# Mastocitosi Sistemica

## DIAGNOSI E INQUADRAMENTO PROGNOSTICO

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blueprint MEDICINES

# Algoritmo diagnostico per pazienti con sospetta mastocitosi sistemica

**QUADRO A**

**Anafilassi o altri elementi clinici di sospetto**

**Lesioni cutanee tipiche?**

S → Biopsia cutanea e analisi istologica

N → **QUADRO B**

MIS?

N → **QUADRO B**

S → Livelli triptasi sierica Persistenti > 11.4 ng/mL

→ Ricerca KIT D816V su sangue periferico

D816V rilevata?

N → Valutazione ECNM/Fuchs score (SCHEDA 4)

Alto rischio?

N → Ricerca criteri WHO/ICC Maggiori e/o minori (SCHEDA 1-3)

S → Ricerca criteri WHO/ICC Maggiori e/o minori (SCHEDA 1-3)

S → Ricerca criteri WHO/ICC Maggiori e/o minori (SCHEDA 1-3)

in accordo a WHO/ICC

N → Valutazione REMA score (SCHEDA 4)

Alta probabilità?

S → **MCAS**

S → **SM**

Valutazione criteri diagnostici per la determinazione della variante (SCHEDA 7)

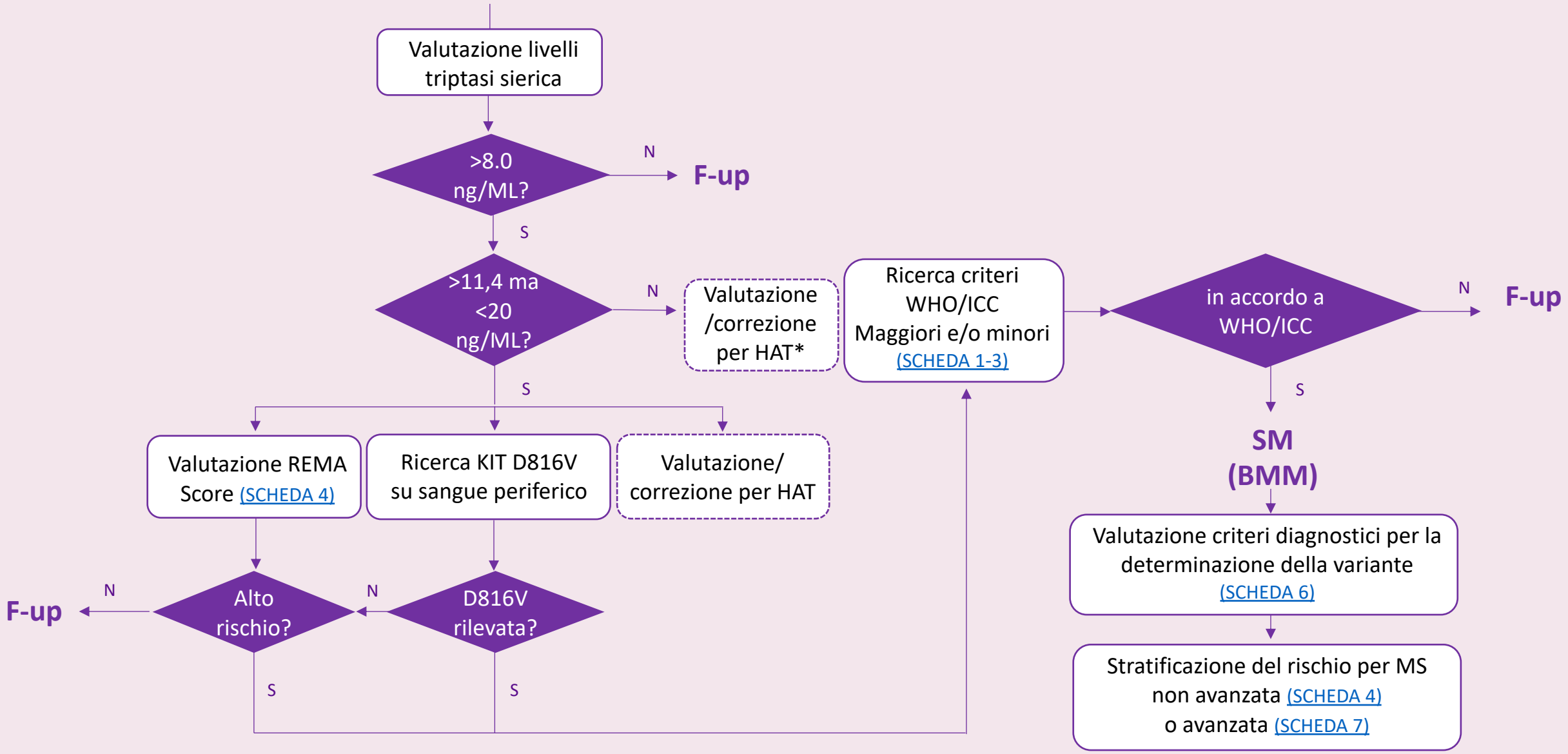
→ Stratificazione del rischio per MS non avanzata (SCHEDA 4) o avanzata (SCHEDA 6)

