Novel Prognostic Risk Scoring System for Patients with Advanced Systemic Mastocytosis Treated with Midostaurin or Avapritinib: Development and Validation of the Revised Mutation-Adjusted Risk Score

Johannes Lübke,[1] Aaron Zakharyan,[2] Jason Gotlib,[3] Julien Rossignol,[4,5] Daniel J. DeAngelo,[6] Deepti H. Radia,[7] Tracy I. George,[8] Michael Deininger,[9] Orianne Debeaupuis,[10] Nicole Naumann,[1] Georgia Metzgeroth,[1] Alice Fabarius,[1] Wolf-Karsten Hofmann,[1] Saša Dimitrijević,[11] Olivier Hermine,[4,5] Juliana Schwaab,[1] Andreas Reiter[1]

[1]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany; [2]Blueprint Medicines Corporation, Cambridge, MA, USA; [3]Division of Hematology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; [4]Imagine Institute, INSERM U1163, Necker-Enfants Malades University Hospital, Paris University, Paris, France; [5]French National Reference Center for Mastocytoses (CEREMAST), Necker-Enfants Malades University Hospital, AP-HP, Paris, France; [6]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [7]Guy's and St Thomas' NHS Foundation Trust, London, UK; [8]ARUP Laboratories, University of Utah, Salt Lake City, UT, USA; [9]Michael Deininger Laboratory, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI, USA; [10]Université Paris Cité, Institut Imagine, Laboratoire d'Immunogénétique des Maladies Autoimmunes Pédiatriques, INSERM UMR1163, Paris, France; [11]Blueprint Medicines (Switzerland) GmbH, Zug, Switzerland

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MARS-R risk calculator

Background, Rationale, and Objectives

- Advanced systemic mastocytosis (AdvSM) is a rare myeloid neoplasm which is driven by *KIT* D816V in >95% of patients
- The changing treatment landscape and availability of KIT inhibitors midostaurin or avapritinib have led to improved prognosis of patients with AdvSM
- Current AdvSM risk scoring systems (e.g., Mutation-Adjusted Risk Score [MARS][1] and International Prognostic Scoring System for Mastocytosis [IPSM][2]) rely solely on categorical variables and do not reflect the use of KIT inhibitors
- We previously developed and internally validated the Revised Mutation-Adjusted Risk Score (MARS-R), a continuous-scale overall survival (OS) risk scoring system for patients with *KIT* D816V-positive AdvSM treated with midostaurin or avapritinib
- The objectives of the current study were:
  - To validate MARS-R with an external patient cohort
  - To compare OS of patients with AdvSM treated with avapritinib and midostaurin after adjustment for MARS-R
  - To compare patients treated with avapritinib in first-line (1L) vs second and subsequent lines (2L+) after adjustment for MARS-R

Methods

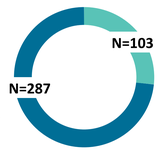
- MARS-R was derived using:
  - A midostaurin cohort from the German Registry on Disorders of Eosinophils and Mast Cells (GREM) (n=120)
  - An avapritinib cohort from the Phase 1 EXPLORER[3] and Phase 2 PATHFINDER[4,5] clinical studies of avapritinib (n=167)
- Together these data sets formed the training cohort (n=287)
- Candidate clinical and genetic candidate risk variables at treatment start were selected via stepwise Cox multivariable modeling
- MARS-R was derived as a weighted sum of the selected predictors (three continuous and five categorical: **Table 1**)[6], normalized to a value of 0 risk level for an average-risk patient (hazard ratio = 1)
- Model discrimination was evaluated by Harrell's C-index and compared to existing risk scoring systems
- External validation was performed on an independent cohort of 103 midostaurin-treated AdvSM from the French "Rare Diseases Reference Center for Mastocytosis (CEREMAST)" (**Figure 1**)
  - 28 of these patients subsequently received avapritinib
- OS according to line of administration of avapritinib (1L or 2L+) was analyzed in the avapritinib cohort
  - Avapritinib given ≥3 months after the last midostaurin and/or cladribine dose was considered as 2L+ treatment

Figure 1. Patient cohorts

Training cohort

From the midostaurin cohort from the German Registry on Disorders of Eosinophils and Mast Cells (GREM)[a] (n=120)

And the avapritinib cohort from the Phase 1 EXPLORER[b,3] and Phase 2 PATHFINDER[c,4,5] clinical studies of avapritinib (n=167)



External validation cohort

From the French "Rare Diseases Reference Center Mastocytosis (CEREMAST)"

Includes 103 midostaurin-treated AdvSM patients, 28 of whom subsequently received avapritinib

[a]Data cutoff date 2024. [b]Data cutoff date January 19, 2023. [c]Data cutoff date September 15, 2023.

