The Revised Mutation-Adjusted Risk Score (MARS-R) for predicting overall survival in patients with advanced systemic mastocytosis treated with midostaurin or avapritinib

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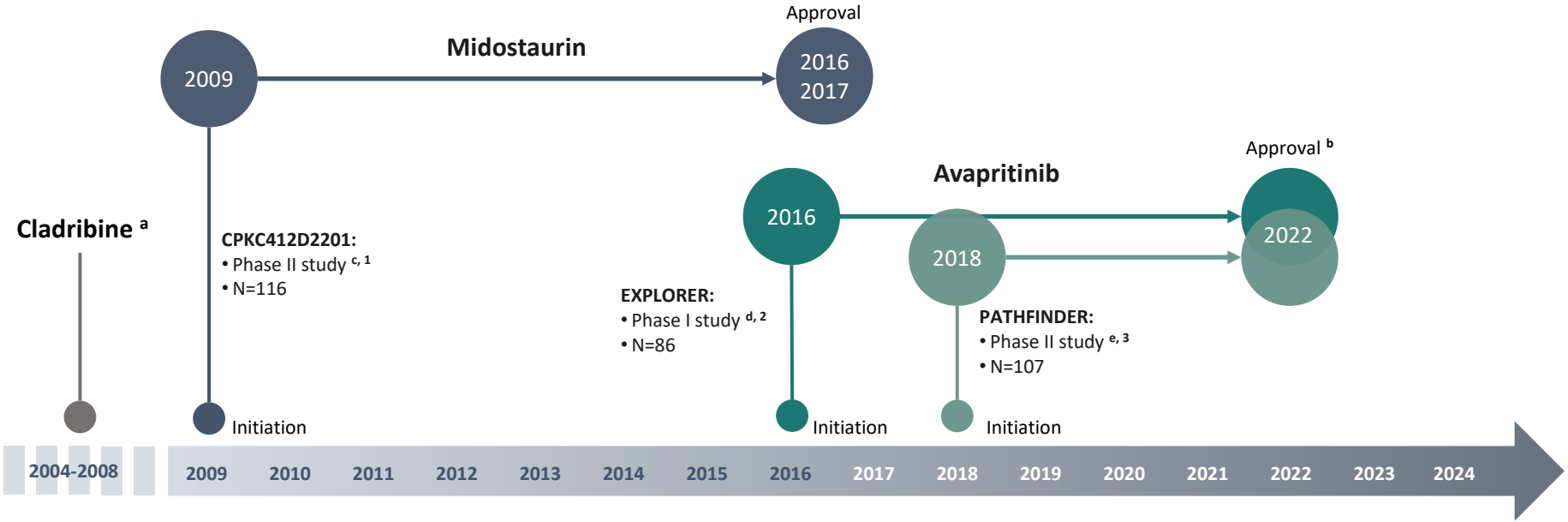
Evolving standard of care in AdvSM

Advanced systemic mastocytosis (AdvSM)

- Rare myeloid neoplasm driven by ***KIT* D816V** in >95% of patients
- Genetically complex disease, especially with associated hematologic neoplasm present and **relevant additional somatic mutations (e.g., *SRSF2, ASXL1, RUNX1, NRAS*)**

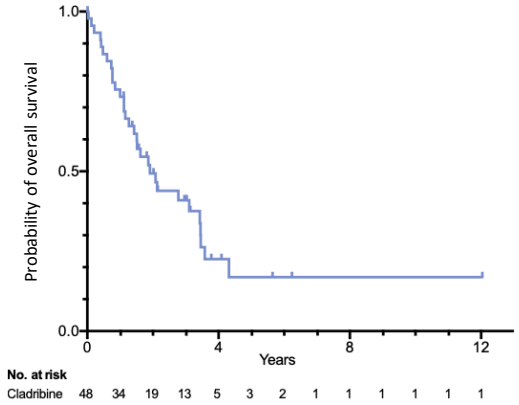


[a] Cladribine is not approved for the treatment of AdvSM. [b] Avapritinib is approved for any line by FDA and after at least 1 systemic therapy by EMA.
[c] Data cutoff date July 9, 2013. [d] Data cutoff date May 27, 2020. [e] Data cutoff date June 23, 2020.
[1] Gotlib J, et al. *N Engl J Med.* 2016;374:2530-2541. [2] DeAngelo DJ, et al. *Nature Med*. 2021;27:2183-2191. [3] Gotlib J, et al. *Nature Med*. 2021;27:2192-2199.

