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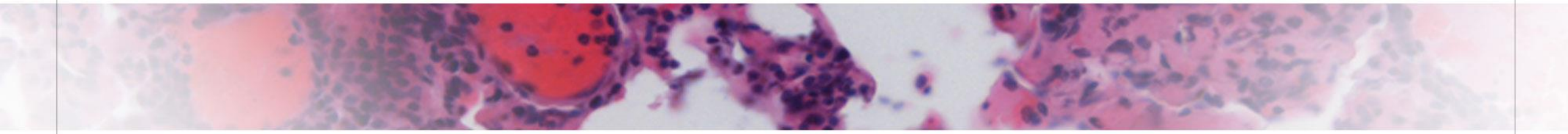

Analysis of Avapritinib Clinical Trial Data Generates A Highly Accurate Predictive Model for Advanced Systemic Mastocytosis *Versus* Indolent Systemic Mastocytosis Based on Peripheral Blood Testing

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Systemic mastocytosis (SM) is a clonal hematologic neoplasm primarily driven by the *KIT* D816V mutation[1–4]

		Advanced SM		
Disease	**ISM**	**ASM**	**SM-AHN**	**MCL**
Frequency	**~85% present with ISM[2,5,6]**	**~15% present with AdvSM[2,5,6]**		
Disease features	**Driven by the *KIT* D816V mutation in ~95% of cases[2–4]**			
	Debilitating symptoms across multiple organ systems, including life-threatening anaphylaxis[7–9]			
	Risk of progression to AdvSM[10]	**Organ damage and reduced life expectancy[1,7,11]**		
Therapies	**Avapritinib 25 mg QD (only approved treatment)[12,13]** *Other off-label symptom-directed therapies[1,14]*	**Avapritinib 200 mg QD (approved)[12,13]** **Midostaurin (approved)[15]** *Other off-label therapies[1]*		

Differing prognoses and treatment approaches highlight the importance of correctly classifying SM

AdvSM, advanced SM; ASM, aggressive systemic mastocytosis; ISM, indolent SM; MCL, Mast cell leukemia; QD, once daily; SM, systemic mastocytosis; SM-AHN, SM with associated hematologic neoplasm.

1. Pardanani A. *Am J Hematol.* 2023;98:1097–1116; 2. Ungerstedt J, et al. *Cancers.* 2022;14:3942; 3. Kristensen T, et al. *Am J Hematol.* 2014;89:493–498; 4. Garcia-Montero AC, et al. *Blood.* 2006;1008:2366–2372; 5. Sperr WR, et al. *Lancet Haematol*. 2019;6:e638–49; 6. Cohen SS, et al. *Br J Haematol.* 2014;166:521–528; 7. Rossignol J, et al. *F1000Research*. 2019;8:1961; 8. Verstovek S. ©International Agency for Research on Cancer. 2023. Systemic Mastocytosis. https://tumourclassification.iarc.who.iwent/chaptercontent/63/20. Accessed 20 January 2023; 9. Khoury JD, et al. *Leukemia.* 2022;36:1703–1719; 10. Mukherjee S, et al. Presented at AAAAI, 2023; Poster 149; 11. Valent P. *Clin Exp Allergy.* 2014;44:914–920; 12. Blueprint Medicines Corporation. AYVAKIT® (avapritinib). Prescribing Information. 2023; 13. Blueprint Medicines Corporation. AYVAKYT® (avapritinib). Summary of Product Characteristics. 2024; 14. Akin C, et al. *J Allergy Clin Immunol*. 2022;149:1912–1918. 15. Novartis Pharmaceuticals Corporation. RYDAPT® (midostaurin). Prescribing Information. 2023

Invasive procedures and clinicopathologic expertise in this rare disease are needed to distinguish between non-advanced and advanced categories[1,2]

ASM[3]

- **Cytopenia:** neutropenia, anemia, thrombocytopenia
- **Hepatopathy**: ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension
- **Spleen:** palpable splenomegaly with hypersplenism ± weight loss ± hypoalbuminemia
- **GI tract:** malabsorption with hypoalbuminemia ± weight loss
- **Bone:** osteolysis ± pathologic fractures ± bone pain

MCL[1]

- >20% mast cells on bone marrow aspirate

SM-AHN[3]

- Criteria met for an additional hematologic neoplasm in addition to SM, including[3]
  - Myeloproliferative neoplasm
  - Chronic myelomonocytic leukemia
  - Myelodysplastic syndrome

Diagnostic methods potentially used to assess organ involvement/damage include the following **invasive and potentially difficult-to-interpret tests:**

