Società Italiana di Ematologia

Convegno interregionale SIE

Delegazioni Emilia Romagna e Toscana

Gli ematologi insieme contro le malattie rare

Le novità in tema di terapie

Michela Rondoni
AUSL Romagna- UOC Ematologia Ravenna

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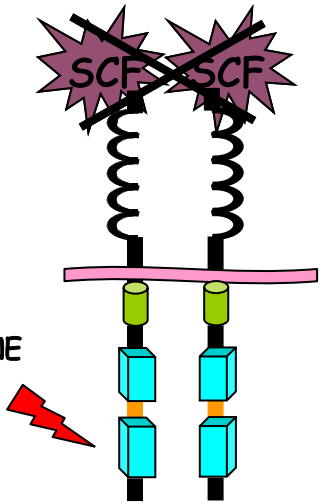
Bologna, Aula Prodi

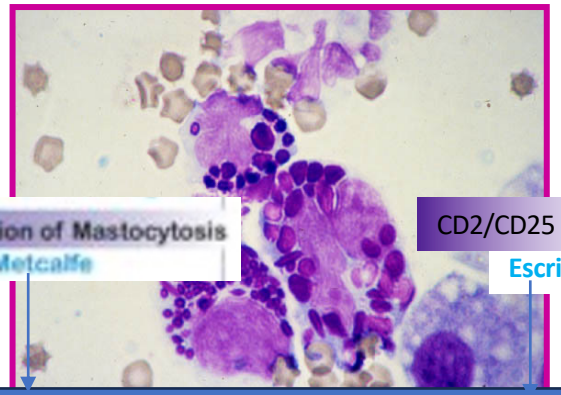
Disclosures of Michela Rondoni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie							X
Astellas						X	X
Pfizer							X
Amgen							X
Blueprint	X					X	
Incyte						X	
Gentili						x	X
Jazz pharmaceuticals	X					X	x

Outline

- ✓ Update studi TKI
- ✓ Criteri di risposta e score di rischio per le scelte terapeutiche in ASM
- ✓ TKI per ISM
- ✓ Nuove molecole





Paul Ehrlich
First described tissue Mast cells

Yosef Yarden
KIT identification and cloning

Classification of Mastocytosis
Metcalfe

CD2/CD25 on MCs
Escribano

WHO 2001-2008

1878 1967 1987 1990 1991 1995 1998 2000 2001 2008 2016 2023

Ginsburg
Mast cell culture

Identification of SCF
Douglas E. Williams

Identification of D816V mutation
Hiroshi Nagata

Working conference
Valent

2-CdA

TK INHIBITORS

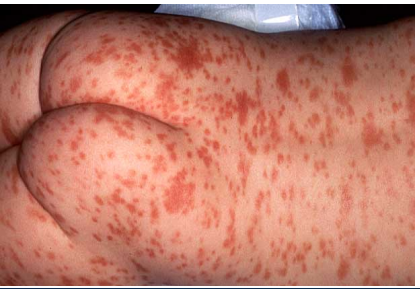
MIDOSTAURINA

AVAPRITINIB

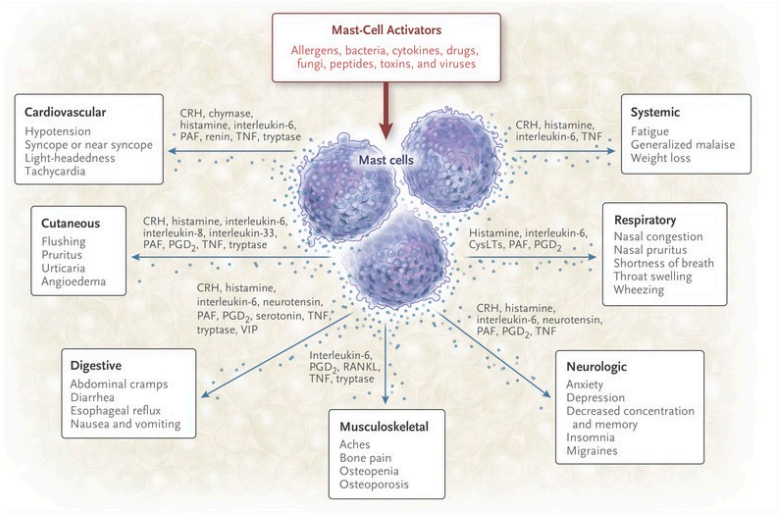
BEZUCLASTINIB

ELENESTINIB

TL-895B

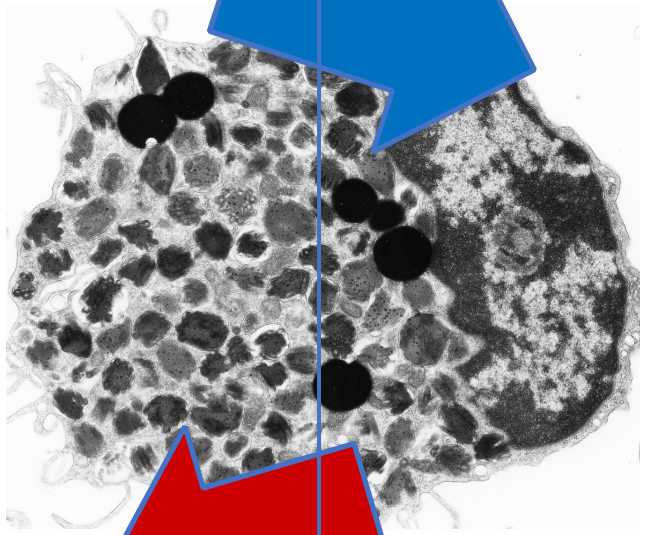


Come trattare i pazienti: Terapia multidisciplinare

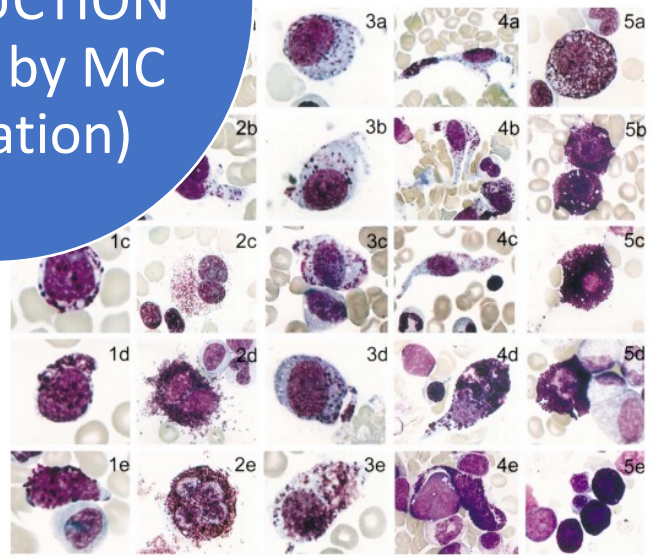


NEJM (2015) 373:163-72

Terapia citoriduttiva

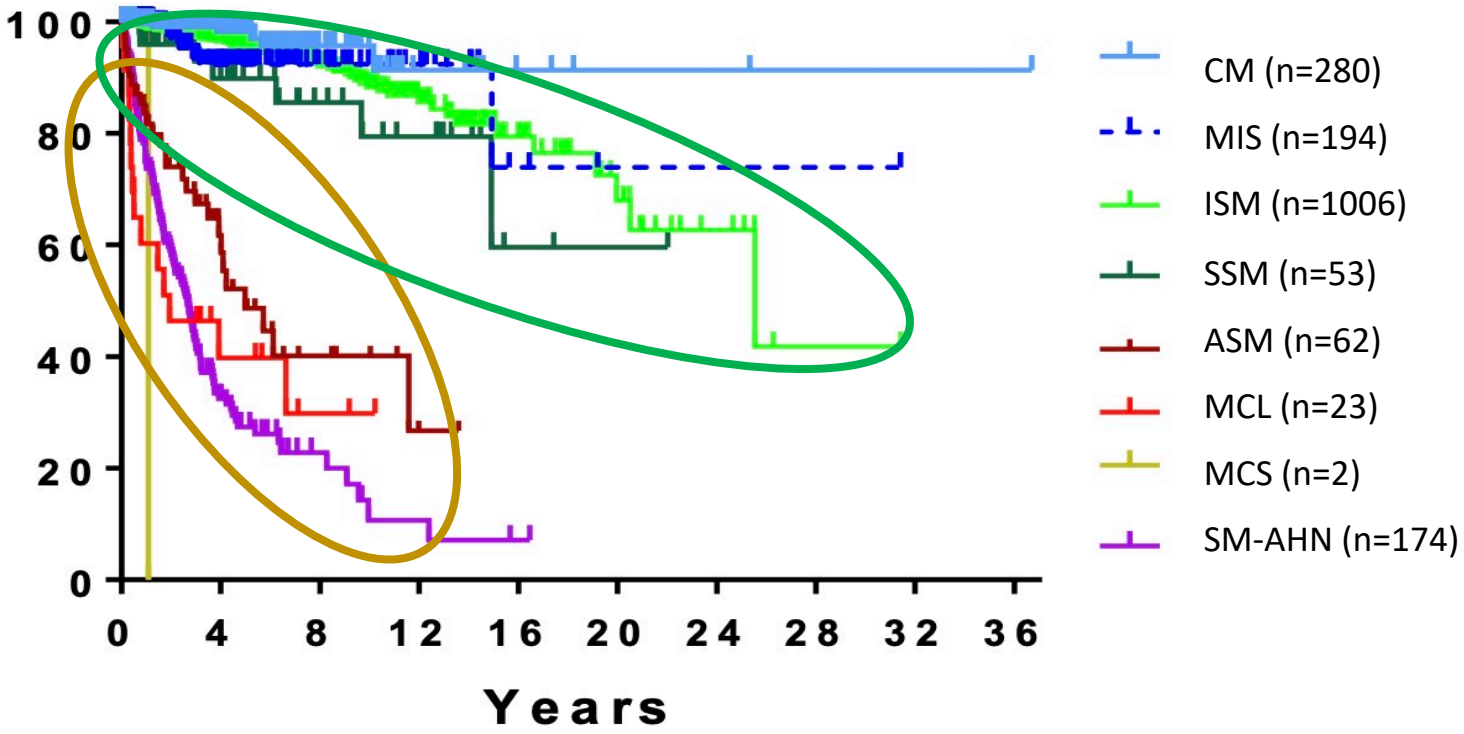


C-FINDINGS (ORGAN DESTRUCTION caused by MC infiltration)



