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Characteristics and outcomes associated with CD2 and CD25 expression on bone marrow mast cells in patients with systemic mastocytosis

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Running heads

CD2/CD25 expression on mast cells in mastocytosis

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Data availability statement:

The data that support the findings of this study are available from the corresponding author [LL] upon reasonable request.

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Main text

Mastocytosis corresponds to a heterogeneous group of hematological disorders characterized by the accumulation of neoplastic mast cells (MCs) in one or more organs. The World Health Organization (WHO) and the International Consensus Classification (ICC) described several variants of mastocytosis, including cutaneous mastocytosis (CM), MC sarcoma (MCS), and systemic mastocytosis (SM)[12]. SM has been subsequently divided into non-advanced SM (including bone marrow (BM) mastocytosis, indolent SM (ISM), and smoldering SM) and advanced SM (Adv-SM). The Adv-SM subgroup includes aggressive SM (ASM), MC leukemia (MCL) and SM with associated hematological neoplasm (SM-AHN).

In the majority of cases, adults with mastocytosis harbor a D816V mutation in the *KIT* tyrosine kinase domain (TKD)[3]. Other *KIT* mutations have been described in the juxtamembrane domain, and some patients have wild-type (WT) *KIT*[4]. Furthermore, an abnormal phenotype for CD2, CD25 or CD30 expression on BMMCs (as assessed with immunohistochemistry or flow cytometry) is considered to be pathognomonic of atypical MC[56]. The WHO and ICC classifications differentiate several morphological patterns, including well-differentiated SM (WDSM), which can occur in any type of SM[7]. WDSM is morphologically characterized by round mast cells with a well-granulated mature appearance, a low prevalence of the *KIT* mutation, and an almost complete lack of expression of CD2 and CD25, whereas CD30 is expressed. Apart from WDSM, few studies have investigated the characteristics and outcomes associated with the expression of CD2 and CD25 in SM. One report found a higher frequency of CD2 expression in SM compared to CM, while another study observed a non-significant trend towards a lower frequency of CD2 expression in Adv-SM compared to ISM[8,9].

Patients with Adv-SM have a worse prognosis than those with non-Adv-SM, and the main therapeutic goal is to prolong survival. Until recently, cladribine was the standard treatment for patients with Adv-SM. Although the marketing authorization of tyrosine kinase inhibitors (TKI) targeting the D816V-mutated KIT receptor (midostaurin and avapritinib) has significantly prolonged survival times in Adv-SM, allogeneic hematopoietic stem cell transplantation remains the only curative therapy[10–12]. Thus, the identification of prognostic factors for time to treatment failure (TTF) and overall survival (OS) is critical for the optimization of patient care. The Mutation-Adjusted Risk Score for Adv-SM (MARS) has become the reference score in this population[13]. However, the prognostic impact of abnormal

phenotypes has not been extensively characterized. The objective of the present study was to investigate the characteristics and outcomes of mastocytosis patients as a function of their BMMCs expression of CD2 and CD25.

All diagnoses of mastocytosis were based on the WHO 2016 classification. The study data were collected by medical staff at the French National Referral Center for Mastocytosis (CEREMAST, France). All the patients were participating in a retrospective, cross-sectional study sponsored by the French Association for Research Initiatives on MCs and Mastocytosis (AFIRMM). The study was approved by the local investigational review board (*CPP G.H. Pitié-Salpêtrière*, Paris, France; reference: 93□00) and was conducted in compliance with the principles of the Declaration of Helsinki.

The study included two cohorts of patients with mastocytosis. The first cohort aimed to investigate the characteristics associated with the expression of CD2 and CD25 on MCs (discovery cohort), while the second cohort aimed to study the prognostic significance associated with the expression of CD2 in a nationwide cohort of patients with Adv-SM treated with midostaurin (midostaurin cohort). The "discovery cohort" (n=81) included adult patients referred to a CEREMAST reference center for the diagnosis of mastocytosis. Patients were prospectively enrolled over a 4-year period between January 2008 and December 2011. MCS patients were included in the Adv-SM group for analyses. Fresh BM aspirates were immunophenotyped at diagnosis. The midostaurin cohort (n=111) included adult patients retrospectively enrolled with the diagnosis of Adv-SM, available CD2/CD25 phenotyping data and the presence of C finding(s). The Cladribine cohort (n=17) included patients from the midostaurin cohort, who have been treated by cladribine prior midostaurin therapy.

