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RESEARCH ARTICLE

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Comparison of prognostic scores according to WHO classification in 170 patients with advanced mastocytosis and C-finding treated with midostaurin

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Abstract

Advanced systemic mastocytosis (AdvSM) encompasses heterogeneous mastocytosis subtypes and is associated with poor outcomes. Although midostaurin was the first tyrosine kinase inhibitor to be approved for AdvSM patients, long-lasting responses are limited. The mutation-Adjusted Risk Score (MARS), the International Prognostic Scoring System for mastocytosis (IPSM) and the Global Prognostic Score for Systemic Mastocytosis (GPSM) have been established to characterize the outcomes of patients with overall AdvSM. However, given the outcome's dependency on the AdvSM

For affiliations refer to page 2136

subtype, prognostic characterization within each subtype is critical. We aimed to study the predictive ability using Harrell's concordance index of prognostic scores according to the AdvSM subtype. We conducted a nationwide retrospective study using the French mastocytosis reference center's registry and included all midostaurin-treated patients with C finding. Overall, 170 patients were identified: 46 aggressive SM (ASM), 11 mast cell leukemia (MCL), and 113 SM with associated hematological neoplasm (SM-AHN). All risk scores improved their discriminative value for overall survival (OS) when combined with the AdvSM subtype. The best predictive value was for adjusted MARS (C-index = 0.689), followed by GPSM (C-index = 0.677) and IPSM (C-index = 0.618). In a multivariable analysis, MARS stratification and the AdvSM subtype were both prognostic for OS. Accordingly, five subgroups of patients with AdvSM and a different median OS were identified: 9.9 months for MCL, 24 months for intermediate/high-risk SM-AHN, 33 months for intermediate/high-risk ASM, 58 months for low-risk SM-AHN and was not reached for low-risk ASM ($p < 0.001$). The AdvSM subtype and the MARS are the most predictive of OS and should prompt specific management.

1 | INTRODUCTION

Mastocytosis is a highly heterogeneous spectrum of diseases characterized by the accumulation of atypical mast cells (MCs) in multiple tissues/organs.[1] The international consensus classification (ICC) and the World Health Organization (WHO) in 2022 distinguish between cutaneous mastocytosis, systemic mastocytosis (SM) and MC sarcoma.[2,3] Depending on the disease site, the MC burden, and the end-organ damage (the so-called "C-findings"), SM can be classified into several subtypes: bone marrow mastocytosis (BMM), indolent SM (ISM), smoldering SM (SSM), aggressive systemic mastocytosis (ASM), systemic mastocytosis associated with hematological neoplasm (SM-AHN), and MC leukemia (MCL).[3,4] The last three entities form the advanced SM (AdvSM) group,[1] which is characterized by the frequent presence of C-findings, a greater risk of transformation into acute myeloid leukemia (AML) in SM-AHN, and thus a poor prognosis.[3]

The *KIT* D816V hot spot mutation is one of the mechanistic hallmarks of the disease and is found in most cases (>90%) of SM. Several translational studies have shown that AdvSM, and in particular SM-AHN, has a complex molecular landscape. In the majority of SM-AHN cases, the *KIT* D816V mutation is detected not only in clonal MCs but also in AHN cells—reflecting clonal multilineage involvement.[5–7] Furthermore, more than 60% of patients with AdvSM (particularly those with SM-AHN) carry at least one somatic mutation (e.g., in *ASXL1*, *CBL*, *JAK2*) in addition to *KIT* D816V.[8–11]

Prior to the approval of KIT-D816V-targeted tyrosine kinase inhibitors (TKIs), patients with AdvSM had few treatment options. Historically, cladribine was the first-line treatment of choice in AdvSM; the drug gave overall response and complete remission rates of 30%–50% and 10%–15%, respectively, but had a high toxicity burden.[12–16] Midostaurin was the first TKI that significantly improved the overall outcomes in *KIT* D816V AdvSM.[17–19] Although the reported overall response rates (according to Valent's criteria) was 60% and the major response rate was 45%, the response rates were lower and the response durations were shorter in patients with SM-AHN than in patients with ASM.[19,20] In fact, SM-AHN can progress from both the AHN and SM components. Midostaurin's main limitations are the long time to first response (3–6 months) and the low proportion of complete responses (CRs).[20] More recently, avapritinib (a highly selective and potent KIT D816V inhibitor) showed high rates and long-lasting responses in all AdvSM subtypes.[21–24] Both midostaurin and avapritinib have been approved by the US Food and Drug Administration and the European Medicines Agency for the indication of AdvSM and now part of AdvSM armamentarium.[23,24]

Several prognostic scores (the International Prognostic Scoring System for Mastocytosis [IPSM], Global Prognostic Score for Systemic Mastocytosis [GPSM], and the Mutation-Adjusted Risk Score [MARS]) have been developed to identify high-risk patients with AdvSM.[25–29] IPSM prognostic variables are: an age ≥ 60 years, a basal serum tryptase (BST) ≥ 125 ng/mL, a leukocyte count of ≥16 G/L, a hemoglobin level ≤ 11 g/dL, a platelet count ≤ 100 G/L and specific mastocytosis skin involvement. The GPSM for overall survival (OS) includes three parameters (hemoglobin ≤ 11.0 g/dL, serum alkaline phosphatase ≥ 140 IU/L, and at least one mutation in *SRSF2*, *ASXL1*, *RUNX1*, or *DNMT3A*). The MARS is a five-variable, WHO-independent prognostic score that defines three AdvSM risk groups based on age (≥60 years), anemia status (hemoglobin level ≤ 10 g/dL), thrombocytopenia status (platelet count ≤ 100 G/L), and the presence of one or more high-risk gene mutations (in *SRSF2*, *ASXL1*, and/or *RUNX1* [S/A/R]).[10] All these scores are predictive of OS. In addition, MARS has proved to accurately predict both SM progression and the occurrence of secondary AML. However, the MARS high-risk group included a high proportion of patients with SM-AHN[26]; this introduces a bias as these patients

are prone to AML transformation. Thus, the specific risk of AML transformation among patients with SM-AHN should be specifically addressed in patients treated with a TKI.

