Indolente systemische Mastozytose
-
eine hämatologische Erkrankung?

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Offenlegung Interessenskonflikte

Beratungs- bzw. Gutachtertätigkeit: Novartis, Blueprint

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Klassifikation der SM nach WHO 2016

- **Indolente systemische Mastozytose (ISM)**
- “Smoldering” Systemische Mastozytose (SSM)
- Systemische Mastozytose mit assoziierter hämatologischer Neoplasie (SM-ASH)
- Aggressive sytemische Mastozytose (ASM)
- Mastzellleukämie (MCL)

Classification ICC 2022 vs WHO2002

ICC

- Cutaneous mastocytosis
  - Urticaria pigmentosa / maculopapular cutaneous mastocytosis
  - Diffuse cutaneous mastocytosis
  - Mastocytoma of skin
- Systemic mastocytosis
  - **Indolent systemic mastocytosis (includes bone marrow mastocytosis)***
  - Smoldering systemic mastocytosis*
  - Aggressive systemic mastocytosis*
  - Mast cell leukemia
  - Systemic mastocytosis with an associated myeloid neoplasm
- Mast cell sarcoma

*diagnosis of these variants require correlation with B and C findings

WHO

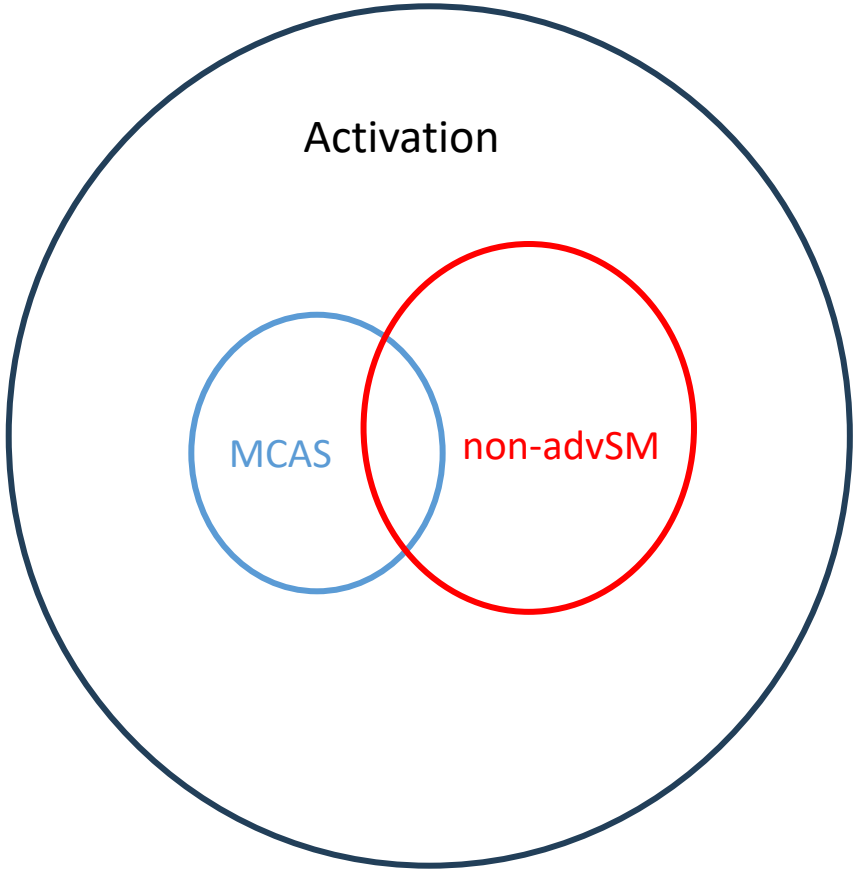
- Cutaneous mastocytosis
  - Urticaria pigmentosa / maculopapular cutaneous mastocytosis
    - Monomorphic
    - Polymorphic
  - Diffuse cutaneous mastocytosis
  - Cutaneous mastocytoma
    - Isolated mastocytoma
    - Multilocalized mastocytoma
- Systemic mastocytosis
  - **Bone marrow mastocytosis**
  - **Indolent systemic mastocytosis**
  - Smoldering systemic mastocytosis
  - Aggressive systemic mastocytosis
  - Systemic mastocytosis with an associated haematologic neoplasm
  - Mast cell leukemia
- Mast cell sarcoma

Classification ICC 2022 vs WHO2002

	ICC	WHO
B-findings	>30% BM cellularity by MCs in histology **and** serum tryptase >200 ng/ml **and/or** KIT D816V VAF >10% in BM or PB leukocytes	>30% of BM cellularity by MC aggregates (assessed on BM biopsy) **and** serum tryptase >200 ng/mL
	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 (not meeting criteria for C-findings) or cytosis. Reactive causes are excluded, and criteria for other myeloid neoplasms are not met.
	Palpable hepatomegaly without ascites or other signs of organ damage **and/or** palpable splenomegaly without hypersplenism and without weight loss **and/or** lymphadenopathy (>2 cm)	Hepatomegaly without impairment of liver function **and/or** splenomegaly without features of hypersplenism including thrombocytopenia **and/or** lymphadenopathy (>1 cm size) on palpation or imaging
	BMM: no B-findings, absence of skin lesions a basal serum tryptase <125 mg ***ISM <2 B-findings*** ***SSM ≥2 B-findings***	***ISM <2 B-findings*** ***SSM ≥2 B-findings***
C-findings	Cytopenias: ANC <1×10⁹/L and/or Hb <100 g/L and/or platelets <100×10⁹/L	
	Hepatopathy: ascites and elevated liver enzymes±hepatomegaly or cirrhotic liver±portal hypertension	
	Spleen: palpable splenomegaly with hypersplenism±weight loss±hypoalbuminemia	
	GI tract: malabsorption with hypoalbuminemia±weight loss	
	Bone: large-sized osteolysis (≥2 cm) with pathologic fracture±bone pain **ASM 1 or more C-findings/SM-AHM/AMN and MCL may not have C-findings**	

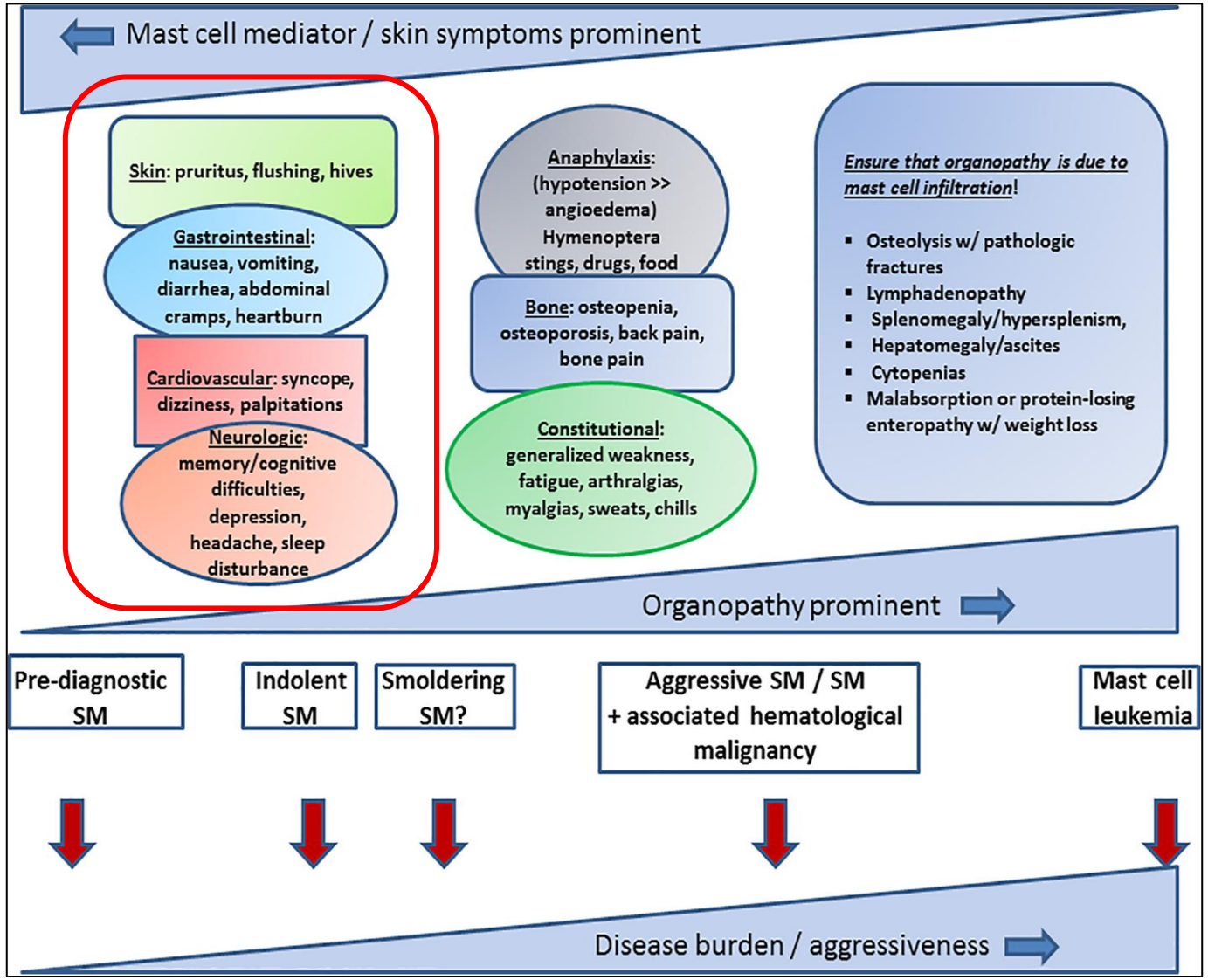
Veitch and Radia, ASH, 2023

Indolent systemic mastocytosis – an allergological diagnosis?



Akin, Blood, 2022

Indolent systemic mastocytosis – an allergological diagnosis?



Paradanani, AJH, 2021

How is a hematological disease defined?

1. the disease-defining cells are derived from haematopoietic cells
2. clonal proliferation of the disease-defining cells
3. clonal evolution/progression into a more aggressive disease

ISM a hematological disease?

1. the disease-defining cells are derived from haematopoietic cells
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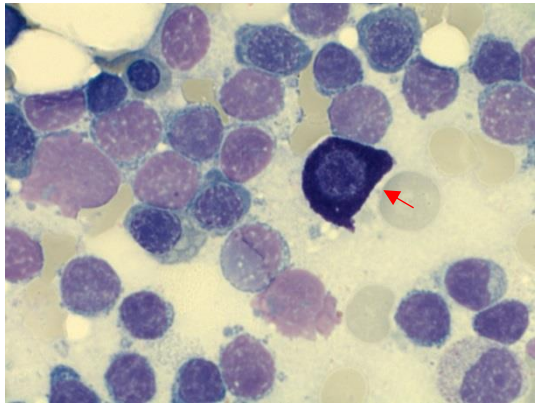
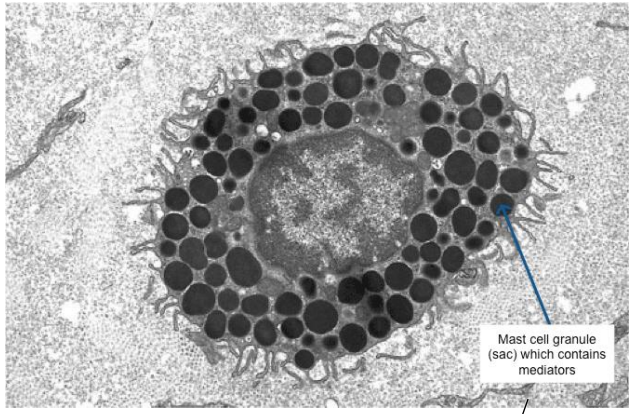
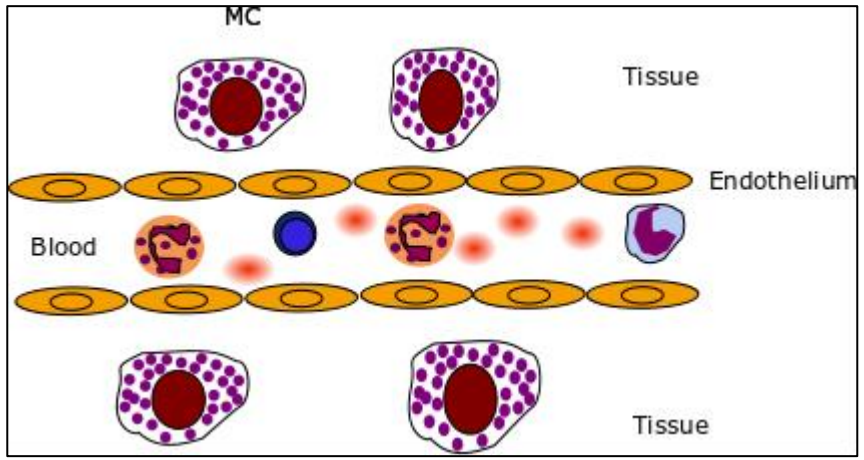
Mast cell biology

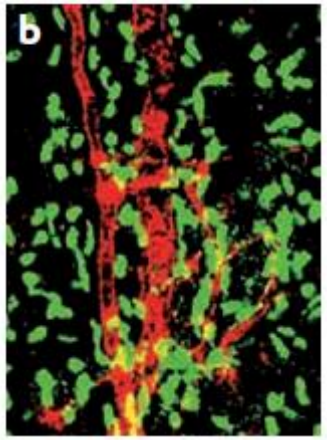




50–200 large granules

1. bioactive amines (Histamine, PGD2 and LTC4)
2. proteoglycans (Heparine)
3. proteases (Tryptase)





- long-lived (month to years)
- highly heterogeneous and phenotypically malleable cells
- in mucosal and epithelial tissues throughout the body
- involved in innate and adaptive immunsystem
- IgE-mediated allergic reactions through the FcεRI receptor

