

Refined Treatment Response Criteria for Indolent Systemic Mastocytosis Proposed by the ECNM-AIM Consortium



Polina Pyatlova, MD^{a,b}, Cem Akin, MD, PhD^c, Iván Alvarez-Twose, MD, PhD^d, Michel Arock, PharmD, PhD^e, Patrizia Bonadonna, MD^f, Knut Brockow, MD^g, Joseph H. Butterfield, MD^h, Sigurd Broesby-Olsen, MD^{i,j}, Melody C. Carter, MD^k, Mariana Castells, MD, PhD^l, Tracy I. George, MD^m, Jason Gotlib, MD, MSⁿ, Georg Greiner, MD, PhD^{o,p,q}, Theo Gülen, MD, PhD^{r,s}, Karin Hartmann, MD^{t,u}, Olivier Hermine, MD, PhD^v, Hans-Peter Horny, MD^w, Mohamed Jawhar, MD^x, Magdalena Lange, MD, PhD^y, Jonathan J. Lyons, MD^z, Marcus Maurer, MD^{a,b}, Dean D. Metcalfe, MD, MS^k, Boguslaw Nedoszytko, PhD^{aa,bb}, Marek Nedoszytko, MD, PhD^{cc}, Alberto Orfao, MD, PhD^{dd}, Andreas Reiter, MD^w, Juliana Schwaab, MD^w, Karl Sotlar, MD^{ee}, Wolfgang R. Sperr, MD^{o,ff}, Massimo Triggiani, MD, PhD^{gg}, Peter Valent, MD^{o,ff}, and Frank Siebenhaar, MD^{a,b} Berlin, Munich, Mannheim, Germany; Ann Arbor, Mich; Toledo, Salamanca, Spain; Paris, France; Verona, Salerno, Italy; Rochester, Minn; Odense, Denmark; Bethesda, Md; Boston, Mass; Salt Lake City, Utah; Stanford, Calif; Vienna, Salzburg, Austria; Stockholm, Sweden; Basel, Switzerland; and Gdansk, Poland

Indolent systemic mastocytosis (ISM) has a favorable prognosis and normal life expectancy. However, many patients suffer from mast cell (MC) mediator-related symptoms, which significantly affect quality of life (QoL). Cutaneous, gastrointestinal, and neurological complaints, musculoskeletal pain, and the presence of skin lesions, anaphylaxis, and osteoporosis are the main

symptoms and signs in ISM and must be assessed in all patients before and during treatment. Validated mastocytosis-specific patient-reported outcome measures (PROMs) should be used for this purpose. Serum tryptase and *KIT* D816V allele burden are recommended as secondary outcome parameters, noting that they do not reflect the severity of signs, symptoms, and related

^aInstitute of Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

^bFraunhofer Institute for Translational Medicine and Pharmacology ITMP, Allergology and Immunology, Berlin, Germany

^cDivision of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, Mich

^dInstituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast) and CIBERONC, Hospital Virgen del Valle, Toledo, Spain

^eDepartment of Hematological Biology, Pitié-Salpêtrière Hospital, Paris Sorbonne University, Paris, France

^fAllergy Unit, Verona University Hospital, Verona, Italy

^gDepartment of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany

^hMayo Clinic, Division of Allergic Diseases, Rochester, Minn

ⁱMastocytosis Centre, Odense University Hospital, Odense, Denmark

^jDepartment of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

^kMast Cell Biology Section, Laboratory of Allergic Diseases, NIAID, NIH, Bethesda, Md

^lDivision of Allergy and Immunology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

^mDepartment of Pathology, University of Utah, Salt Lake City, Utah

ⁿStanford University School of Medicine/Stanford Cancer Institute, Stanford, Calif

^oLudwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria

^pDepartment of Laboratory Medicine, Medical University of Vienna, Vienna, Austria

^qIhr Labor, Medical Diagnostic Laboratories, Vienna, Austria

^rDepartment of Respiratory Medicine and Allergy, Karolinska University Hospital Huddinge, Stockholm, Sweden

^sDepartment of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

^tDivision of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland

^uDepartment of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland

^vImagine Institute Université de Paris, Sorbonne, INSERM U1163, Centre national de référence des mastocytoses, Hôpital Necker, Assistance publique hôpitaux de Paris, Paris, France

^wInstitute of Pathology, Ludwig Maximilians University, Munich, Germany

^xDepartment of Hematology and Oncology, University Hospital Mannheim, Mannheim, Germany

^yDepartment of Dermatology, Venereology and Allergology, Medical University of Gdansk, Gdansk, Poland

^zTranslational Allergic Immunopathology Unit, Laboratory of Allergic Diseases, NIAID, NIH, Bethesda, Md

^{aa}Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, Gdansk, Poland

^{bb}Invicta Fertility and Reproductive Centre, Molecular Laboratory, Gdansk, Poland

^{cc}Department of Allergology, Medical University of Gdańsk, Gdansk, Poland

^{dd}Servicio General de Citometría, Centro de Investigación del Cáncer (IBMCC CSIC/USAL) Instituto Biosanitario de Salamanca (IBSAL), CIBERONC and Department of Medicine, University of Salamanca, Salamanca, Spain

^{ee}Institute of Pathology, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria

^{ff}Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria

^{gg}Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy
M. C. Carter, J. J. Lyons, and D. D. Metcalfe were supported by the Division of Intramural Research, National Institutes of Allergic and Infectious Diseases, and National Institutes of Health. M. Nedoszytko was supported by the Medical University of Gdansk grant 02-0141/07/231. P. Valent was supported by the Austrian Science Fund (FWF) grant # P32470-B.

Conflicts of interest: C. Akin has received grant support from Blueprint and has served as a consultant for Blueprint and Novartis. I. Alvarez-Twose is or recently was a speaker and/or advisor for Blueprint Medicines and Novartis. M. Arock has received research grants from Blueprint and honoraria from AB Science, Blueprint, and Novartis. P. Bonadonna is or recently was a speaker and/or advisor for

Abbreviations used

AIM- American Initiative in Mast Cell Disease
 ASO-qPCR- Allele-specific quantitative polymerase chain reaction
 BM- Bone marrow
 BMD- Bone mineral density
 CR- Complete response
 ddPCR- Droplet digital polymerase chain reaction
 ECNM- European Competence Network on Mastocytosis
 GI- Gastrointestinal
 HcT- Hereditary α -tryptasemia
 ISM- Indolent systemic mastocytosis
 ISM-SAF- Indolent systemic mastocytosis symptom assessment form
 MAS- Mastocytosis activity score
 MC- Mast cell
 MC-QoL- Mastocytosis Quality-of-Life Questionnaire MC-QoL
 MQLQ- Mastocytosis Quality-of-Life Questionnaire MQLQ
 MR- Major response
 MSAF- Mastocytosis symptom assessment form
 NR- No response
 PINP- N-terminal propeptide of type 1 collagen
 PB- Peripheral blood
 PR- Partial response
 PROMs- Patient-reported outcome measures
 QoL- Quality of life
 SCORMA- Scoring mastocytosis index
 sCTX- Cross-linked C-telopeptide of type 1 collagen
 SM- Systemic mastocytosis
 SSM- Smoldering systemic mastocytosis
 WHO- World Health Organization

