

ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification

Jakub Trizuljak¹  | Wolfgang R. Sperr²  | Lucie Nekvindová³  |
 Hanneke O. Elberink⁴  | Karoline V. Gleixner²  | Aleksandra Gorska⁵ |
 Magdalena Lange⁶  | Karin Hartmann^{7,8}  | Anja Illerhaus⁸  |
 Massimiliano Bonifacio⁹  | Cecelia Perkins¹⁰  | Chiara Elena¹¹  |
 Luca Malcovati¹¹  | Anna B. Fortina¹²  | Khalid Shoumariyeh¹³  |
 Mohamad Jawhar¹⁴  | Roberta Zanotti⁹  | Patrizia Bonadonna¹⁵  |
 Francesca Caroppo¹²  | Alexander Zink¹⁶  | Massimo Triggiani¹⁷  |
 Roberta Parente¹⁷  | Nikolas von Bubnoff¹³  | Akif S. Yavuz¹⁸  | Hans Hägglund¹⁹  |
 Mattias Mattsson¹⁹  | Jens Panse²⁰  | Nadja Jäkel²¹  | Alex Kilbertus²²  |
 Olivier Hermine²³  | Michel Arock²⁴  | David Fuchs²⁵  | Vito Sabato²⁶  |
 Knut Brockow¹⁶  | Agnes Bretterklieber²⁷  | Marek Niedoszytko⁵  |
 Björn van Anrooij⁴  | Andreas Reiter¹⁴  | Jason Gotlib¹⁰  |
 Hanneke C. Kluin-Nelemans²⁸  | Jiri Mayer¹  | Michael Doubek¹  | Peter Valent² 

¹Department of Hematology and Oncology, University Hospital, CEITEC Masaryk University, Brno, Czech Republic²Department of Internal Medicine I, Division of Hematology and Hemostaseology, Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria³Institute of Biostatistics and Analyses, Ltd., Spinoff Company of Masaryk University, Brno, Czech Republic⁴Department of Allergology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands⁵Department of Allergology, Medical University of Gdańsk, Gdańsk, Poland⁶Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Gdańsk, Poland⁷Division of Allergy, Department of Dermatology, University of Basel, Basel, Switzerland⁸Department of Dermatology, University of Cologne, Cologne, Germany⁹Department of Medicine, Section of Hematology, University of Verona, Verona, Italy¹⁰Division of Hematology, Department of Medicine, Stanford University, School of Medicine/Stanford Cancer Institute, Stanford, CA, USA¹¹Division of Hematology, Fondazione IRCCS Policlinico San Matteo & University of Pavia, Pavia, Italy¹²Pediatric Dermatology Unit, Department of Medicine, University of Padova, Padova, Italy¹³Department of Hematology, Oncology and Stem Cell Transplantation, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany¹⁴Hämatologie und Onkologie, III. Medizinische Klinik, Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany¹⁵Allergy Unit, Verona University Hospital, Verona, Italy¹⁶Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany¹⁷Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy¹⁸Division of Hematology, Istanbul Medical School, University of Istanbul, Istanbul, Turkey

Abbreviations: ALP, alkaline phosphatase; ASM, aggressive systemic mastocytosis; BM, bone marrow; BMM, bone marrow mastocytosis; CI, confidence interval; CM, cutaneous mastocytosis; ECNM, the European Competence Network on Mastocytosis; ECOG, the Eastern Cooperative Oncology Group; EFS, event-free survival; Hb, hemoglobin; HR, hazard ratio; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; MCS, mast cell sarcoma; MIS, mastocytosis in skin; OS, overall survival; PLT, platelet count; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SMM, smoldering systemic mastocytosis; WBC, white blood count; WHO, the World Health Organization.

¹⁹Department of Medical Sciences, Uppsala University, Section of Hematology, Uppsala University Hospital, Uppsala, Sweden

²⁰Department of Oncology, Haematology, Haemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany

²¹Department of Internal Medicine IV, University Hospital Halle, Halle, Germany

²²Department of Dermatology and Venereology, Kepler University Hospital, Johannes Kepler University, Linz, Austria

²³Department of Hematology, Centre National de Référence des Mastocytoses, Imagine Institute, INSERM U1123, Université Paris Descartes, Sorbonne, Paris Cité, Hôpital Necker, Assistance Publique des Hôpitaux de Paris (APHP), Paris, France

²⁴Laboratory of Hematology, Pitié-Salpêtrière Hospital, Paris, France

²⁵Department of Internal Medicine 3, Hematology and Oncology, Kepler University Hospital, Johannes Kepler University, Linz, Austria

²⁶Faculty of Medicine and Health Sciences, Department of Immunology-Allergology-Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

²⁷Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria

²⁸Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

Correspondence

Michael Doubek, University Hospital Brno and Central European Institute of Technology of Masaryk University Brno, Jihlavská 20, 60200 Brno, Czech Republic.
Email: doubek.michael@fnbrno.cz

Funding information

Supported by the project CEITEC 2020 [LQ1601] from the Ministry of Education, Youth and Sports of the Czech Republic under National Sustainability, TA CR Center of Competence project (TE02000058), MH CR – DRO (FNBr, 65269705), by Deutsche Forschungsgemeinschaft (DFG, RA 2838 to AI), by the Koeln Fortune Program, Faculty of Medicine, University of Cologne (216/2016 to AI) and by the Austrian Science Fund (FWF) grant SFB F4704-B20. Also supported by the Czech Leukemia Study Group for Life (CELL).

Abstract

Background: In indolent systemic mastocytosis (ISM), several risk factors of disease progression have been identified. Previous studies, performed with limited patient numbers, have also shown that the clinical course in ISM is stable and comparable to that of cutaneous mastocytosis (CM). The aim of this project was to compare the prognosis of patients with ISM with that of patients with CM.

Methods: We employed a dataset of 1993 patients from the registry of the European Competence Network on Mastocytosis (ECNM) to compare outcomes of ISM and CM.

Results: We found that overall survival (OS) is worse in ISM compared to CM. Moreover, in patients with typical ISM, bone marrow mastocytosis (BMM), and smoldering SM (SSM), 4.1% of disease progressions have been observed (4.9% of progressions in typical ISM group, 1.7% in BMM, and 9.4% in SSM). Progressions to advanced SM were observed in 2.9% of these patients. In contrast, six patients with CM (1.7%) converted to ISM and no definitive progression to advanced SM was found. No significant differences in OS and event-free survival (EFS) were found when comparing ISM, BMM, and SSM. Higher risk of both progression and death was significantly associated with male gender, worse performance status, and organomegaly.

Conclusion: Our data confirm the clinical impact of the WHO classification that separates ISM from CM and from other SM variants.

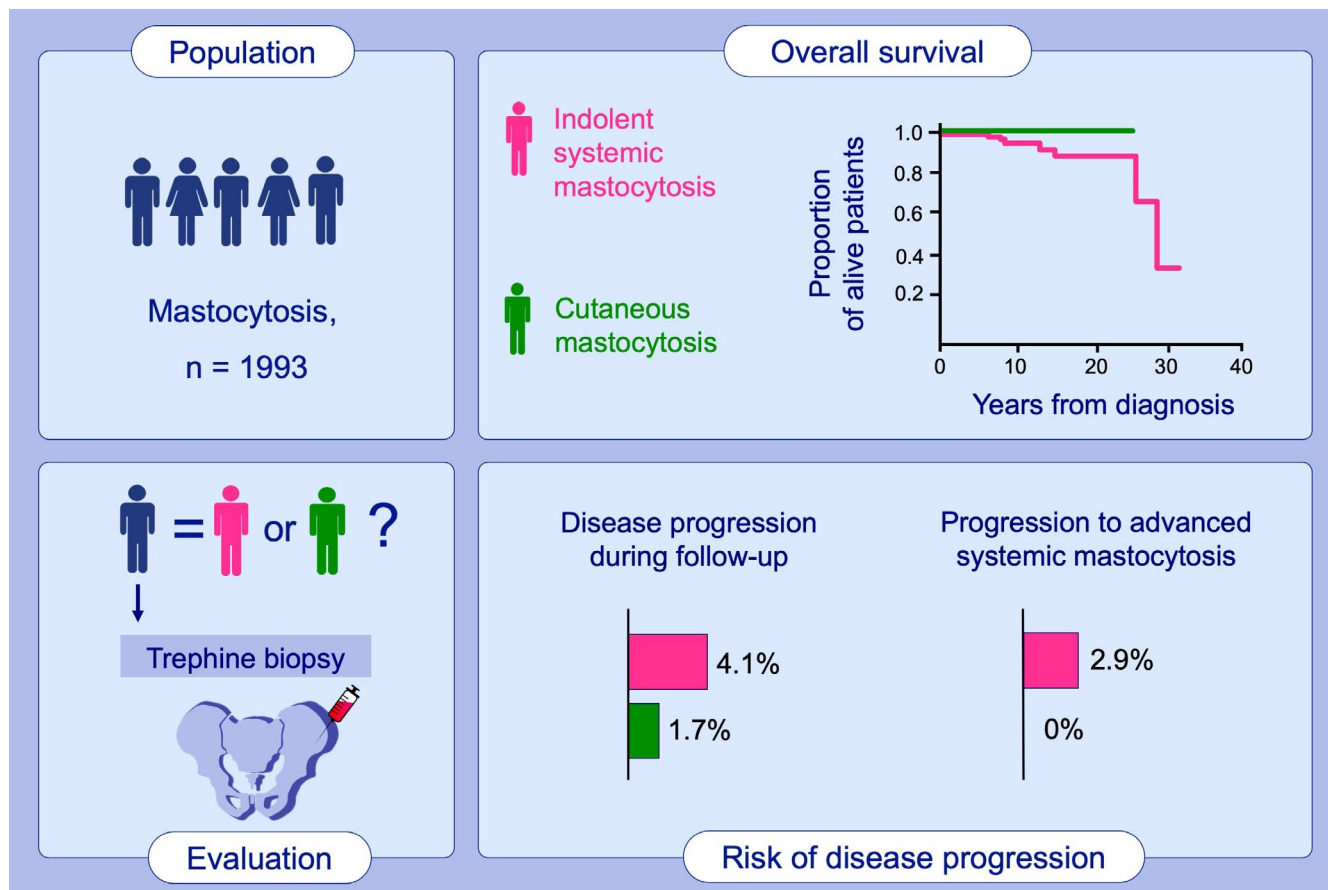
KEYWORDS

cutaneous mastocytosis, indolent systemic mastocytosis, prognostication, survival, WHO classification

1 | INTRODUCTION

Mastocytosis is a rare hematologic disease characterized by abnormal accumulation and expansion of tissue mast cells (MCs) in various organs.^{1–5} According to World Health Organization (WHO) criteria, indolent and advanced forms of mastocytosis can be distinguished.^{1–4} Cutaneous mastocytosis (CM) is typically found in childhood but can also be detected in adults. When detected in children, CM often resolves spontaneously before adolescence.^{1–5} Most adult patients have systemic mastocytosis (SM), often presenting with skin lesions

and almost always with bone marrow (BM) involvement.^{1–7} Indolent SM (ISM) has the highest prevalence.^{1–5} Bone marrow mastocytosis (BMM) represents a subvariant of ISM.^{1–4} In these patients, no skin lesions are detectable and the MC burden as well as serum tryptase levels are usually low. Recently, the smoldering subtype of SM (SSM), a former provisional ISM subvariant, has been designated as a distinct variant of SM by the WHO.^{1,2,4} Advanced mastocytosis includes aggressive SM (ASM), MC leukemia (MCL), and SM with an associated hematologic (non-MC) neoplasm (SM-AHN).^{1–4} The diagnosis of mastocytosis is established in a stepwise approach using the WHO classification and related diagnostic criteria.^{1–12}



GRAPHICAL ABSTRACT

Division of mastocytoses according to updated WHO Classification is clinically relevant. Overall survival is worse in indolent systemic mastocytosis compared to cutaneous mastocytosis. Trephine biopsy is necessary to distinguish indolent systemic mastocytosis from cutaneous mastocytosis.

In a majority of patients with mastocytosis, including CM, ISM, and SSM, the clinical course remains stable over years or even decades.^{1-4,7,13-16} This contrasts with the smaller group of advanced SM, including ASM and MCL, where most patients show a more or less rapid progression of disease, resulting in organ damage.^{1-4,6,7,13-16} During the last decade, several clinical, serological, cytomorphological, immunological, and molecular factors have been reported to be of prognostic importance in CM and SM.^{1-5,16-31} A number of these prognostic variables have been included in the WHO classification.¹⁻⁵

The WHO classification of mastocytosis was initially coined in 2001³ and has been refined in 2008 and 2016.^{1,2,4} The correct classification of mastocytosis is important because it serves as a major tool of prognostication. In the 2016 update of the WHO classification, nonadvanced group was split into patients with typical ISM, patients with SSM, and patients with BMM, a subset that is still considered to represent a provisional subentity of typical ISM.^{1,2,4} However, so far, the clinical implications of the updated WHO classification have not been analyzed in detail.