Abraham and St. John; Nature Review Imm, 2010

Mast cell biology – mast cell subtypes

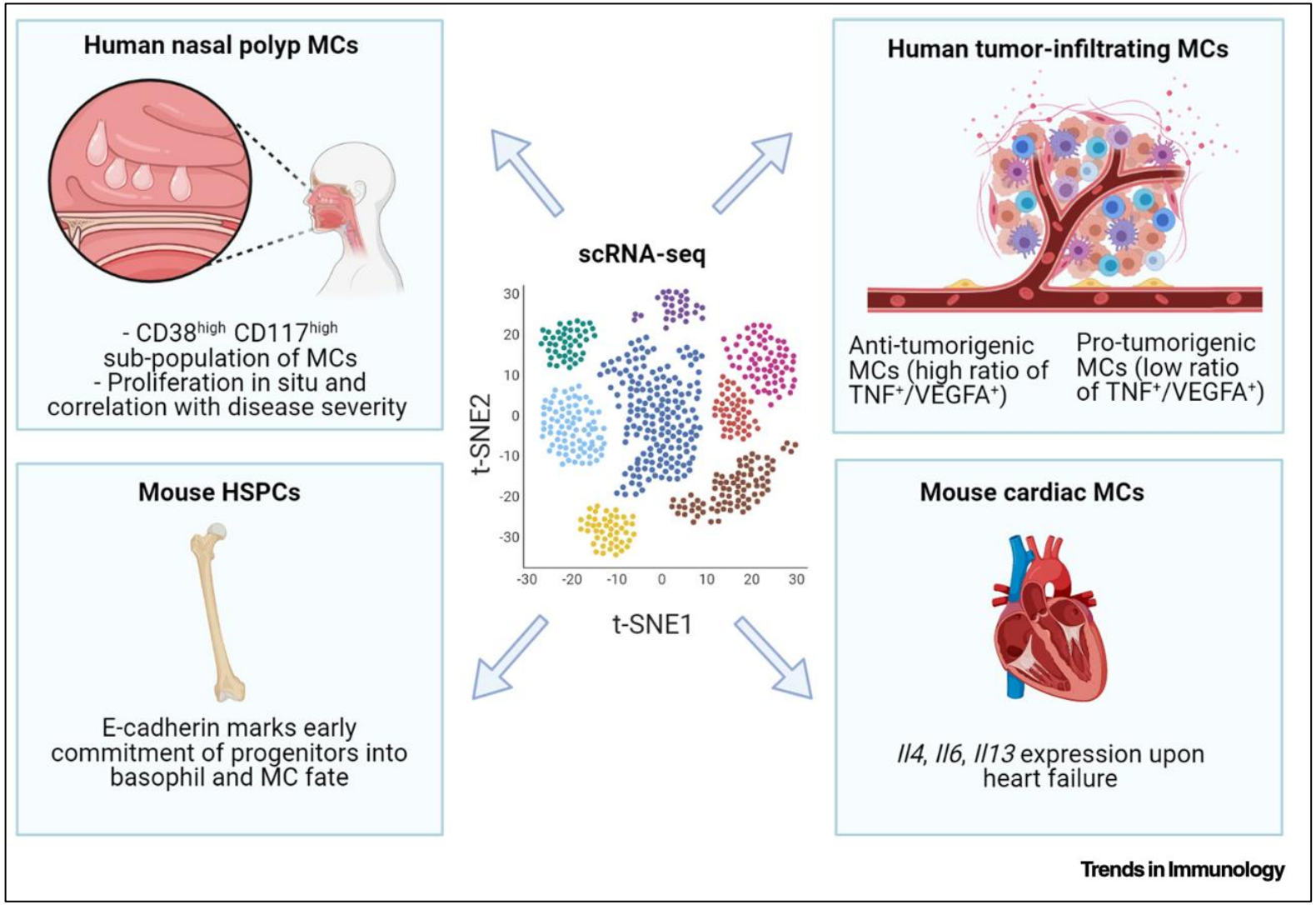
Three MC subpopulations in humans:

1. **Tryptase^{+} chymase^{+}**
    1. expression of tryptase, chymase, carboxypeptidase, and Cathepsin G and are predominantly localized within connective tissues including skin, airway smooth muscle, submucosa of gastrointestinal (GI) tract

2. **Tryptase^{+} chymase^{-}**
    1. dominant MC subtype and are typically found at mucosal surfaces including the respiratory and gastrointestinal (GI) mucosa

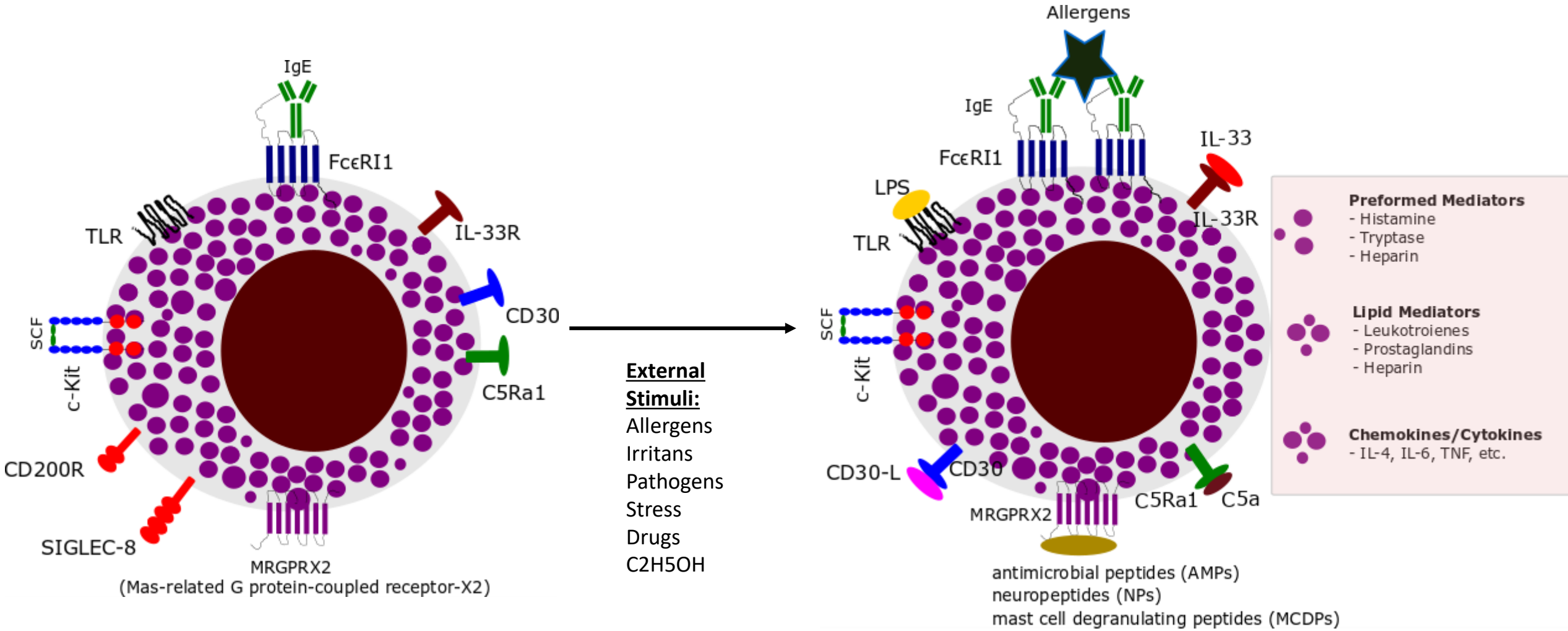
3. **Tryptase^{-} chymase^{+}**
    1. rare MC subtype are identified within the submucosa and mucosa of the stomach, lung, and endometrial tissue

Mast cell biology – new subtypes based on scRNA Seq analysis



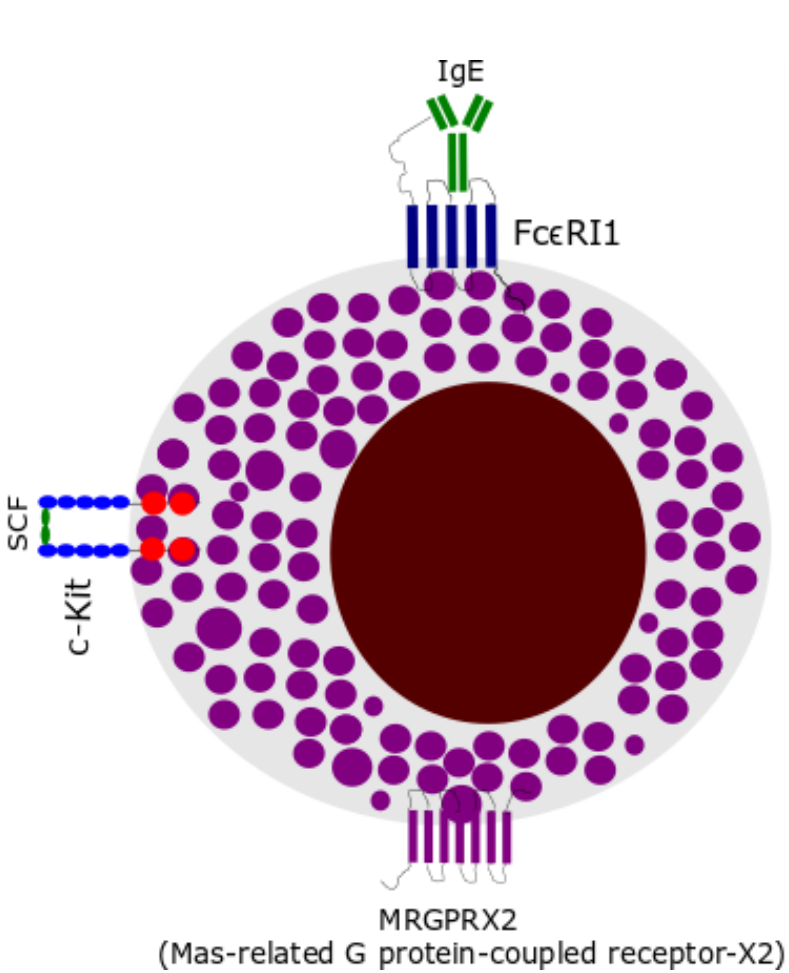
Cildir et al., Trends in Imm, 2021

Normal Mast cells - Activation

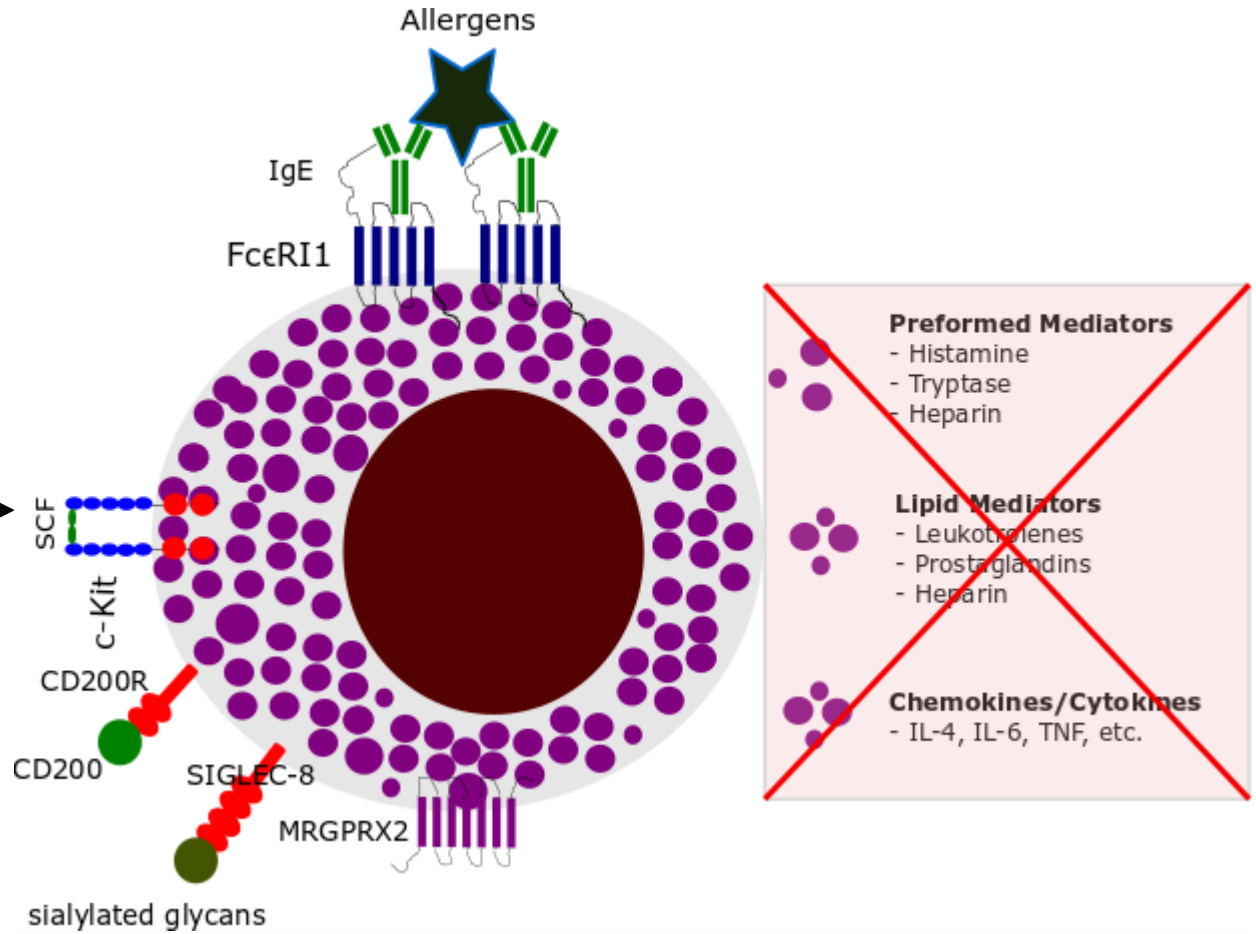


Giannetti A., Ann Allergy Asthma Immunol 127 (2021), Dahlin et al., Allergy, 2021

Normal Mast cells - Silencing

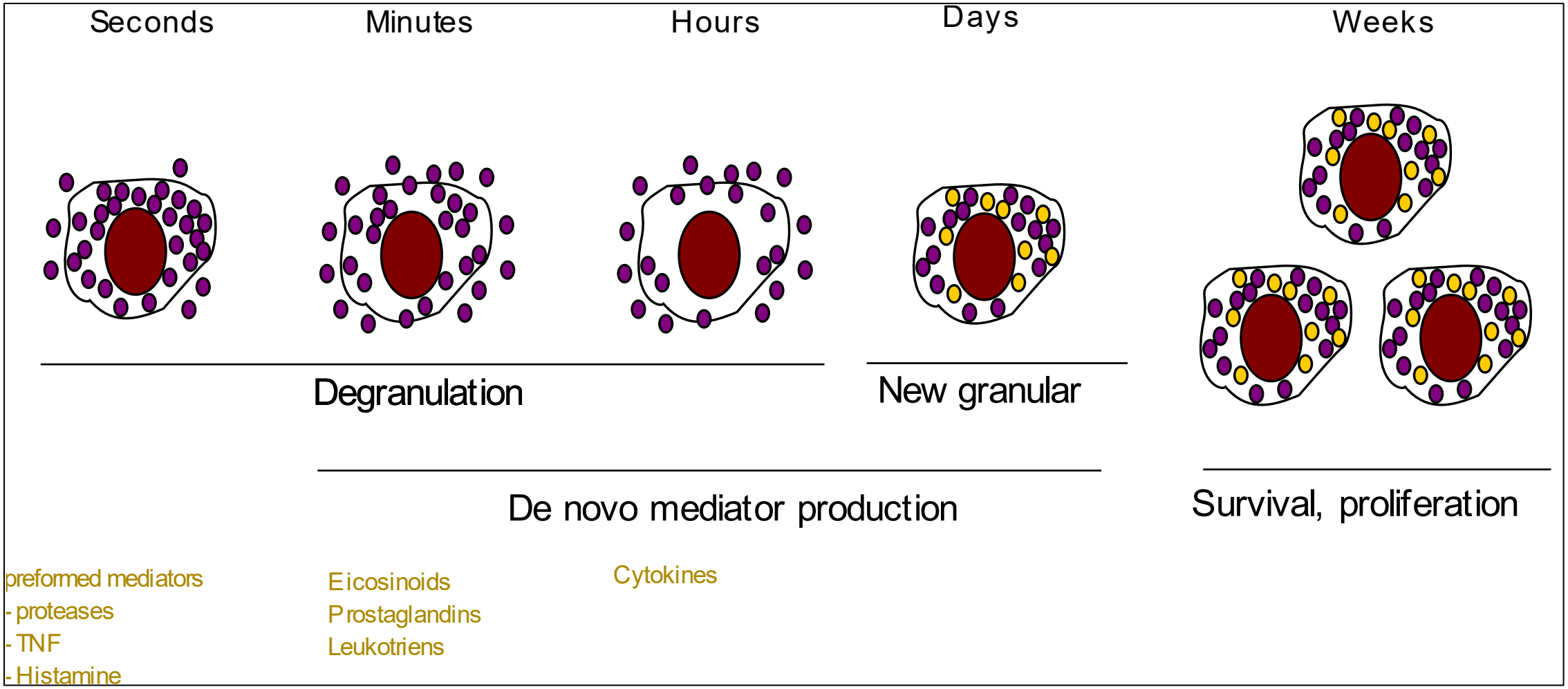


External Stimuli:
Allergens
Irritans
Pathogens
Stress
Drugs
C2H5OH



Giannetti A., Ann Allergy Asthma Immunol 127 (2021), Dahlin et al., Allergy, 2021