- **Bone marrow biopsy**
- Liver biopsy
- Colonoscopy
- Bone biopsy

- **Bone marrow biopsy**

- **Bone marrow biopsy**

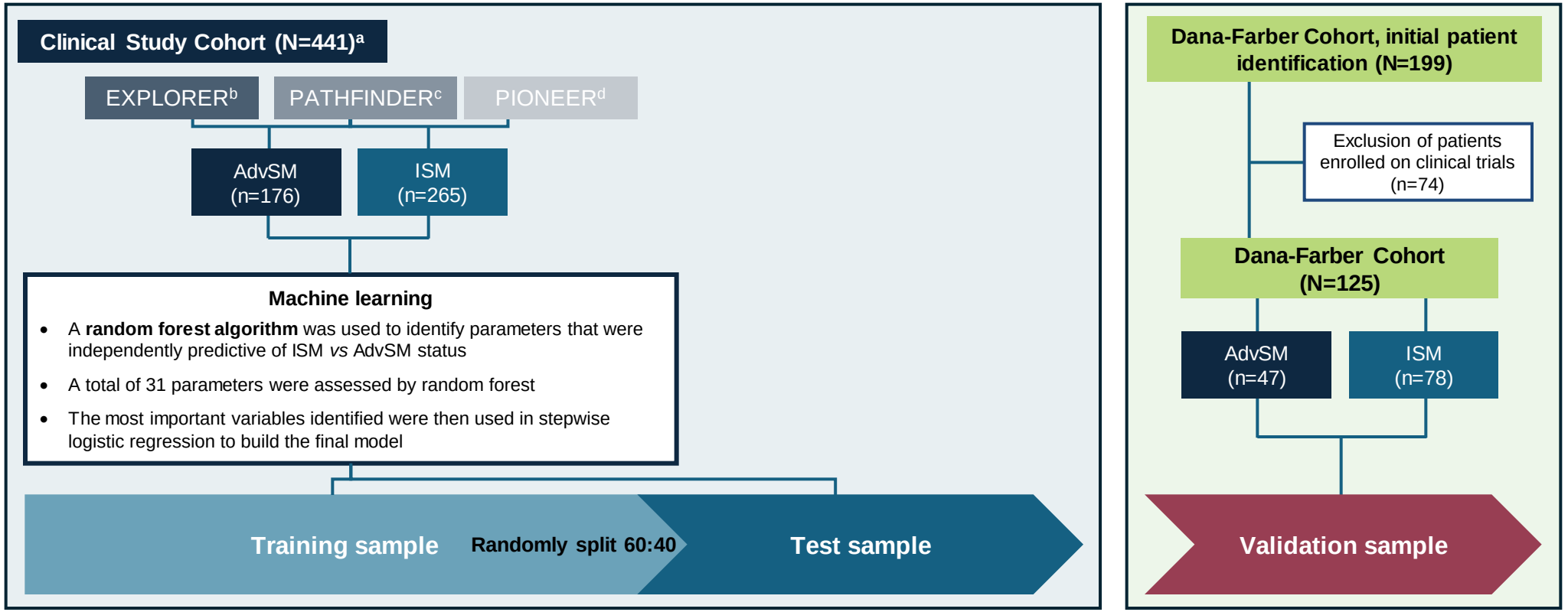
Non-invasive, broadly applicable tools are needed to aid clinicians to help guide SM subtyping and treatment

GI, gastrointestinal.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–1719; 2. Schwaab J, et al. J Allergy Clin Immunol Pract. 2020;8:3121–3127.e1; 3. WHO Classification of Tumours Editorial Board (eds). Hematolymphoid Tumors, 5th edition, International Agency for Research Cancer; Lyon, France: 2022; 4. Pardanani A. *Am J Hematol*. 2023;98:1097–1116

Novel predictive models to help guide care, minimize procedural diagnostic interventions and assist with timely classification of SM

- Predictive models were developed using baseline parameters from adult patients enrolled in three clinical studies of avapritinib[1–3]



[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. [b]In EXPLORER (N=83; 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. [c]PATHFINDER (N=107; NCT03580655). [d]PIONEER (N=251; NCT03731260).
DFCI, Dana Farber Cancer Institute.
1. DeAngelo DJ, et al. *Nat Med*. 2021;27:2183–2191; 2. Reiter A, et al. Presented at EHA 2024, P1023; 3. Gotlib J, et al. NEJM Evid. 2023;2(6)

Approach to generating a mathematical model

- Identify a set of variables (demographic characteristics, clinical findings, laboratory findings) that could potentially help distinguish ISM from AdvSM