The aim of this current project was to compare the prognosis of patients with typical ISM with that of patients with SSM, BMM, and CM regarding OS and EFS, and to perform univariate and multivariate

analysis of factors associated with disease progression in these subgroups of patients. To meet this aim, we examined data in 1993 patients with mastocytosis collected in the dataset of the registry of the European Competence Network on Mastocytosis (ECNM).^{19,32} Details concerning the ECNM registry have been described recently by us¹⁹ and are summarized in the Supplemental Appendix.

2 | PATIENTS AND METHODS

2.1 | Patients' characteristics

A total of 1993 patients entered into the ECNM registry were analyzed (all the nonadvanced SM patients registered at the ECNM registry at the time of the study; Figure S1). Patients had typical ISM (n = 813), SSM (n = 56), BMM (n = 474), CM (n = 359; mastocytoma excluded), and mastocytosis in the skin (MIS; n = 291). MIS is a provisional diagnosis when no BM results are available in adults.³³ In all cases, no C-findings were found, so ASM was always excluded. To analyze overall survival (OS), all patients with a follow-up of at least 1 day were included. As a result, the dataset for analyzing OS

consisted of 1538 patients. The MIS cohort was excluded when calculating event-free survival (EFS). Thus, the dataset for this analysis consisted of 1325 patients. Detailed patients' characteristics are shown in Tables 1 and 2. All patients provided written informed consent to participate.

2.2 | Clinical and laboratory parameters assessed at diagnosis

Clinical and laboratory parameters captured at diagnosis included age, gender, performance status (Eastern Cooperative Oncology Group; ECOG), presence of skin lesions, organomegaly, serum tryptase level, white blood cell count (WBC), platelet count (PLT), hemoglobin (Hb), alkaline phosphatase (ALP), presence of MC infiltrates in BM sections, and presence of *KIT* mutation in codon 816 in BM cells.

2.3 | Estimation of survival

Comparisons of patients' characteristics in WHO subgroups (ISM vs BMM vs SSM vs CM)^{1,2,4} were performed using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Primary endpoints were OS and EFS. OS was calculated from the date of diagnosis to the date of death or last visit. EFS was defined as the time from the date of diagnosis to the date of progression to more advanced or aggressive forms of mastocytosis, death, or last visit. Survival estimates were established according to the method of Kaplan and Meier and compared across different diagnostic variants using the log-rank test. Patients' characteristics and diagnoses were evaluated for association with survival using univariate and multivariate Cox regression analyses. $P < .05$ were considered significant, and the outcomes were accompanied by 95% confidence intervals (CI).

3 | RESULTS

3.1 | Age and gender of patients with ISM and comparison to other forms of mastocytosis

Patients with ISM differed from patients with CM or MIS regarding age (ISM: median age 45.0 years; CM: median 23.0 years; MIS: median 42.0 years; $P < .001$ for ISM vs CM; $P = .013$ for ISM vs MIS). ISM, BMM, and SSM patients were exclusively adults; patients with CM consisted of 55% adults and 45% children. As per definition, patients diagnosed with MIS included only adults as children with skin lesions are usually classified as CM without BM studies.¹⁻³ Patients with ISM were significantly younger than patients with BMM or SSM (ISM: median 45.0 years; BMM: 50.0 years; SSM: 52.0 years; $P < .001$ for both comparisons: ISM vs BMM and ISM vs SSM). Performance status was significantly different in these forms of mastocytosis (the best in BMM, worse in SSM; $P < .001$ for all comparisons).

Furthermore, patients with typical ISM differed from patients with BMM concerning gender distribution (ISM: 65.2% women; BMM: 42.4% women; $P < .001$) (Tables 1 and 2).

3.2 | Comparison of laboratory parameters in patients with ISM, BMM, and SSM

Patients with ISM had significantly higher tryptase levels compared to BMM patients and significantly lower tryptase levels compared to SSM patients (ISM: median 35.0 ng/mL; BMM: median 27.0 ng/mL; SSM: median 200.0 ng/mL; $P < .001$ in comparisons: ISM vs BMM, ISM vs SSM, and BMM vs SSM). Moreover, ISM patients differed from BMM and SSM patients concerning ALP activity levels (ISM: median 75.0 U/L; BMM: median 71.9 U/L; SSM: median 114.0 U/L; $P < .001$ for comparison ISM vs SSM). Differences in Hb levels and PLT counts were marginal, but statistically significant. There were significant differences in the presence of MC infiltrates in BM biopsy sections ($P < .001$ for ISM vs BMM; $P = .006$ for ISM vs SSM). These results are summarized in Tables 1 and 2.

3.3 | Laboratory parameters also differ when comparing ISM with CM and MIS

Patients with ISM differed from patients with CM, adulthood CM (aCM; CM in patients over 18 years of age) and MIS in serum tryptase levels (medians: ISM 35.0 ng/mL; CM 7.6 ng/mL; aCM 9.2 ng/mL; MIS 12.0 ng/mL; $P < .001$ for comparisons: ISM vs CM, ISM vs aCM, and ISM vs MIS), and presence of the *KIT* mutation D816V in BM cells ($P < .001$ for the comparisons ISM vs CM and ISM vs aCM). Differences in Hb levels and PLT counts were marginal, but statistically significant. An interesting observation was that there was no significant difference in these parameters when comparing typical ISM with MIS patients. However, statistically significant differences were found between patients with typical ISM and patients with MIS concerning ALP (ISM: median 75.0 U/L; MIS: median 66.0 U/L; $P = .014$), performance status ($P = .001$), presence of splenomegaly (ISM: 3.6%; MIS: 0%; $P = .007$), and lymphadenopathy (ISM: 1.1%; MIS: 5.8%; $P < .001$). These results are summarized in Table 2.

3.4 | Comparison of clinical parameters in patients with ISM, BMM, and SSM

As expected, given the WHO requirements for the SSM classification, patients with ISM differed from patients with SSM in the frequency of documented organomegaly. Organomegaly (B-finding) was thus more prominent in the SSM subgroup than in ISM patients (splenomegaly: ISM 3.6%, SSM 52.9%, $P < .001$; hepatomegaly: ISM 4.4%, SSM 41.2% yes, $P < .001$; and lymphadenopathy: ISM: 1.1% yes; SSM: 15.7% yes; $P < .001$). There were also significant differences in skin involvement ($P < .001$ for ISM vs SSM) (Table 1).

TABLE 1 Patients' characteristics. Data of patients with indolent systemic mastocytosis (ISM), bone marrow mastocytosis (BMM), and smoldering systemic mastocytosis (SSM)

Characteristics	Statistics/categories	ISM	BMM	SSM	P*	P**
Age (y) (n = 1085)	Median (5. perc; 95. perc)	45.0 (24.0; 67.0)	50.0 (27.0; 70.0)	52.0 (30.0; 73.0)	<.001	<.001
Serum tryptase (ng/mL) (n = 1028)	Median (5. perc; 95. perc)	35.0 (8.9; 183.0)	27.0 (11.0; 128.0)	200.0 (29.5; 575.0)	<.001	<.001
WBC (/μL) (n = 1027)	Median (5. perc; 95. perc)	6600.0 (4 160.0; 10 900.0)	6 400.0 (3 900.0; 10 600.0)	6900.0 (2 900.0; 12 600.0)	.397	.940
Hemoglobin (g/dL) (n = 1032)	Median (5. perc; 95. perc)	13.9 (12.0; 16.0)	14.4 (12.3; 16.4)	13.2 (10.4; 16.6)	<.001	.004
Platelets (×10 ³ /μL) (n = 1025)	Median (5. perc; 95. perc)	269.0 (179.0; 396.0)	247.0 (162.0; 380.0)	230.0 (112.0; 409.0)	<.001	<.001
Alkaline phosphatase (U/L) (n = 873)	Median (5. perc; 95. perc)	75.0 (45.0; 146.0)	71.8 (44.5; 129.0)	114.0 (56.0; 340.0)	.133	<.001
Gender (n = 1085)	Women	427 (65.2%)	160 (42.4%)	31 (58.5%)	<.001	.370
	Men	228 (34.8%)	217 (57.6%)	22 (41.5%)		
Performance status (WHO) (n = 1085)	0—Normal activity	380 (58.0%)	270 (71.6%)	15 (28.3%)	<.001	<.001
	1—Symptoms, but fully ambulatory	255 (38.9%)	96 (25.5%)	32 (60.4%)		
	2—Symptoms, but in bed <50% of the day	9 (1.4%)	6 (1.6%)	5 (9.4%)		
	3—Needs to be in bed >50% of the day, but not bedridden	5 (0.8%)	3 (0.8%)	0 (0.0%)		
	5—Unknown	6 (0.9%)	2 (0.5%)	1 (1.9%)		
Typical skin involvement (n = 1085)	Yes	655 (100%)	0 (0%)	43 (81.1%)	<.001	<.001
	No	0 (0%)	377 (100%)	10 (18.9%)		
MC infiltrates in BM biopsy (n = 1085)	Yes	561 (85.6%)	284 (75.3%)	50 (94.3%)	<.001	0.006
	No ^a	68 (10.4%)	77 (20.4%)	0 (0.0%)		
	Not done ^a	26 (4.0%)	16 (4.2%)	3 (5.7%)		
KIT mutation D816V in BM (n = 1081)	Yes	428 (65.6%)	274 (72.9%)	34 (64.2%)	.614	.636
	No	77 (11.8%)	44 (11.7%)	4 (7.5%)		
	Not done	147 (22.5%)	58 (15.4%)	15 (28.3%)		
Spleen (palpable) (n = 1056)	Yes	23 (3.6%)	15 (4.0%)	27 (52.9%)	.735	<.001
	No	603 (95.1%)	352 (94.9%)	24 (47.1%)		
	Unknown	8 (1.3%)	4 (1.1%)	0 (0.0%)		
Hepatomegaly (palpable) (n = 1054)	Yes	28 (4.4%)	19 (5.1%)	21 (41.2%)	.644	<.001
	No	597 (94.3%)	347 (93.8%)	29 (56.9%)		
	Unknown	8 (1.3%)	4 (1.1%)	1 (2.0%)		
Darier sign positive (n = 787)	Yes	419 (67.0%)	65 (53.7%)	23 (56.1%)	1.000	.279
	No	38 (6.1%)	6 (5.0%)	4 (9.8%)		
	Unknown	168 (26.9%)	50 (41.3%)	14 (34.1%)		
Lymphadenopathy (n = 1047)	Yes	7 (1.1%)	8 (2.2%)	8 (15.7%)	.189	<.001
	No	590 (93.4%)	341 (93.7%)	37 (72.5%)		
	Unknown	35 (5.5%)	15 (4.1%)	6 (11.8%)		

Note: Dataset for overall survival.

Abbreviations: BM, bone marrow; MC, mast cell; WBC, white blood count.

^aPatients without MC infiltrates in the bone marrow biopsy or with no bone marrow biopsy had MCs found in the bone marrow blood smear; therefore, the diagnosis of ISM or BMM has been established.

*ISM vs BMM.

**ISM vs SSM.

Bold *P*-values are statistically significant.

TABLE 2 Patients' characteristics. Data of patients with indolent systemic mastocytosis (ISM), cutaneous mastocytosis (CM), adulthood CM (aCM) and mastocytosis in the skin (MIS)

