·88 (1·27–2·79) | 0·002 |
| Haemoglobin (g/dL) | 1550 | ≤11·0 | 0·01 (0·00–0·31) | 0·019 | .. | .. | 0·01 (0·00–0·04) | <0·0001 | 1·71 (1·13–2·57) | 0·011 |
| Platelets (×10⁹ per L) | 1543 | ≤100 | 0·05 (0·01–0·23) | <0·0001 | 5·78 (0·56–59·52) | 0·14 | 0·17 (0·11–0·27) | <0·0001 | 1·63 (1·13–2·34) | 0·009 |
| Lactate dehydrogenase (U/L) | 1226 | ≥260 | 0·46 (0·04–5·29) | 0·535 | .. | .. | 2·51 (1·27–4·98) | 0·008 | 1·36 (0·82–2·28) | 0·19 |
| Alkaline phosphatase (U/L) | 1295 | ≥100 | 15·19 (3·93–58·71) | <0·0001 | 2·91 (1·60–5·30) | <0·0001 | 2·16 (1·35–3·46) | 0·001 | 0·74 (0·39–1·40) | 0·11 |
| Calcium (mg/dL) | 1216 | ≤8·7 | 0·01 (0·00–0·01) | 0·003 | 0·97 (0·22–4·22) | 0·93 | 0·01 (0·00–0·01) | <0·0001 | 1·48 (0·91–2·41) | 0·12 |
| Neutrophils (%) | 1466 | ≥50 | 11·11 (0·72–171·57) | 0·085 | 2·58 (0·90–7·44) | 0·081 | 0·66 (0·30–1·46) | 0·307 | .. | .. |
| Monocytes (%) | 1420 | ≥0·32 | 16·74 (0·19–1451·66) | 0·216 | .. | .. | 3·20 (1·06–9·69) | 0·040 | 1·43 (0·53–3·83) | 0·44 |
| Eosinophils granulocytes (%) | 1432 | .. | 1·01 (0·94–1·10) | 0·749 | .. | .. | 1·00 (0·99–1·02) | 0·408 | .. | .. |
| Skin involvement | 1641 | .. | 1·06 (0·50–2·28) | 0·877 | .. | .. | 0·44 (0·31–0·65) | <0·0001 | 0·46 (0·30–0·69) | <0·0001 |
| Organomegaly* | 1464 | .. | 3·05 (1·56–5·94) | 0·001 | 1·28 (0·56–2·94) | 0·51 | 1·06 (0·68–1·66) | 0·782 | .. | .. |
| Mediator symptoms | 1639 | .. | 0·66 (0·36–1·20) | 0·171 | .. | .. | 0·61 (0·43–0·85) | 0·004 | 0·87 (0·52–1·48) | 0·25 |
| Allergy | 1418 | .. | 0·74 (0·39–1·43) | 0·376 | .. | .. | 0·43 (0·22–0·84) | 0·014 | 0·48 (0·20–1·19) | 0·23 |

Prognostic variables were examined for their statistical power and independence from each other and from the WHO classification by univariate and multivariate analysis. HR=hazard ratio. *Organomegaly (ie, enlarged spleen, enlarged liver, enlarged lymph nodes, or a combination).

***Table 2:*** **Effect of individual risk factors on overall survival and identification of prognostic variables**

**Sperr WR, et al. *Lancet Haematol*. 2019;6(12):e638-e649.**

# The International Prognostic Scoring System for Mastocytosis (IPSM)

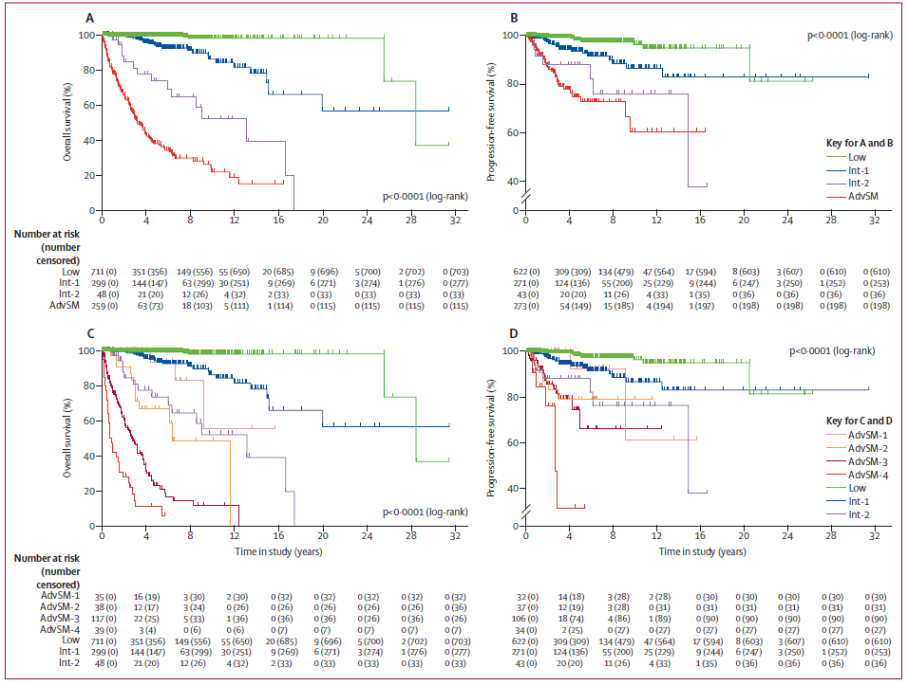


***Figure 3*: Survival outcomes according to the IPSM score in patients with non-advanced and advanced systemic mastocytosis**
Kaplan–Meier curves show the probability of overall survival (A, C) and progression-free survival (B, D) in patients with non-advanced and advanced systemic mastocytosis, defined by the IPSM. Upper panels (A, B) show that patients with non-advanced systemic mastocytosis at low risk (no risk factors [low]) and intermediate risk (one [int-1] or two [int-2] additional risk factors) differed significantly and had a favourable outcome compared with patients with advanced systemic mastocytosis (AdvSM). Lower panels (C, D) show that patients with advanced systemic mastocytosis and no additional risk factors (AdvSM-1) differed significantly from those with one (AdvSM-2), two to three (AdvSM-3), or four to five (AdvSM-4) risk factors. IPSM=international prognostic scoring system for mastocytosis.

**Sperr WR, et al. *Lancet Haematol*. 2019;6(12):e638-e649.**

# Mutation-Adjusted Risk Score (MARS)

**TABLE 4.** Univariable and Multivariable OS Analysis in Training Set on the Basis of Clinical and Molecular Characteristics (Mutation-Adjusted Risk Score, MARS) in Patients With Advanced Systemic Mastocytosis

| | Univariable OS Analysis | | | Multivariable OS Analysis | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Age > 60 years | 3.4 | 2.0 to 5.8 | < .001 | 2.4 | 1.4 to 5.0 | .003 |
| Sex (men *v* women) | 1.7 | 1.1 to 2.5 | .02 | | | |
| WHO classification | | | | | | |
| SM-AHN *v* ASM | 2.3 | 1.3 to 4.0 | .004 | | | |
| MCL *v* SM-AHN | 2.9 | 1.5 to 5.8 | .002 | | | |
| MCL *v* ASM | 3.4 | 2.0 to 5.9 | < .001 | | | |
| Hemoglobin < 10 g/dL | 2.4 | 1.6 to 3.5 | < .001 | 2.0 | 1.3 to 3.0 | .002 |
| Platelets < $100 \times 10^9$/L | 2.4 | 1.6 to 3.5 | < .001 | 1.7 | 1.1 to 2.5 | .017 |
| Mast cell infiltration* > 30% | 1.3 | 0.8 to 1.9 | .3 | | | |
| Serum tryptase > 150 μg/L | 1.7 | 1.1 to 2.5 | .02 | | | |
| Albumin < 35 g/L | 1.9 | 1.3 to 3.0 | .002 | | | |
| Alkaline phosphatase > UNL | 2.6 | 1.6 to 4.1 | < .001 | | | |
| Splenomegaly | 2.0 | 1.0 to 4.2 | .05 | | | |
| S/A/R (1 mutation) | 4.3 | 2.7 to 6.9 | < .001 | 2.5 | 1.6 to 4.5 | < .001 |
| S/A/R (≥ 2 mutations) | 7.6 | 3.5 to 9.9 | < .001 | 4.4 | 2.1 to 7.3 | < .001 |
| Aberrant karyotype | 1.5 | 0.9 to 2.5 | .1 | | | |

