FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE



CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
23-24 ottobre 2026

MAST-CMML: Studio dell' Impatto della componente mastocitaria sulla risposta al trattamento nella Leucemia Mielomonocitica Cronica

.

Daniela Cilloni

Disclosures of Daniela Cilloni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Gentili					X	X	
Blueprint					X		
GSK					X		
BMS					X		
Abbvie					X		
Astellas	X				X		
Daichii Sankyo					X		
Novartis					X	x	

FONDAZIONE
ITALIANA
SINDROMI
MIELODISPLASTICHE

Protocol cover page

PROTOCOL TITLE MAST-CMML Study: Impact of Mast Cell Component on Treatment Response in patients with chronic myelomonocytic leukemia.

PROTOCOL IDENTIFYING NUMBER: MAST-CMML

PROTOCOL VERSION 1.0 DATE 01/09/2026

Studio Osservazionale con farmaco

Systemic mastocytosis is classified as a myeloid neoplasm

Myeloid Neoplasms					
Mastocytosis	Myeloproliferative neoplasms (MPN)	Myeloid/lymphoid neoplasms with eosinophilia	Myelodysplastic syndromes/ myeloproliferative neoplasms (MDS/MPN)	MDS	Myeloid neoplasms with germline predisposition

Cutaneous Mastocytosis (CM)[1]

Systemic Mastocytosis[1]

Mast Cell Sarcoma[1]

Non-Advanced SM[2]

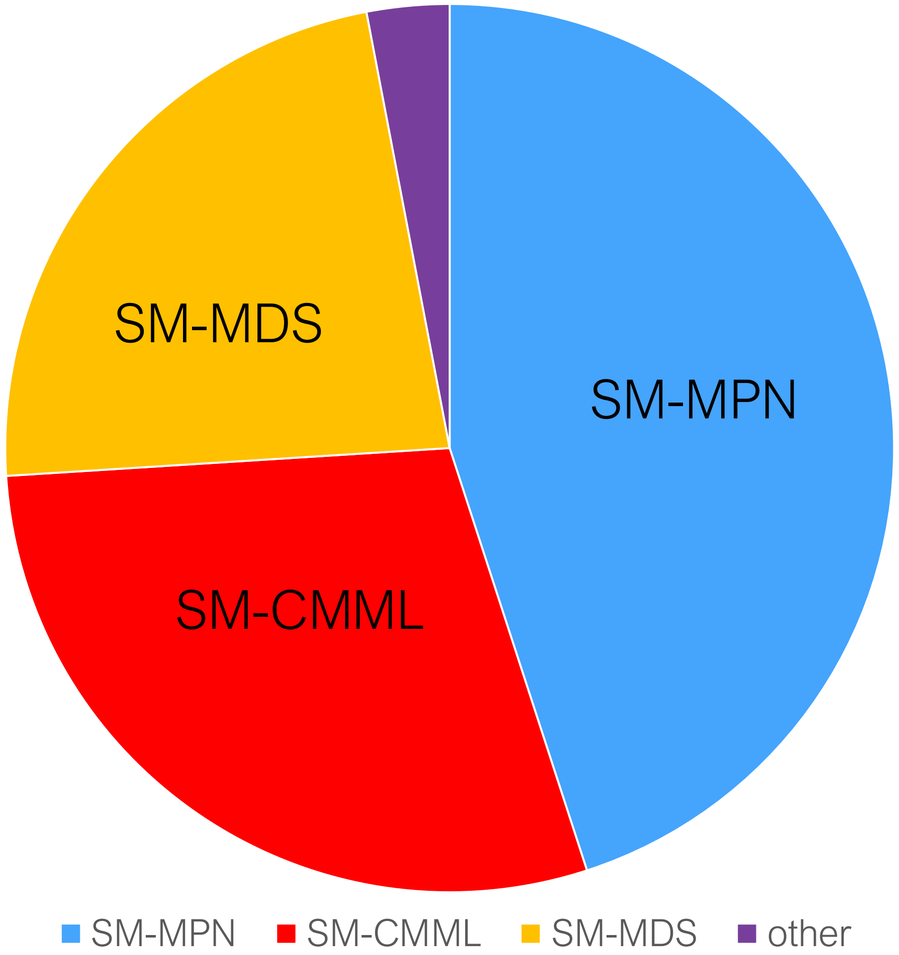
- Indolent SM
- Smoldering SM
- BM mastocytosis