QoL impairment, but indirectly express MC burden. Changes from baseline of 90%, 60%, and 30% indicate complete response >90%, major response 60% to 90%, partial response 30% to 60%, and no response <30% to treatment. To conclude, we recommend the use of PROMs as primary outcome parameters to define treatment response in patients with ISM in clinical trials and in everyday clinical practice. © 2022 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2015-24)

Blueprint Medicines and Novartis. S. Broesby-Olsen is or recently was a study steering committee member for Blueprint Medicines, and a speaker for Novartis and Thermo Fisher. T. I. George has received consultancy with Blueprint Medicines, Incyte, and Celgene/BMS. J. Gotlib has received research grant (funds for administration of clinical trials) from Novartis, Blueprint Medicines, Deciphera, and Cogent Biosciences; is on the advisory board of and has received honoraria from Blueprint Medicines, Novartis, Deciphera, and Cogent Biosciences; and has received reimbursement of travel expenses from Novartis and Blueprint Medicines. K. Hartmann has no relevant conflict of interest in relation to this work. Outside of this work, she has received research funding from Thermo Fisher and consultancy or lecture fees from Allergopharma, ALK-Abello, Blueprint, Deciphera, Leo Pharma, Menarini, Novartis, Pfizer, Takeda, and Thermo Fisher. M. Maurer has no relevant conflict of interest in relation to this work. Outside of it, he is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Alnylam, Amgen, Aquestive, Arcensus, Aralez, ArgenX, AstraZeneca, Astria, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Cogent, FAES, Genentech, GSK, GILInnovation, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, ThirdHarmonicBio, UCB, and Uriach. D. D. Metcalfe is an investigator in a clinical trial for Sanofi US Services. A. Orfao has received grant support from Blueprint, and has served as a consultant for Blueprint and

Key words: Mast cells; Mastocytosis; Symptoms; Signs; Mast cell activation; Response criteria

During the working conference on mast cell (MC) disorders organized by representatives of the European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Disease (AIM) in Vienna in 2020, treatment response criteria in indolent systemic mastocytosis (ISM) were discussed. Two major aims were identified and addressed: (1) to provide tools for the use by health care providers in daily practice for the evaluation of treatment outcomes; (2) to define response criteria to be used in clinical trials for assessing the efficacy of novel treatment options in ISM. Experts involved in mastocytosis management gave their feedback and shared their thoughts. Finally, relevant tools and response criteria for everyday practice and clinical trials were discussed and, based on published data, expert opinion and experience from clinical trials in ISM, consensus statements, and revised response criteria were prepared.

STATUS QUO**Definition, epidemiology, and prognosis of ISM**

Systemic mastocytosis (SM) is a heterogeneous group of disorders characterized by increased numbers and accumulation of neoplastic MCs in various organs, including bone marrow (BM), skin, spleen, lymph nodes, and gastrointestinal (GI) tract.¹⁻⁴ ISM is the most common SM subtype and affects around 90% of adults with mastocytosis. The prognosis and survival in ISM are favorable, with the risk of progression to advanced forms of SM being less than 3% and up to 7% including smoldering SM (SSM).⁵⁻⁷ Up to 95% of patients suffer from MC mediator-related symptoms, which can significantly impact quality of life (QoL).^{3,5,8-13}

Clinical phenotypes, signs, and symptoms of ISM

Clinical manifestations of ISM are highly variable. The signs of ISM include MC accumulation in the skin (typically associated with maculopapular cutaneous lesions) as well as other organs and bone involvement (often associated with osteopenia, osteoporosis, and rarely osteosclerosis). Among symptoms in patients with ISM, the following are often recorded: skin

Novartis. A. Reiter has received research grant (funds for administration of clinical trials) from Blueprint Medicines, Novartis, and Deciphera; is on the advisory board of and has received honoraria and reimbursement of travel expenses from Blueprint Medicines and Novartis. W. R. Sperr received honoraria from Novartis, Pfizer, AbbVie, Daiichi Sankyo, Stem line, Thermo Fisher, Deciphera, Celgene, and Jazz. M. Triggiani has consultancy with Novartis and Blueprint; and is an investigator in a clinical trial for Blueprint. F. Siebenhaar is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Blueprint, Celldex, CogentBio, Genentech, Novartis, Moxie, Sanofi, and Uriach. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication February 16, 2022; revised May 12, 2022; accepted for publication May 15, 2022.

Available online June 18, 2022.

Corresponding author: Frank Siebenhaar, MD, Charité—Universitätsmedizin Berlin, Institute of Allergology, Hindenburgdamm 30, Haus II, 12203 Berlin, Germany. E-mail: frank.siebenhaar@charite.de.

2213-2198

© 2022 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2022.05.037>

symptoms (itching and flushing), GI symptoms (diarrhea, abdominal cramping, nausea, and vomiting), musculoskeletal pain, and neurological symptoms (fatigue/exhaustion, headache, and cognitive dysfunction).^{2-4,14,15}

Secondary osteoporosis and anaphylaxis are common features of mastocytosis, and the latter comes with the risk of recurrent and severe or even life-threatening events. Up to one-third of patients with ISM are diagnosed with osteoporosis/osteopenia.¹⁶⁻²² The risk of anaphylaxis in ISM is much higher than in the general population and varies from 20% to 56% of all patients, with Hymenoptera insect venom being the most frequent trigger.²³⁻²⁶ Anaphylaxis is the most common sign in patients with ISM without skin lesions, with up to 80% being at risk of severe reactions.^{27,28}

Quality-of-life impairment

One-third of patients with ISM exhibit moderately or severely impaired QoL, and only 30% of patients report no impairment in their QoL.^{29,30} ISM affects the private and social life of patients and their performance in school or at work. In many patients, symptoms do not allow for social activities, and patients fear the onset of signs and symptoms, which is often unpredictable. In addition, patients are concerned about the lack of expert knowledge and treatment they may face when consulting their physicians.⁸ Flushing, diarrhea, fatigue, and fear of anaphylaxis were reported to be among the most frequent causes of QoL impairment.^{12,14}

Patient-reported outcome measures for ISM

Several patient-reported outcome measures (PROMs) for assessing the symptom burden and disease-specific QoL in patients with ISM have been developed. Some of them have been translated and validated in different languages, making them available and easy to use all around the globe. Because of the lack of yet available effective treatment options, clinimetric validation of the available tools has not been completed. Thus, minimal clinically important difference, that is, the smallest change that patients perceive as beneficial, has not yet been defined for most of these instruments. However, this is expected to change by upcoming results of clinical trials with novel tyrosine kinase inhibitors.

