Systemic mastocytosis

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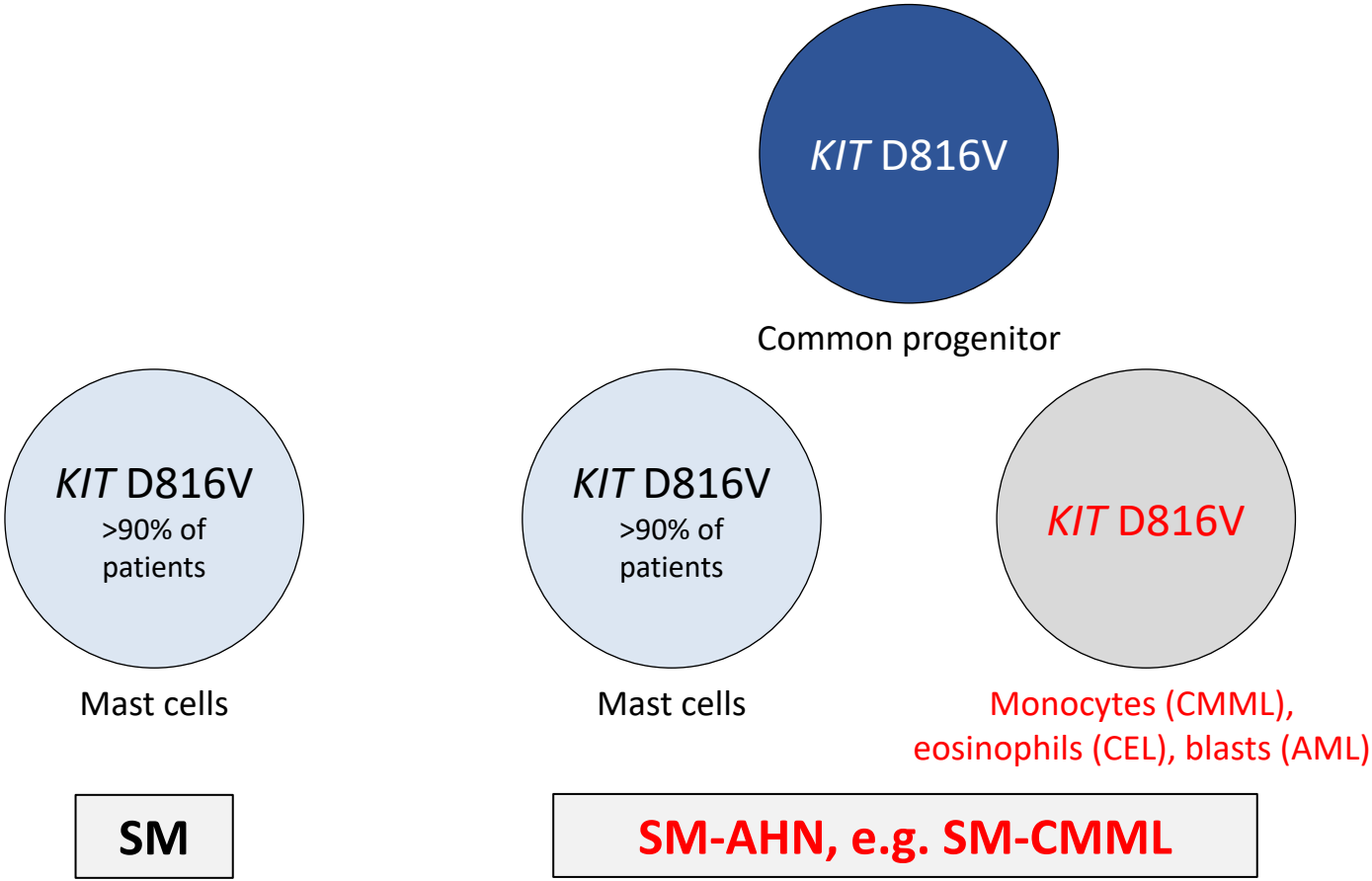
Disclosures

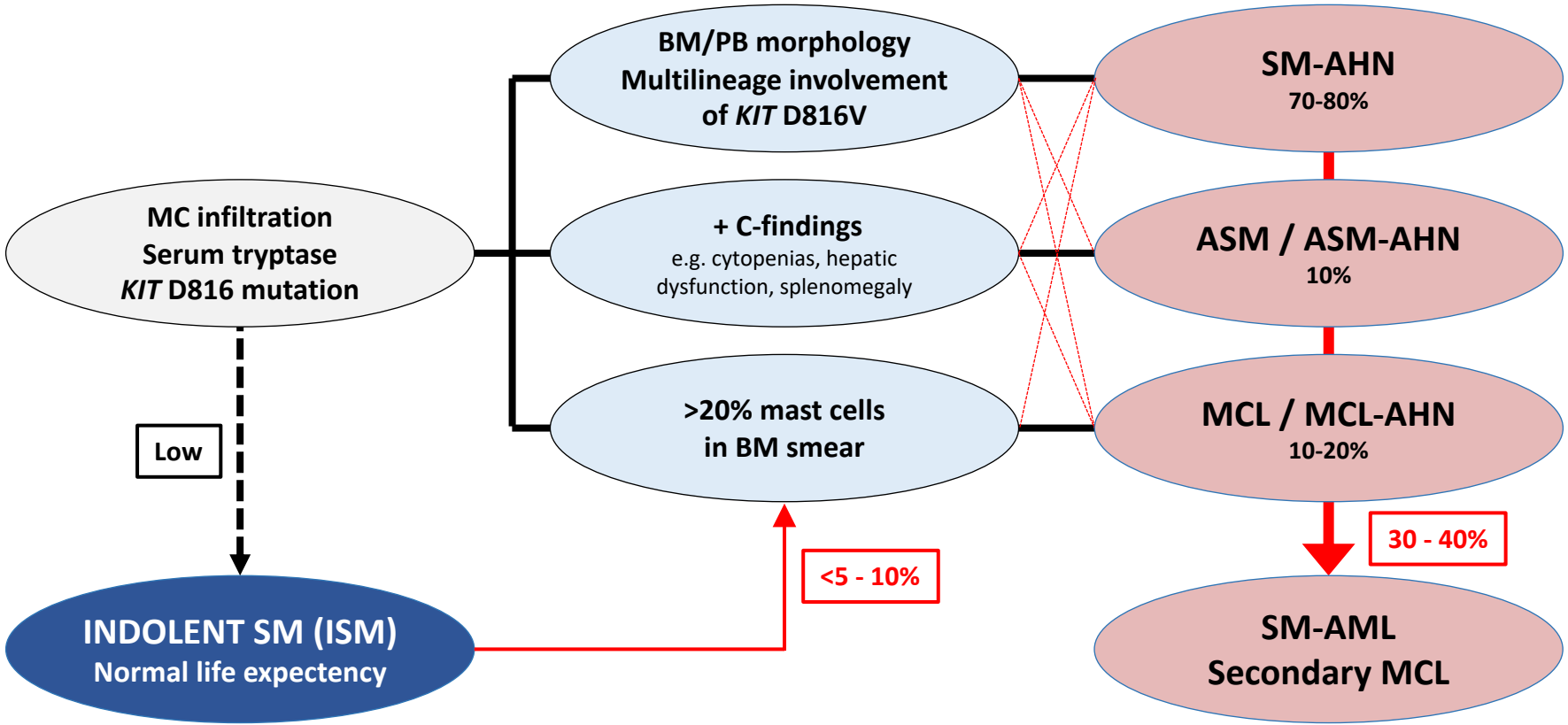
Name of Company	Research support (clinical trials)	Consultant/ Scientific Advisory Board	Honoraria	Travel reimbursement
Blueprint	x	x	x	x
Novartis	x	x	x	x
BMS	x	x	x	x
AOP	x	x	x	x
GSK	x	x	x	x
Abbvie	x	x	x	x
Incyte	x	x		
Cogent	x	x		
Astra Zeneca	x			

