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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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

Introduction

The ECNM is a multi-center cooperative network and initiative of an international group of scientists and clinicians working in the field of mastocytosis.[1,2] Members of the ECNM are dedicated to work together and to merge their clinical and research efforts with the ultimate goal to advance the field, to improve diagnostics, management and prognostication, and to optimize treatment approaches in patients with mastocytosis and related mast cell disorders. Specific aims of the network consortium are to provide all relevant information to doctors and to patients, to establish and update standards for diagnosis and therapy, and to support referrals to specialized centers and experts in various European countries and in the US. The ECNM is a non-profit collaborative effort and network that was established in 2002. The ECNM consists of so-called Reference Centers and Centers of Excellence.[1,2]

In 2012, members of the ECNM initiated a registry project with the aim to collect data from patients with mastocytosis in a comprehensive way, the ECNM registry. The primary goal of the ECNM registry is to collect and merge data from a very large number of patients with mast cell disorders in order to define the frequency, etiology and clinical course of this disease.[3] Additional aims of the ECNM registry studies are to develop new diagnostic and prognostic parameters and biomarkers and to investigate the natural clinical course, the prognosis (progression and survival), and treatment responses in patients with recognized variants and subtypes of mastocytosis.[3] Moreover, information about patient-related (mastocytosis-independent) variables and the impact of these parameters concerning disease course and survival are examined in ECNM projects. Finally, mediator-induced symptoms, the management of mediator-related events and treatment responses are captured in the ECNM registry.

Structure of the Registry and Collection of Data

The ECNM registry represents a web-based collection of data obtained in patients with various forms of mastocytosis.[3] Most of the enrolled patients are seen and managed in the Centers of Excellence of the ECNM. The patients' data are collected retrospectively and prospectively in the participating centers. In each center the data entry is organized by the local principle investigator (PI) and by her/his local team.[3] All data are included in a central, web-based, data-file, the ECNM registry source data file. The quality of the data is checked by regular quality controls, a yearly data-clearing-process and by technical adjustments and updates as needed. Patients are enrolled by using pseudonyms in the registry data-set. As a result, only the members of each participating site who have entered the patients´ data are able to identify the patient through a specific code. The sponsor of the registry is the Medical University of Vienna. The sponsor supports the ECNM registry projects by providing the IT-infrastructure of the network, the core data set and the central coordination and management of the registry. The registry data are stored on the server of the Austrian Control Bank (OeKB Business Services; https://ecnm-registry.oekb-bs.at). The entry mask and entry system are provided by Verdino, an agency specialized on communication and on creating digital solutions (www.verdino.com). Each participating center - the local PI and his/her team - can view its own patients´ data-set entered into the registry and can download the data of their own patients but cannot access or download data of patients enrolled in other participating centers. A general download of data from all patients can only be performed by the coordinator of the ECNM registry. Such downloads are necessary for the annual data-clearing and for the distribution of the entire data-sets for individual (officially defined and approved) projects in each project wave (once a year). The complete data set consists of the initial data obtained at diagnosis and all follow up data.

Participating Centers and Development of ECNM Registry Projects

The registry consortium consists of the coordinators of the registry and the local PIs of each participating center. The Medical University of Vienna runs and coordinates the ECNM registry. The ECNM registry is a contract-based multi-center approach.[3] The consortium contract defines the regulations and rules in the individual ECNM registry projects, regulates the selection and distribution (to individual centers) of these projects, the rights and responsibilities of each participating center, and the publication strategies. Every center, independent of its size, the country and the center-status, can make proposals for registry projects and can present such proposal at an annual ECNM meeting. The minimal criterion required for participation in the ECNM registry projects is inclusion of patients (at least 25 eligible mastocytosis patients in projects enrolling a larger number of patients) in the ECNM registry. Members of the ECNM board coordinate and prepare the distribution of individual ECNM projects. This board consists of the previous and the present/current chair of the ECNM, the coordinator of the ECNM, 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 a major discussion, decisions will be reached by voting. Every single center can decide for each individual ECNM registry project whether or not it will participate. Only thereafter will the core data-sets be distributed to individual centers.

Inclusion and Exclusion Criteria in the ECNM registry

Only patients who had proven mastocytosis based on criteria provided by the World Health Organization (WHO) were included in the ECNM registry.[4-6] The diagnostic criteria of systemic mastocytosis (SM) are shown in this appendix (p 24) and are briefly summarized below in the next paragraph. The diagnosis of cutaneous mastocytosis (CM) was also based on the WHO classification and related consensus criteria.[4,7-9] In adult patients, the diagnosis CM requires a bone marrow (BM) biopsy-proven exclusion of SM. By contrast, in children, CM can usually be diagnosed without a BM examination following established guidelines.[4,7,8] In these patients, a BM biopsy is mandatory to rule out or demonstrate SM and to establish or exclude the diagnosis CM (CM and SM are mutually exclusive diagnoses).[4-8] When no BM studies were available in adults presenting with typical skin lesions, the provisional diagnosis in these patients is mastocytosis in the skin (MIS).[7,8] WHO criteria are as follows:

The diagnosis SM can be established when at least one major and one minor SM criteria or at least three minor SM criteria are demonstrable (appendix p 24).[4-6] When neither B-findings nor C-findings are detectable, the final diagnosis is indolent SM. One B-finding alone will also lead to the diagnosis of indolent systemic mastocytosis. The presence of 2 or 3 B-findings (and absence of C-findings) leads to the diagnosis smoldering systemic mastocytosis and the demonstration of at least one C-finding results in the final diagnosis of aggressive systemic mastocytosis provided that no mast cell leukemia has been diagnosed. B-findings and C-findings are depicted in the appendix p 24. The presence of ≥20% MC in BM smears or peripheral blood smears defines mast cell leukemia.[4-6] It is important to know that organ damage only counts as a C-Finding when the damage is directly induced by a histologically demonstrable malignant MC infiltrate.[4-6] In patients with MC sarcoma (MCS), SM criteria are not met, but the local (uni-focal) MC tumor shows destructive growth and a high-grade MC morphology. In systemic mastocytosis with an associated hematologic neoplasm, the criteria of SM as well as WHO criteria for an AHN are fulfilled by definition.[4-9] Patients not fulfilling the WHO criteria of mastocytosis were excluded from the registry.

Ethics Committee Approval

All patients gave their written informed consent to participate in the ECNM registry project. The registry study was approved by the local ethics committee of the participating centers.

Patients and Centers participating in the current ECNM registry project

The patient cohort used in this study was derived from 25 centers, including 24 European centers and one center in the United States of America (US). As mentioned before, data clearing was performed prior to the final download of the data set. Detailed information on the number of patients provided by each center is shown in the appendix p 25. For calculating patients´ survival, follow up data were analyzed. Only a subset of patients (those in whom follow up data were available) could be included in these analyses. The numbers of patients included in each center for this study and the distribution of patients among WHO categories are shown in the appendix p 25.

Clinical and Laboratory Evaluations at Diagnosis and Follow up Examinations

Clinical and laboratory variables 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 levels (Hb), serum lactate dehydrogenase (LDH), alkaline phosphatase (AP), performance status (according to WHO), presence or absence of urticaria pigmentosa (UP)-like skin lesions, presence or absence of osteopenia and osteoporosis (by osteodensitometry), organomegaly (splenomegaly, hepatomegaly and/or lymphadenopathy, palpable and/or by ultrasound or CT scan), known allergies, and mediator-related symptoms. An overview of these parameters is shown in Supplementary appendix pp 26-29. 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, using the following rank order (from low to high risk according to estimated survival): CM< indolent systemic mastocytosis < smoldering systemic mastocytosis < systemic mastocytosis with an associated hematologic neoplasm < aggressive systemic mastocytosis + aggressive systemic mastocytosis with an associated hematologic neoplasm < mast cell leukemia +MCS.

Data Quality Control and Data Clearing

Data quality was controlled by the coordinators and their team to ensure correct documentation and entry of data and to maintain optimal quality in the data set. The data clearing process was performed once a year. In a first step, the data set files were checked for accuracy, completeness of basic information, consistency, plausibility as well as homogeneity in the ECNM registry dataset. In case of outliers and/or implausibility, queries were generated and sent out to individual centers. After the queries had been solved, the data were checked again before the files were sent out to all participating centers conducting registry studies.

Collection of Patients, Statistical analyses and establishment of the score

Collection of Patients

As mentioned above, the registry represents a web-based collection of data obtained in patients with mastocytosis. The patients' data were collected retrospectively and prospectively in the participating centers. All enrolled data were included in a central web-based data-file, the ECNM registry source data file. As mentioned before, quality of the data was checked by regular quality controls and a yearly data-clearing-process. Patients enrolled in the registry had been diagnosed between Jan 12, 1978 and Mar 16, 2017. However, only one patient in our study cohort was diagnosed before 1980. Overall, 4 (0·45%) of all 1794 patients included were diagnosed before 1990, and only 88 (4·9%) of all 1794 patients were diagnosed before the year 2000. In other words 95·1% of the data is based on patients diagnosed between the year 2000 and 2017. A potential disadvantage of such a long time-period may be that diagnostic assays and tools changed over time. However, the

major diagnostic parameters (including WHO criteria), assays, technologies and standard evaluations did not change in the field of mastocytosis when comparing the years 2000 and 2017.

The data were collected in 4 files i.e. “basic and initial data”, “follow up”, “mediator therapy”, and “cytoreductive therapy”. Each file contained a number of predefined fields for clinical (including weight, size, and symptoms), laboratory data (including peripheral blood counts, laboratory chemistry, and molecular biology) and specific information (including type of therapy, start of therapy) as well as several comment fields where additional information could be included at the discretion of the PI and his team. In the wave 2 data set there were 98 predefined fields and 15 comment fields in the template “basic and initial data”, 84 predefined fields and 11 comment fields in the template “follow up”, 25 predefined fields and 7 comment fields in the template “mediator therapy”, and 58 predefined fields and 23 comment fields in the template for cytoreductive therapy for each patient. Not all predefined fields had to be completed. Likewise, if a patient did not suffer from systemic mastocytosis with an associated hematologic neoplasm but only from SM, the fields for the definition of the AHN-component had not to be completed. In the section “basic and initial data” 2631 patients were entered. For these patients 188076 fields were predefined. Overall 154424 (82%) of these 188076 predefined fields were completed. Follow up visits were documented in 1601 patients (range 1 to 24 follow up visits per patient). Together with the information on death and last visits captured in the section “basic and initial data” survival was calculated in 1794 patients. For the patients in the follow up file 280054 fields were predefined. Overall 207505 (74%) of 280054 predefined fields of were completed. These two files i.e. the “basic and initial data” file and the “follow up” file were used in this study. In the section “mediator therapy” and “cytoreductive therapy” 1894 and 666 patients were entered, respectively. With regard to mediator therapy, information on the use of H1-histamine receptor antagonists (completed in 87%), H2-histamine receptor antagonists (completed in 77%), oral cromolyn sodium (completed in 62%), glucocorticosteroids (completed in 63%), bisphosphonates (completed in 62%), and other supportive therapy (completed in 63%) were collected together with information on start of, end of, and response to therapy. Overall 15391 (51·1%) of 30087 predefined files were completed. In the wave 2 data set information on cytoreductive therapy was entered in 137 patients. Data on the use of interferon-alpha, 2-chlorodeoxyadenosine (2CdA), hydroxyurea, tyrosine kinase inhibitors, polychemotherapy, stem cell transplantation, and other cytoreductive therapy were captured. Overall 6827 (64·1%) of the 10650 predefined fields were completed.

Validation Cohort

For validation of the score, 462 patients from the Spanish Red Española de Mastocitosis (REMA) network that were not included in the ECNM registry were analyzed. These patients were diagnosed with mastocytosis between Jan 22, 1998 and Nov 2, 2017. Of these 462 patients, 18 had CM (3.9%), 384 indolent systemic mastocytosis (83.1%), 11 smoldering systemic mastocytosis (2.4%), 19 aggressive systemic mastocytosis (2.4%), 5 mast cell leukemia (1.1%), and 25 systemic mastocytosis with an associated hematologic neoplasm (5.4%). Detailed information and the characteristics of these patients are provided in table 1 and the appendix p 32.

Survival Analyses

Overall survival was defined as time from diagnosis to death of any cause. Patients still at risk or lost for follow-up were censored at the last date they were known to be alive. The event-free survival was calculated as the time from diagnosis to occurrence of an event. Events were defined as death or progression of disease. Patients still at risk or lost for follow-up were censored. Progression-free survival was defined as time from diagnosis to progression of disease (progression of systemic mastocytosis or in case of systemic mastocytosis with an associated hematologic neoplasm also progression of the AHN from an indolent AHN to aggressive AHN, such as AML). Patients still at risk, lost for follow-up or who died without progression were censored in progression-free survival calculations. Since mast cell leukemia represents the most aggressive MC disorder and no further progression to a more advanced disease can occur (with the exception of the very

rare mast cell leukemia -AML), patients with mast cell leukemia were excluded progression-free survival analyses. MIS is a provisional diagnosis for patients with skin involvement but unknown/unavailable BM data. Thus, it is impossible to prove whether a diagnostic BM infiltration (sufficient to diagnose SM) was present at initial diagnosis. Therefore, these patients were also excluded from analysis of progression-free survival. Univariate Cox regression was applied for all potentially prognostic variables. All variables that showed prognostic significance in univariate analyses were included in multivariate analyses. The proportional hazard assumption was checked by testing interaction whether the hazards of the prognostic factors do change during follow up (depend on the survival time reached). Survival was analyzed by the method of Kaplan and Meier and by the Cox proportional hazard model.[10]

Evaluation of Potential Predictive Variables

A number of categorical and (semi)continuous variables were considered as potential predictors of survival. Only information entered at clinical diagnosis of the mastocytosis was included in the analysis. The patients were categorized according to the diagnosis established based on the WHO classification. Again only information available at diagnosis was used. In case of progression the patients remained in their initial group. Likewise, 17 patients progressed from indolent systemic mastocytosis to systemic mastocytosis with an associated hematologic neoplasm. These patients were included as indolent systemic mastocytosis patients during follow up and were not counted as systemic mastocytosis with an associated hematologic neoplasm patients.

Categorical variables included performance status, gender, skin lesions, organomegaly (hepatomegaly and/or splenomegaly and /or enlarged lymph nodes), allergies, and mediator-related symptoms at diagnosis. The (semi)continuous variables included age at diagnosis, tryptase, WBC, eosinophils, hemoglobin, platelets, AP, LDH, calcium, and albumin at diagnosis. The (semi)continuous variables were categorized by the following procedure: for each of these variables a univariate Cox regression for overall survival was performed. For the calculation of the defining cut off, martingale residuals were computed as described [10]. A lowess function was fit to these residuals with the chosen predictor as independent variable. The cut off was determined at the point where the lowess functions cuts through the zero martingale line. This procedure was started with the variable of highest significance and continued step by step choosing the predictor with the next lower p-value**.** In each case the martingale residuals were computed including all prior established predictors. All variables that showed prognostic significance in univariate analyses were included in multivariate analyses. This analysis was performed separately for non-advanced and advanced disease. The proportional hazard assumption was checked by testing interaction whether the hazards of the prognostic factors do change during follow up (depend on the survival time reached). None of the predictors showed significant interaction and, consequently, the assumption was maintained. The significances of differences in progression rates between patients with AP <100 units/liter and ≥100 units/liter from indolent systemic mastocytosis / smoldering systemic mastocytosis to AdvSM was calculated with the likelihood test. In the table 2 along with 95% CI the Hazard ratios were reported.

Generation of Prognostic Scores

For the generation of the prognostic scores, only variables that were recorded in at least 70% of the patients were included. Hence the multivariate analysis was restricted to these variables. Since their coefficients were almost equal, one point was allocated to each of the predictors in the non-advanced and advanced disease groups. Based on the results we established a score with three risk groups for patients with non-advanced disease: none of the predictive variables (age, AP) positive (low), one point (int-1) or two points (int-2). For advanced disease, multivariate Cox regression revealed 6 significant predictors (age, tryptase, leukocytes, platelets, hemoglobin, and skin involvement). The risk factors age, tryptase, leukocytes, platelets, hemoglobin scored 1 point each, the presence of skin involvement -1 point. Based on clustering of survival functions scores were grouped into -1 to 0, 1, 2 to 3, and 4 to 5 points.