Eighty-one consecutive adult patients with a diagnosis of mastocytosis were included in the discovery cohort (**Supplemental Table 1**); there were 54 patients with non-Adv-SM (including 54 ISM patients) and 27 patients with Adv-SM (including ASM (n=15), SM-AHN (n=8), MCL (n=2) and 2 MCS (n=2)). Sixty-six patients (81.5%) had a *KIT* D816 mutation, 2 had a juxtamembrane mutation, and 13 had a WT *KIT* gene. Of the 81 BM samples immunophenotyped, MCs were detected in 73 (90.1%). Of the 73 samples with detectable BMMCs, the phenotypes were as follows: $CD2^{+}/CD25^{+}$ (n=58, 79.5%), $CD2^{-}/CD25^{+}$ (n=10, 13.7%), $CD2^{-}/CD25^{-}$ (n=5, 6.8%), $CD2^{+}/CD25^{-}$ (n=0, 0%). We next investigated the relationship between the phenotype and the *KIT* genotype. All the patients with a *KIT* TKD mutation and an evaluable phenotype (n=58, 79.4%) expressed CD25. In contrast, only 9 of the 14 patients (64.3%) without a *KIT* TKD mutation were $CD25^{+}$. Specifically, 3 patients

with a WT *KIT* (1 with ISM, 1 with SM-AHN and 1 with MCL) and two patients with a juxtamembrane mutation (1 MCL and 1 MCS) were $CD25^-$ (**Supplemental Figure 1A**). One patient with MCL initially displayed a juxtamembrane *KIT* mutation (Dup 501-502) with $CD25^-$ BMMCs. However, after masitinib therapy (targeting WT and juxtamembrane *KIT* mutations) and remission, the patient relapsed and showed two different BMMCs populations – one $CD25^+$ and the other $CD25^-$ (**Supplemental Figure 1B**). This phenotypic mosaicism was confirmed by immunochemistry, and the appearance of CD25 coincided with the detection of a sub-clonal *KIT* D816H mutation. Sorting of $CD25^+$ BMMCs confirmed that the *KIT* D816H mutation was restricted to this compartment and was absent from the $CD25^-$ population.

Expression of CD2 on BMMCs was significantly more frequent in non-Adv-SM patients (45/50, 90%) than in Adv-SM patients (13/23, 57%, p=0.003, **Supplemental Table 1**). To specifically investigate the association between a lack of CD2 expression on BMMCs and the characteristics and outcomes of patients with Adv-SM, we retrospectively constituted a cohort of 111 midostaurin-treated patients (Table 1), of whom 53 (47.7%) were $CD2^-$ **(Table 1)**. $CD2^-$ patients were more likely to be male (81%, vs. 64% of $CD2^+$ patients, p=0.042) and to present with a low platelet count (114 G/L vs. 148 G/L, respectively; p=0.016), adverse additional mutations (i.e., *SRSF2/ASXL1/RUNX1*; 61%, vs. 39%, respectively; p=0.048) and were more likely to die (72%, vs 36%, respectively; p<0.001). Accordingly, the median OS time was significantly lower in midostaurin-treated $CD2^-$ Adv-SM patients than in midostaurin-treated $CD2^+$ Adv-SM patients (32.1 vs. 49.3 months, respectively; p=0.011, **Figure 1A**). Next, we assessed the prognostic impact of CD2 expression on patients having received cladribine. We identified 17 patients (including 11 $CD2^-$ patients) in the midostaurin cohort who had been treated with cladribine before the initiation of midostaurin. The median TTF was significantly lower in $CD2^-$ patients than in $CD2^+$ patients (3.4 vs. 7.0 months, respectively; p=0.043, **Figure 1B**). Lastly, we studied the prognostic impact of CD2 expression on OS in a multivariable analysis with the other MARS laboratory parameters (**Supplemental Table 2**). In a univariable analysis, the WHO classification, platelet count, hemoglobin level, *SRSF2/ASXL1/RUNX1* mutations and CD2 expression were associated with poor OS. However, in a multivariable analysis, only the platelet count was still associated with poor OS (HR=0.99; p=0.005).

