VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Quali novità terapeutiche nella Mastocitosi Sistemica?

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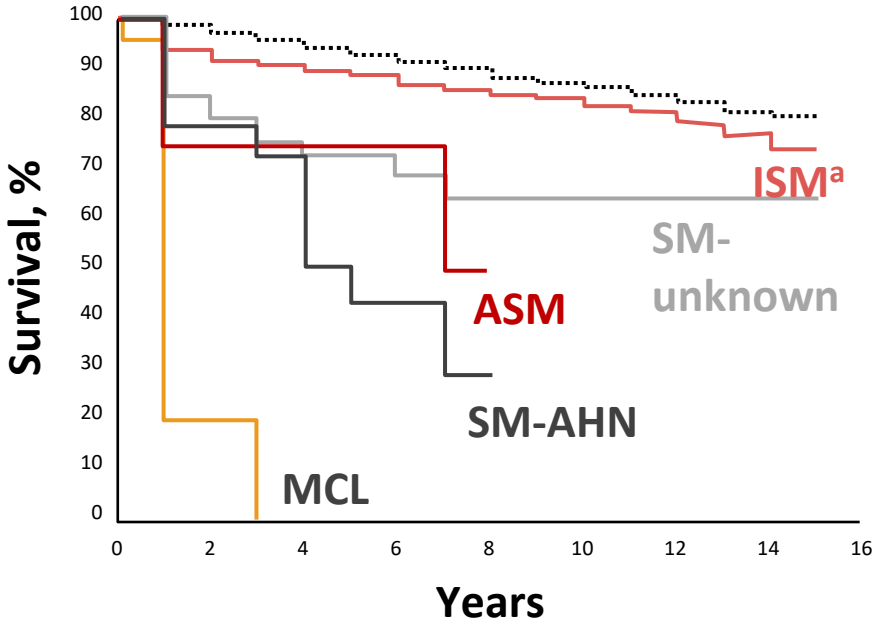
Disclosures of Cristina Papayannidis

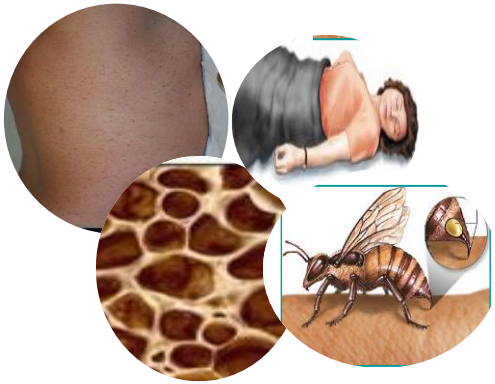
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						X	X
Astellas						X	X
Servier							X
Menarini							X
BMS							X
Pfizer						X	X
Amgen							X
Janssen						X	
GSK						X	
Blueprint						X	
Incyte						X	X
Paladin Labs Inc							X
Jazz pharmaceuticals						X	
Novartis						X	
Delbert Laboratoires						X	

Survival for SM subtypes

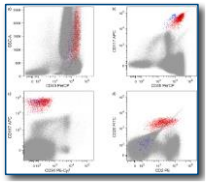


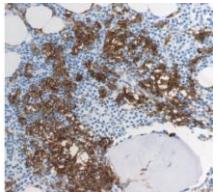
Cohen SS, et al. *Br J Haematol*. 2014

What's the aim of SM therapy?



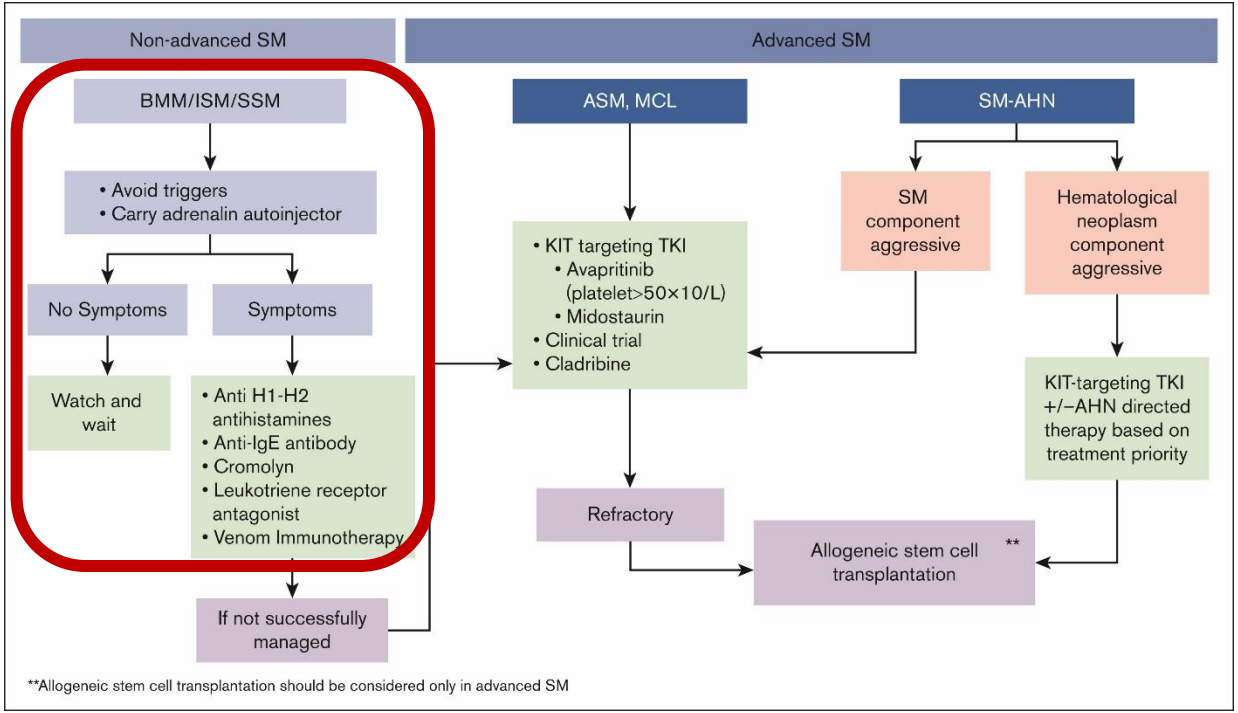
Symptoms management (ISM)





Disease control/ eradication (AdvSM)

