Oncology Learning Network

Advances in the Management of Myeloproliferative Neoplasms and Systemic Mastocytosis:

Diagnosis/Classification, Risk Stratification, and Optimal Therapeutic Selection

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Icahn School of Medicine at Mount Sinai
New York, New York

Faculty Disclosures

- **Mariana Castells, MD, PhD**: Clinical Trial PI—Blueprint, Cogent, Telios; Editor-in-Chief—Current Allergy and Asthma Reports; Board of Directors—American Initiative in Mast Cell Diseases; Author—UpToDate; Data and Safety Monitoring Board—NIH
- **Daniel DeAngelo, MD, PhD**: Consultant—Amgen, Autolus, Agios, Blueprint, Forty-Seven, Gilead, Incyte, Jazz, Novartis, Pfizer, Servier, Takeda; Research Funding—AbbVie, Novartis, Blueprint, Glycomimetrics; Data and Safety Monitoring Board—Daiichi-Sankyo, Mount Sinai MPN Consortium
- **Raajit Rampal, MD, PhD**: Consultant—Incyte, Zentalis, Celgene/Bristol Myers Squibb, Blueprint, AbbVie, CTI, Stemline, Galecto, PharmaEssentia, Jubilant, Constellation/MorphoSys, Sierra Oncology/GSK, Protagonist, Cogent, Sumitomo, Kartos, Servier, Karyopharm; Research Funding—Incyte, Zentalis, Constellation/MorphoSys, Ryvu, Stemline
- **John Mascarenhas, MD**: Consultant—Incyte, Novartis, CTI/Sobi, Geron, Kartos, AbbVie, GSK, Blueprint Medicines, Disc, Karyopharm, Sumitomo, Pfizer, MorphoSys, Galecto, Jubilant, Merck, Roche, PharmaEssentia, Keros; Research Funding—Incyte, Novartis, Bristol Myers Squibb, CTI/Sobi, AbbVie, Geron, Kartos, Karyopharm, Disc

This presentation will discuss the unapproved use of drugs for the treatment of myelofibrosis.

Program Information

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- Supported by an educational grant from Blueprint Medicines Corporation; CTI BioPharma Corp., a Sobi Company; Incyte Corporation; and PharmaEssentia USA Corporation

Learning Objectives

- Incorporate the latest clinical trial data, real-world evidence, and clinical practice guidelines to accurately differentiate, diagnose, and manage MPNs and SM
- Evaluate the mechanisms of action and safety and efficacy of targeted therapies for the treatment of MPNs and SM
- Differentiate SM variants and identify genetic mutations driving targeted treatment algorithms
- Implement strategies to optimize therapeutic selection and/or identify clinical trial opportunities that may be appropriate for patients with MPNs or SM
- Recognize and appropriately manage TRAEs to optimize patient outcomes and improve QoL
- Utilize a multidisciplinary approach to implement appropriate personalized, patient-centered strategies to care for patients with MPNs and SM

MPN = myeloproliferative neoplasm; SM = systemic mastocytosis; TRAE = treatment-related adverse event; QoL = quality of life.

Systemic Mastocytosis

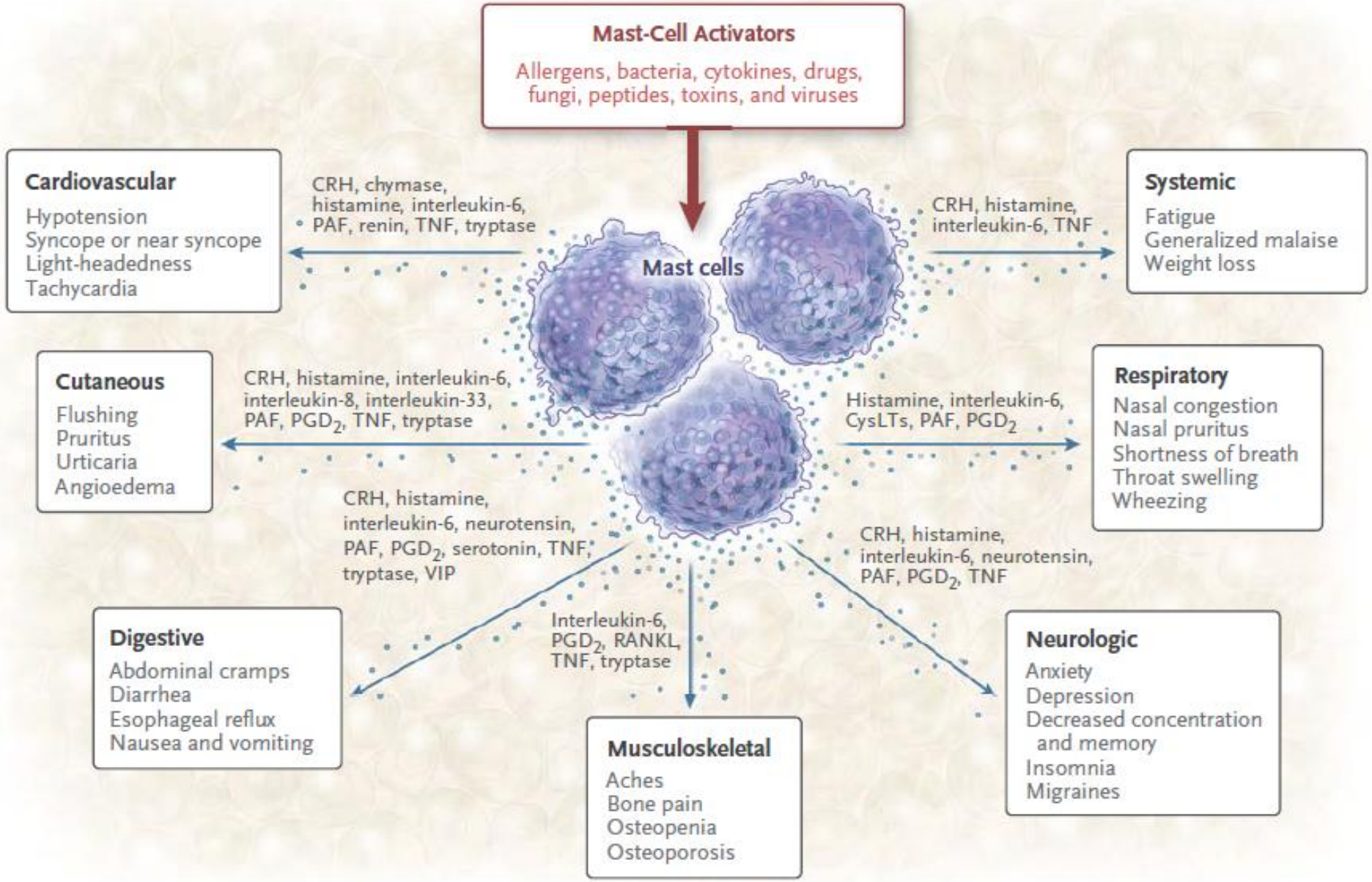
Daniel DeAngelo, MD, PhD, and Mariana Castells, MD, PhD

The Spectrum of Mast Cell Disorders

What Are Mast Cells?

First discovered by Paul Ehrlich, who named these cells “mastzellen”.

Ehrlich P. *Arch mikr Anat*. 1877;13:263-277.



CRH = corticotropin-releasing hormone; TNF = tumor necrosis factor; PAF = platelet-activating factor; PGD_2 = prostaglandin D2; CysLTs = cysteinyl leukotrienes; VIP = vasoactive intestinal polypeptide; RANKL = receptor activator of nuclear factor-κB ligand.

Theoharides TC, et al. *N Engl J Med*. 2015;373(2):163-172.

Diagnostic Criteria of SM: WHO 2022 Update

Major	Multifocal dense infiltrates of mast cells, ≥15 mast cells in aggregates
Minor	1. >25% mast cells with atypical morphology in BM or other organs 2. Activating KIT mutation at 816 or other 3. Aberrant expression of CD2, CD25, or CD30 4. Serum total tryptase >20 ng/mL in the absence of a myeloid disorder or HAT

1 major
+ 1 minor

OR

3 minor criteria

WHO = World Health Organization; BM = bone marrow; HAT = histone acetyltransferase.
Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719.