Terapia anti-mediatori
Terapia sintomatica

Perché trattare i pazienti: Prognosi



Non-advanced mastocytosis

OS>90% at 10 years

→ Control symptoms & prevent complications

Advanced mastocytosis

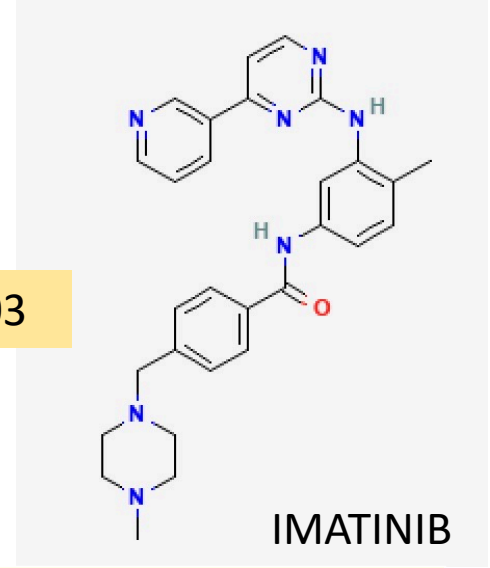
Median OS < 5 years

→ Reverse organ damage & improve survival

Sperr et al. Lancet hematol 2019;6:e638-649

TKI in Systemic Mastocytosis

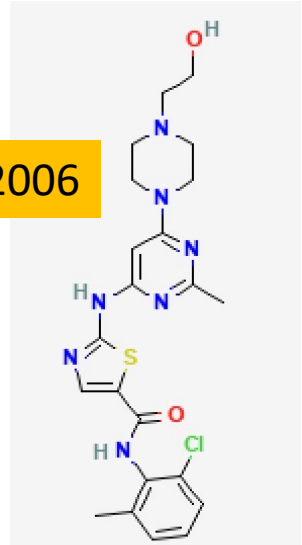
2003



IMATINIB

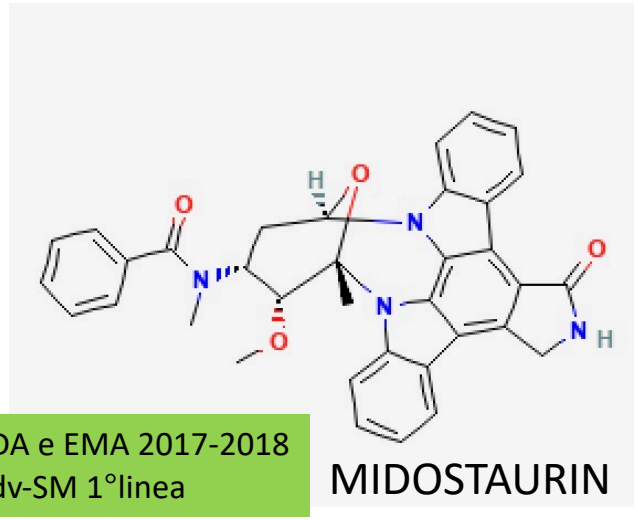
IMATINIB: indicato solo nelle forme con KIT WT o varianti mutate di KIT (D560G, F522C, K509I) o riarrangiamento FIP1L1/PDGFRA
Negli altri casi riportate risposte nel 5% dei casi

2006



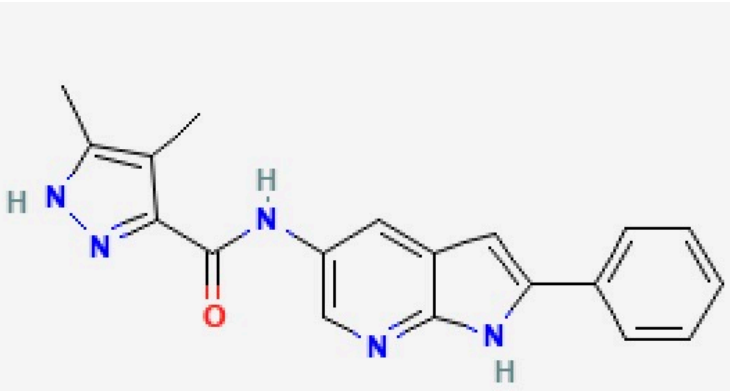
DASATINIB

DASATINIB: efficace nel ridurre i sintomi da infiltrazione d' organo (USO TERAPEUTICO)



Approvato FDA e EMA 2017-2018 per Adv-SM 1°linea

MIDOSTAURIN



Approvato FDA e EMA 2022 per Adv-SM 2° linea
Approvato FDA e EMA 2025 per ISM

AVAPRITINIB

Outline

- ✓ Update studi TKI
- ✓ Criteri di risposta e score di rischio per le scelte terapeutiche in ASM
- ✓ TKI per ISM
- ✓ Nuove molecole

Midostaurin: a multitarget drug

KIT wt
KIT D816V
KIT V560G
KIT K509I
FES

FLT3 wt
FLT3 ITD
FLT3 D835H
FLT3 D835Y
FLT3 N841I
PDGFRA wt
FIP1L1-PDGFRA (F/P)
F/P mutant forms
PDGFRB wt
PDGFRB mutant forms
JAK2
JAK3
AAK1
SYK
AURKA
AURKB
MARK3
PKN1
FGFR3
FGFR3 TDII (K650E)
TEL-FGFR3

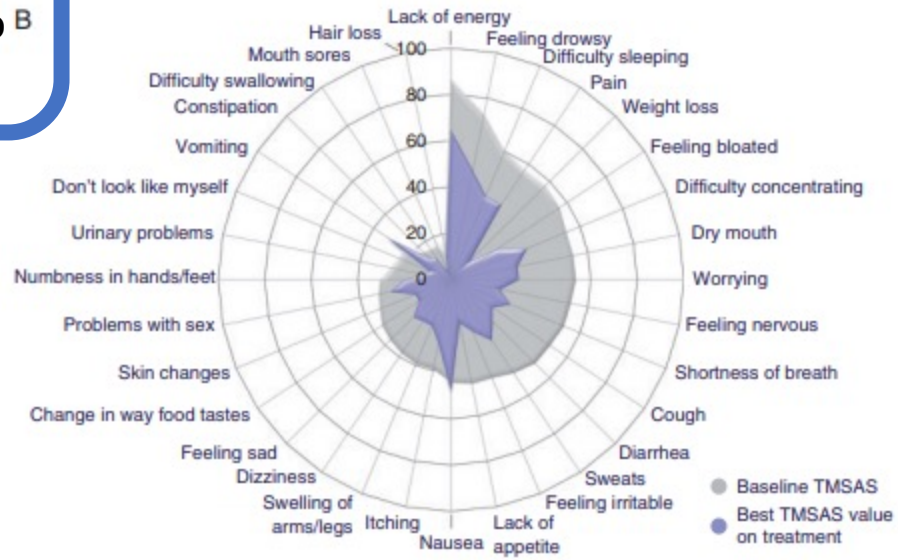
SINGLE AGENT ACTIVITY: ORR 69%

MEDIAN DURATION OF RESPONSE 24.1 MONTHS

IMPROVEMENT OF PATIENTS-REPORTED SYMPTOMS

MANAGEABLE TOXICITY (GRADE 3-4: VOMITING, DIARROEA AND FATIGUE)

NO CR (Valent, 2007)

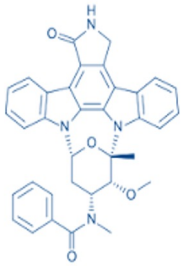


Gotlib J, et al. *N Engl J Med.* 2016;374:2530-2541- Valent, Ann of Allergy, 2018

Long term efficacy of phase 2 trial A2213

AIFA 2018

Approved for treatment as monotherapy of ASM, SM-AHN and MCL patients : **100 mg x 2**



Characteristics	(n = *26*)
Median age, years (range)	64.5 (24–79)
Male, *n* (%)	15 (58)
ECOG performance status, n *(%)*	
0–1	12 (46)
2–3	14 (54)
Time from SM diagnosis (by bone marrow biopsy) to start of study treatment, days (range)	241 (12–1756)
Number of prior therapies, n *(%)*	
None	5 (19)
1	8 (31)
2	6 (23)
⩾3	7 (27)
Types of prior therapies, n *(%)*	
Corticosteroids	14 (54)
Imatinib	10 (39)
2-Chlorodeoxyadenosine	5 (19)
Hydroxycarbamide	4 (15)
Dasatinib	4 (15)
(PEG)-interferon-α	3 (12)
Other[a]	3 (12)
Denileukin difitox	2 (8)
Histopathology review, n *(%)*	
SM subtype	
ASM	3 (12)
SM-AHN	17 (65)
CMML	12 (46)
MDS/MPN-U	3 (12)
MDS	2 (8)
MCL[b]	6 (23)
KIT D816 mutation[c,d], *n* (%)	20 (77)
Other *KIT* mutation[e]	1 (4)
KIT mutation negative[f]	5 (19)
Median tryptase level, ng/ml (range)	323 (22–1255)
Median bone marrow mast cell burden, % (range)	50 (5–95)

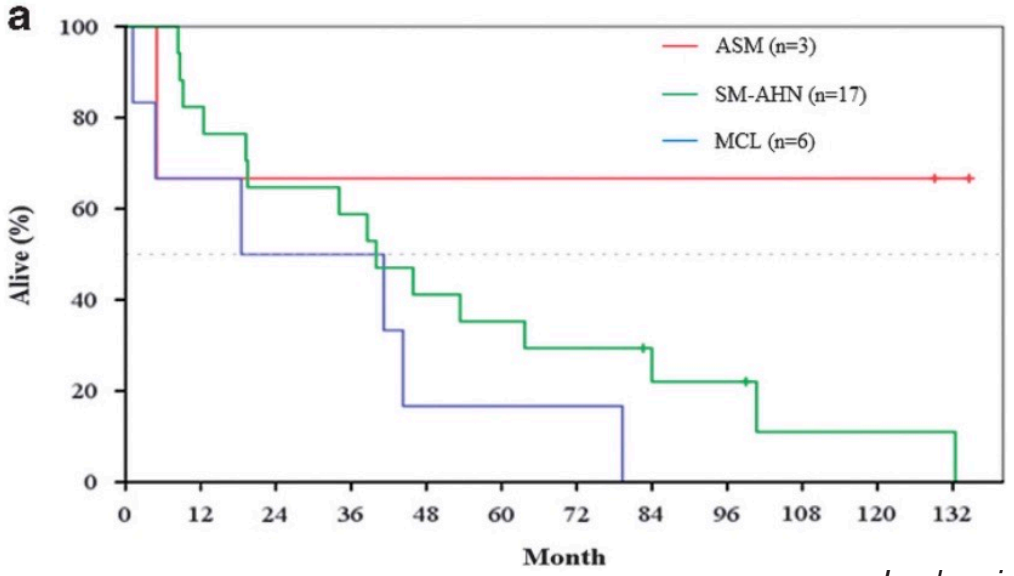
26 pt

ORIGINAL ARTICLE

Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial

DJ DeAngelo[1], TI George[2], A Linder[3], C Langford[3], C Perkins[3], J Ma[3], P Westervelt[4], JD Merker[5], C Berube[3], S Coutre[3], M Liedtke[3], B Medeiros[3], D Sternberg[6,7], C Dutreix[6,7], P-A Ruffie[6,7], C Corless[8], TJ Graubert[9] and J Gotlib[3]

2005-2010



FU 124 mesi

ORR 69%

Leukemia (2018) 32, 470–478

AdvSM subtype according to MARS was predictive of median OS and TTF (CEREMAST STUDY)

170 pt

AdvSM subtype according to MARS score[a]	Median TTF, months (range)	Median OS, months (range)
Low-risk ASM	59.8 (30.5–NR)	NR (NR–NR)
Low-risk SM-AHN	26.1 (13.0–NR)	57.6 (34.4–NR)
Intermediate/high-risk ASM	6.7 (3.9–NR)	33.0 (24.4–NR)
Intermediate/high-risk SM-AHN	8.4 (5.9–12.9)	24.0 (16.9–38.2)
MCL	3.6 (3.1–NR)	9.9 (4.9–NR)

Heiblig, Am J Hematol. 2024;99:2127–2139.

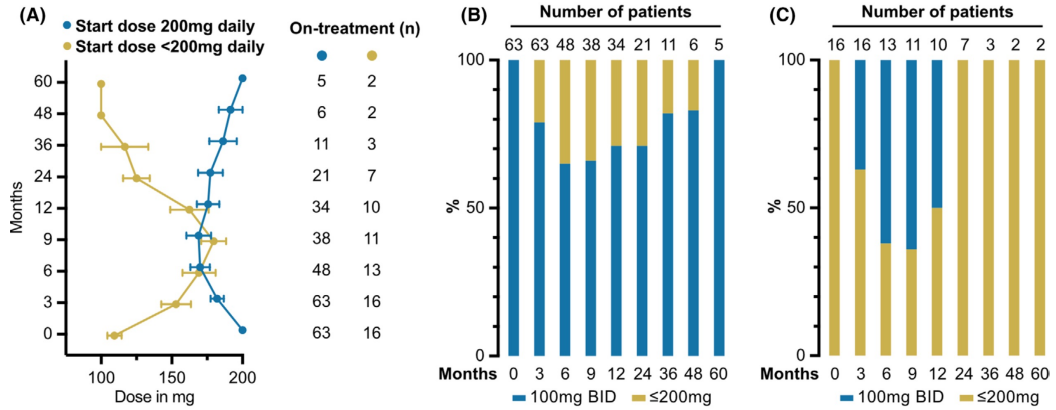
Response to treatment with midostaurin differed significantly across AdvSM subtypes (N=170; median follow-up 19 months).