Laboratory values

The *KIT* D816V mutation is the driver of the disorder and can be identified in both peripheral blood (PB) and BM in more than 90% of patients with typical ISM.³¹⁻³³ A strong correlation between mutation burden in PB and BM has been reported, highlighting the diagnostic value of the former, when highly sensitive techniques, that is, allele-specific quantitative polymerase chain reaction (ASO-qPCR) or droplet digital polymerase chain reaction (ddPCR), are applied. The median burden of *KIT* D816V-mutated cells in ISM has been reported as 0.6% and 0.3% in BM and PB, respectively.³⁴ However, no link between *KIT* D816V mutation burden and clinical signs or symptoms of ISM was identified.³⁴

The basal serum tryptase level is the most frequently applied marker for the diagnosis and monitoring of ISM, with a median value of 35 ng/mL (interquartile range: 8.9-183 ng/mL) recently assessed in a large cohort.³⁵ Several studies have reported a strong correlation between serum tryptase levels and *KIT* D816V allele burden, but not with sign and symptom severity.^{28,36,37} Both

tests are commonly used in the diagnosis of ISM, assessment of MC burden, and long-term monitoring of patients.³⁸

Complete blood counts are usually within the normal range in patients with ISM. In the rare case of eosinophilia, clonal eosinophilia in terms of an associated hematologic neoplasm should be excluded. However, in less than 5%, eosinophilia might also be reactive and usually eosinophil counts do not correlate with the severity of mediator-related symptoms or the risk for anaphylaxis in these cases.³⁵

Histological findings in ISM

BM biopsy with aspiration is an obligatory diagnostic procedure in ISM in accordance with the current World Health Organization (WHO) criteria.^{2-4,37} MC clusters (more than 15 MCs), atypical (spindle-shaped and/or immature) morphology of MCs, and/or aberrant expression of certain cell surface markers, such as CD25 ± CD2 in MCs, are established diagnostic criteria of SM in BM.^{2,4} The MC burden in BM of patients with typical ISM is low, usually less than 5% to 10% in tryptase-stained BM biopsy sections (and less than 1% in BM aspirate smears). BM investigation is the key procedure to exclude advanced forms of SM, including aggressive SM, SM with an associated hematological neoplasm, and MC leukemia.^{2,4,39} Repeated BM investigations are not reasonable for monitoring or assessing symptom burden in patients with ISM.

Histological evaluation of skin lesions, when present, can support the diagnosis of mastocytosis.^{2,40,41} In a subset of patients, MC numbers in lesional skin are increased up to 8-fold compared with healthy skin. However, MC numbers vary substantially from patient to patient and are comparable to healthy controls in some patients with ISM.⁴¹ The site of skin biopsy plays an important role as peripheral skin sites exhibit higher MC numbers.⁴² Specific tissue staining procedures are needed to visualize MCs including metachromatic staining by Giemsa or toluidine blue as nonspecific techniques to detect MCs.^{40,41} In recent years, specific immunohistochemical staining by anti-tryptase antibody became the most commonly used technique for the evaluation of tissue MCs.^{40,41} Tryptase is the preferable marker to be used to assess dermal MC numbers, whereas CD25 expression, a marker of atypical neoplastic MCs, is inconsistently expressed in lesional skin MCs of patients with ISM.

When GI symptoms are present, a biopsy of the GI tract can be helpful. CD117 is the preferred marker as tryptase is typically dim to negative in GI biopsies. Colon, ileum, and duodenum are the most frequently affected gut sites in patients with mastocytosis.⁴³ As in the skin, the number of tissue MCs is highly variable and does not correlate with the organ-specific symptom burden. It is also worth noting that accumulations of tissue MCs can also be detected in various inflammatory disorders or genetic conditions.⁴³⁻⁴⁸

WHAT TO ASSESS IN PATIENTS WITH ISM

Assessment of disease symptoms in ISM

The symptoms to be assessed in patients with ISM are as follows (Table 1): (a) skin (itching and flushing); (b) GI (diarrhea, abdominal pain/cramping, and nausea/vomiting); (c) musculoskeletal pain; and (d) neurological (fatigue/exhaustion, headache, brain fog/difficulty concentrating, and dizziness); (e—optional) others (eg, palpitations).^{2,3,13} Three PROMs were developed for the evaluation of symptoms in patients with ISM, the mastocytosis symptom assessment form (MSAF), the

TABLE I. Parameters to be assessed in indolent systemic mastocytosis and available tools for treatment response monitoring

	Parameter	Method to use/available PROM	Result
Symptoms	Skin symptoms	MAS, ISM-SAF	Domain score
	Itching	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Flushing	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Gastrointestinal symptoms	MAS, ISM-SAF	Domain score
	Diarrhea	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Abdominal cramping	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Muscle/joint pain	MAS, MSAF, ISM-SAF	Intensity of the symptom
	Neurological symptoms		
	Fatigue/exhaustion	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Headache	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Difficulty concentrating	MAS, MSAF, ISM-SAF	Intensity of each symptom
	Other palpitations	MSAF	Intensity of each symptom
	Disease activity/burden	MAS, MSAF, ISM-SAF	Total score
Quality of life		MC-QoL	None/mild/moderate/severe
		MQLQ	None/mild/moderate/severe
Signs	Skin lesions	Are lesions present?	Yes/no
		Area affected	% of lesional skin surface
		Standardized photographs (computed image analyses)	Assess the number and color intensity of lesions
	Anaphylaxis	History of anaphylaxis	Yes/no
	Osteoporosis/osteopenia/fractures	DXA or magnetic resonance imaging	Yes/no
		BMD of at least lumbar spine and femur	T- and Z-scores
		Alternative: sCTX, P1NP	ng/mL
Laboratory values	Tryptase in serum	ImmunoCAP	ng/mL
	<i>KIT</i> D816V mutation	ASO-qPCR or ddPCR in PB	%
		ASO-qPCR or ddPCR in BM (when BM biopsy or aspiration is performed)	%
	Optional: <i>TPSAB1</i> gene	ddPCR in PB	Copy number
Organomegaly	Hepato- and/or splenomegaly and/or lymphadenopathy	Sonography	Organ size
Histological findings in bone marrow (skin, gastrointestinal tract—if applicable)		Biopsy	% MC infiltration; compact MC infiltrates; atypical MC morphology; aberrant expression of CD25 (and/or CD2 and/or CD30); dysmyelopoiesis

ASO-qPCR, Allele-specific quantitative polymerase chain reaction; BM, bone marrow; BMD, bone mineral density; ddPCR, droplet digital polymerase chain reaction; DXA, dual-energy x-ray absorptiometry; ISM-SAF, indolent systemic mastocytosis symptom assessment form;^{49,50} MAS, mastocytosis activity score;¹⁵ MC, mast cell; MC-QoL, Mastocytosis Quality-of-Life Questionnaire MC-QoL;³⁰ MQLQ, Mastocytosis Quality-of-Life Questionnaire MQLQ;¹⁴ MSAF, mastocytosis symptom assessment form;¹⁴ P1NP, aminoterminal propeptide of type 1 collagen; PB, peripheral blood; PROM, patient-reported outcome measure; sCTX, cross-linked C-telopeptide of type 1 collagen.

mastocytosis activity score (MAS), and the ISM symptom assessment form (ISM-SAF). All 3 underwent psychometric evaluation, show high reliability and validity, and are of great value in clinical trials.

The MSAF consists of 14 items, that is, pruritus, dizziness, headache, fatigue, flushing, mediator-release attacks, dyspnea, rhinorrhea, palpitations, nausea and vomiting, abdominal pain, bone pain, concentration problems, and depression. A separate part of the questionnaire identifies the impact of fatigue on everyday life. The tool was developed and validated in the Dutch language.¹⁴

The MAS is a 9-item tool with a 3-domain structure (skin, GI tract, and other symptoms).¹⁵ It is available in German as well as the American English language and is currently being translated and adopted to several other languages. The MAS is recommended to be completed by patients for at least 7 consecutive days, preferably 14 days, to obtain robust data on disease activity and symptom severity. Mean total scores of 2.9, 11.0, 28.1, and 42.4 were seen in patients who self-reported no, mild, moderate, and severe disease activity, respectively; these values can be used and being helpful to interpret the results of the MAS.