Introduction: multilineage involvement of *KIT* D816V



A. Reiter: educational slide

Diagnosis, subtyping and clinical course of SM

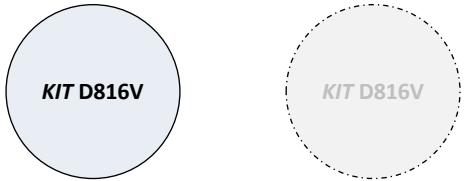


A. Reiter: educational slide

Complex genetics of systemic mastocytosis

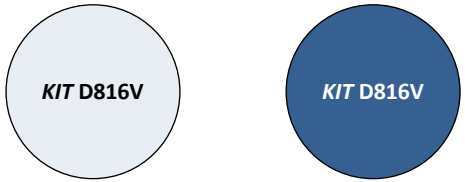
Involvement of mast cell lineage

- ISM
- SSM
- ASM
- MCL



Multilineage involvement

- SSM
- SM-AHN (CMML, MDS/MPN, CEL)
- ASM ± AHN
- MCL ± AHN

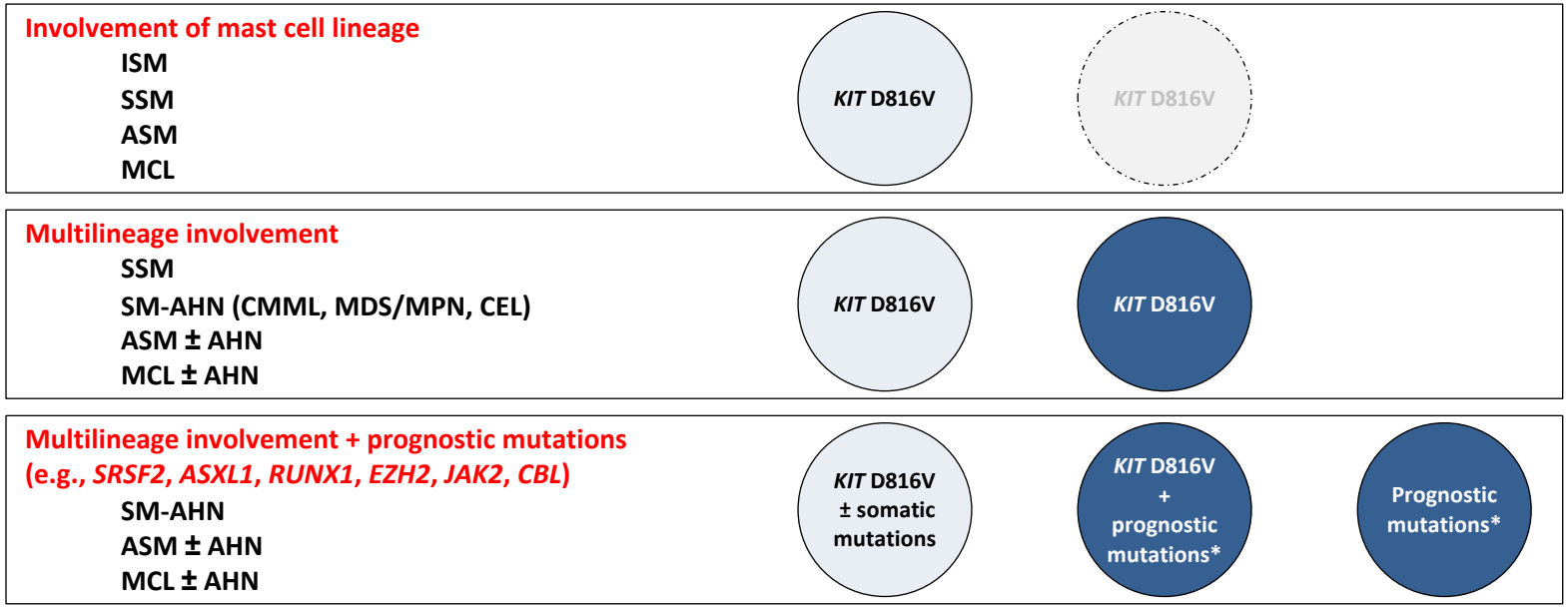


Mast cells **Non-mast cell lineages**

SM: systemic mastocytosis; ISM: indolent SM, SSM: smoldering SM; ASM: aggressive SM; SM-AHN: systemic mastocytosis with associated hematologic neoplasm; MCL: mast cell leukemia; MPN: myeloproliferative neoplasm; ET: essential thrombocythemia; PV: polycythemia vera, MF: myelofibrosis; CMML: chronic myelomonocytic leukemia; MDS/MPN: myelodysplastic/myeloproliferative neoplasm; CEL: chronic eosinophilic leukemia; AML: acute myeloid leukemia

Adapted from Reiter & Gotlib, Blood 2020

Complex genetics of systemic mastocytosis



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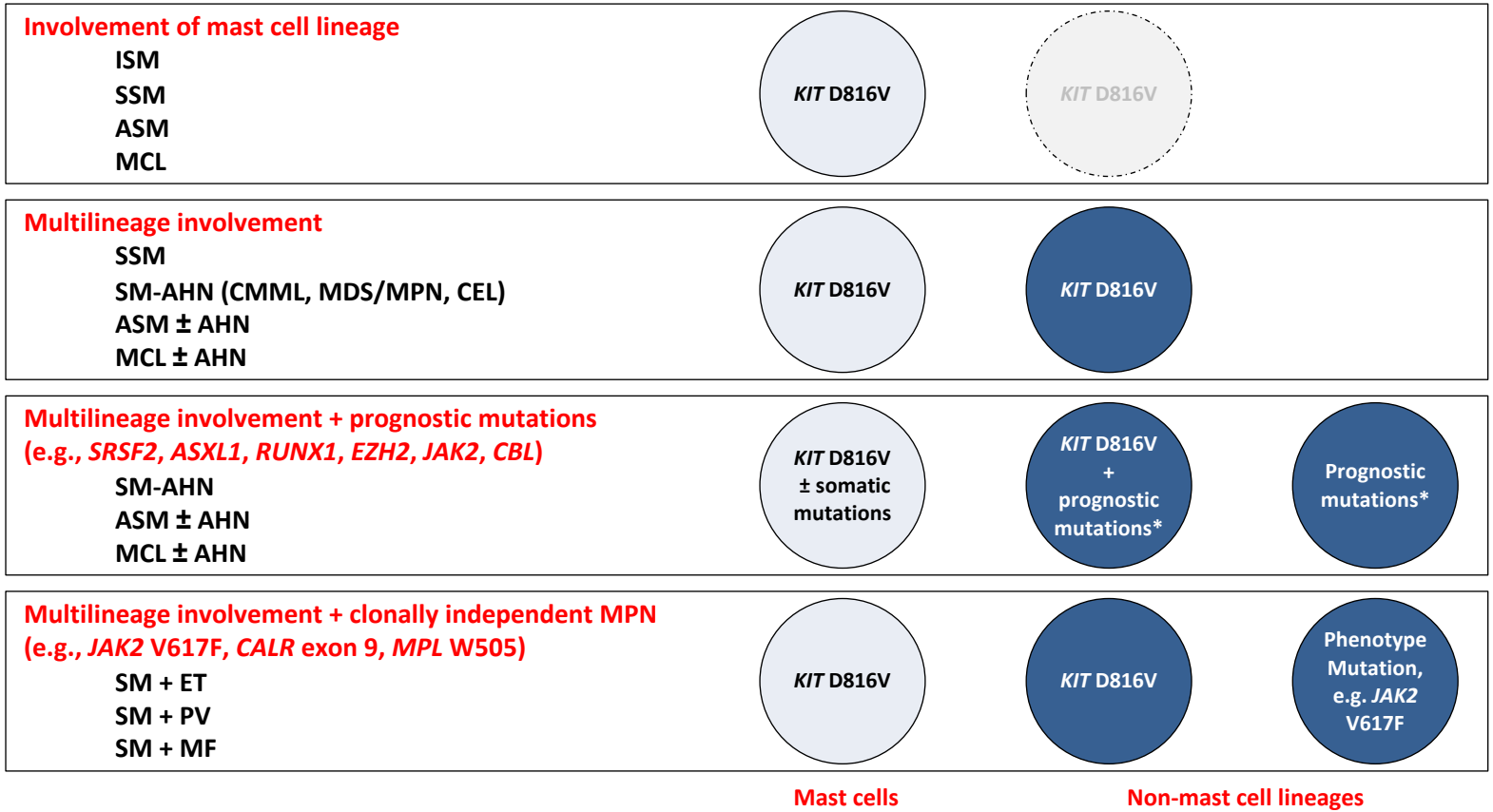
Complex genetics of systemic mastocytosis



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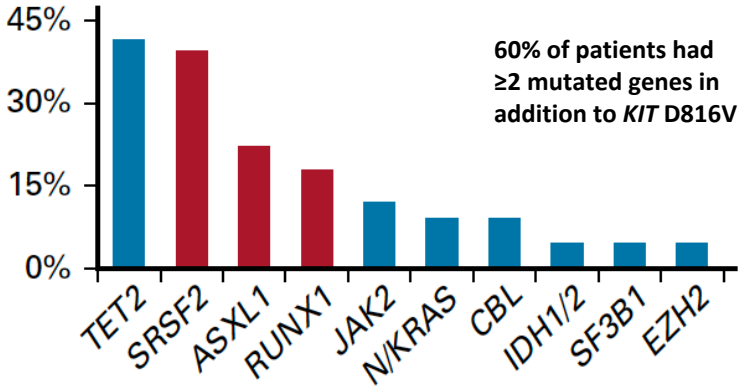
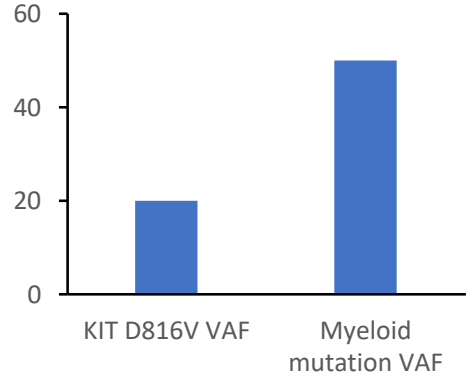
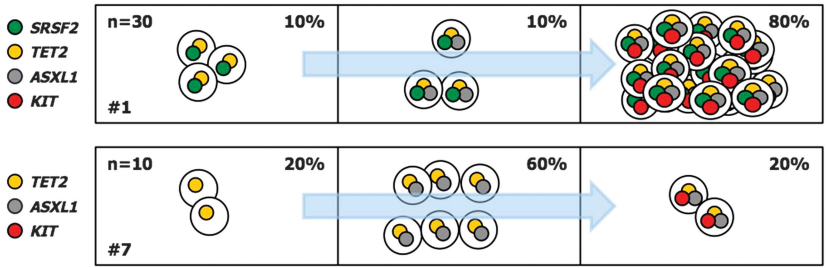
Adapted from Reiter & Gotlib, Blood 2020

