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Original Article

Prognostic Impact of Organomegaly in Mastocytosis: An Analysis of the European Competence Network on Mastocytosis

Johannes Lübke, MD[a], Juliana Schwaab, MD[a], Deborah Christen, MD[b], Hanneke Oude Elberink, MD[c], Bart Span, MD[d], Marek Niedoszytko, MD[e], Aleksandra Gorska, MD[e], Magdalena Lange, MD[f], Karoline V. Gleixner, MD[g,h], Emir Hadzijusufovic, PhD[g,h,i], Oleksii Solomianyi, MD[j], Irena Angelova-Fischer, MD[k], Roberta Zanotti, MD[l], Massimiliano Bonifacio, MD[l], Patrizia Bonadonna, MD[m], Khalid Shoumariyeh, MD[n,o], Nikolas von Bubnoff, MD[n,o,p], Sabine Müller, MD[q], Cecelia Perkins, MD[r], Chiara Elena, MD[s], Luca Malcovati, MD[s], Hans Hagglund, MD[t], Mattias Mattsson, MD[t], Roberta Parente, MD[u], Judit Varkonyi, MD[v], Anna Belloni Fortina, MD[w], Francesca Caroppo, MD[w], Alexander Zink, MD[x], Knut Brockow, MD[x], Christine Breynaert, MD[y], Dominique Bullens, MD[y], Akif Selim Yavuz, MD[z], Michael Doubek, MD[aa], Vito Sabato, MD[bb], Tanja Schug, MD[cc], Dietger Niederwieser, MD[dd], Karin Hartmann, MD[ee,ff], Massimo Triggiani, MD, PhD[gg], Jason Gotlib, MD, MS[r], Olivier Hermine, MD, PhD[hh], Michel Arock, PharmD, PhD[ii], Hanneke C. Kluin-Nelemans, MD[d], Jens Panse, MD[b,jj], Wolfgang R. Sperr, MD, PhD[g,h], Peter Valent, MD[g,h], Andreas Reiter, MD[a,*], and Mohamad Jawhar, MD[a,*] *Mannheim, Aachen, Freiburg, Lübeck, Munich, and Leipzig, Germany; Groningen, The Netherlands; Gdańsk, Poland; Vienna, Linz, and Graz, Austria; Verona, Pavia, Salerno, and Padova, Italy; Stanford, Calif; Uppsala, Sweden; Budapest, Hungary; Leuven and Antwerpen, Belgium; Istanbul, Turkey; Brno, Czechia; Basel, Switzerland; and Paris, France*

What is already known about this topic? Mere presence of organomegaly including splenomegaly, hepatomegaly, and/or lymphadenopathy and potential subsequent organ damage form the basis for dividing patients with systemic mastocyotsis into non-advanced and advanced subgroups.

What does this article add to our knowledge? Organomegalies including lymphadenopathy are often found in advanced systemic mastocyotsis disease forms. The new occurrence of organomegaly is associated with disease progression in systemic mastocyotsis. The number of organomegalies is associated with an adverse outcome.

How does this study impact current management guidelines? We recommend close monitoring through repeated adequate physical/radiography examinations as potential early indicator of progression and adverse outcome and allowing early intervention to prevent further organ damage.

BACKGROUND: Organomegaly, including splenomegaly, hepatomegaly, and/or lymphadenopathy, are important diagnostic and prognostic features in patients with cutaneous mastocytosis (CM) or systemic mastocytosis (SM).

OBJECTIVES: To investigate the prevalence and prognostic impact of 1 or more organomegalies on clinical course and survival in patients with CM/SM.

METHODS: Therefore, 3155 patients with CM (n = 1002 [32%]) or SM (n = 2153 [68%]) enrolled within the registry of

[a]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany
[b]Department of Oncology, Haematology, Haemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany
[c]Department of Allergology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[d]Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[e]Department of Allergology, Medical University of Gdańsk, Gdańsk, Poland
[f]Department of Dermatology, Medical University of Gdańsk, Gdańsk, Poland
[g]Department of Internal Medicine I, Division of Hematology & Hemostaseology, Medical University of Vienna, Vienna, Austria
[h]Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria
[i]Internal Medicine Small Animals, University Clinic for Small Animals, Department/University Clinic for Companion Animals and Horses, University of Veterinary Medicine, Vienna, Austria
[j]University Clinic for Hematology and Oncology, Kepler University Hospital, Johannes Kepler University, Linz, Austria
[k]Department of Dermatology and Venereology, Allergy Center, Kepler University Hospital, Johannes Kepler University Linz, Linz, Austria
[l]Section of Hematology, Department of Medicine, Verona University Hospital, Verona, Italy
[m]Allergy Unit, Verona University Hospital, Verona, Italy
[n]Department of Hematology and Oncology, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[o]German Cancer Consortium (DKTK) Partner Site Freiburg, Freiburg, Germany
[p]Department of Hematology and Oncology, Medical Center, University of Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

the European Competence Network on Mastocytosis were analyzed.

RESULTS: Overall survival (OS) was adversely affected by the number of organomegalies (OS: #0 vs #1 hazard ratio [HR], 4.9; 95% CI, 3.4-7.1, $P < .001$; #1 vs #2 HR, 2.1, 95% CI, 1.4-3.1, $P < .001$; #2 vs #3 HR, 1.7, 95% CI, 1.2-2.5, $P = .004$). Lymphadenopathy was frequently detected in patients with smoldering SM (SSM, 18 of 60 [30%]) or advanced SM (AdvSM, 137 of 344 [40%]). Its presence confered an inferior outcome in patients with AdvSM compared with patients with AdvSM without lymphadenopathy (median OS, 3.8 vs 2.6 years; HR, 1.6; 95% CI, 1.2-2.2; $P = .003$). OS was not different between patients having organomegaly with either ISM or SSM (median, 25.5 years vs not reached; $P = .435$). At time of disease progression, a new occurrence of any organomegaly was observed in 17 of 40 (43%) patients with ISM, 4 of 10 (40%) patients with SSM, and 33 of 86 (38%) patients with AdvSM, respectively.

CONCLUSIONS: Organomegalies including lymphadenopathy are often found in SSM and AdvSM. ISM with organomegaly has a similar course and prognosis compared with SSM. The number of organomegalies is adversely associated with OS. A new occurrence of organomegaly in all variants of SM may indicate disease progression. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2023;11:581-90)

Key words: *Mastocytosis; Systemic mastocytosis; Organomegaly; Splenomegaly; Hepatomegaly; Lymphadenopathy*

INTRODUCTION

Mastocytosis designates a heterogeneous group of disorders characterized by expansion and multifocal accumulation of clonal mast cells (MCs) in various tissues and organs, predominantly in the bone marrow (BM), skin, and visceral organs. The 2022 World Health Organization classification and the International Consensus Classification of myeloid neoplasms and acute leukemias divides the disease into cutaneous mastocytosis (CM) and systemic mastocytosis (SM). SM is divided into indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL).[1-6] ASM, SM-AHN, and MCL are collectively referred to as advanced SM (AdvSM).

[q]Department of Dermatology, Faculty of Medicine, Medical Center, University of Freiburg, Freiburg, Germany
[r]Division of Hematology, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA
[s]Department of Molecular Medicine and Department of Hematology Oncology, University of Pavia and Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[t]Division of Hematology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[u]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy
[v]Department of Hematology, Semmelweis University, Budapest, Hungary
[w]Pediatric Dermatology Unit, Department of Medicine, University of Padova, Padova, Italy
[x]Department of Dermatology and Allergy Biederstein, Faculty of Medicine, Technische Universität München, Munich, Germany
[y]KU Leuven Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group and MASTeL, University Hospitals Leuven, Leuven, Belgium
[z]Division of Hematology, Istanbul Medical School, University of Istanbul, Istanbul, Turkey
[aa]University Hospital and Faculty of Medicine, Brno, Czechia
[bb]Faculty of Medicine and Health Sciences, Department of Immunology-Allergology-Rheumatology, University of Antwerp and Antwerp University Hospital, Antwerpen, Belgium
[cc]Department of Dermatology and Venereology, University Hospital Graz, Graz, Austria
[dd]University Hospital of Leipzig, Leipzig, Germany
[ee]Division of Allergy, Department of Dermatology, University of Basel, Basel, Switzerland
[ff]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland
[gg]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy
[hh]French Reference Center for Mastocytosis (CEREMAST), Hôpital Necker, Assistance Publique Hôpitaux de Paris, Imagine Institute, University Paris Descartes, Paris, France
[ii]Laboratory of Hematology, Pitié-Salpêtrière Hospital, Paris, France
[jj]Center for Integrated Oncology, Aachen Bonn Cologne Düsseldorf (CIO ABCD), Aachen, Germany
*These authors contributed equally to this work.

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Corresponding author: Mohamad Jawhar, MD, Department of Hematology and Oncology, University Hospital Mannheim, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. E-mail: mohamad.jawhar@medma.uni-heidelberg.de.

