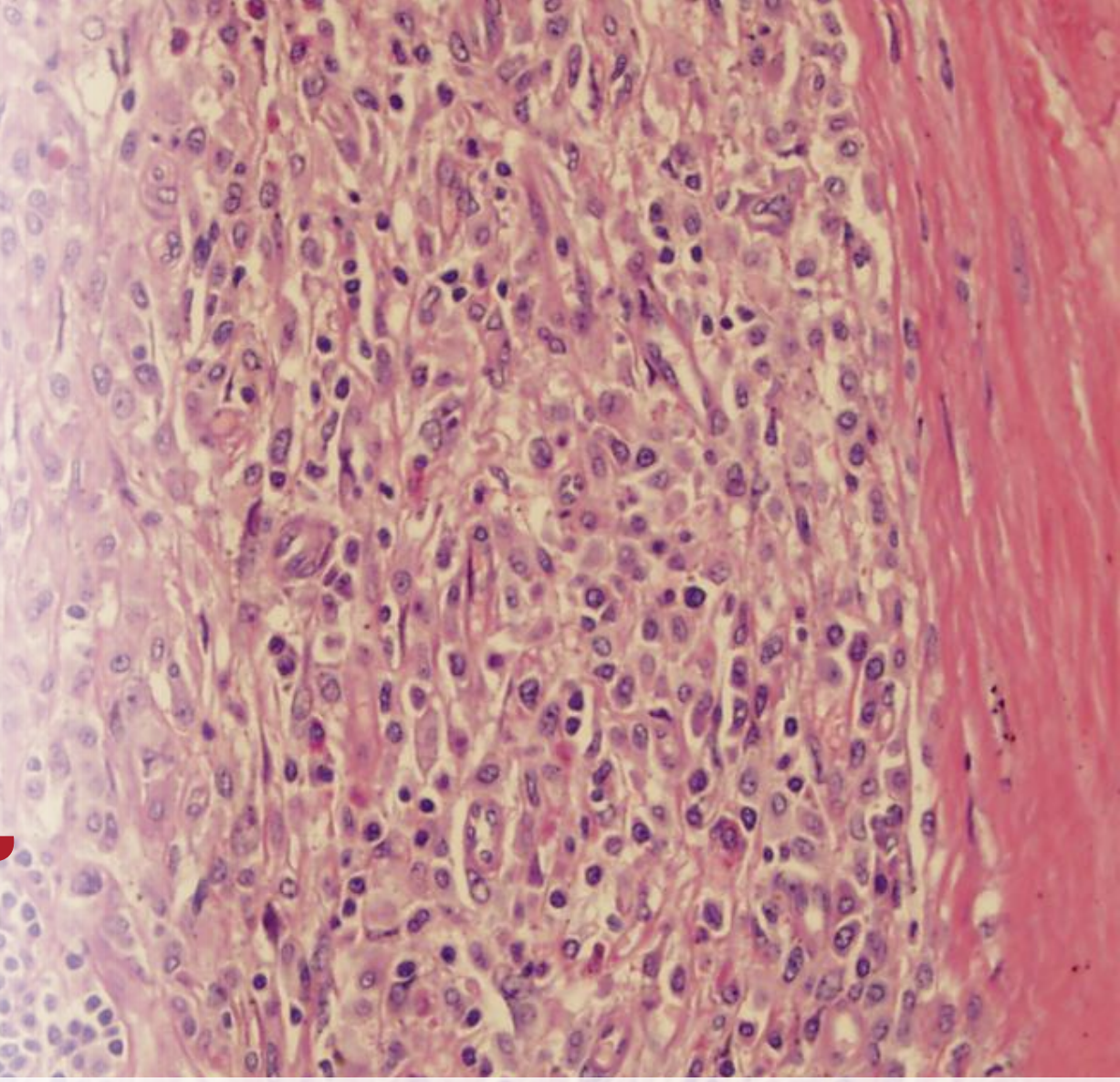
FOR HEMATOLOGISTS AND PATHOLOGISTS

Diagnosing Systemic Mastocytosis



Tracy I. George, MD
Chief Scientific Officer and President-Innovation
Professor of Pathology, University of Utah

ARUP LABORATORIES

AUGUST 2025

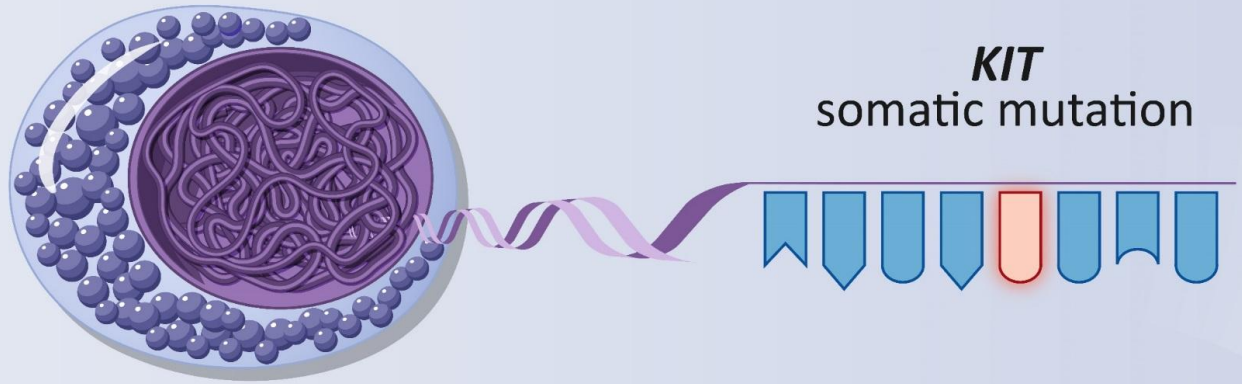
DISCLOSURES

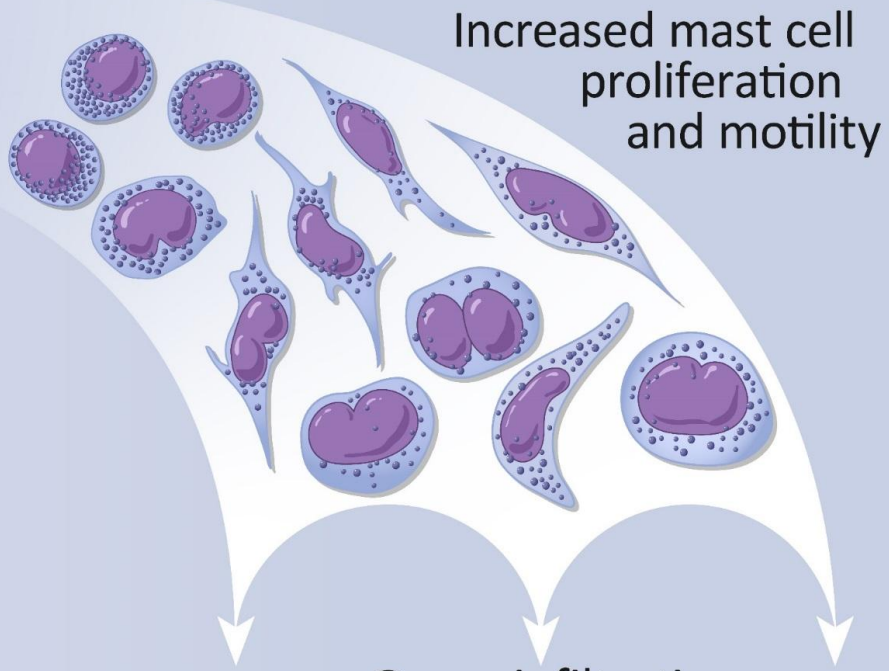
- Blueprint Medicines, consultant
- Cogent Biosciences, consultant

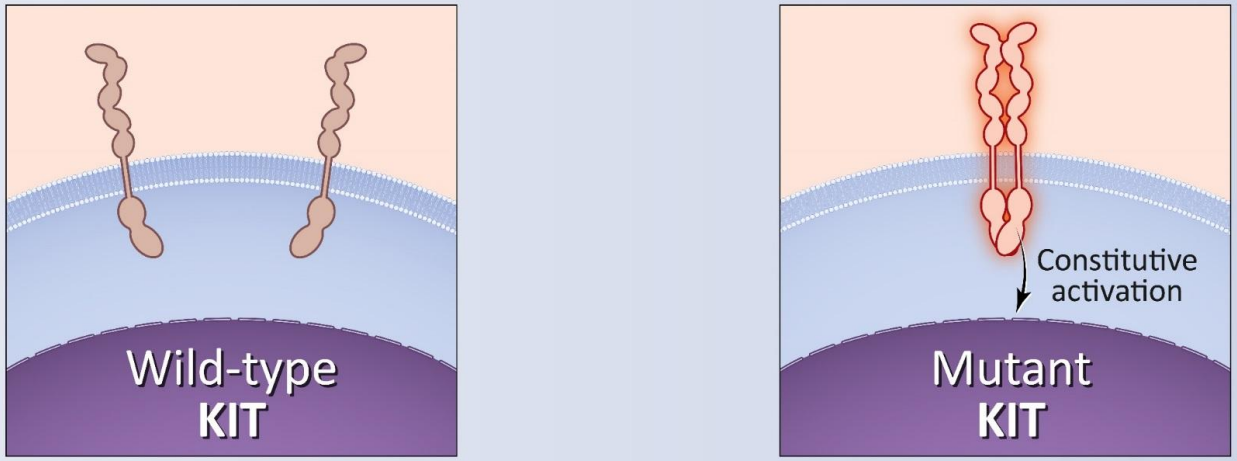
Agenda

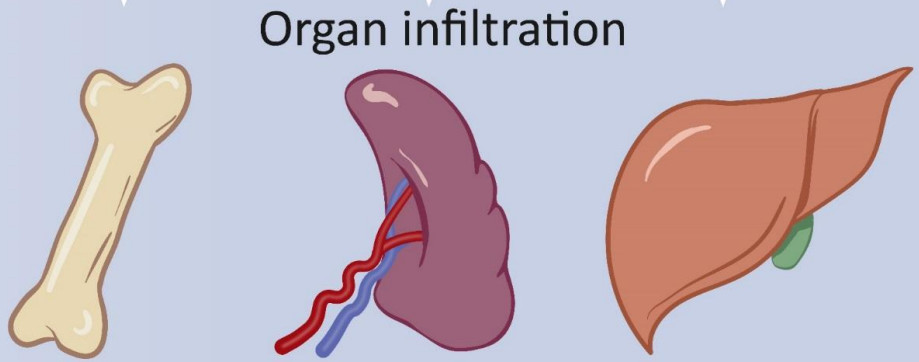
- WHO & ICC Classifications
- Systemic mastocytosis and subtypes
- Association with myeloid neoplasms
- Immunohistochemistry and molecular diagnosis
- Challenges of diagnosis

KIT D816V is present in >95% of patient with systemic mastocytosis



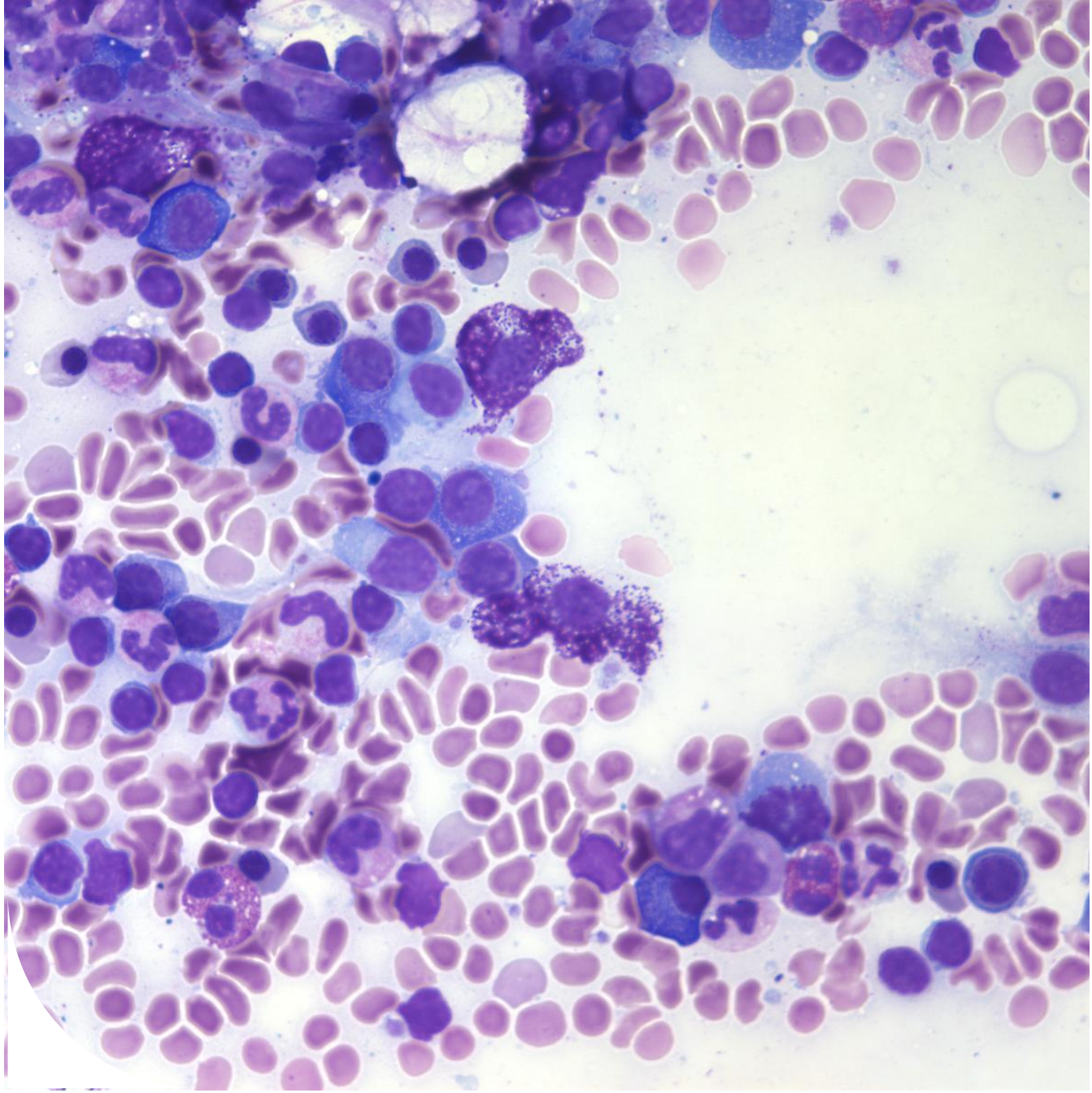






Mastocytosis pathogenesis

WHO & ICC Classifications



Diagnostic criteria for systemic mastocytosis

Major	Multifocal dense aggregates of mast cells
Minor	1) >25% mast cells with atypical morphology
	2) Activating *KIT* mutation
	3) CD2, CD25 and/or CD30 expression on mast cells
	4) Serum total tryptase >20 ng/mL* (unless an associated myeloid neoplasm)

Valent P et al. Leuk Res 2001; Khoury JD et al. Leukemia 2022; Arber DA et al. Blood 2022

