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Advancing Care in Systemic Mastocytosis: From Diagnosis to Targeted Treatment and Multidisciplinary Management

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Disclosures

- **Sarina B. Elmariah, MD, PhD, MPH, FAAD:** Consultant – Bambusa Therapeutics, Blueprint Medicines, Celldex Therapeutics, Disc Medicine, Eli Lilly, Galderma, Incyte, Leo Pharma, New Frontier Bio, Novartis, Pfizer, Regeneron, Sanofi-Genzyme, ZenZema; investigator –Celldex, Galderma
- **Cem Akin, MD, PhD:** Consultant – Blueprint Medicines, Cogent Biosciences; grant/research support – Blueprint Medicines, Cogent Biosciences

Learning Objectives

- Identify the cutaneous and systemic manifestations of SM using current guideline-based criteria to support appropriate initial evaluation and referral for systemic assessment
- Differentiate the mechanisms of action, efficacy, and safety of approved and emerging targeted therapies for SM
- Integrate multidisciplinary management strategies for patients with SM, including coordination across specialties, and patient-centered, symptom-directed care



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Classification of SM and Diagnostic Criteria

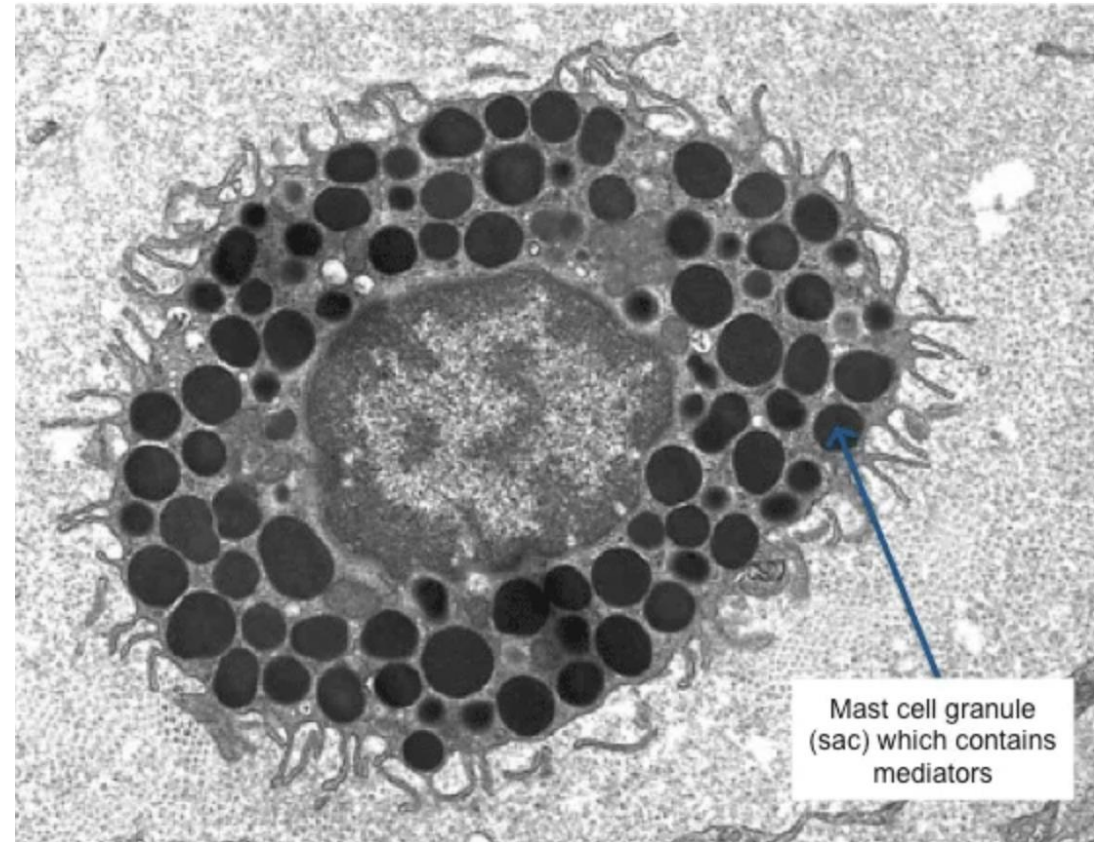
Sarina B. Elmariah, MD, PhD, MPH, FAAD

Overall Agenda

1. Brief review of mast cell function and impact of mediator release
2. Presentation and classification of systemic mastocytosis
3. Diagnostic criteria for systemic mastocytosis
4. Therapeutic landscape and pipeline in systemic mastocytosis
5. The role of the dermatologist in management of systemic mastocytosis

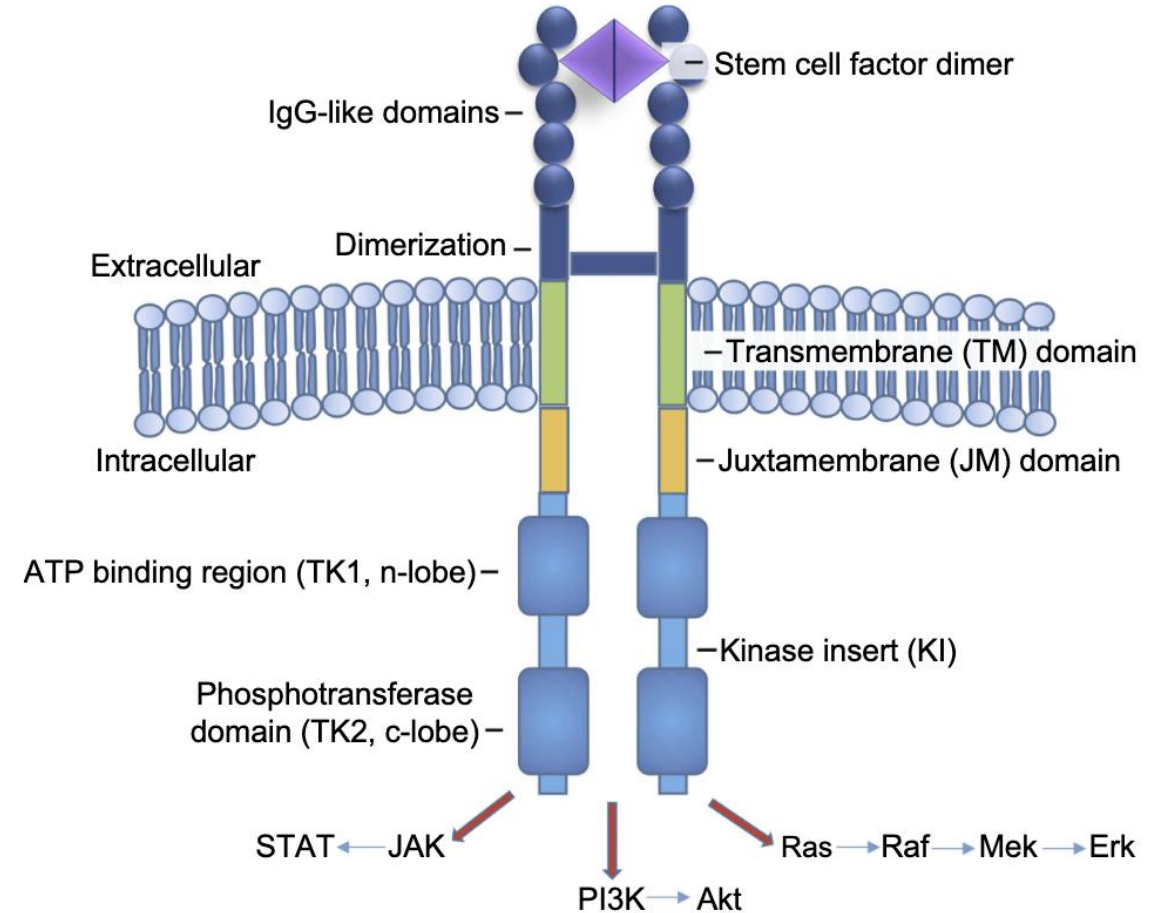
Mast Cell Development and Survival

- Originate from CD34+ progenitor cells in the bone marrow, differentiate along the myeloid pathway, and migrate to peripheral tissues where they fully mature
 - Identified by co-expression of CD117 (KIT) and FcεRI
- Require KIT activation by the ligand stem cell factor (SCF), expressed by fibroblasts and endothelial cells
- Reside in connective tissues and mucosal/barrier tissues (including skin, gut, lung)



KIT Receptor Drives MC proliferation, Differentiation, and Survival

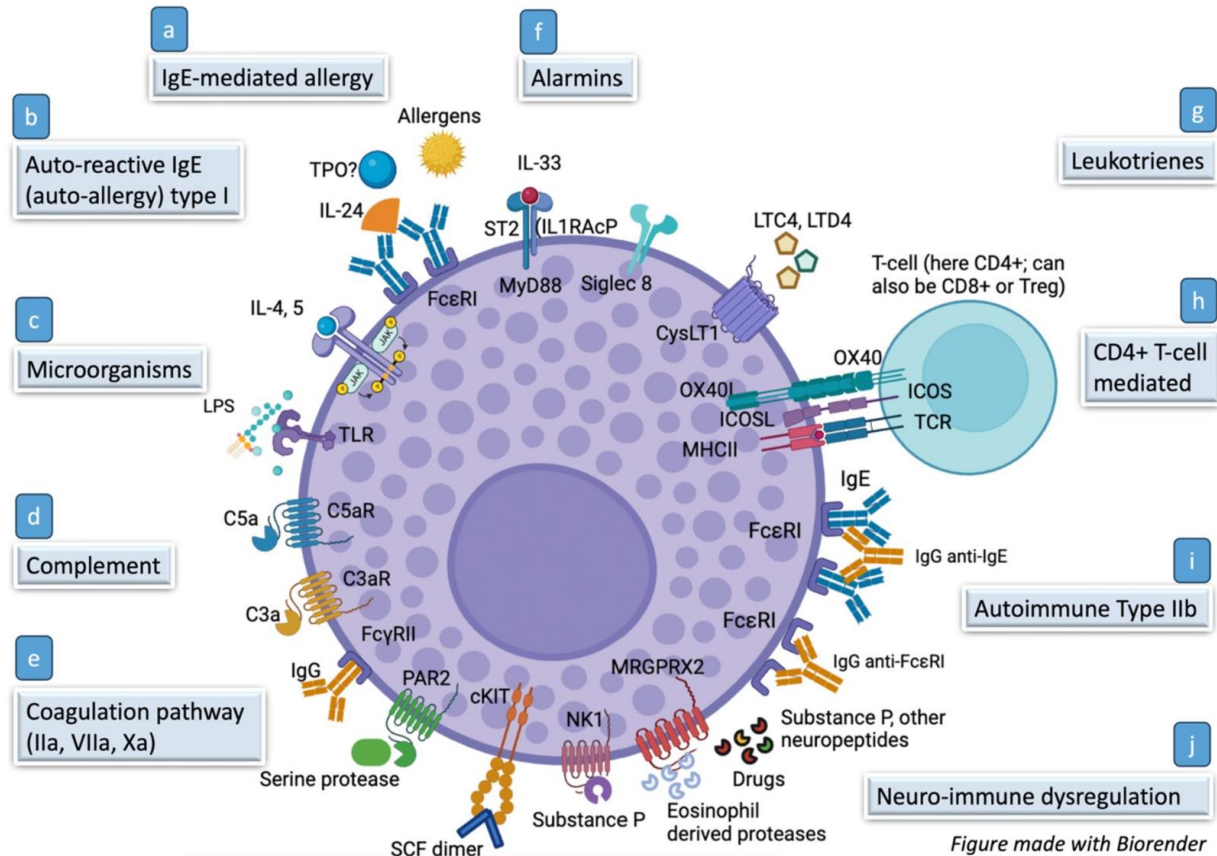
- KIT is a growth factor receptor with intrinsic tyrosine kinase activity
- Normal KIT signaling drives MC proliferation, differentiation, survival, and activation as a functioning part of the immune response
- Gain-of-function mutations (eg. KIT D816V) lead to SCF-independent receptor activation and signaling, resulting in survival, clonal expansion, and uncontrolled activation of MCs



MC = mast cell.

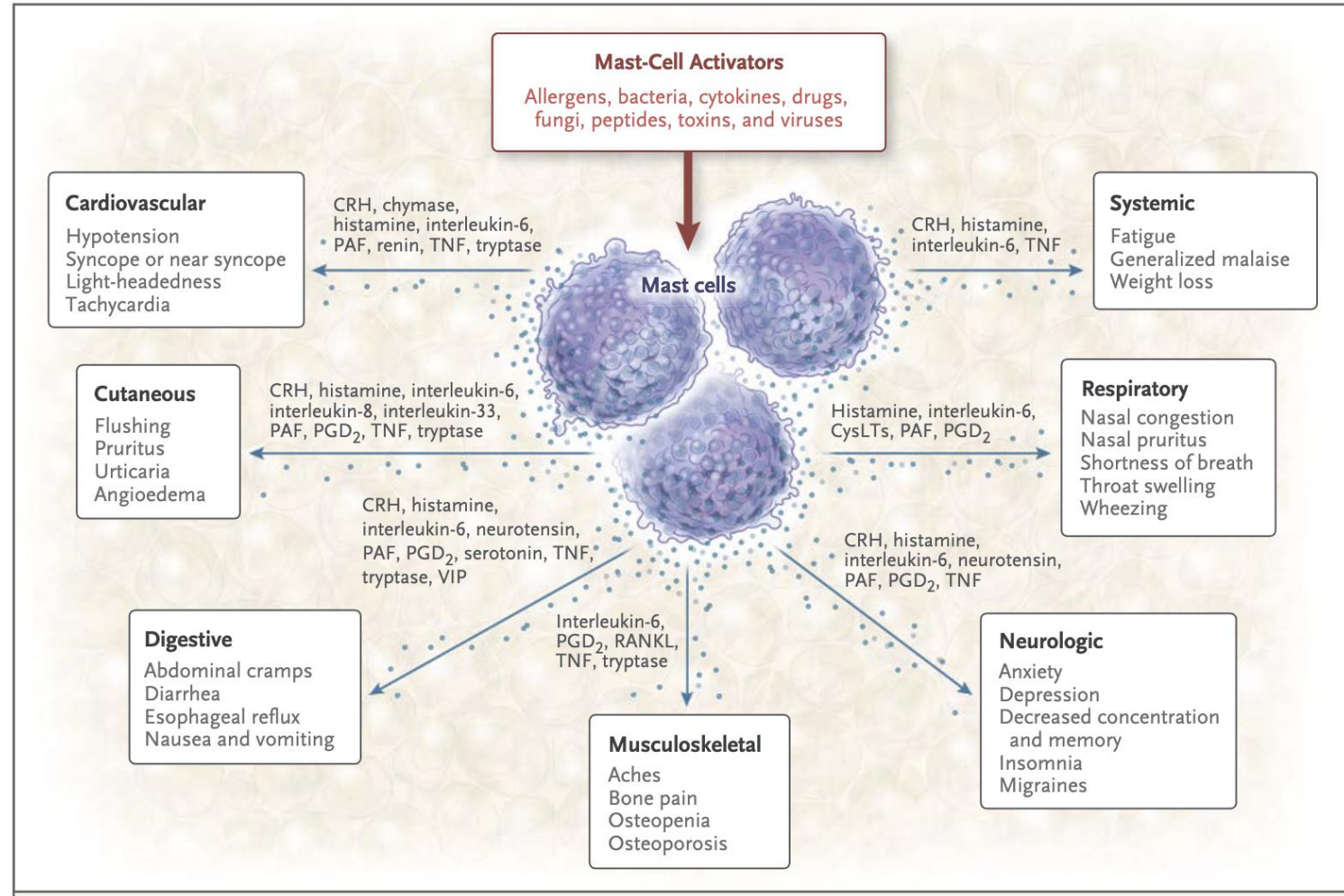
Theoharides TC, et al. *N Engl J Med*. 2015;373(2):163-172. Gilreath JA, et al. *Clin Pharmacol*. 2019;11:77-92. Pardanani A. *Am J Hematol*. 2023;98(7):1097-1116. Metcalfe DD, et al. In: *Mastocytosis*. Springer, 2020.

Mast Cell Degranulation

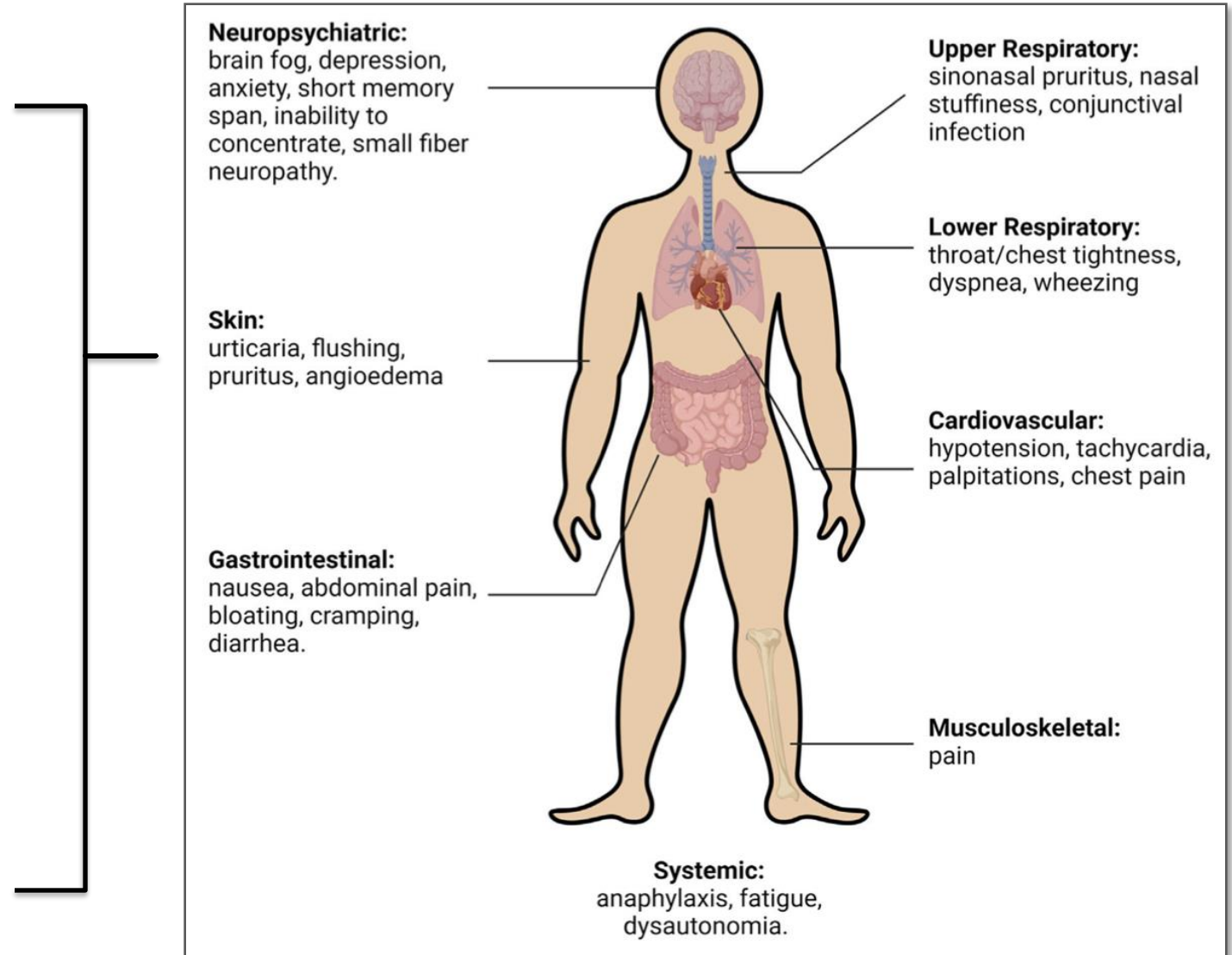


- Triggered by
 - Immunologic factors
 - Non-immunologic factors
- Mast cell mediators act on multiple cell types
- Mast cell degranulation is amplified by other immune cells (eg. eosinophils, activated T-cells) or nerves (eg. neuropeptides)

Mast Cell Mediators



Clinical Manifestations of MC Activation





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Classification of SM and Diagnostic Criteria

Introduction to Signs, Symptoms, Classification, and More

Overview of Mastocytosis

- Heterogeneous group of disorders resulting from proliferation and accumulation of abnormal MCs in one or more organ systems
 - Cutaneous mastocytosis (CM) – skin is always involved
 - *Criteria for SM are not fulfilled*
 - *All variants considered non-advanced by WHO*
- SM – bone marrow and/or multiorgan involvement which *may* or *may not* include skin
 - *Variants may be non-advanced (indolent or smoldering SM) or advanced (aggressive SM, SM with associated hematologic malignancy, mast cell leukemia)*
- Mast cell sarcoma
 - *Advanced, highly aggressive, and fatal variant*

WHO = World Health Organization.