MIS: mastocytosis in the skin
ECNM: European Competence Network on Mastocytosis
REMA: Red Española de Mastocitosis
MCAS: Mast Cell Activation Syndrome

# Algoritmo diagnostico per pazienti con sospetta mastocitosi sistemica

**QUADRO B**

**Anafilassi o altri elementi clinici di sospetto ma assenza di lesioni cutanee/MIS**




*HAT: Hereditary Alpha Tryptasemia; solo se si ha accesso ad un laboratorio che offre il test che valuta l'amplificazione del gene per la triptasi

SCHEDA 1

# Criteri diagnostici per la diagnosi di mastocitosi sistemica

| Criteria Type | Major Criterion | Type of Sample |
|---|---|---|
| Histopathology | Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) | in sections of BM or extracutaneous organ biopsy |

| Criteria Type | Minor Criteria | Type of Sample |
|---|---|---|
| Morphology | >25% of mast cells in infiltrates are spindle-shaped or have atypical morphology, or | in sections of BM or extracutaneous organ biopsy |
| | >25% of mast cells are immature or atypical | BM aspirate smear |
| Molecular genetics | Detection of an activating point mutation at codon 816 of KIT | BM, blood, another extracutaneous organ |
| Phenotype | Mast cells express CD2 and/or CD25 in addition to normal mast cell markers | BM, blood or other extracutaneous organs |
| Blood chemistry | total tryptase persistently >20 ng/mL | Serum from blood |

| WHO 5th Edition [1] | ICC [2] |
|---|---|
| 1 major + 1 minor criteria<br>**or**<br>≥3 minor criteria | Major criterion<br>**or**<br>≥3 minor criteria |

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

SCHEDA 2

# Test diagnostici per mastocitosi sistemica

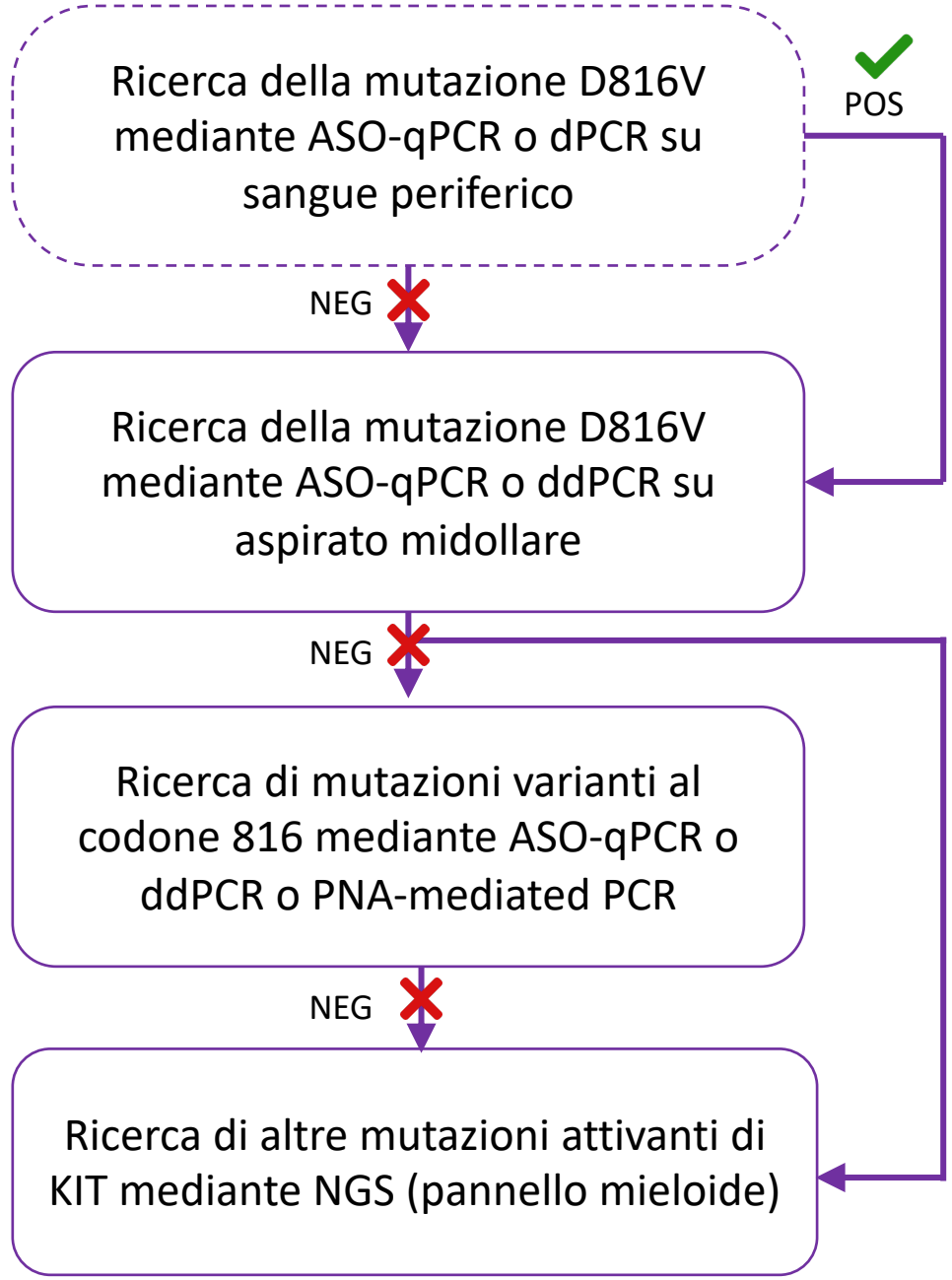
**Su sangue periferico:**
Esame morfologico dello striscio
Emocromo ed esami biochimici
Livelli di triptasi sierica basale
Valutazione del numero di copie TPSAB1 (HAT)[1]
(Analisi molecolare per ricerca mutazione KIT D816V mediante ASO-qPCR o ddPCR)
(Analisi molecolare per ricerca riarrangiamento FIP1L1::PDGFRA se eosinofilia)