Supplementary Results

Basic Characteristics of Patients Included in the Registry

A total of 1794 patients with mastocytosis were included in the dataset. The median observation period in the 1794 patients was 3·4 years (75-25% percentile: 1·4-6·6 years) with a maximum of 36·7 years. The probability to be alive after 5, 10, and 20 years was 87·5% (CI 85·5-89·3), 81·9% (CI 78·7-86·6), and 67·1% (CI 55·9-76·1), respectively (appendix p 9). The progression-free survival and event-free survival are shown in appendix p 9. Regarding the overall survival in patients with CM, no events were recorded. By contrast, in all other cohorts, events were observed, namely in 10 (5·1%) of 194 patients with MIS, 35 (3·4%) of 1006 with indolent systemic mastocytosis, and 5 (9·4%) of 53 with smoldering systemic mastocytosis, resulting in an overall survival after 10 years of 92·8% (CI 85·4-96·0%), 93·5% (CI 90·1-95·8%) and 84·5% (CI 61·1-94·4%), respectively.

Substantial differences regarding clinical and laboratory parameters were observed among WHO categories. In the group of advanced SM, patients were older, had higher tryptase and AP levels, higher WBC, lower hemoglobin concentrations, and lower platelet counts. Moreover, documented allergies were more frequently recorded in indolent systemic mastocytosis patients compared to patients with MIS, smoldering systemic mastocytosis, or advanced SM.

Causes of Death

Overall 194 (10·8%) of 1794 patients died during the observation period, including 49 (3·2%) of 1533 with non-AdvM and 145 (55·6%) of 261 (55·6%) with AdvSM. Marked differences in the cause of death were found when comparing patients with non-AdvM and AdvSM. In most patients with non-AdvM, the causes of death were not related to mastocytosis. These patients died primarily from “other cancers” and cardiovascular events. In contrast, in most patients with AdvSM, namely 109 (75·2%) of 145 patients, the cause of death was related to the underlying mast cell disorder (appendix p 33). Whereas the cause of death was not defined in 76 of these 109 patients, 30 had a progression to systemic mastocytosis with an associated hematologic neoplasm, and 3 died from mastocytosis-related organ failure. All patients with transplant-related death had AdvSMor had progressed to AdvSM prior to stem cell transplantation.

Event-Free Survival

The median event-free survival of all patients was 25·5 (CI=17·6-33·5) years (appendix p 9). Overall, 239 events were recorded. As expected, CM patients had the best outcome with only 6 (2.2%) events in 280 patients, 1 (0·7%) of 153 childhood cutaneous mastocytosis and 5 (3·9%) of 127 adulthood cutaneous mastocytosis patients. More events were documented in cases with MIS (10/194; 5·0%), indolent systemic mastocytosis (62/1006; 6·2%), smoldering systemic mastocytosis (7/53; 13·2%) and AdvSM (154/261; 59·0%). In patients with aggressive systemic mastocytosis, mast cell leukemia, MCS, and systemic mastocytosis with an associated hematologic neoplasm, the median event-free survival was 5·0 (CI 2·6-7·4), 1·9 (CI 0-5·1), 1·1 (only one patient), and 2·7 (CI2·2-3·2) years, respectively ($p<0·0001$; appendix p 11).

Dissection of Clinical Features and Risk-Factors in WHO Subgroups

In AdvSM (aggressive systemic mastocytosis, mast cell leukemia, systemic mastocytosis with an associated hematologic neoplasm), median serum tryptase levels, median AP levels and median age were higher compared to patients with non-advanced mastocytosis (appendix pp 30-31). By contrast, hemoglobin levels, platelet counts, and albumin were higher in patients with non-advanced disease. In the total cohort of SM, female predominance was found (f:m ratio 1:0·8). By

contrast, in advanced mastocytosis, male predominance was detected (appendix p 30). Patients with AdvSM also presented more often with organomegaly compared to non-AdvM (appendix p 30).

The IPSM Mastocytosis Scores are Highly Predictive Concerning event-free survival

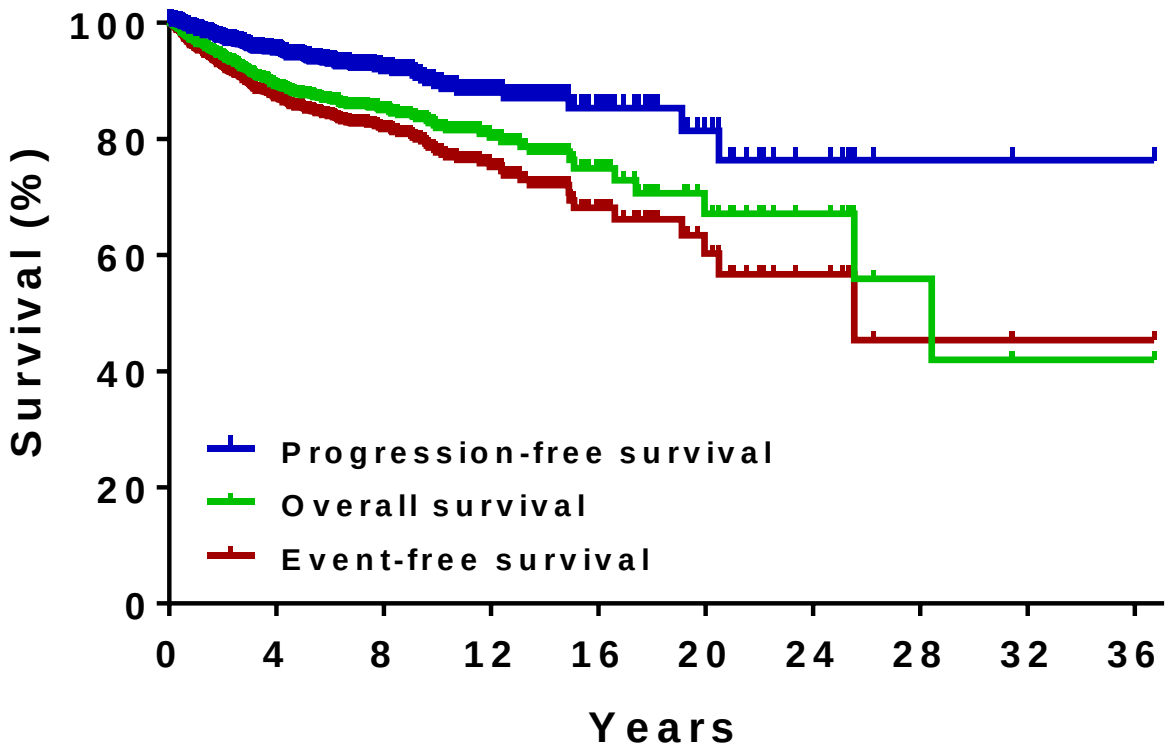
Both scores were also found to be of predictive significance for event-free survival ($p<0{\cdot}0001$; appendix pp 15, 17). The median event-free survival was not reached in the Low and Int-1 group, and was 9·1 (CI=2·7-14·3) years and 2·9 (CI=2·4-3·5) years in the int-2 and AdvSM group, respectively ($p<0{\cdot}0001$; appendix 17). Again, the survival of AdvSM-1 patients was similar to int-1 patients and the survival of AdvSM-2 patients was similar to int-2 patients. The worst outcome was seen in the AdvSM-4 group followed by the AdvSM-3 risk group ($p<0{\cdot}0001$; appendix 17). When applying the scores in distinct categories of mastocytosis i.e. CM, indolent systemic mastocytosis, smoldering systemic mastocytosis, aggressive systemic mastocytosis, mast cell leukemia and systemic mastocytosis with an associated hematologic neoplasm, significant differences were again found (appendix pp 16, 20).

Correlation of the Scores with the WHO Groups

The distribution of the WHO subgroups within different score-based risk groups are shown in the appendix p 38.

Supplementary Figures

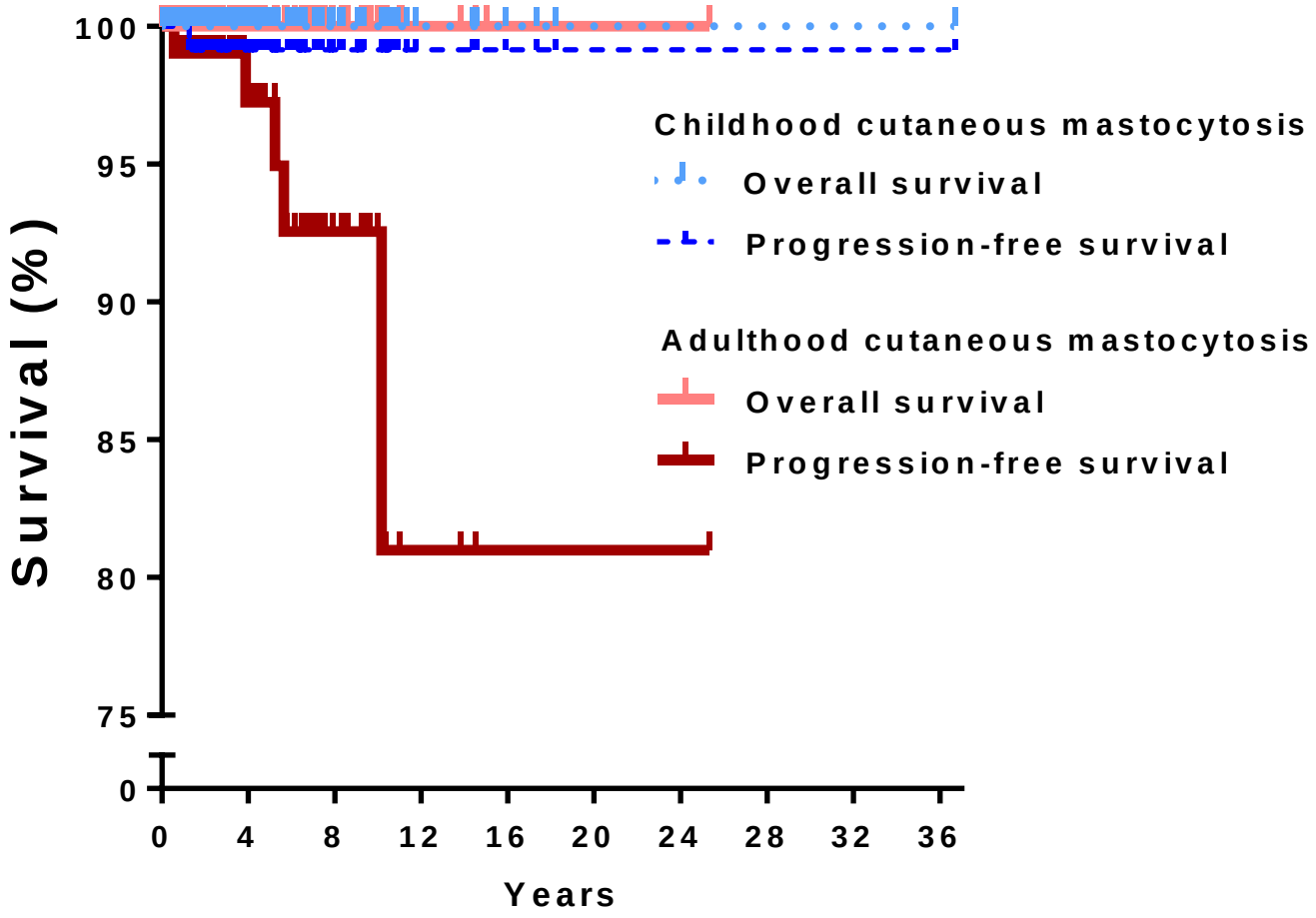
Figure S1
Survival of patients with mastocytosis



Number at risk (number censored)										
Progression-free survival	1577 (0)	687 (831)	288 (1213)	101 (1392)	38 (1453)	18 (1472)	8 (1481)	2 (1487)	1 (1488)	1 (1488)
Overall survival	1794 (0)	789 (860)	326 (1296)	121 (1489)	42 (1563)	19 (1583)	10 (1592)	4 (1597)	1 (1599)	1 (1599)
Event-free survival	1794 (0)	772 (847)	318 (1267)	115 (1453)	41 (1520)	19 (1539)	9 (1548)	3 (1553)	1 (1555)	1 (1555)

Overall survival (green line), event-free survival (red line) and progression-free survival (blue line) of patients with mastocytosis calculated according to the method of Kaplan and Meier. Since mast cell leukemia represents the most aggressive mast cell disorder that cannot progress into a more aggressive mastocytosis and mastocytosis in the skin is a provisional diagnosis for patients with proven skin involvement but unknown/unavailable bone marrow results (no definitive diagnosis available), these patients were excluded from analysis of progression-free survival. After an observation period of 12 years, more than 100 patients are still under observation.

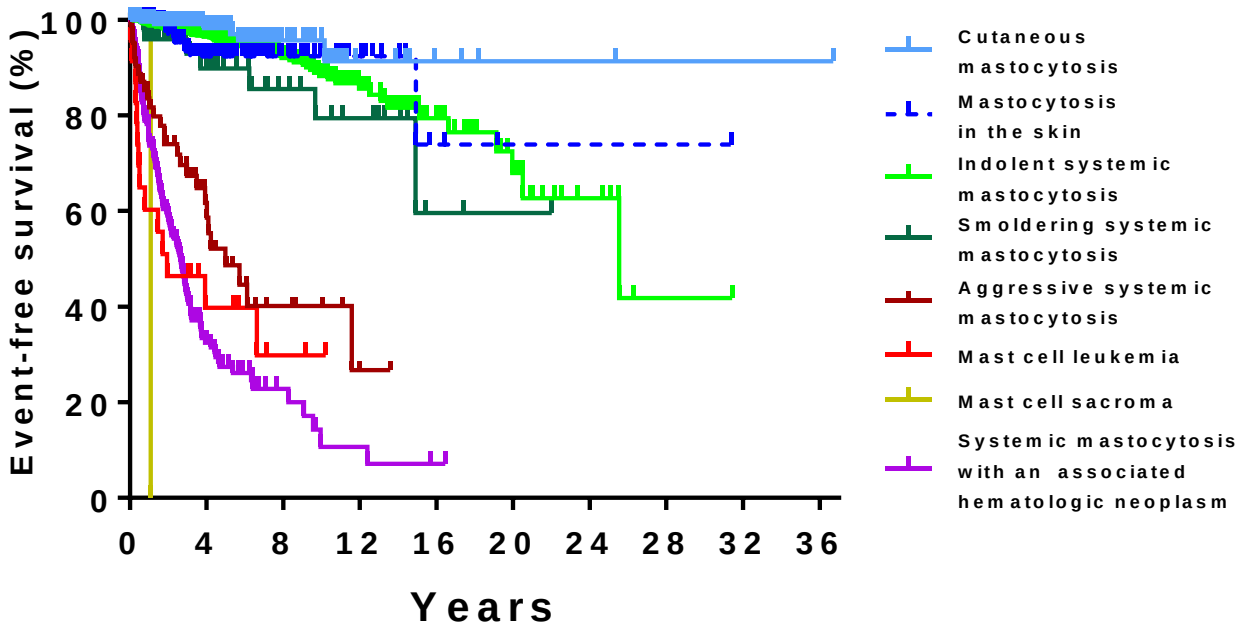
Figure S2
Overall survival and progression-free survival in cutaneous mastocytosis



Number at risk (number censored)										
Childhood cutaneous mastocytosis										
Overall survival	153 (0)	51 (102)	18 (135)	7 (146)	3 (150)	1 (152)	1(152)	1(152)	1(152)	1(152)
Progression-free survival	153 (0)	50 (102)	18 (134)	7 (145)	3 (149)	1 (151)	1 (151)	1 (151)	1 (151)	1 (151)
Adulthood cutaneous mastocytosis										
Overall survival	127 (0)	55 (72)	20 (107)	4 (123)	1 (126)	1 (126)	1 (126)	0 (127)	0 (127)	0 (127)
Progression-free survival	127 (0)	53 (72)	19 (104)	3 (119)	1 (121)	1 (121)	1 (121)	0 (122)	0 (122)	0 (122)

The probability of overall survival and progression-free survival was calculated in 280 patients with cutaneous mastocytosis by the method of Kaplan and Meier. As visible, there was no difference in overall survival between patients with childhood cutaneous mastocytosis (i.e. cutaneous mastocytosis aged <17 years; n=153; light blue dotted line) and adulthood cutaneous mastocytosis (i.e. cutaneous mastocytosis patients aged ≥17 years; n=127; light red solid line). However, there were more progressions (n=5) in patients aged ≥18 years than in the group aged <18 years (n=1). The difference of progression-free survival between childhood cutaneous mastocytosis and adulthood cutaneous mastocytosis showed a tendency towards significance when applying the log rank test (p=0.07).