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Abbreviations used
AdvSM- advanced SM
AHN- associated hematologic neoplasm
ASM- aggressive SM
BM- bone marrow
CM- cutaneous mastocytosis
ECNM- European Competence Network on Mastocytosis
HR- hazard ratio
ISM- indolent SM
MC- mast cell
MCL- MC leukemia
MIS- mastocytosis in the skin
MRI- magnetic resonance imaging
OS- overall survival
PFS- progression-free survival
SM- systemic mastocytosis
SM-AHN- SM with an associated hematologic neoplasm
SSM- smoldering SM

For subcategorization of patients with SM, B- and C-Findings are applied. B-Findings are typically found in SSM and include BM MC infiltration of greater than or equal to 30% and serum tryptase level of greater than or equal to 200 μg/L, signs of dysplasia or myeloproliferation in 1 or more non-MC lineages, and organomegaly (splenomegaly, hepatomegaly, and/or lymphadenopathy) without organ damage. C-Findings are typical features of organ damage caused by an AdvSM and include cytopenia(s) (absolute neutrophil count, $<1 \times 10^9$/L; hemoglobin, <10.0 g/dL; or platelets, $<100 \times 10^9$/L), impaired liver function with abnormal liver enzymes and ascites, skeletal involvement with large osteolytic lesions, splenomegaly with hypersplenism, as well as malabsorption with pronounced weight loss due to gastrointestinal MC infiltrates. The diagnosis of SSM is established when 2 or more B-Findings in the absence of any C-Findings are documented. When at least 1 C-Finding can be documented, the final diagnosis is ASM and if greater than or equal to 20% MCs in BM smears are identified, the final diagnosis is acute MCL. The disease-driving somatic point mutation *KIT* D816V is found in a vast majority of all patients with SM.[7-10]

Patients with CM and ISM have a normal or nearly normal life expectancy. Patients with SSM have a 10-year overall survival (OS) of 85%, whereas patients with AdvSM exhibit a poor subtype-depending median OS of less than 4 years.[11-17] Clinical features, B-Findings, various laboratory parameters, and signs of organ dysfunction (C-Findings) in combination with genetic aberrations create the framework for several recently established multiparametric prognostic scoring systems.[12,18-22]

Organomegaly has also been identified as a poor prognostic parameter in SM.[12,16,18,20,22] However, although organomegaly (splenomegaly, hepatomegaly, lymphadenopathy) is a common feature in patients with SSM and AdvSM,[1,11,23] previous studies about the potential relevance of organomegaly were often limited to smaller cohorts and a more detailed investigation of prevalence and prognostic impact of organomegaly is still lacking.

We therefore sought to investigate the impact of organomegaly on prevalence, clinical features, OS, and progression-free survival (PFS) in a series of 3155 patients enrolled in the registry of the European Competence Network on Mastocytosis (ECNM).

METHODS

ECNM registry

The ECNM registry was established in 2012 as a multidisciplinary, multinational cooperative initiative to analyze basic clinical, laboratory, and prognostic parameters in patients with CM and SM.[24-26] Details about the ECNM registry have been published elsewhere.[26] For the current study, we used a data set including 3115 patients from 26 centers in Europe (12 countries) and 1 in the United States. Data were entered online in a standardized form and checked regularly for plausibility and correctness. The study design adhered to the tenets of the Declaration of Helsinki and was approved by the relevant institutional review boards of the participating centers. All patients gave their written informed consent before entering this study.

Data collection

We included all patients with CM and SM (n = 3115) with at least 1 registry entry regarding splenomegaly (persistently palpable in deep inspiration ≥4 weeks, yes/no), hepatomegaly (persistently palpable in deep inspiration ≥4 weeks, yes/no), and/or central/peripheral lymphadenopathy (persistent palpable or >2 cm in imaging—ultrasound, computed tomography, or magnetic resonance imaging [MRI] ≥4 weeks, yes/no). Other possible hematologic and nonhematologic reasons as possible causes for organomegalies were noted within the data set. For this analysis, we used the data from a validated cohort updated in March 2019. Two patients with MC sarcoma were excluded. Patients diagnosed with maculopapular CM, diffuse CM, cutaneous mastocytoma, and mastocytosis in the skin (MIS) were grouped as CM/MIS (n = 1002 [32%]). The 2153 patients with SM were classified as ISM (n = 1665 [53%]), SSM (n = 68 [2%]), ASM (n = 108 [3%]), SM-AHN (n = 256 [8%]), and MCL (n = 56 [2%]). Diagnosis of a lymphoid neoplasm was established in 8 (3%) cases; of these, 4 (1%) patients were reported with registry-defined lymphadenopathy.

Patients characteristics

Table I and Table E1 in this article's Online Repository at www.jaci-inpractice.org present an overview of mastocytosis-associated disease characteristics at diagnosis in all patients with SM according to the number of organomegalies (#0-#3; #0, n = 1658 [77%]; #1, n = 209 [10%]; #2, n = 171 [8%]; #3, n = 115 [5%]). The median age increased with the number of organomegalies (#0-#3, 48-65 years; P [#0 vs #3] < .001). Dichotomized C-Findings and C-Finding—related laboratory abnormalities or other signs of organ dysfunction and SM-related symptoms analyzed in this study included hemoglobin level, platelet count, absolute neutrophil count, serum alkaline phosphatase, serum albumin, presence of ascites, portal hypertension, weight loss, gastrointestinal symptoms, and osteolytic lesions.

Statistical analyses

All statistical analyses considered clinical and laboratory parameters obtained at the time of diagnosis and progression and usually coincided with the time of BM biopsy. The following parameters were only included dichotomized (yes/no): splenomegaly, hepatomegaly, lymphadenopathy, ascites, portal hypertension, dysmyelopoiesis, osteolytic lesions, and weight loss (>10% over last 6 months). To address the question as to which extent splenomegaly, hepatomegaly, and lymphadenopathy were associated with other SM-relevant parameters, the phi (Φ) coefficient and the eta (η) coefficient were used for nominal-by-nominal and

TABLE I. Demographic and disease characteristics of 2153 patients with SM at diagnosis according to the number of organomegalies

Characteristic	SM #0	SM #1	SM #2	SM #3	P*
No. of patients at diagnosis, n (%)	1658 (77)	209 (10)	171 (8)	115 (5)	
Age (y), median (range)	48 (0-91)	54 (0-87)	62 (1-82)	65 (27-87)	<.001
Sex: male, n (%)	724 (44)	120 (57)	112 (66)	73 (64)	<.001
C-Findings, n (%)					
Hemoglobin (<10 g/dL)	35 (2)	30 (15)	48 (29)	42 (38)	<.001
Platelets (<100 × 10^9/L)	38 (2)	33 (17)	63 (38)	49 (44)	<.001
ANC (<1 × 10^9/L)	29 (2)	6 (3)	5 (3)	2 (2)	NS
Alkaline phosphatase (>150 U/L)	58 (4)	40 (24)	87 (60)	69 (69)	<.001
Albumin level (<34 g/L)	36 (3)	15 (10)	36 (28)	26 (28)	<.001
Ascites	6 (0)	13 (7)	44 (29)	55 (49)	<.001
Portal hypertension	5 (0)	8 (5)	16 (12)	25 (25)	<.001
Weight loss (>10% over last 6 mo)	30 (2)	40 (20)	71 (43)	64 (59)	<.001
Large osteolytic lesions	31 (2)	13 (8)	15 (12)	11 (12)	<.001
B-Finding–related parameters, n (%)					
Serum tryptase level (>200 μg/L)	47 (3)	29 (15)	56 (36)	50 (46)	<.001
Splenomegaly	0 (0)	108 (53)	158 (92)	115 (100)	<.001
Hepatomegaly	0 (0)	76 (37)	143 (85)	115 (100)	<.001
Lymphadenopathy	0 (0)	25 (15)	41 (31)	115 (100)	<.001
Additional finding					
KIT D816V AB,† median (range)	1 (0.0-37)	15 (0.0-47)	17 (0.0-50)	23 (0.0-50)	<.001

AB, Allele burden; *ANC*, absolute neutrophil count; *NS*, not significant.
*For distinct *P* values, see Table E1.
†*KIT* D816V AB available in 64, 22, 21, and 17 patients with 0, 1, 2, or 3 organomegalies, respectively.

nominal-by-interval association, respectively. OS was considered from the date of diagnosis to date of death or date of last follow-up (if alive). PFS was defined as the time from diagnosis to progression, death, or date of last follow-up (if progression-free). Disease progression was determined as follows: (1) from ISM to SSM or AdvSM, (2) from SSM to AdvSM, and (3) from AdvSM to a more aggressive AdvSM subtype (secondary MCL or secondary acute myeloid leukemia). OS and PFS probabilities were estimated by the method described by Kaplan and Meier and compared using the log-rank test. For categorical variables, Fisher exact test was used to assess the statistical significance of differences among groups. For calculating the level of significance in differences seen in continuous variables, the Mann-Whitney *U* test was used. *P* values of less than .05 (2-sided) were considered as significant. To assess the relationship between continuous and ordinary data, the Spearman rank correlation was used. Data management and statistical analyses were done by using SPSS software (SPSS version 20.0; IBM Corporation, Armonk, NY).