Abbreviations: AHN, associated hematologic neoplasm; ASM, aggressive systemic mastocytosis; HR, hazard ratio; MCL, mast cell leukemia; OS, overall survival; S/A/R, *SRSF2*, *ASXL1*, and/or *RUNX1*; SM, systemic mastocytosis; UNL, upper normal limit.

*Mast cell infiltration in bone marrow histology.

**Jawhar M, et al. *J Clin Oncol*. 2019;37(31):2846-2856.**

# MARS

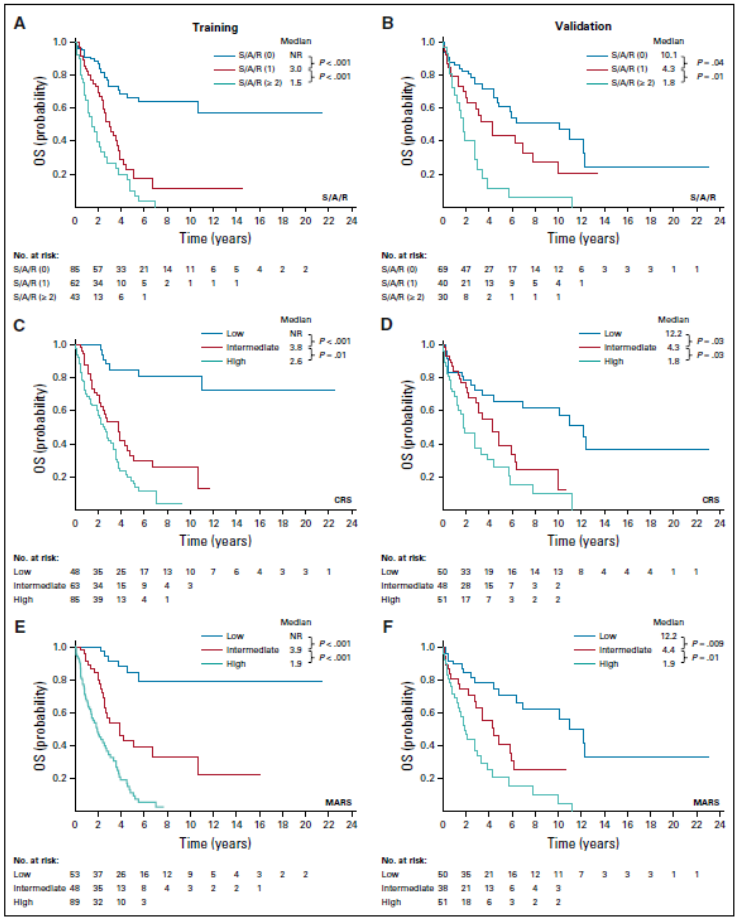


**FIG 2.** Overall survival (OS) for the training set (left) and the validation set (right) of patients with advanced systemic mastocytosis (AdvSM). Patients in both sets are grouped by (A and B) *SRSF2*, *ASXL1*, and *RUNX1* (S/A/R) mutation–based stratification, (C and D) the clinical risk score (CRS), and (E and F) the mutation-adjusted risk score (MARS).

**Jawhar M, et al. *J Clin Oncol*. 2019;37(31):2846-2856.**

# Global Prognostic Score (GPS)

| | PFS | OS |
|---|---|---|
| Haemoglobin ≤110 g/L | .. | 1·0 |
| Platelet count ≤100 × $10^9$ cells per L | 1·0 | .. |
| Serum alkaline phosphatase ≥140 IU/L | .. | 1·5 |
| Serum baseline tryptase ≥125 µg/L | 2·0 | .. |
| Serum β2-microglobulin ≥2·5 µg/mL | 3·5 | .. |
| Presence of *SRSF2, ASXL1, RUNX1, DNMT3A* gene mutations | .. | 1·0 |
| GPSM | | |
| Low risk | 0 | 0 |
| Intermediate risk | 1·0–3·5 | 1·0–1·5 |
| High risk | >3·5 | ≥2·0 |

GPSM=global prognostic score model. PFS=progression-free survival. OS=overall survival.

***Table 2:*** **GPSM scores for predicting PFS and OS in patients with systemic mastocytosis**

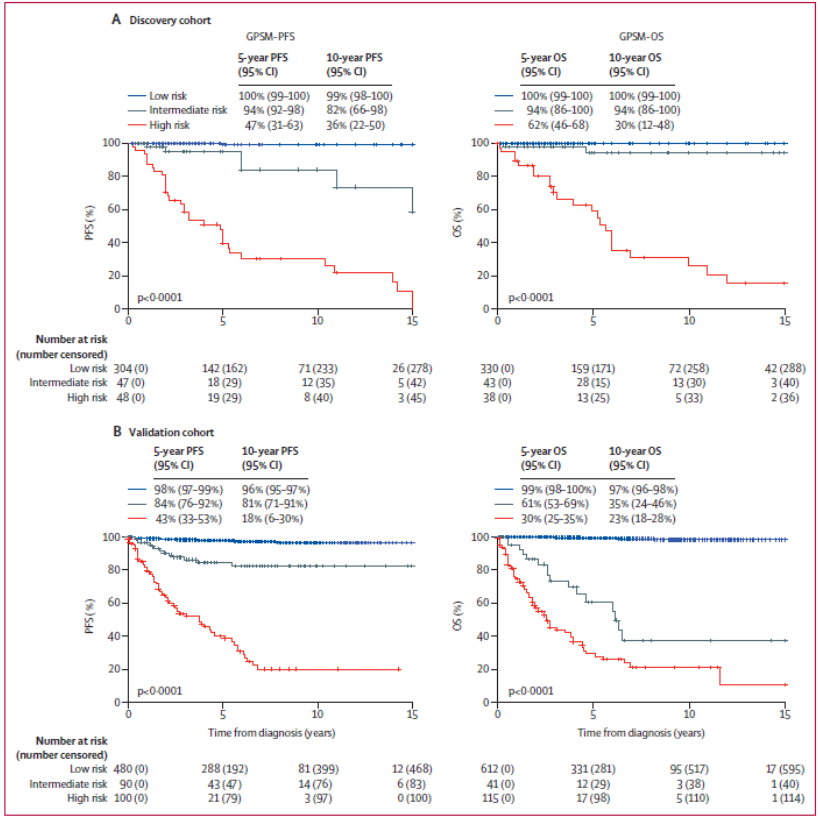


***Figure 1:*** **PFS and OS Kaplan-Meier estimates in patients with systemic mastocytosis stratified according to proposed GPSM scores in the discovery (A) and validation (B) cohorts**
GPSM=global prognostic score for mastocytosis. PFS=progression-free survival. OS=overall survival.