Among responders (n=86), almost two-thirds (61%) discontinued midostaurin

Of these, 73% discontinued due to relapse, 23% due to intolerance, and 4% switched to allo-HSCT

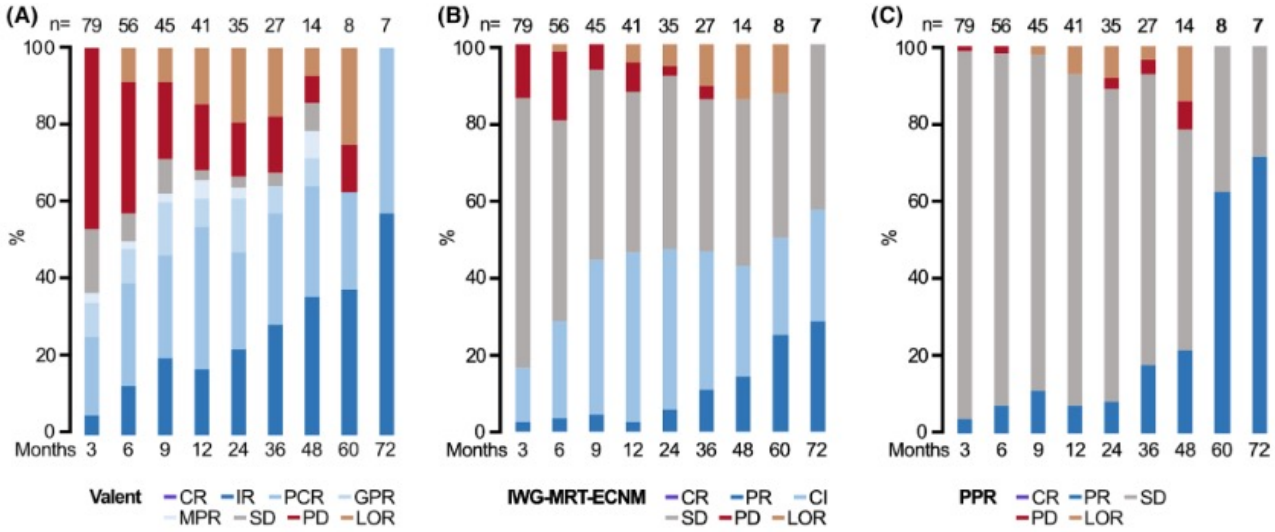
Midostaurin in daily clinical practice (GREM STUDY)

79 pt

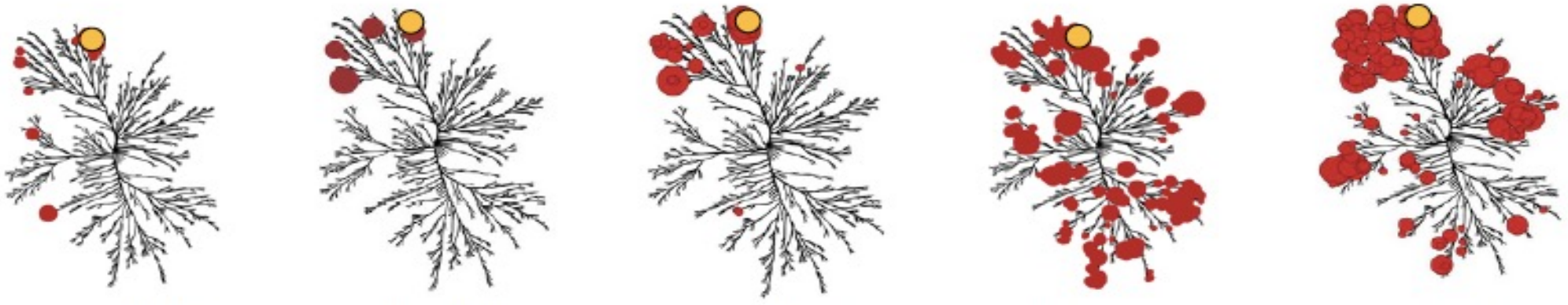


96 adverse events (AE) led to dose adjustment
nausea/emesis (n = 22, 23%)
neutropenia (n = 8, 8%)

2009 - 2021
125 AdvSM→ 79 pt
Median treatment duration 1.0 year (range 0.1–11.4)
Progression (MCL or AML occurred in 11%
31/79 patients (39%) remained on-treatment
Lack of Response/progression 39%
Death 6%
AEs 13%



Avapritinib is the only targeted therapy designed for potent and selective inhibition of the underlying driver, *KIT* D816V (and PDGFRA D842V)



Binding to KIT Binding to other kinases (size is proportional to binding)

KIT D816V biochemical IC_{50}				
avapritinib*	imatinib*	masitinib#	midostaurin*	ripretinib#
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Evans E, et al. Science Translational Medicine (2017) 1;9(414);Gotlib J, et al. NEJM (2016) 374:2530

PATHFINDER: Study design and patient disposition

- International, multicenter, open-label, single-arm, phase 2 study designed to assess the efficacy and safety of avapritinib in adult patients with a centrally confirmed AdvSM diagnosis

Eligibility

- Centrally confirmed AdvSM diagnosis per WHO criteria
- ≥18 years of age
- ECOG PS 0–3
- Platelets ≥50×10^9/L

Primary endpoint:

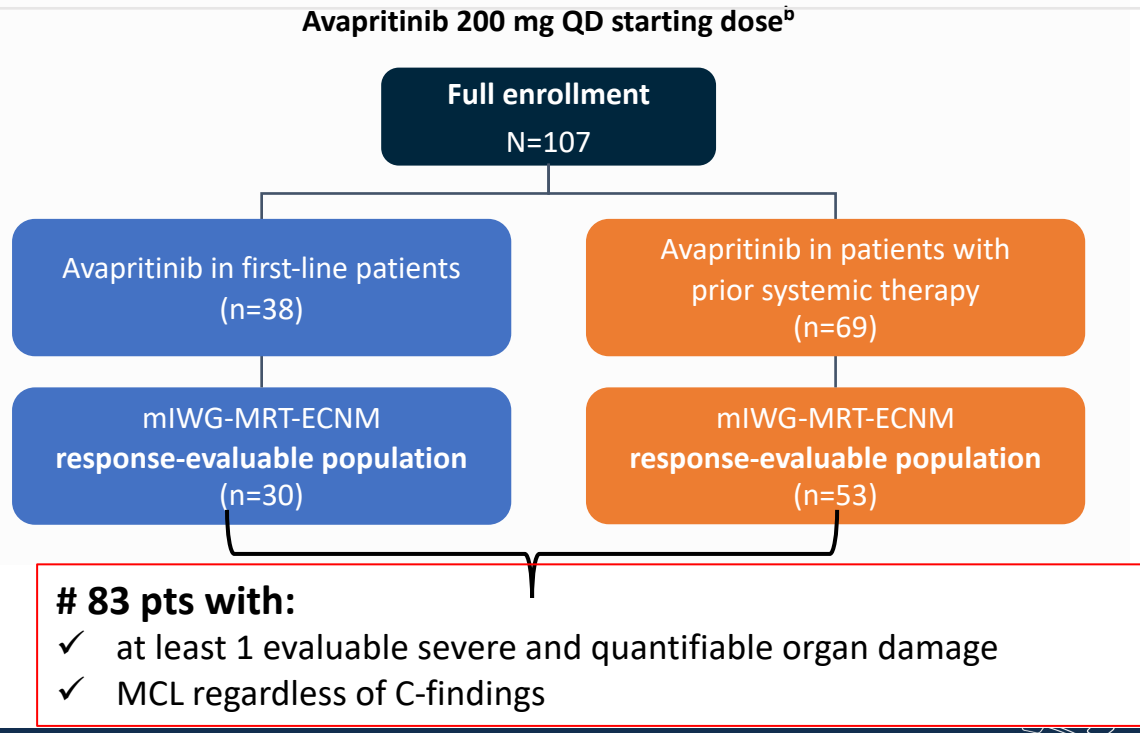
- Centrally adjudicated ORR by mIWG-MRT-ECNM criteria

Secondary endpoints

- Biomarkers of objective disease burden measures[a]
- Duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety

Exploratory endpoints

- Bone density (BD)
- Levels of bone turnover markers (PINP, TRAcP-5b)



PATHFINDER: Response rate and time-to-response

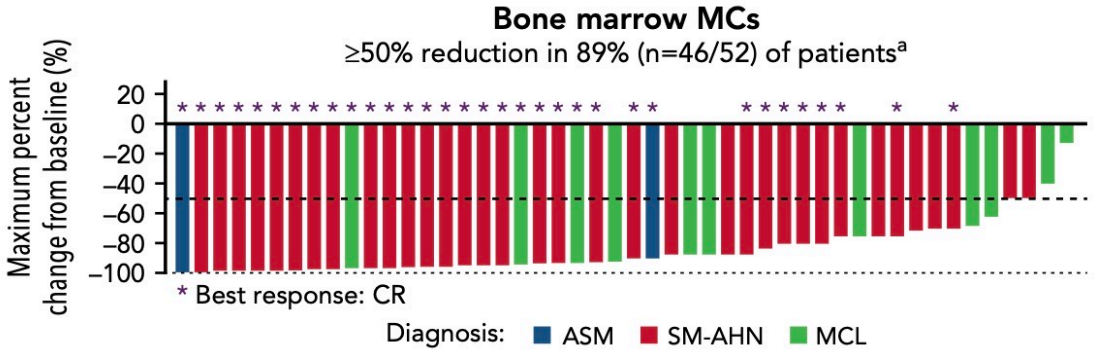
IWG-MRT-ECNM

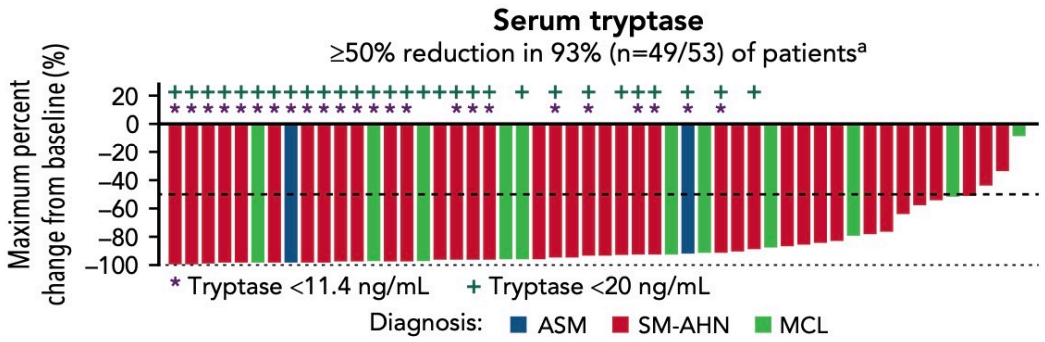
		AdvSM subtype		
	All (n=83)	ASM (n=13)	SM-AHN (n=55)	MCL (n=15)
ORR[a], % (n)	**73 (n=61)**	77 (n=10)	75 (n=41)	67 (n=10)
95% CI	63–83	46–95	61–85	38–88
CR/CRh[b]	**27 (n=22)**	15 (n=2)	31 (n=17)	20 (n=3)
PR[c]	42 (n=35)	62 (n=8)	36 (n=20)	47 (n=7)
CI	5 (n=4)	0	7 (n=4)	0
SD	17 (n=14)	23 (n=3)	15 (n=8)	20 (n=3)
PD[d]	2 (n=2)	0	2 (n=1)	7 (n=1)
NE	7 (n=6)	0	9 (n=5)	7 (n=1)
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)
Median time to CR+CRh (range), months	9.1 (1.8–26)	2.8 (1.8–3.7)	9 (1.8–25.8)	20 (9.3–26.0)
Median DOR[e] (95% CI)	NR (37–NR)	NR (27–NR)	NR (37–NR)	NR (NR–NR)
24-month DOR[e], % (95% CI)	89 (81–97)	89 (68–100)	87 (76–98)	100 (100–100)