The current strategy



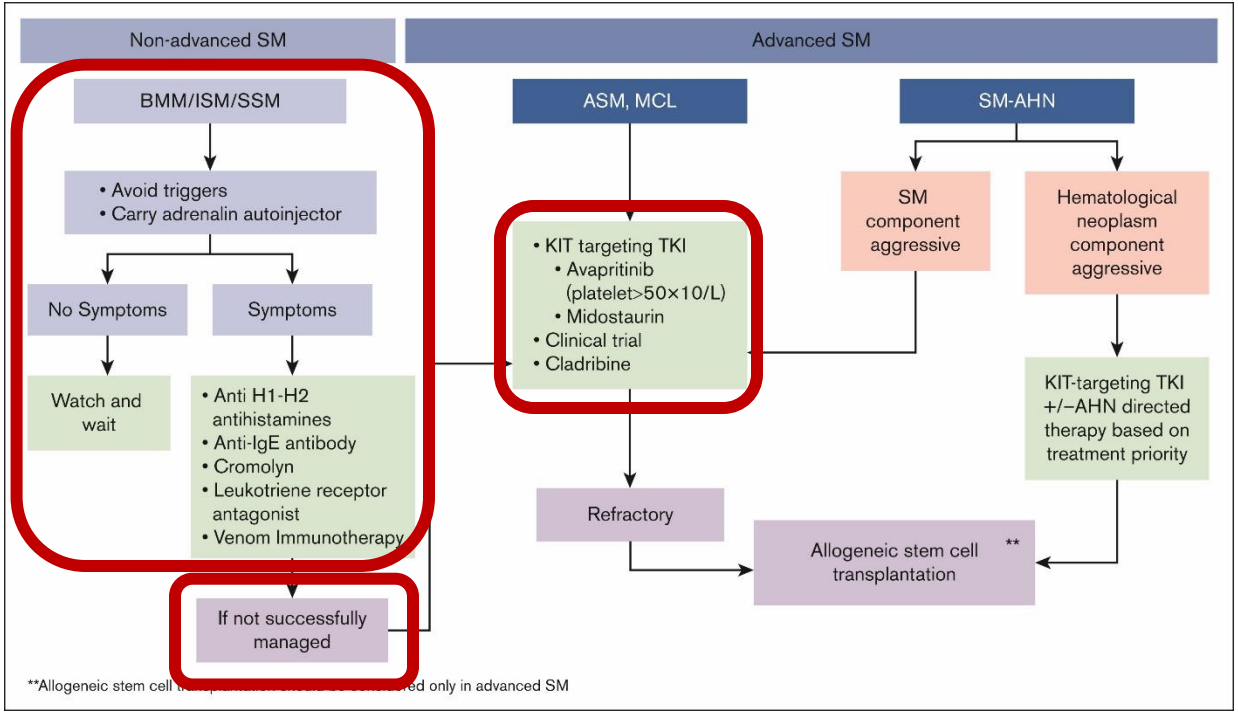
Ustun C et al, Blood Adv 2025

Anti-mediator therapy may not be sufficient

Organ Involvement/Symptoms	Stepwise Treatment[e,f]
Skin: Pruritus, flushing, urticaria, angioedema dermatographism	1. H1 blockers and H2 blockers 2. Leukotriene receptor antagonist 3. Aspirin 4. Ketotifen[c] 5. Topical cromolyn sodium (cream/ointment 1%–4%)[c]
Gastrointestinal: Diarrhea, abdominal cramping, nausea, vomiting	1. H2 blockers 2. Cromolyn sodium 3. Proton pump inhibitors 4. Leukotriene receptor antagonist 5. Ketotifen[c]
Neurologic: Headache, poor concentration and memory, brain fog	1. H1 blockers and H2 blockers 2. Cromolyn sodium 3. Aspirin 4. Ketotifen[c]
Cardiovascular: Pre-syncope, tachycardia	1. H1 blockers and H2 blockers 2. Corticosteroids 3. Omalizumab
Pulmonary: Wheezing, throat swelling	1. H1 blockers and H2 blockers 2. Corticosteroids 3. Omalizumab
Naso-ocular: Nasal stuffiness, nasal pruritus, conjunctival injection	1. H1 blockers 2. Corticosteroids 3. Cromolyn sodium

