Updates on Myelofibrosis and Systemic Mastocytosis

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Disclosures

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Acknowledgement

-Jason Gotlib, M.D.

Learning Objectives

- To Recognize the heterogeneity of disease phenotype and treatment in Myelofibrosis
- To Discuss the use of newer JAK inhibitors in Myelofibrosis
- To Explain the disease manifestations and diagnosis of Systemic Mastocytosis
- To Appraise the current treatment landscape for Systemic Mastocytosis

Case 1: Cytopenic Myelofibrosis

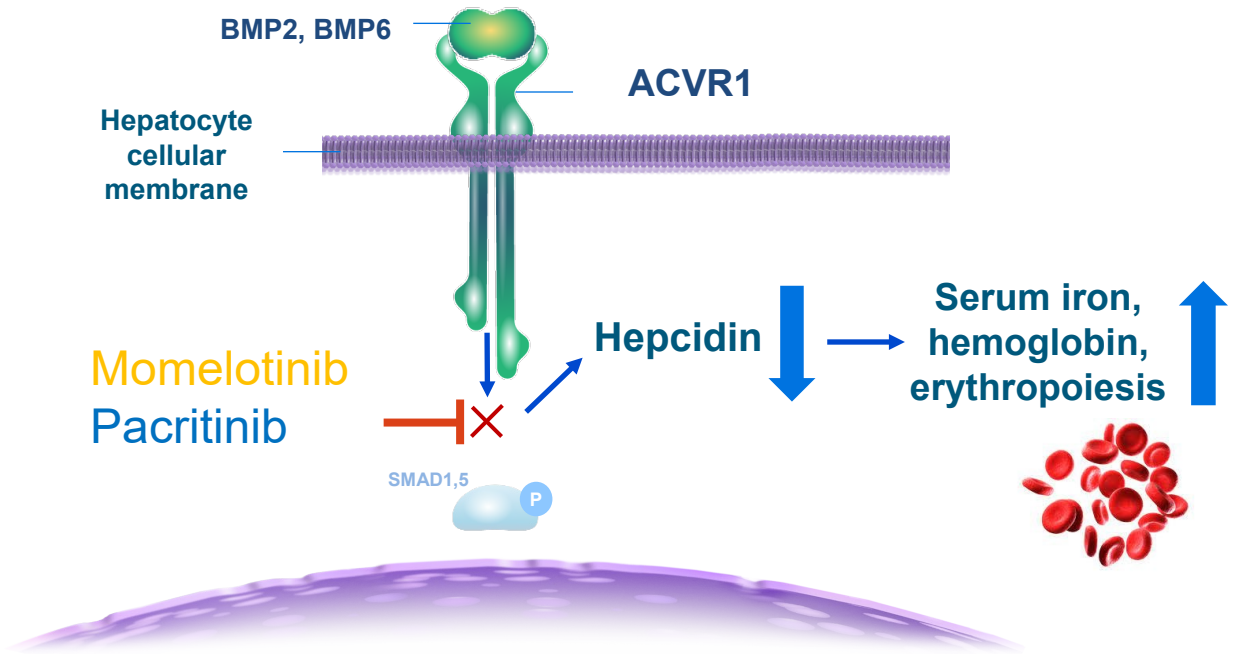
76 yo M presents with fatigue, weight loss, and abdominal fullness

- Exam: Splenomegaly (12 cm below costal margin)
- **CBC: WBC 2.3k (3% blasts), Hb 6.5 g/dL, platelets 41k**
- Bone marrow biopsy: 90% cellular marrow with myeloid expansion, dysplastic megakaryocytes in clusters, and MF-3 fibrosis with 5% myeloid blasts
- Cytogenetics: Normal Karyotype
- Myeloid NGS panel: JAK2 V617F+, ASXL1+

Diagnosis: Primary Myelofibrosis, Cytopenic subtype
Risk Stratification: DIPSS+ High Risk, MIPSS70+v2.0 Very High Risk

How can we manage cytopenic MF?

Momelotinib and Pacritinib Inhibit ACVR1



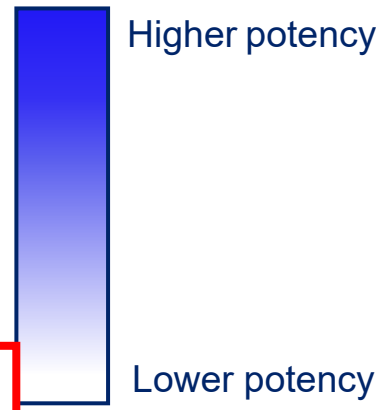
Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF[3,4]

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

Chifotides HT, et al. *J Hematol Oncol*. 2022;15(1):7. 2. Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458. 3. Asshoff M, et al. *Blood*. 2017;129(13):1823-1830. 4. Oh ST, et al. *Blood Adv*. 2020;4(18):4282-4291.

ACVR1 Inhibition

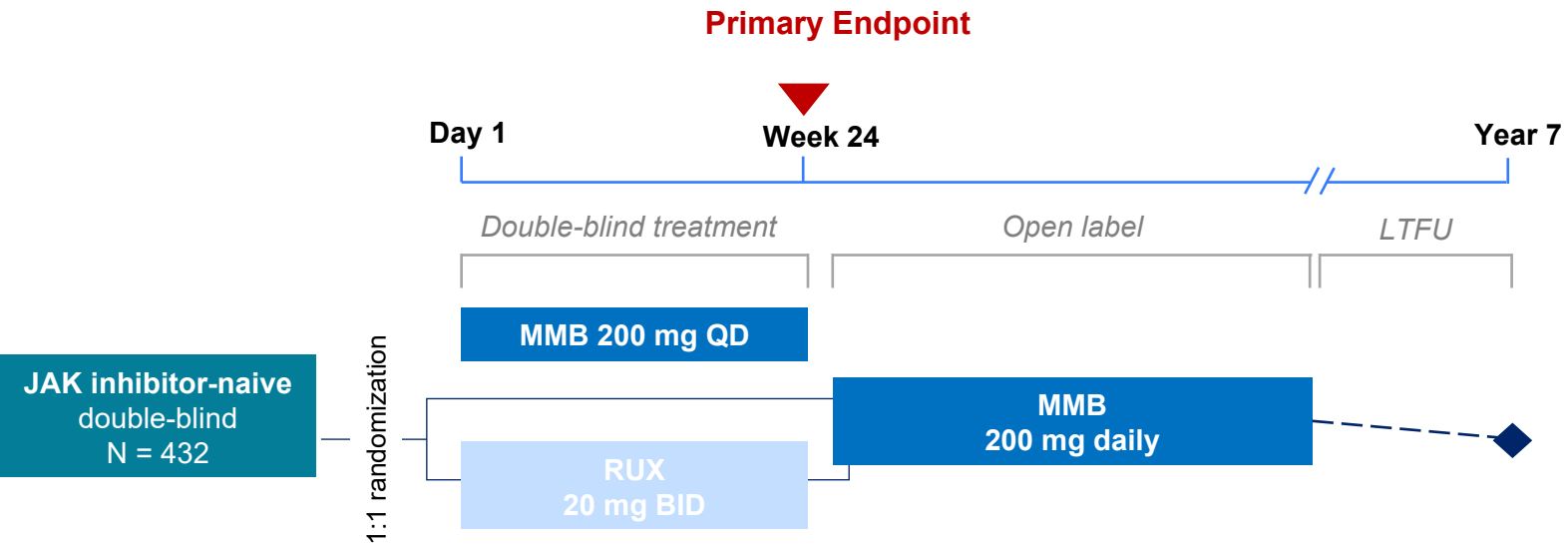
	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	**20.4**	**22.6**	**70.2**	**312.0**	**>1000**
Replicate 2 ACVR1 IC_{50} (nM)	**32.4**	**10.8**	**34.9**	**235.0**	**>1000**
Mean ACVR1 IC_{50} (nM)	**26.4**	**16.7**	**52.6**	**273.5**	**>1000**
Potency[b] (C_{max}:IC_{50})	**N/A**	**12.7**	**3.2**	**1.0**	**<0.01**



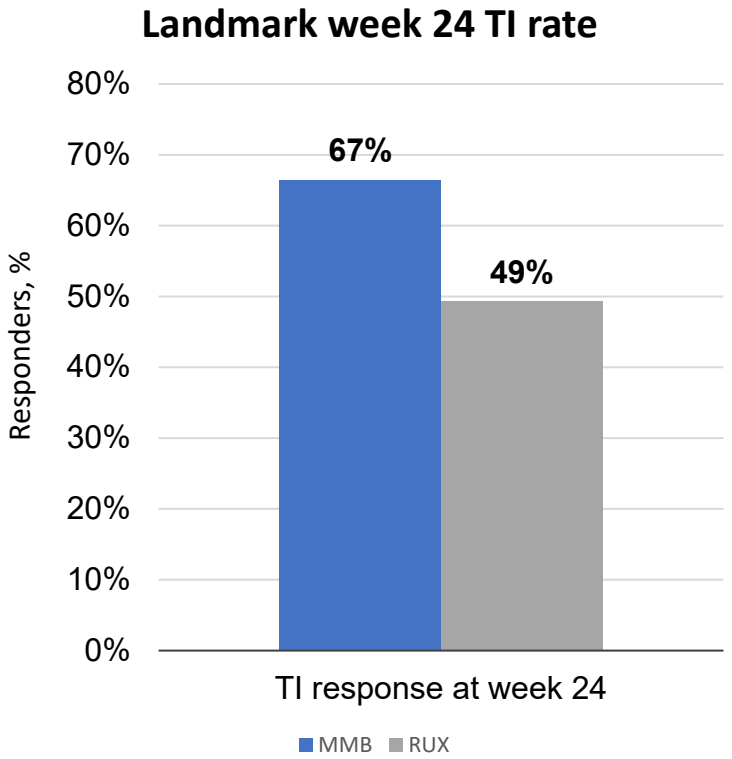
[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

ACVR1= Activin A receptor type 1; FED=fedratinib; IC_{50}=half maximal inhibitory concentration; MOM=momelotinib; PAC=pacritinib; RUX=ruxolitinib.

SIMPLIFY-1: A Phase 3 Study of Momelotinib Versus Ruxolitinib in Untreated Myelofibrosis Patients.