Mast cells – Mediator release



Mast cells – physiological roles

Innate immunity

- assist in innate defense against bacterial
  - mediated through toll-like receptors (TLRs) on the mast cell surface
  - complement activation

- phagocytose bacteria (*Salmonella typhi*)

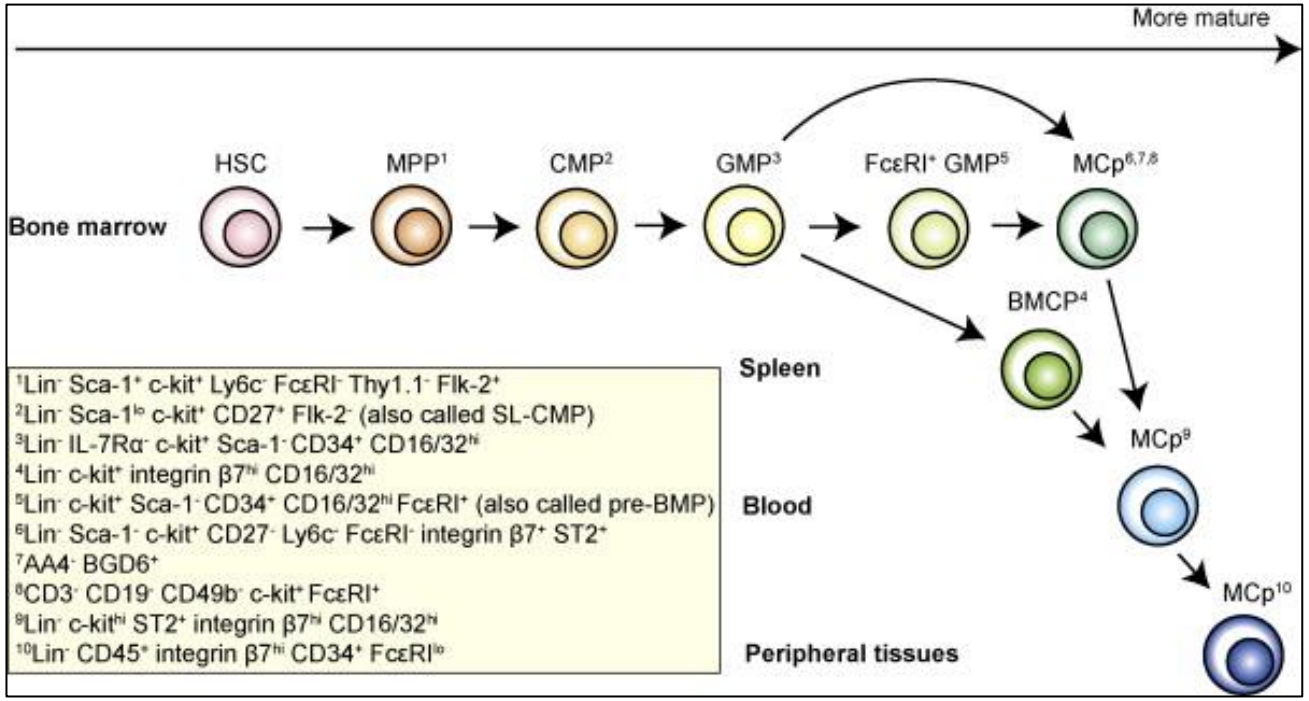
- early defense aggainst virus infection
  - Relase cytokines and chemotactic mediators

- produce antimicrobial peptides (cathelicidins) and amplify complement activation

- MC protease can degrade and thus protect against some toxins

- MC cytokines are crucial to the early and effective recruitment of neutrophils and other leukocytes to sites of infection

Differentiation from hematopoietic stem cells to mast cells



- hematopoietic stem cells (HSCs) in the bone marrow (BM) and yolk sac in both mice and humans
- Circulating mast cell progenitors move to target tissue
- 7 mont after aloogeneic PBSCT mast cells are dornor-derived
- in vitro CD34+ cells BM cells give rise to mast cells

Grootens et al., Blood Adv, 2018

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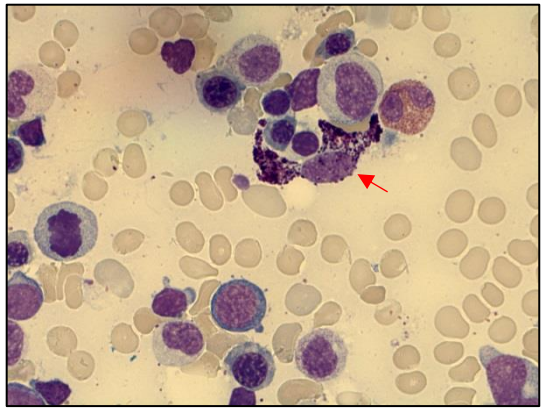
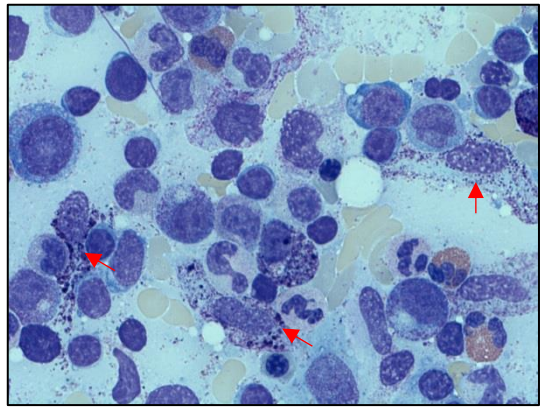
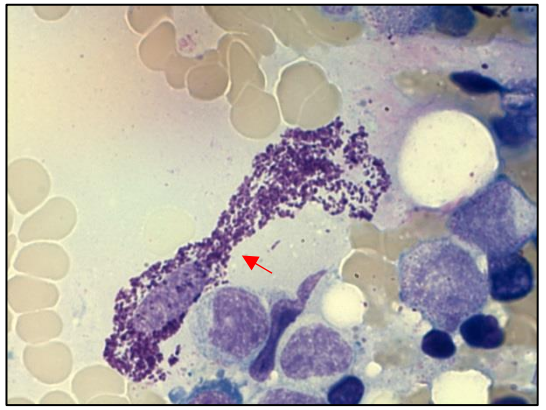
Atypical Mast cells

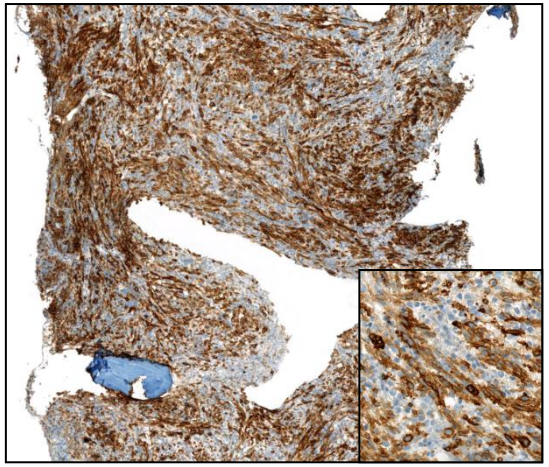
Bone marrow aspirate



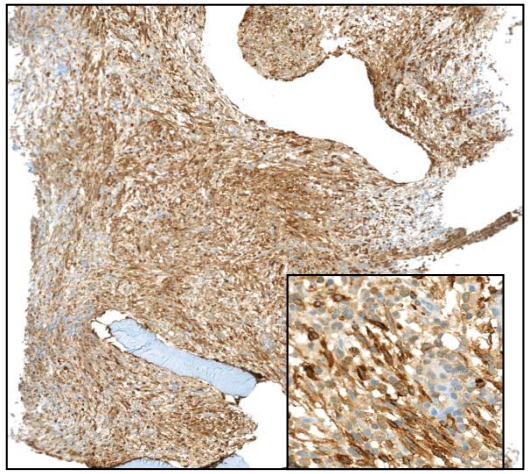




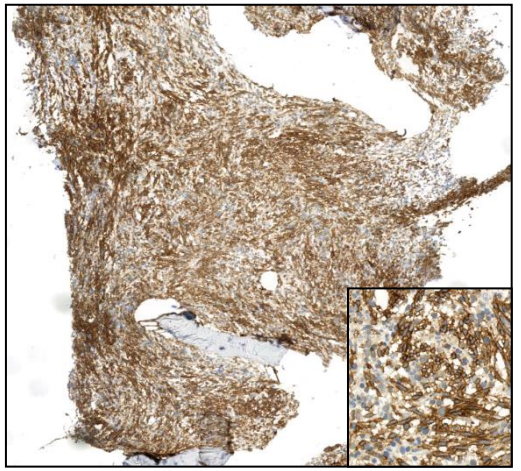
Bone marrow biopsy



CD117



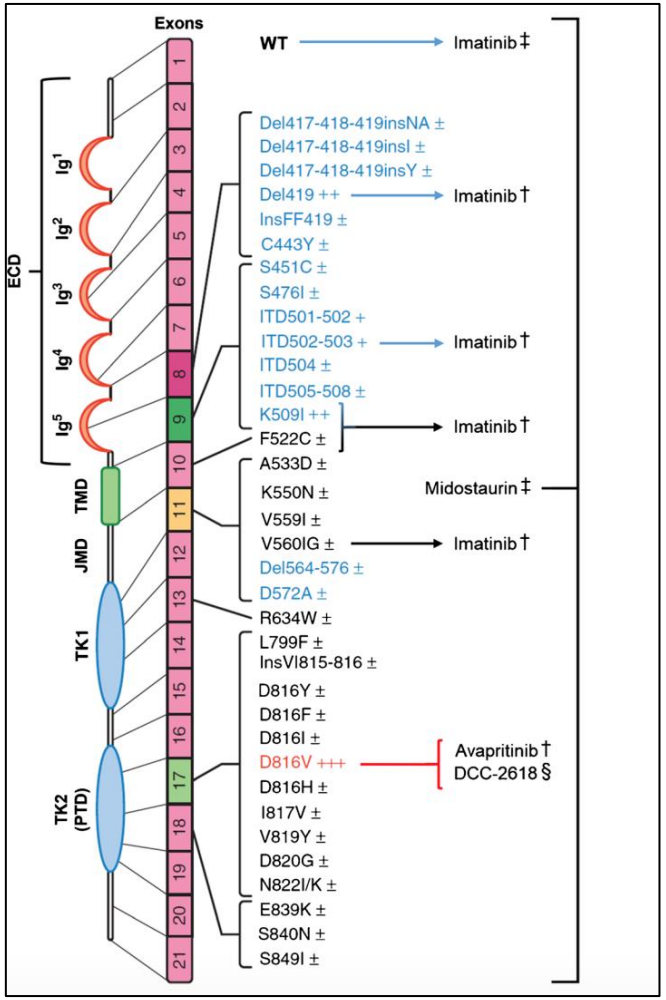
Tryptase

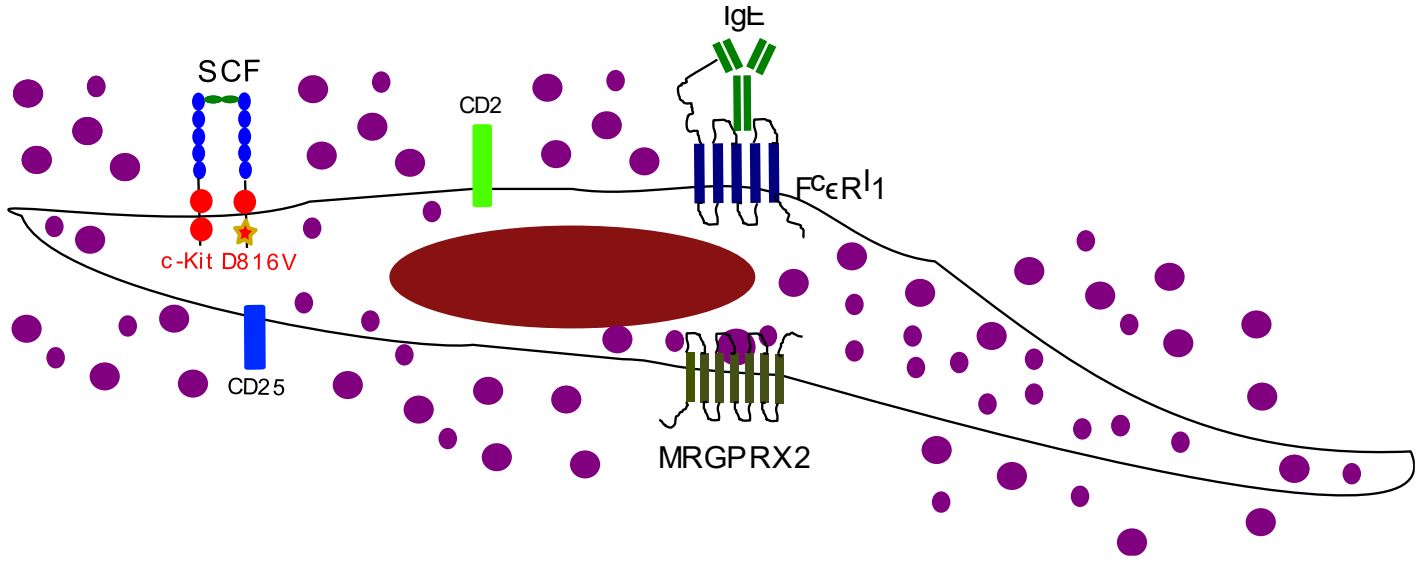


CD25

Pathogenesis – c-Kit Mutations

c-Kit Mutationen
(>90% der Patienten)