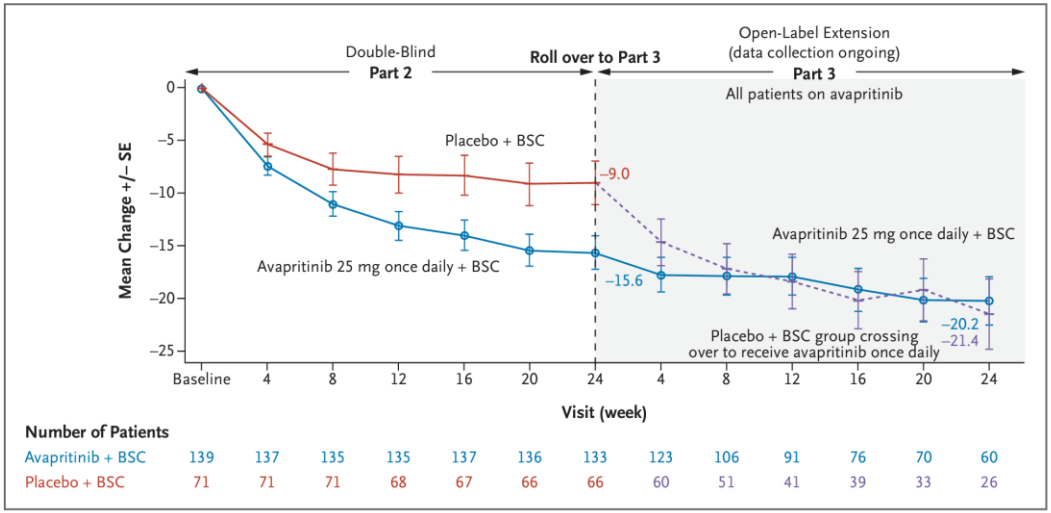
NCCN Version 2. 2026

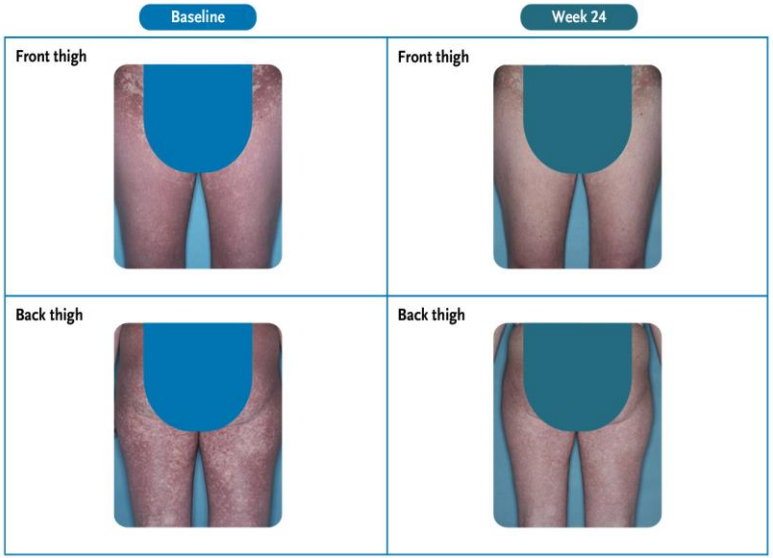
The current strategy



Ustun C et al, Blood Adv 2025

Avapritinib approved by FDA and EMA in ISM patients





Gotlib J et al, NEJM Evidence 2023

New drugs in clinical development in ISM patients with uncontrolled symptoms

Elenestinib (BLU-263)
Bezuclastinib
TL-895

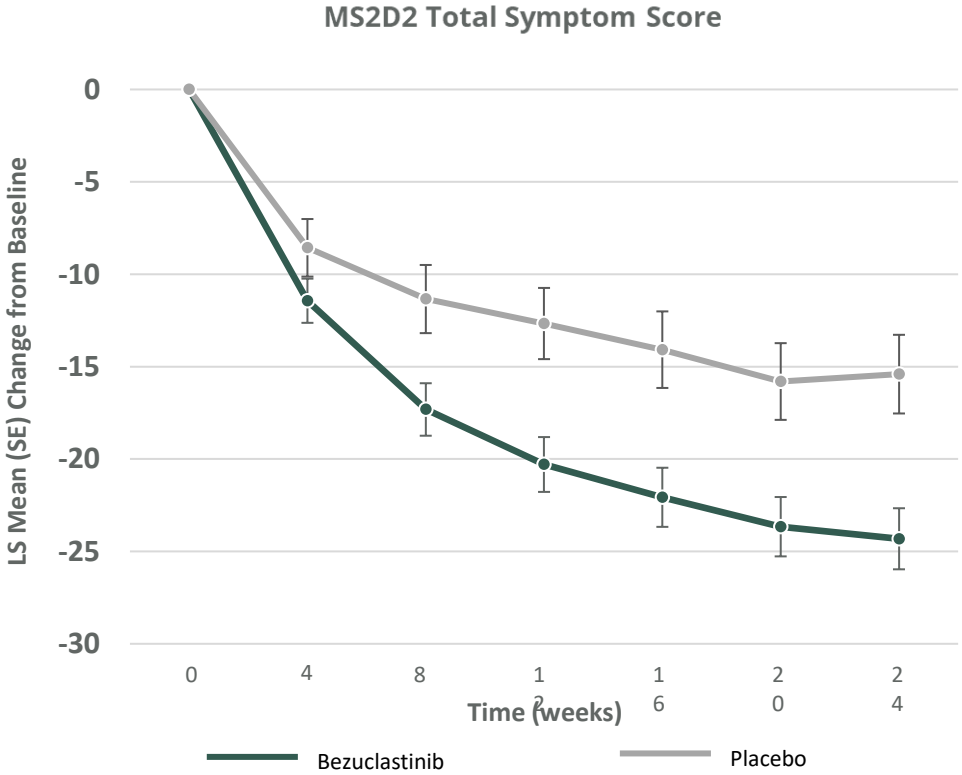
ISM with uncontrolled symptoms

SUMMIT Part 2: Double-Blind, Placebo-Controlled Randomized Clinical Study Evaluating Bezuclastinib in Non-Advanced Systemic Mastocytosis Patients

Primary Endpoint	• Mean change in TSS at Week 24
Key Secondary Endpoints*	• ≥ 50% Reduction in Serum Tryptase • ≥ 50% Reduction in KIT D816V VAF • ≥ 50% Reduction in TSS • ≥ 50% Reduction in Bone Marrow MC • ≥ 30% Reduction in TSS

NCT04910685, NCT05186753, NCT04655118

Bezuclastinib induces clinically meaningful decreases in patient-reported symptoms and objective measures of disease burden



Mean Change in TSS at Week 24 [95 % CI]		
Bezuclastinib	**Placebo**	**P-Value**
-24.32 *(-27.56, -21.08)*	-15.41 *(-19.58, -11.24)*	0.0002
-8.91 *(-13.56, -4.26)*		

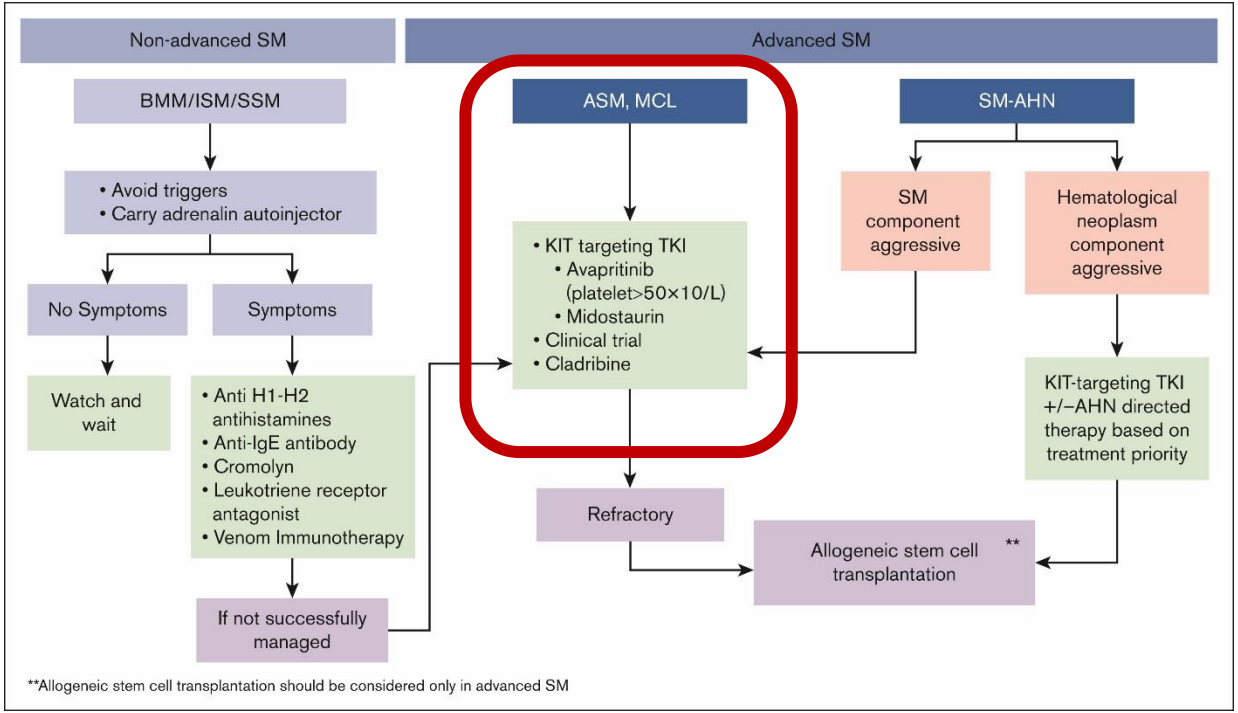
≥50% Reduction in Serum Tryptase at Week 24		
Bezuclastinib	**Placebo**	**P-Value**
87.4%	0%	<0.0001