The recently published ISM-SAF is a 12-item tool, which was successfully used in patients with ISM undergoing treatment with a selective KIT inhibitor. The ISM-SAF was developed by Adelphi Values and Blueprint Medicines and has been translated and linguistically validated in English and other languages to be used in multicenter clinical trials.^{49,50} Total score or separate scores for skin and GI domains are assessed over a minimum period of 7 days to reflect total disease and domain symptom burden, respectively.

Apart from these PROMs, there are other simpler criteria for assessing symptom burden that could be applied in daily practice. One is a grading system provided by the EU/US consensus group.⁴⁰ In their proposal, skin symptoms and (other) mediator-related symptoms are classified as grades 0, 1, 2, 3, and 4 based on the need to introduce treatment, efficacy of therapy, and (the need to recommend) hospitalization. This grading system has been validated and is independent of patient reporting, but not widely used.

Assessment of quality of life in ISM

Two disease-specific QoL tools, the Mastocytosis Quality-of-Life Questionnaire MC-QoL (MC-QoL) and the Mastocytosis Quality-of-Life Questionnaire MQLQ (MQLQ), were developed according to the current recommendations for assessing patient-reported outcomes and health-related QoL in clinical trials, that is, these tools have undergone item generation, item selection, and final validation (Table I).^{14,30,51,52}

The MC-QoL is a 27-item questionnaire with a recall period of 2 weeks that covers 4 domains: symptoms, emotions, social life/functioning, and skin. Overall mastocytosis-related QoL impairment is assessed by the total score and reflects none, mild, moderate, and severe QoL impairment with cutoffs for the latter three being 29, 50, and 71 points, respectively. Separate scores for each domain can also be calculated. Originally developed and validated in the German and American English languages, it is now available in 34 culturally adapted versions free of charge for academic noncommercial use (MOXIE, Berlin, Germany). The MC-QoL is applicable for international clinical trials and everyday clinical practice worldwide.³⁰

The MQLQ is a 49-item questionnaire, developed and validated in a Dutch population. It includes the role of mastocytosis in 8 domains: fatigue and mental health, anaphylaxis, bone symptoms, unfamiliarity (low awareness), flushing, general symptoms, skin symptoms, and triggers.¹⁴

Assessment of signs of disease in ISM

Skin lesions. In ISM, skin lesions are maculopapular, reddish-brown, of variable number, and usually symmetrically distributed on the trunk and thighs.⁴¹ Diagnostic criteria of cutaneous involvement in mastocytosis include typical lesions associated with Darier's sign (wheal-and-flare response of cutaneous mastocytosis lesions due to mechanical irritation) as the major criterion. Additional criteria are increased numbers of MCs in lesional skin and the presence of an activating *KIT* mutation in lesional skin tissue.⁴¹ Of note, histological and immunohistochemical findings in the affected skin areas of patients with ISM can be difficult to interpret as MC numbers may only be slightly increased or normal and as neoplastic MCs can hardly be identified. Both confluence and spontaneous disappearance of lesions can indicate disease progression and should be assessed in combination with other parameters of the disease.^{53,54}

Several scoring approaches were used in the past to assess skin involvement in mastocytosis. For example, the SCORMA (SCORing MASTocytosis) index was developed to assess the extent of skin involvement and changes in lesions in combination with subjective (patient-reported) symptoms.⁵⁵ Brockow et al⁵⁶ proposed to evaluate the affected skin area with a technique that is also used to assess burns. The percentage of lesional skin surface in the most involved hand-sized area can also be assessed.⁵⁶ These scores are subjective and do not include the color intensity of the lesions, but can be easily used in everyday practice. However, a standardized and robust approach is needed to be applied in clinical trials, such as computed image analysis (Table I).

Bone involvement. Osteoporosis, defined by the bone mineral density (BMD) T-score of the lumbar spine and/or femur -2.5 or less, is a common finding and seen in approximately 30% of patients with ISM (Table I).²¹ No correlation between serum tryptase levels and bone involvement was observed in ISM.¹⁸ Thus, all patients with ISM should be screened and monitored for osteoporosis. As a second step, other reasons for bone impairment, including thyroid dysfunction and osteomalacia, should be excluded. A 5-year follow-up showed improvement in BMD and serum collagen C-telopeptide (sCTX) Z-scores in patients with ISM under first-line treatment with bisphosphonates.⁵⁷ Several additional serum markers of bone turnover, such as bone-specific alkaline phosphatase, osteocalcin, C-terminal propeptide of type 1 collagen, N-terminal propeptide of type 1 collagen (P1NP), cross-linked N-telopeptide of type 1 collagen, and tartrate-resistant acid phosphatase 5b, may be used to assess early response to treatment in ISM patients with osteoporosis. Two of these markers, P1NP and sCTX, were recommended to be included in interventional studies for disease monitoring and treatment response by the International Osteoporosis Foundation.⁵⁸ However, further research is needed to better understand the etiology of skeletal disease in mastocytosis and the role of serum markers of bone formation and resorption.²²

Anaphylaxis. The risk of anaphylaxis in ISM, predominantly in patients with lower tryptase levels, is higher as compared with the general population.^{3,13,28,59,60} ISM patients with a history of anaphylaxis are more likely to develop recurrent episodes and should be monitored. The underlying mechanisms of anaphylaxis in mastocytosis are not fully understood.^{13,61} Several triggers such as insect venom, food, stress, exercise, temperature changes, infections, and drugs were identified, with insect venom being the most common one. In some patients with SM, an underlying IgE-dependent allergy is detected.⁶²⁻⁶⁴ However, in many cases, the trigger remains unknown. In a subset of patients with ISM, the presenting symptom of disease is unprovoked anaphylaxis. These patients frequently do not exhibit typical skin lesions of mastocytosis, and serum tryptase values are often <20 ng/mL.⁶⁵ Many factors may influence the risk of anaphylaxis and its severity, including the exposure to specific triggers or combinations of triggers, IgE-dependent and IgE-independent (eg, MRXPRX2-dependent) pathways of MC activation, *TPSAB1* gene copy number encoding α -tryptase, and gender.⁶⁶ Elevated venom-specific IgE levels can be detected, but levels are often lower compared with sensitized non-mastocytosis patients, which makes this parameter difficult to use for diagnosis and monitoring.⁶⁷⁻⁷⁰ The rate of a false-negative skin prick test also may be high in certain patients with SM.⁷¹ Standardized uniformly

TABLE II. Recommended “to do” list for primary and follow-up ISM assessment in everyday practice and clinical trials for treatment response monitoring

