Systemic Mastocytosis: Recognizing and Managing a Rare Disease

FLASCO Clinical Oncology Series: Rare Disease

August 22nd, 2026

Samuel B. Reynolds, MD

Clinical Assistant Member and ECDGA Cancer Center Lead

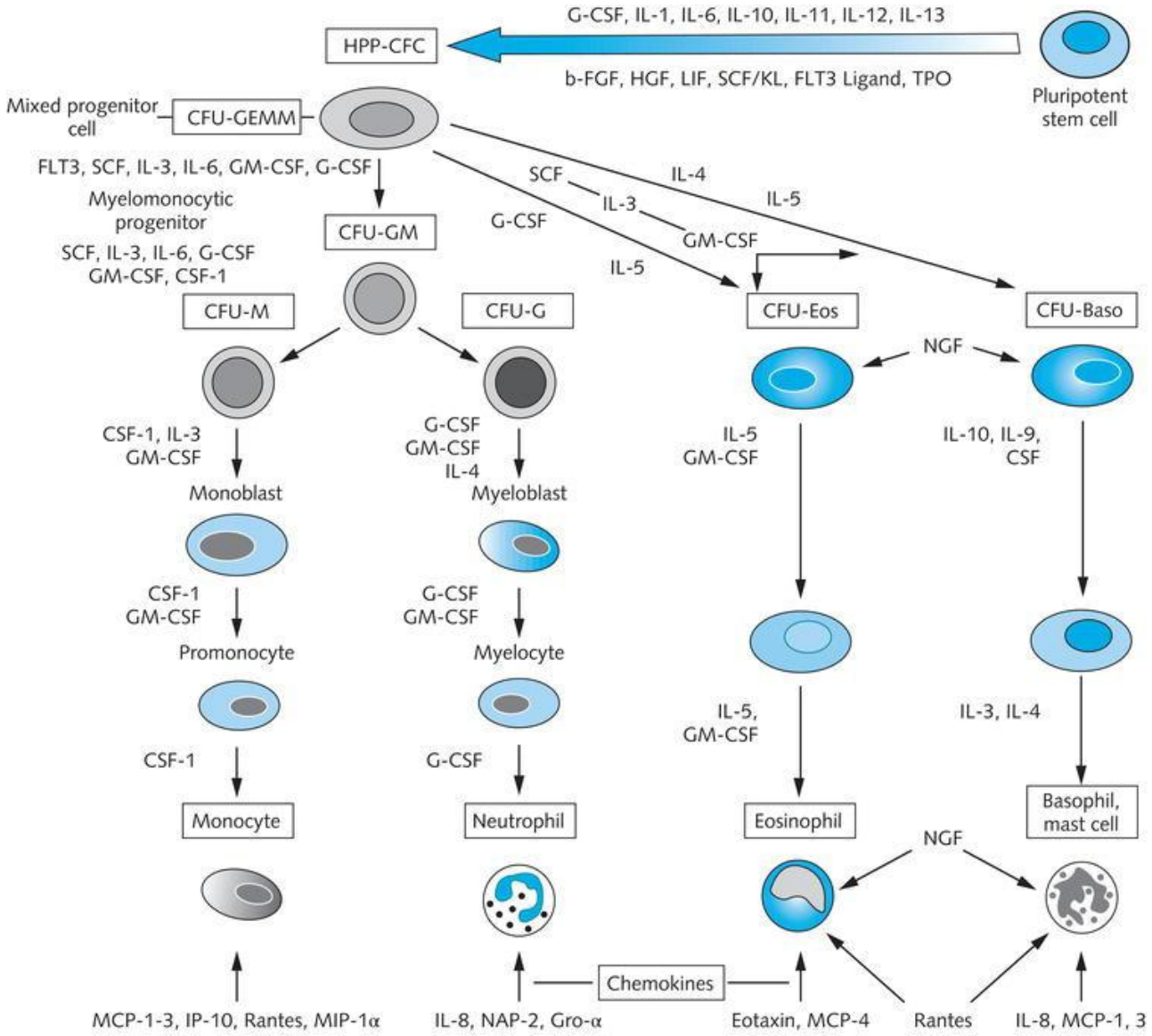
Moffitt Cancer Center

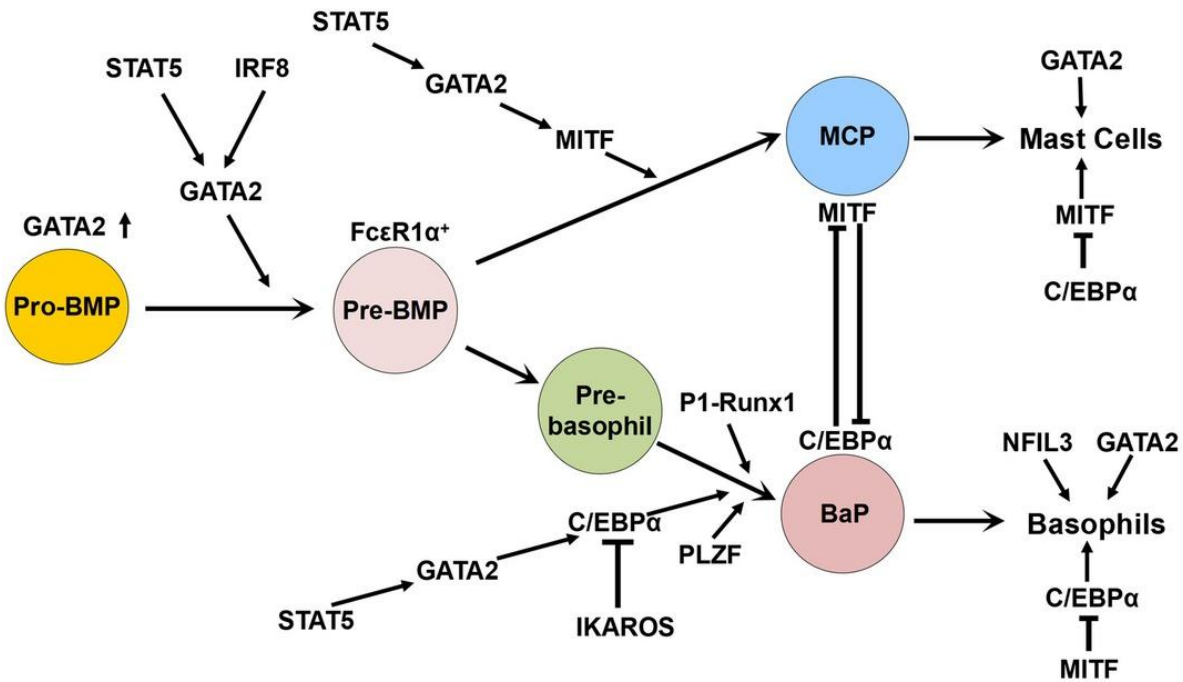
Outline

- Recognition and diagnosis of SM
- SM Classification
- Treatment in SM by subtype
- Evolving treatments and the importance of multidisciplinary care

Where do mast cells come from?

