original reports

Superior Efficacy of Midostaurin Over Cladribine in Advanced Systemic Mastocytosis: A Registry-Based Analysis

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abstract

PURPOSE On the basis of data from the German Registry on Disorders of Eosinophils and Mast Cells, we compared the efficacy of midostaurin and cladribine in patients with advanced systemic mastocytosis (AdvSM).

PATIENTS AND METHODS Patients with AdvSM (n = 139) were treated with midostaurin only (n = 63, 45%), cladribine only (n = 23, 17%), or sequentially (midostaurin-cladribine, n = 30, 57%; cladribine-midostaurin, n = 23, 43%). Prognosis was assessed through the Mutation-Adjusted Risk Score (MARS). Besides the comparison of efficacy between midostaurin and cladribine on response (eg, organ dysfunction, bone marrow mast cell [MC] infiltration, and tryptase), overall survival (OS), and leukemia-free survival, we focused on the impact of treatment on involved non-MC lineages, for example, monocytes or eosinophils, and the *KIT* D816V expressed allele burden.

RESULTS Midostaurin only was superior to cladribine only with effects from responses on MC and non-MC lineages conferring on a significantly improved OS (median 4.2 *v* 1.9 years, $P = .033$) and leukemia-free survival (2.7 *v* 1.3 years, $P = .044$) on the basis of a propensity score–weighted analysis of parameters included in MARS. Midostaurin compensated the inferior efficacy of cladribine in first- and second-line treatment. On midostaurin in any line, response of eosinophilia did not improve its baseline adverse prognostic impact, whereas response of monocytosis proved to be a positive on-treatment parameter. Multivariable analysis allowed to establish three risk categories (low/intermediate/high) through the combination of MARS and the reduction of the *KIT* D816V expressed allele burden of ≥ 25% at month 6 (median OS not reached *v* 3.0 years *v* 1.0 year; $P < .001$).

CONCLUSION In this registry-based analysis, midostaurin revealed superior efficacy over cladribine in patients with AdvSM. In midostaurin-treated patients, the combination of baseline MARS and molecular response provided a compelling three-tier risk categorization (MARSv2.0) for OS.

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INTRODUCTION

Systemic mastocytosis (SM) is a rare hematologic neoplasm characterized by multifocal accumulation of neoplastic mast cells (MCs) in the bone marrow (BM), skin, and visceral organ systems.[1-4] Advanced SM (AdvSM) comprises SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL), and median survival is < 3-4 years.[5-10] A common feature of AdvSM is the heterogeneous multilineage involvement (> 70%-80%) of the canonical *KIT* D816V mutation in both MC and diverse non-MC lineages, for example, neutrophils, monocytes, and eosinophils,[11-14] morphologically diagnosed as chronic myelomonocytic leukemia, chronic eosinophilic leukemia, acute myeloid leukemia (AML), and others.[5,6,9]

On the basis of a phase-II-trial,[15,16] the multikinase-inhibitor midostaurin received approval for frontline treatment of AdvSM by the US Food and Drug Administration in 2016 and the European Medicines Agency in 2017. The purine analog cladribine has been widely used off-label in AdvSM on the basis of several retrospective analyses with limited number of patients.[17-20] *KIT* D816V independent somatic mutations, for example, in *SRSF2*, *ASXL1*, and *RUNX1* (*S/A/R* gene panel), and cytogenetic aberrations are frequently identified in AdvSM and confer an inferior response to treatment, more rapid disease progression, for example, into secondary MCL or secondary AML, and reduced overall survival (OS).[6,21-27]

Established response criteria are predominantly anchored to SM-related parameters (BM MC burden and serum tryptase levels) and improvement or normalization of organ damage (C-findings).[15,22,28] A more granular response assessment also taking into account the AHN compartment, for example, monocytosis and eosinophilia, has not yet been established.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Advanced systemic mastocytosis is characterized by frequent multilineage involvement and presence of *KIT* D816V in > 90% of patients. In a registry-based analysis, we sought to compare the impact of the multikinase/KIT inhibitor midostaurin and the purine analog cladribine on response of mast cell (MC) and non-MC lineages, overall disease progression, and survival. Moreover, clinical and genetic variables should be identified for early prediction of long-term outcome.

Knowledge Generated

With the exception of response rates, midostaurin is superior to cladribine in first- and second-line treatment on all other criteria including response of non-MC lineages, molecular response, leukemia-free survival, and overall survival. A new dynamic prognostic score (MARSv2.0) was generated through combination of prognostic baseline parameters (Mutation-Adjusted Risk Score) and molecular response at 6 months.

Relevance

This first cross-assessment, to our knowledge, of midostaurin versus cladribine and the MARSv2.0 will substantially affect the treatment algorithms in advanced systemic mastocytosis.

On the basis of registry data, we here analyzed the impact of monotherapy with midostaurin and cladribine and sequential treatment of these agents on baseline and on-treatment parameters associated with the MC compartment, the non-MC compartment, the *KIT* D816V expressed allele burden (EAB), OS, leukemia-free survival (LFS), and event-free survival (EFS).

PATIENTS AND METHODS

Study Population

On the basis of data from the German Registry on Disorders of Eosinophils and Mast Cells, a total of 139 patients with AdvSM were included (recruitment time 2003-2020). Diagnosis and subtyping of AdvSM were established according to the revised WHO 2017 classification (Data Supplement, online only).[1,4,29] Treatment cohorts included patients receiving (1) midostaurin only ($mido^{only}$, n = 63, 45%), (2) cladribine only ($clad^{only}$, n = 23, 17%) and (3) sequential treatment (n = 53, 38%; midostaurin-cladribine, $mido^{clad}$, n = 30, 57%; cladribine-midostaurin, $clad^{mido}$, n = 23, 43%; Fig 1). The study design adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the Medical Faculty of Mannheim, Heidelberg University. Written informed consent was provided by all patients.

Diagnostic Evaluations and Follow-Up Studies

All BM biopsies were evaluated by reference pathologists of the European Competence Network on Mastocytosis (ECNM).[30] Distinct peripheral blood counts were defined as monocytosis (> 1.0×10^9/L), mild eosinophilia (0.5-1.5×10^9/L), and hypereosinophilia (> 1.5×10^9/L). Mutational analyses on *KIT* D816V EAB by allele-specific quantitative real-time polymerase chain reaction (sensitivity 0.01%-0.1%) and identification of additional somatic mutations by next-generation deep amplicon sequencing were performed as previously reported.[6,11]

Evaluation of Response

Response according to modified Valent criteria. Response assessment included regular monitoring of C-findings, serum tryptase, and a BM biopsy around month 6 on midostaurin or within 2 months after the last cladribine course.[15,19] The main reason for not using the more recently established International Working Group-Myeloproliferative Neoplasms Research and Treatment & ECNM (IWG-MRT-ECNM) consensus response criteria was that the combined retrospective/prospective collection of data did not allow to adequately address the complex IWG-MRT-ECNM criteria.