Variables	
Age	Monocyte count (absolute)
Albumin	Medical history of anaphylaxis
Alkaline phosphatase	Neutrophil count (absolute)
ALT	Platelets
Ascites (Y/N)	Pleural Effusion (Y/N)
AST	Race
Basophil count (absolute)	Sex
Bilirubin, total	Palpable spleen (Y/N)
BMI	Tryptase
Bone marrow biopsy mast cell percentage (core)	NGS panel presence of Tier 1 *KIT* mutation with VAF>1% (Y/N)
Country	NGS panel presence of any Tier 1 mutation with a VAF>1% (Y/N)
Creatinine	NGS panel number of non-*KIT* genes with a Tier 1 mutation
KIT D816V VAF in the peripheral blood	NGS panel presence of Tier 1 *ASXL1* mutations with VAF>1% (Y/N)
Eosinophil count (absolute)	*DNMT3A* Tier 1 VAF>1% (Y/N)
Hemoglobin	*EZH2* Tier 1 VAF>1% (Y/N)
LDH	*RUNX1* Tier 1 VAF>1% (Y/N)
Lymphocyte count (absolute)	*SETBP1* Tier 1 VAF>1% (Y/N)
	SRSF2 Tier 1 VAF>1% (Y/N)

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; LDH, lactate dehydrogenase; NGS, next-generation sequencing; VAF, variant allele frequency.

Approach to generating a mathematical model

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AST	Race
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	SRSF2 Tier 1 VAF>1% (Y/N)

Removed variables with too many missing values

BMI had 19 missing values

LDH had 86 missing values

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; LDH, lactate dehydrogenase; NGS, next-generation sequencing; VAF, variant allele frequency.

Approach to generating a mathematical model

- Identify a set of variables (demographic characteristics, clinical findings, laboratory findings) that could potentially help distinguish ISM from AdvSM

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	SRSF2 Tier 1 VAF>1% (Y/N)

Remove "subjective" variables of palpable spleen and bone marrow biopsy mast cell percentage

Reasoning:

- High inter-observer variability
- High test-retest variability (bone marrow biopsy)
- Requires a set of skills that community clinicians may not have (allergists – spleen palpation, pathologists – mast cell quantitation)

Benefits:

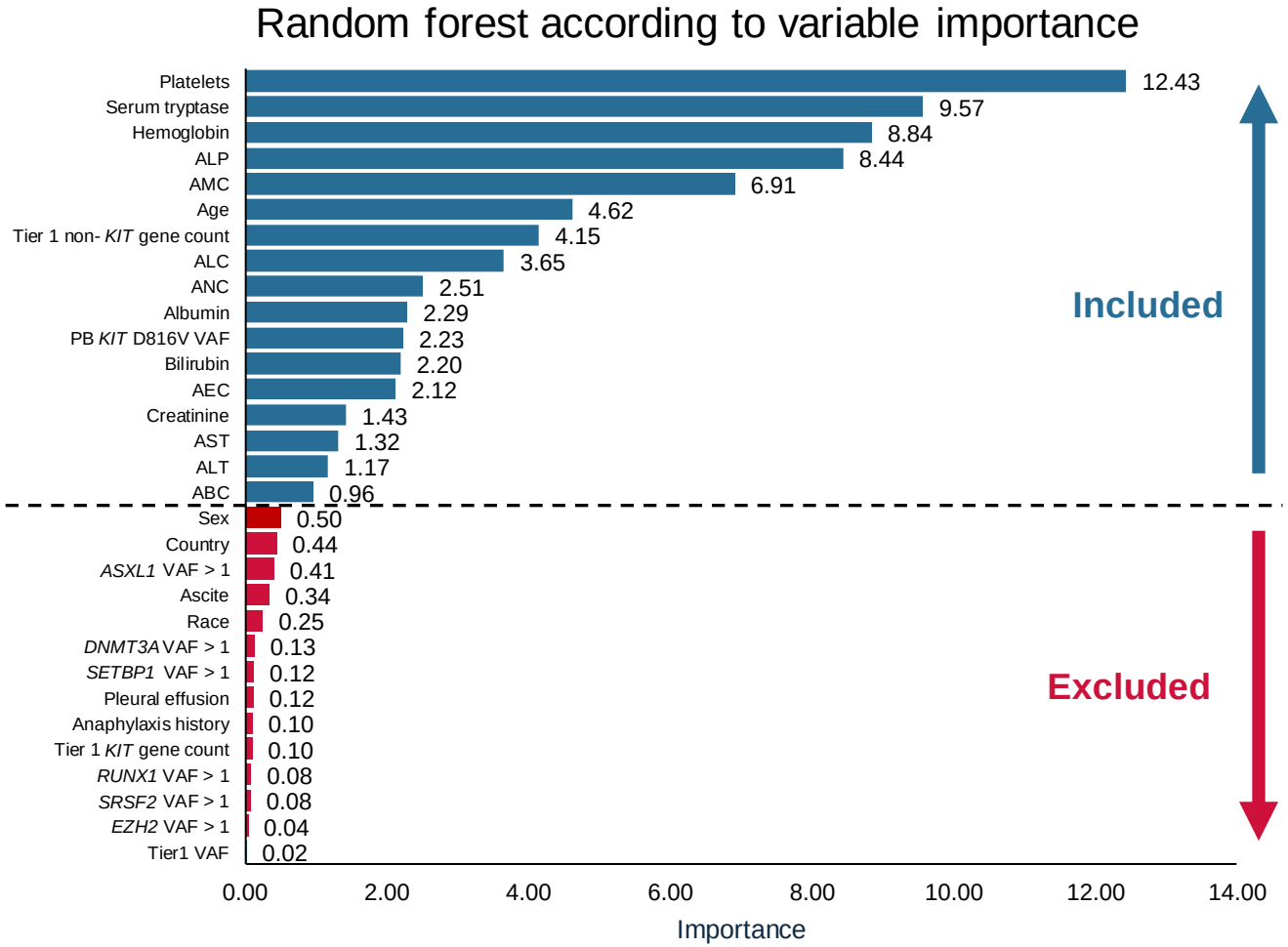
- Enhances generalizability of eventual model (e.g., can be employed even in resource-limited settings)