Table 1. Development of the Revised Mutation-Adjusted Risk Score (MARS-R)

Variable	Reference	Range[a]	HR[b] (95% Wald CI)	Coefficients (w_j)
Age, years	—	f(x)=max(38, min(x,86))	1.051 (1.028–1.073)	w_{age}
Monocyte count (×10⁹/L)	—	f(x)=max(x,9.0)	1.294 (1.070–1.565)	$w_{monocytes}$[c]
Platelet count (×10⁹/L)	—	f(x)=max(x,250)	0.998 (0.996–0.999)	$w_{platelets}$
ASXL1	Mutated	—	1.723 (1.122–2.645)	w_{ASXL1}
RUNX1	Mutated	—	1.700 (1.102–2.622)	w_{RUNX1}
SETBP1	Mutated	—	2.550 (1.238–5.252)	w_{SETBP1}
Sex	Female	—	0.536 (0.354–0.812)	w_{sex}
Skin involvement	Presence	—	0.661 (0.440–0.992)	w_{skin}

$$\text{MARS-R} = \text{norm}\left(\sum_{\text{variables}_j} w_j \cdot x_j\right)^{d}$$

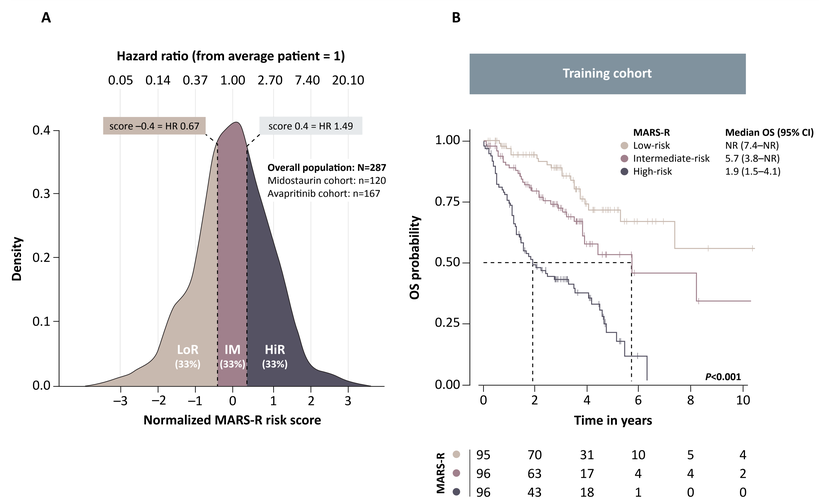
[a]Truncation at 38 and 86 years of age (1st and 99th percentile), at 9×10⁹/L for monocyte count (99th percentile) and at 250×10⁹/L for platelet count (80th percentile). [b]HR >1 is unfavorable. [c]The coefficient was normalized. [d]MARS-R was calculated as a normalized linear combination, where each observed variable x_j for a given patient is weighted by a coefficient w_j. The final sum is normalized.
CI, confidence interval; HR, hazard ratio; max, maximum; min, minimum.

Results

Development and performance of MARS-R

- MARS-R generates a continuous unique score per patient which is used to generate three different risk categories; low risk, intermediate risk, and high risk; (**Figure 2A**)
- Each risk category was associated with distinct median OS (NR vs 5.7 vs 1.9 years, *P*<0.001) (**Figure 2B**)
- MARS-R[6] consistently outperforms other prognostic models (MARS[1], IPSM[2], WHO[7])
- In all three MARS-R risk groups, avapritinib demonstrated longer OS than midostaurin (**Table 2**)

Figure 2. The MARS-R is individualizing risk assessment in AdvSM



CI, confidence interval; HiR, high-risk; HR, hazard ratio; IM, intermediate-risk; LoR, low-risk; MARS-R, Revised Mutation-Adjusted Risk Score; NR, not reached; OS, overall survival.