RESULTS

Prevalence of organomegaly

Organomegaly was found to be rare in CM/MIS (n = 57 [6%]) and ISM (n = 129 [8%]) but was frequently recorded in patients with SSM (n = 56 [88%]) and AdvSM (n = 306 [73%]). No significant differences were observed within the various subtypes of AdvSM (ASM, n = 78 [72%]; SM-AHN, n = 184 [78%]; MCL ± AHN, n = 44 [79%]) (Figure 1). In SSM and throughout all AdvSM subtypes, splenomegaly was the most common organomegaly, followed by hepatomegaly and lymphadenopathy. CM/MIS and ISM showed a more homogeneous distribution (Figure 1). In AdvSM, the concurrent presence of splenomegaly in patients with hepatomegaly (194 of 215 [90%]) was more prevalent than *vice versa* (194 of 273 [71%]). Lymphadenopathy without splenomegaly and hepatomegaly was observed in only 18 patients with AdvSM (4%). Multiple organomegalies were rare in CM/MIS (1 organomegaly [#1], n = 49 [5%]; 2 organomegalies [#2], n = 7 [1%]; 3 organomegalies [#3], n = 1 [0.1%]) and ISM (#1, n = 97 [6%]; #2, n = 23 [1%]; #3, n = 9 [0.5%]) but frequent in SSM (#1, n = 28 [41%]; #2, n = 23 [34%]; #3, n = 9 [13%]) and AdvSM (#1, n = 84 [20%]; #2, n = 125 [30%]; #3, n = 97 [23%]).

Association between organomegaly and clinical, laboratory, and molecular parameters

In patients with AdvSM, the heat map indicated a strong association between splenomegaly and hepatomegaly with ascites ($\Phi = 0.334$, $\Phi = 0.383$), portal hypertension ($\Phi = 0.234$, $\Phi = 0.249$), weight loss ($\Phi = 0.341$, $\Phi = 0.303$), alkaline phosphatase ($\eta = 0.281$, $\eta = 0.353$), and the albumin level ($\eta = 0.218$, $\eta = 0.285$). The *KIT* D816V allele burden was associated with splenomegaly in patients with ISM ($\eta = 0.534$) and with splenomegaly and hepatomegaly in patients with SSM ($\eta = 0.442$, $\eta = 0.442$). An association between lymphadenopathy and eosinophilia as previously described[27] was identified only in the SSM subgroup ($\eta = 0.394$) (see Figure E1 and Tables E2 and E3 in this article's Online Repository at www.jaci-inpractice.org). Overall, the presence and numbers of C-Findings and other related laboratory abnormalities or clinical symptoms (continuous and dichotomized) were associated with the numbers of organomegalies ($P < .001$) with the exception of the absolute neutrophil count. Similar observations were made for the serum tryptase level more than 100 μg/L (#0-#3, 12%-79%; *P* [#0 vs #3] < .001) and the median *KIT* D816V allele burden (#0-#3, 1%-23%; *P* [#0 vs #3] < .001).

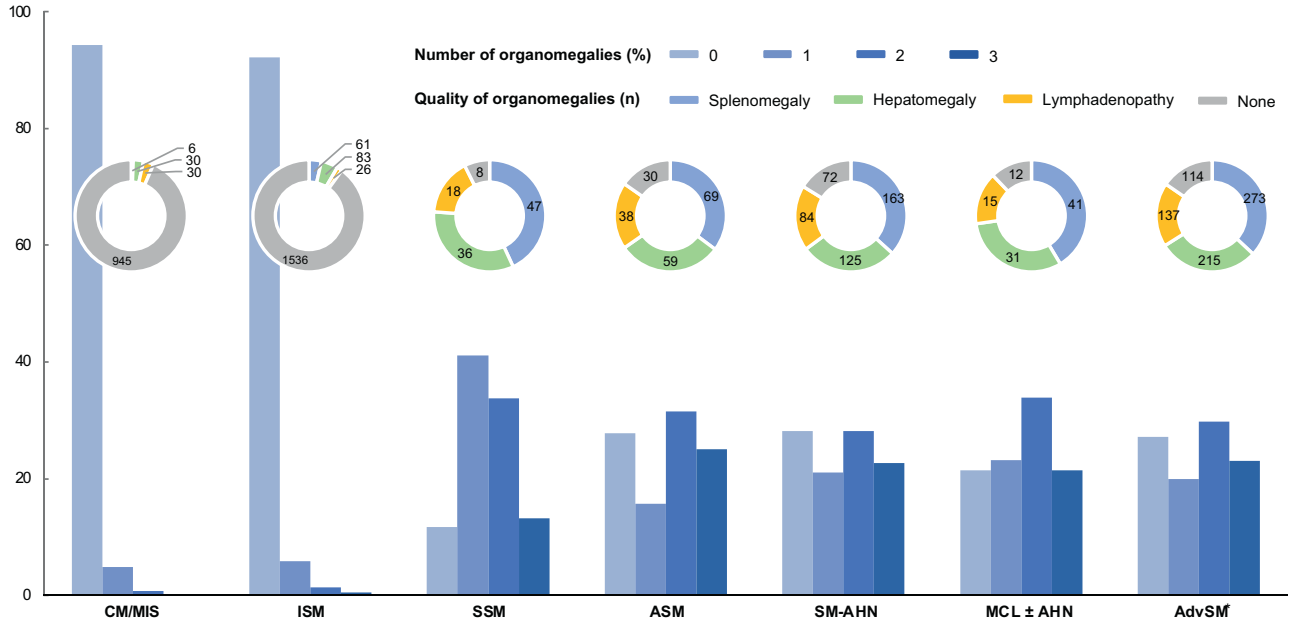


FIGURE 1. Prevalence of organomegaly in mastocytosis. The bar chart reflects the distinct frequencies (%) of the number of organomegalies (#0-#3), and the doughnut charts reflect the frequency (n) of the different organomegalies (splenomegaly, hepatomegaly, lymphadenopathy) depending on the various subtypes (CM, ISM, SSM, ASM, SM-AHN, MCL ± AHN, AdvSM). *AdvSM compromises ASM, SM-AHN, and MCL ± AHN.

Presence and absence of lymphadenopathy in AdvSM

Comparison of patients with AdvSM with (n = 137 [40%]) or without (n = 207 [60%]) lymphadenopathy revealed a strong association of lymphadenopathy with several characteristics of high disease burden (number of C-Findings, serum tryptase level, BM MC infiltration, *KIT* D816V allele burden [$P < .05$; see Table E4 in this article's Online Repository at www.jaci-inpractice.org], and OS [3.8 vs 2.6 years, hazard ratio (HR), 1.6 with 95% CI, 1.2-2.2, $P = .003$]) (Figure 2).

Impact of organomegaly on disease progression

During a median follow-up of 4.0 years (range, 0.0-33.4), progression was observed from ISM to SSM (n = 12) or AdvSM (n = 28) in 40 of 1665 patients (2%), from SSM to AdvSM in 10 of 68 patients (15%), and from AdvSM to a more aggressive AdvSM subtype (eg, secondary MCL or acute myeloid leukemia) in 86 of 420 patients (20%) (Figure 3). At the time of progression, a previously unknown organomegaly was observed in 38% to 43% of patients (≥2 newly enlarged organ sites in 8% of patients with ISM and 13% of patients with AdvSM), with new splenomegaly being the most common event. Most patients with a dynamic (expanding) organomegaly had at diagnosis no signs of an enlarged organ (ISM, n = 15 [88%]; SSM, n = 2 [50%]; AdvSM, n = 23 [70%]).

Number of organomegalies and outcome

Inferior OS and PFS were associated with multiple organomegalies (pooled over strata: $P < .001$ and $P < .001$, respectively; Figure 4, *A* and *B*). The median OS values depending on the number of organomegalies were as follows: #0, 26.9 years, 95% CI (19.1-34.7); #1, 12.4 years, 95% CI (9.4-15.4); #2, 4.7 years, 95% CI (2.8-6.5); #3, 2.8 years, 95% CI (2.1-3.5); median PFS: #0, 26.9 years, 95% CI (20.3-33.5); #1, 12.4 years, 95% CI (7.9-16.8); #2, 3.9 years, 95% CI (2.5-5.3); #3, 2.4 years, 95% CI (1.4-3.4). The HRs for OS were as follows: #0 versus #1 HR, 4.9, 95% CI (3.4-7.1), $P < .001$; #1 versus #2 HR, 2.1, 95% CI (1.4-3.1), $P < .001$; #2 versus #3 HR, 1.7, 95% CI (1.2-2.5), $P = .004$. An adverse impact on OS was observed in ISM in association with splenomegaly ($P = .001$) and/or hepatomegaly ($P < .001$) and in patients with AdvSM in association with lymphadenopathy ($P = .025$). Tables E5 and E6 in this article's Online Repository at www.jaci-inpractice.org list the results of OS analyses in all subcategories of mastocytosis.