B- and C-Findings in Systemic Mastocytosis

B-Findings = Indication of high burden of MCs, and expansion of the genetic defect into various myeloid lineages without impairment of organ function
B = Borderline Benign

1. Infiltration grade (MCs) in bone marrow > 30% in histology and serum total tryptase level > 200 ng/mL
2. Hypercellular marrow with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias or WHO criteria for an MDS or MPD
3. Organomegaly: palpable hepatomegaly, splenomegaly, or lymphadenopathy (on CT or US: > 2 cm) without impaired organ function
4. KIT D816V mutation with VAF >10%

C-Findings = Indication of impaired organ function due to MC infiltration (has to be confirmed by biopsy in most cases)
C = Consider Cytoreduction

1. Cytopenia(s): ANC < 1000/µL or Hb < 10 g/dL or Plt < 100,000/µL
2. Hepatomegaly with ascites and impaired liver function
3. Palpable splenomegaly with hypersplenism
4. Malabsorption with hypoalbuminemia and weight loss
5. Skeletal lesions: large-sized osteolyses or/and severe osteoporosis causing pathologic fractures
6. Life-threatening organopathy in other organ systems that is definitively caused by an infiltration of the tissue by neoplastic MCs

MDS = myelodysplastic syndrome; MPD = myeloproliferative disorder; CT = computed tomography scan; US = ultrasound scan; VAF = variant allele fraction; Plt = platelet.

Valent P, et al. *Leuk Res*. 2001;25(7):603-625. Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719.

What Are the Subtypes of SM?

Indolent SM (ISM)

Meets criteria for SM; no C-findings; no B-findings; no evidence of AHN or MCL
Includes a subtype called bone marrow mastocytosis (BMM)

Smoldering SM (SSM)

Meets criteria for SM; no C-findings; ≥2 B-findings; no evidence of AHN or MCL
Generally has a higher burden of mast cell infiltration than ISM

Advanced SM (AdvSM)

Aggressive SM (ASM)

Meets criteria for SM; ≥1 C-finding; no evidence of AHN or MCL

SM with an associated hematological neoplasm (SM-AHN)

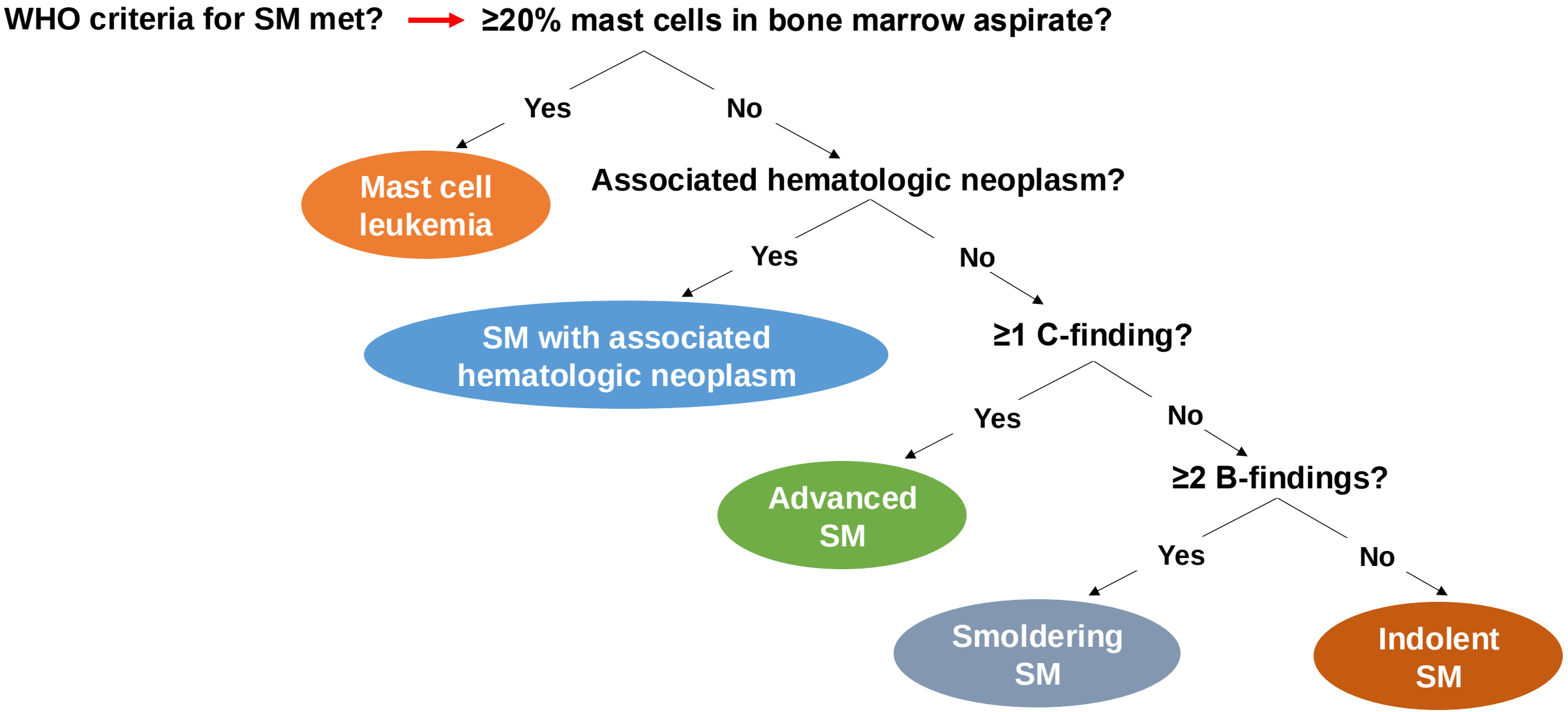
Meets criteria for SM and also meets criteria for AHN as distinct entity (per WHO)

Mast cell leukemia (MCL)

Meets criteria for SM; ≥20% mast cells in bone marrow; diffuse bone marrow infiltration, usually dense, by atypical immature mast cells; aleukemic MCL variant (<10% circulating mast cells)

Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719.

How Is the Subtype of SM Determined?



Adapted from: Pardanani A. *Am J Hematol*. 2023;98(7):1097-1116.

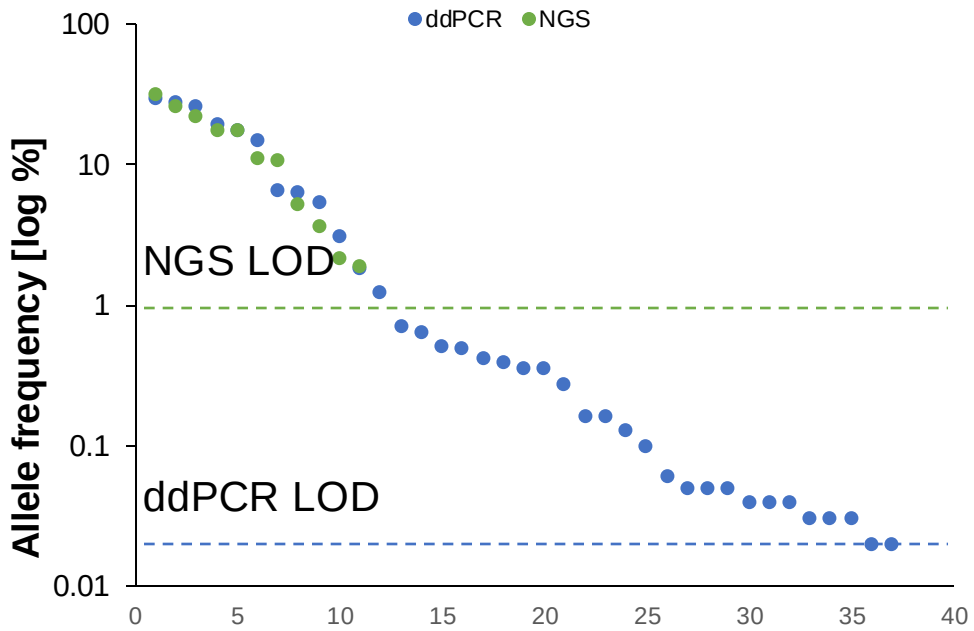
KIT Mutation

- *KIT* D816V
  - Approximately 90-95% of all SM patients
  - **Diagnostic** marker and **therapeutic** target
  - Poor oncogenic driver mutation
    - Associated mast cell phenotype
      - Promote mast cell ***differentiation***
      - Little effects on mast cell proliferation and oncogenesis

Are there additional driver mutations that potentiate malignant transformation?