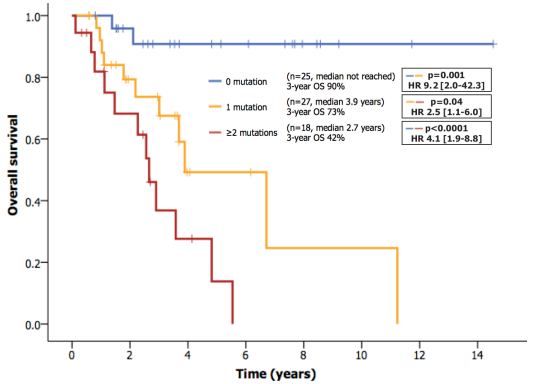
Impact of additional somatic mutations in AdvSM







- *KIT* D816V alone was not identified in a single colony.
- In contrast, colonies with additional mutations were frequent.
- Mutations in *TET2*, *SRSF2* or *ASXL1* precede *KIT* D816V.
- *KIT* D816V is a strong phenotype modifier



Schwaab et al., Blood 2013; Jawhar et al., Leukemia 2015 & 2016; Jawhar et al., Blood 2017

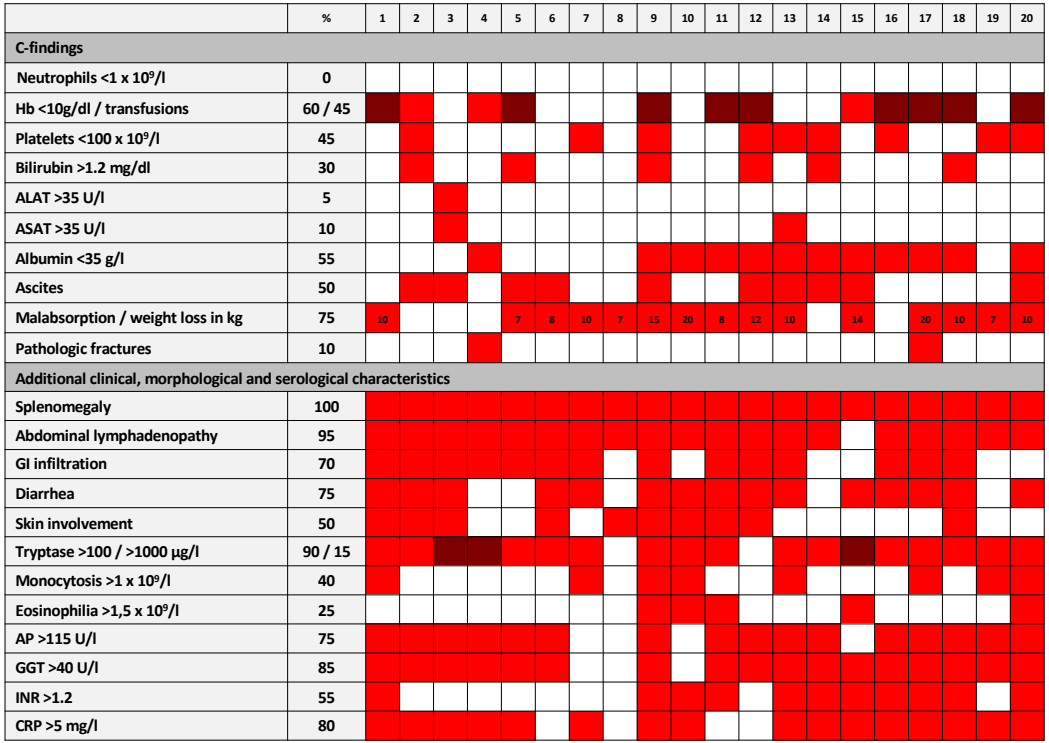
The path to diagnosis and subclassification of SM

Symptoms	Anaphylaxis/flushs Fatigue Diarrhea Skin
Blood counts	Normal
Serum	Tryptase (elevated)
Organ involvement/damage	Osteoporosis

Adapted from Reiter & Gotlib, Blood 2020

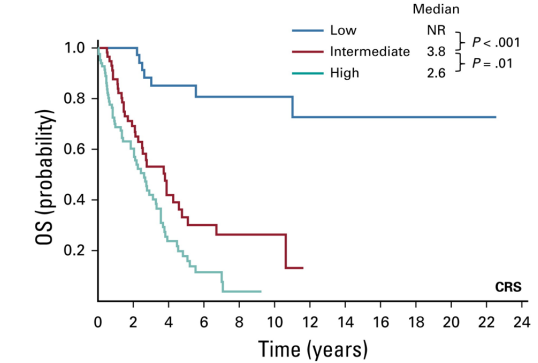
The path to diagnosis and subclassification of SM

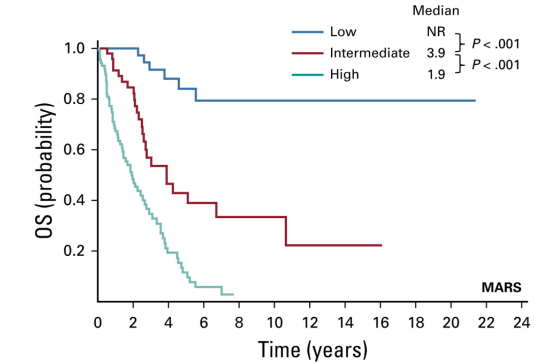
Symptoms	Anaphylaxis/flushs Fatigue Diarrhea Skin **Weight loss**
Blood counts	**Anemia** **Thrombocytopenia** **Monocytosis** **Eosinophilia**
Serum	**Tryptase (elevated)** **Albumin (low)** **AP (elevated)** LDH (normal/elevated)
Organ involvement/damage	Osteoporosis **Splenomegaly** **Hepatomegaly** **Lymphadenopathy** **Portal hypertension** **Ascites** **Osteosclerosis**



Adapted from Reiter & Gotlib, Blood 2020

Prognosis of advanced SM: CRS and MARS



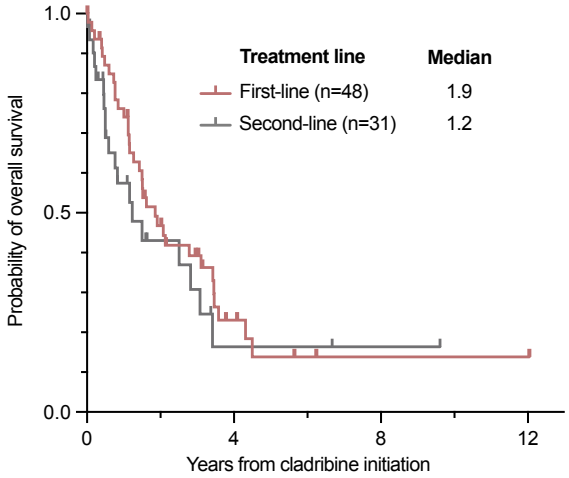


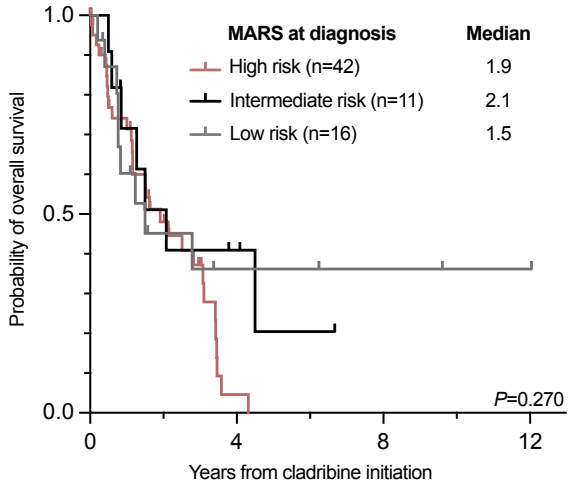
Age >60 years	1.5
Anemia <10g/dl	1
Platelets <100 x 10^9/l	1
AP >UNL	1
Low	**0 – 1.5**
Intermediate	**2 – 2.5**
HIgh	**3 – 4.5**

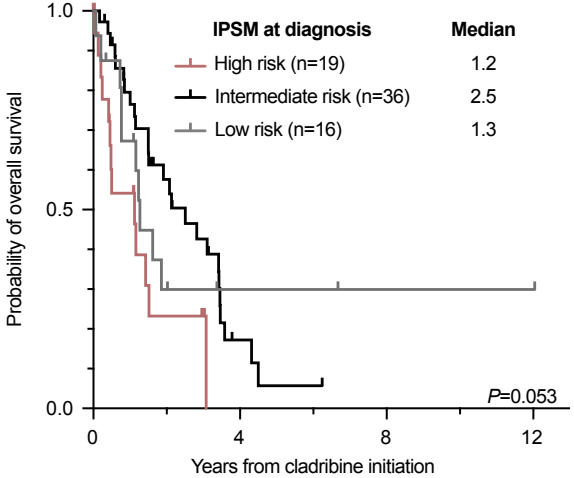
Age >60 years	1
Anemia <10g/dl	1
Platelets <100 x 10^9/l	1
***SRSF2/ASXL1/RUNX1* = 1**	**1**
***SRSF2/ASXL1/RUNX1* >1**	**2**
Low	**0 - 1**
Intermediate	**2**
HIgh	**3 - 5**