Organomegaly with/without dysfunction and outcome

In patients with splenomegaly, the number of cytopenias (hemoglobin <10 g/dL, platelets $<100 \times 10^9$/L, leukocytes $<4 \times 10^9$/L) was adversely associated with OS ($P < .001$; see Figure E2, *A*, in this article's Online Repository at www.jaci-inpractice.org). In patients with hepatomegaly, the OS was adversely impacted by the number of variables indicating liver dysfunction (albumin <34 g/dL or alkaline phosphatase >150 U/L, acites, portal hypertension; $P < .001$; Figure E2, *B*).

Validation of a previously published clinical risk score

On the basis of one of the first clinical risk score for SM (based on clinical parameters only),[16] we stratified 1480 patients according to presence or absence of splenomegaly and elevated serum alkaline phosphatase. On the basis of the weighted score assigning 1 point each to splenomegaly and alkaline phosphatase more than 150 U/L, median OS of low- (0 point, n = 1164), intermediate- (1 point, n = 172), and high-risk (2 points,

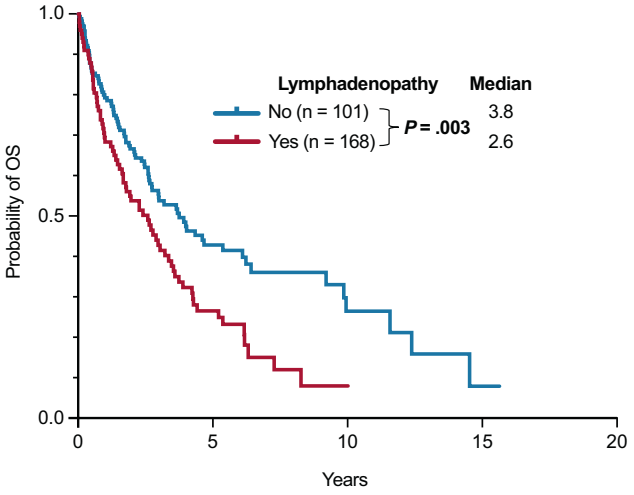


FIGURE 2. Kaplan-Meier estimates of the OS of patients with AdvSM depending on the presence and absence of lymphadenopathy.

n = 144) patients was 26.9, 12.4, and 2.6 years, respectively ($P < .001$) (Figure 5).

Comparison between ISM with or without organomegaly and SSM

OS and PFS were significantly different ($P = .002$ and $P < .001$) when patients with ISM were stratified according to presence/absence of organomegaly (#0, n = 1064; #1, n = 64; #2, n = 15; #3, n = 4). OS and PFS of patients with ISM and at least 1 organomegaly were similar to those of patients with SSM ($P = .435$ and $P = .810$) (Figure 6). However, as expected, patients with SSM suffered significantly more often from further B-Findings: dysmyelopoiesis ($P = .005$), BM MC infiltration ($P < .001$), increased serum tryptase levels ($P < .001$), and splenomegaly ($P = .004$) (Table II).

DISCUSSION

Organomegaly, including splenomegaly, hepatomegaly, and/or lymphadenopathy, as well as signs of SM-induced organ damage (eg, hypoalbuminemia, elevated alkaline phosphatase, portal hypertension, hypersplenism, and ascites) form the basis for dividing SM into subsets through assignment of B-Findings (organomegaly, high burden of clonal cells, and signs of myelodysplasia or myeloproliferation) and C-Findings (relevant organ damage).[1,2,11] Here, we reported on a large series of patients with at least 1 data entry about the presence and prognostic implications of organomegaly collected within the ECNM registry.

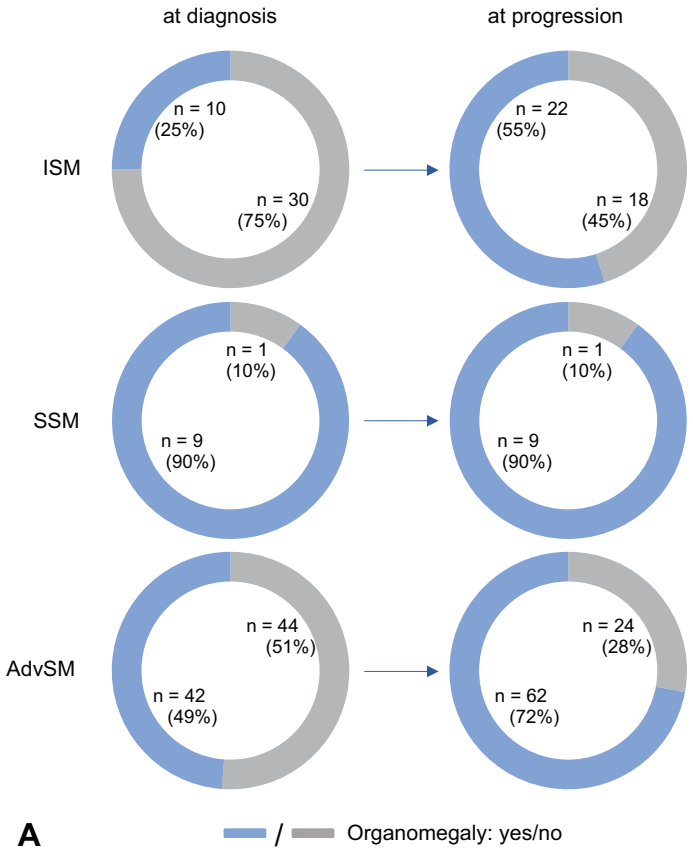
We could identify a minority of patients with CM/MIS presenting with organomegaly. Of these, most patients were diagnosed with MIS. MIS is an initial diagnosis that requires further diagnostic steps (eg, BM biopsy) leading to the final diagnosis of CM or SM. Recently, a palpable spleen was identified as predictor for SM in patients with MIS in univariate analysis.[28] Taken together, this rather heterogeneous group of patients with CM/MIS could therefore include patients of a more advanced disease status.

Organomegaly is common in SSM and AdvSM but is only rarely observed in ISM.[12,16,18-20,29,30] Patients with 3 organomegalies had the most aggressive disease phenotype and the worst OS and PFS. The negative impact of splenomegaly with hypersplenism and hepatomegaly with liver impairment (dysfunction) on OS validated the concept of B- and C-Findings that robustly distinguishes between non-advanced and advanced SM. The new occurrence of organomegaly at the time of progression highlights the importance of repeated adequate physical/radiography examination during follow-up as potential early indicator of progression and allowing early intervention. Because of the retrospective design, the presence of a yet-undetected organomegaly at time of diagnosis cannot be excluded, for example, possibly missed because of an inadequate physical examination or because of the patients' physical conditions. Although the current SM classification criteria state that hepatic or splenic involvement is based on physical examination, imaging techniques such as ultrasound could help in diagnosis, elucidating the underlying cause of organomegaly, quantification at diagnosis, and monitoring under therapy.

Splenomegaly is a major clinical feature in patients with myeloproliferative neoplasms and is included in diagnostic criteria, for example, for myelofibrosis, and prognostic scoring systems, for example, for chronic myeloid leukemia.[31-33] A pooled analysis on OS in ruxolitinib-treated patients with myelofibrosis indicated an association between spleen size reduction (measured by MRI or computed tomography) and improvement of survival.[34,35] In accordance to myelofibrosis, splenomegaly is included as a reliable and valid parameter for response assessment in SM by an expert panel of the ECNM. For an objective assessment, MRI/computed tomography–based volumetry is recommend at least in clinical trials.[36,37] In a recent study of patients with SM, splenomegaly was divided into no splenomegaly (<450 mL), mild splenomegaly (450-1200 mL), and marked splenomegaly (≥1200 mL) measured by MRI. Interestingly, splenomegaly greater than or equal to 450 mL was an independent prognostic variable in univariate and multivariable analyses ($P = .02$).[16] In the current study, we could validate an easily accessible clinical risk score based on the 2 variables splenomegaly and elevated alkaline phosphatase.[16] In several subsequent World Health Organization–independent SM risk scores, the prognostic significance of organomegaly was validated in univariate analyses. However, in multivariable analyses, an independent prognostic significance at diagnosis was not demonstrated by any of these scores.[12,18,20,22]

Spleen size enlargement is often caused by invasion of neoplastic/cancer cells and/or extramedullary hematopoiesis. The precise prevalence of splenic involvement by MCs in SM or SM-AHN is unknown, because splenectomy is rarely performed in these patients. It therefore often remains unknown in patients with SM-AHN whether splenomegaly is derived from the SM, the AHN, or from both disease components. Additional (nonhematologic) causes of splenomegaly include, among others, autoimmune diseases (eg, rheumatoid arthritis or lupus erythematosus) and acute and chronic infections, which should be carefully ruled out and were not mentioned in any patient with splenomegaly enrolled in this study.