Our study provides valuable diagnostic and prognostic information. All patients with a non-TKD genotype lacked CD25 expression on their BMMCs. Therefore, the absence of

these immunophenotypic and molecular criteria (i.e., TKD mutation) may prompt physicians to screen for other *KIT* mutations. In this context, based on the MCs morphology and the expression of CD30 on MCs, a WDSM should be considered. In addition, we confirmed previous report regarding the association between the absence of CD2 expression in Adv-SM compared with ISM patients. This observation could be explained by previous study reporting that the lack of CD2 may be associated with the loss of CD2-CD58 interaction[14]. This could lead to the absence of homotypic aggregation, resulting in the spreading of SM into extramedullary organs. We also provided further findings on the association between the lack of CD2 expression on BMMCs, adverse additional mutations and poor outcomes. In addition to the potential increased risk of spreading of CD2-negative tumoral MCs, this finding might be explained by lower platelet levels and a tendency towards a higher frequency of *KIT* D816V-negative status among CD2-negative patients, which have been associated with poor prognosis[15]. Besides the potential interest from a pathophysiological perspective, the poor prognostic significance of CD2 absence may serve as a cost-effective tool for identifying high-risk Adv-SM patients, especially when next-generation sequencing (and thus the MARS score) is not available. Further studies are required to determine whether this prognostic impact is present in patients treated with avapritinib.

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Table

Table 1: Characteristics of the patients with advanced systemic mastocytosis, according to their expression of CD2 on bone marrow mast cells.

		CD2 expression		
Variable	Overall, N = 111[1] (% total)	Negative, N = 53[1]	Positive, N = 58[1]	**p-value**
Age (years)	68 [60; 76]	70 [65; 76]	68 [59; 74]	0.3[2]
Sex (male)	80 (72%)	43 (81%)	37 (64%)	**0.042**[3]
WHO classification				0.3[4]
ASM	27 (24%)	10 (37%)	17 (63%)	
MCL	9 (8%)	3 (33%)	6 (67%)	
SM-AHN	75 (68%)	40 (53%)	35 (47%)	
AHN subtypes				0.5[4]
CMML	34 (45%)	17 (50%)	17 (50%)	
MDS	23 (31%)	15 (65%)	8 (35%)	
MPN	6 (8.0%)	2 (33%)	4 (67%)	
MDS/MPNu	12 (16%)	6 (50%)	6 (50%)	
AML transformation	21 (28%)	13 (62%)	8 (38%)	0.4[3]
AHN progression	20 (28%)	14 (70%)	6 (30%)	0.13[3]
Allo-HSCT	14 (13%)	7 (50%)	7 (50%)	0.9[3]
Hepatomegaly	72 (71%)	33 (46%)	39 (54%)	0.6[3]
Splenomegaly	85 (83%)	42 (49%)	43 (51%)	>0.9[3]
Adenopathy	59 (65%)	26 (44%)	33 (56%)	0.3[3]
Cutaneous mastocytosis	52 (53%)	20 (39%)	32 (61%)	0.059[3]
Portal hypertension - ascites	40 (38%)	22 (55%)	18 (45%)	0.3[3]
Malabsorption, weight loss	67 (64%)	38 (57%)	29 (43%)	**0.035**[3]
Osteolytic lesions	29 (28%)	15 (52%)	14 (48%)	0.7[3]
Response to midostaurin	60 (58%)	31 (52%)	29 (48%)	0.4[3]
Causes of midostaurin discontinuation				0.10[4]
allo-HSCT	4 (5%)	2 (50%)	2 (50%)	
relapse/refractory	60 (74%)	35 (58%)	25 (42%)	
intolerance	17 (21%)	5 (29%)	12 (71%)	
Hemoglobin level (g/dL)	10.10 [9.12; 11.90]	9.95 [8.60; 11.70]	10.25 [9.30; 12.35]	0.3[2]
Leukocyte count ($x10^9$/L)	8 [4; 13]	8 [5; 13]	7 [4; 11]	0.3[2]
Neutrophil count ($x10^9$/)	4.2 [2.0; 7.2]	5.7 [2.2; 8.7]	4.0 [1.9; 6.2]	0.2[2]
Eosinophil count ($x10^9$/L)	0.35 [0.06; 1.29]	0.33 [0.07; 1.01]	0.37 [0.06; 1.84]	0.5[2]
Monocyte count ($x10^9$/L)	1.00 [0.46; 1.81]	1.00 [0.37; 1.89]	0.83 [0.50; 1.54]	0.7[2]
Basophil count ($x10^9$/)	0.00 [0.00; 0.02]	0.00 [0.00; 0.00]	0.00 [0.00; 0.03]	0.4[2]
Lymphocyte count ($x10^9$/L)	1.22 [0.80; 1.90]	1.21 [0.76; 1.85]	1.27 [0.94; 1.90]	0.4[2]

