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Mastocitosi Sistemica

Mastocytosis is defined by **abnormal proliferation of clonal MCs** in different tissues, including skin, bone marrow (BM), GI tract, liver, and/or spleen.

It is frequently associated with somatic gain-of function mutations in KIT, leading to constitutive KIT activation independent of its ligand SCF.

Based on the pathology, clinical presentations, and organ involvement, mastocytosis is divided into three major groups by both the 2022 ICC and WHO 5th edition classifications

CM, typically diagnosed in pediatric patients, is limited to the skin and generally carries a good prognosis,

MCS is a highly aggressive, destructive proliferation of neoplastic MCs that tends to metastasize

Table 2. Types and subtypes of mastocytosis per 2022 ICC [9,33] and WHO 5th edition # [10,49].

	2022 ICC	WHO 5th Edition
CM	Maculopapular CM (MPCM; previously known as urticaria pigmentosa) Monomorphic Polymorphic	Urticaria pigmentosa/Maculopapular CM Monomorphic Polymorphic
	Diffuse CM (DCM)	Diffuse CM
	Mastocytoma of the skin *	Cutaneous mastocytoma Isolated mastocytoma Multilocalized mastocytoma
SM	Indolent SM (Includes bone marrow mastocytosis **)	Bone marrow mastocytosis **
		Indolent SM
	Smoldering SM	Smoldering SM
	Aggressive SM	Aggressive SM
	SM with an associated myeloid neoplasm	SM with an associated hematologic neoplasm
	Mast cell leukemia	Mast cell leukemia
MCS	Mast cell sarcoma	Mast cell sarcoma

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Epidemiologia

- La prevalenza in Europa è stimata 1/10000
- Nessuna preferenza di sesso;
- Più frequente nei soggetti di razza caucasica;
- Nella maggior parte dei casi non è osservata familiarità,
- La mastocitosi cutanea è più comune in età pediatrica mentre la mastocitosi sistemica è tipica dell'età adulta