Drawbacks:

- Removes two presumably very powerful predictors, potentially decreasing performance of the model

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; LDH, lactate dehydrogenase; NGS, next-generation sequencing; VAF, variant allele frequency.

17 variables were independently predictive of AdvSM *versus* ISM classification



35 variables were assessed in the Clinical Study Cohort (N=441)

↓

Parameters with low inter-rater reliability (**splenomegaly** and **BM MC percentage**) or high frequency of missing baseline parameters (**BMI** and **LDH**) were **removed**

↓

17/35 variables were **independently predictive of ISM *versus* AdvSM** classification

↓

Independently predictive variables were used in stepwise logistic regression to develop the final models in the Training sample (n=265)

ABC, absolute basophil count; AEC, absolute eosinophil count; ALC, absolute lymphocyte count; ALP, alkaline phosphatase; AMC, absolute monocyte count; ANC, absolute neutrophil count; BM MC, bone marrow mast cell; PB, peripheral blood.

Model 1 was highly predictive of AdvSM *versus* ISM

Training
Training sample (n=265)

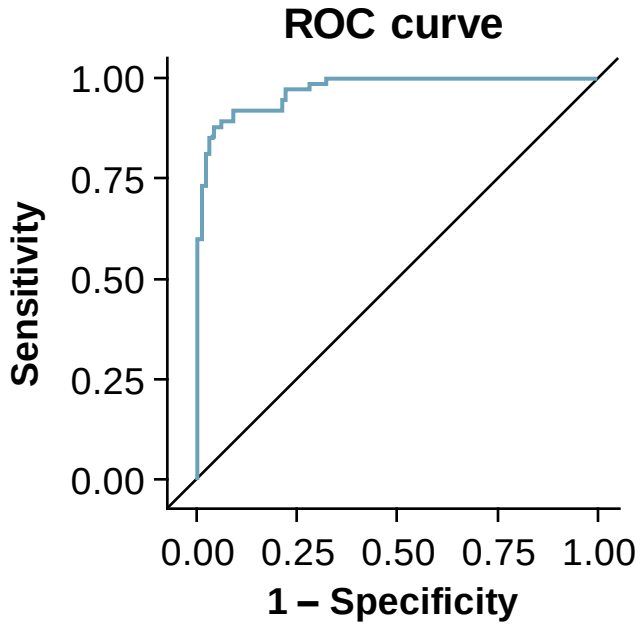
- Model 1 included age, platelets, absolute monocyte count, hemoglobin, alkaline phosphatase, tryptase, and total bilirubin

P(AdvSM) = *f*(platelets) + *f*(tryptase) + *f*(hemoglobin) + *f*(alkaline phosphatase) + *f*(absolute monocytes) + *f*(age) + *f*(total bilirubin)

ISM if **0 ≤P<0.5**
AdvSM if **0.5≤P≤1**[a]

Test
Test sample (n=176)

- Model 1 predicted AdvSM versus ISM with an **area under the curve (AUC) of 0.97 in the independent test data**



Model 1 uses age and a combination of objectively and easily measured parameters in the peripheral blood to distinguish between AdvSM and ISM with a high degree of accuracy

[a]Thresholds for classifying ISM or AdvSM are currently preliminary and will be further refined.
ROC, receiver operating characteristic.