Reduction of* KIT *D816V EAB (molecular response). Serial monitoring of the *KIT* D816V EAB for midostaurin (reduction ≥ 25% at month 6, defined as prognostically relevant molecular response) and cladribine (within 2 months after the last course).[22]

Response of monocytosis and/or eosinophilia. Response of monocytosis/eosinophilia was defined for monocytes as < 1.0×10^9/L and/or an individual relative reduction of ≥ 50% and for eosinophils as < 0.5×10^9/L and/or an individual relative reduction of ≥ 50%. A normalization was defined as monocytes < 1.0×10^9/L or eosinophils < 0.5×10^9/L (Fig 1).

Statistical Analyses

OS was defined as time from diagnosis/treatment initiation to death or date of last follow-up (if alive). LFS was defined as time from diagnosis/treatment initiation to date of progression to secondary MCL or secondary AML/death or date of last follow-up (if leukemia-free). EFS was defined as the time from diagnosis/treatment initiation to date of any new event defined as disease progression by modified Valent

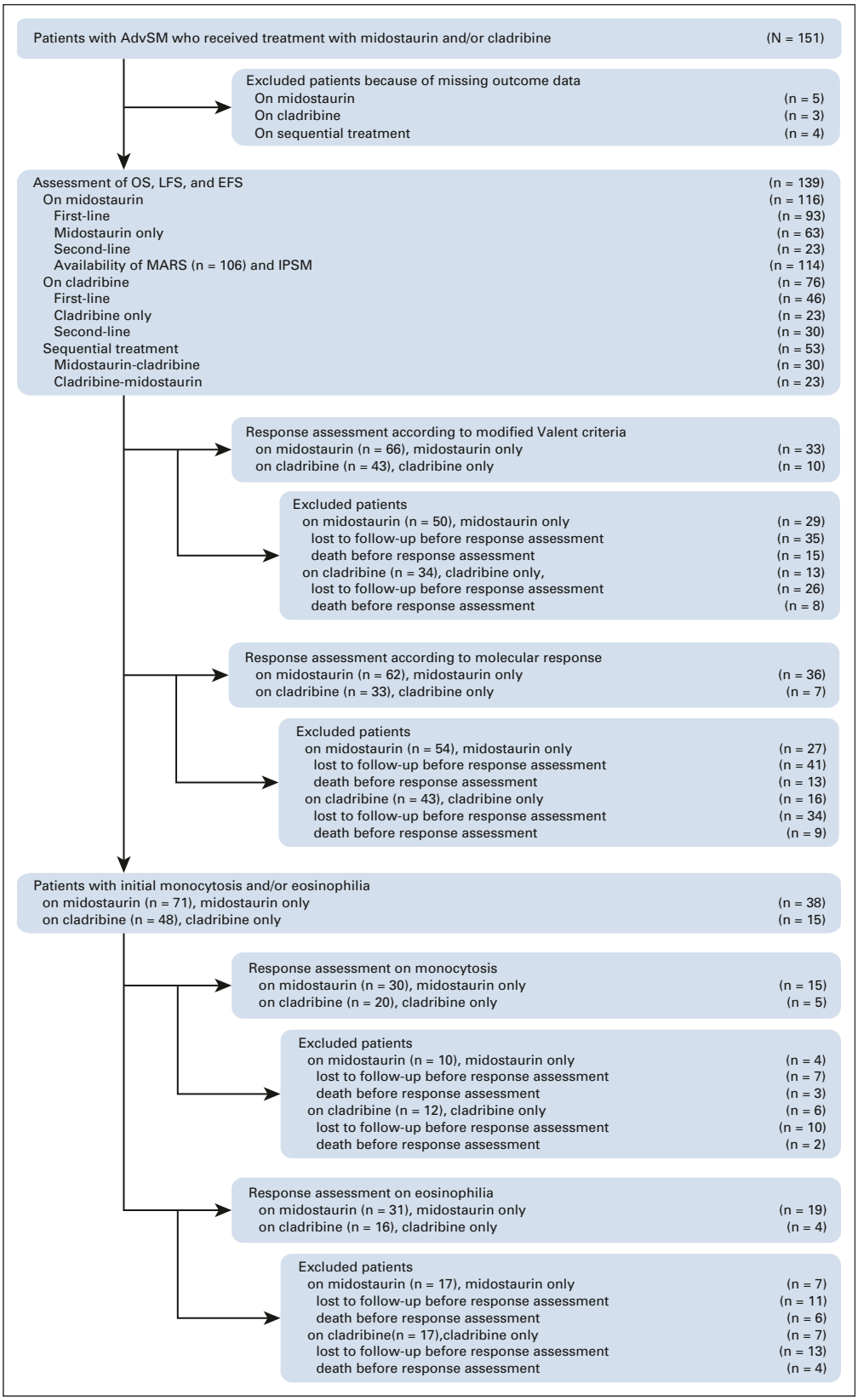

FIG 1. Study profile. Patients were selected from the German Registry on Eosinophils and Mast Cells. AdvSM, advanced systemic mastocytosis; EFS, event-free survival; IPSM, International Prognostic Scoring System for Systemic Mastocytosis; LFS, leukemia-free survival; MARS, Mutation-Adjusted Risk Score; OS, overall survival.

criteria[15,19]/death/or date of last follow-up (if event-free). The Kaplan-Meier method with log-rank test was used for group comparisons. To account for differences in demographic and disease characteristics between patients who received midostaurin versus cladribine, propensity score analysis including the variables age, hemoglobin, platelets, and *S/A/R*-positivity (variables of the Mutation-Adjusted Risk Score [MARS][6]) was performed. For the estimation of hazard ratios and multivariable analysis, the cox proportional-hazard regression model was used. The Mann-Whitney *U*-test was used to compare continuous variables and medians of distributions. For categorical variables, Fisher's exact test was used. All tests were two-sided, with $P < .050$ considered as statistically significant. Statistical analyses were performed with SPSS (version 20.0; IBM-Corporation, Armonk, NY), GraphPad Prism (version 8; GraphPad, San Diego, CA), and SAS (version 9; SAS-Institute, Cary, NC).

RESULTS

Dose and Duration of Treatment

The starting dose of midostaurin was 100 mg twice a day, and the median dose during follow-up was 150 mg/d in both first- and second-line treatment. During follow-up, the dose was modified according to efficacy and toxicity, with nausea/vomiting and thrombocytopenia being the most relevant adverse events for dose adjustments. Median duration of first-line (n = 93) or second-line (n = 23) midostaurin was 0.8 years (range: 0.0-10.1 years) or 0.5 years (range: 0.0-10.4 years), respectively. The dose of cladribine was 0.14 mg/kg/d subcutaneously or intravenously from day 1-5 of a 28-day course. Median 3 cycles (range: 1-8 cycles) were applied at a median interval between cycles of 1.1 months (range: 0.7-7.8 months). There was no difference between first- and second-line treatment. The main reason for dose reduction, for example, application only on days 1-3, or extension of intervals, was prolonged myelosuppression.