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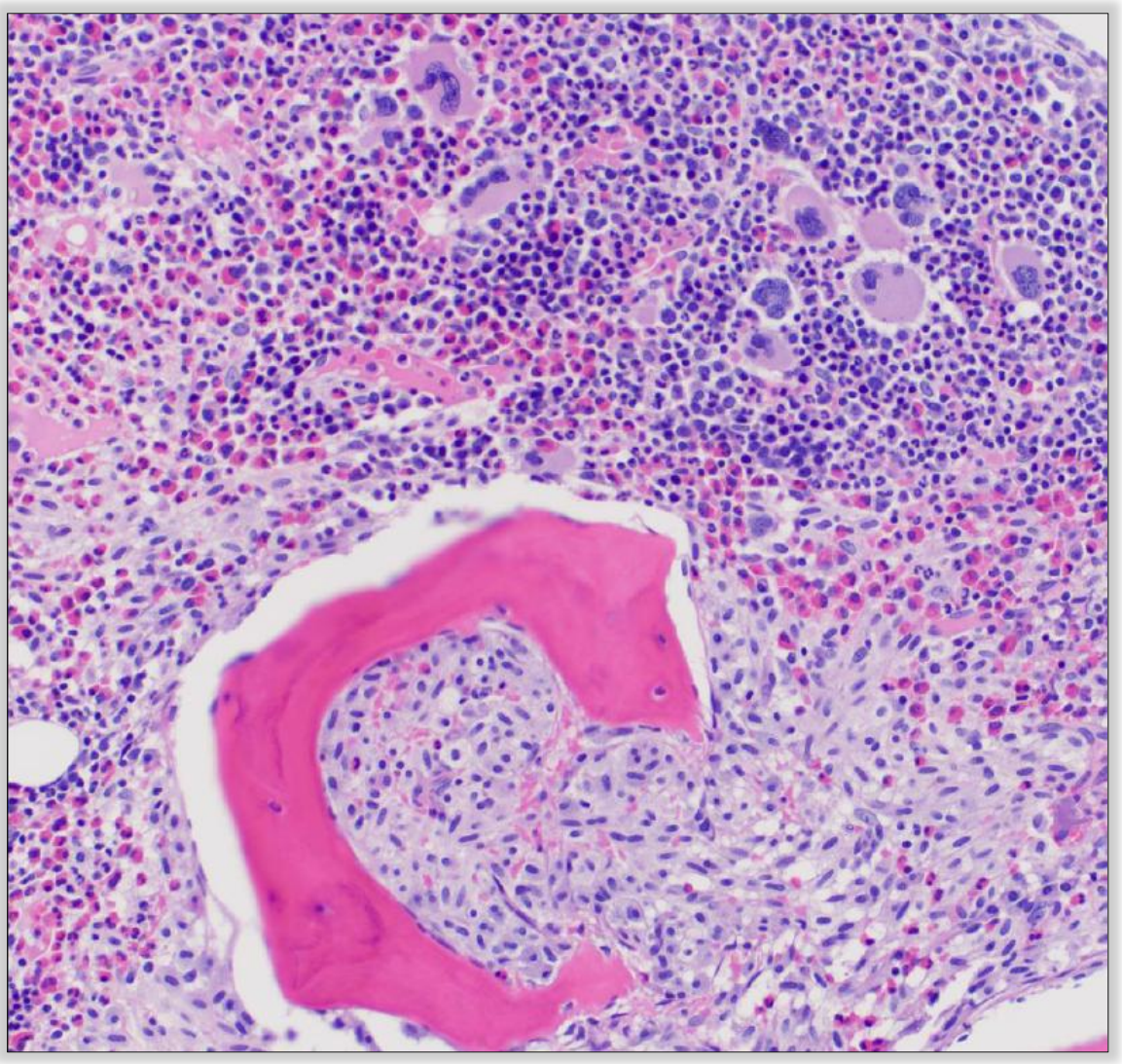
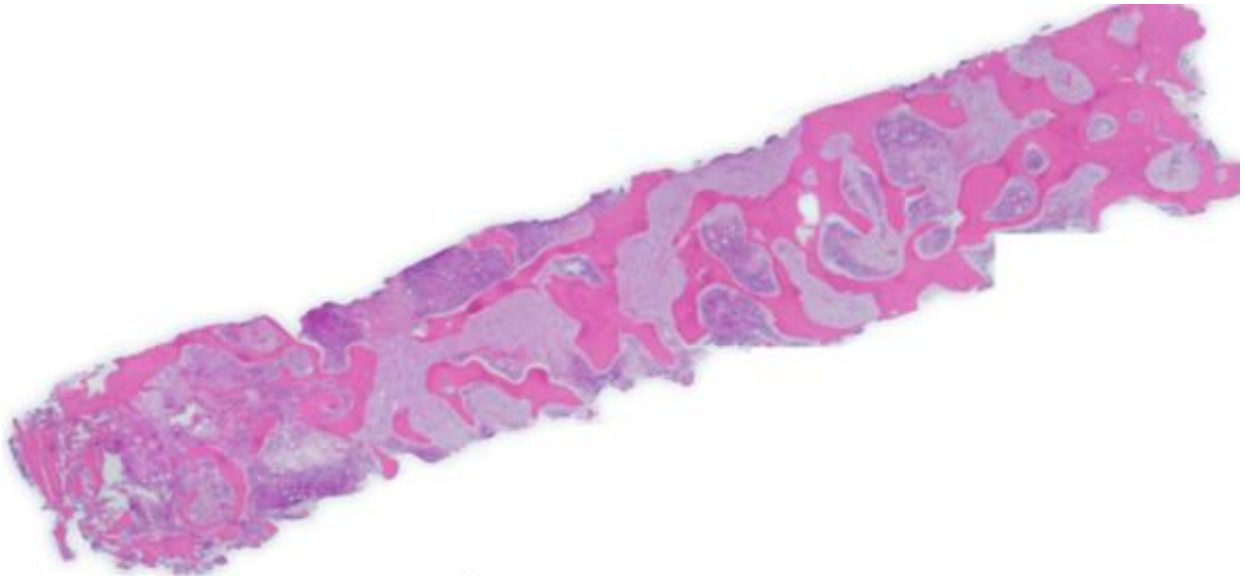
	WHO 5th edition	ICC
Requirements for diagnosis	1 Major + 1 Minor *or* 3 Minor criteria	1 Major *or* 3 Minor criteria
Major criterion		Requires mast cell identification by CD117 and/or tryptase
***KIT* mutation**		If *KIT* negative, the presence of TK gene fusions must be excluded
Serum total tryptase	Adjust if HaT+	

Valent P et al. Leuk Res 2001; Khoury JD et al. Leukemia 2022; Arber DA et al. Blood 2022; Valent P et al JACI Pract 2024; Lyons JJ et al. Nat Genet 2016

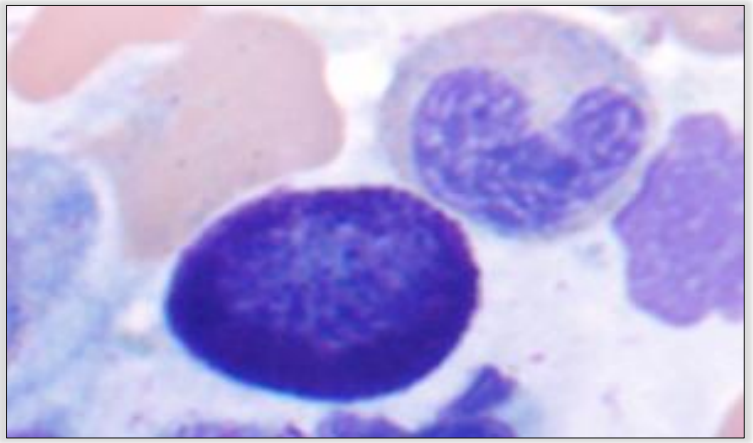
Major criterion: multifocal dense mast cell aggregates



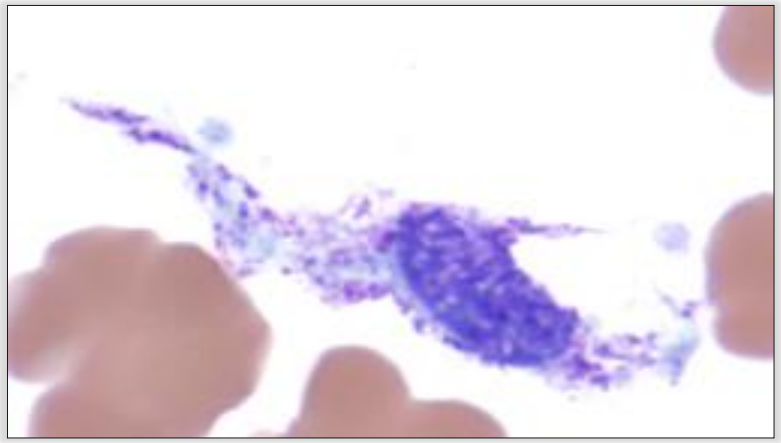


Atypical mast cell morphology

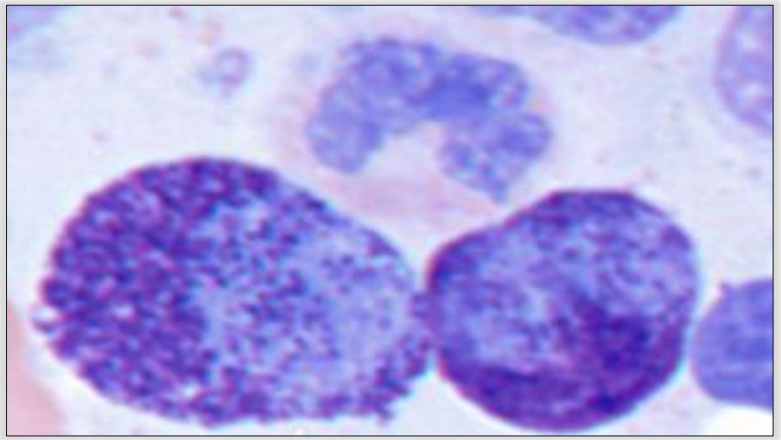
Normal/well-differentiated



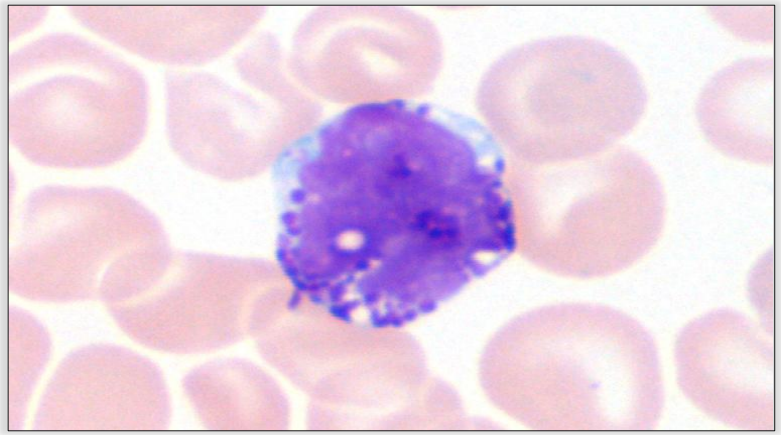
Atypical type I



Atypical type II



Metachromatic blast



George TI and Horny H-P. Hematol Oncol N Am 2011

Classification of Mastocytosis

WHO 5th EDITION	ICC
Mastocytosis	

Cutaneous mastocytosis
• Urticaria pigmentosa/maculopapular cutaneous mastocytosis
  ○ Monomorphic
  ○ Polymorphic
• Diffuse cutaneous mastocytosis
• Cutaneous mastocytoma
  ○ Isolated mastocytoma
  ○ Multilocalized mastocytoma
	Cutaneous mastocytosis
	• Urticaria pigmentosa/maculopapular cutaneous mastocytosis
	• Diffuse cutaneous mastocytosis
	• Mastocytoma of skin

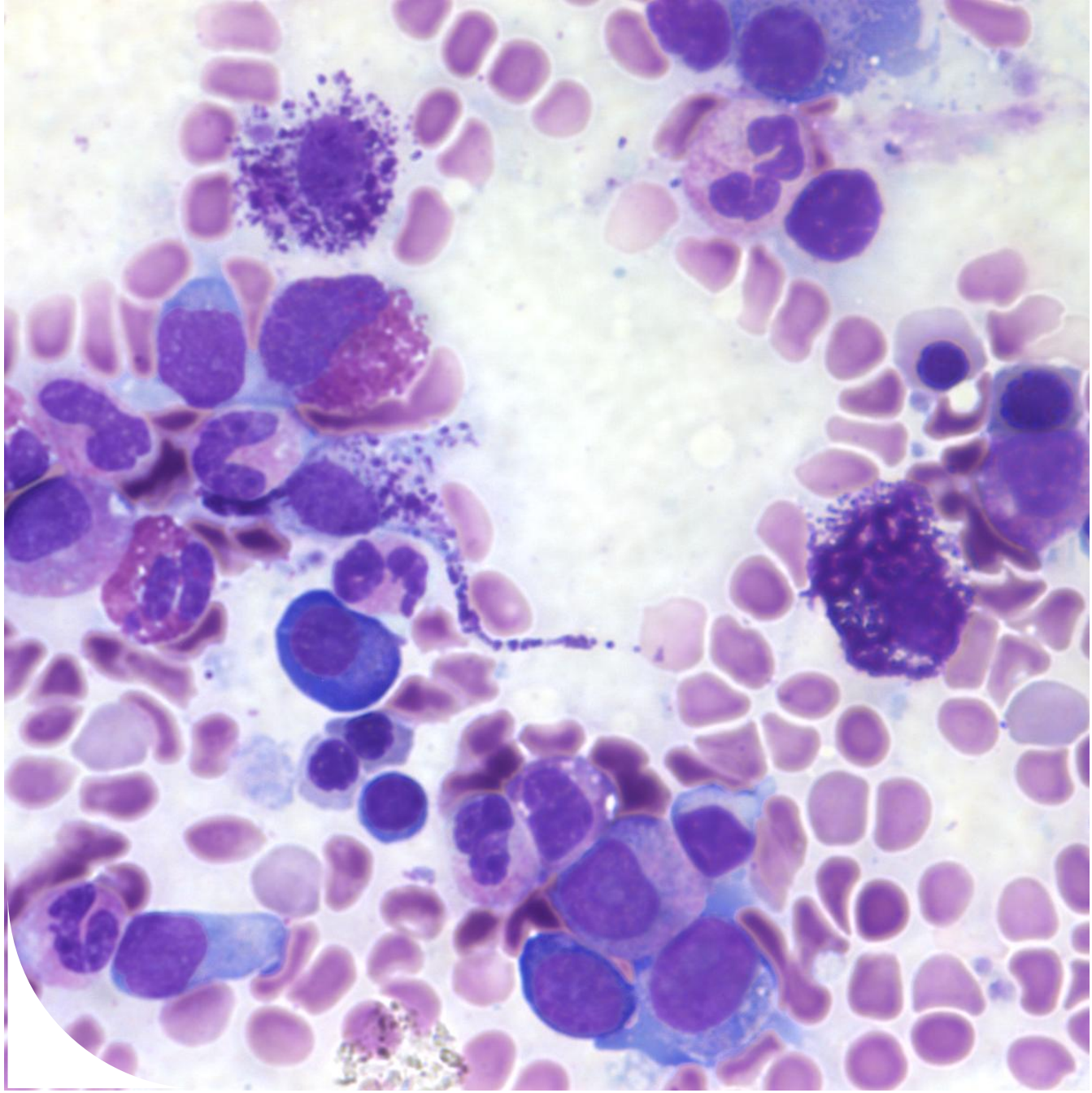
Systemic mastocytosis (SM) • Bone marrow mastocytosis • Indolent SM • Smoldering SM • Aggressive SM • Mast cell leukemia • SM with an associated hematologic neoplasm (SM-AHN)	Systemic mastocytosis (SM) • Indolent SM ○ Bone marrow mastocytosis • Smoldering SM • Aggressive SM • Mast cell leukemia • SM with an associated myeloid neoplasm (SM-AMN)
Mast cell sarcoma	Mast cell sarcoma