Advanced SM[2]

- Aggressive SM
- Mast Cell Leukemia (MCL)
- **Associated Hematologic Neoplasm (AHN)**

- ISM represents the vast majority of systemic mastocytosis (~ 95% of SM patients)[3]
- Up to **67%** of patients with advanced systemic mastocytosis have an associated neoplasm[2]

SM-AHN: subtypes



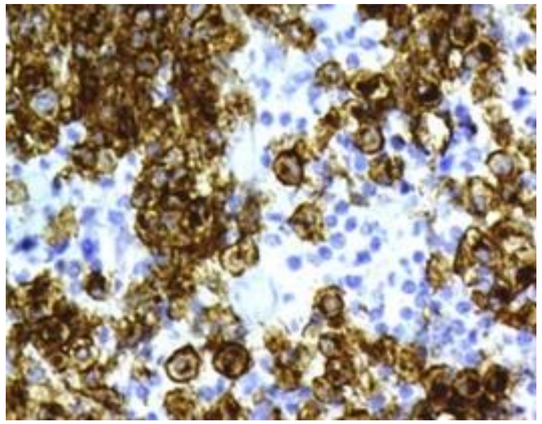
	percentage (%)	Median OS (months)	Leukemia trasnformation (%)
SM-MPN	45	31	11
SM-CMML	29	15	6
SM-MDS	23	13	29
other	3	NA	NA

SM-MPN displayed a 2- to 3-fold better life expectancy (*P* = .003),
Leukemic transformation was more frequent in SM-MDS (29%; *P* =.02)

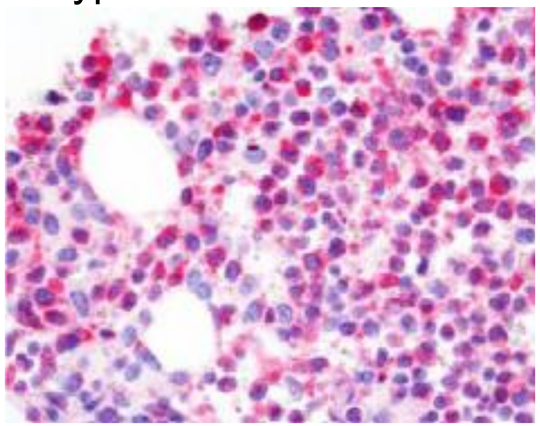
Pardanani A, Blood 2009:114;28:2206

It is critical to utilize the appropriate markers to make an accurate diagnosis

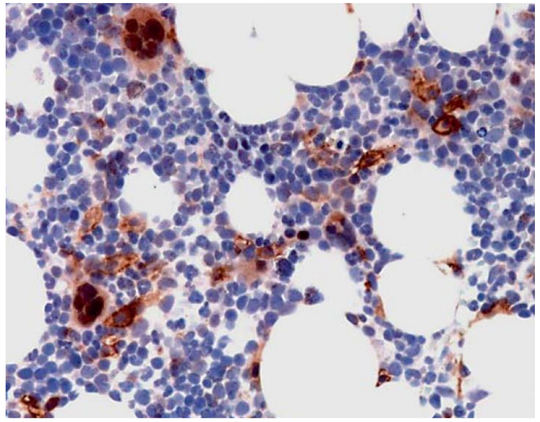
CD117 in mast cells[1]



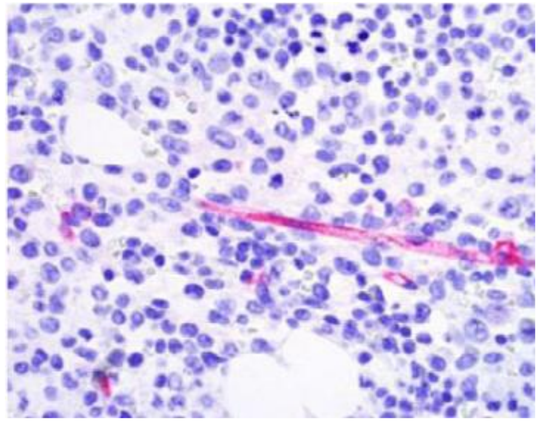
Tryptase in mast cells[2,a]



CD25 in mast cells[3]



CD34 in mast cells[2,a]



IHC with markers for mast cell tryptase, CD117, and CD25 should be performed to quantify **mast cell burden**[4]