Variable	Overall, N = 111[1] (% total)	CD2 expression		p-value
		Negative, N = 53[1]	Positive, N = 58[1]	
Platelet count (x10^9/)	126 [78; 172]	114 [73; 140]	148 [91; 196]	**0.016**[2]
Albumin level (g/L)	35.7 [30.9; 40.2]	35.7 [31.9; 39.7]	36.5 [30.8; 41.0]	0.5[2]
Tryptase level ≥200 ng/mL	47 (43%)	20 (43%)	27 (57%)	0.3[3]
Alkaline phosphatase level > ULN	48 (67%)	24 (50%)	24 (50%)	0.7[3]
KIT mutation				0.3[4]
D816V	100 (92%)	46 (46%)	54 (54%)	
D816X	3 (3%)	2 (67%)	1 (33%)	
wild type	5 (5%)	4 (80%)	1 (10%)	
Abnormal karyotype	10 (15%)	6 (60%)	4 (40%)	0.7[4]
SRSF2/ASXL1/RUNX1				**0.048**[3]
Zero S/A/R mutations	42 (51%)	14 (33%)	28 (67%)	
1 or more S/A/R mutations	40 (49%)	22 (55%)	18 (45%)	
CD25	107 (99%)	52 (49%)	55 (51%)	>0.9[4]
MARS category				0.15[3]
low risk	28 (31%)	9 (32%)	19 (68%)	
intermediate risk	20 (22%)	9 (45%)	11 (55%)	
high risk	43 (47%)	24 (56%)	19 (44%)	
ISPM category				>0.9[4]
low risk	8 (11%)	4 (50%)	4 (50%)	
intermediate risk 1	27 (38%)	14 (52%)	13 (48%)	
intermediate risk 2	37 (51%)	19 (51%)	18 (49%)	
Time since diagnosis (months)	26 [10; 48]	27 [12; 45]	24 [9; 50]	0.9[2]
Time since initiation of midostaurin therapy (months)	20 [8; 42]	19 [8; 38]	21 [7; 42]	0.9[2]
Deaths	59 (53%)	38 (64%)	21 (36%)	**<0.001**[3]

