San Giuseppe Moscati - Avellino
Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione

1ST SYMPOSIUM ON INNOVATIVE THERAPIES IN HEMATOLOGY

Avellino, Hotel de la Ville
March 30-31, 2023

Targeted Treatments for Mastocytosis

Massimo Triggiani

Division of Clinical Immunology and Rheumatology
University of Salerno

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						X	
Blueprint Medicines						X	
Cogent						X	

Mast Cell Disorders

	Mastocytosis	Mast Cell Hyperplasia	Primary MCAS (Clonal)	Secondary MCAS	Hereditary α Tryptasemia
Bone Marrow Mast Cells	↑	↑	N/↑	N	N
Mediator Release	↑	↑	↑↑	↑↑	N
Kit Mutations	+ ↑ prolif.	-	+ ↑ activation	- ↑ activation	- *TPSAB1* Duplication
CD2/CD25 Expression	+	-	+	-	-
Morphology Alterations	+	-	+/-	-	-
Serum Tryptase	↑↑	N	N ↑ Acute	N ↑ Acute	↑↑

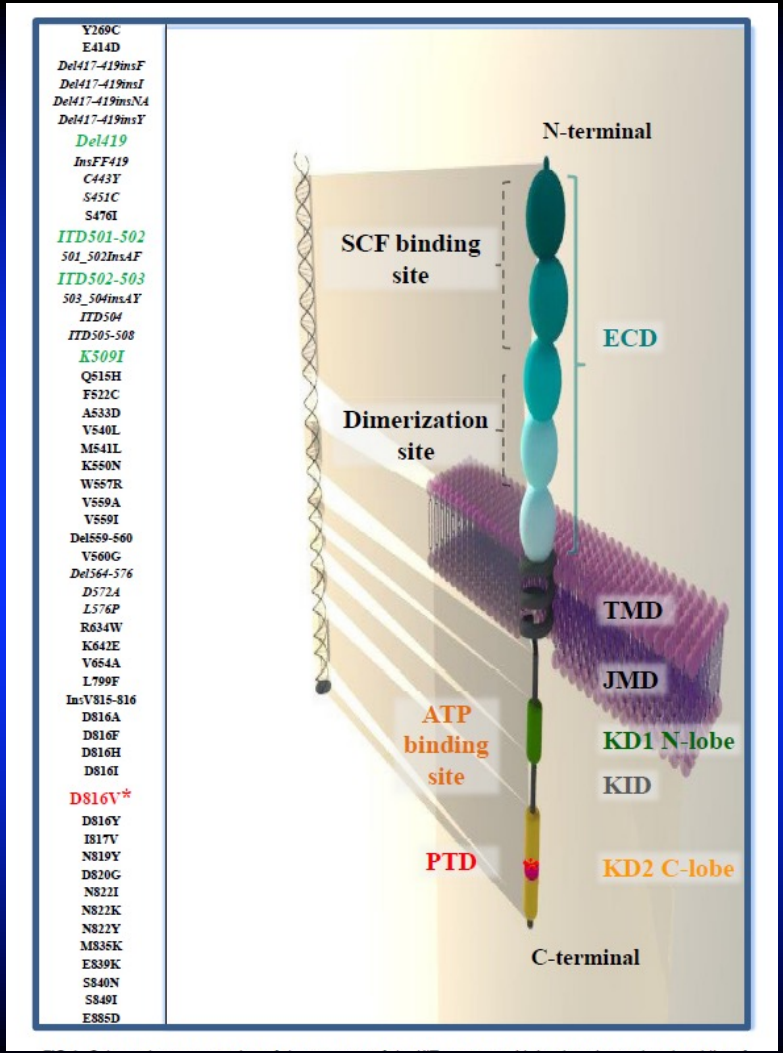
Mastocitosi

Malattia inquadrata nell'ambito delle patologie dei mastociti (*Mast Cell Disorders*) caratterizzata da proliferazione clonale ed iperreattività di queste cellule e da una marcata eterogeneità del fenotipo clinico e del decorso

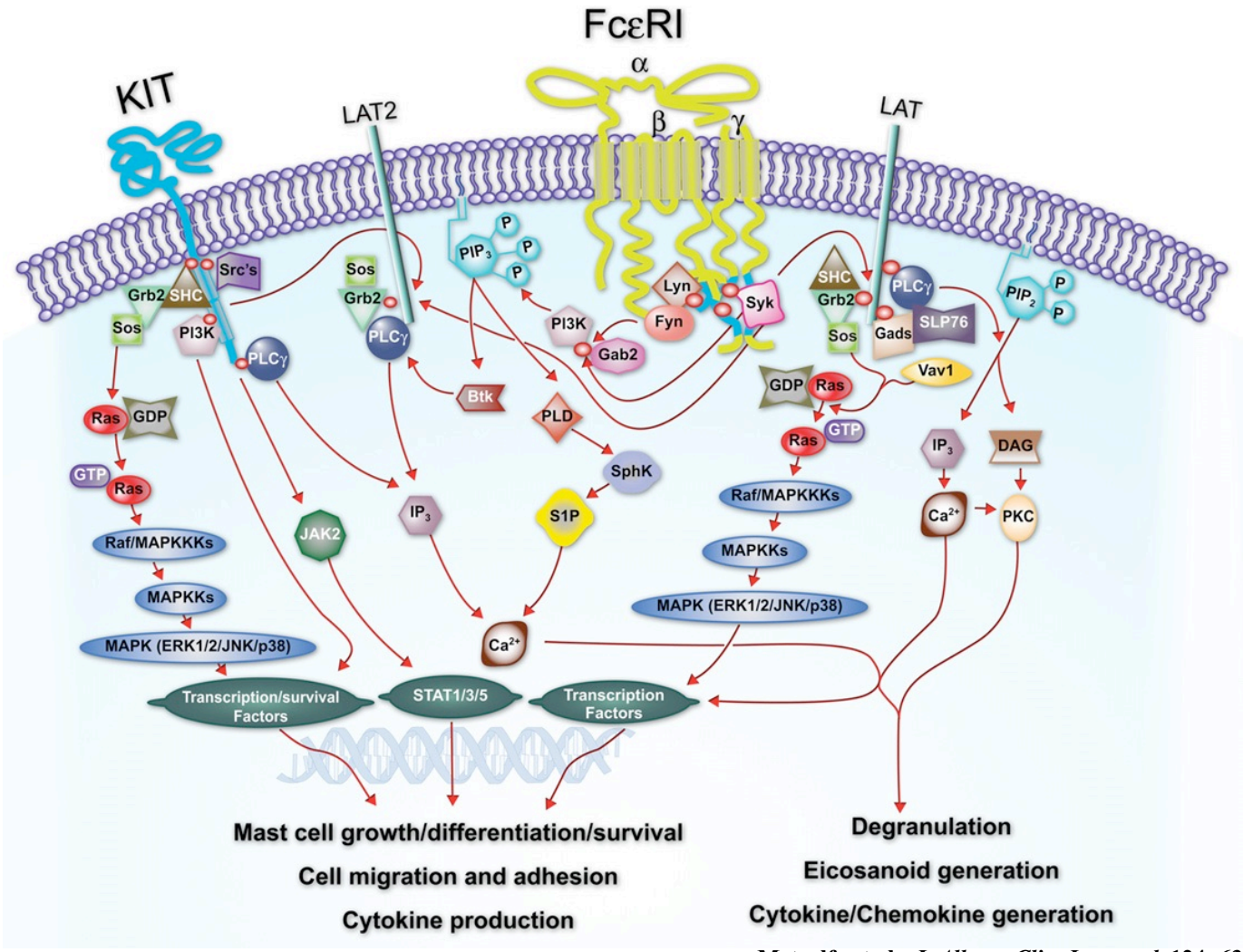
Quasi sempre associate a mutazioni somatiche *gain-of-function* del recettore per SCF (KIT, CD117). La più frequente è la D816V (>90% dei pazienti adulti)

Le correlazioni tra il genotipo (relativamente costante) e l'estrema variabilità clinica non sono attualmente definite