Akin C, Metcalfe DD. *Annu Rev Med.* 2004;55:419-432. Andersen PK, et al. *Int J Epidemiol.* 2012;41(3):861-870. Metcalfe DD. *J Invest Dermatol.* 1991;96(3 Suppl):2S-4S. Valent P, et al. *Br J Haematol.* 2003;122(5):695-717.

Mastocytosis Classification

- In 2022, the classification and diagnostic criteria for mastocytosis were revised by the WHO 5th edition and the International Consensus Classification (ICC)

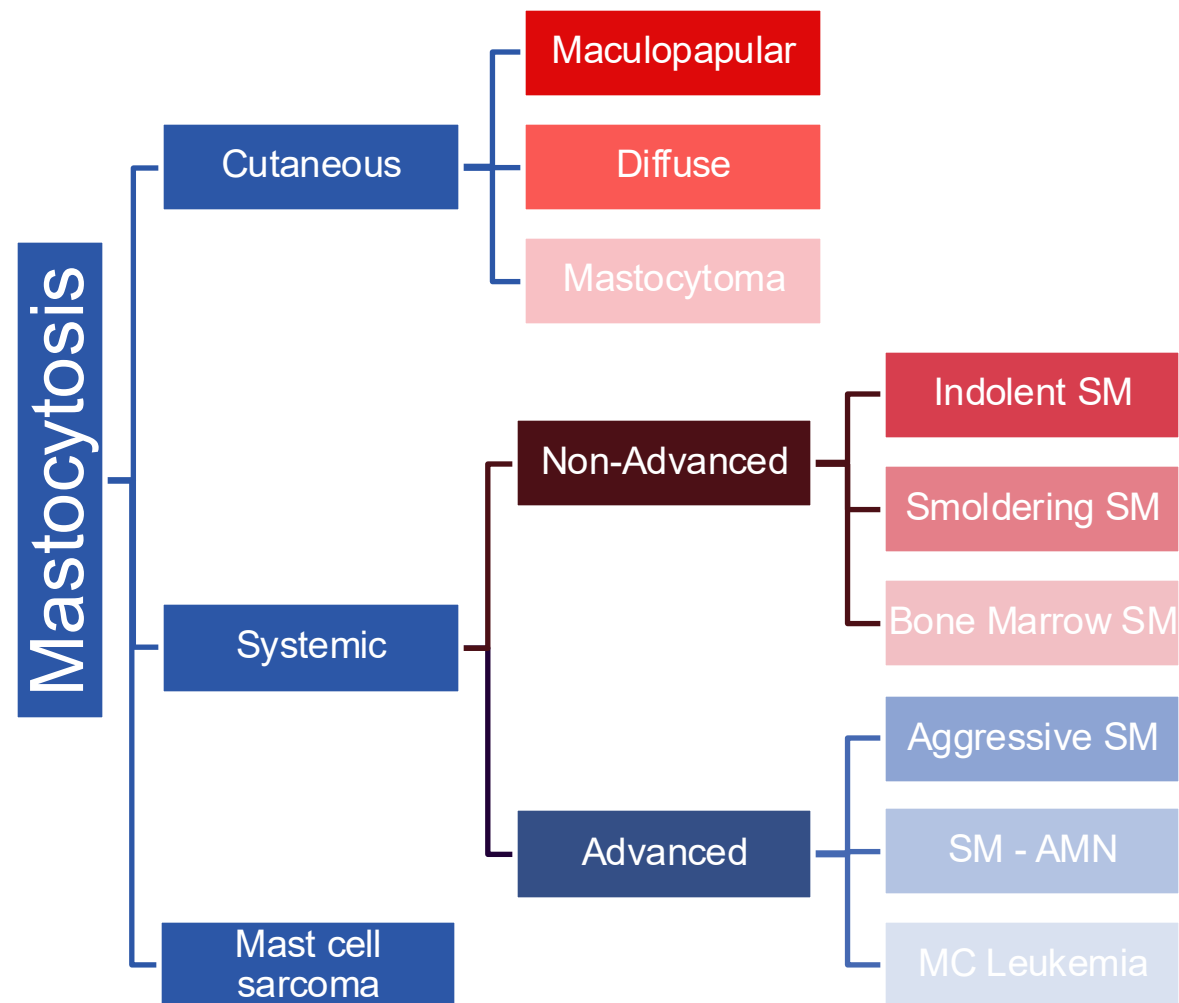
WHO 5th Edition ^{1,a}	International Consensus Classification (ICC) ²
Cutaneous mastocytosis	
• Urticaria pigmentosa/maculopapular cutaneous mastocytosis	• Urticaria pigmentosa/maculopapular cutaneous mastocytosis
‣ Monomorphic	• Diffuse cutaneous mastocytosis
‣ Polymorphic	• Mastocytoma of skin
• Diffuse cutaneous mastocytosis	
• Cutaneous mastocytoma	
‣ Isolated mastocytoma	
‣ Multilocalized mastocytoma	
Systemic mastocytosis	
• Bone marrow mastocytosis (BMM) ^b	• Indolent SM
• Indolent SM	‣ Bone marrow mastocytosis ^b
• Smoldering SM	• Smoldering SM
• Aggressive SM	• Aggressive SM
• SM with an associated hematologic neoplasm ^c	• SM with an associated myeloid neoplasm (SM-AMN) ^c
• Mast cell leukemia	• Mast cell leukemia
Mast cell sarcoma	

SM-AMN = SM with associated myeloid neoplasm.

Gotlib J, et al. *J Natl Compr Canc Netw*. 2024;22(2D):e240030. Khoury JD, et al. *Leukemia*. 2022;36:1703-1719. Arber DA, et al. *Blood*. 2022;140:1200-1228.

Mastocytosis Classification

- Prevalence of SM is estimated at up to ~1 in 5,000 adults
- Non-advanced SM represents majority of patients (~85%)
 - Of patients with non-adv SM, ISM (~95%) is the most common, followed by SSM (5%)
- Advanced SM arises in a minority of patients (~15%)
 - Up to 67% of patients with advanced SM have an associated neoplasm



ISM = indolent SM.

Akin C, Metcalfe DD. *Annu Rev Med.* 2004;55:419-432. Andersen PK, et al. *Int J Epidemiol.* 2012;41(3):861-870. Metcalfe DD. *J Invest Dermatol.* 1991;96(3 Suppl):2S-4S. Valent P, et al. *Br J Haematol.* 2003;122(5):695-717.

Who Develops Mastocytosis?

Prevalence: 1-2 per 10,000

Annual incidence: 1 per 100,000

- **Pediatric**

- Onset occurs before 2 years of age in > 50% of pediatric mastocytosis
- Equal gender distribution
- CM is more common than SM
 - Maculopapular CM -- 40-75%
 - Cutaneous mastocytoma -- 20–50%
 - Diffuse CM (DCM) -- 3–11%
- Great prognosis
 - Majority experience resolution by adolescence
 - Persistence into adulthood is usually associated with systemic involvement

- **Adult**

- Mean age at onset reported between 20-61 years
- Slight female predominance (50-60% female)
- SM is much more common (> 95%)
 - CM is rare – maculopapular >> diffuse> mastocytoma
- Variable prognosis depending on variant (non-advanced vs advanced)

Characteristics & Comorbidities of Adult Patients with SM

Table 1. Demographic characteristics in 2040 individuals with mastocytosis, age ≥ 20 years at diagnosis.

All subjects	<i>n</i>	%
Sex		
Male	829	40.6
Female	1211	59.4
Age at diagnosis		
Median, IQR	50, 37-64	
Mean, SD	50.6, 17.4	
20–29	284	13.9
30–39	328	16.1
40–49	388	19.0
50–59	365	17.9
60–69	345	16.9
70–79	227	11.1
80–89	91	4.5
90+	12	0.6

Table 4. CCI and comorbidities in individuals with a mastocytosis diagnosis and comparators age ≥ 20 years at index date.

	Cases		Comparators		OR	95% CI	<i>p</i>	Total	
	<i>n</i>	%	<i>n</i>	%				<i>n</i>	%
Charlson Comorbidity Index (CCI)									
0	1623	79.6	8,970	88.0	0.53	0.47–0.60	<0.001	10593	86.6
1	167	8.2	555	5.4	1.55	1.29–1.85	<0.001	722	5.9
2+	250	12.3	668	6.6	1.99	1.71–2.32	<0.001	918	7.5
Morbidities within CCI									
Myocardial infarction	34	1.7	146	1.4	1.17	0.80–1.70	0.483	180	1.5
Congestive heart failure	34	1.7	163	1.6	1.04	0.72–1.51	0.901	197	1.6
Peripheral vascular disease	22	1.1	67	0.7	1.64	1.02–2.67	0.057	89	0.7
Cerebrovascular disease	64	3.1	259	2.5	1.24	0.94–1.64	0.145	323	2.6
Dementia	6	0.3	46	0.5	0.65	0.28–1.53	0.418	52	0.4
Chronic pulmonary disease	69	3.4	186	1.8	1.88	1.42–2.49	<0.001	255	2.1
Connective tissue disease-rheumatic disease	12	0.6	74	0.7	0.81	0.44–1.49	0.593	86	0.7
Peptic ulcer disease	16	0.8	58	0.6	1.38	0.79–2.41	0.323	74	0.6
Mild liver disease	11	0.5	49	0.5	1.12	0.58–2.16	0.864	60	0.5
Diabetes without complications	76	3.7	226	2.2	1.71	1.31–2.22	<0.001	302	2.5
Diabetes with complications	12	0.6	42	0.4	1.43	0.75–2.72	0.361	54	0.4
Paraplegia and hemiplegia	20	1.0	27	0.3	3.73	2.09–6.66	<0.001	47	0.4
Renal disease	21	1.0	44	0.4	2.39	1.42–4.04	0.001	65	0.5
Cancer	173	8.5	379	3.7	2.40	2.00–2.89	<0.001	552	4.5
Moderate or severe liver disease	1	0.0	7	0.1	0.71	not estimated	not estimated	8	0.1
Metastatic carcinoma	22	1.1	39	0.4	2.83	1.68–4.80	<0.001	61	0.5
AIDS/HIV	3	0.1	1	0.0	15.01	not estimated	not estimated	4	0.0

ISM Is the Most Common Presentation of SM

Table IV. Incidence rate (1997–2010), cumulative incidence (1997–2010) and prevalence (1 January, 2011) of mastocytosis by subtype.

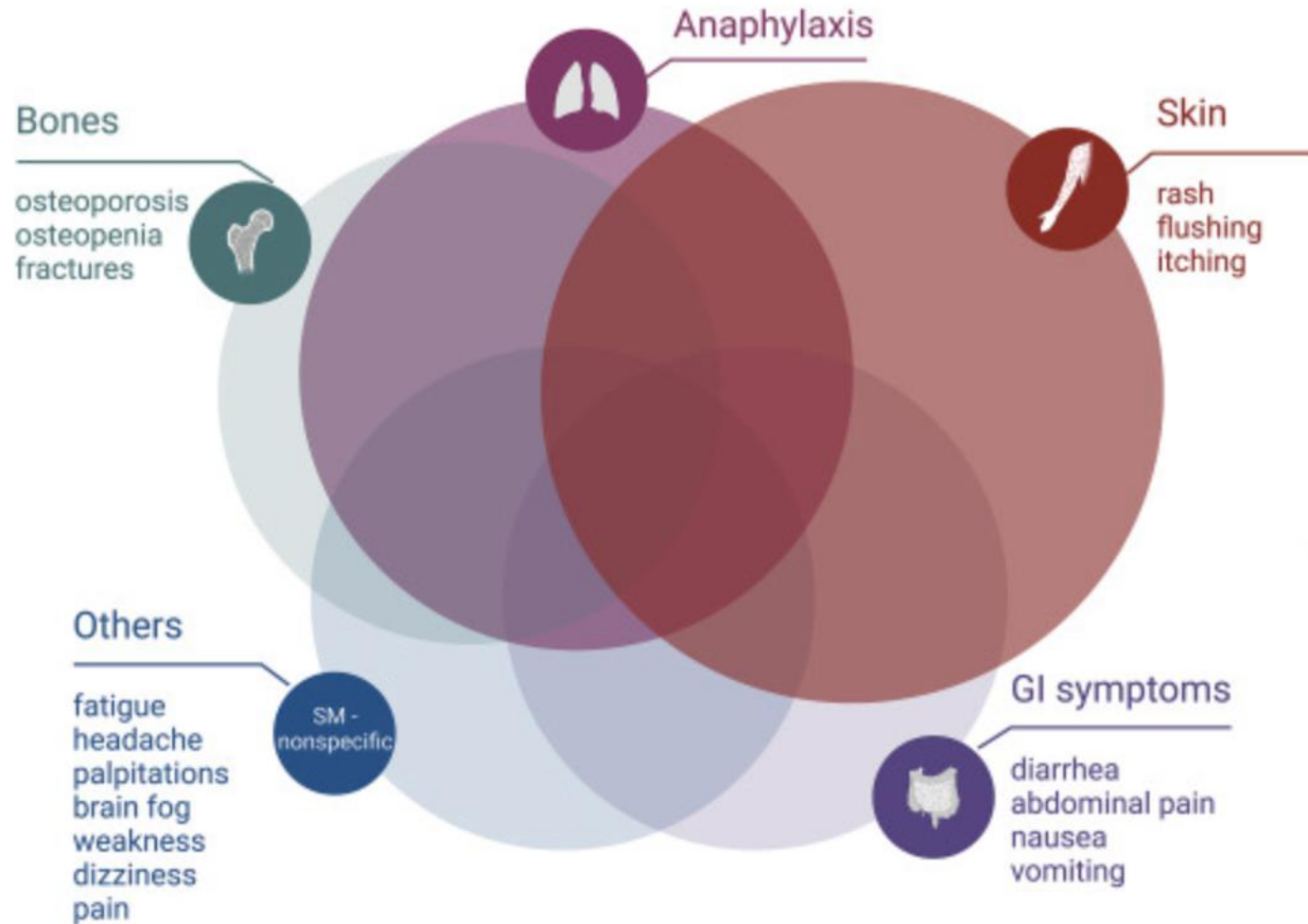
Subtype	Incidence rate per 100 000 (95% CI)	Cumulative incidence per 100 000 (95% CI)*	Prevalence per 100 000 (95% CI)†
ISM (including UP)	0.73 (0.67–0.80)	10.23 (9.32–11.21)	8.24 (7.44–9.10)
SM (unk)	0.10 (0.08–0.13)	1.39 (1.07–1.77)	0.96 (0.71–1.28)
ASM	0.01 (0.006–0.03)	0.18 (0.09–0.34)	0.09 (0.03–0.21)
SM-AHNMD	0.04 (0.03–0.06)	0.55 (0.36–0.80)	0.31 (0.18–0.50)
MCL	0.01 (0.003–0.02)	0.11 (0.04–0.25)	0.00
Total	0.89 (0.82–0.97)	12.46 (11.45–13.54)	9.59 (8.73–10.52)

ISM, indolent systemic mastocytosis; UP, urticaria pigmentosa; SM (unk), systemic mastocytosis, subtype unknown; ASM, aggressive systemic mastocytosis; SM-AHNMD, systemic mastocytosis with associated clonal haematological non-mast cell lineage disease; MCL, mast cell leukaemia; 95% CI, 95% confidence interval.

*Mean population (15 years and older) in Denmark from 1997 to 2011 was 4 397 709.21.

†Population in Denmark (15 years and older) on 1 January 2011 was 4 565 541.

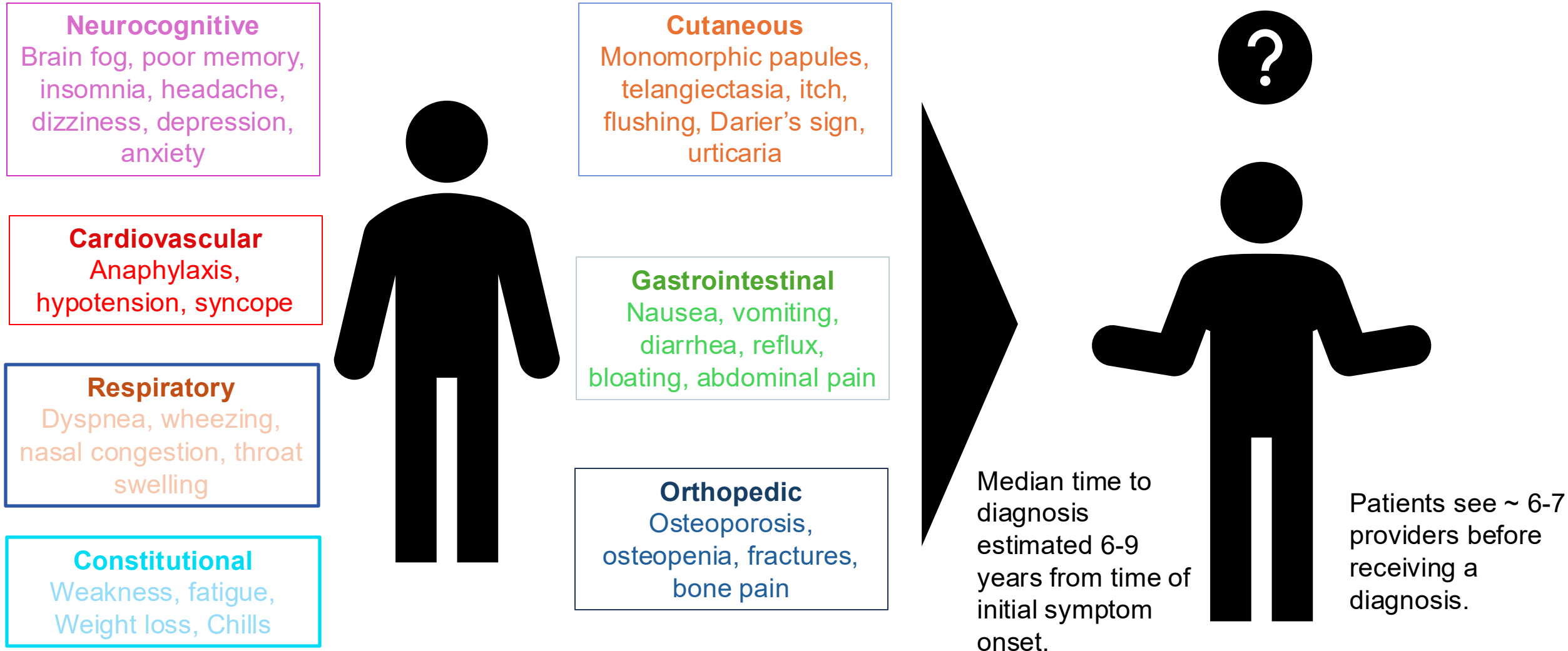
ISM Manifests with Widespread Signs & Symptoms



GI = gastrointestinal.

Pyatilova P, Siebenhaar F. *Immunol Allergy Clin North Am.* 2023;43(4):751-762.