The median time between cladribine and second-line midostaurin was 0.6 years (range: 0.0-7.7 years) and between midostaurin and second-line cladribine 0.5 years (range: 0.0-2.4 years), respectively ($P = .220$). Main reasons for physician-decision–based switch from midostaurin to cladribine were resistance/progression with or without intolerance in 26/30 (87%) or intolerance only in 4/30 (13%) patients, respectively, whereas respective numbers as reasons for the switch from cladribine to midostaurin were 17/23 (74%) and 6/23 (26%).

OS, LFS, and EFS

Median survival of the entire cohort from diagnosis was 3.8 years (ASM, n = 22, not reached; SM-AHN, n = 92, 3.7 years; MCL ± AHN, n = 25; 2.0 years). The median OS from start of midostaurin or cladribine in first-line was 3.1 or 1.6 years, respectively. On mido^{only}, median OS, LFS, and EFS was 4.2, 2.7, and 1.6 years, and on clad^{only} 1.9, 1.3, and 1.0 years, respectively ($P = .033$, $P = .044$, and $P = .047$, respectively). The significantly better OS and LFS of midostaurin over cladribine were still evident when the respective analyses were performed from the time of diagnosis (Data Supplement). Patients on mido^{only} or clad^{only} revealed no significant differences upon prognostically relevant baseline characteristics nor upon other major disease-specific features (Data Supplement). The mean propensity score for midostaurin and cladribine was estimated with 0.739 (0.668-0.829) and 0.734 (0.689-0.796), respectively (difference of means 0.005; 95% CI, –0.010 to 0.021; $P = .504$). OS and LFS of sequential treatment with mido^{clad} or clad^{mido} were not different because superior OS on first- and second-line midostaurin (3.5 and 1.5 years, respectively) compensated for the inferior OS on first- and second-line cladribine (1.9 and 1.2 years, respectively; Figs 2A-2D).

Response According to Modified Valent Criteria and Monitoring of *KIT* D816V EAB

In evaluable midostaurin-treated patients in any line, the overall response rate (ORR) according to modified Valent criteria[15,19] was 35% (23/66) and OS was significantly better in responders than in nonresponders (7.9 *v* 3.1 years, $P = .031$). A molecular response was achieved in 42/62 (68%) patients and OS was significantly better in responders than in nonresponders (median OS 4.8 *v* 1.0 years, $P < .001$; Data Supplement). In evaluable cladribine-treated patients in any line, ORR was 40% (17/43) and also significantly better in responders than in nonresponders (median OS 3.4 *v* 1.5 years, $P = .025$). A molecular response occurred in 15/33 (45%) patients, which was not associated with a favorable median OS (3.1 *v* 1.5 years, $P = .367$; Data Supplement). Although the ORR according to modified Valent criteria was similar, the proportion of patients with molecular response was significantly higher on midostaurin. These differences were even more pronounced in mido^{only} versus clad^{only} patients ($P = .006$ *v* $P = .224$ for relative *KIT* D816 EAB reduction and 74% [n = 23] *v* 29% [n = 2], $P = .022$ for the proportion of KIT responders; Data Supplement).

Prognostic Impact of Presence and Response of Monocytosis and Eosinophilia

Independent of treatment, monocytosis at baseline was not associated with adverse survival. On midostaurin in any line, absolute numbers of monocytes decreased from median 2.2×10^9/L (range: 1.0-7.1) to 1.0×10^9/L (range: 0.2-7.6; $P = .007$; Data Supplement). Responders (overall response, n = 22/30, 73%; complete normalization, n = 16/30, 53%) revealed a lower frequency of mutations in *SRSF2* (88% *v* 55%), *ASXL1* (50% *v* 18%), and *RUNX1* (25% *v* 18%), and a better OS (median 4.2 *v* 2.2 years, $P = .002$; Figs 3A-3C; Data Supplement). In contrast to monocytosis, hypereosinophilia at baseline was associated with an inferior