<i>Primary investigation</i>	- Sign and symptom evaluation: - Anaphylaxis (yes/no, history of anaphylaxis, history of Hymenoptera stings) - Skin lesions (yes/no, standardized photographs*) - Osteoporosis (yes/no, BMD of at least the lumbar spine and femur) Spontaneous fractures (yes/no, anamnesis) - Specific PROMs for symptom assessment at least 7 days, preferably 14 days, before intervention is applied* <i>Optional: TPSAB1</i> gene copy number - Specific PROMs for mastocytosis-associated quality-of-life impairment (quality of life for the last 2 weeks is being assessed) - Laboratory values to assess baseline MC burden: - Serum tryptase level <i>KIT</i> D816V mutation burden in blood and bone marrow (when BM biopsy or aspiration is performed) - Hepato- and/or splenomegaly, lymphadenopathy - Bone marrow evaluation, including <i>KIT</i> D816V mutation burden, for diagnostic purposes and MC burden assessment - Skin, gastrointestinal tract biopsies or other affected organ may be considered
<i>Follow-up</i>	<i>Primary outcome</i> - Sign and symptom evaluation: - Anaphylaxis (when present before, yes/no)† - Skin lesions (standardized photographs*, percentage of affected area) - Osteoporosis (BMD at least 6 months after treatment initialization) - Use specific PROMs for continues symptom assessment under treatment (eg, MAS, MSAF, ISM-SAF) - Specific PROMs for mastocytosis-related quality-of-life assessment at predefined endpoints (eg, MC-QoL, MQLQ) <i>Secondary outcome</i> - Laboratory values to assess MC burden response to treatment: - Serum tryptase level <i>KIT</i> D816V mutation burden in blood - Hepato- and/or splenomegaly, lymphadenopathy - Follow-up bone marrow biopsies (skin, gastrointestinal tract—if applicable) could be considered (ie, presence of any B-finding in BM at baseline)

BMD, Bone mineral density; ISM-SAF, indolent systemic mastocytosis symptom assessment form; MAS, mastocytosis activity score; MC, mast cell; MC-QoL, Mastocytosis Quality-of-Life Questionnaire MC-QoL; MQLQ, Mastocytosis Quality-of-Life Questionnaire MQLQ; MSAF, mastocytosis symptom assessment form; PROMs, patient-reported outcome measures.

*Applies for clinical trials only.

†Interpreted with caution due to the multifactorial pathogenesis of anaphylaxis; total and specific IgE may be considered to be measured, and specific novel biomarkers are needed.

accepted grading systems and biomarkers for anaphylaxis severity are missing, and tools for monitoring anaphylaxis are currently unavailable.⁷²

Assessment of mast cell burden in ISM

Laboratory parameters. Serum tryptase level and a sensitive and quantitative assessment of the *KIT* D816V mutation (preferably by quantification of the allele burden by sensitive techniques, such ASO-qPCR or ddPCR) are recommended to be included in the diagnostic workup of all patients with ISM (Table I). Tryptase levels of more than 20 ng/mL and the presence of the activating *KIT* D816V mutation are criteria of SM and detectable in the majority of patients with ISM, whereas lower tryptase levels do not exclude the disease.^{73,74} The presence of the *KIT* D816V mutation results in uncontrolled MC growth and accumulation in various organs. Both markers, serum tryptase and *KIT* D816V mutation allele burden, show strong correlation and reflect the overall MC burden in ISM.^{73,74} Of note, *KIT* D816V allele burden is typically (very) low in ISM; thus, high *KIT* D816V allele burden in PB serves as an indication for multilineage involvement and therefore also has important prognostic value.⁷⁵

Histological findings. Evaluation of MC numbers in affected organs such as the skin, BM, and GI tract is of limited value in ISM as compared with advanced forms of mastocytosis,

because they do not reflect or correlate with symptom burden and severity.⁷⁶ In everyday practice, BM evaluation should be included in the diagnostic workup of all patients suspected to have ISM (Table I).^{2,4,76} In clinical trials, skin and/or GI tract biopsies, if cutaneous lesions or GI symptoms are present, can be additionally included in the diagnostic workup of patients with ISM, especially when organ-specific treatment effects are expected or special research questions are addressed. Repeated biopsies can serve to assess secondary treatment outcome parameters. Whenever organ biopsies are performed, appropriate immunohistochemical staining procedures with antibodies against tryptase, KIT/CD117, and CD25 should be performed. Tryptase and KIT/CD117 serve to assess the amount, distribution (compact MC infiltrates in extracutaneous tissues = major diagnostic criterion for SM), and morphology (atypical MC morphology ≥25% = minor diagnostic criterion for SM) of MCs. An aberrant expression of CD25 also serves as a minor diagnostic criterion for SM. In immunohistochemistry, CD25 has a higher sensitivity as compared with CD2 and CD30.⁷⁶⁻⁷⁸

RECOMMENDATIONS FOR ISM MONITORING IN EVERYDAY PRACTICE AND CLINICAL TRIALS

Primary investigations

A BM investigation is part of the diagnostic workup in all patients with suspected ISM according to the current WHO

TABLE III. Proposed grading and definition of treatment response criteria

Grade	Definition
Complete response (CR)*	Improvement by >90%
Major response (MR)*	Improvement by >60%
Partial response (PR)*	Improvement to 30%-60%
No response (NR)	<30% improvement

*Continuous response when no relapse occurs after cessation of treatment. However, the treatment-free period of response needs to be defined.

criteria.^{2,4,76} A baseline serum tryptase level ≥ 20 ng/mL and an activating *KIT* D816V mutation are minor diagnostic criteria for SM and helpful in preliminary screening for ISM.^{2,4,76} In addition, up to one of the following B-findings can be present in ISM: more than 30% MC infiltration in the BM biopsy and serum tryptase level >200 ng/mL; signs of dysmyelopoiesis or myeloproliferation without evidence of an additional hematological neoplasm and/or organomegaly (hepatomegaly and/or splenomegaly and/or lymphadenopathy) without organ impairment.^{2,4,76} Two or more B-findings are required to diagnose SSM and to distinguish this variant from ISM.^{2,4,76} Taken together, BM findings, serum tryptase levels, and *KIT* D816V allele burden reflect MC numbers, but are not helpful in identifying disease-related signs and symptoms of ISM (skin lesions, osteoporosis, anaphylaxis, and symptom burden).

Monitoring of patients with ISM should primarily focus on the assessment of signs and symptoms as well as on mastocytosis-related QoL impairment (Table II). Validated prospective mastocytosis-specific PROMs to assess symptom burden in clinical trials are available and should be used for at least 7 days, preferably 14 days, before treatment initiation. Patients should be provided with native language versions of the PROMs used (Table I). QoL is one of the most important patient-reported impacts and should be included as part of the clinical assessment in all ongoing studies. Moreover, improvement in QoL is the main goal of currently developed treatments. Therefore, specific PROMs for mastocytosis-related QoL impairment, reflecting the QoL status for the last 2 weeks, should be always considered in both everyday practice and clinical trials.

Skin and bone involvement should be graded.³⁷ In everyday practice, the affected skin area and the percentage of lesional skin surface in the most involved hand-sized area are valuable parameters to assess disease progression and response to treatments.^{37,56} For example, the SCORMA index is an easy-to-use tool for scoring the extent of skin involvement in routine clinical practice.⁵⁵ Clinical trials, however, require a more systematic and standardized approach, for example, standardized photodocumentation with further machine-learning-based and/or expert consensus evaluation.

When osteoporosis is diagnosed, BMD T-score of at least 2 regions, the lumbar spine and femur, should be documented and monitored.^{40,76} Several blood markers, such as sCTX and P1NP, are considered to be an alternative tool for bone involvement prediction and rating, but are not yet defined as robust markers for osteoporosis grading.