Model 2 still highly predictive with fewer variables and C-findings removed

Training
Training sample (n=265)

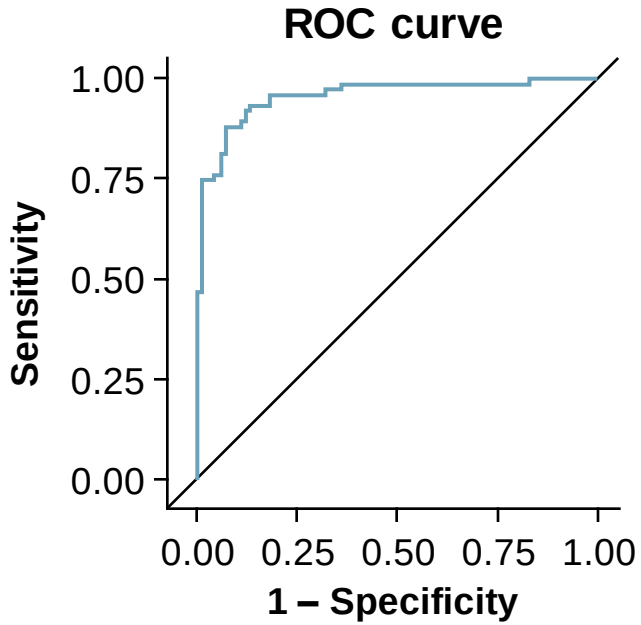
- Model 2 included age, alkaline phosphatase, tryptase, total bilirubin, albumin, absolute monocyte count, absolute lymphocyte count

P(AdvSM) = *f*(age) + *f*(alkaline phosphatase) + *f*(tryptase) + *f*(total bilirubin) + *f*(albumin) + *f*(absolute monocyte count) + *f*(absolute lymphocyte count)

ISM if **0 ≤P<0.5**
AdvSM if **0.5≤P≤1**[a]

Test
Test sample (n=176)

- Model 2 predicted AdvSM versus ISM with an **AUC of 0.96 in the independent test data**



As C-findings are already used for AdvSM diagnosis, parameters such as pleural effusion, ascites, hemoglobin, ANC, and platelets were removed. Model 2 exhibited a high degree of accuracy, despite using fewer parameters than Model[1]

[a]Thresholds for classifying ISM or AdvSM are currently preliminary and will be further refined.
ROC, receiver operating characteristic.

Clinical study cohort: Most patients with ISM misclassified as AdvSM had high disease burden

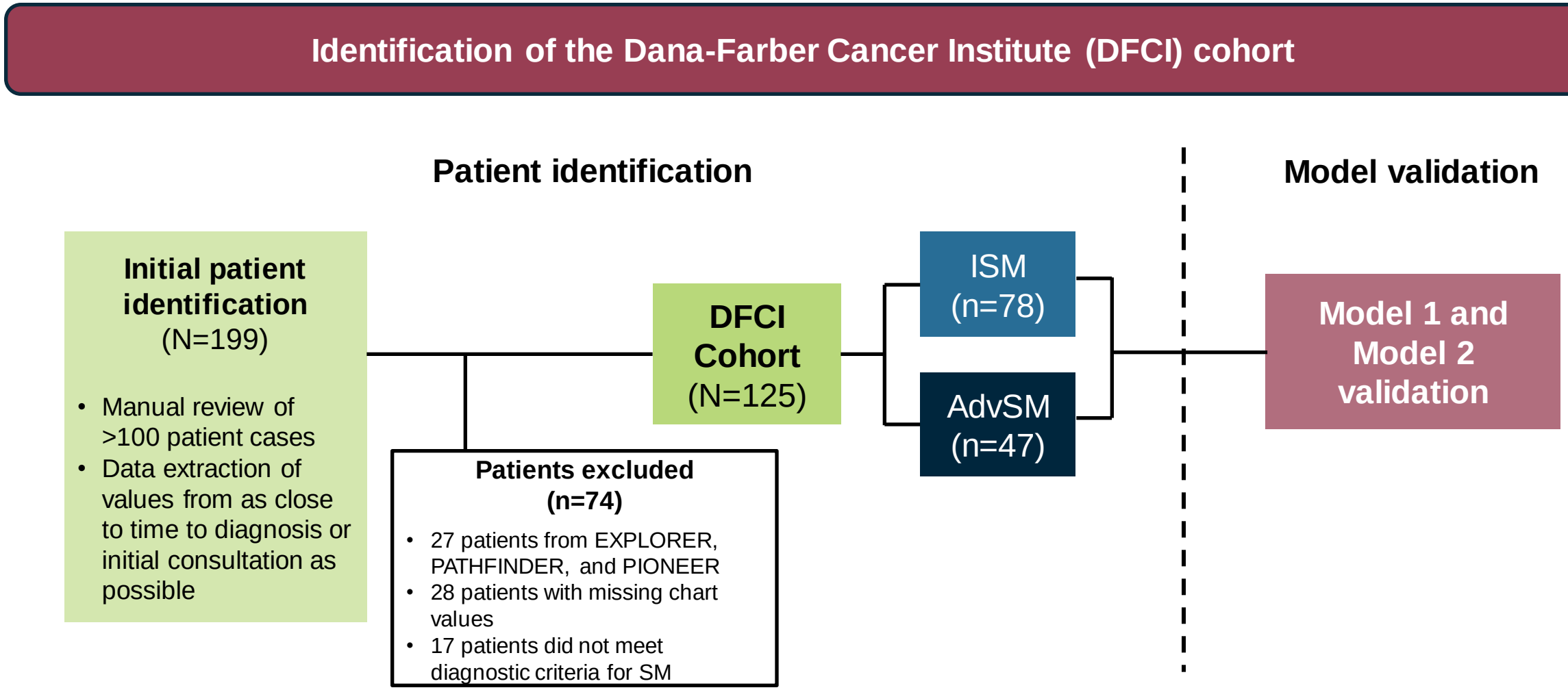
- Patients misclassified as having AdvSM *versus* ISM (per expert-adjudicated classification[a]) generally had high disease burden – mathematical modelling may provide objective prediction to aid expert classification