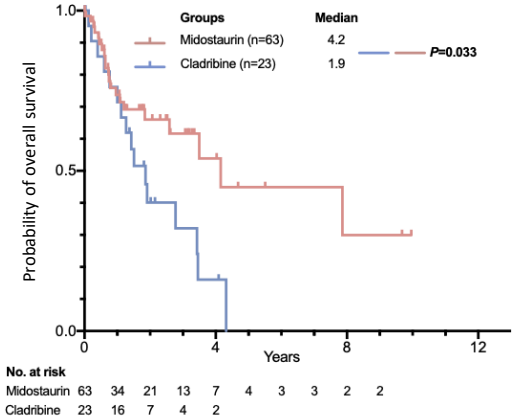
Study rationale for developing a new risk scoring system

Study rationale:

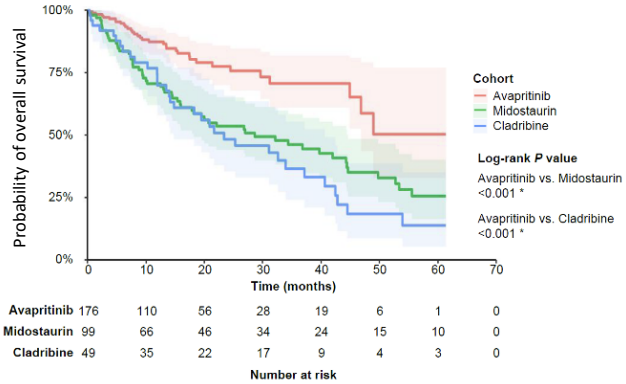
A. **Changing treatment landscape** led to **improved prognosis** of patients with AdvSM.



Cladribine [a, 1]



Midostaurin vs. cladribine [a, 2]



Avapritinib [b] **vs. midostaurin / cladribine** [a, 3]

[a] Cladribine is not approved for the treatment of AdvSM.
[b] Avapritinib is approved for any line by FDA and after at least 1 systemic therapy by EMA.
[1] Lübke J, et al. *Ann Hematol.* 2023;102:2077-2085. [2] Lübke J, et al. *J Clin Oncol.* 2022;40:1783-1794. [3] Lübke J, et al. *DGHO* 2022. Abstract V52.

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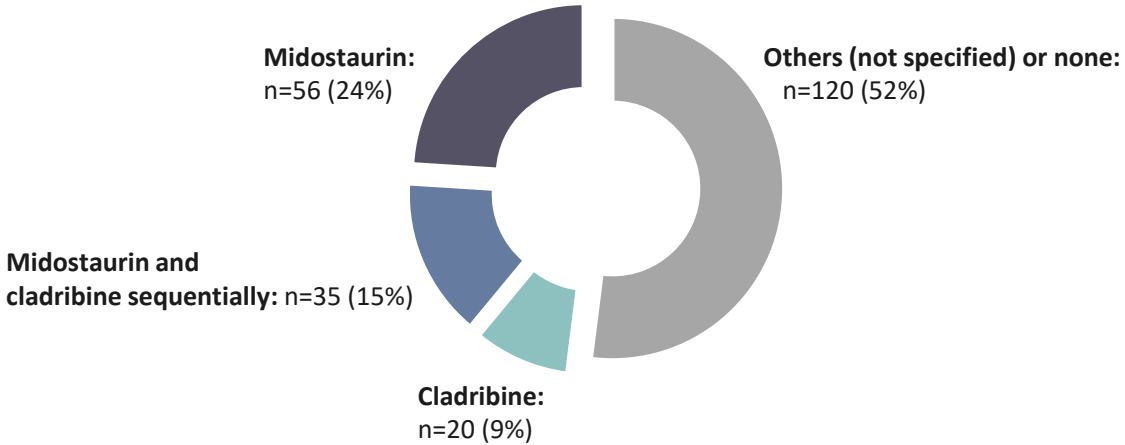
Patient population of the MARS training set (N=231) [1]



IPSM, International Prognostic Scoring System for Mastocytosis; MARS, mutation-adjusted risk score.

[1] Jawhar M, et al. *J Clin Oncol*. 2019;37:2846-2856. [2] Sperr WR, et al. *Lancet Haemtol*. 2019;6:e638-e649.

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C. Current AdvSM risk scoring systems (e.g., MARS [1], IPSM [2]) **rely solely on categorical variables**, which may **oversimplify complex data** and fail to capture important relationships - such as **linear**, **exponential**, or other patterns - between risk factors and outcomes.

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Study objective

Study rationale:

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C. Current AdvSM risk scoring systems (e.g., MARS [1], IPSM [2]) **rely solely on categorical variables**, which may **oversimplify complex data** and fail to capture important relationships - such as **linear**, **exponential**, or other patterns - between risk factors and outcomes.

Study objective:

→ To develop the **Revised Mutation-Adjusted Risk Score (MARS-R)**, a **continuous-scale OS risk scoring system** for patients with ***KIT* D816V-positive AdvSM** treated with **midostaurin or avapritinib, independent of WHO-defined subgroups.**