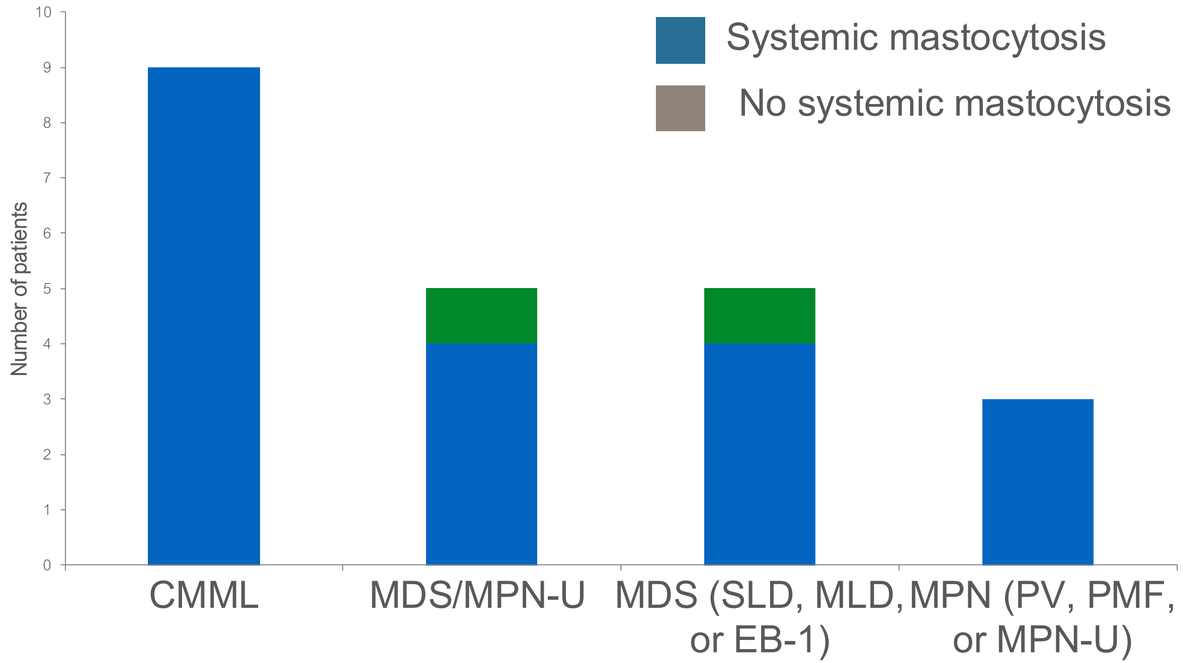
- **CD117** and **tryptase** are expressed on mast cells and can be used to quantify and characterize mast cells in the bone marrow[4,5]
- Aberrant expression of **CD2** and **CD25** can be used to identify systemic mastocytosis mast cells[4]
- **CD34 staining is optional;** may be used to detect an increase in the proportion of myeloblasts, especially in SM-AHN[4]
- **CD30** is a marker recently introduced as a minor diagnosis criterion. CD30, is expressed in neoplastic mast cells in the majority of patients with advanced systemic mastocytosis (85%), whereas in most patients with indolent systemic mastocytosis only a few if any mast cells stained positive for this marker

1. Mallya KP et al. *J Clin Diagn Res.* 2013;7(10):2276–2277; 2. Valent P et al. *Leukemia Res Rep.* 2014;3(1):8–13; 3. Horny HP et al. *Pathobiology.* 2010;77:169–180. Copyright © 2010 Karger Publishers, Basel, Switzerland; 4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Systemic Mastocytosis V.1.2020. © National Comprehensive Cancer Network, Inc. 2020. All rights reserved. Accessed August 13, 2020. To view the most recent and complete version of the guideline, go online to NCCN.org; 5. Stoecker MM, Wang E. *Arch Pathol Lab Med*. 2012;136(7):8322–838.