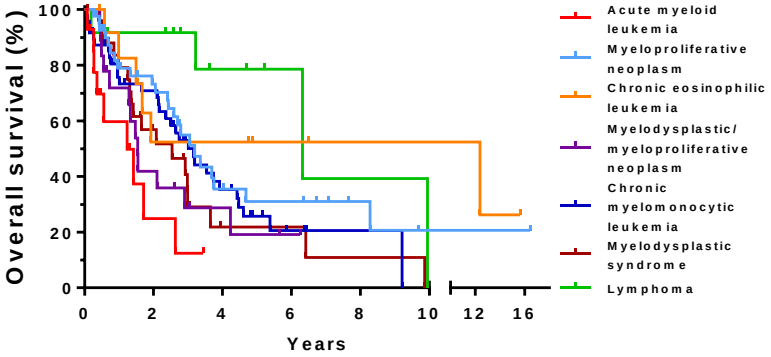
Figure S3
Event-free survival in different WHO subgroups of mastocytosis



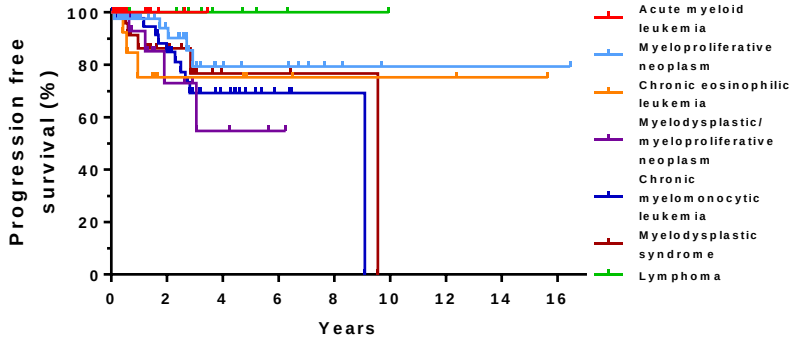
Number at risk (number censored)										
Cutaneous mastocytosis	280 (0)	103 (174)	37 (283)	10 (264)	4 (270)	2 (272)	22 (272)	1 (273)	1 (273)	1 (273)
Mastocytosis in the skin	194 (0)	78 (107)	27 (158)	14 (171)	3 (181)	1 (183)	1 (183)	1(183)	0 (184)	0 (184)
Indolent systemic mastocytosis	1006 (0)	501 (478)	219 (744)	77 (876)	31 (918)	15 (931)	6 (939)	1 (943)	0 (944)	0 (944)
Smoldering systemic mastocytosis	53 (0)	29 (20)	16 (32)	10 (37)	2 (44)	1 (45)	0 (46)	0 (46)	0 (46)	0 (46)
Aggressive systemic mastocytosis	62 (0)	20 (22)	7 (29)	1 (34)	0 (35)	0 (35)	0 (35)	0 (35)	0 (35)	0 (35)
Mast cell leukemia	23 (0)	6 (4)	2 (7)	0 (9)	0 (9)	0 (9)	0 (9)	0 (9)	0 (9)	0 (9)
Mast cell sarcoma	2 (0)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)	0 (1)
Systemic mastocytosis with an associated hematologic neoplasm	174 (0)	34 (41)	8 (79)	3 (60)	1 (61)	0 (62)	0 (62)	0 (62)	0 (62)	0 (62)

The probability of event-free survival of the different subgroups of mastocytosis defined by WHO criteria was calculated according the method of Kaplan and Meier. The differences in event-free survival were statistically significant as assessed by log rank test ($p<0.0001$). The estimated survival of non-advanced mastocytosis i.e. cutaneous mastocytosis, mastocytosis in the skin, indolent systemic mastocytosis and smoldering systemic mastocytosis was longer compared to that of patients with advanced systemic mastocytosis, i.e.: aggressive systemic mastocytosis , mast cell leukemia, mast cell sarcoma and systemic mastocytosis with an associated hematologic neoplasm. These two groups of patients thus formed two prognostically distinct clusters. For event-free survival of the different with an associated hematologic neoplasm please see Supplementary Figure S5C.

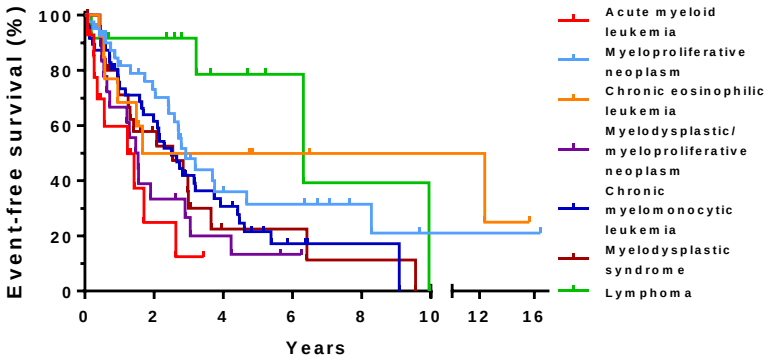
Figure S4
Overall survival, event-free survival and progression-free survival of patients with systemic mastocytosis with an associated hematologic neoplasm according to the subtype of the associated hematologic neoplasm



Number at risk (number censored)								
Acute myeloid leukemia	14 (0)	2 (4)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)
Myeloproliferative neoplasm	41 (0)	25 (6)	9 (11)	7 (12)	3 (16)	1 (17)	1 (17)	1 (17)
Chronic eosinophilic leukemia	13 (0)	5 (3)	5 (3)	3 (5)	2 (6)	2 (6)	1 (6)	0 (7)
Myelodysplastic/myeloproliferative neoplasm	18 (0)	7 (1)	3 (3)	1 (4)	0 (5)	0 (5)	0 (5)	0 (5)
Chronic myelomonocytic leukemia	48 (0)	29 (6)	12 (10)	3 (15)	1 (17)	0 (17)	0 (17)	0 (17)
Myelodysplastic syndrome	26 (0)	11 (5)	2 (8)	2 (8)	1 (8)	0 (8)	0 (8)	0 (8)
Lymphoma	12 (0)	10 (1)	4 (6)	2 (8)	1 (8)	0 (8)	0 (8)	0 (8)



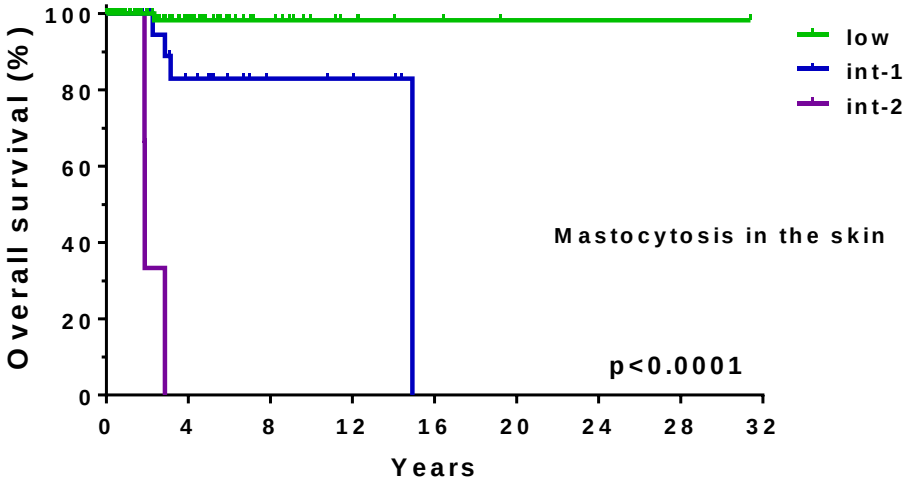
Number at risk (number censored)									
Acute myeloid leukemia	14 (0)	2 (12)	0 (14)	0 (14)	0 (14)	0 (14)	0 (14)	0 (14)	0 (14)
Myeloproliferative neoplasm	41 (0)	25 (14)	9 (27)	7 (29)	3 (33)	1 (35)	1 (35)	1 (35)	1 (35)
Chronic eosinophilic leukemia	13 (0)	5 (5)	5 (5)	3 (7)	2 (8)	2 (8)	2 (8)	1 (9)	0 (10)
Myelodysplastic/myeloproliferative neoplasm	18 (0)	6 (9)	3 (11)	1 (13)	0 (14)	0 (14)	0 (14)	0 (14)	0 (14)
Chronic myelomonocytic leukemia	48 (0)	26 (17)	11 (28)	3 (36)	1 (38)	0 (38)	0 (38)	0 (38)	0 (38)
Myelodysplastic syndrome	26 (0)	11 (12)	2 (20)	2 (20)	1 (21)	0 (21)	0 (21)	0 (21)	0 (21)
Lymphoma	12 (0)	10 (12)	4 (8)	2 (10)	1 (11)	0 (12)	0 (12)	0 (12)	0 (12)



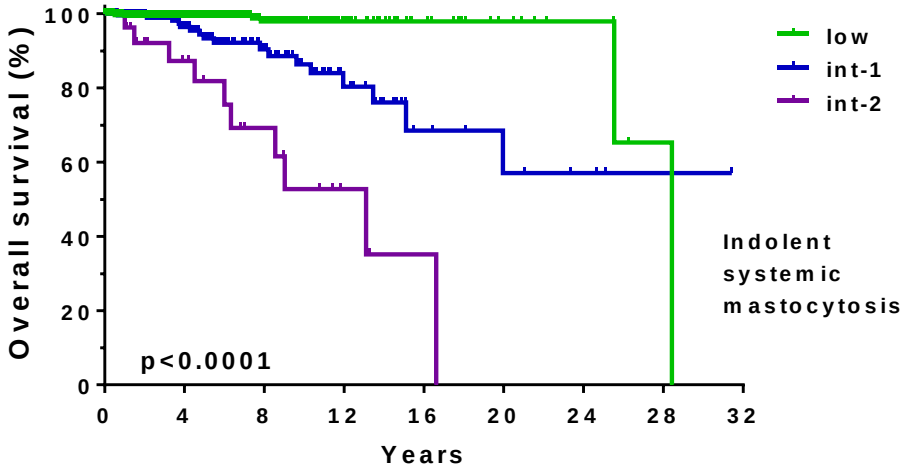
Number at risk (number censored)								
Acute myeloid leukemia	14 (0)	2 (4)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)
Myeloproliferative neoplasm	41 (0)	25 (6)	9 (11)	7 (12)	3 (16)	1 (17)	1 (17)	1 (17)
Chronic eosinophilic leukemia	13 (0)	5 (2)	5 (2)	3 (4)	2 (5)	2 (5)	2 (5)	0 (6)
Myelodysplastic/myeloproliferative neoplasm	18 (0)	6 (0)	3 (1)	1 (2)	0 (3)	0 (3)	0 (3)	0 (3)
Chronic myelomonocytic leukemia	48 (0)	26 (5)	11 (8)	3 (12)	1 (14)	0 (14)	0 (14)	0 (14)
Myelodysplastic syndrome	26 (0)	11 (5)	2 (8)	2 (8)	1 (8)	0 (8)	0 (8)	0 (8)
Lymphoma	12 (0)	10 (1)	4 (6)	2 (8)	1 (8)	0 (8)	0 (8)	0 (8)

The probability of overall survival, progression-free survival and event-free survival was calculated by the method of Kaplan and Meier. Overall, the outcome in systemic mastocytosis with an associated hematologic neoplasm is poor. Patients with SM-AML had the worst outcome. In contrast, patients with lymphoma-type AHN did slightly better.

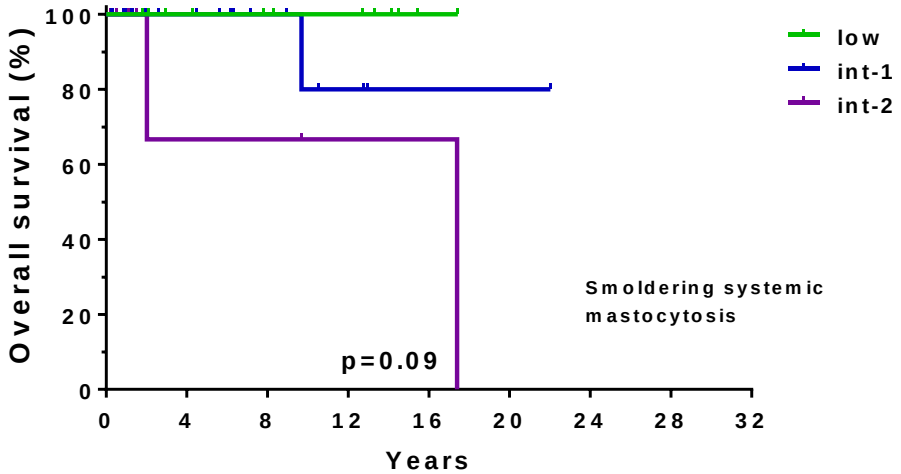
Figure S5
Overall survival of patients with mastocytosis in the skin, indolent systemic mastocytosis and smoldering systemic mastocytosis according to the predictive scoring system (IPSM) for all patients with mastocytosis



Number at risk (number censored)									
low	89 (0)	42 (46)	14 (74)	6 (82)	3 (85)	1 (87)	1 (87)	1(87)	0 (88)
int-1	28 (0)	13 (12)	5 (20)	4 (21)	0 (24)	0 (24)	0 (24)	0 (24)	0 (24)
Int-2	5 (0)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)



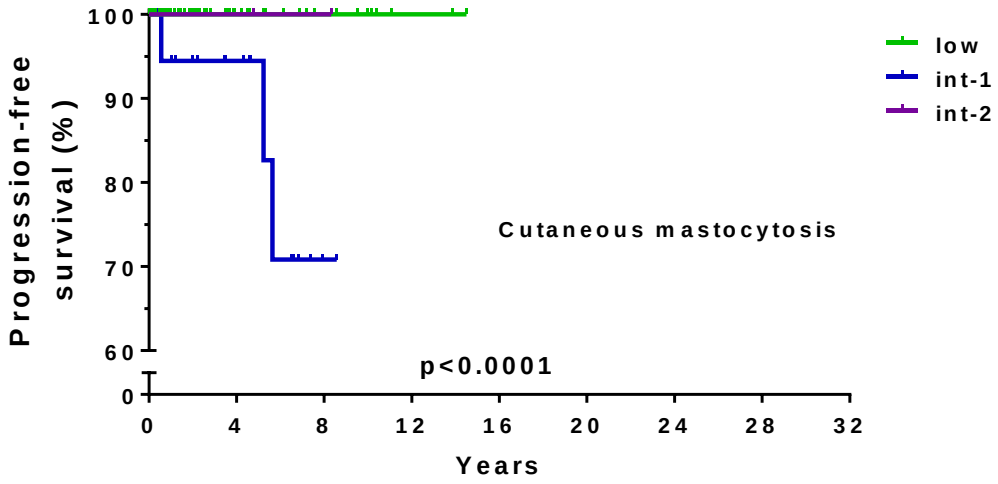
Number at risk (number censored)									
low	553 (0)	283 (267)	120 (428)	41 (507)	16 (532)	8 (540)	4 (544)	1 (546)	0 (546)
int-1	227 (0)	107 (115)	50 (167)	22 (191)	8 (203)	5 (205)	3 (207)	1 (209)	0 (210)
Int-2	33 (0)	17 (13)	9 (18)	3 (22)	1 (23)	0 (23)	0 (23)	0 (23)	0 (23)



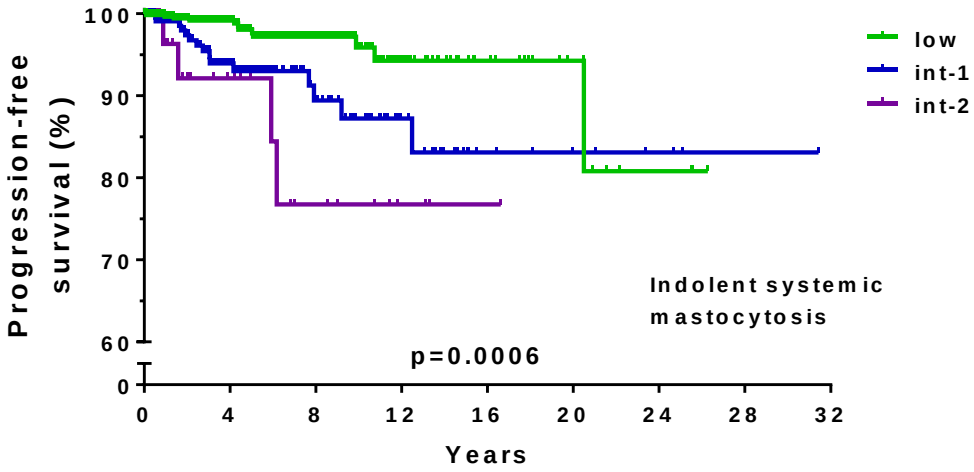
Number at risk (number censored)									
low	12 (0)	9 (3)	7 (5)	6 (6)	1 (11)	0 (12)	0 (12)	0 (12)	0 (12)
int-1	21 (0)	12 (9)	6 (15)	3 (17)	1 (19)	1 (19)	0 (20)	0 (20)	0 (20)
Int-2	8 (0)	2 (5)	2 (5)	2 (5)	1 (6)	0 (6)	0 (6)	0 (6)	0 (6)

Overall survival of patients with mastocytosis in the skin, indolent systemic mastocytosis and smoldering systemic mastocytosis was calculated separately by the method of Kaplan and Meier. Moreover, each subgroup was further divided in low, intermediate (int)-1, and int-2. In patients with mastocytosis in the skin and indolent systemic mastocytosis the differenced in overall survival among the low, int-1, and int-2 risk groups was found to be significant as assessed by log rank test ($p<0.0001$). In patients with smoldering systemic mastocytosis only a tendency towards significance was observed ($p=0.09$), most probably due to the low number of patients and events (n=3) in this group.