Anaphylaxis is an important clinical sign of ISM. Identifying the severity of anaphylaxis remains challenging. Nevertheless, anaphylaxis in mastocytosis is often severe and includes signs and symptoms of the cardiovascular system, such as hypotensive

syncope. There are several anaphylaxis grading systems in use; however, none has proven superiority over the other. Thus, further studies in mastocytosis patients with anaphylaxis would be desirable. Moreover, based on recent reports that individual patients experience reproducibly stereotypic anaphylactic events irrespective of the cause, monitoring the number of anaphylactic episodes could provide a better standardization of response assessment in clinical practice and clinical trials than grading their severity.⁷⁹

Follow-up

The primary aim of ISM treatment is disease control by symptom reduction and improvement of mastocytosis-related QoL. To do so, signs and symptoms of the disease as well as QoL should be monitored continuously during the course of treatment (Table II). In this regard, response of anaphylaxis should be interpreted with caution as the occurrence of anaphylactic episodes may depend on the presence of known triggers, avoidance behavior of the patient, immunotherapy for Hymenoptera venoms, and/or prophylactic treatment with omalizumab. Monitoring of osteopenia/osteoporosis in ISM should not differ from general recommendations and requires long, that is, at least 6-month, follow-up periods after treatment initialization.⁸⁰

The mechanisms of symptom improvement are not completely defined, and may depend on the drug being applied and rely on MC depletion and/or inhibition. Although tryptase levels and *KIT* D816V allele burden do not correlate with symptom severity at baseline, their value as surrogate parameters for symptom reduction remains to be investigated. Taking together, serum tryptase levels and *KIT* D816V allele burden should be considered as secondary outcome parameters to indirectly monitor MC burden and, possibly, symptom reduction.⁴⁰ BM investigations, contrary to laboratory values, are less useful in symptom response assessment due to low MC numbers in BM of most patients with ISM. In fact, repeated BM biopsies do not answer the main research question in ISM and restrict the access of patients to participate in clinical trials. Thus, follow-up BM investigations should be considered only when any B-finding in BM is present, that is, >30% MC in BM histopathology, myeloproliferation, or signs of dysmyelopoiesis, as these patients are at higher risk of progression to SSM and/or advanced SM.

DEFINITION OF COMPLETE, MAJOR, PARTIAL, AND NO RESPONSE TO TREATMENT

Clinically significant response of symptoms has been defined as a 30% reduction from baseline when using disease-specific PROMs. For now, according to the ECRM consensus, changes from baseline of 90%, 60%, and 30% are recommended to be used as outcome parameters for assessing treatment efficacy, indicating complete response (CR) >90%, major response (MR) 60% to 90%, partial response (PR) 30% to 60%, and no response (NR) <30% (Table III). When achieved response persists after treatment cessation, the term *continuous* response can be applied, whereas the treatment-free period of response remains to be defined and will depend on the pharmacodynamics and the disease-modifying capacities of investigated drugs.

CURRENT LIMITATIONS AND UNMET NEEDS FOR REFINING RESPONSE CRITERIA FOR ISM

Several unmet needs have to be addressed to improve the use of response criteria in ISM.

First, skin evaluation would highly profit from the use of specific equipment with further computed image analysis.⁸¹ Easy and cost-effective approaches are required. Several approaches, including SCORMA index and identifying the percentage of lesional skin surface in the most involved hand-sized area, have been proposed.^{55,56} However, these tools do not include evaluation of color intensity of the lesions.

Secondly, serum bone turnover markers for predicting osteoporosis and defining treatment response are needed. Two of them, PINP and sCTX, were suggested to be included in intervention studies by the International Osteoporosis Foundation.⁵⁸ However, the role of serum bone formation and resorption markers is not completely defined, and their value for use in secondary osteoporosis associated with mastocytosis remains to be elucidated.

Thirdly, despite plenty of available mastocytosis-specific PROMs, only a few are available in multiple culturally adopted and linguistically validated versions, which limits their use around the globe. The variety of different PROMs restricts study-to-study comparison. Moreover, a one-time and quick-to-complete PROM to assess symptom severity and/or disease burden remains an unmet need.

Fourthly, tools for monitoring anaphylaxis severity and response to treatment are needed. The role and relevance of increased *TPSAB1* gene copy number encoding α -tryptase, hereditary α -tryptasemia (H α T), need to be further evaluated as a potential factor influencing symptom severity in mastocytosis. Thus, screening for the prevalence of H α T in future clinical trials in mastocytosis should be considered because concomitant H α T could affect the response to treatment.

Finally, clinimetric evaluation of PROMs and cutoffs for symptom response should be achieved and updated after first studies with targeted treatments are completed.

CONCLUSIONS

The primary goal of ISM treatment is symptom reduction and improvement of mastocytosis-related QoL impairment. Cutaneous, GI, and neurological symptoms, musculoskeletal pain, and the presence of skin lesions, anaphylaxis, and osteoporosis are the main drivers of disease burden in ISM and should be assessed in all patients, before initiation and over the course of treatment. Validated mastocytosis-specific PROMs are recommended to assess symptom burden and QoL impairment. Treatment responses assessed by changes from baseline of 90%, 60%, and 30% indicate CR >90%, MR 60% to 90%, PR 30% to 60%, and NR <30%. Laboratory values (serum tryptase and *KIT* D816V allele burden) and histological findings (MC numbers in BM, skin, GI tract, or other affected organs) can be investigated, but are limited outcome parameters because they neither reflect symptom/sign severity nor QoL impairment.

REFERENCES

- Akin C, Valent P. Diagnostic criteria and classification of mastocytosis in 2014. *Immunol Allergy Clin North Am* 2014;34:207-18.
- Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603-25.
- Valent P, Sperr WR, Schwartz LB, Horny HP. Diagnosis and classification of mast cell proliferative disorders: delineation from immunologic diseases and non-mast cell hematopoietic neoplasms. *J Allergy Clin Immunol* 2004;114:3-11. quiz: 2.
- Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood* 2017;129:1420-7.
- Trizuljak J, Sperr WR, Nekvindova L, Elberink HO, Gleixner KV, Gorska A, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. *Allergy* 2020;75:1927-38.
- Munoz-Gonzalez JJ, Alvarez-Twose I, Jara-Acevedo M, Zanotti R, Perkins C, Jawhar M, et al. Proposed global prognostic score for systemic mastocytosis: a retrospective prognostic modelling study. *Lancet Haematol* 2021;8:e194-204.
- Munoz-Gonzalez JJ, Alvarez-Twose I, Jara-Acevedo M, Henriques A, Vinas E, Prieto C, et al. Frequency and prognostic impact of KIT and other genetic variants in indolent systemic mastocytosis. *Blood* 2019;134:456-68.
- Jensen B, Broesby-Olsen S, Bindslev-Jensen C, Nielsen DS. Everyday life and mastocytosis from a patient perspective—a qualitative study. *J Clin Nurs* 2019;28:1114-24.
- Russell N, Jennings S, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: part 2—patient clinical experiences and beyond. *J Allergy Clin Immunol Pract* 2019;7:1157-65.e6.
- Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. *J Allergy Clin Immunol Pract* 2014;2:70-6.
- Jennings SV, Slee VM, Zack RM, Verstovsek S, George TI, Shi H, et al. Patient perceptions in mast cell disorders. *Immunol Allergy Clin North Am* 2018;38:505-25.
- Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One* 2008;3:e2266.
- Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med* 2015;373:163-72.
- van Anrooij B, Kluijn-Nelemans JC, Safy M, Flokstra-de Blok BM, Oude Elberink JN. Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis. *Allergy* 2016;71:1585-93.
- Siebenhaar F, Sander B, Ho LHT, Ellrich A, Maurer M, Weller K. Development and validation of the mastocytosis activity score. *Allergy* 2018;73:1489-96.
- van Doormaal JJ, Arends S, Brunekreef KL, van der Wal VB, Sietsma J, van Voorst Vader PC, et al. Prevalence of indolent systemic mastocytosis in a Dutch region. *J Allergy Clin Immunol* 2013;131:1429-31.e1.
- van der Veer E, van der Goot W, de Monchy JG, Kluijn-Nelemans HC, van Doormaal JJ. High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. *Allergy* 2012;67:431-8.
- Rossini M, Zanotti R, Bonadonna P, Artuso A, Caruso B, Schena D, et al. Bone mineral density, bone turnover markers and fractures in patients with indolent systemic mastocytosis. *Bone* 2011;49:880-5.
- Escribano L, Alvarez-Twose I, Sanchez-Munoz L, Garcia-Montero A, Nunez R, Almeida J, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. *J Allergy Clin Immunol* 2009;124:514-21.
- Pieri L, Bonadonna P, Elena C, Papayannidis C, Grifoni FI, Rondoni M, et al. Clinical presentation and management practice of systemic mastocytosis. A survey on 460 Italian patients. *Am J Hematol* 2016;91:692-9.
- Barete S, Assous N, de Gennes C, Grandpeix C, Feger F, Palmerini F, et al. Systemic mastocytosis and bone involvement in a cohort of 75 patients. *Ann Rheum Dis* 2010;69:1838-41.
- Rabenhorst A, Christopeit B, Leja S, Gerbaulet A, Kleiner S, Forster A, et al. Serum levels of bone cytokines are increased in indolent systemic mastocytosis associated with osteopenia or osteoporosis. *J Allergy Clin Immunol* 2013;132:1234-7.e7.
- Gulen T, Hagglund H, Dahlen B, Nilsson G. High prevalence of anaphylaxis in patients with systemic mastocytosis—a single-centre experience. *Clin Exp Allergy* 2014;44:121-9.
- Florian S, Krauth MT, Simonitsch-Klupp I, Sperr WR, Fritsche-Polanz R, Sonneck K, et al. Indolent systemic mastocytosis with elevated serum tryptase, absence of skin lesions, and recurrent severe anaphylactoid episodes. *Int Arch Allergy Immunol* 2005;136:273-80.
- Gonzalez de Olano D, de la Hoz Caballer B, Nunez Lopez R, Sanchez Munoz L, Cuevas Agustin M, Dieguez MC, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). *Clin Exp Allergy* 2007;37:1547-55.
- Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63:226-32.