Systemic mastocytosis may be missed in patients with suspected myeloid neoplasms

Concomitant, undiagnosed systemic mastocytosis has been identified upon detection of KIT mutations in patients with confirmed or suspected myeloid neoplasms

Myeloid neoplasm and KIT D816V (n=22)[a]

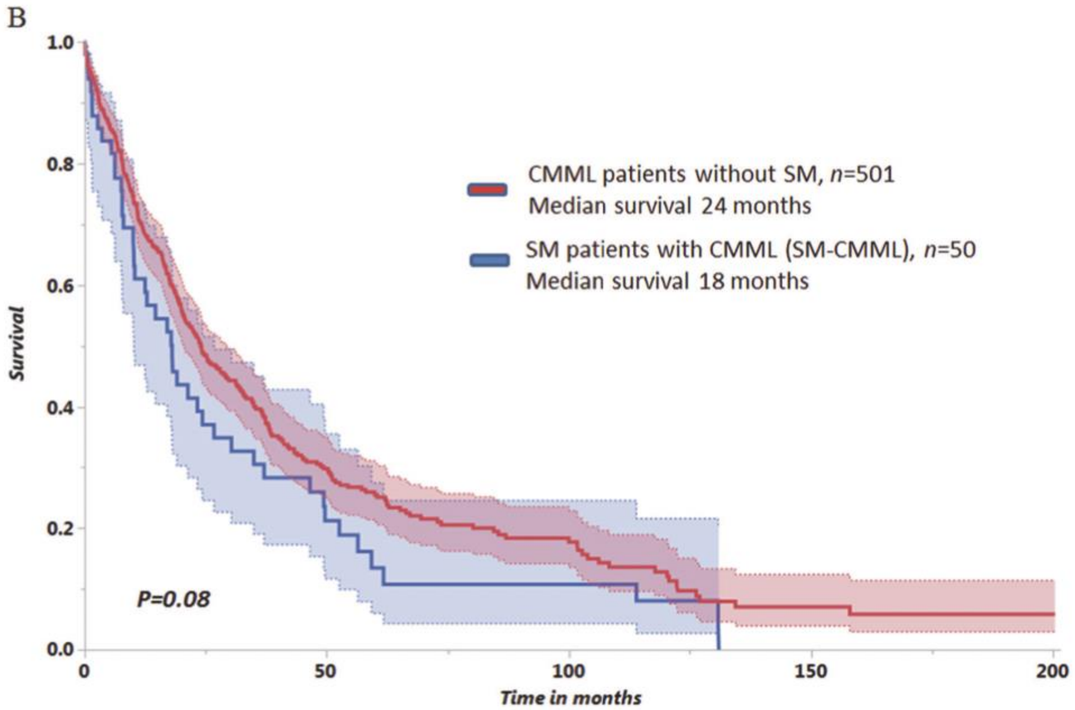


- Nearly all patients with KIT mutation diagnosed with a chronic myeloid neoplasm (20/22, 91%) were confirmed to have SM-AHN*
- **In 35% of those confirmed** (7/20), there was no clinical or pathologic suspicion of a systemic mast cell disorder, and a diagnosis of **SM-AHN was not rendered upon initial pathologic review**

Craig JW et al. *Modern Pathol*. 2020;10.1038/s41379-019-0447-x. Accessed February 12, 2020.

A comparison of clinical and molecular characteristics of patients with systemic mastocytosis with chronic myelomonocytic leukemia to CMML alone

Mrinal M. Patnaik[1] · Rangit Vallapureddy[1] · Terra L. Lasho[1] · Katherine P. Hoversten[1] · Christy M. Finke[1] · Rhett P. Ketterling[2] · Curtis A. Hanson[2] · Naseema Gangat[1] · Ayalew Tefferi[1] · Animesh Pardanani[1]