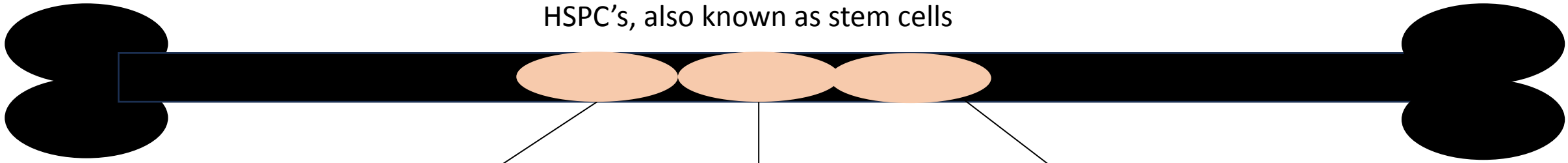
What are their functions?





Chia SL, et al., *Immunol Rev*, 2023
Gao J, *Immunol Rev* , 2025
Scadden, D.T. *Stem Cells,* 2024

HSPC's, also known as stem cells



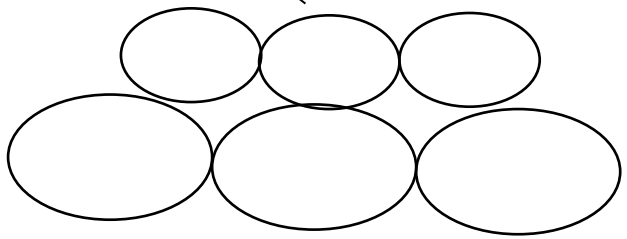
RBC's

Essential in oxygen binding, transport and delivery

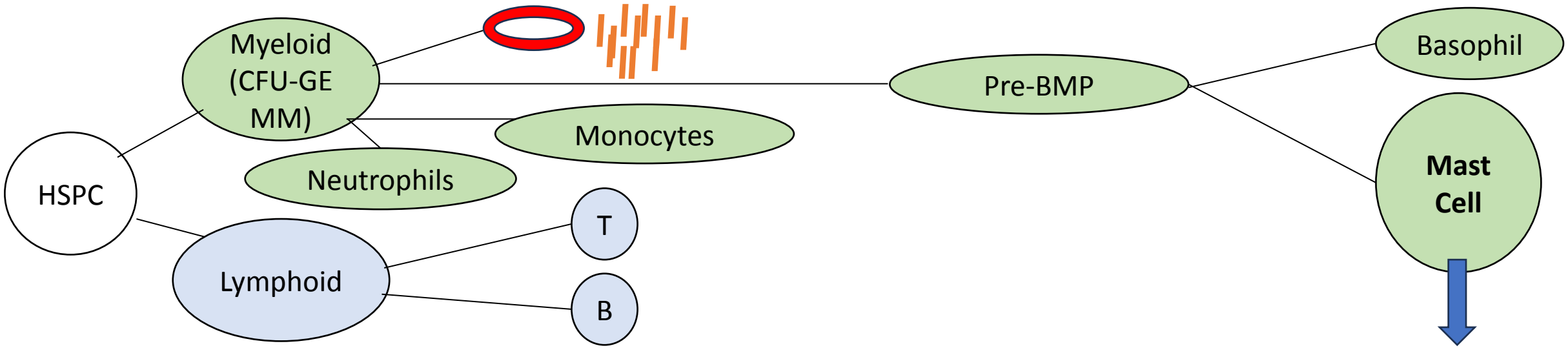
Platelets

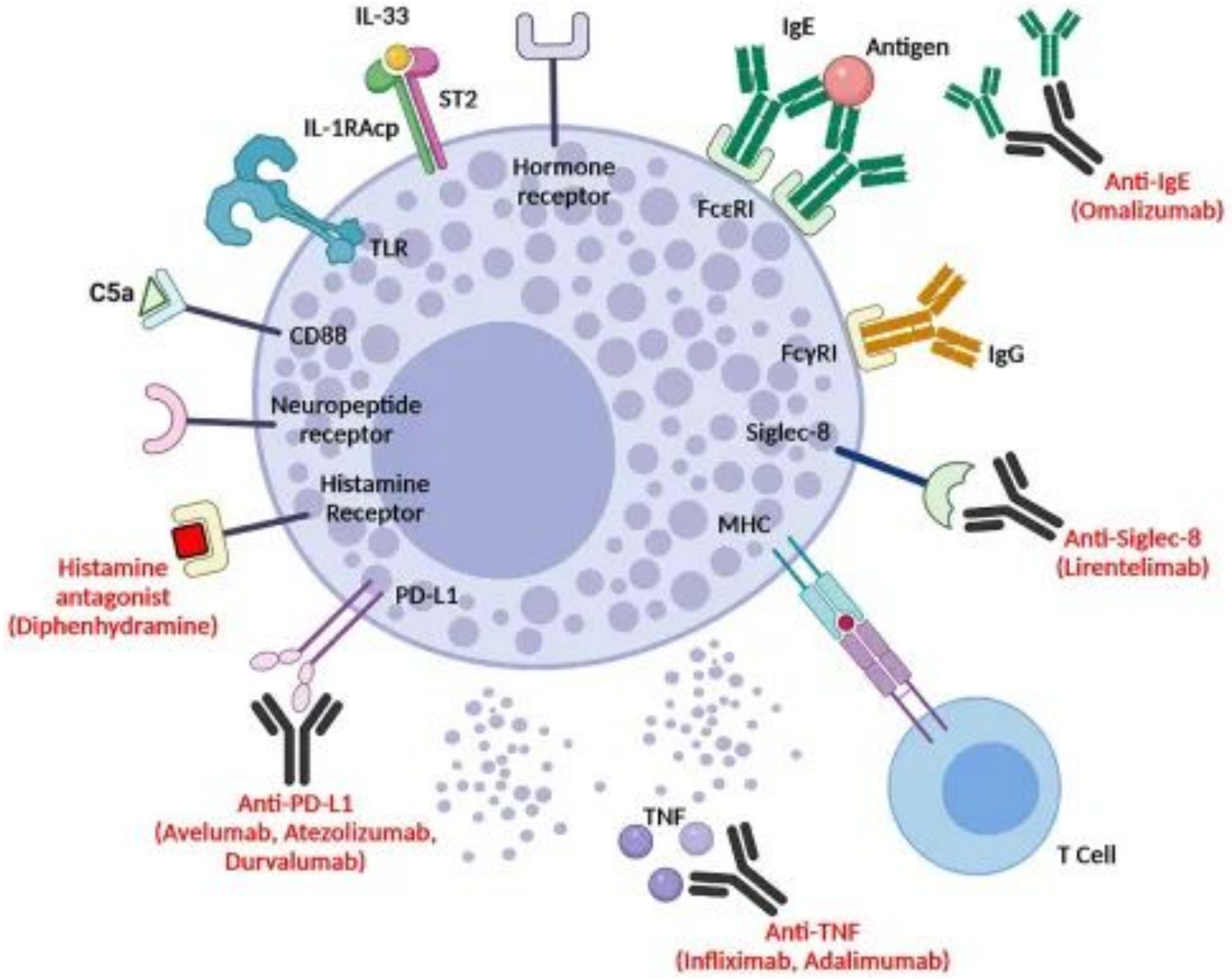
Primary hemostasis

White blood cells***



Diverse, multifaceted





Activators

Complement (C5a)