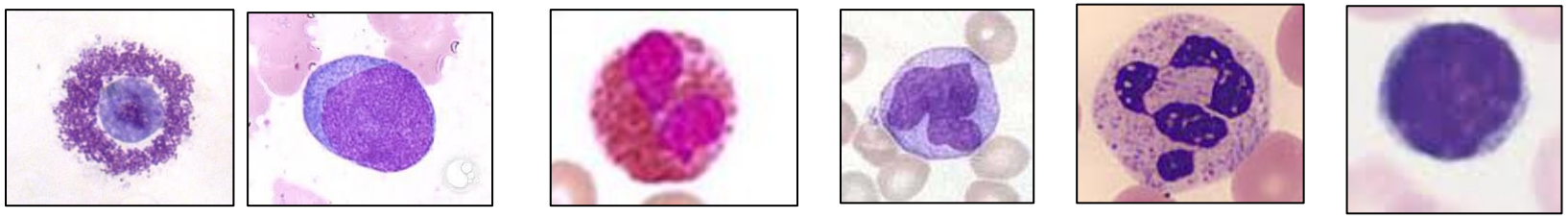


- unrestrained growth of MCs
- lowered threshold for activation (degranulation)

Baird and Gotlib, Current Hematologic Malignancy Reports (2018)

Systemic Mastocytosis - Pathogenesis

FACS- purified populations of BM MCs (n = 113) and other BM cell compartments (n = 67) from adults with SM

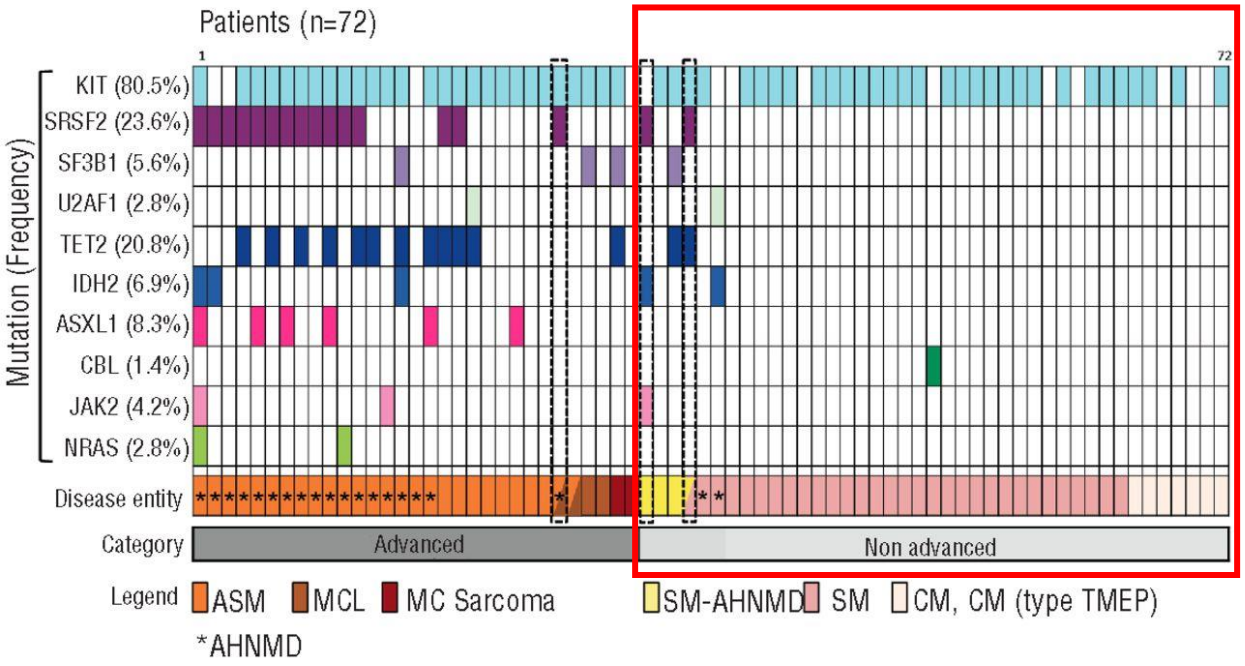


Category	Mast cells	CD34⁺ HPCs	Eosinophils	Monocytes	Neutrophils	Lymphocytes
MCL	2/2 (100)	2/2 (100)	1/1 (100)	NA	1/1 (100)	N
ISM	43/43 (100)	9/38 (24)	9/42 (21)	4/37 (11)	3/37 (8)	1/10 (10)
ASM	5/5 (100)	3/4 (75)	4/5 (80)	3/4 (75)	4/5 (80)	3/4 (75)
SM-AHNMD	9/9 (100)	6/9 (67)	6/9 (67)	5/8 (63)	4/7 (57)	2/5 (40)

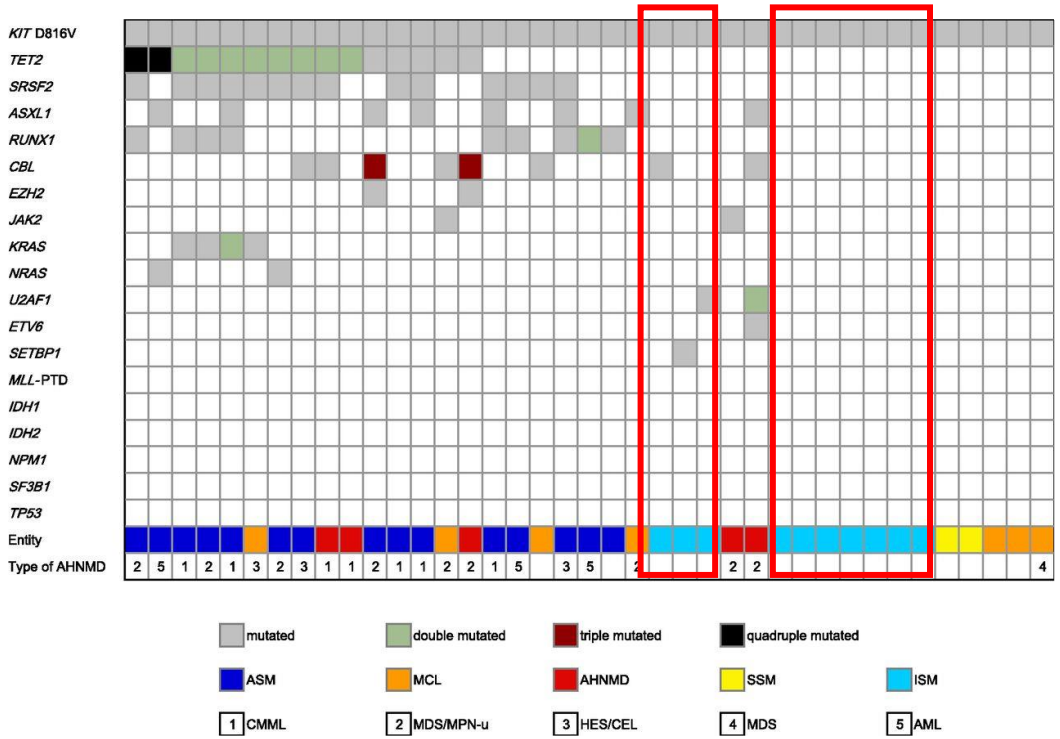
Garcia-Mentero et al., Blood, 2006

Systemic Mastocytosis - Pathogenesis

additional somatic mutations



- 39 Patienten mit SM: ISM (n=10), SSM (n=2), SM-AHN (n=5), ASM (n=15), MCL (n=7)



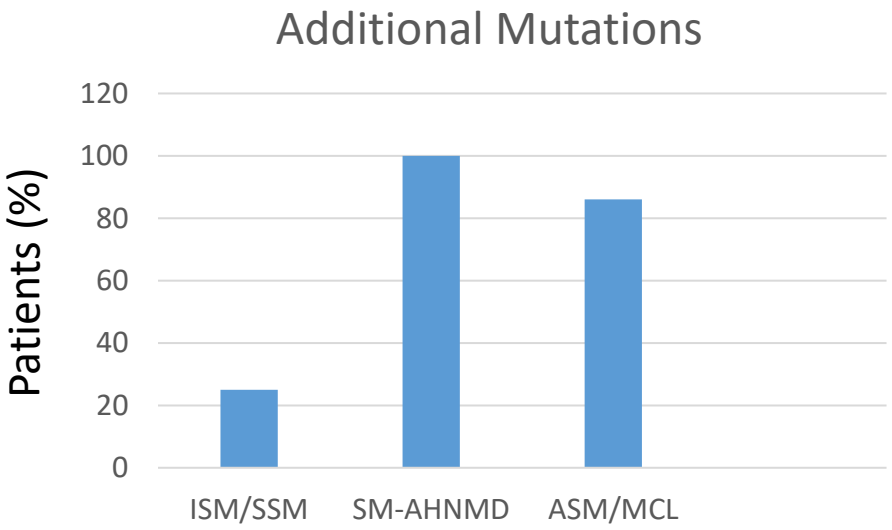
Most frequent mutations: TET2, SRSF2, ASXL1, RUNX1, and CBL

Hanssens et al. Haematologica 2014

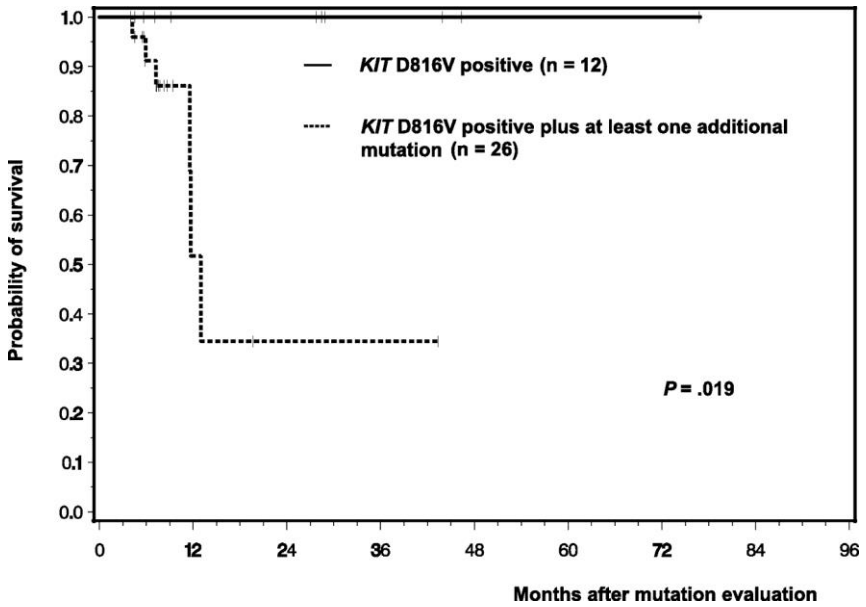
Schwaab et al., Blood, 2013

Systemic Mastocytosis - Pathogenesis

additional somatic mutations



Survival



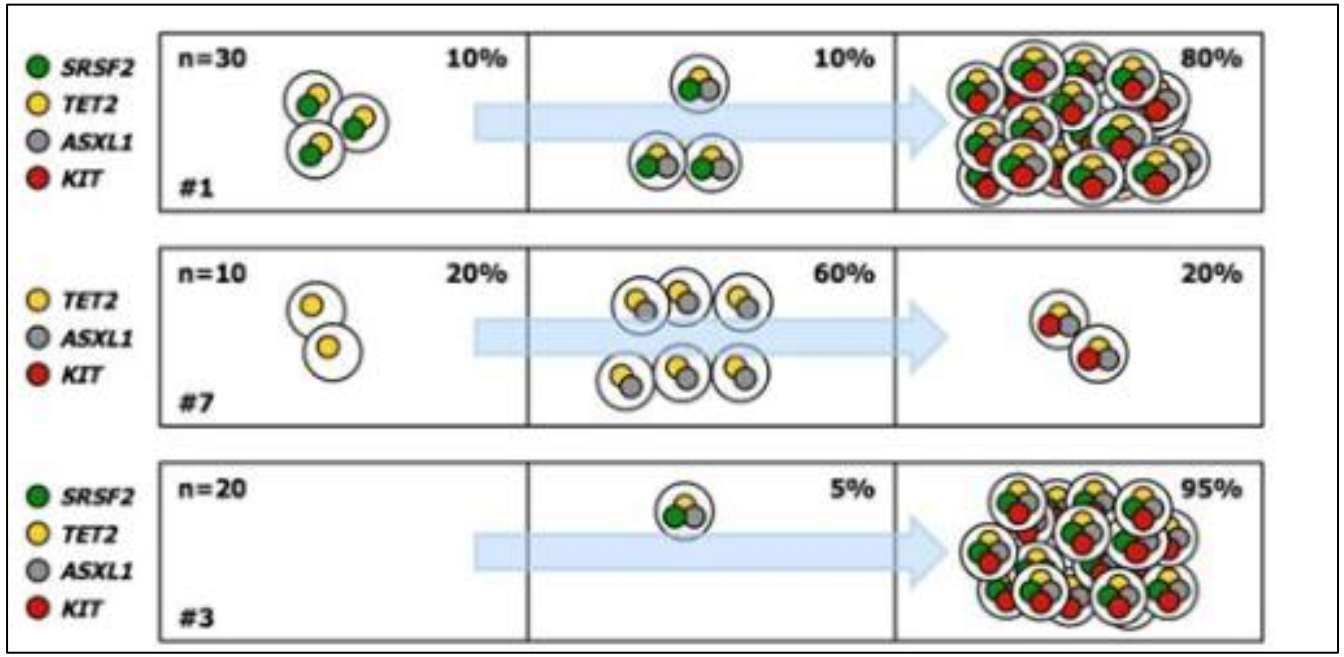
Kaplan-Meier estimates of overall survival of 38 SM patients with respect to the individual mutation status irrespective of disease subtype: 12 patients with KIT D816V alone (ISM, n = 7; SSM, n = 2; ASM, n = 3) vs 26 patients with KIT D816V