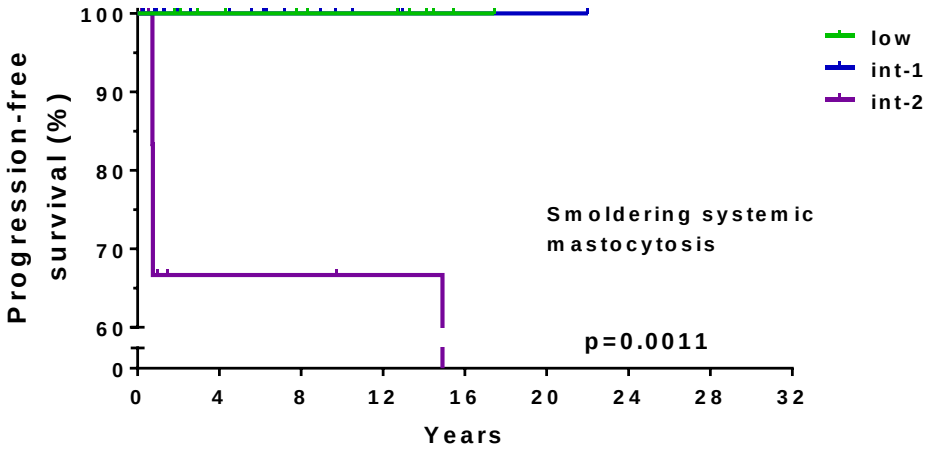
Figure S6
Progression-free survival of patients with cutaneous mastocytosis, indolent systemic mastocytosis and smoldering systemic, according to the predictive scoring system for all patients with mastocytosis



Number at risk (number censored)									
Low	57 (0)	17 (40)	8 (49)	2 (55)	0 (57)	0 (57)	0 (57)	0 (57)	0 (57)
int-1	23 (0)	11 (14)	1 (19)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)
Int-2	2 (0)	0 (2)	1 (1)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)



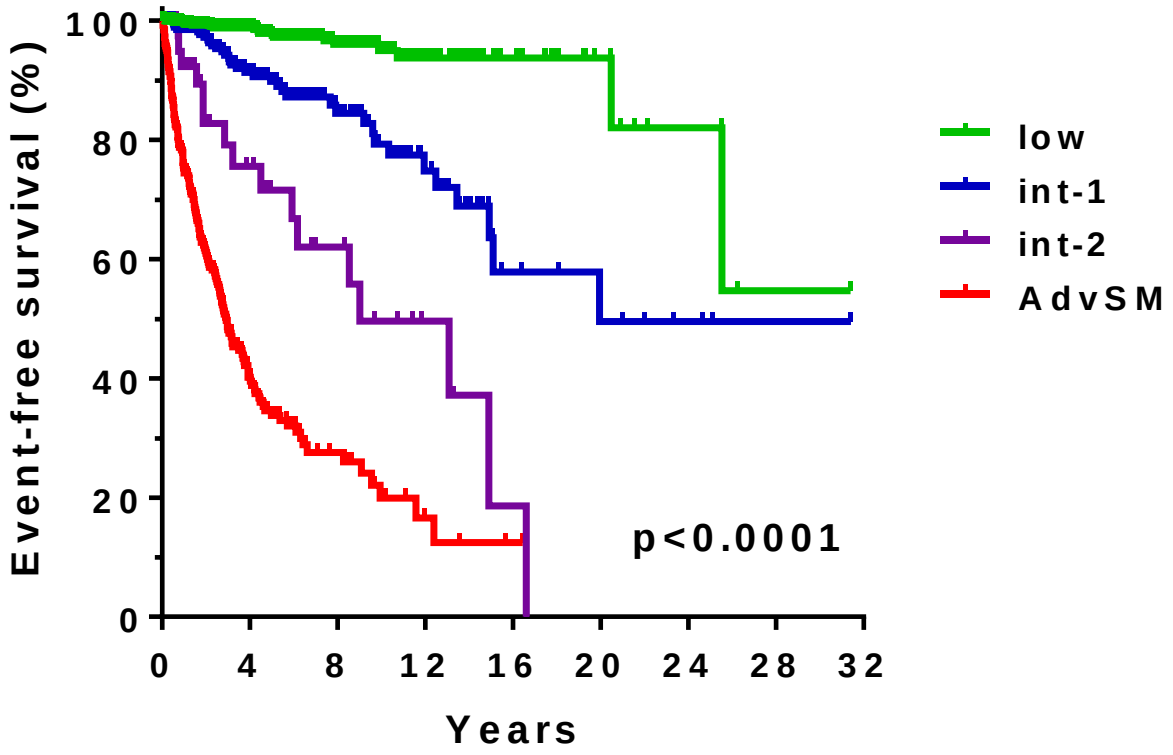
Number at risk (number censored)									
low	553 (0)	283 (266)	119 (425)	39 (503)	16 (526)	8 (534)	3 (528)	0 (541)	0 (541)
int-1	227 (0)	101 (115)	48 (165)	22 (190)	8 (203)	5 (206)	3 (208)	1 (210)	0 (211)
Int-2	33 (0)	16 (15)	8 (21)	3 (26)	1 (28)	0 (29)	0 (29)	0 (29)	0 (29)



Number at risk (number censored)									
low	12 (0)	8 (4)	7 (5)	6 (5)	1 (11)	0 (12)	0 (12)	0 (12)	0 (12)
int-1	21(0)	11 (10)	6 (15)	3 (18)	1 (20)	1 (20)	0 (21)	0 (21)	0 (21)
Int-2	8 (0)	2 (4)	2 (4)	1 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)

Progression-free survival of patients with cutaneous mastocytosis, indolent systemic mastocytosis and smoldering systemic, was calculated separately by the method of Kaplan and Meier. Since mastocytosis in the skin is a provisional term for patients with proven skin involvement but unknown/ unavailable bone marrow these patients were excluded from the analysis. Each subgroup of non-advanced disease was further divided in low, Intermediate (int)-1, and int-2. In patients with cutaneous mastocytosis, indolent systemic mastocytosis and smoldering systemic the differences in Progression-free survival among the low, int-1, and int-2 risk groups was found to be significant as assessed by log rank test .

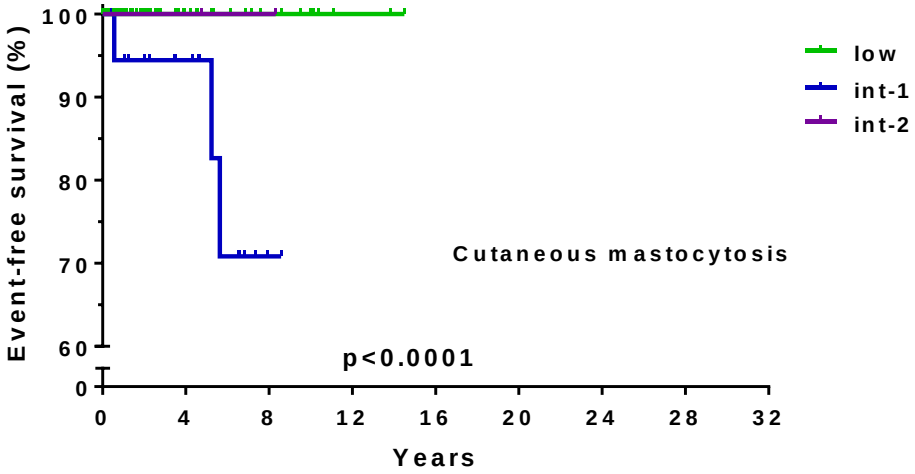
Figure S7
Event-free survival of patients with mastocytosis according to the predictive score



Number at risk (number censored)									
low	711 (0)	351 (353)	148 (548)	53 (642)	20 (675)	9 (686)	4 (690)	1 (692)	0 (693)
int-1	299 (0)	137 (144)	59 (215)	28 (241)	9 (256)	6 (258)	3 (261)	1 (263)	0 (264)
int-1	48 (0)	20 (20)	11 (26)	4 (31)	1 (32)	0 (32)	0 (32)	0 (32)	0 (32)
AdvSM	259 (0)	60 (67)	17 (95)	4 (103)	1 (105)	0 (106)	0 (106)	0 (106)	0 (106)

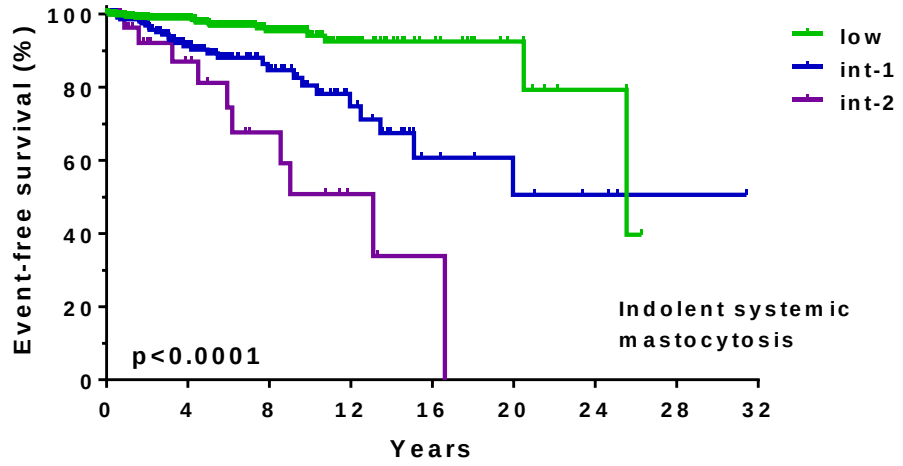
Event-free survival of patients with mastocytosis was calculated according to the method of Kaplan and Meier. The event-free survival was calculated in low, intermediate (int)-1, int-2 risk patients and AdvSM defined by the predictive scoring system. The survival differed significantly between the groups as assessed by log rank test.

Figure S8
Event-free survival of patients with mastocytosis in the skin, indolent systemic mastocytosis and smoldering systemic mastocytosis according to the predictive scoring system for all patients with mastocytosis



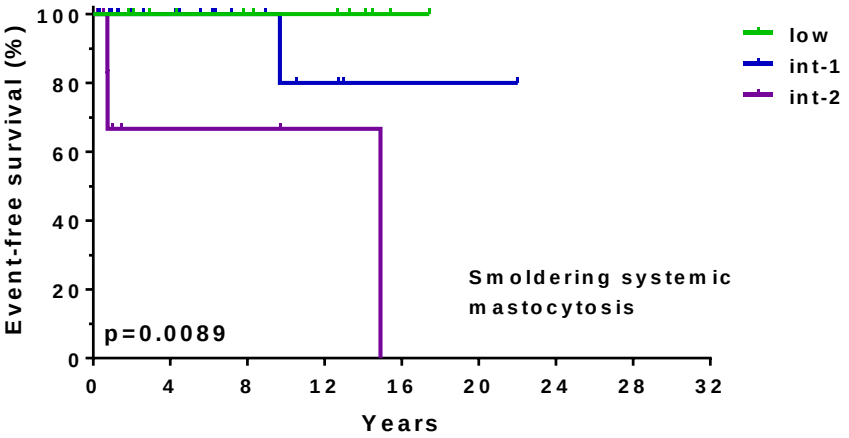
Number at risk (number censored)

Low	57 (0)	17 (40)	8 (49)	2 (55)	0 (57)	0 (57)	0 (57)	0 (57)	0 (57)
int-1	23 (0)	11 (11)	1 (19)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)	0 (20)
Int-2	2 (0)	2 (0)	1 (1)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)



Number at risk (number censored)

Low	533 (0)	283 (264)	119 (421)	39 (499)	16 (522)	8 (530)	3 (534)	0 (536)	0 (536)
int-1	227 (0)	101 (111)	48 (159)	22 (181)	8 (192)	5 (194)	3 (198)	1 (198)	0 (199)
Int-2	33 (0)	16 (14)	8 (19)	3 (22)	1 (23)	0 (23)	0 (23)	0 (23)	0 (23)

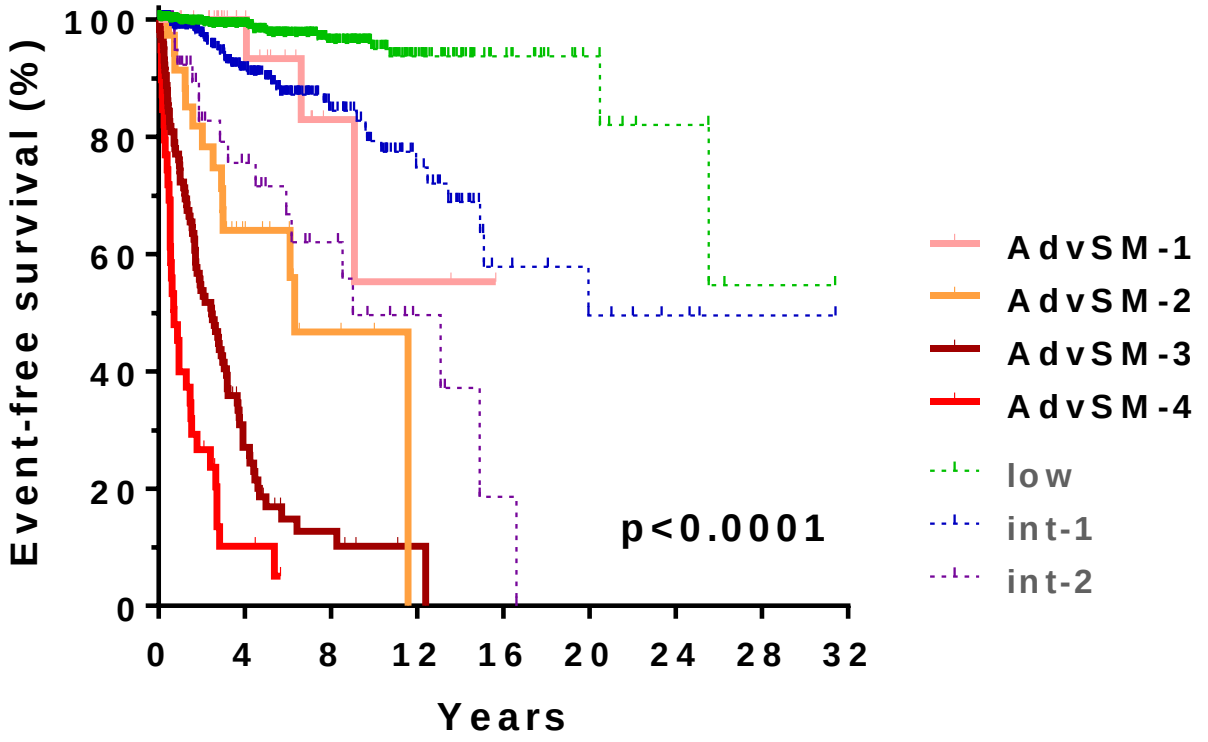


Number at risk (number censored)

low	12 (0)	8(4)	7 (5)	6 (6)	1 (11)	0 (12)	0 (12)	0 (12)	0 (12)
int-1	21 (0)	11 (10)	6 (15)	3 (17)	1 (19)	1 (19)	0 (20)	0 (20)	0 (20)
Int-2	8 (0)	2 (4)	2 (4)	1 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)

Event-free survival of patients with mastocytosis in the skin, indolent systemic mastocytosis and smoldering systemic mastocytosis was calculated separately by the method of Kaplan and Meier. Moreover, each subgroup was further divided in low, intermediate (int)-1, and int-2. In patients with mastocytosis in the skin, indolent systemic mastocytosis and smoldering systemic mastocytosis the differences in event-free survival among the low, int-1, and int-2 risk groups was found to be significant as assessed by log rank test.