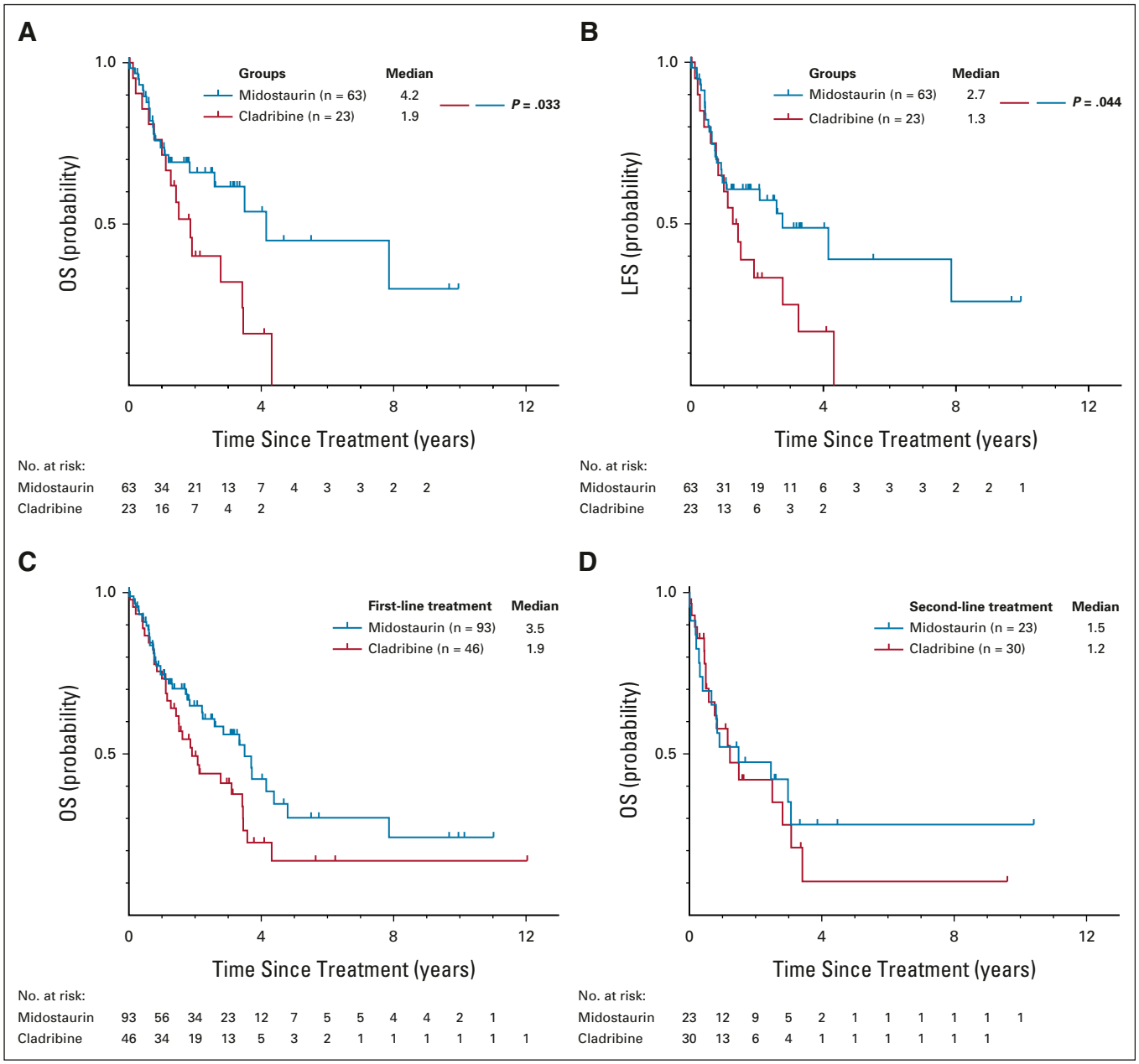

FIG 2. Kaplan-Meier estimates of (A) OS and (B) LFS in patients treated with midostaurin or cladribine only. Kaplan-Meier estimates of OS in patients treated with (C) midostaurin or cladribine first-line and (D) midostaurin or cladribine second-line. LFS, leukemia-free survival; OS, overall survival.

survival (median OS 0.8 *v* 3.5 years; $P = .009$; Data Supplement). Absolute numbers of eosinophils declined from median 1.3×10^9/L (range: 0.5-13.2) to median 0.2×10^9/L (range: 0.0-2.5; $P < .001$; Data Supplement). The frequently occurring overall response (26/31, 84%; complete normalization 20/31, 65%) did not improve OS.

On cladribine in any line, overall response was observed in 5/20 (25%; complete normalization, 5/20, 25%) patients with monocytosis and in 10/16 (63%; complete normalization, 9/20, 56%) patients with eosinophilia. A significant decrease of absolute cell counts could not be observed (Data Supplement). In conclusion, response of eosinophilia and monocytosis was observed on both drugs but only the response of monocytosis on midostaurin conferred into improved OS.

Validation of the Risk Scoring Systems MARS and International Prognostic Scoring System in Mastocytosis

On midostaurin in any line, median OS according to MARS (n = 106) was not reached in low- (n = 27, 25%), 3.3 years in intermediate- (n = 17, 16%), and 1.2 years in high-risk patients (n = 62, 59%, $P < .001$). According to International Prognostic Scoring System in Mastocytosis (IPSM, n = 114), median OS was not reached in AdvSM-1/-2

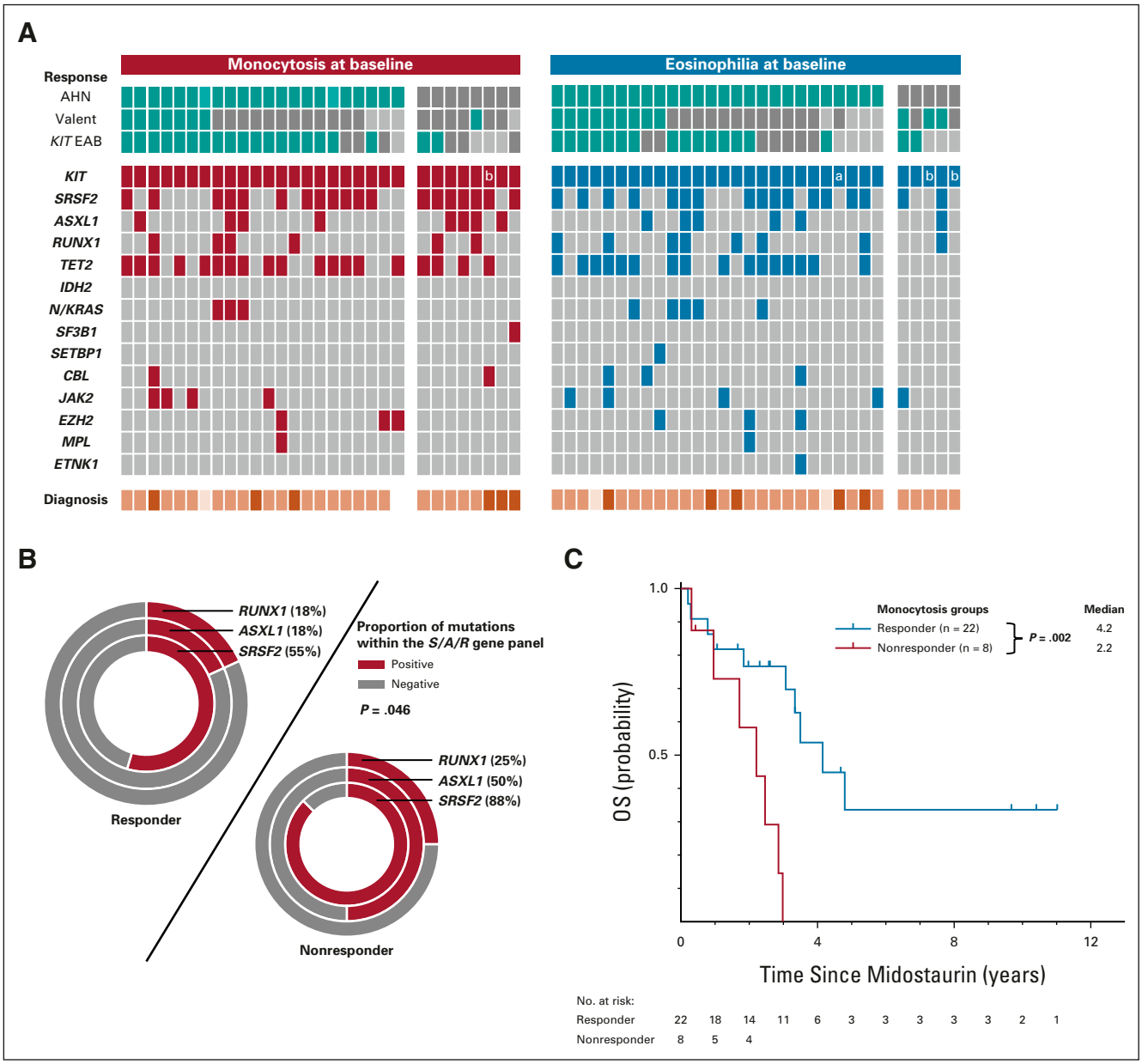

FIG 3. (A) Alignment of response status, mutational profile, and diagnosis in patients with monocytosis (n = 30) and eosinophilia (n = 31). Each column represents an individual patient. Bright, medium, and dark orange for diagnosis of aggressive systemic mastocytosis, systemic mastocytosis with an AHN, and mast cell leukemia with/without an AHN, respectively. Teal for responders. [a]*KIT* variants D816N and D816H identified, and no myeloid gene panel analysis available. [b]*KIT* variant D816Y identified. (B) Number of mutations in *SRSF2*, *ASXL1*, and *RUNX1* in patients with monocytosis: responders versus nonresponders. (C) Kaplan-Meier estimates of OS in patients depending on response status of monocytosis. AHN, associated hematologic neoplasm; EAB, expressed allele burden; OS, overall survival.