The so-called C-findings are indicators of organ damage associated with mastocytosis. The C-finding criteria are classified by the WHO and ICC, and the presence of at least one of these criteria results in the diagnosis of ASM. The C-findings include cytopenia, hepatopathy with ascites and elevated liver enzymes or cirrhotic liver, hypersplenism, malabsorption with hypoalbuminemia, and large-sized osteolysis (≥2 cm) with pathologic fracture. Not all AdvSM patients have C-finding, and identifying these criteria is critical for several reasons. Indeed, in SM-AHN, the subtype of mastocytosis component must be specified (e.g., ASM-AHN, ISM-AHN, etc.) as survival and management differ significantly depending on the aggressiveness of the SM component. Similarly, patients with MCL but without C-finding (referred to as chronic MCL in the WHO 2022 classification) have significantly different survival compared with patients with acute MCL (characterized by the presence of one or more C-findings). To our knowledge, no prognostic score specifically includes patients with AdvSM and the mandatory presence of at least one C-finding.

The identification of high-risk patients with C-finding(s) within each AdvSM subtype is critical for optimizing follow-up and treatment plans. We therefore conducted a comprehensive nationwide study to evaluate the prognostic value of the IPSM, GPSM, and MARS (including OS and time to treatment failure [TTF]) for each AdvSM subtype in midostaurin-treated patients in France.

2 | METHODS

2.1 | Study population

The study data were collected by medical staff at the French National Referral Center for Mast Cell Disorders (*Centre de Référence Maladies Rares des Mastocytoses* [CEREMAST, Paris, France]), using an electronic case report form. All the patients registered at the CEREMAST were participating in a retrospective, cross-sectional study sponsored by the French Association for Research Initiatives on Mast Cells and Mastocytoses (*Association Française pour les Initiatives de Recherche sur le Mastocyte et les Mastocytoses* [AFIRMM]). The study was approved by the local investigational review board (*CPP Groupe Hospitalier Pitié-Salpêtrière*, Paris, France; reference: 93–00) and was conducted in compliance with the principles of the Declaration of Helsinki. All patients with AdvSM included in the study met the WHO's 2016 or 2022 diagnostic criteria for mastocytosis. Diagnostics were carried out locally in accordance with current recommendations.

The main inclusion criteria were, (i) a diagnosis of AdvSM, (ii) the presence of one or more C-findings according to WHO classification, (iii) treatment with midostaurin for AdvSM and, (iv) the availability of at least 12 months of follow-up data for surviving patients. The main exclusion criteria were (1) chronic MCL (i.e., no C-finding), (2) SM-AHN with non-advanced SM component (i.e., no C-finding), (3) treatment with midostaurin for SM-AML, and (4) MC sarcoma.

2.2 | Outcomes and prognostic factors

We sought to describe the clinical and laboratory characteristics of midostaurin-treated AdvSM patients with C-finding. The outcome variables included OS and TTF after the initiation of midostaurin. The putative prognostic factors were the MARS, the AdvSM diagnosis according to the WHO classification and the following baseline characteristics (selected on the basis of their clinical relevance): sex, a BST ≥ 200 ng/mL, the white blood cell count, and the serum alkaline phosphatase level. The methodology used for MARS computation and next generation sequencing (NGS) assessment is described in Data S2. Due to the retrospective nature of the study, the response to midostaurin (defined according to Valent criteria) was assessed at physician discretion based on clinical and biological parameters. Treatment response was only considered for SM component. Treatment failure was defined as treatment intolerance, absence or loss of response to midostaurin at physician's discretion. AHN progression was defined in the manuscript by associated myeloid disease progression according to treating physician.

2.3 | Statistical methods

Data were quoted as the median (interquartile range [IQR]) for continuous variables and as the frequency (percentage) for categorical variables, overall and by group. Groups were compared using a non-parametric Kruskal-Wallis rank sum test for continuous variables (given the relatively small size of the subgroups) and in a chi-squared or Fisher's exact test (as appropriate) for categorical variables. The threshold for statistical significance was set to $p < 0.05$.

The OS and TTF for each group were analyzed using the Kaplan–Meier method, with the number of patients at risk, the number of events, and the median (95% confidence interval [CI]) survival time. Stratified log-rank tests were used if applicable for pairwise inter-group comparisons of OS and TTF.

We used Cox proportional-hazards models to investigate prognostic factors and the strength of association with patient outcomes (i.e., OS and TTF). We first selected explanatory variables with $p < 0.2$ in a univariate analysis. Given the risk of a type I error, we also reported the Bonferroni correction as a q-value. Next, we included the variables as prognostic factors in multivariable models. Both univariate and multivariable estimates of the hazard ratio (HR) (95% CI) were reported. The multivariable models' assumptions were checked by plotting the Schoenfeld residuals.

To check the consistency of the risk score, our sensitivity analyses included univariable and multivariable Cox proportional hazard models with the individual MARS items. We also stratified our main model by ASM and SM-AHN subgroups, in order to investigate the robustness of the MARS' prognosis value for patients with AdvSM.