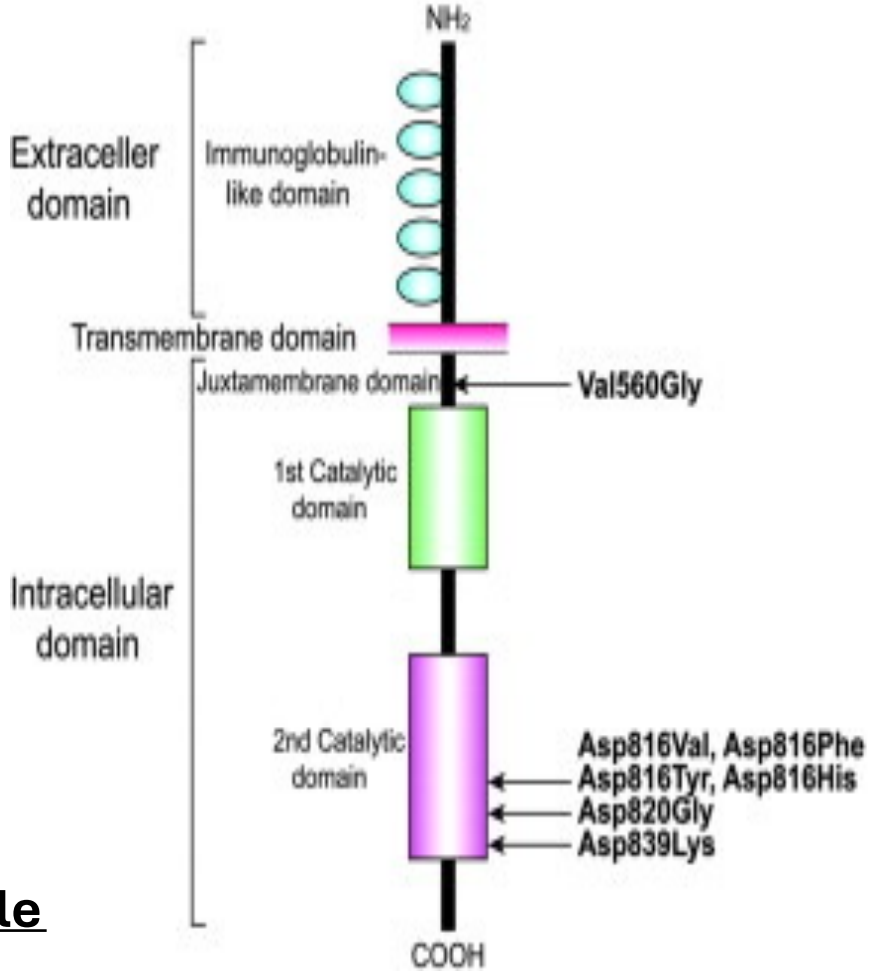
Patogenesi

- >90% delle mastocitosi dell'adulto e l'85% delle mastocitosi infantili sono causate da una **mutazione del gene c-KIT** codificante per il recettore tirosin-chinasico dello Stem Cell Factor;
- **La più frequente è la mutazione puntiforme D816V, nell'esone 17**, che determina una gain-of-function del dominio catalico;
- Il recettore diviene pertanto costitutivamente attivo, con conseguente incremento dell'attivazione e sopravvivenza dei mastociti.

Tale mutazione rende la malattia resistente all'Imatinib

- Altre e più rare mutazioni possono interessare la stessa porzione intracellulare ma anche i domini extracellulare, trans e iuxtamembrana;

Tali mutazioni rendono la malattia sensibile all'Imatinib



Presentazione clinica

The heterogeneous clinical presentation of SM is related to MC-released mediators, MC burden, and associated hematological disorders.

- **Constitutional symptoms**, when present, may include weight loss, pain, nausea, headache, malaise, or fatigue.

- **Mediator-associated symptoms** occur both in indolent and advanced SM. These symptoms, ranging from diarrhea and abdominal pain to skin changes and musculoskeletal issues, can mimic those of other conditions, complicating SM diagnosis

- Extensive involvement with neoplastic MCs is associated with **organ dysfunction**.

DIAGNOSI

	2022 ICC	WHO 5th Edition
Major criterion	Multifocal dense infiltrates of tryptase- and/or CD117 positive MCs (≥15 MCs in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).	Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s).
Minor criteria	In bone marrow biopsy or in section of other extracutaneous organs, >25% of MCs are spindle shaped or have an atypical immature morphology.	At least 25% of all MCs are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in MC infiltrates detected in sections of bone marrow or other extracutaneous organs.
	KIT D816V mutation or other activating *KIT* mutation detected in bone marrow, peripheral blood, or other extracutaneous organs.	Activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT* in bone marrow or another extracutaneous organ(s).
	MCs in bone marrow, peripheral blood, or other extracutaneous organs express CD25, CD2, and/or CD30, in addition to MC markers.	MCs in bone marrow, blood, or another extracutaneous organs express one or more of the following: CD2 and/or CD25 and/or CD30.