Jawhar et al., JCO 2020

Survival in cladribine treated patients



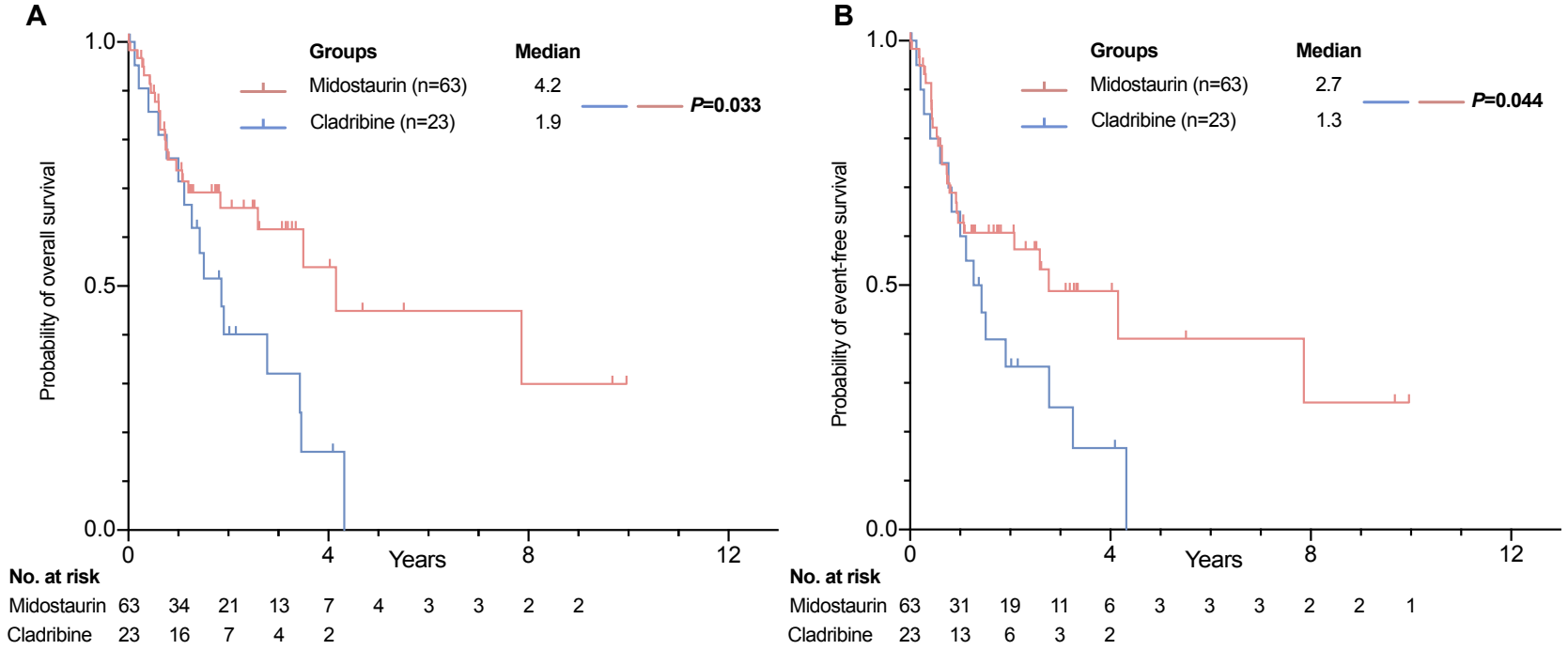




*Cladribine is not approved for the treatment of AdvSM

Lübke et al., Annals of Haematology 2023

OS and EFS in patients with AdvSM treated with midostaurin only vs. cladribine* only



Difference of mean propensity scores 0.005 (0.739 and 0.734), *P*=0.504

OS = Overall survival, EFS = Event-free survival
*Cladribine is not approved for the treatment of AdvSM

Lübke et al. J Clin Oncol. 2022 Jun 1;40(16):1783-1794
[1]based on historical data from the German Registry on Disorders of Eosinophils and Mast Cells

Key avapritinib studies in AdvSM

Phase 1 open study EXPLORER[1]

Primary study objectives: MTD, RP2D, safety

Part 1: Dose escalation (n=32)

3+3 dose escalation design avapritinib 30-400 mg QD

Part 2: Dose expansion (n=54)

- **Avapritinib 300 mg QD**
- **Avapritinib 200 mg QD**

Phase 2 open study PATHFINDER[3]

Primary study objective: ORR (CR/CRh/PR/CI)

Enrolled (N=107)[2]

Avapritinib 200* mg QD Starting Dose[3]

- **Evaluable, Cohort 1 (n=74*)[3]**
  AdvSM with ≥1 evaluable C-finding
- **Non-Evaluable, Cohort 2 (n=33)[3]**
  AdvSM without evaluable C-finding

EMA approval population with 200 mg starting dose and prior systemic therapy (PST)[2]: Efficacy Population n=47[2] Safety Population n=67[2]

Responses confirmed by central pathology review and adjudicated by the steering committee

*2 patients received a starting dose other than 200 mg

AdvSM, advanced systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; MTD, maximum tolerated dose; ORR, overall response rate; PR, partial remission; QD, once daily; RP2D, recommended phase 2 dose; PST, prior systemic therapy

1. DeAngelo DJ et al. Nat Med. 2021; 27 (12): 2183-2191; 2. AYVAKYT Summary of Product Characteristics. Blueprint Medicines, October 2022; 3. Gotlib et al. Nature Medicine 2021; 27:2192-2199

Baseline characteristics for efficacy poulation

	Patients with ≥1 prior therapy (n=69)	Treatment-naïve patients (n=38)	All AdvSM (N=107)
Age, median years (range)	68 (31–86)	68 (39–88)	68 (31–86)
Female, n (%)	27 (39)	18 (47)	27 (39)
ECOG performance status, n (%)			
0–1	48 (70)	31 (82)	79 (74)
2–3	21 (30)	7 (18)	28 (26)
AdvSM subtype per central assessment, n (%)			
ASM	14 (20)	7 (18)	21 (20)
SM-AHN	43 (62)	28 (74)	71 (66)
CMML[a]	22 (32)	11 (29)	33 (31)
MDS/MPN-U	16 (23)	13 (34)	29 (27)
CEL	3 (4)	3 (8)	6 (6)
Other	3 (4)	1 (3)	4 (4)
MCL	12 (17)	3 (8)	15 (14)
KIT D816V mutation by central assay, n (%)	76 (92)	36 (95)	103 (96)
KIT D816V VAF[b], median percent (range)	20 (0–47)	6 (0–45)	16 (0–47)
S/A/R mutation per central assay[c], n (%)	25 (36)	23 (61)	48 (45)
BM mast cell burden, median percentage (range)	50 (1–95)	35 (3–90)	40 (1–95)
Serum tryptase level, median ng/mL (range)	312 (24–1600)	178 (37–1336)	262 (24–1600)
Spleen volume, median mL (range)	830 (44–2652)	863 (149–2897)	839 (44–2897)
One prior systemic therapy, n (%)	42 (61)	0	42 (39)
Prior antineoplastic therapy, n (%)			
Midostaurin	58 (84)	0	58 (54)
Cladribine	12 (17)	0	12 (11)
Imatinib	5 (7)	0	5 (5)
Interferon	10 (14)	0	7 (7)

