High Accuracy of Peripheral Blood Testing Using Machine Learning–Derived Models to Differentiate Advanced *Versus* Indolent Systemic Mastocytosis: Analysis of Avapritinib and Elenestinib Trial Data

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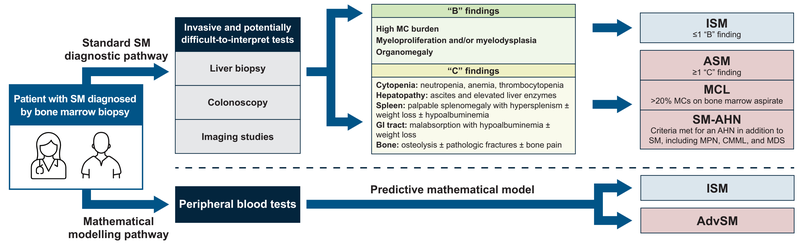
Introduction

- Systemic mastocytosis (SM) is a clonal hematologic neoplasm driven by the *KIT* D816V mutation in ~95% of cases[1-3]
- The prevalence of SM has been estimated at up to 1 in 5000 people[4-7]
- The two most common subtypes of SM are indolent SM (ISM) and advanced SM (AdvSM; **Figure 1**)[8-10]
  - ISM accounts for ~85% of patients with SM[2,5,11] and is characterized by debilitating symptoms across multiple organ systems, life-threatening anaphylaxis, and potential progression to AdvSM[1,12,13]
  - AdvSM is characterized by organ damage and associated shortened overall survival[9,10,14]
- Classification of SM per World Health Organization-defined criteria requires a high level of clinical and hematopathologic expertise as well as invasive diagnostic techniques (**Figure 1**)[9,10]
- Machine learning might identify algorithms that can assist clinicians in the accurate classification of SM; however, this requires large and well-characterized data sets
- To achieve this, we amassed such a dataset by combining patient-level baseline data from:
  - Clinical trials of avapritinib, a potent and highly selective KIT D816V inhibitor[15] approved in the US and Europe for the treatment of ISM and AdvSM (in Europe after ≥1 prior systemic therapy)[16,17]
  - HARBOR, an ongoing, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of elenestinib (a next-generation, potent, and highly selective KIT D816V inhibitor with limited central nervous system penetration) plus symptom-directed therapy in patients with ISM and smoldering SM[18]
  - Patients with AdvSM and ISM treated at the Dana-Farber Cancer Institute (DFCI)
- These data allowed us to use machine learning to develop and validate predictive models that distinguish AdvSM from ISM using only patient demographics and widely available peripheral blood tests

Figure 1. Clinical work-up and classification of the newly diagnosed SM patient[1,9,10,19]

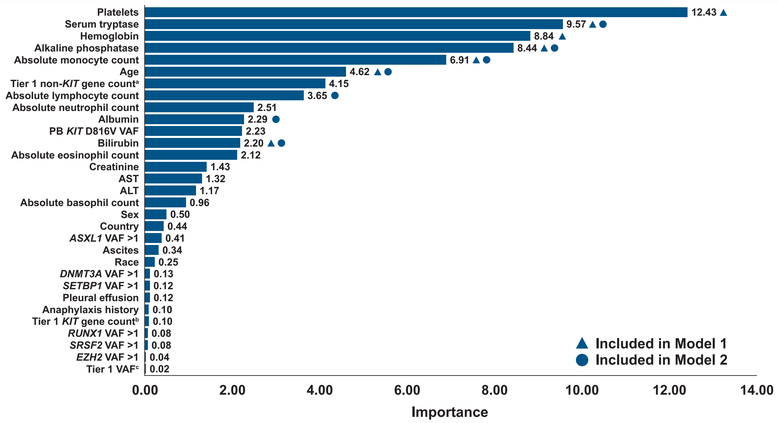


AdvSM, advanced systemic mastocytosis; AHN, associated hematological neoplasm; ASM, aggressive systemic mastocytosis; CMML, chronic myelomonocytic leukemia; GI, gastrointestinal; ISM, indolent systemic mastocytosis; MC, mast cell; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; SM, systemic mastocytosis.

Methods

- A random forest algorithm was applied to data from clinical trials of avapritinib (N=441) to identify parameters independently predictive of ISM *versus* AdvSM (**Figure 2**)
- The clinical trials of avapritinib included patients from PATHFINDER (NCT03580655; AdvSM), EXPLORER (NCT02561988; AdvSM and ISM), and PIONEER (NCT03731260; ISM)

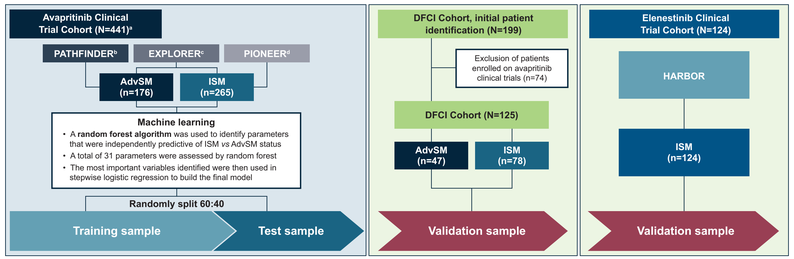
Figure 2. Random forest algorithm with variables ranked by Gini index importance in determining AdvSM *versus* ISM



[a]Represents the number of tier 1 mutations in non-*KIT* genes (e.g., *SRSF2*, *ASXL1*, *RUNX1*). [b]A binary variable indicating whether a tier 1 mutation was detected in the *KIT* gene. [c]A binary variable indicating whether a tier 1 mutation with a VAF >1% was detected in any gene assessed by the TruSight Myeloid Sequencing Panel. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PB, peripheral blood; VAF, variant allele frequency.