**Muñoz-González JI, et al. *Lancet Haematol*. 2021;8(3):e194-e204.**

# Mayo Alliance Prognostic System (MAPS)

**Table 2. Univariate analysis of risk factors for overall survival among 580 patients with SM**

| Variables | All patients univariate P (n = 580) | ISM univariate P (n = 291) | Advanced SM univariate P (n = 289) |
|---|---|---|---|
| Median age | **<.001** | **<.001** | **<.001** |
| Age >60 y | **<.001** | **<.001** | **<.001** |
| Males | **<.001** | .4 | .17 |
| Anemia sex adjusted | **<.001** | **<.001** | **<.001** |
| n eval = 574 | | n eval = 285 | |
| Leukocyte count | **<.001** | .3 | **.03** |
| n eval = 573 | | n eval = 284 | |
| Platelet count | **<.001** | .4 | **<.001** |
| n eval = 567 | | n eval = 280 | n eval = 287 |
| Platelet count < 150 × $10^9$/L | **<.001** | .08 | **<.001** |
| n eval = 567 | | n eval = 280 | n eval = 287 |
| Urticaria pigmentosa | **<.001** | .7 | **<.001** |
| n eval = 577 | | n eval = 288 | |
| Mast cell mediator symptoms | **<.001** | **.009** | .58 |
| n eval = 349 | | n eval = 153 | n eval = 196 |
| Palpable hepatomegaly | **<.001** | **.03** | **.01** |
| n eval = 579 | | | n eval = 288 |
| Palpable splenomegaly | **<.001** | **.006** | **<.001** |
| n eval = 578 | | n eval = 290 | n eval = 288 |
| Serum albumin | **<.001** | .4 | **<.001** |
| n eval = 389 | | n eval = 157 | n eval = 232 |
| Serum albumin <3.5 g/dL | **<.001** | .2 | **.01** |
| n eval = 389 | | n eval = 157 | n eval = 232 |
| Serum ALP | **<.001** | **<.001** | **<.001** |
| n eval = 547 | | n eval = 269 | n eval = 278 |
| Serum ALP > UNL | **<.001** | **.001** | **<.001** |
| n eval = 547 | | n eval = 269 | n eval = 278 |
| KITD816V | .4 | .1 | .16 |
| n eval = 357 | | n eval = 172 | n eval = 185 |
| ASXL1 mutated | **<.001** | No adverse mutations | **<.001** |
| n eval = 150 | | | n eval = 107 |
| RUNX1 mutated | **.03** | No adverse mutations | .05 |
| n eval = 150 | | | n eval = 107 |
| NRAS mutated | **.002** | No adverse mutations | **<.001** |
| n eval = 150 | | | n eval = 107 |
| Adverse mutations | **<.001** | No adverse mutations | **<.001** |
| n eval = 150 | | | n eval = 107 |
| Abnormal karyotype | **<.001** | .3 | **<.001** |
| n eval = 53 | | n eval = 8 | n eval = 45 |

Bold indicates statistical significance (P < .05).

**Figure 1. Clinical risk model.** (A) "Clinical" risk model for SM (n = 543) based on number of risk factors: (1) advanced SM vs ISM/SSM (HR, 2.7); (2) age >60 years (HR, 2.5); (3) platelets <150 × $10^9$/L (HR, 2.5); (4) anemia below sex-adjusted normal (HR, 2.2); and (5) serum ALP above normal range (HR, 2.1). HR (95% CI) values listed are calculated against the next lower risk level. (B-C) Application of the clinical risk model in advanced SM (n = 277) vs ISM/SSM (n = 266), respectively.

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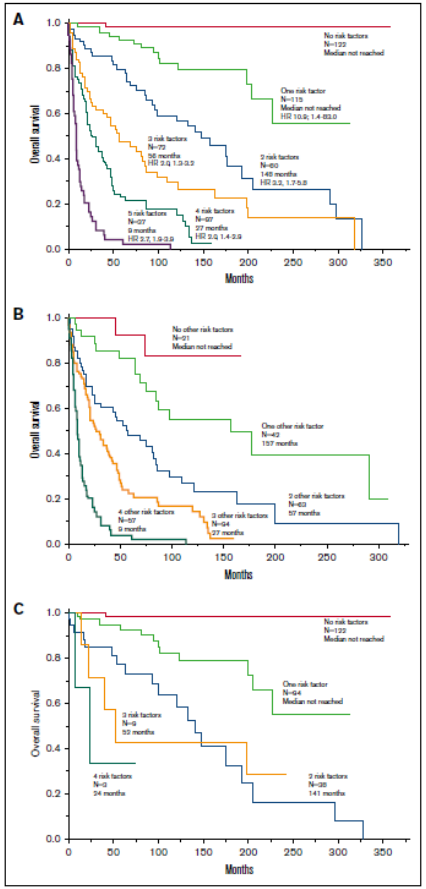



**Pardanani A, et al. *Blood Adv*. 2018;2(21):2964-2972.**

# Visual Aids to Facilitate SM Identification among Dermatologists

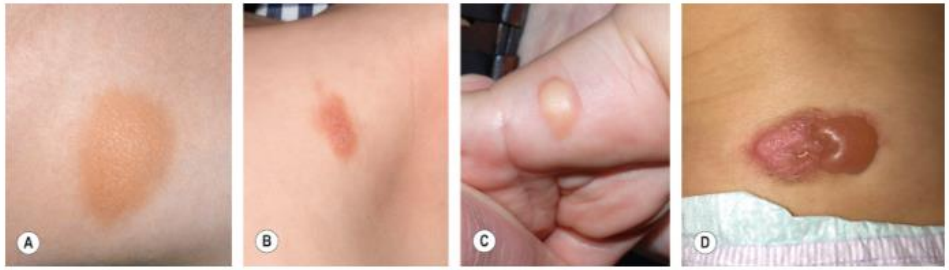


FIG. 118.4

**Mastocytomas in young children .**

Tan ( **A** ) and pink–tan ( **B** ) plaques with a leathery surface. **C** Swelling and a subtle rim of erythema resulting from urtication of a yellowish nodule on the wrist. **D** Bullae formation within a pink–brown plaque on the back.

A, Courtesy Antonio Torrelo, MD; B–D Courtesy Julie V. Schaffer, MD.

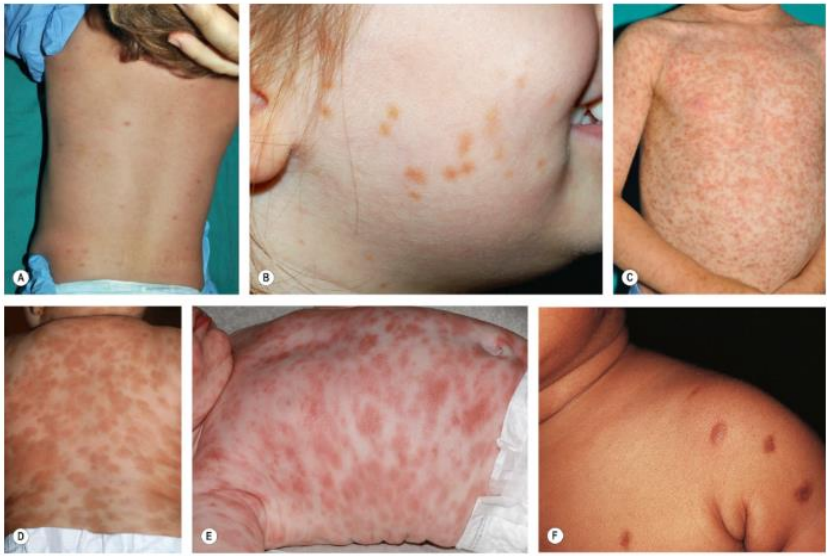


FIG. 118.5

**Maculopapular cutaneous mastocytosis in children .**

Patients can present with variable numbers and sizes of papules, which may be scattered ( **A** ), clustered ( **B** ), or nearly confluent ( **C** ), as well as predominantly plaques ( **D, E** ) or papulonodules ( **F** ). As in solitary lesions, the degree of associated hyperpigmentation can vary. Note the Darier sign ( **C , D** ).