Characteristics	Statistics/ categories	ISM	CM	aCM	MIS	P*	P**	P***
Age (yrs) (n = 1108)	Median (5. perc; 95. perc)	45.0 (24.0; 67.0)	23.0 (0.6; 60.0)	37.0 (22.0; 60.0)	42.0 (17.0; 69.0)	<.001	<.001	.013
Serum tryptase (ng/mL) (n = 1007)	Median (5. perc; 95. perc)	35.0 (8.9; 183.0)	7.6 (2.7; 27.8)	9.2 (2.7; 26.9)	12.0 (2.7; 64.0)	<.001	<.001	<.001
WBC (/μL) (n = 966)	Median (5. perc; 95. perc)	6 600.0 (4 160.0; 10 900.0)	7 000.0 (4 510.0; 12 800.0)	6300.0 (4 510.0; 12 800.0)	6 690.0 (4 410.0; 11 000.0)	.025	.484	.343
Hemoglobin (g/dL) (n = 975)	Median (5. perc; 95. perc)	13.9 (12.0; 16.0)	13.5 (10.8; 15.9)	13.9 (12.1; 15.9)	13.8 (11.7; 15.8)	<.001	.807	.194
Platelets (×10 ³ /μL) (n = 967)	Median (5. perc; 95. perc)	269.0 (179.0; 396.0)	276.5 (173.0; 434.0)	258.0 (173.0; 386.0)	254.0 (183.0; 390.0)	.022	.081	.231
Alkaline phosphatase (U/L) (n = 754)	Median (5. perc; 95. perc)	75.0 (45.0; 146.0)	76.0 (40.0; 357.0)	68.0 (40.0; 148.0)	66.0 (42.0; 135.0)	.126	.063	.014
Gender (n = 1108)	Women	427 (65.2%)	143 (59.1%)	92 (69.2%)	137 (64.9%)	.101	.423	1.000
	Men	228 (34.8%)	99 (40.9%)	41 (30.8%)	74 (35.1%)			
Performance status (WHO) (n = 1106)	0—Normal activity	380 (58.0%)	166 (68.9%)	79 (59.8%)	153 (72.9%)	.007	.409	.001
	1—Symptoms, but fully ambulatory	255 (38.9%)	74 (30.7%)	52 (39.4%)	53 (25.2%)			
	2—Symptoms, but in bed <50% of the day	9 (1.4%)	0 (0.0%)	0 (0.0%)	2 (1.0%)			
	3—Needs to be in bed >50% of the day, but not bedridden	5 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			
	4—Unable to get out of bed	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)			
	5—Unknown	6 (0.9%)	1 (0.4%)	1 (0.4%)	1 (0.5%)			
MC infiltrates in BM biopsy (n = 1108) ^a	Yes	561 (85.6%)	2 (0.8%)	2 (1.5%)	0 (0.0%)	<.001	<.001	<.001
	No	68 (10.4%)	133 (55.0%)	128 (96.2%)	10 (4.7%)			
	Not done	26 (4.0%)	107 (44.2%)	3 (2.3%)	201 (95.3%)			
C-kit mutation D816V in BM (n = 1103)	Yes	428 (65.6%)	24 (10.0%)	24 (18.3%)	7 (3.3%)	<.001	<.001	<.001
	No	77 (11.8%)	81 (33.8%)	79 (60.3%)	9 (4.3%)			
	Not done	147 (22.5%)	135 (56.3%)	28 (21.4%)	195 (92.4%)			
Spleen (palpable) (n = 1053)	Yes	23 (3.6%)	3 (1.3%)	3 (2.3%)	0 (0.0%)	.113	.600	.007
	No	603 (95.1%)	208 (93.3%)	125 (94.7%)	165 (84.2%)			
	Unknown	8 (1.3%)	12 (5.4%)	4 (3.0%)	31 (15.8%)			
Hepatomegaly (palpable) (n = 1051)	Yes	28 (4.4%)	8 (3.6%)	7 (5.3%)	6 (3.1%)	.845	.644	.829
	No	597 (94.3%)	202 (91.0%)	121 (91.7%)	159 (81.1%)			
	Unknown	8 (1.3%)	12 (5.4%)	4 (3.0%)	31 (15.8%)			
Darier sign positive (n = 1069)	Yes	419 (67.0%)	178 (74.8%)	85 (64.9%)	141 (68.4%)	.761	.240	.337
	No	38 (6.1%)	18 (7.6%)	12 (9.2%)	17 (8.3%)			
	Unknown	168 (26.9%)	42 (17.6%)	34 (26.0%)	48 (23.3%)			

(Continues)

TABLE 2 (Continued)

Characteristics	Statistics/ categories	ISM	CM	aCM	MIS	P*	P**	P***
Lymphadenopathy (n = 1043)	Yes	7 (1.1%)	7 (3.2%)	2 (1.6%)	11 (5.8%)	.052	.657	<.001
	No	590 (93.4%)	188 (85.5%)	122 (94.6%)	138 (72.3%)			
	Unknown	35 (5.5%)	25 (11.4%)	5 (3.9%)	42 (22.0%)			

Note: Dataset for overall survival.

Abbreviations: BM, bone marrow; MC, mast cell; NA, not applicable; WBC, white blood count.

*The diagnosis ISM can be established based on the presence of three minor criterion even in the absence of the major criterion (dense mast cell infiltrate); not every mast cell infiltrate is diagnostic even if it is clearly visible; a loose infiltrate without densely packed atypical mast cells does not qualify as a major SM criterion.

*ISM vs CM.

**ISM vs aCM.

***ISM vs MIS.

Bold P-values are statistically significant.

3.5 | Overall survival is better in patients with CM compared to patients with ISM

One thousand five hundred thirty-eight patients were analyzed for OS. Median follow-up of patients with ISM (n = 655) was 4.3 years (range 0.0-31.4). Twenty-two patients (3.4%) died during this period. Causes of death were disease-related (n = 5; progression to more advanced SM); cardiovascular (n = 7); secondary cancer (n = 6); unknown (n = 4). Median OS was 28.4 years (95% CI: 24.1-32.7 years). Median follow-up of patients with BMM (n = 377) was 3.2 years (range 0.0-20.5). Thirteen patients (3.4%) died in this group. Causes of death were secondary cancer (n = 4); cardiovascular (n = 4); liver failure (n = 1); unknown (n = 4). Median OS was 19.9 years (95% CI: 15.2-24.7) in the BMM group. Median follow-up of patients with SSM (n = 53) was 4.3 years (range 0.3-22.0); five patients (9.4%) died in this cohort (disease-related cause (n = 2; progression to more advanced SM); secondary cancer (n = 1); infection (n = 1); unknown (n = 1)). At the time of analysis, median OS was not reached in the SSM group. There were no significant differences among ISM, BMM, and SSM both in length of follow-up (P = .206) and in percentage of surviving patients (P = .262). There was no significant difference in OS when comparing ISM and BMM (P = .727) and borderline when comparing ISM and SSM (P = .050) (Figures S2 and S3).

Median follow-up of patients with CM (n = 242) was 3.0 years (range 0.0-25.3 years; median in aCM was 3.1 years). No patient with childhood CM or aCM died during follow-up. Median follow-up of patients with MIS (n = 211) was 3.0 years (range 0.0-36.7 years). There were 10 (4.7%) deaths among patients with MIS. Causes of death were secondary cancer (n = 2), cardiovascular (n = 2), kidney failure (n = 1), accident (n = 1), infection (n = 1), unknown (n = 3). Median OS was not reached both in patients with CM and MIS. A significant difference in OS was found between patients with ISM and CM (P = .024), but no significant difference in OS was found when comparing ISM patients with the aCM (P = .092) and MIS subgroup (P = .17). However, there was a

clear trend to better survival in aCM patients compared with ISM (Figure 1; Figures S4 and S5).

3.6 | Progression of disease and event-free survival

A total of 1325 patients were analyzed for EFS. Median follow-up of patients with typical ISM (n = 653) was 4.2 years (range 0.0-31.4); patients with BMM (n = 377) 3.2 years (range 0.0-20.5); and patients with SSM (n = 53) 4.3 years (range 0.3-22.0). In these patients, progressions were as follows: typical ISM to SSM (n = 11; 1.7%), typical ISM to aggressive SM (ASM) (n = 8; 1.2%), typical ISM to SM-AHN (n = 12; 1.8%), typical ISM to MC sarcoma (MCS like progression fulfilling ASM criteria) (n = 1; 0.1%), SSM to ASM (n = 4; 7.5%), SSM to SM-AHN (n = 1; 1.9%), BMM to ASM (n = 1; 0.2%), BMM to SM-AHN (n = 5; 1.3%), and BMM to SSM (n = 1; 0.2%). Median follow-up of patients with CM (n = 242) was 2.8 years (aCM also 2.8 years). Only six patients with CM (1.7%; all aCM patients) eventually converted to ISM, and no further progression to advanced SM was found. Summary of progressions is shown in Table 3. No statistically significant difference was found when comparing EFS in ISM, BMM, SSM, CM, and aCM. EFS estimates are shown in Figures S6-S10.

3.7 | Identification of independent prognostic variables in multivariate analyses

In multivariate analyses including parameters shown in Tables 1 and 2, age (HR 1.06, 1.04-1.09; P < .001), gender (female gender protective; HR 0.5, 0.28-0.86; P = .013), performance status (HR 2.11, 1.19-3.72; P = .010), and lymphadenopathy (HR 4.96, 1.76-13.96; P = .002) were statistically significant predictors of EFS (Table 4). Regarding OS, performance status (HR 2.02, 1.05-3.91; P = .036); splenomegaly (HR 3.39, 1.15-10.03 P = .027), and age (HR 1.11, 1.08-1.14;

$P < .001$) were found to be significant. Results of multivariate analyses are summarized in Table 3.

4 | DISCUSSION

The term mastocytosis denotes a heterogeneous group of rare disorders characterized by abnormal growth and accumulation of MCs in various organs.¹⁻⁵ Indolent SM (ISM) is the most prevalent subtype of mastocytosis in adults. However, so far, little is known about the clinical outcome of this group, especially when comparing to adult patients with CM, BMM, or SSM. In the present study, we examined clinical and laboratory features as well as the prognosis of patients with typical ISM and compared the outcomes in this group with OS and EFS in patients with CM, BMM, and SSM. These studies were performed in 1993 patients with mastocytosis collected in the ECRM registry (no well-differentiated SM among these patients). Our data show that ISM is a unique subset with distinct clinical features and distinct prognosis which is worse compared to CM regarding OS. However, our data also show that the differences in OS and EFS are subtle if any when comparing typical ISM with BMM and SSM.

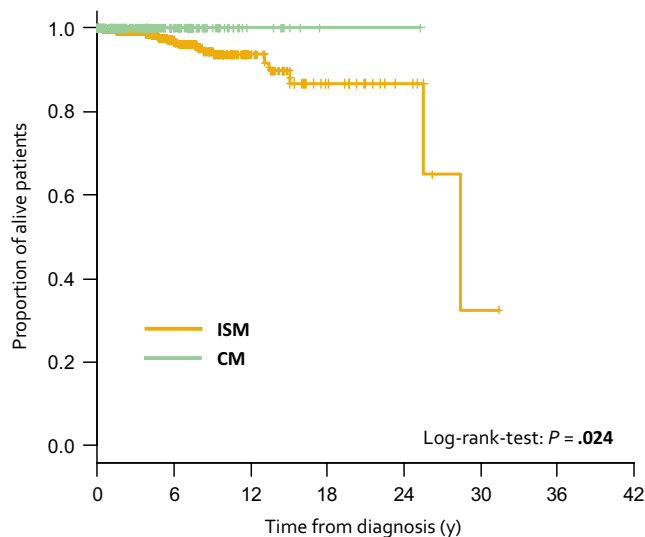


FIGURE 1 Overall survival (OS) of indolent systemic mastocytosis patients (ISM, $n = 655$) and cutaneous mastocytosis patients (CM, $n = 242$). $P = .024$ as determined by log-rank-test. Hazard ratio (HR) 0.0 (95% confidence interval: 0.0)

There has been a long-lasting debate about the necessity to perform a BM biopsy in all adult patients with MIS and about the clinical and prognostic implications of separating CM from SM. In particular, it was not clear whether patients with ISM have a less favorable prognosis compared to CM—actually the OS in ISM seems to be similar to that in the healthy, age-matched population.⁶ We found that patients with ISM have inferior OS compared to CM patients. However, there was also a significant difference in age when comparing these patients. In particular, patients in the ISM subgroup were significantly older compared to patients with CM which is due to the fact that in the CM group, 45% of the patients were children. On the other hand, adult patients with CM were also detected in the registry, and these patients were also found to have a better prognosis compared to ISM patients. Most importantly, even in adults with CM, no cases of death were recorded, contrasting the ISM group. Based on this observation, it seems clear that definitive statements about the prognosis in MIS can only be delivered when a BM biopsy is performed to clarify the final correct diagnosis: SM vs CM. Therefore, we recommend a BM study in all adult patients with MIS.

We also found that there is no significant difference when OS is compared in patients with MIS and ISM, which may point to the fact that many patients with the provisional diagnosis of MIS have in fact an unrecognized (not yet diagnosed) SM, mostly ISM. This assumption is supported by the fact that indeed ISM is diagnosed in many patients once these adult patients agree to a BM biopsy study.

In the recent WHO update, ISM has been separated from SSM and from BMM, which was recognized as a provisional subset of ISM and is now considered a provisional SM variant. Unexpectedly, the OS in these subgroups (ISM, BMM, and SSM) was very similar. Regarding OS of ISM patients, we confirmed data of a previous study published by the Mayo group.^{6,34} In the Mayo cohort, OS of patients with ISM was 25.1 years and thus slightly shorter compared to an OS of 28.4 years in our study. The prognosis of SSM patients also appeared to be better in our analysis, with a median OS not reached in our study and a median OS of 10 years in the Mayo cohort.^{6,34} These differences may have several explanations. One could be that the awareness for mastocytosis and therapy has improved in recent years (when the ECRM registry was established), whereas the Mayo data are based in part on a cohort of cases that was collected in an earlier time period. Another possibility may be that our patients

		Progressions		Progressions to advanced SM	P-value (ISM vs CM)
ISM ($n = 1083$)	Typical ISM ($n = 653$)	4.9%	4.1%	2.9%	<.001
	BMM ($n = 377$)	1.7%			
	SMM ($n = 53$)	9.4%			
CM ($n = 242$)			1.7%	0	

Abbreviations: BMM, bone marrow mastocytosis; CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; SMM, smoldering systemic mastocytosis.