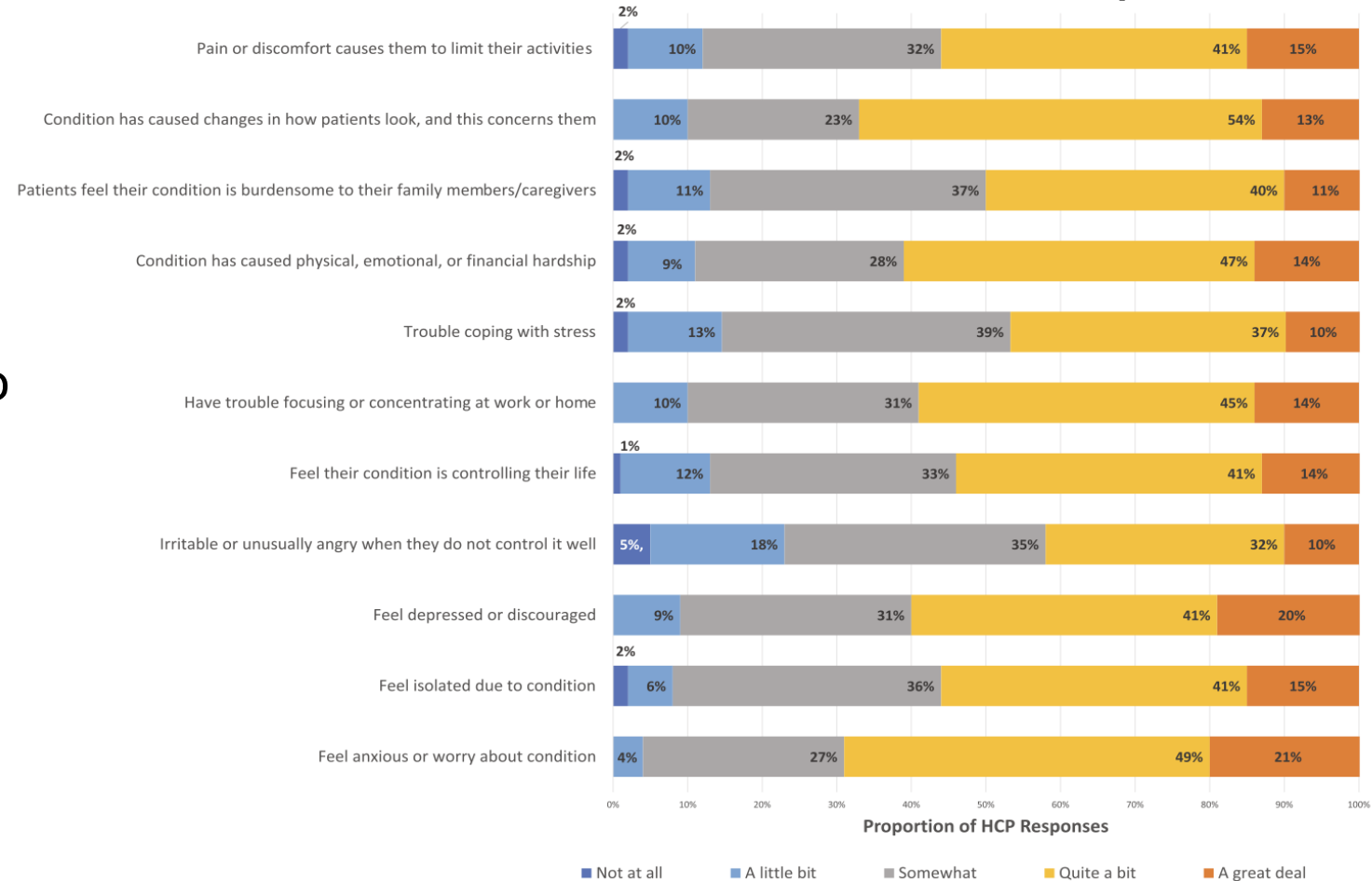
Heterogenous S/Sx Lead to Delays in Diagnosis



Heterogenous S/Sx Lead to Reduced QoL

- Patients with SM struggle with
 - Depression, anxiety, and fear
 - Reduced work productivity
 - Economic instability
 - Family and caregiver strain
 - Extensive polypharmacy
 - DALY of ISM is comparable to lymphoma, leukemia

Survey of HCPs caring for patients with ISM highlights the burden patients face



QoL = quality of life; DALY = disability-adjusted life year.

Mesa RA, et al. *Cancer*. 2022;128(20):3691-3699. Jennings SV, et al. *Immunol Allergy Clin North Am*. 2018;38(3):505-525. Gilreath JA, et al. *Cil Pharmacol*. 2019;11:77-92. Moura DS, et al. *PLoS One*. 2011;6(10):e26375. Mouine M, et al. *J Allergy Clin Immunol Pract*. 2025;13(4):923-929.

Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis

Table 1 The correlation between the individual domains of the mastocytosis quality-of-life questionnaire, independent measures (convergent validation) and the RAND-36 general quality-of-life questionnaire (discriminant validation)

Domain	Items (n)	Cronbach's α	Convergent validation (Spearman's r ; P score)	Discriminant validation (Spearman's r ; P score)
Fatigue, mental health	12	0.958	MSAF fatigue score r 0.823; P < 0.001	RAND36 energy-fatigue r -0.789; P < 0.001
Anaphylaxis	6	0.841	Müeller grade r 0.352; P < 0.001	RAND36 Total score r -0.317; P < 0.001
Skin	6	0.917	Consensus skin grading r 0.357; P < 0.001	RAND36 Total score r -0.320; P < 0.001
Bones	5	0.855	Lumbar BMD r 0.207; P : 0.011	RAND36 Total score r -0.547; P < 0.001
Unfamiliarity	7	0.846	–	RAND36 Total score r -0.513; P < 0.001
Flushing	3	0.904	Consensus mediator grading r 0.474; P < 0.001	RAND36 Total score r -0.526; P < 0.001
General symptoms	6	0.854	Consensus mediator grading r 0.591; P < 0.001	RAND36 Total score r -0.659; P < 0.001
Triggers	4	0.865	–	RAND36 Total score r -0.616; P < 0.001

Table 3 The items of the final mastocytosis symptom assessment form and the scoring of these items by 164 indolent systemic mastocytosis patients

Step 1: The severity of symptoms on a scale from 0 to 10			
	%	MI	OI
Itchy skin	83	4.48	3.73
Dizziness	69	3.93	2.72
Headache	72	4.16	2.99
Fatigue (during the last week)	81	5.42	4.40
Runny nose	57	4.07	2.33
Shortness of breath	58	4.00	2.31
Chest pain/palpitations	61	3.25	1.98
Nausea/vomiting	36	3.55	1.26
Diarrhoea, stomach ache, cramps	68	4.25	2.87
Bone pain/ muscle pain	80	5.17	4.14
Concentration problems	69	4.37	3.02
Depression, sombreness	60	3.59	2.17
	Percentage > 0	Mean, SD	
Attacks, with or without loss of consciousness, per month	26%	1.62 ± 7.2	
Flushing, per week	59%	4.68 ± 10.2	
Step 2: The influence fatigue has, scale from 0 to 10, on:			
	%	MI	OI
Activities (general)	70	4.96	3.49
Mood/temper	69	3.99	2.77
Mobility	56	4.40	2.48
Chores	67	4.89	3.27
Relationships	57	4.35	2.48
Happiness	59	4.35	2.58

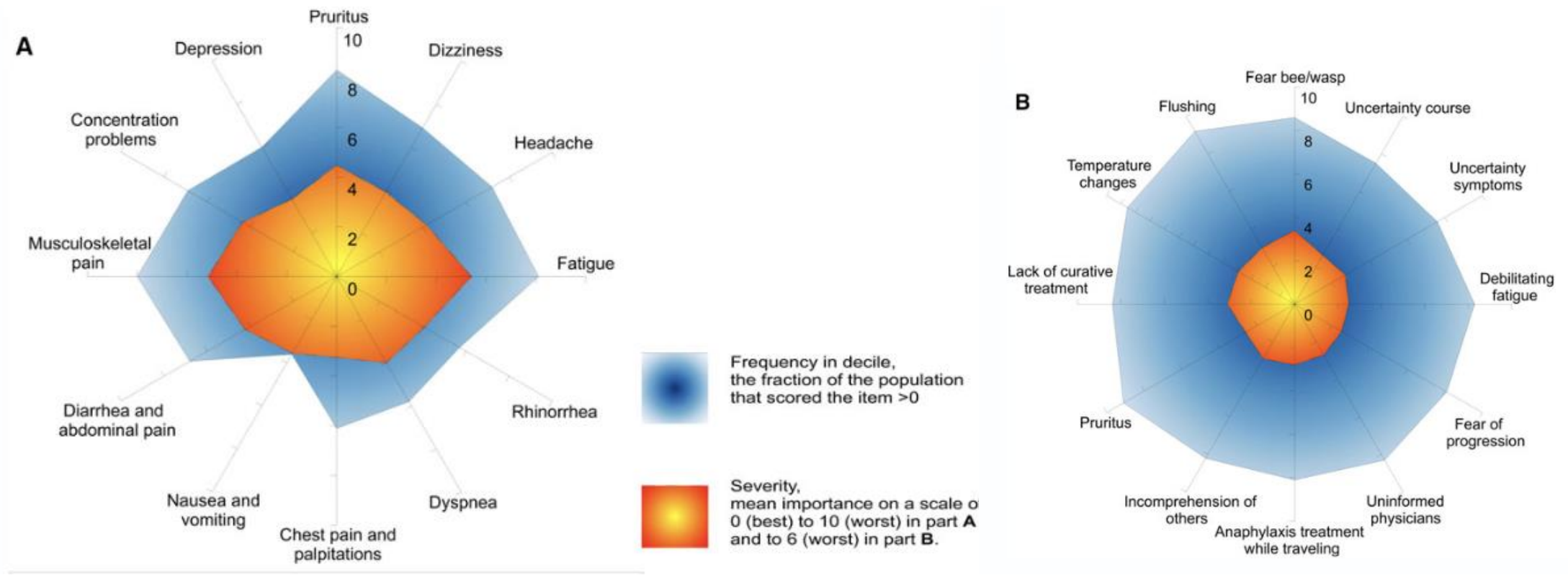
% = percentage of patients reporting this as an issue; MI = mean importance score ranging in burden from 0 (absent) to 10 (most severe); OI = overall importance score, the frequency of the symptom multiplied with the mean importance.

Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis

Table 2 The scoring of the 49-item final mastocytosis quality-of-life questionnaire by 164 indolent systemic mastocytosis patients, sorted on overall importance

Domain identification					Domain identification				
I Fatigue and mental health			II Anaphylaxis		I Fatigue and mental health			II Anaphylaxis	
III Bone symptoms			IV Unfamiliarity		III Bone symptoms			IV Unfamiliarity	
V Flushing			VI General symptoms		V Flushing			VI General symptoms	
VII Skin symptoms			VIII Triggers		VII Skin symptoms			VIII Triggers	
Domain	Short item descriptions	%	MI	OI	Domain	Short item descriptions	%	MI	OI
I	Debilitating fatigue	84	3.1	2.6	IV	Lack of knowledge of mastocytosis by some physicians	82	2.9	2.4
I	Decreased stamina	76	2.5	1.9	IV	The difficulty for others to understand mastocytosis	83	2.7	2.3
I	Feeling worn-out after only mild exertion	75	2.5	1.9	IV	Fear of doctors prescribing a drug triggering anaphylaxis	75	1.9	1.5
I	Clouding of consciousness	75	2.2	1.6	IV	Incomprehension of mastocytosis by your social surrounding	68	1.9	1.3
I	Reduced ability to concentrate	72	2.1	1.5	IV	Physician unfamiliarity with mastocytosis hindering treatment	62	1.8	1.1
I	Inability to pay attention to conversations	73	2	1.4	V	A feeling of intense, glowing heat	75	2.6	2
I	Impaired short-term memory	70	2.1	1.4	V	Flushing attacks	75	2.2	1.6
I	Social life suffering under mastocytosis	69	2	1.4	V	Physically exhausting flushing attacks	69	2	1.4
I	Needing to go to bed earlier on workdays	61	1.9	1.2	VI	Uncertainty about the course of your mastocytosis	82	3	2.7
I	Reduced capability to work under stressful conditions	62	1.8	1.1	VI	Uncertainty whether or not a symptom fits mastocytosis	89	3	2.6
I	Suffering from sombre feelings	70	1.6	1.1	VI	Fear of progression	91	2.6	2.4
I	Work requiring more energy	58	1.9	1.1	VI	Frustration by the current lack of curative treatment	83	2.5	2.1
II	Fear when spotting a bee or wasp	86	3.4	3	VI	Lower back pain	77	2.4	1.9
II	Worrying about treatment of anaphylaxis while travelling	81	2.8	2.3	VI	Abdominal pain	68	1.8	1.2
II	Having to rely on family members during anaphylaxis	68	2.4	1.6	VI	Diarrhoea	64	1.8	1.1
II	The burden of carrying a epinephrine auto-injector	68	2	1.4	VII	Pruritus	81	2.5	2.1
II	Anaphylactic attacks being stressful	54	1.9	1	VII	Skin abnormalities increasing in number or size over time	72	2.2	1.6
II	Family's anxiety when spotting a bee or wasp	46	2.2	1	VII	Skin abnormalities becoming more visible over time	71	2.1	1.5
II	The burden of anaphylactic reactions	52	1.9	1	VII	Embarrassment for your skin abnormalities	67	1.9	1.3
III	Fear of falling and incurring fractures	70	1.9	1.4	VII	Skin abnormality being cosmetically unappealing	64	1.8	1.2
III	Avoiding certain activities for fear of fractures	54	2	1.1	VII	Nocturnal pruritus	65	1.7	1.1
III	Avoiding lifting for fear of back pain or fractures.	62	1.7	1.1	VIII	Temperature change as a trigger for mastocytosis symptoms	76	2.7	2
III	Fear of incurring fractures while sporting	66	1.5	1					
III	Height loss	59	1.7	1					

Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis



SM Is Likely Underdiagnosed and Undermanaged!

- To make an early and accurate diagnosis and to reduce patient, family, and caregiver burdens, we must
 - Recognize the diverse signs and symptoms
 - Have a lower threshold to screen for SM – making the diagnosis is more than half the battle!
 - Understand the classification of SM
 - Important for prognosis, counseling, and management
 - Engage a multidisciplinary medical team

What Drives Most SM?... Understanding KIT

- SCF activates the KIT receptor, leading to maturation of progenitor cells into mast cells
- > 50 KIT mutations have been identified
 - Gain-of-function mutations in the KIT proto-oncogene cause KIT activation independent of SCF binding, leading to uncontrolled proliferation of MC
 - KIT D816V is the most common mutation
 - >80% of adult patients with SM, 20-40% of childhood patients with SM, and 20-40% of adult patients with CM
 - KIT Del419 mutations are next most common
 - ~15-20% of childhood cases
 - <3% in adult SM, representing
 - Other variants are rare

Systemic Mastocytosis Classification

- SM is divided into 6 different subvariants based on the mast cell burden, organ involvement, and SM-related organ damage

2022 CLASSIFICATION OF MASTOCYTOSIS

WHO 5th Edition ^{1,a}		International Consensus Classification (ICC) ²	
Systemic mastocytosis			
Non-advanced	• Bone marrow mastocytosis (BMM) ^b	• Indolent SM	
	• Indolent SM	▸ Bone marrow mastocytosis ^b	
	• Smoldering SM	• Smoldering SM	
Advanced	• Aggressive SM	• Aggressive SM	
	• SM with an associated hematologic neoplasm ^c	• SM with an associated myeloid neoplasm (SM-AMN) ^c	
	• Mast cell leukemia	• Mast cell leukemia	

Diagnostic Criteria for SM



Major criterion

- ≥ 15 MC aggregates in BM or extracutaneous organ
- ICC also requires CD117 and MC tryptase staining

2022 DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS^{a,1,2}

Major	Multifocal dense aggregates of mast cells ^b
Minor	<ul style="list-style-type: none">• $>25\%$ mast cells with atypical morphology^c• <i>KIT</i> D816V or other activating <i>KIT</i> mutation^d• CD2, CD25, and/or CD30 expression on mast cells^e• Serum total tryptase >20 ng/mL^f

WHO 5th Edition ¹	ICC ^{2,9}
1 major + 1 minor criteria	1 major criterion
OR	OR
≥ 3 minor criteria	≥ 3 minor criteria

Minor criterion

- Any *KIT* mutations that cause ligand-independent activation (D816V is most common)
- Analysis can be performed on BM, EC tissue, or peripheral blood

BM = bone marrow; EC = endothelial cell.

Gotlib J, et al. *J Natl Compr Canc Netw*. 2024;22(2D):e240030. Khoury JD, et al. *Leukemia*. 2022;36:1703-1719. Arber DA, et al. *Blood*. 2022;140:1200-1228.

Diagnostic Evaluation in SM

- History, physical exam, and ROS are critical!
 - Assess cutaneous lesions
 - Assess for organ accumulation: HSM, LAD
 - Other sx to elicit: Weight loss, malabsorption, GI ulcers, migraines, back pain, fractures
- If skin lesions are present, skin biopsy to assess mast cell density (> 4-8x normal skin)
 - Special stains (Giemsa, toluidine blue, or Leder), anti-tryptase or CD117 IHC, consider other markers
 - KIT D816V mutation analysis (tissue or blood)
- Blood tests
 - Serum tryptase
 - > 20 ng/ml: Need BM biopsy
 - >15 but < 20 ng/ml: Consider bone marrow biopsy if REMA = 2 or above, KIT D816V mutation is detected in peripheral blood, or if there are systemic symptoms
 - < 15 ng/ml: monitor with serial exams
 - CBCd – anemia (30-50%); leukopenia (20%), leukocytosis (20%), eosinophilia (30-40%), thrombocytopenia (20%)
 - CMP with LFTs and alk phos elevations; low albumin
 - D816V mutational analysis
 - KIT mutation variant allele frequency (VAF) analysis may be helpful
- BM biopsy is required to assess involvement and distinguish ISM from other variants associated with hematologic malignancy

First Things First, Baseline Serum Tryptase!

- Serum tryptase is an important marker for MC activation and disease burden
- BST predominantly reflects the constitutive release of pro-tryptases into the peripheral circulation by resident tissue MCs → can be helpful when considering most MC disorders, not just SM
 - Please note: Elevations in tryptase are not specific to mast cell disease, may also increase due to chronic kidney disease, parasitic infections, and myeloid neoplasms
 - H₂T is the leading cause of elevated tryptase
- Although WHO criteria specify BST > 20 ng/ml, ~ 30% of ISM pts have BST <20 ng/mL → if high clinical suspicion, pursue further work up for SM if BST ≥ 8 ng/ml

BST = baseline serum tryptase.

Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719. Theoharides TC, et al. *N Engl J Med*. 2015;373(2):163-172. Arber DA, et al. *Blood*. 2022;140(11):1200-1228. Pardanani A. *Am J Hematol*. 2023;98(7):1097-1116. Pongdee T, et al. *J Allergy Clin Immunol Pract*. 2022;10(9):2436-2437. Chovanec J, et al. *Blood Adv*. 2023;7:1796-1810. McMurray JC, et al. *Blood*. 2024;144(4):408-419; Sánchez-Muñoz L, et al. *Mod Pathol*. 2011;24(9):1157-1168. Akin C, et al. *Ann Allergy Asthma Immunol*. 2025:S1081-1206(25)00336-9.

Next, KIT D816V Analysis Should Be Performed – High Sensitivity Assay Preferred!