Rein L et al, ASH 2025

Open questions (I)

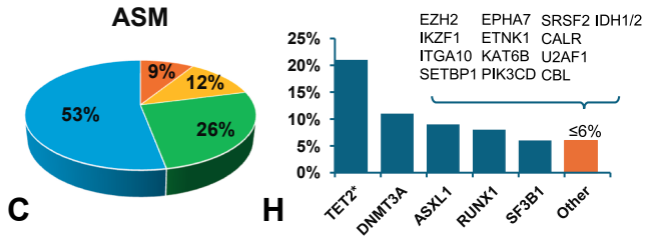
- ✓ What is the role of TKIs in preventing disease progression, if any?
- ✓ TKIs in ISM: how long?
- ✓ TKIs in ISM: for which patients? Need for a shared and objective evaluation of symptoms burden over time

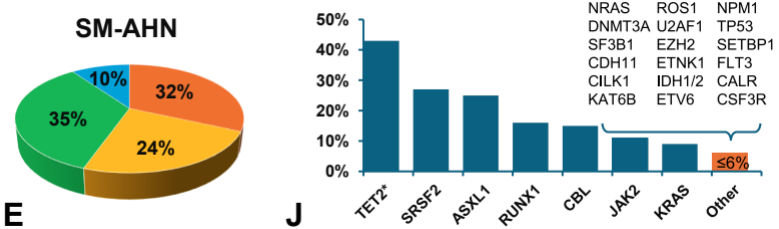
The current strategy

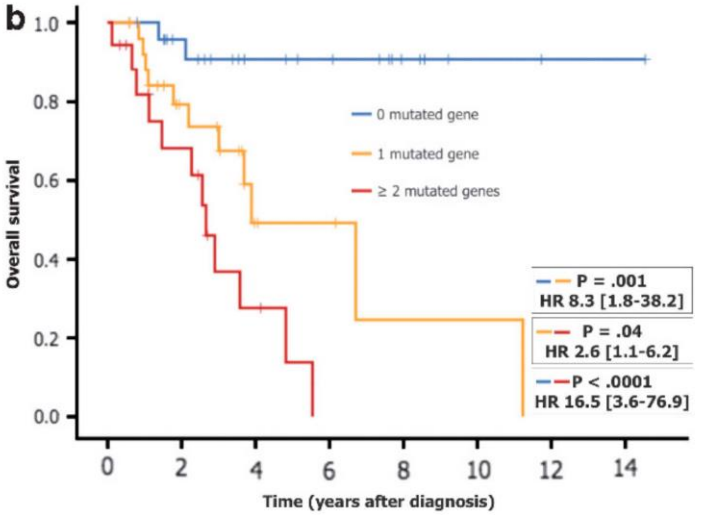


Ustun C et al, Blood Adv 2025

Beyond *KIT*







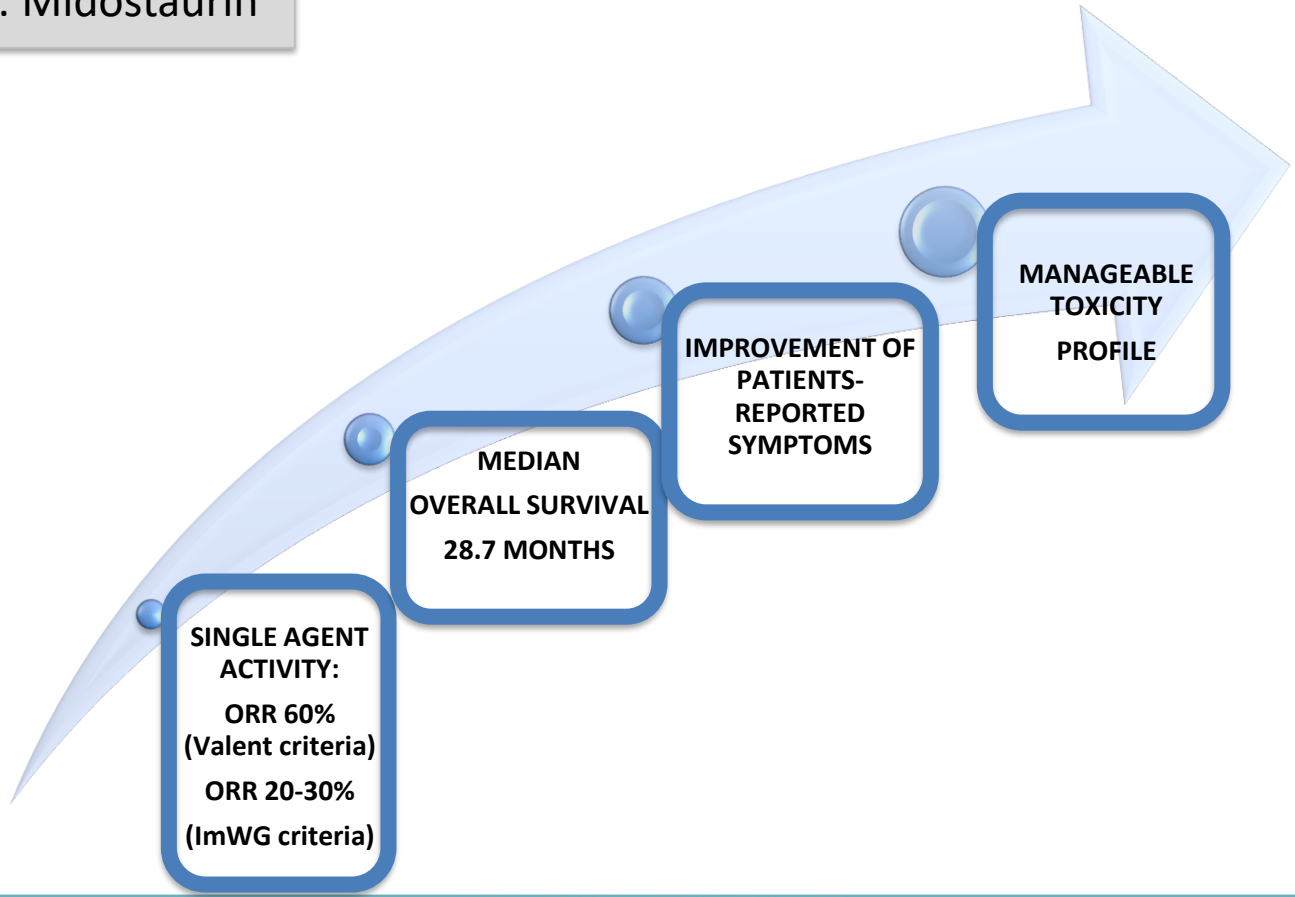
- ≥3 mutated genes
- 2 Mutated genes
- 1 Mutated gene
- Non Mutated