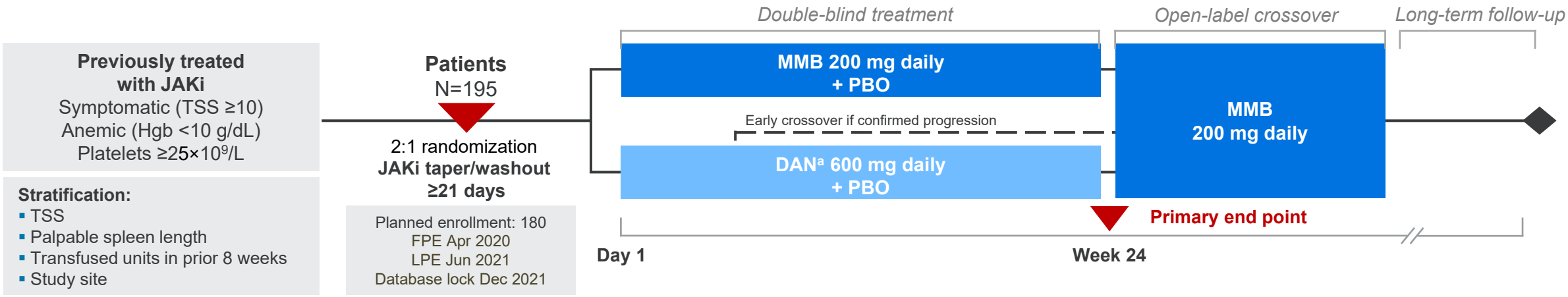


Secondary Endpoint: TI



Mesa RA, et al. J Clin Oncol. 2017;35:3844-3850.

MOMENTUM: A Phase 3 Study of Momelotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients



MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

TEAEs in ≥10% of Patients During OL MMB Treatment with No New Safety Signals Detected

	MMB→MMB (n=93)		DAN→MMB (n=41)	
	% of patients			
Grade ≥3 adverse events	49.5		46.3	
Serious adverse events	31.2		29.3	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
Nonhematologic (preferred term)				
Weight decreased	7.5	0	14.6	0
Diarrhea	14.0	1.1	12.2	0
Pyrexia	14.0	0	7.3	0
Hypertension	3.2	0	12.2	2.4
Asthenia	11.8	3.2	0	0
Hematologic (preferred term)				
Thrombocytopenia	14.0	8.6	17.1	14.6
Anemia	10.8	8.6	7.3	2.4
Neutropenia	5.4	5.4	4.9	0
Other				
COVID-19 (pneumonia)	10.8	5.4	0	0
Peripheral sensory neuropathy	2.2	0	2.4	0

DAN, danazol; MMB, momelotinib; OL, open-label; TEAE, treatment-emergent adverse event.

Transfusion Independence (TI): Analysis of PERSIST-2

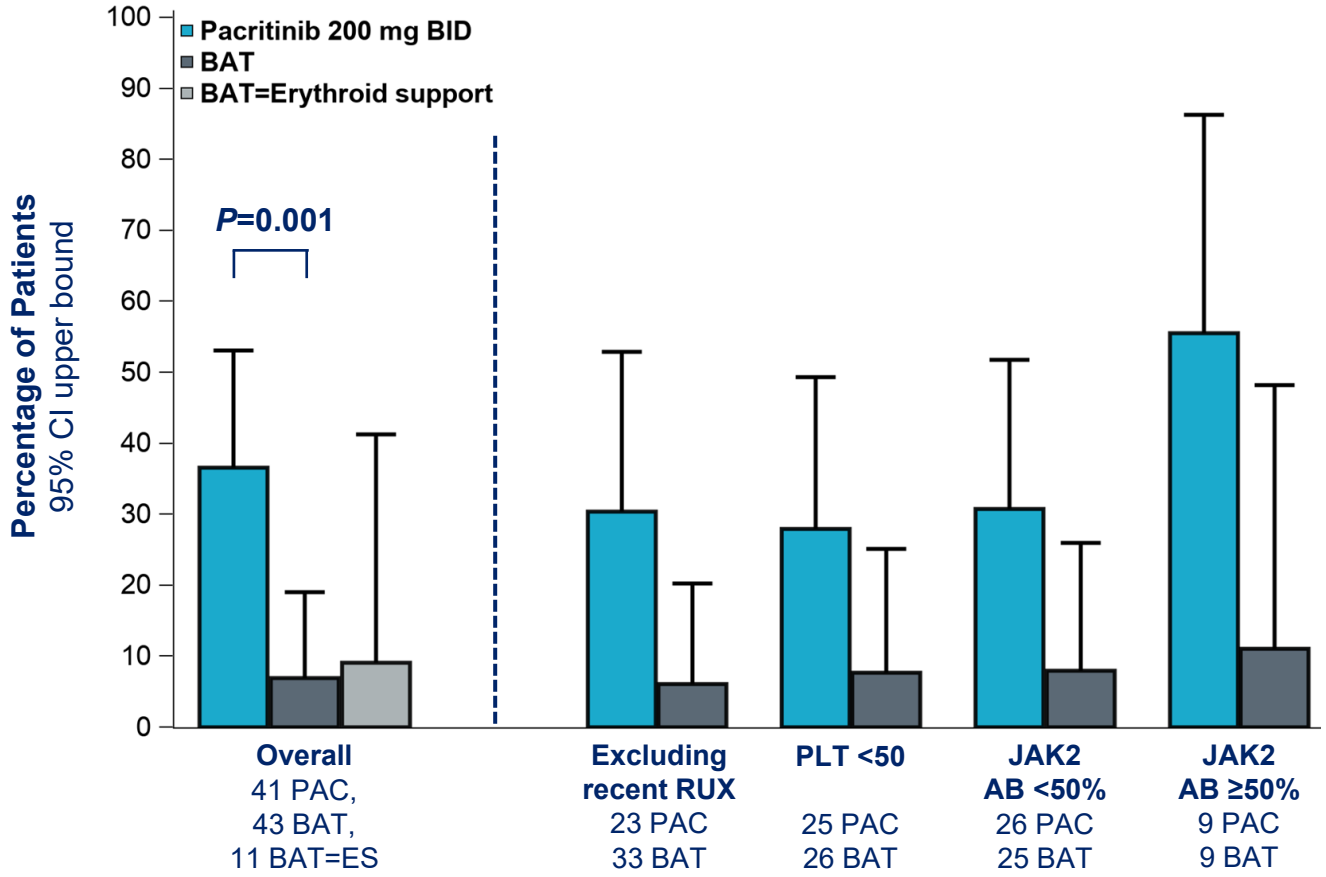
TI Conversion Rate

Pacritinib N=41	BAT N=43	*P*-value
37%	7%	0.001

TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT

- Erythroid support agents were prohibited on the pacritinib arm

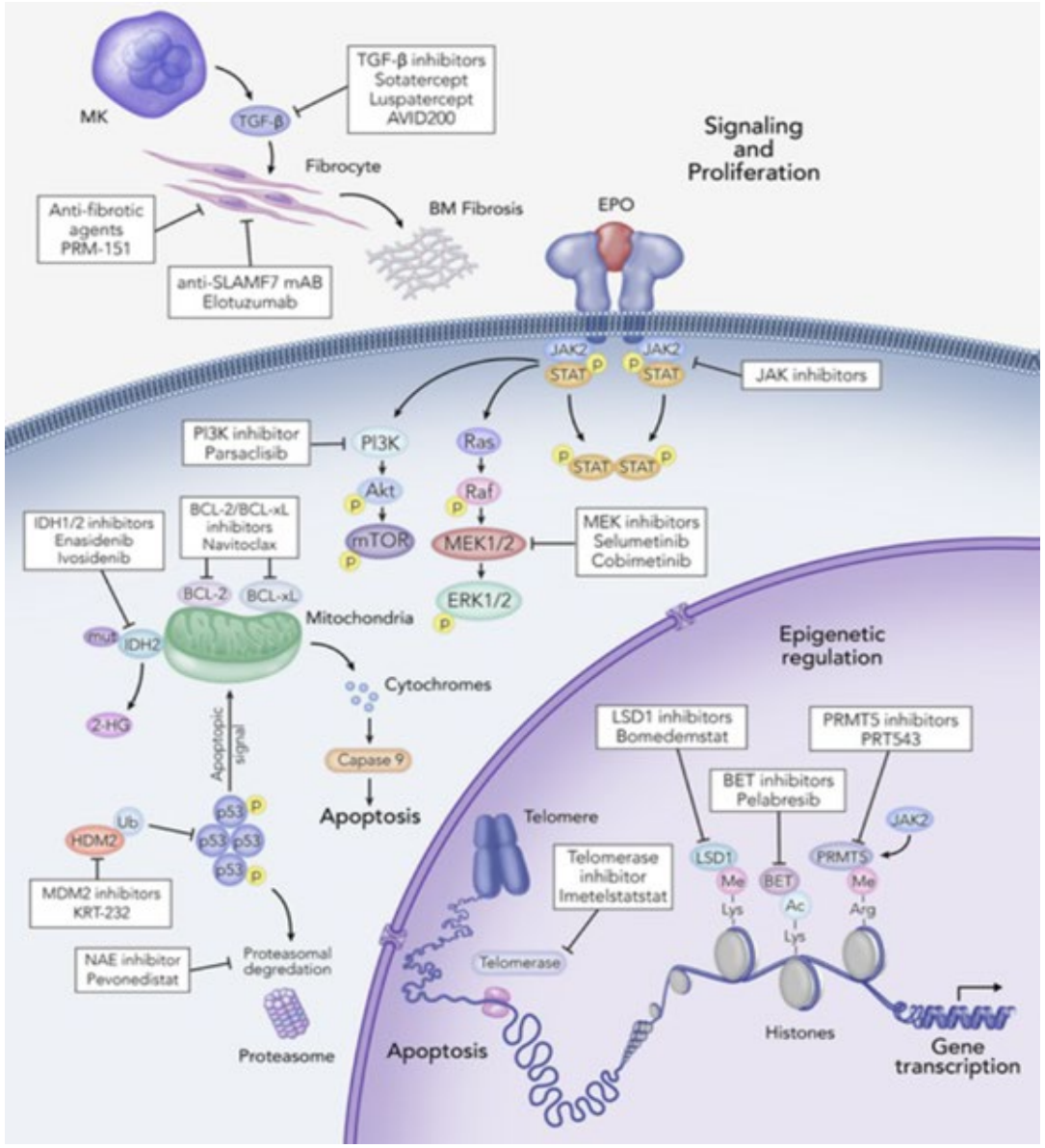
Rate of TI (Gale criteria) through Week 24



AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

Oh ASH 2022

Add-on to Ruxolitinib/Post-Ruxolitinib Therapeutic Approaches in Clinical Development



Drug	Mechanism	Phase
Pelabresib	BET inhibitor	III
Navitoclax	BCL-XL-BCL-2 inhibitor	III
Imetelstat	Telomerase inhibitor	III
Bomedemstat	LSD1 inhibitor	II
Navtemadlin	MDM2 inhibitor	III

- Single Agent
- Add-on to ruxolitinib
- Both single agent or add-on to ruxolitinib

Pettit et al. *Am Soc Clin Oncol Educ Book*. 2022

Case 2: Systemic Mastocytosis

67 y/o male presents with chief complaint of diarrhea, as well as fatigue, abdominal bloating and weight loss of 20lbs over 3 months

Work-up tryptase of 234. CBC notable for WBC 18.3 K/mcL, Hgb 9.6 g/dL PLT 289K/mcL,

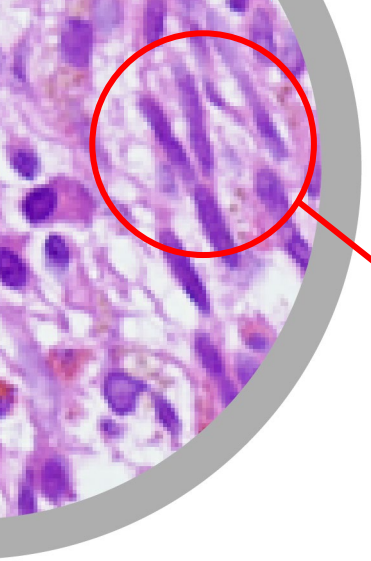
20% monocytes, Albumin 2.8 g/dL (nml 3.8-5.0); LFTs otherwise unremarkable

A bone marrow examination is performed which reveals: systemic mastocytosis (50-60% of marrow cellularity by CD117 staining), as well as a hypercellular marrow with maturing trilineage hematopoiesis with myeloid dyspoiesis and dysmegakaryopoiesis.