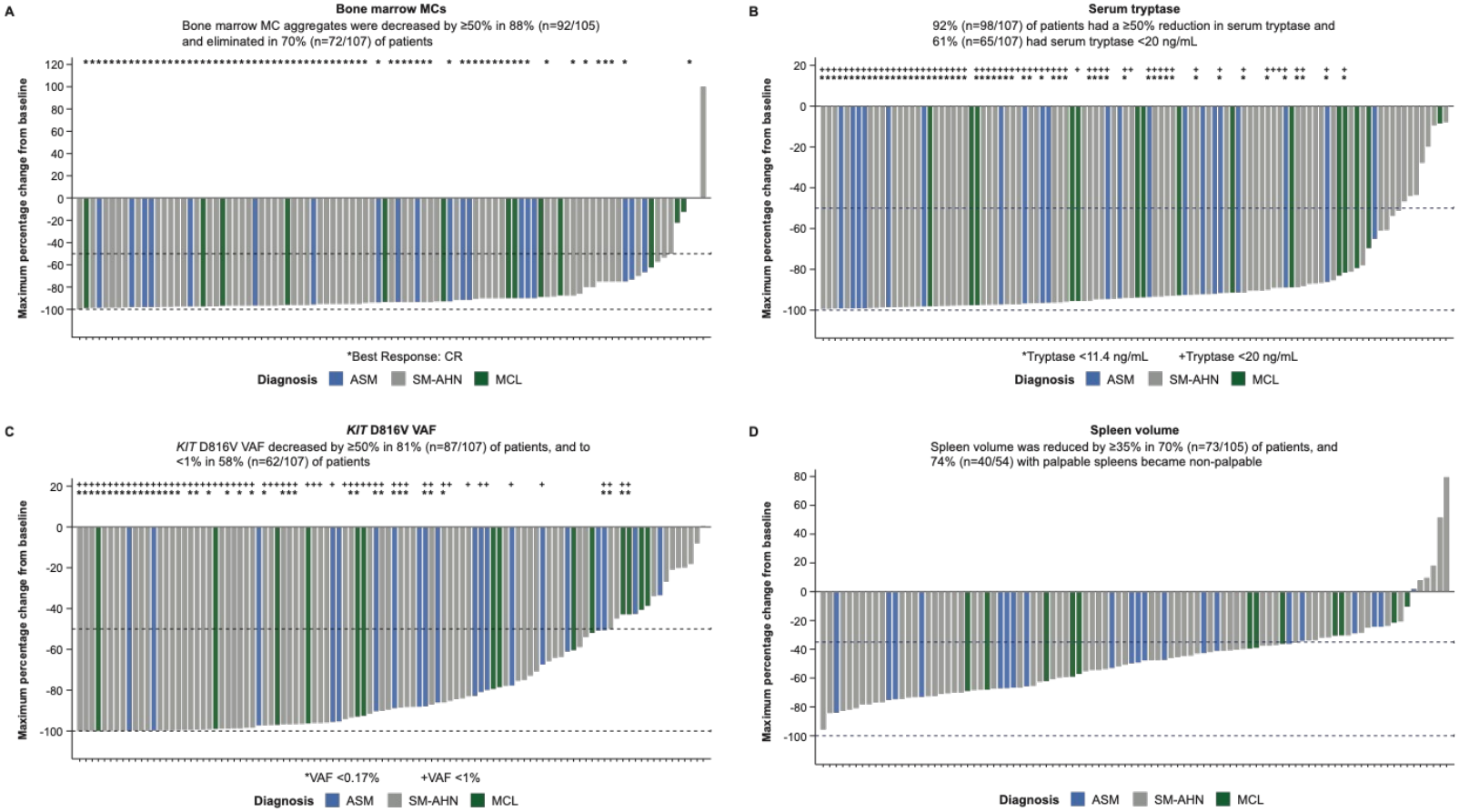
Gotlib et al., P1023, EHA 2023

Efficacy in response-evaluable patients

		AdvSM subtype			Treatment-naïve		After ≥1 prior therapy	
	All (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)	All (n=30)	SM-AHN (n=22)	All (n=53)	SM-AHN (n=33)
ORR[a] 95% CI	73 (n=61) 63–83	77 (n=10) 46–95	75 (n=41) 61–85	67 (n=10) 38–88	90 (n=27) 74–98	91 (n=20) 71–99	64 (n=34) 50–77	64 (n=21) 45–80
CR/CRh[b]	27 (n=22)	15 (n=2)	31 (n=17)	20 (n=3)	40 (n=12)	50 (n=11)	19 (10)	18 (n=6)
PR[c]	42 (n=35)	62 (n=8)	36 (n=20)	47 (n=7)	50 (n=15)	41 (n=9)	38 (n=20)	33 (n=11)
CI	5 (n=4)	0	7 (n=4)	0	0	0	8 (n=4)	12 (n=4)
SD	17 (n=14)	23 (n=3)	15 (n=8)	20 (n=3)	10 (n=3)	9 (n=2)	21 (n=11)	18 (n=6)
PD[d]	2 (n=2)	0	2 (n=1)	7 (n=1)	0	0	4 (n=2)	3 (n=1)
NE	7 (n=6)	0	9 (n=5)	7 (n=1)	0	0	11 (n=6)	15 (n=5)
Median TTR (range), months	2.3 (0.3–15)	2.1 (0.3–15)	2.1 (0.5–12)	7.3 (1.7–12.2)	3.7 (0.3–15.0)	3.1 (0.5–12.2)	2.0 (0.5–14.6)	1.9 (0.5–8.2)
Median time to CR+CRh (range), months	9.1 (1.8–26)	2.8 (1.8–3.7)	9 (1.8–26)	20 (9.3–26)	7.5 (2.0–25.8)	6.1 (2.0–25.8)	12.1 (1.8–15.0)	12.1 (1.8–26.0)
Median DOR[e] (95% CI)	NR (37–NR)	NR (27–NR)	NR (37–NR)	NR (NR–NR)	NR (37–NR)	37 (37–NR)	NR (NR–NR)	NR (NR–NR)
24-month DOR[e], % (95% CI)	89 (81–97)	89 (68–100)	87 (76–98)	100 (100–100)	92 (81–100)	89 (74–100)	87 (75–99)	85 (69–100)

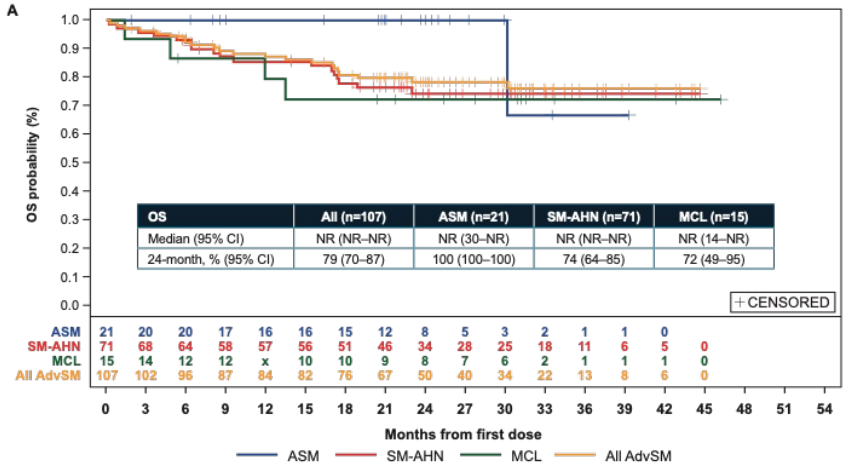
Gotlib et al., P1023, EHA 2023

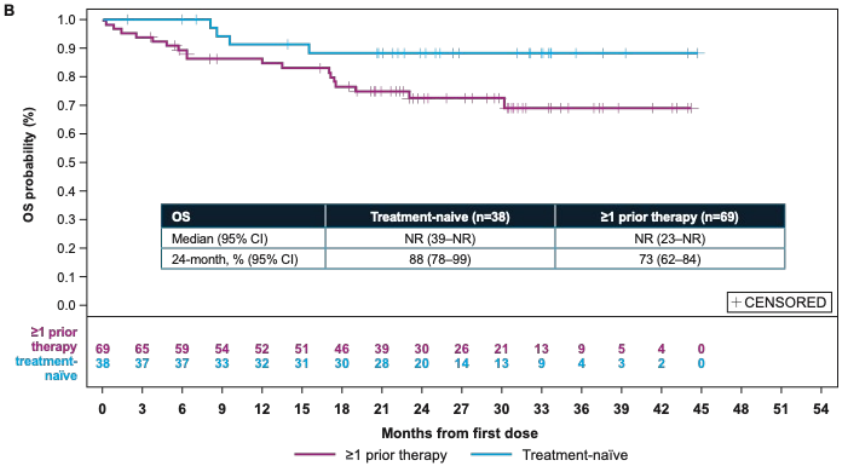
Reductions in objective measures of disease burden



Gotlib et al., P1023, EHA 2023

Overall survival by disease subtype and by treatment history

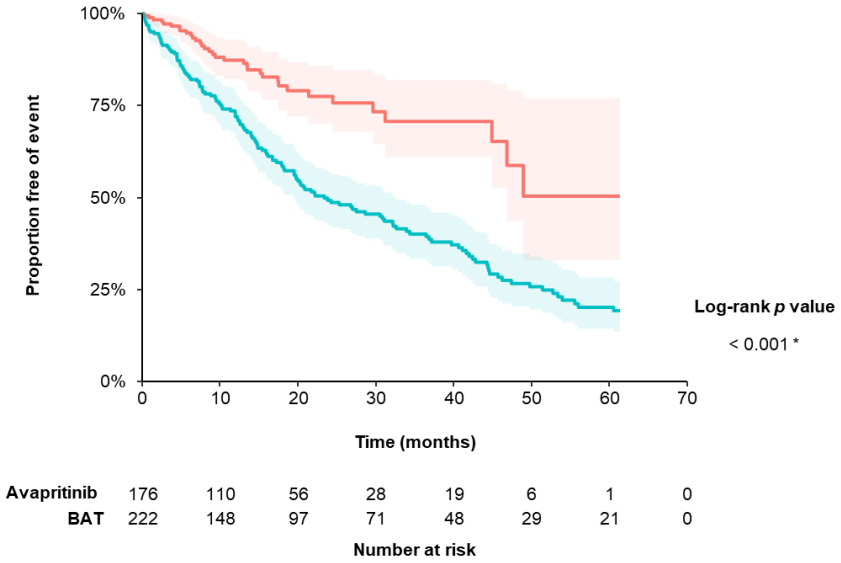




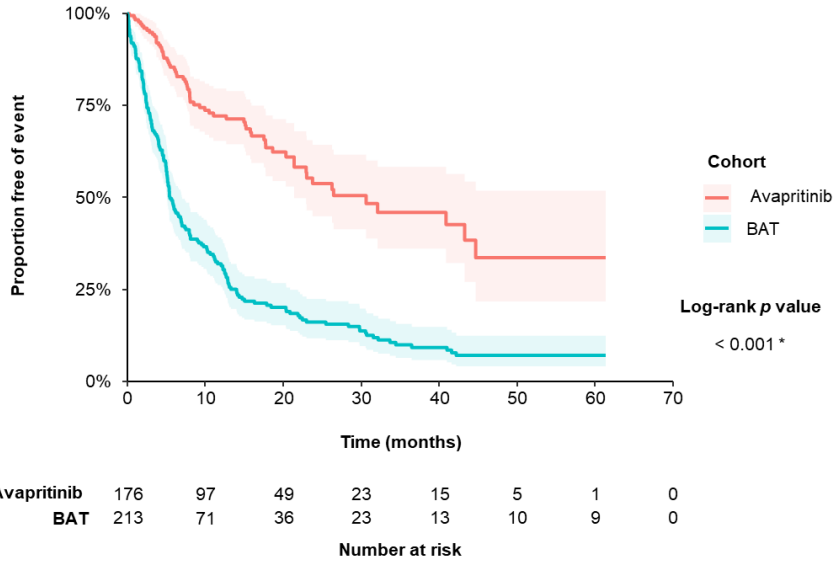
Gotlib et al., P1023, EHA 2023

OS and DOT among avapritinib patients compared to real world patients receiving best available therapy (retrospective study)

OS among avapritinib patients compared to BAT cohort[1]



DOT among avapritinib patients compared to BAT cohort[1]



❖ **Median OS[a]:**

49.0 (46.9, NE) for avapritinib[b] vs **26.8** (18.2, 39.7) for BAT cohort[c]

[a]Weighted by IPTW; [b]Avapritinib cohort: n=172 patients form Explorer/Pathfinder contributing to 172 lines of treatment; [c]BAT cohort: n=136 patients contributing to 210 LOT.