27. Pardanani A, Tefferi A. Systemic mastocytosis in adults: a review on prognosis and treatment based on 342 Mayo Clinic patients and current literature. *Curr Opin Hematol* 2010;17:125-32.
28. Gulen T, Ljung C, Nilsson G, Akin C. Risk factor analysis of anaphylactic reactions in patients with systemic mastocytosis. *J Allergy Clin Immunol Pract* 2017;5:1248-55.
29. Pulfer S, Ziehefreund S, Gebhard J, Hindelang B, Biedermann T, Brockow K, et al. Health-related quality of life and influencing factors in adults with non-advanced mastocytosis—a cross-sectional study and qualitative approach. *J Allergy Clin Immunol Pract* 2021;9:3166-75.e2.
30. Siebenhaar F, von Tschirnhaus E, Hartmann K, Rabenhorst A, Staubach P, Peveling-Oberhag A, et al. Development and validation of the mastocytosis quality of life questionnaire: MC-QoL. *Allergy* 2016;71:869-77.
31. Jara-Acevedo M, Teodosio C, Sanchez-Munoz L, Alvarez-Twose I, Mayado A, Caldas C, et al. Detection of the KIT D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications. *Mod Pathol* 2015;28:1138-49.
32. Arock M, Sotlar K, Akin C, Broesby-Olsen S, Hoermann G, Escribano L, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. *Leukemia* 2015;29:1223-32.
33. Kristensen T, Vestergaard H, Bindslev-Jensen C, Moller MB, Broesby-Olsen S, Mastocytosis Centre OUH. Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol* 2014;89:493-8.
34. Broesby-Olsen S, Kristensen T, Vestergaard H, Brixen K, Moller MB, Bindslev-Jensen C, et al. KIT D816V mutation burden does not correlate to clinical manifestations of indolent systemic mastocytosis. *J Allergy Clin Immunol* 2013;132:723-8.
35. Kluin-Nelemans HC, Reiter A, Illerhaus A, van Anrooij B, Hartmann K, Span LFR, et al. Prognostic impact of eosinophils in mastocytosis: analysis of 2350 patients collected in the ECRM Registry. *Leukemia* 2020;34:1090-101.
36. Kristensen T, Broesby-Olsen S, Vestergaard H, Bindslev-Jensen C, Moller MB, Mastocytosis Centre Odense University Hospital. Serum tryptase correlates with the KIT D816V mutation burden in adults with indolent systemic mastocytosis. *Eur J Haematol* 2013;91:106-11.
37. Erben P, Schwaab J, Metzgeroth G, Horny HP, Jawhar M, Sotlar K, et al. The KIT D816V expressed allele burden for diagnosis and disease monitoring of systemic mastocytosis. *Ann Hematol* 2014;93:81-8.
38. Hoermann G, Gleixner KV, Dinu GE, Kundi M, Greiner G, Wimazal F, et al. The KIT D816V allele burden predicts survival in patients with mastocytosis and correlates with the WHO type of the disease. *Allergy* 2014;69:810-3.
39. Horny HP, Sotlar K, Valent P. Differential diagnoses of systemic mastocytosis in routinely processed bone marrow biopsy specimens: a review. *Pathobiology* 2010;77:169-80.
40. Valent P, Akin C, Escribano L, Fodinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435-53.
41. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 2016;137:35-45.
42. Weber A, Knop J, Maurer M. Pattern analysis of human cutaneous mast cell populations by total body surface mapping. *Br J Dermatol* 2003;148:224-8.
43. Doyle LA, Sepehr GJ, Hamilton MJ, Akin C, Castells MC, Hornick JL. A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients. *Am J Surg Pathol* 2014;38:832-43.
44. Zimmermann N, Abonia JP, Dreskin SC, Akin C, Bolton S, Happel CS, et al. Developing a standardized approach for assessing mast cells and eosinophils on tissue biopsies: A Work Group Report of the AAAAI Allergic Skin Diseases Committee. *J Allergy Clin Immunol* 2021;148:964-83.
45. Giannetti MP, Akin C, Hufdri R, Hamilton MJ, Weller E, van Anrooij B, et al. Patients with mast cell activation symptoms and elevated baseline serum tryptase level have unique bone marrow morphology. *J Allergy Clin Immunol* 2021;147:1497-501.e1.
46. Hamilton MJ, Zhao M, Giannetti MP, Weller E, Hufdri R, Novak P, et al. Distinct small intestine mast cell histologic changes in patients with hereditary alpha-tryptasemia and mast cell activation syndrome. *Am J Surg Pathol* 2021;45:997-1004.
47. Konnikova L, Robinson TO, Owings AH, Shirley JF, Davis E, Tang Y, et al. Small intestinal immunopathology and GI-associated antibody formation in hereditary alpha-tryptasemia. *J Allergy Clin Immunol* 2021;148:813-21.e7.
48. Lyons JJ, Sun G, Stone KD, Nelson C, Wisch L, O'Brien M, et al. Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities. *J Allergy Clin Immunol* 2014;133:1471-4.
49. Padilla B, Shields AL, Taylor F, Li X, McDonald J, Green T, et al. Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) in a phase 2 clinical study. *Orphanet J Rare Dis* 2021;16:434.
50. Taylor F, Akin C, Lamoureux RE, Padilla B, Green T, Boral AL, et al. Development of symptom-focused outcome measures for advanced and indolent systemic mastocytosis: the AdvSM-SAF and ISM-SAF ((c)). *Orphanet J Rare Dis* 2021;16:414.
51. Baiardini I, Bousquet PJ, Brzoza Z, Canonica GW, Compalati E, Fiocchi A, et al. Recommendations for assessing patient-reported outcomes and health-related quality of life in clinical trials on allergy: a GA(2)LEN taskforce position paper. *Allergy* 2010;65:290-5.
52. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.
53. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991;96(Suppl):2S-4S. discussion: 4S, 60S-5S.
54. Brockow K, Scott LM, Worobec AS, Kirshenbaum A, Akin C, Huber MM, et al. Regression of urticaria pigmentosa in adult patients with systemic mastocytosis: correlation with clinical patterns of disease. *Arch Dermatol* 2002;138:785-90.
55. Heide R, van Doorn K, Mulder PG, van Toorenbergen AW, Beishuizen A, de Groot H, et al. Serum tryptase and SCORMA (SCORing MASTocytosis) Index as disease severity parameters in childhood and adult cutaneous mastocytosis. *Clin Exp Dermatol* 2009;34:462-8.
56. Brockow K, Akin C, Huber M, Metcalfe DD. Assessment of the extent of cutaneous involvement in children and adults with mastocytosis: relationship to symptomatology, tryptase levels, and bone marrow pathology. *J Am Acad Dermatol* 2003;48:508-16.
57. Onnes MC, van Doormaal JJ, van der Veer E, Versluis JB, Arends S, Oude Elberink HNG. Fracture risk reduction by bisphosphonates in mastocytosis? *J Allergy Clin Immunol Pract* 2020;8:3557-64.
58. Vasikaran S, Cooper C, Eastell R, Griesmacher A, Morris HA, Trenti T, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. *Clin Chem Lab Med* 2011;49:1271-4.
59. Broesby-Olsen S, Farkas DK, Vestergaard H, Hermann AP, Moller MB, Mortz CG, et al. Risk of solid cancer, cardiovascular disease, anaphylaxis, osteoporosis and fractures in patients with systemic mastocytosis: a nationwide population-based study. *Am J Hematol* 2016;91:1069-75.
60. van Anrooij B, van der Veer E, de Monchy JG, van der Heide S, Kluin-Nelemans JC, van Voorst Vader PC, et al. Higher mast cell load decreases the risk of Hymenoptera venom-induced anaphylaxis in patients with mastocytosis. *J Allergy Clin Immunol* 2013;132:125-30.
61. Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. *J Allergy Clin Immunol* 2009;124:639-46. quiz: 47-8.
62. Bonadonna P, Lombardo C, Zanotti R. Mastocytosis and allergic diseases. *J Invest Allergol Clin Immunol* 2014;24:288-97. quiz 3 p preceding 297.
63. Bonadonna P, Bonifacio M, Lombardo C, Zanotti R. Hymenoptera allergy and mast cell activation syndromes. *Curr Allergy Asthma Rep* 2016;16:5.
64. Valent P, Akin C, Nedoszytko B, Bonadonna P, Hartmann K, Nedoszytko M, et al. Diagnosis, Classification and Management of Mast Cell Activation Syndromes (MCAS) in the era of personalized medicine. *Int J Mol Sci* 2020;21:9030.
65. Carter MC, Desai A, Komarow HD, Bai Y, Clayton ST, Clark AS, et al. A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 2018;141:180-188.e3.
66. Glover SC, Carter MC, Korosec P, Bonadonna P, Schwartz LB, Milner JD, et al. Clinical relevance of inherited genetic differences in human tryptases: Hereditary alpha-tryptasemia and beyond. *Ann Allergy Asthma Immunol* 2021;127:638-47.
67. Gulen T, Akin C. Anaphylaxis and mast cell disorders. *Immunol Allergy Clin North Am* 2022;42:45-63.
68. Jarkvist J, Salehi C, Akin C, Gulen T. Venom immunotherapy in patients with clonal mast cell disorders: IgG4 correlates with protection. *Allergy* 2020;75:169-77.
69. Michel J, Brockow K, Darsow U, Ring J, Schmidt-Weber CB, Grunwald T, et al. Added sensitivity of component-resolved diagnosis in hymenoptera venom-allergic patients with elevated serum tryptase and/or mastocytosis. *Allergy* 2016;71:651-60.
70. Vos B, van Anrooij B, van Doormaal JJ, Dubois AEJ, Oude Elberink JNG. Fatal anaphylaxis to yellow jacket stings in mastocytosis: options for identification and treatment of at-risk patients. *J Allergy Clin Immunol Pract* 2017;5:1264-71.