	Elevated serum tryptase level, persistently >20 ng/mL. In cases of SM-AMN, an elevated tryptase does not count as an SM minor criterion.	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).
NOTE:	**The major criterion alone is enough, or in the absence of the major criterion, at least 3 of the 4 minor criteria must be present.**	**The major plus at least 1 minor, or 3 minor criteria must be fulfilled for diagnosis of SM.**

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Systemic mastocytosis (SM) is subdivided into six subtypes. The diagnosis of these variants of SM requires correlation with B ('burden of disease') and C ('cytoreduction-requiring') findings.

Table 3. B- and C-findings by the 2022 ICC and the 5th WHO (Modified) [9,10,49].

	2022 ICC [9]	WHO 5th Edition [10,49]
B-findings	High MC burden (>30% of BM cellularity by MC aggregates, as assessed on BM biopsy) and serum tryptase >200 ng/mL.	High MC burden: Infiltration grade (MC) in BM ≥30% in histology (IHC) and/or serum tryptase ≥200 ng/mL and/or *KIT* D816V VAF ≥10% in BM or PB leukocytes.
	Cytopenia (not meeting criteria for C findings) or -cytosis. Reactive causes are excluded, and criteria for other myeloid neoplasms are not met.	Signs of myeloproliferative and/or myelodysplasia: 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).
	Hepatomegaly without impairment of liver function, or splenomegaly without features of hypersplenism including thrombocytopenia, and/or lymphadenopathy (>1 cm size) on palpation or imaging.	Organomegaly: palpable hepatomegaly without ascites or other signs of organ damage and/or palpable splenomegaly without hypersplenism and without weight loss and/or palpable lymphadenopathy or visceral lymph node enlargement found by imaging (>2 cm).
C-findings *	BM dysfunction manifested by one or more cytopenia(s): ANC <1 × 10^9/L, Hb <10 g/dL, PLT <100 × 10^9/L, but no obvious non-MC hematopoietic malignancy.	One or more cytopenia(s): ANC <1 × 10^9/L, Hb <10 g/dL, or PLT <100 × 10^9/L.
	Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension.	Hepatopathy: ascites and elevated liver enzymes ± hepatomegaly or cirrhotic liver ± portal hypertension.
	Palpable splenomegaly with hypersplenism.	Spleen: Palpable splenomegaly with hypersplenism ± weight loss ± hypalbuminemia
	Malabsorption with weight loss due to GI MC infiltrates.	GI tract: malabsorption with hypoalbuminemia ± weight loss.
	Skeletal involvement with large osteolytic lesions and/or pathological fractures.	Bone: large-sized osteolysis (≥2 cm) with pathologic fracture ± bone pain.