Recommendations for Histopathology and *KIT* D816V Mutation Testing

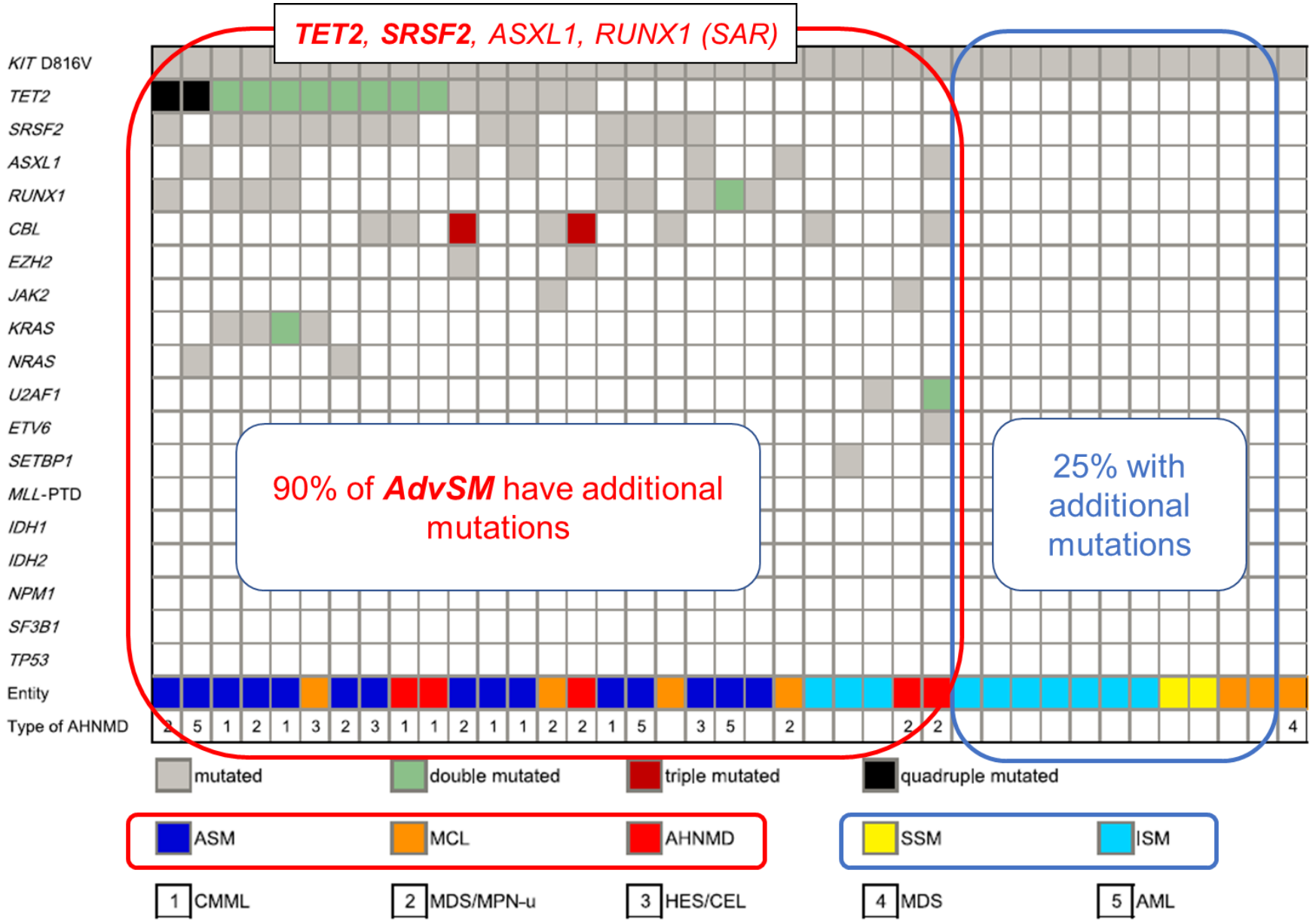
- Increased detection of *KIT* D816V mutation in peripheral blood samples using digital droplet PCR (ddPCR) compared with next-generation sequencing (NGS) in patients with indolent systemic mastocytosis



KIT D816V: 28% (NGS) vs 95% (ddPCR)

LOD = lower limit of detection.

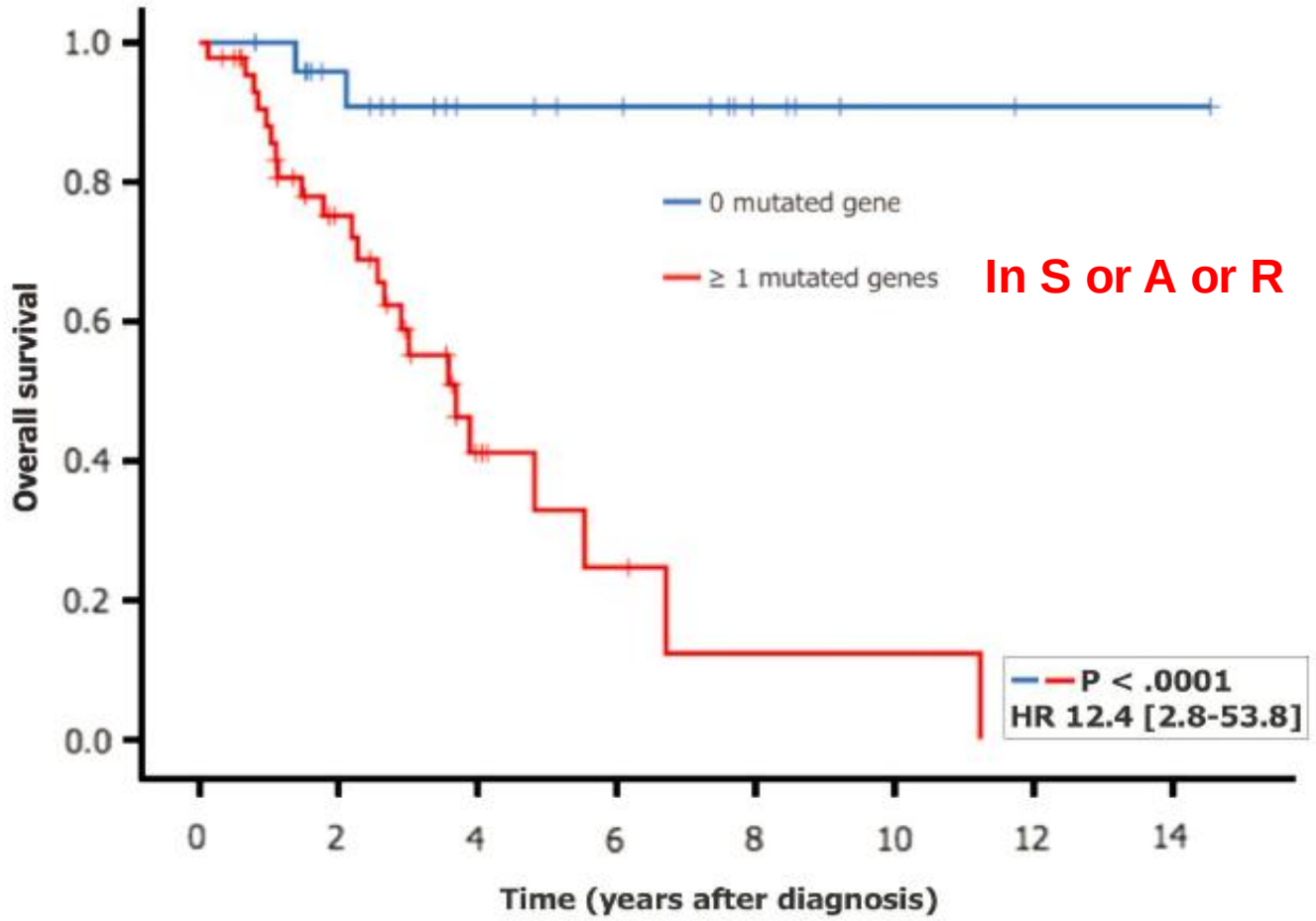
George TI, et al. Presetned at: American Hematology Society Annual Meeting and Exposition; December 5-8, 2020; Virtual. Abstract 3004.