71. Gulen T, Moller Westerberg C, Lyberg K, Ekoff M, Kolmert J, Bood J, et al. Assessment of in vivo mast cell reactivity in patients with systemic mastocytosis. *Clin Exp Allergy* 2017;47:909-17.
72. Muraro A, Worm M, Alviani C, Cardona V, DunnGalvin A, Garvey LH, et al. EAACI guideline: anaphylaxis (2021 update). *Allergy* 2022;77:357-77.
73. Sperr WR, Jordan JH, Fiegl M, Escribano L, Bellas C, Dirnhofer S, et al. Serum tryptase levels in patients with mastocytosis: correlation with mast cell burden and implication for defining the category of disease. *Int Arch Allergy Immunol* 2002;128:136-41.
74. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006;26:451-63.
75. Garcia-Montero AC, Jara-Acevedo M, Alvarez-Twose I, Teodosio C, Sanchez-Munoz L, Muniz C, et al. KIT D816V-mutated bone marrow mesenchymal stem cells in indolent systemic mastocytosis are associated with disease progression. *Blood* 2016;127:761-8.
76. Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. *Hemasphere* 2021;5:e646.
77. Sotlar K, Horny HP, Simonitsch I, Krokowski M, Aichberger KJ, Mayerhofer M, et al. CD25 indicates the neoplastic phenotype of mast cells: a novel immunohistochemical marker for the diagnosis of systemic mastocytosis (SM) in routinely processed bone marrow biopsy specimens. *Am J Surg Pathol* 2004;28:1319-25.
78. Berezowska S, Flaig MJ, Rueff F, Walz C, Haferlach T, Krokowski M, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. *Mod Pathol* 2014;27:19-29.
79. Slapnicar C, Lebovic G, McParland A, Dozois M, Vadas P. Reproducibility of symptom sequences across episodes of recurrent anaphylaxis. *J Allergy Clin Immunol Pract* 2022;10:534-538.e1.
80. Ebina K, Hirao M, Tsuboi H, Nagayama Y, Kashii M, Kaneshiro S, et al. Effects of prior osteoporosis treatment on early treatment response of romosozumab in patients with postmenopausal osteoporosis. *Bone* 2020;140:115574.
81. Maurer M, Siebenhaar F, Hartmann K, Reiter A, Radia D, Deininger MW, et al. Avapritinib improves overall symptoms, skin lesions and quality of life in patients with advanced systemic mastocytosis in the PATHFINDER study. *Allergy* 2021;76:18-22.