Leukemia 2018:32:1850-1856

SM-CMML: the abnormal mast cells were not appreciated on initial evaluation

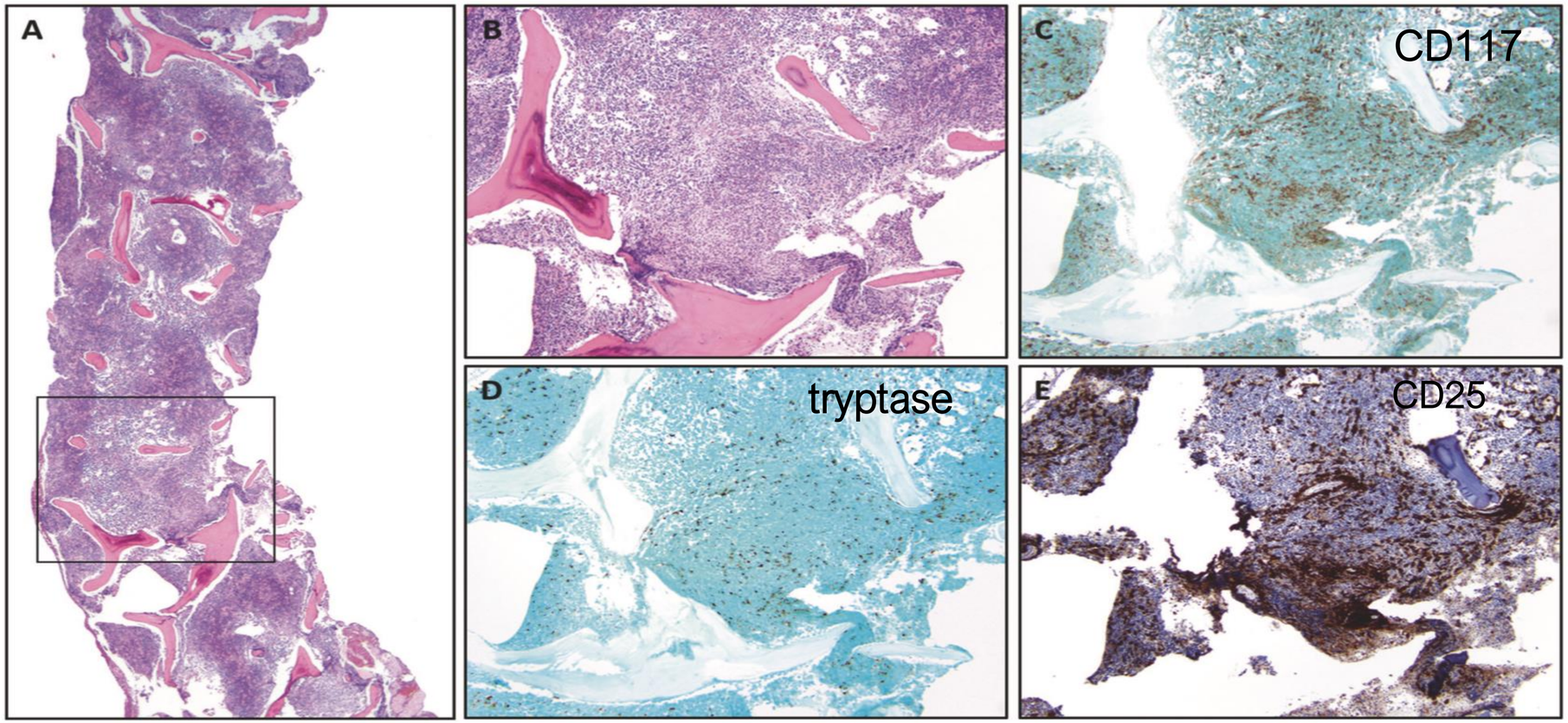


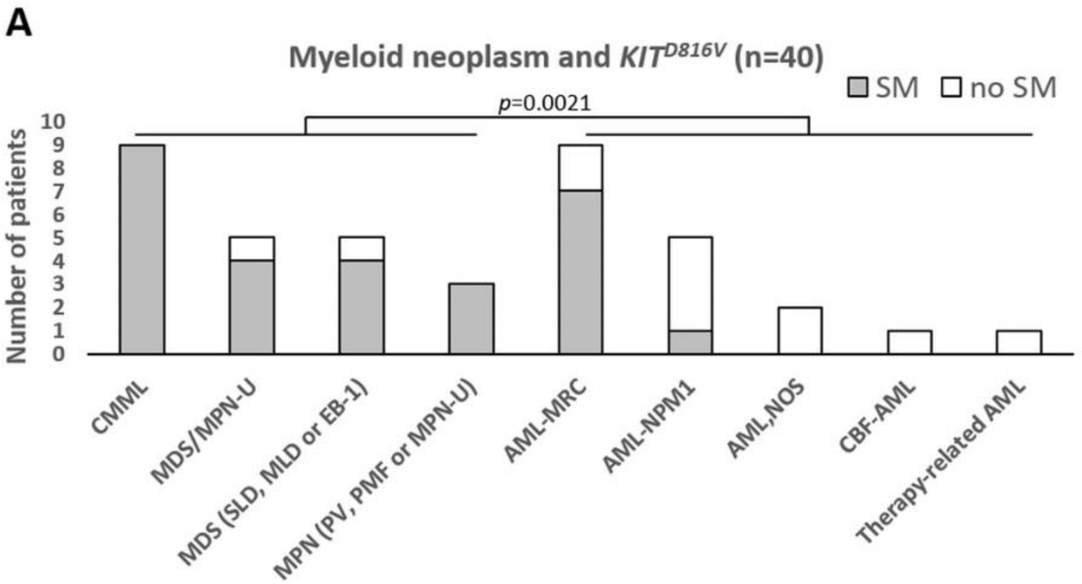
Fig. 3 Bone marrow biopsy from a patient with chronic myelomonocytic leukemia and systemic mastocytosis. a The abnormal mast cells were not appreciated on initial evaluation, given extensive involvement by chronic myelomonocytic leukemia (hematoxylin and eosin (H&E), 20×). **b–e** Additional immunostaining revealed large clusters and loose aggregates of spindled, CD25-positive mast cells (**b** H&E; **c** CD117; **d** mast cell tryptase; **e** CD25; all 200×). Some degranulated forms are not highlighted by mast cell tryptase (**d**).