KIT Mutations in Mastocytosis

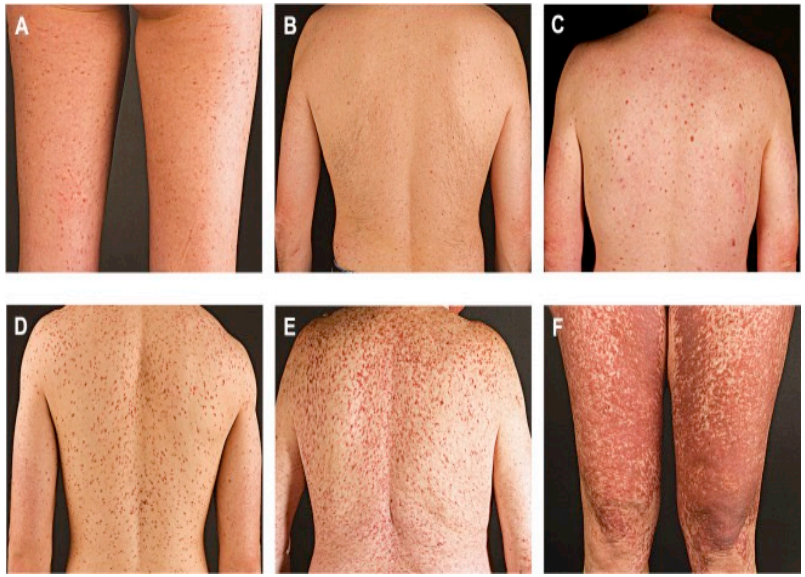


Arock M et al. JACI 2022: 149: 1855



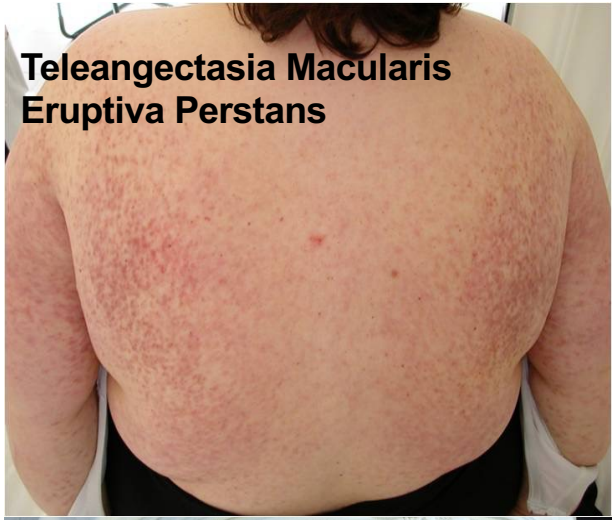
Metcalfe et al. *J. Allergy Clin. Immunol.* 124: 639, 2009

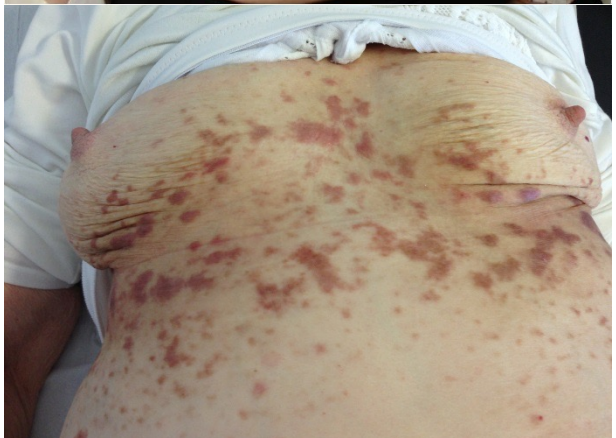
Mastocytosis: Heterogeneity of Skin Lesions



Hartmann K et al.
J Allergy Clin Immunol 2016

Triggiani M, personal archive





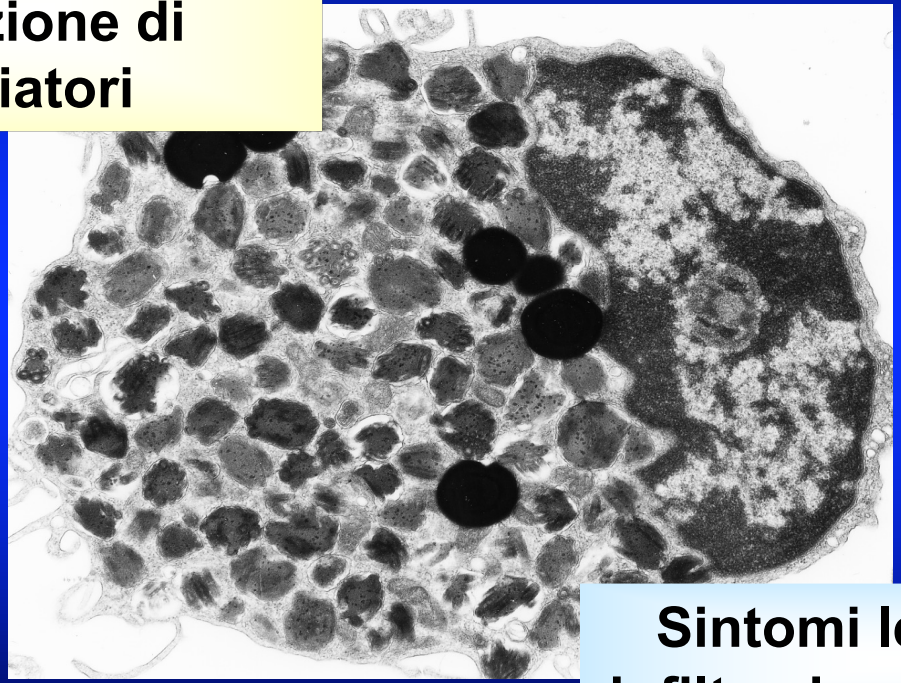
CLASSIFICATION 2020 (proposed)

- Cutaneous Mastocytosis (CM)
- Indolent Systemic Mastocytosis (ISM)
  - Bone Marrow Mastocytosis
- Smoldering Systemic Mastocytosis (SSM)
- SM with an Associated Hematologic (Non Mast Cell) Neoplasm (SM-AHN)
- Aggressive Systemic Mastocytosis (ASM)
- Mast Cell Leukemia (MCL)
- Mast Cell Sarcoma (MCS)