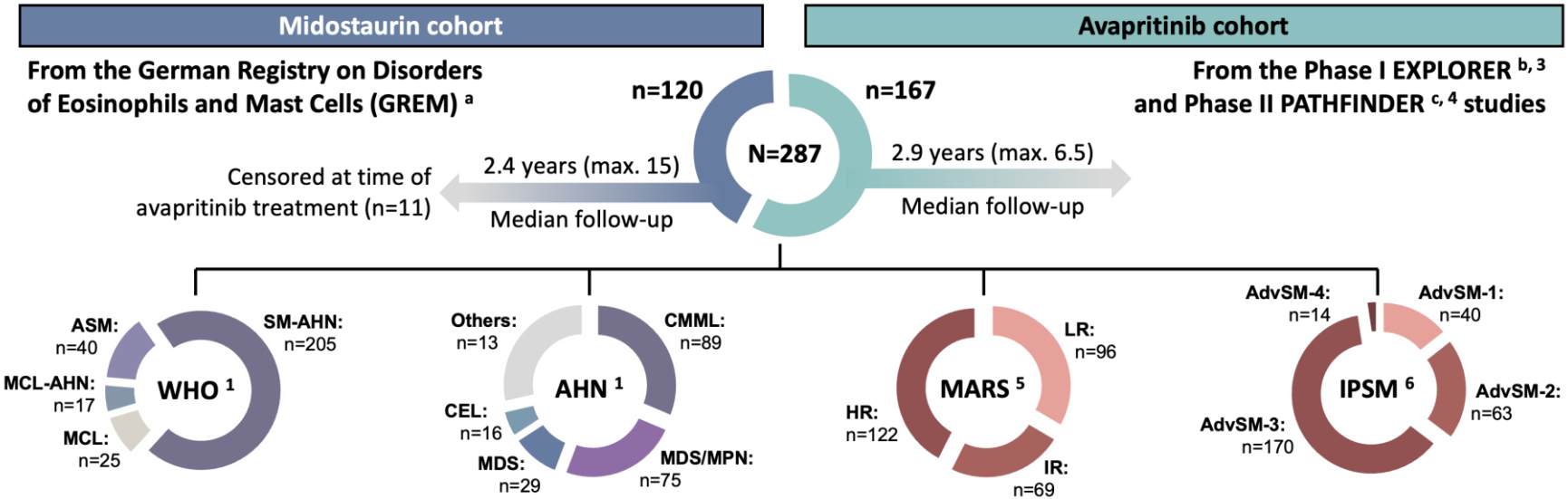
ICC, International Consensus Classification; IPSM, International Prognostic Scoring System for Mastocytosis; MARS, mutation-adjusted risk score; OS, overall survival; WHO, World Health Organization.

[1] Jawhar M, et al. *J Clin Oncol*. 2019;37:2846-2856. [2] Sperr WR, et al. *Lancet Haemtol*. 2019;6:e638-e649.

Patient cohorts

Inclusion criteria:

- **Diagnosis:** Confirmed **AdvSM** according to the **WHO** [1] **classification**
- **Genetics:** Presence of the ***KIT* D816V** mutation [2]
- **Treatment history:** Treatment with either **midostaurin** or **avapritinib**

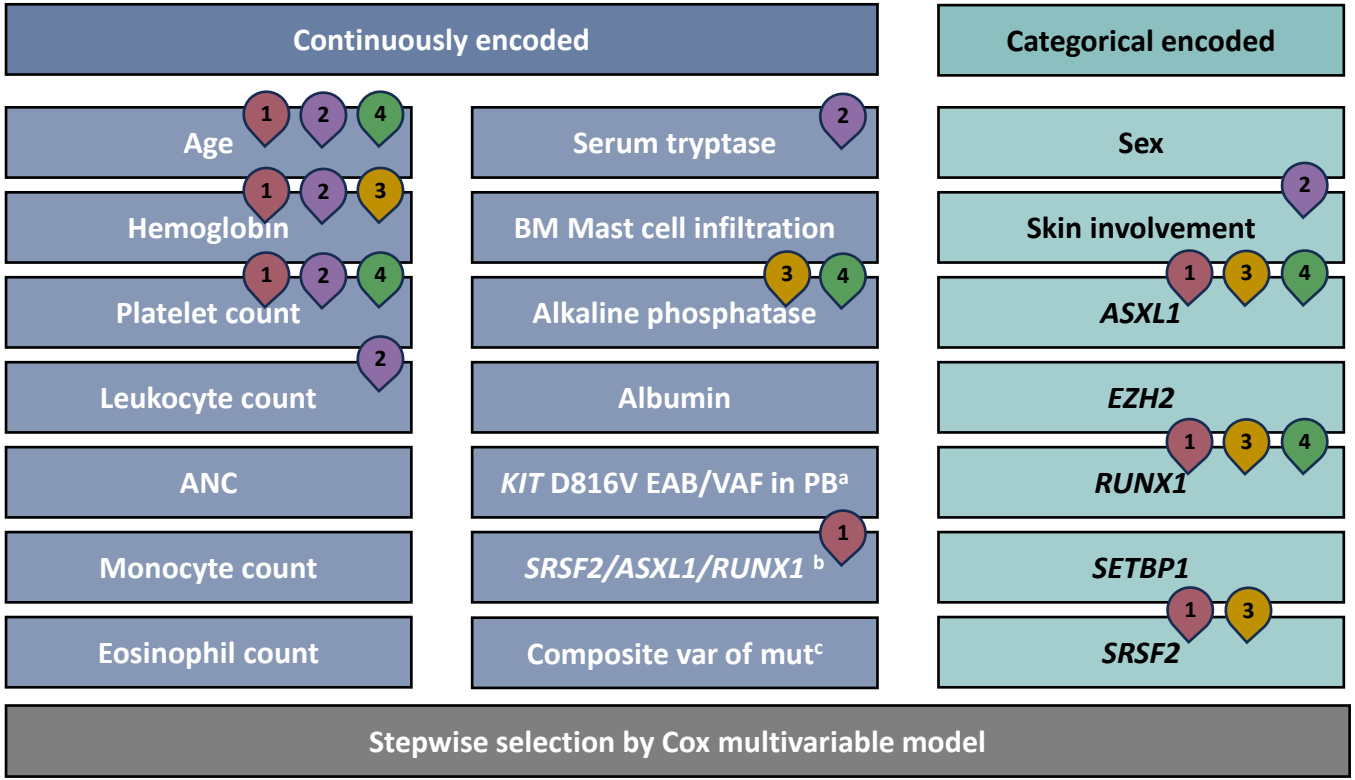


Midostaurin and avapritinib cohorts were balanced regarding WHO diagnosis, existing risk scoring systems, and C-findings.