PAMPs
Fc Receptors (IgE & IgG)
Neuropeptides
Hormones
Serine Proteases
Cytokines (IL-33)

Responses

Rheumatoid Arthritis
IL-8, TNF, IL-10

Multiple Sclerosis
IL-17, tryptase, chymase

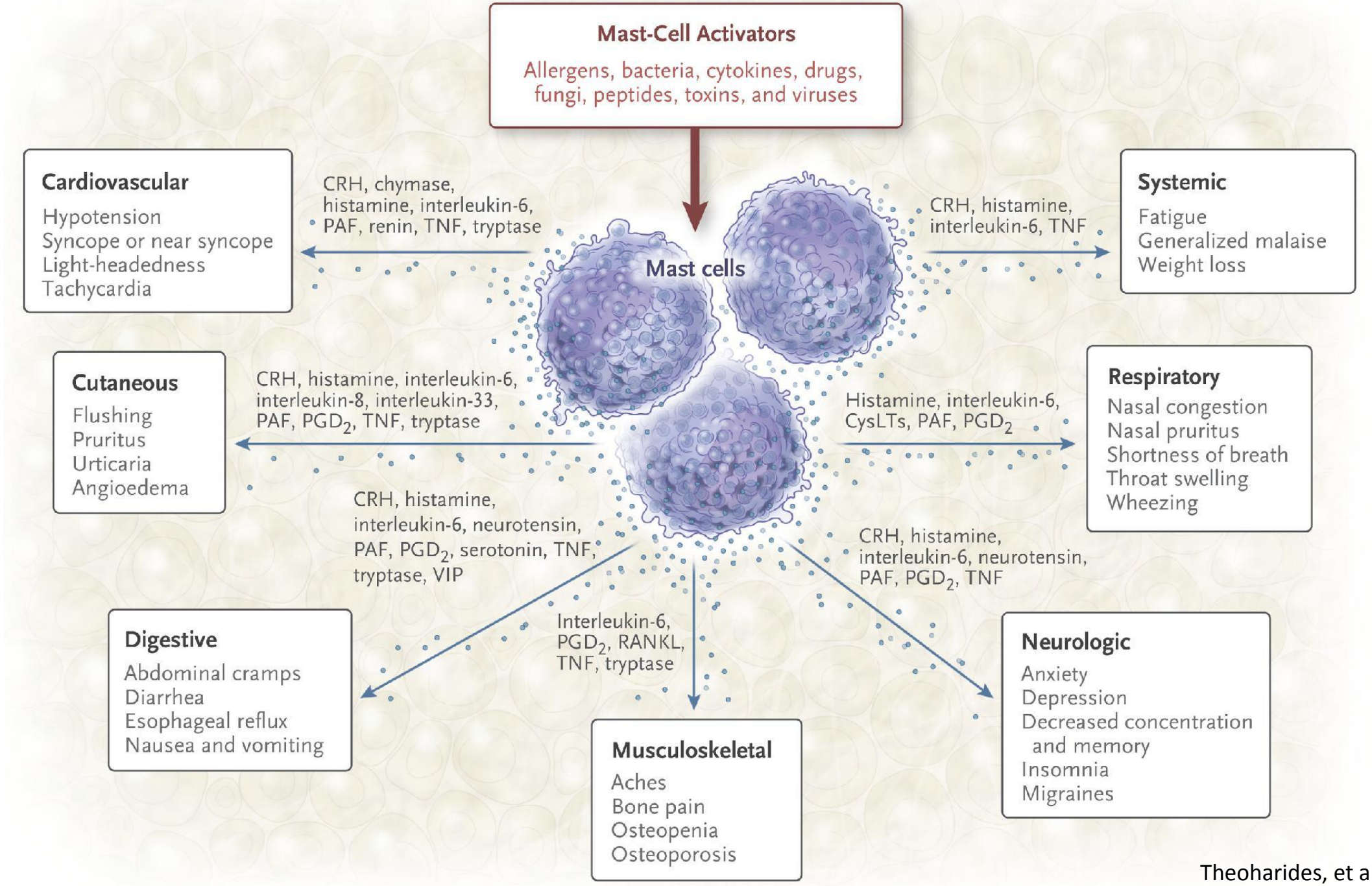
Type 1 Diabetes
IL-6

Inflammatory Bowel Disea
TNF, histamine

Therapeutics

Anti-IgE
Anti-Siglec-8
Anti-TNF
Anti-PD-L1/PD-L2
Histamine antagonists

Noto, et al., *Front. Cell Dev. Biol*, 2021



Theoharides, et al., *NEJM*, 2015

How do we formally diagnose mast cell disorders?