Table 2. OS with midostaurin and avapritinib across MARS-R risk groups

MARS-R risk category	Median OS (95% CI)		*P* value
	Midostaurin	Avapritinib	
Low-risk	7.4 (3.5–NR)	NR (NR–NR)	*P*=0.012
Intermediate-risk	3.8 (3.1–NR)	NR (NR–NR)	*P*=0.079
High-risk	1.7 (1.2–3.5)	4.1 (1.6–NR)	*P*=0.079

CI, confidence interval; MARS-R, Revised Mutation-Adjusted Risk Score; NR, not reached; OS, overall survival.

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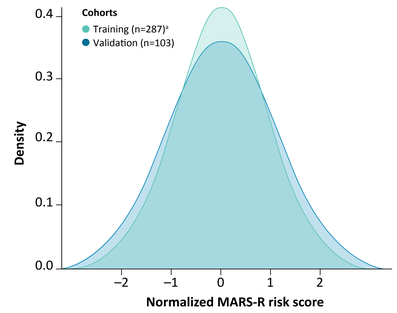
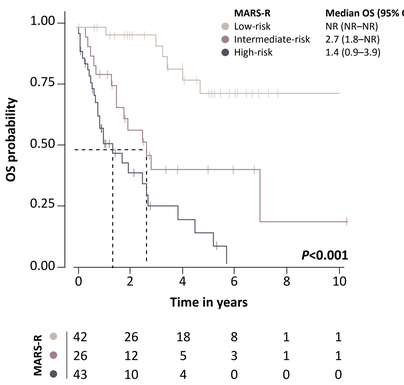
- The MARS-R risk score distribution was very similar between the training cohort (n=287) and the external validation cohort (n=103) (**Figure 3**)
- In the external validation cohort, the median OS differed significantly across MARS-R risk groups (NR vs 2.7 vs 1.4 years, *P*<0.001) (**Figure 4**)

Figure 3. External validation of the MARS-R



[a]The training cohort (n=287) is the avapritinib cohort (n=167) and the midostaurin cohort (n=120) combined (**Figure 1**).
MARS-R, Revised Mutation-Adjusted Risk Score.

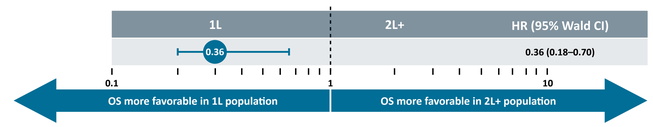
Figure 4. OS by MARS-R risk groups in validation cohort (n=103)



CI, confidence interval; MARS-R, Revised Mutation-Adjusted Risk Score; NR, not reached; OS, overall survival.

- Avapritinib was administered as 1L and 2L+ therapy in 69% and 31% of patients, respectively
- 1L avapritinib was associated with superior OS compared with 2L+ therapy (HR 0.36; 95% CI 0.18–0.70) after adjustment for baseline OS risk (by MARS-R) (**Figure 5**)

Figure 5. OS with 1L and 2L+[a] avapritinib



[a]2L+ indicates patients who were treated with at least 1 systemic therapy prior to receiving avapritinib.
1L, first-line; 2L+, second-line; CI, confidence interval; HR, hazard ratio; MARS-R, Revised Mutation-Adjusted Risk Score; OS, overall survival.

Conclusions

- The MARS-R was developed and internally validated using both categorical and continuous variables from *KIT* D816V-positive AdvSM patients treated with the KIT inhibitors midostaurin or avapritinib
- Patients can be categorized into three distinct risk categories
  - Avapritinib is associated with improved OS vs midostaurin across all three categories
- A web-based calculator is available for a standardized application of the MARS-R: www.mars-r.com
- In the era of KIT inhibitor therapy, the MARS-R can serve as an important new tool helping to make treatment decisions for *KIT* D816V-positive patients based on the risk score
- MARS-R was developed and internally validated using EXPLORER/PATHFINDER and GREM patients (n=287), and externally validated in the CEREMAST cohort (n=103)
- While previous studies of avapritinib demonstrate prolonged OS regardless of line of therapy[5,6], here we report that the first-line use of avapritinib was associated with improved OS when compared with second-line or later use, after adjustment for baseline MARS-R risk