Hoermann G et al, J ALLERGY CLIN IMMUNOL PRACT 2025

Response assessment criteria

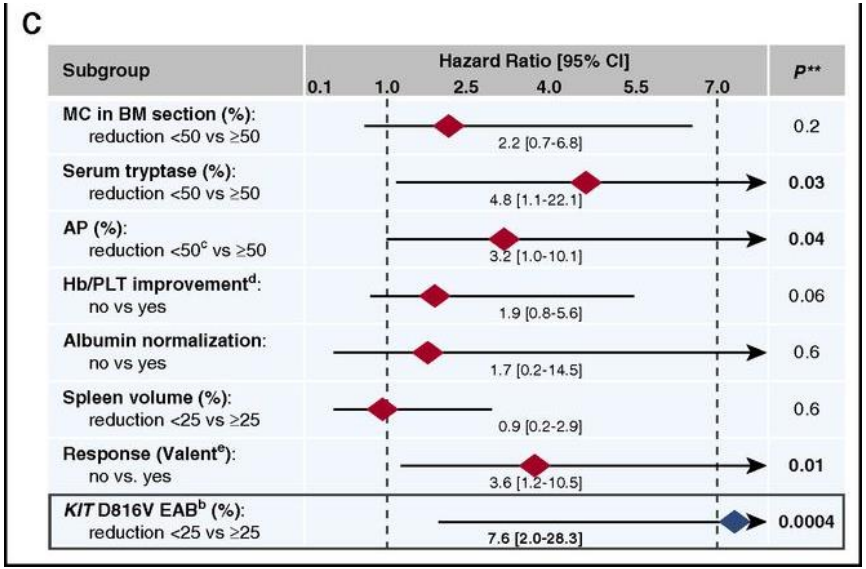
Response Assessment	mIWG-MRT-ECNM Response Criteria*	Pure Pathological Response Criteria
Complete Remission (CR)	✓ Absence of neoplastic MC aggregates in bone marrow ✓ Serum tryptase ≤ 20 ng/mL ✓ Remission of peripheral blood counts ✓ Complete resolution of all mIWG C-findings	✓ Absence of neoplastic MC aggregates in bone marrow ✓ Serum tryptase < 20 ng/mL ✓ Remission of peripheral blood counts
Partial Remission (PR)	✓ Reduction of neoplastic MC in bone marrow by ≥ 50% ✓ Reduction of serum tryptase by ≥ 50% ✓ Resolution of ≥ 1 mIWG C-finding	✓ Reduction of neoplastic MC in bone marrow by ≥ 50% ✓ Reduction of serum tryptase by ≥ 50%
Clinical Improvement (CI)	✓ Resolution of ≥1 mIWG C-finding in the absence of CR, CRh, PR, or PD	Not a part of PPR Criteria

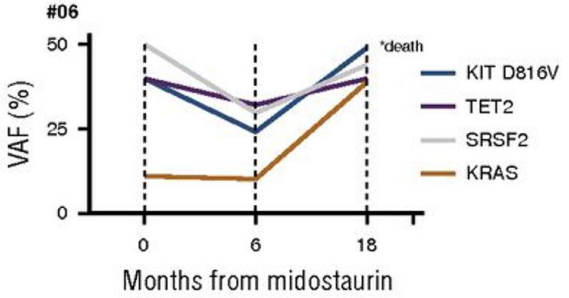
The first player: Midostaurin

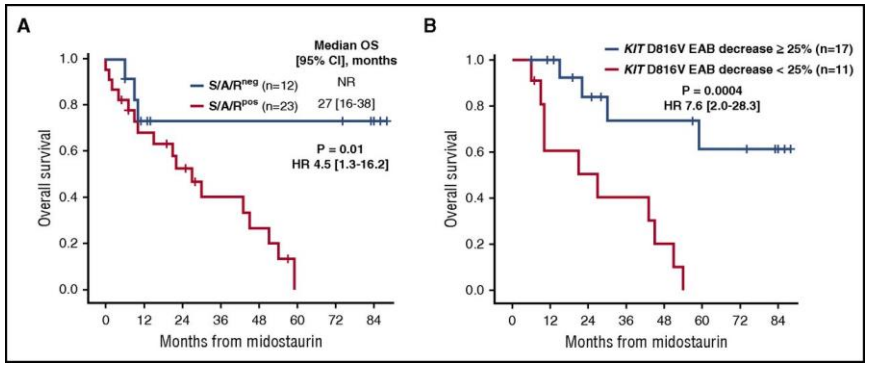


Gotlib J et al, NEJM 2016

What did we learn from Midostaurin experience?







Jawhar M et al, Blood 2017

Avapritinib is now approved after a 1st line of systemic therapy

Best confirmed response, n (%)	Patients with ≥1 prior systemic therapy				Treatment-naïve patients			
		AdvSM subtype				AdvSM subtype		
	All (n = 53)	ASM (n = 8)	SM-AHN (n = 33)	MCL* (n = 12)	All (n = 30)	ASM (n = 5)	SM-AHN (n = 22)	MCL* (n = 3)
ORR†	**35 (66)**	6 (75)	22 (67)	7 (58)	**26 (87)**	4 (80)	19 (86)	3 (100)
95% CI	**52-79**	35-97	48-82	28-85	**69-96**	28-100	65-97	29-100
Best response								
CR/CRh	**12 (23)**	3 (38)	7 (21)	2 (17)	**13 (43)**	1 (20)	11 (50)	1 (33)
CR	**6 (11)**	0	4 (12)	2 (17)	**8 (27)**	1 (20)	6 (27)	1 (33)
CRh	**6 (11)**	3 (38)	3 (9)	0	**5 (17)**	0	5 (23)	0
PR	**19 (36)**	3 (38)	11 (33)	5 (42)	**13 (43)**	3 (60)	8 (36)	2 (67)
CI	**4 (8)**	0	4 (12)	0	**0**	0	0	0
SD	**10 (19)**	2 (25)	5 (15)	3 (25)	**3 (10)**	1 (20)	2 (9)	0
PD	**2 (4)**	0	1 (3)	1 (8)	**0**	0	0	0
NE	**6 (11)**	0	5 (15)	1 (8)	**1 (3)**	0	1 (5)	0
Median TTR, months	**2.1**	3.0	2.0	2.0	**3.1**	1.8	2.4	9.2
Median time to CR/CRh, months	**14.9**	3.7	14.8	23.2	**9.0**	25.9	6.1	9.3

95% CI, 95% confidence interval; AdvSM, advanced systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; MCL-AHN, mast cell leukemia with an associated hematologic neoplasm; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE, not evaluable; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm.
*The MCL subtype includes patients with the subtypes MCL (n = 11) and MCL-AHN (n = 4). †CR + CRh + PR + CI.