TABLE 3 Disease progressions

TABLE 4 Multivariate analysis of the influence of selected parameters on event-free survival (EFS) and overall survival (OS)

Variable	Multivariate analysis of the influence of selected parameters on EFS		Multivariate analysis of the influence of selected parameters on OS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (y)	1.06 (1.04; 1.09)	<.001	1.11 (1.08; 1.14) ^a	<.001
Serum tryptase (ng/mL)	1.00 (1.00; 1.00) ^a	.093	1.00 (1.00; 1.00) ^a	.253
Platelets ($\times 10^3/\mu\text{L}$)	1.00 (0.99; 1.00) ^a	.485	1.00 (1.00; 1.00) ^a	.943
Gender (female vs male)	0.50 (0.28; 0.86)	.013	0.54 (0.27; 1.05)	.070
Performance status: symptoms/need to be in bed (vs normal activity)	2.11 (1.19; 3.72)	.010	2.02 (1.05; 3.91)	.036
Spleen (palpable) (yes vs no)	1.37 (0.55; 3.41)	.492	3.39 (1.15; 10.03)	.027
Hepatomegaly (palpable) (yes vs no)	1.99 (0.86; 4.60)	.106	1.36 (0.48; 3.85)	.563
Lymphadenopathy (yes vs no)	4.96 (1.76; 13.96)	.002	0.54 (0.27; 1.05)	.070

Note: Results of Cox regression multivariate analysis of the influence of selected parameters on PFS and OS in indolent systemic mastocytosis (ISM), bone marrow mastocytosis (BMM), smoldering systemic mastocytosis (SSM) and cutaneous mastocytosis (CM). Statistically significant parameters ($P < .05$) from univariate Cox analyses were put into multivariate Cox analysis. Performance status is binarized: symptoms/need to be in bed vs normal activity. N = 1043.

Abbreviations: HR, hazard ratio; CI, confidence interval.

^aElevated vs normal.

Bold P-values are statistically significant.

were diagnosed at an earlier time point in their lifetime compared to the Mayo patients.

So far, most studies evaluating risk factors in SM were based on less than 400 patients, which is an important point as SM is an extremely heterogeneous disease, and even in defined subtypes, the clinical course and organ involvements may differ substantially between patients' subsets. In the current study, 1538 patients were examined for OS and 1325 for EFS. In multivariate analysis, gender, performance status, and lymphadenopathy were statistically significant predictors of EFS; and performance status, splenomegaly, and lymphadenopathy for OS. So far, it is unclear whether all adult patients with MIS and lower tryptase level should have a BM investigation in order to define whether they are suffering from CM or SM, or even an advanced form of SM. Our data show that the OS is worse in adult patients with ISM compared to adults with CM, although statistical significance was not reached.

In the new WHO classification, typical ISM has been separated from SSM.^{1,2,4} Although several observations have already supported this split, validation was still lacking. Our study confirms that the proposed split into ISM, SSM, and BMM is meaningful. In fact, slightly higher progression rates and slightly shorter OS were found in the SSM cohort compared to ISM. On the other hand, these differences were not significant statistically and no differences were found when comparing OS and EFS in ISM and BMM patients. In this regard, it should be mentioned that BMM is still regarded a special

subvariant of ISM. On the other hand, BMM patients exhibit unique clinical features and are frequently overlooked, which is a clinical challenge as exactly these patients may suffer from severe systemic mediator-induced symptoms, especially when a concomitant allergy is present.

The Spanish Network on Mastocytosis published that ISM in adults has a low disease progression rate and that a majority of their patients had a normal life expectancy.¹⁶ According to their analysis, the presence of *KIT* mutations in multiple hematopoietic lineages and increase in serum beta2-microglobulin are the most powerful independent parameters predicting conversion into a more aggressive form of disease.¹⁶ Multilineage involvement and beta2-microglobulin concentrations were not analyzed in our study but may correlate with the smoldering state (SSM) of SM. Therefore, we believe that indeed multilineage involvement with *KIT* D816V is of prognostic significance in SM. More recently, this assumption has also been confirmed in several independent studies, including studies examining the mutant allele burden in SM. For example, Hoermann et al published that *KIT* D816V allele burden predicts survival in SM and correlates with the WHO type of the disease, and with the tryptase levels.²⁹ In our study, the *KIT* D816V allele burden was not analyzed. However, we believe that multilineage involvement and the *KIT* D816V allele burden should be added to prognostication and should probably also count as signs or even criterion of the smoldering state in SM in the future.

An interesting aspect in our study was that the prognosis of patients with SSM was similar to OS and EFS compared to ISM which contrasts previous studies.¹⁶ There are several explanations for this discrepancy. First, it may well be that only a subset of patients with SSM (eg those with clearly elevated *KIT* D816V burden and/or multilineage involvement and/or elevated ALP) has a higher risk to progress. Alternatively, the different numbers of patients analyzed in the different studies may explain this discrepancy.

An interesting aspect was that the progression patterns were different when comparing patients with CM, BMM, ISM, and SSM. For example, in CM, only six patients developed typical ISM and no further progression of these "CM-to-ISM" patients was seen. In BMM, progression to ASM, SSM, and SM-AHN, but no progression to typical ISM with skin lesions was found. In this regard, it is worth noting that many patients with ASM and SM-AHN lack skin lesions. By contrast, in typical ISM, transitions to SSM, ASM, MCS (MCS like progression fulfilling ASM criteria), and SM-AHN were recorded. Together, these data suggest that clinically relevant progression may occur in ISM and even in BMM. In BMM, a close follow-up may especially be required in cases with higher or rapidly increasing tryptase levels, in order to detect or exclude disease transformation.

5 | CONCLUSIONS

Our data confirm the clinical impact of the WHO classification that separates CM from ISM variants. The different prognosis of ISM and CM gives a sufficient reason for a BM investigation in all adult patients with skin lesions (MIS) and point at the need to recommend a regular follow-up in these cases. Precise differentiation of individual SM subgroups is also recommended for routine clinical practice. On the other hand, we also show that although ISM, BMM, and SSM display unique clinical features, especially the performance status which is worse in SSM, the prognosis is similar regarding OS and EFS.

CONFLICT OF INTEREST

WRS received honoraria from Novartis, Pfizer, AbbVie, Daiichi Sankyo, Amgen, Thermo Fisher, Deciphera, Incyte, Celgene, Jazz and travel grants from Pfizer and Roche. HOE received honoraria from ALK-Abelló, Chiesi, MEDA Pharma, Novartis, Blueprint. KVG received honoraria from Novartis, Roche, BMS, Sanofi, Incyte and travel grants from Roche and AbbVie. ML received honoraria from Novartis. KH received honoraria from Novartis, ALK, Blueprint, Deciphera and research funding from Euroimmun. MB received honoraria from Amgen, Incyte, Pfizer and research funding from Novartis. CE received honoraria from Novartis and Pfizer. MJ received honoraria from Novartis, Blueprint, Deciphera. RZ is consultant Deciphera and Novartis. AZ received honoraria or participated in trials from AbbVie, Almirall, Beiersdorf Dermo Medical, Bencard Allergie, BMS, Celgene, Eli Lilly, GSK, Janssen-Cilag, Miltenyi Biotec, Novartis, Sanofi-Aventis, Takeda Pharma. MT received honoraria from Deciphera, Blueprint, Novartis. NB

received honoraria from Astra Zeneca, Amgen, Novartis and BMS and research funding from Novartis. JP received honoraria from Alexion, BMS, Boehringer Ingelheim, Grünenthal, MSD, Novartis, Pfizer, Chugai. DF received honoraria from Novartis, Pfizer, Roche travel grants from Roche. VS received honoraria from Novartis, Termofisher, Shire, Stallergens. KB received honoraria from Novartis, Phadia (Thermo Fisher), Meda, BioMarin Pharmaceutical Inc outside. BA received honoraria from Novartis. AR received honoraria from Novartis, BMS, Deciphera, Blueprint, Baxalta/Shire and research funding from Novartis. JG received honoraria from Blueprint, Deciphera, Gilead, Incyte, Novartis and research funding from Blueprint, Celgene, CTI BioPharma, Deciphera, Gilead, Incyte, Pharmacyclics, Promedior, Seattle Genetics. JM received honoraria from Novartis, Gilead, BMS. MD received honoraria from Roche, AbbVie, Novartis, Gilead, AOP Pharmaceuticals, Janssen-Cilag. PV has received honoraria from Novartis, Pfizer, Deciphera, Incyte, Blueprint, Celgene and research funds from Pfizer, Incyte, Celgene. JT, LN, AG, AI, CP, LM, ABF, FC, KS, RP, MN, PB, ASY, HH, MM, NJ, AK, OH, MA, AB, HCKN have nothing to disclose.

AUTHOR CONTRIBUTIONS

JT, WRS, MD, PV designed analyses, interpreted results, and wrote the manuscript; LN performed statistical analyses; HOE, KVG, AG, ML, KH, AI, MB, CP, CE, LM, ABF, KS, MJ, RZ, PB, FC, AZ, MT, RP, NvB, ASY, HH, MM, JP, NJ, AK, OH, MA, DF, VS, KB, EA, MN, BvA, AR, JG, KCN, and JM collected data, supervised the study, and edited the manuscript.

ORCID

Jakub Trizuljak  <https://orcid.org/0000-0002-8948-5387>
 Wolfgang R. Sperr  <https://orcid.org/0000-0003-3288-8027>
 Lucie Nekvindová  <https://orcid.org/0000-0002-8866-2310>
 Hanneke O. Elberink  <https://orcid.org/0000-0003-2844-2196>
 Karoline V. Gleixner  <https://orcid.org/0000-0001-5753-0203>
 Magdalena Lange  <https://orcid.org/0000-0002-6967-1393>
 Karin Hartmann  <https://orcid.org/0000-0002-4595-8226>
 Anja Illerhaus  <https://orcid.org/0000-0003-0521-203X>
 Massimiliano Bonifacio  <https://orcid.org/0000-0003-0716-1686>
 Cecelia Perkins  <https://orcid.org/0000-0002-1277-7699>
 Chiara Elena  <https://orcid.org/0000-0003-2699-7462>
 Luca Malcovati  <https://orcid.org/0000-0002-1460-1611>
 Anna B. Fortina  <https://orcid.org/0000-0001-5791-0775>
 Khalid Shoumariyeh  <https://orcid.org/0000-0001-7969-1972>
 Mohamad Jawhar  <https://orcid.org/0000-0001-6312-237X>
 Roberta Zanotti  <https://orcid.org/0000-0003-2871-9730>
 Patrizia Bonadonna  <https://orcid.org/0000-0003-0476-1934>
 Francesca Caroppo  <https://orcid.org/0000-0003-3583-0816>
 Alexander Zink  <https://orcid.org/0000-0002-5424-0523>
 Massimo Triggiani  <https://orcid.org/0000-0001-7318-2093>
 Roberta Parente  <https://orcid.org/0000-0002-4187-6477>
 Nikolas von Bubnoff  <https://orcid.org/0000-0001-9593-8947>
 Akif S. Yavuz  <https://orcid.org/0000-0001-9049-4654>
 Hans Häggglund  <https://orcid.org/0000-0002-4382-4945>

Mattias Mattsson  <https://orcid.org/0000-0002-9510-8801>
 Jens Panse  <https://orcid.org/0000-0001-6316-3112>
 Nadja Jäkel  <https://orcid.org/0000-0001-6162-515X>
 Alex Kilbertus  <https://orcid.org/0000-0002-4686-5582>
 Olivier Hermine  <https://orcid.org/0000-0003-2574-3874>
 Michel Arock  <https://orcid.org/0000-0001-6714-7478>
 David Fuchs  <https://orcid.org/0000-0003-3909-0499>
 Vito Sabato  <https://orcid.org/0000-0002-1321-314X>
 Knut Brockow  <https://orcid.org/0000-0002-2775-3681>
 Agnes Brettertklieber  <https://orcid.org/0000-0002-6288-7693>
 Marek Niedoszytko  <https://orcid.org/0000-0003-1089-1911>
 Björn van Anrooij  <https://orcid.org/0000-0003-0149-5087>
 Andreas Reiter  <https://orcid.org/0000-0002-6338-2136>
 Jason Gotlib  <https://orcid.org/0000-0001-8253-6156>
 Hanneke C. Kluin-Nelemans  <https://orcid.org/0000-0003-2617-9427>
 Jiri Mayer  <https://orcid.org/0000-0003-0567-9887>
 Michael Doubek  <https://orcid.org/0000-0002-1269-6282>
 Peter Valent  <https://orcid.org/0000-0001-7017-6640>