Juliana Schwaab et al. Blood 2013;122:2460-2466

Systemic Mastocytosis - Pathogenesis

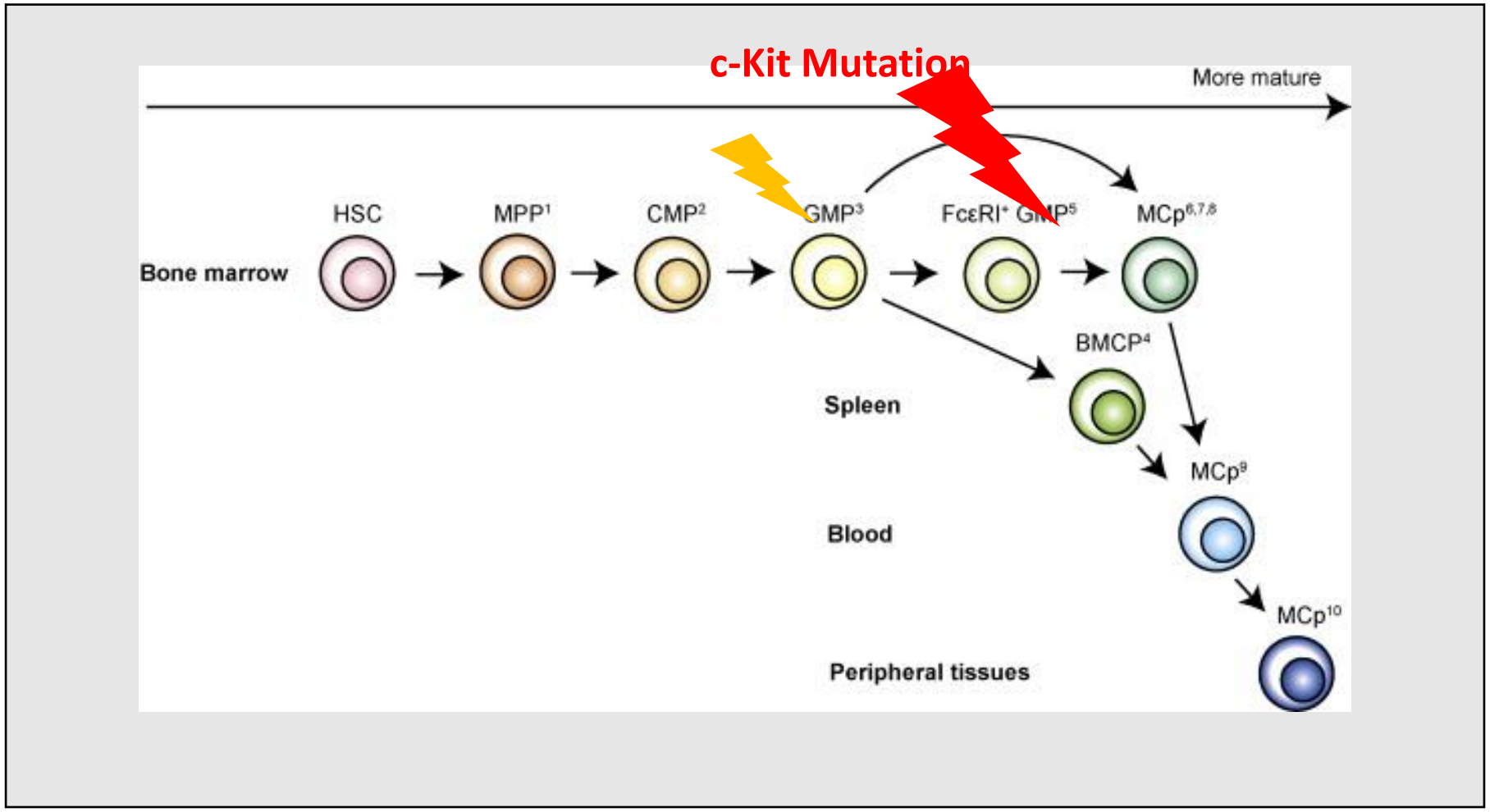
- Clonale Evolution -

- mutation status of CFU-GM using NGS in
  - indolent SM (ISM, *n*=4)
  - smoldering SM (SSM, *n*=2)
  - aggressive SM (ASM, *n*=1)
  - SM-AHNMD (*n*=5)
  - ASM-AHNMD (*n*=7)



Jawhar et al., Leukemia, 2015

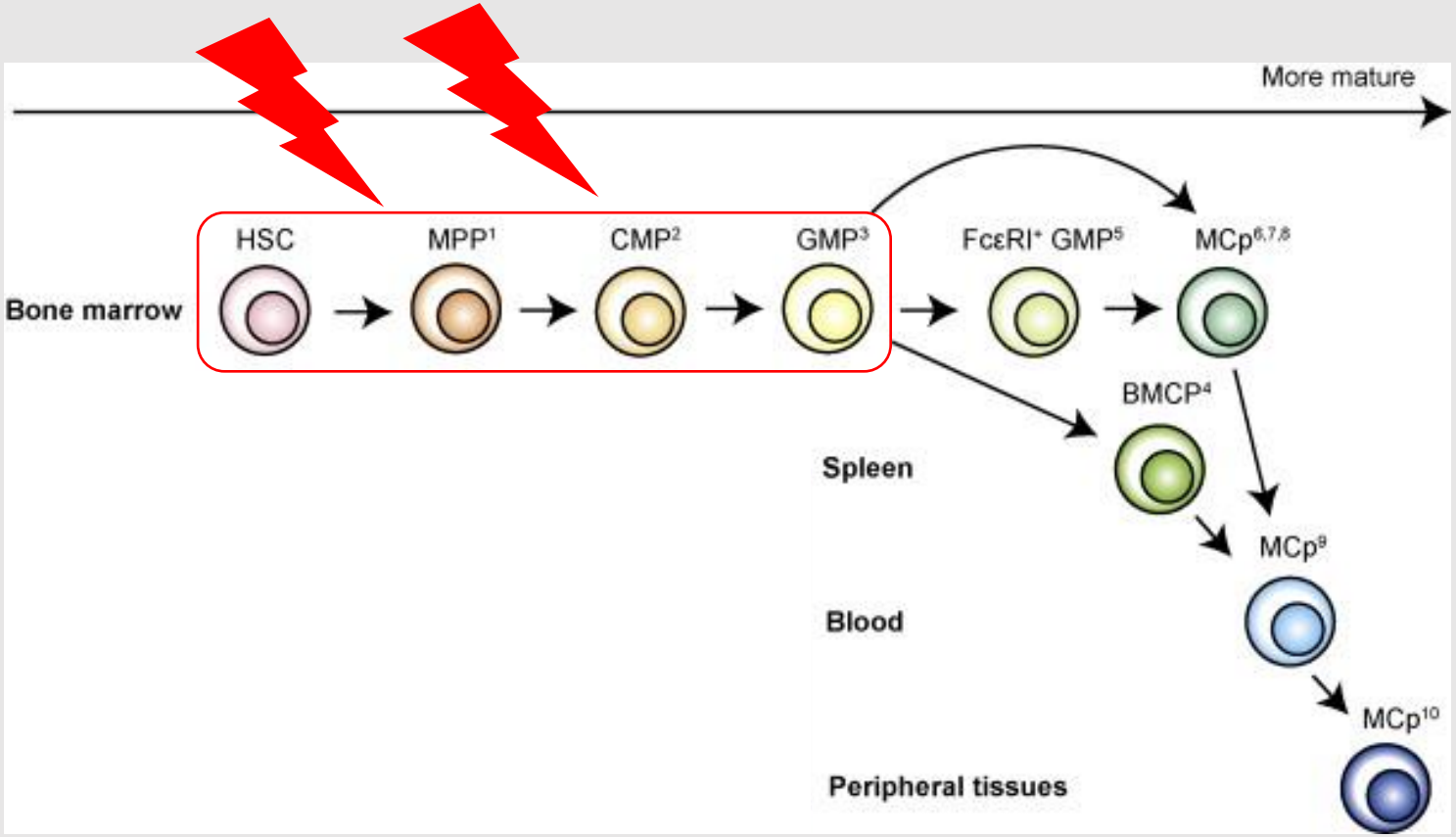
Pathogenesis – ISM/SSM



Dahlin and Hallgren, Mol Imm, 2015

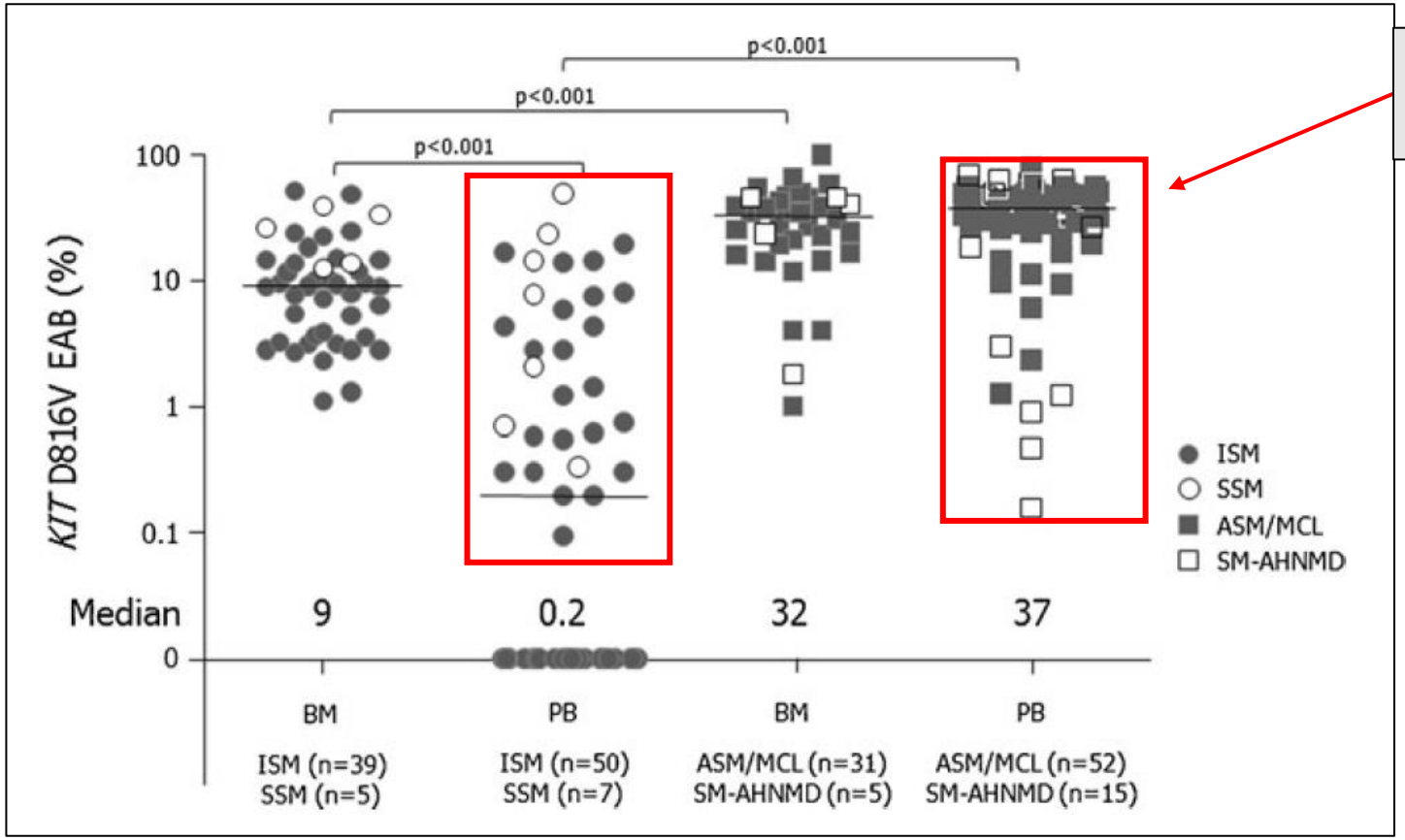
Pathogenesis - advSM

1. Hit – somat. Mutation **2. Hit - c-Kit Mutation**



Dahlin and Hallgren, Mol Imm, 2015

c-Kit Mutation Burden in Peripheral Blood

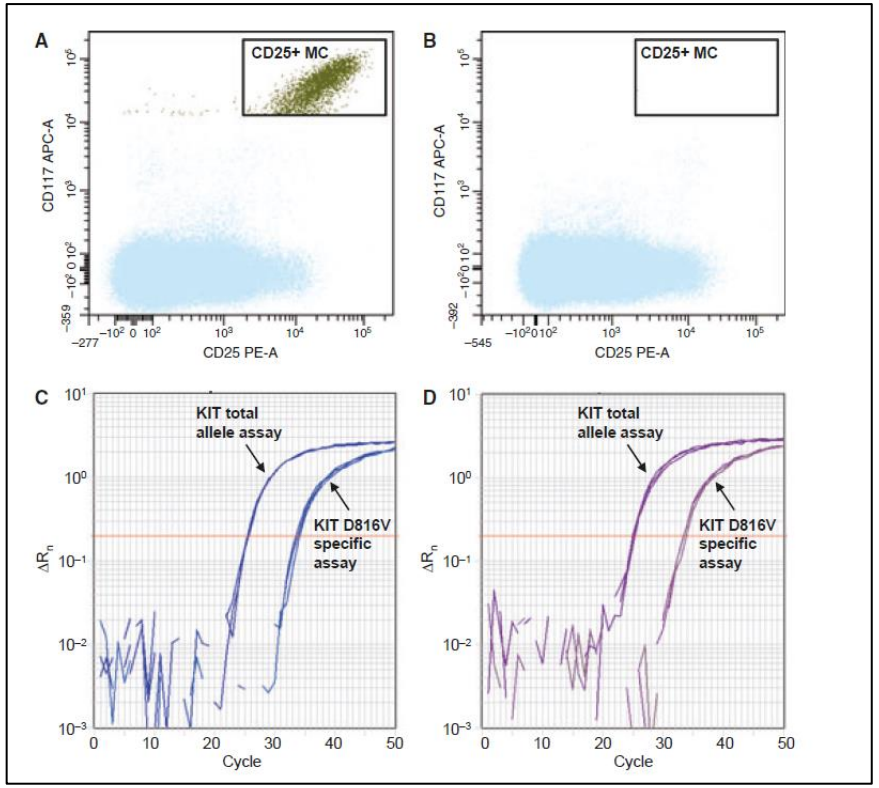


Indicator for multi-lineage Involvement

Erben et al., Ann Hematol, 2014

c-Kit Mutation Burden

- 25 patients with ISM
- RT-PCR and Flow cytometry on unfractionated cells from BM and PB