ADVANCED

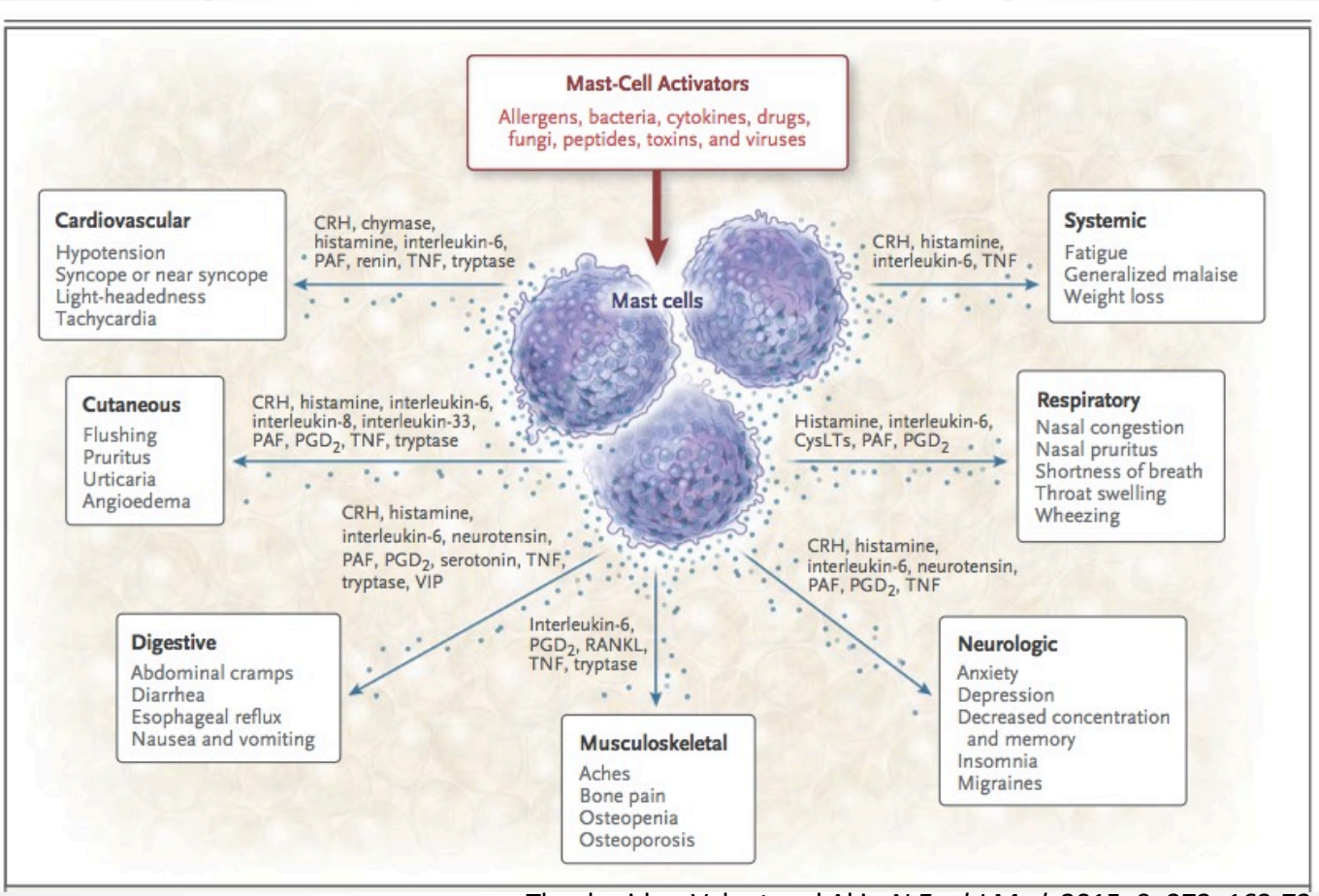
Il Mastocita

Sintomi legati alla secrezione di mediatori



Sintomi legati alla infiltrazione d'organo

Spectrum of mediator related symptoms



Theoharides, Valent and Akin *N Engl J Med.* 2015: 9; 373: 163-72

Diagnostic Criteria of Systemic Mastocytosis

Table 2.

Proposed Refined Major and Minor SM Criteria.

Major criterion:	Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria:	a. ≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in sections of bone marrow or other extracutanous organs[a]
	b. KIT-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*[b] in bone marrow or another extracutaneous organ
	c. Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30[c]
	d. Baseline serum tryptase concentration >20 ng/mL (in the case of an unrelated myeloid neoplasm, an elevated tryptase does not count as an SM criterion. In the case of a known HαT, the tryptase level should be adjusted[d]
	If at least 1 major and 1 minor or 3 minor criteria are fulfilled → the diagnosis is SM

[a]In tissue sections, an abnormal mast cell morphology counts in both a compact infiltrate and a diffuse (or mixed diffuse + compact) mast cell infiltrate. However, the spindle-shaped form does not count as an SM criterion when mast cells are lining vascular cells, fat cells, nerve cells, or the endosteal-lining cell layer. In the bone marrow smear, an atypical morphology of mast cells does not count as SM criterion when mast cells are located in or adjacent to bone marrow particles. Morphologic criteria of atypical mast cells have been described previously.[6]

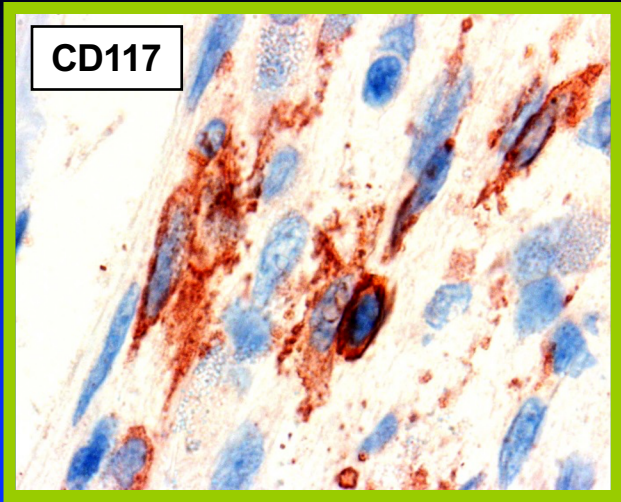
[b]Any type of *KIT* mutation counts as minor SM criterion when published solid evidence for its transforming behavior is available. A list of such *KIT* mutations (including variants in *KIT* codons 417, 501–509, 522, 557–560, 642, 654, 799, 816, 820, 822) is provided in Supplemental Digital Content, Table S6, http://links.lww.com/HS/A201 (KIT-activating mutations are labeled in bold).

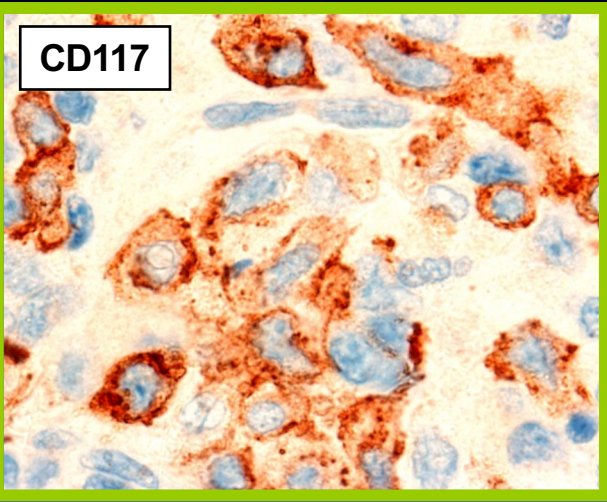
[c]All 3 markers fulfill this minor SM criterion when expression in mast cells can be confirmed by either flow cytometry or by immunohistochemistry or by both techniques.

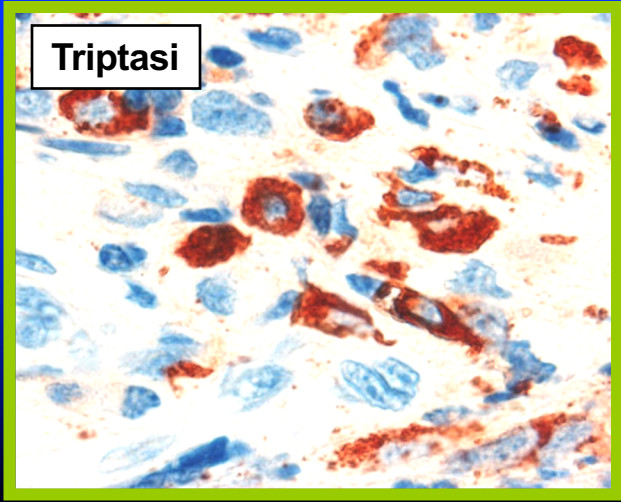
[d]Although the optimal way of adjustment may still need to be defined, one way is to divide the basal tryptase level by 1 plus the extra copy numbers of the alpha tryptase gene. Example, when the tryptase level is 30 and 2 extra copies of the alpha tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 10 (30/3 = 10) and thus is not a minor SM criterion.

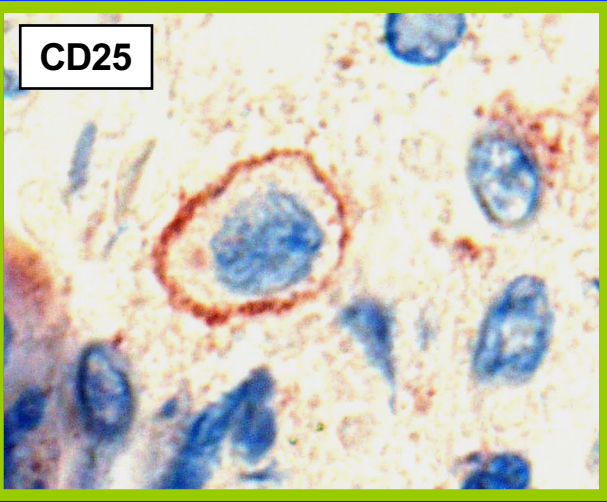
HαT = hereditary alpha-tryptasemia; SM = systemic mastocytosis.

Valent P et al Hemasphere 2021: 5: 11


CD117


CD117


Triptasi


CD25

B- and C-Findings (update 2021)

Table 4.

Proposed Refined B-findings and C-findings.