Molecular genetics reveal: *cKIT*, *TET2*, *NRAS* mutations

Diagnosis: Systemic Mastocytosis with Associated Hematologic Neoplasm (SM-AHN)/CMML-0

What are the treatment options for the patient?



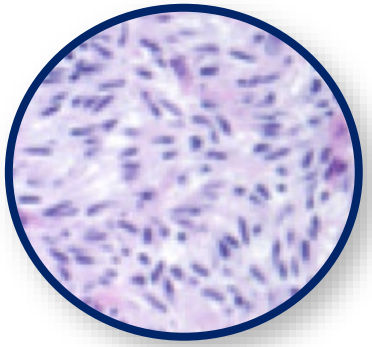
WHO Diagnostic Criteria for Systemic Mastocytosis

Major
- Mast cell aggregates (≥ 15) in the marrow or other extracutaneous tissue

Minor
- Spindle-shaped mast cells
- *KIT* D816V or other activating *KIT* mutation
- CD25 +/- CD2 expression on mast cells
- Serum tryptase > 20 ng/mL

Diagnosis requires:
1 major + 1 minor or ≥ 3 minor criteria)[1]

~65%



Indolent SM (ISM)

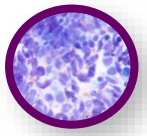
0 or 1 B-findings

Smoldering SM (SSM)

2 or more B-findings

Advanced SM

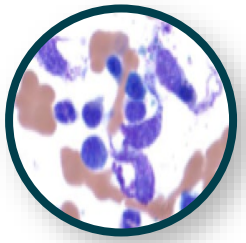
~10%



Aggressive SM (ASM)

≥1 or more C-findings

~25%



SM with an Associated Hematologic Neoplasm (SM-AHN)

Presence of SM and a myeloid neoplasm

1%

Mast Cell Leukemia (MCL)

≥20% mast cells on BM aspirate

[1]Horny H-P, *et al*, WHO Classification, 2017

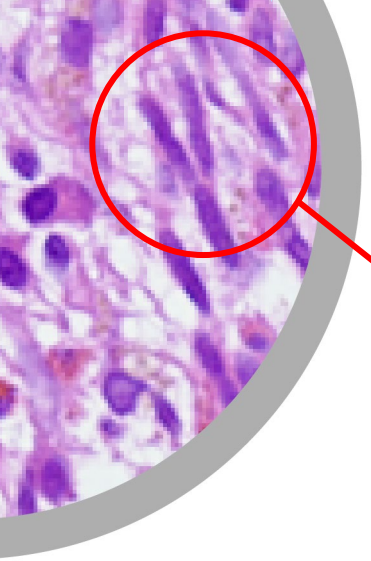
B Findings

B Findings

1. BM biopsy showing >30% infiltration by mast cells (focal, dense aggregates) and/or serum total tryptase level >200 ng/mL

2. Signs of dysplasia or myeloproliferation, in non-mast cell lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts.

3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.



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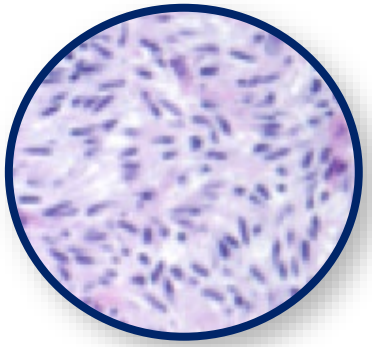

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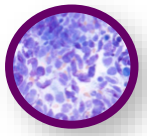

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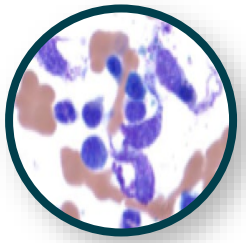

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[1]Horny H-P, *et al*, WHO Classification, 2017

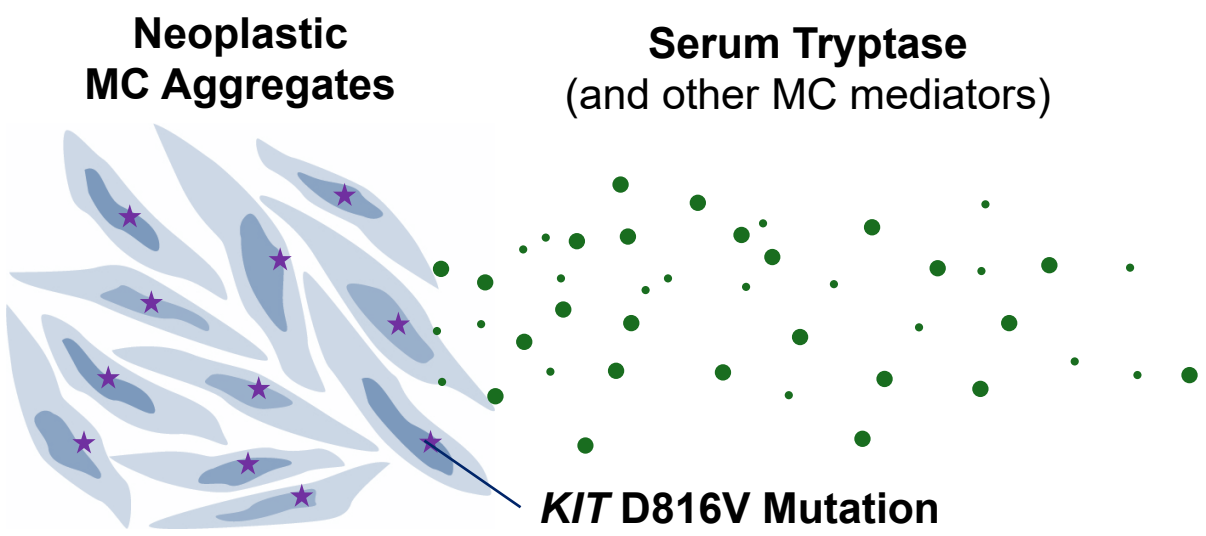
Advanced Systemic Mastocytosis (AdvSM) is a Rare Hematologic Neoplasm with Poor Outcomes

Patients with AdvSM often have organ damage (C-findings) due to neoplastic mast cell infiltration

Mast cell activation leads to severe mediator symptoms and poor quality of life

Clinically and biologically heterogeneous

Poor survival, generally ranges from < 6 months to ~3-4 years

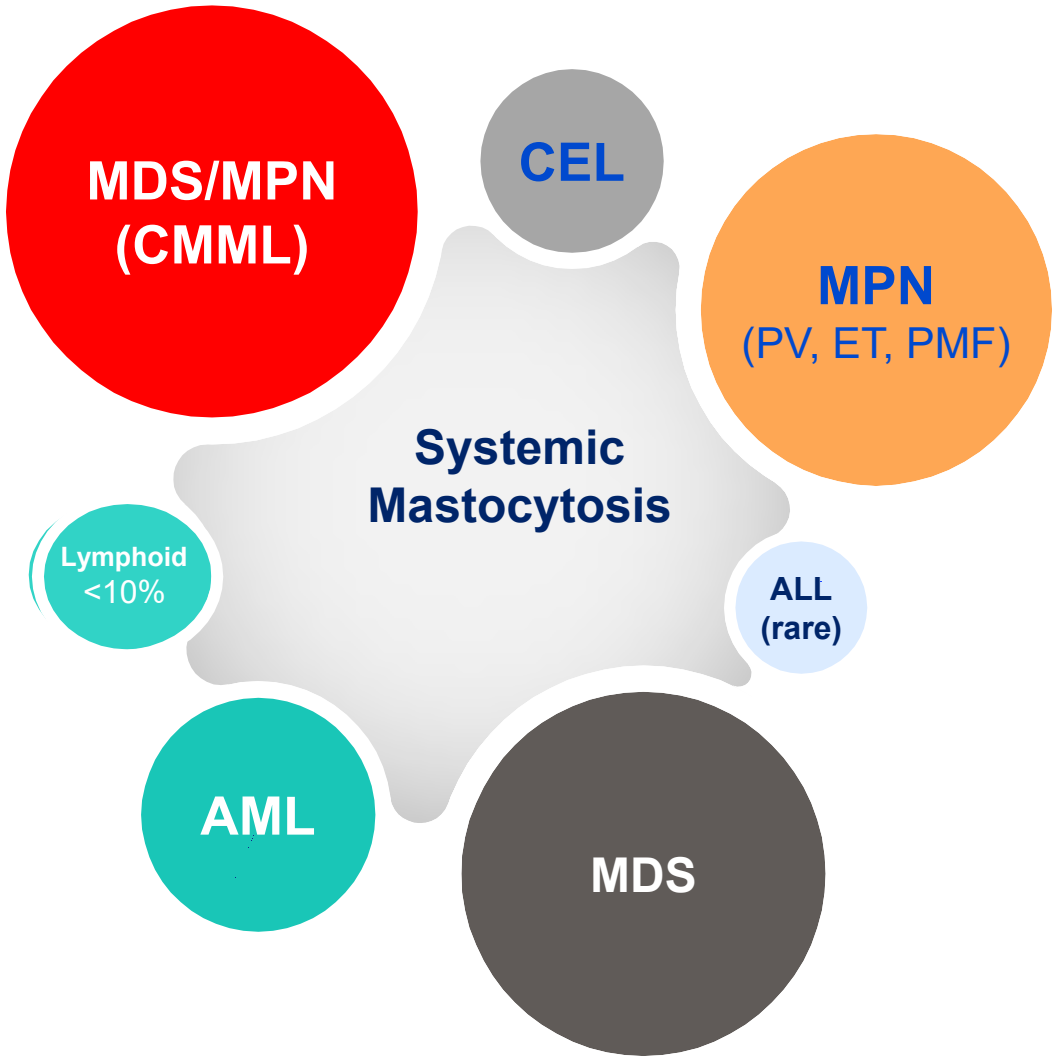


Organ Damage (C-findings)