Patients with liver involvement can present with ascites and other signs of portal hypertension such as variceal bleeding. In 7 patients, MC infiltrates in liver biopsies proved that liver dysfunction was caused by SM (data of the "German Registry on



	ISM	SSM	AdvSM
Number of patients with disease progression, n (%)	40 (2)	10 (15)	86 (20)
With newly occurred organomegaly, n (%)	17 (43)	4 (40)	33 (38)
New splenomegaly, n (%)	12 (30)	1 (10)	19 (22)
New hepatomegaly, n (%)	6 (15)	2 (20)	19 (22)
New lymphadenopathy, n (%)	2 (5)	3 (30)	8 (9)
≥2 organomegalies, n (%)	3 (8)	1 (10)	11 (13)

B

FIGURE 3. Disease progression in SM with newly occurred organomegaly. (**A**) Number of patients with/without identification of an organomegaly at time of diagnosis and progression. (**B**) Number of patients with newly occured organomegaly at time of progression.

Disorders of Eosinophils and Mast Cells"). Further potential reasons for liver enlargement could be involvement by the AHN and non-hematologic disorders (eg, [non-]alcoholic fatty liver disease, obstruction of the gallbladder or bile ducts, and liver cysts). The latter ones were mentioned in only a minority of patients in our ECNM registry (n = 17, <1%, with fatty liver disease being the most common one). Because we could not exclude co-contribution of liver enlargement through the SM and/or AHN component, these patients were not excluded in the respective analyses. Presence of hepatomegaly in absence of splenomegaly and lymphadenopathy had a negative impact on OS compared with patients without any organomegalies (10 years OS, 23% vs 86%; $P = .001$). However, in a recently published analysis based on the ECNM data set, hepatomegaly itself had no impact on OS in multivariate analysis.[12]

In contrast to splenomegaly or hepatomegaly, lymphadenopathy is uncommon in patients with myeloid neoplasms. This and previous reports have highlighted the association between lymphadenopathy and AdvSM and an adverse outcome.[38] Yet, the exact prevalence and the clinical/prognostic impact of lymphadenopathy in mastocytosis remained unclear. Within the ECNM registry, information on lymphadenopathy was missing

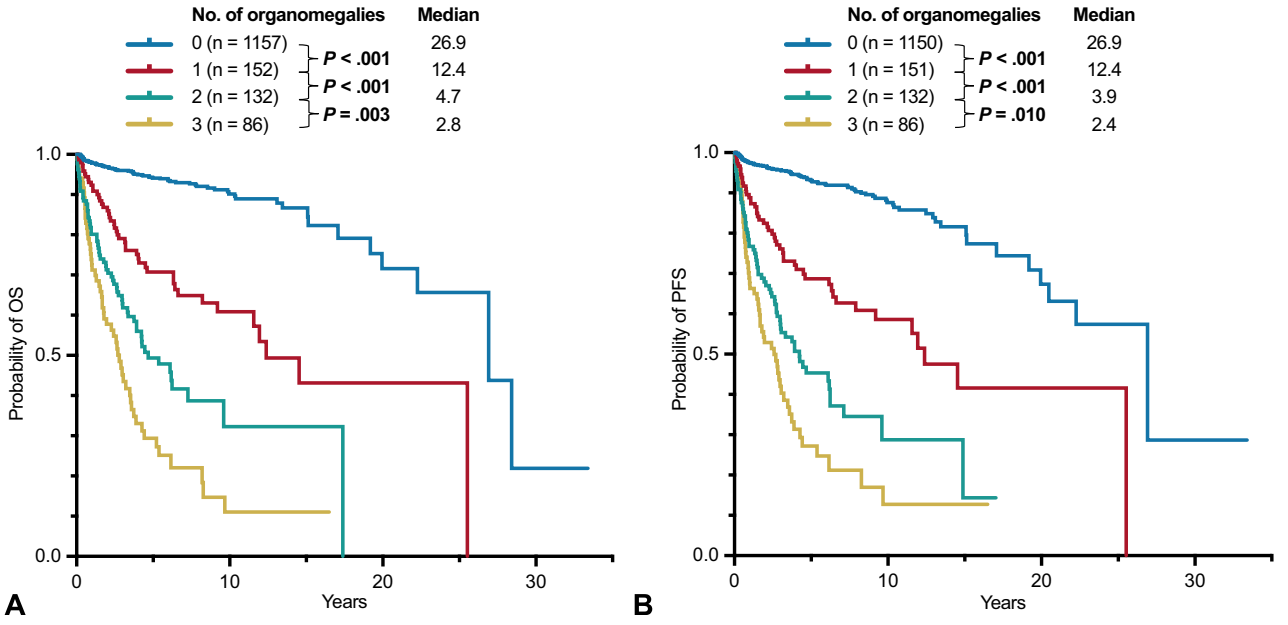


FIGURE 4. Kaplan-Meier estimates of the (**A**) OS and (**B**) event-free survival in SM depending on the number of organomegalies (#0-#3).

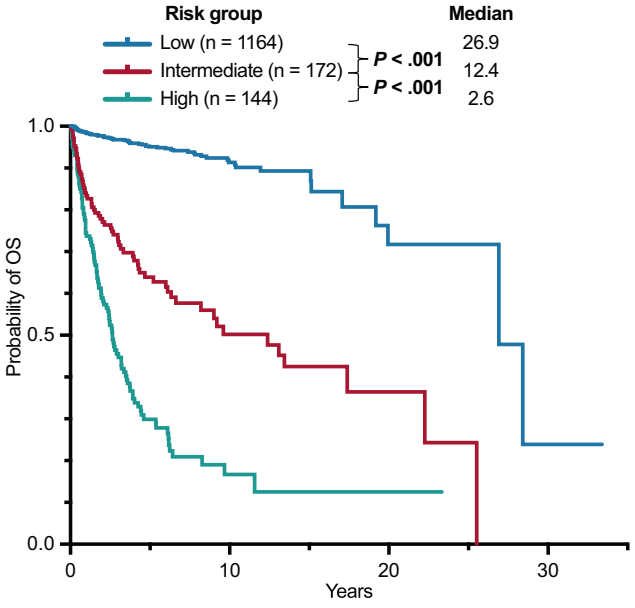


FIGURE 5. Kaplan-Meier estimates of the OS in 1480 patients with SM depending on the presence of splenomegaly (1 point) and elevated alkaline phosphatase (>150 U/L, 1 point); low risk, 0 point (n = 1164); intermediate risk, 1 point (n = 172), and high risk, 2 points (n = 144).

in approximately 15% of patients. This lack of data on lymphadenopathy is best explained by the retrospective nature of this registry-based analysis and by the fact that lymphadenopathy is usually not suspected in CM and ISM. In our series, lymphadenopathy was frequently recorded, particularly in AdvSM, and was frequently found in association with splenomegaly and hepatomegaly. Therefore, we recommend that SM be included as differential diagnosis not only in patients with splenomegaly but also in patients with otherwise unexplained lymphadenopathy. Of note, lymphadenopathy due to lymphatic AHN was found in only less than 1% of patients in this study. In cases with concurrent presence of lymphadenopathy and peripheral blood eosinophilia, certain tyrosine kinase fusion genes such as *PDGFRA* rearrangements should be ruled out. Identification of such rearrangements would prompt diagnosis as "myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions" according to 2022 World Health Organization classification and 2022 International Consensus Classification of Myeloid Neoplasms and Acute Leukemias.[5,6] Other non-malignant causes for lymphadenopathy include immune system disorders such as lupus erythematosus or rheumatoid arthritis. None of them was noted within the patient charts. In-depth analyses on the extension of lymphadenopathy (central vs peripheral) and the response to therapy could not be further evaluated because of the registry-based binary assessment of organomegaly (yes/no).