A, C, Courtesy Antonio Torrelo, MD; B, D, E Courtesy Julie V. Schaffer, MD.

**Bolognia JL, et al. *Dermatology*. 5th ed. Elsevier; 2024.**

# Visual Aids to Facilitate SM Identification among Dermatologists

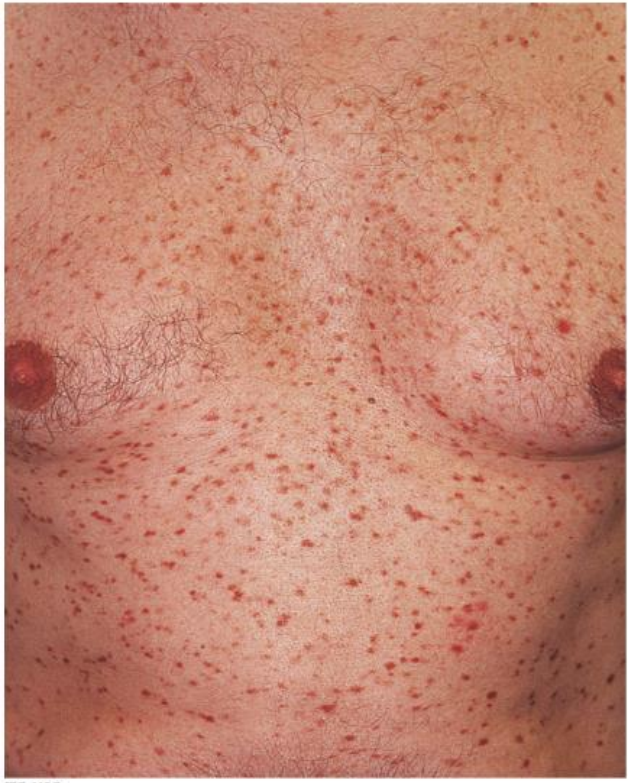


FIG. 118.7

Adult maculopapular mastocytosis ("urticaria pigmentosa") .

Numerous reddish-brown macules and papules.

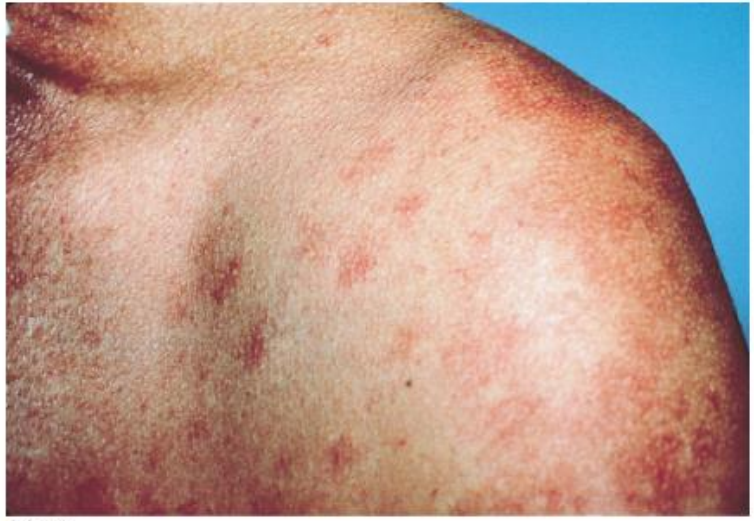


FIG. 118.8

Telangiectasia macularis eruptiva perstans .

Multiple lesions composed of telangiectasias are present.

**Bolognia JL, et al. *Dermatology*. 5th ed. Elsevier; 2024.**

# Key Learning Points

- We now have harmonized diagnostic criteria and definitions
- B-findings and C-findings affect diagnosis, prognosis, and workup/treatment
- There are multiple prognostic tools
- There is a range of dermatologic manifestations in children and adults

# Current and Emerging Therapies for SM

# National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines in Oncology for Systemic Mastocytosis

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Systemic Mastocytosis V.1.2026.
 Accessed February 17, 2026.
To view the most recent and complete version of the guideline, go online to NCCN.org.
NCCN makes no warranties of any kind whatsoever regarding their content, use, or application, and disclaims any responsibility for their application or use in any way.

**Image source: https://en.wikipedia.org/wiki/Ludwig_Wittgenstein.**

# NCCN Guidelines®: First- and Later-Line Care

**Acute Flares**

If anaphylaxis, then epi!

**Chronic Symptoms**

| | |
|---|---|
| Anti-mast cell mediators: | H1 and H2 antihistamines (eg, cetirizine 10-20 mg PO twice daily; famotidine 20 mg PO twice daily)<br>Anti-leukotriene receptor (montelukast)<br>Leukotriene generation blockers (ASA, zafirlukast) |
| Mast cell stabilizers: | Cromolyn sodium (GI), ketotifen, omalizumab |
| Cytoreduction: | Avapritinib, midostaurin, cladribine, pegylated INF-$\alpha$2 |

**Cutaneous Management and Monitoring**

**ASA = aspirin; IFN = interferon.**

# C-KIT Receptor Structure and Function

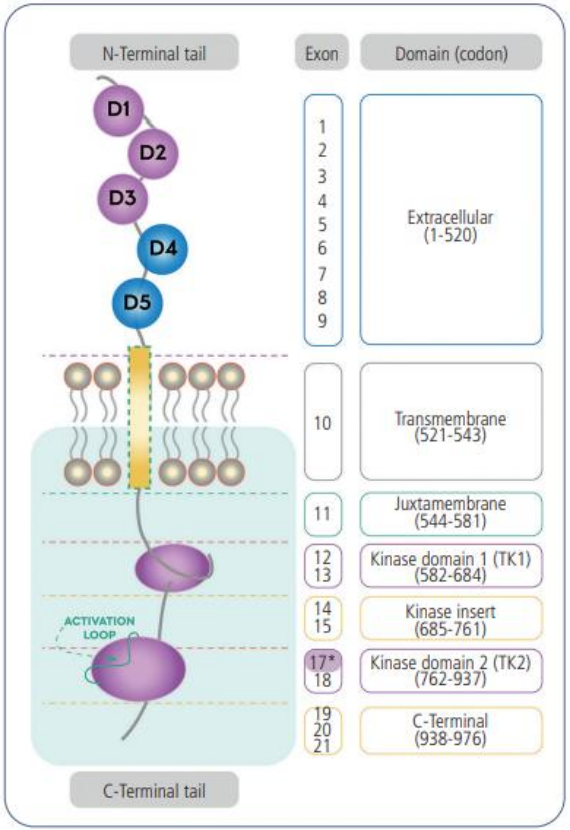



**Figure 1.** Structure of the KIT receptor.
*Exon 17: the most common *KIT* mutation Asp816Val (D816V) is localized here.