- Cytopenias
- Liver function abnormalities
- Ascites, pleural effusions
- Splenomegaly with hypersplenism
- Malabsorption with hypoalbuminemia and weight loss
- Large osteolytic bone lesions +/- pathologic fractures

Shomali and Gotlib, Hematology Am Soc Hematol Educ Program, 2018

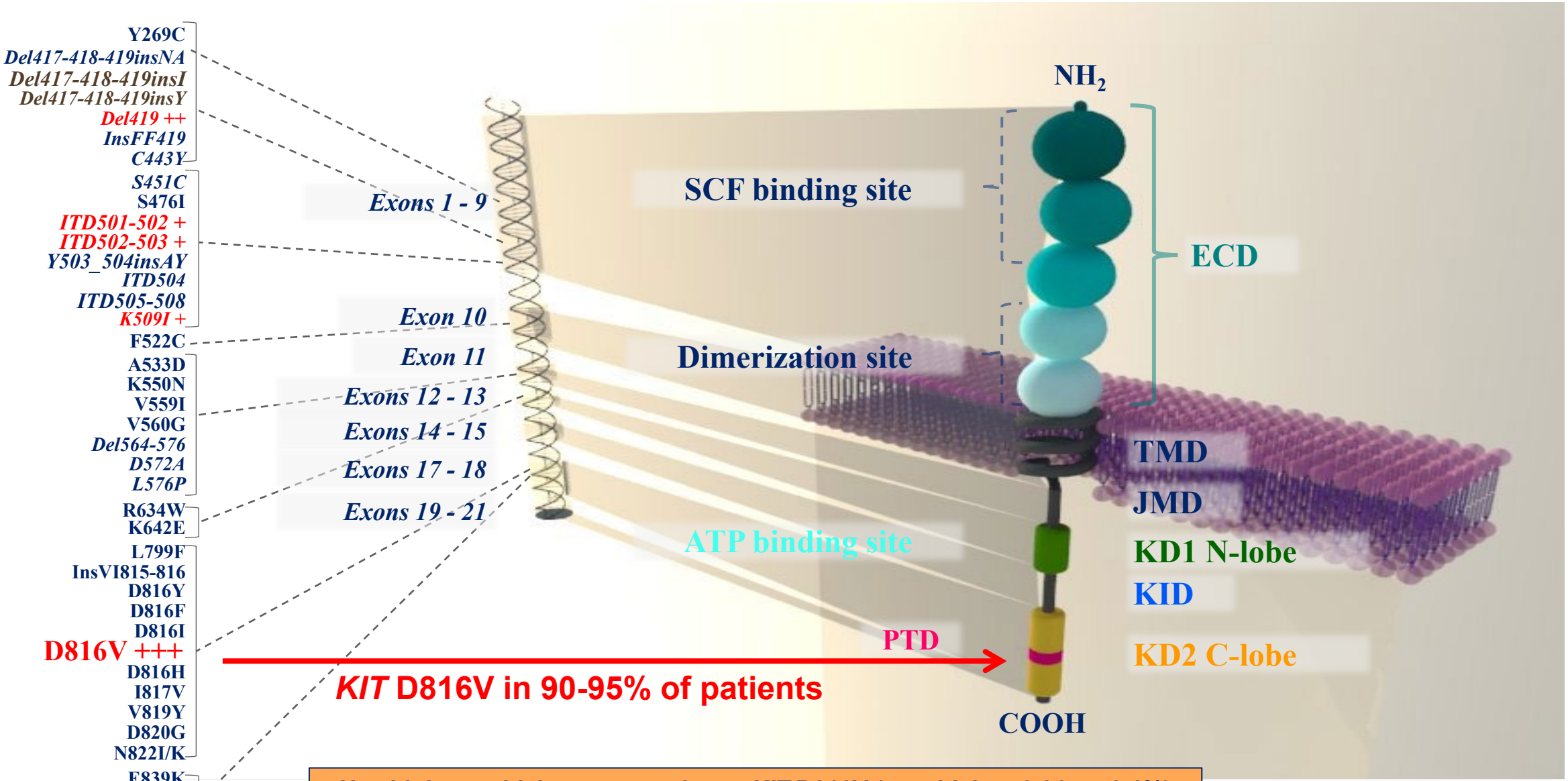
SM with an Associated Hematologic Neoplasm (SM-AHN)



Myeloid AHN: ~90% of cases

[1]Sotlar *et al*, *J Pathol*, 2010

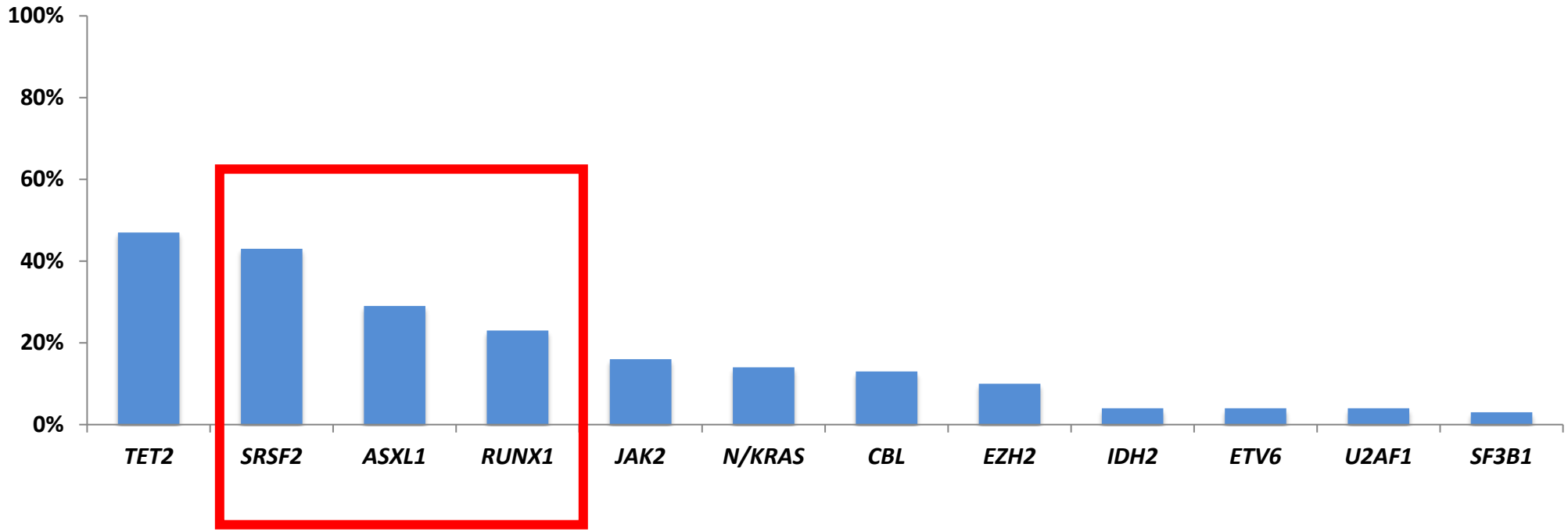
KIT D816V is Found in ~95% of SM Patients



Use high-sensitivity assay to detect *KIT* D816V (sensitivity ~0.01 to 0.1%)
e.g. *KIT* D816V allele-specific PCR; digital droplet PCR

Slide courtesy of Prof. M. Arock

Advanced Systemic Mastocytosis: Mutations Beyond *KIT* D816V



High Risk Mutations: *SRSF2 / ASXL1 / RUNX1 (S/A/R)*

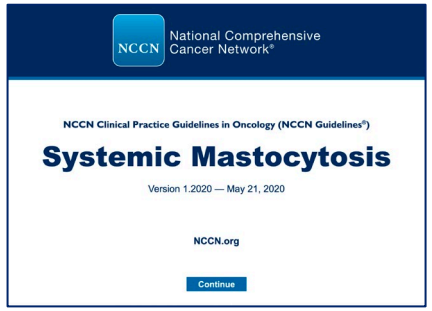
Jawhar *et al.*, *Leukemia* 2015
Jawhar *et al.*, *Leukemia* 2016

Mastocytosis: Clinical Issues

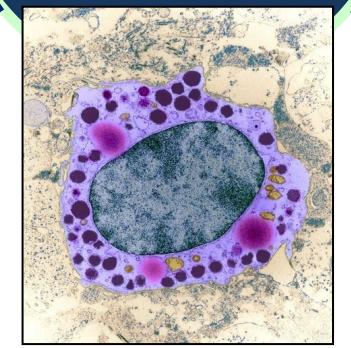
Skin lesions
Maculopaular
Cutaneous
Mastocytosis

Mediator Symptoms
Flushing
Diarrhea
Brain fog
Anaphylaxis

- H1, H2 Blockers
- Cromolyn
- EpiPen



Neoplastic mast cells

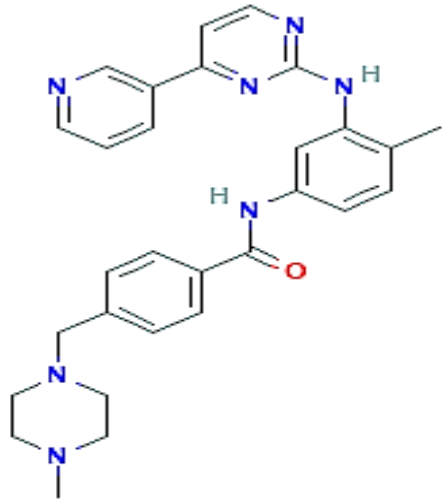


Organ damage

Associated myeloid neoplasm

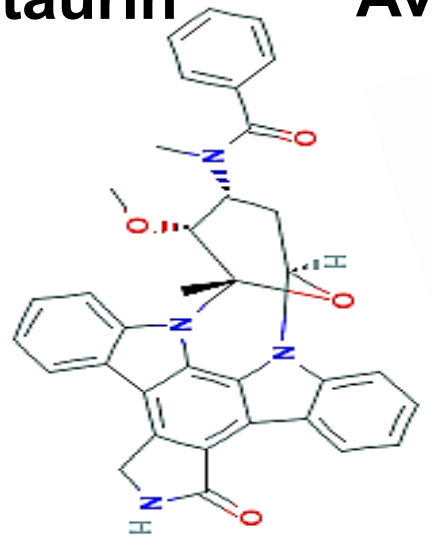
KIT-targeting TKIs: Status 2024

Imatinib



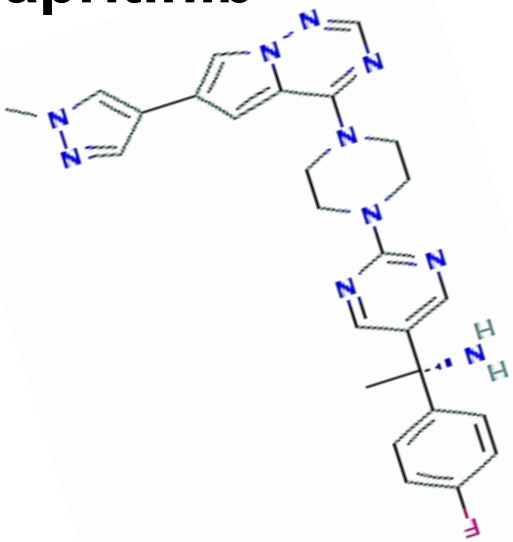
Approved in 2006 for ASM **lacking *KIT* D816V** mutation or with **unknown *KIT* mutation status**