REFERENCES

- Horny H-P, Akin C, Arber DA, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Arber DA, Hasserjian RP, LeBeau MM, Orazi A, Siebert R, eds. *WHO classification of tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press; 2017:61-70.
- Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420-1427.
- Valent P, Horny H-P, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001;25:603-605.
- Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. *Cancer Res*. 2017;77(6):1261-1270.
- Sperr WR, Valent P. Diagnosis, progression patterns and prognostication in mastocytosis. *Expert Rev Hematol*. 2012;5:261-274.
- Lim K-H, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113(23):5727-5736.
- Arock M, Valent P. Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. *Expert Rev Hematol*. 2010;3:497-516.
- Sperr WR, Escribano L, Jordan J-H, et al. Morphologic properties of neoplastic mast cells: delineation of stages of maturation and implication for cytological grading of mastocytosis. *Leuk Res*. 2001;25:529-536.
- Escribano L, Díaz-Agustín B, Bellas C, et al. Utility of flow cytometric analysis of mast cells in the diagnosis and classification of adult mastocytosis. *Leuk Res*. 2001;25:563-570.
- Longley BJ, Reguera MJ, Ma Y. Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy. *Leuk Res*. 2001;25:571-576.
- Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med*. 1987;316:1622-1626.
- Sperr WR, Jordan J-H, Fiegl M, 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;128:136-141.
- Akin C, Metcalfe DD. Systemic mastocytosis. *Annu Rev Med*. 2004;55:419-432.
- Metcalfe DD. Mast cells and mastocytosis. *Blood*. 2008;112(4):946-956.
- Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. *Blood*. 2010;116(26):5812-5817.
- Escribano L, Álvarez-Twose I, Sánchez-Muñoz L, 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(3):514-521.
- Sperr WR, Horny HP, Valent P. Spectrum of associated clonal hematologic non-mast cell lineage disorders occurring in patients with systemic mastocytosis. *Int Arch Allergy Immunol*. 2002;127(2):140-142.
- Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol*. 1991;96(3):2S-4S.
- Valent P, Oude Elberink JNG, Gorska A, et al. The data registry of the European Competence Network on Mastocytosis (ECNM): set up, projects and perspectives. *J Allergy Clin Immunol Pract*. 2019;7(1):81-87.
- Lennert K, Parwaresch MR. Mast cells and mast cell neoplasia: a review. *Histopathology*. 1979;3(5):349-365.
- Sotlar K, Cerny-Reiterer S, Petat-Dutter K, et al. Aberrant expression of CD30 in neoplastic mast cells in high-grade mastocytosis. *Mod Pathol*. 2011;24(4):585-595.
- Valent P, Cerny-Reiterer S, Herrmann H, et al. Phenotypic heterogeneity and target expression profiles of normal and neoplastic mast cells. *Best Pract Res Clin Haematol*. 2010;23(3):369-378.
- Escribano L, Orfao A, Díaz-Agustín B, et al. Indolent systemic mast cell disease in adults: immunophenotypic characterization of bone marrow mast cells and its diagnostic implications. *Blood*. 1998;91(8):2731-2736.
- Escribano L, Orfao A, Villarrubia J, et al. Sequential immunophenotypic analysis of mast cells in a case of systemic mast cell disease evolving to a mast cell leukemia. *Cytometry*. 1997;30(2):98-102.
- Teodosio C, Mayado A, Sánchez-Mun-oz L, et al. The immunophenotype of mast cells and its utility in the diagnostic work-up of systemic mastocytosis. *J Leukoc Biol*. 2015;97:49-59.
- Pardanani A, Reichard KK, Zblewski D, et al. CD123 immunostaining patterns in systemic mastocytosis: differential expression in disease subgroups and potential prognostic value. *Leukemia*. 2016;30:914-918.
- Pardanani A, Finke C, Abdelrahman RA, et al. Increased circulating IL-2Ra (CD25) predicts poor outcome in both indolent and aggressive forms of mastocytosis: a comprehensive cytokine-phenotype study. *Leukemia*. 2013;27:1430-1433.
- Hoermann G, Gleixner KV, Dinu GE, 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(6):810-813.
- Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. *Blood*. 2013;122(14):2460-2466.
- Jawhar M, Schwaab J, Schnittger S, et al. Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V+ advanced systemic mastocytosis. *Leukemia*. 2016;30:136-143.
- Greiner G, Witzeneder N, Berger A, et al. CCL2 is a KIT D816V-dependent modulator of the bone marrow microenvironment in systemic mastocytosis. *Blood*. 2017;129(3):371-382.
- Valent P, Arock M, Bonadonna P, et al. European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update, and future perspectives. *Wien Klin Wochenschr*. 2012;124(23-24):807-814.

33. Hartmann K, Escribano L, Grattan C, 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 Allergology and Clinical Immunology. *J Allergy Clin Immunol*. 2016;137(1):35-45.
34. Pardanani A. Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management. *Am J Hematol*. 2015;90:250-262.

How to cite this article: Trizuljak J, Sperr WR, Nekvindová L, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. *Allergy*. 2020;00:1-12. <https://doi.org/10.1111/all.14248>

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Supplemental information to:

Clinical Features and Survival of Patients with Indolent Systemic Mastocytosis defined by the Updated WHO Classification

Jakub Trizuljak¹, Wolfgang R. Sperr², Lucie Nekvindová³, Hanneke Oude Elberink⁴, Karoline V. Gleixner², Aleksandra Gorska⁵, Magdalena Lange⁶, Karin Hartmann⁷, Anja Illerhaus⁸, Massimiliano Bonifacio⁹, Cecelia Perkins¹⁰, Chiara Elena¹¹, Luca Malcovati¹¹, Anna Belloni Fortina¹², Khalid Shoumariyeh¹³, Mohamad Jawhar¹⁴, Roberta Zanotti⁹, Patrizia Bonadonna¹⁵, Francesca Caroppo¹², Alexander Zink¹⁶, Massimo Triggiani¹⁷, Roberta Parente¹⁷, Nikolas von Bubnoff¹³, Akif Selim Yavuz¹⁸, Hans Häggglund¹⁹, Mattias Mattsson¹⁹, Jens Panse²⁰, Nadja Jäkel²¹, Alex Kilbertus²², Olivier Hermine²³, Michel Arock²⁴, David Fuchs²⁵, Vito Sabato²⁶, Knut Brockow¹⁶, Agnes Bretterkieber²⁷, Marek Niedoszytko⁵, Björn van Anrooij⁴, Andreas Reiter¹⁴, Jason Gotlib¹⁰, Hanneke C. Kluin-Nelemans²⁸, Jiri Mayer¹, Michael Doubek¹, Peter Valent²

¹University Hospital, Department of Hematology and Oncology, and CEITEC Masaryk University, Brno, Czech Republic; ²Department of Internal Medicine I, Division of Hematology and Hemostaseology, and Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria; ³Institute of Biostatistics and Analyses, Ltd., spinoff company of Masaryk University, Brno, Czech Republic; ⁴Department of Allergology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ⁵Department of Allergology, Medical University of Gdańsk, Gdańsk, Poland; ⁶Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Gdańsk, Poland; ⁷Division of Allergy, Department of Dermatology, University of Basel, Basel, Switzerland; ⁸Department of Dermatology, University of Cologne, Cologne, Germany; ⁹Department of Medicine, Section of Hematology, University of Verona, Verona, Italy; ¹⁰Division of Hematology, Department of Medicine, Stanford University School of Medicine/Stanford Cancer Institute, Stanford, CA, USA; ¹¹Division of Hematology, Fondazione IRCCS Policlinico San Matteo & University of Pavia, Italy; ¹²Pediatric Dermatology Unit, Department of Medicine, University of Padova, Padova, Italy; ¹³Department of Hematology, Oncology and Stem Cell Transplantation, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany; ¹⁴Hämatologie und Onkologie, III. Medizinische Klinik, Universitätsmedizin Mannheim, Universität Heidelberg, Mannheim, Germany; ¹⁵Allergy Unit, Verona University Hospital, Verona, Italy; ¹⁶Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany; ¹⁷Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy; ¹⁸Division of Hematology, Istanbul Medical School, University of Istanbul, Istanbul, Turkey; ¹⁹Department of Medical Sciences, Uppsala University and Section of Hematology, Uppsala University Hospital, Uppsala, Sweden; ²⁰Department of Oncology, Haematology, Haemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany; ²¹Department of Internal Medicine IV, University Hospital Halle, Germany; ²²Department of Dermatology and Venereology, Kepler University Hospital, Johannes Kepler University, Linz, Austria; ²³Imagine Institute, INSERM U1123, Université Paris Descartes, Sorbonne, Paris Cité, Département of Hematology, Centre national de référence des mastocytoses, Hôpital Necker, Assistance publique des hôpitaux de Paris (APHP), Paris, France; ²⁴Laboratory of Hematology, Pitié-Salpêtrière Hospital, Paris, France; ²⁵Department of Internal Medicine 3, Hematology and Oncology, Kepler University

Hospital, Johannes Kepler University, Linz, Austria; ²⁶Faculty of Medicine and Health Sciences, Department of Immunology-Allergology-Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium; ²⁷Department of Dermatology and Venereology, Medical University of Graz, Graz, Austria; ²⁸Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Table of Contents

The European Competence Network on Mastocytosis (ECNM) and the ECNM Registry

Background

Structure of the registry

Participating centers

Inclusion and exclusion criteria

Ethics committee approval

Patients

Diagnostic evaluations at diagnosis and

Follow up examinations

Data quality control and data clearing

Supplemental Tables

Table S1. Criteria of systemic mastocytosis.

Table S2. B findings and C findings.

Table S3. Information captured at diagnosis (A, B), information captured at follow up (C, D).

Supplemental Results

Figure S1. Analysed data structure.

Figure S2. Overall survival of patients with indolent systemic mastocytosis (ISM) and bone marrow mastocytosis (BMM).

Figure S3. Overall survival of patients with indolent systemic mastocytosis (ISM) and smouldering systemic mastocytosis (SSM).

Figure S4. Overall survival of patients with indolent systemic mastocytosis (ISM) and mastocytosis of skin (MIS).

Figure S5. Progression-free survival of patients with indolent systemic mastocytosis (ISM) and bone marrow mastocytosis (BMM).

Figure S6. Progression-free survival of patients with indolent systemic mastocytosis (ISM) and smouldering systemic mastocytosis (SSM).

Figure S7. Progression-free survival of patients with indolent systemic mastocytosis (ISM) and cutaneous mastocytosis (SSM).

Figure S8. Event-free survival of patients with indolent systemic mastocytosis (ISM) and cutaneous mastocytosis (CM).

Figure S9. Event-free survival of patients with indolent systemic mastocytosis (ISM) and adulthood cutaneous mastocytosis (aCM).

Figure S10. Event-free survival: cutaneous mastocytosis (CM) versus indolent systemic mastocytosis (ISM) versus bone marrow mastocytosis (BMM) versus smouldering systemic mastocytosis (SMM).

References

The European Competence Network on Mastocytosis (ECNM) and the ECNM Registry

Background

The ECNM is a major collaborative network and initiative of a group of scientists and clinicians who are working together in the field of mastocytosis in Europe. The members of this network are dedicated to merge their ideas and research efforts, with the ultimate goal to improve awareness, recognition, diagnostics, prognostication and therapy in patients with mast cell disorders. Specific aims of the ECNM are to provide and distribute new relevant information to physicians and patients, to organize access to essential diagnostic assays, to promote research and collaborative scientific projects, to establish state-of-the art standards for diagnosis and therapy of mastocytosis patients, and to facilitate referrals to specialized centers and experts in various countries. The ECNM is a non-profit cooperative network and was established in 2002. It consists of so-called Reference Centers and Centers of Excellence.^{1,2} In 2012, our network members initiated a registry project collecting data from patients with mastocytosis, the ECNM registry. The primary goal of the ECNM registry is to collect and merge data from a larger number of patients with mast cell disorders including all variants of mastocytosis with the aim to learn more about the incidence, pathogenesis and course of this disease. Further major goals of the registry are to identify new diagnostic and prognostic biomarkers, to study the natural course of disease, and to define treatment response of patients with various forms of mastocytosis.^{2,3} Moreover, information about patient-related variables (like age or gender) and their impact as prognostic parameters are studied in the registry. Finally, data regarding mediator-related effects and symptoms, the management of mediator-induced symptomatology and treatment responses are collected.

Structure of the Registry and Collection of Data

The registry is a web-based collection of data (core data set) of patients with mastocytosis. Most patients are seen and managed in the Centers of Excellence of the ECNM. Patients' data are collected retrospectively and prospectively in individual centers by the local principle investigator (PI) and her/his team, and are included in a central web-based data file, creating the ECNM registry source data set. This data set undergoes regular quality controls, a yearly data-clearing-process and technical adjustment and updating as needed. Patients are entered through pseudonyms in the central database. Thus, only the physicians (and their teams) in the local centers that have entered the patients' data can identify their own patients through a specific identifying number. The sponsor of the ECNM registry is the Medical University of

Vienna.³ The sponsor supports the ECNM registry projects by providing the IT-infrastructure of the network, the central (core) data set, and the central management of the registry data set. The registry data are stored on the server of the Austrian Control Bank (OeKB Business Services; <https://ecnm-registry.oekb-bs.at>). The OeKB Business Services is specialized on IT project management and software development. The entry mask and entry system are provided by Asoluto, an agency for communication and digital solutions (www.asoluto.com). Each participating center can view its own patients entered in the registry and can download the data of its own patients but cannot access or download data of patients from other centers unless conducting an official ECNM registry project. Only the coordinator of the registry can perform a general download. Such downloads are necessary for the regular data clearing and for the distribution of the entire data sets to individual centers so that the centers can perform ECNM registry projects. The general download is performed in each project wave (once a year). The complete data set consists of the initial data (at diagnosis), all follow up data and all data regarding therapy.