Khoury JD et al. Leukemia 2022; Arber DA et al. Blood 2022

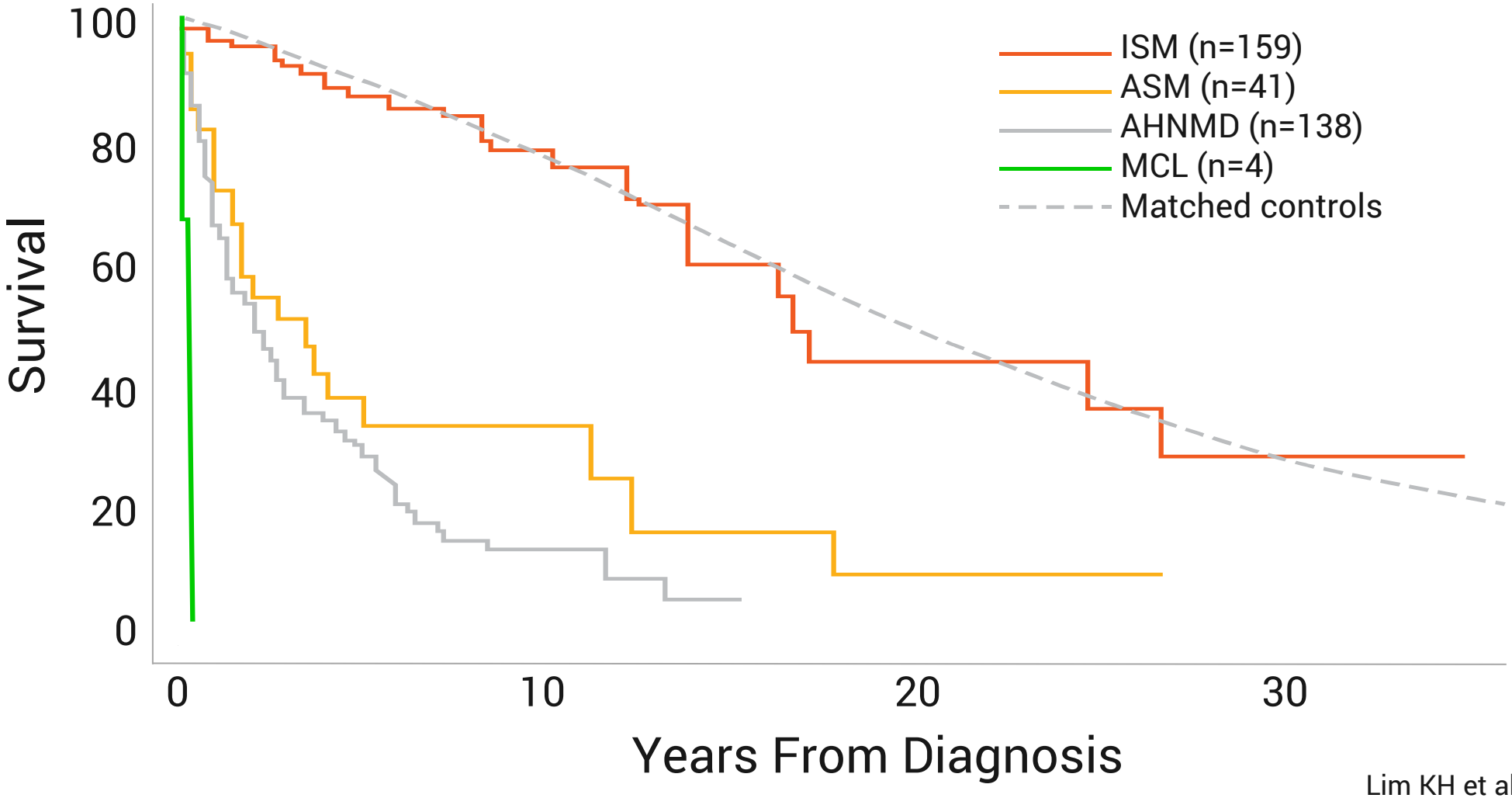
	WHO 5th edition	ICC
B	≥30% MC in BM **and/or** Serum tryptase ≥200 ng/mL **and/or** ***KIT* p.D816V VAF ≥ 10% in BM/PB**	>30% MCs in BM **and** Serum tryptase >200 ng/mL
B	Signs of myeloproliferation and/or myelodysplasia not meeting criteria for an AHN	Cytopenia(s) not meeting criteria for C-findings. Reactive causes excluded. Criteria for other myeloid neoplasms not met
B	Hepatomegaly w/o ascites or organ damage and/or Splenomegaly w/o hypersplenism and w/o weight loss and/or Lymphadenopathy **>2cm**	Hepatomegaly w/o impaired liver function, or Splenomegaly w/o hypersplenism and/or Lymphadenopathy (**>1cm**)
C	≥1 cytopenia (ANC <1.0 x 10^9/L, Hb <10g/dL and/or PLT <100 x 10^9/L)	same
C	Hepatopathy: ascites and elevated LFTs +/- hepatomegaly or cirrhosis +/- portal hypertension	Palpable hepatomegaly w/ impaired liver function, ascites and/or portal hypertension
C	Palpable splenomegaly w/ hypersplenism +/- weight loss +/- hypoalbuminemia	Palpable splenomegaly w/ hypersplenism
C	Malabsorption w/ hypoalbuminemia +/- weight loss	Malabsorption w/ weight loss due to GI MC infiltrates
C	Large osteolysis (**≥ 2cm**) +/- fracture +/- bone pain	Skeletal involvement w/ large osteolysis +/- fractures

Khoury JD et al. Leukemia 2022; Arber DA et al. Blood 2022

Systemic mastocytosis and subtypes



Overall Survival



Lim KH et al. Blood 2009

Mastocytosis classification

Cutaneous mastocytosis (CM)

Systemic mastocytosis (SM)	
Bone marrow mastocytosis (BMM) Indolent SM	*More indolent*
Smoldering SM	
SM with an associated hematologic neoplasm (SM-AHN)	*"Advanced"*
Aggressive SM	
Mast cell leukemia	
Mast cell sarcoma	

Mastocytosis classification

Non AdvSM	Diagnostic features
BMM	0 B-findings, no skin lesions, serum tryptase <125 ng/mL
ISM	<2 B-findings, typical skin lesions
SSM	≥2 B-findings, often high MC burden

Advanced Systemic Mastocytosis

Mast cell leukemia

≥ 20% mast cells on aspirate/PB*

SM + AHN/AMN

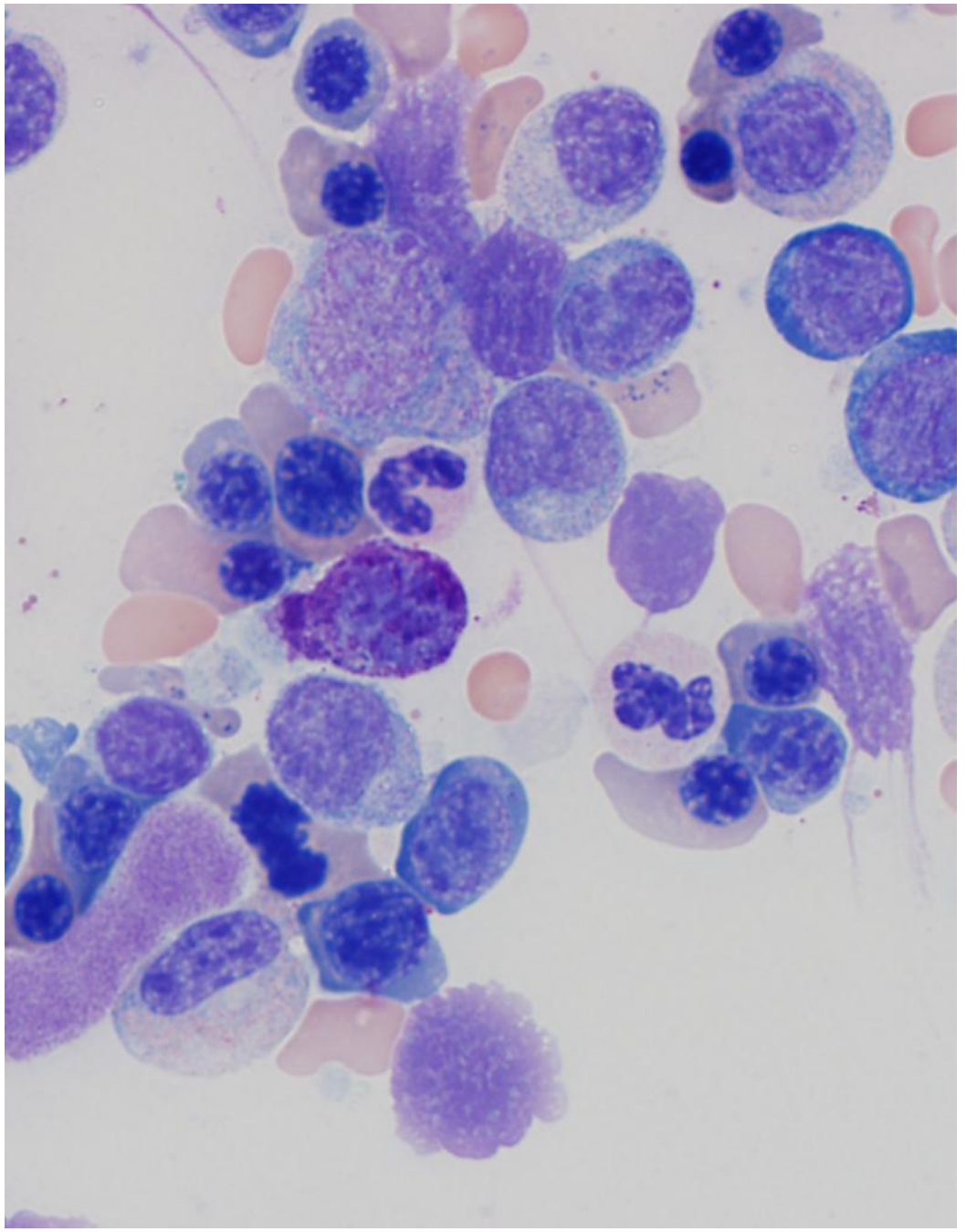
- Meets WHO criteria for an associated hematological neoplasm
- Meets SM criteria

ASM (1+ C-findings)

- Cytopenias
- Hepatomegaly with impaired liver function
- Skeletal involvement → osteolytic lesions and/or pathological fractures
- Splenomegaly with hypersplenism
- Malabsorption due to GI mast cell infiltrates

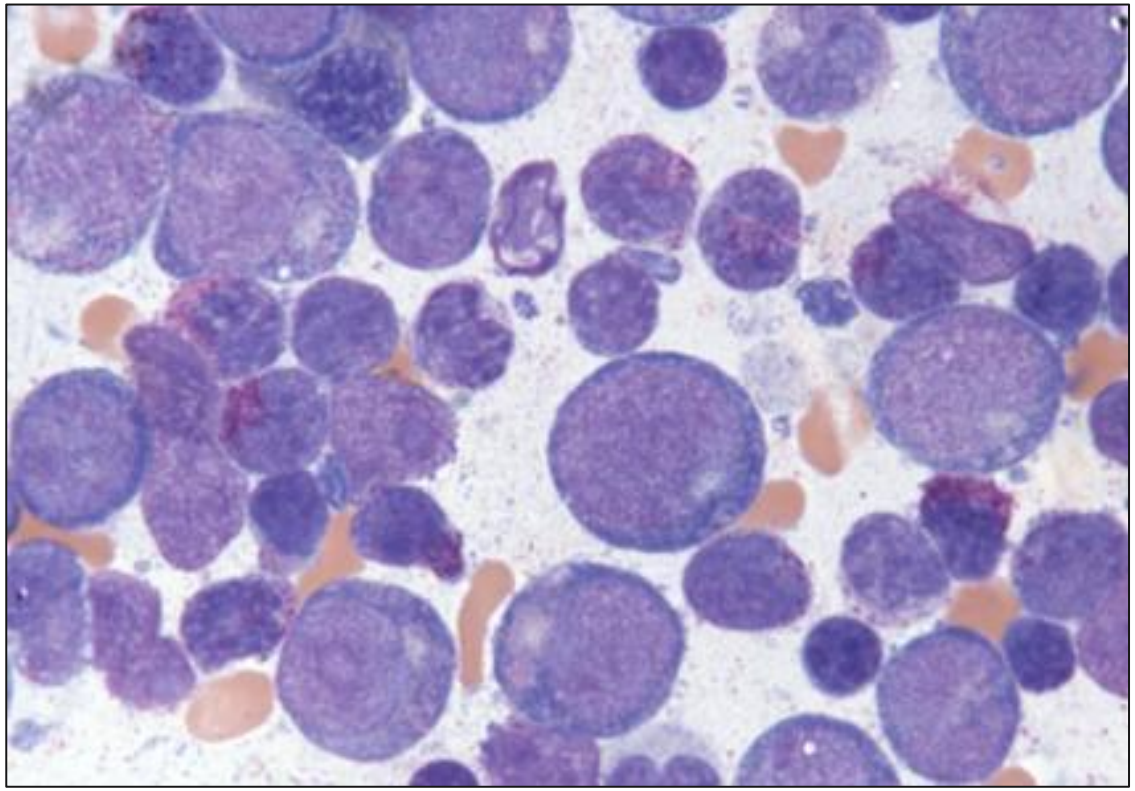
*MCs must be immature per ICC only

Association with myeloid neoplasms



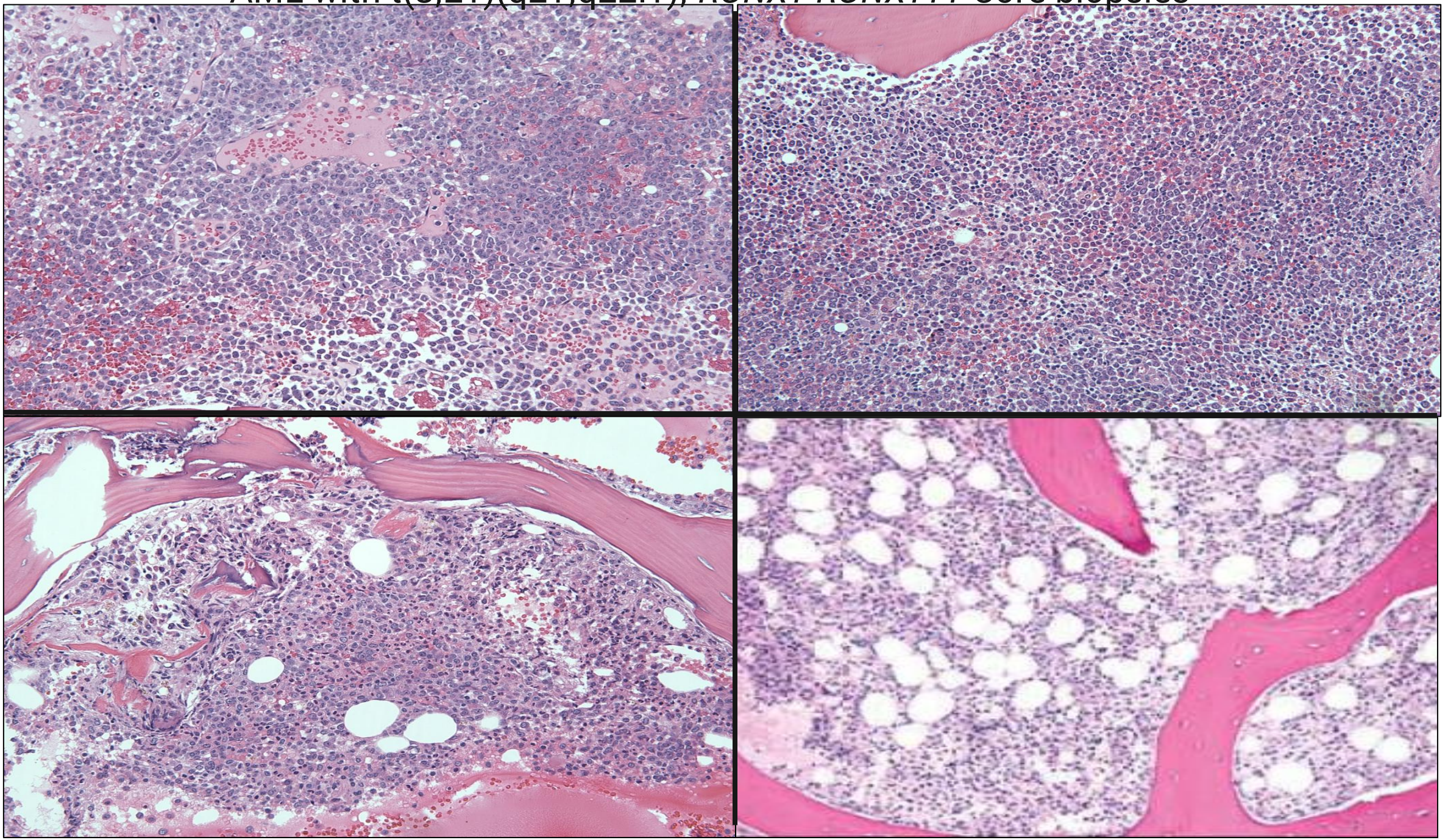
Prevalence of systemic mastocytosis in select myeloid malignancies

- Most pts with AdvSM are SM-AHN
- Of AHN, 85% are myeloid malignancies (AML, MDS, CMML, MPN)
- 5-6% of AHNs: AML with t(8;21)(q22;q22)/*RUNX1-RUNX1T1*