- Important variables were then used in stepwise logistic regression to build two distinct models (Model 1 and Model 2), both of which employed a combination of age plus routinely measured parameters in the peripheral blood to distinguish AdvSM from ISM
- Models were trained and tested on the avapritinib clinical trial data (N=441) split 60:40 between training and test cohorts and included adult patients as shown in **Figure 3**
- Models were then validated in independent cohorts of patients with AdvSM and ISM from DFCI (N=125), as well as patients with ISM treated with elenestinib in HARBOR (NCT04910685; N=124)

Figure 3. Study design



[a]In total, 441/444 patients were used in model development including 265 patients with ISM, 29 patients with ASM, 119 patients with SM-AHN, and 28 patients with MCL. In total, 3 patients were not included (2 patients with SSM and 1 patient who did not have SM). [b]PATHFINDER: N=107; NCT03580655. [c]In EXPLORER (N=93; NCT02561988), 69 patients had AdvSM, 14 patients had ISM, 2 patients had SSM, and 1 patient did not have SM. Patients who had SSM and patients who did not have SM (n=3) were not included in the analyses. [d]PIONEER: N=251; NCT03731260. DFCI, Dana-Farber Cancer Institute; SSM, smoldering systemic mastocytosis.

Results

- Model 1 predicted AdvSM *versus* ISM using the following objective parameters:

$$f(\text{platelets}) + f(\text{tryptase}) + f(\text{hemoglobin}) + f(\text{alkaline phosphatase}) + f(\text{absolute monocytes}) + f(\text{age}) + f(\text{total bilirubin}) = \text{P(AdvSM)} \begin{cases} 0 \le P < 0.5 \rightarrow \text{ISM} \\ 0.5 \le P < 1 \rightarrow \text{AdvSM} \end{cases}$$

- As C-findings such as thrombocytopenia and anemia are already used for AdvSM diagnosis,[20] Model 2 was developed
- Model 2 predicted AdvSM *versus* ISM using the following objective parameters:

$$f(\text{age}) + f(\text{alkaline phosphatase}) + f(\text{tryptase}) + f(\text{total bilirubin}) + f(\text{albumin}) + f(\text{absolute monocyte count}) + f(\text{absolute lymphocyte count}) = \text{P(AdvSM)} \begin{cases} 0 \le P < 0.5 \rightarrow \text{ISM} \\ 0.5 \le P < 1 \rightarrow \text{AdvSM} \end{cases}$$

- A fixed threshold of 0.5 was used for classification to enable direct comparison across datasets and models; however, additional work is underway to optimize thresholds based on cohort characteristics and clinical relevance
- Model 1 and Model 2 demonstrated high accuracy in distinguishing AdvSM from ISM in both the training and external validation cohorts (**Table 1** and **Figure 4**)

Table 1. Area under the receiver operating characteristic curve in Model 1 and Model 2 across all cohorts

	AUC Model 1	Correctly classified patients Model 1	AUC Model 2	Correctly classified patients Model 2
Avapritinib Clinical Trial Cohort (n=441)	0.97	93%	0.96	93%
DFCI Cohort (n=125)	0.92	89%	0.90	86%
Elenestinib Clinical Trial Cohort (n=124)	0.99	98%	0.98	98%

AUC, area under the curve.

- In all three datasets, patients with ISM misclassified as having AdvSM demonstrated features of high disease burden not typically observed in ISM (**Table 2**)

Table 2. Comprehensive evaluation of misclassified patients with ISM across all cohorts

	Patients misclassified as AdvSM by Model 1	Patients misclassified as AdvSM by Model 2
Patients misclassified, n (%) (Percentage of total patients with ISM analyzed, n=467)	22 (5)	22 (5)
Age (years), median (range)	62 (47.2–83.9)	64 (47.2–83.9)
Disease burden measures		
Median (range) serum tryptase, ng/mL	210 (33–612)	193 (22–612)
Median (range) *KIT* D816V VAF in peripheral blood, %	6.07 (0.09–41.7) [n=16]	5.39 (0.11–41.7) [n=15]
Median (range) bone marrow mast cells on core biopsy, %	22.5 (7–70) [n=16]	25.0 (5–70) [n=15]

- Similarly, patients with AdvSM that were misclassified as ISM generally had lower disease burden measures (**Table 3**)

Table 3. Comprehensive evaluation of misclassified patients with AdvSM across all cohorts