Participating Centers and Development of ECNM Registry Projects

The registry consortium consists of the registry coordinators and the local PI of each participating center. The Medical University of Vienna runs and coordinates the ECNM registry. The ECNM registry is a contract-based multi-center long-term project. The consortium contract regulates the selection and distribution of ECNM registry projects, the rights and responsibilities of each participating center, co-authorships, and the publication strategy. Every center - independent of size, country or center-status - can make suggestions for a study and can present a proposal in an Annual ECNM meeting. The minimal criterion is inclusion of patients (25 eligible mastocytosis patients or more for larger studies) in the ECNM registry. The board of the ECNM (ECNM Board) coordinates and prepares the distribution of ECNM projects. This board consists of the previous and current chairs of the ECNM, the ECNM coordinator, and the coordinators of the ECNM registry. A decision board panel checks and approves the submitted projects. This board consists of the ECNM decision board, additional experts who included more than 100 eligible patients in the registry and members of the scientific advisory board (SAB) of the ECNM. In case of discussion concerning project strategies, decisions are reached by voting. Every single center can decide for each single project whether or not it will participate. Only thereafter will the data-sets be prepared and distributed to individual centers.

Inclusion and Exclusion Criteria

Only patients with proven mastocytosis were included in the ECNM registry. The diagnosis of mastocytosis was established according to criteria provided by the World Health Organization (WHO).⁴⁻⁶ The criteria of systemic mastocytosis (SM) are shown in Supplementary Table S1 and B and C findings in Supplementary Table S2.

The diagnosis of cutaneous mastocytosis (CM) was established based on published consensus criteria.⁷⁻⁹ In adults, the diagnosis CM requires a BM-based exclusion of SM. By contrast, in almost all children, CM can be diagnosed without BM studies, following established criteria and algorithms.⁷⁻⁹ In adult patients, a bone marrow (BM) biopsy was mandatory to rule out SM and to establish the diagnosis CM.^{4-6,10-12} If no BM studies were available (e.g., patient refused a consent) the provisional diagnosis of mastocytosis in the skin (MIS) was established. The diagnosis systemic mastocytosis (SM) was included in the registry when at least one major and one minor or at least three minor SM criteria were fulfilled (see Table 1).^{4-6,10-12} When neither B- nor C-findings were found, the disease was classified as indolent SM (ISM). When at least 2 B-findings were recorded, the diagnosis smouldering SM (SSM) was included, and when at least one C-finding was recorded the patient was classified as aggressive SM (ASM). B Findings and C Findings are shown in Supplementary Table S2. When $\geq 20\%$ MC were found in BM or peripheral blood smears, the diagnosis mast cell leukaemia (MCL) was established.^{4-6,10-12} It is important to know that organ damage only counts as C-finding when organ damage is caused by a devastating MC infiltrate that is confirmed by histology.^{4-6,10-12} In patients with MC sarcoma (MCS), SM criteria are not fulfilled, but the local (unifocal) MC tumor shows destructive growth and a high-grade histology. In SM with an associated hematologic neoplasm (SM-AHN) the criteria of SM and the criteria of an AHN had to be fulfilled. All these criteria were checked before the patients were included in the ECNM registry. Patients not fulfilling the WHO criteria of mastocytosis are excluded from the registry.

Ethics committee approval

All patients gave their written informed consent to participate. The registry study was approved by the local ethics committee of each participating center.

Patients

The patients' cohort used in this study was derived from 25 centers, including 24 European centers and one center in the USA (Stanford University, CA, USA). A routine data clearing

process was performed prior to the final data-download. To include patients in survival analyses, sufficient follow up data were mandatory. Thus, only a subset of patients could be employed for studying follow up and survival data. The number of patients selected for the analyses in this study is shown in Figure S1.

Diagnostic Evaluations at Diagnosis and Follow up Examinations

Clinical and laboratory features were assessed at diagnosis and during follow up. These parameters, included age, serum tryptase levels, white blood counts (WBC), percentage of eosinophils, platelet counts (PLT), hemoglobin (Hb), serum lactate dehydrogenase (LDH), alkaline phosphatase (ALP), performance status (according to WHO), presence or absence of urticaria pigmentosa (UP)-like skin lesions, presence or absence of osteoporosis (documented by osteodensitometry), organomegaly, known allergies, and mediator-related symptoms. At diagnosis, a BM examination was performed and included conventional morphology (cytology on Wright Giemsa-stained BM smears), conventional BM histology, immunohistochemistry (using antibodies against tryptase, KIT and CD34), cytogenetic studies, and *KIT* mutations analysis to detect or exclude *KIT* D816V.

An overview of these parameters is shown in Supplementary Tables S3A, S3B and S3C. During follow up, BM investigations were repeated in case of suspected progression. Progression was defined as a shift from a lower-risk category to a higher risk disease-category. Based on estimated survival times, the following rank order (from low to high risk disease) was employed for defining progressions: CM<ISM<SSM<SM-AHN<ASM+ASM-AHN<MCL+MCS. Patients with MCL who developed and AML were not considered to progress further as MCL has a very poor prognosis that may not be influenced by a concomitant AHN even if it is an AML.

Data quality control and data clearing

Data and data quality were supervised by the coordinators and their team in order to ensure standard documentation and standard data-quality. The data clearing process was done once a year. In a first step, the files were checked for accuracy, completeness of basic information, consistency, plausibility and homogeneity. In case of outliers or non-plausible data, queries were generated and sent out in order to solve the issues. After the queries were solved the data were checked again before the files were provided for carrying out this project.

Supplemental Tables

Table S1: Criteria of systemic mastocytosis

Major Criterion

1. Multifocal dense MC infiltrates (≥ 15 MC/infiltrate) in the bone marrow or in another extracutaneous organ

Minor Criteria

1. $>25\%$ spindle-shaped cells in MC-infiltrates; or $>25\%$ of all MC are atypical MC (type I and/or type II) in bone marrow smears
2. Expression of CD2 and/or CD25 in bone marrow MC
3. Serum tryptase level >20 ng/ml (does not count in cases with an AHN)
4. *KIT* point mutation at codon 816 (mostly D816V) in bone marrow or in another extracutaneous organ

Abbreviations: AHN, associated hematologic neoplasm; MC, mast cell

The diagnosis of Systemic Mastocytosis (SM) can be established when at least 1 major and 1 minor or 3 minor criteria are fulfilled

Table S2: B findings and C findings

B-Findings:

-
1. Infiltration grade (MC) in BM>30% and serum tryptase >200 (!) ng/ml
 2. Dysmyelopoiesis: Hypercellular marrow with signs of myelodysplasia or myeloproliferation, but no criteria for MDS or MPN. Blood picture normal or slightly abnormal
 3. Organomegaly (without impairment of organ function): Hepatomegaly (without ascites), splenomegaly (palpable), lymphadenopathy (>2 cm in CT or US)
-

When 2 or 3 B-Findings but no C-Findings are recorded, the final diagnosis is smouldering SM

C-Findings:

-
1. One or more Cytopenias: ANC<1000/ μ l; Hb<10 g/dl; PLT<100000/ μ l
 2. Hepatopathy: Enlarged liver with ascites, elevated liver enzymes +/- portal hypertension
 3. Organopathy of Spleen: Splenomegaly with hypersplenism
 4. Malabsorption with hypalbuminemia and weight loss
 5. Large osteolysis and/or severe osteoporosis & pathologic fractures
-

In case of detectable signs of organfunction impairment due to infiltration by neoplastic MC (i.e. a C-finding) the final diagnosis is aggressive systemic mastocytosis

Abbreviations: ANC, absolute neutrophil count; BM, bone marrow; CT, computed tomography; Hb, haemoglobin; MC, mast cell; PLT, platelets; US, ultrasound

Table S3A: Information captured at diagnosis.

Basic data	Mastocytosis criteria	Peripheral blood findings	Laboratory findings
• Patientcode • Patient-ID • Initials if possible • Gender • Date or year of birth • Center • Date of first symptoms • Date of first visit • Performance status (WHO) • Material stored • Type of material • Height • Weight • Patient lost to follow up • Date of last follow-up (contact) • Patient died • Date of death • Reason of death	• Date of visit • Skin involvement • if yes • if yes: typical, atypical • if typical maculopapulous or diffuse • % skin involved • Darier sign positive • monomorphic mast cell infiltration in the skin • <i>KIT</i> D816V positive in the skin • MC-infiltrates in BM biopsy (tryptase IHC) • % MC infiltrates (BM) by IHC • % spindle shaped MC in compact MC infiltrates in BM by IHC • loose infiltrate with predominantly spindle shaped MC by IHC (minor criterium) • MC present in smears • % MC in BM smears (MWG, WG) • % spindle shaped MC of all MC in bm smears • <i>KIT</i> mutation D816V in bm • <i>KIT</i> D816V allele burden • Other <i>KIT</i> mutation • Mutations in genes other than <i>KIT</i> • CD2 positive BM MC (by FACS) • CD25 positive BM MC (by FACS or IHC) • CD30 positive BM MC (by IHC or FACS) • Other surface markers • Multilineage involvement • Well differentiated morphology of MC • Serum tryptase • Diagnosis of Mastocytosis • Type of SM • Type of AHN	• Date of visit • WBC • % ANC • % eosinophils • % monocytes • % mast cells • Haemoglobin • Platelets • Basophils • Lymphocytes • Progenitors*	• Date of visit • LDH • Alkaline phosphatase • Calcium • Albumin • Fibrinogen • IgM • IgA • IgG • IgM kappa • IgM lambda • IgA kappa • IgA lambda • IgG kappa • IgG lambda • β-Microglobulin • Cholesterol

Abbreviations: AHN, associated hematologic neoplasm; ANC, absolute neutrophil count; BM, bone marrow; FACS, fluorescence activated cell sorting, flow cytometry; Ig, immunoglobulin; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MC, mast cell; MWG, modified Wright-

Giemsa stain; SM, systemic mastocytosis; WBC, white blood count; WG, Wright-Giemsa stain; WHO, World Health Organization

Table S3B: Information captured at diagnosis.

Clinical findings	Bone marrow	B & C findings	Mediator symptoms
• Date of visit • Spleen (palpable) • Hepatomegaly (palpable) • Lymphadenopathy (palpable or >2 cm in US/CT)	• Date of visit • Karyotype • % of blasts in BM smears	• Date of visit • Osteolysis due to MC infiltration • Number • Size • Dysmyelopoiesis • Ascites • Portal hypertension • Malabsorption • Weight loss ($\geq 10\%$ within last 12 months)	• Date of visit • Skin lesions • Flushing • Pruritus • Blistering/bullae • Constitutional/cardiovascular • Hypotension • Osteopenia/osteoporosis (symptoms) • Bone pain • T-Score • GI-tract symptoms • Abdominal Cramping • Diarrhoea • Ulcus duodeni • Ulcus ventriculi • Headache • Allergy • Type of allergen • Specific IgE • Therapy

Abbreviations: BM, bone marrow; CT, computed tomography; MC, mast cell; MC, mast cell; US, ultrasound

Table S3C: Information captured at follow up.

Basic data	Mastocytosis criteria	Peripheral blood findings	Laboratory findings
• Patientcode • Patient-ID • Initials if possible • Gender • Date or year of birth • Center • Date of first symptoms • Date of first visit • Performance status (WHO) • Material stored • Type of material • Height • Weight • Patient lost to follow up • Date of last follow-up (contact) • Patient died • Date of death • Reason of death	• Date of visit • Skin involvement • if yes • if yes: typical, atypical • if typical maculopapulous or diffuse • % skin involved • Darier sign positive • monomorphic mast cell infiltration in the skin • <i>KIT</i> D816V found in the skin • MC-infiltrates in BM biopsy (tryptase IHC) • % MC infiltrates (BM) by IHC • % spindle shaped MC in compact MC infiltrates in BM by IHC • loose infiltrate with predominantly spindle shape MC by IHC (minor criterion) • MC present in smears • % MC in BM smears (MWG, WG) • % spindle shaped MC of all MC in BM smears • <i>KIT</i> mutation D816V in BM • <i>KIT</i> D816V allele burden • Other <i>KIT</i> mutation • Mutations in genes other than <i>KIT</i> • CD2 positive BM MC (by FACS) • CD25 positive BM MC (by FACS or IHC) • CD30 positive BM MC (by IHC or FACS) • Other surface markers • Multilineage involvement • Well differentiated morphology of MC • Serum tryptase • Diagnosis of Mastocytosis • Type of SM • AHNMD	• Date of visit • WBC • % ANC • % eosinophils • % monocytes • % mast cells • Haemoglobin • Platelets • Basophils • Lymphocytes • Progenitors	• Date of visit • LDH • Alkaline phosphatase • Calcium • Albumin • Fibrinogen • IgM • IgA • IgG • IgM kappa • IgM lambda • IgA kappa • IgA lambda • IgG kappa • IgG lambda • β-Microglobulin • Cholesterol

Abbreviations: AHNMD, associated clonal, hematologic non-mast-cell lineage disease; ANC, absolute neutrophil count; BM, bone marrow; FACS, fluorescence activated cell sorting, flow cytometry; Ig, immunoglobulin; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MC, mast cell; MWG, modified Wright-Giemsa stain; SM, systemic mastocytosis; WBC, white blood

count; WG, Wright-Giemsa stain; WHO, World Health Organization

Table S3D: Information captured at follow up.