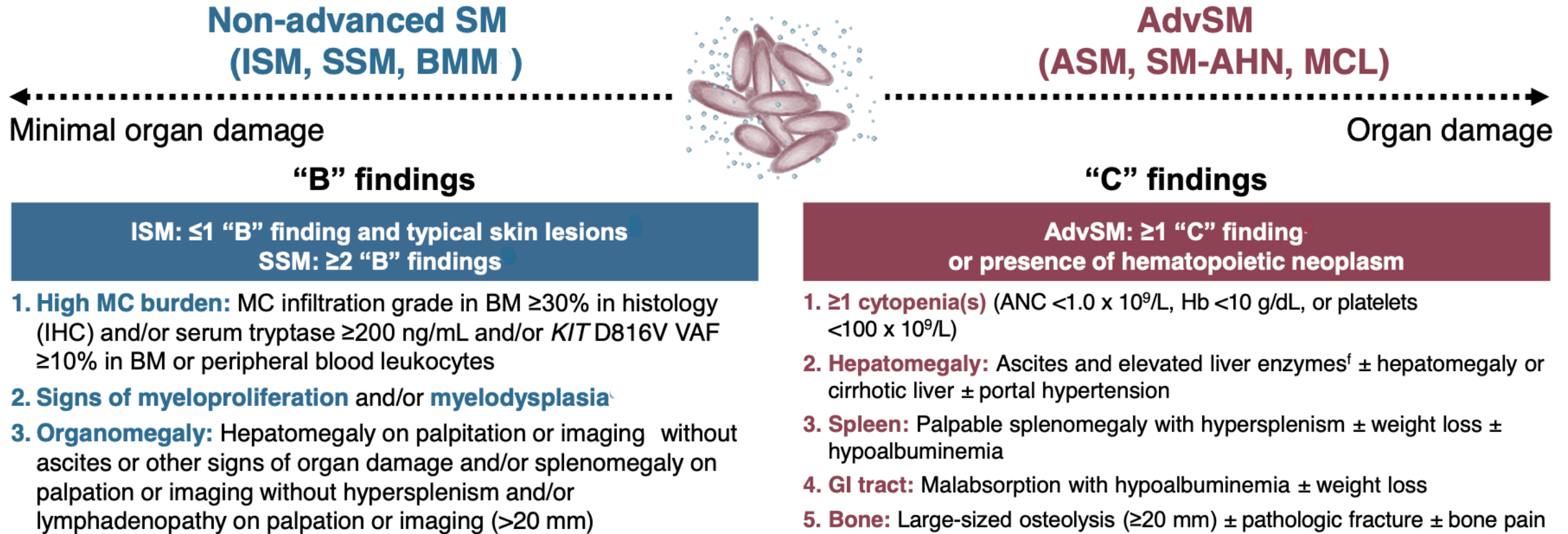
The high-sensitivity (limit of detection $\leq 0.03\%$ VAF) KIT D816V assays are available at several university-based and commercial laboratories.

- Laboratories that offer high-sensitivity KIT D816V assays
 - ARUP Laboratories/ Utah of Utah Laboratories
 - Quest Diagnostics
 - Virant Diagnostics
 - Labcorp
 - Mayo Clinic Laboratories
 - OHSU/Knight Diagnostic Laboratories
 - If in doubt, call your local laboratory and ask if they are able to do a send out test for the high-sensitivity analysis
- Important notes
 - SM should not be ruled out on the ddx due to undetectable KIT D816V since assays have limitations and may be less sensitive if MC burden is low. **If clinical suspicion remains high, pursue SM work up further!**
 - ddPCR is more sensitive than NGS techniques – identifies KIT D816V in >20% more patients than NGS, but ~15% of patients with ISM will still be negative by ddPCR on peripheral blood

NGS = next generation sequencing.

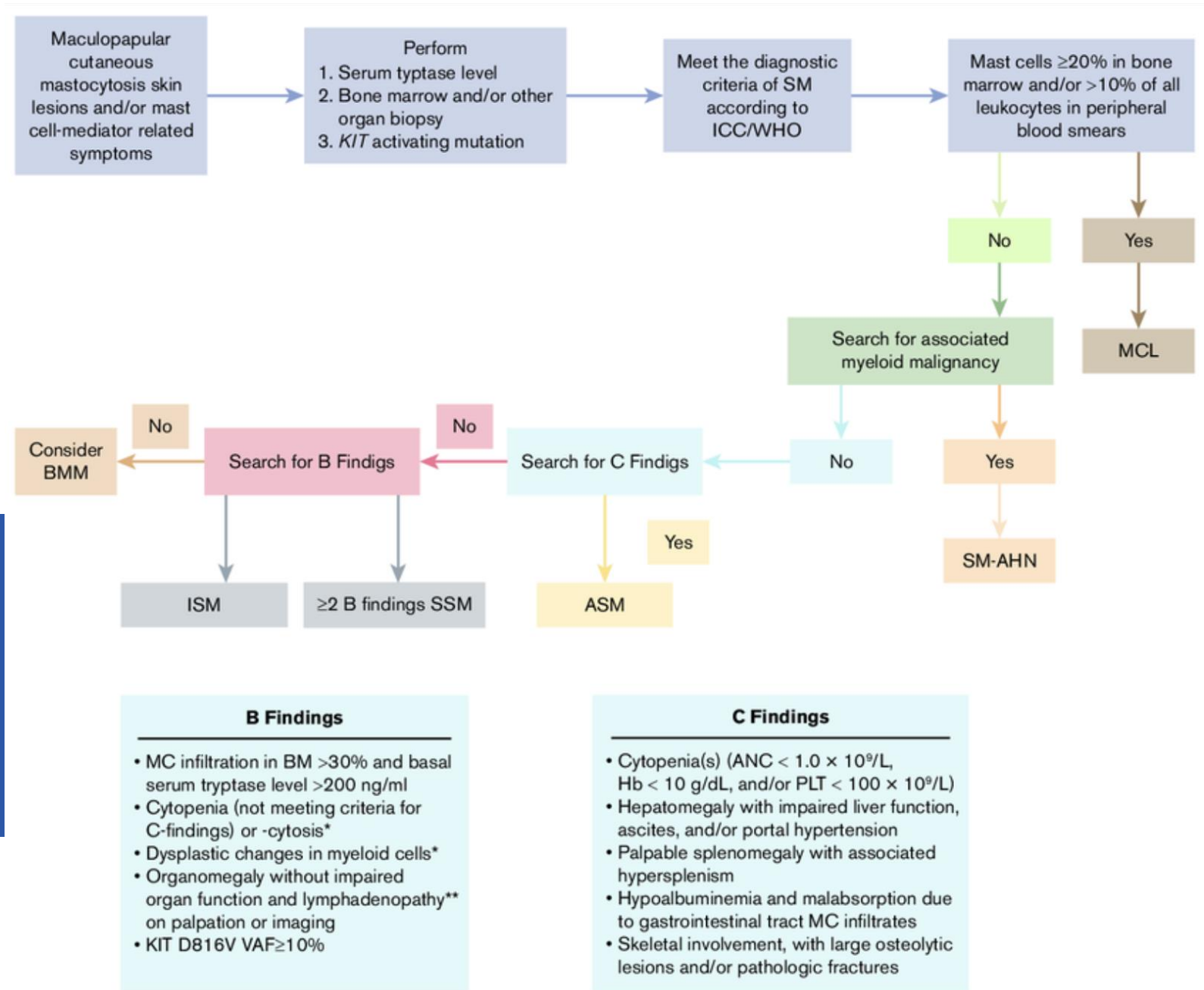
Rossignol J, et al. *F1000Res*. 2019;8:F1000 Faculty Rev-1961. Pardanani A. *Am J Hematol*. 2023;98(7):1097-1116. Khoury JD, et al. *Leukemia*. 2022;36:1703-1719. Verstovsek S. *Eur J Haematol*. 2013;90(2):89-98. Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

SM Subtyping Requires Burden of Disease and Organ Damage Assessment



BMM = bone marrow mastocytosis.

Rossignol J, et al. *F1000Res*. 2019;8:F1000 Faculty Rev-1961. Pardanani A. *Am J Hematol*. 2023;98(7):1097-1116. Khoury JD, et al. *Leukemia*. 2022;36:1703-1719. Verstovsek S. *Eur J Haematol*. 2013;90(2):89-98.



B findings:
MC accumulation in organs

C findings:
Organ damage or dysfunction

A Deeper Dive into Cutaneous Involvement in ISM

- Adult patients with cutaneous maculopapular lesions (either adult-onset or failure to regress after childhood) are more likely to have SM
- Approximately 90% of adult-onset patients with CM have SM upon further diagnostic evaluation
- Cutaneous mastocytosis is diagnosed when
 - Individuals with cutaneous infiltration who meet the diagnostic criteria for CM
 - Assumes that a patient has undergone full work up and SM has been ruled out
- Mastocytosis in skin is considered a provisional diagnosis for patients with CM who have not undergone full evaluation for SM



SM: Indolent Systemic Mastocytosis

- Most common subtype of SM
 - Accounts for ~70-80% of cases of all SM
- Cutaneous involvement is common
- Prognosis is excellent, but QoL may be reduced
 - Least aggressive, but longer duration of symptoms before diagnosis
 - No increased mortality
 - Progression to more severe subtypes occurs in only 1–5% of cases

ISM: Clinical Manifestations

- Skin involvement is more common than not
- Heterogeneous clinical presentation
 - Maculopapular presentation is most common (~80%)
 - Recurrent flushing of torso, extremities, or face
 - In my experience, patients often report pruritus or 'sensitive skin' without persistent erythema, wheals, or apparent flushing



ISM: Clinical Manifestations

- Widespread or mottled erythematous appearance with variable levels of hyperpigmentation



ISM: Clinical Manifestations

- Can appear with diffuse CM-like lesions which may manifest as mildly edematous or indurated, and in some patients sclerodermoid-appearing due speckling



Mastocytosis: Flushing



Mastocytosis: Excoriations and Hyperpigmentation



ISM: Extracutaneous Clinical Manifestations

Always obtain a thorough review of systems!

- Extracutaneous symptoms include
 - Fatigue (45-70%)
 - GI (40-80%): Abdominal pain, or cramping, distention, constipation, and diarrhea
 - Ortho/MS (~30-42%): Non-inflammatory musculoskeletal pain, fractures, osteoporosis, osteopenia
 - Cardiac (~30%): Palpitations, hypotension, syncope
 - Neuro (>50%): Headaches, migraines, brain fog, reduced short term memory
 - Psych (>50%): Depression, anxiety, irritability
 - Hepatomegaly (7.7%), splenomegaly (3.6-8.0%), lymphadenopathy (5-20%) are rare in ISM

Smoldering SM

- Considered non-advanced or indolent
- Accounts for ~2-9% of adult SM
- Clinical presentation
 - Mast cell burden is high (>2 B symptoms)
 - Hepatic involvement with HSM but no extensive organ damage
- Less frequent cutaneous symptoms, but may have MPCM lesions, flushing, pruritus or burning



MPCM = maculopapular cutaneous mastocytosis.

Ustun C, et al. *Blood Adv.* 2025;9(9):2048-2062. Tse KY, et al. *J Allergy Clin Immunol Glob.* 2024;3(4):100316. Images from the Mast Cell Disease Society.

Advanced SM Subtypes

- Subtypes are defined by the presence of at least one C-finding (organ damage)
 - **Aggressive systemic mastocytosis (ASM) (4-12%)**: Evidence of organ dysfunction, such as low blood counts or liver issues
 - **SM with an associated hematologic neoplasm (SM-AHN) (8-20%)**: SM alongside another separate blood cancer or disorder, such as a myeloid leukemia.
 - **Mast cell leukemia (MCL)**: Rarest and most aggressive form
- Majority of patients do not have cutaneous findings
- Require disease modifying therapies to reduce mast cell burden and limit organ damage
 - May include KIT inhibitors or chemotherapies

SM with Associated Hematologic Neoplasm

- SM-AHN accounts for up to 40% of SM
 - 2nd most common variant
- Any subtype of SM (ISM, SSM, or ASM), arising in association with a 2nd hematologic malignancy (myeloid >> lymphoid/plasma cell neoplasms)
- Majority do not have cutaneous involvement
- Prognosis is poor
 - Leukemic transformation is observed in ~13% of patients
 - 24-month median survival
- KIT D816V mutation is present in roughly 90% of cases
- Additional mutations in myeloid panels (eg. ASXL1, TET2, or SRSF2) identify AHN component

Clinical Impact of Skin Lesions in Mastocytosis: A Multicenter Study of the European Competence Network on Mastocytosis

- **ECNM Registry** recruited >2000 patients between 2002–2017
- This study examined the frequency and prognostic value of cutaneous lesions in mastocytosis patients in the ECNM Registry
- **1,510 patients with mastocytosis** examined in total
 - 1,195 (**79.1%**) patients presented with **skin lesions**
 - 891 of 1,146 (78%) patients who underwent bone marrow biopsy were + for multifocal MC infiltrates by IHC
 - KIT D816V mutation identified in 724 of 946 (76.5%)
 - Flow cytometry on BM aspirates showed CD2+ in 435 of 613 (71.0%) and CD25+ in 762 of 854 (89.2%)
- SM was established in 1,036 of 1,510 patients (68.6%) based on WHO criteria
- BM biopsy was not performed in 165 of 1,510 (10.9%) patients who were aged <18 years → classified as having CM (n = 162) or having mastocytosis in skin (MIS) (n=3) following consensus guidelines

Table 1. Patients' Characteristics

Characteristics	All (n = 1,510)	CM (n = 286)	MIS (n = 188)	SM+ (n = 721)	SM– (n = 315)
Age at first visit, median (IQR)	44.3 (31.5–55.8)	6.0 (1.2–32.6) ^{1,2,3}	40.0 (31.3–9.6) ^{2,3,4}	46.3 (36.7–5.3) ^{1,3,4}	57.2 (45.4–65.5) ^{1,2,4}
Age at first symptoms, median (IQR)	36.0 (22.6–49.5)	2.5 (0.2–27.9) ^{1,2,3}	33.2 (23.5–44.6) ^{3,4}	35.8 (25.2–46.7) ^{3,4}	52.6 (42.4–63.9) ^{1,2,4}
Duration of disease, y, median (IQR)	4.0 (0.8 – 10.2)	2.0 (0.5–5.2) ^{1,2,3}	4.8 (1.0–10.7) ^{2,3,4}	7.5 (2.4–15.0) ^{1,3,4}	1.0 (0.3–3.3) ^{1,2,4}
Male/female	664 (44%)/846 (56%)	136 (48%)/150 (52%) ^{1,2,4}	63 (34%)/125 (66%) ^{3,4}	272 (38%)/449 (62%) ⁴	193 (61%)/122 (39%) ^{1,2,3}
Skin involvement	1,195 (79.1%)	286 (100%)	188 (100%)	721 (100%)	—
BM biopsies (n = 1,146)					
MC infiltrates positive ⁵	891 (78%)	3 (2%) ⁶	0 (0%)	630 (89%)	258 (85%)
No diagnostic MC infiltrates = negative	255 (22%)	124 (98%) ^{2,3,7}	8 (100%) ^{2,3}	76 (11%) ^{2,4}	47 (15%) ^{3,4}
BM smears (n = 950)					
MC infiltrates positive ⁵	669 (70%)	30 (26%)	3 (25%)	442 (78%)	194 (75%)
Negative	281 (30%)	84 (74%) ^{2,3}	9 (75%) ^{2,3}	125 (22%) ^{3,4}	63 (25%) ^{3,4}
KIT (n = 946)					
Positive	724 (77%)	20 (19%)	6 (43%)	488 (86%)	210 (82%)
Negative	222 (23%)	86 (81%) ^{2,3}	8 (57%) ^{2,3}	81 (14%) ^{3,4}	47 (18%) ^{3,4}
CD2+ MFC (n = 613)					
Positive	435 (70%)	47 (54%)	4 (50%)	264 (76%)	120 (70%)
Negative	178 (30%)	40 (46%) ^{1,2}	4 (50%)	83 (24%) ⁴	51 (30%)
CD25+ MFC (n = 854)					
Positive	762 (89%)	48 (48%)	4 (40%)	477 (96%)	233 (95%)
Negative	92 (11%)	53 (52%) ^{2,3}	6 (60%) ^{2,3,4}	21 (4%) ^{3,4}	12 (5%) ^{3,4}
Patient died, n (%)	159/1,044 (15.0%)	0 (0.0%) ^{1,2,3}	6 (5%) ^{2,3,4}	67 (13%) ^{1,3,4}	86 (38%) ^{1,2,4}
5-year survival		100%	97.4%	93.3%	71.6%
10-year survival		100%	97.4%	87.8%	66.1%

Abbreviations: BM, bone marrow; CM, cutaneous mastocytosis; IQR, interquartile range; MC, mast cell; MFC, multicolor flow cytometry; MIS, mastocytosis in the skin; SM+, systemic mastocytosis with skin involvement; SM–, systemic mastocytosis without skin involvement.

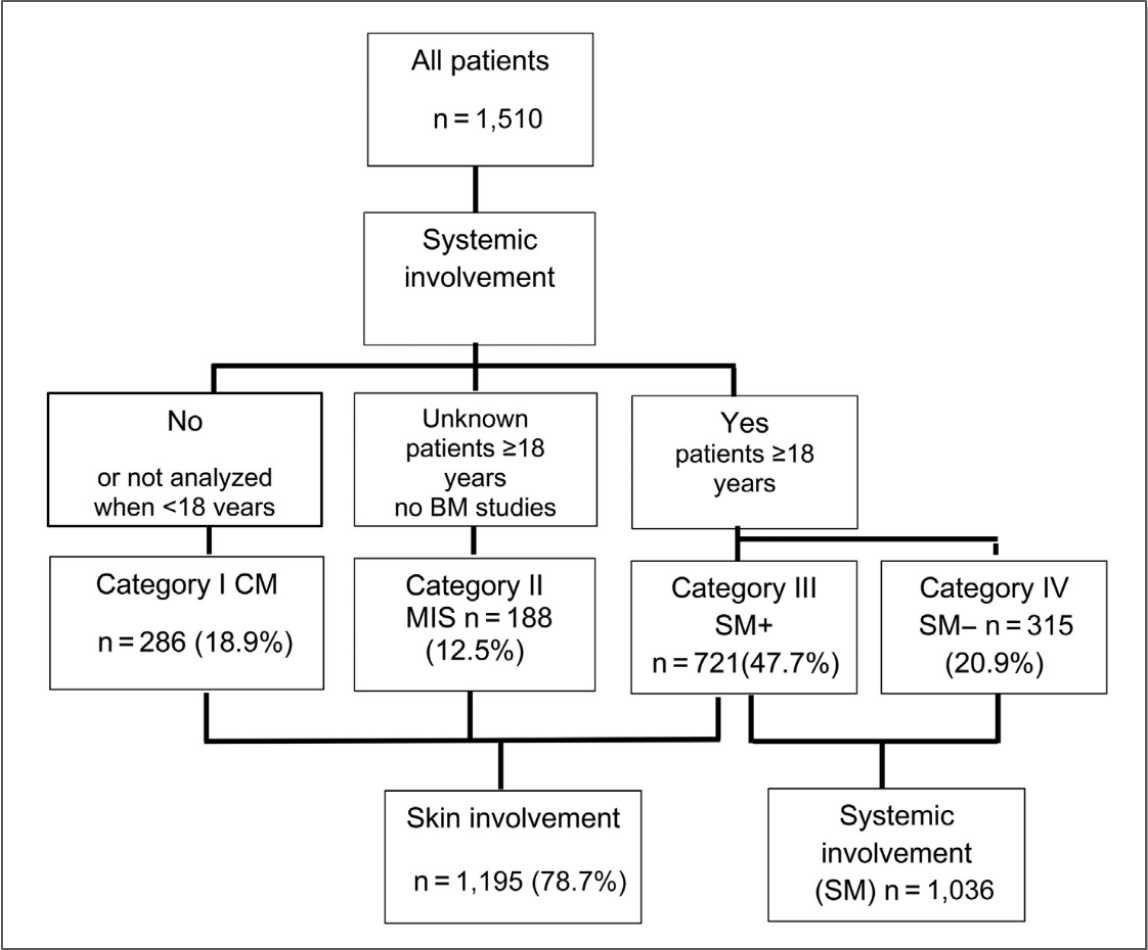


Table 2. SM Subtypes in Patients with SM+ and SM–

All Patients with SM (N = 1,036)	SM+ (n = 721)	SM– (n = 315)
ISM (n = 634)	634 (100.0%)	0
SSM (n = 33)	29 (87.9%)	4 (12.1%)
BMM (n = 199)	0	199 (100%)
SM-AHN ¹ (n = 112)	32 (28.6%)	80 (71.4%)
ASM (n = 45)	21 (46.7%)	24 (53.3%)
MCL (n = 13)	5 (38.5%)	8 (61.5%)

Abbreviations: ASM, aggressive systemic mastocytosis; ASM-AHN, aggressive systemic mastocytosis with associated hematologic (non-mast cell) neoplasm; BMM, bone marrow mastocytosis; ISM, indolent systemic mastocytosis; ISM-AHN, indolent systemic mastocytosis with associated hematologic (non-mast cell) neoplasm; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with associated hematologic (non-mast cell) neoplasm; MIS, mastocytosis in the skin; SM, systemic mastocytosis; SM+, SM with skin involvement; SM–, SM without skin involvement; SM-AHN, SM with an associated hematologic neoplasm; SSM, smoldering SM.