We used Cox model adjusted or unadjusted on the WHO classification of mastocytosis to compare the discriminative values of the risk scores IPSM, GPSM, and MARS with Harrell's concordance index.[30]

We did not impute missing data; all analyses were performed on complete cases from the full analysis set. All statistical analyses were performed using R software (version 4.3.0).[31]

3 | RESULTS

3.1 | Characteristics of the study population

We identified 170 midostaurin-treated patients with C finding(s) between May 2009 and March 2023: 46 with ASM, 11 with MCL, and 113 with SM-AHN (Table 1). The sex ratio was significantly different between subtypes, with male/female ratios of 61%/39%, 27%/73%, and 74%/26% for ASM, MCL, and SM-AHN, respectively ($p = 0.004$). The median [IQR] age for the whole cohort was 69 years [61;75]; there were no significant differences in age between the ASM, SM-AHN and MCL groups (median [IQR]: 67 [55;72], 68 [63;77], and 70 [64;76], respectively, $p = 0.07$). Chronic myelomonocytic leukemia (CMML) was the most frequent neoplasm among the patients with SM-AHN (52%), followed by myelodysplastic syndromes (MDSs, 25%), myeloproliferative neoplasms (MPNs, 11%), and unclassified MDS/MPN (12%, Table 1). With regard to clinical C-findings, i.e., portal hypertension/ascites, malabsorption and osteolytic lesions, theses complications were found in 35%, 67%, and 22% of evaluable AdvSM patients, respectively, with no significant differences between AdvSM subgroups (Table 1).

3.2 | Laboratory variables

The median hemoglobin level was similar between disease groups (10.2, 10.1, and 9.9 g/dL for ASM, MCL and SM-AHN, respectively, $p = 0.3$; Table 1). In contrast, the median platelet count was higher in ASM (148 vs. 120 G/L for both MCL and SM-AHN, respectively, $p = 0.045$). A BST ≥ 200 ng/mL was more frequent in MCL (80% of the patients) than in ASM (45%) and SM-AHN (37%, $p = 0.006$).

The *KIT* D816V point mutation was found in 92% of patients, with no significant difference between the subgroups. Cytogenetic abnormalities were observed in 14 (18%) patients with SM-AHN. S/A/R molecular status was available in 126/170 patients. High-risk mutations (at least 1 S/A/R mutation) were predominantly found in the SM-AHN group (62%), relative to ASM (33%) and MCL (25%) ($p = 0.023$). Accordingly, the MARS risk group distribution varied between subgroups with the proportion of patients with an intermediate (int)/high-risk patient being higher in SM-AHN (81%) compared with MCL (60%) and ASM (53%) ($p = 0.026$). Besides *KIT* and S/A/R mutations, the most frequent additional mutations observed in patients with available NGS analysis were *TET2* (51%), *JAK2* (13%), *U2AF1* (9%), *CBL* (9%), *DNMT3A* (8%), and *IDH2* (8%) (Figure S1A). No additional mutation was found in 35.5% and 7.5% of patients with ASM and SM-AHN, respectively.

Among the patients evaluable for therapeutic response, 72/158 (46%) were primary refractory and 42/158 (27%) including 11 ASM, 2 MCL, and 29 SM-AHN patients, relapsed during the follow-up (Table 1). The response to midostaurin differed significantly as a function of the AdvSM subtype (73% in ASM vs. 27% in MCL, and 50% in SM-AHN, $p = 0.006$). Overall, 128/158 (81%) evaluable patients have discontinued midostaurin. The causes for midostaurin withdrawal were relapse in 42/128 (33%) patients, refractory disease in 53/128 (41%) patients, intolerance in 27/128 (21%) patients, allogeneic stem cells transplantation (ASCT) in 4/128 (3%) patients, and not available in 2/128 (2%) patients.

After a median follow-up time of 19 months after midostaurin initiation, 86 patients (51%) had died; the proportion of deaths was higher for MCL (55%) and SM-AHN (57%) than for ASM (35%, $p = 0.042$). Accordingly, the median OS time was 69, 9.9, and 32 months for ASM, MCL, and SM-AHN, respectively ($p = 0.001$), and the TTF was 30, 3.6, and 9 months, respectively ($p < 0.001$; Figure 1). The same outcomes profiles were observed for the median OS time since diagnosis (72 vs. 9.9 vs. 37 months, in ASM, MCL, and SM-AHN, respectively, $p = 0.004$, Figure S1B). Among SM-AHN, 56% (63/113) died during follow-up, of which 84% (53/63) was related to disease progression: evolution to AML in 21/63 patients (33%), AHN component progression in 8/63 patients (13%), and SM component progression in 24/63 patients (38%).

During the follow-up period, 21 patients out of 170 received avapritinib after midostaurin exposure ($n = 5$ with ASM, $n = 15$ with SM-AHN, and $n = 1$ with MCL). Two patients received avapritinib in post-ASCT settings (one patient for relapse and one patient for maintenance therapy). Censoring at the time of avapritinib onset did not impact significantly observed outcome (Figure S1C). In addition, 19 patients underwent ASCT during follow-up (including 2 ASM and 17 SM-AHN patients). In this specific subset of patients, median OS was 88 months but did not reach statistical significance compared with non-transplanted patients (47 months, $p = 0.15$) (Figure S2A). In patients evaluable for response ($n = 18$), 55% (10/18) were in response prior to transplantation. Censoring at the time of transplant did not influence significantly OS while considering WHO and WHO/MARS subclassifications (Figure S2B,C).