CMML = chronic myelomonocytic leukemia; MDS/MPN-u = myelodysplastic/myeloproliferative neoplasm unclasssified; HES/CEL = hypereosinophilic syndrome/chronic eosinophilic leukemia; AML = acute myeloid leukemia.

Schwaab J, et al. *Blood*. 2013;122(14):2460-2466.

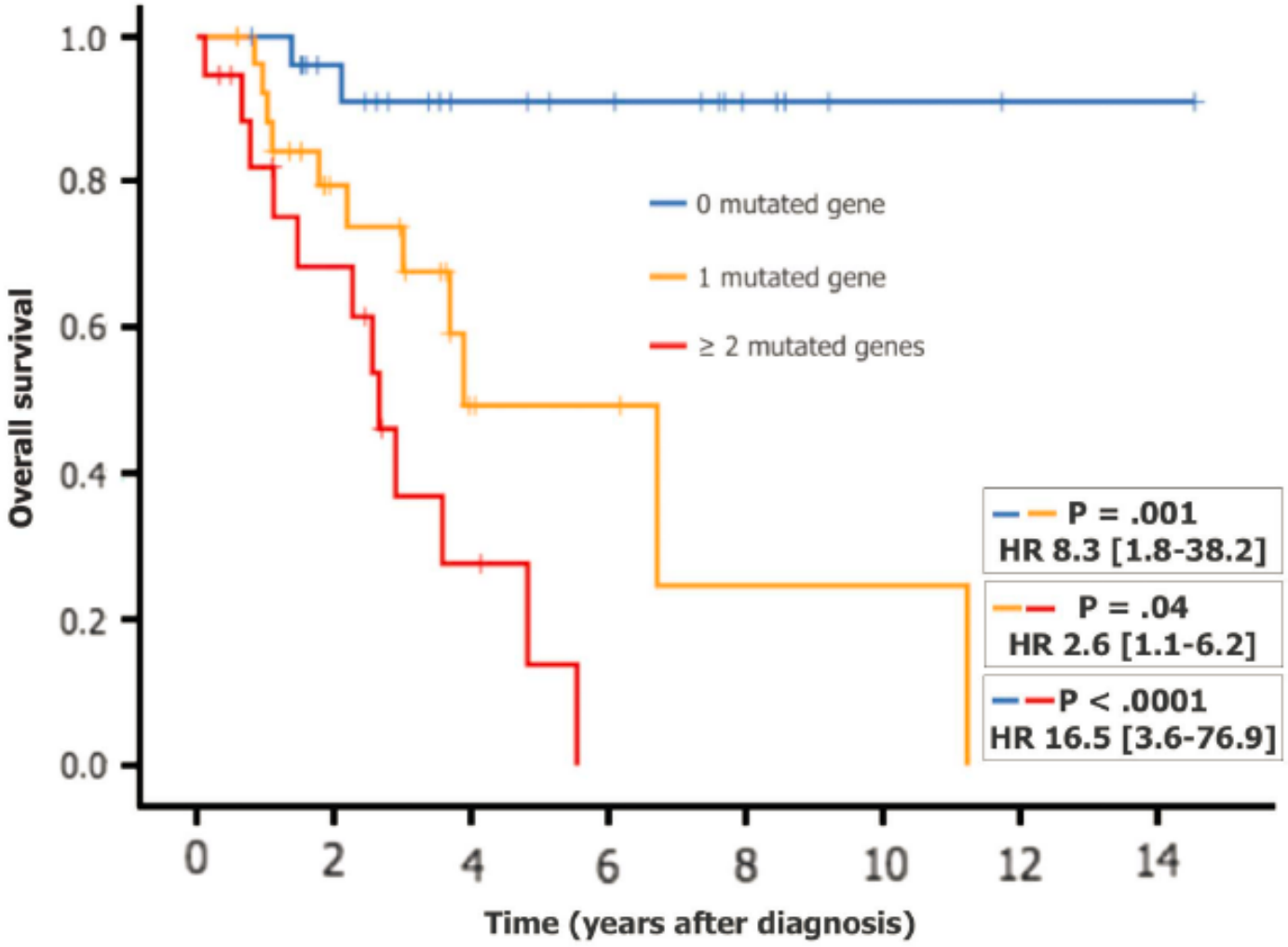
SARSF2, ASXL1, RUNX1: High-Risk Mutations in SM



S = *SARSF2*; A = *ASXL1*; R = *RUNX1*.

Jawhar M, et al. *Leukemia*. 2016;30(1):136-143.

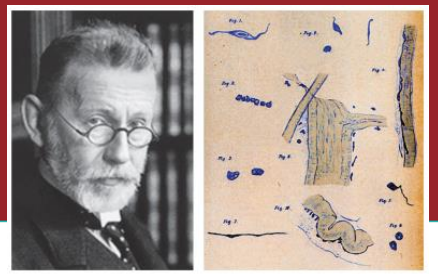
SARSF2, ASXL1, RUNX1: High-Risk Mutations in SM