(n = 24, 21%), 5.1 years in AdvSM-3 (n = 61, 54%), and 1.3 years in AdvSM-4 (n = 29, 25%) patients (P = .001; Figs 4A and 4B).

A Dynamic Prognostic Score Derived From Baseline Prognostic Status (MARS and IPSM) and On-Treatment Molecular Response to Midostaurin

In multivariable analysis, molecular response was the only independent on-treatment risk parameter (Table 1). Assignment of one point to MARS high-risk or IPSM AdvSM-3/4 and one point to lack of molecular response allowed the generation of two new dynamic scores on the basis of three risk categories (low-, intermediate-, and high-risk; Figs 4C and 4D). In the intermediate-risk group of both scores, patients at high-risk with molecular response had a better OS than patients at low-/intermediate-risk without molecular response (P = .018 and P = .003, respectively; data not shown).

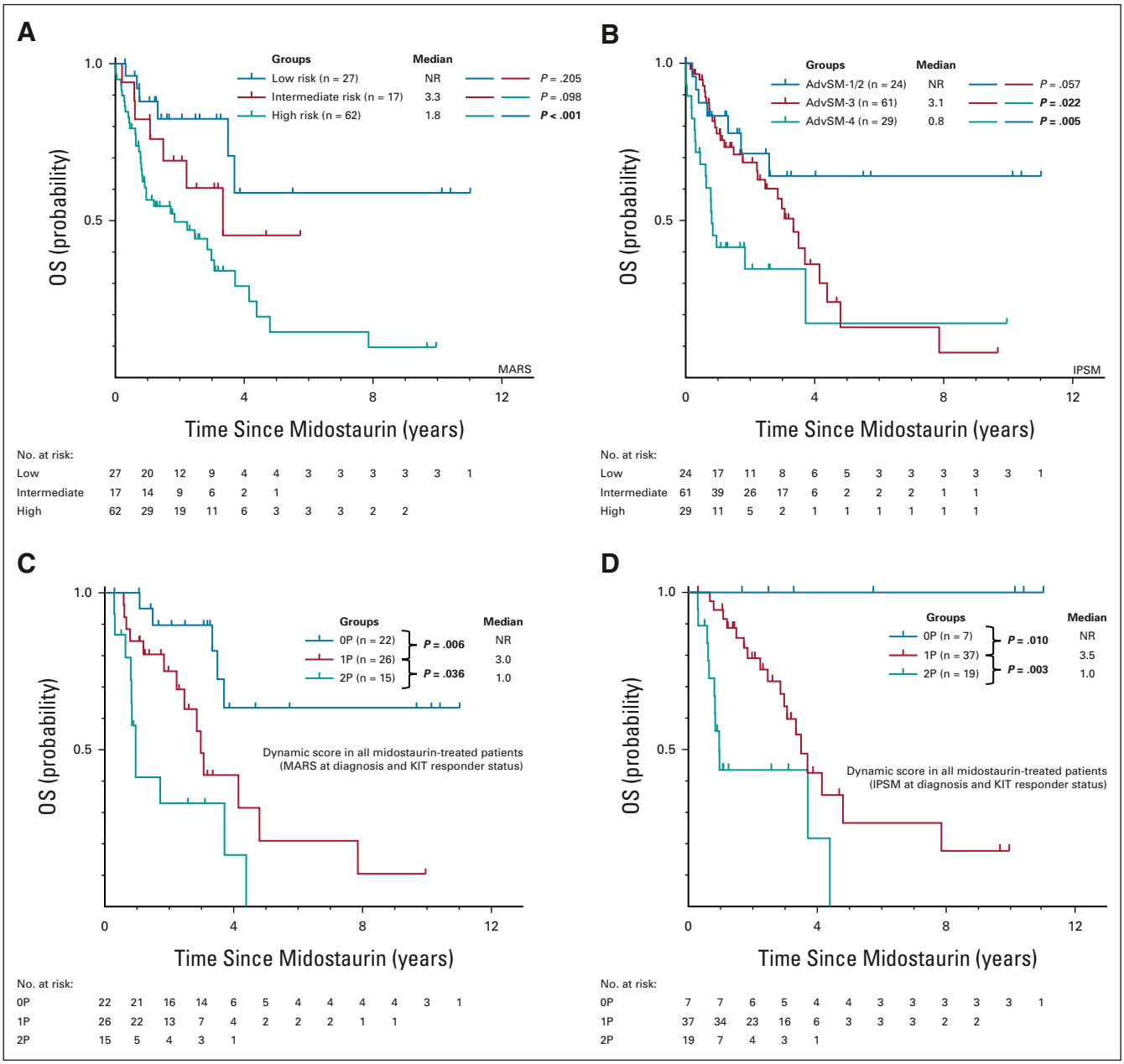

FIG 4. (A) MARS and (B) IPSM for up-front treatment stratification with midostaurin. (C and D) Kaplan-Meier estimates of OS of midostaurin-treated patients on the basis of a new dynamic on-treatment score with 0, 1, or 2 points (1 point each for MARS high risk or AdvSM3-4 and KIT nonresponse status at the time of response assessment). AdvSM, advanced systemic mastocytosis; IPSM, International Prognostic Scoring System in Mastocytosis; MARS, Mutation-Adjusted Risk Score; NE, not evaluable; NR, not reached; OS, overall survival; P, points.

DISCUSSION

AdvSM has an aggressive clinical course with a median survival of < 3-4 years. Smaller series from single institutions[7,18-20,31-33] and a national registry[17] reported achievement of partial responses and clinical improvements on the purine analog cladribine. In the absence of other effective therapies, cladribine was elevated to a status of first-line treatment option, although its impact on long-term outcomes such as progression and OS is limited. This changed with approval of the multikinase-inhibitor midostaurin by the US Food and Drug Administration in 2016 and the European Medicines Agency in 2017 following a phase-II-trial reporting an ORR of 60% according to modified Valent criteria and 28% according to IWG-MRT-ECNM criteria.[15,16,28,34] In subsequent reports, distinct baseline, for example, additional somatic mutations, and on-treatment parameters, for example, molecular response, have been identified as prognostic variables on midostaurin but have not yet been evaluated on cladribine.[22]

Because AdvSM is a rare hematologic neoplasm, there is no expectation of a head-to-head comparison of midostaurin

TABLE 1. Univariate and Multivariable Overall Survival Analyses Regarding the Prognostic Impact of Several On-Treatment Parameters for Midostaurin-Treated Patients