[a] Data cutoff date 2024. [b] Data cutoff date January 19, 2023. [c] Data cutoff date September 15, 2023.
AHN, associated hematologic neoplasm; ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; HR, high risk; IR, intermediate risk; LR, low risk; max., maximum; MDS, myelodysplastic neoplasms; MPN, myeloproliferative neoplasms; WHO, World Health Organization.

[1] Khoury JD, et al. *Leukemia.* 2022;36:1703-1719. [2] Naumann N, et al. *Cancers (Basel).* 2024;16:593. [3] DeAngelo DJ, et al. *Nature Med*. 2021;27:2183-2191. [4] Gotlib J, et al. *Nature Med*. 2021;27:2192-2199.
[5] Jawhar M, et al. *J Clin Oncol*. 2019;37:2846-2856. [6] Sperr WR, et al. *Lancet Haemtol*. 2019;6:e638-e649.

Selection of clinical and genetic candidate risk variables



AdvSM (Training cohort)

1. MARS (N=231, 2019) [1]
2. IPSM (N=259, 2019) [2]

SM (Training cohort)

3. GPSM (N=422, 2021) [3]
4. MAPS (N=145, 2018) [4]

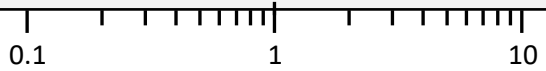
[a] *KIT* D816V was measured on RNA or DNA level in midostaurin- or avapritinib-treated patients, respectively.
[b] The number of mutations within the *SRSF2/ASXL1/RUNX1* gene panel was tested.
[c] A composite variable consisting of the number of additional somatic mutations was tested.
ANC, absolute neutrophil count; BM, bone marrow; EAB, expressed allele burden; GPSM, global prognostic score for mastocytosis; MAPS, Mayo alliance prognostic system for mastocytosis; mut, mutations; PB, peripheral blood; VAF, variant allele burden; var, variable.

[1] Jawhar M, et al. *J Clin Oncol*. 2019;37:2846-2856. [2] Sperr WR, et al. *Lancet Haemtol*. 2019;6:e638-e649. [3] Munoz-Gonzalez JI, et al. *Lancet Haematol*. 2021;8:e193-e204 . [4] Pardanani A, et al. *Blood Adv*. 2018;2:2964-2972.

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

Continuously scaled

	Reference	Range [a]	Favorable	Unfavorable	HR (95% Wald CI)	Coefficients (w_j)
Age (years)	-	f(x)=max(38, min(x,86))	1.1		1.051 (1.028-1.073)	w_{age}
Monocyte count (x10^9/L)	-	f(x)=max(x,9.0)	1.3		1.294 (1.070-1.565)	$W_{monocytes}$ [b]
Platelet count (x10^9/L)	-	f(x)=max(x,250)	0.9		0.998 (0.996-0.999)	$w_{platelets}$