Gotlib J et al, Blood Advances 2026

Avapritinib demonstrated rapid, robust and sustained response with 4 years median follow-up

	Overall population				First-line			
	All (n=107)	ASM (n=21)	SM-AHN (n=71)	MCL (n=15)	All (n=38)	ASM (n=7)	SM-AHN (n=28)	MCL (n=3)
Median follow-up, months (95% CI)	49 (44–52)	43 (21–46)	52 (47–56)	54 (43–59)	49 (44–55)	44 (21–49)	50 (45–57)	51 (42–NR)
Median TTR, months (95% CI)	2.3 (0.3–20.3)	2.1 (0.3–15.0)	2.1 (0.5–20.3)	7.3 (1.7–12.2)	3.1 (0.3–15.0)	1.8 (0.3–15.0)	2.4 (0.5–12.2)	9.2 (9.2–9.3)
Median DOR, months (95% CI)	57.8 (46.1–NR)	NR (26.5–NR)	54.5 (42.6–NR)	NR (NR–NR)	NR (37.1–NR)	NR (NR–NR)	NR (31.2–NR)	NR (29.0–NR)
Median PFS,[a] months (95% CI)	51.3 (38.7–NR)	NR (NR–NR)	45.1 (31.4–61.6)	NR (12.0–NR)	NR (39.4–NR)	NR (NR–NR)	48.1 (25.4–NR)	NR (38.2–NR)

DOR, duration of response; NR, not reached; PFS, progression-free survival; TTR, time to response.

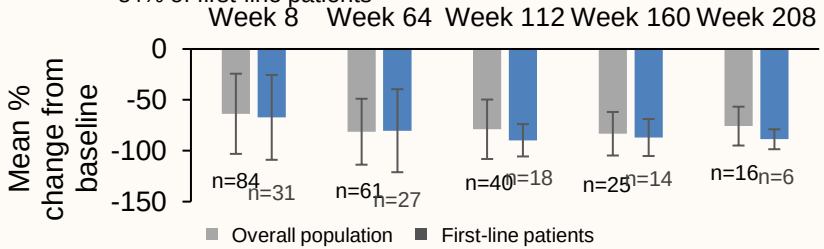
Final database lock: March 13, 2025. DOR, TTR, and PFS were assessed in the response-evaluable population. [a]PFS was defined as the time from first dose to the time of initial documentation of progressive disease or death due to any cause, whichever occurred first.

Gotlib J et al, Blood Advances 2026

Durable reductions in all biomarkers of disease burden were observed

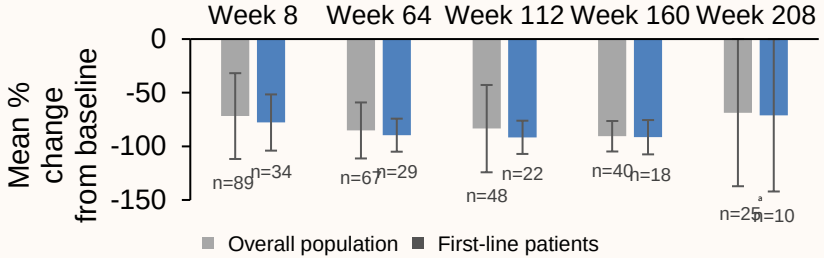
BM MC

- Clearance of BM MC aggregates was seen in 74% of all patients and 84% of first-line patients



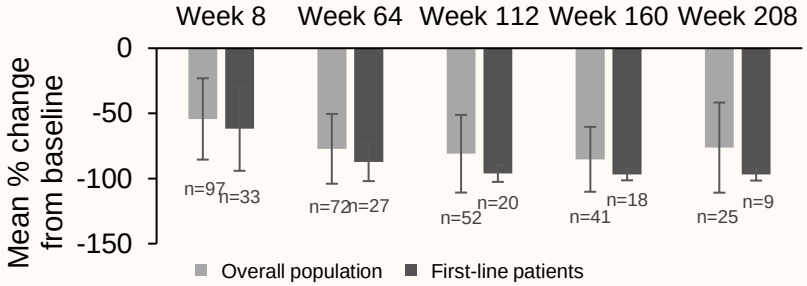
Serum tryptase

- A reduction in serum tryptase to <20 ng/ml was observed in 65% of all patients and 79% of first-line patients



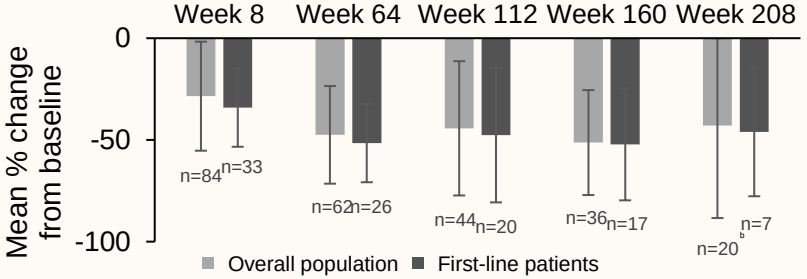
KIT D816V VAF

- A total of 64% of all patients and 67% of first-line patients had post-baseline *KIT* D816V VAF of <1%



Spleen volume

- In patients with baseline palpable spleens, clinical resolution was observed in 78% of the overall population and 72% of first-line patients

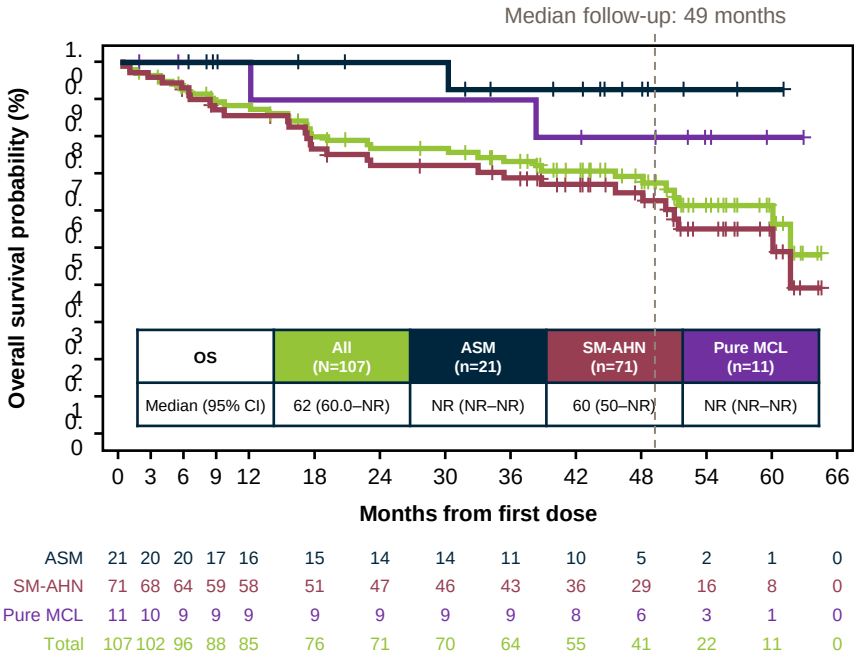


Final database lock: March 13, 2025. Error bars = ±SD. [a]SD = 85.5. [b]SD = 45.5