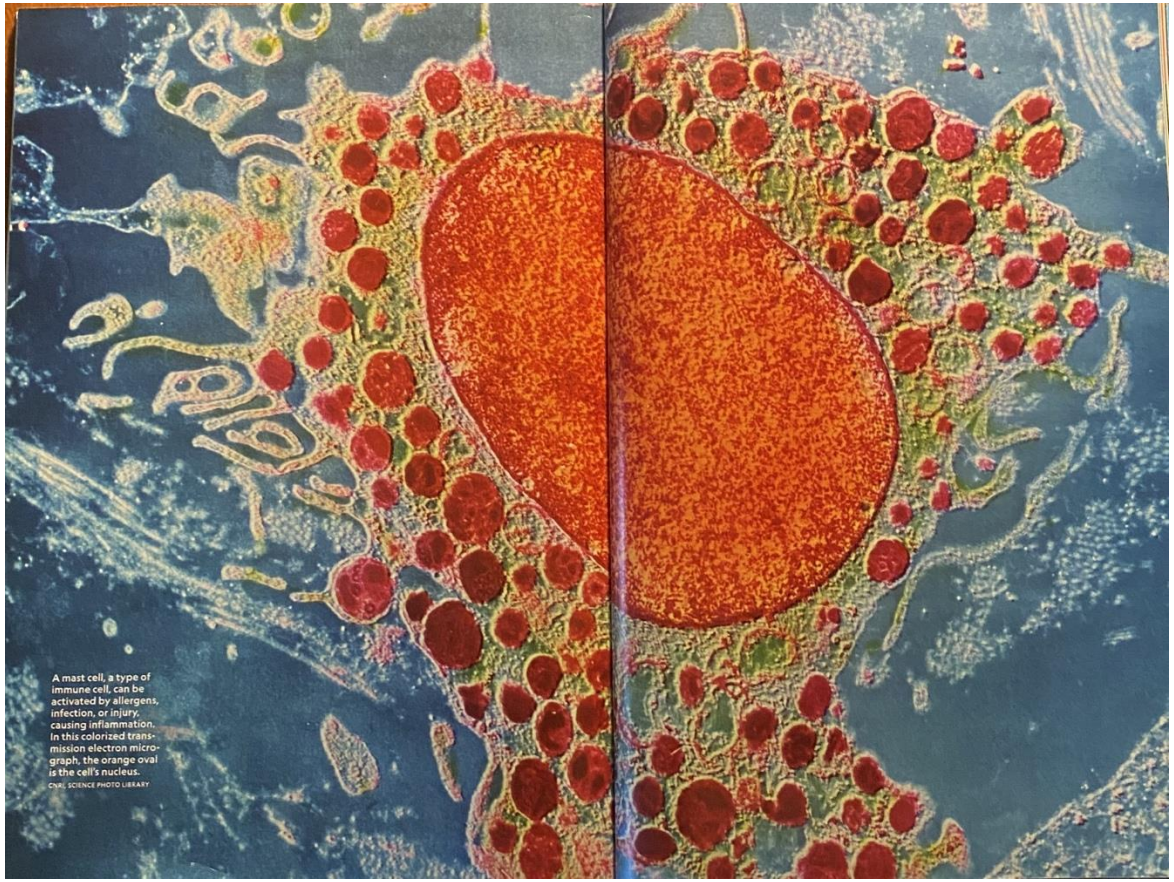


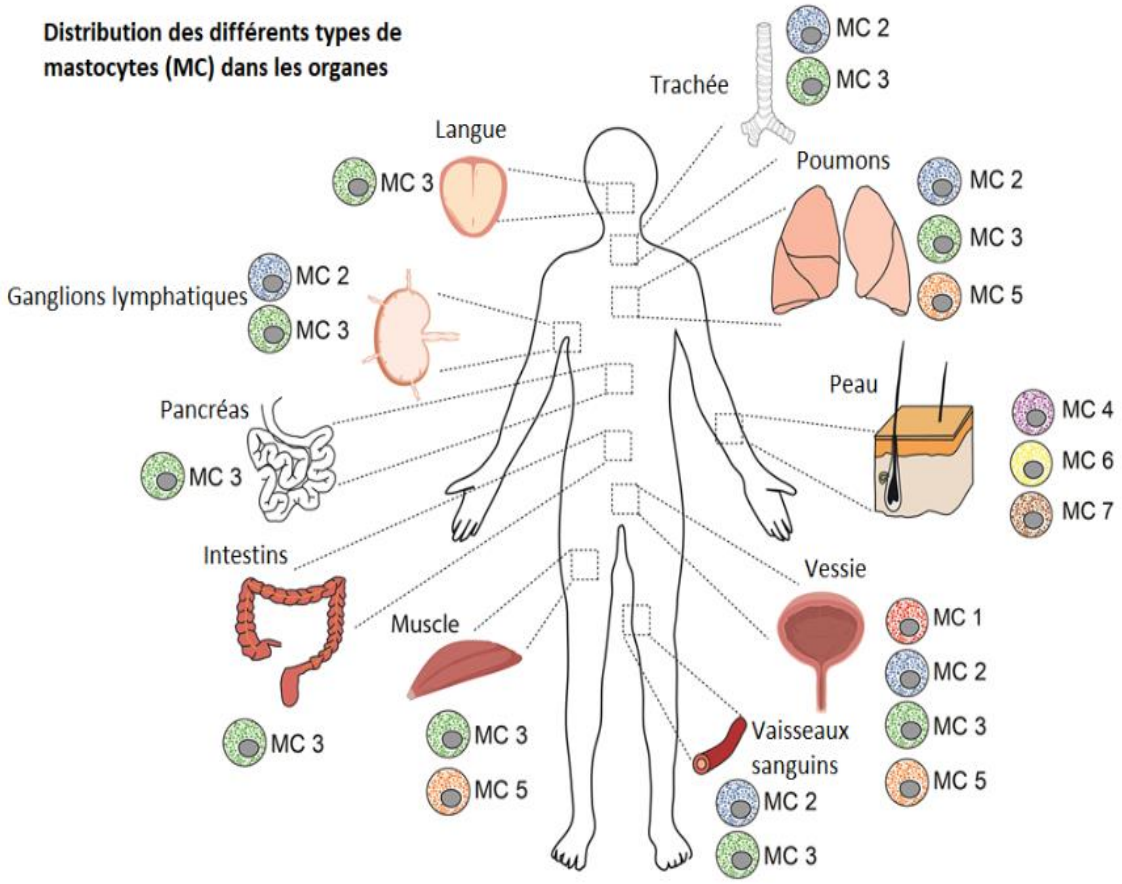
Jawhar M, et al. *Leukemia*. 2016;30(1):136-143.

Systemic Mastocytosis

Mast Cells in the Human Body

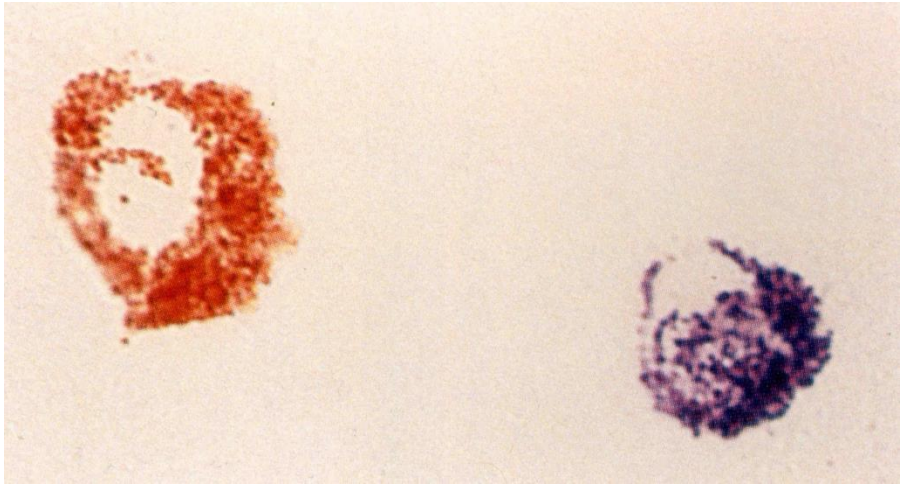




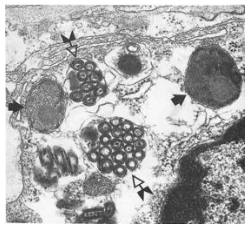


Ehrlich P. *Arch mikr Anat*. 1877;13:263-277. Tauber M, et al. *J Exp Med*. 2023;220(10):e20230570. Erratum in: *J Exp Med*. 2024;221(2):e2023057001172024c. Science Photo Library. Accessed November 18, 2024. https://sciencephotogallery.com/featured/mast-cell-tem-cnri.html?product=metal-print.