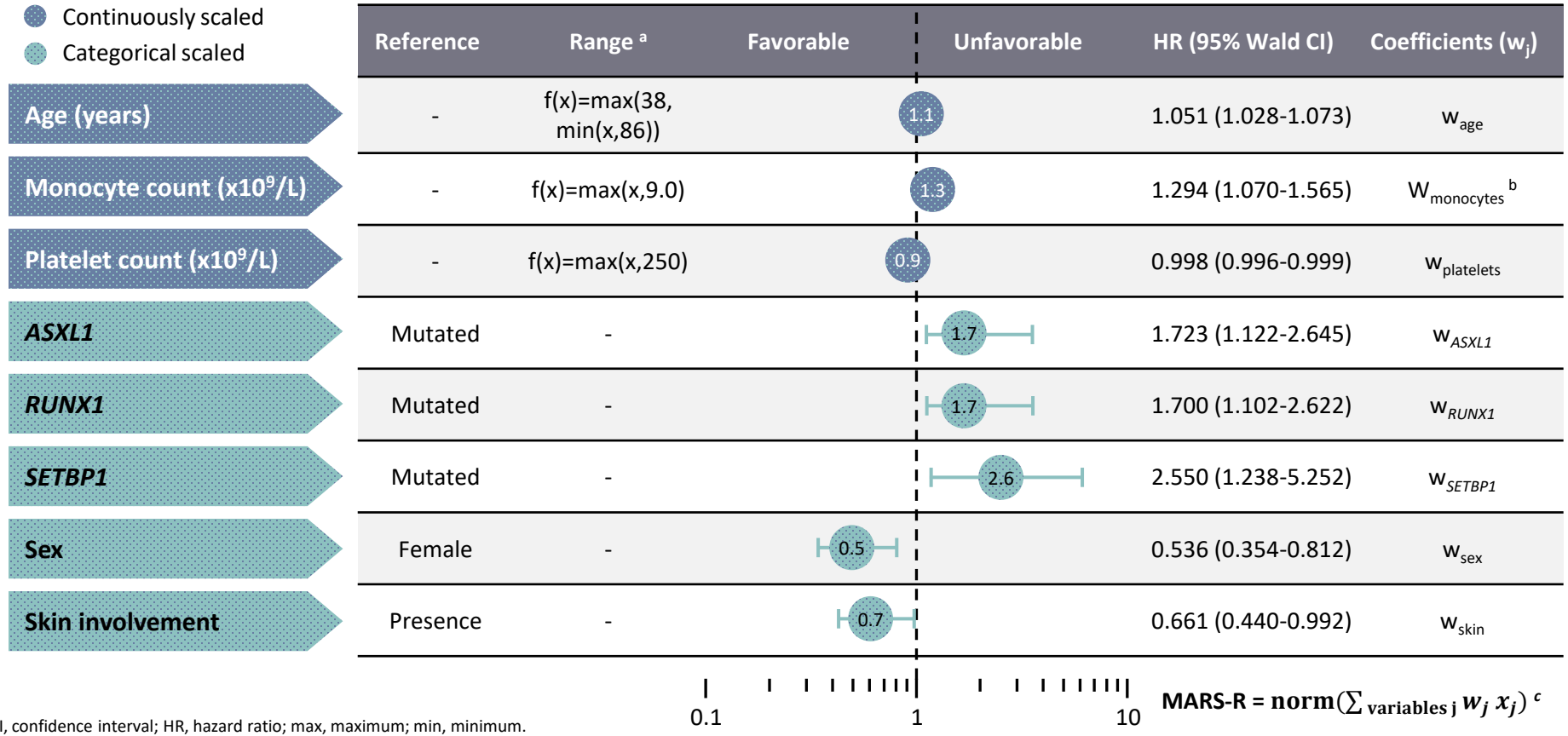
CI, confidence interval; HR, hazard ratio; max, maximum; min, minimum.

[a] Truncation at 38 and 86 years for age (1st and 99th percentile), at 9 x10^9/L for monocyte count (99th percentile) and at 250 x10^9/L for platelet count (80th percentile).

[b] The coefficient was normalized.

[c] 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.

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



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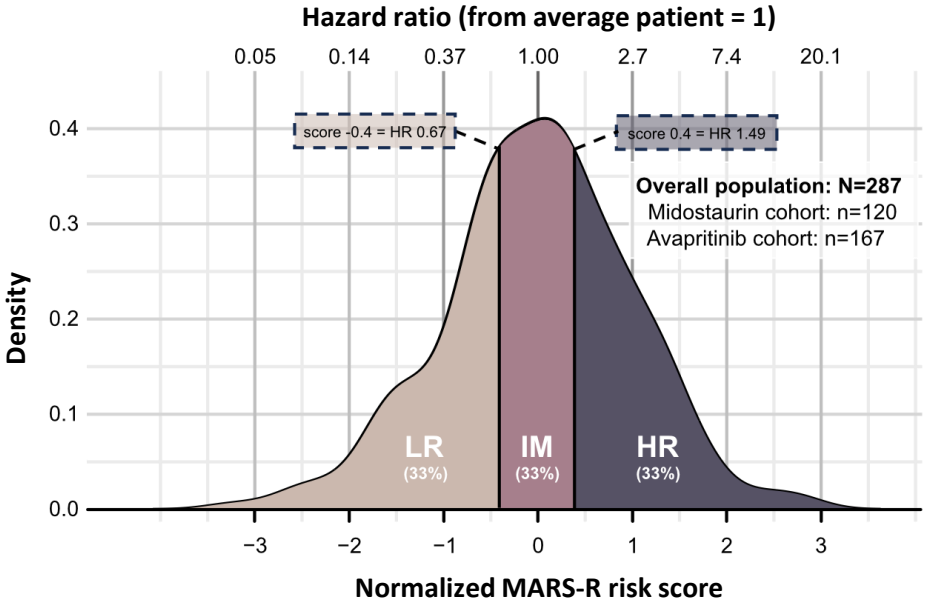
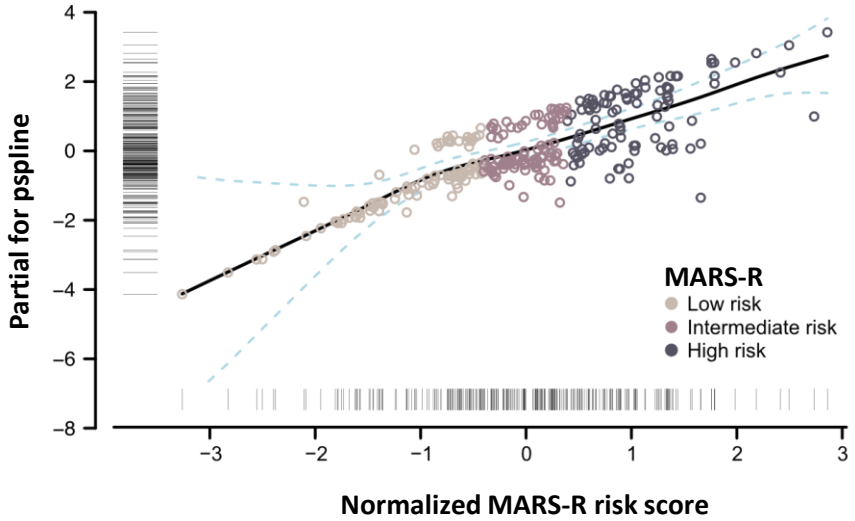
The MARS-R is individualizing risk assessment in AdvSM