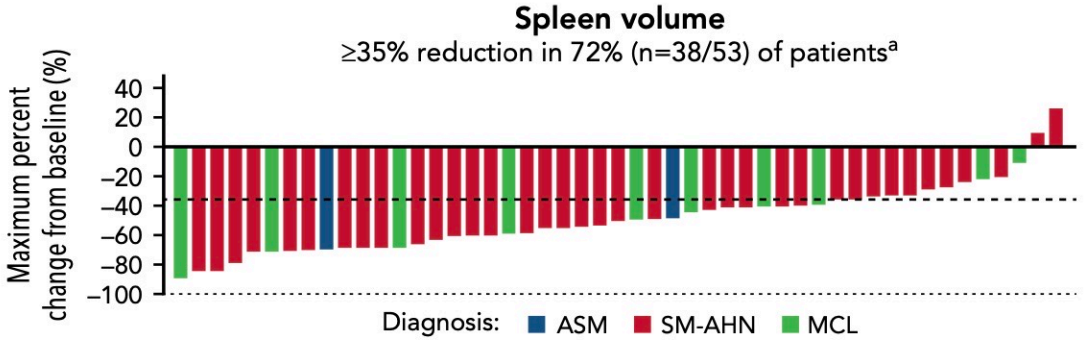
[a]CR+CRh+PR+CI. [b]CRh requires full resolution of all evaluable C-findings, elimination of BM mast cell aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as absolute neutrophil count >0.5×10^9/L with normal differential, platelet count >50×10^9/L, and Hgb level >8.0 g/dL). [c]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both BM MCs and serum tryptase. [d]Two patients had PD as best response. [e]The denominator is based on patients with overall response.

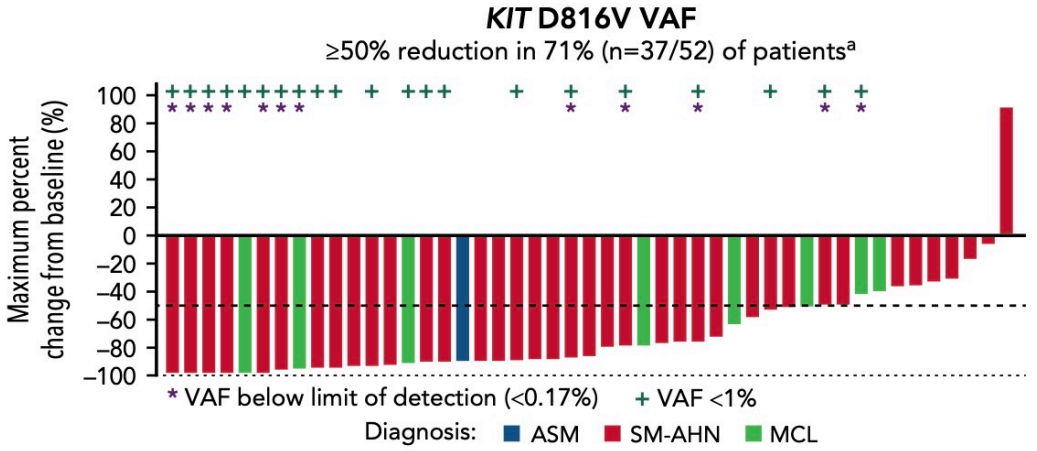
De Angelo DJ et al, Nat Med 2021; 27:2192

Efficacy of Avapritinib in AdvSM patients





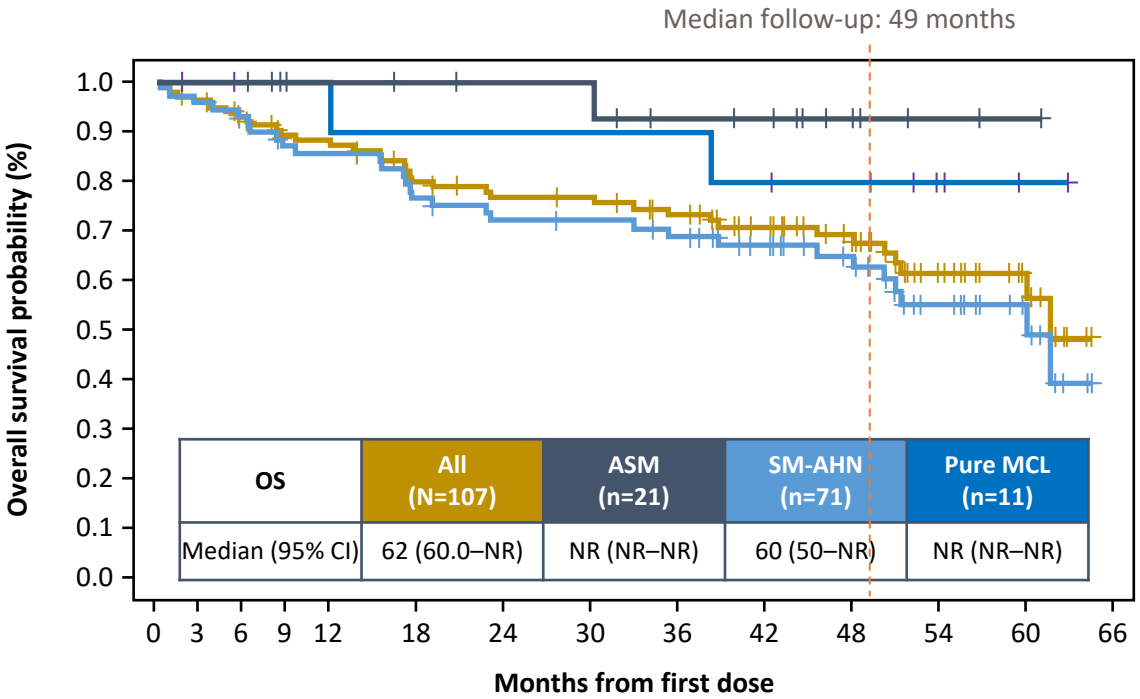




Gotlib J et al, Blood 2022;140(15):1667-1673

PATHFINDER: Update with 4 years median follow-up

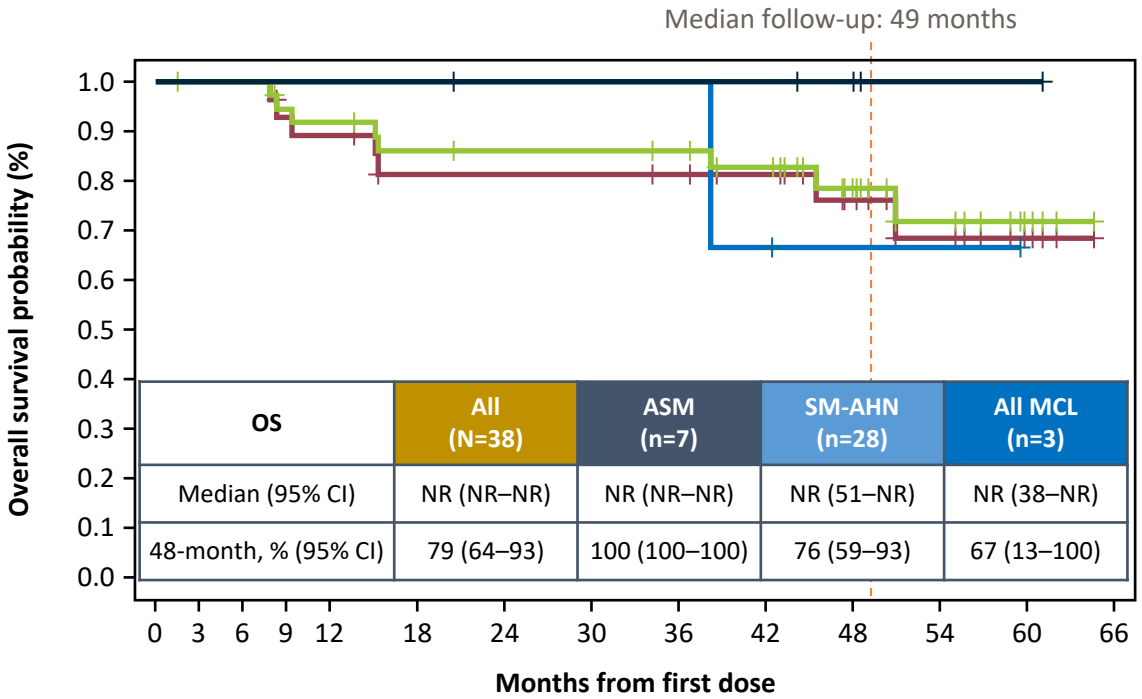
OS in overall population



OS	All (N=107)	ASM (n=21)	SM-AHN (n=71)	Pure MCL (n=11)
Median (95% CI)	62 (60.0–NR)	NR (NR–NR)	60 (50–NR)	NR (NR–NR)

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

OS in first-line patients



OS	All (N=38)	ASM (n=7)	SM-AHN (n=28)	All MCL (n=3)
Median (95% CI)	NR (NR–NR)	NR (NR–NR)	NR (51–NR)	NR (38–NR)
48-month, % (95% CI)	79 (64–93)	100 (100–100)	76 (59–93)	67 (13–100)

ASM	7	6	6	6	6	6	5	5	5	5	3	1	1	0
SM-AHN	28	28	28	25	24	21	21	21	20	18	13	8	3	0
All MCL	3	3	3	3	3	3	3	3	3	2	1	1	0	0
Total	38	37	37	34	33	30	29	29	28	25	17	10	4	0

- **Median OS according to MARS score**: not reached in low/intermediate, 48 months in high MARS score (n = 41)

Reiter et al, ASH 2025
Gotlib et al, Blood Adv 2026

Final database lock: March 13, 2025.

PATHFINDER – disease progression

- Disease progression was observed in **21 patients**, including **6 with progression to AML**
- # 19 of 21 had an initial diagnosis of **SM-AHN** or **MCL-AHN**

Patient number	Diagnosis	Age	Avapritinib dose		Baseline disease burden				Best response*	AML progression (yes/no)
			Baseline dose (mg)	Average daily dose (mg)	BM blasts (%)	BM MC %)	Serum tryptase (µg/L)	*KIT* D816V in PB (%)		
1	SM-CMML-0	71	200	98	1	15	488	44	PR	Y
2	SM-CMML-1	47	200	200	5	1	47	42.86	PD	Y
3	SM-CEL	76	200	84	4	20	464	38.41	PR	N
4	SM-CMML-0	79	200	50	2	20	1116	3.85	CRh	N
5	MCL-CMML-1	67	200	111	5	80	728	0.06	SD	Y
6	SM-CMML-0	78	200	103	2	20	49	2.7	PR	Y
7	SM-CMML-1	54	200	86	4	30	37	0.13	CRh	Y
8	SM-CMML-0	69	200	48	1	75	604	36.26	SD	Y
9	SM-CMML-0	63	200	74	1	40	107	2.88	PR	N
10	SM-MDS/MPN-U	69	200	73	1	70	116	41.75	SD	N
11	SM-MDS/MPN-U	79	200	65	1	90	160	18.72	PR	N
12	SM-MPN	72	200	200	3	20	176	6	PR	N
13	SM-MDS-RS-MLD	77	200	200	1	30	568	47.76	PD	N
14	ASM	64	200	110	1	75	226	11.6	PR	N
15	SM-CMML-0	85	200	59	1	80	107	25.36	PD	N
16	SM-CMML-0	74	200	100	1	30	508	39.88	PR	N
17	SM-MPN	64	200	200	3	15	312	21.92	PD	N
18	SM-CMML-1	73	200	65	7	10	87	16.4	PR	N
19	MCL-MDS/MPN-U	37	200	240	1	80	1600	0.02	PD	N
20	SM-MDS-MLD	65	200	200	2	15	122	0.01	SD	N
21	MCL	69	200	93	2	90	382	15.77	SD	N