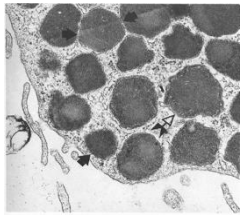
Mast Cell Heterogeneity



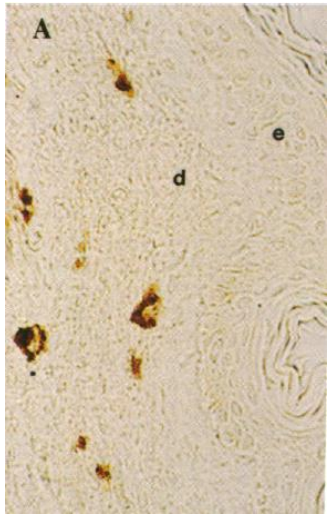
MCt **Tryptase**



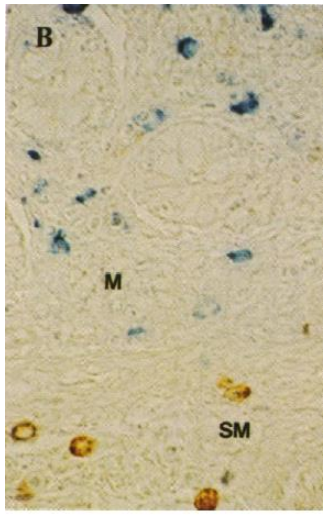
MCtc **Tryptase Chymase Carboxypeptidase**



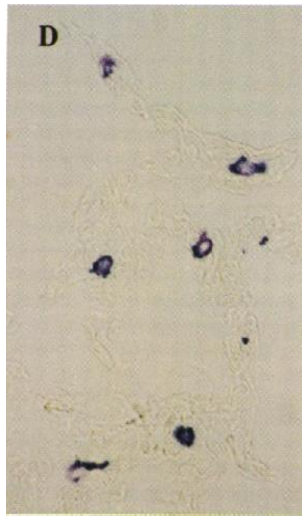
SKIN: 88% MCtc



GATROINTESTINAL TRACT: MCt/MCtc



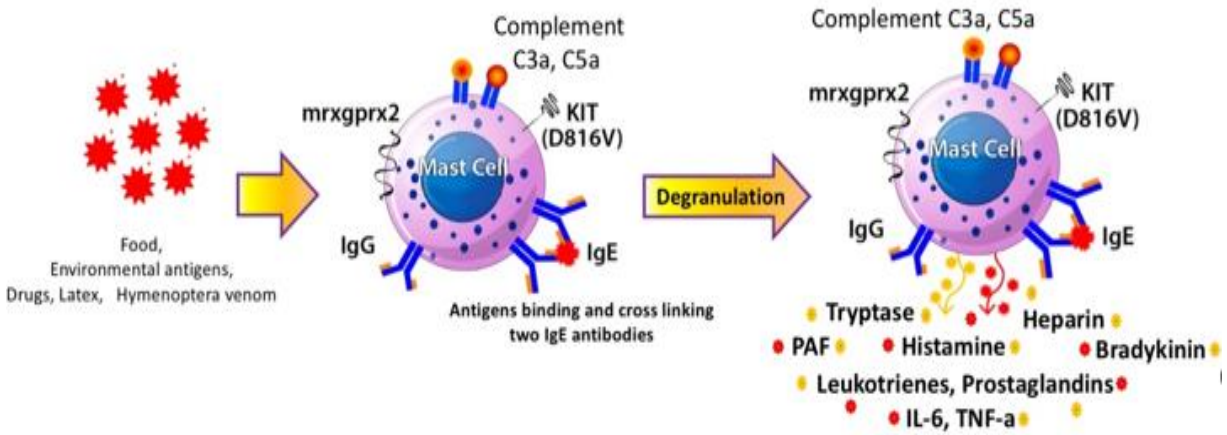
LUNG ALVEOLI: 93% MCt



Mast cells/melanocytes interactions

Castells MC, et al. *J Immunol*. 1987;138(7):2184-2189. Personal photo used with permission from Dan Friend.

Mast Cell Activation and Mediators



Biomarkers: Skin Test
Tryptase

Mediators of Anaphylaxis

Histamine	→	Skin + Blood vessels
PGD_2	→	Brain + Flushing Vasodialation
Tryptase	→	Fibrinogen αchain C3a + C5a
Bradykinin	→	Hypotension + Swelling
Leukotrines	→	Bronchospasm + Swelling
PAF	→	Vasodilation

IgG = immunoglobulin G; IgE = immunoglobulin E; IL-6 = interleukin 6.

Jimenez-Rodriguez TW, et al. *J Asthma Allergy*. 2018;11:121-142. Pathak AK. July 21, 2018. Accessed November 18, 2024. https://www.slideshare.net/slideshow/hypersensitivity-reactions-106906746/106906746.

Classification of Mastocytosis

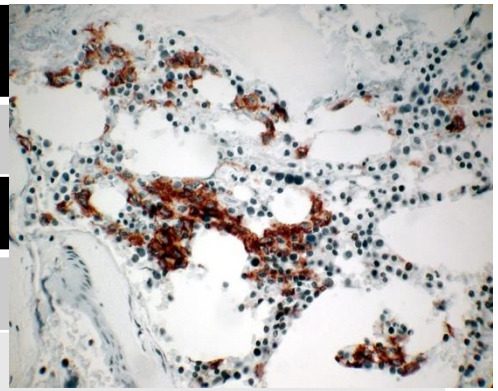
WHO 5th Edition	International Consensus Classification (ICC)
Cutaneous mastocytosis	
• Urticaria pigmentosa/maculopapular cutaneous mastocytosis (MPCM) - Monomorphic - Polymorphic	• Urticaria pigmentosa/maculopapular cutaneous mastocytosis
• Diffuse cutaneous mastocytosis	• Diffuse cutaneous mastocytosis
• Cutaneous mastocytoma - Isolated mastocytoma - Multilocalized mastocytoma	• Mastocytoma of skin
Systemic mastocytosis	
• Bone marrow mastocytosis (BMM)	• Indolent SM • Bone marrow mastocytosis
• Indolent SM	• Smoldering SM
• Smoldering SM	• Aggressive SM
• Aggressive SM	• SM with an associated myeloid neoplasm (SM-AMN)
• SM with an associated hematologic neoplasm	• Mast cell leukemia
• Mast cell leukemia	
Mast cell sarcoma	

Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719. Leguit RJ, et al. *Virchows Arch*. 2023;482(1):99-112.

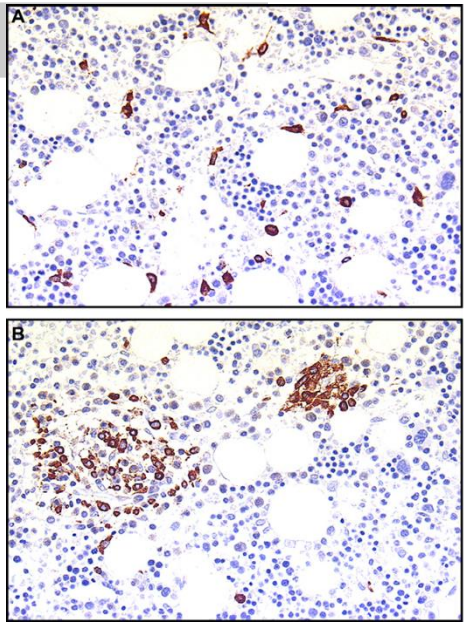
Diagnostic Criteria for Systemic Mastocytosis

Major	Multifocal dense aggregates of mast cells
Minor	>25% mast cells with atypical morphology

WHO 5th edition	**ICC**
1 major + 1 minor criteria	1 major criterion
OR	OR
≥3 minor criteria	≥3 minor criteria



- Well-differentiated systemic mastocytosis (WDSM): *KIT* D816V mutation negative
- SM with and without cutaneous involvement with hymen optera anaphylaxis
- Monoclonal mast cell activation syndrome (MMCAS): no aggregates, *KIT* D816V mutation positive



Monoclonal Mast Cell Activation Disorder

Systemic Mastocytosis

Alvarez-Twose I, et al. *J Allergy Clin Immunol*. 2016;137(1):168-178.e1. Bonadonna P, et al. *Curr Allergy Asthma Rep*. 2016;16(1):5. Arock M, et al. *Eur J Haematol*. 2015;94(6):474-490. Akin A, et al. *J Allergy Clin Immunol.* 2010;126(6):1099-1104.e4.