¹Patients with SM-AHN included cases with ISM-AHN, ASM-AHN, and MCL-AHN.

- More than half of the patients with skin lesions had systemic involvement
- Majority of patients with SM had skin involvement
- Maculopapular lesion-type was detected in 95% of patients with SM

Table 3. Differences in Skin Involvement in Patients with CM, MIS, and SM+ Regarding Diagnostic MC Infiltrates and Detectable *KIT* D816V Mutation in Skin Biopsies

Disease Variant	% Involved Skin (n = 723)	Diagnostic MC Infiltrates in the Skin, n/n (%) (814/845)	<i>KIT</i> Mutation in the Skin, n/n (%) (49/55)
CM	38.5 (10.0–70.0) ¹	178/181 (98.3)	3/4 (75.0)
Subtypes	Comparison of subtypes: <i>P</i> < 0.001	Comparison of subtypes: <i>P</i> = 0.233	Comparison of subtypes: <i>P</i> = 1.000
MPCM	40.0 (20.0–74.5)	159/162 (98.1)	3/4
DCM	45.0 (27.5–70.0)	7/7	0/0
Mastocytoma	5.0 (2.0–5.0)	12/12	—
MIS	40.0 (20.0–60.0) ¹	138/147 (93.9)	7/9 (77.8)
SM+	50.0 (25.0–75.0)	498/517 (96.3)	39/42 (92.9)
Subtypes	Comparison of subtypes: <i>P</i> = 0.045 ²	Comparison of subtypes: <i>P</i> = 0.774	Comparison of subtypes: <i>P</i> = 0.910
ASM	51.5 (14.0–75.0)	10/10	1/1
ISM	50.0 (25.0–72.0)	455/474 (96.0)	33/36 (94.1)
MCL	—	2/2	0/0
SM-AHN	50.0 (24.0–62.5)	13/13	2/2
SSM	70.0 (40.0–80.0)	18/18	3/3

Abbreviations: ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; DCM, diffuse cutaneous mastocytosis; IQR, interquartile range; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; MIS, mastocytosis in the skin; MPCM, maculopapular cutaneous mastocytosis; SM+, systemic mastocytosis with skin involvement; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; SSM, smoldering systemic mastocytosis.

Data are presented as n (%) and median (IQR).

¹Significantly (*P* < 0.05) different from SM+; post hoc test: Bonferroni correction.

²ASM, MCL, and SM-AHN were not included in this analysis because of the low number of cases.

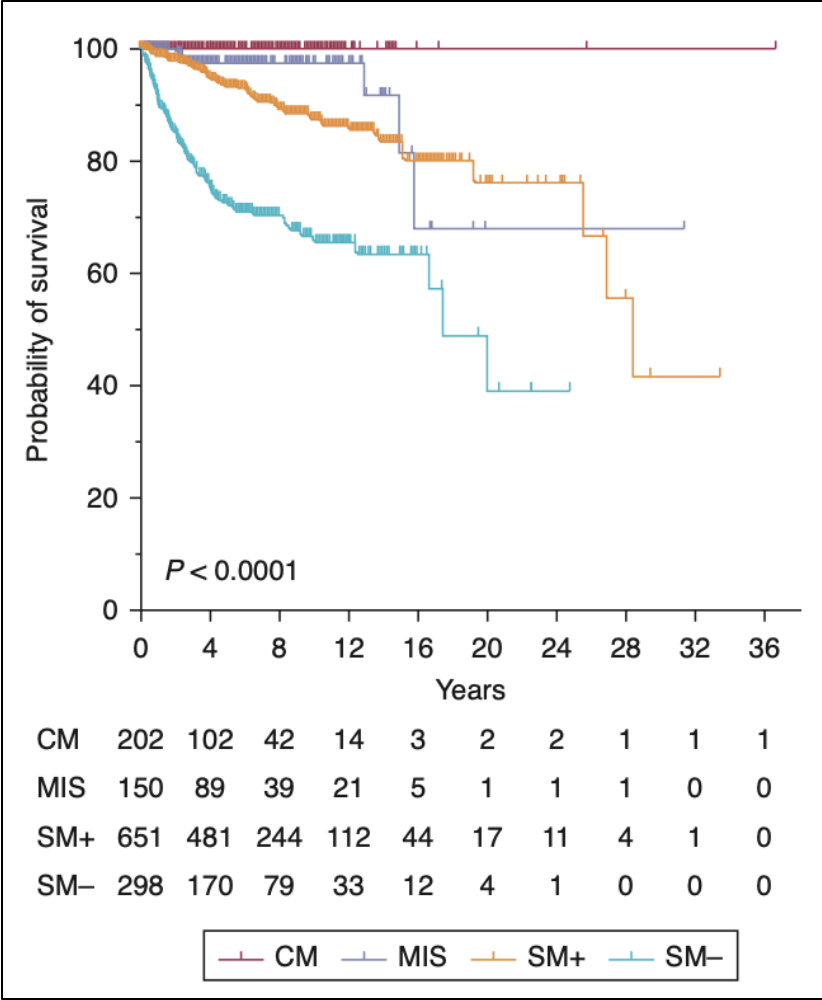
Table 4. Changes in the Clinical Laboratory Parameters Found when Comparing Baseline Data with Last Follow-Up Data (Median and Range or IQR) in the Four Mastocytosis Categories

Clinical Variable	Measure	Timepoint	All	CM	MIS	SM+	SM−
Years since the first visit	Median (range)		4.2 (0.5–34.1)	3.4 (0.5–34.1)	3.7 (0.5–29.6)	4.8 (0.5–30.5)	3.7 (0.5–19.5)
% of skin involved (n = 239)	Median (IQR)	Baseline	50 (30–70) ¹	48 (25–76)	40 (19–61) ¹	50 (30–70) ¹	—
		Follow-up	40 (18–70)	48 (14–72)	36 (17–51)	50 (20–75)	—
Serum tryptase, µg/l (n = 765)	Median (IQR)	Baseline	28.2 (15.1–58.9) ¹	8.9 (4.7–15.9)	11.5 (6.4–23.3)	40.9 (22.1–94.0) ¹	37.9 (19.2–98.1) ¹
		Follow-up	25.9 (13.1–56.0)	9.5 (4.5–16.0)	13.1 (7.0–24.5)	38.3 (20.0–74.3)	24.9 (13.0–47.3)
Darier's sign positive (n = 326)	n (%)	Baseline	305/326 (93.6)	60/65 (92.3)	64/73 (87.7)	181/188 (96.3)	—
		Follow-up	295/326 (90.5)	59/65 (90.8)	64/73 (87.7)	172/188 (91.5)	—

Abbreviations: CM, cutaneous mastocytosis; IQR, interquartile range; MIS, mastocytosis in the skin; SM+, systemic mastocytosis with skin involvement; SM−, systemic mastocytosis without skin involvement.

¹Significant changes from baseline to follow-up ($P < 0.05$).

- Serum tryptase levels were significantly higher in SM than those with CM
- No significant difference in tryptase levels between pts with or without skin lesions
- Absence of skin lesions is associated with reduced survival in SM



Key Learning Points



- Systemic mastocytosis is not rare (~1:5000)!
- Most adults with evidence of cutaneous mastocytosis have systemic involvement
- Recognize the signs, symptoms, and burden, both with non-adv SM and adv SM
- Diagnostic work up should include
 - Serum tryptase (BST < 20 ng/ml doesn't exclude SM, consider further evaluation in > 8 ng/ml)
 - KIT D816V mutational analysis should be performed using a highly sensitive assay



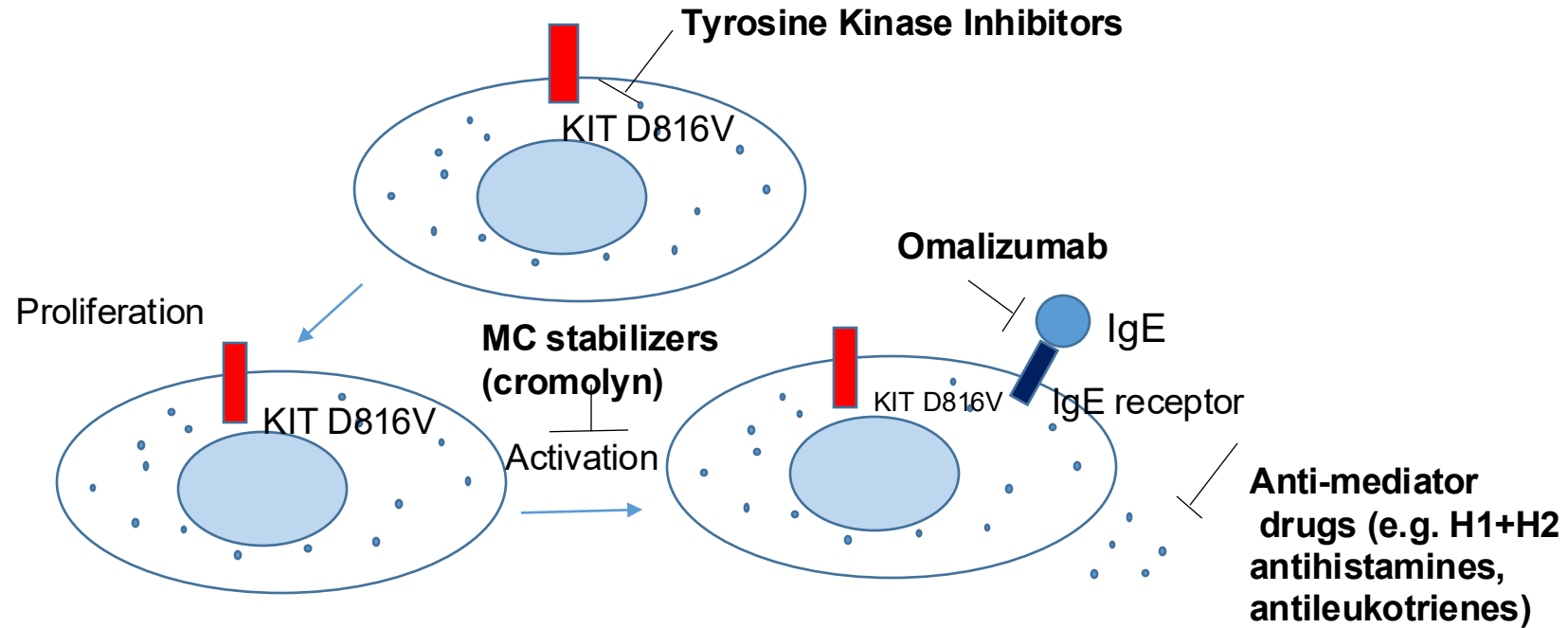
masterclasses in dermatology
saturday morning live

PRESENTED BY THE **derm**atologist

Current and Emerging Targeted Therapies for SM

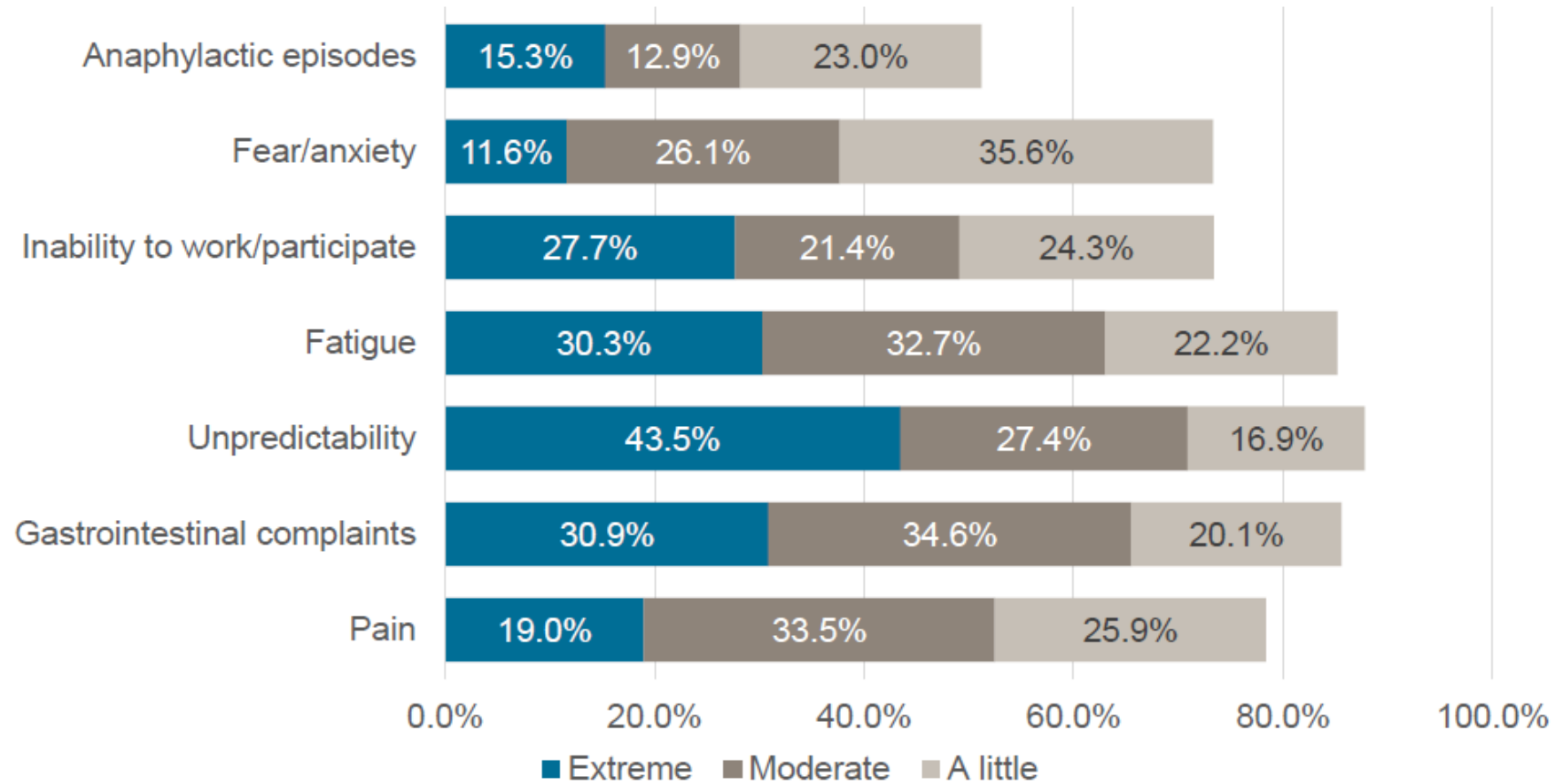
Cem Akin, MD, PhD

Treatment Modalities in Mastocytosis



- Also treat associated co-morbidities
 - Osteoporosis
 - Venom allergy

Impact on QoL in Patients with Mast Cell Disorders



Tyrosine Kinase Inhibitors in Systemic Mastocytosis

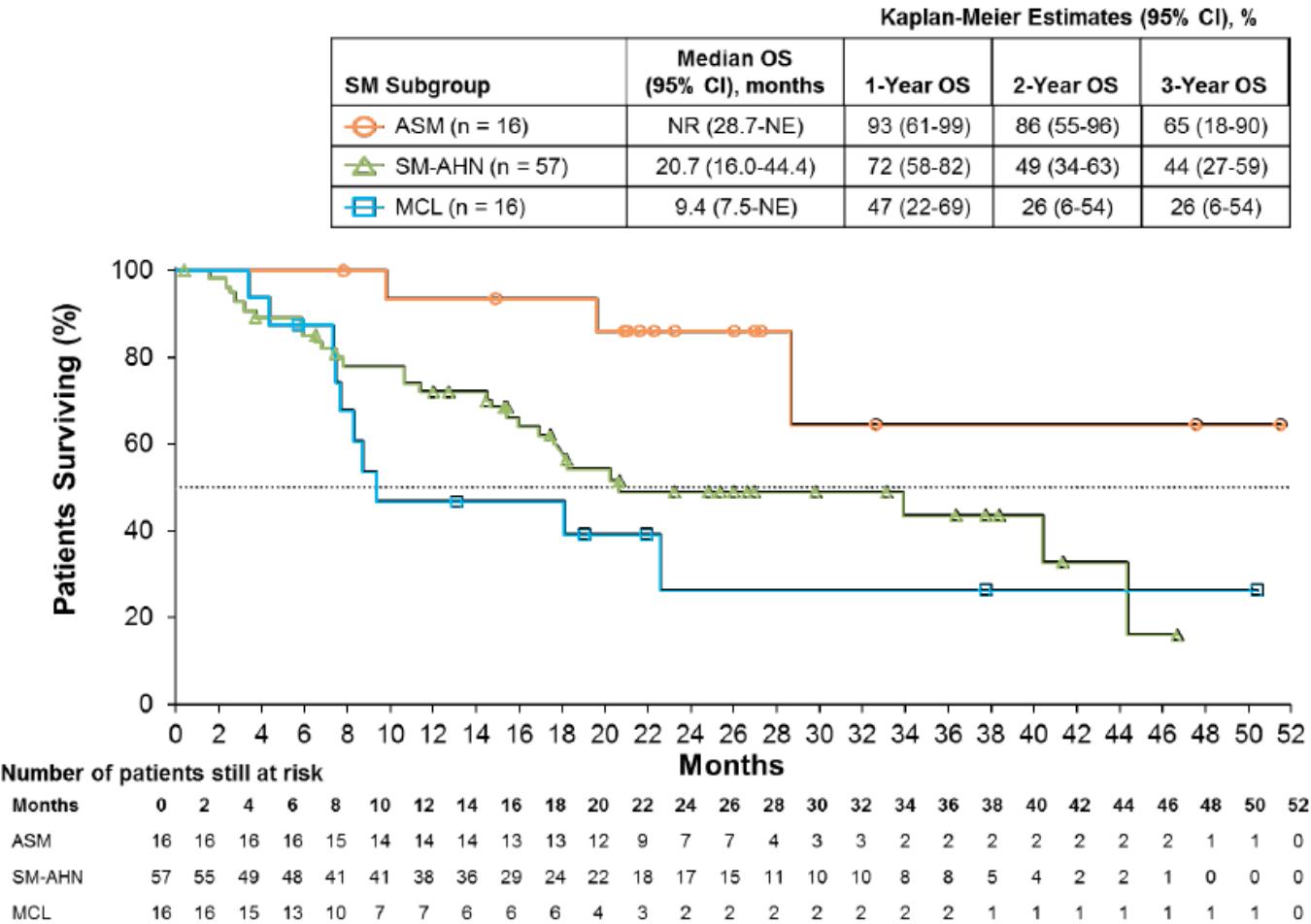
- WT KIT or non-codon D816V
 - Imatinib (FDA indication for advanced SM)
- Both WT and D816V KIT
 - Midostaurin (FDA indication for advanced SM)
- Primarily D816V KIT
 - Avapritinib (FDA indication for advanced and indolent SM)
 - Bezuclastinib (SUMMIT clinical trial)
 - BLU-263 (HARBOR clinical trial)

WT = wild type; FDA = Food and Drug Administration.