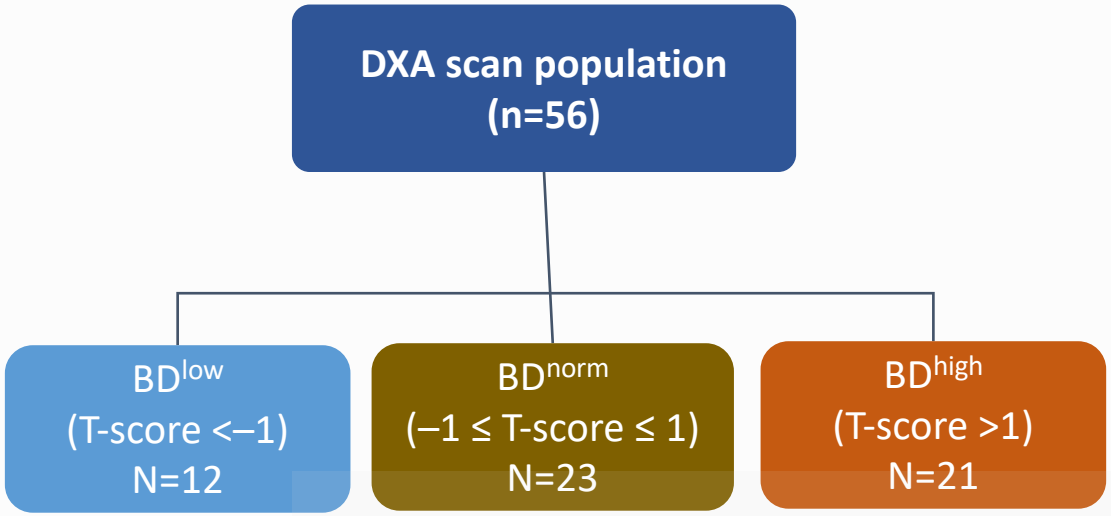
Gotlib et al, Blood Adv 2026

PATHFINDER - bone density analysis in patients evaluated by DXA scans

- Serial DXA scans were optional, and were available in **52% of enrolled patients** at baseline and at ≥2 FUP visits
- Baseline demographic parameters and markers of MC disease burden in patients with serial DXA scans were not significantly different from those without serial DXA scans

Low bone density was observed in **21%** of patients

High bone density was observed in **38%** of patients

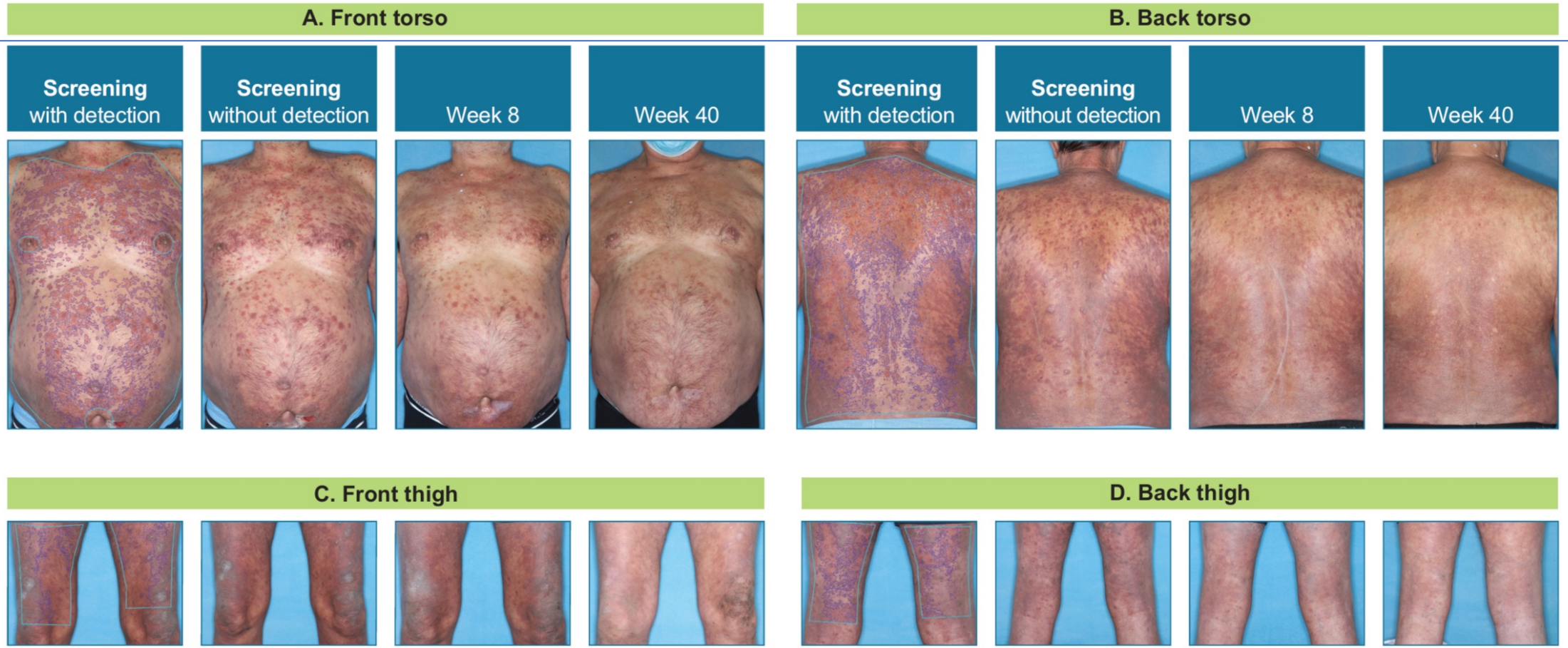


- **Mean lumbar T-scores significantly improved** in the BD^{low} group and did not worsen in the BD^{high} and BD^{norm} groups

Bone turnover marker analysis (n=47) included:

- PINP: a biomarker of osteoblast activity/bone formation[1]
- TRAcP-5b: a biomarker associated with osteoclast activity/bone resorption[2,3]

PATHFINDER - skin lesion analysis



- Reductions in skin lesion area and improvement in color in the front (A) and back (B) torso, and front C) and back (D) things were maintained through Week 40

PATHFINDER – intracranial bleeding and cognitive effects

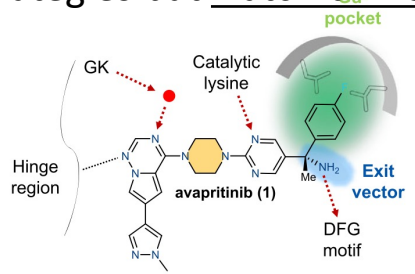
- After protocol amendment, patients with **baseline platelet counts of <50×10^9/L** were excluded from enrollment
- **Mitigation strategies** (platelet count monitoring, guidance for treatment interruption, dose reduction, or treatment discontinuation) were implemented

➡ ICB occurred in 4 patients (**4%**) enrolled in PATHFINDER

- ✓ 2 patients with intracranial hemorrhages
- ✓ 2 patients with subdural hematomas

- None of the patients died due to their ICBs

✓ Avapritinib **penetrates the blood-brain**; observed **cognitive effects** are generally mild and reversible with mitigation strategies but watchful monitoring is recommended



Measure	avapritinib	BLU-263
Rat Brain Penetration (Kp,uu homogenate)	40%	2.4%

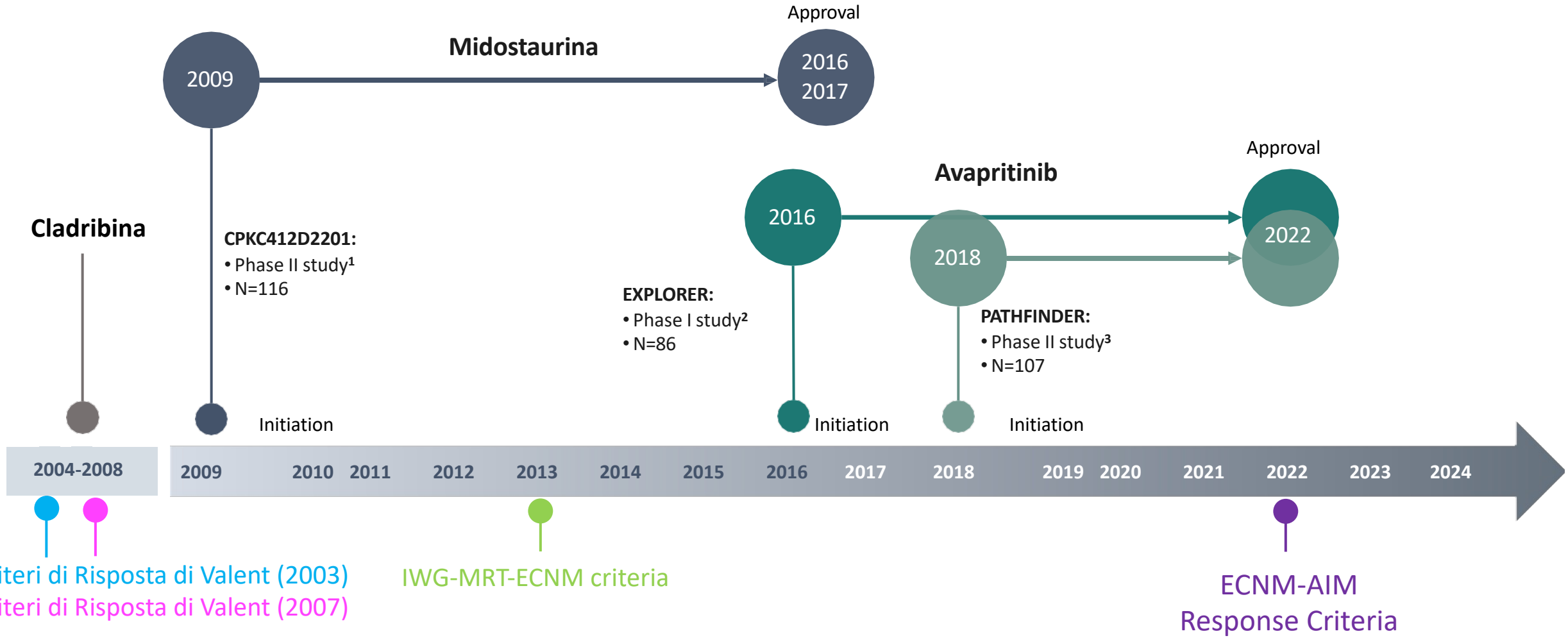
- Cognitive effects observed in **34% of patients**, considered **treatment-related in 28%**
- **Most** cognitive effects were **Grade 1 or 2**
- The most frequent were cognitive disorder (≥ gr.3: 5%), memory impairment (0%), confusional state (<1%)

- Cognitive effects were generally managed through **dose modification**
- Treatment **discontinuation due to cognitive effects** occurred in 4 patients overall

➢ **Alert**: in standard practice, patients are less frequently evaluated than in clinical trials

Outline

- ✓ Update studi TKI
- ✓ Criteri di risposta e score di rischio per le scelte terapeutiche in ASM
- ✓ TKI per ISM
- ✓ Nuove molecole



C-findings + TRIPTASI + MCs in BOM, **no c-kit mutation**

[1] Gotlib J, et al. *N Engl J Med.* 2016;374:2530-2541. [2] DeAngelo DJ, et al. *Nature Med*. 2021;27:2183-2191. [3] Gotlib J, et al. *Nature Med*. 2021;27:2192-2199.

