Novel Machine Learning-Based Model Predicts Presence of Associated Hematologic Neoplasms in Advanced Systemic Mastocytosis

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Poster Number PS1999

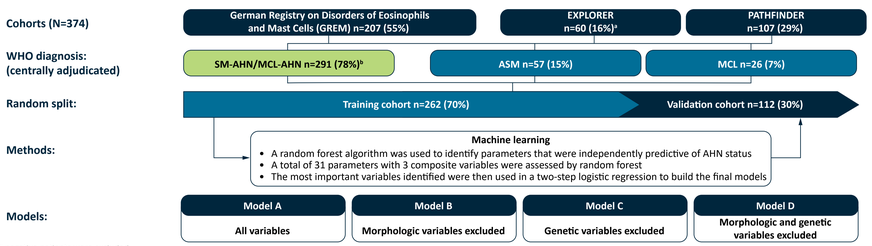
Background, Rationale, and Objectives

- Advanced systemic mastocytosis (AdvSM) is a rare clonal hematologic neoplasm driven by the *KIT* D816V mutation in approximately 95% of cases
- AdvSM comprises three subtypes: aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL)
- SM-AHN is the most common and heterogeneous AdvSM subtype (~60–80% of cases)
  - AHN subtypes include chronic myelomonocytic leukemia (CMML), myelodysplastic/myeloproliferative neoplasms, unclassifiable (MDS/MPN-U), myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), chronic eosinophilic leukemia (CEL), and acute myeloid leukemia (AML)
- Identification of AHN at diagnosis is challenging because SM may dominate the clinico-morphologic picture and obscure the AHN
  - This may result in SM-AHN being underrecognized or misdiagnosed
- Accurate detection of AHN is critical for clinical management, as it influences treatment selection, dosing strategy, and prognosis
- In routine practice, complete morphologic and genetic data may not be available, highlighting the need for models that remain applicable across different diagnostic settings
- The objective of this study was to develop and validate tiered machine learning models that estimate the likelihood of AHN in patients with AdvSM

Patients and Methods

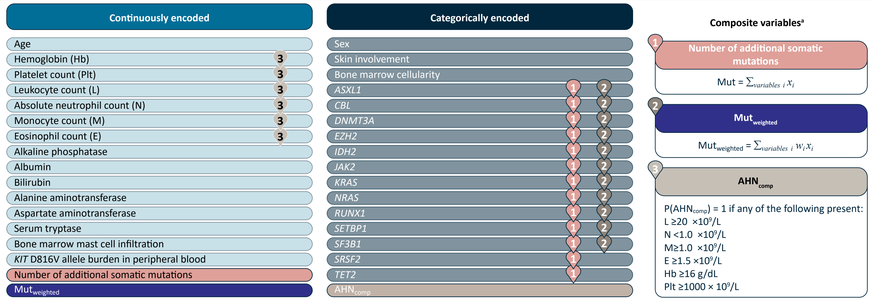
- This study (**Figure 1**) included patients from the German Registry on Disorders of Eosinophils and Mast Cells (GREM) and from the EXPLORER and PATHFINDER clinical trials of avapritinib
- Diagnoses of AdvSM, including assessment of the presence or absence of an AHN, were established according to the 2016 WHO criteria by central review in the EXPLORER and the PATHFINDER clinical trials
- All AHNs were of myeloid origin
- Bone marrow and tissue samples underwent central review by reference pathologists
- Baseline clinical and genetic variables (n=33), including composite variables, were assessed at diagnosis (GREM) or at start of avapritinib (EXPLORER/PATHFINDER) (**Figure 2**)
- Random forest–guided variable selection followed by two-step logistic regression was used to generate models that were robust to variable data availability
- Patients with model-predicted probabilities of 0.5≤P<1.0 were classified as having AHN

Figure 1. Study overview



[a]Nine *KIT*-negative patients were excluded.
[b]SM-AHN n=273 (73%), MCL-AHN n=18 (5%).
AHN subtypes: CMML n=107 (29%); MDS/MPN n=86 (23%); MDS n=44 (12%); CEL n=28 (7%); others n=109 (29%).
Diagnoses of AdvSM were assigned according to 2016 World Health Organization (WHO) criteria.
AdvSM, advanced systemic mastocytosis; AHN, associated hematologic neoplasm; ASM, aggressive systemic mastocytosis; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; MCL, mast cell leukemia; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic/myeloproliferative neoplasms; SM, systemic mastocytosis.