3.3 | Prognostic impact of MARS, IPSM, and GPSM adjusted to WHO classification

We aimed to compare the predictive value for OS of the MARS, IPSM, and GPSM scores, with or without adjustments for WHO classification (Table S1). For OS, the C-index was the greatest for the MARS than for both the GPSM and IPSM (C-index = 0.647 vs. 0.630 for GPSM and 0.564 for IPSM) indicating that the proportion of concordant peers (between observed survival time and predicted risk score) was more accurate for MARS. In addition, all prognostic scores adjusted for WHO classification had higher C-indexes compared with prognostic scores alone. Finally, MARS combined with WHO subtype had the highest C-index (C-index = 0.689 vs. 0.677 and 0.618 for adjusted GPSM and IPSM, respectively). OS and TTF according to the IPSM and GPSM risk groups are reported in Figures S3 and S4.

TABLE 1 Characteristics of the patients according to WHO classification (ASM, MCL, or SM-AHN).

Variable	Overall, $N = 170$[a]	WHO classification			p-value
		ASM, $N = 46$[a]	MCL, $N = 11$[a]	SM-AHN, $N = 113$[a]	
Age (years)	69 [61; 75]	67 [55; 72]	68 [63; 77]	70 [64; 76]	**0.070**[b]
Male sex	115 (68%)	28 (61%)	3 (27%)	84 (74%)	**0.004**[b]
Prior treatment with cladribine	31 (21%)	12 (30%)	3 (30%)	16 (16%)	0.14[b]
AHN subtypes					
CMML	59 (52%)	–	–	59 (52%)	
MDS	28 (25%)	–	–	28 (25%)	
MPN	12 (11%)	–	–	12 (11%)	
Unclassified MDS/MPN	14 (12%)	–	–	14 (12%)	
Clinical characteristics					
Hepatomegaly	110 (73%)	31 (79%)	6 (60%)	73 (72%)	0.4[c]
Splenomegaly	128 (84%)	34 (89%)	6 (60%)	88 (85%)	0.10[c]
Cutaneous mastocytosis	72 (51%)	25 (63%)	3 (33%)	44 (48%)	0.2[c]
Adenopathy	90 (67%)	24 (71%)	5 (71%)	61 (66%)	0.9[c]
Portal hypertension/ascites	54 (35%)	10 (25%)	4 (40%)	40 (38%)	0.3[c]
Malabsorption, weight loss	99 (67%)	24 (63%)	5 (50%)	70 (70%)	0.4[c]
Osteolytic lesions	32 (22%)	9 (19%)	2 (18%)	21 (18%)	0.9[c]
Response to midostaurin in evaluable patients	86 (54%)	32 (73%)	3 (27%)	51 (50%)	**0.006**[c]
Cause of midostaurin discontinuation (% of evaluable patients)					0.5[c]
Allogeneic stem cell transplantation	4 (3%)	0 (0%)	0 (0%)	4 (4%)	
Relapse	42 (27%)	11 (25%)	2 (18%)	29 (28%)	
Refractory	53 (34%)	7 (16%)	6 (55%)	40 (39%)	
Intolerance	27 (17%)	8 (18%)	2 (18%)	17 (17%)	
Not available	2 (1%)	1 (2%)	0 (0%)	1 (1%)	
Biological characteristics					
Hemoglobin (g/dL)	10.00 [9.00; 11.70]	10.20 [9.30; 12.40]	10.10 [8.55; 11.20]	9.90 [8.80; 11.50]	0.3[b]
Leukocyte count ($\times 10^9$/L)	9 [5; 14]	7 [5; 11]	8 [6; 13]	10 [5; 16]	0.2[b]
Neutrophil count ($\times 10^9$/L)	4.4 [2.1; 7.2]	4.9 [3.3; 7.1]	4.4 [3.5; 5.7]	4.1 [1.7; 7.9]	>0.9[b]
Eosinophil count ($\times 10^9$/L)	0.60 [0.11; 1.82]	0.6 [0.23; 1.23]	0 [0.0; 0.01]	0.60 [0.14; 2.60]	**0.036**[b]
Monocyte count ($\times 10^9$/L)	1.08 [0.50; 1.93]	0.75 [0.42; 1.46]	0.50 [0.19; 0.71]	1.32 [0.62; 2.18]	**0.010**[b]
Basophil count ($\times 10^9$/L)	0 [0.00; 0.03]	0 [0.00; 0.03]	0 [0.00; 0.02]	0 [0.00; 0.03]	>0.9[b]
Lymphocyte count ($\times 10^9$/L)	1.30 [0.81; 2.18]	1.67 [0.68; 2.46]	1.48 [0.86; 2.13]	1.26 [0.90; 2.05]	0.7[b]
Platelet count ($\times 10^9$/L)	124 [75; 177]	148 [85; 251]	120 [108; 163]	120 [72; 160]	**0.045**[b]
Albumin (g/L)	35 [31; 40]	35 [32; 39]	31 [30; 34]	36 [31; 40]	0.5[b]
Tryptase ≥ 200 ng/mL	74 (45%)	26 (57%)	8 (80%)	40 (37%)	**0.006**[c]
Alkaline phosphatase > ULN	65 (66%)	15 (63%)	7 (78%)	43 (65%)	0.8[c]
Molecular characteristics					
KIT mutation					0.093[c]
D816V	152 (92%)	43 (96%)	7 (70%)	102 (93%)	
D816 (other)	5 (3%)	1 (2%)	1 (10%)	3 (3%)	
Wild type	8 (5%)	1 (2%)	2 (20%)	5 (5%)	
Abnormal karyotype	15 (16%)	1 (7%)	0 (0%)	14 (18%)	0.5[c]

(Continues)

TABLE 1 (Continued)