ECNM-AIM Response Criteria (2022)

C-findings:

. Applicabile solo a casi di AdvSM che presentavano al baseline C-findings valutabili (Chronic MCL)

. Possono essere confusi con componente AHN, AE farmaci, altre comorbidità

. Potenziale discordanza tra persistenza di C-findings e clearance delle MCs nel BM

Complete remission with full (CR) or partial (CRh) hematologic recovery[a]
- BM MC aggregates eliminated and tryptase <20 ng/ml

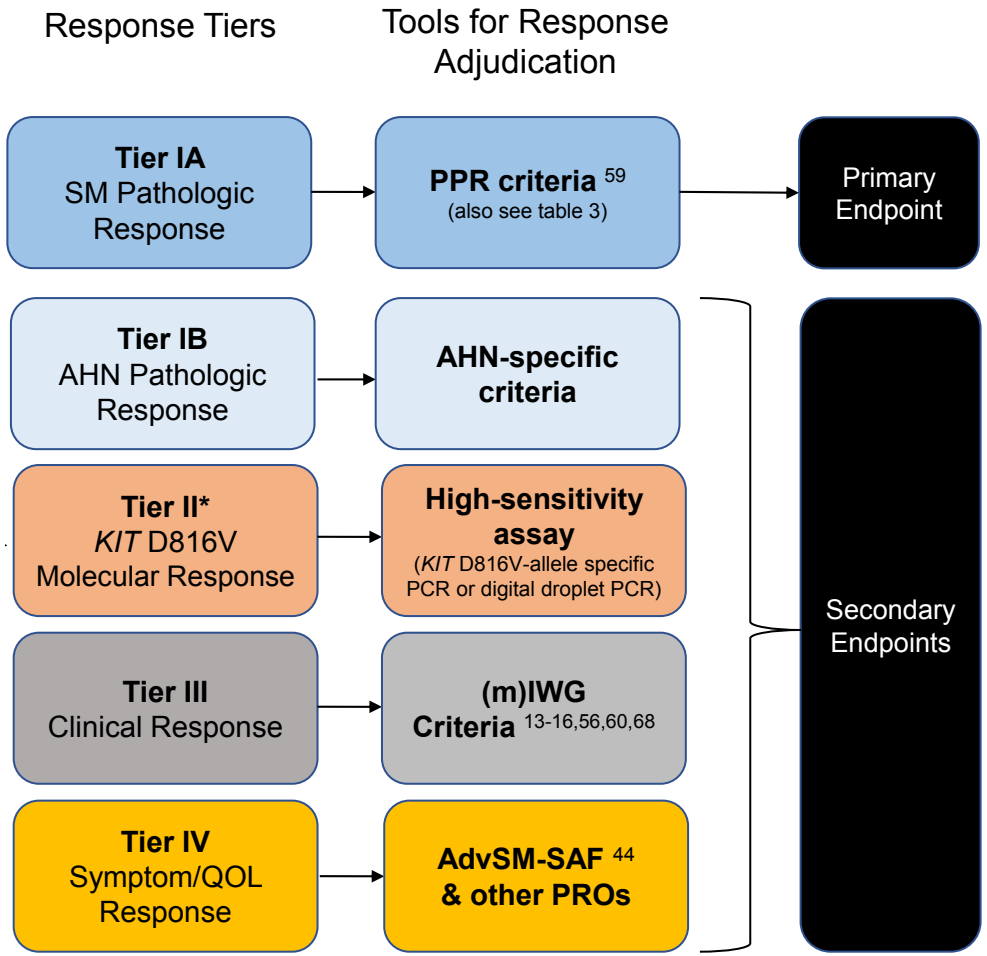
Molecular complete remission (mCR/mCRh)
- *and KIT* D816V mutant allele fraction falls below LOD by sensitive assay[b]

Partial remission (PR)
- ≥50% reduction in BM MCs and tryptase

Stable disease (SD)
- Not in a CR, PR, or PD

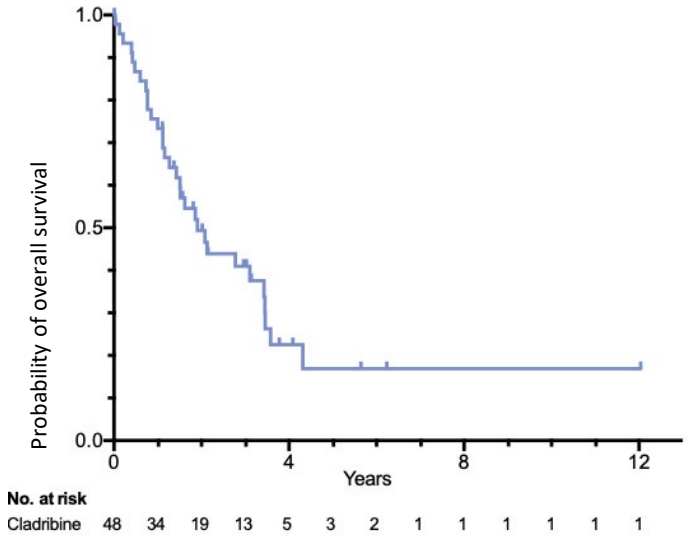
Progressive disease (PD)
- Transformation to AML

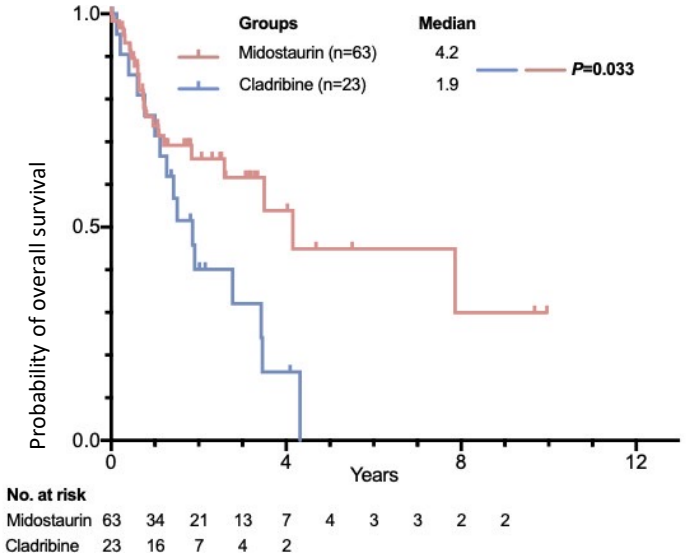
Pure Pathologic Response

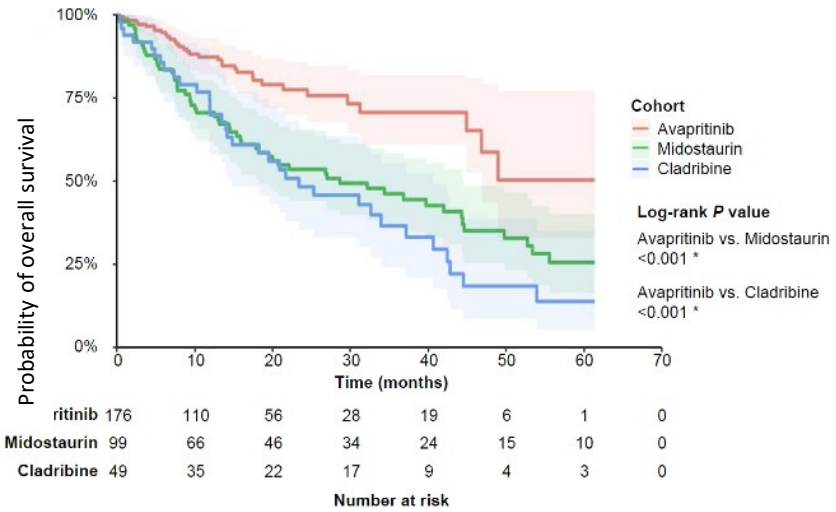


Gotlib, J et al. J Allergy Clin Immunol Pract. 2022;10(8):2025-2038.

I TKI hanno sicuramente determinato un **miglioramento della prognosi** (OS)







Cladribina[1]

Midostaurina vs. cladribina[2]

Avapritinib vs. midostaurina / cladribina[3]

[1] Lübke J, et al. *Ann Hematol.* 2023;102:2077-2085. [2] Lübke J, et al. *J Clin Oncol.* 2022;40:1783-1794. [3] Lübke J, et al. *DGHO* 2022. Abstract V52.

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

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

MARS-R

SCOPO: sviluppare il **Revised Mutation-Adjusted Risk Score (MARS-R)**, uno score prognostico, basato su scala continua, per pazienti con **AdVSM** con mutazione **D816V** di *KIT* trattati con **midostaurina o avapritinib**, indipendente dalle sottoclassi diagnostiche definite secondo WHO.

CRITERI DI INCLUSIONE:

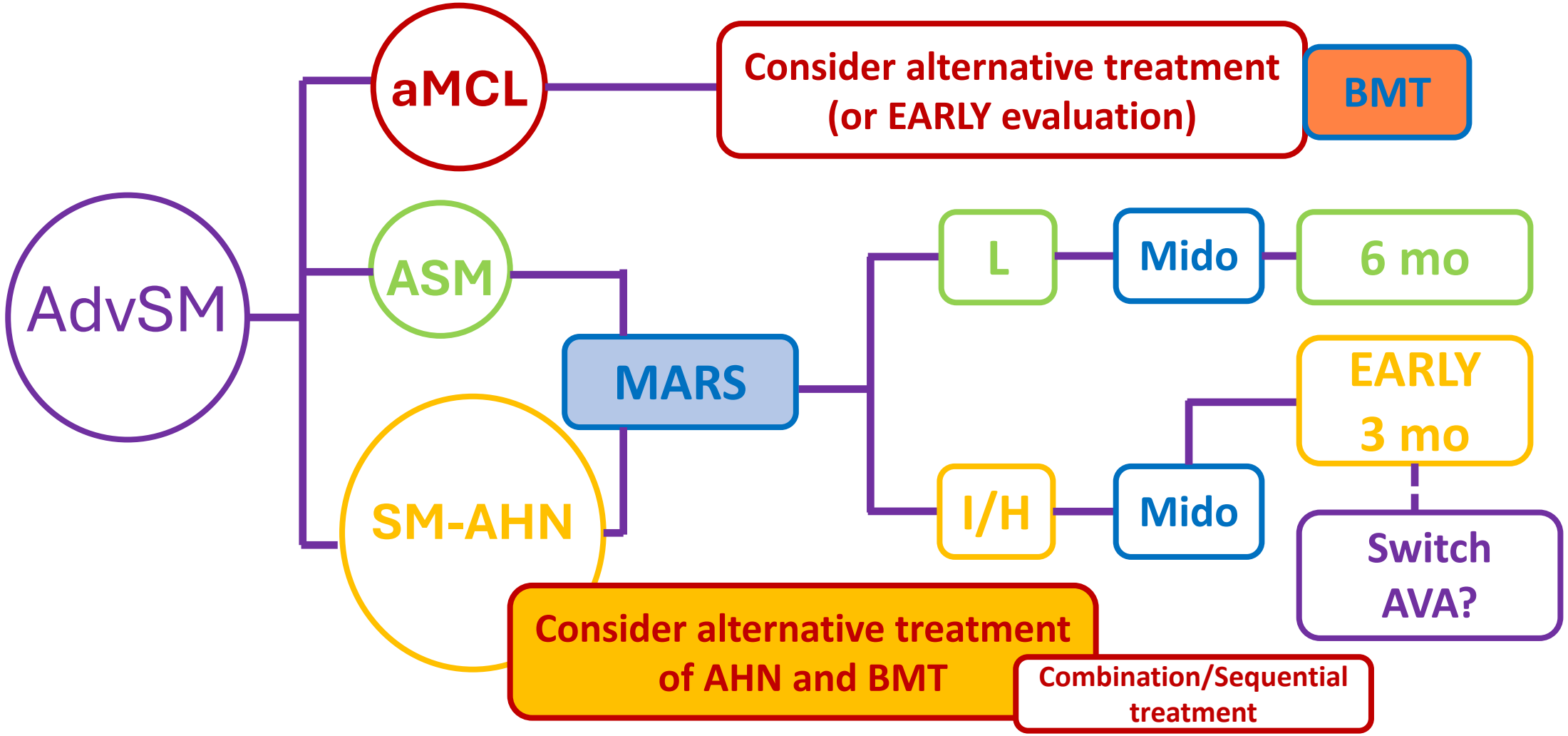
- **AdvSM** secondo classificazione WHO
- Presenza della mutazione **D186V** di *KIT*
- Terapia con **midostaurina** o **avapritinib**

Age/Hb/Plts/VAF Kit/SAR & 2> more HR mut^{ns}

Skin lesions/Sex

Lübke J et al., EHA 2025, Oral Presentation S216.