❖ **Median DOT[a]:**

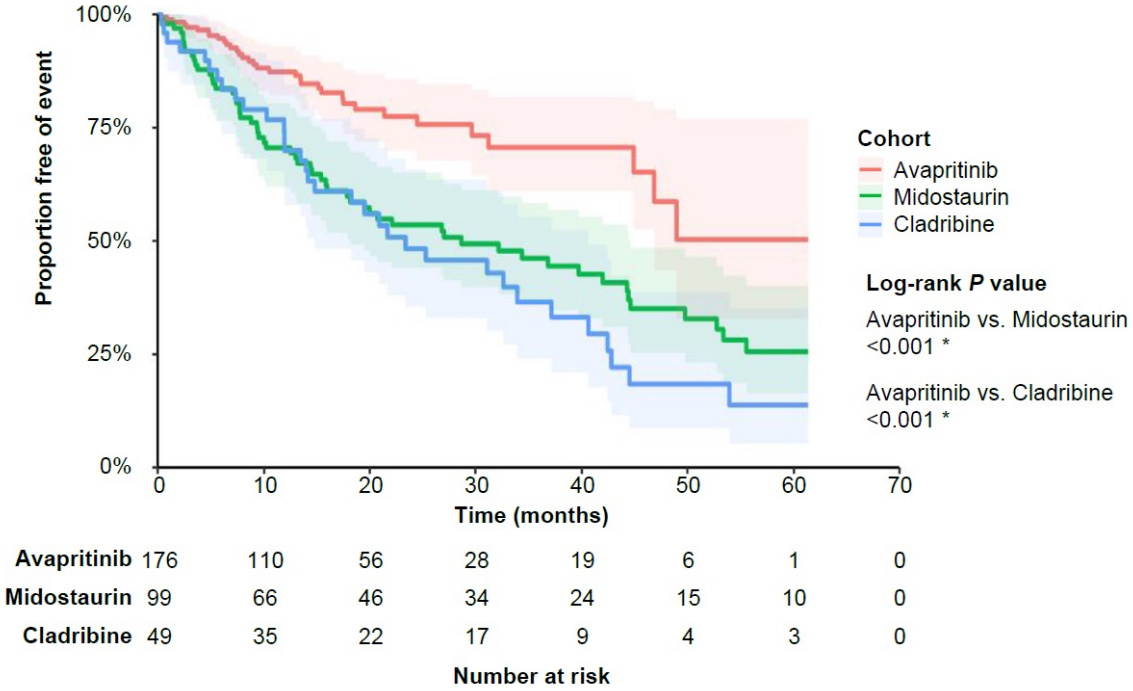
23.8 (20.3, 40.9) for avapritinib[b] vs **5.4** (5.0, 7.5) for BAT cohort[c]

[a]Weighted by IPTW; [b]Avapritinib cohort: n=173 patients from Explorer/Pathfinder contributing to 173 lines of treatment; [c]BAT cohort: n=131 patients contributing to 201 LOT.

BAT, best available therapy; DOT, duration of treatment; IPTW, inverse probability of treatment weighting; LOT, line of treatment; NE, not evaluated; OS, overall survival.
Observational retrospective external control study.

Reiter et al., Leukemia 2022

Unweighted KM curve for OS of patients with AdvSM treated with avapritinib versus midostaurin or cladribine



*P<0.05
Abbreviations: AdvSM: advanced systemic mastocytosis; KM: Kaplan-Meier; OS: overall survival.
Note: The follow-up times for the midostaurin and cladribine cohorts were truncated to match the maximum follow-up time of the avapritinib cohort. In the midostaurin cohort, 94 patients contributed 99 lines of therapy to the analysis. In the cladribine cohort, 44 patients contributed 49 lines of therapy to the analysis.

Reiter et al. EHA Congress 2022, June 9-12, Poster #1014

Platelets monitoring and management reduced risk of ICBs

EXPLORER[1]

n=69

- **Starting Dose**: 30-400 mg
- **Platelets**:
  - no restriction
- **9 ICB** Events
  - 400 mg[#]: 1
  - 300 mg: 6
  - 200 mg: 2

Risk factor analysis [§,2] Protocol amendment, 2019

PATHFINDER[3]

n=107

- **Starting Dose**: 200 mg
- **Platelet**:
  - restricted to $> 50 \times 10^9$/l
  - platelets monitoring
- **1 ICB event** (prior to protocol amendment, platelets $<50 \times 10^9$/l)
  - 200 mg: 1

SmPC[4]

Assess ICH risk before treatment, especially:

- In patients with potential increased risk including those with thrombocytopenia, vascular aneurysm or a history of ICH or CVA within the prior year.

Platelet monitoring for patients with AdvSM

Perform platelet counts before initiating avapritinib

Avapritinib is not recommended in patients with platelet counts <50 x 10^9/L

After treatment initiation:

Perform platelet counts every 2 weeks for the first 8 weeks regardless of baseline platelet count

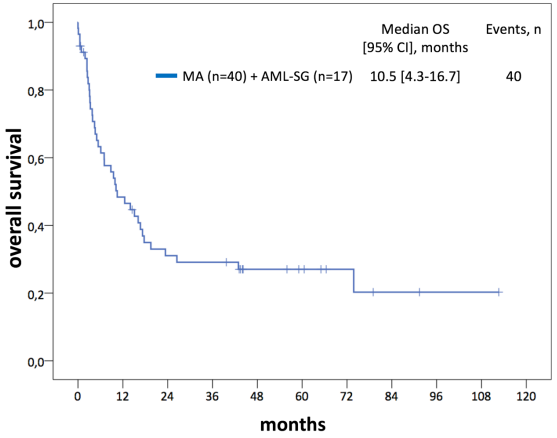
After 8 weeks of treatment, monitor platelet count:

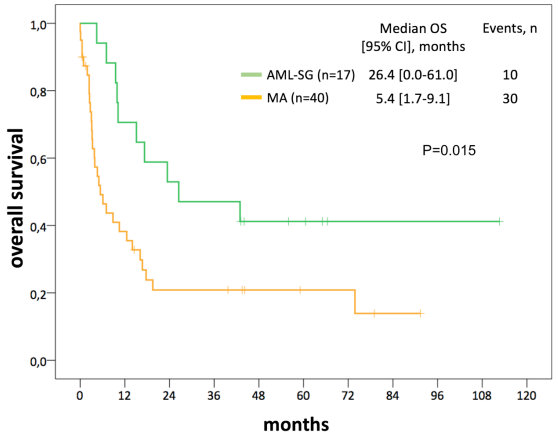
- Every 2 weeks* if values are less than 75 x 10^9/L
- Every 4 weeks if values are between 75-100 x 10^9/L
- As clinically indicated if values are >100 x 10^9/L

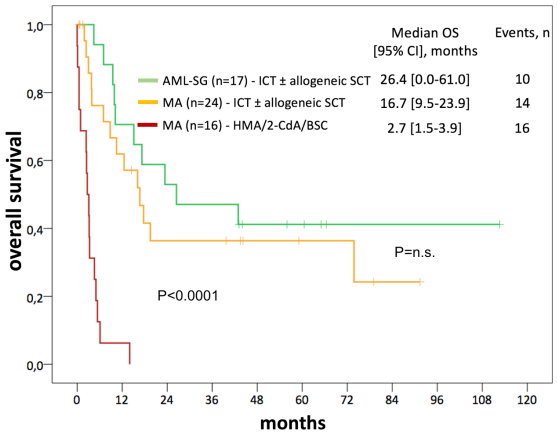
If any ICH event occurs, permanently discontinue avapritinib

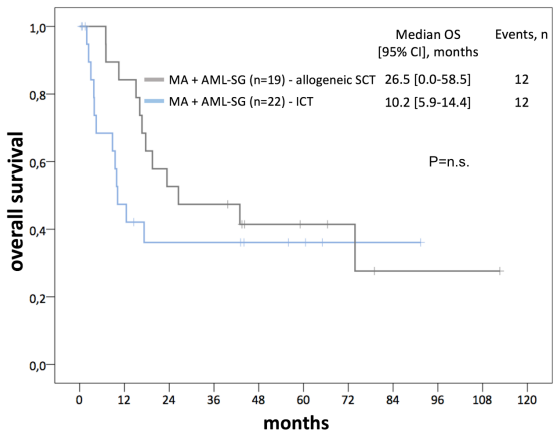
[#] starting dose. [§]In A logistic regression analysis of potential risk factors for ICB events in EXPLORER and PATHFINDER (including platelet counts, starting dose, concomitant anti-thrombotic therapy, INR, and aPTT levels) identified thrombocytopenia (platelet counts <50,000/μL) as the only statistically significant risk factor (p=0.0292), with an odds ratio of 13.552 (95% CI: 1.3901, 141.142).[2] *Or more frequently as clinically indicated.
AdvSM, advanced systemic mastocytosis; CVA, cerebrovascular accident; ICB, intracranial bleeding; ICH, intracranial haemorrhage.
1. DeAngelo DJ et al. Nat Med. 2021; 27 (12): 2183-2191 **Data cut off May 27th, 2020;** 2. Data not published. (REF-MED-0672). Blueprint Medicines Corporation, Cambridge, MA. 2021. a. Regression analysis conducted April 2019; 3. Gotlib J et al. Nat Med. 2021; 27 (12) 2192-2199 **Data cut off June 23rd, 2020;** 4. AYVAKYT Summary of Product Characteristics. Blueprint Medicines October 2022.