	Univariate		Multivariable	
Characteristic	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
MC in BM section (%): reduction < 50 *v* ≥ 50 (n = 40)	0.8 (0.3 to 1.8)	NS		
Serum tryptase (%): reduction < 50 *v* ≥ 50[a] (n = 66)	1.7 (0.7 to 4.0)	NS		
Hb/Plt normalization[b]: no or progression *v* yes (n = 52)	1.8 (0.7 to 4.4)	NS		
Albumin normalization: no or progression *v* yes (n = 35)	3.3 (1.3 to 8.6)	.012	0.5 (0.1 to 4.1)	NS
AP (%): reduction < 50 *v* ≥ 50[a] (n = 49)	1.3 (0.6 to 2.8)	NS		
Vitamin B12 (%): reduction < 50 *v* ≥ 50[a] (n = 23)	2.9 (0.7 to 13.3)	NS		
Monocytosis response: no or progression *v* yes (n = 30)	2.2 (1.1 to 4.4)	.032	1.1 (0.3 to 4.8)	NS
Eosinophilia response: no or progression *v* yes (n = 31)	0.5 (0.6 to 3.4)	NS		
Modified Valent response: no *v* yes (n = 66)	2.8 (1.1 to 7.2)	.039	4.9 (0.5 to 44.8)	NS
KIT response (%): reduction < 25 *v* ≥ 25 (n = 62)	5.0 (2.2 to 11.2)	< .001	17.8 (1.8 to 179.1)	.008

Abbreviations: AP, alkaline phosphatase; BM, bone marrow; Hb, hemoglobin; HR, hazard ratio; MC, mast cell; NS, not significant; Plt, platelets.
[a]Or normalization.
[b]Cheson criteria for transfusion were considered, if necessary.

versus cladribine.[9,35] Statistically optimized comparisons between data from clinical trials and registry-based data therefore remain the second-best option, for example, similar to the approval process of blinatumomab in refractory adult B-cell acute lymphoblastic leukemia.[36] Compared with the strict design of randomized trials, primary limitations of registry-based data sets include (1) patient selection, (2) the variable adherence to treatment itself and clinical and laboratory controls at certain time points, and (3) the incomplete documentation of data across different centers. By contrast, registry-based data are closer to real life and observation time can be indefinitely extended. This allows reporting of long-term data and also the outcome of sequential treatment strategies.

The reliability and validity of our registry data has been demonstrated individually[6,7,9,21-25,27,37-39] and also in relation to several projects of the ECNM.[5,6,40-45] For the current analyses, salient strengths include (1) a comprehensive data set of clinical and molecular parameters from baseline and on-treatment from a high number of patients of whom > 70% were repeatedly seen at the same institution, (2) evaluation of almost all BM biopsies by ECNM reference pathologists,[9,30] and (3) the use of widely acknowledged statistical methodologies through propensity score analyses as an optimal approach for comparing outcomes across cohorts with balanced distributions and the best possible approximation of a randomized trial.[46-48]

The ORR according to modified Valent criteria was not different between midostaurin and cladribine but midostaurin was superior regarding the response of the AHN (monocytes/eosinophils), *KIT* D816V EAB, LFS, EFS, and OS. Midostaurin apparently compensated the inferior efficacy of cladribine in first- and second-line settings. A response according to modified Valent criteria to either midostaurin or cladribine resulted in a significantly improved survival. The reasons why similar response rates resulted in statistically different LFS, EFS, and OS are manifold: (1) MARS and IPSM were predictive for LFS, EFS, and OS with midostaurin- but not in cladribine-treated patients (data for cladribine-treated patients not shown). (2) In midostaurin-treated patients, statistical analyses revealed a strong association between LFS/EFS/OS and molecular response, which is not included in the modified Valent criteria, but was shown to be the only independent on-treatment risk factor in a multivariable analysis. (3) The significantly better EFS of midostaurin over cladribine highlights that the durability of response is more important than the achievement of a distinct response at a certain time point. The reasons for drug selection in first- and second-line were mainly on the basis of variable drug availability at referring centers and the limited possibility for inclusion of patients into the clinical trial (Data Supplement).

Regarding the complex topic of response assessment, major under-rated aspects of AdvSM involve the heterogeneity of phenotype and genetics. In at least 60%-80% of patients with AdvSM, presence of an AHN reflects a multimutated stem-cell neoplasm rather than a pure MC neoplasm. *KIT* D816V-positive MC and tryptase represent the MC compartment, whereas *KIT* D816V-positive neutrophils, monocytes, or eosinophils belong to the non-MC compartment. A clear attribution of hematologic (eg, anemia and thrombocytopenia) and gastrointestinal (eg, portal hypertension, splenomegaly, and ascites) C-findings but also of the *KIT* D816V EAB to SM versus AHN is difficult as patients are variably affected by involvement of both disease components. On midostaurin in any line, a complete normalization of eosinophilia was observed in almost