B-findings	C-findings (SM-induced Organ Damage)
High MC burden: Infiltration grade (MC) in BM ≥30% in histology (IHC) and/or serum tryptase ≥200 ng/mL[a] and/or *KIT* D816V VAF ≥10% in BM or PB leukocytes	-
Signs of myeloproliferation and/or myelodysplasia[b]: Hypercellular BM with loss of fat cells and prominent myelopoiesis ± left shift and eosinophilia ± leukocytosis and eosinophilia and/or discrete signs of myelodysplasia (<10% neutrophils, erythrocytes, and megakaryocytes)	Cytopenia/s: ANC < 1×10^9/L Hb < 10 g/dL PLT < 100×10^9/L (one or more found)
Organomegaly: Palpable hepatomegaly without ascites or other signs of organ damage or/and palpable splenomegaly without hypersplenism and without weight loss or/and lymphadenopathy palpable or visceral LN-enlargement found in ULS or CT (>2 cm)	Hepatopathy: Ascites and elevated liver enzymes[c] ± hepatomegaly or cirrhotic liver ± portal hypertension Spleen: Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia GI tract: Malabsorption with hypoalbuminemia ± weight loss Bone: Large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain

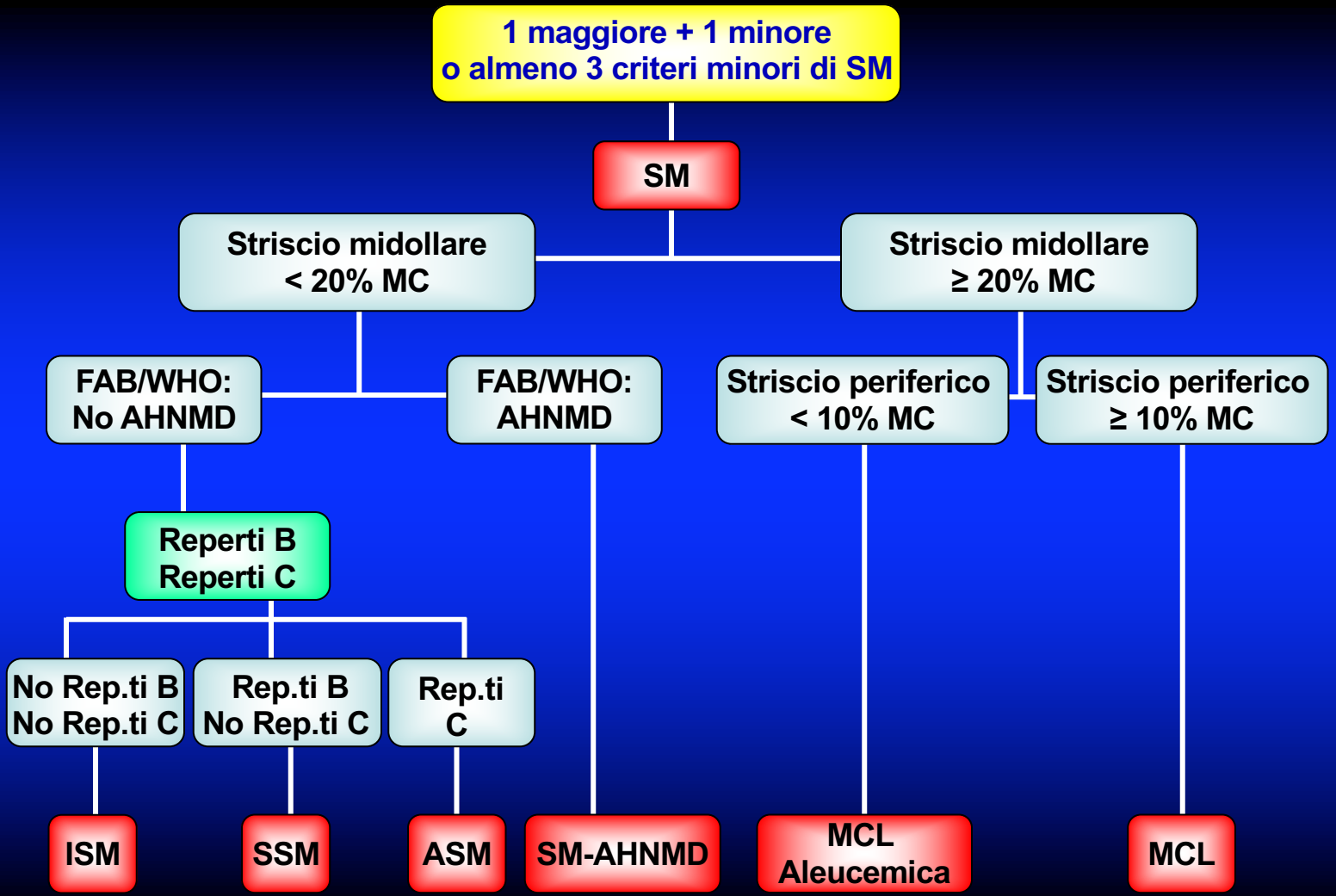
[a]In the case of a known HαT, the basal serum tryptase level should be adjusted. Although the optimal way of adjustment still needs to be defined, one way is to divide the basal tryptase level by 1 plus the extra copy numbers of the alpha tryptase gene. Example, when the tryptase level is 300 and 2 extra copies of the alpha tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 100 (300/3 = 100) and would thus not qualify as a B-finding.

[b]Signs of myeloproliferation and/or myelodysplasia must be discrete and stable (neither disappear nor progress) and must not reach diagnostic criteria of an MPN, MDS, or MPN/MDS in which case the diagnosis changes to SM-AHN. The presence of a myeloid AHN excludes B-findings and SSM by definition.

[c]Alkaline phosphatase levels are typically elevated in patients with advanced SM and SM-induced liver damage. In some of these patients, only elevated liver enzymes but no (clinically relevant) ascites is found.

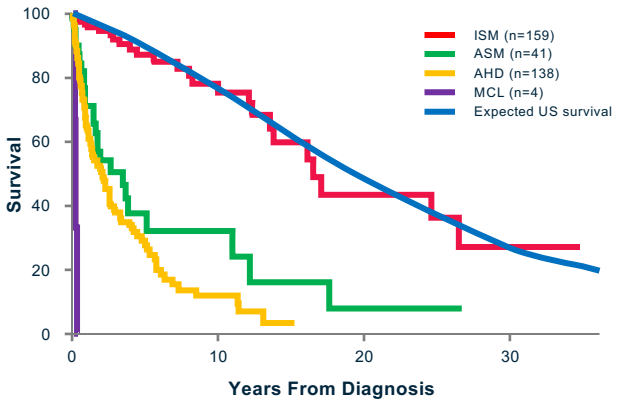
AHN = associated hematologic neoplasm; ANC = absolute neutrophil count; BM = bone marrow; CT = computed tomography; GI = gastrointestinal; HαT = hereditary alpha-tryptasemia; Hb = hemoglobin; IHC = immunohistochemistry; LN = lymph node; MC = mast cells; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; PB = peripheral blood; PLT = platelet count; SM = systemic mastocytosis; SSM = smoldering systemic mastocytosis; ULS = ultrasound; VAF = variant allele frequency.

Valent P et al Hemasphere 2021: 5: 11


1 maggiore + 1 minore
o almeno 3 criteri minori di SM
SM
Striscio midollare
< 20% MC
Striscio midollare
≥ 20% MC
FAB/WHO:
No AHNMD
FAB/WHO:
AHNMD
Striscio periferico
< 10% MC
Striscio periferico
≥ 10% MC
Reperti B
Reperti C
No Rep.ti B
No Rep.ti C
Rep.ti B
No Rep.ti C
Rep.ti
C
ISM
SSM
ASM
SM-AHNMD
MCL
Aleucemica
MCL

Reduced Overall Survival in Advanced Mastocytosis

Expected US survival compared with WHO classification of SM[1,2]