**Su aspirato midollare:**
Esame morfologico dello striscio
Analisi immunofenotipica[2]
Analisi molecolare per ricerca/conferma mutazione KIT D816V mediante ASO-qPCR o ddPCR
(Analisi molecolare per ricerca altre mutazioni attivanti di KIT se D816V non rilevata)[3]
Analisi citogenetica (se si sospetta AHN?)

**Su biopsia midollare:**
Analisi immunoistochimica[4]

[1] se il test è disponibile/accessibile; opportuno per correggere i livelli di triptasi basale in caso di amplificazione
[2] CD34, CD45, CD2, CD25, CD117, CD30
[3] vedere tabella; per mutazioni non D816V è ammesso l'utilizzo di pannelli NGS
[4] triptasi, chimasi, CD34, CD117, CD2, CD25, CD30

# SCHEDA 3A Algoritmo di analisi molecolare per KIT 816V e altre mutazioni attivanti di KIT



SCHEDA 3B

# Varianti oncogeniche di KIT che si qualificano come criterio minore in assenza di D816V

| Varianti oncogeniche di KIT | |
|---|---|
| Del417-419insF | V559I |
| Del417-419insI | Del559-560 |
| Del417-419insNA | V560G |
| Del417-419insY | K642E |
| Del419 | V654A |
| InsFF419 | L799F |
| ITD501-502 | D816A |
| 501_502InsAF | D816F |
| ITD502-503 | D816H |
| 503_504insAY | D816I |
| ITD504 | D816V |
| ITD505-508 | D816Y |
| K509I | D816T |
| F522C | D820G |
| W557R | N822I |
| V559A | N822K |

da Valent et al, Hemasphere. 2021 Nov; 5(11): e646

SCHEDA 4

## ECNM/Fuchs SCORE

| Prognostic Variable | Points |
|---|---|
| **Tryptase(ng/mL) level** | |
| **<10** | -1 |
| **≥10<15** | 0 |
| **≥15<20** | 1 |
| **≥20** | 3 |
| **Bone symptoms or osteoporosis** | +1 |
| **Constitutional or cardiovascular symptoms** | +1 |

| Risk Groups | Points |
|---|---|
| **LOW** | ≤0 |
| **Medium/intermediate** | 1-2 |
| **HIGH** | 3-5 |