How are they subclassified?

Clinical characteristics and presenting data:

- Suspected mast cell over-activation
- Elevated serum tryptase Mastocytosis in the skin (MIS) in an adult without prior SM

Conduct biopsy of marrow or extracutaneous tissue

- Comprehensive myeloid genomic and/or transcriptomic profiling, including for *KIT* D816V
- *FIP1L1::PDGFRA* if concurrent eosinophilia
- Mast cell characterization by immunophenotyping or IHC

Proceed to subclassify mast cell disorder utilizing standardized diagnostic criteria for SM

NCCN., *Systemic Mastocytosis*, 2025

Diagnostic Criteria for SM

Major	Dense multifocal aggregates of at least 15 mast cells in sampled tissue
Minor	Atypical morphology in >25% of biopsied tissue
	Aberrant expression of ≥1 of CD2, CD25 or CD30
	KIT D816V mutation identified in tissue or peripheral blood
	**Serum tryptase of >20 ng/mL

**If SM-AHN is absent
**In the presence of HCT; adjust the tryptase level by dividing tryptase by gene copy number

WHO 5th Ed	**ICC**
1 major + 1 minor	1 major
≥3 minor	≥3 minor

NCCN., *Systemic Mastocytosis*, 2025
Rets and T.I. George, *Int J Lab Hematolo*, 2026

Clinical characteristics and presenting data:

- Suspected mast cell over-activation
- Elevated serum tryptase Mastocytosis in the skin (MIS) in an adult without prior SM

Conduct biopsy of marrow or extracutaneous tissue

- Comprehensive myeloid genomic and/or transcriptomic profiling, including for *KIT* D816V
- *FIP1L1::PDGFRA* if concurrent eosinophilia
- Mast cell characterization by immunophenotyping or IHC

Proceed to subclassify mast cell disorder utilizing standardized diagnostic criteria for SM

***KIT* WT with normal cellular morphology + immunophenotype**

Consider alternate diagnoses, including peripheral MCAS

CD2/CD25/CD30+ or *KIT* D816V but normal morphology

MMAS

Isolated MIS not meeting WHO/ICC

Cutaneous Mastocytosis (CM)

≥3 minor criteria, 1 major + 1 minor (WHO) or 1 major (ICC)

Systemic Mastocytosis (SM)

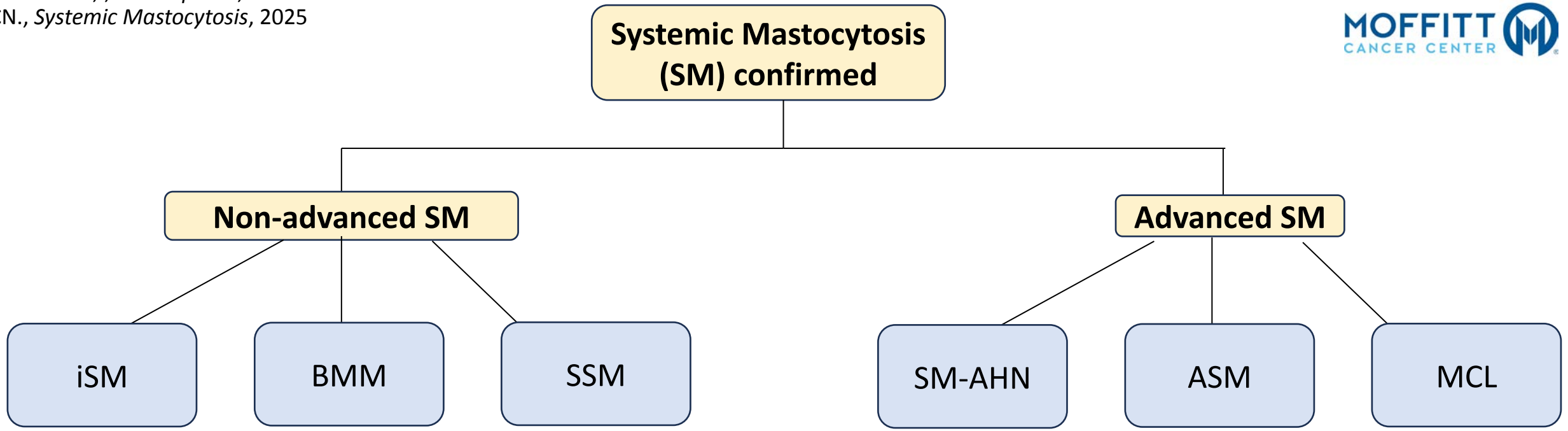
NCCN., *Systemic Mastocytosis*, 2025

MOFFITT CANCER CENTER

How do we further subclassify systemic mastocytosis?

What are the therapeutic implications of this process?

Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025



B-Findings

WHO 5th Ed	ICC
High mast cell burden by BM% (≥30), tryptase (≥200 ng/mL), *KIT* VAF (≥10%) in BM or PBMC's	>30% mast cells by BMBx AND tryptase >200 ng/mL
Myeloproliferation or dysplasia	Cytopenia(s) not d/t C findings
Hepatomegaly, splenomegaly or LAD without end-organ damage	Hepatomegaly without impaired liver function, splenomegaly

C-Findings

- ≥1 cytopenia (ANC <1000, Hgb <10, Plts <100)
- Hepatic, splenic or gastrointestinal dysfunction
- Large bone osteolysis (>20 mm), fracture or pain

Indolent systemic mastocytosis (iSM)