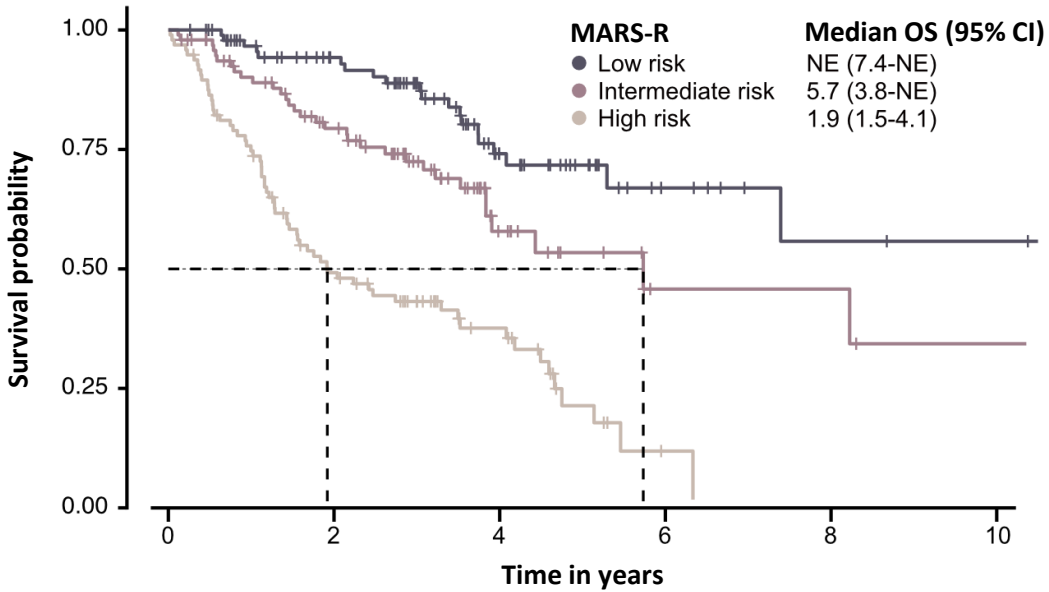
- The **MARS-R** provides a **continuous score** with a **virtually unique value per patient**
- **Negative** or **positive scores** reflect **worse or better OS** compared to the **average-risk AdvSM patient**





- Smoothing splines modeling the functional MARS-R risk representation shows a consistent linear progression across the entire scale
- **Equal percentile-based cutoffs** to the **continuous MARS-R scale** were applied to generate **three different risk categories**

Overall survival according to MARS-R categories



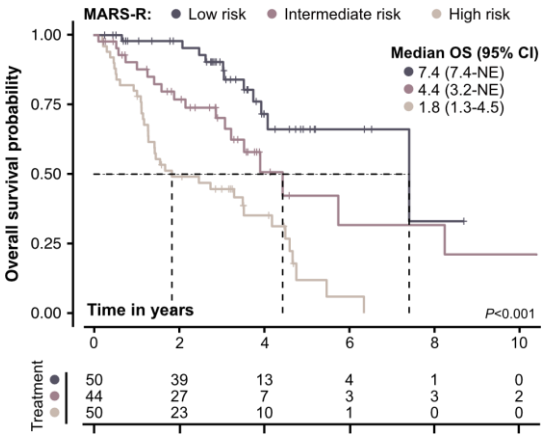
Overall survival (%)

By year	MARS-R categories LR	IR	HR
1	97	90	75
2	94	79	49
3	89	72	43
4	74	58	38
5	72	53	21
6	67	46	12
7	67	46	-
8	56	46	-
9	56	34	-
10	56	34	-

HR, high risk; IR, intermediate risk; LR, low risk; NE, not estimable.

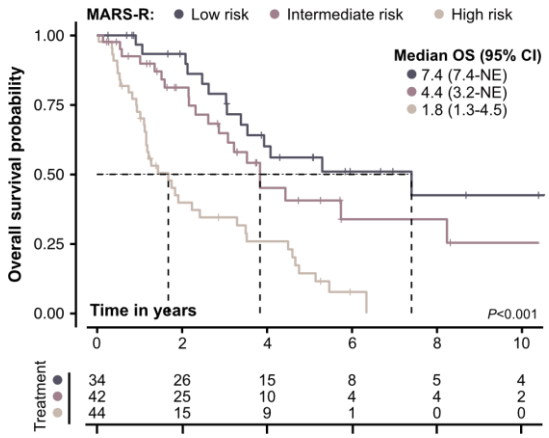
The MARS-R has been internally validated

Validation cohort (50% random split)



The **MARS-R** can be **independently** applied to *KIT* D816V-positive AdvSM patients **at time of midostaurin** or **avapritinib start.**