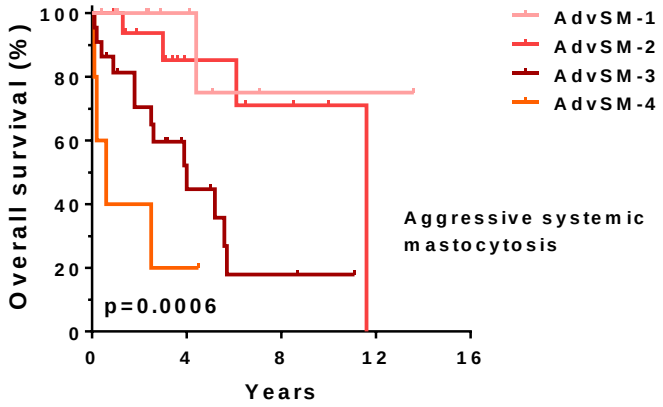
Figure S9
Event-free survival of patients with mastocytosis according the predictive scoring systems of all patients and advanced patients



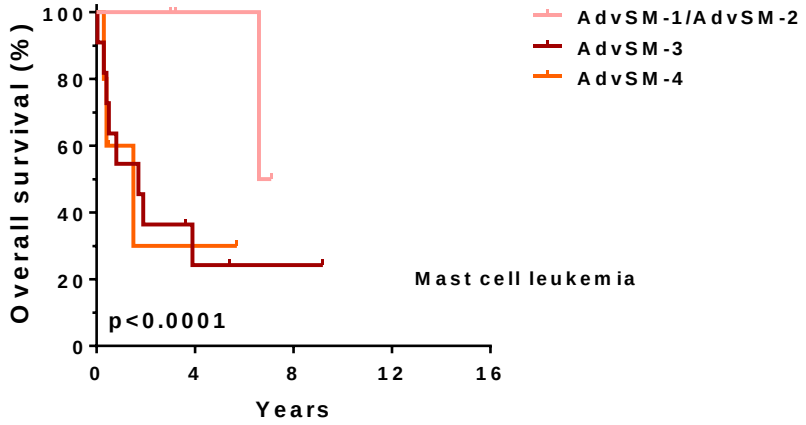
Number at risk (number censored)									
AdvSM-1	35 (0)	16 (19)	3 (30)	2 (30)	0 (32)	0 (32)	0 (32)	0 (32)	0 (32)
AdvSM-2	38 (0)	12 (15)	3 (22)	0 (24)	0 (24)	0 (24)	0 (24)	0 (24)	0 (24)
AdvSM-3	117 (0)	20 (23)	5 (29)	1 (32)	0 (32)	0 (32)	0 (32)	0 (32)	0 (32)
AdvSM-4	39 (0)	3 (3)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)	0 (5)
Low	711 (0)	351 (353)	148 (548)	53 (642)	20 (675)	9 (686)	4 (690)	1 (692)	0 (693)
int-1	299 (0)	137 (144)	59 (215)	28 (241)	9 (256)	6 (258)	3 (261)	1 (263)	0 (264)
int-2	48 (0)	20 (20)	11 (26)	4 (31)	1 (32)	0 (32)	0 (32)	0 (32)	0 (32)

The probability of event-free survival was calculated by the method of Kaplan and Meier. event-free survival differed significantly among the cohort without risk factors (AdvSM-1), patients with one risk factor (AdvSM-2), those with two to three risk factors (AdvSM-3), or four to five risk factors (AdvSM-4) ($p<0.0001$). The event-free survival of AdvSM-1 and AdvSM-2 risk patients was similar to patients in the groups intermediate (int)-1 and int-2, respectively.

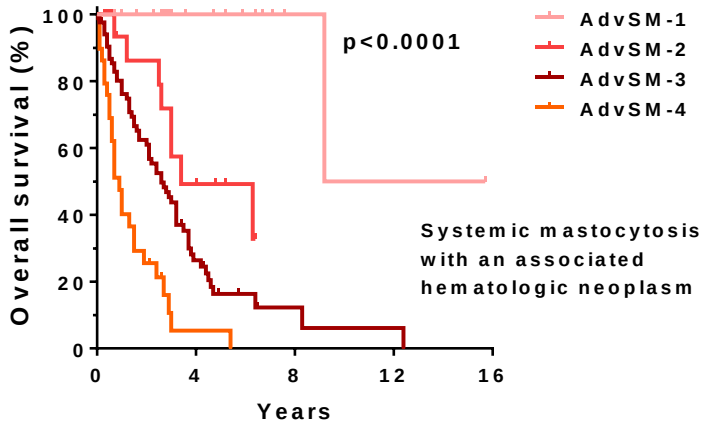
Figure S10
Overall survival of patients with advanced systemic mastocytosis according to the further separation of the AdvSM risk group.



Number at risk (number censored)					
AdvSM-1	11 (0)	5 (6)	1 (9)	1 (9)	0 (11)
AdvSM-2	18 (0)	6 (10)	3 (12)	0 (14)	0 (14)
AdvSM-3	22 (0)	7 (6)	2 (7)	0 (9)	0 (9)
AdvSM-4	5 (0)	1 (0)	0 (1)	0 (1)	0 (1)



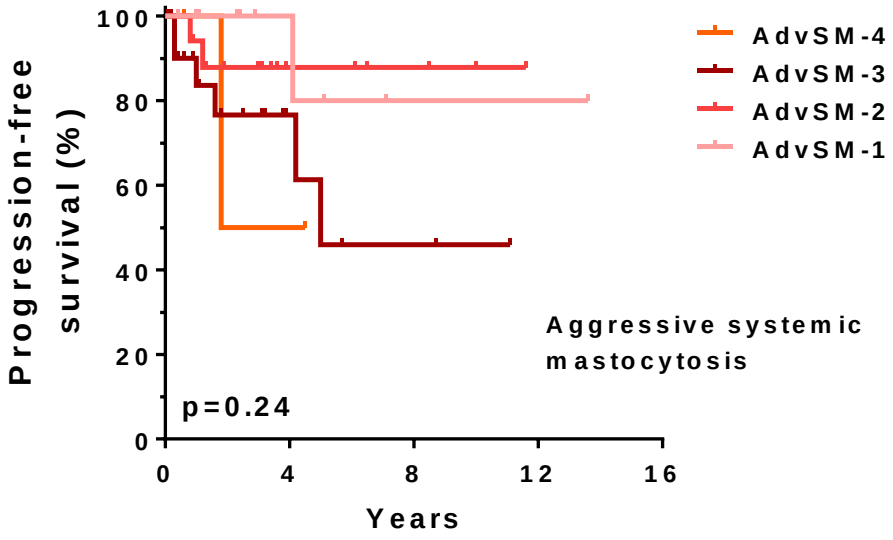
Number at risk (number censored)					
AdvSM-1/2	4 (0)	2 (2)	0 (3)	0 (3)	0 (3)
AdvSM-3	11 (0)	2 (1)	1 (2)	0 (3)	0 (3)
AdvSM-4	5 (0)	1 (1)	0 (2)	0 (2)	0 (2)



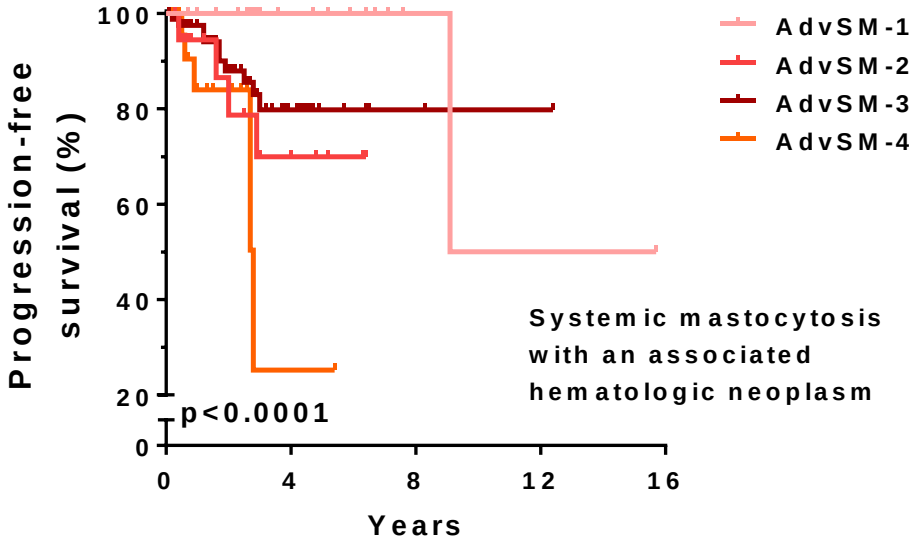
Number at risk (number censored)					
AdvSM-1	21 (0)	9 (12)	2 (19)	1 (19)	0 (20)
AdvSM-2	19 (0)	6 (6)	0 (11)	0 (11)	0 (11)
AdvSM-3	84 (0)	14 (18)	2 (24)	1 (24)	0 (24)
AdvSM-4	29 (0)	1 (3)	0 (3)	0 (3)	0 (3)

Overall survival of patients with aggressive systemic mastocytosis, mast cell leukemia, and systemic mastocytosis with an associated hematologic neoplasm was calculated separately by the method of Kaplan and Meier. Moreover, each subgroup was further divided in AdvSM-1, AdvSM-2, AdvSM-3, and AdvSM-4 risk group in aggressive systemic mastocytosis and systemic mastocytosis with an associated hematologic neoplasm. In mast cell leukemia the AdvSM-1 and AdvSM-2 group were merged due to the low number of individuals in each group. In patients with aggressive systemic mastocytosis, mast cell leukemia, and systemic mastocytosis with an associated hematologic neoplasm the differences in overall survival were found to be significant as assessed by log rank test.

Figure S11
Progression-free survival of patients with aggressive systemic mastocytosis and systemic mastocytosis with an associated hematologic neoplasm



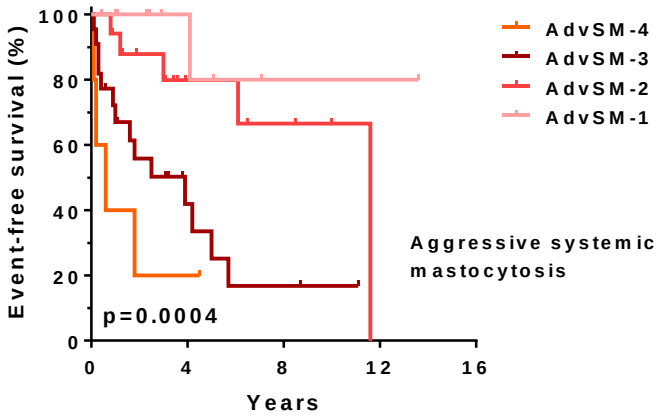
Number at risk (number censored)					
AdvSM-1	11 (0)	5 (6)	1 (9)	1 (9)	0 (10)
AdvSM-2	18 (0)	6 (10)	3 (13)	0 (16)	0 (16)
AdvSM-3	22 (0)	5 (13)	2 (14)	0 (16)	0 (16)
AdvSM-4	5 (0)	1 (3)	0 (4)	0 (4)	0 (4)



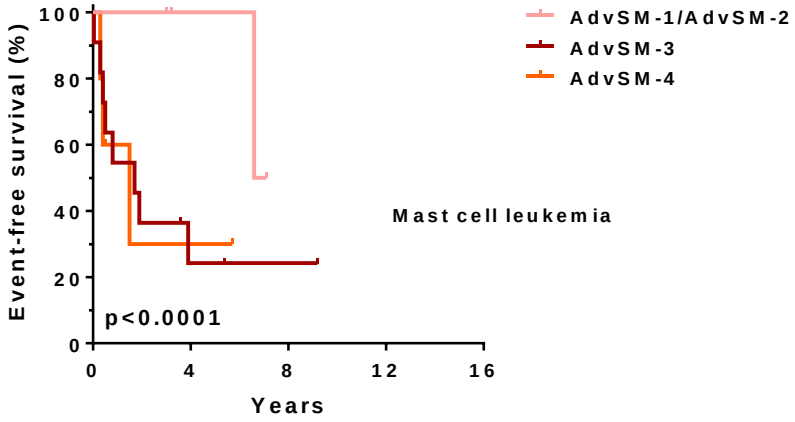
Number at risk (number censored)					
AdvSM-1	21 (0)	9 (12)	2 (19)	1 (19)	0 (21)
AdvSM-2	19 (0)	6 (9)	0 (15)	0 (15)	0 (15)
AdvSM-3	83 (0)	13 (61)	2 (72)	1 (73)	0 (74)
AdvSM-4	29 (0)	1 (22)	0 (23)	0 (23)	0 (23)

Progression-free survival of patients with aggressive systemic mastocytosis and systemic mastocytosis with an associated hematologic neoplasm was calculated by the method of Kaplan and Meier. Since mast cell leukemia represents the most aggressive mast cell disorder and a progression to a higher disease state is not possible these patients were excluded from the analysis. Both subgroups of advanced disease were further divided into AdvSM-1, AdvSM-2, AdvSM-3, and AdvSM-4 risk groups. The differences in progression-free survival among the AdvSM-1, AdvSM-2, AdvSM-3, and AdvSM-4 risk groups in patients with systemic mastocytosis with an associated hematologic neoplasm were found to be significant as assessed by log rank test ($p<0.0001$). In aggressive systemic mastocytosis the differences in progression-free survival did not reach the level of significance.

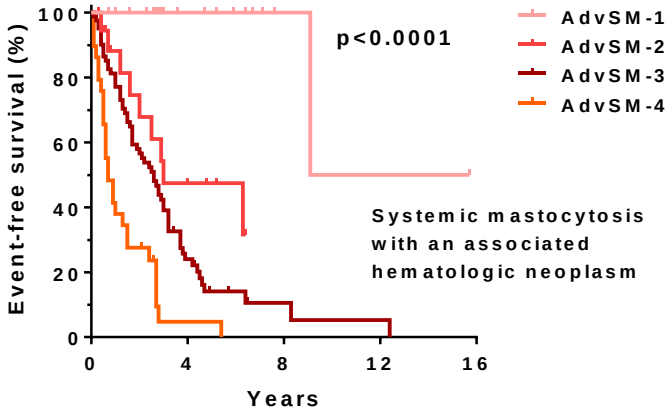
Figure S12
Event-free survival of patients with advanced systemic mastocytosis according to the further separation of the AdvSM risk group.