Clinical findings	Bone marrow	B & C findings	Mediator symptoms
• Date of visit • Spleen (palpable) • Hepatomegaly (palpable) • Lymphadenopathy (palpable or >2 cm in US/CT)	• Date of visit • Karyotype • % Blasts in BM smears	• Date of visit • Osteolysis due to MC infiltration • Number • Size • Dysmyelopoiesis • Ascites • Portal hypertension • Malabsorbtion • Weight loss ($\geq 10\%$ within last 12 months)	• Date of visit • Skin lesions • Flushing • Pruritus • Blistering/bullae • Constitutional/ cardiovascular • Hypotension • Osteopenia/osteoporosis (symptoms) • Bone pain • T-score • GI-tract symptoms • Cramping • Diarrhoea • Ulcus duodeni • Ulcus ventriculi • Headache • Allergy • Type of allergen • Specific IgE • Therapy

Abbreviations: BM, bone marrow; CT, computed tomography; MC, mast cell; MC, mast cell; US, ultrasound

Supplemental Results

Figure S1. Analysed data structure.

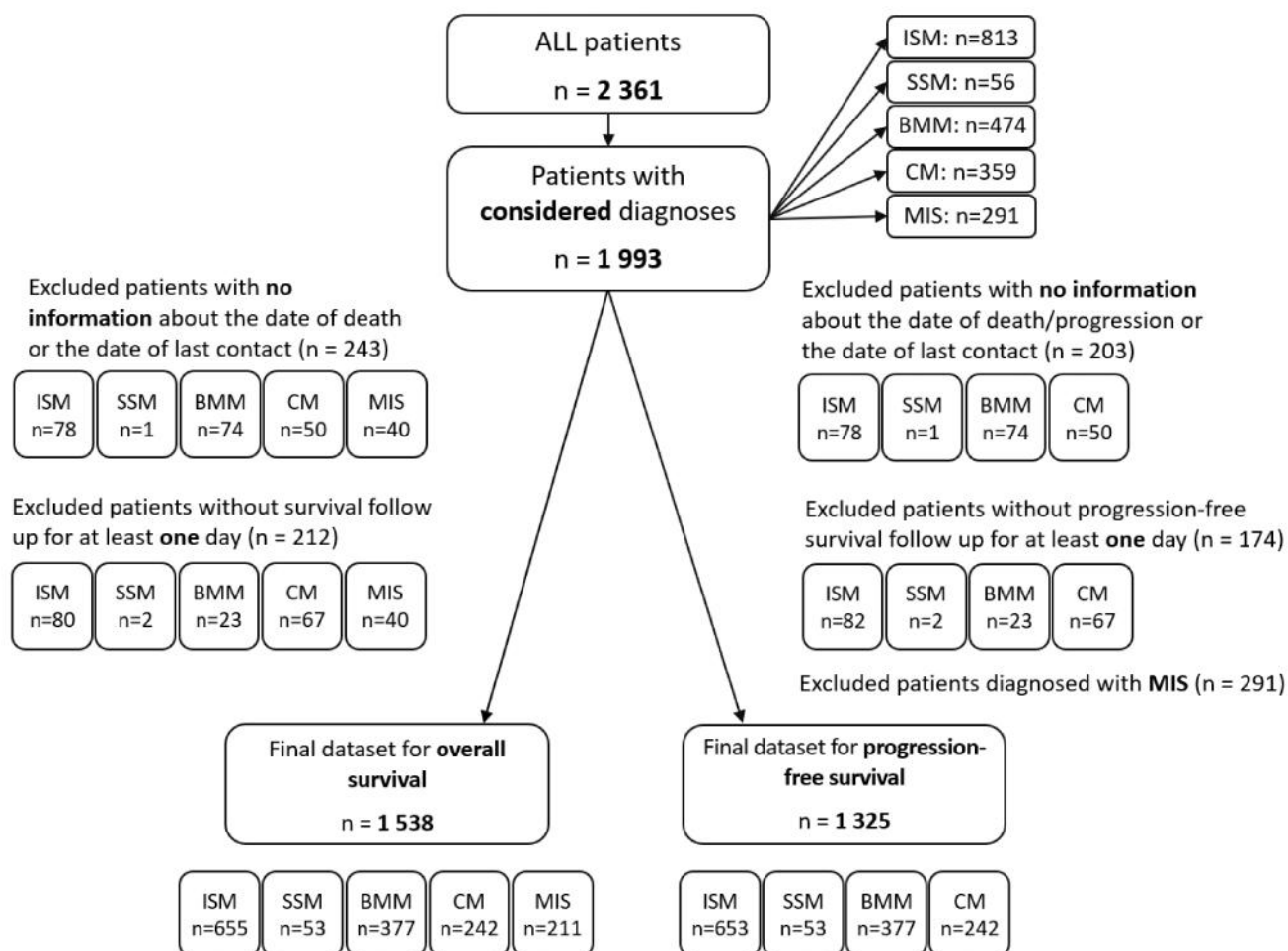


Figure S2. Overall survival: ISM vs. BMM. Overall survival of patients with indolent systemic mastocytosis (ISM; n=655) and bone marrow mastocytosis (BMM; n=377). Kaplan-Meier curves. Log-rank-test: $p=0.727$. Hazard ratio (HR) BMM vs. ISM 1.40 (95% confidence interval: 0.70; 2.80).

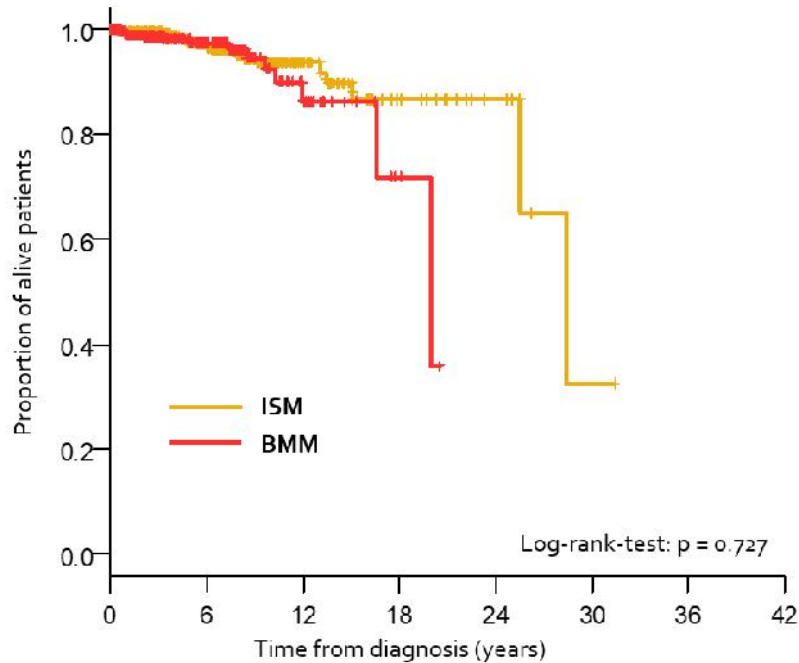


Figure S3. Overall survival: ISM vs. SSM. Overall survival of patients with indolent systemic mastocytosis (ISM; n=655) and smouldering systemic mastocytosis (SSM; n=53). Kaplan-Meier curves. Log-rank-test: $p=0.050$. Hazard ratio (HR) SSM vs. ISM 2.45 (95% confidence interval: 0.92; 6.51).

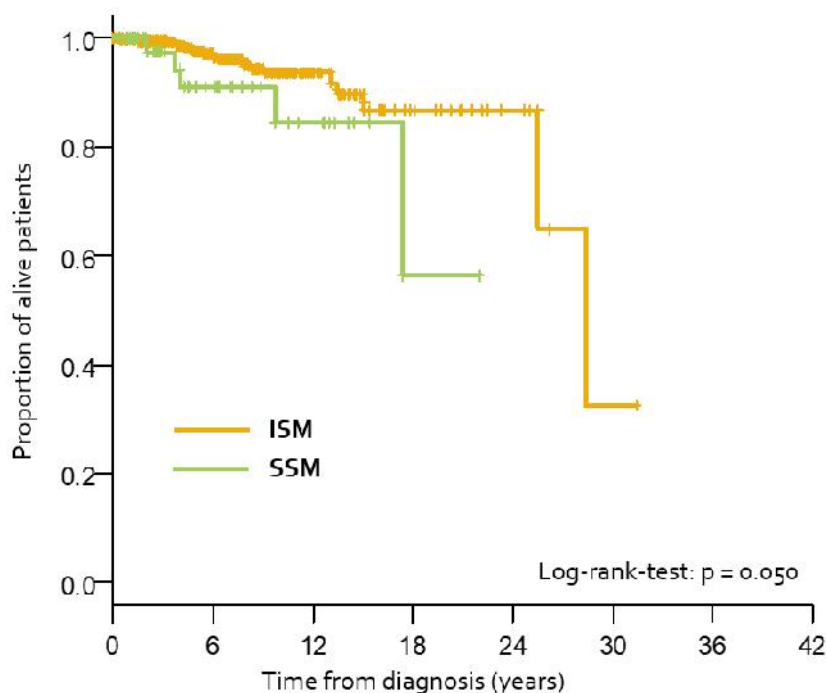


Figure S4. Overall survival: ISM vs. MIS. Overall survival of patients with indolent systemic mastocytosis (ISM; n=655) and mastocytosis in the skin (MIS; n=211). Kaplan-Meier curves. Log-rank-test: $p=0.172$. Hazard ratio (HR) MIS vs. ISM 1.70 (95% confidence interval: 0.80; 3.63).

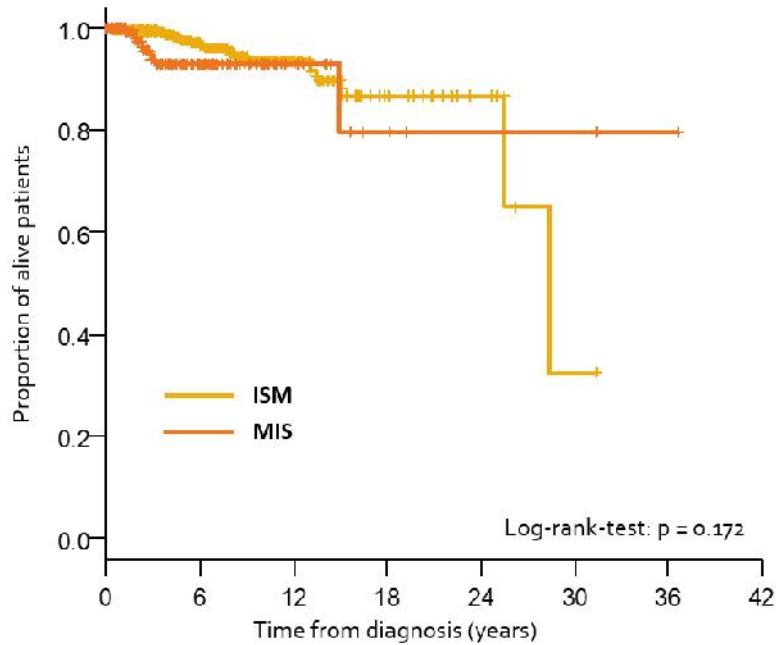


Figure S5. Overall survival: ISM vs. aCM. Overall survival of patients with indolent systemic mastocytosis (ISM; n=655) and adulthood cutaneous mastocytosis (aCM; n=133). Kaplan-Meier curves. Log-rank-test: $p=0.092$.

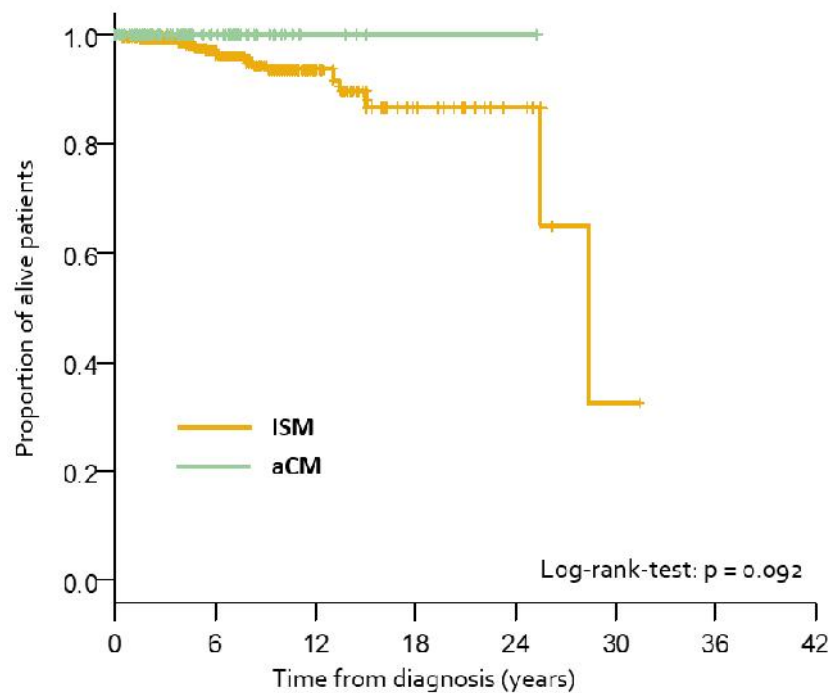


Figure S6. Event-free survival: ISM vs. BMM. Event-free survival of patients with indolent systemic mastocytosis (ISM; n=653) and bone marrow mastocytosis (BMM; n=377). Kaplan-Meier curves. Log-rank-test: $p=0.268$. Hazard ratio (HR) BMM vs. ISM 1.32 (95% confidence interval: 0.79; 2.23).