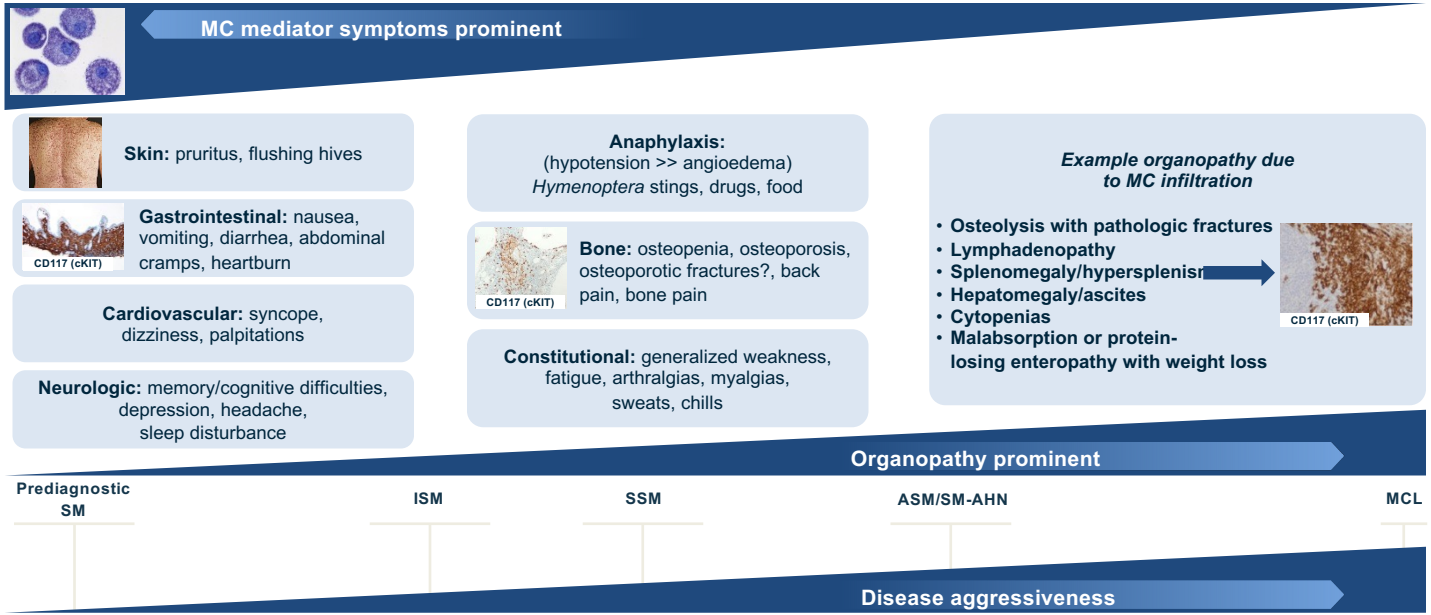


Median OS (mo)[1,2]	
ISM	198
SSM	120
ASM	41
SM-AHN	24
MCL	2

AdvSM[3]

1.Pardanani A. Am J Hematol. 2016;91(11):1146-1159.
2.Lim KH et al. Blood. 2009;113(23):5727-5736.
3.Valent P et al. Cancer Res. 2017;77(6):1261-1270.

Clinical Spectrum of Systemic Mastocytosis



Clinical spectrum of patients with clonal MC disorders. Please refer to Tables I and II for the WHO classification of mastocytosis. "Prediagnostic" SM refers to an abnormal clonal bone marrow mast cell (BMMC) infiltrate that falls short of the diagnostic threshold for SM (generally satisfies 1-2 minor criteria only).[1]

1. Pardanani A. *Am J Hematol.* 2016;91(11):1146-1159. 2. Metcalfe DD. *Blood*. 2008;112(4):946-956. 3. Hartmann K et al. *J Allergy Clin Immunol.* 2016;137(1):35-45.
4. Ammannagari N et al. *Ann Hematol*. 2013;92(11):1573-1575. 5. Behdad A et al. *Arch Pathol Lab Med*. 2013;137(9):1220-1223.

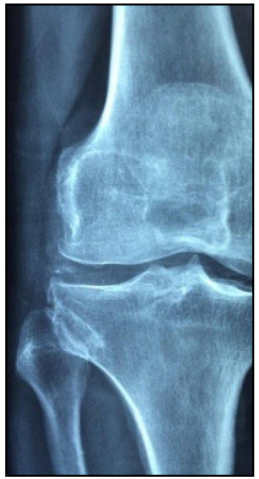
Bone Involvement in Mastocytosis

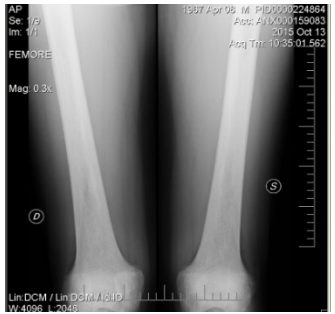
SM

Osteopenia

Osteoporosis

Fractures



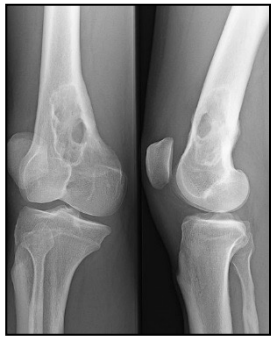


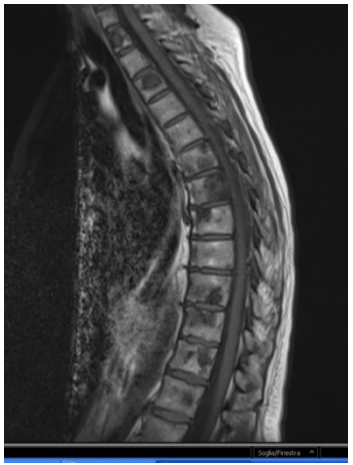
AdvSM

Osteosclerosis

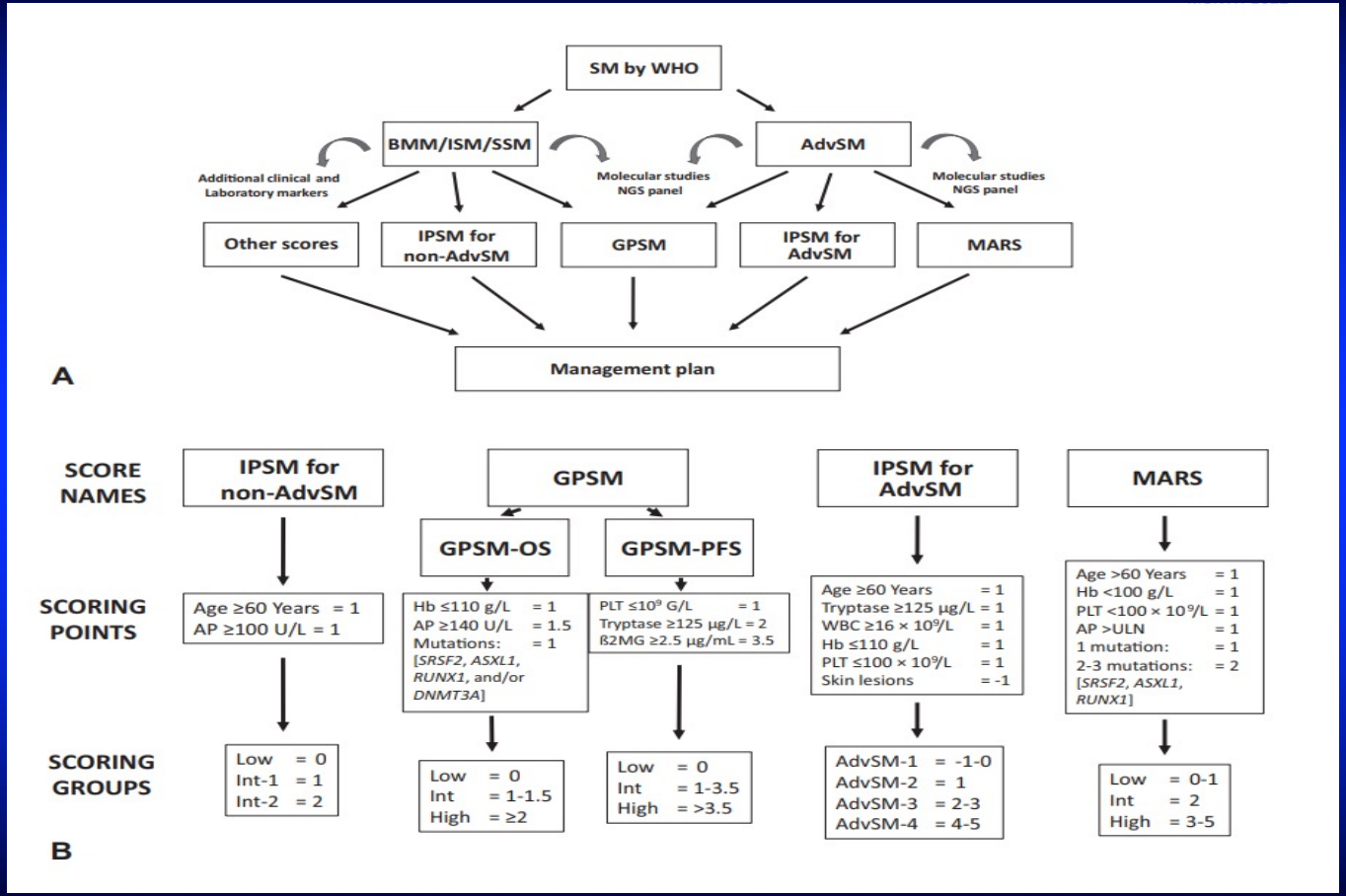
Osteolysis

Fractures





Personalized Management Plan in SM



Valent P et al. JACI Pract 2022

I. Diagnostic value of serum markers in SM

Serum marker	Normal values	Indolent SM (n=1531)	AdvSM (n=310)	p - value
Alkaline phosphatase	<126 U/l range	73 (19-786)	162 (20-1,696)	<0.0001
Tryptase	<20 µg/l range	31 (1-2,100)	170 (20-1,696)	<0.0001
LDH	220 U/l range	165 (77-3,187)	183 (9-2,152)	0.003
B2-microglobulin	<2.5 mg/l range	1.8 (0.2-7.1) n=336	3.3 (1.2-17.2) n=70	<0.0001
Albumin	>35 g/l range	45 (11-60)	39 (18-57)	<0.0001
Cholesterol	220 mg/dl range	190 (70-320) n=363	130 (63-380) n=60	<0.0001