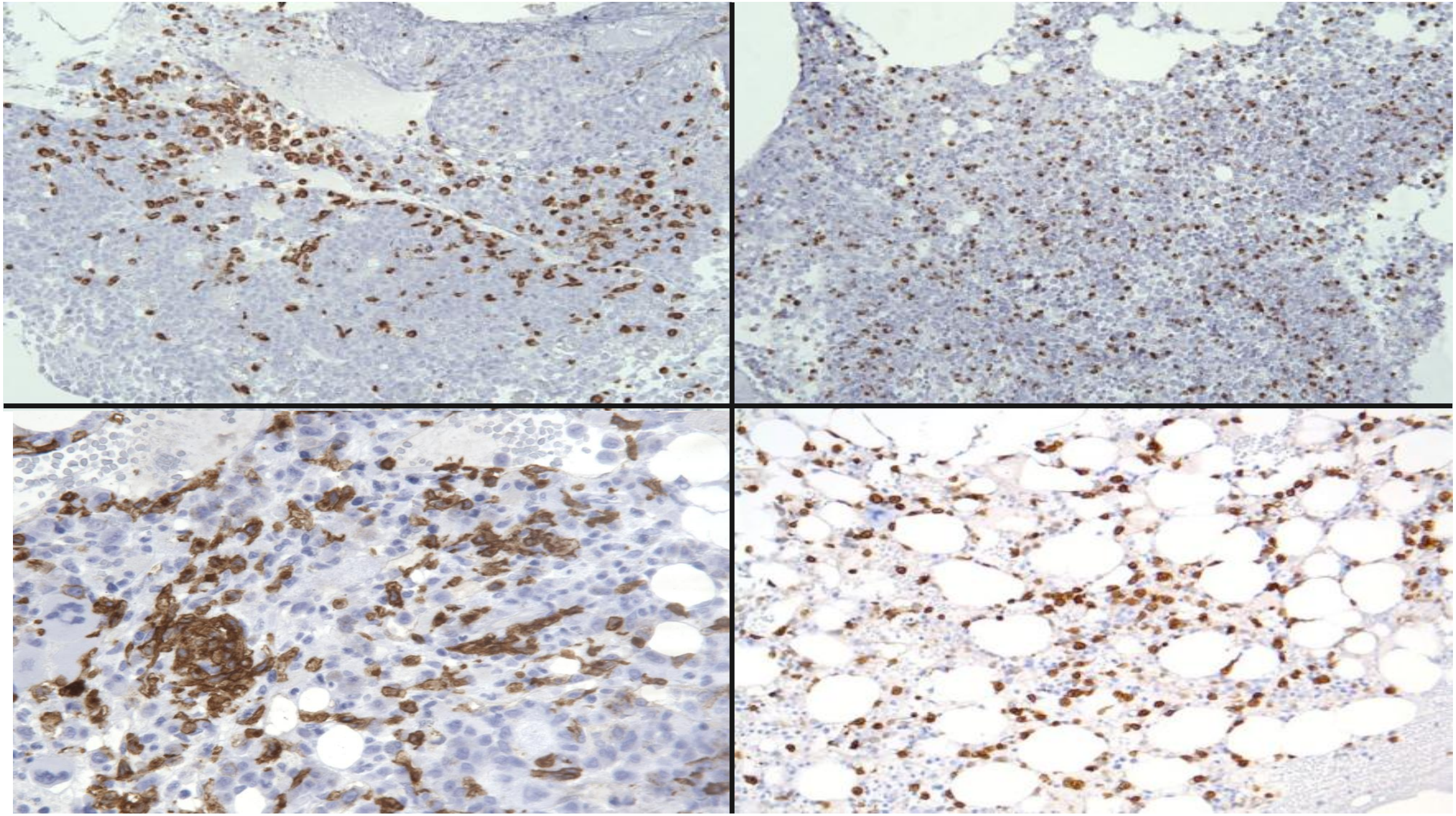


Arredondo et al. Am J Hematol 2010
Pullarkat et al. J Hematopathol 2009
Sperr et al. Clin Cancer Res 2005
Pullarkat et al. Leuk Res 2007
Wong et al. Am J Hematol 1991
Nagai et al. Exp. Hematol 2007
Escribano et al. J Allergy Clin Immunol 2004
Bernd et al. J Clin Pathol 2004

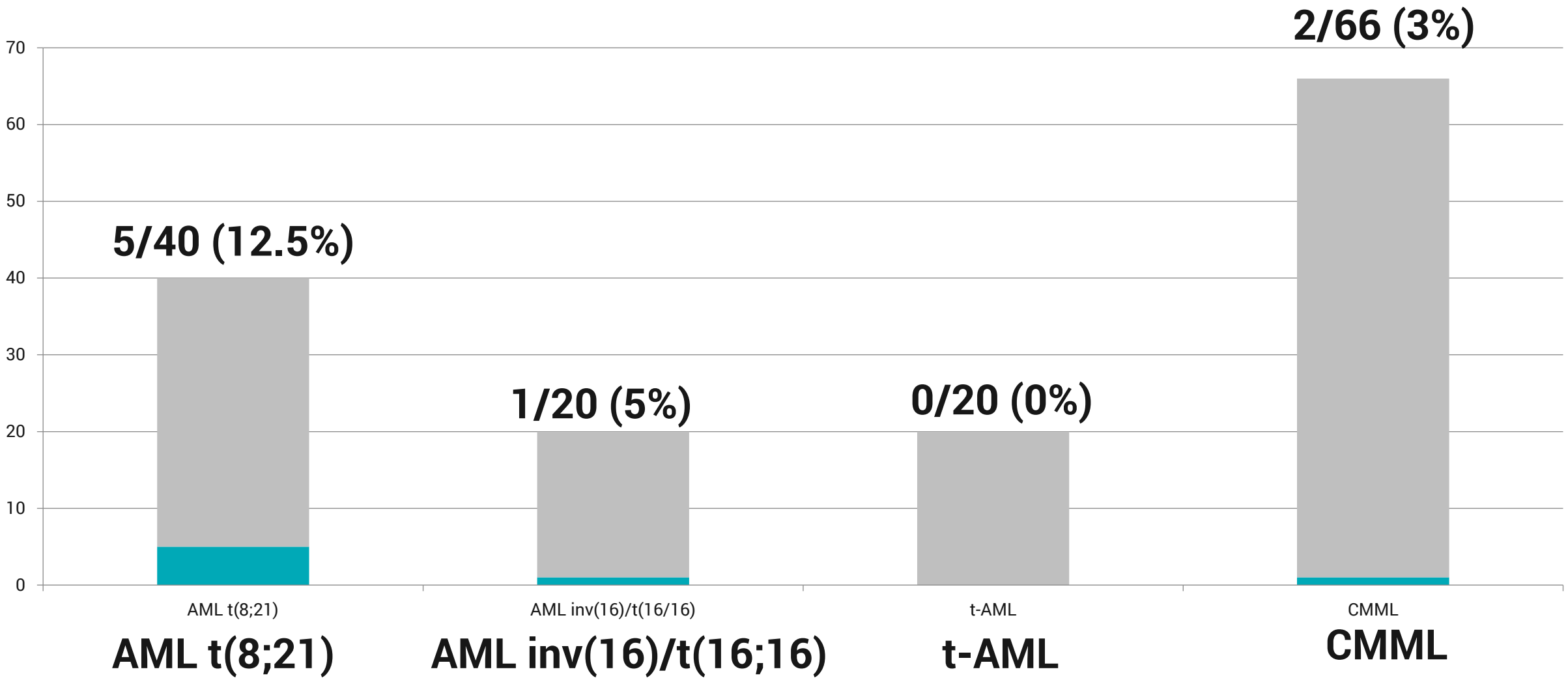
AML with t(8;21)(q21;q22.1); *RUNX1-RUNX1T1* Core biopsies



Tryptase immunohistochemistry



Prevalence of Systemic Mastocytosis in Select Myeloid Malignancies from a Single Institution



Johnson RC et al. Am J Clin Pathol 2013

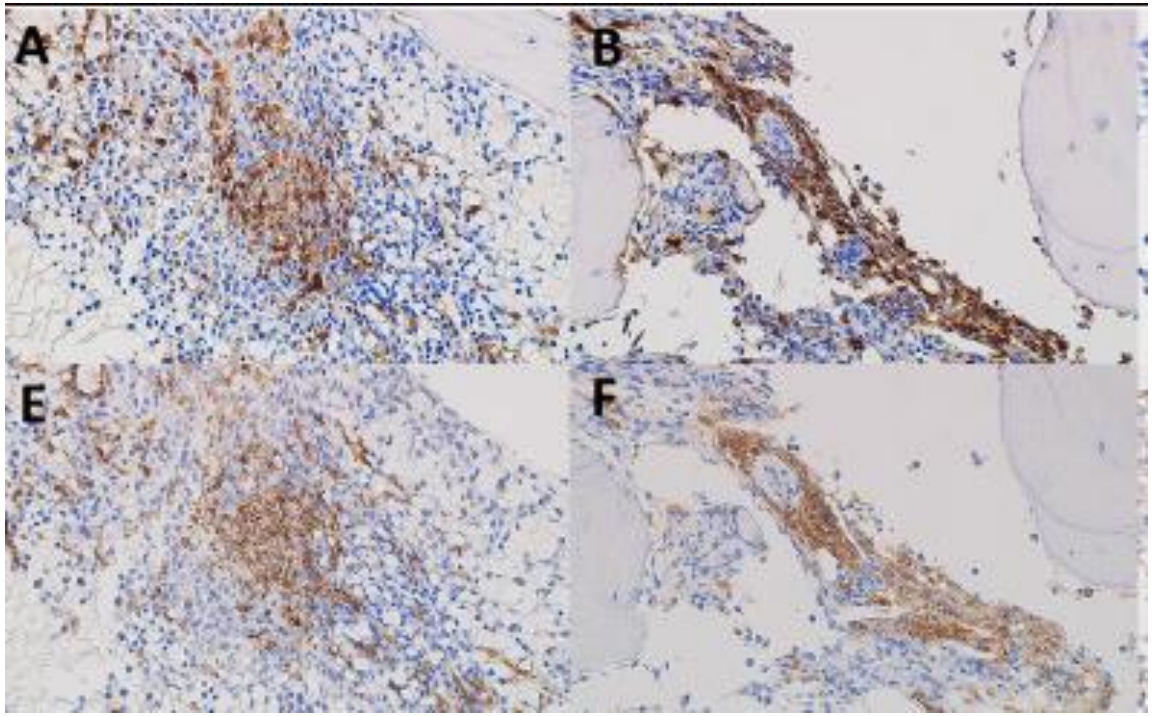
Utility of *KIT* mutations in myeloid neoplasms to detect hidden mast cells in BM