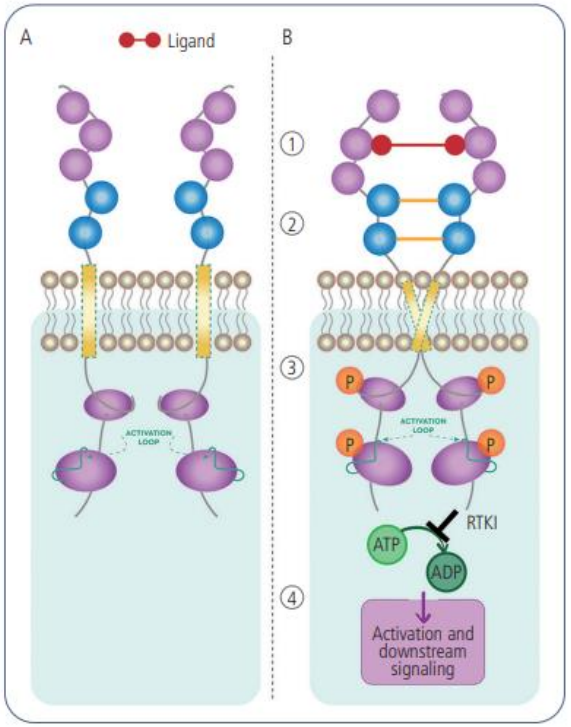



**Figure 2.** Immunological processes occurring during c-kit activation. A, Inactive c-kit (monomer). B, Active c-kit (homodimerization). The following consecutive processes occur: 1, Binding of stem cell factor (SCF) to D1-D3 domains; 2, Conformational changes; 3, Autophosphorylation, which entails that ATP binds to the ATP binding region, the TK1 domain (N-lobe); and 4, Activation of downstream signaling by full activated c-kit.
⊢ Inhibits the action of.
ATP indicates adenosine triphosphate; ADP, adenosine diphosphate; RTKI, receptor tyrosine kinase inhibitor.

Carpio-Escalona LV, et al. *J Investig Allergol Clin Immunol*. 2025;35(5):328-340.

# Mechanism of TKIs and Their Role in Treatment

- Since the c-KIT receptor drives activation, migration, development, and…
- Some mutations increase receptor kinase activity, then…
- The obvious strategy is to block that kinase

Doing so should prevent both acute exacerbations and limit chronic symptoms

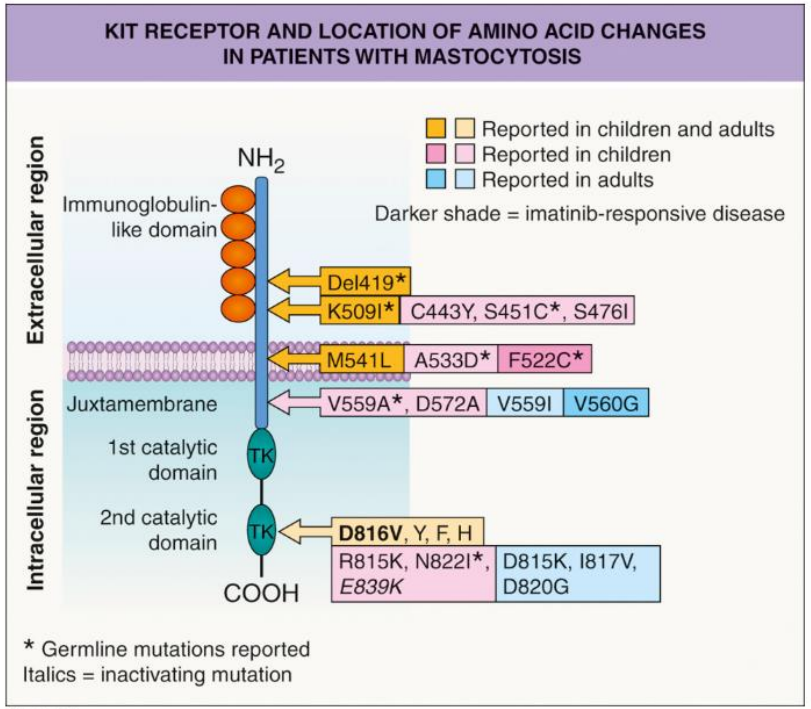



FIG. 118.2

KIT receptor and location of amino acid changes (due to *KIT* mutations) in pediatric and adult patients with mastocytosis .

**TKIs = tyrosine kinase inhibitors.**

**Bolognia JL, et al. *Dermatology*. 5th ed. Elsevier; 2024.**

# Available and Emerging TKIs

- Approved agent
  - Avapritinib: Indications and clinical trial data
- Investigational therapeutics for ISM and AdvSM
  - Elenestinib
  - Bezuclastinib
  - Ripretinib
  - BLU-808
- Treatment-related adverse events

# Phase 2 PIONEER Study

ORIGINAL ARTICLE

## Avapritinib versus Placebo in Indolent Systemic Mastocytosis

Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

# Avapritinib for ISM

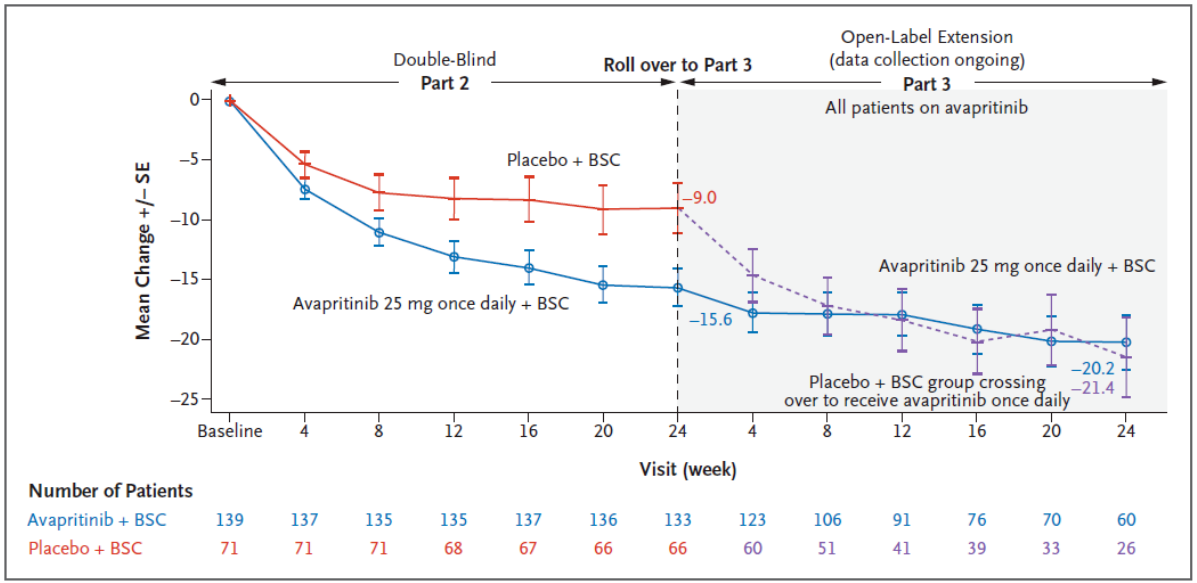
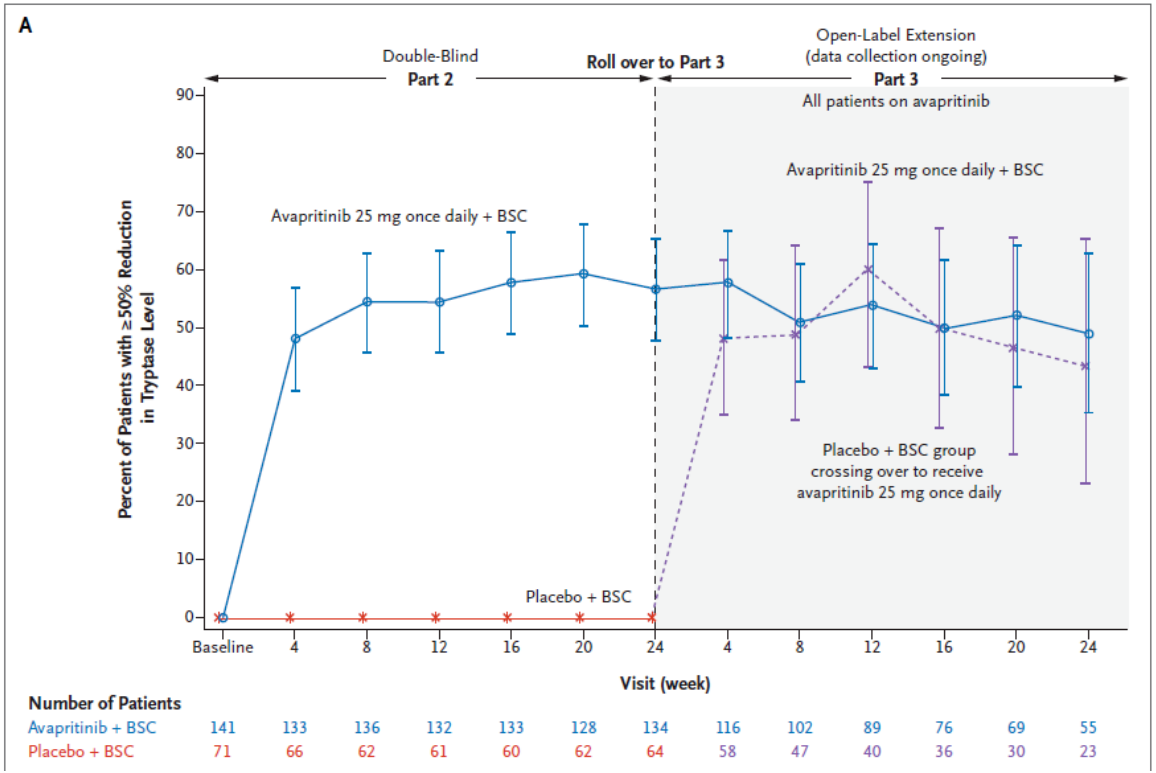