Sensitivität: 0.002 and 0.005%

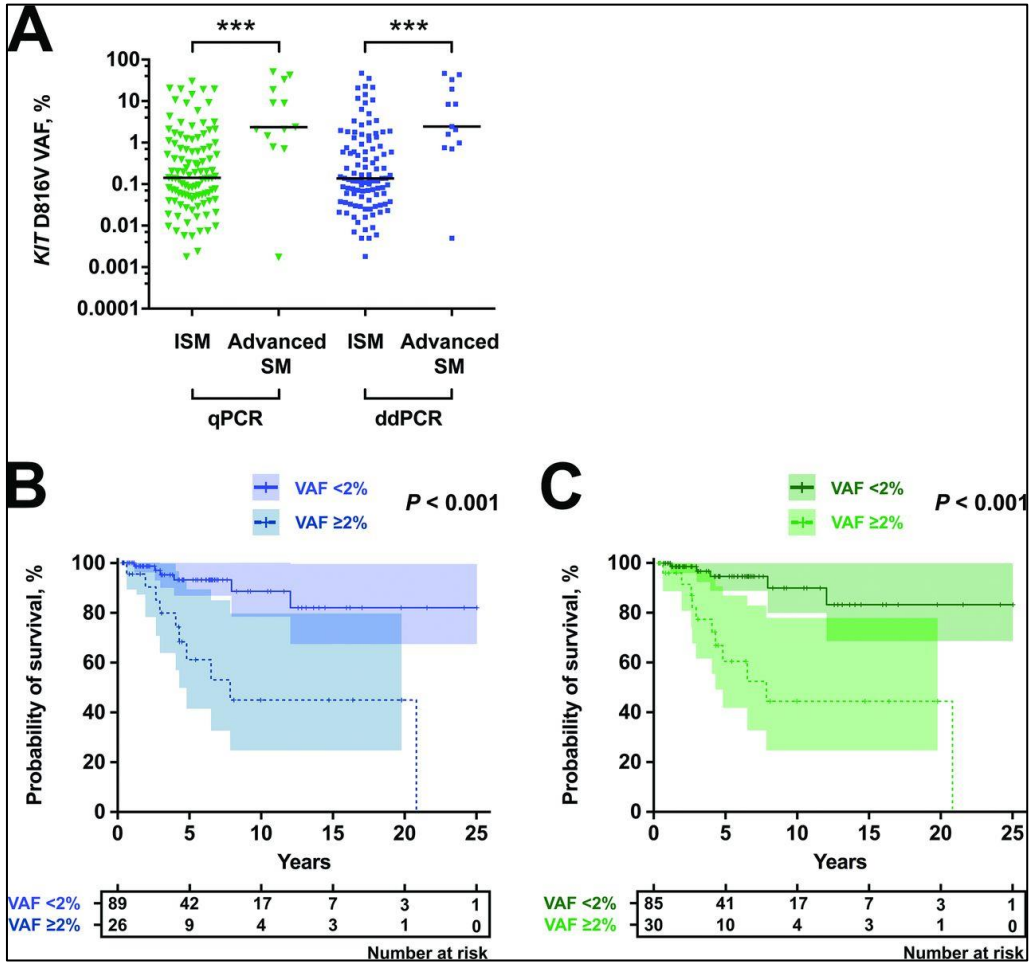
Sensitivität: 0.003%

Detection of circulating KIT D816V mutation-positive non-mast cells

Kristensen et al., Ann Hematol, 2012

c-Kit Mutationsanalyse

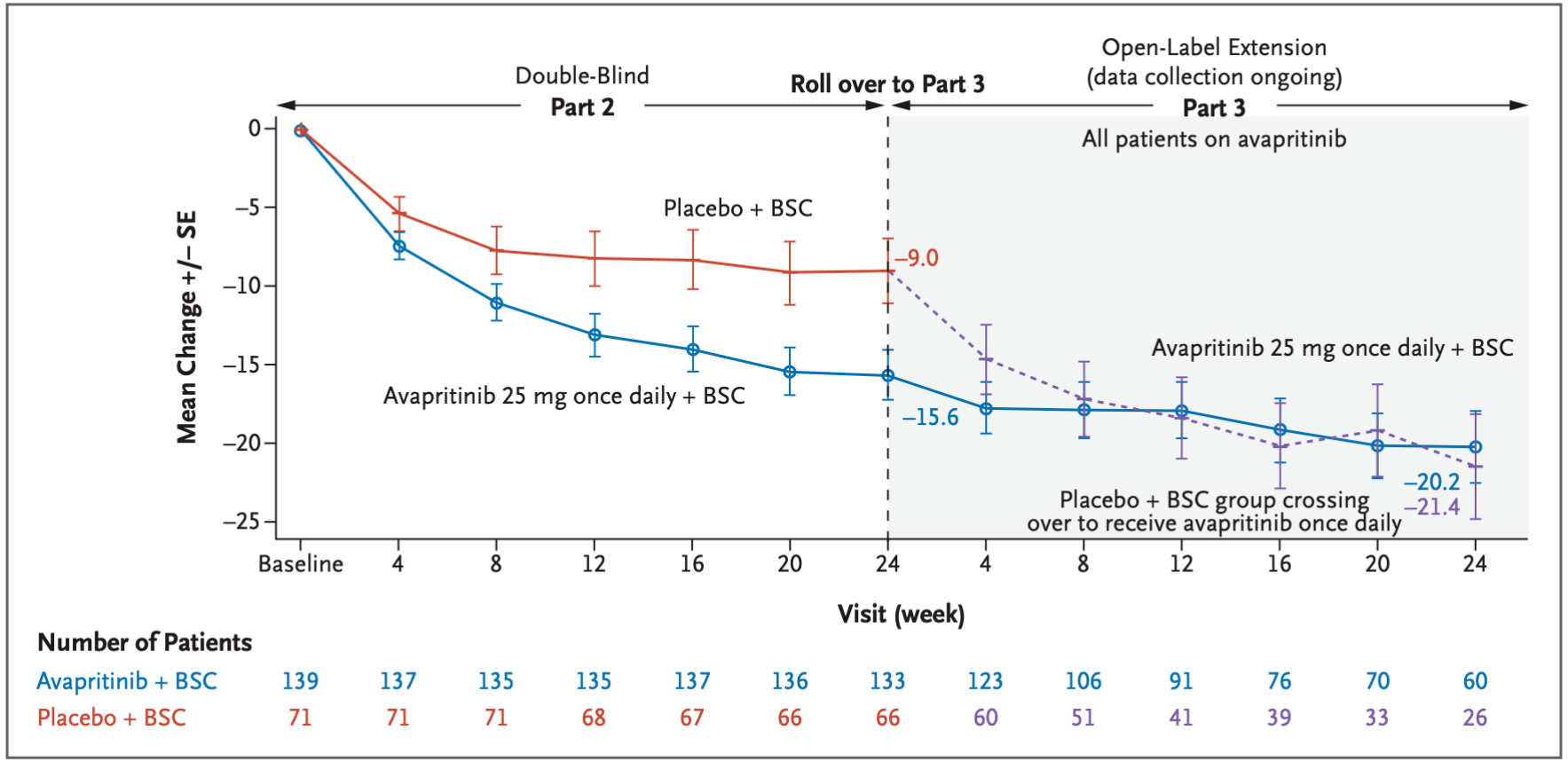
Methode	Sensitivität
Sanger-Sequenzierung	10-20%
Allel-spezifische RT-PCR	0.1-2%
Digital PCR	0.001



Greiner et al., Clin Chem, 2018

c-Kit inhibition in ISM patients

ISM Symptom Assessment Form Total Symptom Score over Time with Avapritinib versus Placebo



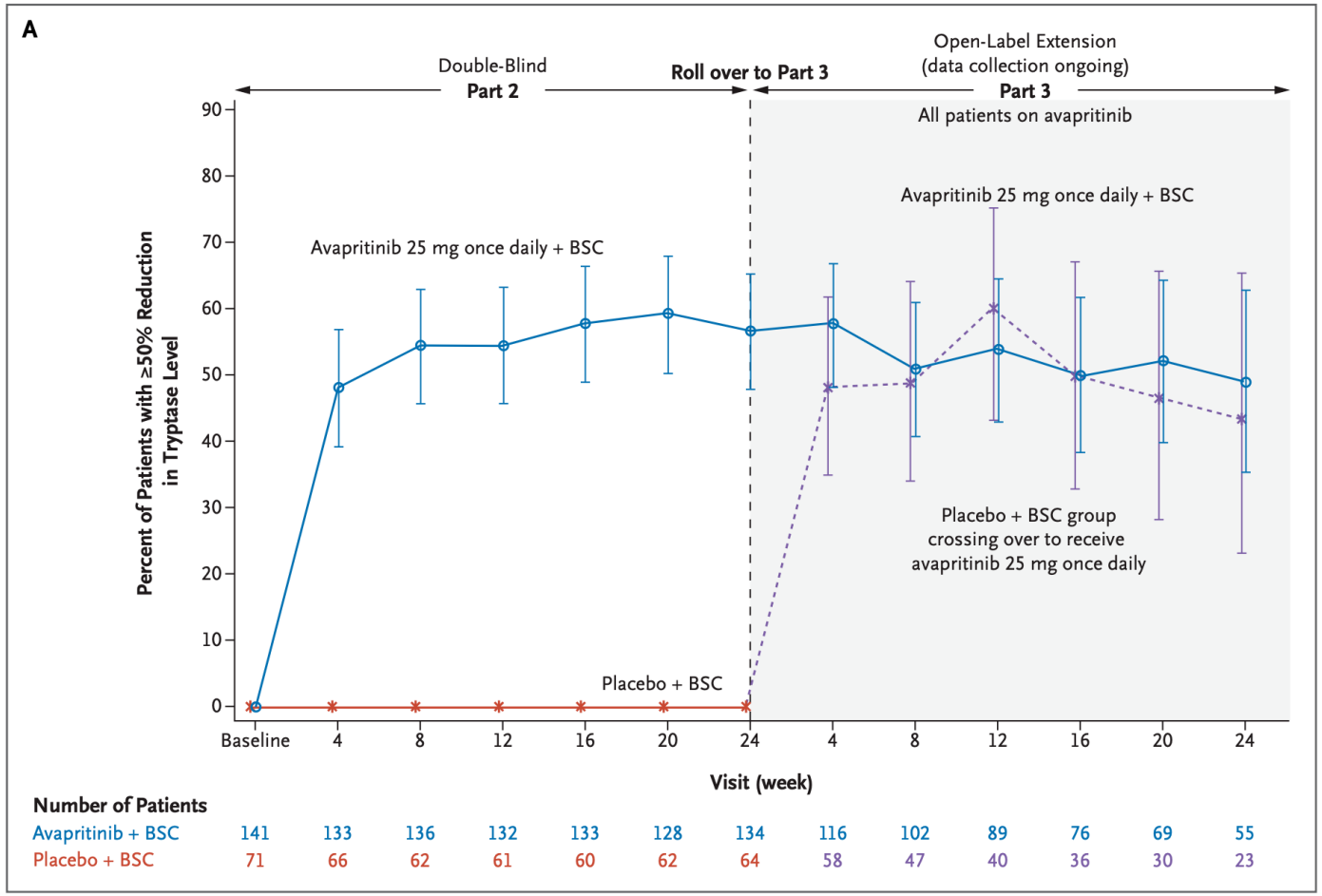
Number of Patients

Avapritinib + BSC	139	137	135	135	137	136	133	123	106	91	76	70	60
Placebo + BSC	71	71	71	68	67	66	66	60	51	41	39	33	26

Gotlib et al., NEJM Evid 2023

c-Kit inhibition in ISM patients

Reduction in Serum Tryptase over Time



Gotlib et al., NEJM Evid 2023

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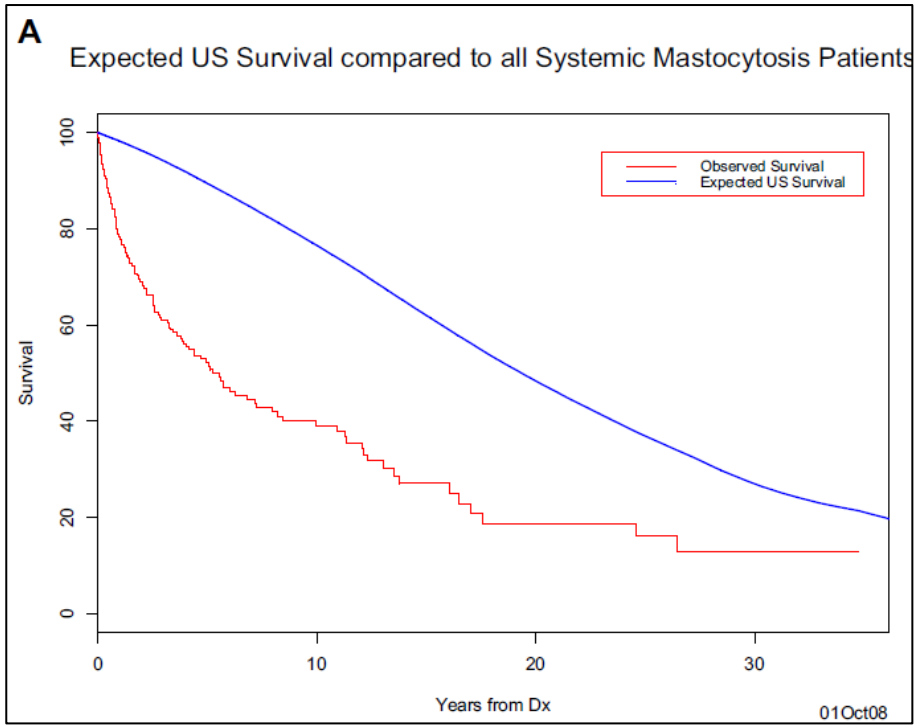
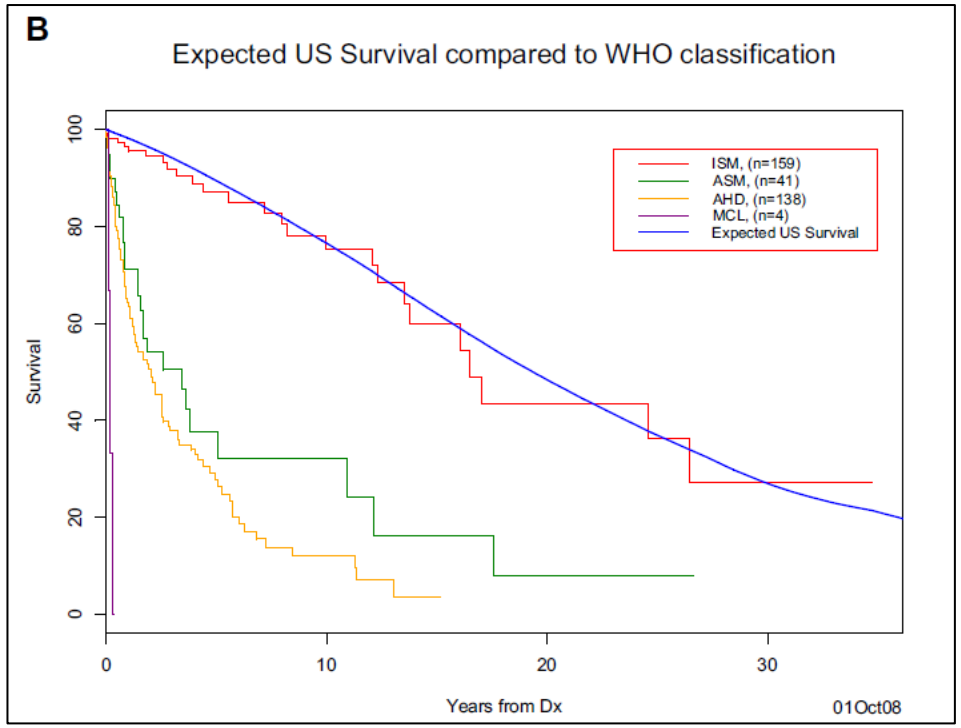
Prognose der SM

- 342 consecutive adults with SM (1976 – 2007)