* C-findings in 2022 ICC has no changes, adopted from prior 2016 WHO classification [7]. ANC, absolute neutrophil count; BM, bone marrow; Hb, hemoglobin; PB, peripheral blood; PLT, platelets.

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-**Bone marrow mastocytosis (BMM):** requires fulfilling of SM criteria, serum tryptase (BST) <12,5 ng/mL, absence of skin lesions, B- or C-findings, lack of dense SM infiltrates in an extramedullary organ, and exclusion of MCL or AHN

-**Indolent SM (ISM**) is defined by meeting the criteria for SM, no or only one B-finding, no evidence of C-findings, and no evidence of MCL or associated hematological neoplasm (AHN)

-**Smoldering SM (SSM**): defined by meeting the SM criteria, having ≥2 B-findings, and no C-findings or AHN

-**Aggressive SM (ASM**): requires fulfilling the SM criteria and the presence of ≥1 C-finding

-**SM associated hematologic neoplasm (SM AHN**) must satisfy criteria both for SM and for another WHO-defined hematologic neoplasm such as myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), or lymphoproliferative disorder.

-**Mast Cell Leukemia (MCL).** It is diagnosed based on meeting SM criteria and the presence of ≥20% atypical MCs in BM aspirate. In cases of suboptimal aspirate (dry tap) MCL can be diagnosed on a BM biopsy showing a dense, diffuse infiltration of atypical immature MCs. The WHO 5th edition distinguishes the more common aleukemic MCL variant (<10% MCs in peripheral blood) from the "classic" leukemic variant (≥10% circulating MCs)

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REMA score

REMA score proposed to predict clonal MCAD in patients in the absence of skin lesions

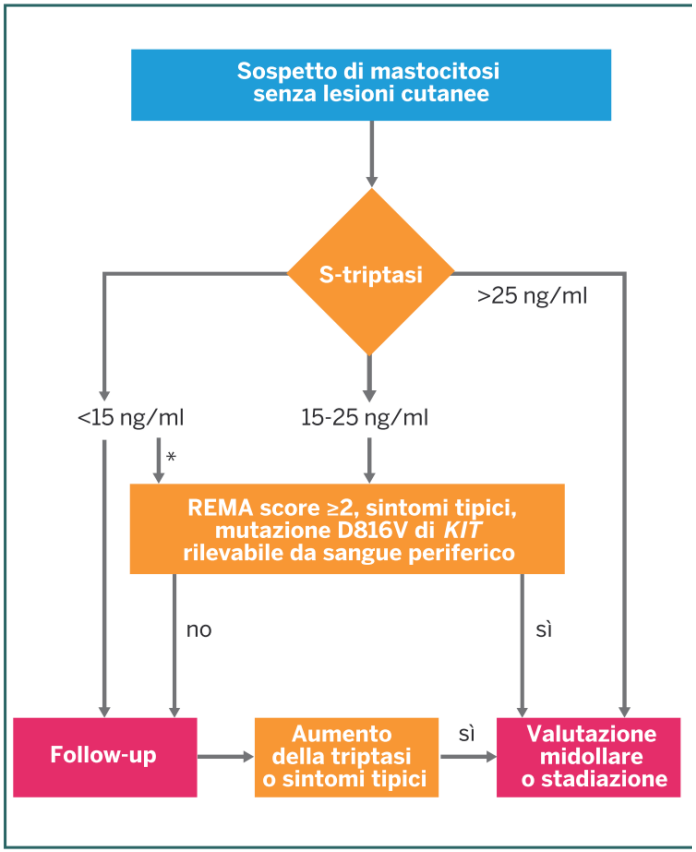
Parametro	Score
Genere	
Maschio	+1
Femmina	−1
Sintomi clinici	
Assenza di orticaria angioedema	+1
Orticaria e angioedema	−2
Presincope e/o sincope	+3
Triptasi[a]	
<15 ng/ml	−1
>25 ng/ml	+2