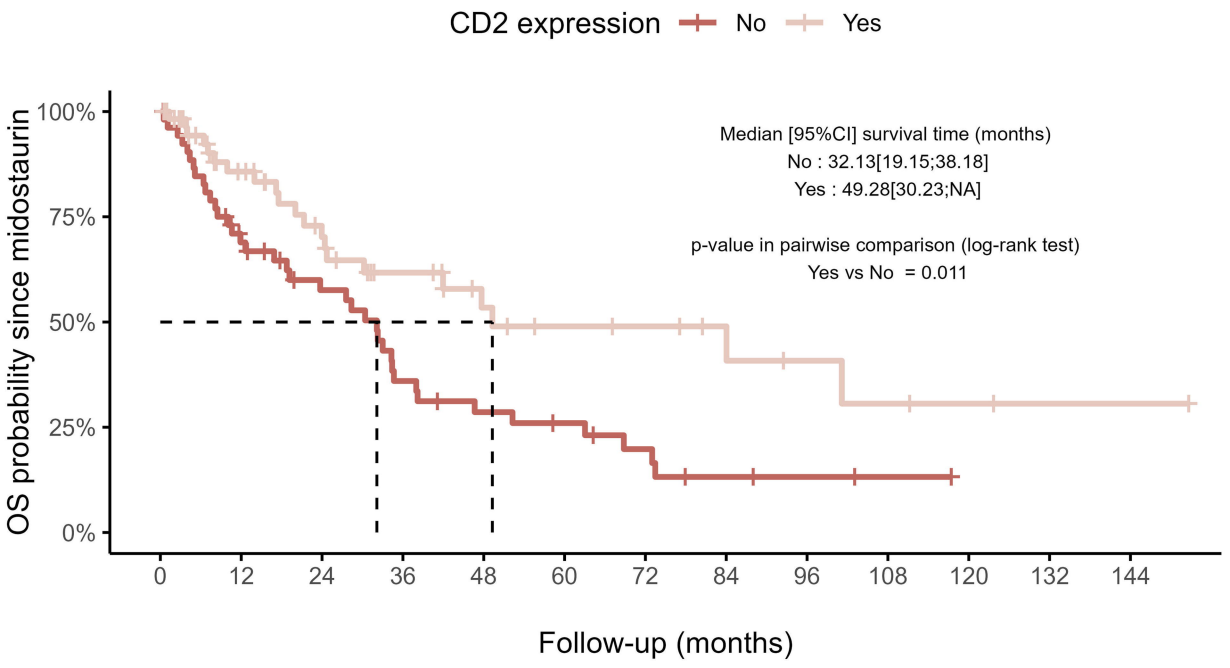
Table 1: WHO: World Health Organization. ASM: aggressive systemic mastocytosis. SM-AHN: systemic mastocytosis with an associated hematological neoplasm. MCL: mast cell leukemia. CMML: chronic myelomonocytic leukemia. MDS: myelodysplastic syndrome. MPN: myeloproliferative neoplasm. MDS/MPNu: myelodysplastic syndrome/myeloproliferative neoplasm unclassified. AML: acute myeloid leukemia. Allo-HSCT: allogeneic hematopoietic stem cell transplantation. MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis. IPSM: International Prognostic Scoring System. IPSM score includes: age 60 years or older, a concentration of tryptase 125 ng/mL or higher, a leukocyte count of 16 × 10^9/L or higher, hemoglobin of 11 g/dL or lower, a platelet count of 100 × 10^9/L or lower and skin involvement (Sperr et al. Lancet Haematology, 2019). ULN: upper limit of normal. Response to midostaurin was defined according to Valent criteria per physician discretion based on clinical and biological parameters. All *KIT* sequencing in the midostaurin cohort was performed by nested PCR (Polivka et al., JACI 2024) or by droplet digital PCR. D816X corresponds to two D816Y and one D816H mutations. [1]median [IQR]; n (%). [2]Wilcoxon's test. [3]Pearson's chi-

squared test. [4]Fisher's exact test. Data were quoted as the median [interquartile range (IQR)] for continuous variables and the frequency (percentage) for categorical variables. Groups were compared in a non-parametric Wilcoxon test for continuous variables and in a Chi-squared or Fisher's exact test (as appropriate) for categorial variables. The threshold for statistical significance was set to $p<0.05$. All statistical analyses were performed using R software (version 4.3.0)

Figure legend

Figure 1: Outcomes of advanced systemic mastocytosis patients treated with midostaurin or cladribine according to CD2 expression on mast cells (A) Kaplan-Meier estimates of overall survival (OS), according to CD2 expression on bone marrow mast cells in midostaurin-treated patients with advanced systemic mastocytosis (Adv-SM). **(B)** Kaplan-Meier estimates of time to treatment failure (TTF), according to CD2 expression on bone marrow mast cells in cladribine-treated patients with Adv-SM. The OS and TTF since the start of treatment for each group were analyzed using the Kaplan-Meier estimator. Estimates of hazard functions were compared using the log-rank test