## SCORE MODEL TO PREDICT CLONAL MAST CELL ACTIVATION DISORDERS (MCAD) – REMA SCORE

| Prognostic Variable | Points |
|---|---|
| **Gender** | |
| **Male** | +1 |
| **Female** | -1 |
| **Clinical Symptoms** | |
| **Absence of hives, pruritus and angioedema** | +1 |
| **Hives, pruritus and angioedema** | -2 |
| **Presyncope and/or syncope** | +3 |
| **Baseline Serum Tryptase** | |
| **<15ng/mL** | -1 |
| **>25ng/mL** | +1 |

| Risk Groups | Points |
|---|---|
| **LOW PROBABILITY** | <2 |
| **HIGH PROBABILITY** | ≥2 |

SCHEDA 5

# Criteri diagnostici per le varianti di mastocitosi sistemica

| VARIANTS OF SM | Diagnostic Criteria |
|---|---|
| **Bone marrow mastocytosis** | • As indolent systemic mastocytosis but with bone marrow involvement and no skin lesions |
| **Indolent systemic mastocytosis** | • Meets the general criteria for systemic mastocytosis<br>• No C-findings<br>• No evidence of an associated hematologic neoplasm<br>• Low mast cell burden<br>• Skin lesions are frequently present |
| **Smoldering systemic mastocytosis** | • Meets the general criteria for systemic mastocytosis<br>• ≥2 B-findings; no C-findings<br>• No evidence of an associated hematologic neoplasm<br>• High mast cell burden<br>• Does not meet the criteria for mast cell leukemia |
| **Systemic mastocytosis with an associated hematologic neoplasm** | • Meets the general criteria for systemic mastocytosis<br>• Meets the criteria for an associated hematologic neoplasm (ie, a myelodysplastic syndrome, AML, myeloproliferative neoplasm, lymphoma, or another hematologic neoplasm classified as a distinct entity in the WHO classification) |
| **Aggressive systemic mastocytosis** | • Meets the general criteria for systemic mastocytosis<br>• ≥1 C-findings<br>• Does not meet the criteria for mast cell leukemia<br>• Skin lesions are usually absent |
| **Mast cell leukemia** | • Bone marrow aspirate smears show ≥20% mast cells<br>• In classic cases, mast cells account for ≥10% of the peripheral blood white blood cells, but the aleukemic variant (in which mast cells account for <10%) is more common<br>• Mast cell variants include: Acute MCL [≥1 C-finding(s)] vs. chronic MCL (no C-findings) MCL with an AHN vs. MCL without an AHN Primary (de novo) vs. secondary MCL (arising from another SM variant<br>• Skin lesions are usually absent |

1. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.
2. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

SCHEDA 6

# Stratificazione del rischio per pazienti con forma non-avanzata di mastocitosi sistemica

## MAYO ALLIANCE PROGNOSTIC SYSTEM (MAPS)

| Prognostic Variable | Points |
|---|---|
| Age >60 years | 1 |
| Advanced SM vs. ISM/SSM | 2 |
| Platelets <150 x 109/L | 1 |
| Serum alkaline phosphatase (ALP) > normal range | 1 |
| Adverse mutation (ASXL1, RUNX1, and NRAS) | 1 |

| Risk Groups | Points |
|---|---|
| LOW | ≤2 |
| INTERMEDIATE-1 | 3 |
| INTERMEDIATE-2 | 4 |
| HIGH | ≥5 |

## INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MASTOCYTOSIS (IPSM) SCORE

| Prognostic Variable | Points |
|---|---|
| Age ≥60 years | 1 |
| Alkaline phosphatase ≥100 U/L | 1 |

| Risk Groups | Points |
|---|---|
| LOW | 0 |
| INTERMEDIATE-1 | 1 |
| INTERMEDIATE-2 | 2 |