Searched myeloid neoplasms for NGS results of KIT+ mutations

IHC for tryptase and CD117 on 49 pts

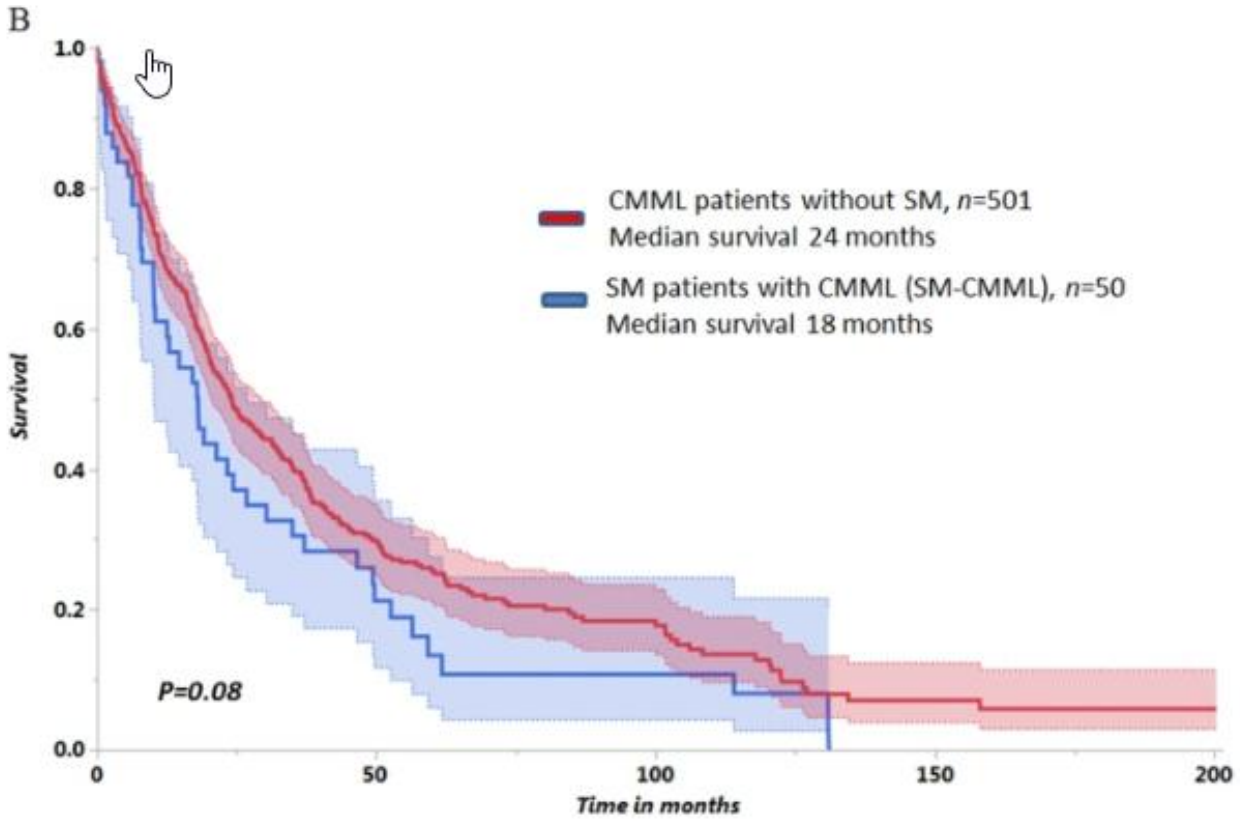
AML= 38
CMML=6

SM-AHN 4 (8%): AML t(8;21), CMML, MPN, AML in CR



DH Kim et al. Clin Lymphoma Myeloma Leuk 2024

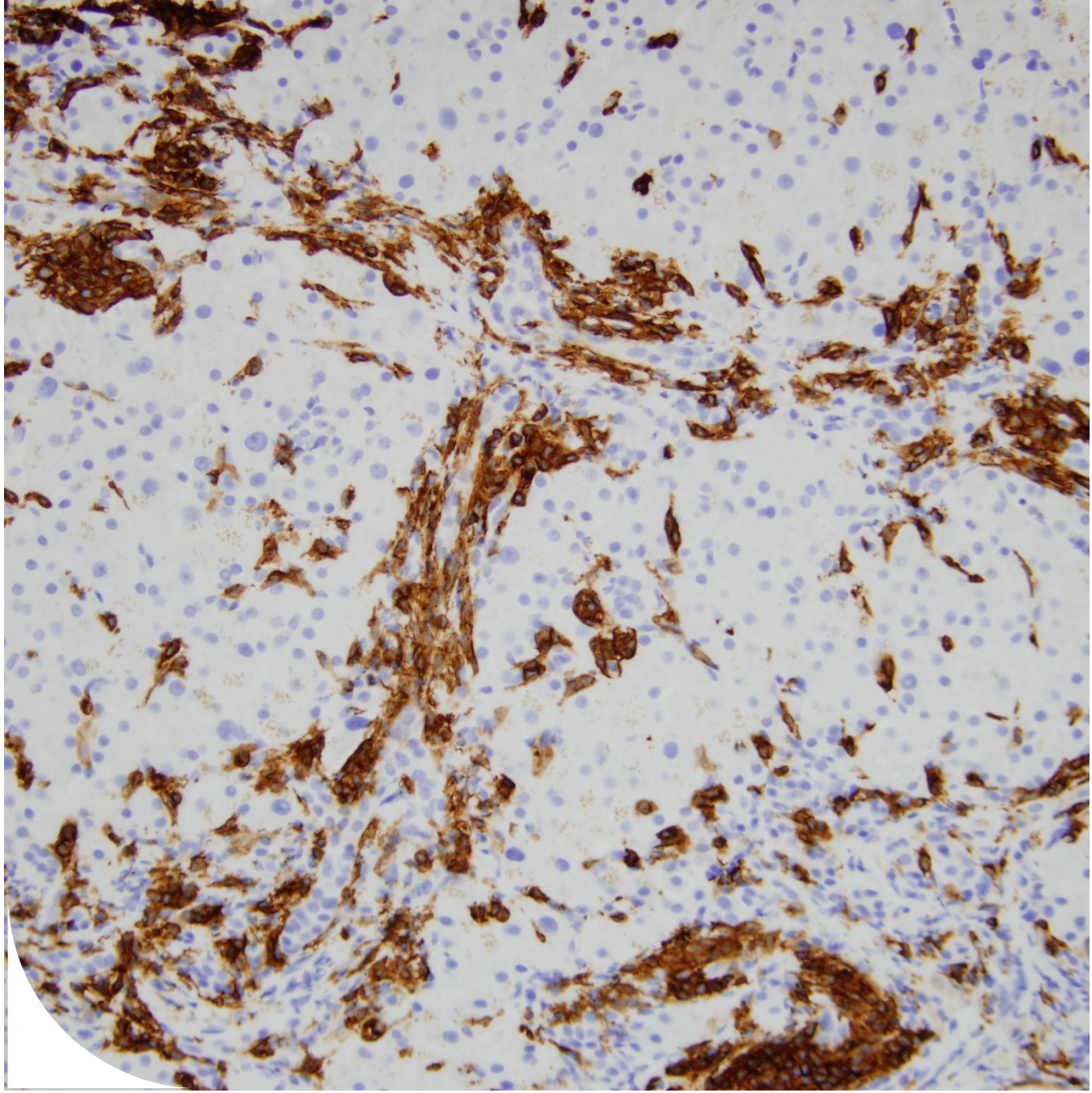
SM-CMML has worse survival than CMML

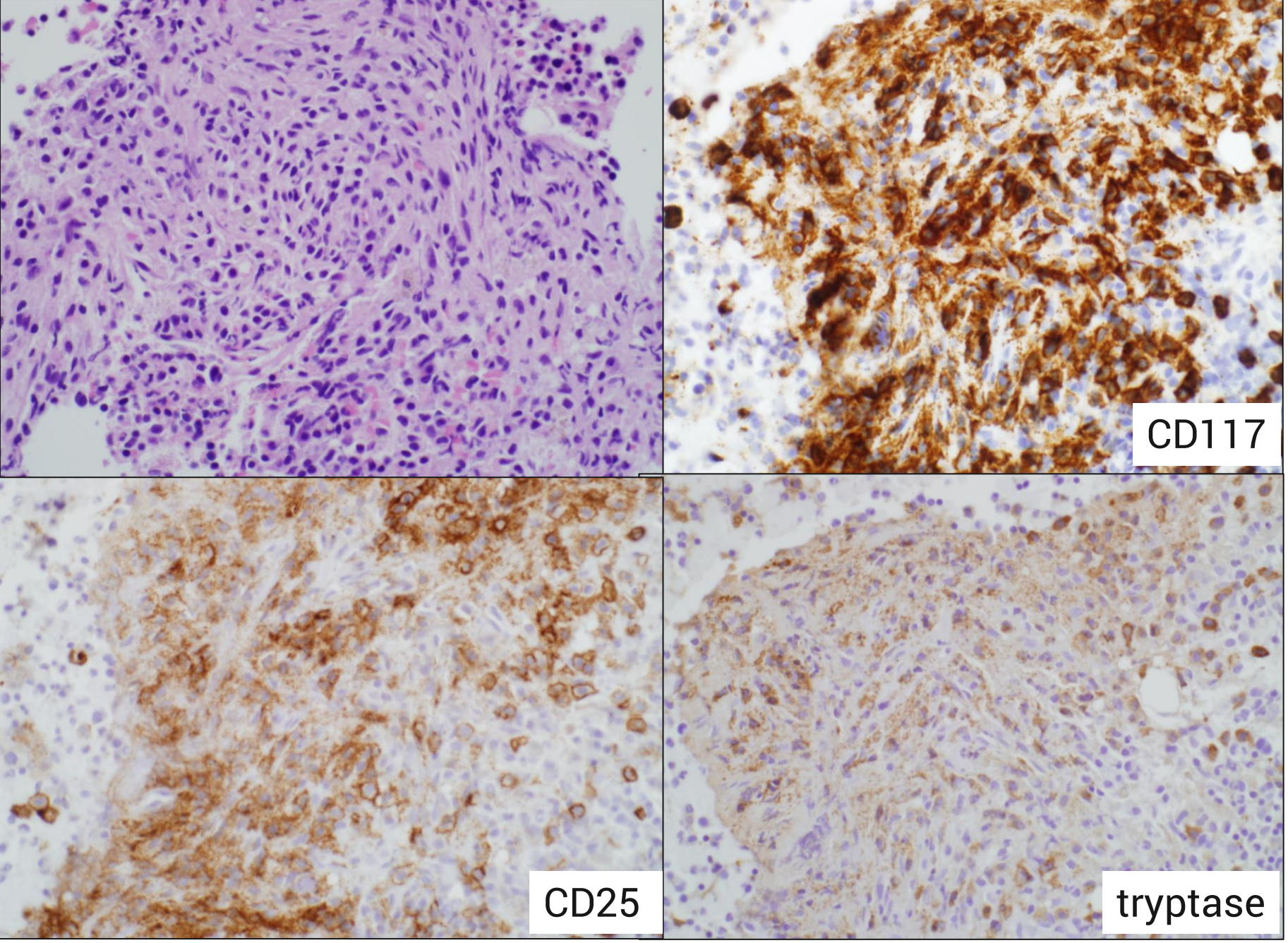


	SM-CMML	CMML	*P* values
Number	50	501	
Age (yr); median (range)	70 (45-88)	72 (18-95)	0.03
PB blasts%; median (range)	0 (0-9)	0 (0-19)	0.03
LDH IU/mL; median (range)	167 (79-926)	237 (140-338)	0.04
WHO CMML-0; n(%)	38 (79)	265 (56)	0.003
CBL; n(%)	10 (27)	36 (13)	0.03
KIT D816V; n(%)	43 (86)	3(1)	0.0001

Patnaik MM et al. Leukemia 2018

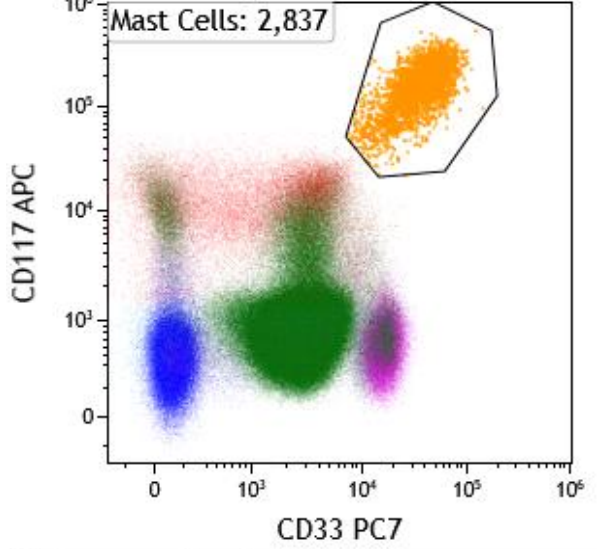
Immunohistochemistry and molecular diagnosis



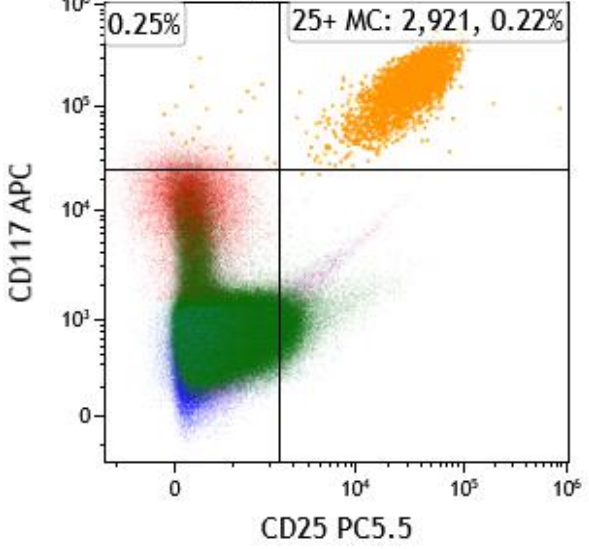


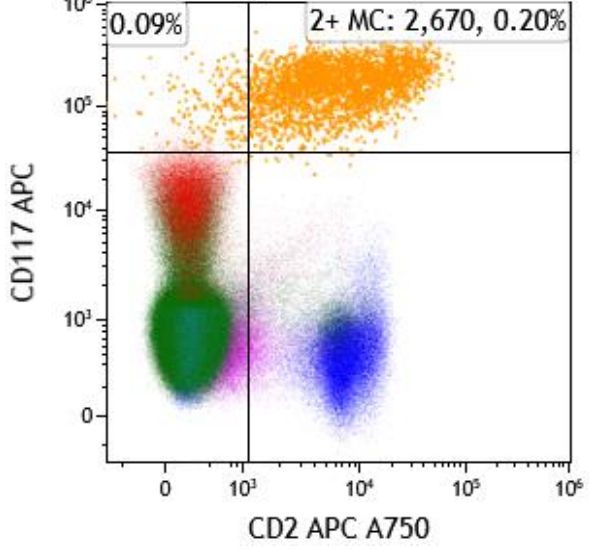
BM core biopsy

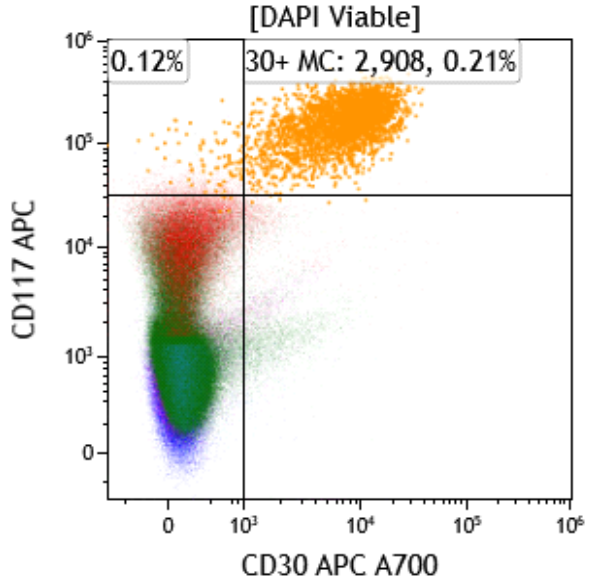
Aberrant expression of CD2 and/or CD25 and/or CD30 in mast cells

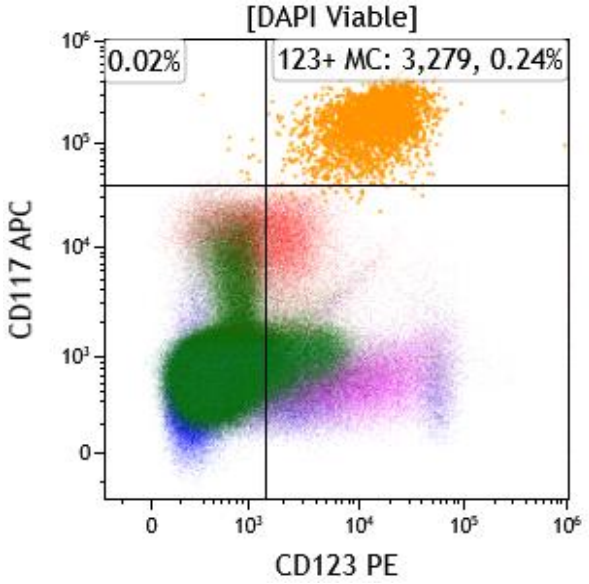


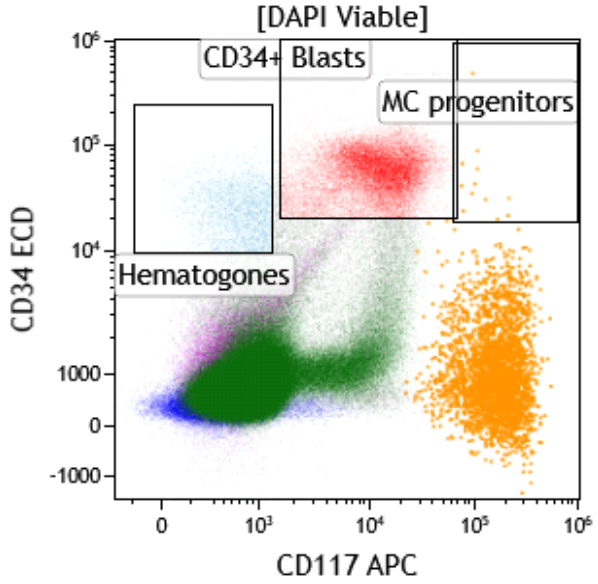
Gate	Number	%Gated
All	1,357,935	100.00
Mast Cells	2,837	0.21









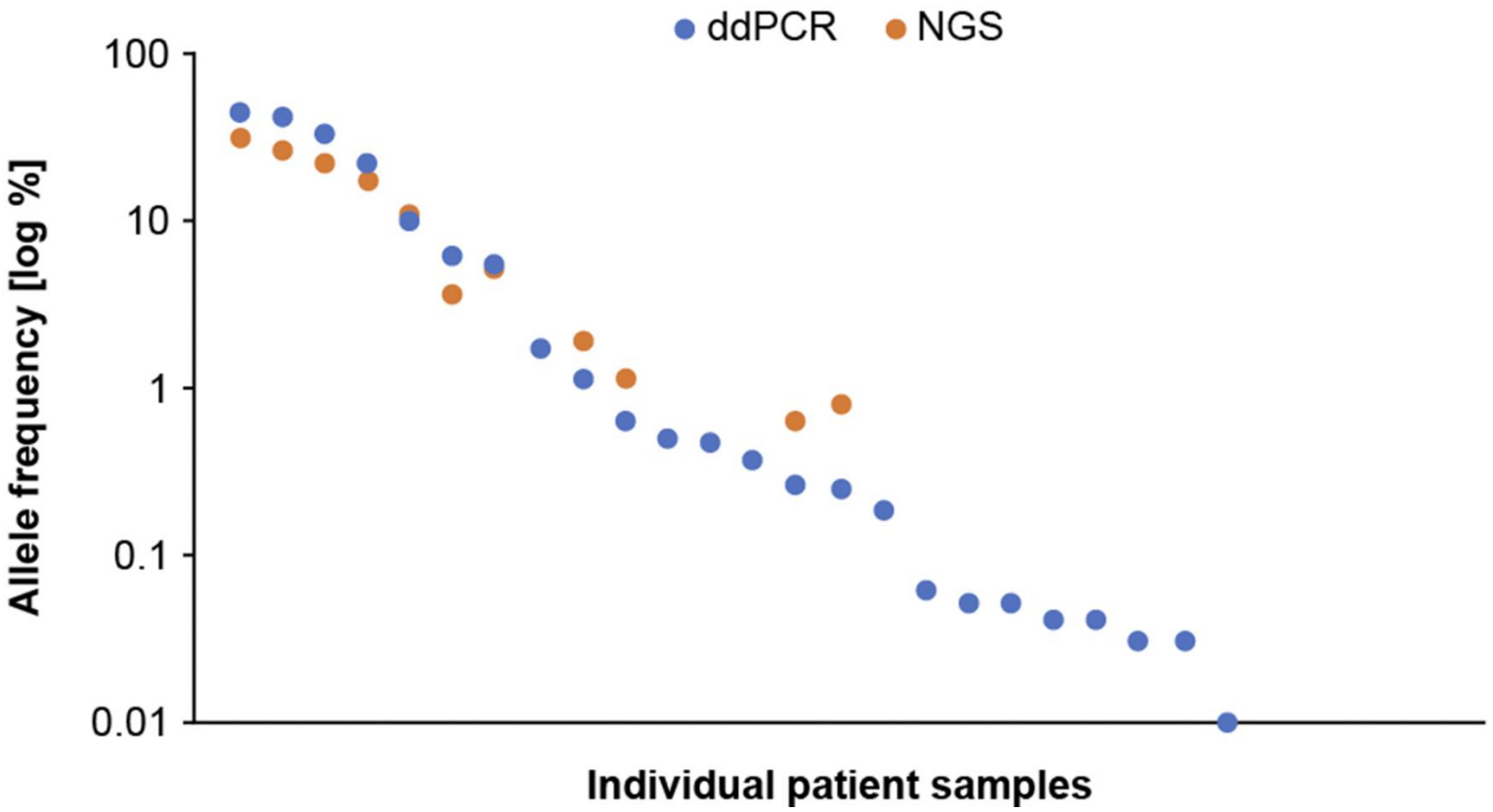


Gate	Number	%Gated
All	1,357,935	100.00
CD34+ Blasts	25,580	1.88
Hematogones	5,415	0.40
MC progenitors	116	0.01