The strong prognostic impact of organmegaly was also evident in patients with non-advanced SM. In particular, OS and PFS of patients with ISM with organomegaly were found to be similar to those of patients with SSM and significantly better than in patients with ISM without organomegaly. Nevertheless, these data clearly demonstrate that the combination of organomegaly with other factors, for example, multilineage involvement by flow cytometry, increased *KIT* D816V allele burden, cytogenetic analysis, and/or the hybrid clinical-molecular risk model containing high-risk clinical and molecular parameters, help to better stratify this obviously rather heterogeneous group of patients with ISM/SSM.[12,19,20,22]

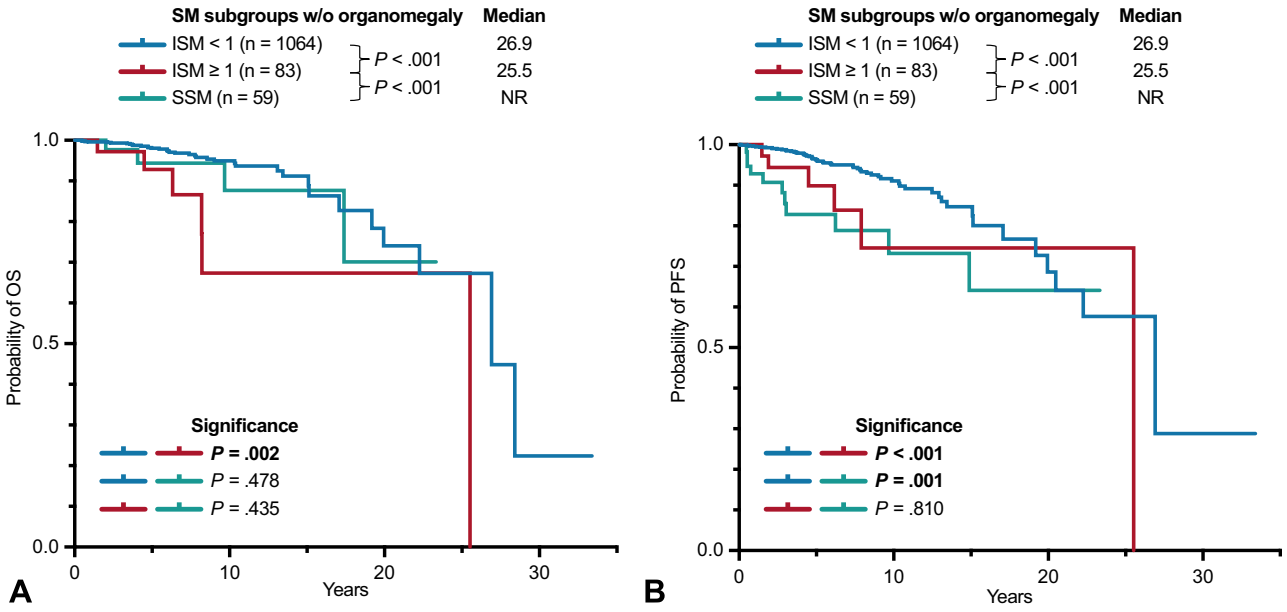


FIGURE 6. Kaplan-Meier estimates of the (**A**) OS and (**B**) event-free survival of ISM with (≥1, red) and without (<1, blue) organomegaly in comparison to SSM (green). *NR*, Not reported.

TABLE II. Summarized clinical, laboratory, histological, and molecular characteristics of 1665 patients with ISM, stratified by the presence of OM and 68 patients with SSM

Characteristics	ISM with <1 OM	ISM with ≥1 OM	SSM	*P**	*P*†	*P*‡
No. of patients	1536	129	68			
Age (y), median (range)	47.4 (5.0-83.3)	48.4 (0.3-81.9)	56.4 (25.2-79.2)	NS	<.001	.013
Sex: male, n (%)	66 (43.0)	70 (54.3)	30 (44.1)	.013	NS	NS
B-Findings, n (%)						
Dysmyelopoiesis	16 (1)	7 (6)	12 (19)	<.001	<.001	.005
MC infiltration in BM biopsy (%), median (range)	5 (0-85)	10 (1-60)	35 (5-90)	.023	<.001	<.001
Serum tryptase level (µg/L), median (range)	29 (1-885)	47 (4-264)	200 (3-2100)	.002	<.001	<.001
>100 µg/L	147 (10)	27 (22.0)	52 (81)	<.001	<.001	<.001
>200 µg/L	30 (2)	4 (3)	34 (50)	NS	<.001	<.001
Splenomegaly	0 (0)	61 (48)	47 (69)	<.001	<.001	.004
Hepatomegaly	0 (0)	83 (64)	36 (53)	<.001	<.001	NS
Lymphadenopathy	0 (0)	26 (22)	18 (30)	<.001	<.001	NS
Outcome						
Follow-up (y), median (range)	4.9 (0.1-33.4)	5.1 (0.1-25.5)	4.1 (0.3-23.3)	NS	NS	NS
Progression	30 (2)	10 (8)	10 (15)	<.001	<.001	NS
Death	36 (2)	9 (7)	4 (6)	.002	NS	NS
Disease related	9 (25)	2 (22)	3 (75)			
Other, n (%)	27 (75)	7 (78)	1 (25)			

NS, Not significant; *OM*, organomegaly.
**P* values refer to Mann-Whitney *U* test or Fisher exact test comparing patients with ISM with no OM with patients who are diagnosed with at least 1 OM.
†*P* values refer to Mann-Whitney *U* test or Fisher exact test comparing patients with ISM with no OM with patients with SSM.
‡*P* values refer to Mann-Whitney *U* test or Fisher exact test comparing patients with ISM who are diagnosed with at least 1 OM with patients with SSM.

CONCLUSIONS

(1) The presence of splenomegaly, hepatomegaly, and lymphadenopathy is common in AdvSM and associated with a poor OS and PFS, (2) a new occurrence of organomegaly may indicate disease progression in all SM variants, (3) ISM with organomegaly has a similar course and prognosis compared with SSM, and (4) in contrast to other myeloid neoplasms, lymphadenopathy is a common feature in SM, particularly in SSM and AdvSM.

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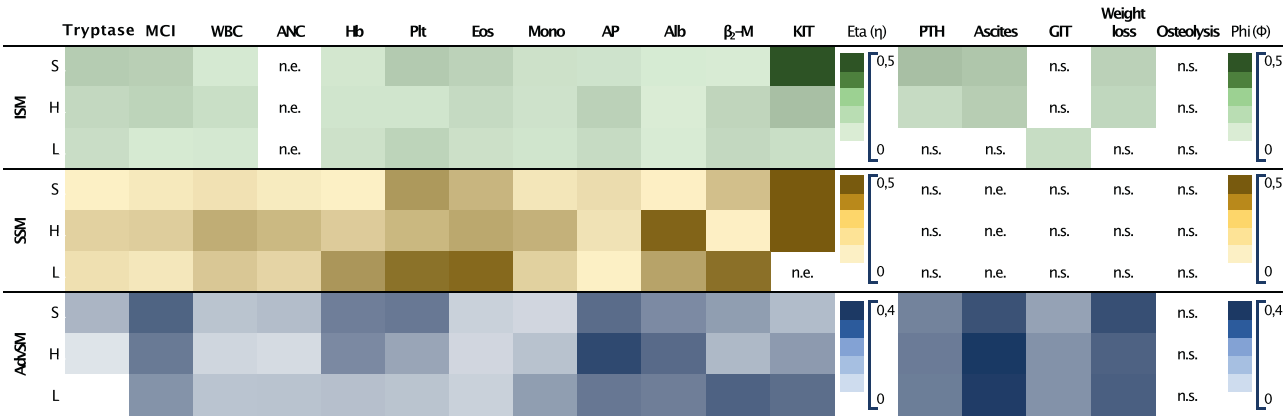

FIGURE E1. The heat map displays the association of splenomegaly, hepatomegaly, and lymphadenopathy with SM-related parameters. The more intensive the color is, the stronger the *eta* (η) and *phi* (Φ) coefficient indicating nominal-by-interval and nominal-by-nominal association, respectively. *Alb*, Albumin; *ANC*, absolute neutrophil cells; *AP*, alkaline phosphatase; *β2-M*, β_2 microglobulin; *Eos*, eosinophils; *Eta*, eta coefficient; *GIT*, gastrointestinal symptoms; *H*, hepatomegaly; *Hb*, hemoglobin; *KIT*, *KIT* D816V expressed allele burden; *L*, lymphadenopathy; *MCI*, mast cell infiltration; *Mono*, monocytes; *n.e.*, not evaluable; *n.s.*, not significant; *Phi*, phi coefficient; *Plt*, platelets; *PHT*, portal hypertension; *S*, splenomegaly; *WBC*, white blood cell (leukocytes); *weight loss*, weight loss ≥10%.