Mast Cell Mediators and Related Symptoms in Mastocytosis

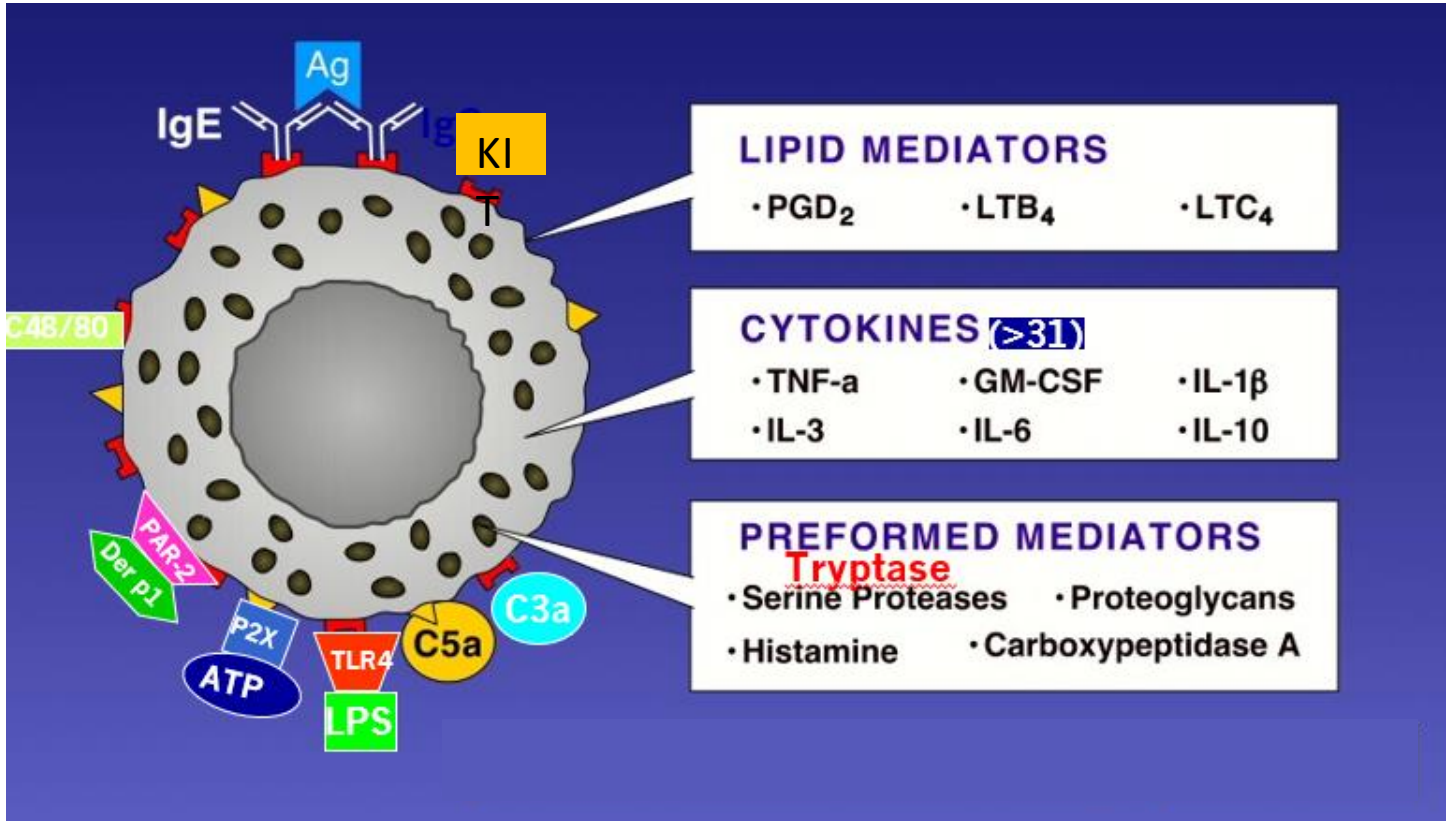


Table 1 Mast cell mediators and related symptoms

	Mediator(s)	Measured in mastocytosis
Systemic		
Vasodilation/hypotension	Histamine	+
	Prostaglandin D2	+
Hypertension	Chymase	–
Fatigue/cachexia/weight loss	TNF-α	+
Fever	IL-6	+
	IL-1	–
Fibrosis	IL-1	–
	IL-13	–
	TGF-β	–
Skin		
Flushing	Histamine	+
	Prostaglandin D2	+
Urticaria/angioedema	Histamine	+
	Prostaglandin D2	+
	Leukotriene C4	–
Gastrointestinal		
Abdominal pain	Histamine	+
Peptic		
Colic		
Diarrhea	Histamine	+
Malabsorption		
Bone		
Bone pain		
Osteoporosis/osteopenia	IL-6	+
	Heparin	–
	Tryptase	+
	TGF-β	–
Central nervous system		
Mixed CNS syndrome	Prostaglandin D2	+
	Histamine	+

CNS = central nervous system.

McNeil BD, et al. *Nature*. 2015;519(7542):237-241. Dwyer DF, et al. *Nat Immunol*. 2017;17(7):878-887. Escribano L, et al. *Ann Hematol*. 2002;81(12):677-690.

Symptoms and Signs of Mastocytosis

Cardiovascular
- Anaphylaxis with hypotension and syncope
- Dizziness
- Palpitations

Gastrointestinal
- Abdominal pain or cramping
- Diarrhea
- Heartburn or reflux
- Nausea and/or vomiting
- Gastroesophageal reflux
- Hepatosplenomegaly

Musculoskeletal
- Bone pain
- Muscle pain
- Osteoporosis/osteopenia/osteosclerosis
- Osteochondroma

Skin: Urticaria Pigmentosa
- Darier's sign
- Flushing
- Pruritis

Neuropsychiatric
- Depression
- Anxiety
- Brain fog
- Lack of focus
- Memory loss
- Migraines

Systemic
- Anaphylaxis
- Fatigue
- Weight loss
- Lymphadenopathy

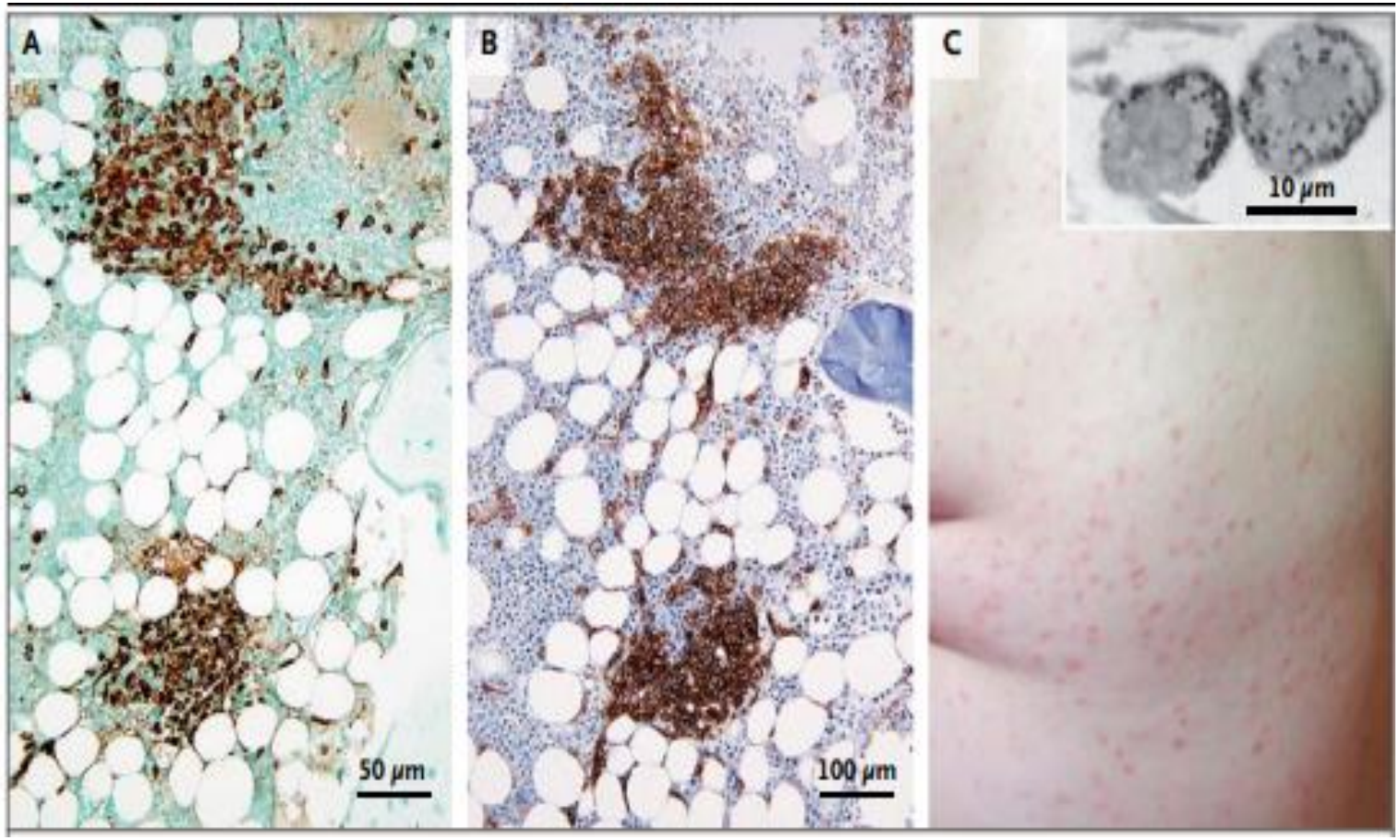
Respiratory
- Dyspnea
- Nasal congestion
- Wheezing
- Throat swelling