Patient characteristic	Model 1 (n=31)		Model 2 (n=33)	
	ISM Misclassified as AdvSM (n=14)	AdvSM Misclassified as ISM (n=17)	ISM Misclassified as AdvSM (n=12)	AdvSM Misclassified as ISM (n=21)
Age (years), median (range)	64 (52–72)	59 (38–77)	64 (51–72)	59 (31–81)
Female, n (%)	11 (79)	9 (53)	7 (58)	12 (57)
Disease burden measures				
Median serum tryptase (central), ng/mL (range)	194.0 (46.0–501.6)	129.0 (19.9–524.0)	187.0 (21.8–501.6)	70.5 (12.4–334.0)
Median *KIT* D816V VAF in peripheral blood, % (range)[b]	10.83 (undetectable–41.70)	1.44 (undetectable–42.98)	7.70 (undetectable–41.70)	0.79 (undetectable–40.20)
Median bone marrow mast cells, % (range)	23 (7–70)	18 (1–80)	25 (5–70)	20 (5–90)
Median haemoglobin g/L (range)	120 (104–134)	129 (116–167)	125 (113–161)	123 (86–144)
Median platelet count 1x10^3 platelets/µL (range)	233 (101–341)	178 (60–602)	259 (101–341)	153 (60–602)

[a]Per WHO 2016 guidelines, in effect when patients were enrolled on studies.[1] [b]A *KIT* D816V VAF in peripheral blood of less than the limit of detection, 0.022%, is considered undetectable.