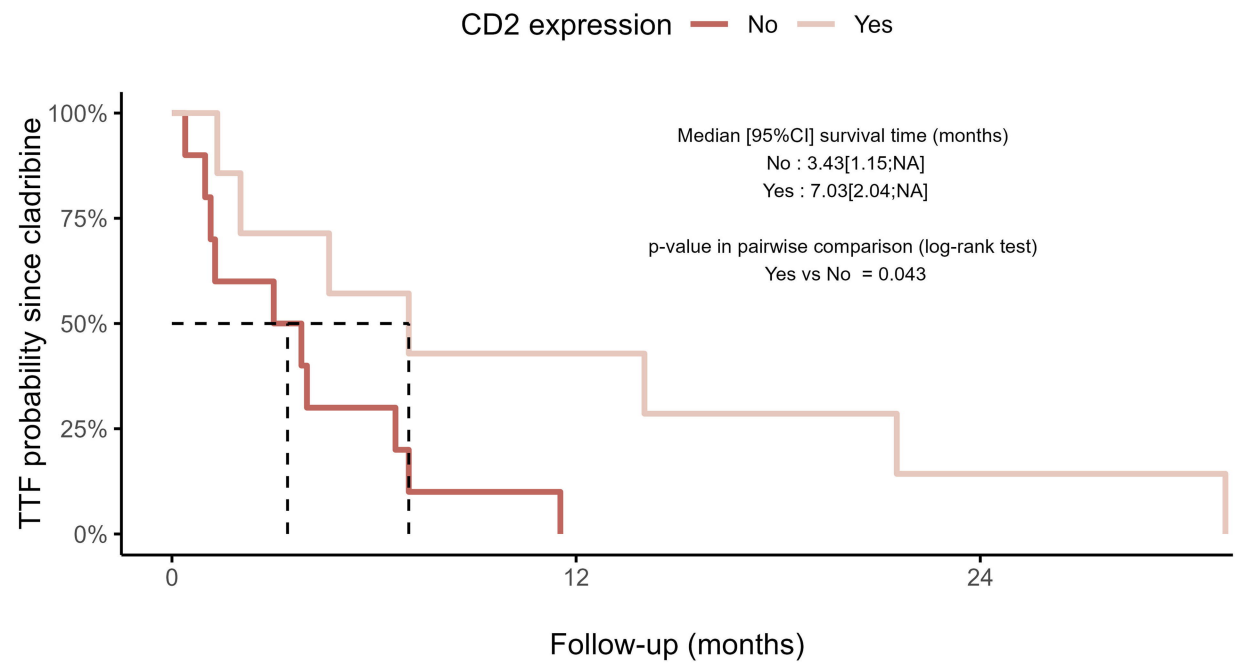
A



Number at risk (number of events)

	53 (0)	33 (16)	24 (21)	15 (30)	11 (33)	9 (34)	6 (36)	3 (38)	2 (38)	1 (38)	0 (38)	0 (38)	0 (38)
	58 (0)	37 (7)	26 (13)	18 (16)	12 (18)	9 (19)	8 (19)	6 (19)	4 (20)	3 (21)	2 (21)	1 (21)	1 (21)

B



Number at risk (number of events)

	10 (0)	0 (10)	0 (10)
	7 (0)	3 (4)	1 (6)

Online supplementary

Supplemental Table 1: demographic, clinical and laboratory characteristics of mastocytosis patients in the discovery cohort.

	Total	**Non-advanced[1]**	**Advanced[2]**	**p-value**
	N = 81	**N = 54**	**N = 27**	
Age (years); median [IQR]	51 [23]	47 [22]	60 [26]	**0.003[5]**
Sex (male); n (%)	39 (48%)	21 (39%)	18 (67%)	**0.02[6]**
WHO classification; n (%)				-
ISM	54 (67%)	54 (100%)		
ASM	15 (18%)		15 (55%)	
SM-AHN[3]	8 (11%)		8 (30%)	
MCL	2 (2%)		2 (7%)	
MCS	2 (2%)		2 (7%)	
Phenotype[4]; n (%)				**0.003[6]**
Detectable	**73 (86%)**	**50 (86%)**	**23 (85%)**	
CD2+	58/73 (79%)	45/50 (90%)	13/23 (57%)	
CD2-	15/73 (21%)	5/50 (10%)	10/23 (43%)	
CD2+/CD25+	58/73 (79%)	45/50 (90%)	13/23 (57%)	
CD2+/CD25-	0/73 (0%)	0/50 (0%)	0/23 (0%)	
CD2-/CD25+	10/73 (14%)	4/50 (8%)	6/23 (26%)	
CD2-/CD25-	5/73 (7%)	1/50 (2%)	4/23 (17%)	
Undetectable	**12 (14%)**	**8 (14%)**	**4 (15%)**	
***KIT* genotype;** n (%)				0.13[6]
TKD-mutations	66 (82%)	45 (83%)	21 (77%)	
wild type	13 (16%)	9 (17%)	4 (15%)	
non-TKD mutations	2 (2%)	0 (0%)	2 (7%)	
Death; n (%)				**<0.001[7]**
Yes	11 (14%)	1 (2%)	10 (37%)	
No	70 (86%)	53 (98%)	17 (63%)	