Variable	Overall, $N = 170$[a]	WHO classification			p-value
		ASM, $N = 46$[a]	MCL, $N = 11$[a]	SM-AHN, $N = 113$[a]	
SRSF2/ASXL1/RUNX1 mutations					**0.023**[c]
0 mutations	57 (45%)	20 (67%)	3 (75%)	34 (37%)	
1 mutation	39 (31%)	7 (23%)	1 (25%)	31 (34%)	
≥*2* mutations	30 (24%)	3 (10%)	0 (0%)	27 (29%)	
MARS risk groups					
Low risk	37 (27%)	16 (47%)	2 (40%)	19 (19%)	**0.026**[c]
Intermediate risk	28 (20%)	5 (15%)	1 (20%)	22 (22%)	
High risk	72 (53%)	13 (38%)	2 (40%)	57 (58%)	
Acute myeloid leukemia transformation	26 (15%)	1 (2%)	0 (0%)	25 (22%)	**0.001**[c]
Allogeneic stem cell transplantation	19 (12%)	2 (4%)	0 (0%)	17 (16%)	0.068[c]
Duration of follow-up since the diagnosis of AdvSM (months)	26 [9; 51]	39 [19; 65]	7 [5; 15]	25 [9; 48]	**0.002**[b]
Duration of follow-up since the initiation of midostaurin (months)	19 [7; 42]	31 [15; 61]	7 [4; 15]	17 [6; 38]	**0.002**[b]
Deaths	86 (51%)	16 (35%)	6 (55%)	64 (57%)	**0.042**[d]

Abbreviations: AdvSM, Advanced masstocytosis; AHN, associated hematological neoplasm; ASM, aggressive mastocytosis; CMML, chonic myelomonocytic leukemia; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; SM-AHN, Systemic mastocytosis with associated hematological; ULN, upper limits of normal; WHO, World Health Organization.
[a]Median [25%; 75%]; *n* (%).
[b]Kruskal-Wallis rank sum test.
[c]Fisher's exact test.
[d]Pearson's Chi-squared test.

3.4 | The prognostic impact of MARS stratification and the AdvSM subtype

In a multivariable analysis, we sought to assess the influence of each MARS criterion and the AdvSM subtypes on OS. We found that the following variables were associated with OS: age > 60 years (HR = 3.01, $p < 0.001$) and AdvSM subtype (HR = 3.21 for SM-AHN, $p = 0.002$, Table S2). Accordingly, MARS stratification had a significant impact on OS (HR = 3.39 for an intermediate risk, and 3.23 for a high risk, $p = 0.001$, Table 2), as did the subtype of AdvSM (HR = 2.18 for SM-AHN, $p = 0.021$). When assessed specifically in each subtype of AdvSM, the MARS had prognostic value among ASM patients (HR = 13.8 and 5.88 for intermediate- and high-risk groups, respectively, $p = 0.037$, Table S3). There was a non-significant trend for patients with SM-AHN (HR = 2.43 and 2.93 for the intermediate- and high-risk groups, respectively, $p = 0.063$, Table S4).

Overall, the prognostic value of MARS stratification on the median OS time was significant when comparing low-risk versus intermediate/high-risk but not when comparing intermediate and high-risk subgroups ($p < 0.001$, Figure S5). The same profile was observed when investigating MARS stratification in patients with ASM: not reached (NR-NR) for a low-risk, 39 (19-NR) for an intermediate-risk, and 69 (24-NR) months for a high-risk, ($p = 0.01$, Figure S6A) and in patients with SM-AHN (58 [34-NR] for a low risk, 24 [11-NR] for an intermediate risk and 24 [16–38] months for a high risk; $p = 0.035$, Figure S6B). Thus, as outcomes were similar in the intermediate and high-risk groups, we pooled them for both ASM and SM-AHN (Tables S5 and S6). After this stratification, five AdvSM subgroups were identified for both OS and TTF (Figure 2). Indeed, the OS was 9.9 months for MCL, 24 months for int/high-risk SM-AHN, 33 months for int/high-risk ASM, 58 months for low-risk SM-AHN, and NR for low-risk ASM ($p < 0.001$). The subgroup was a prognostic factor for TTF (3.6 months for MCL, 8.4 months for intermediate/high-risk SM-AHN, 6.7 months for intermediate/high-risk ASM, 26 months for low-risk SM-AHN, and 60 months for low-risk ASM, $p < 0.001$). Similarly, censoring at the time of avapritinib onset did not impact significantly OS in WHO/MARS subclassification (Figure S7).

3.5 | Outcomes for the AHN component

We next sought to identify factors associated with AHN progression in midostaurin-treated patients with SM-AHN. In all, 27 (31%)