Treatment algorithm for systemic mastocytosis

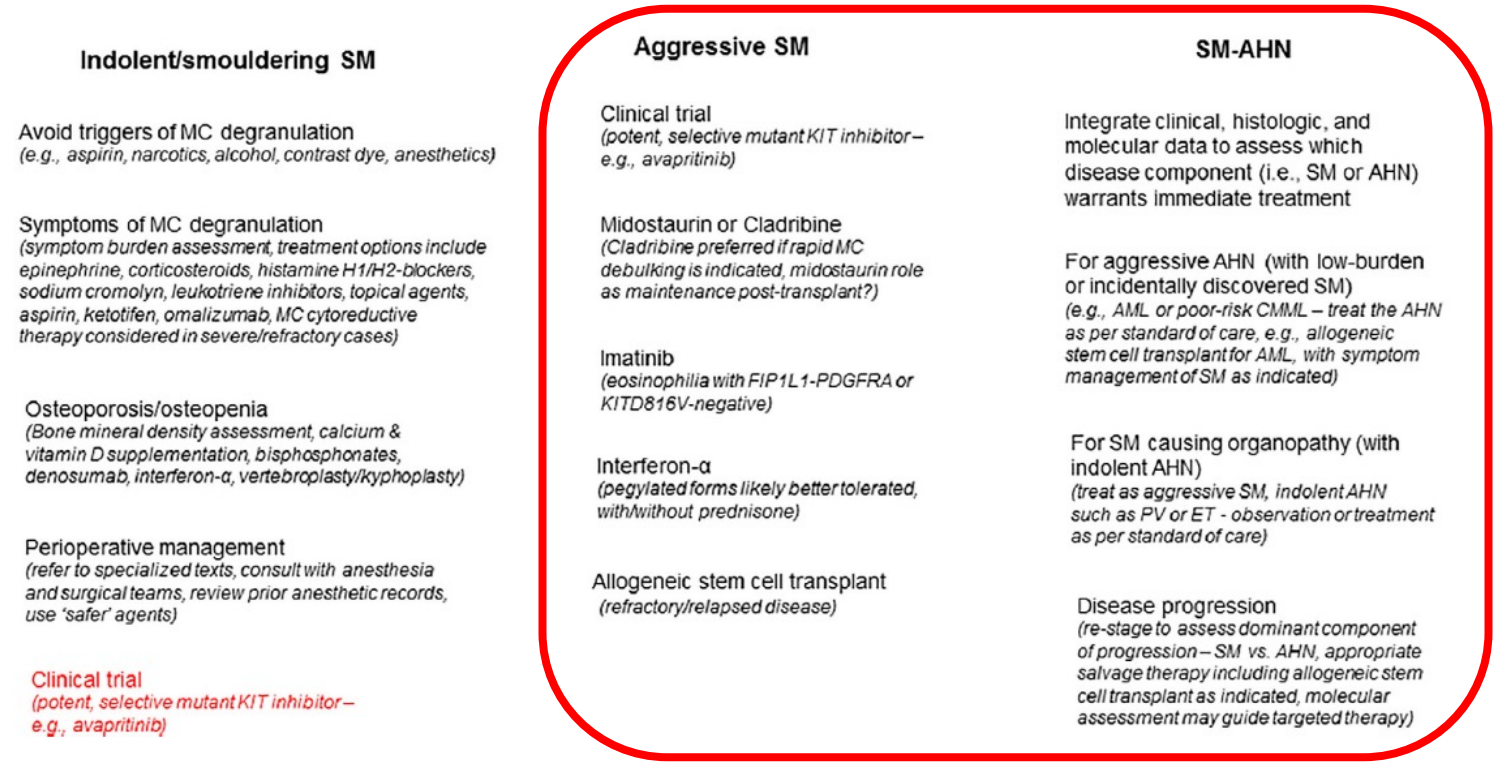
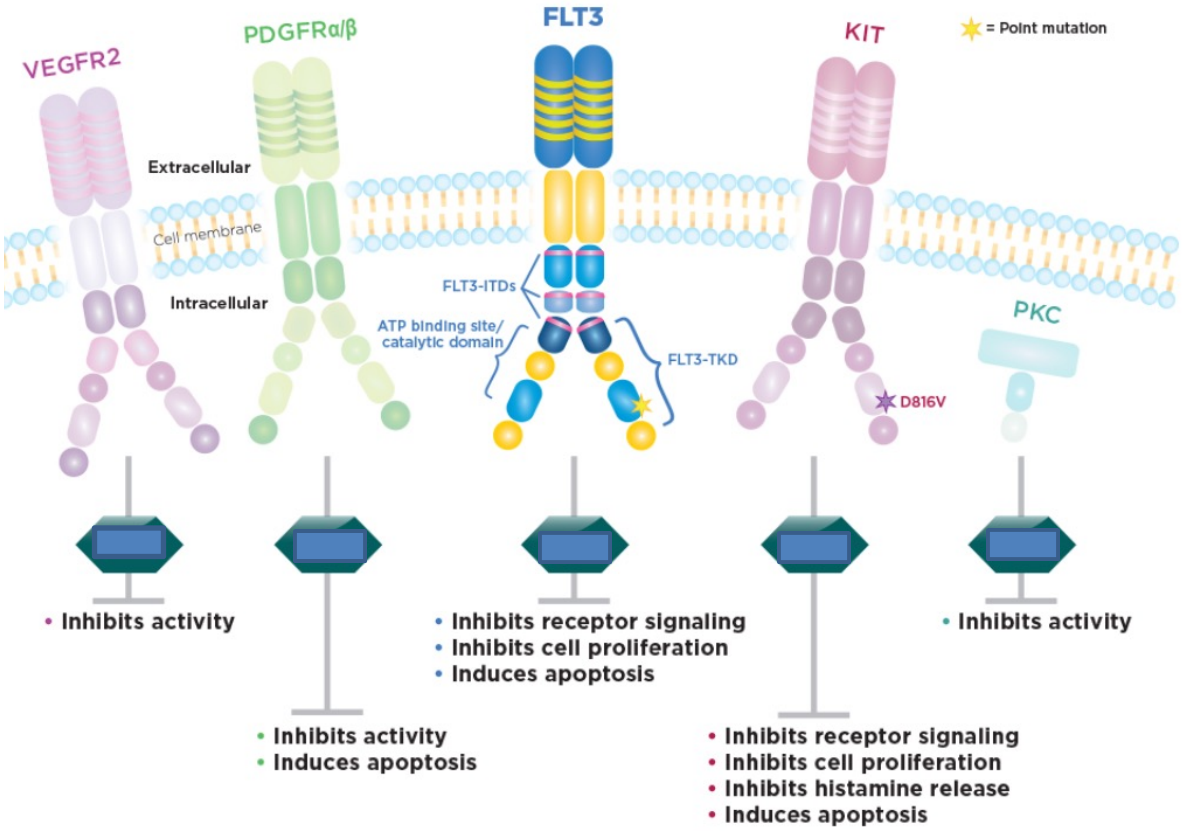


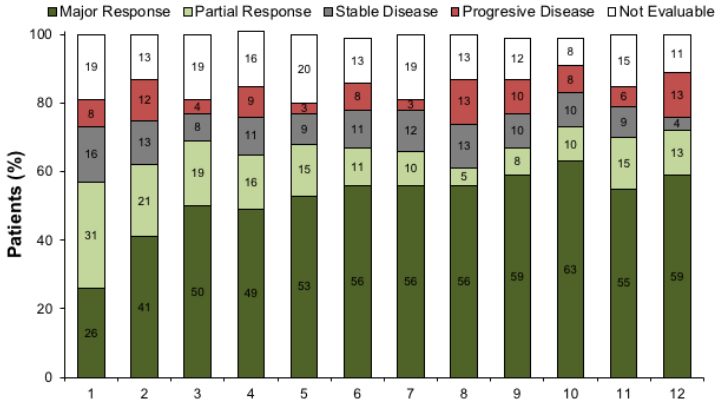
FIGURE 6 Algorithm for the treatment of systemic mastocytosis