Figure 2. Indolent Systemic Mastocytosis Symptom Assessment Form Total Symptom Score over Time with Avapritinib versus Placebo.

Analysis was on the basis of the intent-to-treat population; however, patients using high-dose glucocorticoids (three patients treated with avapritinib and one in the placebo group) were included in this analysis, but per the prespecified statistical analysis plan, these patients were not included in the primary end point calculation because of the potential for high-dose glucocorticoids to influence symptoms. Total symptom score ranges from 0 to 110, with higher numbers indicating more severe symptoms. The "I" bars represent the standard error. BSC denotes best supportive care; and SE, standard error.

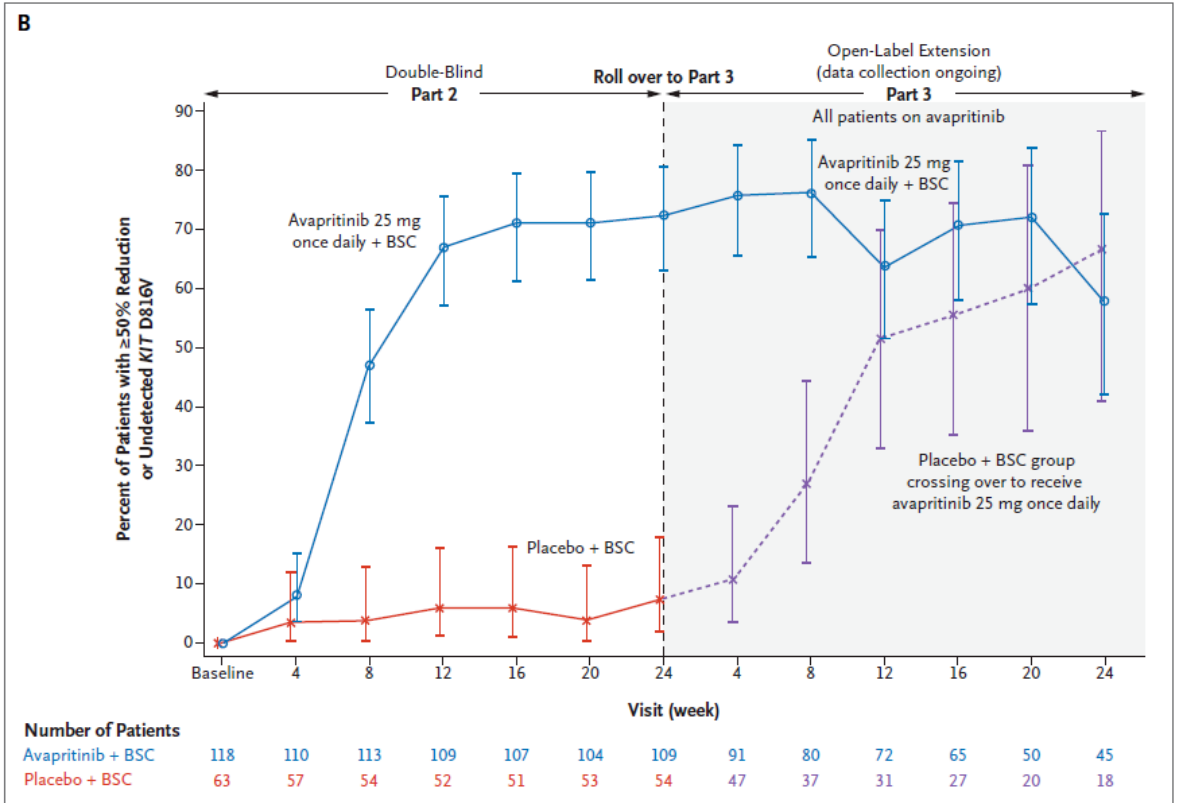
**Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.**