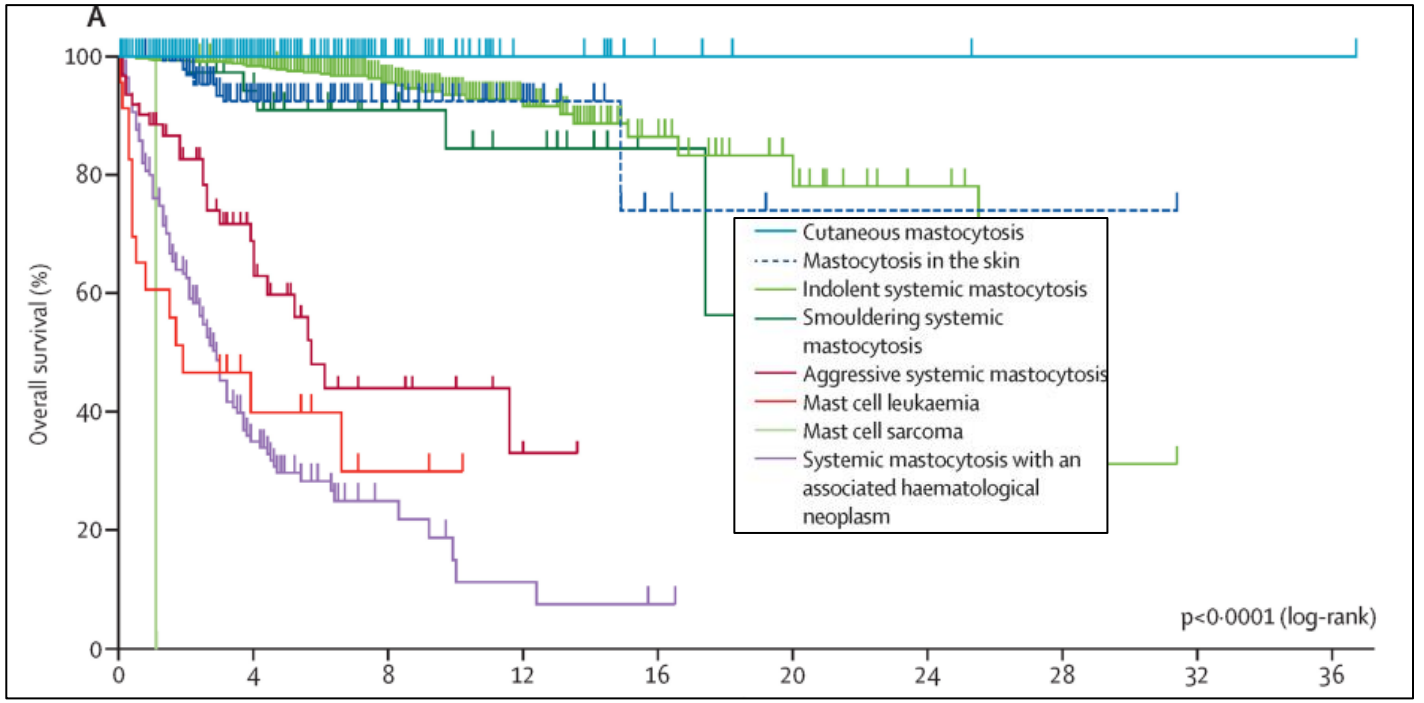
Risk Factors:

1. advanced age,
2. weight loss
3. Anemia
4. Thrombocytopenia
5. hypoalbuminemia,
6. excess bone marrow blasts as independent

Lim et al., Blood. 2009

Prognosis

N = 1641



Evaluated N = 1,006 patients with ISM
Multi-center study (ECNM registry)
Median follow-up 3.4 years

Speer et al., Lancet Hematology, 2019

Prognosis - IPSM=international prognostic scoring system for mastocytosis

	Patients (n)	Risk population	Risk of patients with non-advanced mastocytosis				Risk of patients with advanced systemic mastocytosis			
			Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
			HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Male sex	1641	..	2·01 (1·14–3·55)	0·016	1·47 (0·67–3·14)	0·35	1·74 (1·20–2·54)	0·004	1·12 (0·67–1·86)	0·48
Age (years)	1641	≥60	1·11 (1·08–1·14)	<0·0001	10·75 (5·68–20·32)	<0·0001	1·04 (1·03–1·06)	<0·0001	2·14 (1·42–3·22)	<0·0001
Tryptase (ng/mL)	1530	≥125	3·01 (1·59–5·70)	<0·0001	1·61 (0·72–3·72)	0·24	1·66 (1·18–2·35)	0·0004	1·81 (1·20–2·75)	0·005
Leukocytes (×10⁹ per L)	1543	≥16	2·08 (0·26–16·65)	0·491	..	..	1·94 (1·20–3·14)	0·007	1·88 (1·27–2·79)	0·002
Haemoglobin (g/dL)	1550	≤11·0	0·01 (0·00–0·31)	0·019	..	..	0·01 (0·00–0·04)	<0·0001	1·71 (1·13–2·57)	0·011
Platelets (×10⁹ per L)	1543	≤100	0·05 (0·01–0·23)	<0·0001	5·78 (0·56–59·52)	0·14	0·17 (0·11–0·27)	<0·0001	1·63 (1·13–2·34)	0·009
Lactate dehydrogenase (U/L)	1226	≥260	0·46 (0·04–5·29)	0·535	..	..	2·51 (1·27–4·98)	0·008	1·36 (0·82–2·28)	0·19
Alkaline phosphatase (U/L)	1295	≥100	15·19 (3·93–58·71)	<0·0001	2·91 (1·60–5·30)	<0·0001	2·16 (1·35–3·46)	0·001	0·74 (0·39–1·40)	0·11
Calcium (mg/dL)	1216	≤8·7	0·01 (0·00–0·01)	0·003	0·97 (0·22–4·22)	0·93	0·01 (0·00–0·01)	<0·0001	1·48 (0·91–2·41)	0·12
Neutrophils (%)	1466	≥50	11·11 (0·72–171·57)	0·085	2·58 (0·90–7·44)	0·081	0·66 (0·30–1·46)	0·307	..	..
Monocytes (%)	1420	≥0·32	16·74 (0·19–1451·66)	0·216	..	..	3·20 (1·06–9·69)	0·040	1·43 (0·53–3·83)	0·44
Eosinophils granulocytes (%)	1432	..	1·01 (0·94–1·10)	0·749	..	..	1·00 (0·99–1·02)	0·408	..	..
Skin involvement	1641	..	1·06 (0·50–2·28)	0·877	..	..	0·44 (0·31–0·65)	<0·0001	0·46 (0·30–0·69)	<0·0001
Organomegaly*	1464	..	3·05 (1·56–5·94)	0·001	1·28 (0·56–2·94)	0·51	1·06 (0·68–1·66)	0·782	..	..
Mediator symptoms	1639	..	0·66 (0·36–1·20)	0·171	..	..	0·61 (0·43–0·85)	0·004	0·87 (0·52–1·48)	0·25
Allergy	1418	..	0·74 (0·39–1·43)	0·376	..	..	0·43 (0·22–0·84)	0·014	0·48 (0·20–1·19)	0·23

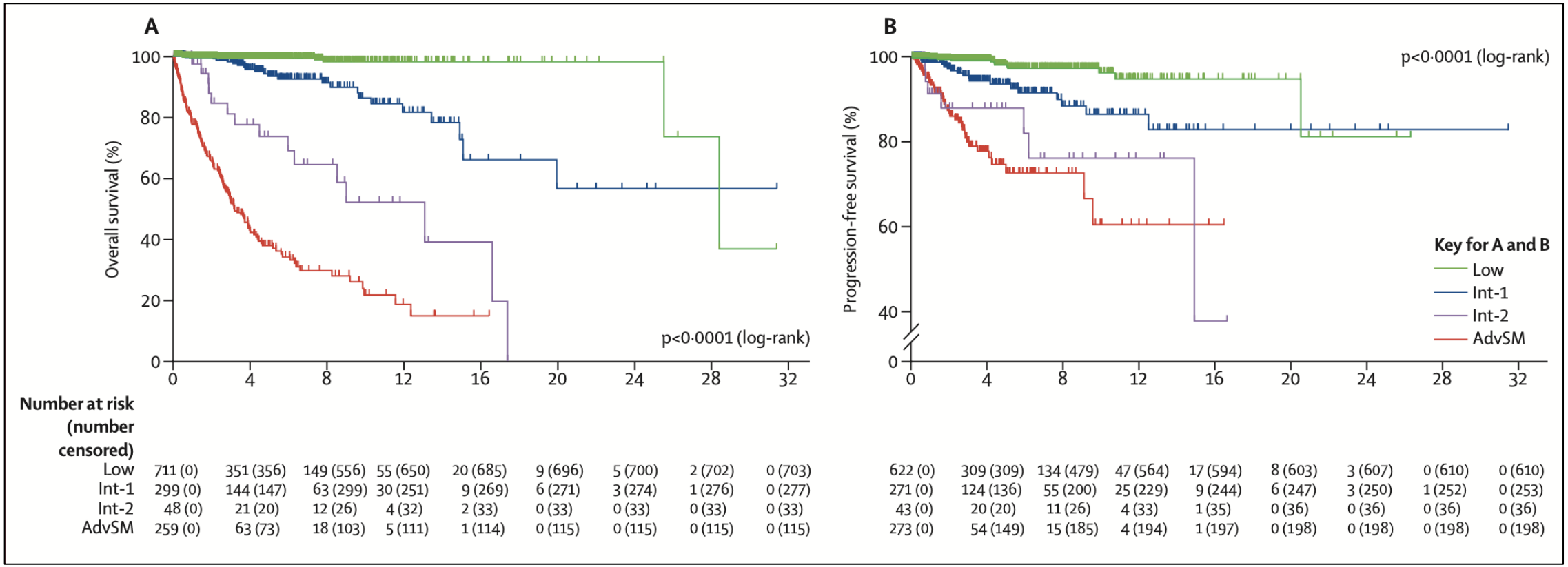
Prognostic variables were examined for their statistical power and independence from each other and from the WHO classification by univariate and multivariate analysis. HR=hazard ratio. *Organomegaly (ie, enlarged spleen, enlarged liver, enlarged lymph nodes, or a combination).

Table 2: **Effect of individual risk factors on overall survival and identification of prognostic variables**

Speer et al., Lancet Hematology, 2019

Prognosis - IPSM=international prognostic scoring system for mastocytosis

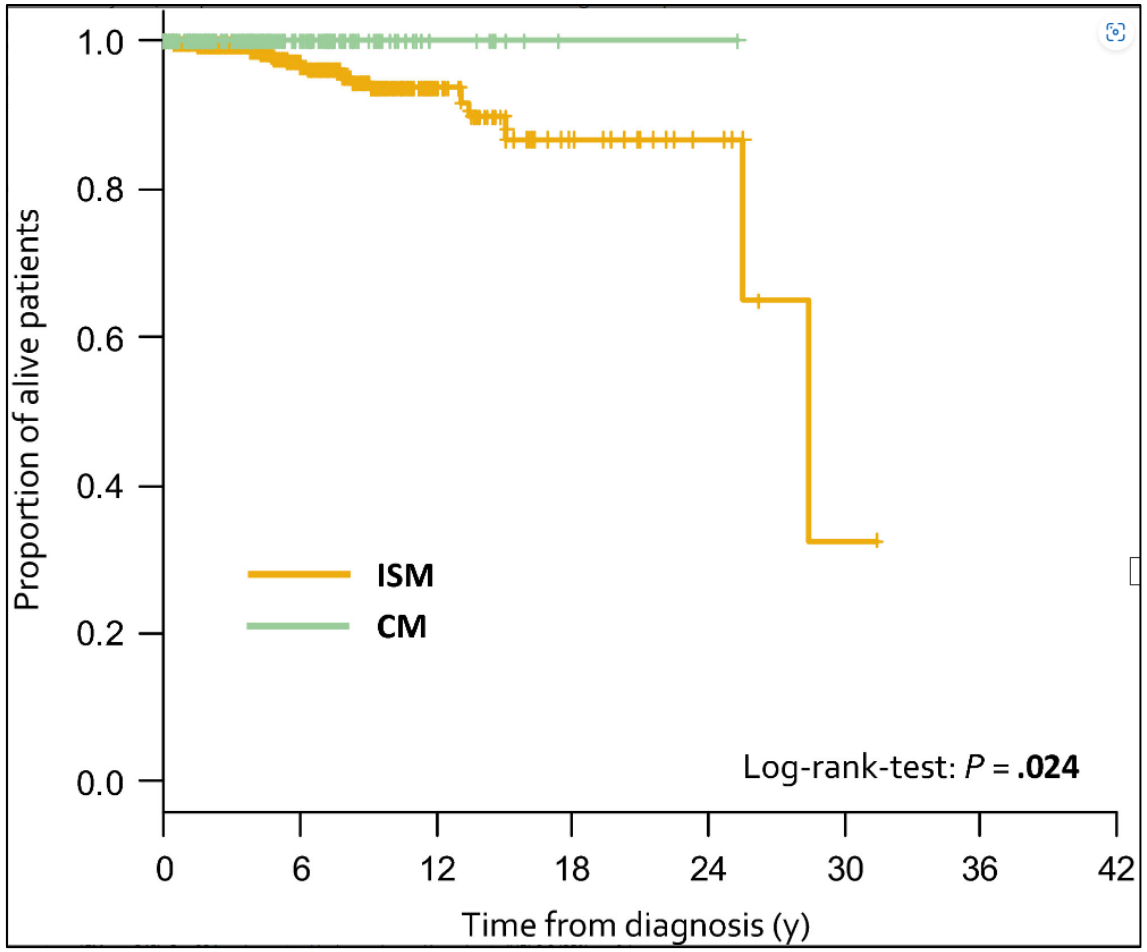
Non-adv SM



Speer et al., Lancet Hematology, 2019

Prognosis CM vs. ISM

1993 patients from the registry of the European Competence Network on Mastocytosis (ECNM)



median follow-up ISM = 4.3 years

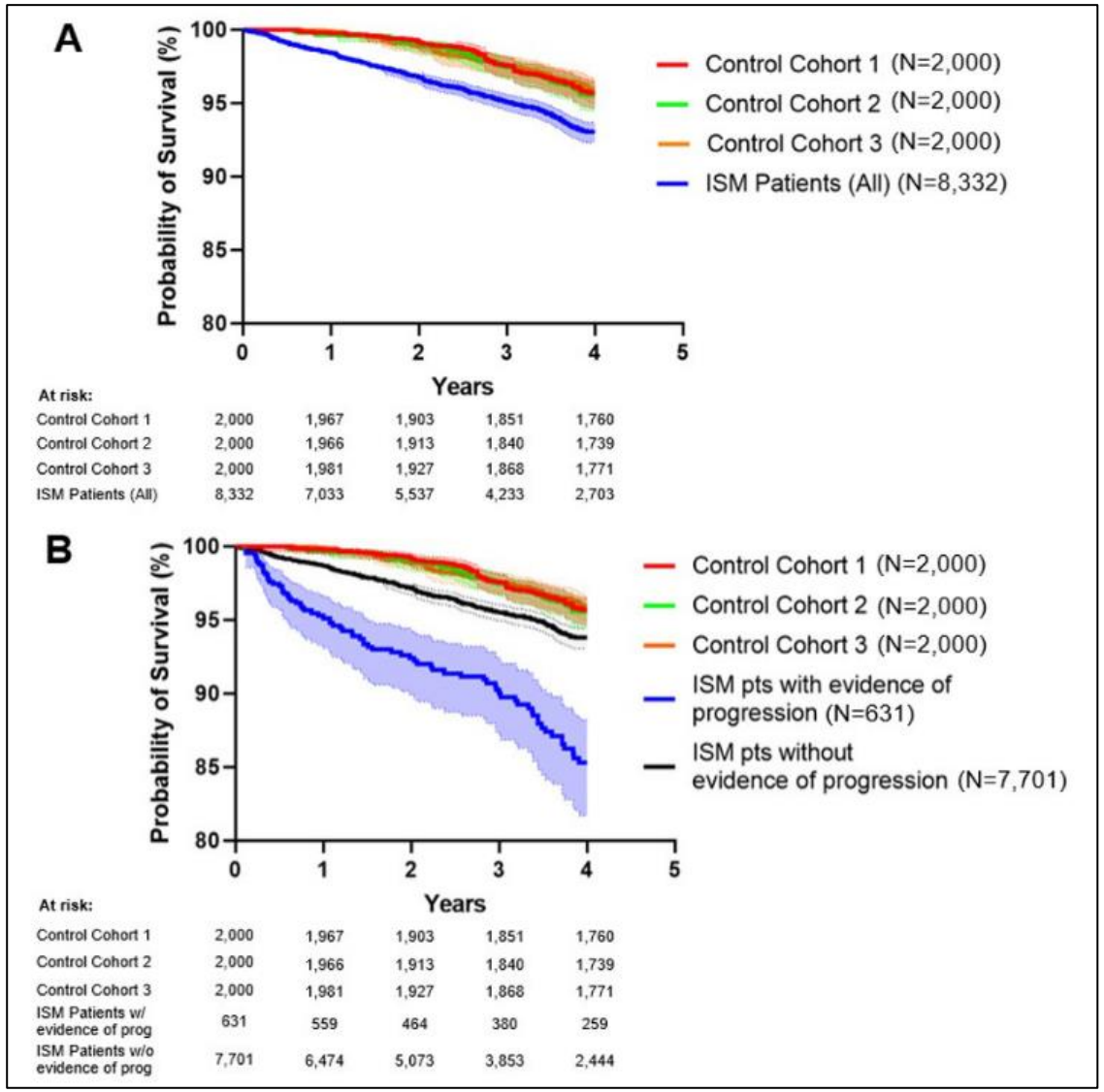
ISM: 3.4% died
(causes of death:
disease-related (n = 5; progression advSM)
cardiovascular (n = 7)
secondary cancer (n = 6)
unknown (n = 4).