Pardanani A. Am J Hematol 2021: 96, 508-525

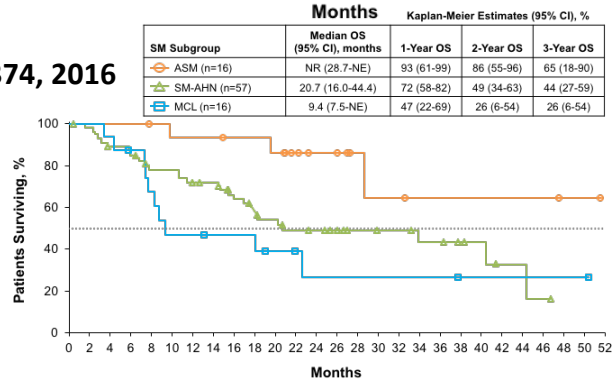
Midostaurin is a Multiple Kinase Inhibitor



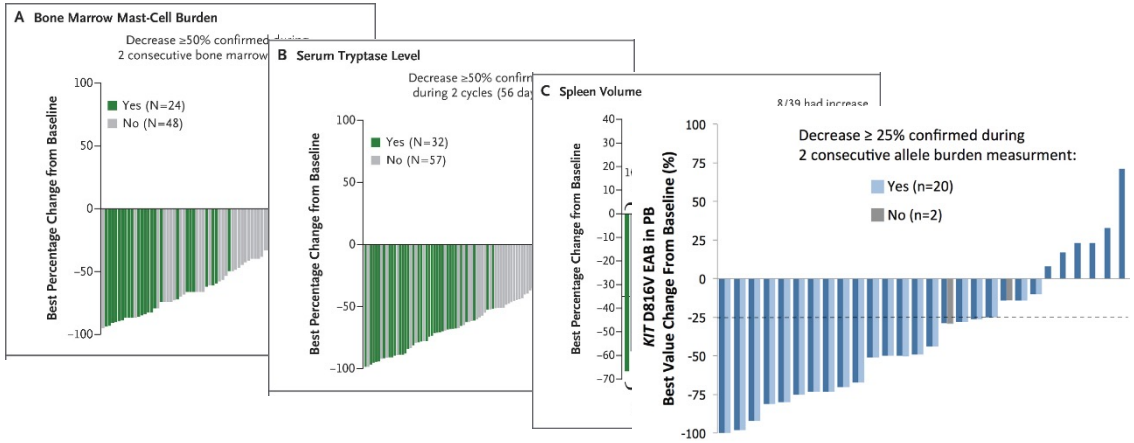
Activity of midostaurin in advanced SM



Gotlib *et al.*, NEJM 374, 2016

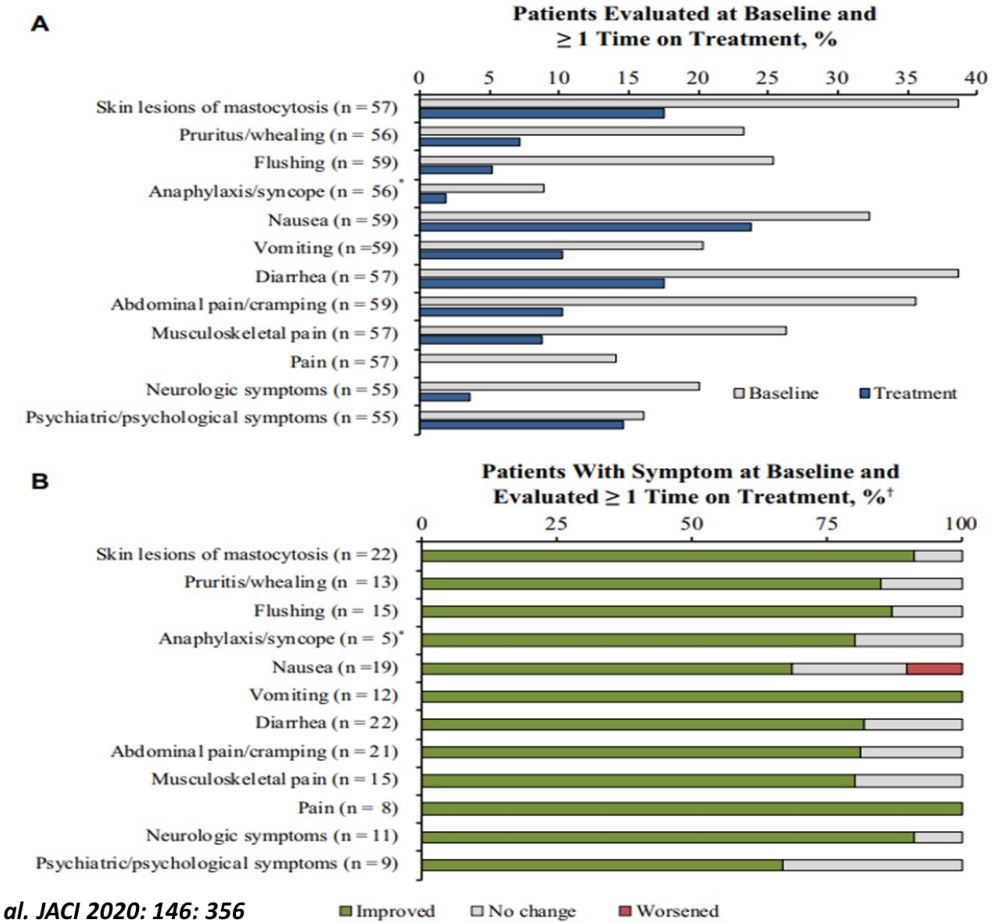


Midostaurin – disease modifying activity



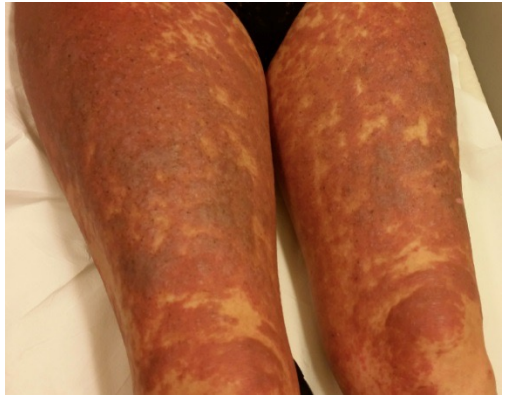
Gotlib J *et al*., *N Engl J Med*. 2016;374(26):2530-2541
Jawhar *et al*., Blood. 2017;130(2):137-145

Midostaurin Improves Mediator-Related Symptoms in Mastocytosis

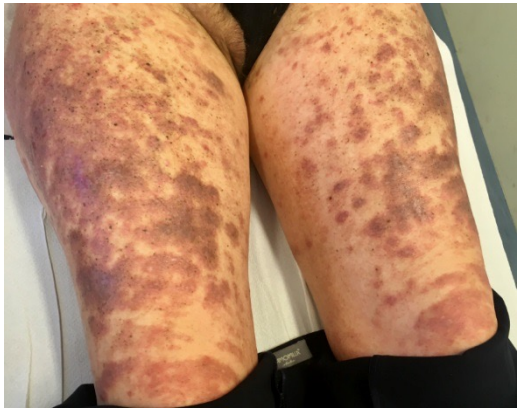


Hartmann K et al. JACI 2020: 146: 356

Before Treatment



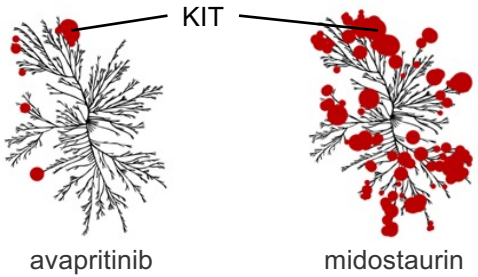
After 3 mo Midostaurin



Parente R, unpublished

Avapritinib

Potent and highly selective inhibitor of D816V mutant *KIT*



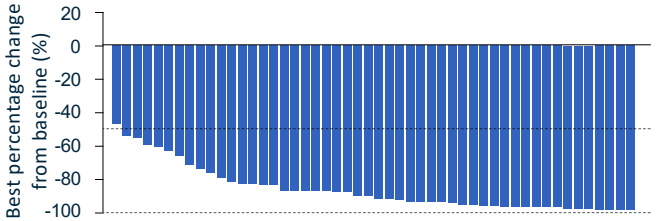
KIT D816V biochemical IC_{50}	
0.27 nM	2.9 nM