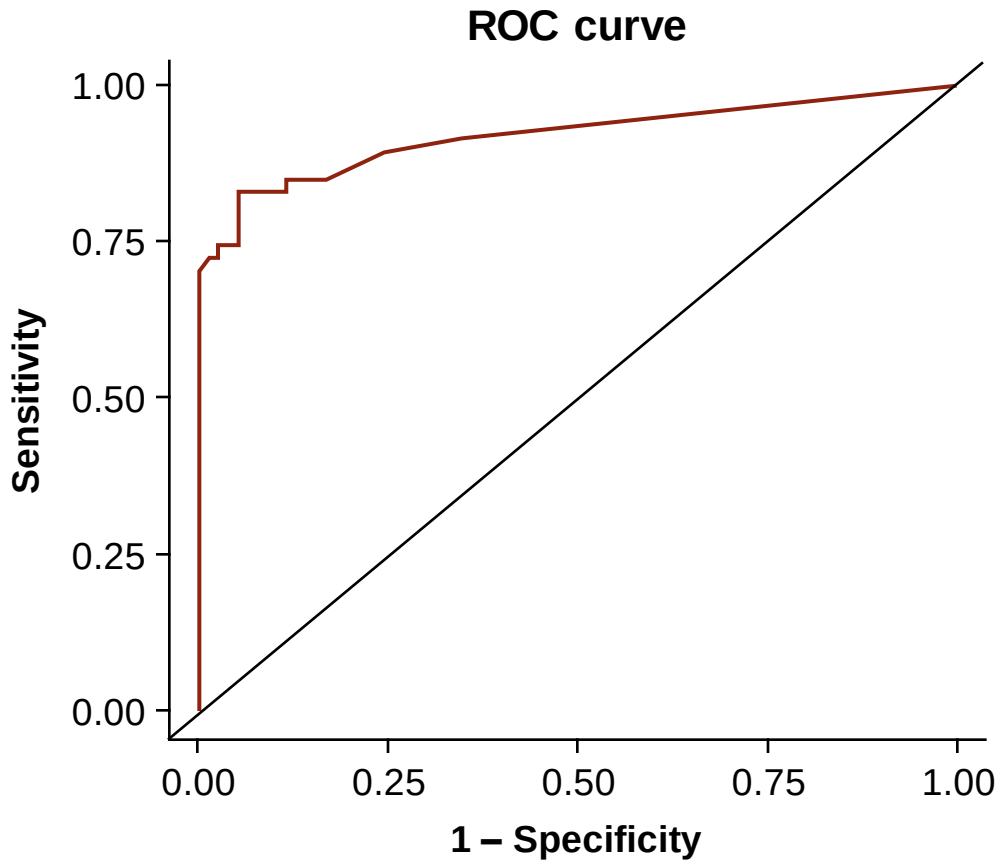
1. Horny HP et al. Mastocytosis. In: Sverdlow SH et al (eds), WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th Edition, International Agency for Research on Cancer 2017, Lyon, France

Model validation: Dana-Farber Cancer Institute (DFCI) cohort overview

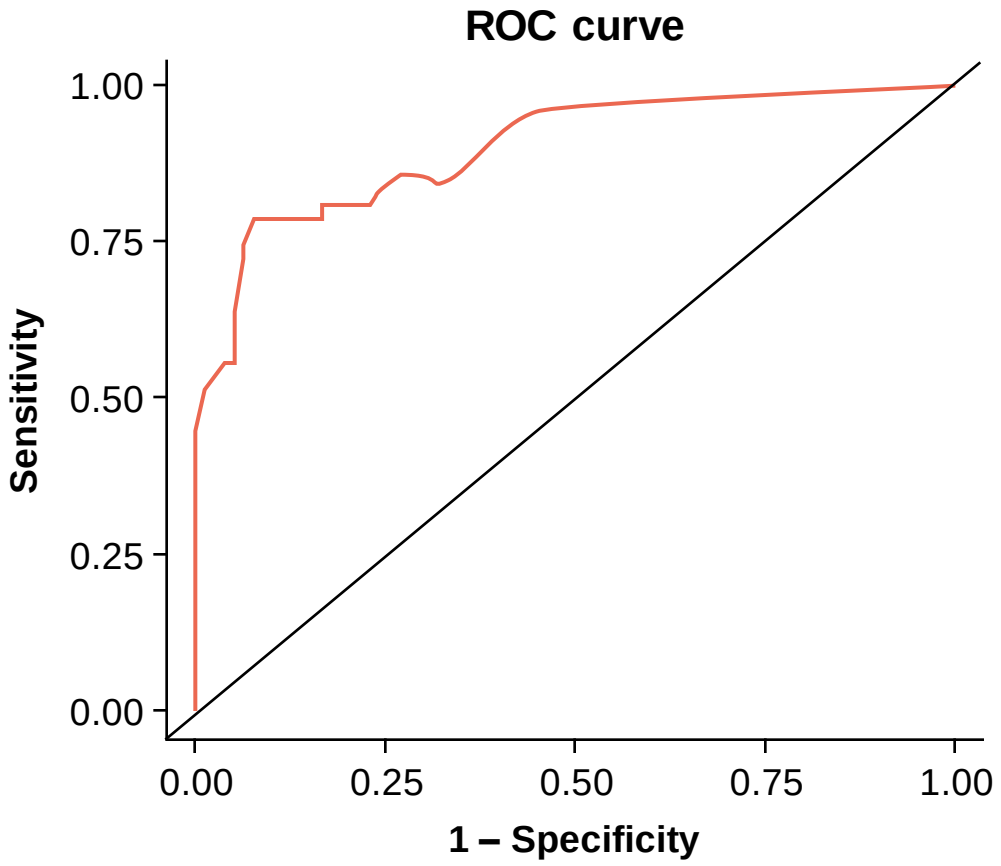


Model validation: DFCI cohort

Model 1: AUC 0.92



Model 2: AUC 0.90



ROC, receiver operating characteristic

Model validation: Most patients with ISM misclassified as AdvSM in the independent DFCI cohort had high disease burden