Score <2: bassa probabilità di MCAD clonale
Score ≥2: alta probabilità di MCAD clonale

Sensibilità: 0,92
Valore predittivo positivo: 0,89

Specificità: 0,81
Valore predittivo negativo: 0,87

[a]*Triptasi sierica basale; MCAD,* mast cell activation disorders



I livelli di triptasi correlano con il burden mastocitario, quindi con l'entità della malattia.

PROGNOSI

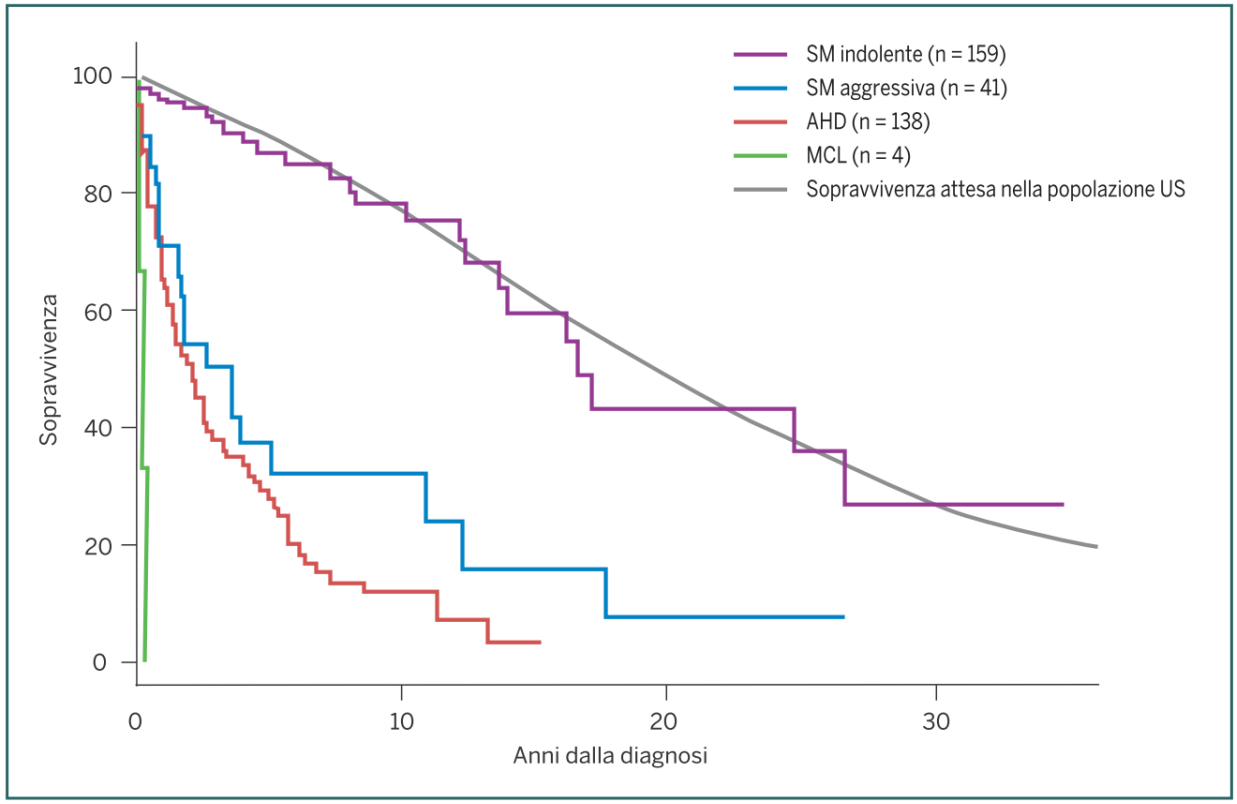


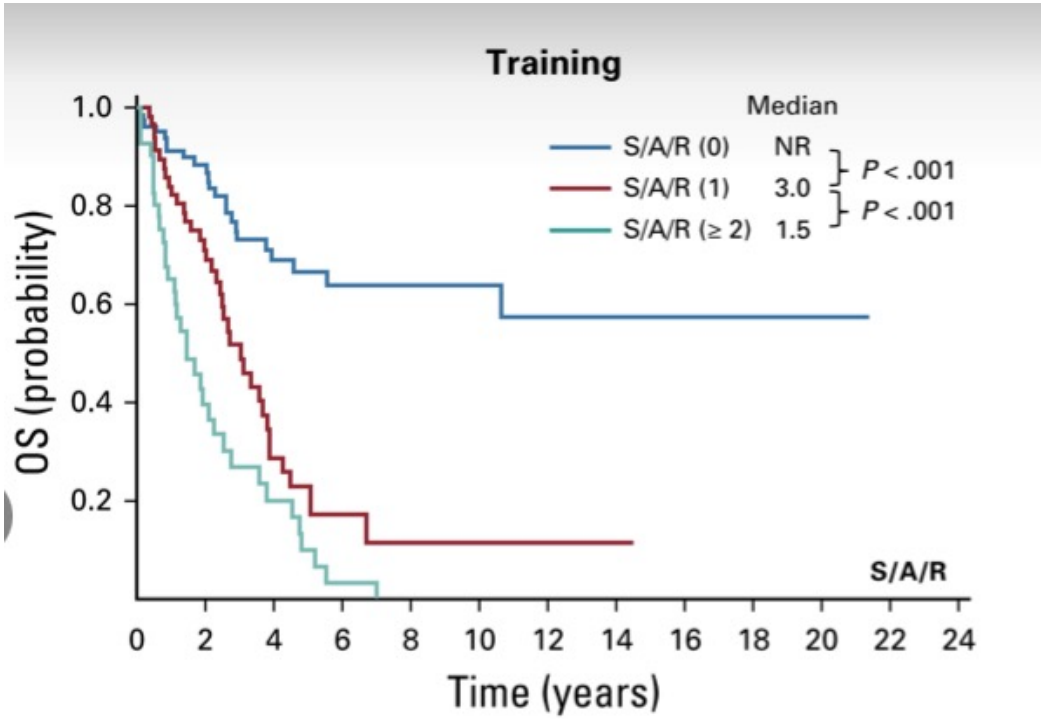
Figura 3. *Curve di sopravvivenza per le forme avanzate di mastocitosi sistemica (SM) (modificata da[18]). AHD (AHNMD), neoplasia ematologica associata (acronimi sostituiti da AHN secondo la classificazione WHO aggiornata); MCL, leucemia mastocitica; US,* United States

La mutazione KIT non è l'unica alterazione genica presente nei casi di SM.

Molte mutazioni aggiuntive possono essere associate, e in particolare le cosiddette mutazioni S/A/R (SRSF2, ASXL1 e RUNX1) sono associate a un outcome molto negativo.

Il mutation-adjusted risk score è un punteggio prognostico validato, a cinque parametri, indipendente dai criteri WHO, che definisce tre gruppi di rischio tra i pazienti con advSM (low - intermediate - high risk), potendo migliorare la stratificazione del trattamento.

-Età > 60 aa
-Hb < 10 g/dL
-Plt < 100000/mmc
-Presenza di una mutazione ad alto rischio
-Presenza di due o più mutazioni ad alto rischio