SCHEDA 7

# Stratificazione del rischio per pazienti con forma avanzata di mastocitosi sistemica

**MAPS**

**MUTATION-ADJUSTED RISK SCORE (MARS) FOR ADVANCED SYSTEMIC MASTOCYTOSIS**

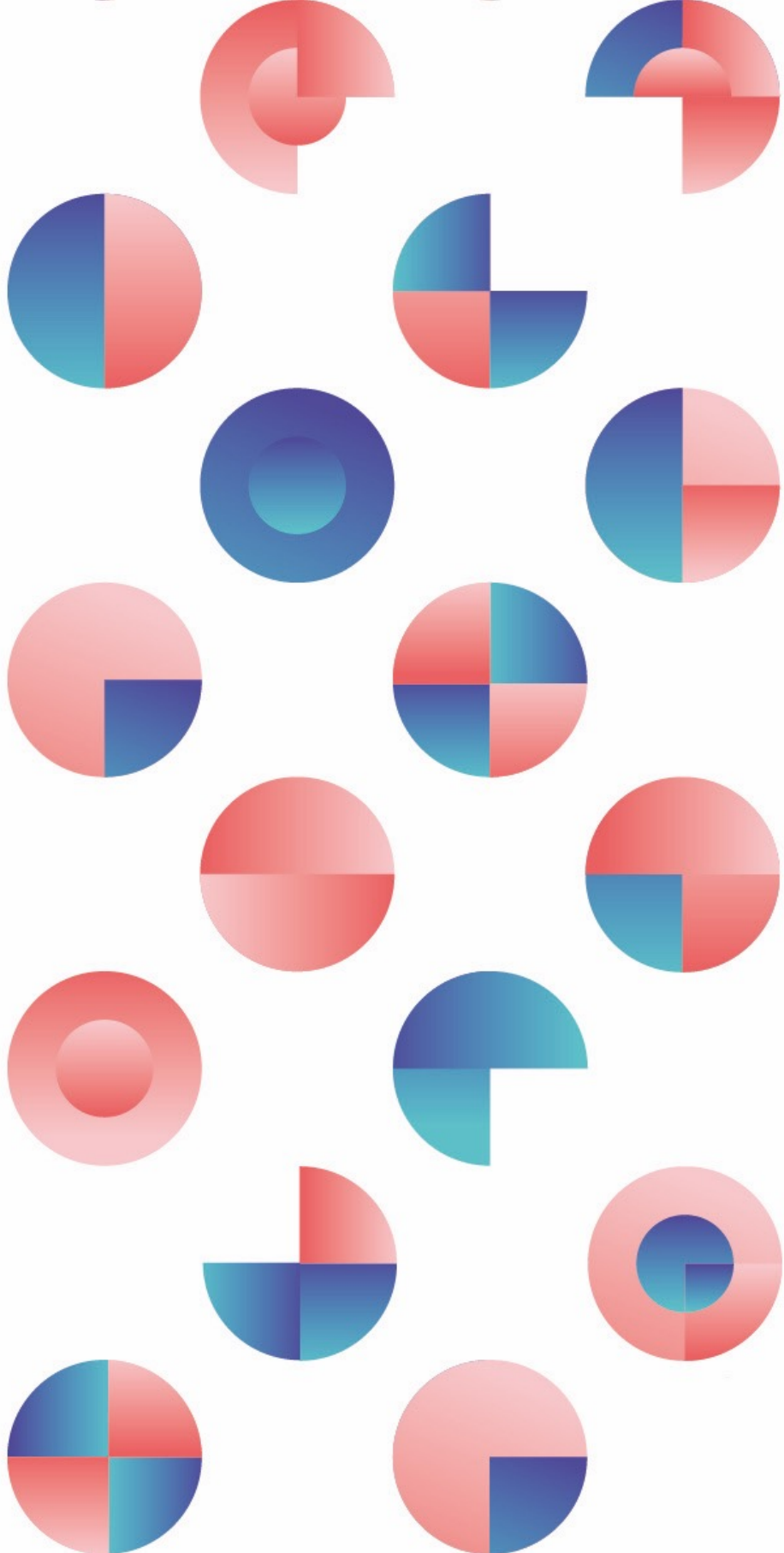
| Prognostic Variable | Points |
|---|---|
| Age >60 years | 1 |
| Hemoglobin <10 g/dL | 1 |
| Platelets <100 x 109/L | 1 |
| One S/A/R (SRSF2, ASXL1, or RUNX1) mutation | 1 |
| ≥2 S/A/R mutation | 2 |

| Risk Groups | Points |
|---|---|
| LOW | 0-1 |
| INTERMEDIATE | 2 |
| HIGH | 3-5 |

**IPSM SCORE FOR ADVANCED SYSTEMIC MASTOCYTOSIS**

| Prognostic Variable | Points |
|---|---|
| Age ≥60 years | 1 |
| Hemoglobin <11 g/dL | 1 |
| Platelets <100 x 109/L | 1 |
| Tryptase ≥125 ng/mL | 1 |
| Leukocytes ≥16 × $10^9$/L | 1 |
| Skin involvement | -1 |

| Risk Groups | Points |
|---|---|
| AdvSM-1 | -1 - 0 |
| AdvSM-2 | 1 |
| AdvSM-3 | 2-3 |
| AdvSM-4 | ≥4 |



Il presente documento è il prodotto finale del progetto *Real-case based diagnostic and management challenges for patients with Systemic Mastocytosis*, condotto nel corso del 2023 e 2024 dal Working Party GIMEMA sulle Neoplasie Mieloproliferative Croniche.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