Gotlib J et al, Blood Advances 2026

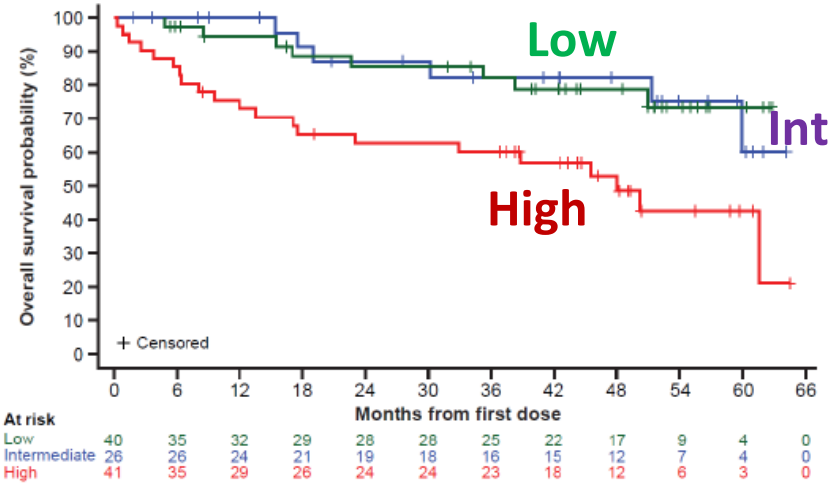
OS was >5 years in the overall population

OS in overall population



ASM	21	20	20	17	16	15	14	14	11	10	5	2	1	0
SM-AHN	71	68	64	59	58	51	47	46	43	36	29	16	8	0
Pure MCL	11	10	9	9	9	9	9	9	9	8	6	3	1	0
Total	107	102	96	88	85	76	71	70	64	55	41	22	11	0

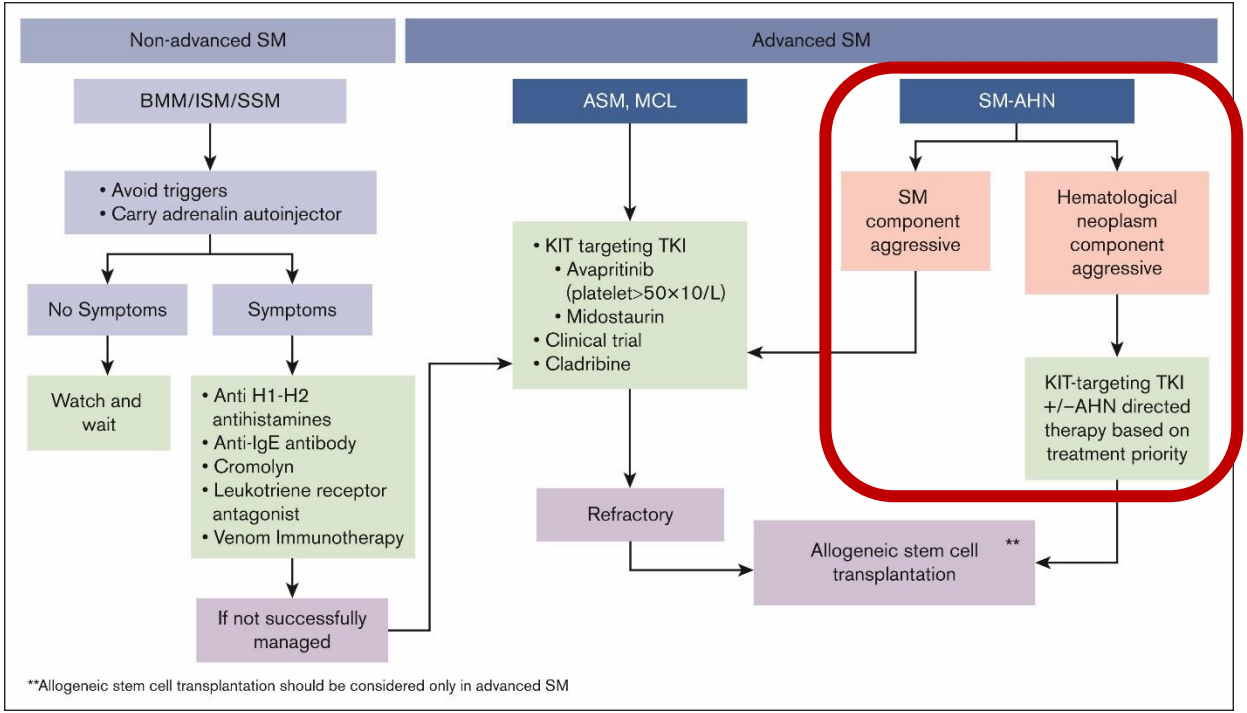
MARS score and OS

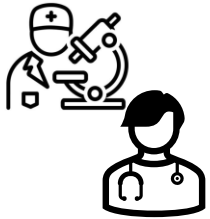


MARS, Mutation-Adjusted Risk Score; OS, overall survival.