Supplemental table 1: WHO: World Health Organization. SM: systemic mastocytosis. ISM: indolent systemic mastocytosis. ASM: aggressive systemic mastocytosis. SM-AHN: systemic mastocytosis with an associated hematological neoplasm. MCL: mast cell leukemia. MCS: mast cell sarcoma. [1]Non-advanced = ISM. [2]Advanced = ASM, MCL, MCS, SM-AHN. [3]The AHN diagnoses were chronic myelomonocytic leukemia (n=2), myelodysplasia (n=2), myeloproliferative neoplasia (n=1), acute myeloid leukemia (n=1), hairy cell leukemia (n=1), and lymphoplasmacytic lymphoma (n=1). **[4]**Including 4 patients with partial expression of CD2 and 2 patients with bimodal expression of CD2. [5]Wilcoxon's rank sum test. [6]Pearson's chi-

squared test [7]Fisher's exact test. Data were quoted as the median [interquartile range (IQR)] for continuous variables and the frequency (percentage) for categorical variables. Groups were compared in a non-parametric Wilcoxon test for continuous variables and in a Chi-squared or Fisher's exact test (as appropriate) for categorial variables. The threshold for statistical significance was set to $p<0.05$. All *KIT* sequencing in the discovery cohort was performed by sequencing from RNA extraction as reported in Polivka et al., JACI 2024. Immunophenotyping was performed using anti-CD2 (clone L303.1) and anti-CD25 (clone 2A3) antibodies.

Supplemental Table 2: Univariable and multivariable analyses of OS after midostaurin initiation, according to the WHO diagnostic classification, hemoglobin level, platelet count, CD2 expression, and number of *S/A/R* mutations.

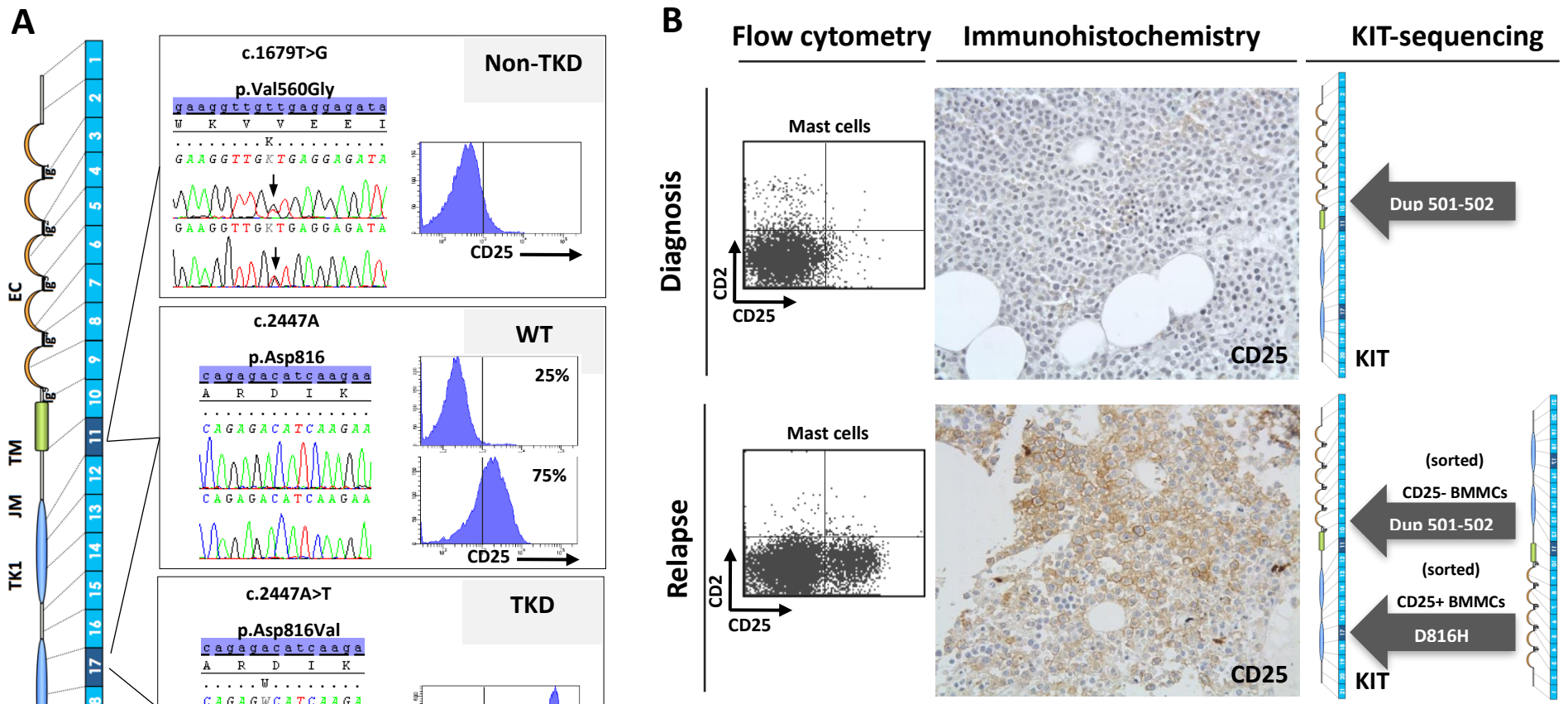
		Univariable analysis				Multivariable analysis			
Characteristic	**N**	**HR**[1]	**95%CI**[1]	**p-value**	**q-value**[2]	**N**	**HR**[1]	**95%CI**[1]	**p-value**
WHO classification				**<0.001**	<0.001				0.11
ASM	27	—	—			17	—	—	
MCL	9	8.77	2.96, 26.0			3	4.38	0.42, 45.2	
SM-AHN	75	3.43	1.61, 7.30			62	2.96	0.89, 9.87	
Hemoglobin (g/dL)	110	0.79	0.68, 0.90	**<0.001**	0.003	82	0.85	0.71, 1.02	0.069
Platelet count (x10^9/L)	111	1.0	0.99, 1.00	**<0.001**	0.002	82	0.99	0.99, 1.00	**0.005**
CD2 expression				**0.010**	0.084				0.9
No	53	—	—			36	—	—	
Yes	58	0.51	0.30, 0.86			46	0.96	0.48, 1.92	
SRSF2/ASXL1/RUNX1 mutations				**0.032**	0.3				0.068
S/A/R 0	42	—	—			42	—	—	
S/A/R 1	25	2.59	1.29, 5.22			25	2.26	1.08, 4.75	
S/A/R >= 2	15	1.60	0.65, 3.94			15	0.96	0.37, 2.46	
Alkaline phosphatase > ULN				0.4	>0.9				
No	24	—	—						
Yes	48	1.32	0.70, 2.51						
Tryptase ≥ 200 ng/mL				0.8	>0.9				
No	62	—	—						
Yes	47	0.93	0.55, 1.57						
Leukocyte count (x10^9/L)	108	1.01	0.98, 1.04	0.6	>0.9				