Drugs@FDA: FDA-Approved Drugs. Accessed Oct 6, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021588s047lbl.pdf.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212608s012lbl.pdf

Midostaurin in Advanced Mastocytosis: Survival per Subgroup

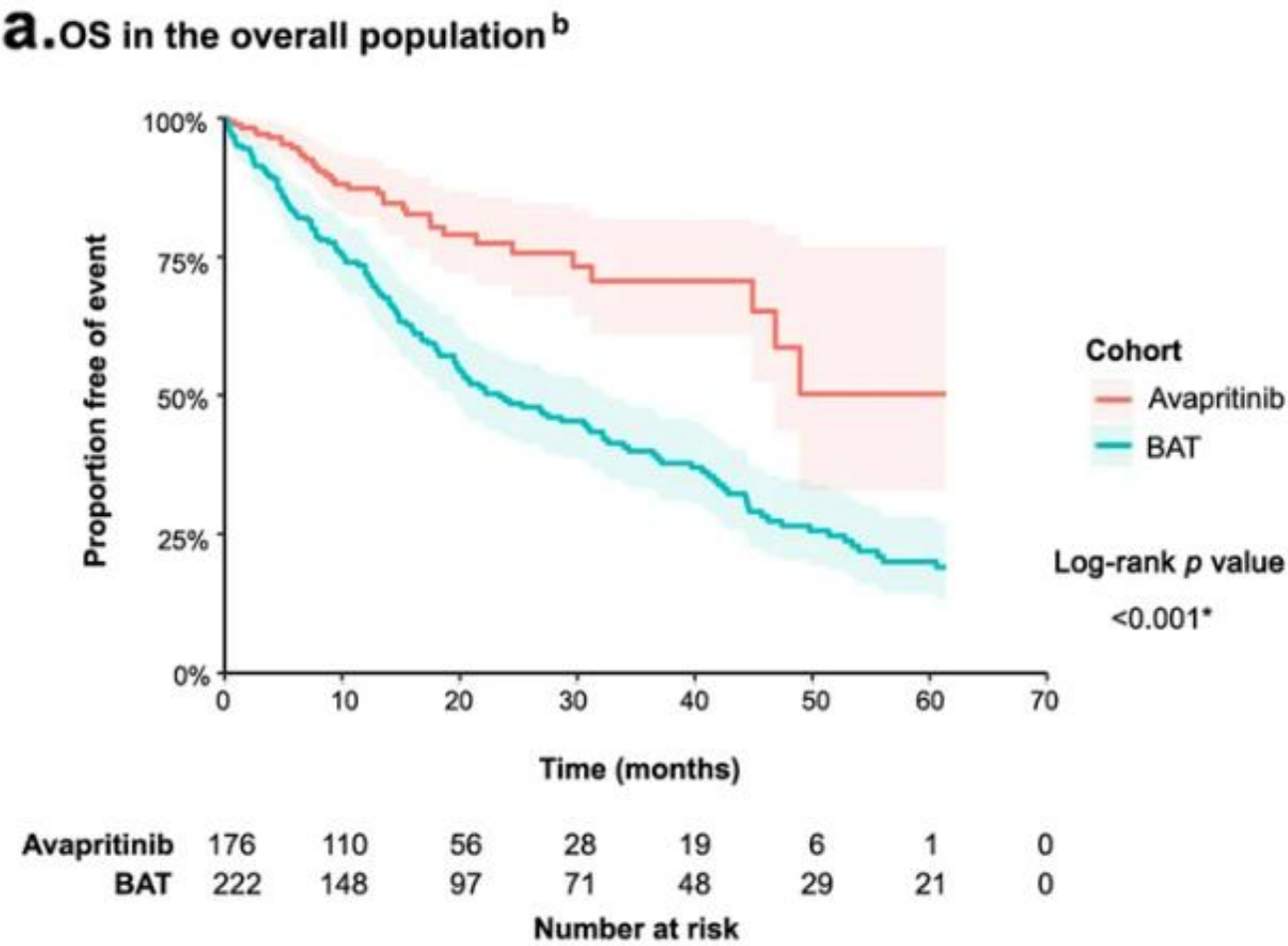


FDA approved on 4/27/2017 for ASM, SM-AH, and MCL

Avapritinib in Advanced SM (EXPLORER and PATHFINDER Studies)

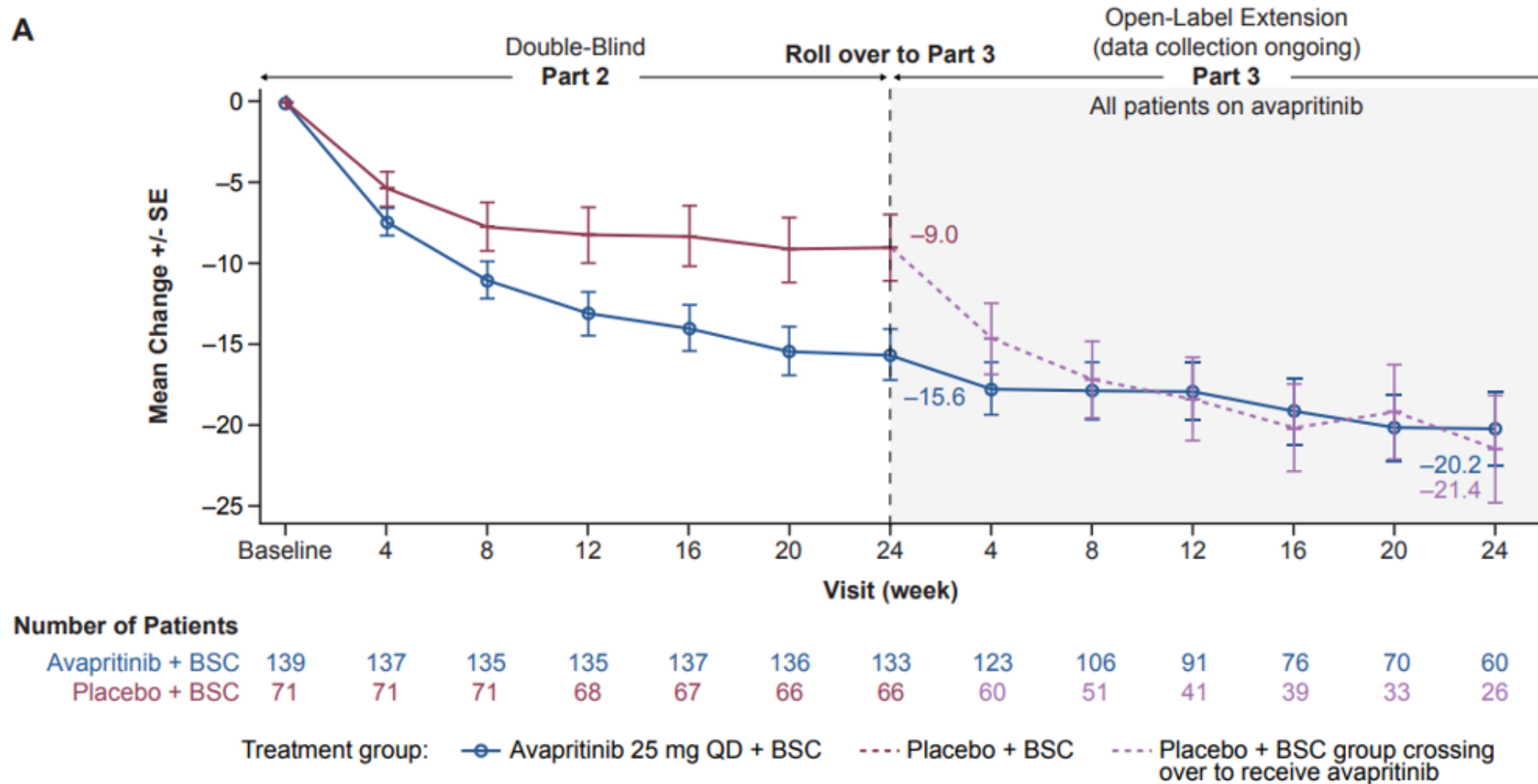
- 131 patients
- Overall response rate: 75%
- Complete response rate: 36% and 17%
- Time to response: 2 months
- Reductions in bone marrow mast cell burden, tryptase levels, symptoms, skin lesions
- Adverse events
 - Peripheral and/or periorbital edema 50%
 - Diarrhea 23%
 - Nausea 18%
 - In EXPLORER: 13% intracranial bleeds (in patients with platelets <50K)
 - Cognitive dysfunction 11%

Avapritinib vs Best Available Therapy in Advanced SM: Effect on Survival

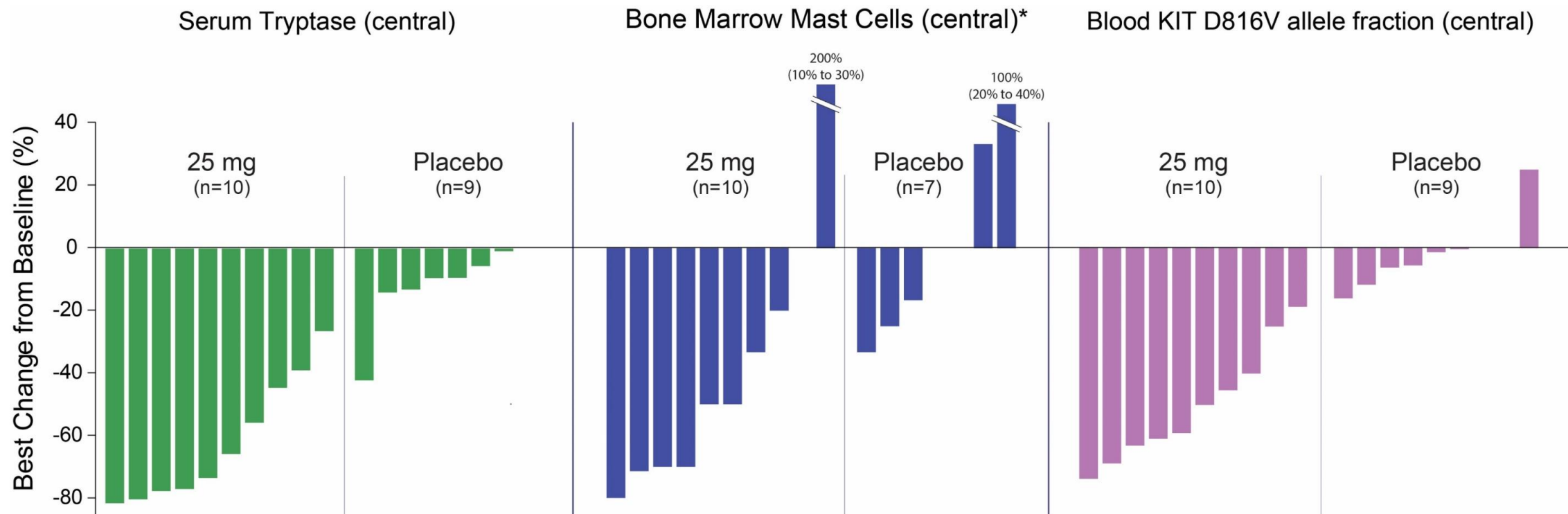


BAT = best available therapy.
Reiter A, et al. *Leukemia*. 2022;36(8):2108-2120.

Avapritinib vs Placebo in ISM: Effect on Symptom Scores (Primary Endpoint)



Objective Reductions in Mast Cell Burden at 25 mg vs Placebo



*Bone marrow MC assessment in SM may have variability in sampling due to patchy nature of disease. No patient on study has progressed to advanced disease.
#patient received high dose IV steroids.
Akin C, et al. Presented at: American Academy of Allergy Asthma and Immunology Annual (AAAAI) Meeting; March 16, 2020; virtual.

Improvement of Skin Lesions with Avapritinib



Baseline

Avapritinib: Safety Profile

	Avapritinib 25 mg QD (N=141)	Placebo (N=71)
Any AEs^{a,b}, n (%)	128 (90.8)	66 (93.0)
Grade 1–2 AEs	98 (69.5)	51 (71.8)
Grade 1–2 related AEs	74 (52.5)	30 (42.3)
Grade ≥3 AEs	30 (21.3)	15 (21.1)
Grade ≥3 related AEs	3 (2.1)	2 (2.8)
SAEs, n (%)	7 (5.0)	8 (11.3)
Any grade TRAEs	77 (54.6)	32 (45.1)
Most frequently reported 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)
TRAEs leading to discontinuation	2 (1.4)	1 (1.4)

AE = adverse event; TRAE = treatment-related adverse event.

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

Longer-Term Safety and Efficacy of Avapritinib in ISM

- 226 patients with median follow up of 35.3 months (up to 63.6 months)
- In part 3, dose escalation to 50 mg was allowed
- Improvements in skin symptoms and QoL persisted with no new safety signals observed



Figure 3. Longer-term efficacy for (A) TSS and (B) MC-QoL in the avapritinib 25 mg QD subset at 96 and 144 weeks

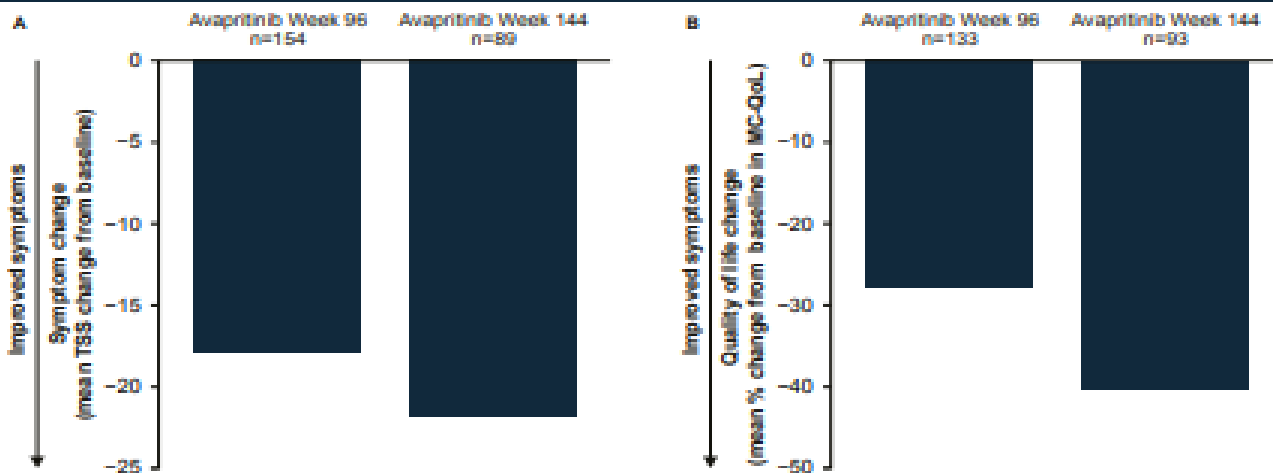


Table 2. Safety profile of avapritinib

	Part 2 ^a		Parts 1, 2, 3 combined
	Avapritinib 25 mg QD + BSC (n=141)	Placebo + BSC (n=71)	All patients who initiated avapritinib 25 mg QD + BSC (N=226) ^b
Median length of follow-up (months) ^c	5.6	5.6	35.3
Any AEs, n (%)	128 (91)	66 (93)	224 (99)
Any TRAEs, n (%)	77 (55)	32 (45)	168 (74)
Grade ≥3 AEs	30 (21)	15 (21)	103 (46)
Grade ≥3 TRAEs	3 (2)	2 (3)	14 (6)
Serious AEs	7 (5)	8 (11)	45 (20) ^d
Serious TRAEs	0 (0)	0 (0)	3 (1) ^e
TRAEs leading to discontinuation	2 (1)	1 (1)	7 (3)
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	29 (13)
Periorbital edema	9 (6)	2 (3)	22 (10)
Headache	11 (8)	7 (10)	21 (9)
Nausea	9 (6)	6 (8)	18 (8)
Fatigue	6 (4)	2 (3)	16 (7)
Diarrhea	4 (3)	2 (3)	14 (6)
Alopecia	5 (4)	3 (4)	13 (6)
Dizziness	4 (3)	5 (7)	11 (5)

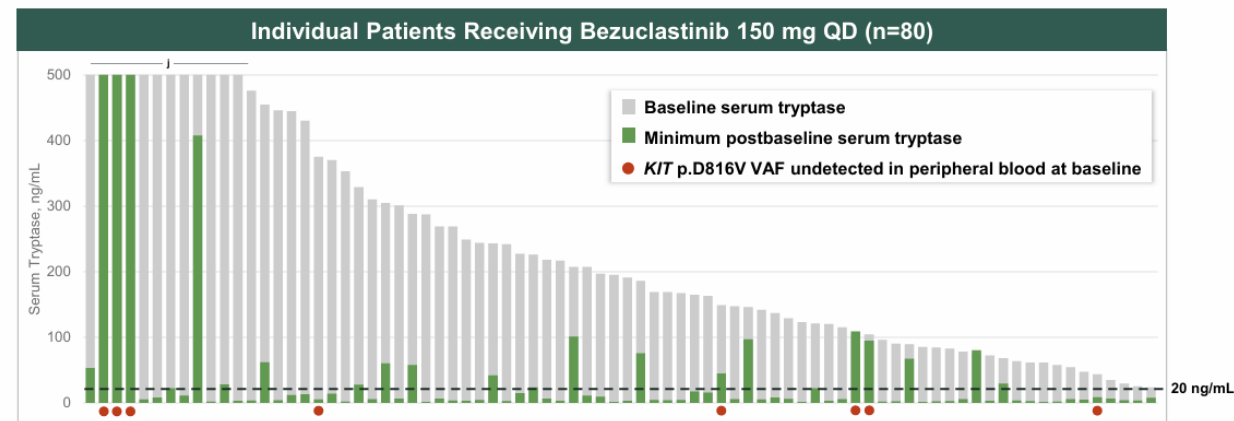
TSS = total symptom score; MC-QoL = mastocytosis quality of life questionnaire.

Akin C, et al. *J Allergy Clin Immunol*. 2026;158(2):421-431.

Bezuclastinib in Advanced SM (Investigational)

- Response rates
 - Overall response: 65%
 - Complete remission: 10%

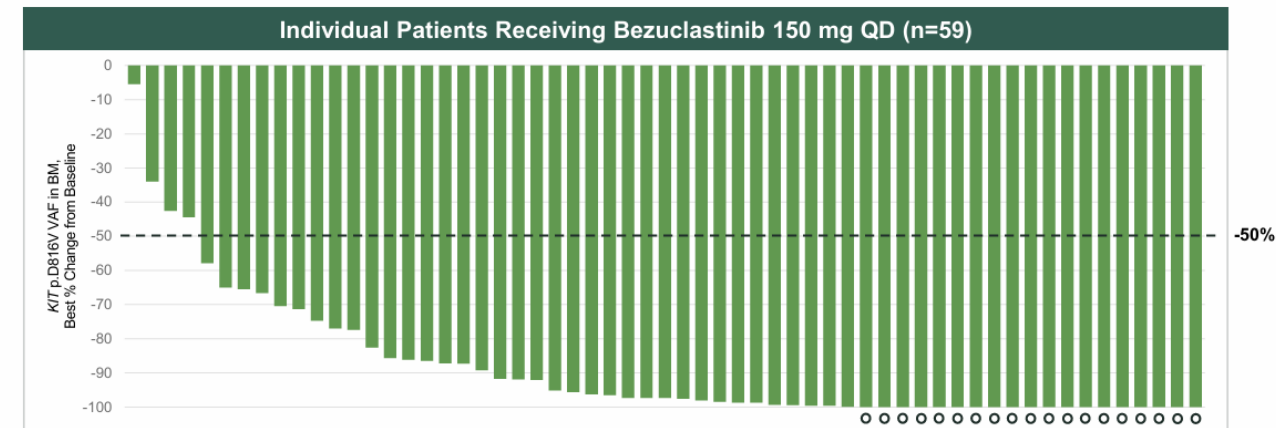
Bezuclastinib Reduced Serum Tryptase to Below Diagnostic Threshold Levels



- **89%** of patients achieved $\geq 50\%$ reduction of serum tryptase postbaseline
 - **71%** achieved serum tryptase reduction to < 20 ng/mL (diagnostic threshold) postbaseline
 - **64%** achieved serum tryptase reduction to < 11.4 ng/mL (normal level) postbaseline

[†]Patients with serum tryptase levels > 500 ng/mL, axis is truncated for visual purposes.