Outcome of *KIT* D816$^{pos.}$/CBF$^{neg.}$ SM-AML



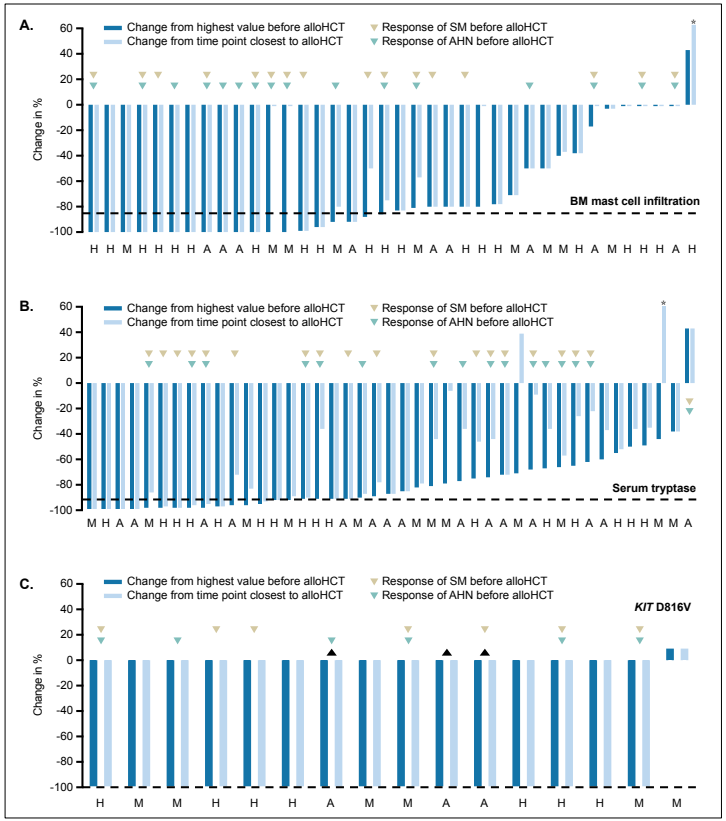






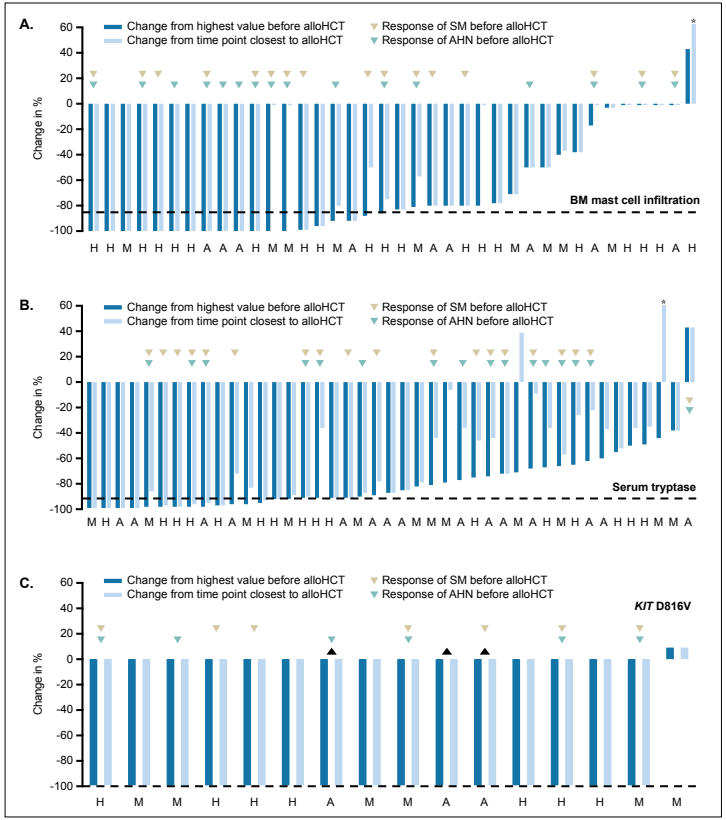
Jawhar et al., Leukemia 2019

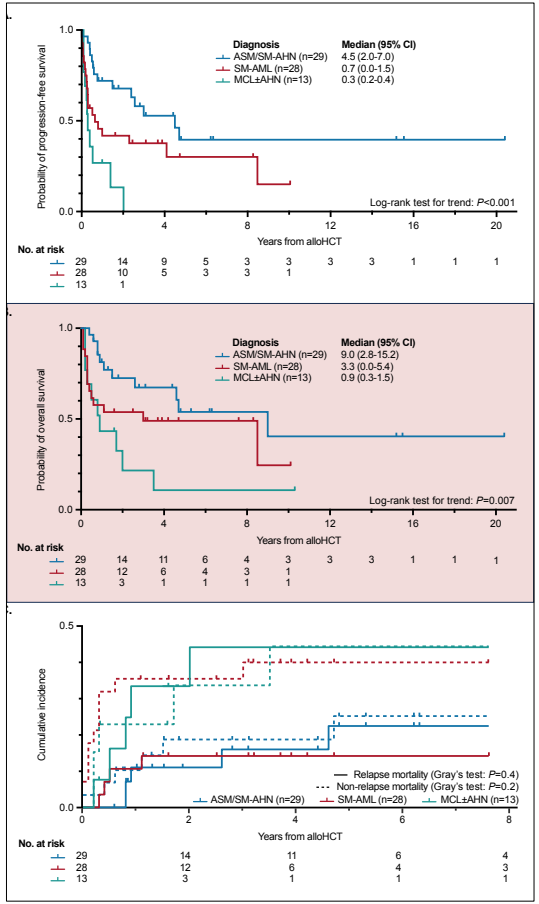
Allogeneic HCT in AdvSM



Lübke et al., Leukemia 2024

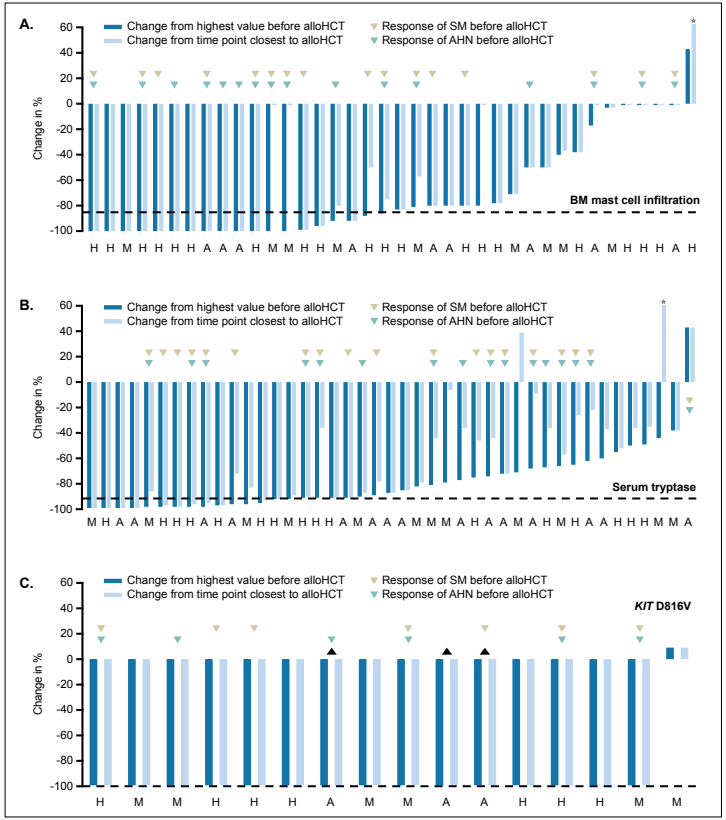
Allogeneic HCT in AdvSM

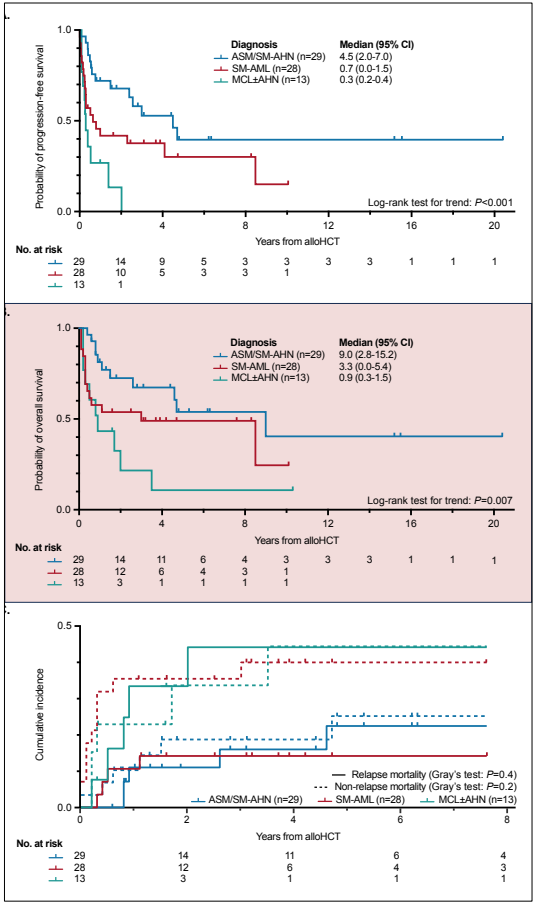




Lübke et al., Leukemia 2024

Allogeneic HCT in AdvSM



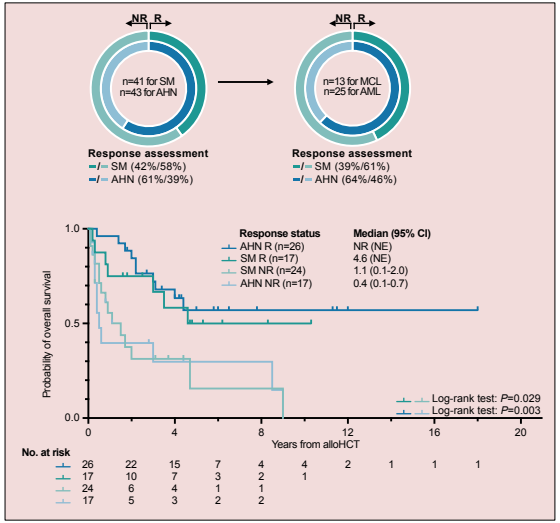


Adverse impact on OS

- **Absence of *KIT* D816V** (10/61, 16%, HR 2.9 [1.2-6.5], *P*<0.001)
- **Complex karyotype** (9/60, 15%, HR 4.2 [1.8-10.0], *P*=0.016)

No impact on OS

- HLA-match
- Conditioning type
- Transplantation at centers reporting above-average Tx (≥7)



Lübke et al., Leukemia 2024

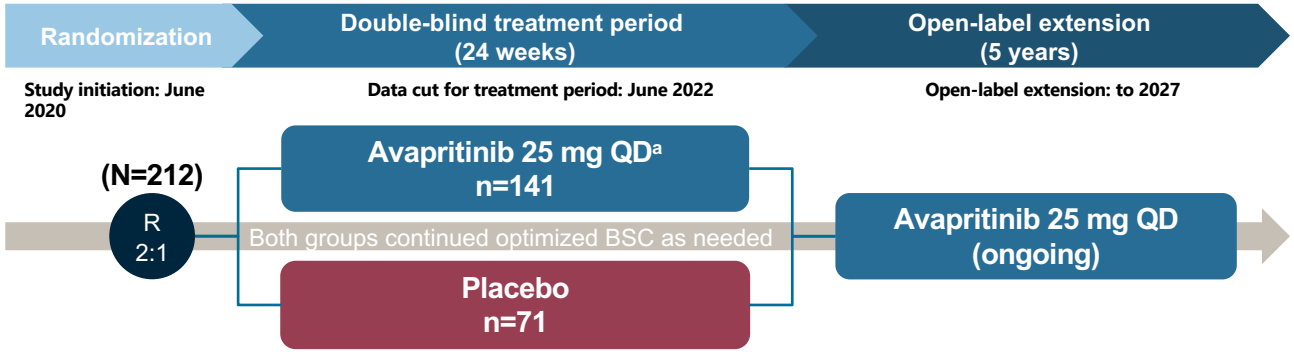
Conclusion

- In AdvSM, **multilineage involvement of *KIT* D816V** and presence of **additional somatic mutations** in 60-80% of patients
- **MARS** predicts prognosis by age, cytopenias and additional somatic mutations (*SRSF2*, *ASXL1*, *RUNX1*)
- Available targeted treatment with **midostaurin** and **avapritinib**. On avapritinib, high overall response rates and improved survival
- Ongoing clinical trials with **elenestinib** and **bezuclastinib**
- In eligible patients, **alloHCT** should remain the treatment goal. Outcome of alloHCT rather depends on phenotype and response to prior treatment than on transplant procedures
- Avapritinib is also approved for patients with **indolent SM** (response of symptoms, MC infiltration, tryptase and *KIT* D816V VAF)

Registrational PIONEER study: Randomized, double-blind, placebo-controlled study in patients with ISM

Screening period

- Best supportive care medications (BSC) optimized for up to a month
  - Antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.
- Eligibility
  - Age ≥18 years
  - ISM by central pathology review
  - Moderate to severe symptoms (TSS ≥28) after ≥2 BSC medications



Symptoms
Primary endpoint

- Mean change in ISM-SAF Total Symptom Score (**TSS**) from baseline to Week 24
- Mean change in **individual symptom scores** of ISM-SAF
- Mean change in **most severe symptom score**