Supplemental table 2: WHO: World Health Organization. ASM: aggressive systemic mastocytosis. MCL: Mast cells leukemia. SM-AHN: systemic mastocytosis with an associated hematological neoplasm. *S/A/R*: *SRSF2/ASXL1/RUNX1*. ULN: upper limit of normal. [1]HR: hazard ratio; CI: confidence interval. [2]Bonferroni correction for multiple testing. We used Cox proportional hazard models to investigate prognostic factors and the strength of associations with OS. We first selected explanatory variables with p<0.2 in a univariable 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 univariable and multivariable estimates of the hazard ratio (HR) [95%CI] were reported. The multivariable models' assumptions were checked by plotting the Schoenfeld residuals.

Supplemental Figure 1: Correlation between CD25 expression and the mast cell genotype in patients with systemic mastocytosis.

(A) Distribution of the CD25 expression pattern and immunogenetic *KIT* status in a series of 73 patients. **(B)** An illustrative case of MCL with a $CD25^-$ immunophenotype and a Dup 501-502 *KIT*-genotype at diagnosis. The disease showed a clonal evolution at relapse, with the emergence of a D816H mutation (in addition to the Dup 501-502 abnormality) associated with the start of partial CD25 expression (detected in both flow cytometry and immunochemistry experiments). The D816H *KIT* mutation segregated with the $CD25^+$ BMMC compartment after electronic sorting and was absent from the $CD25^-$ BMMC population.



Antigen expression	TKD mutation	Absence of TKD mutation	
	D816	JM mutations	WT
CD25-	-	2 / 2 (100%) **	3/12 (25%) ***
CD25+	58/58 (100%)*	-	9/12 (75%)

* 1 case harboring a D816H mutation
** 1 MCL and 1 MCS
*** 1 ISM, 1 SM-AHN, 1 MCL