Bezuclastinib Reduced *KIT* p.D816V Variant Allele Frequency (VAF) in Bone Marrow and Blood

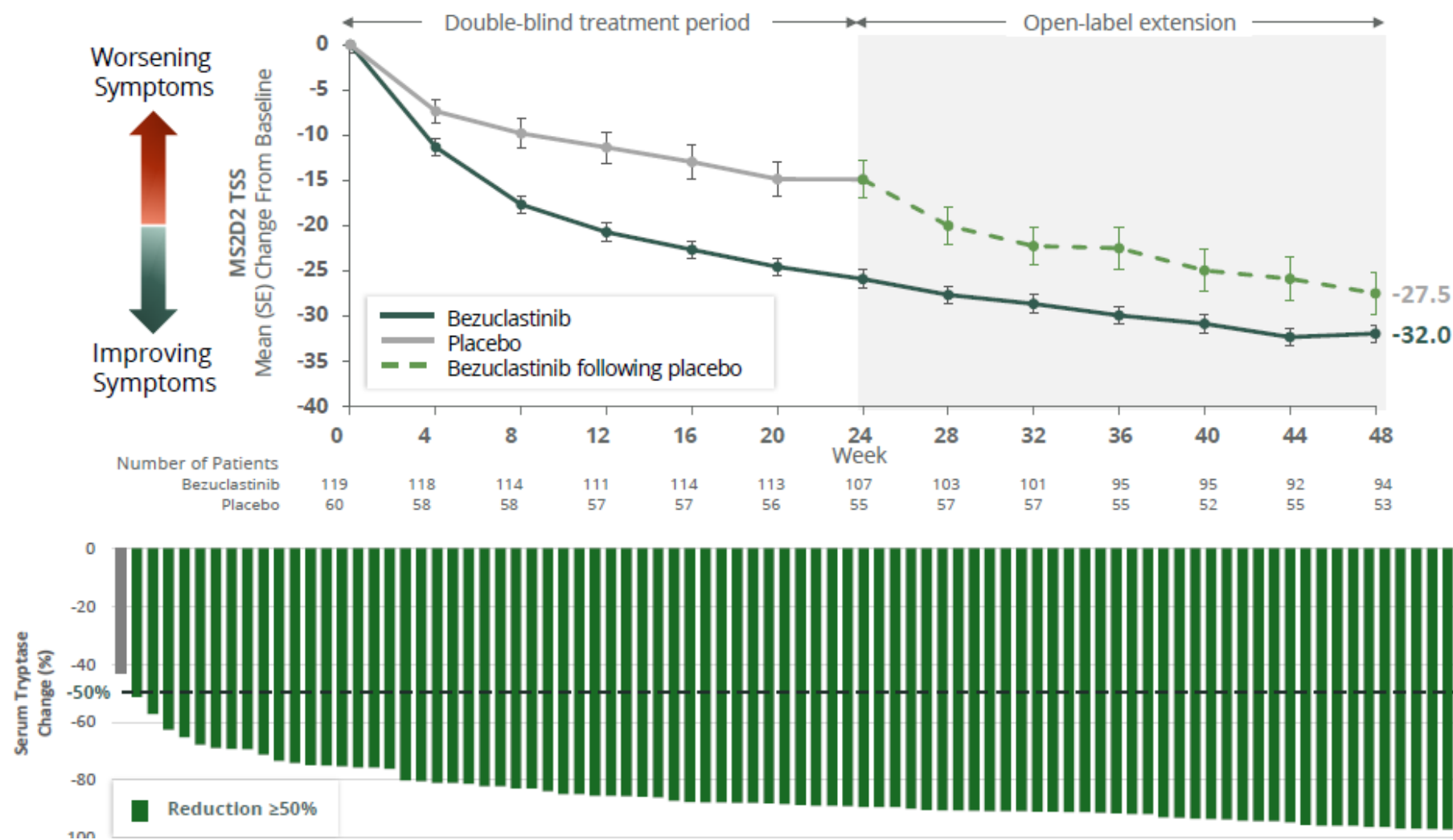


- **93%** of patients achieved $\geq 50\%$ reduction of *KIT* p.D816V VAF in BM postbaseline
 - **32%** achieved undetectable^k levels of *KIT* p.D816V VAF in BM postbaseline
- Peripheral blood results were consistent with reductions observed in BM

^kDroplet digital PCR limit of detection=0.03%.

○ *KIT* p.D816V VAF undetectable^k in BM postbaseline

Bezuclastinib in Non-Advanced SM (Investigational)



Bezuclastinib Demonstrated a Favorable and Manageable Safety Profile

	Bezuclastinib 100mg QD (N=118)	Placebo (N=60)
TEAEs, n (%)	116 (98.3)	53 (88.3)
SAEs, n (%)	5 (4.2)	3 (5.0)
Reductions due to TRAEs, n (%)	13 (11.0)	0
DCs due to TRAEs, n (%)	7 (5.9)	0
TEAEs ≥ 10% that occurred in greater frequency in bezuclastinib arm, n (%)		
Hair color changes	82 (69.5)	3 (5.0)
Altered taste*	28 (23.7)	0
Nausea	26 (22.0)	8 (13.3)
ALT/AST increased*	26 (22.0)	4 (6.6)
Headache	21 (17.8)	7 (11.7)
Alopecia	14 (11.9)	2 (3.3)
ALP increased	12 (10.2)	2 (3.3)

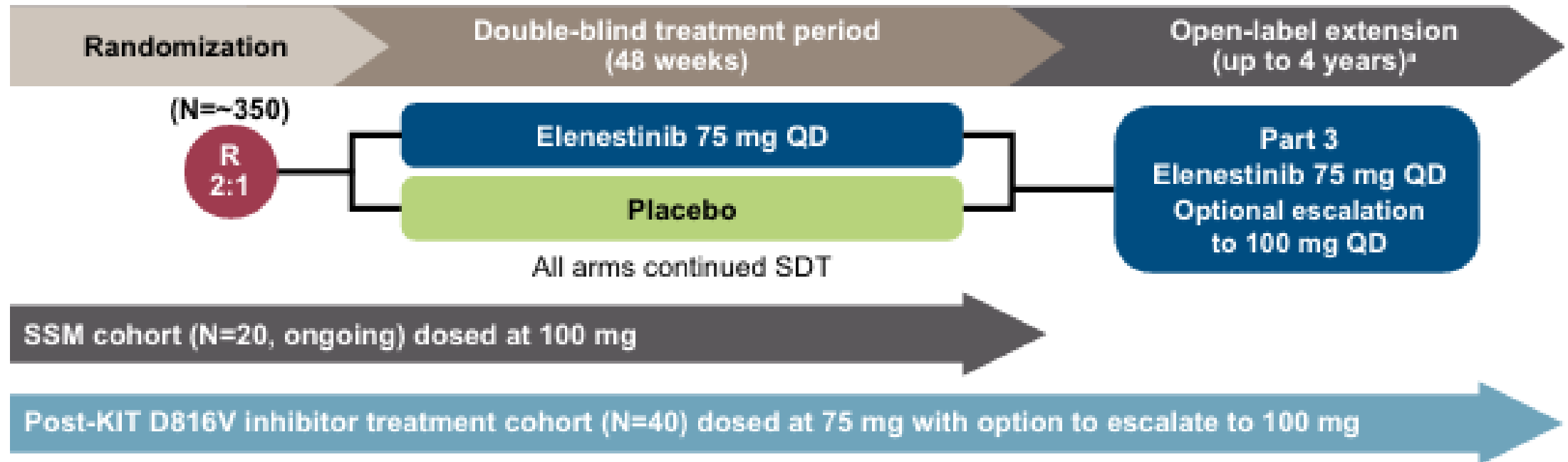
- Majority of TEAEs were of low grade (70% Gr1) and reversible
- Variety of AEs occurred more often in placebo group: Dizziness (10% vs 12%), fatigue (7% vs 12%), arthralgia (6% vs 15%), diarrhea (13% vs. 18%)
- The only hepatic AEs reported were transient and manageable lab abnormalities
- Only 5.9% of patients experienced ≥Gr 3 ALT/AST elevations, and no patients with transaminase AEs required hospitalization or treatment intervention
- All DCs due to treatment-related AEs were due to transaminase elevations and all subjects fully resolved

*Pooled terms. Data cut-off May 22, 2025.

SAE = serious AE; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DC = discontinuation.

Rein L, et al. *Blood*. 2025;146(suppl 1):80.

HARBOR (Elenestinib) Study Design

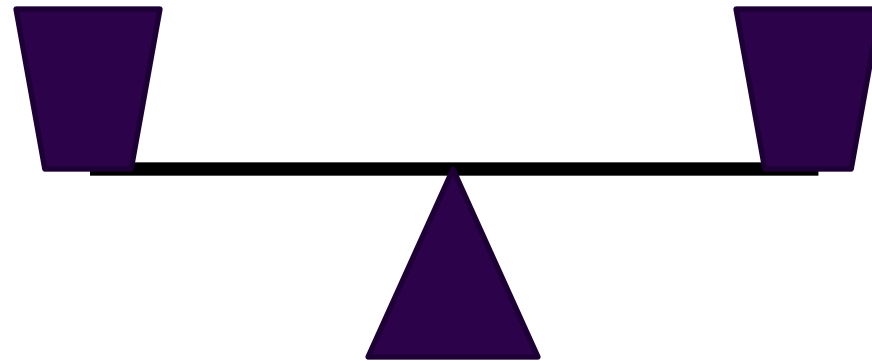


^aUp to a total of 5 years treatment between Parts 2 and 3.
QD, once daily; R, randomized.

- Key secondary endpoints include bone density and anaphylaxis

Risk vs Benefit Considerations in TKI Treatment of Patients with ISM

- Improved symptoms
 - Improved quality of life
 - Decreased skin lesions
 - Decreased polypharmacy
- Adverse events, patient-specific factors and preferences*
 - Unknown long-term safety
 - Reproductive and/or teratogenic risk
 - Need for monitoring



TKI = tyrosine kinase inhibitor.

Akin C. *J Allergy Clin Immunol*. 2017;140(2):349-355.

ECNM/AIM Guidelines for Management of Mon-Advanced SM

Drug or preventive measure

Basic management:

1. Avoidance of any triggers
2. Basic therapy with HR1 blocker plus HR2 blocker

Additional therapies and measures:

3. Adding a proton pump inhibitor to the HR2 blocker
4. Adding cromolyn sodium
5. Adding ketotifen, aspirin, or a leukotriene receptor antagonist (eg, montelukast)
6. Adding ultraviolet light therapy†
7. Adding corticosteroids

Additional specific therapies:

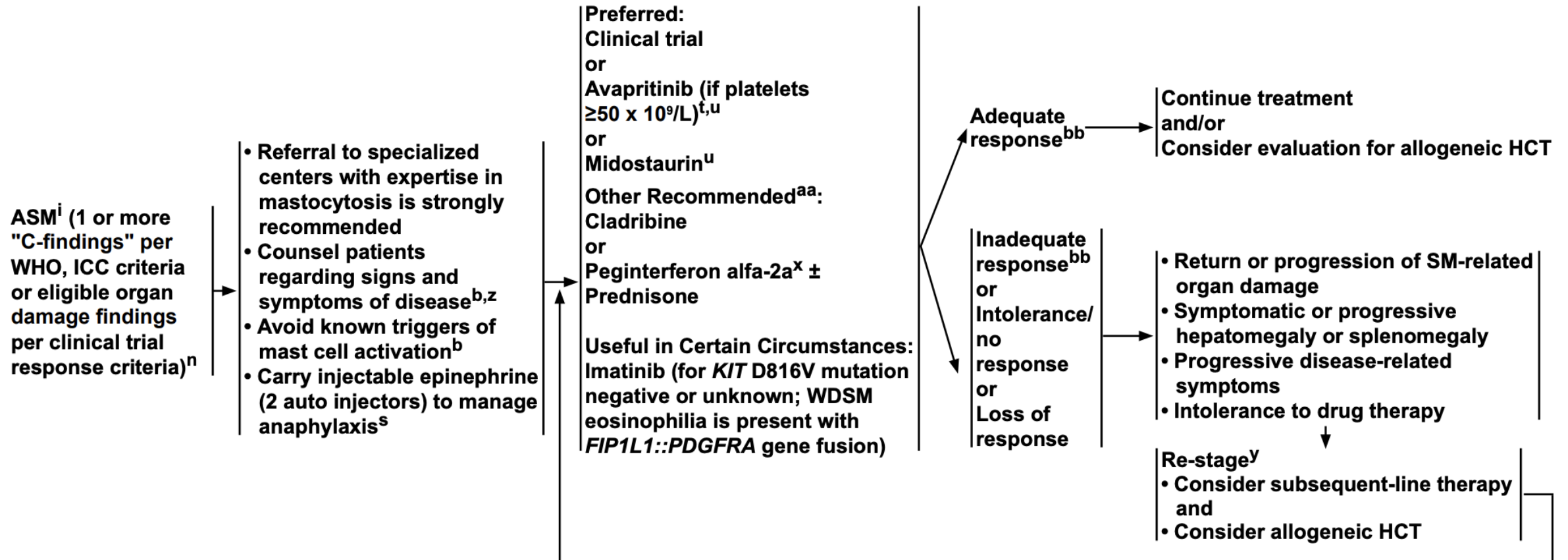
8. Insect venom immunotherapy
9. Omalizumab therapy
10. Adrenaline and other emergency drugs used in anaphylaxis
11. Midostaurin or avapritinib

ECNM/AIM = European Competence Network on Mastocytosis/American Initiative in Mast Cell Diseases; HR = histamine receptor.

Valent P, et al. *J Allergy Clin Immunol Pract.* 2022;10(8):1999-2012.e6.

Treatment of Advanced SM

TREATMENT FOR AGGRESSIVE SYSTEMIC MASTOCYTOSIS¹



If SM-AHN, determine if AHN or SM component needs to be prioritized, and treat AHN according to its guidelines

HCT = hematopoietic cell transplantation; NCCN = National Comprehensive Cancer Network.

Referenced from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Systemic Mastocytosis V.3.2026. ©National Comprehensive Cancer Network, Inc. 2026. All rights reserved. Accessed October 6, 2026. To view the most recent and complete version of the guideline, go online to NCCN.org.



masterclasses in dermatology
saturday morning live

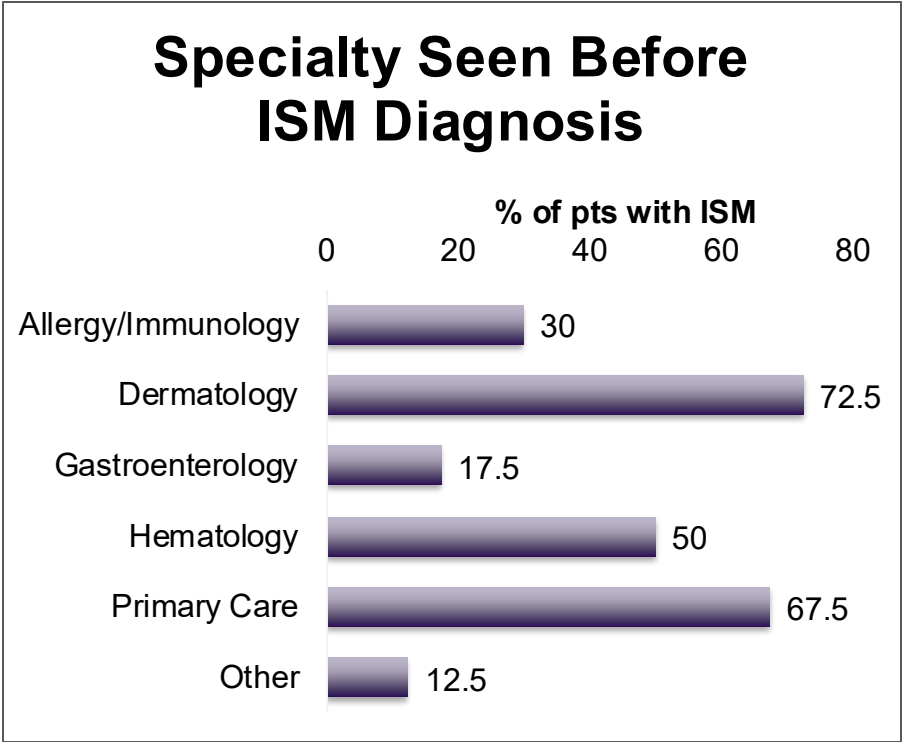
PRESENTED BY THE **dermatologist**

Multidisciplinary Collaboration in Systemic Mastocytosis

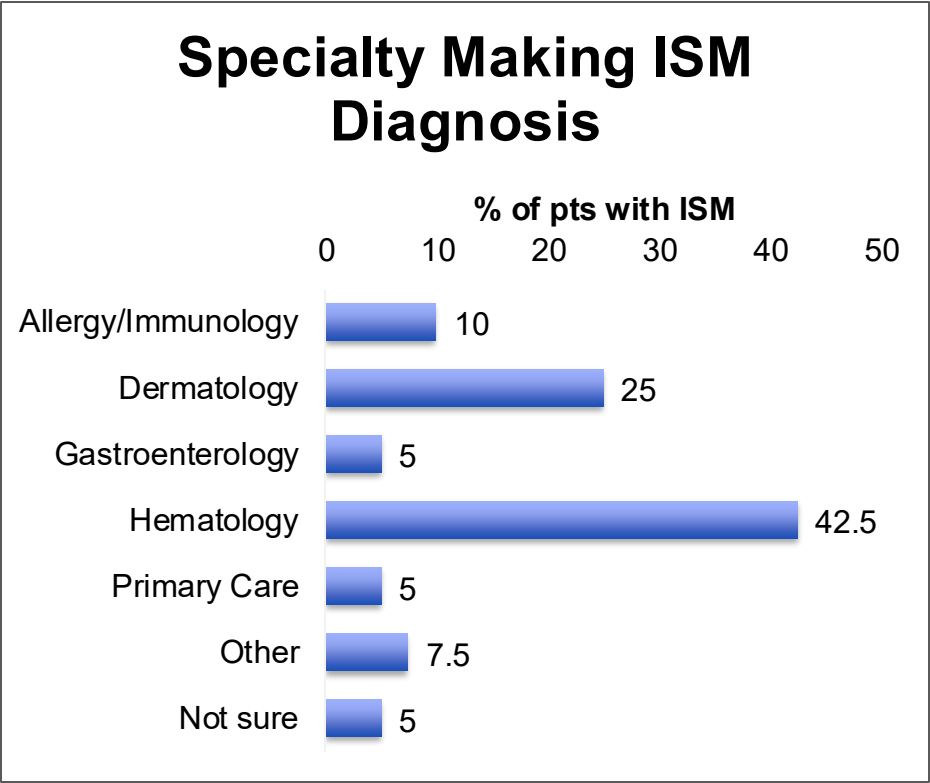
Sarina B. Elmariah, MD, PhD, MPH, FAAD

The role of dermatology in SM is key!
Dermatology may be the gateway to
early diagnosis and management...