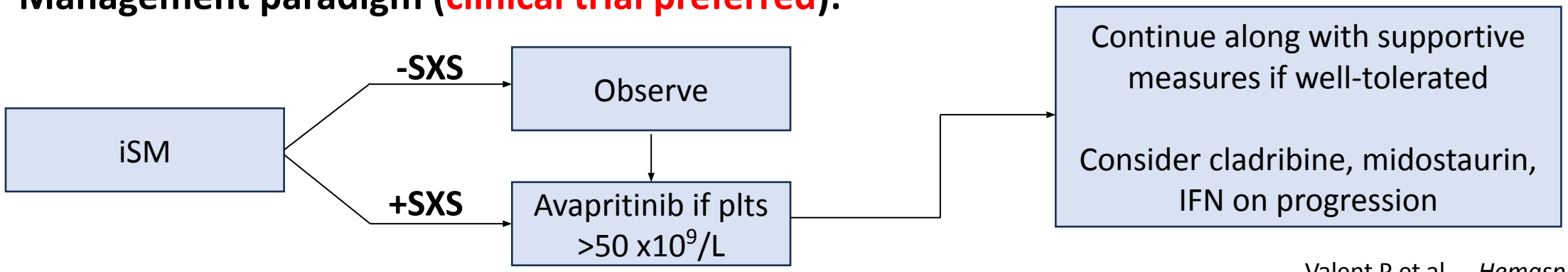
Criteria:

- SM
- +/- skin lesions
- ≤1 B-finding
- iSM with no skin lesions: ≤1 B-finding and/or tryptase >125 ng/mL

Key considerations:

- Conduct baseline DEXA scan
- Carry 2 epinephrine autoinjectors
- Counsel patients on trigger avoidance and assess QOL utilizing MSAF

Management paradigm (clinical trial preferred):



Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025
B van Anrooij, *Allergy*, 2016

Smoldering Systemic Mastocytosis (SSM)

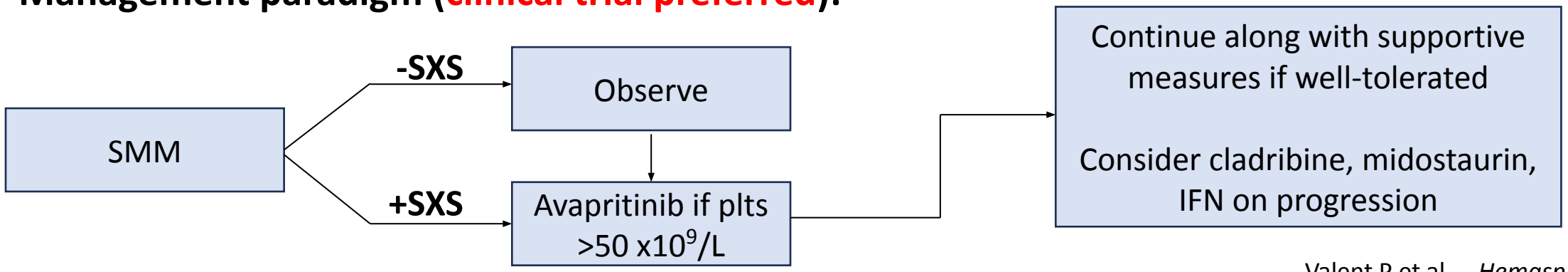
Criteria:

- SM
- ≥2 B-findings
- C findings absent

Key considerations:

- Conduct baseline DEXA scan
- Carry 2 epinephrine autoinjectors
- Counsel patients on trigger avoidance and assess QOL utilizing MSAF

Management paradigm (clinical trial preferred):



Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025
B van Anrooij, *Allergy*, 2016

Bone Marrow Mastocytosis (BMM)

Criteria:

- SM
- Skin lesions absent
- B-findings absent
- Tryptase <125 ng/mL
- EM SM absent

Key considerations:

- Conduct baseline DEXA scan
- Carry 2 epinephrine autoinjectors
- Counsel patients on trigger avoidance and assess QOL utilizing MSAF

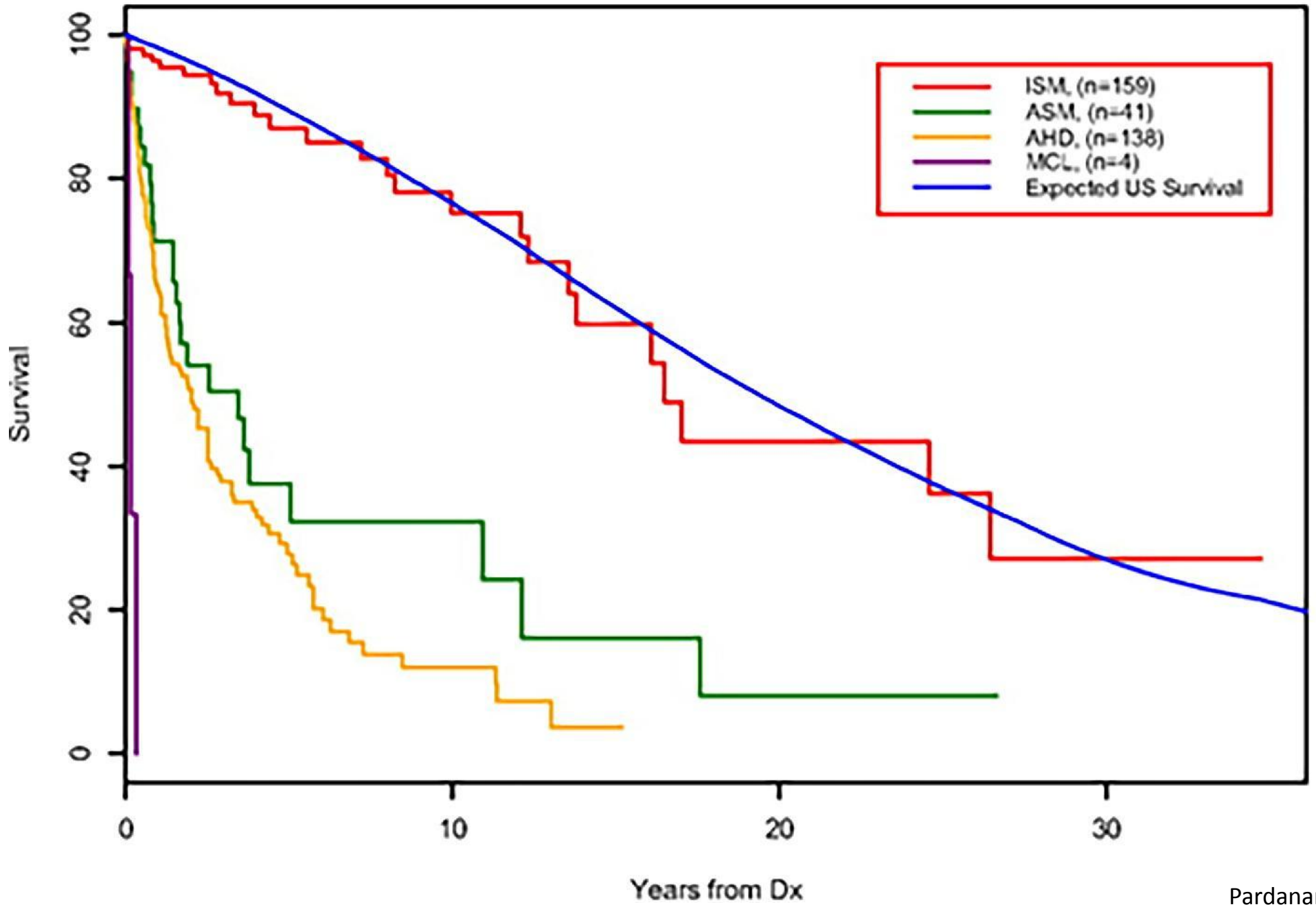
Important Notes:

- The ICC classifies BMM as an iSM subtype
- Generally, this is a more favorable-risk variant
- Management follows the iSM/SMM paradigm

Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025
B van Anrooij, *Allergy*, 2016

Knowing that the management of iSM, SMM and BMM is similar…

How do we manage the more aggressive SM variants?



Pardanani A, *Am J Hematol*, 2023

Aggressive Systemic Mastocytosis (ASM)

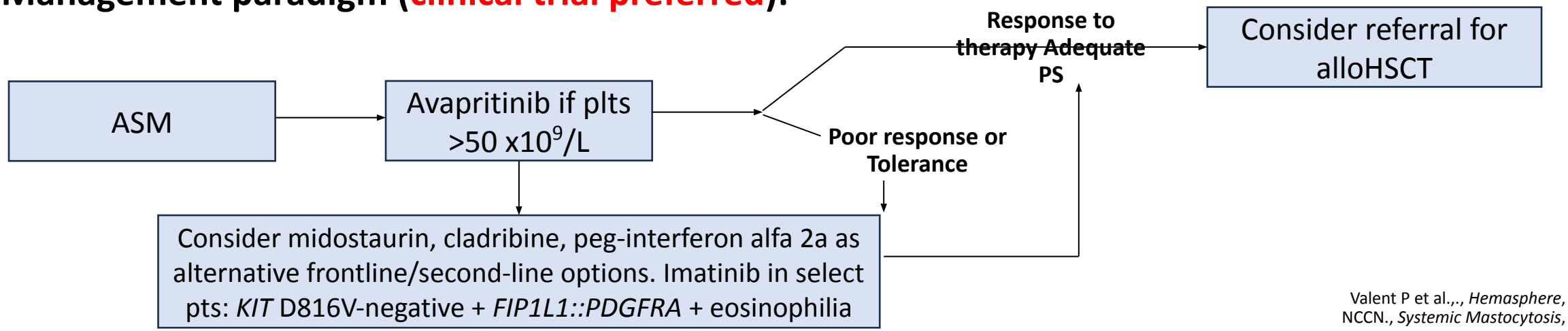
Criteria:

- SM
- ≥C finding

Key considerations:

- Conduct baseline DEXA scan
- Carry 2 epinephrine autoinjectors
- Counsel patients on trigger avoidance and assess QOL utilizing MSAF

Management paradigm (clinical trial preferred):



Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025

Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)

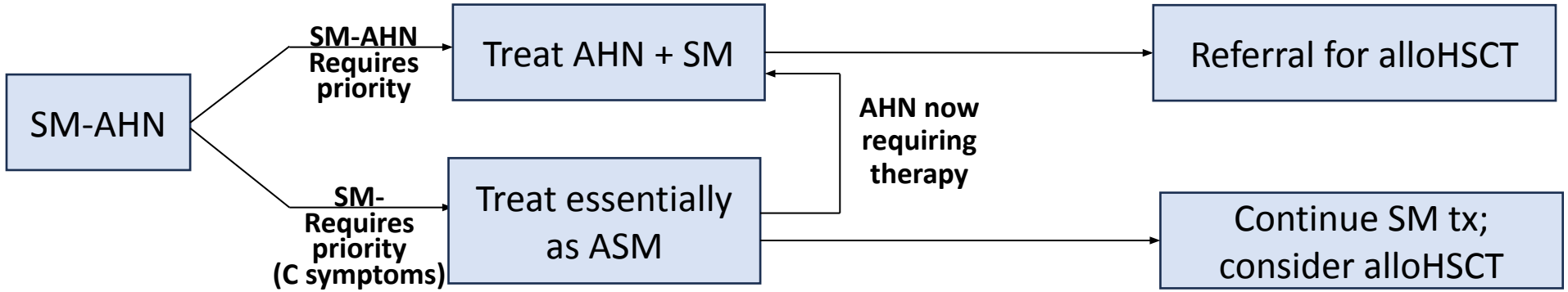
Criteria:

- SM
- WHO-defined hematologic malignancy

Key considerations:

- Conduct baseline DEXA scan
- Carry 2 epinephrine autoinjectors
- Counsel patients on trigger avoidance and assess QOL utilizing MSAF