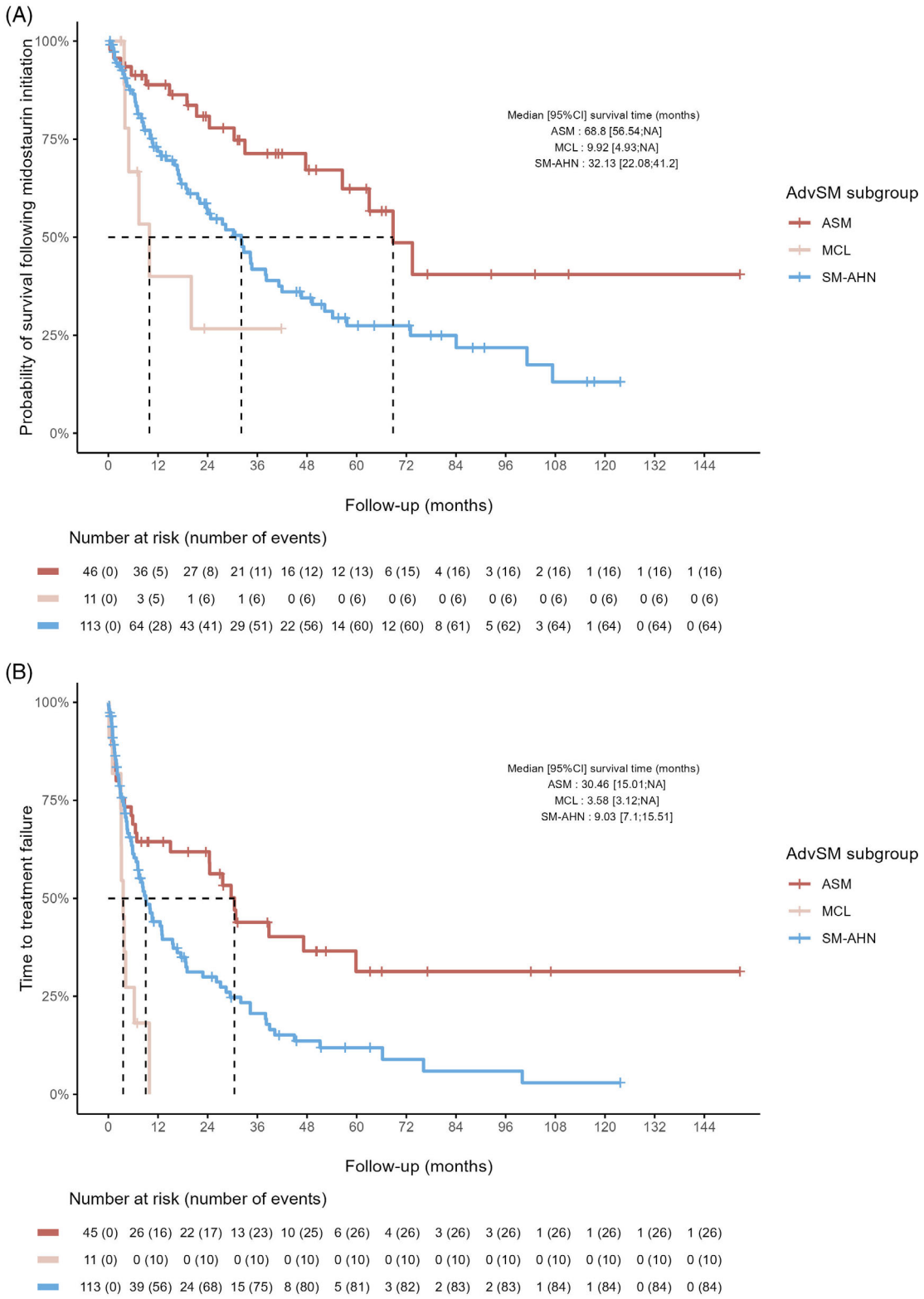

FIGURE 1 Overall survival (A) and time to treatment failure (B) according to AdvSM subtype since the initiation of midostaurin. ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis associated with hematological neoplasm. [Color figure can be viewed at wileyonlinelibrary.com]

patients experienced AHN progression; with progression being associated with a higher mortality rate (89% vs. 58% for non-progressive patients, $p = 0.004$, Table S7). The groups of patients with and without AHN progression differed significantly with regard to several variables: sex, the polynuclear neutrophil count, and the tryptase level. In contrast, the AHN subtype, the MARS category and the response

TABLE 2 Univariate and multivariable analysis of OS after midostaurin initiation according to sex, MARS groups, tryptase level, leukocyte count, alkaline phosphatase and WHO diagnosis.

	Univariable analysis					Multivariable analysis		
Characteristic	**N**	**HR**	**95% CI**	***p*-value**	***q*-value**[a]	**HR**	**95% CI**	***p*-value**
Sex	159			**0.002**	0.012			0.082
Female		—	—			—	—	
Male		2.28	1.30, 4.00			1.73	0.91, 3.31	
Tryptase ≥200 ng/mL	154			0.5	>0.9			
No		—	—					
Yes		0.86	0.54, 1.35					
Leukocyte count ($\times 10^9$/L)	149	1.01	0.98, 1.04	0.5	>0.9			
Alkaline phosphatase > ULN	90			0.3	>0.9			
No		—	—					
Yes		1.34	0.75, 2.39					
MARS category	132			**<0.001**	<0.001			**0.001**
Low risk		—	—			—	—	
Intermediate risk		3.75	1.65, 8.50			3.39	1.48, 7.75	
High-risk		3.91	1.88, 8.14			3.23	1.54, 6.78	
WHO classification	159			**0.001**	0.009			**0.021**
ASM		—	—			—	—	
SM-AHN		2.29	1.32, 3.97			2.18	1.06, 4.49	

ASM, aggressive mastocytosis; CI, confidence interval; HR, hazard ratio; SM-AHN, Systemic mastocytosis with associated hematological; ULN, upper limits of normal; WHO, World Health Organization; HR, hazard ratio; CI, confidence interval.
[a]Bonferroni correction for multiple testing.

to midostaurin were not significantly associated with AHN progression ($p = 0.8$, 0.9 and 0.11, respectively).

Lastly, we assessed AML transformation in patients with SM-AHN throughout the follow-up period (Table S8). AML transformation was observed in 25 (22%) patients and was associated with a high mortality rate (88% vs. 48% in patients without AML transformation, $p < 0.001$). Three factors, at the time of midostaurin initiation, were associated with AML transformation: polynuclear neutrophil count (2.8 vs. 4.6 G/L in the absence of AML transformation, $p = 0.032$), abnormal cytogenetic findings (40% vs. 11%, respectively, $p = 0.007$) and portal hypertension or ascites (68% vs. 29%, respectively, $p < 0.001$). Detailed cytogenetics abnormalities observed in SM-AHN cohort are provided in Table S9.