Patient characteristic	Model 1 (n=14)		Model 2 (n= 17)	
	ISM Misclassified as AdvSM (n=6)	AdvSM Misclassified as ISM (n=8)	ISM Misclassified as AdvSM (n=7)	AdvSM Misclassified as ISM (n=10)
Age (years), median (range)	63.0 (47–83)	64.1 (47–77)	66.5 (47–83)	63.1 (47–77)
Female, n (%)	5 (83)	6 (75)	5 (71)	8 (80)
Disease burden measures				
Median serum tryptase (central), ng/mL (range)	159.5 (33.2–341)	63.6 (21.5–377)	110 (64–341)	44 (20–149)
Median *KIT* D816V VAF in peripheral blood, % (range)[a]	7.8 (0–41.8)	0.8 (0–39.9)	13.9 (0–47)	0.8 (0–39.9)
Median bone marrow mast cells, % (range)	15 (4–30)	10 (5–30)	5 (1–30)	15 (5–40)
Median hemoglobin g/L (range)	121 (104–136)	136 (116–181)	135 (111–161)	117 (77–181)
Median platelet count 1x10^3 platelets/µL (range)	182 (126–333)	482 (179–804)	186 (126–234)	261 (47–804)

[a]A *KIT* D816V VAF in peripheral blood of less than the limit of detection, 0.022%, is considered undetectable.

1. Horny HP et al. Mastocytosis. In: Sverdlow SH et al (eds), WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th Edition, International Agency for Research on Cancer 2017, Lyon, France

Conclusions

- Pathologic diagnosis of SM is only the first step. Following this, it is important to categorize SM subtype to determine prognosis and treatment
- Using B-findings and C-findings to categorize SM subtypes is cumbersome and complicated
- Two predictive mathematical models used age and peripheral blood laboratory parameters (N=265) to distinguish between ISM and AdvSM with a high degree of accuracy
  - Model 1 correctly classified **93.0% of patients in the Clinical Study Cohort** and **88.8% in the independent validation cohort** (DFCI)
  - Model 2 correctly classified **92.5% of patients in the Clinical Study Cohort** and **86.4% in the independent validation cohort** (DFCI)
- Both models remained highly accurate when tested on an independent validation cohort of patients
  - However, the current threshold used (0.5) may not be fully optimized. Further enhancements could increase the success rate even further

Conclusions (cont.)

- Most patients with clinically diagnosed ISM who were misclassified as AdvSM had high-risk disease characteristics
  - Over half of these patients possessed ***KIT*** **D816V VAFs >6%** and **tryptase >100 ng/mL**
  - The number of patients with ISM misclassified as AdvSM by our model suggest that the 'high-risk' ISM population may be larger than previously thought
- These models are broadly applicable irrespective of clinical practice setting or provider expertise and can assist clinicians in accurately determining a patient's SM diagnosis, thus ensuring that patients receive the appropriate treatment and follow up
  - A web-based tool will be made available to allow broad access to these models

SSM, smoldering SM.

SM Variant Type Probability Calculator

DISCLAIMER: This tool is intended to aid healthcare providers in the differentiation between indolent systemic mastocytosis (SM) and advanced SM. This tool is for informational purposes only and should not be used without confirming the patient's diagnosis based on the World Health Organization (WHO) 2024 diagnostic criteria (5th ed.) [1, 2] or as a substitute for clinical judgement.

Instructions:

- **Required Fields:** Please enter values for Tryptase, Alkaline Phosphatase (U/L), Absolute Monocyte Count (x10^9 cells/L or cells/µL), Age (years), Absolute Lymphocyte Count (x10^9 cells/L or cells/µL), Albumin (g/L or g/dL), and Total Bilirubin (µmol/L or mg/dL).
- **Optional Fields:** If you have Platelets (10^9/L) and Hemoglobin (g/L or g/dL), enter them to use Formula 1. If not, Formula 2 will be used.

Enter values here:

Tryptase: [ng/mL]

Alkaline Phosphatase (U/L):

Absolute Monocyte Count: [x10^9 cells/L]

Age (years):

Absolute Lymphocyte Count: [x10^9 cells/L]

Albumin: [g/L]

Total Bilirubin: [µmol/L]

Platelets (10^9/L):

Hemoglobin: [g/L]

Calculate | Clear | Example 1 | Example 2

Acknowledgements

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- We also thank the investigators and clinical trial teams who participated in the studies
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