Figure 2. Candidate variables

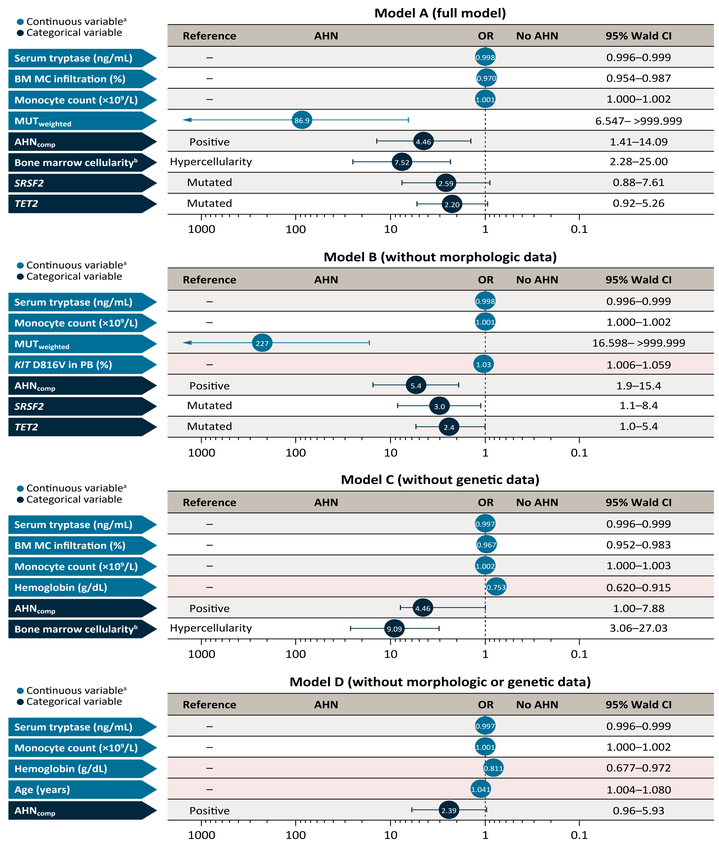


[a]Based on statistical weighting of variables.
w_i, weighting coefficient; x_i, variable.

Results

- Overall, 374 patients (167 from EXPLORER/PATHFINDER and 207 from GREM) were included
- Median (range) age at treatment initiation was 69 (26–88) years and 229 patients (61%) were male
- Prior treatments in the EXPLORER/PATHFINDER population (n=167) were midostaurin n=77 (46%), cladribine n=21 (13), hypomethylating agents n=9 (5%), and chemotherapy n=19 (11%). Some patients had received more than one drug. 71 patients (43%) were treatment-naïve
- Odds ratios (ORs) were calculated for each variable included in each model (**Figure 3**) predicting AHN by:
  - Full model (A): lower serum tryptase, higher monocytes, fewer bone marrow (BM) mast cell (MC) aggregates, BM hypercellularity, higher $MUT_{weighted}$, AHN_{comp}, *SRSF2* mutation, and *TET2* mutation
  - Model B: lower serum tryptase, higher monocytes, higher $MUT_{weighted}$, higher peripheral blood (PB) *KIT* D816V allele burden, AHN_{comp}, and *SRSF2* and *TET2* mutations
  - Model C: lower serum tryptase, higher monocytes, fewer BM MC aggregates, lower hemoglobin, AHN_{comp}, and BM hypercellularity
  - Model D: lower serum tryptase, higher monocytes, lower hemoglobin, higher age, and AHN_{comp}
- Model performance was comparable when next-generation sequencing was performed on BM vs PB