ISM, BMM, SSM => advSM 2.9%
CM => advSM 0%

Trizuljak et al., Allergy, 2020

Prognosis

8,332 patients (out of 230 Million patients) with ISM in US



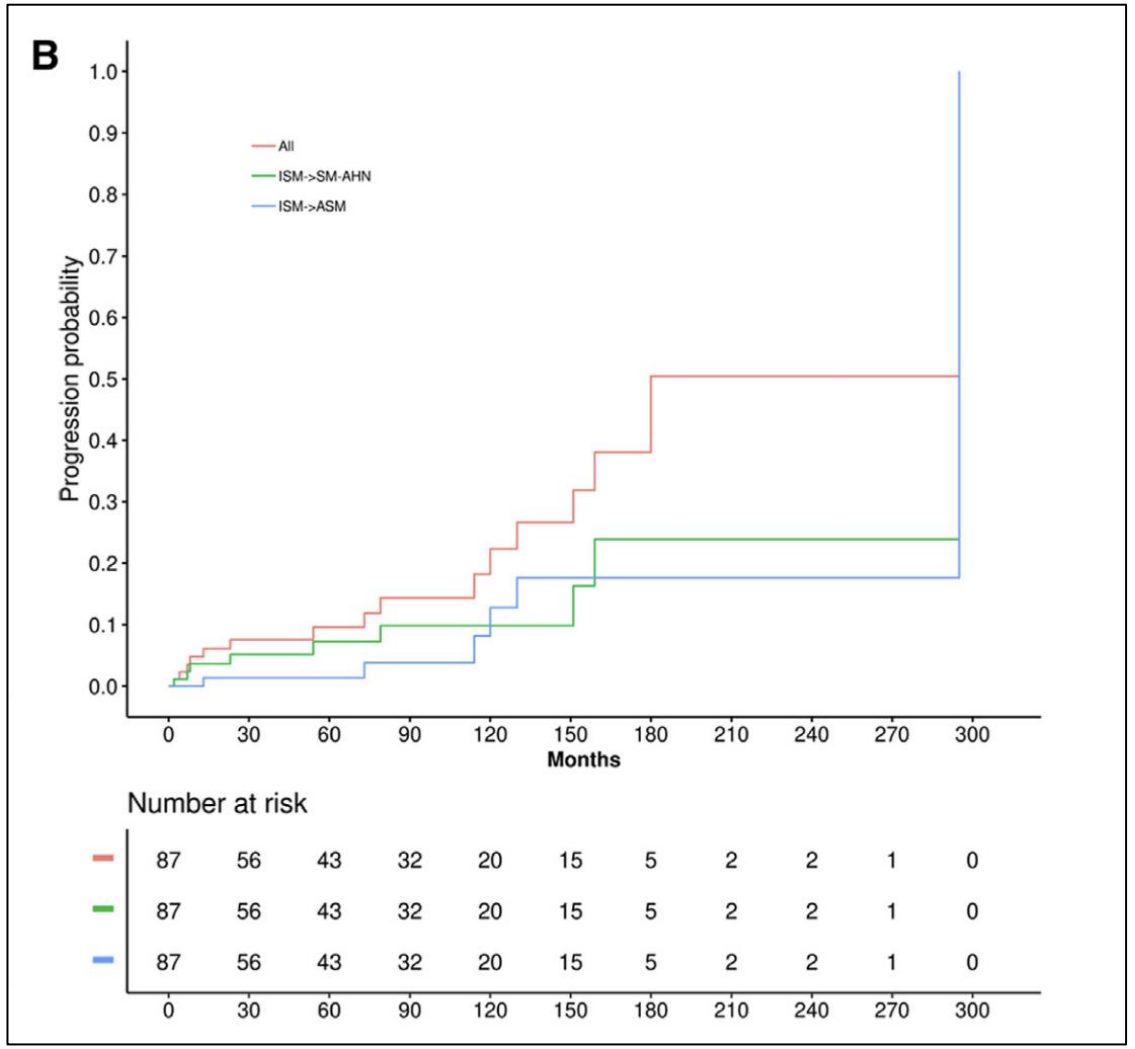
OS non SM vs. ISM
p<0.0001, with a log-rank hazard ratio of 1.64

Excess mortality among ISM patients without evidence of disease progression (P = 0.0005, with a log-rank HR of 1.53, 95% CI 1.23 – 1.90)

Progression from non-advSM to advSM

- retrospective analysis
- 116 patients with confirmed SM
  - 77% ISM
  - 2% SSM
  - 12% SM-AHN
  - 9% aggressive SM

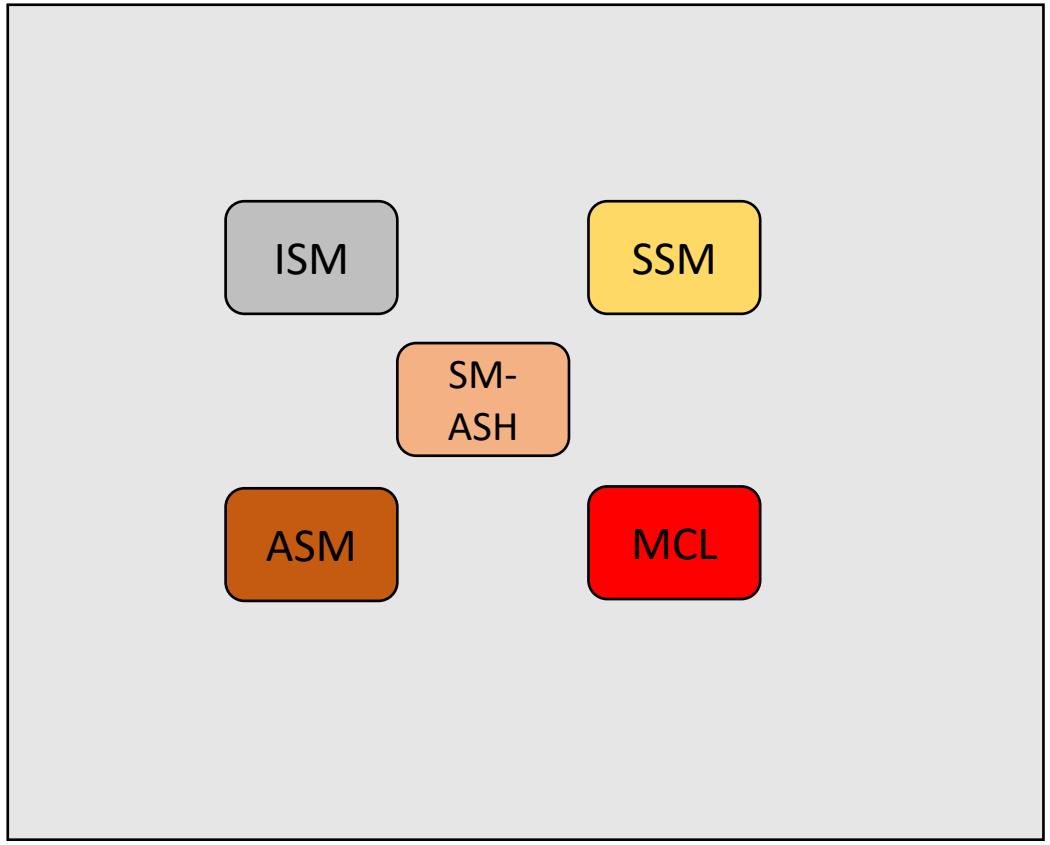
- 16 from 87 non-advSM patients progressed to advSM
  - ISM to ASM, n = 6
  - ISM to SM-AHN, n = 8
  - SSM to SM-AHN, n = 11
  - ISM to MCL, n = 1



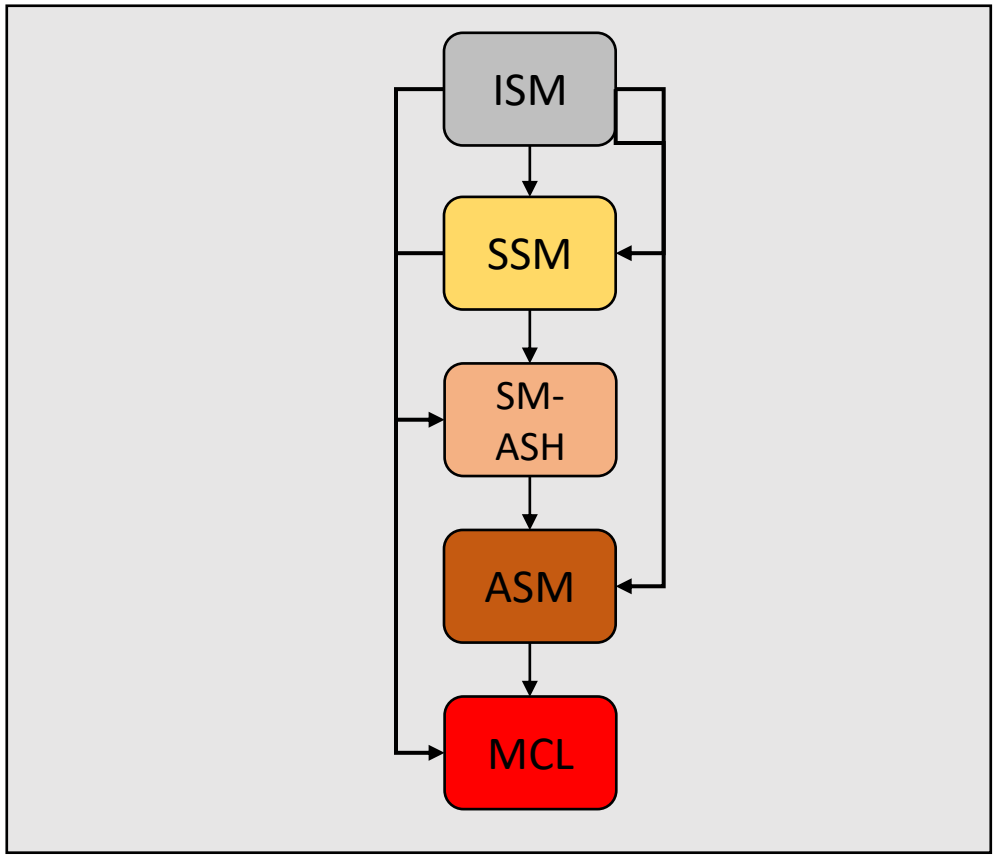
Tse et al., J Aller Clinic Immun, 2024

Progression from non-advSM to advSM

Eigenständige Entitäten



Kontinuum

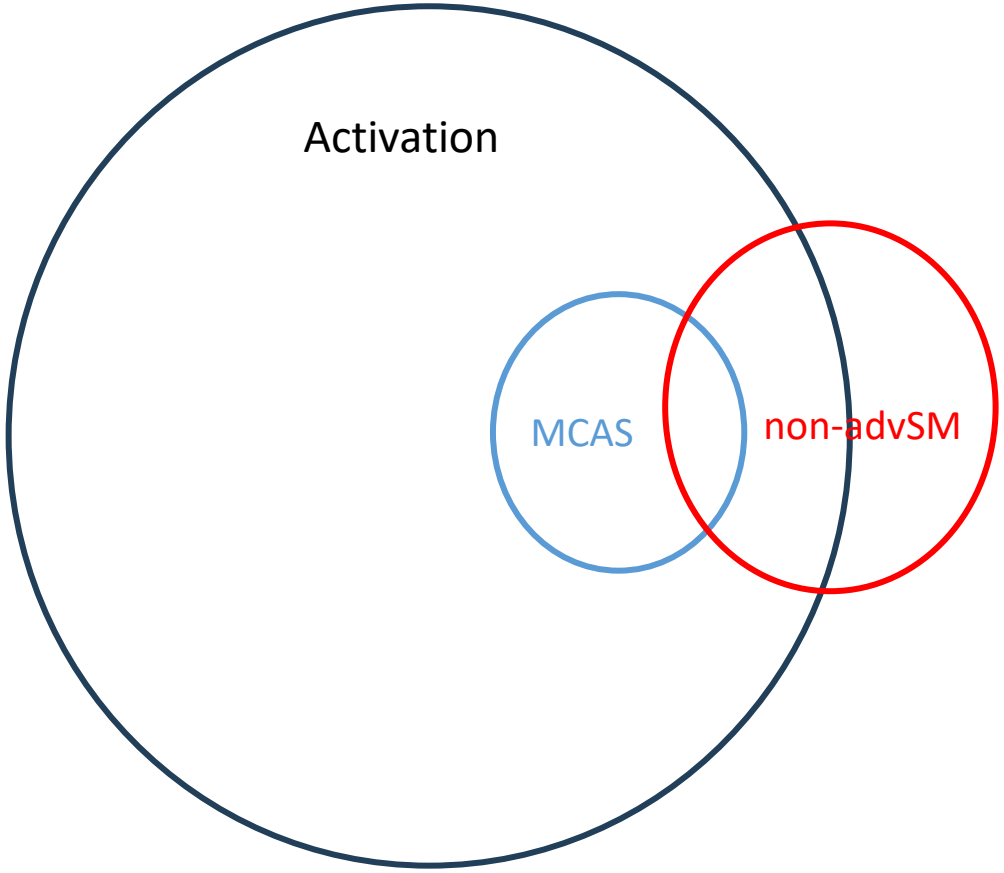


Valent et al, Ann Rev Path, 2023

How is a hematological diesease defined?

1. the disease-defining cells are derived from haematopoietic cells
2. clonal proliferation of the disease-defining cells
3. clonal evolution/progression into a more aggressive disease

Indolent systemic mastocytosis is a hematological diagnosis!



- Age > 60 years
- AP > 100
- Multi-lineage involvement
  - c-Kit VAF > 2% (>6%??)
- Beta-2-microglobuline
- additional mutations?