Number at risk (number censored)					
AdvSM-1	11 (0)	5 (6)	1 (9)	1 (9)	0 (10)
AdvSM-2	18 (0)	6 (9)	3 (11)	0 (13)	0 (13)
AdvSM-3	22 (0)	5 (6)	2 (6)	0 (8)	0 (8)
AdvSM-4	5 (0)	1 (0)	0 (1)	0 (1)	0 (1)



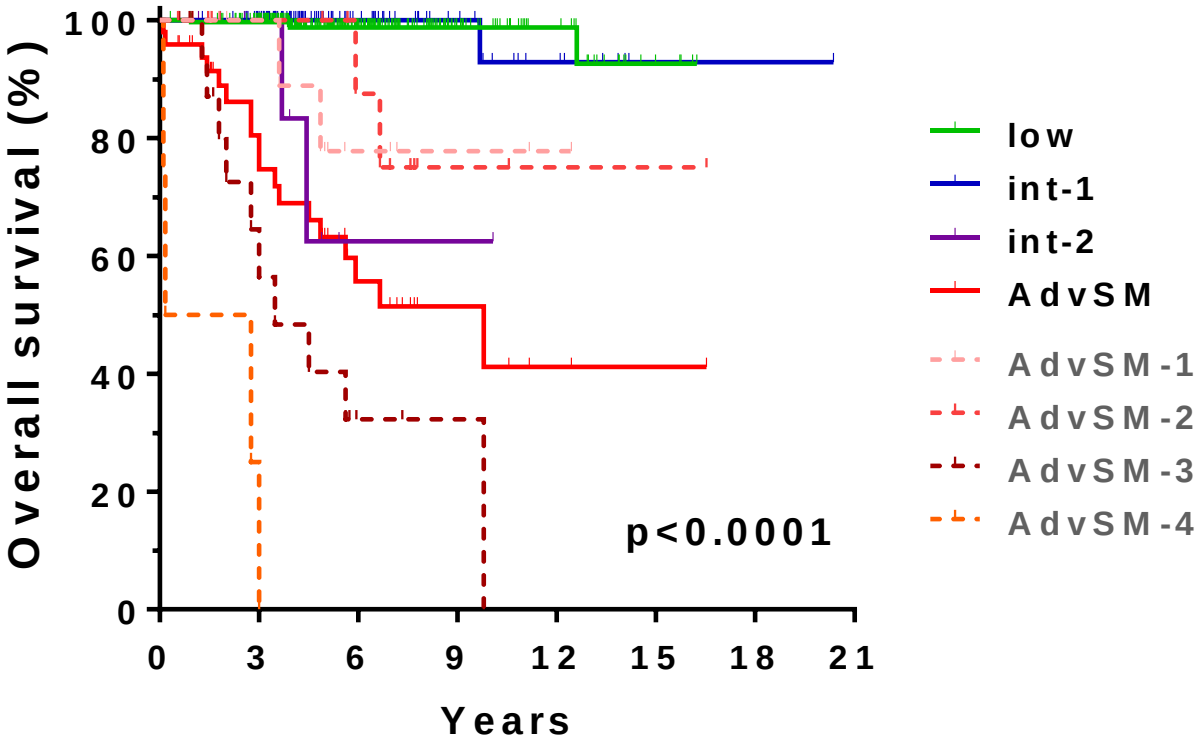
Number at risk (number censored)					
AdvSM-1/2	4 (0)	2 (2)	0 (3)	0 (3)	0 (3)
AdvSM-3	11 (0)	2 (1)	1 (2)	0 (3)	0 (3)
AdvSM-4	5 (0)	1 (1)	0 (2)	0 (2)	0 (2)



Number at risk (number censored)					
AdvSM-1	21 (0)	9 (12)	2 (19)	1 (19)	0 (20)
AdvSM-2	19 (0)	5 (6)	0 (10)	0 (10)	0 (10)
AdvSM-3	84 (0)	13 (16)	2 (21)	1 (21)	0 (21)
AdvSM-4	29 (0)	1 (2)	0 (2)	0 (2)	0 (2)

Event-free survival of patients with aggressive systemic mastocytosis, mast cell leukemia, and systemic mastocytosis with an associated hematologic neoplasm was calculated by the method of Kaplan and Meier. Moreover, each subgroup was further divided into AdvSM-1, AdvSM-2, AdvSM-3, and AdvSM-4 risk group in aggressive systemic mastocytosis and SM-AHN. In mast cell leukemia the AdvSM-1 and AdvSM-2 group were merged due to the low number of individuals in each group. In patients with aggressive systemic mastocytosis, mast cell leukemia, and systemic mastocytosis with an associated hematologic neoplasm the differences in event free survival were found to be significant as assessed by log rank test.

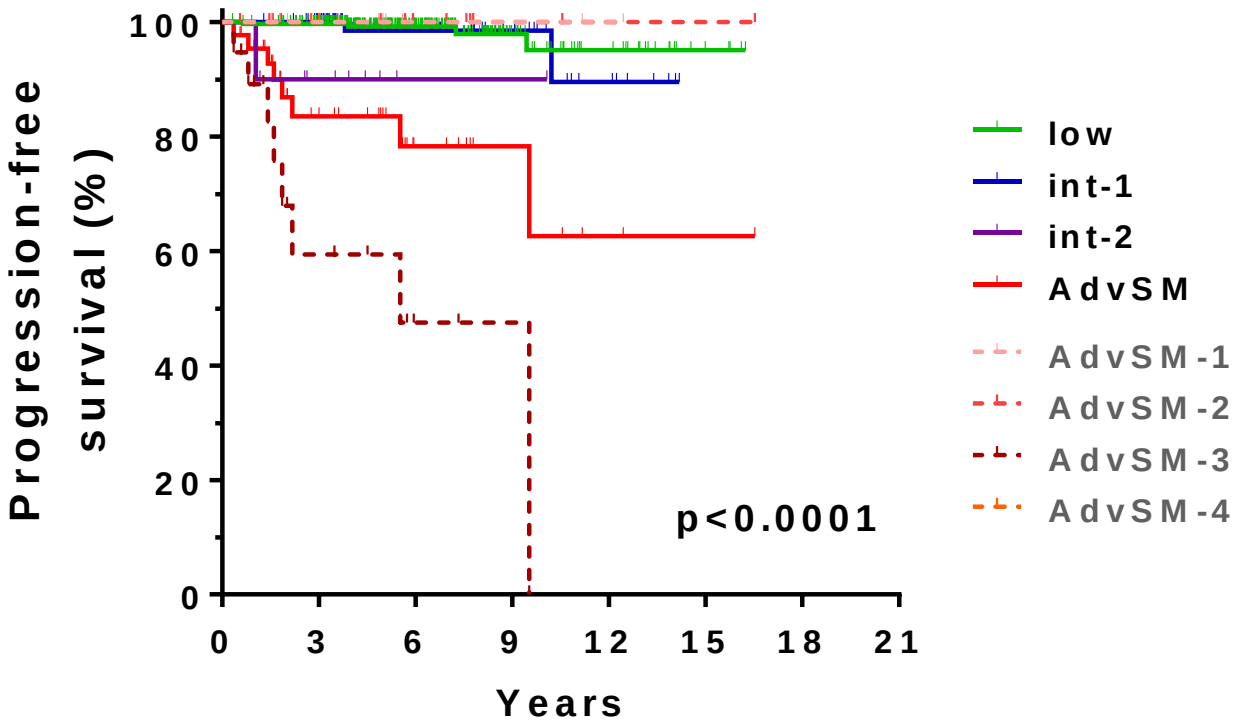
Figure S13
Overall survival according to the predictive scoring system in the REMA validation cohort



Number at risk (number censored)								
low	304 (0)	279 (24)	126 (175)	44 (257)	20 (281)	4 (296)	0 (300)	0 (300)
int-1	99 (0)	91 (8)	32 (67)	16 (83)	8 (90)	1 (97)	1 (97)	0 (98)
int-2	10 (0)	7 (3)	1 (7)	1 (7)	0 (8)	0 (8)	0 (8)	0 (8)
AdvSM	49 (0)	28 (13)	13 (20)	5 (27)	2 (29)	1 (30)	0 (31)	0 (31)
AdvSM-1	12 (0)	9 (3)	4 (6)	2 (8)	1 (9)	0 (10)	0 (10)	0 (10)
AdvSM-2	14 (0)	10 (4)	7 (6)	2 (10)	1 (11)	1 (11)	0 (12)	0 (12)
AdvSM-3	19 (0)	8 (6)	2 (8)	1 (9)	0 (9)	0 (9)	0 (9)	0 (9)
AdvSM-4	4 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The probability of overall survival was calculated by the method of Kaplan and Meier. Both scores were also found to be of prognostic significance for overall survival. The survival of the AdvSM-1 and AdvSM-2 risk patients was similar to patients in group intermediate-1 (int-1) and int-2, respectively.

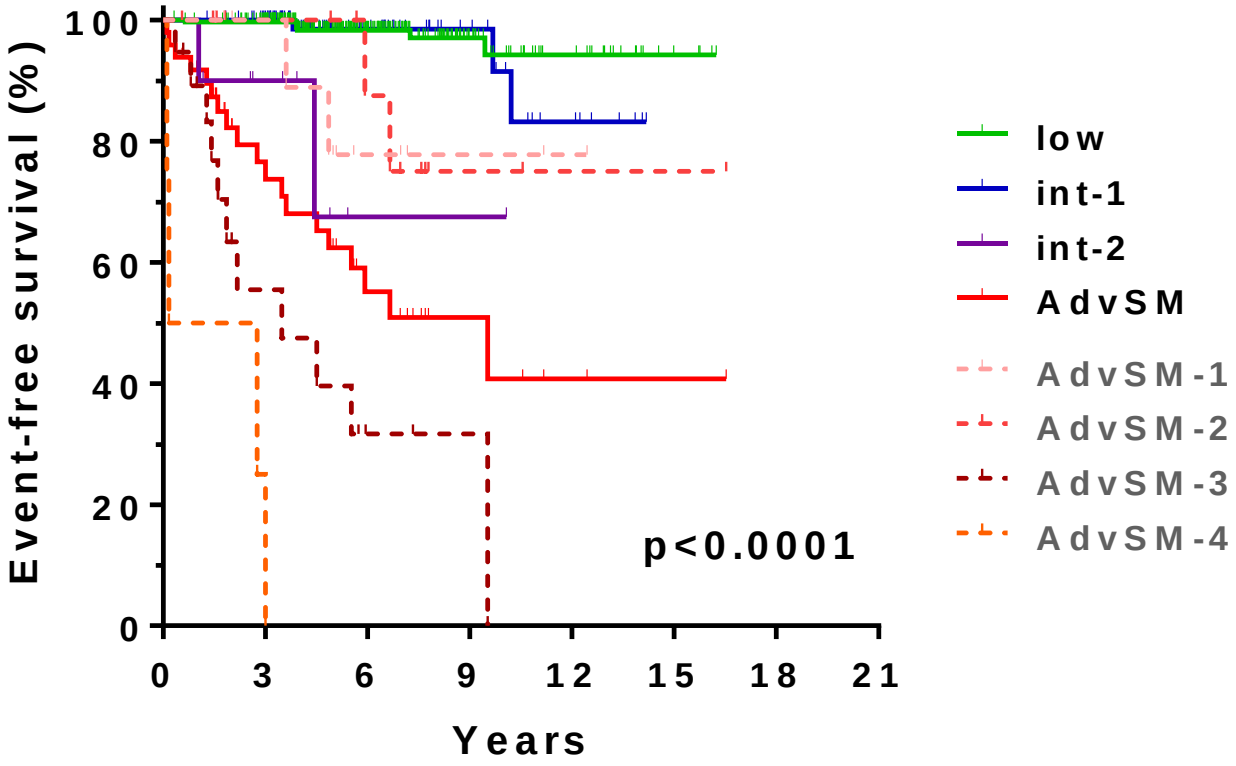
Figure S14
Progression-free survival according to the predictive scoring system in the REMA validation cohort



Number at risk (number censored)								
low	304 (0)	279 (24)	125 (177)	42 (259)	19 (281)	4 (296)	0 (300)	0 (300)
int-1	99 (0)	91 (8)	32 (66)	16 (82)	7 (90)	0 (97)	0 (97)	0 (97)
int-2	10 (0)	6 (3)	1 (8)	1 (8)	0 (9)	0 (9)	0 (9)	0 (9)
AdvSM	44 (0)	24 (14)	10 (27)	5 (32)	2 (34)	1 (35)	1 (35)	0 (36)
AdvSM-1	10 (0)	7 (3)	2 (8)	2 (8)	1 (9)	0 (9)	0 (9)	0 (9)
AdvSM-2	13 (0)	9 (4)	6 (7)	2 (11)	1 (12)	1 (12)	1 (12)	0 (13)
AdvSM-3	19 (0)	7 (3)	2 (10)	1 (11)	0 (11)	0 (11)	0 (11)	0 (11)
AdvSM-4	2 (0)	1 (1)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)	0 (2)

The probability of progression-free survival was calculated by the method of Kaplan and Meier. Since mast cell leukemia represents the most aggressive mast cell disorder that cannot progress into a more aggressive form of mastocytosis and mastocytosis in the skin is a provisional diagnosis for patients with proven skin involvement but unknown/unavailable bone marrow but no definitive diagnosis, these patients were excluded from analysis of progression-free survival. Both scores were also found to be of prognostic significance for progression-free survival.

Figure S15
Event-free survival according to the predictive scoring system in the REMA validation cohort



Number at risk (number censored)								
low	304 (0)	279 (28)	125 (304)	42 (257)	19 (179)	4 (294)	0 (298)	0 (298)
int-1	99 (0)	91 (8)	32 (66)	16 (82)	7 (89)	0 (96)	0 (96)	0 (96)
int-2	10 (0)	6 (3)	1 (7)	1 (7)	0 (8)	0 (8)	0 (8)	0 (8)
AdvSM	49 (0)	27 (12)	13 (19)	5 (26)	2 (28)	1 (29)	0 (30)	0 (30)
AdvSM-1	12 (0)	9 (3)	4 (6)	2 (8)	1 (9)	0 (10)	0 (10)	0 (10)
AdvSM-2	14 (0)	10 (4)	7 (6)	2 (10)	1 (11)	1 (11)	0 (12)	0 (12)
AdvSM-3	19 (0)	7 (5)	2 (7)	1 (8)	0 (8)	0 (8)	0 (8)	0 (8)
AdvSM-4	4 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The probability of event-free survival was calculated by the method of Kaplan and Meier. Both scores were also found to be of prognostic significance for event-free survival. The survival of the AdvSM-1 and AdvSM-2 risk patients was similar to patients in group intermediate-1 (int-1) and int-2, respectively.

Supplementary Tables

Table S1

Criteria of Systemic Mastocytosis

Major SM Criterion

1. Multifocal dense mast cell infiltrates (≥15 mast cells/infiltrate) in the bone marrow or in another extra-cutaneous organ

Minor SM Criteria

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

AHN, associated hematologic neoplasm; mast cells, mast cell

The diagnosis systemic mastocytosis is established if 1 major and at least 1 minor, or 3 minor criteria are fulfilled.[4-9]

Table S2

B-Findings and C-Findings

B-Findings:

1. Infiltration grade with mast cells in the bone marrow >30% and serum tryptase >200 ng/ml
2. Dysmyelopoiesis: a hypercellular bone marrow with signs of myelodysplasia or myelo-proliferation, but no criteria for myelodysplastic syndrome or myeloproliferative neoplasm. Blood picture normal or slightly abnormal
3. Organomegaly (without impaired organ function/organ damage): 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 smoldering systemic mastocytosis

C-Findings:

1. One or more marked cytopenias: ANC<1.0x10^9/L; Hb<10 g/dL; PLT<100x10^9/L
2. Hepatopathy: Enlarged liver with ascites, elevated liver enzymes +/- portal hypertension
3. Organopathy of spleen: splenomegaly with hypersplenism
4. Malabsorption with hypalbuminemia and substantial weight loss
5. Large osteolysis and/or osteolyses with pathologic fractures

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

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

Table S3:
Centers and numbers of patients included in the registry and in the current study

	Centers	Patients included in		Patients included in this study								
		the registry	this study*	Childhood cutaneous mastocytosis	Adulthood cutaneous mastocytosis	Mastocytosis in the skin	Indolent systemic mastocytosis	Smoldering systemic mastocytosis	Aggressive systemic mastocytosis	Mast cell leukemia	Mast cell sarcoma	Systemic mastocytosis with an associated hematologic neoplasm
1	Johannes Kepler University, Austria	78	64	0	10	21	29	1	1	0	0	2
2	Karolinska University Hospital, Huddinge	3	3	0	0	0	2	0	1	0	0	0
3	Klinik, Universitätsmedizin Mannheim, Universität Heidelberg, Germany	90	78	0	2	0	28	6	7	4	0	31
4	Medical University of Gdansk, Poland	246	167	29	43	1	87	3	2	1	0	1
5	Medical University of Vienna, Austria	225	212	2	20	27	125	3	8	4	2	21
6	Stanford University School of Medicine, California, USA	130	120	0	3	20	43	4	12	5	0	33
7	Technische Universität München, Germany	82	43	13	4	8	18	0	0	0	0	0
8	Université Paris Descartes, Sorbonne; Ecole Normale Supérieure de Cachan, France	123	52	1	0	0	25	4	5	2	0	15
9	University Hospital Brno, Czech Republic	46	39	0	2	2	27	0	6	0	0	2
10	University Hospital Freiburg, Germany	99	67	7	3	11	32	3	4	1	0	6
11	University Hospital Graz, Austria	35	31	0	1	14	14	0	0	0	0	2
12	University Hospital of Leipzig, Germany	35	29	0	0	0	21	2	4	1	0	1
13	University Hospital RWTH Aachen, Germany	42	14	0	0	0	11	2	0	0	0	1
14	University Hospitals Leuven, Belgium	25	22	13	0	4	5	0	0	0	0	0
15	University of Antwerp, Belgium	40	10	1	2	0	7	0	0	0	0	0
16	University of Cologne, Germany	114	79	9	8	19	34	2	2	0	0	5
17	University of Groningen, The Netherlands	414	370	40	11	22	252	5	2	2	0	36
18	University of Istanbul, Turkey	52	45	0	6	0	23	3	4	3	0	6
19	University of Padova, Italy	83	26	22	0	2	2	0	0	0	0	0
20	University of Pavia and Fondazione IRCCS Policlinico San Matteo, Italy	102	90	1	7	18	47	8	3	0	0	6
21	University of Salerno, Italy	91	63	15	2	21	19	3	0	0	0	3
22	Uppsala University, Sweden	45	31	0	0	0	28	1	0	0	0	2
23	Verona University Hospital, Italy	161	139	0	3	4	127	3	1	0	0	1
	All patients	2361	1794	153	127	194	1006	53	62	23	2	174

*In 1794/2361 follow up data were recorded. These patients were included in the study.