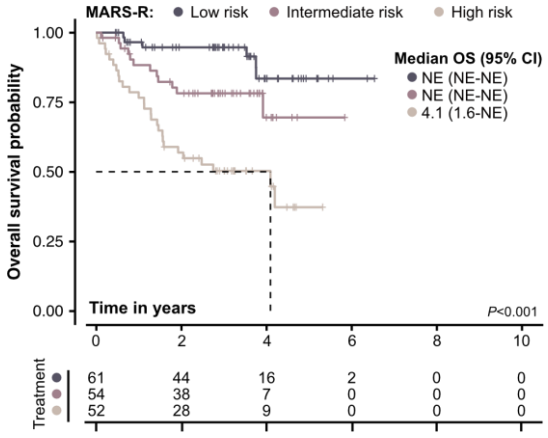
Midostaurin treatment (GREM)



Overall survival (%)

By year	1	2	3	4	5
MARS-R LR	97	93	79	60	56
MARS-R IR	92	81	65	45	41
MARS-R HR	72	40	35	26	14

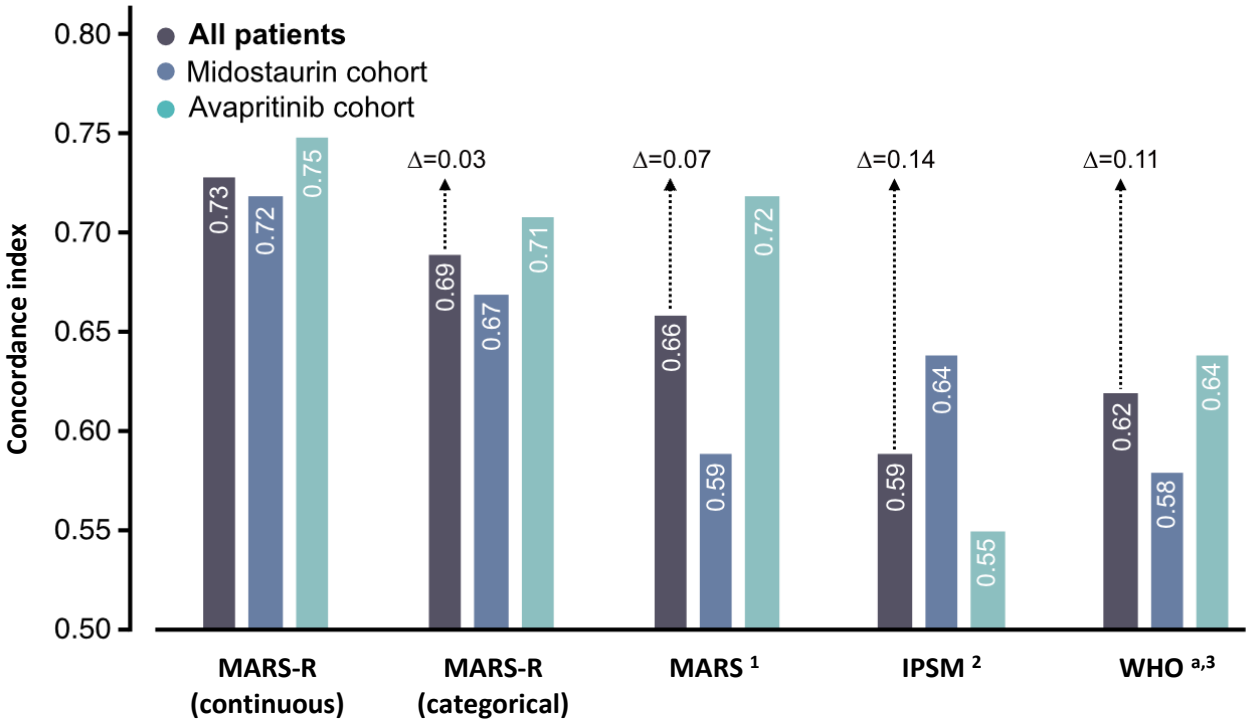
Avapritinib treatment



Overall survival (%)

By year	1	2	3	4	5
MARS-R LR	97	95	95	83	83
MARS-R IR	88	78	78	69	69
MARS-R HR	77	57	50	50	37

The MARS-R is a better discriminator of the risk

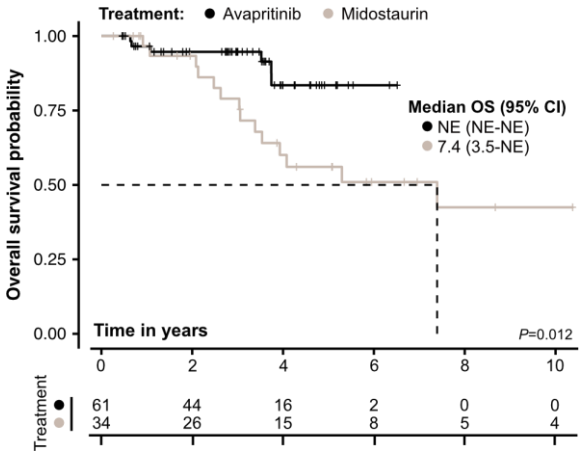


The **MARS-R** consistently **outperforms** other prognostic models, **independent of treatment** with **midostaurin** and/or **avapritinib**.