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TERAPIA

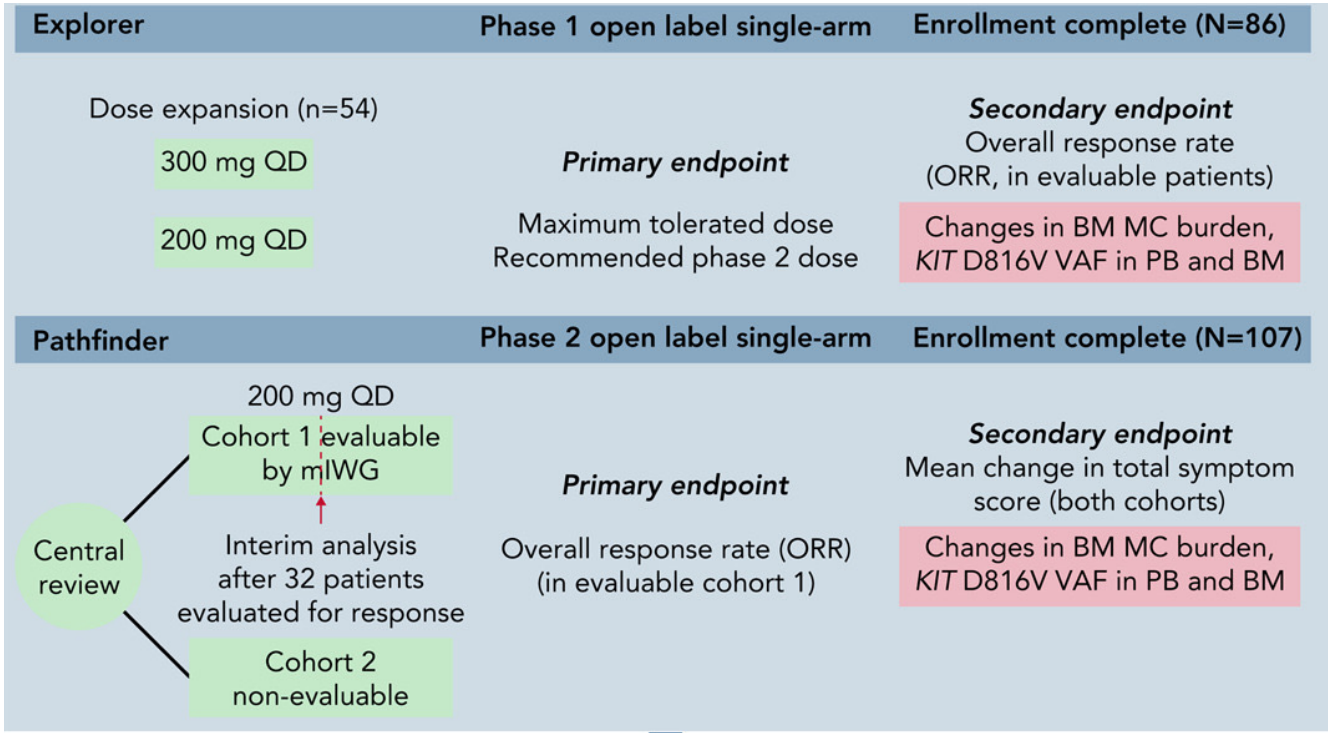
Non-Advanced SM*: ISM, BMM, and SSM:* The treatment focuses primarily on the prevention and treatment of anaphylactic reactions and symptom relief using histamine receptor blockers and MC-stabilizing agents (**antihistamines, cromolyn, aspirin, corticosteroids, and leukotriene receptor antagonists**).

Advanced SM *(ASM, SM-AHN, and MCL):* advanced subtypes are characterized by MC infiltration in organs, requiring the use of TKIs and/or cytoreductive agents to control/decrease MC burden.

- **Imatinib**: useful in those types of systemic mastocytosis that do not have mutations of the codon 816 on the c-kit gene and carry the wild-type kit. The common mutation KIT D816V is resistant to imatinib.
- **Midostaurin:** effectively inhibits both wild-type and D816V-mutated *KIT.* Its clinical response rates in ASM are similar regardless of subtype, *KIT* mutation status or prior therapy exposure
- **Avapritinib**: a potent, highly selective inhibitor of KIT D816V. Avapritinib treatment was associated with a marked reduction in symptoms and marrow MC burden, decreased tryptase level, spleen volume and *KIT* D816V VAF and improved overall survival compared to midostaurin and cladribine
- Available therapeutic options beyond TKIs include **interferon α, cladribine, and allogeneic stem cell transplant** (employed particularly for selected younger patients).

Avapritinib

Avapritinib in <u>advanced systemic mastocytosis</u>: **EXPLORER and PATHFINDER**



200 mg was ultimately chosen as the recommended phase 2 dose based on a composite of safety/tolerability, pharmacokinetics, efficacy, and reductions in measures of MC burden.

The ORR was 75%, including 19% with a CR/CRh. The mean total symptom scores (TSSs) improved rapidly after treatment initiation

Avapritinib in ISM

PIONEER: is a phase 2, multipart, randomized, placebo-controlled, double-blind trial. It assessed the safety and efficacy of **avapritinib 25 mg once daily plus BSC versus placebo plus BSC** in patients with moderate to severe **ISM.**

The trial has three parts. In part 1, a dose of 25 mg once daily was identified as the recommended dose in part 2 and in part 3. Part 2 of the PIONEER trial, which assessed the safety and efficacy of avapritinib 25 mg once daily plus BSC versus placebo plus BSC in patients with moderate to severe ISM. Part 3 is an ongoing, open-label extension of the trial that is evaluating the safety and efficacy of avapritinib 25 mg once daily for up to 5 years.