Therapeutic Options for AdvSM : conclusions



Heiblig M, Am J Hematol. 2024;99(12):2327-38

Outline

- ✓ Update studi TKI
- ✓ Criteri di risposta e score di rischio per le scelte terapeutiche in ASM
- ✓ TKI per ISM
- ✓ Nuove molecole

NEJM Evidence

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DOI: 10.1056/EVIDoa2200339

ORIGINAL ARTICLE

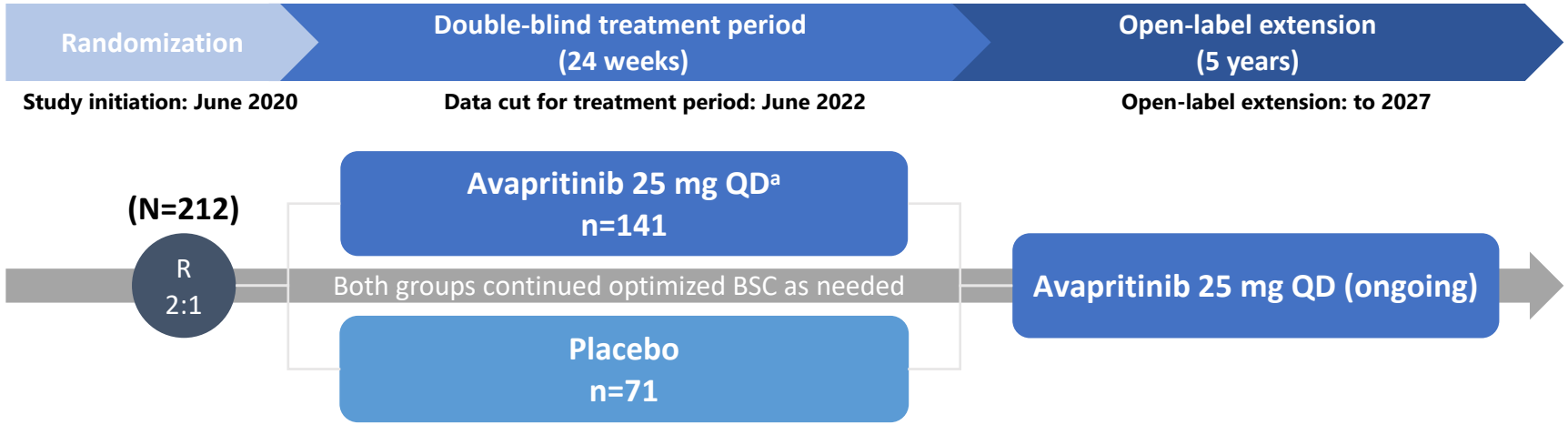
Avapritinib versus Placebo in Indolent Systemic Mastocytosis

Jason Gotlib, M.D.,[1] Mariana Castells, M.D., Ph.D.,[2] Hanneke Oude Elberink, M.D., Ph.D.,[3] Frank Siebenhaar, M.D.,[4,5] Karin Hartmann, M.D.,[6,7] Sigurd Broesby-Olsen, M.D.,[8] Tracy I. George, M.D.,[9] Jens Panse, M.D.,[10,11] Iván Alvarez-Twose, M.D., Ph.D.,[12] Deepti H. Radia, M.R.C.P.I., F.R.C.Path.,[13] Tsewang Tashi, M.D.,[14] Cristina Bulai Livideanu, M.D.,[15] Vito Sabato, M.D., Ph.D.,[16] Mark Heaney, M.D.,[17] Paul Van Daele, M.D.,[18] Sonia Cerquozzi, M.D.,[19] Ingunn Dybedal, M.D., Ph.D.,[20] Andreas Reiter, M.D.,[21] Thanai Pongdee, M.D.,[22] Stéphane Barete, M.D., Ph.D.,[23] Celalettin Ustun, M.D.,[24] Lawrence Schwartz, M.D., Ph.D.,[25] Brant R. Ward, M.D., Ph.D.,[25] Philippe Schafhausen, M.D.,[26] Peter Vadas, M.D., Ph.D.,[27] Prithviraj Bose, M.D.,[28] Daniel J. DeAngelo, M.D., Ph.D.,[29] Lindsay Rein, M.D.,[30] Pankit Vachhani, M.D.,[31] Massimo Triggiani, M.D., Ph.D.,[32] Patrizia Bonadonna, M.D.,[33] Mark Rafferty, M.Bch.B., M.R.C.P., F.R.C.Path.,[34] Nauman M. Butt, M.D.,[35] Stephen T. Oh, M.D., Ph.D.,[36] Friederike Wortmann, M.D.,[37] Johanna Ungerstedt, Ph.D.,[38] Mar Guilarte, M.D., Ph.D.,[39] Minakshi Taparia,[40] Andrew T. Kuykendall, M.D.,[41] Cecilia Arana Yi, M.D.,[42] Princess Ogbogu, M.D.,[43] Caroline Gaudy-Marqueste, M.D., Ph.D.,[44] Mattias Mattsson, M.D., Ph.D.,[45] William Shomali, M.D.,[1] Matthew P. Giannetti, M.D.,[46] Ilda Bidollari, M.D.,[47] Hui-Min Lin, Ph.D.,[47] Erin Sulllivan, Ph.D.,[47] Brenton Mar, M.D.,[47] Robyn Scherber, M.D.,[47] Maria Roche, M.S.,[47] Cem Akin, M.D., Ph.D.,[48] and Marcus Maurer, M.D.[4,5]

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**

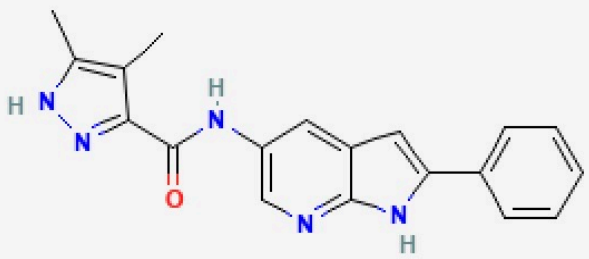
Biomarkers of mast cell burden
Key secondary endpoints

- ≥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**

TKI in Indolent SM : Avapritinib



AVAPRITINIB

Approvato FDA e EMA 2022
per Adv-SM 2° linea
Approvato FDA e EMA 2025
per ISM

- Score for enrollment: 28
- Daily ISM-SAF TSS

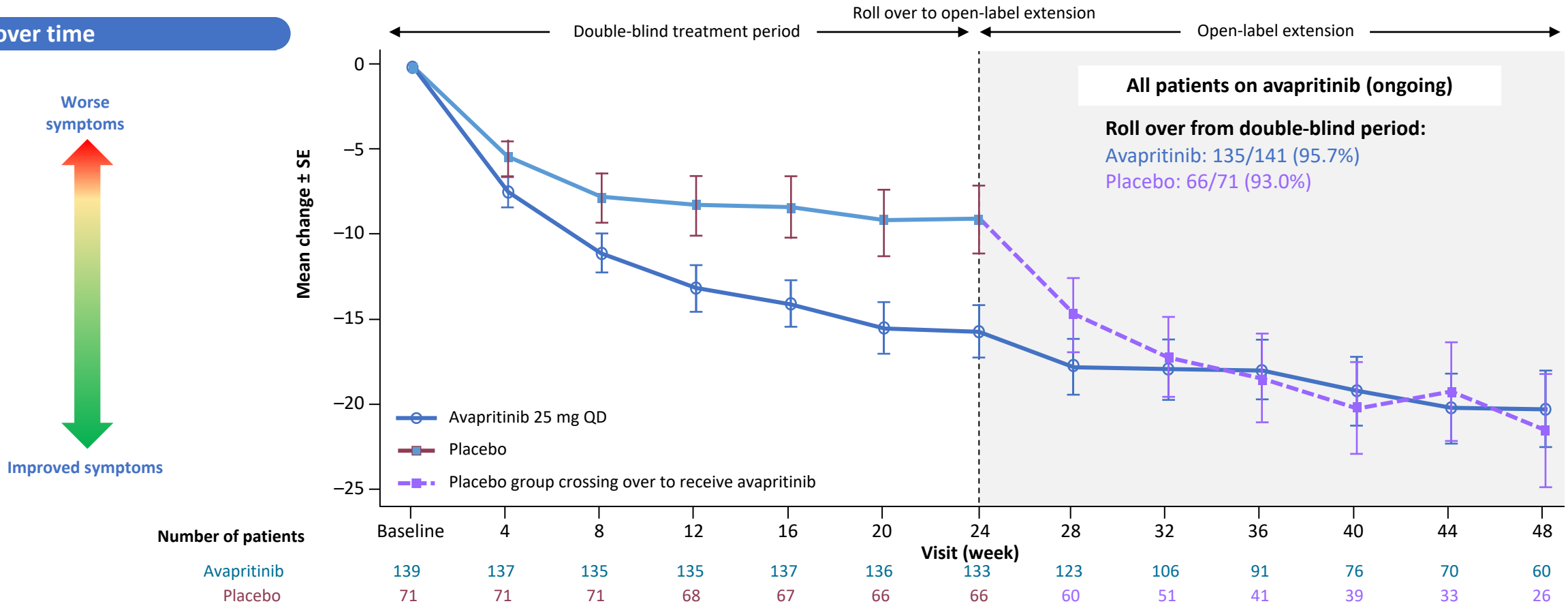
ISM Symptom Assessment Form (ISM-SAF)

ISM Symptom	Scoring
Abdominal pain Diarrhea Nausea	Scored 0–10 daily on handheld device 0 = no symptom 10 = **worst imaginable** symptom Analyzed as a 14-day moving average
Spots Itching Flushing	
Brain Fog Headache Dizziness	
Bone pain Fatigue	

- Total Symptom Score (TSS) based on severity of 11 ISM symptoms

TKI in Indolent SM : Avapritinib

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.