Table S4A

Information captured at diagnosis

Basic data	Mastocytosis criteria	Peripheral blood findings	Laboratory findings
• Patient code	• Date of visit	• Date of visit	• Date of visit
• Patient-ID	• Skin involvement (yes/no)	• WBC	• LDH
• Patients' initials	• In case of skin involvement:	• % ANC	• Alkaline phosphatase
• Gender	- Typical/atypical skin lesions	• % Eosinophils	
• Date or year of birth (age at diagnosis)	- Maculopapular/diffuse	• % Monocytes	• Calcium
	- % skin involved	• % Mast cells	• Albumin
• Center	- Darier sign positive /negative	• % Basophils	• Fibrinogen
• Date of first symptoms	- Monomorphic morphology of MC infiltrates	• % Lymphocytes	• IgM
• Date of first visit	- *KIT* D816V positive in the skin	• % Progenitors*	• IgA
• Performance status (WHO)	• MC-infiltrates in bm biopsy (tryptase IHC) (yes/no)	• Hemoglobin	• IgG
• Is material stored (yes/no)	- % MC infiltrates (bm) by IHC	• Platelets	• IgM kappa
• Type of material stored	- % spindle shaped MC in compact MC infiltrates in bm by IHC		• IgM lambda
• Height	- loose infiltrate with predominantly spindle-shaped MC by IHC		• IgA kappa
• Weight	• MC present in smears (yes/no)		• IgA lambda
• Patient lost to follow up (yes/no)	- % MC in bm smears (MWG, WG)		• IgG kappa
• Date of last follow-up	- % spindle shaped MC of all MC in bm smears		• IgG lambda
• Patient died (yes/no)	• *KIT* mutation D816V in bm cells (yes/no)		• Beta-2-micro-globuline
	• *KIT* D816V allele burden		
• Date of death	• Other *KIT* mutation		• Cholesterol
• Reason of death	• Mutations in genes other than *KIT*		
	• CD2 positive bm MC (by FACS) (yes/no)		
	• CD25 positive bm MC (by FACS or IHC) (yes/no)		
	• CD30 positive bm MC (by IHC or FACS) (yes/no)		
	• Other surface markers if recorded		
	• Multilineage involvement with *KIT* D816V		
	• Well differentiated (WD) morphology of MC (yes/no)		
	• Basal serum tryptase level (ng/ml)		
	• Diagnosis of Mastocytosis – if SM-AHN:		
	- Type of SM		
	- Type of AHN		

AHN, associated hematologic neoplasm; ANC, all neutrophil count; bm, bone marrow; FACS, fluorescence activated cell sorting; ID, identification number; IgA, immunoglobulin-A; IgG, immunoglobulin-G; IgM, immunoglobulin-M; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MC, mast cell; MWG, May-Grünwald-Giemsa; SM, systemic mastocytosis; WBC, white blood cell count; WG, Wright-Giemsa WHO, World Health Organization; *Progenitors=metamyelocytes+myelocytes+promyelocytes+blasts.

Table S4B

Information captured at diagnosis

Clinical findings	Bone marrow	B- & C-findings[#]	Mediator symptoms
• Date of visit	• Date of visit	• Date of visit	• Date of visit
• Spleen (palpable; yes/no)	• Karyotype	• Osteolysis due to MC infiltration (yes/no)	• Skin lesions (yes/no)
• Hepatomegaly (palpable yes/no)	• % Blasts in bm smears	• Number of osteolysis	- Flushing (grading*)
• Lymphadenopathy (palpable or >2 cm in US/CT yes/no)		• Size of osteolysis	- Pruritus
		• Dysmyelopoiesis (yes/no)	- Blistering/bullae
		• Ascites (yes/no)	• Constitutional/cardiovascular symptoms (grading*)
		• Portal hypertension (yes/no)	• Hypotension (grading*)
		• Malabsorption (yes/no)	• Osteopenia/osteoporosis (symptoms; yes/no)
		• Weight loss (≥10% within last 12 months)	• Bone pain (grading*)
			• T-Score
			• GI-tract symptoms (yes/no)
			- Abdominal cramping (grading)
			- Diarrhea (grading*)
			- Duodenal ulcer (grading*)
			- Gastric ulcer (grading*)
			• Headache (grading*)
			• Allergy (yes/no)
			• Type of allergen
			• Specific IgE
			• Therapy

[#]Only B- or C-findings not included in other section of the registry i.e. "Peripheral blood findings" and "Clinical findings" were captured in this section.

*Grading of symptoms was performed following generally accepted guidelines.[7]

bm, bone marrow; CT, computed tomography; GI, gastrointestinal; IgE, immunoglobulin E; US, ultrasound

Table S4C

Information captured in the follow up

Basic data	Mastocytosis criteria	Peripheral blood findings	Laboratory findings
• Date of visit	• Date of visit	• Date of visit	• Date of visit
• Progression of disease	• Skin involvement (yes/no)	• WBC	• LDH
	• In case of skin involvement	• % ANC	• Alkaline phosphatase
• Performance status (WHO	- Typical/atypical	• % Eosinophils	
• Is material stored (yes/no)	- Maculopapular/diffuse	• % Monocytes	• Calcium
	- % skin involved	• % Mast cells	• Albumin
	- Darier sign positive /negative	• % Basophils	• Fibrinogen
• Type of material stored	- Monomorphic morphology of MC infiltrates	• % Lymphocytes • % Progenitors*	• IgM
• Weight	- *KIT* D816V positive in the skin	• Hemoglobin	• IgA
	• MC-infiltrates in bm biopsy (tryptase IHC) (yes/no)	• Platelets	• IgG
	- % MC infiltrates (bm) by IHC		• IgM kappa
	- % spindle shaped MC in compact MC infiltrates in bm by IHC		• IgM lambda
	- loose infiltrate with predominantly spindle-shaped MC by IHC		• IgA kappa
	• MC present in smears (yes/no)		• IgA lambda
	- % MC in bm smears (MWG, WG)		• IgG kappa
	- % spindle shaped MC of all MC in bm smears		• IgG lambda
	• *KIT* mutation D816V in bm cells (yes/no)		• Beta-2-Micro-globuline
	• *KIT* D816V allele burden		
	• Other *KIT* mutation		• Cholesterol
	• Mutations in genes other than *KIT*		
	• CD2 positive bm MC (by FACS) (yes/no)		
	• CD25 positive bm MC (by FACS or IHC) (yes/no)		
	• CD30 positive bm MC (by IHC or FACS) (yes/no)		
	• Other surface markers if captured		
	• Multilineage involvement with *KIT* D816V		
	• Well differentiated (WD) morphology of MC (yes/no)		
	• Serum tryptase		
	• Diagnosis of Mastocytosis		
	- Type of SM - Type of AHN		

AHN, associated hematologic neoplasm; ANC, all neutrophil count; bm, bone marrow; FACS, fluorescence activated cell sorting; ID, identification number; IgA, immunoglobulin-A; IgG, immunoglobulin-G; IgM, immunoglobulin-M; IHC, immunohistochemistry; LDH, lactate dehydrogenase; MC, mast cell; MWG, May-Grünwald-Giemsa; SM, systemic mastocytosis; WBC, white blood cell count; WG, Wright-Giemsa WHO, World Health Organization; *Progenitors=metamyelocytes+myelocytes+promyelocytes+blasts.

Table S4D

Information captured in the follow up

Clinical findings	Bone marrow	B- & C-findings[#]	Mediator symptoms
• Date of visit	• Date of visit	• Date of visit	• Date of visit
• Spleen (palpable; yes/no)	• Karyotype	• Osteolysis due to MC infiltration (yes/no)	• Skin lesions (yes/no)
• Hepatomegaly (palpable yes/no)	• % Blasts in bm smears	• Number of osteolysis	- Flushing (grading*)
• Lymphadenopathy (palpable or >2 cm in US/CT yes/no)		• Size of osteolysis	- Pruritus
		• Dysmyelopoiesis (yes/no)	- Blistering/bullae
		• Ascites (yes/no)	• Constitutional/cardiovascular symptoms (grading*)
		• Portal hypertension (yes/no)	• Hypotension (grading*)
		• Malabsorption (yes/no)	• Osteopenia/osteoporosis (symptoms; yes/no)
		• Weight loss (≥10% within last 12 months)	• Bone pain (grading*)
			• T-Score
			• GI-tract symptoms (yes/no)
			- Abdominal cramping (grading*)
			- Diarrhea (grading*)
			- Duodenal ulcer (grading*)
			- Gastric ulcer (grading*)
			• Headache (grading*)
			• Allergy (yes/no)
			• Type of allergen
			• Specific IgE
			• Therapy

[#]Only B- or C-findings not included in other section of the registry i.e. "Peripheral blood findings" and "Clinical findings" were captured in this section.

*Grading of symptoms was performed following generally accepted guidelines.[7]

bm, bone marrow; CT, computed tomography; GI, gastrointestinal; IgE, immunoglobulin E; US, ultrasound

Table S5

Clinical characteristics of the patients included in follow up examinations

Disease category	n (%)	f	m	f:m-ratio	Age years	Organomegaly n yes/no (% yes)	Allergies n yes/no (% yes)	Skin lesions n yes/no (% yes)	Mediator symptoms n yes/no (% yes)
Childhood cutaneous mastocytosis	153 (8·5)	69	124	1:1·2	1 (0·15-17)	6/81 (6·9)	9/75 (10·7)	153/0 (100)	91/62 (59·5)
Adulthood cutaneous mastocytosis	127 (7·1)	187	124	1:0·5	37 (18-76)	8/109 (6·8)	28/82 (26·1)	127/0 (100)	96/30 (76·2)
Mastocytosis in the skin	194 (10·8)	126	68	1:0·5	43 (18-87)	15/122 (10·9)	52/104 (33·3)	194/0 (100)	126/68 (64·9)
Indolent systemic mastocytosis	1006 (56·1)	577	429	1:0·7	47 (17-83)	74/846 (8·0)	374/509 (42·4)	732/274 (72·8)	780 (77·6)
Smoldering systemic mastocytosis	53 (3·0)	31	22	1:0·7	52 (25-79)	35/15 (70·0)	14/30 (31·8)	43/10 (81·1)	45/8 (84·9)
Aggressive systemic mastocytosis	62 (3·5)	31	31	1:1·0	58 (15-83)	43/15 (74·1)	12/42 (22·2)	32/30 (51·6)	49/13 (79·0)
Mast cell leukemia	23 (1·3)	10	13	1:1·3	54 (27-90)	16 /5 (76·2)	5/15 (25·0)	8/15 (34·8)	16/7 (69·6)
Mast cell sarcoma	2 (0·1)	2	0	1:0	19 (8-30)	0/2 (0·0)	0/2 (0)	0/2 (0)	0 (0·0)
Systemic mastocytosis with an associated hematologic neoplasm	174 (9·7)	50	124	1:2·5	64 (22-83)	123/36 (77·4)	10/138 (6·8)	57/117 (32·8)	114 (65·5)
all patients	1794 (100)	983	811	1:0·8	46 (0·15-90)	320/1231 (20·6)	505/997 (33·6)	1346/448 (75·5)	1317/475 (73·5)

Abbreviations: f, female; n, number of patients in the group; m, male

Table S6

Laboratory parameters in patients included in follow up examinations

Subtype	Tryptase, ng/ml	WBC x10^9/L	Hb g/dL	PLT x10^9/L	LDH U/L	AP U/L	Albumin U/L	Ca mg/dL
Childhood cutaneous mastocytosis	**6·3** (1-98·1)	**8·4** (2·8-15·1)	**12·3** (9·9*-15·1)	**339** (214-551)	**248** (129-457)	**212** (79-1729)	**45** (37-64)	**9·9** (9·2-11·7)
Adulthood cutaneous mastocytosis	**9·4** (1·3-126)	**6·3** (3·5-13·0)	**13·8** (8·1*-17·2)	**253** (139-553)	**177** (110-399)	**68** (33-212)	**45** (36-66)	**9·5** (8·8-10·5)
Mastocytosis in the skin	**12** (1-141)	**6·6** (2·3-17·7)	**13·8** (8·7*-17·3)	**253** (152-481)	**167** (82-1164)	**66** (36-290)	**45** (36-67)	**9·4** (8·0-10·7)
Indolent systemic mastocytosis	**31** (3-885)	**6·6** (1·0-19·5)	**14·0** (8·7*-18·2)	**261** (26$^{\#}$-589)	**166** (76-662)	**74** (22-317)	**45** (28-68)	**9·4** (7·8-11·7)
Smoldering systemic mastocytosis	**200** (60-819)	**6·9** (1·6-13·0)	**13·2** (9·3-16·7)	**230** (75-422)	**159** (100-334)	**114** (36-345)	**46** (34-64)	**9·3** (7·6-10·0)
Aggressive systemic mastocytosis	**175** (9-1432)	**6·4** (1·4-38·9)	**11·3** (5·8-16·4)	**131** (5-681)	**171** (89-587)	**161** (63-1696)	**37** (18-50)	**8·9** (7·5-10·4)
Mast cell leukemia	**397** (114-4530)	**8·5** (2·0-53·3)	**9·8** (7·7-14·0)	**128** (18-399)	**158** (97-2152)	**194** (55-1121)	**37** (26-49)	**8·9** (7·9-9·6)
Mast cell sarcoma	**3·3** (1, 5·6)	**10·0** (8·1, 12·0)	**9·2** (8·8, 9·6)	**400** (301, 499)	**293** (293)	**100** (100)	**40** (40)	**9·3** (9·3)
Systemic mastocytosis with an associated hematologic neoplasm	**150** (2-1022)	**9·4** (0·6-95·0)	**10·8** (4·0-16·4)	**110** (5-969)	**186** (81-8121)	**207** (39-1407)	**40** (34-49)	**9·1** (7·2-10·9)
All patients	**29** (1-4530)	**6·7** (0·6-95·0)	**13·7** (4·0-18·2)	**254** (5-969)	**169** (76-8121)	**80** (22-1729)	**45** (18-68)	**9·4** (7·2-11·7)

All parameters are provided as median and range (in brackets) in all patients per group examined in this study. Abbreviations: AP, alkaline phosphatase; Ca, calcium; Hb, hemoglobin; LDH, lactate dehydrogenases; PLT, platelets; pts, patients; WBC, white blood cell count

*In cutaneous mastocytosis, mastocytosis in the skin, and indolent systemic mastocytosis there were several patients with anemia due to iron deficiency, in indolent systemic mastocytosis there were 2 cases with thalassemia trait, and 1 case of protoporphyrin