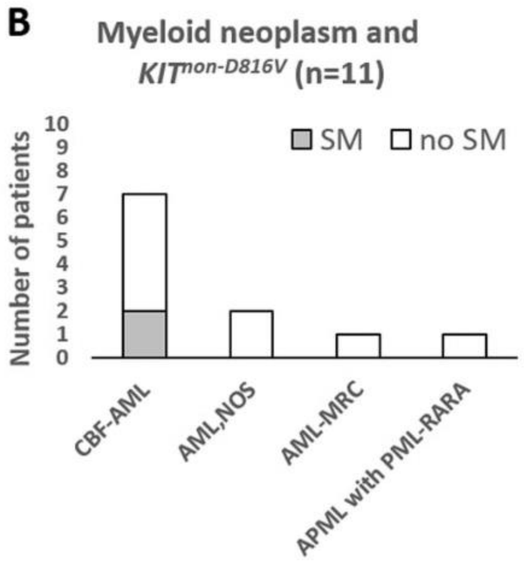
Craig J et al. Modern Pathology (2020) 33:1135–1145

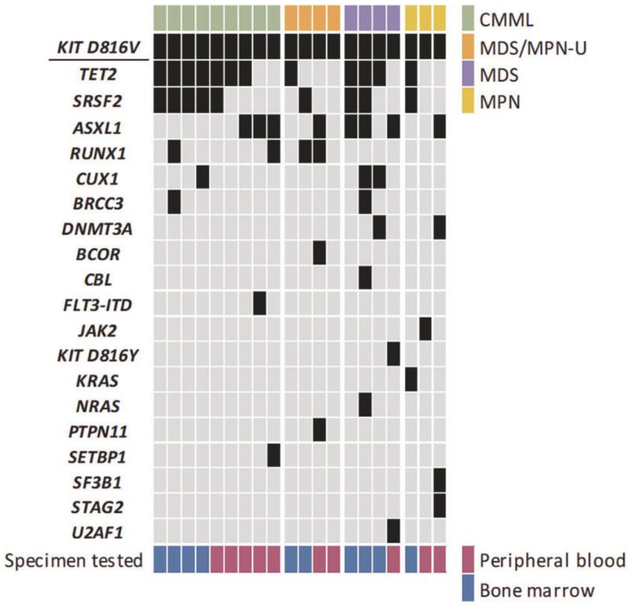
Detection of the *KIT*^{D816V} mutation in myelodysplastic and/or myeloproliferative neoplasms and acute myeloid leukemia with myelodysplasia-related changes predicts concurrent systemic mastocytosis

Jeffrey W. Craig[1] · Robert P. Hasserjian[2,3] · Annette S. Kim[3,4] · Jon C. Aster[3,4] · Geraldine S. Pinkus[3,4] · Jason L. Hornick[3,4] · David P. Steensma[3,5] · R. Coleman Lindsley[3,5] · Daniel J. DeAngelo[3,5] · Elizabeth A. Morgan[3,4]