Courtesy of David Ng (Univ Utah)

Increased detection of KIT D816V in ISM using a high sensitivity ddPCR assay (95%) vs NGS (28%)

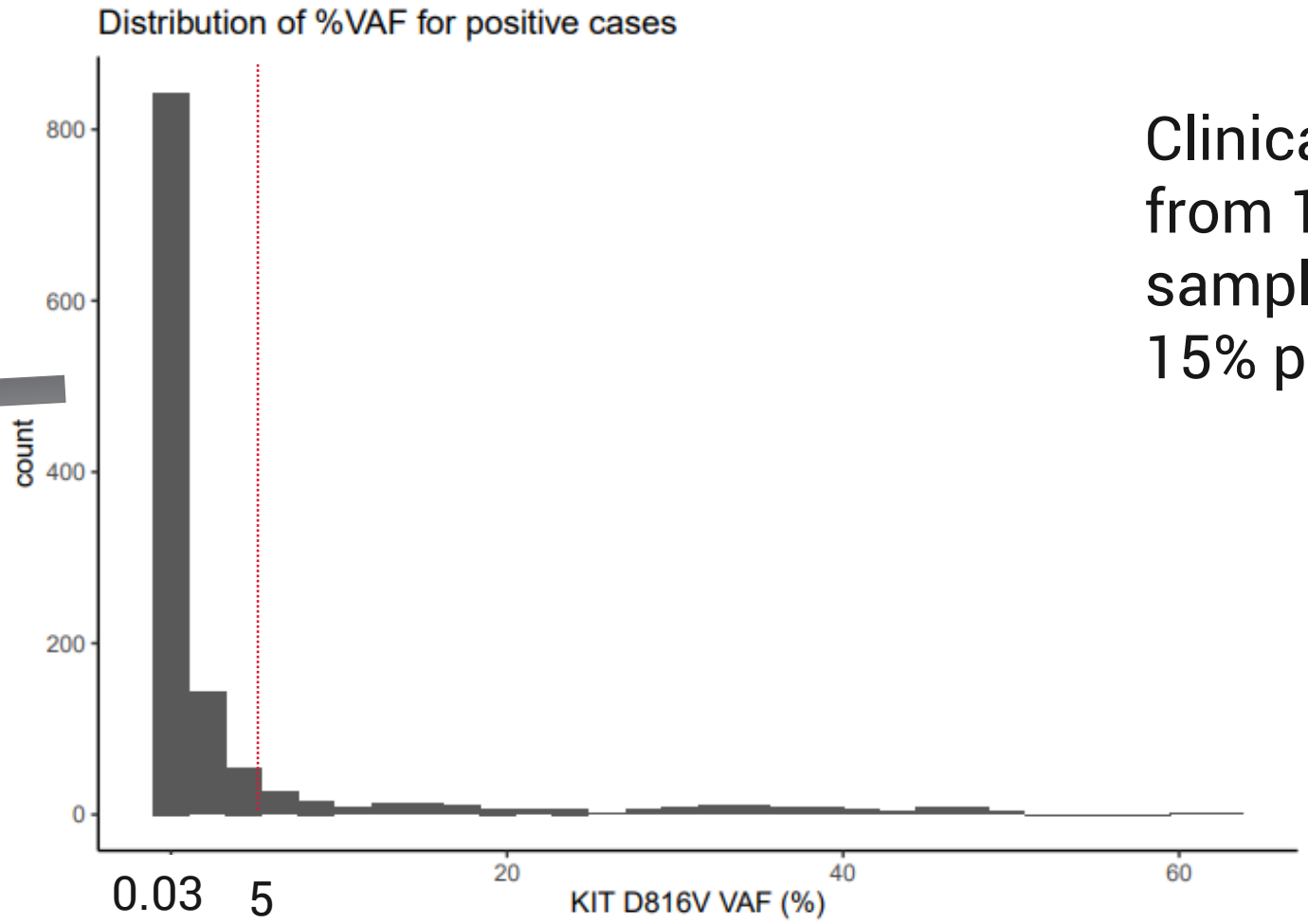
Figure. Performance of central ddPCR and NGS detection of *KIT* D816V VAF in PB samples from patients enrolled in part 1 of PIONEER



George TI et al. Blood 2020, abstract.

High sensitivity *KIT* D816V testing by ddPCR

1031/1232 (84%) of positive samples with <5% VAF



Clinical testing performed from 1/2021-3/2024: 8,272 samples (PB, BM) with a 15% positivity rate overall.

Shean R et al. Am J Clin Pathol 2025.

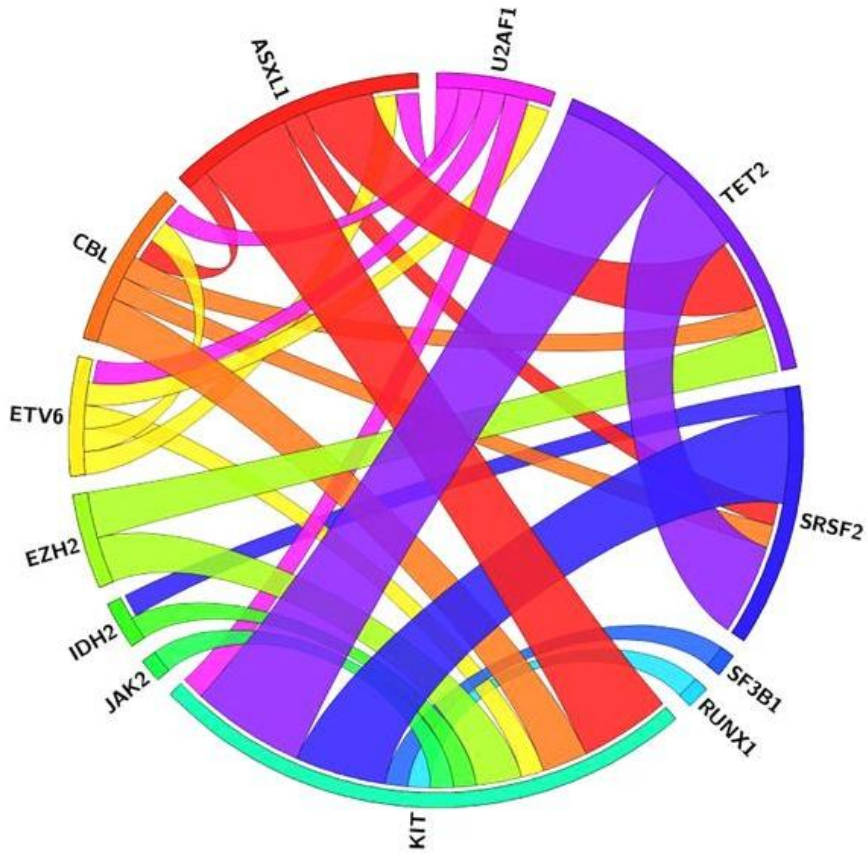
Detection of the *KIT* D816V mutation: higher rates of discordance in PB vs BM in nonAdvSM

Disease subtype	% Discordant with blood	P value
BMM (n=86)	44/86 (51%)	<.0001
ISM (n=102)	15/102 (15%)	<.0001
SSM (n=7)	0/7 (0%)	NA
AdvSM (n=37)	2/37 (5%)	<.0001
SM TOTAL (n=232)	61/232 (26%)	<.0001

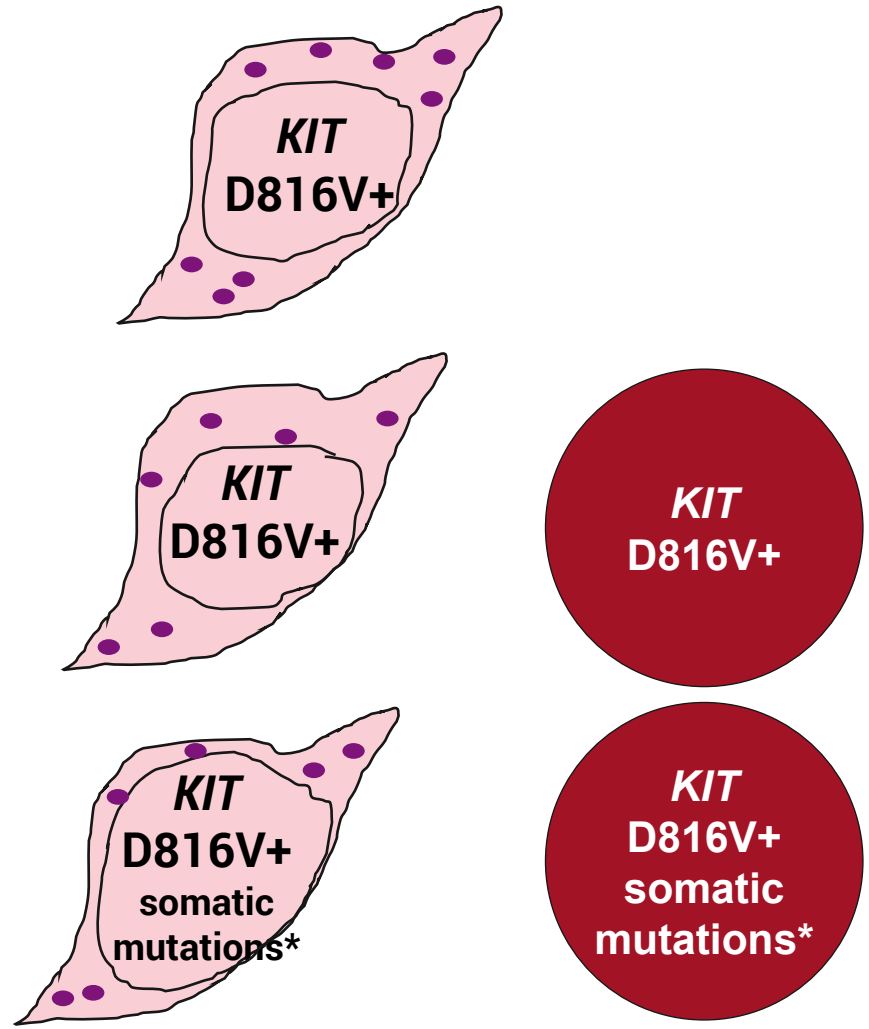
Navarro-Navarro P et al. Allergy 2023.

Advanced systemic mastocytosis is a multimutated myeloid neoplasm

- **ISM/SSM**- 0 additional mutations
- **SM-AHN**- 1-4 additional mutations; *TET2, **S**RSF2, **A**SXL1, CBL, EZH2, **R**UNX1*
- *SAR: adverse prognosis for OS*



Jawhar M et al. Leukemia 2015. Jawhar M et al. Leukemia 2016.



Involvement of mast cell lineage

- **ISM**
- SSM
- MCL

Multilineage involvement

- ISM
- **SSM**
- **SM-AMN**

PB *KIT* D816V qPCR

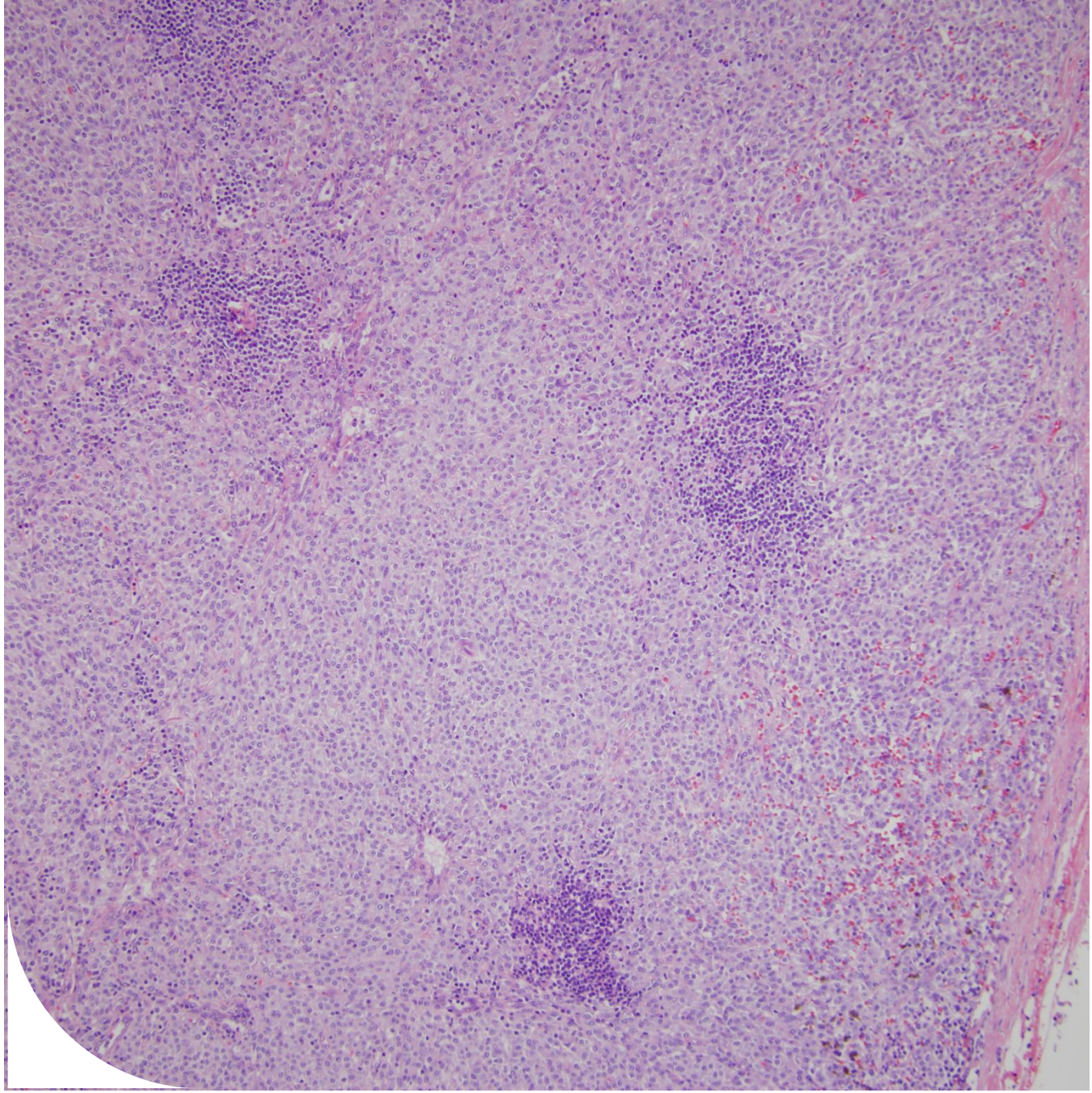
Multilineage involvement + multi-mutated

- **SM-AHN/AMN**
- **MCL ± AHN/AMN**

*additional somatic mutations:
e.g., *SRSF2*, *ASXL1*, *RUNX1*, *CBL*, *JAK2*, *EZH2*

Slide adapted from A. Reiter with permission. Reiter A, George TI, Gotlib. Blood 2020.