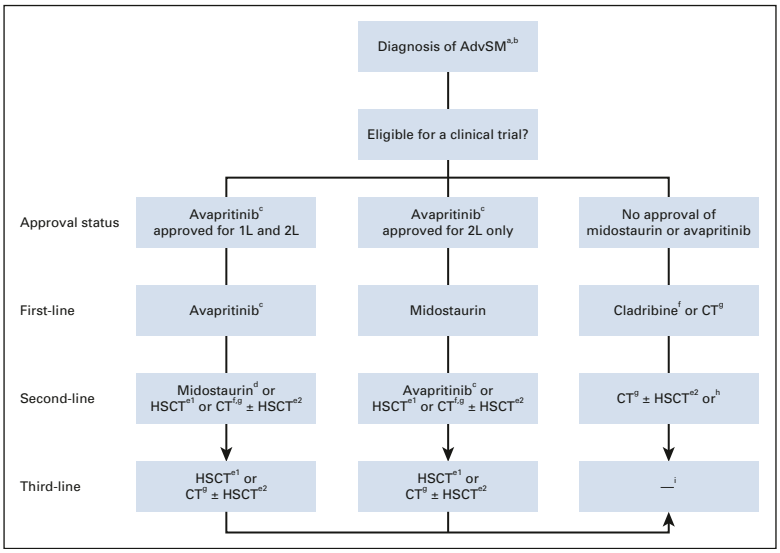

FIG 5. Algorithm for treatment of AdvSM. [a]AdvSM without C-findings and without significant progression over months: consider careful watch-and-wait, interferon-alpha, or hydroxyurea. [b]Imatinib: although imatinib was the first approved TKI for treatment of ASM, it must be emphasized that *KIT* D816V (> 90% of patients) confers primary resistance to imatinib. The efficacy may be most promising in patients with a well-differentiated SM morphology: CD25 negative/low, CD30-positive, and *KIT* D816V-negative. Some patients exhibit mutations in the juxtamembrane region of *KIT*. [c]On the basis of results from EXPLORER[49] and PATHFINDER[50] trials. Before and during treatment with avapritinib, the platelet count should be $> 50 \times 10^9$/L to mitigate the potential for intracranial bleeding. If $< 50 \times 10^9$/L, consider second-line treatment. Alternative first-line options should be considered in patients with *KIT* D816V-negative AdvSM. [d]The second-line efficacy of midostaurin after avapritinib has not yet been evaluated in clinical trials. [e]In eligible patients, an allogeneic HSCT should be considered for patients (1) with a significant and durable response to treatment with TKI, and (2) with resistance to TKI and rapidly progressing AHN component, which is generally considered to require an allogeneic HSCT, for example, AML, MDS, MDS/MPNu, or CEL, with or without previous CT (poly-CT with or without cladribine or hypomethylating agents with or without venetoclax). [f]SM-directed CT, for example, cladribine alone or poly-CT ± cladribine. [g]AHN-directed CT (see e), on the basis of disease component requiring more immediate therapy, for example, AML, MDS, MDS/MPNu, or CEL. [h]Consider off-label use or compassionate use of midostaurin or avapritinib. [i]Supportive/palliative care ± steroids ± hydroxyurea. 1L, first-line; 2L, second-line; AdvSM, advanced systemic mastocytosis; AHN, associated hematologic neoplasm; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CT, chemotherapy; MDS, myelodysplastic syndrome; MDS/MPNu, myelodysplastic/myeloproliferative neoplasm, unclassifiable; SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor.

all patients but responses did not translate into improved OS. We therefore conclude that in these patients, the strong adverse prognostic impact of eosinophilia[49] could not be overcome by midostaurin treatment. By contrast, a response of monocytosis on midostaurin resulted in a significantly improved OS/LFS.

The serial measurement of (minimal/measurable) residual disease through high-sensitivity assays such as quantitative real-time polymerase chain reaction or digital-droplet polymerase chain reaction and reported either as relative reduction of the allele burden at certain time points or as absence (below detection level) of the mutation in terms of complete molecular remission may become as relevant and recommendable as it is already in practice in many other hematologic neoplasms. Within the phase-I trial (EXPLORER, NCT02561988[50]) and an interim analysis of the phase-II clinical trial (PATHFINDER, NCT03580655[51]), avapritinib, a highly selective KIT inhibitor, produced an ORR of approximately 75% according to IWG-MRT-ECNM criteria including marked responses in BM MC burden, serum tryptase, and splenomegaly. In addition, molecular remissions with *KIT* D816V variant allele frequency < 1% were reported in 30% (in BM) and 35% (in peripheral blood) of patients with AdvSM, respectively. In our series,

we primarily confirmed that the > 25% reduction of the *KIT* D816V EAB at month 6 as an independent marker for OS. The significantly better OS of patients with the combination high-risk patients (MARS/IPSM)[6,22] with molecular response versus low-/intermediate-risk (MARS/IPSM) patients without molecular response further supports the importance of achievement of a molecular response. High-risk patients according to the new dynamic score should be seen as candidates for early switch to potentially more effective second-line treatment, for which avapritinib is currently the most promising agent.[39] Eligible patients should be considered for allogeneic hematopoietic stem-cell transplantation.[52,53] The complex concept of first- and second-line treatment of AdvSM depending on the variable approval status of midostaurin and avapritinib is provided in Figure 5.

Furthermore, it could be confirmed that a higher proportion of nonresponders were positive for additional somatic mutations in *S/A/R*, suggesting a major impact of additional somatic mutations on primary resistance and progression.[6,22,23,39] Recent data on single-cell–derived myeloid progenitor cells using granulocyte macrophage colony-forming units revealed that neither midostaurin nor avapritinib had an inhibitory effect on multimutated *KIT* D816V-negative clones.[39] The reported molecular or even complete molecular responses on midostaurin or avapritinib may therefore not prevent from selection and outgrowth of one or more *KIT* D816V-negative subclones as basis of a progressive AHN, necessitating alternative therapeutic strategies against the *KIT* D816V-negative subclone.

We conclude that in AdvSM: (1) Midostaurin is superior to cladribine in first- and second-line treatment and compensates for the inferior efficacy of cladribine in the sequential setting. (2) Midostaurin in any line is superior against monocytosis/eosinophilia but a response does not compensate for the poor prognosis of eosinophilia. (3) Not monocytosis per se, but the lack of response is associated with poor prognosis. (4) MARS and IPSM are predictive for OS on midostaurin in any line but not on cladribine. (5) On treatment, the sequential assessment of the *KIT* D816V allele burden at the RNA or DNA level is strongly recommended. (6) The combination of MARS or IPSM with molecular response provides a three-tier risk categorization (MARSv2.0) for OS potentially conferring on treatment modifications.

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The data sets used and/or analyzed during the current study are available from the corresponding author (A.R.) on reasonable request.