Figure 3. Models evaluated in the study



[a]For continuous variables, the ORs reflect the change in odds per unit increase. [b]Models A and C accounted for missing variables for cellularity. New parameters compared with Model A are highlighted in red.
SRSF2 and *TET2* are the additional somatic mutations referred to in **Figures 2 and 4**. AHN_{comp} positive is defined as the presence of any of the parameters listed in **Figure 2**. The linear predictor is calculated as a linear combination, where each observed variable x_i for a given patient is weighted by a coefficient w_i. The resulting linear predictor is then converted into a probability using the log transformation. Figure shows adjusted associations within the multivariable models.
AHN, associated hematologic neoplasm; BM, bone marrow; CI, confidence interval; MC, mast cell; OR, odds ratio; PB, peripheral blood.

Figure 4. Relationship between AHN score and number of mutations

- The composite variable "Mut" mainly distinguishes 0 vs ≥1 mutation, with little added risk increase beyond the first mutation (**Figure 4A**)
- The composite variable "$Mut_{weighted}$" provides a more continuous association with AHN (**Figure 4B**)

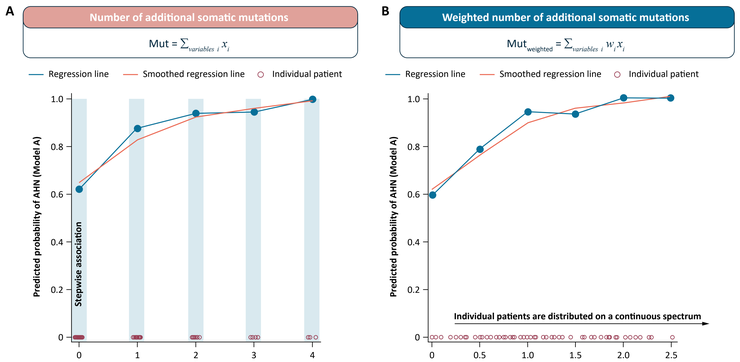
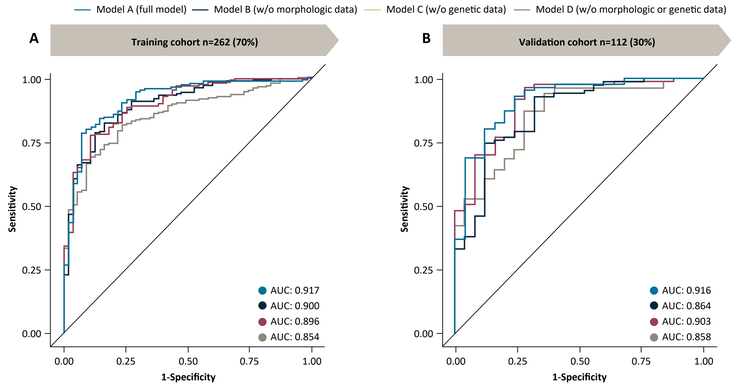


Figure 5. Performance of the models in training and validation cohorts

- ROC curves showed strong discriminatory performance between AHN and no AHN in AdvSM, with the highest performance observed for Model A (full model) and preserved discriminatory ability across all models in both the training (**Figure 5A**) and validation (**Figure 5B**) cohorts



AUC, area under the receiver operating characteristic curve; w/o, without.

Conclusions

- Tiered machine learning models identified AHN with high sensitivity across varying diagnostic settings
- The presence of AHN in AdvSM can be predicted with high accuracy using adaptable models that retain performance even in cases where blood is the only sample available
- These models provide an important tool supporting accurate diagnoses of AdvSM and may improve real-world recognition of AHN in AdvSM

Acknowledgments
This study was funded by Blueprint Medicines Corporation, Cambridge, MA, a wholly owned subsidiary of Sanofi. Editorial support, under the guidance of the authors, was provided by Richard Murphy, PhD, an employee from the Publications and Medical Affairs Division of Omnicom Health Medical Communications and was funded by Blueprint Medicines Corporation, a wholly owned subsidiary of Sanofi, in accordance with Good Publication Practice, GPP 2022 (*Ann Intern Med* 2022;175:1298–1304). The sponsor reviewed and provided feedback on the presentation. However, the authors had full editorial control and provided final approval of all content.