4 | DISCUSSION

Treatment with *KIT* D816V targeted TKIs has dramatically changed the prognosis for patients with AdvSM.[17,18,23,24] Given that two TKIs have now been approved to treat such patients, the optimization of treatment and follow-up of midostaurin-treated patients requires reliable data on prognosis, including duration of response and OS. In clinical practice, the WHO classification for SM is widely used for prognostic purposes because of the difference in survival between ASM, SM-AHN, and MCL.[2] For example, Lübke et al. found a median OS time from start of midostaurin of 4.2, 2.7, and 1.6 years for ASM, SM-AHN, and MCL respectively, which are in line with our results.[32] However, the AdvSM classification had limited overall prognostic value due to the heterogeneity of outcomes within each AdvSM subtype; hence, a specific score was needed in a homogenously treated cohort.

Three prognostic scores have been developed specifically for AdvSM (IPSM, GPSM, and MARS). These scores include clinical, laboratory, and molecular variables (for GPSM and MARS only). However, only the prognostic value of MARS has been confirmed specifically in midostaurin-treated patients with AdvSM.[32] To the best of our knowledge, the specific outcome by MARS risk group and by AdvSM subtype has not previously been investigated in a homogenous cohort of midostaurin-treated patients. In addition, previous studies included patients with MCL or SM-AHN regardless of the presence of C-findings, or did not specify whether patients were necessarily carriers of C-finding(s). This study is the first to specifically address the predictive value of prognostic scores based on AdvSM subtype in midostaurin-treated patients with at least one C-finding.

Herein, we confirmed the prognostic value of the MARS and GPSM scores, although the latter appears slightly less effective. The IPSM score, which has the lowest C-index, benefits from using only simple clinical and laboratory parameters, making it more accessible in hospitals and countries where molecular testing is not readily available. Regarding the validity of MARS for each AdvSM subtype, we

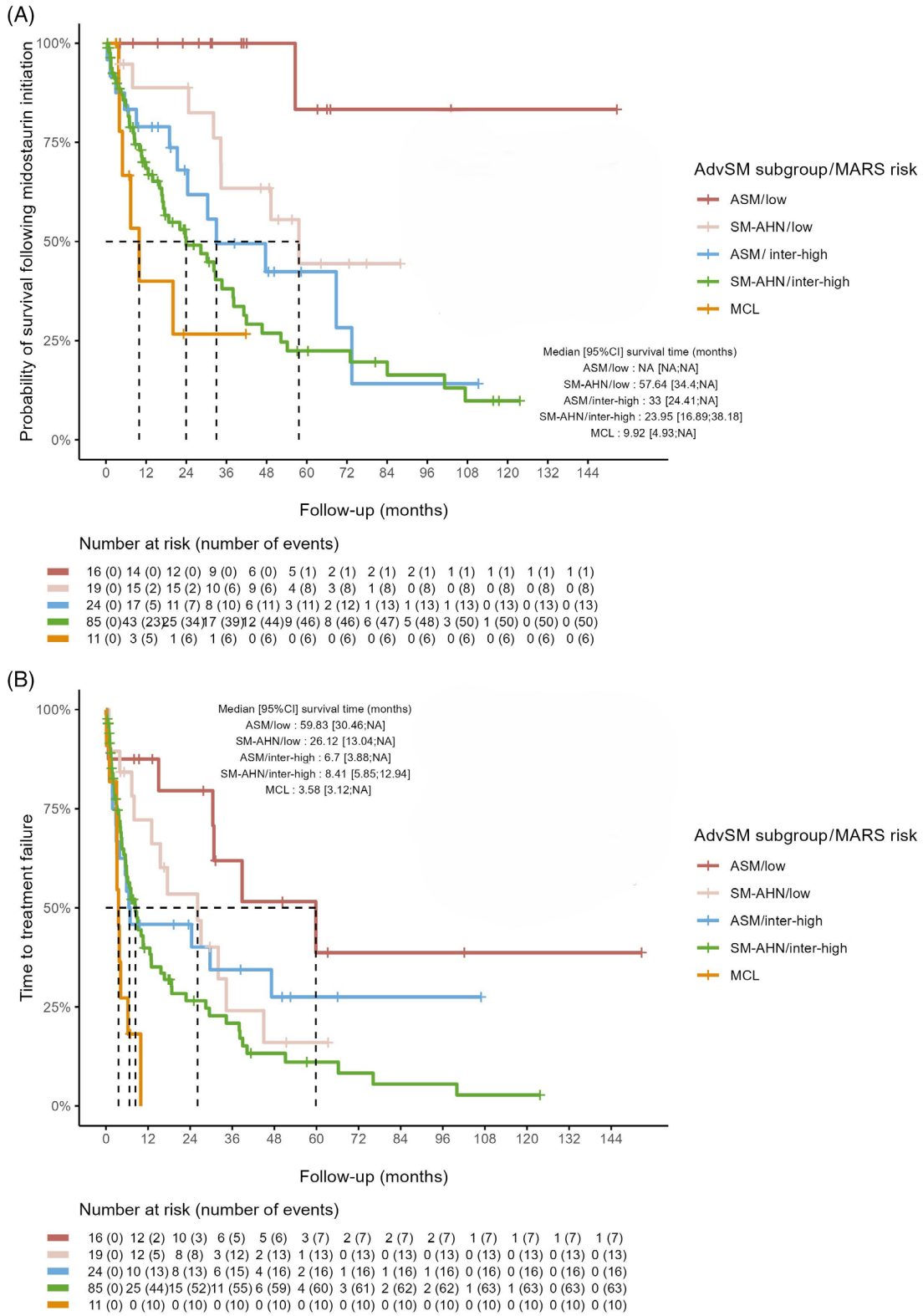

FIGURE 2 Overall survival (A) and time to treatment failure (B) according to AdvSM subtype and MARS groups since the initiation of midostaurin. ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; SM-AHN, systemic mastocytosis associated with hematological neoplasm; MARS, mutation-adjusted risk score. [Color figure can be viewed at wileyonlinelibrary.com]

have confirmed its prognostic value for both ASM and SM-AHN subtypes with respect to OS and TTF. However, we did not find a significant difference between intermediate and high-risk subpopulations. Overall, we identified five subgroups of patients with different outcomes and highlighted the heterogeneity of AdvSM as a disease entity.