- Primary end point: mean change in TSS from baseline to week 24 in the intent-to-treat (ITT) population: avapritinib-treated patients had a decrease in mean TSS of 15.6 points compared with a decrease of 9.2 points in the placebo group.
- Secondary end points: (all assessed from baseline to week 24) proportion of patients with ≥50% reductions in serum tryptase levels; with ≥50% reductions in KIT D816V VAF in peripheral blood, with ≥50% reduction in TSS; with ≥30% reduction in TSS; and with ≥50% reduction in bone marrow core biopsy mast-cell burden

Masitinib

E' stata valutata la sicurezza e l'efficacia di Masitinib (6 mg/kg al giorno per 24 settimane) rispetto al placebo nei pazienti affetti da ISM e SSM gravemente sintomatici che non rispondevano ai trattamenti sintomatici ottimali.

L'endpoint primario era la risposta cumulativa (miglioramento del 75% o superiore rispetto al basale entro le settimane 8-24) in almeno un sintomo basale grave. Per 24 settimane, Masitinib è stato associato a una risposta cumulativa del 18.7% nell'endpoint primario rispetto al 7.4% per il placebo.

I risultati hanno indicato che Masitinib è un farmaco efficace e ben tollerato per il trattamento della mastocitosi sistemica indolente o smouldering gravemente sintomatica.

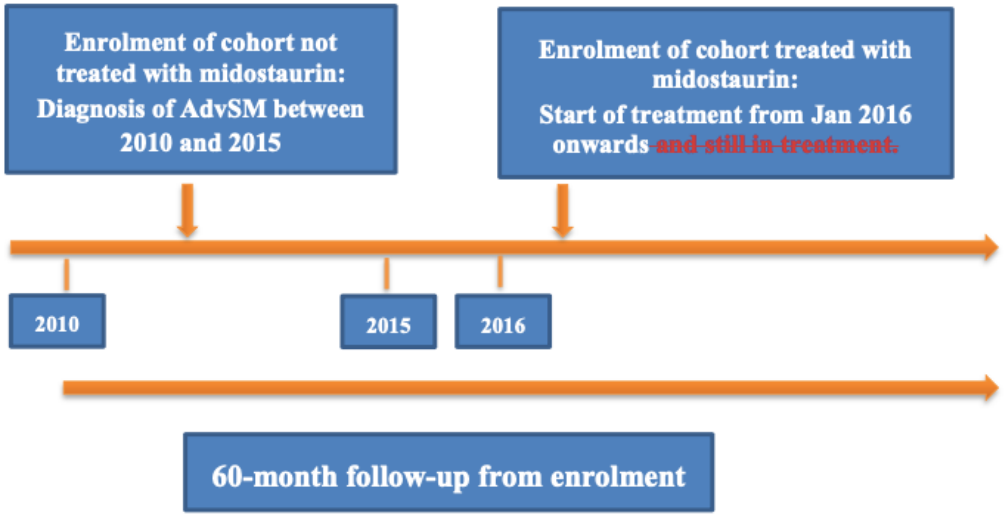
OVIDIO

This is a local, multicenter, non-randomized, observational study in an adult population of men and women diagnosed with AdvSM. This study will consider two cohorts:

-Patients treated with midostaurin starting from Jan 2016. The data collection period will be of 5 years starting from the beginning of treatment with midostaurin for AdvSM.

-Patients not treated with midostaurin for AdvSM (diagnosis between Jan 2010 and Dec 2015). The data collection period will be of 5 years from the initial diagnosis of AdvSM.

The purpose of this non-interventional study is to follow patients with advanced systemic mastocytosis (AdvSM) and to describe the **profile and disease burden** of a cohort of patients subsequently treated and not treated with midostaurin in clinical practice according to local label. Treatment with midostaurin will be independent from participation in this observational study and shall not be initiated for the purpose of participation in the study.



The secondary objectives of the study are to:

-evaluate the effectiveness of midostaurin in patients with AdvSM treated with midostaurin

-evaluate the effectiveness of treatment in patients with AdvSM not treated with midostaurin,

-evaluate the impact of treatment with midostaurin on quality of life in patients with AdvSM,

-evaluate the safety of midostaurin in patients with AdvSM