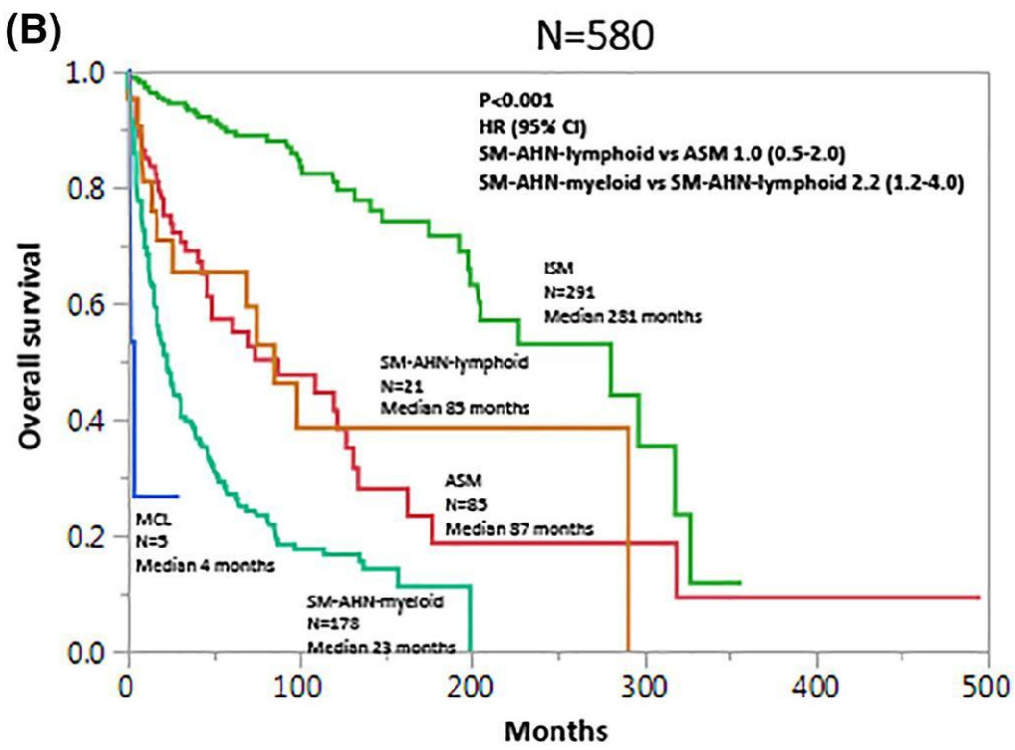
Management paradigm (clinical trial preferred):

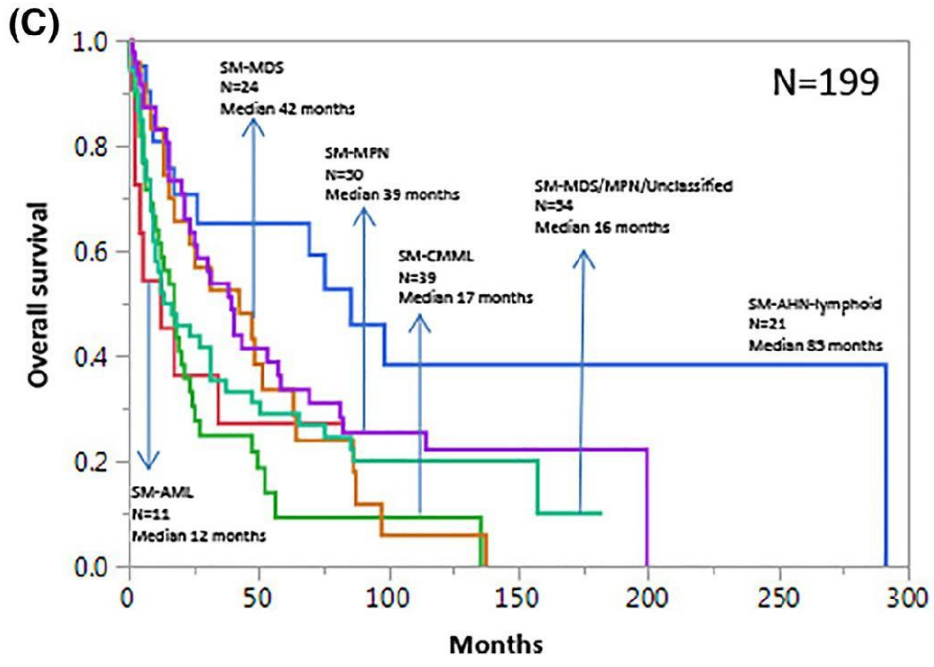


Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025

What is the breakdown amongst hematologic neoplasms?

- **Study:**
  - 580 patients
  - Single-institution
  - Stratified by WHO SM criteria
- **Key Findings:**
  - Amongst 199 pts with SM-AHN:
    - 178 myeloid (89.4%)
    - 21 lymphoid (10.6%)
  - OS: MPN>MDS/MPN>MDS=CMML> AML
- **Takeaways in SM-AHN:**
  - Myeloid more common, subtype varies
  - Lymphoid neoplasms in SM-AHN fare better than myeloid





Tefferi A, *Am J Hematol*, 2018

Mast cell leukemia (MCL)

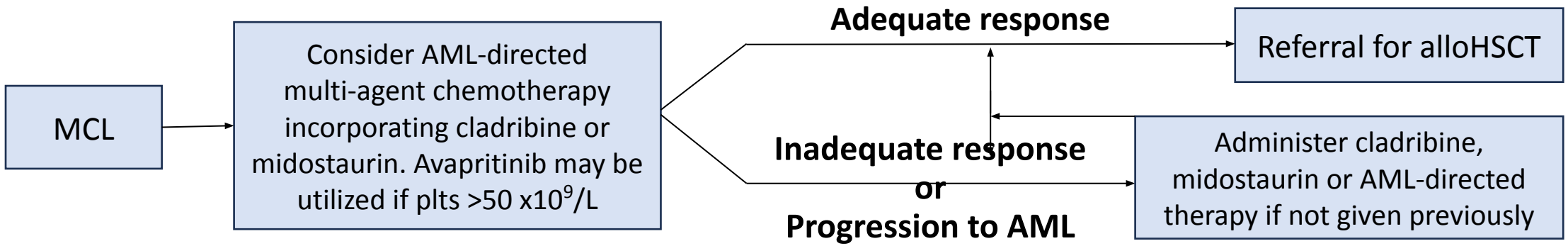
Criteria:

- SM
- ≥20 mast cells on BM
- Peripheral mast cell percentage is more variable

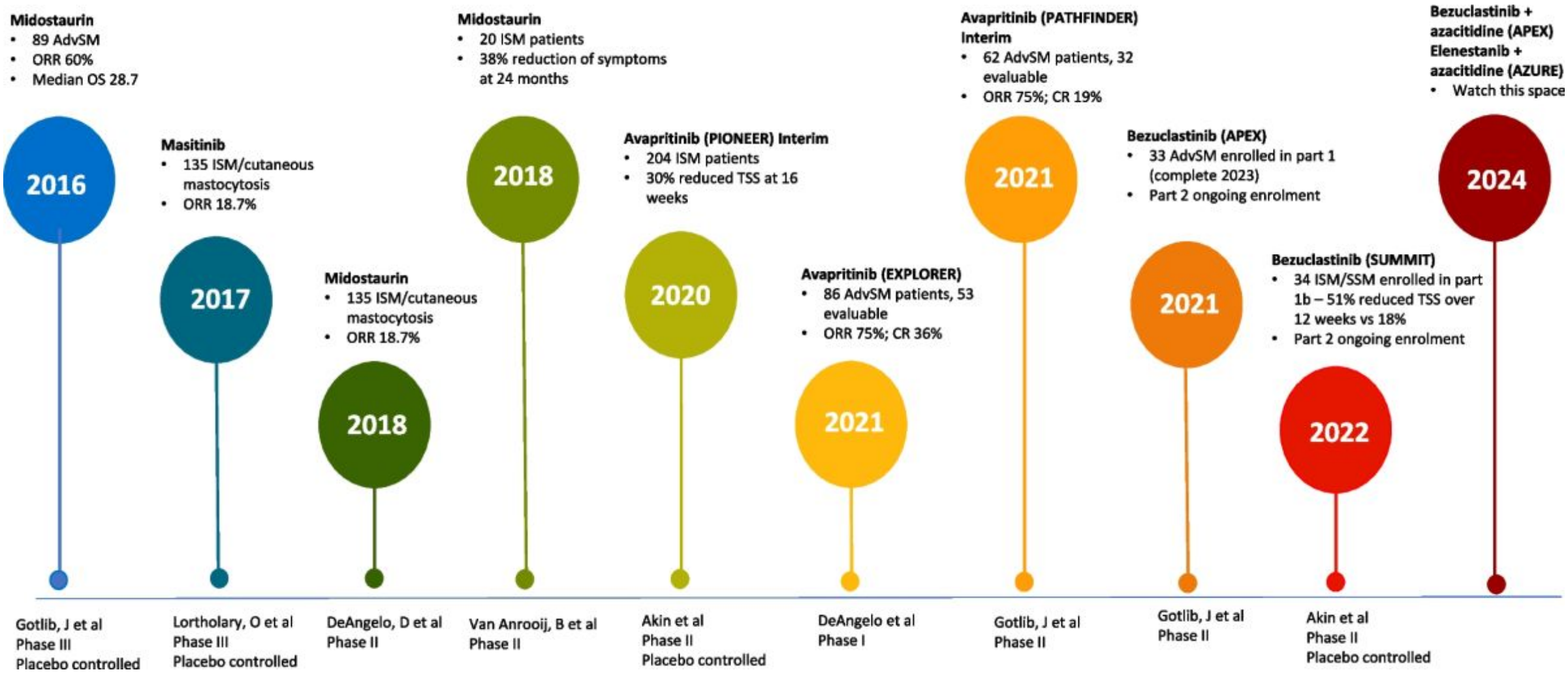
Key considerations:

- Conduct baseline DEXA scan
- Carry 2 epinephrine autoinjectors
- Counsel patients on trigger avoidance and assess QOL utilizing MSAF

Management paradigm (clinical trial preferred):



Valent P et al.,., *Hemasphere*, 2021
NCCN., *Systemic Mastocytosis*, 2025



Farmer, I., Radia, D.H., *Curr Hematol Malig Rep*, 2024.

Takeaways

- Recognition of SM is complex and may be recognized by many specialists outside of Hematology
- Management is:
  - Multidisciplinary
  - Nuanced
  - Evolving as clonal architecture evolves
- Enroll patients on clinical trials whenever possible

References

- Chia SL, Kapoor S, Carvalho C, Bajénoff M, Gentek R. Mast cell ontogeny: From fetal development to life-long health and disease. *Immunol Rev*. 2023; 315: 31-53. doi:10.1111/imr.13191
- Scadden, D.T. (2024). Stem cells. In Molecular Hematology (eds D. Provan and H.M. Lazarus).
- Gao, J., Zhao, D., Nouri, H.R., Chu, H.W. and Huang, H. (2025), Transcriptional Regulation of Mouse Mast Cell Differentiation and the Role of Human Lung Mast Cells in Airway Inflammation. Immunol Rev, 331: e70026.
- Noto CN, Hoft SG and DiPaolo RJ (2021) Mast Cells as Important Regulators in Autoimmunity and Cancer Development. Front. Cell Dev. Biol. 9:752350. doi: 10.3389/fcell.2021.752350
- Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. N Engl J Med. 2015 Nov 5;373(19):1885-6. doi: 10.1056/NEJMc1510021. PMID: 26535528.
- Gerds et al., NCCN Guidelines on systemic mastocytosis, v3.2026 [Accessed 16 Jul 2026; available from https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf].
- Rets and T. I. George, " Diagnosing Systemic Mastocytosis: State of the Art," International Journal of Laboratory Hematology 48, no. 3 (2026): 551–560, https://doi.org/10.1111/ijlh.70011.

References

- Valent P, et al. Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal. Hemasphere. 2021 Oct 13;5(11):e646. doi: 10.1097/HS9.0000000000000646. PMID: 34901755; PMCID: PMC8659997.
- van Anrooij B, Kluin-Nelemans JC, Safy M, Flokstra-de Blok BM, Oude Elberink JN. Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis. Allergy. 2016 Nov;71(11):1585-1593. doi: 10.1111/all.12920. Epub 2016 Jun 23. PMID: 27089859.
- Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023; 98(7): 1097-1116.
- Tefferi, A., Shah, S., Lasho, T.L., Patnaik, M.M., Reichard, K.K., Hanson, C.A., Ketterling, R.P. and Pardanani, A. (2018), Practice-relevant demarcation of systemic mastocytosis associated with another hematologic neoplasm. Am J Hematol, 93: E383-E386.
- Farmer, I., Radia, D.H. Systemic Mastocytosis: State of the Art. Curr Hematol Malig Rep 19, 197–207 (2024).

MOFFITT CANCER CENTER

Thank you!