Midostaurin



Approved in 2017 for 1L in AdvSM

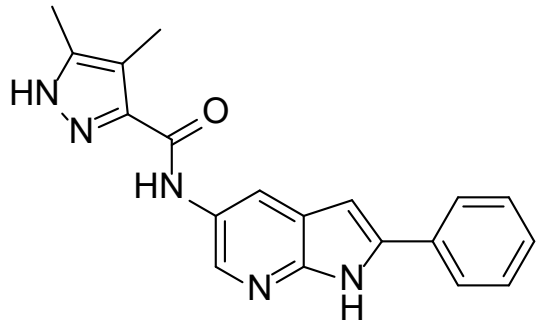
Avapritinib



FDA-approved for 1L in AdvSM (2021); Approved for ISM

BLU-263
***HARBOR* (NCT04910685)**

Bezuclastinib (CGT9486)



Phase II study in advanced SM
NCT04996875
APEX

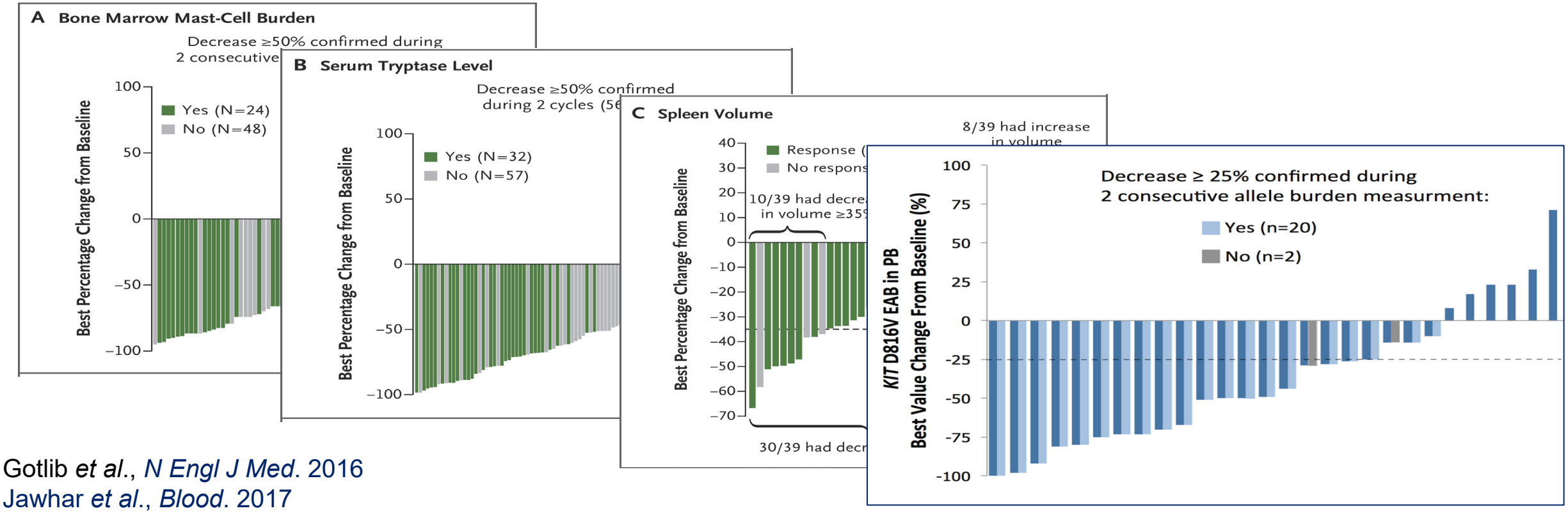
ISM/SSM trial:
NCT05186753
SUMMIT

Global Midostaurin Trial: Efficacy & Impact on Mast Cell Burden

	ALL PTS, N=89
ORR %	**60**
Complete	0
Major	45
Partial	15

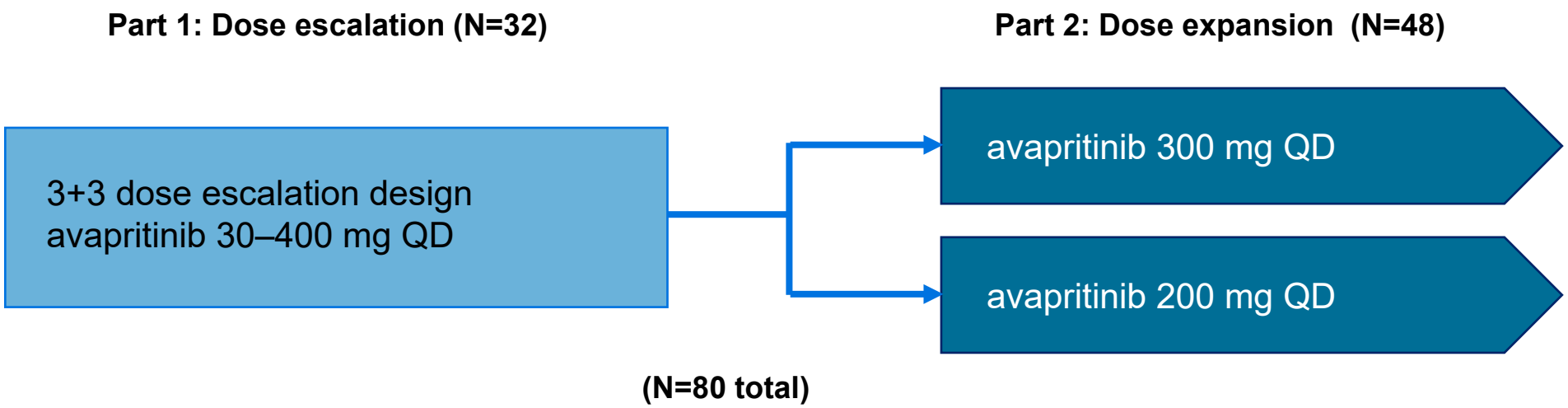
ASM N=16	SM-AHN N=57	MCL N=16
75%	58%	50%

Median duration of response: 24.1 months



Gotlib *et al*., *N Engl J Med*. 2016
Jawhar *et al*., *Blood*. 2017

Phase I EXPLORER Study Design



Key entry criteria:

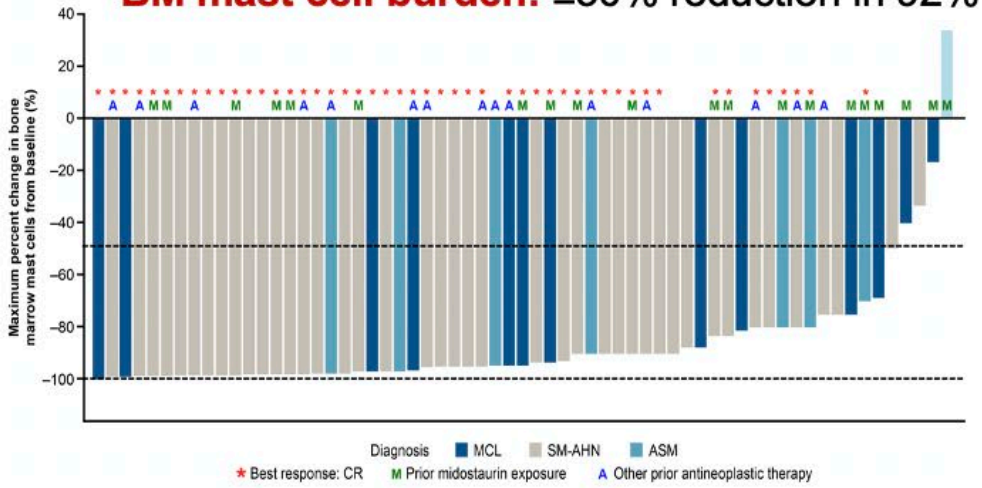
- AdvSM (ASM, SM-AHN, or MCL) or relapsed/refractory myeloid malignancy per local assessment
- Age ≥18 years, ECOG performance status 0–3, platelets ≥50 x 10^9/L

Study objectives:

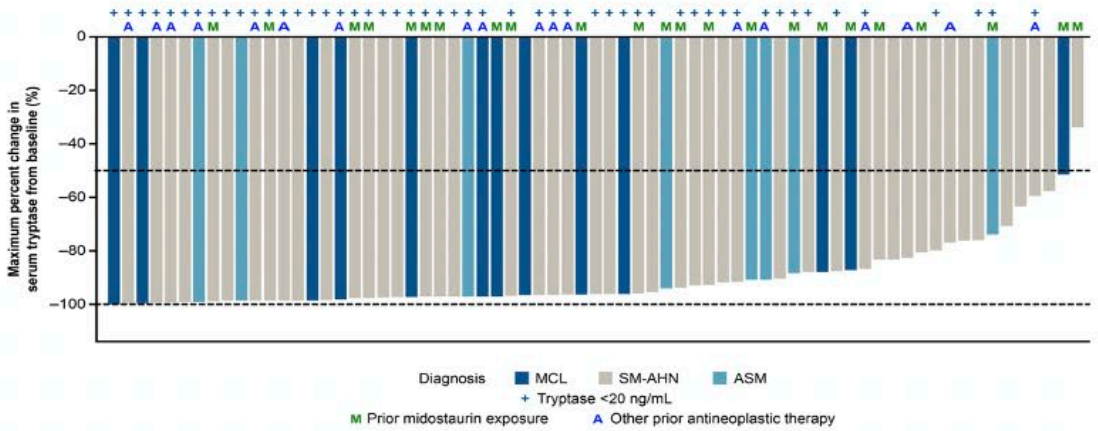
- RP2D and safety, ORR per mIWG-MRT-ECNM, pharmacokinetics, changes in serum tryptase and blood/bone marrow *KIT* D816V mutant allele fraction, and patient-reported outcomes