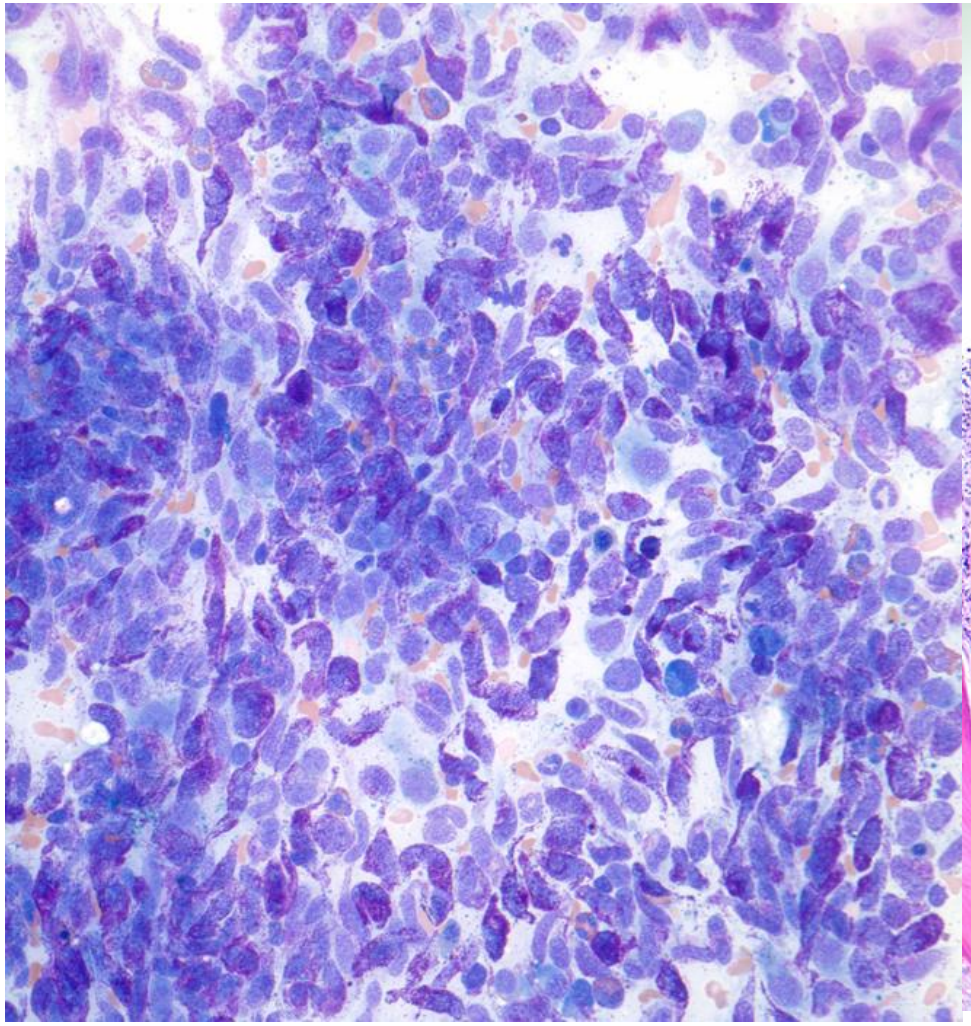
Challenges of diagnosis

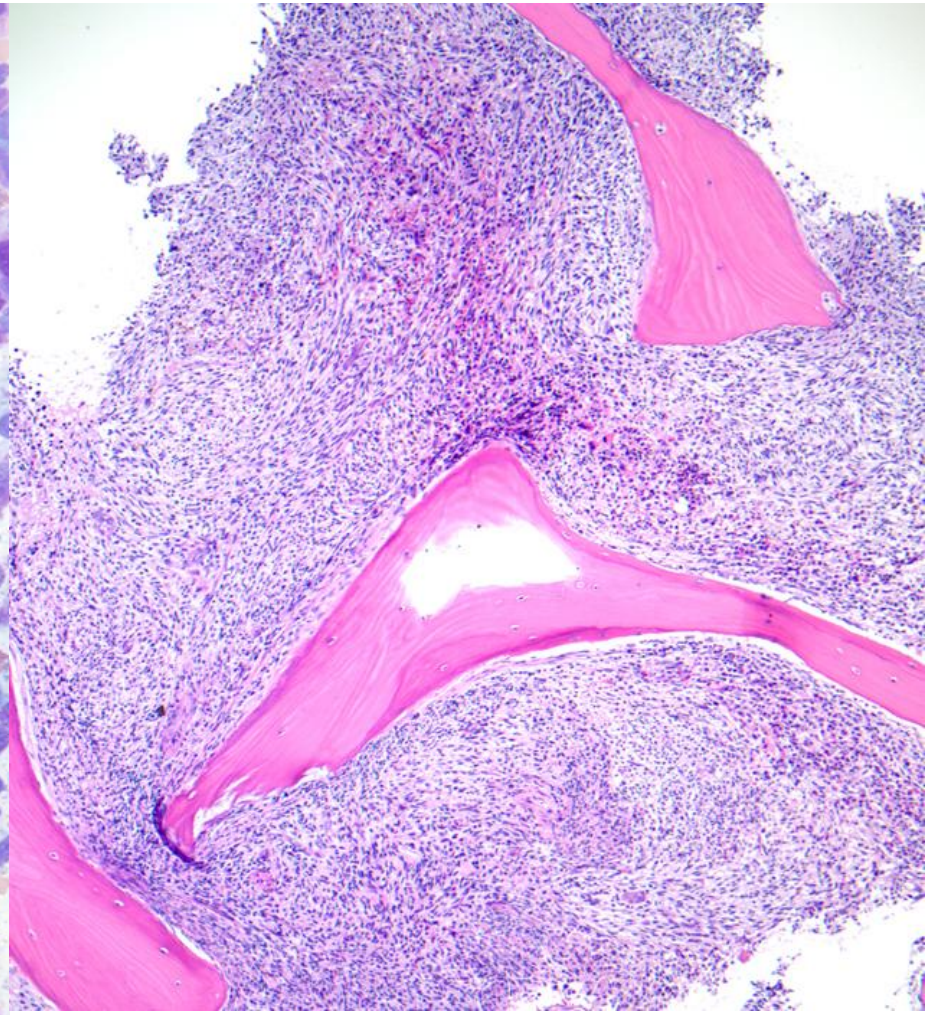


Challenges diagnosing mast cell disease

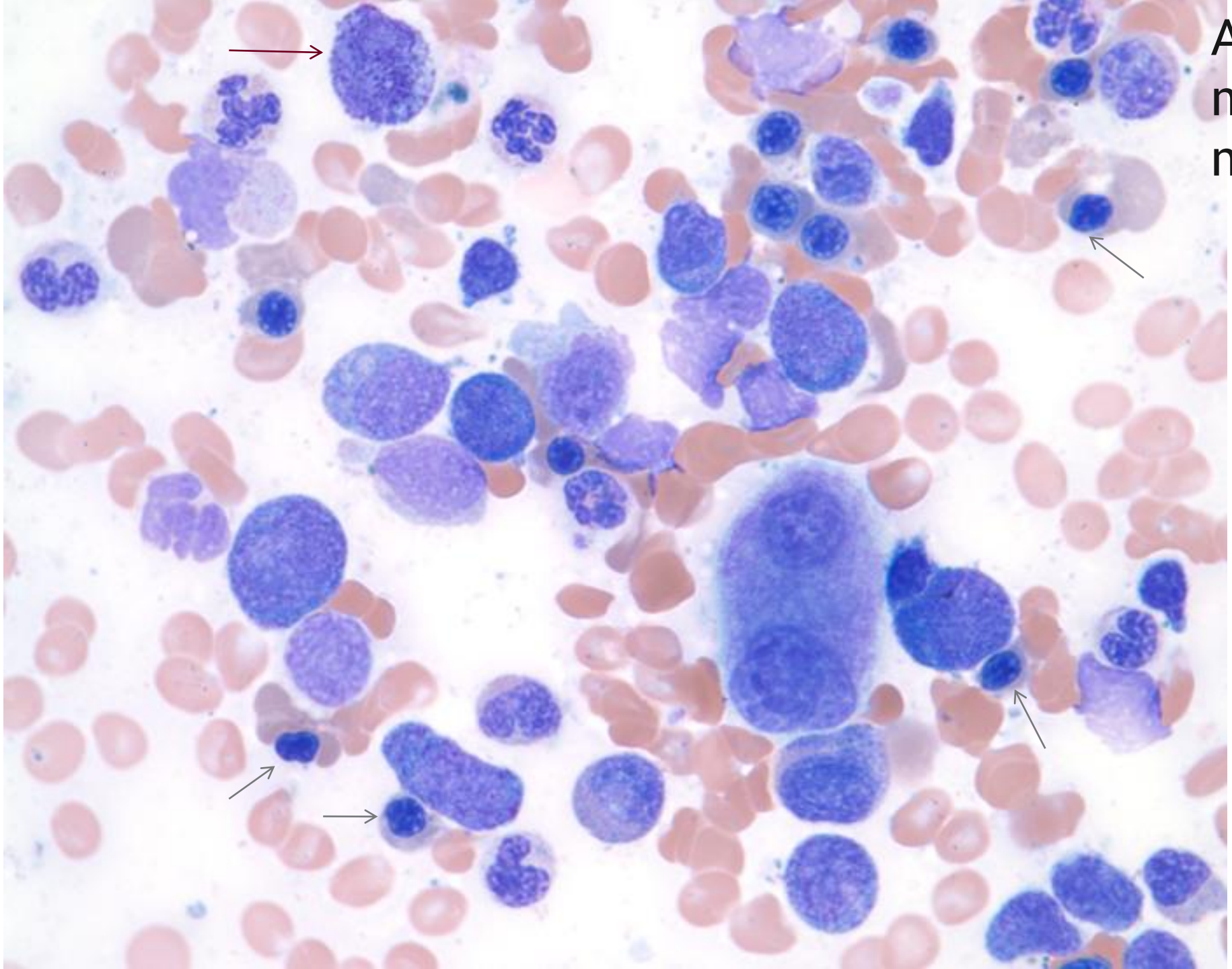
1) Under recognition of AHN/AMN in SM
2) Under recognition of SM in AHN/AMN
3) Recognizing immature mast cells
4) Morphologic mimics
5) Using less sensitive methods for detection of *KIT* p.D816V

Recognizing AHN in the presence of SM



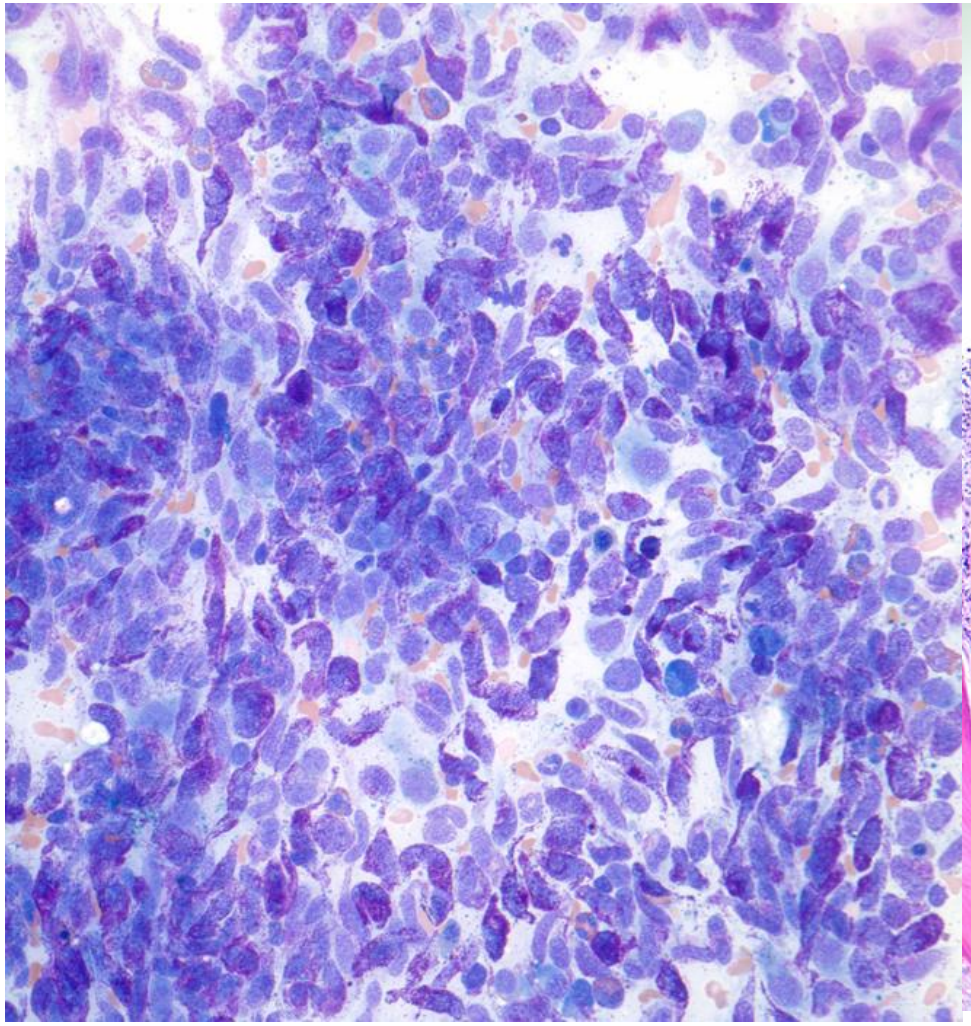


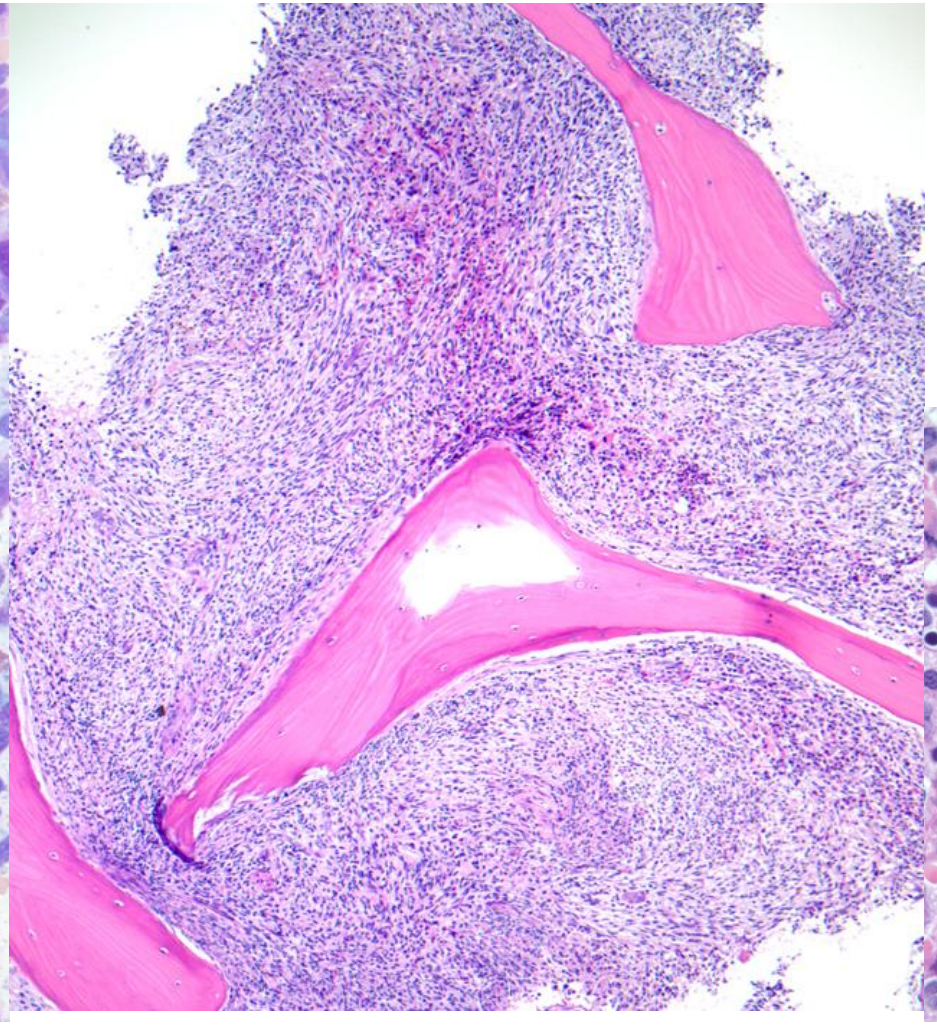
MCL

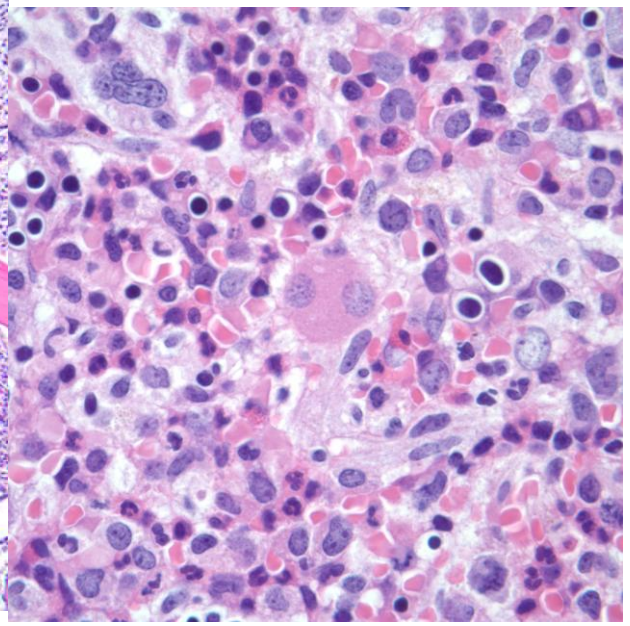


After 3 months on midostaurin

MCL-MDS







Clues to diagnosing AHN when SM is present

	PB blast%	Cytopenias	-cytoses	Dysplasia	BM biopsy cellularity away from MC aggregates	Abnormal karyotype	PB KIT D816V qPCR	BM KIT D816V qPCR	Additional somatic mutations
ISM	0	No	No	No	Normocellular	No	Low	Low	0-1
SSM	0	No	No	Variable	Normocellular/ Hypercellular	No	Low	High	0-1
ASM	0	Yes	No	No	Normocellular	No	Low	High	≥3
MCL	0	Variable	Variable	No	Normocellular	No	Variable	High	≥3
ISM-AHN	Variable	Yes	Variable	Variable	Hypercellular	Yes	High	High	≥3
ASM/ MCL-AHN	Variable	Yes	Variable	Variable	Hypercellular	Yes	High	High	≥3