First, midostaurin-treated patients with acute MCL had a particularly dismal prognosis; in our study, the median TTF was 3.6 months. Although some MCL patients may respond, most of them experienced early treatment failure and no durable responses were observed. Midostaurin does not appear to be an appropriate treatment for MCL, either as a bridge to ASCT or as long-term treatment in ASCT-ineligible patients.

Secondly, patients with SM-AHN had a lower response rate to midostaurin than patients with ASM, as also observed in the midostaurin phase II trial.[23] In fact, the studies' outcomes were similar: the median progression-free survival time in the phase II study was 11.0 months, and the median TTF in our study was 9.0 months. However, by distinguishing between MARS risk groups, we observed two types of outcomes among patients with SM-AHN: a low-risk group of patients with a longer response (median TTF: 26.0 months) and an intermediate/high-risk group with a shorter response (median TTF: 8.4 months). As the response rate between 3.0 and 6.0 months after midostaurin therapy did not appear to be significantly different in the phase II trial, we believe that SM-AHN patients in the int/high-risk group should be evaluated early at 3.0 months after the initiation of first-line treatment midostaurin, so that other therapeutic options can be considered if necessary, including AHN therapy and/or other TKI followed by ASCT.[17,19,22,23]

Finally, as shown by the results of prospective and observational studies, midostaurin-treated patients with ASM had the best outcomes. However, the int/high-risk subgroup benefited much less from midostaurin than the low-risk ASM subgroup did, with a median TTF of 6.7 months and 60.0 months, respectively. As in patients with SM-AHN, almost half of all the int/high-risk ASM patients progressed or failed to tolerate their treatment in the first 6.0 months; hence, these patients should be closely monitored, and those with a non-optimal early response should be considered for other therapeutic interventions.

Recently, DeAngelo et al. reported on the long-term efficacy of avapritinib in the EXPLORER study of patients with AdvSM. With a median time to first response of 2.3 months, the median duration of response was not reached in any of the WHO SM subgroups and was not significantly influenced by the presence of S/A/R mutations.[24] The prognostic value of the five risk-groups reported here remains to be investigated in patients treated with new TKIs such as avapritinib.

The European Society for Blood and Marrow Transplantation (EBMT) have recently issued recommendations for the management of patients with AdvSM.[33] These recommendations are crucial as they facilitate uniform patient care for AdvSM, and it encompassed treatment lines and indications for ASCT according to AdvSM subtypes. However, it did not specify the use of a particular prognostic score for each subtype and its corresponding management. Our study data could assist physicians in decision making by demonstrating that under midostaurin, the survival of patients with ASM or SM-AHN is significantly impacted by the MARS score. This suggests that in addition to the EBMT decision-making algorithm, adaptation of monitoring and treatment type based on MARS for patients with ASM and SM-AHN could be implemented.

AHN progression (including AML transformation) is a major determinant of survival in patients with SM-AHN.[13,34] In our study, we observed AML transformation at some point in 19.8% of the SM-AHN subgroup. The response to midostaurin did not reduce the risk of AHN progression, and the MARS was not predictive of AHN progression or leukemic transformation in the patients with SM-AHN. In the original publication, MARS was predictive of AML transformation when applied to all AdvSM patients.[26] However, due to a higher prevalence of int/high-risk in SM-AHN patients (which are at higher risk of AML transformation), a diagnostic bias may explain the prognostic value of MARS. We observed that liver C-findings (ascites/portal hypertension) and the presence of an abnormal karyotype prior to midostaurin treatment were significantly associated with the development of AML during follow-up. It remains to be determined whether these prognostic factors for AML transformation remain prognostic in patients treated with avapritinib. Indeed, the identification of patients at risk of transformation may enable early ASCT to be considered. In our study, 19 patients underwent ASCT. The median OS time for this group was not significantly different compared with non-transplanted patients (88.0 vs. 47.0 months, $p = 0.15$, Figure S2). This finding may be related to the limited power of our study regarding the specific issue of post-ASCT survival in this population. In addition, as a recent study has shown, the absence of AdvSM response prior to ASCT is associated with poor prognosis and could explain the outcomes observed in our cohort.[35–37]

In conclusion, the subtypes of AdvSM together with the MARS are predictive of both OS and TTF. Based on these variables, five subgroups of AdvSM patients with distinct outcomes have been identified, highlighting the need for specific management. Further studies are critically needed to determine if this prognostic characterization remains relevant in AdvSM patients treated with other TKIs.

AUTHOR CONTRIBUTIONS

MH and JR performed research, analyzed data and wrote the paper. CG, PG, CBL, SB, YC, JA, FB, PD, RL, OT, LT, DL, LB, CC, GD, TB, CG, LP, LF, CM, HB DB, CGM, MG, ELM, AN, DR, RJ, TJM, JB, PV, LL, LMC, MT, OK, RMJ, FP, FC, FR, QC, PZ, MPG, EWH, JFV, CL, CH, ID, SDS, JMTD, MW, AS, MA, CB, and OL performed research, reviewed, and edited the manuscript. JL performed the statistical analysis. OH and JR designed research and gave final approval.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author (JR) upon reasonable request.

PATIENT CONSENT STATEMENT

Complete written informed consent was obtained from the patient for the publication of this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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