Avapritinib: Phase I EXPLORER: Reduction in Measures of Mast Cell Burden

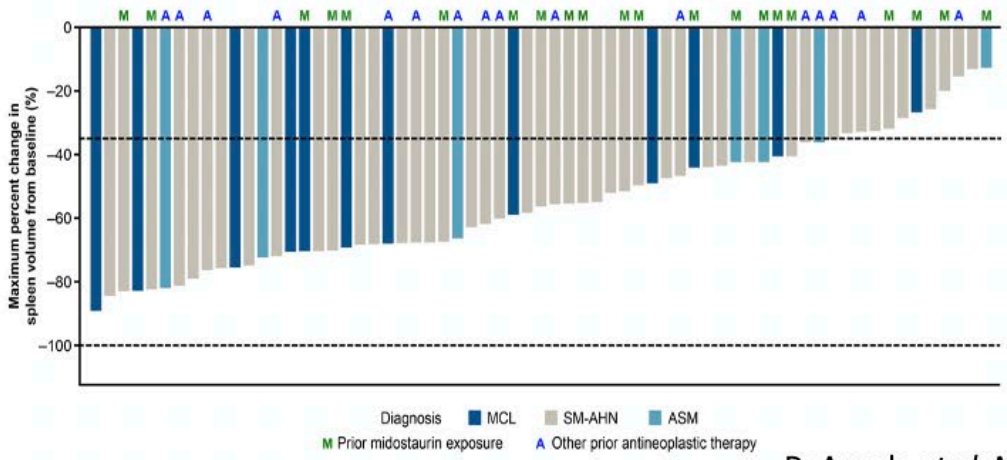
BM mast cell burden: ≥50% reduction in 92%



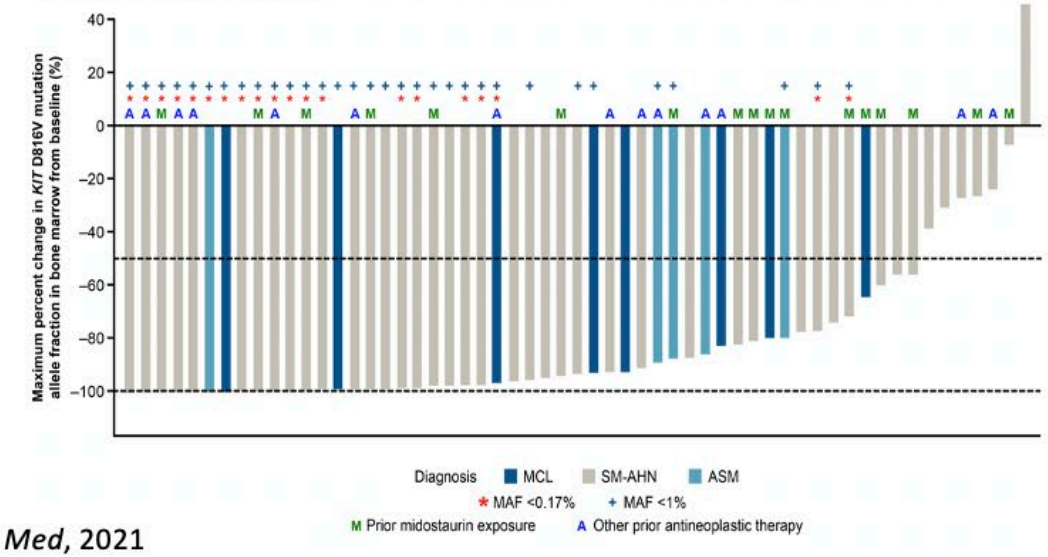
Serum tryptase: ≥50% reduction in 99%



Spleen volume: ≥35% reduction in 82%

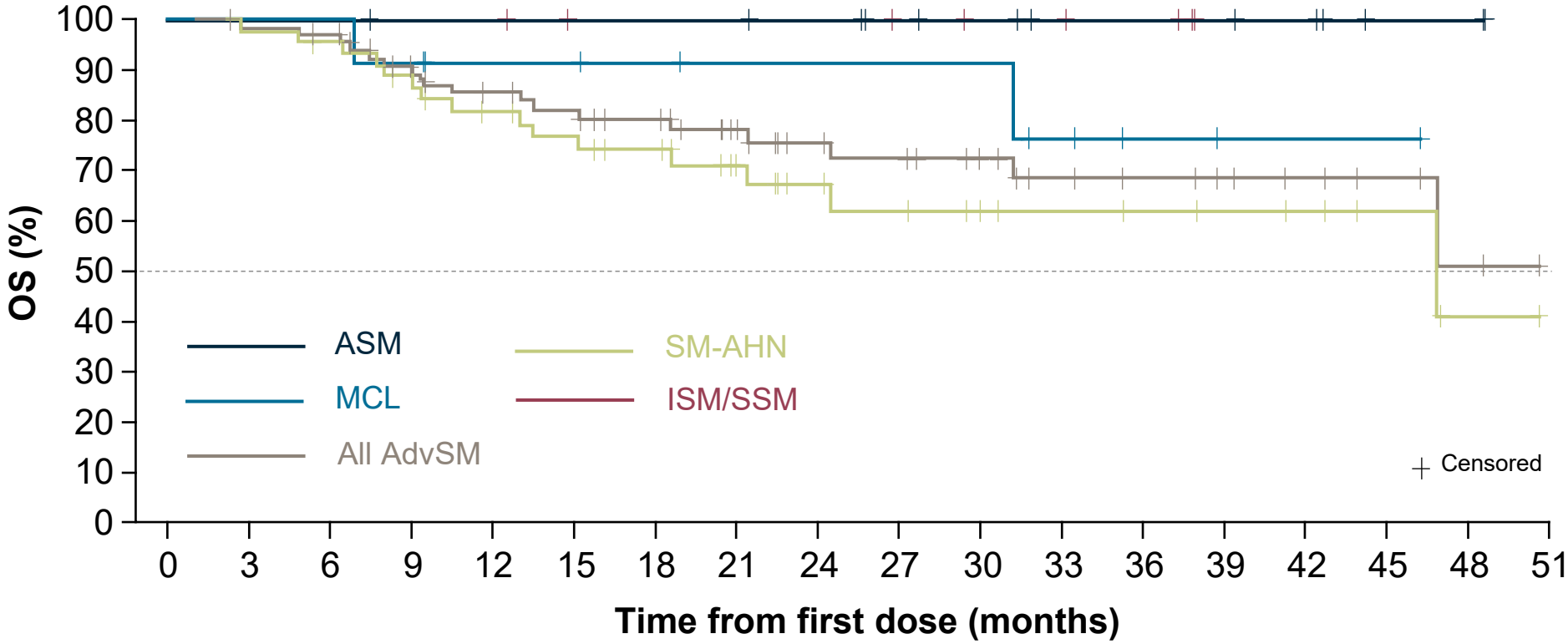


***KIT* D816V VAF:** ≥50% reduction in 80%; undetectable in 30%



DeAngelo *et al*, *Nature Med*, 2021

EXPLORER: Kaplan-Meier estimates of overall survival (safety population)



- Median OS was not reached in the overall AdvSM safety population with a median duration of follow-up of 23 months
- Estimated 24-month OS rates were: **all AdvSM**, 76%; **ASM**, 100%; **SM-AHN**, 67%; and **MCL**, 92%

Midostaurin: **all AdvSM**, 53%; **ASM**, 86%; **SM-AHN**, 49%; and **MCL**, 26%

DeAngelo *et al*, *Nature Med*, 2021

Phase I EXPLORER: Adverse events (safety population)

Treatment-related AEs (N=86)[a]	All grades	Grade ≥3
Non-hematologic AEs in ≥20% of patients, n (%)		
Periorbital edema/eyelid edema	57 (66)	2 (2)
Cognitive effects[b]	34 (40)	2 (2)
Diarrhea	24 (28)	1 (1)
Nausea	29 (34)	2 (2)
Fatigue	24 (28)	4 (5)
Peripheral edema	26 (30)	0
Vomiting	19 (22)	1 (1)
Hair color changes	22 (26)	1 (1)
Hematologic AEs in ≥10% of patients, n (%)		
Anemia	35 (41)	18 (21)
Thrombocytopenia	26 (30)	18 (21)
Neutropenia	12 (14)	10 (12)

[a]Safety data includes all patients regardless of starting dose. [b]Includes memory impairment, cognitive disorder, confusional state and encephalopathy. AE, adverse event.

- Most AEs were Grade 1 and 2; 14 patients (16%) discontinued treatment due to disease progression, of which 6 (7%) were due to progression to acute myeloid leukemia
- 9 patients (10%) discontinued due to treatment-related AEs
- 63 (73%) patients experienced AEs leading to dose reduction, most commonly cytopenias
- Intracranial bleeding was reported in 10 (12%) patients, including 2 (2%) in the absence of severe thrombocytopenia
  - 5 were asymptomatic (Grade 1)
  - 3 were Grade 2; 1 was Grade 3
  - 1 was Grade 5
  - 2 events occurred following head trauma (Grade 2 and Grade 5) and 1 in the context of progressive MCL (Grade 2)

DeAngelo *et al*, *Nature Med*, 2021

Avapritinib as first-line therapy in patients with advanced systemic mastocytosis: Efficacy and safety from the PATHFINDER clinical study

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December 10 to December 13, 2022
Abstract #625

Avapritinib as first-line therapy in patients from PATHFINDER

Eligibility

- Central AdvSM diagnosis per WHO criteria[1]
  - **SM-AHN excluding AML and high or very high-risk MDS**
- ≥18 years of age
- ECOG PS 0–3
- **Platelets ≥50×10⁹/L[a]**

Avapritinib 200 mg QD starting dose[b]

Full enrolment
N=107

Avapritinib as second line or later therapy (n=69)

mIWG-MRT-ECNM response-evaluable population (n=49)

Prior therapies included midostaurin, cladribine, and interferon

Avapritinib as first-line therapy (n=38)

mIWG-MRT-ECNM response-evaluable population (n=25)

Current analysis

Primary Endpoint

- Central adjudicated ORR by mIWG-MRT-ECNM criteria (requires at least one evaluable C-finding - organ damage)

Secondary Endpoints

- Objective disease burden measures[c]
- DOR, PFS, OS, and safety

[a]Implemented in 2019 to reduce risk of intracranial bleeding. [b]2 patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD. [c]Disease burden measures include bone marrow MCs, serum tryptase, *KIT* D816V variant allele fraction, and spleen volume. No type 1 error control for these endpoints.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR, overall response rate; OS, overall survival; PFS, progression free survival; QD, once daily; WHO, World Health Organization.