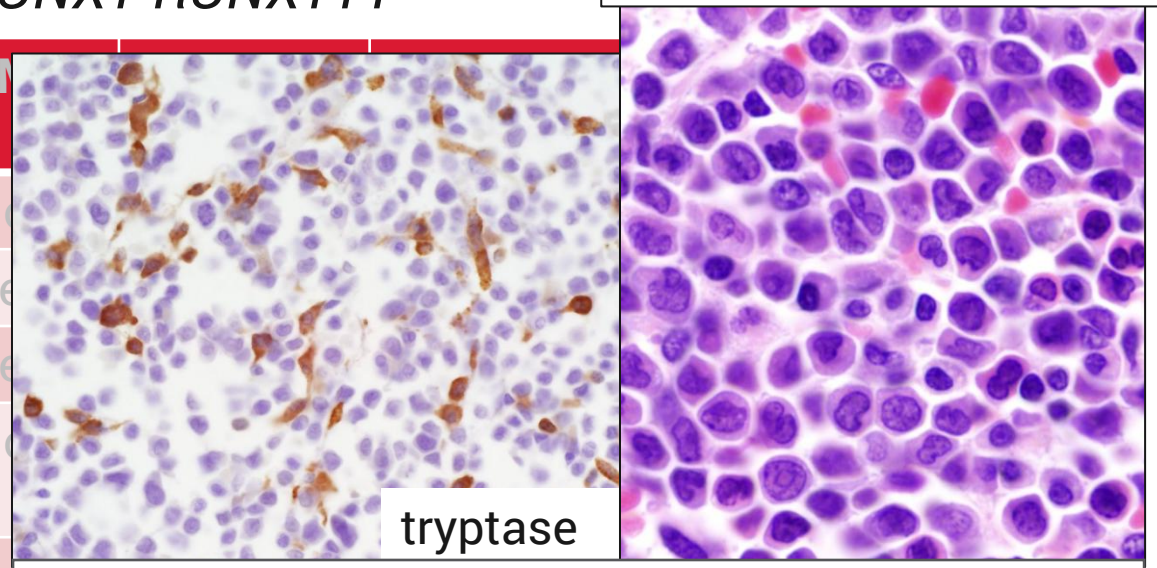
From Society for Hematopathology/EAHP presentation 2019

Recognizing SM in the presence of an AHN

SM-AML with t(8;21)(q21;q22.1); *RUNX1-RUNX1T1*

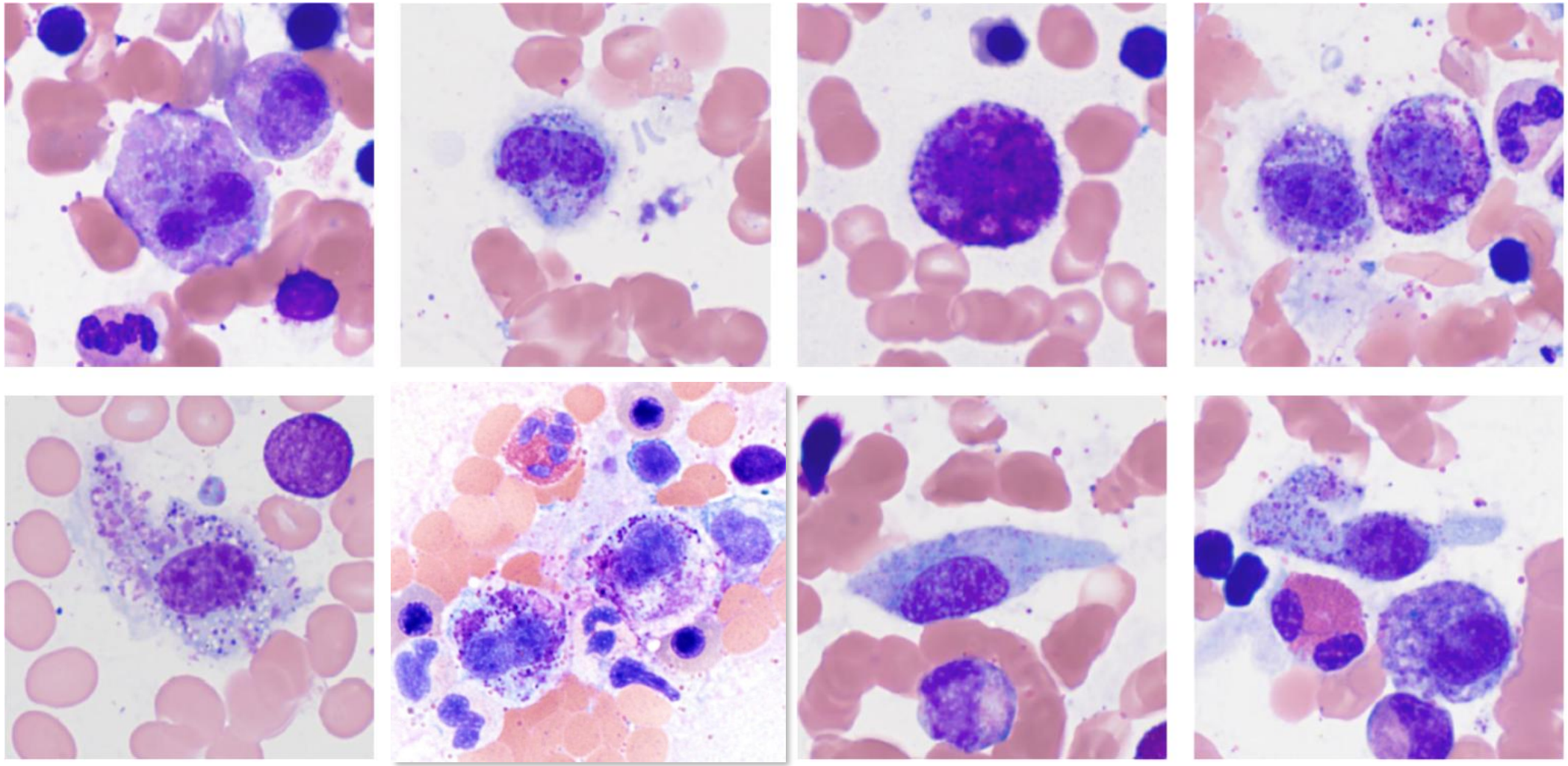
Case	Age/ Sex	Initial Dx	AML Relapse	EN
20	44F	AML	Yes	No
29	29F	SM-AML	Yes	Ye
59	10F	AML	No	Ye
108	30F	SM-AML	Yes	No
206	36F	SM-AML	Yes	No
236	13F	AML	Yes	No
254	50F	AML	Yes	Ye

Diagnostic bone marrow

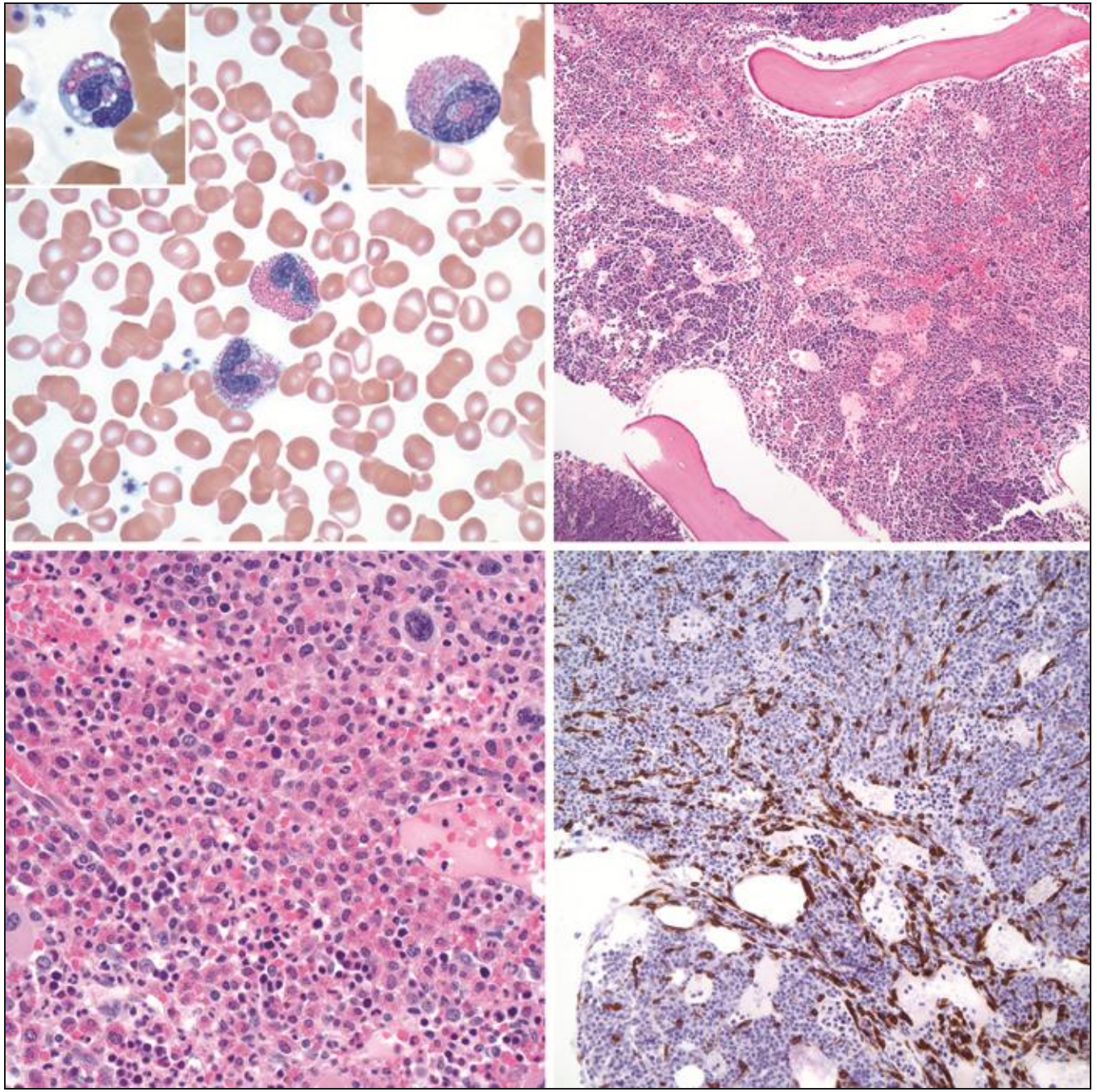


1. *Systemic mastocytosis often subtle and only revealed by immunohistochemistry at diagnosis*
2. *Mast cells increase over time, becoming diagnostic for SM later in disease course (e.g. day14 bone marrow, relapse)*

Recognizing neoplastic mast cells on smears

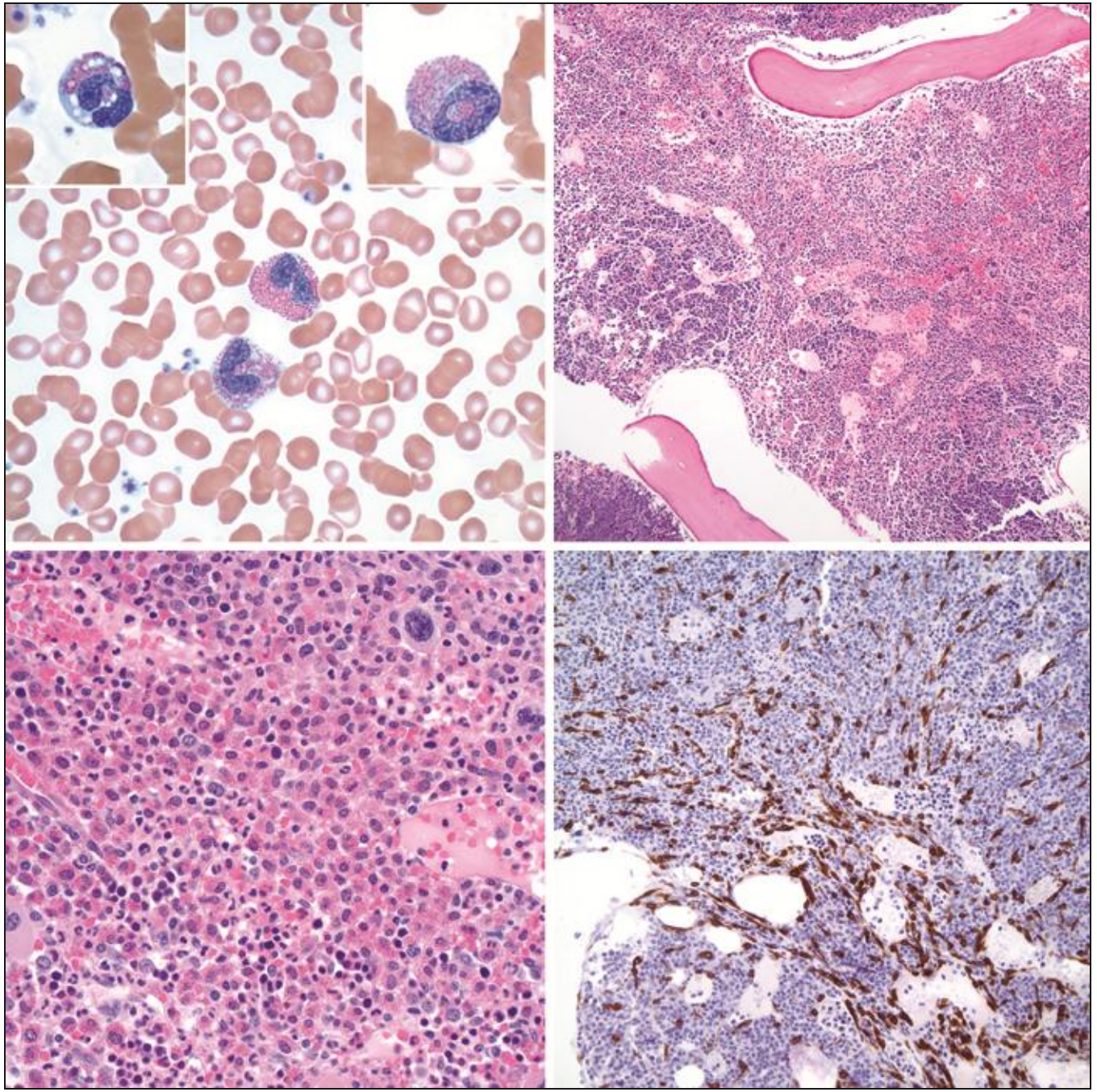


Courtesy of Anton Rets (Univ Utah)



Diagnosis?

CD117



Chronic eosinophilic leukemia with *FIP1L1-PDGFRA*

CD117

Conclusions

01	WHO & ICC Classifications
02	Systemic mastocytosis and subtypes
03	Association with myeloid neoplasms
04	Immunohistochemistry and molecular diagnosis
05	Challenges of diagnosis

Thank you!

American
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