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REFERENCES

1. Arber DA, Orazi A, Hasserjian R, et al: The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127: 2391-2405, 2016
2. Pardanani A: Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. Am J Hematol 94:363-377, 2019
3. Valent P, Horny HP, Escribano L, et al: Diagnostic criteria and classification of mastocytosis: A consensus proposal. Leuk Res 25:603-625, 2001
4. Valent P, Akin C, Metcalfe DD: Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood 129:1420-1427, 2017
5. Sperr WR, Kundi M, Alvarez-Twose I, et al: International prognostic scoring system for mastocytosis (IPSM): A retrospective cohort study. Lancet Haematol 6: e638-e649, 2019
6. Jawhar M, Schwaab J, Alvarez-Twose I, et al: MARS: Mutation-adjusted risk score for advanced systemic mastocytosis. J Clin Oncol 37:2846-2856, 2019
7. Jawhar M, Schwaab J, Meggendorfer M, et al: The clinical and molecular diversity of mast cell leukemia with or without associated hematologic neoplasm. Haematologica 102:1035-1043, 2017
8. Lim KH, Tefferi A, Lasho TL, et al: Systemic mastocytosis in 342 consecutive adults: Survival studies and prognostic factors. Blood 113:5727-5736, 2009
9. Schwaab J, Cabral do OHN, Naumann N, et al: Importance of adequate diagnostic work-up for correct diagnosis of advanced systemic mastocytosis. J Allergy Clin Immunol Pract 8:3121-3127.e1, 2020
10. Reiter A, George TI, Gotlib J: New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. Blood 135:1365-1376, 2020
11. Erben P, Schwaab J, Metzgeroth G, et al: The KIT D816V expressed allele burden for diagnosis and disease monitoring of systemic mastocytosis. Ann Hematol 93:81-88, 2014
12. Jawhar M, Schwaab J, Schnittger S, et al: Molecular profiling of myeloid progenitor cells in multi-mutated advanced systemic mastocytosis identifies KIT D816V as a distinct and late event. Leukemia 29:1115-1122, 2015
13. Sotlar K, Colak S, Bache A, et al: Variable presence of KITD816V in clonal haematological non-mast cell lineage diseases associated with systemic mastocytosis (SM-AHNMD). J Pathol 220:586-595, 2010
14. Wang SA, Hutchinson L, Tang G, et al: Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease: Clinical significance and comparison of chomosomal abnormalities in SM and AHNMD components. Am J Hematol 88:219-224, 2013
15. Gotlib J, Kluin-Nelemans HC, George TI, et al: Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 374:2530-2541, 2016
16. Tzogani K, Yu Y, Meulendijks D, et al: European Medicines Agency review of midostaurin (Rydapt) for the treatment of adult patients with acute myeloid leukaemia and systemic mastocytosis. ESMO Open 4:e000606, 2019
17. Barete S, Lortholary O, Damaj G, et al: Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood 126:1009-1016, 2015
18. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al: Cladribine therapy for systemic mastocytosis. Blood 102:4270-4276, 2003
19. Lim KH, Pardanani A, Butterfield JH, et al: Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol 84:790-794, 2009
20. Tefferi A, Kittur J, Farrukh F, et al: Cladribine therapy for advanced and indolent systemic mastocytosis: Mayo Clinic experience in 42 consecutive cases. Br J Haematol 196:975-983, 2022
21. Schwaab J, Schnittger S, Sotlar K, et al: Comprehensive mutational profiling in advanced systemic mastocytosis. Blood 122:2460-2466, 2013
22. Jawhar M, Schwaab J, Naumann N, et al: Response and progression on midostaurin in advanced systemic mastocytosis: KIT D816V and other molecular markers. Blood 130:137-145, 2017
23. Jawhar M, Schwaab J, Schnittger S, et al: Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V(+) advanced systemic mastocytosis. Leukemia 30:136-143, 2016
24. 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 30:2342-2350, 2016
25. Naumann N, Jawhar M, Schwaab J, et al: Incidence and prognostic impact of cytogenetic aberrations in patients with systemic mastocytosis. Genes Chromosomes Cancer 57:252-259, 2018
26. Naumann N, Lübke J, Shomali W, et al: Clinical and histopathological features of myeloid neoplasms with concurrent Janus kinase 2 (JAK2) V617F and KIT proto-oncogene, receptor tyrosine kinase (KIT) D816V mutations. Br J Haematol 194:344-354, 2021
27. Naumann N, Lübke J, Baumann S, et al: Adverse prognostic impact of the KIT D816V transcriptional activity in advanced systemic mastocytosis. Int J Mol Sci 22:2562, 2021
28. Chandesris MO, Damaj G, Canioni D, et al: Midostaurin in advanced systemic mastocytosis. N Engl J Med 374:2605-2607, 2016
29. Horny HP, Akin C, Arber D, et al: Mastocytosis, in Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France, IARC Press, 2017, pp 62-69
30. Jawhar M, Schwaab J, Horny HP, et al: Impact of centralized evaluation of bone marrow histology in systemic mastocytosis. Eur J Clin Invest 46:392-397, 2016
31. Pardanani A, Hoffbrand AV, Butterfield JH, et al: Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine. Leuk Res 28:127-131, 2004
32. Tefferi A, Li CY, Butterfield JH, et al: Treatment of systemic mast-cell disease with cladribine. N Engl J Med 344:307-309, 2001
33. Bohm A, Sonneck K, Gleixner KV, et al: In vitro and in vivo growth-inhibitory effects of cladribine on neoplastic mast cells exhibiting the imatinib-resistant KIT mutation D816V. Exp Hematol 38:744-755, 2010
34. DeAngelo DJ, George TI, Linder A, et al: Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia 32:470-478, 2018
35. Cohen SS, Skovbo S, Vestergaard H, et al: Epidemiology of systemic mastocytosis in Denmark. Br J Haematol 166:521-528, 2014
36. Barlev A, Lin VW, Katz A, et al: Estimating long-term survival of adults with Philadelphia chromosome-negative relapsed/refractory B-precursor acute lymphoblastic leukemia treated with blinatumomab using historical data. Adv Ther 34:148-155, 2017
37. Jawhar M, Dohner K, Kreil S, et al: KIT D816 mutated/CBF-negative acute myeloid leukemia: A poor-risk subtype associated with systemic mastocytosis. Leukemia 33:1124-1134, 2019
38. Schwaab J, Jawhar M, Naumann N, et al: Diagnostic challenges in the work up of hypereosinophilia: Pitfalls in bone marrow core biopsy interpretation. Ann Hematol 95:557-562, 2016
39. Lübke J, Naumann N, Kluger S, et al: Inhibitory effects of midostaurin and avapritinib on myeloid progenitors derived from patients with KIT D816V positive advanced systemic mastocytosis. Leukemia 33:1195-1205, 2019
40. Kluin-Nelemans HC, Jawhar M, Reiter A, et al: Cytogenetic and molecular aberrations and worse outcome for male patients in systemic mastocytosis. Theranostics 11:292-303, 2021

41. Fuchs D, Kilbertus A, Kofler K, et al: Scoring the risk of having systemic mastocytosis in adult patients with mastocytosis in the skin. J Allergy Clin Immunol Pract 9:1705-1712.e4, 2021
42. Trizuljak J, Sperr WR, Nekvindova L, et al: Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. Allergy 75:1927-1938, 2020
43. Zanotti R, Bonifacio M, Lucchini G, et al: Refined diagnostic criteria for bone marrow mastocytosis: A proposal of the European Competence Network on Mastocytosis. Leukemia 36:516-524, 2022
44. 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 137:35-45, 2016
45. Nedoszytko B, Arock M, Lyons JJ, et al: Clinical impact of inherited and acquired genetic variants in mastocytosis. Int J Mol Sci 22:411, 2021
46. Concato J, Shah N, Horwitz RI: Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 342:1887-1892, 2000
47. Benson K, Hartz AJ: A comparison of observational studies and randomized, controlled trials. N Engl J Med 342:1878-1886, 2000
48. Booth CM, Tannock IF: Randomised controlled trials and population-based observational research: Partners in the evolution of medical evidence. Br J Cancer 110:551-555, 2014
49. Kluin-Nelemans HC, Reiter A, Illerhaus A, et al: Prognostic impact of eosinophils in mastocytosis: Analysis of 2350 patients collected in the ECNM registry. Leukemia 34:1090-1101, 2020
50. DeAngelo DJ, Radia DH, George TI, et al: Safety and efficacy of avapritinib in advanced systemic mastocytosis: The phase 1 EXPLORER trial. Nat Med 27: 2183-2191, 2021
51. Gotlib J, Reiter A, Radia DH, et al: Efficacy and safety of avapritinib in advanced systemic mastocytosis: Interim analysis of the phase 2 PATHFINDER trial. Nat Med 27:2192-2199, 2021
52. Ustun C, Reiter A, Scott BL, et al: Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. J Clin Oncol 32:3264-3274, 2014
53. Ustun C, Gotlib J, Popat U, et al: Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. Biol Blood Marrow Transplant 22:1348-1356, 2016

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Superior Efficacy of Midostaurin Over Cladribine in Advanced Systemic Mastocytosis: A Registry-Based Analysis

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