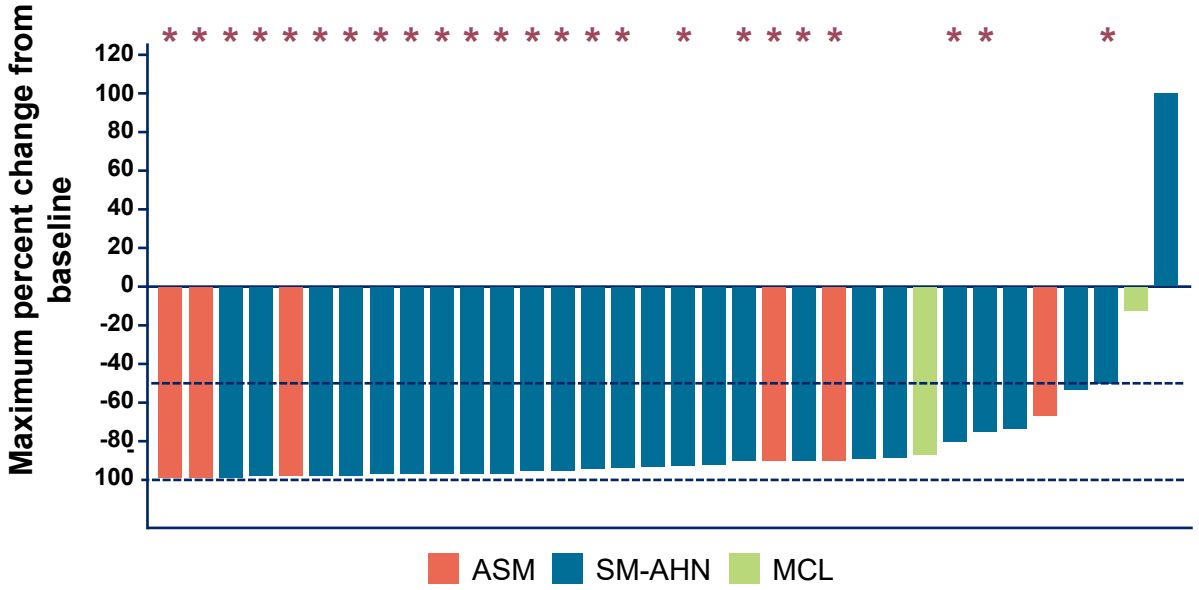
1. Horny HP et al. Mastocytosis. In: Sverdlow SH et al. World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2016.

Reduction in disease burden observed across subtypes

Bone marrow MCs[a]

Bone marrow MCs decreased by ≥50% in 84% of patients (32/38), including 25 of 28 patients with SM-AHN

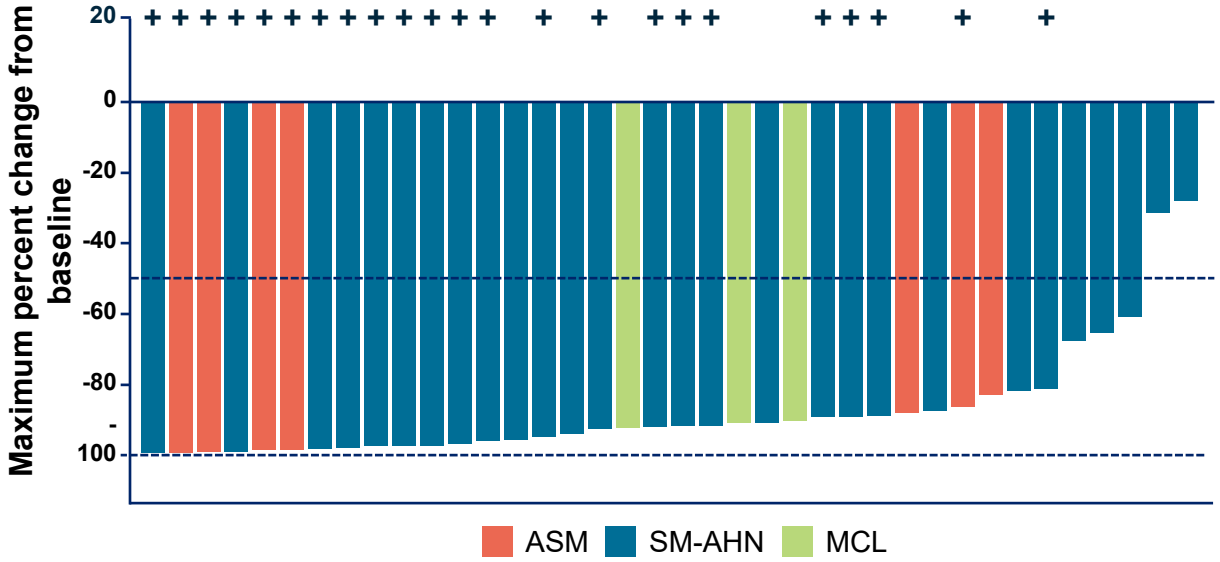
MC aggregates total clearance in 63% of patients (24/38), including 19 of 28 patients with SM-AHN



* Best response: CR

Serum tryptase[a]

- **Serum tryptase level decreased by ≥50% in 95% of patients (36/38),** including 26 of 28 patients with SM-AHN
- **60% of patients (22/37) had CR (decrease to <20 ng/mL) in serum tryptase,** including 18 of 28 patients with SM-AHN



\+ Tryptase <20 ng/mL

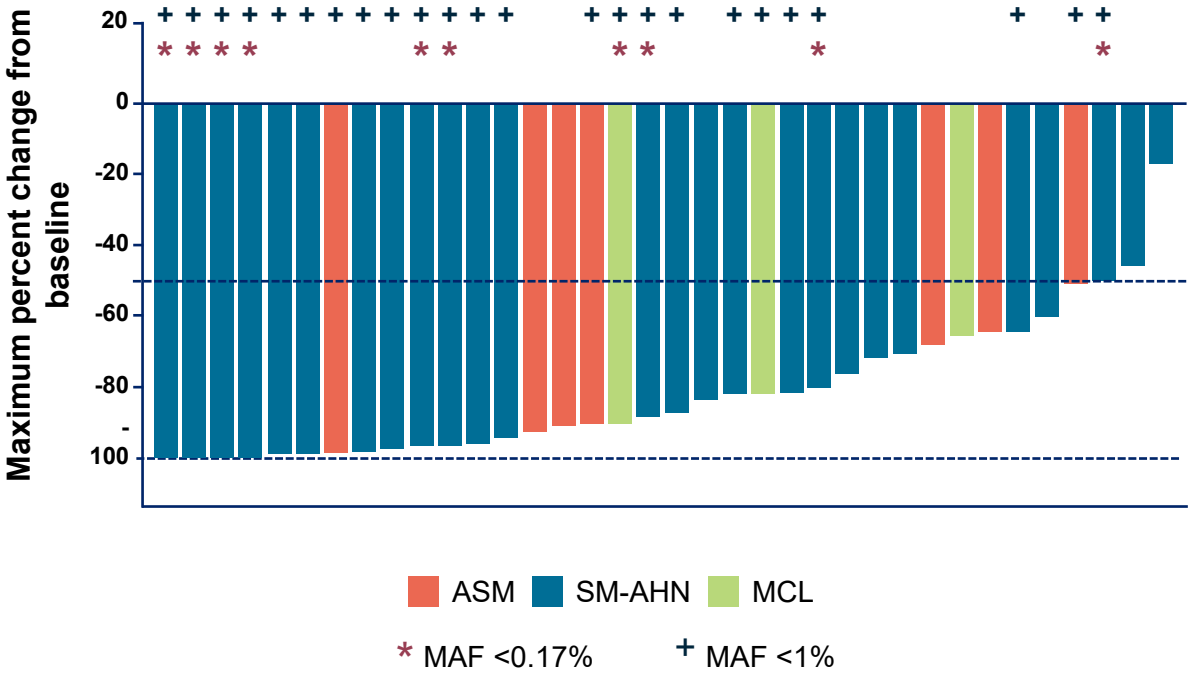
Data cut off: April 20, 2021.

[a]Only patients with post-baseline measurements were included in both waterfall plots. There was no type I error control.

Reduction in disease burden observed across subtypes

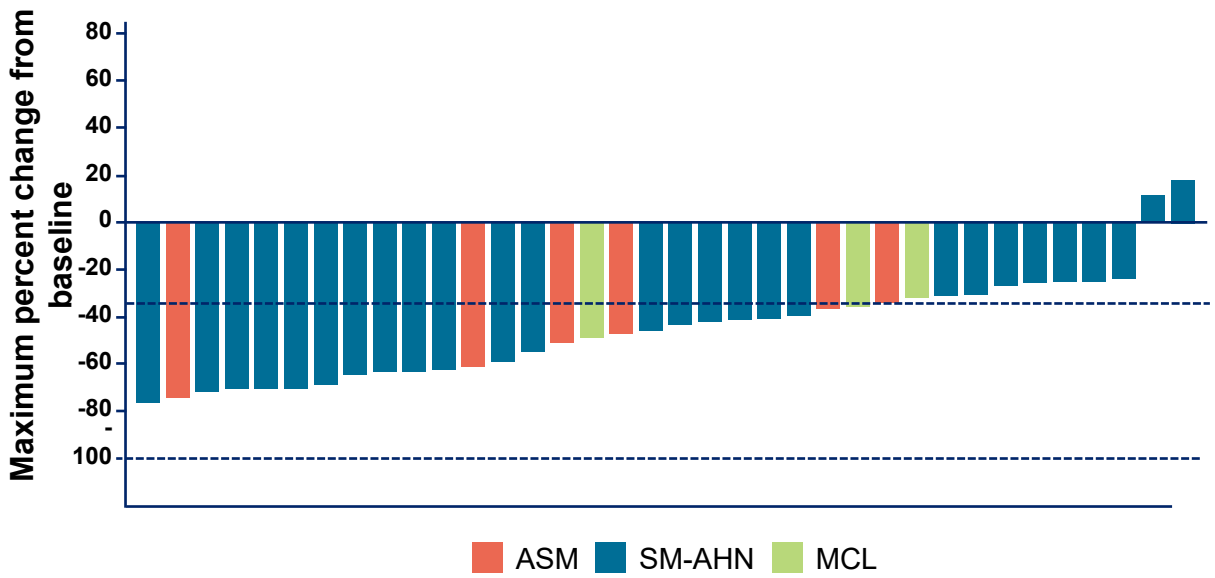
KIT D816V variant allele fraction in peripheral blood[a]

- ***KIT* D816V VAF[b] decreased by ≥50% in 89% of patients (34/38)**, including 24 of 28 patients with SM-AHN
- ***KIT* D816V VAF[b] decreased below 1% in 63% of patients (24/38)**, including 19 of 28 patients with SM-AHN



Spleen volume[a]

- **Spleen volume decreased by ≥35% in 66% of patients (25/38),** including 18 of 28 patients with SM-AHN
- **61% (n=11/18) of patients whose spleen was palpable at baseline became non-palpable during treatment,** including 10 of 28 patients with SM-AHN