KIT mutation different from D816V







40 pts with KIT mutation by NGS
91% had associated mastocytosis

18 AML with KIT mutation
44% % had associated mastocytosis

Modern Pathology (2020) 33:1135–1145

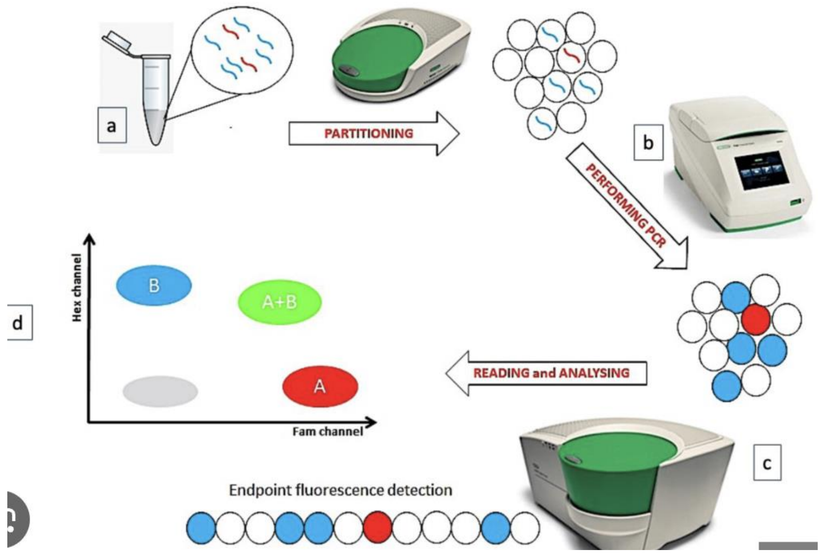
Next generation sequencing (NGS)

Sequencing of 30 genes that are commonly involved in myeloid neoplasia

ABL1	KIT
ASXL1	KRAS
BRAF	MPL
CALR	NPM1
CBL	NRAS
CEBPA	PTPN11
CSF3R	RUNX1
DNMT3	SETBP1
ETV6	SF3B1
EZH2	SRSf2
FLT3	TET2
HRAS	TP53
IDH1	U2AF1
IDH2	WT1
JAK2	ZRSR2

Low Sensitivity

Not recommended for KITD816V detection in mastocytosis



ddPCR for KIT detection

Different scenarios for a negativity in PB

1) The mutational load is below the detection limit, making it a false negative.

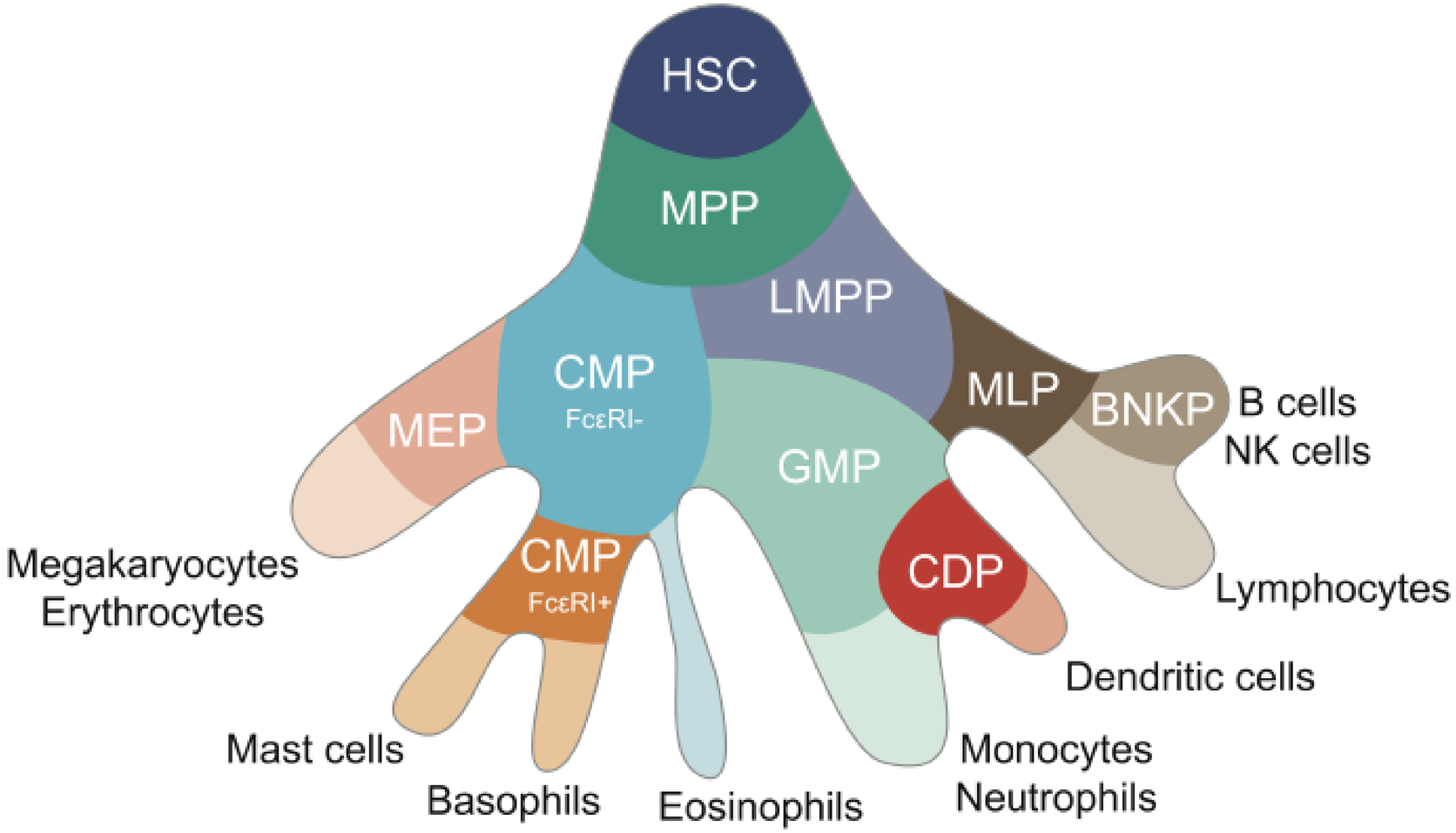
2) the sample is truly negative.