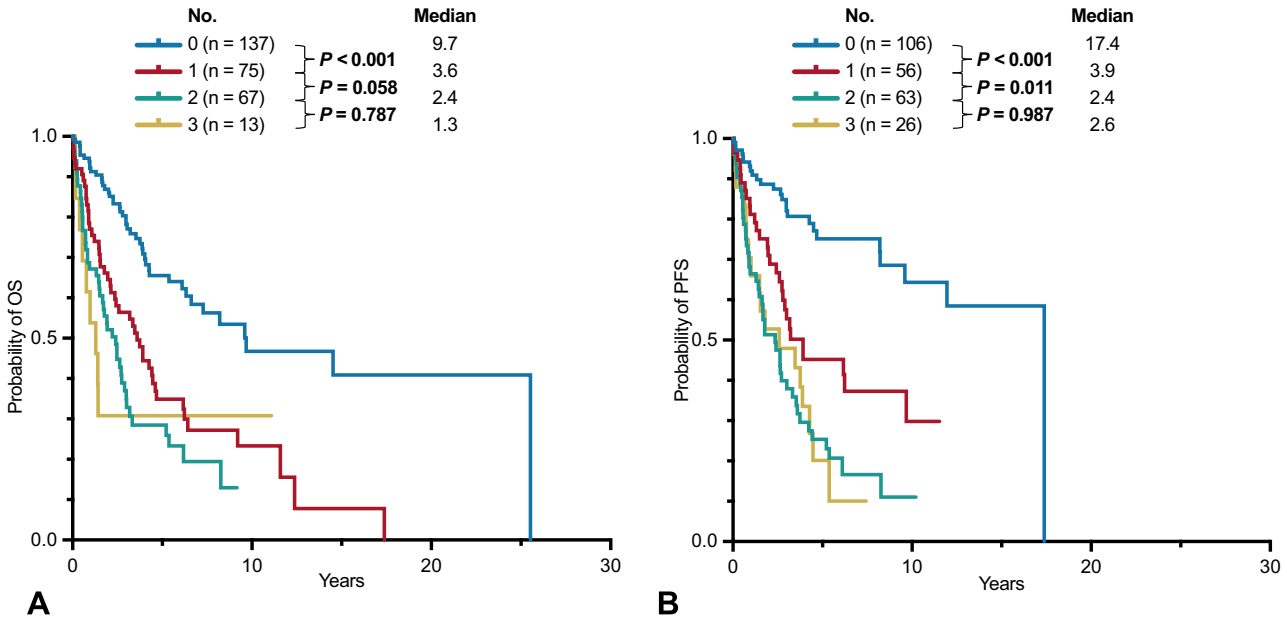

FIGURE E2. Kaplan-Meier estimates of the OS of (**A**) patients with splenomegaly depending on the number of cytopenias indicating hypersplenism and (**B**) patients with hepatomegaly depending on the number of variables indicating liver function impairment.

TABLE E1. Demographic and disease characteristics of 2153 patients with SM at diagnosis according to the number of organomegalies with distinct *P* values

Characteristics	SM #0	SM #1	SM #2	SM #3	*P#0 vs #1*	*P#0 vs #2*	*P#0 vs #3*	*P#1 vs #2*	*P#1 vs #3*	*P#2 vs #3*
No. of patients at diagnosis, n (%)	1658 (77)	209 (10)	171 (8)	115 (5)						
Age (y), median (range)	48 (0-91)	54 (0-87)	62 (1-82)	65 (27-87)	<.001	<.001	<.001	<.001	<.001	.003
Sex: male, n (%)	724 (44)	120 (57)	112 (66)	73 (64)	<.001	<.001	<.001	NS	NS	NS
C-Findings, n (%)										
Hemoglobin (<10 g/dL)	35 (2)	30 (15)	48 (29)	42 (38)	<.001	<.001	<.001	<.001	<.001	NS
Platelets (<100 × 10^9/L)	38 (2)	33 (17)	63 (38)	49 (44)	<.001	<.001	<.001	<.001	<.001	NS
ANC (<1 × 10^9/L)	29 (2)	6 (3)	5 (3)	2 (2)	NS	NS	NS	NS	NS	NS
Alkaline phosphatase (>150 U/L)	58 (4)	40 (24)	87 (60)	69 (69)	<.001	<.001	<.001	<.001	<.001	NS
Albumin level (<34 g/L)	36 (3)	15 (10)	36 (28)	26 (28)	<.001	<.001	<.001	<.001	<.001	NS
Ascites	6 (0)	13 (7)	44 (29)	55 (49)	<.001	<.001	<.001	<.001	<.001	<.001
Portal hypertension	5 (0)	8 (5)	16 (12)	25 (25)	<.001	<.001	<.001	.015	<.001	.009
Weight loss (>10% over last 6 mo)	30 (2)	40 (20)	71 (43)	64 (59)	<.001	<.001	<.001	<.001	<.001	.013
Osteolytic lesions	31 (2)	13 (8)	15 (12)	11 (12)	<.001	<.001	<.001	NS	NS	NS
B-Findings, n (%)										
Serum tryptase level (>200 μg/L)	47 (3)	29 (15)	56 (36)	50 (46)	<.001	<.001	<.001	<.001	<.001	NS
Splenomegaly	0 (0)	108 (53)	158 (92)	115 (100)	<.001	<.001	<.001	<.001	<.001	.003
Hepatomegaly	0 (0)	76 (37)	143 (85)	115 (100)	<.001	<.001	<.001	<.001	<.001	<.001
Lymphadenopathy	0 (0)	25 (15)	41 (31)	115 (100)	<.001	<.001	<.001	<.001	<.001	<.001
Additional finding										
KIT D816V AB,* median (range)	1 (0.0-37)	15 (0.0-47)	17 (0.0-50)	23 (0.0-50)	<.001	<.001	<.001	NS	NS	NS

AB, Allele burden; *ANC*, absolute neutrophil count; *GI*, gastrointestinal; *H*, hepatomegaly; *L*, lymphadenopathy; *NS*, not significant; *PB*, peripheral blood; *S*, splenomegaly.
**KIT* D816V AB available in 64, 22, 21, and 17 patients with 0, 1, 2, or 3 organomegalies, respectively.

TABLE E2. Association (*eta* coefficient) between organomegaly and a subset of laboratory and molecular parameters

	ISM			SSM			AdvSM		
Clinical parameters	S	H	L	S	H	L	S	H	L
Serum tryptase level	0.105	0.063	0.046	0.009	0.089	0.052	0.138	0.061	0.020
MC infiltration in BM biopsy	0.096	0.082	0.012	0.029	0.099	0.034	0.299	0.254	0.203
White blood cells	0.013	0.045	0.015	0.049	0.190	0.117	0.114	0.082	0.113
Absolute neutrophil cells	NE	NE	NE	0.023	0.159	0.078	0.124	0.075	0.115
Hemoglobin	0.018	0.025	0.036	0.009	0.104	0.256	0.242	0.220	0.120
Platelets	0.134	0.025	0.083	0.252	0.162	0.367	0.256	0.168	0.114
Eosinophils	0.085	0.061	0.040	0.167	0.205	0.394	0.090	0.080	0.090
Monocytes	0.037	0.034	0.026	0.037	0.177	0.092	0.080	0.117	0.182
Alkaline phosphatase	0.029	0.090	0.057	0.061	0.047	0.009	0.281	0.353	0.258
Albumin	0.010	0.000	0.004	0.012	0.407	0.220	0.218	0.285	0.243
β_2 microglobulin	0.006	0.078	0.063	0.137	0.012	0.371	0.182	0.133	0.302
KIT D816V EAB	0.534	0.148	0.045	0.442	0.442	NE	0.127	0.189	0.277

H, Hepatomegaly; *KIT D816V EAB*, *KIT* D816V expressed allele burden; *L*, lymphadenopathy; *NE*, not evaluable; *S*, splenomegaly.

TABLE E3. Association (*phi* coefficient) between organomegaly and a subset of clinical parameters

	ISM			SSM			AdvSM		
Clinical parameters	**S**	**H**	**L**	**S**	**H**	**L**	**S**	**H**	**L**
Portal hypertension	0.147	0.057	NS	NS	NS	NS	0.234	0.249	0.245
Ascites	0.123	0.103	NS	NE	NE	NE	0.334	0.383	0.378
GI symptoms	NS	NS	0.050	NS	NS	NS	0.175	0.205	0.204
Weight loss (>10% over last 6 mo)	0.088	0.069	NS	NS	NS	NS	0.341	0.303	0.307
Osteolysis	NS	NS	NS	NS	NS	NS	−0.096	−0.010	−0.092
Serum tryptase level >100 μg/L	0.123	0.084	0.059	NS	NS	NS	0.359	0.272	0.209
Hemoglobin <10 g/dL	NS	NS	NS	NS	NS	0.363	0.129	0.112	NS
Platelets $<100 \times 10^9$/L	0.158	0.081	NS	NS	NS	NS	NS	NS	NS
ANC $<1 \times 10^9$/L	NS	NS	NS	NE	NE	NE	−0.119	NS	−0.136
AP >150 U/L	NS	NS	NS	NS	NS	NS	0.352	0.352	0.355
Albumin <34 g/dL	NS	0.091	0.100	NE	NE	NE	0.199	0.258	0.186

ANC, Absolute neutrophil count; *AP*, alkaline phosphatase; *GI*, gastrointestinal; *H*, hepatomegaly; *L*, lymphadenopathy; *NE*, not evaluable; *NS*, not significant; *S*, splenomegaly.