These indolent systemic mastocytosis patients presented with thrombocytopenia because of a hepatic disorder, idiopathic thrombocythemia and protoporphyrin

Table S7

Characteristics of 462 patients of the Spanish network on mastocytosis, REMA (Red Española de Mastocitosis)

	n (%)	f	m	f:m-ratio	age years	tryptase ng/ml	WBC $x10^9$/L	Hb g/dL	PLT $x10^9$/L	AP U/L
Cutaneous mastocytosis	**18** (3·9)	15	3	**1:0·20**	**33** (17-62)	**5** (2-19)	**6·45** (3·90-9·40)	**13·0** (11·7-17·2)	**237** (134-431)	**61·5** (44-125)
Indolent systemic mastocytosis	**384** (83·1)	198	186	**1:0·94**	**46** (17-79)	**29** (6-644)	**6·40** (2·70-6·20)	**14·2** (9·9-17·5)	**235** (99-480)	**68** (17-332)
Smoldering systemic mastocytosis	**11** (2·4)	4	7	**1:1·75**	**52** (21-72)	**267** (161-380)	**6·40** (3·90-10·70)	**13·2** (11·1-15·3)	**214** (123-321)	**133** (49-553)
Aggressive systemic mastocytosis	**19** (4·1)	8	11	**1:1·38**	**61** (25-77)	**279** (72-2036)	**5·90** (2·03-20·10)	**11·4** (8·4-14·6)	**199** (59-463)	**211** (68-1972)
Mast cell leukemia	**5** (1·0)	2	3	**1:1·50**	**65** (27-73)	**196** (91-660)	**4·20** (2·14-13·40)	**9·4** (8·7-12)	**197** (7-354)	**82** (46-365)
Systemic mastocytosis with an associated hematologic neoplasm	**25** (5·4)	6	19	**1:3·17**	**61** (24-73)	**82** (6-390)	**10·40** (1·79-96·30)	**14·0** (8·5-17·3)	**161** (13-813)	**124** (51-1310)
All patients	**462** (100)	233	229	**1:0·98**	**47** (17-79)	**31** (2-2036)	**6·44** (1·79-96·30)	**14·1** (8·4-17·5)	**233** (7-813)	**70·5** (17-1972)

All parameters are provided as median and range (in brackets) in all patients per group examined in this study. Abbreviations: AP, alkaline phosphatase; f, female; Hb, hemoglobin; ISM, indolent systemic mastocytosis; m, male; n, number of patients in the group; PLT, platelets; pts, patients; WBC, white blood cell count

Table S8

Cause of death in the 194 patients with mastocytosis that died during the observation period.

	Childhood cutaneous mastocytosis	Adulthood cutaneous mastocytosis	Mastocytosis in the skin	Indolent systemic mastocytosis	Smoldering systemic mastocytosis	Non-AdvM	Aggressive systemic mastocytosis	Mast cell leukemia	Mast cell sarcoma	Systemic mastocytosis with an associated hematologic neoplasm	AdvSM	All pts
n	**153**	**127**	**194**	**1006**	**53**	**1533**	**62**	**23**	**2**	**174**	**261**	**1794**
Patients died, n (%)	**0 (0·0)**	**0 (0·0)**	**10 (5·2)**	**34 (3·4)**	**5 (9·4)**	**49 (3·2)**	**24 (38·7)**	**14 (60·9)**	**1 (50·0)**	**106 (60·9)**	**145 (55·6)**	**194 (10·8)**
Cause of death is disease related, n (%)	**0 (0·0)**	**0 (0·0)**	**1 (10·0)**	**8 (23·5)**	**2 (40·0)**	**11 (22·4)**	**16 (66·7)**	**9 (64·3)**	**1 (100)**	**83 (78·3)**	**109 (75·2)**	**120 (61·9)**
Not further defined	0	0	0	3	2	5	10	9	1	56	76	81
Progression to/of systemic mastocytosis with an associated hematologic neoplasm	0	0	0	3	0	3	6	0	0	24	30	33
Anaphylaxis	0	0	1	2	0	3	0	0	0	0	0	3
Systemic mastocytosis related organ damage	0	0	0	0	0	0	0	0	0	3	3	3
Cause of death is tx related, n (%)	**0 (0·0)**	**0 (0·0)**	**0 (0·0)**	**1 (2·9)**	**0 (0·0)**	**1* (2·0)**	**0 (0·0)**	**2 (14·3)**	**0 (0·0)**	**6 (5·7)**	**8 (5·5)**	**9 (4·6)**
Not further defined	0	0	0	0	0	0	0	1	0	1	2	2
Infection during tx	0	0	0	1	0	1	0	1	0	3	4	5
Graft versus host disease	0	0	0	0	0	0	0	0	0	2	2	2
Cause of death is not disease related, n (%)	**0 (0·0)**	**0 (0·0)**	**7 (70·0)**	**17 (50·0)**	**3 (60·0)**	**27 (55·1)**	**2 (8·3)**	**3 (21·4)**	**0 (0·0)**	**11 (10·4)**	**16 (11·0)**	**43 (22·2)**
Not further defined	0	0	1	2	1	4	0	0	0	3	3	7
Cancer	0	0	2	8	1	11	1	0	0	3	4	15
Cardiovascular	0	0	2	7	0	9	0	1	0	1	2	11
Infection	0	0	1	0	1	2	1	2	0	1	4	6
Accident	0	0	1	0	0	1	0	0	0	1	1	2
Respiratory arrest	0	0	0	0	0	0	0	0	0	1	1	1
Liver failure (not related to SM)	0	0	0	0	0	0	0	0	0	1	1	1
Cause of death is unknown, n (%)	**0 (0·0)**	**0 (0·0)**	**2 (20·0)**	**8 (23·5)**	**0 (0·0)**	**10 (20·4)**	**6 (25·0)**	**0 (0·0)**	**0 (0·0)**	**6 (5·7)**	**16 (8·3)**	**22 (11·3)**

*the patients underwent stem cell transplantation after progression from ISM to SM-AHN; Abbreviations: AdvSM, advanced systemic mastocytosis n, number of patients; non-AdvM, non-advanced mastocytosis; tx, stem cell transplantation

Table S9
Evolution patterns and numbers of progression events in patients with mastocytosis

Diagnosis	Progression		Number of patients in subgroups	Median time to progression (years)	Number of patients n
	from	to			
Childhood cutaneous mastocytosis	Maculopapular cutaneous mastocytosis	Indolent systemic mastocytosis	1	1·3	1
Adult cutaneous mastocytosis	Maculopapular cutaneous mastocytosis	Indolent systemic mastocytosis	5	5·2	5
Indolent systemic mastocytosis	Indolent systemic mastocytosis	Smoldering systemic mastocytosis	12	5·5	39
	Indolent systemic mastocytosis	Aggressive systemic mastocytosis	9	3·0	
	Indolent systemic mastocytosis	Mast cell sarcoma like progression fulfilling aggressive systemic mastocytosis criteria	1	7·9	
	Indolent systemic mastocytosis	Systemic mastocytosis with an associated hematologic neoplasm[1]	17	1·9	
Smoldering systemic mastocytosis	Smoldering systemic mastocytosis	Aggressive systemic mastocytosis	4	4·6	5
	Smoldering systemic mastocytosis	Systemic mastocytosis with an associated hematologic neoplasm[2]	1	0·7	
Aggressive systemic mastocytosis	Aggressive systemic mastocytosis	mast cell leukemia	5	1·8	11
	Aggressive systemic mastocytosis	Systemic mastocytosis with an associated hematologic neoplasm [3]	6	1·3	
Systemic mastocytosis with an associated hematologic neoplasm	Indolent systemic mastocytosis with an associated hematologic neoplasm	Aggressive systemic mastocytosis-associated hematologic neoplasm	3	2·3	27
	Aggressive systemic mastocytosis with an associated hematologic neoplasm	Mast cell leukemia associated hematologic neoplasm	7	1·2	
	Aggressive systemic mastocytosis - chronic myelomonocytic leukemia	Mast cell leukemia with an acute myeloid leukemia	1	2·8	
	Systemic mastocytosis-chronic eosinophilic leukemia [4]	Systemic mastocytosis-acute myeloid leukemia	1	1·0	
	Systemic mastocytosis-myeloproliferative neoplasm[5]	Systemic mastocytosis-acute myeloid leukemia	4	2·4	
	Systemic mastocytosis-chronic myelomonocytic leukemia[6]	Systemic mastocytosis-acute myeloid leukemia	4	2·2	
	Systemic mastocytosis-myelodysplastic/myeloproliferative overlap syndrome[7]	Systemic mastocytosis -acute myeloid leukemia	2	1·6	
	Systemic mastocytosis-myelodysplastic syndrome[8]	Systemic mastocytosis -acute myeloid leukemia	5	1·0	
All patients				2·2	88

Disease evolution was examined by analyzing progression-related events defined by a shift from a known disease category in a higher-graded (more advanced) form of mastocytosis or AHN during follow up. Abbreviations: n, number

[1] i.e. aggressive systemic mastocytosis-chronic myelomonocytic leukemia, n=3; indolent systemic mastocytosis-non hodgkins lymphoma, n=3; indolent systemic mastocytosis-acute myeloid leukemia, n=2; indolent systemic mastocytosis-chronic myeloid leukemia, n=2; indolent systemic mastocytosis-myeloproliferative neoplasm, n=2; indolent systemic mastocytosis-chronic myelomonocytic leukemia, n=1; indolent systemic mastocytosis-other, n=1; smoldering systemic mastocytosis-chronic myelomonocytic leukemia, n=1; smoldering systemic mastocytosis-other, n=2

[2] i.e. smoldering systemic mastocytosis-chronic myelomonocytic leukemia

[3] i.e. aggressive systemic mastocytosis-acute myeloid leukemia, n=3; acute myeloid leukemia-chronic myelomonocytic leukemia, n=2; aggressive systemic mastocytosis-myelodysplastic/myeloproliferative overlap syndrome, n=1

[4] i.e. aggressive systemic mastocytosis-chronic eosinophilic leukemia, n=1

[5] i.e. aggressive systemic mastocytosis-myeloproliferative neoplasm, n=3; mast cell leukemia-myeloproliferative neoplasm, n=1

[6] i.e. aggressive systemic mastocytosis-chronic myelomonocytic leukemia, n=2; indolent systemic mastocytosis-chronic myelomonocytic leukemia, n=2

[7] i.e. aggressive systemic mastocytosis-myelodysplastic/myeloproliferative overlap syndrome, n=2

[8] i.e. aggressive systemic mastocytosis-myelodysplastic syndrome, n=2; indolent systemic mastocytosis-myelodysplastic syndrome n=3

Table S10

Probability of progression from non-AdvM to AdvSM

	All pts n	**Pts with progression to AdvSM n**	**Pts with progression to AdvSM %**
Adulthood cutaneous mastocytosis	127	0	0·0
Mastocytosis in the skin	194	1	0·5
Indolent systemic mastocytosis *	1006	29	2·9
Smoldering systemic mastocytosis	53	5	9·4
Non-AdvM	1380	35	2·5

*In 2 ISM patients a progression to AdvSM (mast cell leukemia) was observed after progression to SSM

Abbreviations: AdvSM, advanced systemic mastocytosis; pts, patients; n, number of patients; non-AdvM, advanced mastocytosis

Table S11

Change in diagnosis in mastocytosis in the skin patients

		n	% of all MIS pts			% of pts with final diagnosis according to WHO criteria	Years until diagnosis was made or last contact; median (range)
MIS pts with a change of diagnosis according to WHO criteria	Maculopapular cutaneous mastocytosis	16	8·3			32·7	1·7 (0·1-10·1)
	Indolent systemic mastocytosis	30	15·5			61·2	2·1 (0·12-22·4)
	Smoldering systemic mastocytosis	1	0·5	}	25·3	2·0	8·4
	Aggressive systemic mastocytosis	1	0·5			2·0	4·1
	Systemic mastocytosis with an associated hematologic neoplasm	1	0·5			2·0	2·0
Mastocytosis in the skin pts without change of diagnosis according to WHO criteria		145	74·7			-	2·6 (0·0-15·6)
		194	100				

In 49/194 patients with mastocytosis in the skin (25·3%) a change in diagnosis was reported based on bone marrow biopsy results

Abbreviations: pts, patients; n, number of patients

Table S12

Progression of patients with indolent systemic mastocytosis / smoldering systemic mastocytosis to AdvSM

		Progression to			
AP	No progression to AdvSM	Aggressive systemic mastocytosis	Mast cell sarcoma like Aggressive systemic mastocytosis	Systemic mastocytosis with an associated hematologic neoplasm	All patients
<100	670 (98·1%)	4 (0·6%)	1 (0·1%)	8 (1·2%)	683 (100%)
≥100	159 (93%)	5 (2·9%)	0 (0%)	7 (4·1%)	171 (100%)

The differences in the rate of progressions between patients with AP <100 units/liter and patients with AP ≥100 units/liter was found to be significant as assessed by maximum-likelihood test (p=0·009). Abbreviations: AdvSM, Advanced systemic mastocytosis; AP, alkaline phosphatase; ASM, aggressive systemic mastocytosis; ISM, indolent systemic mastocytosis; MCS, mast cell sarcoma; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SSM, smoldering systemic mastocytosis

Table S13

Correlation between WHO subgroups and the IPSM

Score Category	Childhood cutaneous mastocytosis n (%)	Adulthood cutaneous mastocytosis n (%)	Mastocytosis in the skin n (%)	Indolent systemic mastocytosis n (%)	Aggressive systemic mastocytosis n (%)	Mast cell leukemia n (%)	Mast cell sarcoma n (%)	Systemic mastocytosis with an associated hematologic neoplasm n (%)
low	57 (70)	89 (73)	553 (68)	12 (29)	0	0	0	0
int-1	23 (28)	28 (23)	227 (28)	21 (51)	0	0	0	0
int-2	2 (2)	5 (4)	33 (4)	8 (20)	0	0	0	0
AdvSM	0 (0)	0 (0)	0 (0)	0 (0)	62 (100)	23 (100)	2 (100)	174 (100)
AdvSM-1					11 (20)	3 (15)	0 (0)	21 (13)
AdvSM-2					18 (32)	1 (5)	2 (100)	19 (12)
AdvSM-3					22 (39)	11 (55)	0 (0)	84 (55)
AdvSM-4					5 (9)	5 (25)	0 (0)	29 (20)

Abbreviations: AdvSM, Advanced systemic mastocytosis; IPSM, international prognostic scoring system; int-1, intermediate risk group-1; int-2, intermediate risk group-2; low, low risk group; n, number of patients in the group of mastocytosis patients; WHO, world health organization

Table S14

Comparison of basic demographic data obtained in the ECNM registry with data obtained in two other cohort studies

Study group/center	ECNM	Mayo	Mannheim
number of pts	1794	580	108
median age	46 (0.15-90)	55 (18-88)	64 (27–82)
n (%) males	811 (45·2)	351 (52·0)	57 (53·0)
n (%) non-AdvM	1553 (85·5)	291 (50·2)	41 (38·0)
n (%) AdvSM	261 (14·5)	289 (49.8)	67 (62·0)

AdvSM; advanced systemic mastocytosis; ECNM, European Competence Network on Mastocytosis, pts, patients; non-AdvM, non-advanced mastocytosis

* Pardanani A, Shah S, Mannelli F, et al. Mayo alliance prognostic system for mastocytosis: clinical and hybrid clinical-molecular models. *Blood Adv* 2018; 2:2964–72

** Jawhar M, Schwaab J, Hausmann D, et al. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. *Leukemia* 2016; 30:2342–50

References

1 Valent P, Arock M, Bischoff SC, et al. The European Competence Network on Mastocytosis (ECNM). *Wien Klin Wochenschr* 2004;116: 647-51.

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: 807-14.

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 Pract* 2019;7: 81-87.

4 Valent P, Horny HP, Escribano L et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal *Leuk Res* 2001; 25: 603-25.

5 Horny HP AC, Arber DA, Peterson LA, et al. Mastocytosis. In: Swerdlow SH CE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Arber DA, Hasserjian RP, Le Beau MM, Orazi A, Siebert R. , editor. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2017. p. 62-9.

6 Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood* 2017; 129:1420-7.

7 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: 435-53.

8 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: 35-45

9 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.

10 Therneau TM. Extending the Cox model. Technical Report Nr 58, Mayo Clinic, Rochester, Minnesota, 1996.