Biomarkers of mast cell burden
Key secondary endpoints

- ≥50% reduction in **serum tryptase** levels
- ≥50% reduction in ***KIT* D816V VAF** in peripheral blood (or below level of detection [<0.02%] for patients with a detectable mutation at baseline)
- ≥50% reduction in in bone marrow **mast cell aggregates**

Quality of life

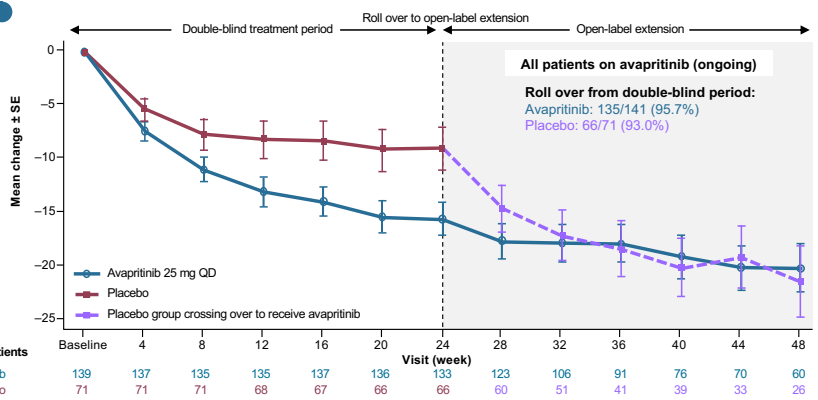
- Mean % change in QoL score, as measured by **MC-QoL**

[a]The recommended dose of avapritinib for the double-blind period and open-label extension was identified based on efficacy and safety results from Part 1 that included 4 cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10) and placebo (n=9). Patients treated with high dose steroids within 7 days of primary endpoint (n=4) were excluded from the week 24 analysis, but included at other timepoints of the study. Percentages were calculated based on available data at the timepoint. One-sided P-values are reported for primary and key secondary endpoints. ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MC-QoL, Mastocytosis Quality of Life Questionnaire; QD, once daily; QoL, quality of life; R, randomized; TSS, total symptom score; VAF, variant allele fraction.

Adapted from Gotlib et al., NEJM evidence 2023

Avapritinib in indolent SM

TSS over time



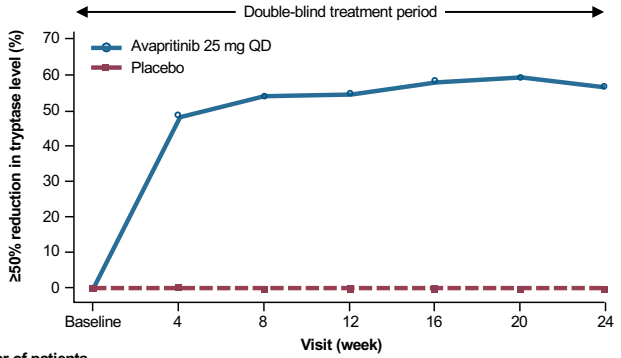
Number of patients	Baseline	4	8	12	16	20	24	28	32	36	40	44	48
Avapritinib	139	137	135	135	137	136	133	123	106	91	76	70	60
Placebo	71	71	71	68	67	66	66	60	51	41	39	33	26

Primary endpoint

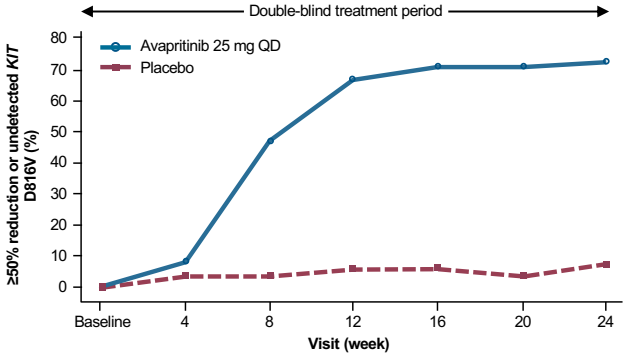
A one-sided P-value of <0.025 was needed to declare avapritinib as superior in reducing TSS versus placebo.

SE, standard error of the mean.

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Mean change in TSS (95% CI)	−15.58 (−18.61, −12.55)	−9.15 (−13.12, −5.18)	0.003



Number of patients	Baseline	4	8	12	16	20	24
Avapritinib	141	133	136	132	133	128	134
Placebo	71	66	62	61	60	62	64



	Baseline	4	8	12	16	20	24
Avapritinib	118	110	113	109	107	104	109
Placebo	63	57	54	52	51	53	54

Adapted from Gotlib et al., NEJM evidence 2023

Conclusion

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