SM Is Often Seen, but Overlooked by Dermatologists



Journey to ISM diagnosis	ISM-SAF severity score			P value
	Score <28 (n = 21)	Score ≥28 (n = 19)	Total (N = 40)	
Time to diagnosis (y)				.20
≤2	15 (71.4)	9 (47.4)	24 (60.0)	
>2	6 (28.6)	10 (52.6)	16 (40.0)	
Visits for symptoms to diagnosis				.11
1-5	14 (66.7)	7 (36.8)	21 (52.5)	
6 or more	7 (33.3)	12 (63.2)	19 (47.5)	
Difficulty to ISM diagnosis				.35
Easy	8 (38.1)	3 (15.8)	11 (27.5)	
Neither easy nor difficult	4 (19.0)	5 (26.3)	9 (22.5)	
Moderately or extremely difficult	9 (42.9)	11 (57.9)	20 (50.0)	
Specialty seen before ISM diagnosis				
Allergist/immunologist	7 (33.3)	5 (26.3)	12 (30.0)	.74
Dermatologist	13 (61.9)	16 (84.2)	29 (72.5)	.16
Gastroenterologist	4 (19.0)	3 (15.8)	7 (17.5)	>.99
Hematologist	14 (66.7)	6 (31.6)	20 (50.0)	.06
Primary care doctor	13 (61.9)	14 (73.7)	27 (67.5)	.51
Other	3 (14.3)	2 (10.5)	5 (12.5)	>.99
Specialty diagnosed ISM				.77
Allergy/immunology	3 (14.3)	1 (5.3)	4 (10.0)	
Dermatology	3 (14.3)	7 (36.8)	10 (25.0)	
Gastroenterology	1 (4.8)	1 (5.3)	2 (5.0)	
Hematology	10 (47.6)	7 (36.8)	17 (42.5)	
Primary care	1 (4.8)	1 (5.3)	2 (5.0)	
Other	2 (9.5)	1 (5.3)	3 (7.5)	
Not sure	1 (4.8)	1 (5.3)	2 (5.0)	
Specialty caring for ISM now				.64
Allergy/immunology	5 (23.8)	5 (26.3)	10 (25.0)	
Dermatology	2 (9.5)	0 (0.0)	2 (5.0)	
Hematology	10 (47.6)	13 (68.4)	23 (57.5)	
Primary care	2 (9.5)	1 (5.3)	3 (7.5)	
Other/not sure	2 (9.5)	0 (0.0)	2 (5.0)	
Duration of ISM diagnosis (y)				.76
<1	3 (14.3)	2 (10.5)	5 (12.5)	
1-4	8 (38.1)	5 (26.3)	13 (32.5)	
5-9	6 (28.6)	6 (31.6)	12 (30.0)	
≥10	4 (19.0)	6 (31.6)	10 (25.0)	



Skin Symptoms Are Present & Bothersome When Patients See the Dermatologist

TABLE III. Comparison of symptoms of the surveyed cohort with indolent systemic mastocytosis (ISM) by the ISM Symptom Assessment Form (ISM-SAF) severity score

	ISM-SAF severity score			
Symptoms by body system*	Score <28 (n = 21)	Score ≥28 (n = 19)	Total (N = 40)	P value
Symptoms at time of diagnosis				
Skin	16 (76.2)	19 (100.0)	35 (87.5)	.049
Gastrointestinal	6 (28.6)	12 (63.2)	18 (45.0)	.05
Fatigue	5 (23.8)	15 (78.9)	20 (50.0)	.001
Neurological	7 (33.3)	17 (89.5)	24 (60.0)	<.001
Pain (muscle, joint, bone)	6 (28.6)	11 (57.9)	17 (42.5)	.11
Respiratory	2 (9.5)	1 (5.3)	3 (7.5)	>.99
Bone (osteoporosis/osteopenia)	4 (19.0)	6 (31.6)	10 (25.0)	.47
Anaphylaxis (severe reaction)	6 (28.6)	5 (26.3)	11 (27.5)	>.99
Most severe symptoms at time of diagnosis				.38
Skin	11 (52.4)	12 (63.2)	23 (57.5)	
Gastrointestinal	3 (14.3)	3 (15.8)	6 (15.0)	
Fatigue	0 (0.0)	2 (10.5)	2 (5.0)	
Neurological	1 (4.8)	0 (0.0)	1 (2.5)	
Bone (osteoporosis/osteopenia)	1 (4.8)	0 (0.0)	1 (2.5)	
Anaphylaxis (severe reaction)	2 (9.5)	2 (10.5)	4 (10.0)	
None of the above	3 (14.3)	0 (0.0)	3 (7.5)	

Current/present symptoms

Skin	18 (85.7)	19 (100)	37 (92.5)	.23
Gastrointestinal	8 (38.1)	14 (73.7)	22 (55.0)	.03
Fatigue	5 (23.8)	17 (89.5)	22 (55.0)	<.001
Neurological	8 (38.1)	18 (94.7)	26 (65.0)	<.001
Pain (muscle, joint, bone)	8 (38.1)	16 (84.2)	24 (60.0)	.004
Respiratory (difficulty breathing)	0 (0.0)	2 (10.5)	2 (5.0)	.22
Bone (osteoporosis/osteopenia)	7 (33.3)	10 (52.6)	17 (42.5)	.34
Anaphylaxis (severe reaction)	5 (23.8)	6 (31.6)	11 (27.5)	.73

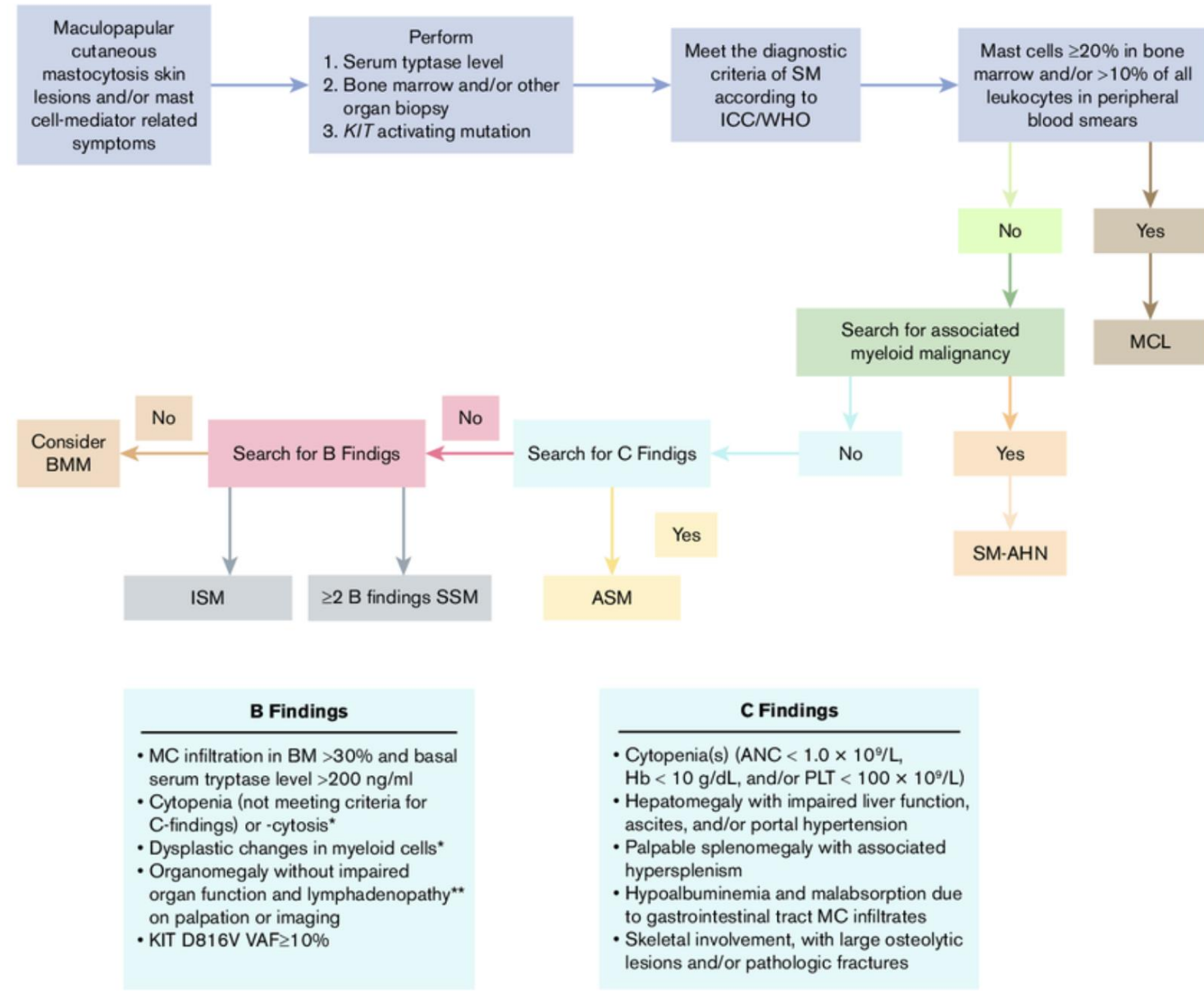
Most severe symptoms currently

				.27
Skin	11 (52.4)	8 (42.1)	19 (47.5)	
Gastrointestinal	2 (9.5)	4 (21.1)	6 (15.0)	
Fatigue	0 (0.0)	2 (10.5)	2 (5.0)	
Neurological	1 (4.8)	1 (5.3)	2 (5.0)	
Pain	1 (4.8)	1 (5.3)	2 (5.0)	
Bone (osteoporosis/osteopenia)	0 (0.0)	2 (10.5)	2 (5.0)	
Anaphylaxis (severe reaction)	3 (14.3)	1 (5.3)	4 (10.0)	
None of the above	3 (14.3)	0 (0.0)	3 (7.5)	

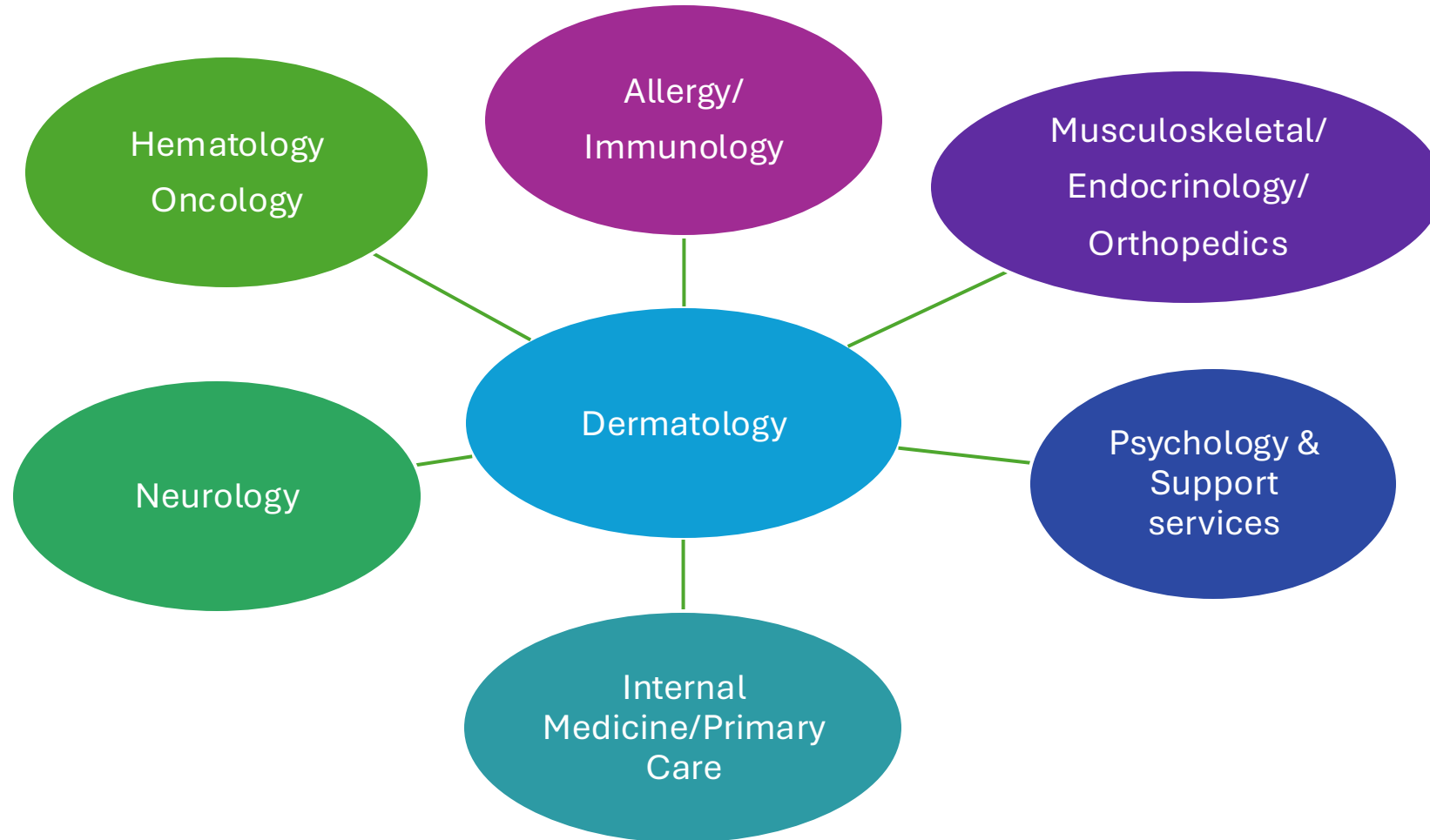
The Role of Dermatology in SM Is Early and Ongoing

- Early and timely diagnosis of suspicious skin lesions for cutaneous mastocytosis
 - Skin biopsy for mast cell burden – requires morphology and special stains!
 - Screening for serum tryptase or KIT mutation analysis
- Management of cutaneous S/SX and risks of anaphylaxis
 - Antihistamines, mast cell stabilizers, leukotriene inhibitor, PPIs
 - Anti-IgE/omalizumab
 - Tyrosine kinase inhibitors – collaborate with hematology and/or allergy
 - Cytoreductive agents – collaborate with hematology and/or allergy
- Ongoing monitoring for skin cancer risk!!
- Referral to specialties
 - Hematology/oncology – monitoring, coordination of care, possible bone marrow biopsy
 - Allergy immunology/pulmonary/GI
 - Endocrinology/internal medicine

Diagnostic Overview



Collaborative and Multidisciplinary Expertise Is Critical for the SM Population



If You Overlook SM, You Overlook...

- Increased risk of anaphylaxis (50%)
- Increased risk of osteoporosis (20%), osteopenia (25%), potential fractures (30% lifetime risk)
- Potential for disease progression to advanced SM variant (5%)
- Increased risk of melanoma and other skin cancers
 - Significantly elevated lifetime risks of all skin cancers compared to controls, with the highest risk observed for MM: HR 2.49, 95% CI: 1.88-3.31 $P<.001$
 - Risk of MM was highest within the first year postdiagnosis (HR: 3.54, 95% CI 1.86-6.73, $P<.001$)

MM = multiple myeloma.

Bergström A, et al. *J Am Acad Dermatol*. 2025;93(3):835-837. Degboe Y, et al. *Bone*. 2017;105:219-225..Vander Veer E, et al. *Allergy*. 2012;67(3):431-438. Trizuliak J, et al *Allergy*. 2020;75(8):1927-1938.

Anaphylaxis Occurs in ~50% of Patients with SM

- Mastocytosis is a key risk factor for severe anaphylaxis
 - Triggers for anaphylaxis include hymenoptera stings (19–60%), foods (3–16%), and drugs (5–9%)
 - Don't forget to Rx and encouraged patient to carry epinephrine injection-pens!
- In patients with recurrent idiopathic anaphylaxis, screen BST, high sensitivity KIT D816V testing, and bone marrow!



HαT + Mastocytosis Intersection

12.6%

HαT prevalence in mastocytosis

French referral cohort

5.7%

Control prevalence

same study

43.0% vs 24.4%

Anaphylactic reactions

HαT+ vs HαT– mastocytosis

A high basal tryptase in systemic mastocytosis may reflect two biological components:

Mast-cell burden

+

**Inherited α-tryptase gene
dosage**

**Finding HαT does not exclude mastocytosis—and finding
mastocytosis does not make HαT irrelevant!**

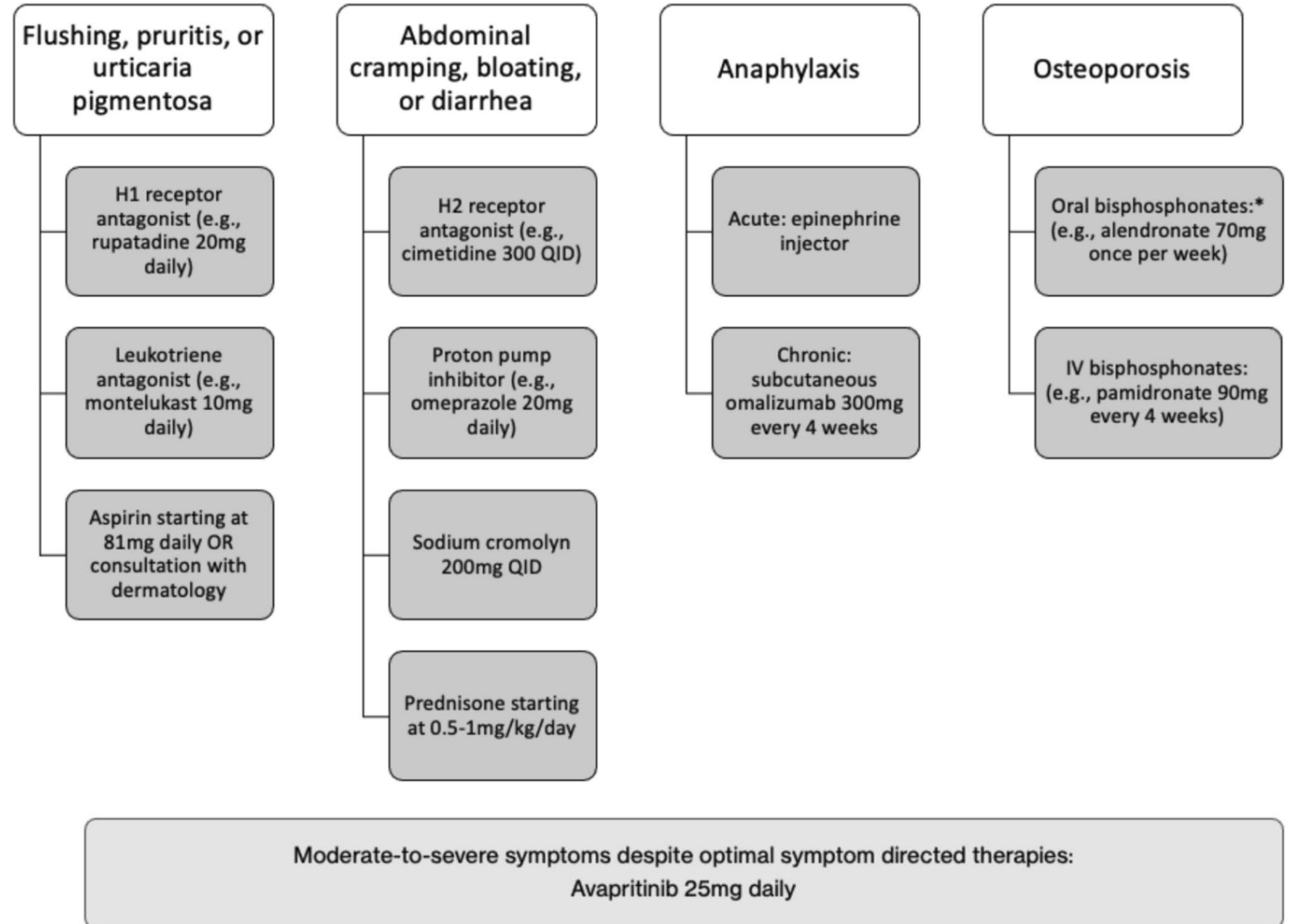
ISM S/Sx Management

Management focus has often been on mediator-directed symptomatic treatment

- Safety
- Mediator control
- Comorbidity management



Now, there are options for disease-directed control



A Clinician's Guide to ISM

DIAGNOSIS & KEY INDICATORS

Diagnosis Requires: 1 Major + 1 Minor OR 3 Minor Criteria



Major Criterion:
Multifocal mast cell clusters
(>15) in bone marrow

Key Minor Criteria



Abnormal cell
morphology



KIT
mutation



CD25
expression



Serum tryptase
 >20 ng/ml



When to Suspect Systemic Mastocytosis



Unexplained
anaphylaxis



Severe venom
reactions



Unexplained
osteoporosis

TREATMENT FOR NON-ADVANCED ISM

First-Line: Symptom-Based Management



H1/H2
antihistamines



Leukotriene
modifiers



Mast cell stabilizers
(cromolyn)

Second-Line: Targeted Therapy



Avapritinib: FDA-approved targeted treatment
for patients with refractory symptoms

Management Requires an Interdisciplinary Team



Allergy
Immunology



Hematology



Dermatology



Gastroenterology



Primary
Care

Key Learning Points



- Dermatology may be the first encounter in a patient with SM's journey
- Most adults with evidence of cutaneous mastocytosis have systemic involvement
 - Be comfortable with screening (BST, KIT mutation analysis), and referrals
- Collaborative effort with other specialties is paramount for management of signs/symptoms and risks for complications of associated disease