# Avapritinib for ISM



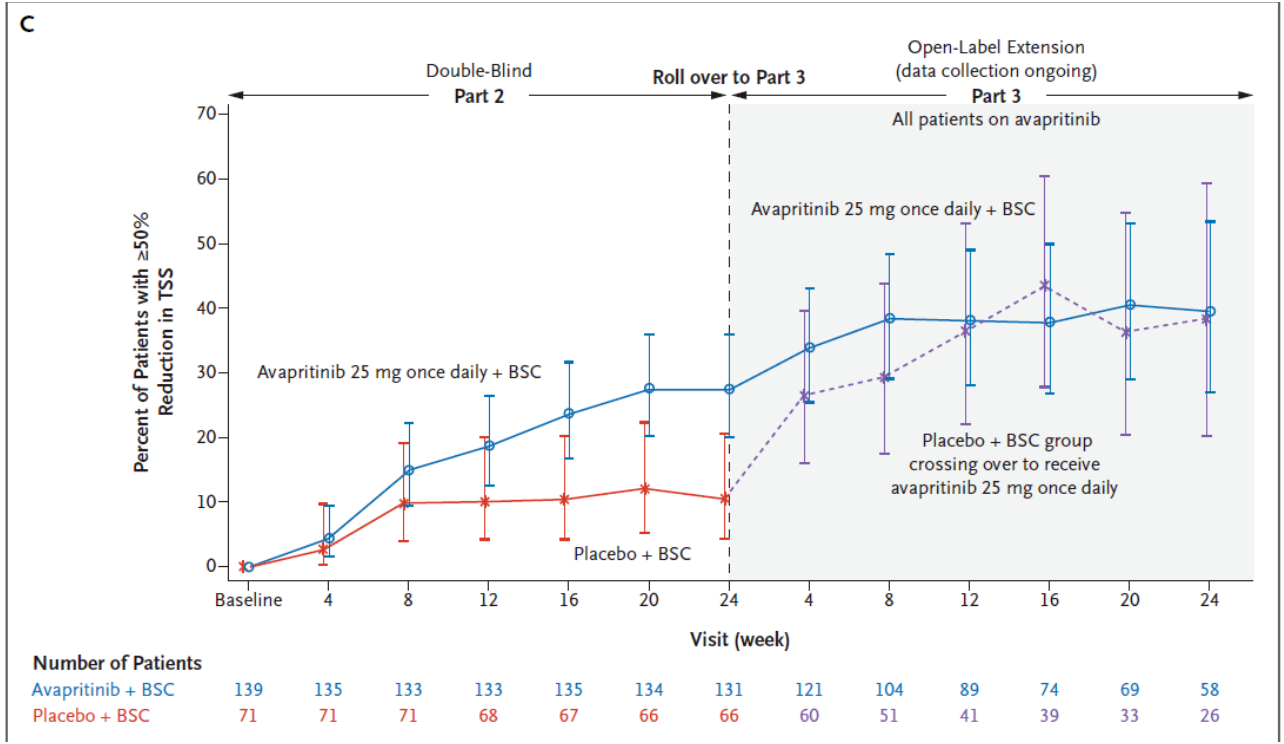

Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

# Avapritinib for ISM



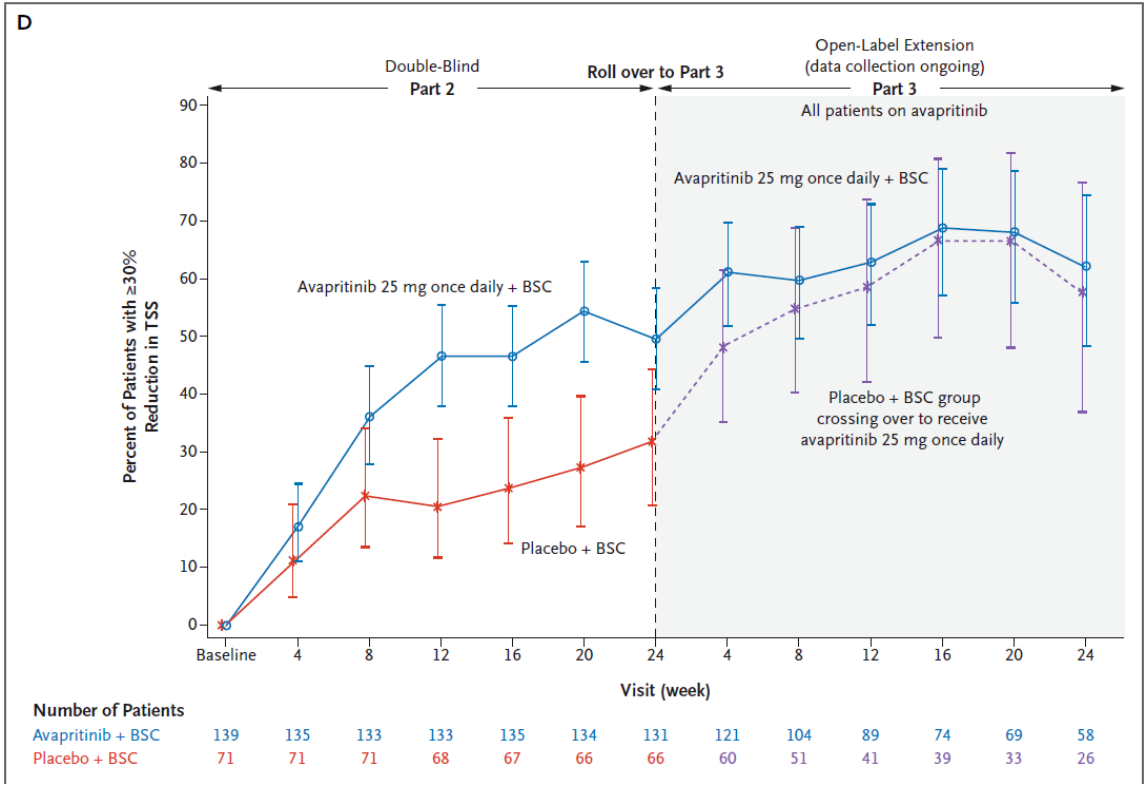

Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

# Avapritinib for ISM




Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

# Avapritinib for ISM




Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

# Avapritinib Safety Summary: PIONEER 2

**Table 2. Safety Summary.***

| Summary of Adverse Events | Avapritinib 25 mg Once Daily† (n=141) | Placebo‡ (N=71) |
|---|---|---|
| Any AEs§ — n (%) | 128 (90.8) | 66 (93.0) |
| Most common AEs (≥5% of patients) — n (%) | | |
| Headache | 27 (19.1) | 14 (19.7) |
| Nausea | 18 (12.8) | 12 (16.9) |
| Covid-19 | 17 (12.1) | 8 (11.3) |
| Dizziness | 16 (11.3) | 6 (8.5) |
| Diarrhea | 15 (10.6) | 8 (11.3) |
| Fatigue | 14 (9.9) | 6 (8.5) |
| Flushing | 13 (9.2) | 3 (4.2) |
| Edema peripheral | 12 (8.5) | 3 (4.2) |
| Arthralgia | 11 (7.8) | 5 (7.0) |
| Pruritus | 11 (7.8) | 5 (7.0) |
| Face edema | 10 (7.1) | 1 (1.4) |
| Blood alkaline phosphatase increased | 9 (6.4) | 1 (1.4) |
| Periorbital edema | 9 (6.4) | 2 (2.8) |
| Abdominal pain | 8 (5.7) | 4 (5.6) |
| Insomnia | 8 (5.7) | 2 (2.8) |
| Alanine aminotransferase increased | 7 (5.0) | 2 (2.8) |
| Alopecia | 6 (4.3) | 4 (5.6) |
| Hypertension | 6 (4.3) | 5 (7.0) |
| Nasopharyngitis | 6 (4.3) | 5 (7.0) |
| Vomiting | 6 (4.3) | 4 (5.6) |
| Urinary tract infection | 5 (3.5) | 5 (7.0) |
| Grades 1 and 2 AEs — n (%) | 98 (69.5) | 51 (71.8) |
| Grade ≥3 AEs — n (%) | 30 (21.3) | 15 (21.1) |
| AEs with incidence ≥2 times that of placebo (≥5% of patients) — n (%) | | |
| Flushing | 13 (9.2) | 3 (4.2) |
| Edema peripheral | 12 (8.5) | 3 (4.2) |
| Face edema | 10 (7.1) | 1 (1.4) |
| Blood alkaline phosphatase increased | 9 (6.4) | 1 (1.4) |
| Periorbital edema | 9 (6.4) | 2 (2.8) |
| Insomnia | 8 (5.7) | 2 (2.8) |
| Serious AEs¶ — n (%) | 7 (5.0) | 8 (11.3) |
| AEs leading to dose interruption — n (%) | 12 (8.5) | 9 (12.7) |
| AEs leading to dose reduction — n (%) | 2 (1.4) | 1 (1.4) |

* There were no statistically significant differences in the incidence of AEs between avapritinib and placebo. AE denotes adverse event.

**Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.**

# Avapritinib for ISM: Treatment-Related Adverse Events

**Table S5.** Summary of treatment-related adverse events (TRAEs)*.

| | Avapritinib 25 mg *qd*† (n=141) | Placebo‡ (N=71) |
|---|---|---|
| Any TRAEs, n (%) | 77 (54.6) | 32 (45.1) |
| Grade 1 to 2 TRAEs | 74 (52.4) | 30 (42.3) |
| Grade ≥3 TRAEs | 3 (2.1) | 2 (2.8) |
| Most common TRAEs (≥5% of patients) | | |
| Headache | 11 (7.8) | 7 (9.9) |
| Nausea | 9 (6.4) | 6 (8.5) |
| Peripheral edema | 9 (6.4) | 1 (1.4) |
| Periorbital edema | 9 (6.4) | 2 (2.8) |
| Dizziness | 4 (2.8) | 5 (7.0) |
| Related SAEs | 0 | 0 |
| TRAEs leading to discontinuation | 2 (1.4) | 1 (1.4) |

Note: There were no statistically significant differences in the incidence of AEs between avapritinib and placebo.
*TRAE refers to treatment-related AEs as assessed by investigators;
†Avapritinib 25 mg orally qd plus BSC (termed avapritinib); ‡Placebo plus BSC (termed placebo);
AEs, adverse events; *qd*, once daily; SAEs, serious adverse events; TRAEs, treatment-related adverse events.

**Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.**

# Avapritinib All-Cause Serious Adverse Events (SAEs): PIONEER 2

**Table S6.** Summary of All Cause SAEs*.

| All cause SAEs, n (%) | Avapritinib 25 mg *qd*† (n=141)§ | Placebo‡ (n=71)‖ |
|---|---|---|
| Abdominal pain | 1 (0.7) | 0 |
| Acute myeloid leukemia | 1 (0.7) | 0 |
| Anaphylactic reaction | 1 (0.7) | 1 (1.4) |
| Bacteremia | 1 (0.7) | 0 |
| COVID-19 pneumonia | 1 (0.7) | 1 (1.4) |
| Chest pain | 1 (0.7) | 0 |
| Pelvic hematoma | 1 (0.7) | 0 |
| Adenovirus infection | 0 | 1 (1.4) |
| Allergy to vaccine | 0 | 1 (1.4) |
| COVID-19 | 0 | 1 (1.4) |
| Foot deformity | 0 | 1 (1.4) |
| Hypertension | 0 | 1 (1.4) |
| Mastocytosis | 0 | 1 (1.4) |
| Mental status changes | 0 | 1 (1.4) |
| Tachycardia | 0 | 1 (1.4) |

*Patients may have experienced more than one SAE (events reported in a different system class / preferred term per MedDRA v.25.0), therefore the number of events reported may be greater than the overall number of patients reporting SAEs; †Avapritinib 25 mg orally *qd* plus BSC (termed avapritinib); ‡Placebo plus BSC (termed placebo). §7 patients experienced one SAE each; ‖6 patients experienced one SAE each; 1 patient experienced tachycardia and hypertension; 1 patient experienced pneumonia and mental status changes.
BSC, best supportive care; COVID-19, Coronavirus disease 2019; *qd*, once daily; SAEs, serious adverse events.

**Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.**

# Investigational Therapeutics for ISM and AdvSM

- Elenestinib = a new-generation KIT D816V inhibitor
- Bezuclastinib = a new-generation inhibitor of KIT with mutations in exons 9, 11, 17, and 18, including, D816V; limited CNS penetration
- Ripretinib = a type II switch-pocket control inhibitor (approved for and used in patients with advanced GIST) that antagonizes KIT with exon 17 mutations, including D816V
- BLU-808 = a small-molecule wild-type (wt) KIT inhibitor
- **Each of these agents is showing promise for treatment of systemic mastocytosis in Phase 1 and 2 trials**

**CNS = central nervous system; GIST = gastrointestinal stromal tumor.**
**Costanzo G, et al. *Curr Opin Allergy Clin Immunol*. 2025;25(4):277-292.**

**Table 1.** The table shows the present, past, and imminent history of cytoreductive and biological therapy for systemic mastocytosis. The mechanism of action, the main trials conducted, the indications available based on the studies carried out, and, in brackets, those for which some data are available in the literature, the main adverse reactions, approvals, warnings and an essential bibliography are specified. Where not reported, references are available in the text

| Name | Mechanism of action | Relevant trial | Main adverse events | Indications | Notes | Essential references |
|---|---|---|---|---|---|---|
| Cladibrine | Purine analogue | none | Myelosuppression, increased opportunistic infection | advSM (non-AdvSM) | \ | [45] |
| Interferon-alfa | Cytokine | (63) | Fatigue, flu-like symptoms, cytopenia, hypothyroidism, neuropsychiatric | advSM | \ | [45] |
| Hydroxyurea | Oral ribonucleotide reductase inhibitor | none | Myelosuppression | advSM | \ | [45] |
| Nilotinib (AMN107) | c-KITi | NCT00109707 | Myelosuppression and increased opportunistic infection | advSM | Little used | [69] |
| Thalidomide | IKKα-i | (73) | myelosuppression | advSM | Little used | [73] |
| Avapritinib (BLU-285) | c-KITi | EXPLORER (NCT02561988), PATHFINDER (NCT05155605), NCT04695431, PIONEER (NCT03731260) | Fatigue/asthenia, cognitive impairment, oedema, and diarrhoea | advSM ISM | FDA/EMA: advSM<br>FDA/EMA: ISM<br>Not recommended in patients with platelet counts $<50 \times 10^9$/L | [93,185] |
| Midostaurin (PKC412) | c-KITi | NCT00782067, (76), NCT01920204 | Nausea/vomiting, diarrhoea | advSM (nonadvSM) | FDA/EMA: advSM | [81] |
| Imatinib mesylate (STI 571) | c-KITi | (186) | Nausea/vomiting, diarrhoea | advSM | FDA: ASM without the D816V c-Kit mutation or with c-Kit mutational status unknown | [45,96] |
| Dasatinib (BMS-354825) | c-KITi | (105) | Nausea/vomiting, diarrhoea | advSM | little used | See trial |
| Omalizumab | anti-IgE | (123 124) XOLMA, ACTRN12613001096741, | Rash on the injection site | prevent MC-activation-related symptoms | Associated to VIT | [125] |
| Ripretinib (DCC-2618) | c-KITi | NCT02571036, | Palmar-plantar erythrodysesthesia and alopecia, nausea, fatigue, diarrhoea | advSM | Novel | [137] |
| Bezuclastinib (CGT9486) | c-KITi | APEX (NCT04996875), (SUMMIT, NCT05186753) | Air colour changes, cytopenias, increased ALT/AST, fatigue, periorbital and peripheral oedema | advSM ISM | Novel | [144] |
| Masitinib | c-KITi | (151), NCT04333108 | Oedema, nausea, diarrhoea, muscle spasms, and rash | nonadvSM | Novel | [150] |

**Costanzo G, et al. *Curr Opin Allergy Clin Immunol*. 2025;25(4):277-292.**

# Key Learning Points

- Avapritinib is proven and approved for ISM
  - Avapritinib provided sustained and durable improvements in skin manifestations of indolent SM after a median follow-up of 3 years
- Avapritinib is generally well-tolerated and safe
- A number of KIT inhibitors, specific for wt or mutant KIT, are on the way

# Multidisciplinary Management of SM

# Role of the Dermatologist in Diagnosis and Risk Stratification

- Understanding the full spectrum of disease for early identification
  – (You are the vanguard at the border and at first encounter!)
- Recognizing cutaneous clues to systemic disease
  – (You have the trained eyes and mind!)
- Patient education and shared decision-making strategies
- <u>Timely referral and coordinated care</u>
  – Primary care, hematology, allergy/immunology, maternal/fetal medicine, anesthesiology, psychiatry, etc

**Image source: https://screenrant.com/lotr-movies-council-elrond-changes-hurt-book-fate-theme-explainer/.**

# Key Learning Points

- Mastocytosis is complex
- The symptoms appear in a number of organ systems
- It's reasonable to coordinate efforts among specialists and other caregivers
- It's, therefore, a team effort
- You're the scout, ranger, and rightful monarch of your domain, as well as a member of the team

**Image sources: https://askmiddlearth.tumblr.com/post/44766092094/aragorn-the-tracker; https://en.wikipedia.org/wiki/Aragorn.**

masterclasses in dermatology
annual meeting
PRESENTED BY THE dermatologist

# Thank You!