	Patients misclassified as ISM by Model 1	Patients misclassified as ISM by Model 2
Patients misclassified, n (%) (Percentage of total patients analyzed with AdvSM, n=223)	17 (8)	21 (9)
Age (years), median (range)	59 (38.0–77.0)	57 (38.0–69.0)
Disease burden measures		
Median (range) serum tryptase, ng/mL	129 (20–524)	71 (12–334)
Median (range) *KIT* D816V VAF in peripheral blood, %	1.44 (0.00–42.98) [n=15]	0.79 (0.00–40.20) [n=21]
Median (range) bone marrow mast cells on core biopsy, %	17.5 (1.0–80.0) [n=16]	20.0 (5.0–90.0) [n=20]

Figure 4. Expert- and model-predicted diagnosis of SM

A) Avapritinib Clinical Trial Cohort (includes patients with AdvSM and ISM from the EXPLORER, PATHFINDER, and PIONEER trials)

Model 1

Central pathology diagnosis by WHO 2016 criteria	Model-predicted diagnosis: ISM	Model-predicted diagnosis: AdvSM
ISM	**251 patients** predicted as ISM by both the model and WHO 2016 criteria	**14 patients** predicted as AdvSM by model but ISM by WHO 2016 criteria
AdvSM	**17 patients** predicted as ISM by model but AdvSM by WHO 2016 criteria	**159 patients** predicted as AdvSM by both the model and WHO 2016 criteria

Model 2

Central pathology diagnosis by WHO 2016 criteria	Model-predicted diagnosis: ISM	Model-predicted diagnosis: AdvSM
ISM	**253 patients** predicted as ISM by both the model and WHO 2016 criteria	**12 patients** predicted as AdvSM by model but ISM by WHO 2016 criteria
AdvSM	**21 patients** predicted as ISM by model but AdvSM by WHO 2016 criteria	**155 patients** predicted as AdvSM by both the model and WHO 2016 criteria

B) DFCI cohort

Model 1

Central pathology diagnosis by WHO 2016 criteria	Model-predicted diagnosis: ISM	Model-predicted diagnosis: AdvSM
ISM	**72 patients** predicted as ISM by both the model and WHO 2016 criteria	**6 patients** predicted as AdvSM by model but ISM by WHO 2016 criteria
AdvSM	**8 patients** predicted as ISM by model but AdvSM by WHO 2016 criteria	**39 patients** predicted as AdvSM by both the model and WHO 2016 criteria

Model 2

Central pathology diagnosis by WHO 2016 criteria	Model-predicted diagnosis: ISM	Model-predicted diagnosis: AdvSM
ISM	**71 patients** predicted as ISM by both the model and WHO 2016 criteria	**7 patients** predicted as AdvSM by model but ISM by WHO 2016 criteria
AdvSM	**10 patients** predicted as ISM by model but AdvSM by WHO 2016 criteria	**37 patients** predicted as AdvSM by both the model and WHO 2016 criteria

C) Elenestinib Clinical Trial Cohort[a] (includes patients with ISM from the HARBOR trial)

Model 1

Central pathology diagnosis by WHO 2016 criteria	Model-predicted diagnosis: ISM	Model-predicted diagnosis: AdvSM
ISM	**122 patients** predicted as ISM by both the model and WHO 2016 criteria	**2 patients** predicted as AdvSM by model but ISM by WHO 2016 criteria

Model 2

Central pathology diagnosis by WHO 2016 criteria	Model-predicted diagnosis: ISM	Model-predicted diagnosis: AdvSM
ISM	**121 patients** predicted as ISM by both the model and WHO 2016 criteria	**3 patients** predicted as AdvSM by model but ISM by WHO 2016 criteria

[a]Due to trial eligibility criteria, only patients centrally–diagnosed with ISM were eligible for the Elenestinib Clinical trial Cohort. WHO, World Health Organization.

Web-based SM Variant Type Probability Calculator

- The SM Variant Type Probability Calculator is available for public use (https://www.advsmcalc.com) and can be employed to calculate the predictive results of Model 1 and Model 2 for any patient with SM

Scan the QR code to view the **Calculator** and **Interactive Poster**

Conclusions

- After making the initial diagnosis of SM, it is important to ascertain the patient's SM subtype so that prognosis and treatment can be determined
- We have successfully created and validated two predictive models that can assist clinicians in distinguishing AdvSM from ISM with a high degree of accuracy
- In addition to their high level of accuracy, these models are also easy to use in the clinic, requiring only a patient's age and set of routinely measured peripheral blood laboratory parameters
- Most patients with clinically diagnosed ISM who were misclassified as AdvSM by the models demonstrated features of high disease burden. These findings suggest that the 'high-risk' ISM population may be larger than previously thought
- The accuracy of these models when tested across multiple independent patient cohorts highlights their expected broad applicability in a variety of clinical practice settings
- A web-based tool is available that allows for broad access to these models

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Disclosures

Dr Volpe has served on a data monitoring committee for Merck. For all author disclosures, please contact medinfo@blueprintmedicines.com.

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