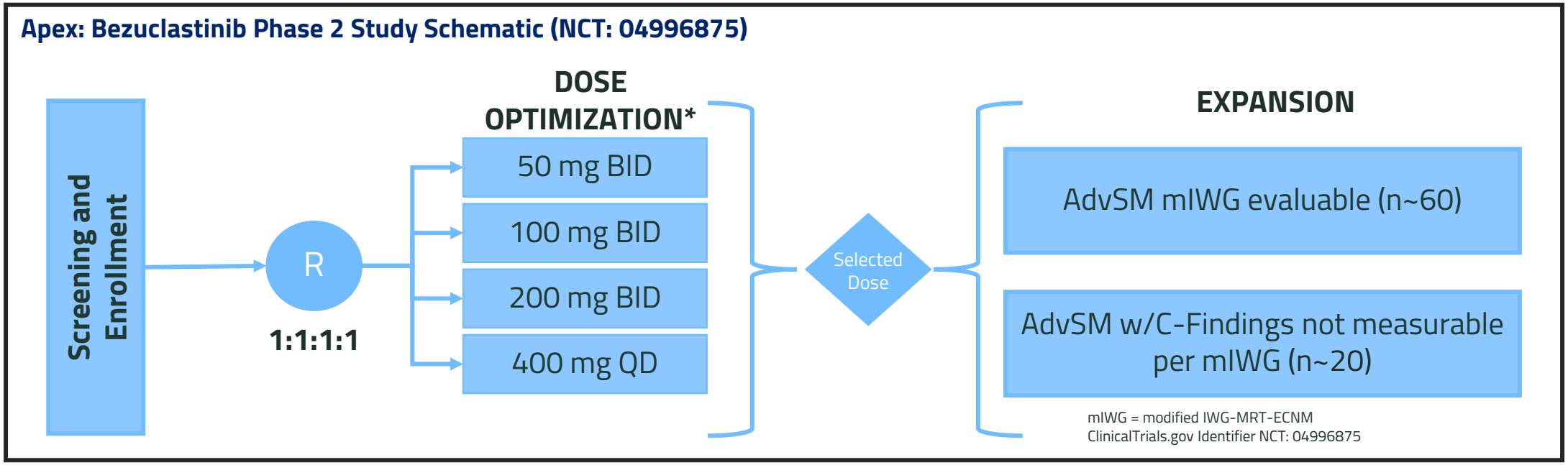
Data cut off: April 20, 2021.

[a]There was no type I error control.

[b]*KIT* D816V VAF measured in peripheral blood using a ddPCR assay with detection limit of 0.17%, consistent with prior presentations on AdvSM.

ddPCR, droplet digital polymerase chain reaction.

Apex: Phase 2, open-label, 2-part clinical study to evaluate safety, efficacy, PK, and PD of the KIT inhibitor bezuclastinib in patients with AdvSM

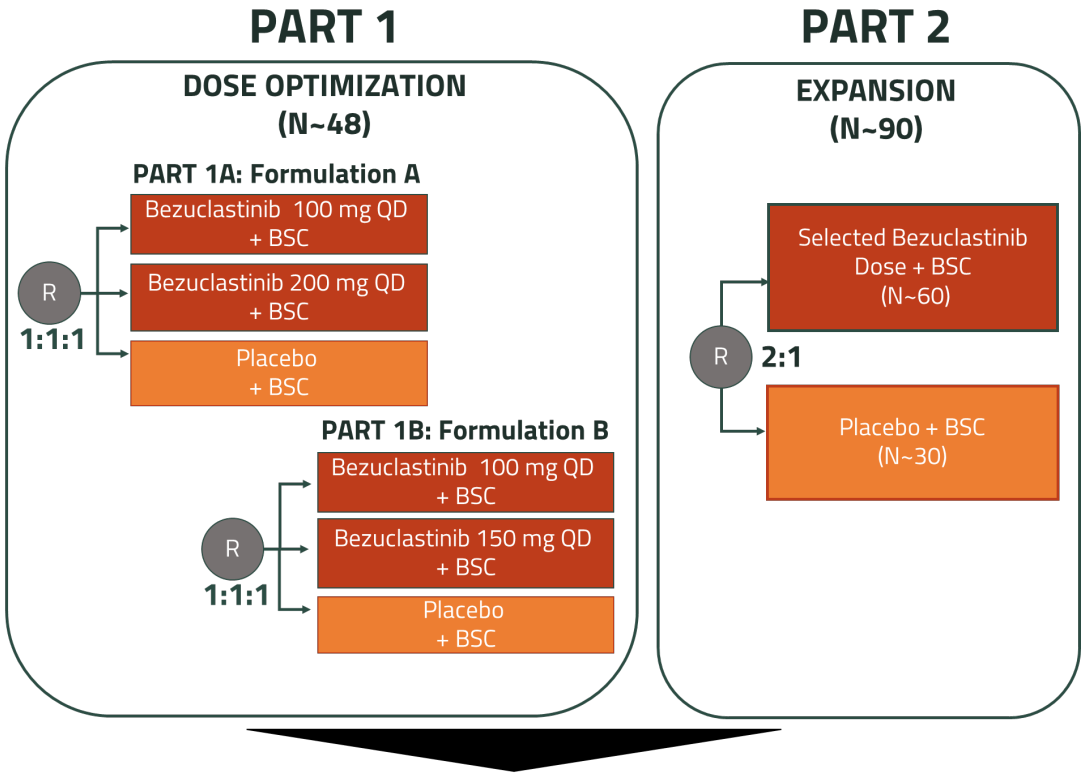


- **Part 1 (dose optimization):** Patients will be randomized to receive 1 of 4 doses of bezuclastinib
  - A panel of expert clinicians and pathologists will determine patient eligibility and approve patient enrollment during the Screening Period based on clinical history and pathology
  - Clinical activity will be assessed according to mIWG response criteria by the central response review committee (CRRC)
  - *Interim analysis (IA) will be performed after ~28 patients have completed at least 2 cycles of treatment

- **Part 2 (expansion):** Patients will receive bezuclastinib at the optimal dose selected in Part 1
- Bezuclastinib is administered orally, once or twice daily for 28 days of each 4-week cycle
- Severity of adverse events will be graded using the NCI-CTCAE v5.0

Summit: A Multi-Part, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of the Safety and Efficacy of Bezuclastinib in participants with Nonadvanced Systemic Mastocytosis

Key Inclusion Criteria	Key Exclusion Criteria
• Diagnosed with 1 of the following World Health Organization (WHO) classifications for SM (ISM, including BMM, or SSM)[12] • Inadequate control of symptoms despite a stable regimen of at least 2 antimediator therapies • Eastern Cooperative Oncology Group (ECOG) Performance Status 0 to 2	• Diagnosed with mastocytosis of the skin without systemic involvement • Received prior treatment with any targeted KIT inhibitor with the exception of approved agents for the treatment of SM • Received prior cytoreductive therapy or investigational agent for <14 days or 5 half-lives of the drug and for cladribine, interferon alpha, pegylated interferon, or antibody therapy <28 days or 5 half-lives of the drug (whichever is longer), before starting screening assessments • Active, uncontrolled, systemic bacterial, fungal, or viral infections at screening • Need for treatment with systemic corticosteroids (i.e., >10 mg/day prednisone or equivalent) • Patient on stable dose of prednisone ≤10 mg/day (or equivalent) are eligible



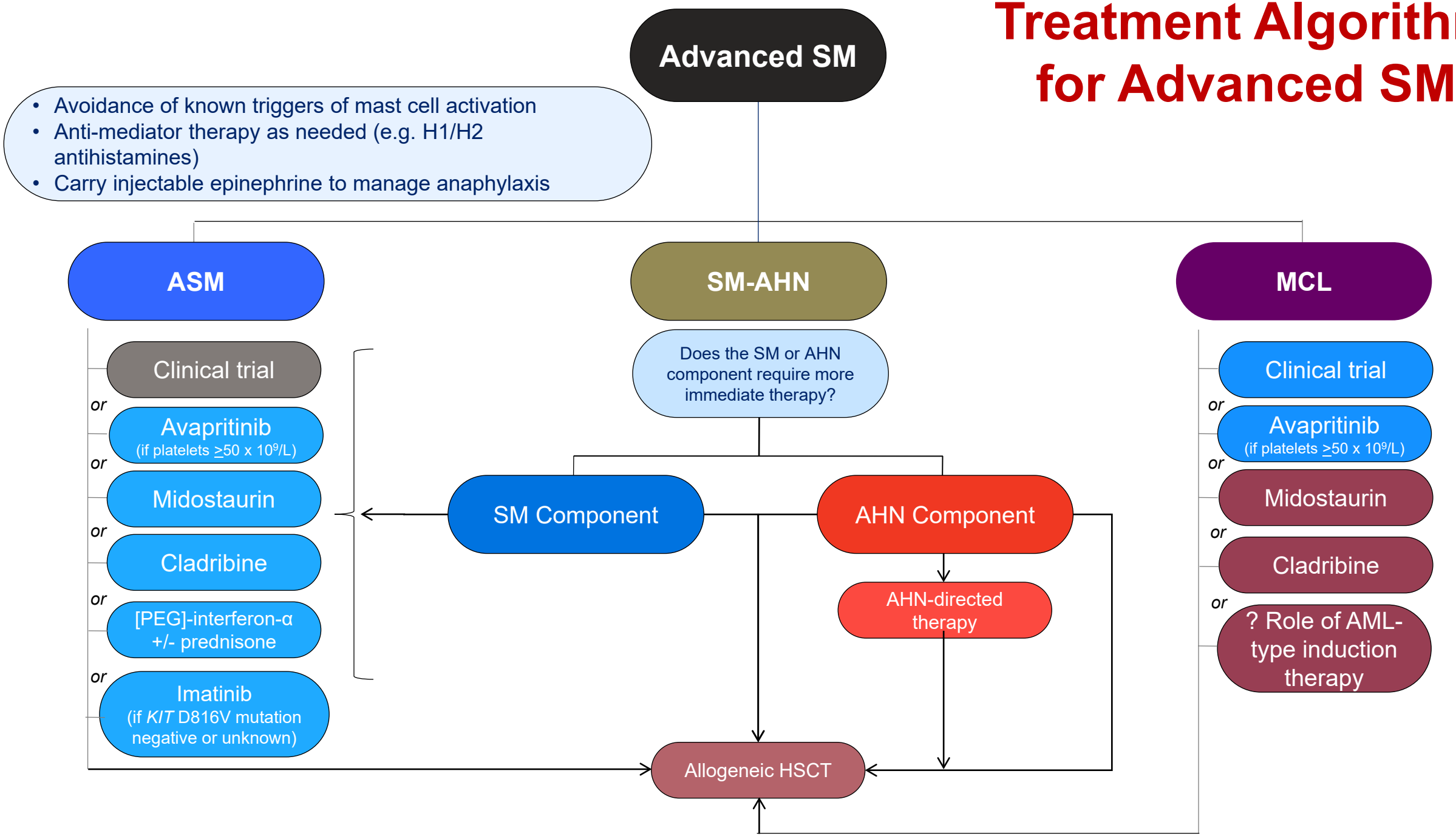
PART 3

EXTENSION

- Continued open-label dosing for patients who were randomized to active drug in Part 1 or Part 2
- Patients randomized to receive placebo in Part 1 or Part 2 can cross-over to receive active drug

Clinical Trials Identifier: NCT05186753

Treatment Algorithm for Advanced SM



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Questions?

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