[a] Patients were grouped into 4 different subgroups: ASM, MCL, SM-AHN, and MCL-AHN.
The Δ symbol denotes the difference in Harrell's Concordance index between the continuously scaled MARS-R and alternative models.
[1] Jawhar M, et al. *J Clin Oncol*. 2019;37:2846-2856. [2] Sperr WR, et al. *Lancet Haemtol*. 2019;6:e638-e649. [3] Khoury JD, et al. *Leukemia.* 2022;36:1703-1719.

Avapritinib demonstrates longer OS vs midostaurin in all 3 MARS-R risk groups

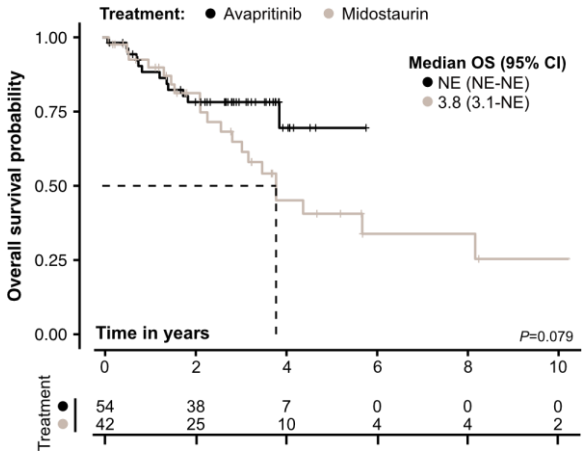
Low risk



Overall survival (%)

By year	1	2	3	4	5
Ava	97	95	95	83	83
Mido	97	93	79	60	56

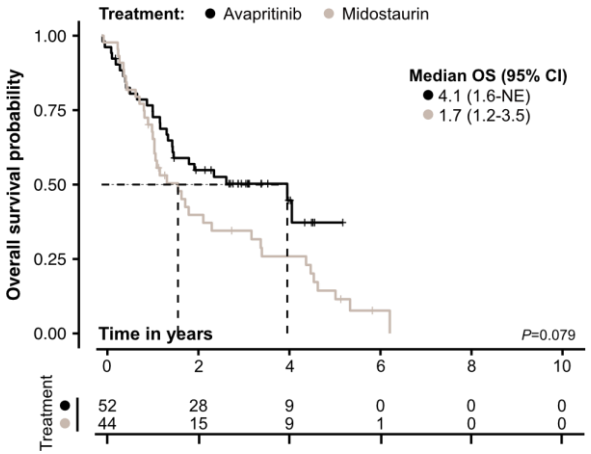
Intermediate risk



Overall survival (%)

By year	1	2	3	4	5
Ava	88	78	78	70	70
Mido	92	81	65	45	41

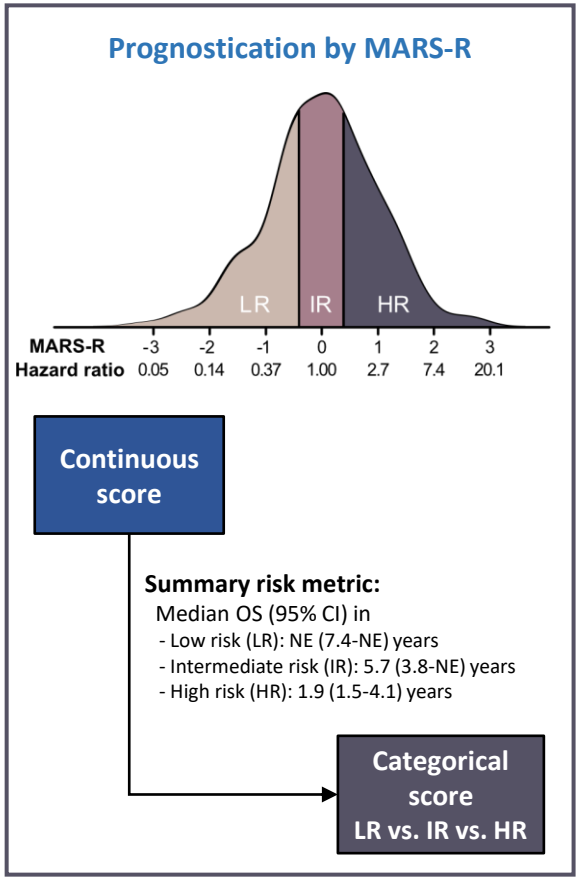
High risk



Overall survival (%)

By year	1	2	3	4	5
Ava	77	57	50	50	37
Mido	72	40	35	26	14

Conclusions



- The MARS-R was developed using both categorical and continuous variables from patients treated with the KIT inhibitors midostaurin or avapritinib
- Patients can be categorized into 3 distinct risk categories
- This new model offers advantages over the existing models:
  - A continuous score that provides an individual value for each patient
  - Captures the continuum of OS risk in patients with AdvSM
  - Highly reproducible and applicable to patients receiving midostaurin or avapritinib
- In the era of KIT inhibitor therapy, the MARS-R can serve as an important new tool helping treatment decisions for *KIT* D816V-positive patients based on the risk score

Acknowledgments

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- We thank the investigators and clinical trial teams for their contributions to the studies
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