Gotlib J et al, Blood Advances 2026

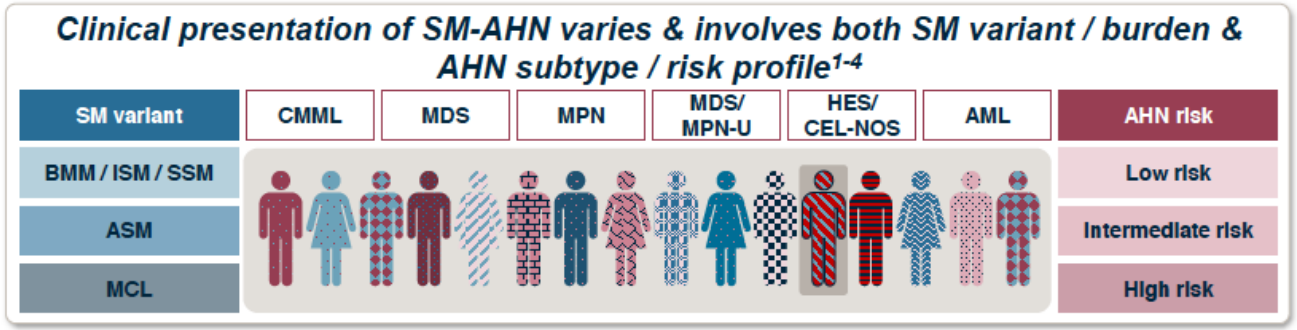
The current strategy





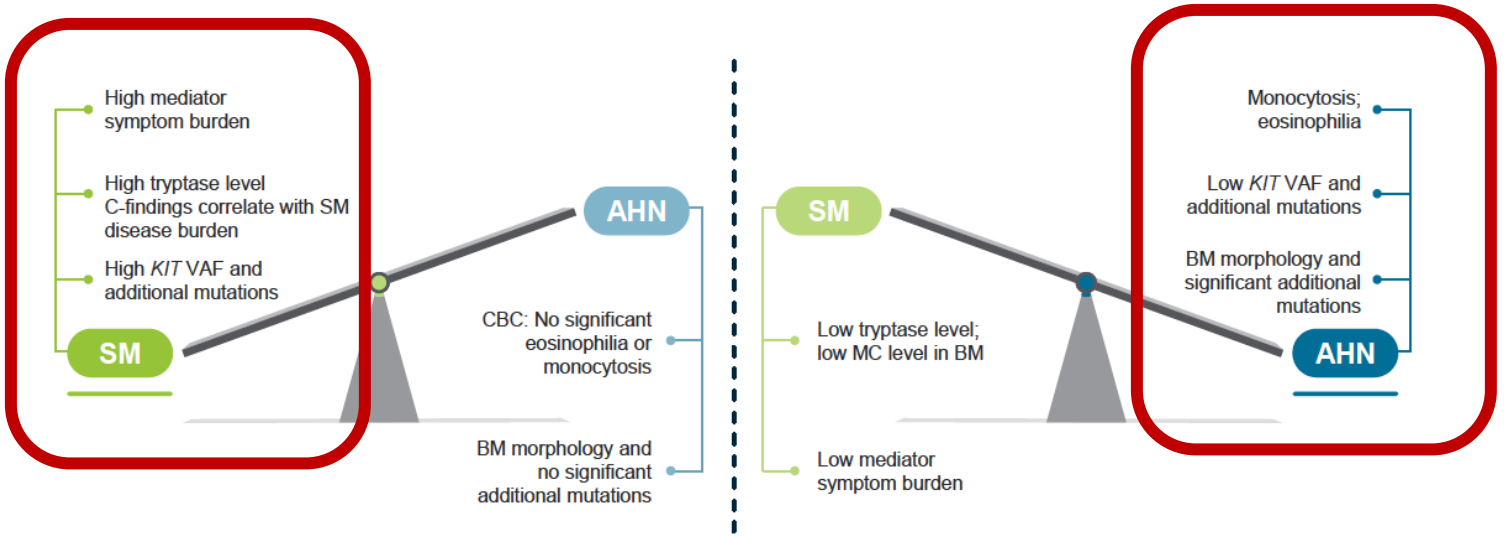
Ustun C et al, Blood Adv 2025

Clinical heterogeneity of SM-AHN



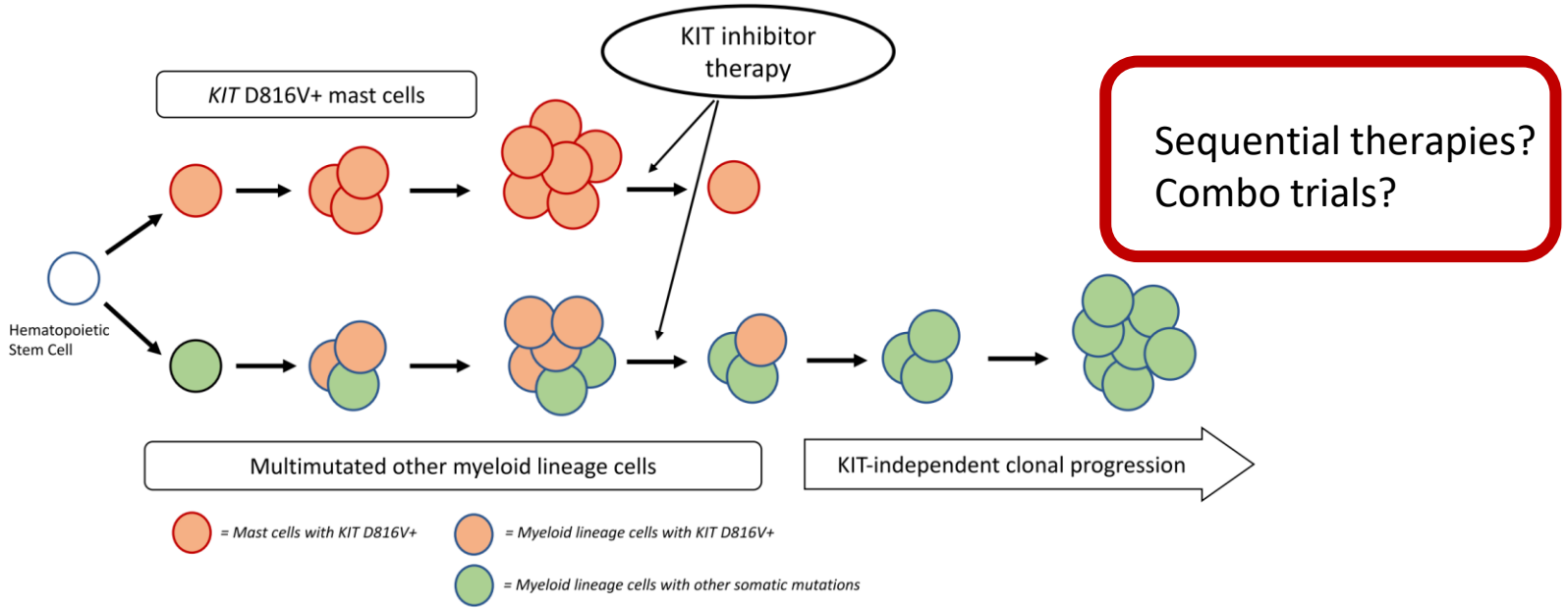
Schwaab J et al, J Allergy Clin Immunol Pract 2020; Valent P et al, HemaSphere 2021; Shouval R et al, Lanect Haematol 2021; Tremblay D et al Oncologist 2021

How do we choose treatment in SM-AHN patients?



Radia DH et al, Hematology 2023

Potential consequences of KIT inhibition in SM-AHN



Sequential therapies?
Combo trials?

Tashi T et al, Immunol Allergy Clin N Am 2023

Open questions (II)

- ✓ How long should TKIs be delivered?
- ✓ What's the role of MRD monitoring?
- ✓ SM-AHN is still a diagnostic and therapeutic challenge→interaction between clinicians and pathologists is mandatory. Combo trials are ongoing.

Thank you!

Prof P.L.Zinzani

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