3) the patient may have a *KIT* mutation different from D816V that cannot be detected with the chosen method

Repeat the exam with **highly sensitive** method.
If the negative result was obtained on PB sample, the analysis should be repeated on a high-quality BM sample.

If the result is negative in both BM and PB despite using a sensitive technique and the mast cell infiltrate is evident, then it is appropriate to look for other *KIT* mutations different from D816V.

What is the cell of origin of mastocytosis?



MPP: Multipotent progenitor
CMP: common myeloid progenitor

Grootens J. et al. / EBioMedicine 43 (2019) 150–

Primary Objective

The primary objective of the study is to assess whether the presence of a mast cell component is associated with a different response rate to HMA therapy and different clinical outcome in CMML patients

Primary endpoint

- **Overall response rate (ORR),** according to the IWG MDS/MPN 2015 response criteria.

Response categories will include Overall response rate (ORR), according to the IWG MDS/MPN 2015 response criteria.9 Response categories will include Complete Response (CR), Complete Cytogenetic Response (CCyR), Partial Response (PR), Marrow Complete Response (mCR), Clinical Benefit, Stable Disease (SD), Progressive Disease

Secondary endpoints

- **Overall survival (OS)**

defined as the time from HMA treatment initiation to death from any cause. OS will be estimated using the Kaplan–Meier method and compared according to the presence or absence of a mast cell component. The OS probability at 24 months, with its 95% confidence interval, will also be reported as a prespecified descriptive summary measure.

- **Progression-free survival (PFS**)

defined as the time from HMA treatment initiation to disease progression according to the 2015 MDS/MPN IWG criteria, or death from any cause, whichever occurs first.

- **Rate of treatment discontinuation during HMA therapy**

Exploratory endpoints

- Prevalence of KIT D816V mutation in the study population
- Identification of clinical, pathological, and molecular features associated with the presence of mastocytosis/mast cell component in CMML
- Exploratory analysis of biomarkers potentially associated with response to HMA therapy in CMML with mast cell involvement.

400 patients from 01/01/2027 – 31/12/-2032

28 centri FISIM

Inclusion criteria

•Patients aged > 18 yrs
•Patients able to provide written informed consent
•Diagnosis of CMML according to WHO 2022 including CMML-1 or CMML-2
•No previous CMML-specific therapies, except hydroxyurea administered for cytoreduction
•before enrollment.

Exclusion criteria

•Absence or scarcity of biological material (BM or PB)
•Unable to provide written informed consent
•Previous allogeneic stem cell transplantation
•CMML-specific therapies (excluding hydroxyurea) before enrollm

28 centri aderenti

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Salerno	UOC Ematologia e Trapianti - AOU San Giovanni di Dio e Ruggi d'Aragona, Università di Salerno	**Carmine Selleri**
Bologna	UOC Ematologia - IRCCS AOU di Bologna	**Stefania Paolini**
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