TABLE E4. Demographic and disease characteristics of 344 patients with AdvSM at diagnosis according to the presence/absence of lymphadenopathy

Characteristics	**L+**	**L−**	***P***
No. of patients at diagnosis, n (%)	137 (40)	207 (60)	
Age (y), median (range)	66 (26-87)	63 (16-91)	.006
Sex: male, n (%)	91 (66)	125 (60)	NS
C-Findings, n (%)			
Hemoglobin (g/dL), median (range)	10 (6-16)	11 (4-17)	.023
<10 g/dL	53 (41)	73 (36)	NS
Platelets ($\times 10^9$/L), median (range)	99 (9-958)	159 (9-901)	.034
$<100 \times 10^9$/L	67 (51)	75 (37)	.009
ANC ($\times 10^9$/L), median (range)	5 (0-85)	4 (0-72)	NS
$<1 \times 10^9$/L	2 (2)	15 (8)	.016
Alkaline phosphatase (U/L), median (range)	233 (39-1407)	121 (20-1696)	<.001
>150 U/L	89 (75)	72 (40)	<.001
Albumin level (g/L), median (range)	38 (16-51)	40 (21-57)	<.001
<34 g/L	33 (29)	21 (14)	.002
Ascites	68 (51)	31 (16)	<.001
Portal hypertension	28 (24)	13 (7)	<.001
Weight loss (>10% over last 6 mo)	85 (66)	69 (35)	<.001
GI symptoms	76 (59)	75 (38)	<.001
Osteolytic lesions	13 (11)	31 (18)	NS
B-Findings, n (%)			
Dysmyelopoiesis	94 (71)	107 (58)	.013
MC infiltration in BM biopsy (%), median (range)	40 (1-100)	20 (0-90)	.002
Serum tryptase level (μg/L), median (range)	200 (9-1690)	117 (2-4980)	NS
Serum tryptase level (>100 μg/L)	96 (74)	98 (54)	<.001
Serum tryptase level (>200 μg/L)	65 (50)	62 (34)	.004
Splenomegaly	118 (87)	103 (50)	<.001
Hepatomegaly	104 (78)	69 (34)	<.001
Other relevant findings			
Leukocytes ($\times 10^9$/L), median (range)	10.0 (1-89)	7.2 (1-95)	.019
Monocytes ($\times 10^9$/L), median (range)	0.9 (0-19)	0.4 (0-10)	.004
Eosinophils ($\times 10^9$/L), median (range)	0.3 (0-17)	0.1 (0-35)	NS
KIT D816V AB (%), median (range)	22 (0-50)	12 (0-47)	.047
Outcome			
Follow-up (y), median (range)	1.8 (0.0-10.0)	2.0 (0.0-15.6)	NS
Death	73 (54)	83 (40)	.015

AB, Allele burden; *ANC*, absolute neutrophil count; *GI*, gastrointestinal; *L*, lymphadenopathy; *NS*, not significant.

TABLE E5. Kaplan-Meier estimates of OS depending on the different occurrence of organomegaly

Occurrence of organomegaly	CM		ISM		SSM		ASM		SM-AHN		MCL ± AHN		AdvSM	
	n	*P**	n	*P**	n	*P**	n	*P**	n	*P**	n	*P**	n	*P**
0 vs ≥1	464 vs 31	.464	1064 vs 83	**.002**	7 vs 52	.292	22 vs 55	.868	56 vs 142	.127	8 vs 38	**.033**	86 vs 235	.545
≤1 vs ≥2	493 vs 4	.784	1128 vs. 19	**<.001**	32 vs 27	.587	35 vs 42	.813	96 vs 102	**.003**	18 vs 28	.107	149 vs 172	.078
≤2 vs 3	496 vs 1	.866	1143 vs 4	**<.001**	50 vs 9	.42	63 vs 14	.336	150 vs 48	**.003**	35 vs 11	.650	248 vs 73	**.009**
0 vs 1 vs 2 vs 3†	466 vs 27 vs 3 vs 1	.911	1064 vs 64 vs 15 vs 4	**<.001**	7 vs 25 vs 18 vs 9	.420	22 vs 13 vs 28 vs 14	.336	56 vs 40 vs 54 vs 48	**.008**	8 vs 10 vs 17 vs 11	.167	86 vs 63 vs 99 vs 73	.057
≤1 vs 2 vs 3†	493 vs 3 vs 1	.963	1128 vs 15 vs 4	**<.001**	32 vs 18 vs 9	.710	35 vs 28 vs 14	.619	96 vs 54 vs 48	**.003**	18 vs 17 vs 11	.264	149 vs 99 vs 73	**.027**
0 vs 1-2 vs 3†	466 vs 30 vs 1	.765	1064 vs 79 vs 4	**<.001**	7 vs 43 vs 9	.459	22 vs 41 vs 14	.577	56 vs 94 vs 48	**.009**	8 vs 27 vs 11	.104	86 vs 162 vs 73	**.031**
0 vs 1 vs ≥2†	466 vs 27 vs 4	.765	1064 vs 64 vs 19	**<.001**	7 vs 25 vs 27	.564	22 vs 13 vs 42	.915	56 vs 40 vs 102	.011	8 vs 10 vs 28	.083	86 vs 63 vs 172	.182
S‡ (N/Y)	495 vs 2	.811	1106 vs 41	**.001**	19 vs 40	.131	29 vs 48	.904	70 vs 128	.160	11 vs 35	.287	110 vs 211	.440
H‡ (N/Y)	483 vs 13	.607	1095 vs 52	**<.001**	28 vs 31	.866	36 vs 41	.628	99 vs 99	**.001**	18 vs 28	**.005**	153 vs 168	.101
L‡ (N/Y)	476 vs 21	.581	1134 vs 13	.208	42 vs 17	.760	55 vs 22	.594	133 vs 65	**.018**	32 vs 14	.890	220 vs 101	**.025**
S§ (N/Y)	497 vs 0	NE	1124 vs 23	.545	44 vs 15	.360	67 vs 10	.675	170 vs 28	.054	39 vs 7	.339	276 vs 45	.180
H§ (N/Y)	488 vs 9	.666	1112 vs 35	.164	51 vs 8	.456	75 vs 2	.501	193 vs 5	.208	43 vs 3	.427	311 vs 10	.543
L§ (N/Y)	479 vs 18	.613	1141 vs 6	.644	57 vs 2	.809	76 vs 1	.460	191 vs 7	.290	46 vs 0	NE	313 vs 8	.201
S and H (N/Y)	495 vs 2	.811	1131 vs 16	**<.001**	38 vs 21	.423	42 vs 35	.751	106 vs 92	**.005**	21 vs 25	**.035**	169 vs 152	.161
S and L (N/Y)	496 vs 1	.866	1141 vs 6	**.001**	46 vs 13	.564	60 vs 17	.423	142 vs 56	**.004**	32 vs 14	.890	234 vs 87	**.005**
H and L (N/Y)	494 vs 18	.829	1142 vs 5	**.001**	48 vs 11	.564	59 vs 18	.367	148 vs 50	**.002**	35 vs 11	.650	242 vs 79	**.009**

H, Hepatomegaly; *L*, lymphadenopathy; *NE*, not evaluable; *(N/Y)*, no/yes; *S*, splenomegaly.

In the first 7 rows, patients are divided by the number of organomegalies including splenomegaly, hepatomegaly, and lymphadenopathy. Significant *P* values are presented in bold face.

**P* values refer to the log-rank test.

†*P* values were compared pooled over strata. *P* values compared pairwise over strata are reported in Table E6.

‡Irrespective of other organomegalies occurring.

§Only the described organomegaly is occurring.

TABLE E6. Selected Kaplan-Meier estimates of OS depending on the number of organomegalies

		CM	ISM	SSM	ASM	SM-AHN	MCL ± AHN	AdvSM
No. of organomegalies	**n**	***P****	***P****	***P****	***P****	***P****	***P****	***P****
0 vs 1 vs 2 vs 3	0 vs 1	.499	.145	.407	.783	.787	.127	.564
	0 vs 2	.825	**<.001**	.157	.679	.144	.078	.779
	0 vs 3	.862	**<.001**	.414	.958	**.007**	**.044**	.058
	1 vs 2	NE	**.044**	.777	.982	.092	.476	.452
	1 vs 3	NE	**.007**	.806	.377	**.005**	.745	**.012**
	2 vs 3	NE	.454	.414	.350	.114	.812	**.048**
≤1 vs 2 vs 3	≤1 vs 2	.829	**<.001**	.963	.904	.073	.144	.524
	≤1 vs 3	.865	**<.001**	.631	.455	**.001**	.266	**.009**
0 vs 1-2 vs 3	0 vs 1-2	.477	**<.001**	.314	.775	.503	.062	.911
	1-2 vs 3	NE	**.032**	.519	.310	**.009**	.996	**.011**
0 vs 1 vs ≥2	0 vs ≥2	.779	**<.001**	.145	.838	**.019**	**.034**	.274
	1 vs ≥2	NE	**.012**	.862	.700	**.013**	.465	.095

NE, Not evaluable.

Values represent *P* values. Significant *P* values are presented in bold face.

**P* values refer to the log-rank test. *P* values are compared pairwise over strata.