Evans EK et al. Sci Transl Med. 2017;9(414)

Clinical proof-of-concept in Phase 1 EXPLORER clinical trial[1-3]

m-IWG-MRT-ECNM ORR: 83%[2*]

Serum tryptase reduction in all patients[2]



1. DeAngelo et al. ASH 2017 (Plenary Session)
2. Deininger et al. EHA 2018
3. Gotlib et al. ECNM 2018

Granted FDA Breakthrough Therapy Designation for AdvSM

m-IWG-MRT-ECNM, modified International Working Group Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis criteria; ORR, overall response rate
*Data previously reported at EHA 2018. Data cutoff date: April 30, 2018,

Efficacy of Avapritinib in AdvSM

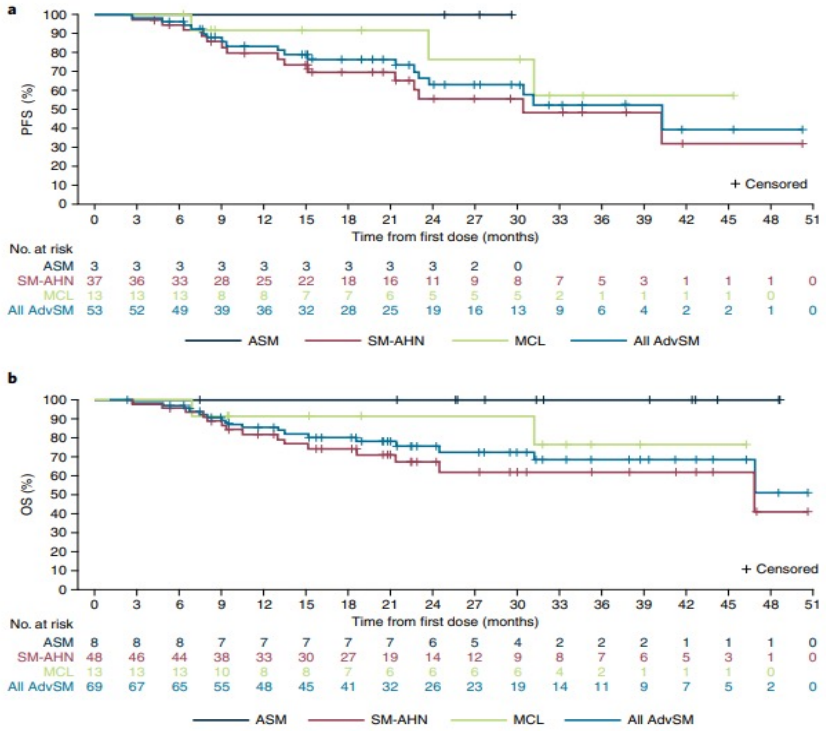
Table 3 | Overall response rates by centrally adjudicated mIWG-MRT-ECNM response criteria

Best confirmed response by mIWG-MRT-ECNM criteria, *n* (%)	By AdvSM subtype				All AdvSM, by midostaurin history		All AdvSM, by prior therapy history	
	All AdvSM (*n* = 53)	ASM (*n* = 3)	SM-AHN (*n* = 37)	MCL (*n* = 13)	Prior midostaurin exposure (*n* = 17)	Midostaurin naïve (*n* = 36)	Any prior therapy (*n* = 32)	No prior therapy (*n* = 21)
ORR (CR + CRh + PR + CI), *n* (%)	40 (75)	3 (100)	28 (76)	9 (69)	10 (59)	30 (83)	22 (69)	18 (86)
95% CI	62–86	29–100	59–88	39–91	33–82	67–94	50–84	64–97
Best response								
CR or CRh	19 (36)	2 (67)	14 (38)	3 (23)	3 (18)	16 (44)	9 (28)	10 (48)
CR	8 (15)	0	5 (14)	3 (23)	2 (12)	6 (17)	4 (13)	4 (19)
CRh	11 (21)	2 (67)	9 (24)	0	1 (6)	10 (28)	5 (16)	6 (29)
PR	18 (34)	1 (33)	13 (35)	4 (31)	6 (35)	12 (33)	11 (34)	7 (33)
CI	3 (6)	0	1 (3)	2 (15)	1 (6)	2 (6)	2 (6)	1 (5)
SD	12 (23)	0	8 (22)	4 (31)	6 (35)	6 (17)	9 (28)	3 (14)
PD	0	0	0	0	0	0	0	0
NE	1 (2)	0	1 (3)	0	1 (6)	0	1 (3)	0

AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; mIWG_MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL, mast cell leukemia; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.

DeAngelo DJ et al. Nat Med 2021: 27: 2183-2191

Avapritinib in AdvSM



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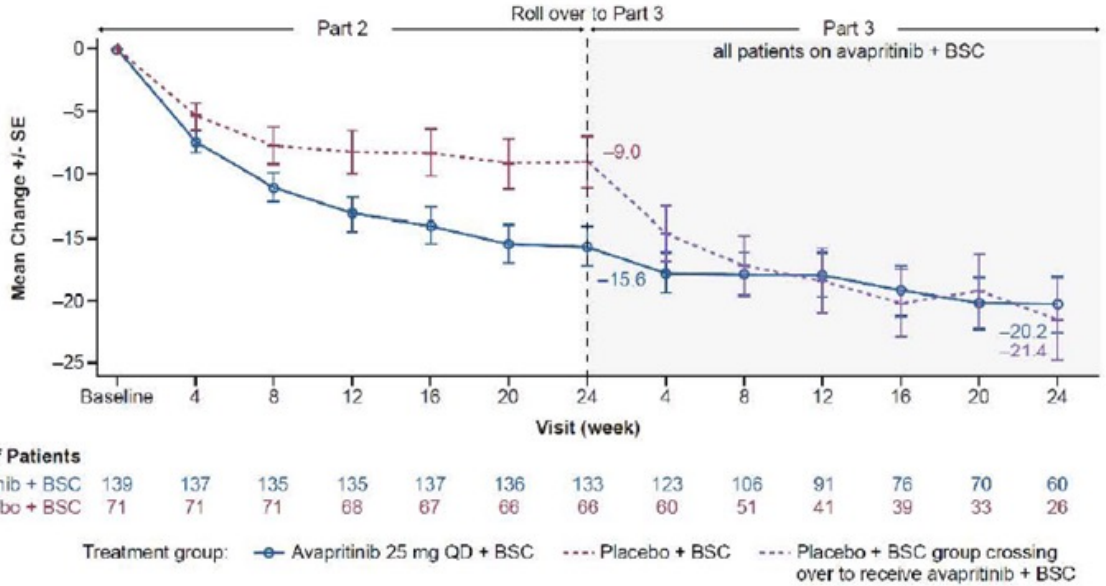
Avapritinib in Indolent Systemic Mastocytosis

Figure. ISM-SAF TSS over time*



ASH 2023, submitted

Conclusioni

- **La mastocitosi è una patologia clonale dei mastociti associata a mutazioni somatiche di *Kit* caratterizzata da quadri clinici estremamente eterogenei**
- **Le manifestazioni cliniche della mastocitosi sono determinate dalla secrezione di mediatori vasoattivi (anafilassi !) e dall'infiltrazione mastocitaria d'organo**
- **Le forme di mastocitosi avanzata (ASM, AHNM, MCL) hanno una prognosi infausta**
- **La diagnosi e la stadiazione precoce della malattia consentono una corretta valutazione prognostica e l'implementazione di un efficace approccio terapeutico**
- **Midostaurina ed avapritinib sono efficaci *targeted-treatments* per le mastocitosi avanzate**

Division of Allergy and Clinical Immunology
University of Salerno
Italy

Roberta Parente
Chiara Cardamone
Domenico Ciotta
Isabella Carrieri
Francesco Chiurillo
Giulia Fabozzi
Anna Tortora

Tiziana Della Vista

Division of Hematology
University of Salerno
Italy

Prof. Carmine Selleri
Valentina Giudice
Luca Pezzullo

mtriggiani@unisa.it