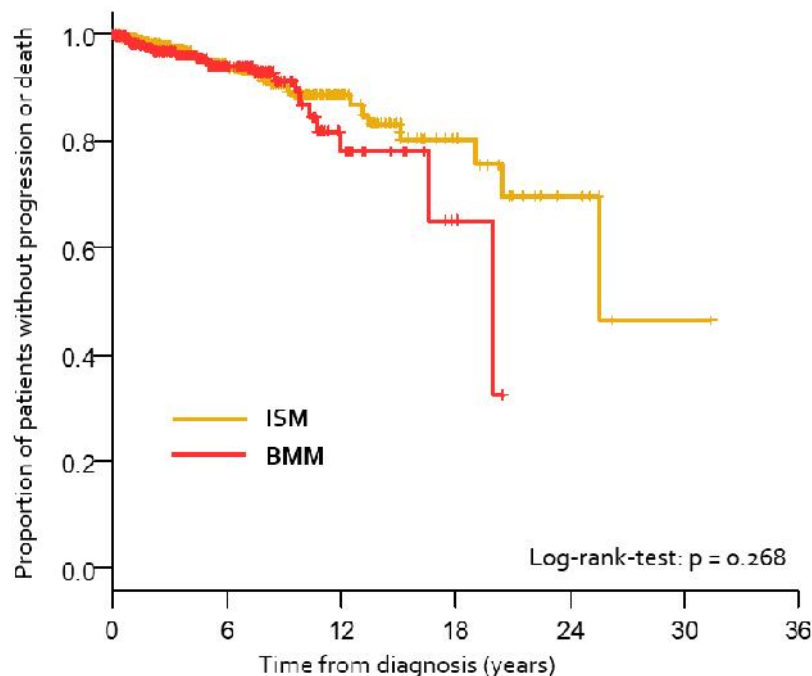


Figure S7. Event-free survival: ISM vs. SSM. Event-free survival of patients with indolent systemic mastocytosis (ISM; n=653) and smouldering systemic mastocytosis (SSM; n=53). Kaplan-Meier curves. Log-rank-test: $p=0.108$. Hazard ratio (HR) SSM vs. ISM 1.89 (95% confidence interval: 0.84; 4.23).

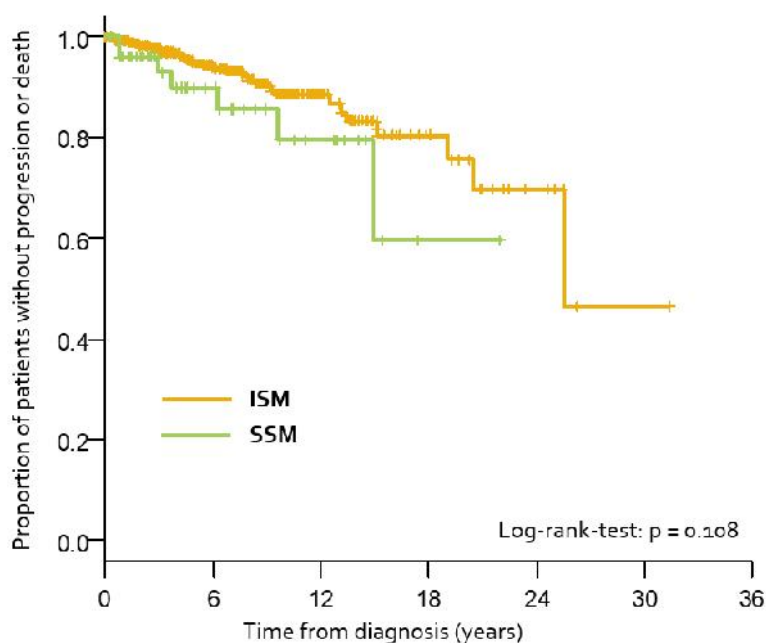


Figure S8. Event-free survival: ISM vs. CM. Event-free survival of patients with indolent systemic mastocytosis (ISM; n=653) and cutaneous mastocytosis (CM; n=242). Kaplan-Meier curves. Log-rank-test: $p=0.394$. Hazard ratio (HR) 0.72 (95% confidence interval: 0.32; 1.62).

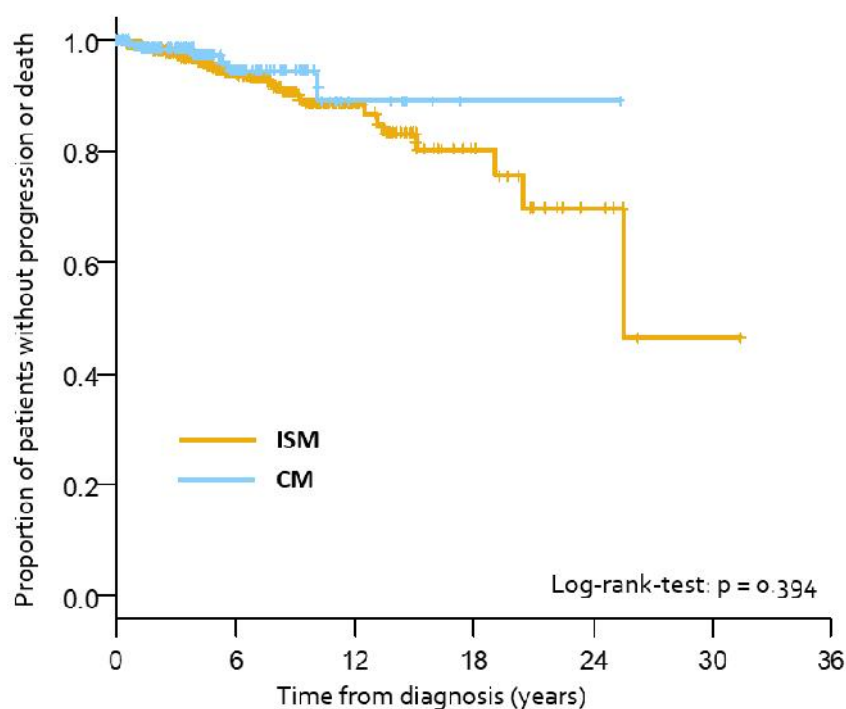


Figure S9. Event-free survival: ISM vs. aCM. Event-free survival of patients with indolent systemic mastocytosis (ISM; n=653) and adulthood cutaneous mastocytosis (aCM; n=133). Kaplan-Meier curves. Log-rank-test: $p=0.818$. Hazard ratio (HR) 0.89 (95% confidence interval: 0.22; 3.51).

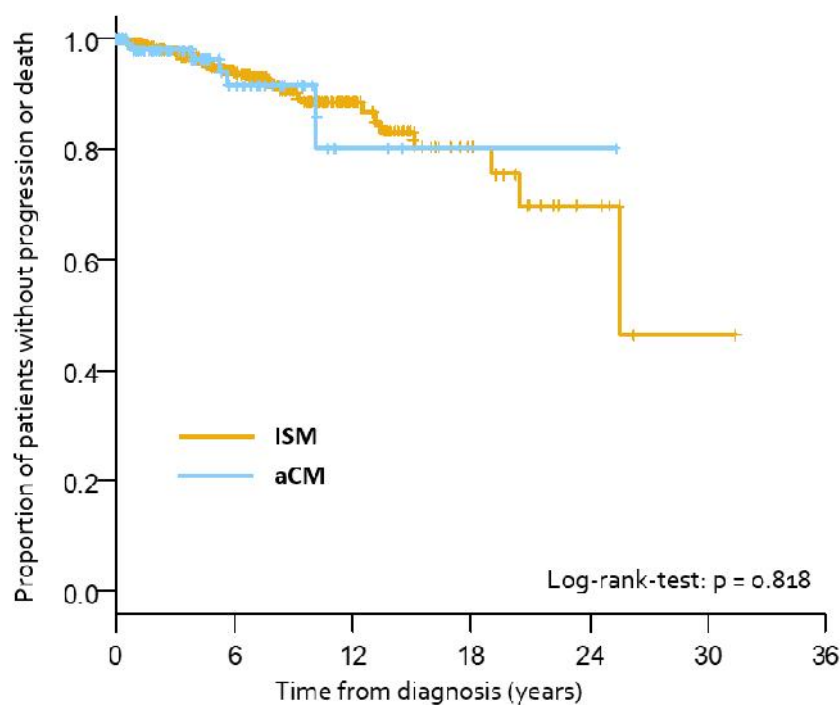
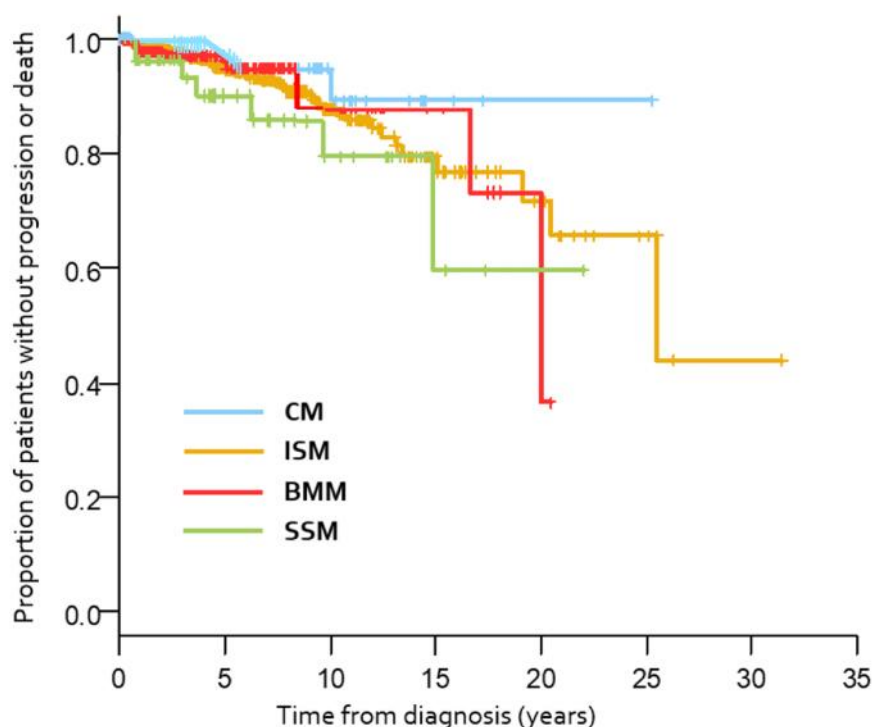


Figure S10. Event-free survival: CM vs. ISM vs. BMM vs. SMM (n=1325). BMM – bone marrow mastocytosis; CM – cutaneous mastocytosis; ISM – indolent systemic mastocytosis; SMM – smouldering mastocytosis.



Reference

1. Valent P, Arock M, Bischoff SC, et al. The European Competence Network on Mastocytosis (ECNM). *Wien Klin Wochenschr.* 2004;116(19-20):647-651.
2. Valent P, Arock M, Bonadonna P, et al. European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update, and future perspectives. *Wien Klin Wochenschr.* 2012;124(23-24):807-814.
3. Valent P, Oude Elberink JNG, Gorska A, et al. The data registry of the European Competence Network on Mastocytosis (ECNM): set up, projects and perspectives. *J Allergy Clin Immunol Practice.* 2019;7(1):81-87.
4. Valent P, Horny HP, Li CY, et al. Mastocytosis. World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues. eds: Jaffe ES, Harris NL, Stein H, Vardiman JW: vol 1. 2001. pp 291-302.
5. Horny HP, Metcalfe DD, Bennett JM, et al. Mastocytosis. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, eds. *IARC Press*, Lyon 2008, pp 54-63.
6. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127:2391-2405.
7. Valent P, Horny HP, Escibano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk. Res.* 2001;25:603-625.

8. Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest*. 2007;37(6):435-453.
9. Hartmann K, Escribano L, Grattan C, 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 Allergology and Clinical Immunology. *J Allergy Clin Immunol*. 2016;137(1):35-45.
10. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol*. 1991;96:2S-4S.
11. Valent P. Biology, classification and treatment of human mastocytosis. *Wien Klin Wochenschr*. 1996;108:385-397.
12. Valent P, Akin C, Sperr WR, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. *Br J Haematol*. 2003;122:695-717.