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

Avapritinib in Indolent SM safety

- Majority of AEs were Grade 1 or 2 with a low rate of discontinuation
- SAEs were reported more frequently in the placebo group (no treatment-related SAEs in either group)
- Edema adverse events were higher in the avapritinib group (majority Grade 1, and did not result in discontinuation)

	Avapritinib 25 mg QD (N=141)	Placebo (N=71)
Any AEs[a,b], n (%)	128 (90.8)	66 (93.0)
Grade 1–2 AEs	98 (69.5)	51 (71.8)
Grade 1–2 related AEs	74 (52.5)	30 (42.3)
Grade ≥3 AEs	30 (21.3)	15 (21.1)
Grade ≥3 related AEs	3 (2.1)	2 (2.8)
SAEs, n (%)	7 (5.0)	8 (11.3)
Any grade TRAEs	77 (54.6)	32 (45.1)
Most frequently reported TRAEs (≥5% of patients)		
Headache	11 (7.8)	7 (9.9)
Nausea	9 (6.4)	6 (8.5)
Peripheral edema	9 (6.4)	1 (1.4)
Periorbital edema	9 (6.4)	2 (2.8)
Dizziness	4 (2.8)	5 (7.0)
TRAEs leading to discontinuation	2 (1.4)	1 (1.4)

Outline

- ✓ Update studi TKI
- ✓ Criteri di risposta e score di rischio per le scelte terapeutiche in ASM
- ✓ TKI per ISM
- ✓ Nuove molecole

A Phase 2/3 Study of BLU-263, a Highly Potent and Selective Tyrosine Kinase Inhibitor, in Patients With Indolent Systemic Mastocytosis (ISM) and Monoclonal Mast Cell Activation Syndrome (mMCAS)

Elenestinib (BLU-263): A next-generation, potent, selective KIT D816V inhibitor

- **Elenestinib** is a novel, investigational, oral, next-generation tyrosine kinase inhibitor that is non-brain penetrant[1,2]
- **Potently** and **selectively** inhibits KIT D816V while **preferentially sparing** wild-type KIT

	KIT D816V phosphorylation IC_{50}	WT KIT proliferation IC_{50}	WT KIT phosphorylation IC_{50}
Elenestinib	3.1 nM	95.9 nM	82.6 nM
Avapritinib	3.1 nM	85.8 nM	89.5 nM
Bezuclastinib	3.4 nM	26.4 nM	32.5 nM

- **Well-characterized** product formulation allowing for **once-daily** (QD) dosing[1,2]

Selectivity profiles of KIT D816V inhibitors in clinical development or approved for systemic mastocytosis

Drug:	Elenestinib	Avapritinib	Bezuclastinib
Kinome tree[a]:			
Selectivity S-score: (fraction of kinome bound by drug, more selective = lower s-score)	0.035	0.035	0.057
	First in human 2020, investigational	First in human Oct 2015, approved	First in human Mar 2015, investigational

IC_{50}, half-maximal inhibitory concentration; QD, once daily; WT, wild-type.

1. Dave N et al. Presented at AACR 2021. Poster #CT122; 2. Castells M et al. Presented at EHA 2022. Poster #1017

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.

Current study sites

- Australia
- Austria
- Belgium
- France
- Germany
- Italy
- Netherlands
- Portugal
- Spain
- Switzerland
- UK
- USA
- Denmark

Primary endpoints	Secondary endpoints
• **Part 1** – Determination of RD – PK and PD • **Part 2** – Proportion of patients who achieve a ≥ 30% reduction in ISM-SAF TSS from baseline at Week 25 • **Parts 1 and 3** – Safety and tolerability – Mean change in ISM-SAF TSS[a,c]	• **Part 1** – Mean change in ISM-SAF Individual Symptom Scores[a] • **Part 2** – ≥ 50% reduction in measures of MC burden[b] – Mean change in ISM-SAF • **Parts 1 and 2** – Mean change in measures of MC burden[a,b] • **Part 3** – Mean change in serum tryptase and *KIT* D816V VAF in the blood[c] – Mean change in ISM-SAF Individual and Lead Symptom Scores from baseline

Bezuclastinib: Highly Selective and Potent KIT D816V Inhibitor

Kinase Inhibition Profile of Clinical Stage and Approved KIT D816V Agents; Cell IC_{50} (nM)

Compound	KIT V560G/D816V (HMC 1.2)	WT KIT	PDGFRα	PDGFRβ	CSF1R	FLT3	KDR
Bezuclastinib	14	121	> 10,000	> 10,000	> 10,000	> 1000	> 1000
Avapritinib	13	114	53	10	249	305	> 1000
BLU-263	6	355	21	6	161	345	> 1000

Summit
NONADVANCED SM

- A multi-part, randomized, double-blind, placebo-controlled Phase 2 clinical study comparing the safety and efficacy of bezuclastinib plus best supportive care (BSC) with placebo plus BSC in patients with nonadvanced systemic mastocytosis (NonAdvSM), including indolent systemic mastocytosis and smoldering systemic mastocytosis.
- NCT05186753

Apex
ADVANCED SM

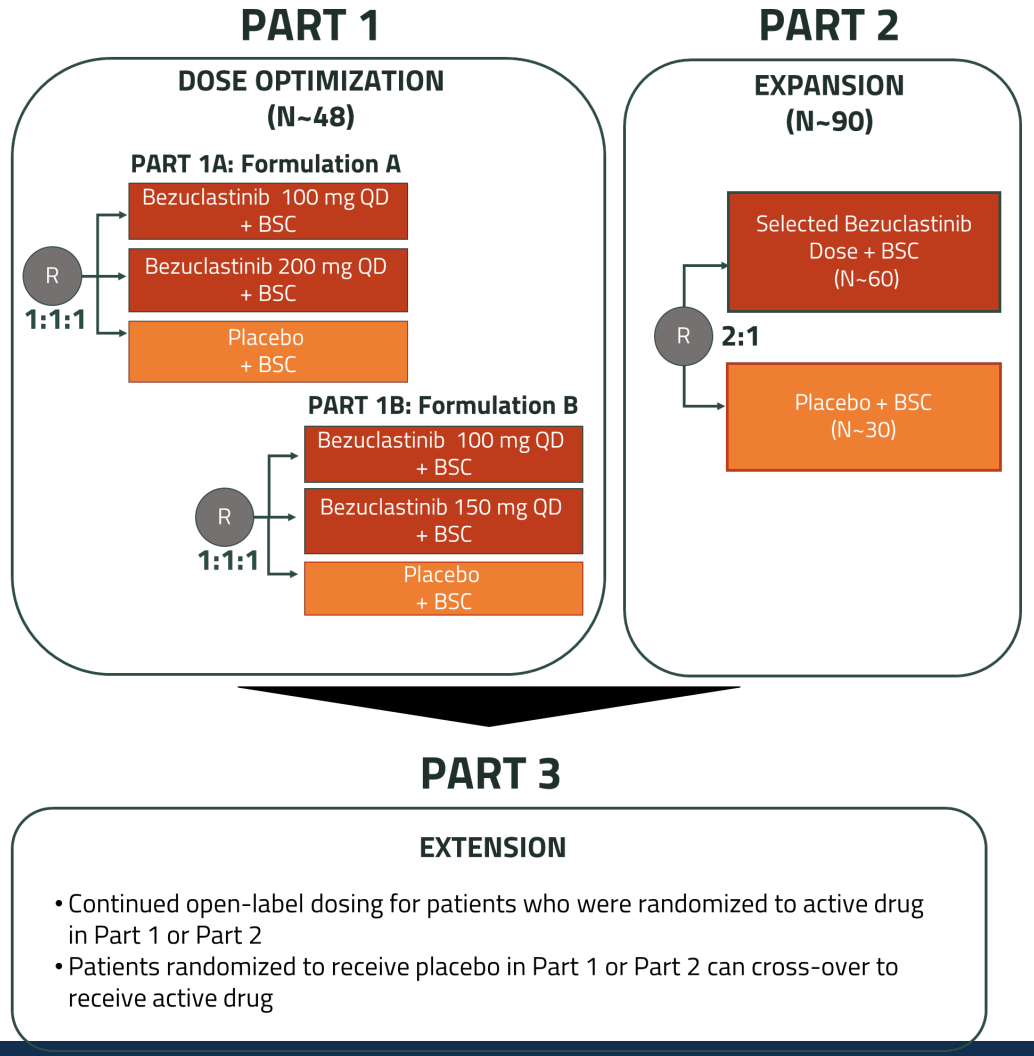
An open-label, two-part Phase 2 study investigating bezuclastinib for the treatment of patients with Advanced Systemic Mastocytosis (AdvSM), including patients with Aggressive SM (ASM), SM with Associated Hematologic Neoplasm (SM-AHN), and Mast Cell Leukemia (MCL)

NCT04996875

References: 1Guarnieri A. et al. Abstract P257 Molecular Cancer Therapeutics, 2021. 20(12_Supplement), P257-P257. 2Giles FJ et al, Leukemia. 2009;23(10):1698-1707. 3Liu S, Kurzrock R. Seminars in Oncology. 2015;42(6):863-875

Summit: A Multi-Part, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of the Safety and Efficacy of Bezuclastinib in Patients with Indolent and Smoldering SM

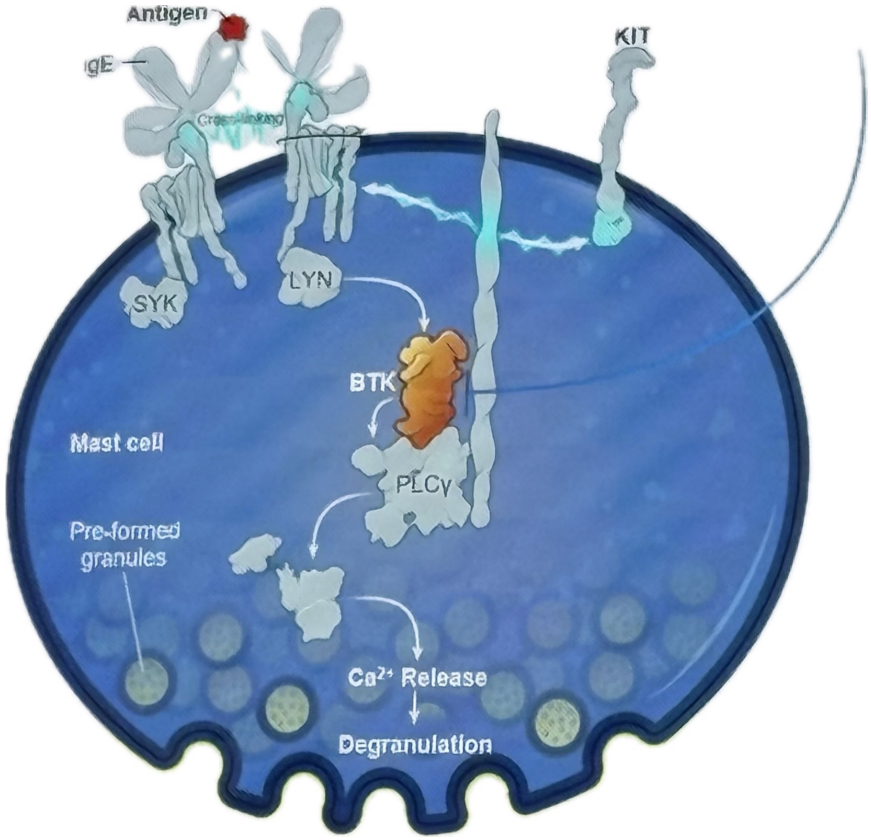
Study Design



BTK Inhibitor TL-895

CLINICAL TRIAL PROTOCOL: STUDY TL-895-201

Study Title:	**A Phase 2 Multicenter Study of TL-895 in Subjects with Relapsed/Refractory Myelofibrosis, Janus Kinase Inhibitor Intolerant Myelofibrosis, Janus Kinase Inhibitor Treatment Ineligible Myelofibrosis, or Indolent Systemic Mastocytosis**
Study Number:	TL-895-201
Version:	Protocol Amendment 8.1, dated 13 February 2024
Study Phase:	2



BTKis prevent IgE-mediated degranulation and cytokine release in primary human mast cells and basophils.

Thank you!

Prof. F. Lanza

Clinical Team
Giovanni Marconi
Beatrice Zannetti
Arbana Dizdari
Alessandro Lucchesi
Federica Monaco
Eliana Liardo
Letizia Zannoni

Hemolymphopathology Unit
Loredana Cardinale

Dermatologist
Paola Sgubbi
Renato Calista

Allergologists
Gabriele Cortellini
Francesca Emiliani

Rheumatologist
Marco Bruschi

Molecular Biology Team
Simona Soverini
Manuela Mancini
Cecilia Monaldi

Maria Rita Sciumè-**Milano**
Patrizia Bonadonna- **Vicenza**
Roberta Zanotti, Massimiliano Bonifacio, Ilaria Tanasi-**Verona**
Chiara Elena-**Pavia**
Michela Rondoni-**Ravenna**
Alessandro Vannucchi,Francesco Mannelli-**Firenze**
Massimo Triggiani, Roberta Parente- **Salerno**
Cristina Papayannidis, Simona Soverini, Chiara Sartor-**Bologna**
Marianna Criscuolo, Livio Pagano-**Roma**