Hamilton MJ, et al. *Front Allergy*. 2024;5:1401187.

Mastocytosis Tissue Diagnosis

Bone Marrow Biopsy

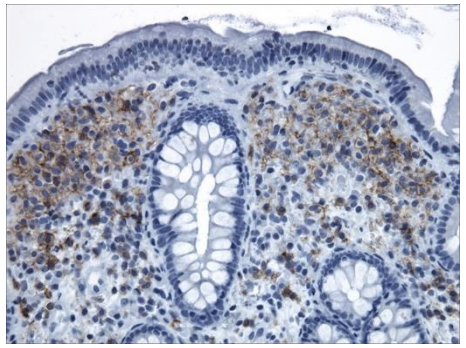
Urticaria Pigmentosa Skin Biopsy



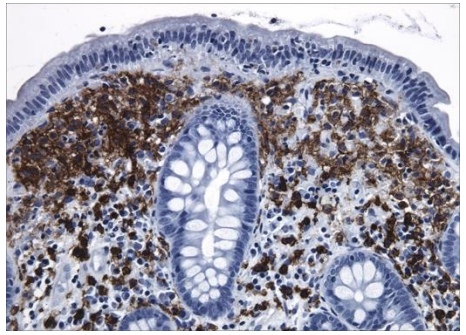
Tryptase **CD 25**

Gastrointestinal Biopsy

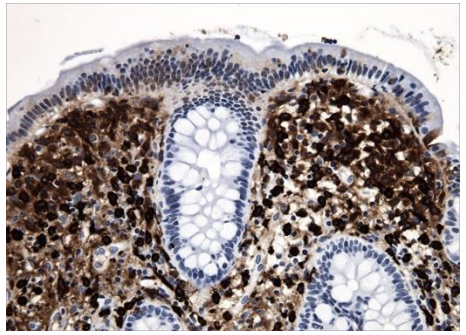
Tryptase



KIT



CD25

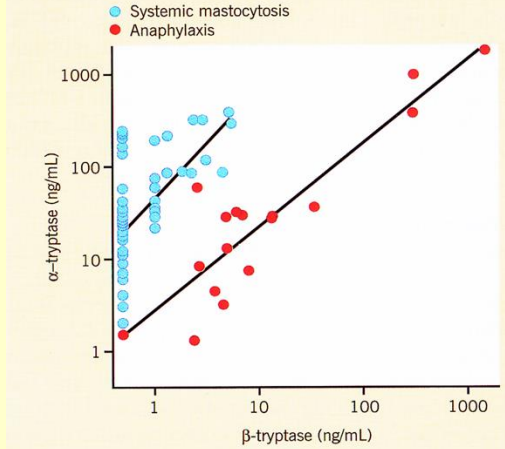


Theoharides TC, et al. *N Engl J Med*. 2015;373(2):163-172.

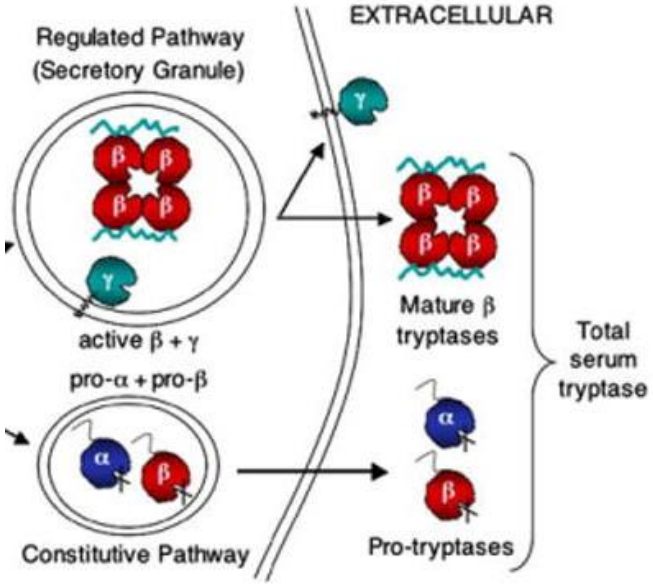
Tryptases

- **Total tryptase**
  - Mostly inactive pro-tryptase at baseline
  - Reflect mast cell burden at baseline
- **Mature β-tryptase**
  - Measure of MC activation
- **Total:Mature tryptase ratio**
  - >20 in SM at baseline
- **27% of Caucasians lack an alpha tryptase gene**
- **Low baseline tryptase**
  - (Significant elevation: >20% baseline + 2 ng)

Normal tryptase in 10% mastocytosis patients.

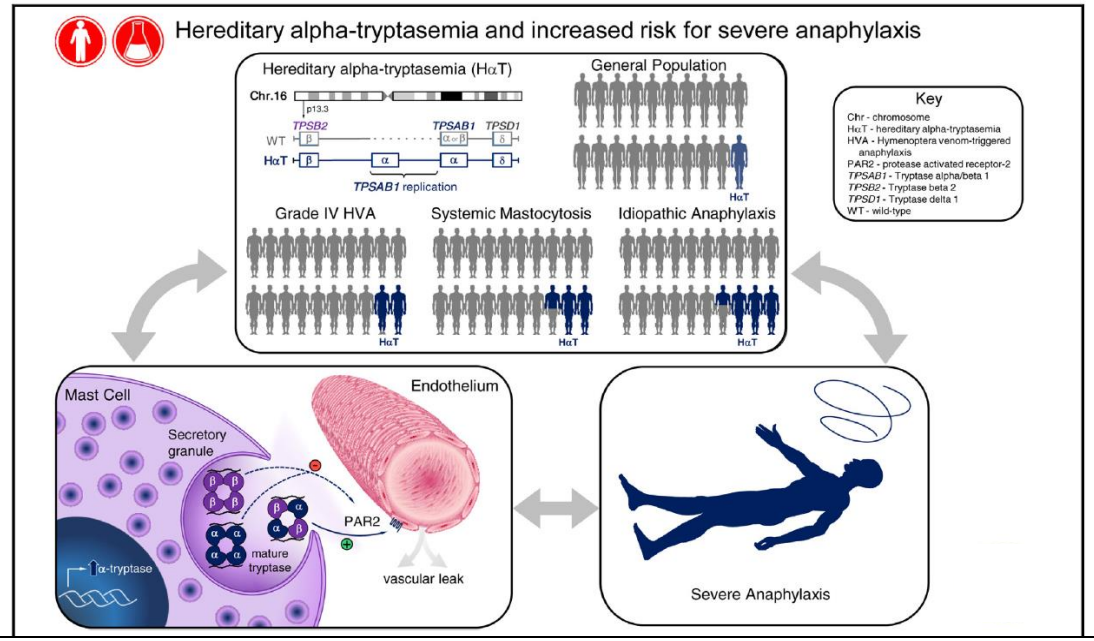


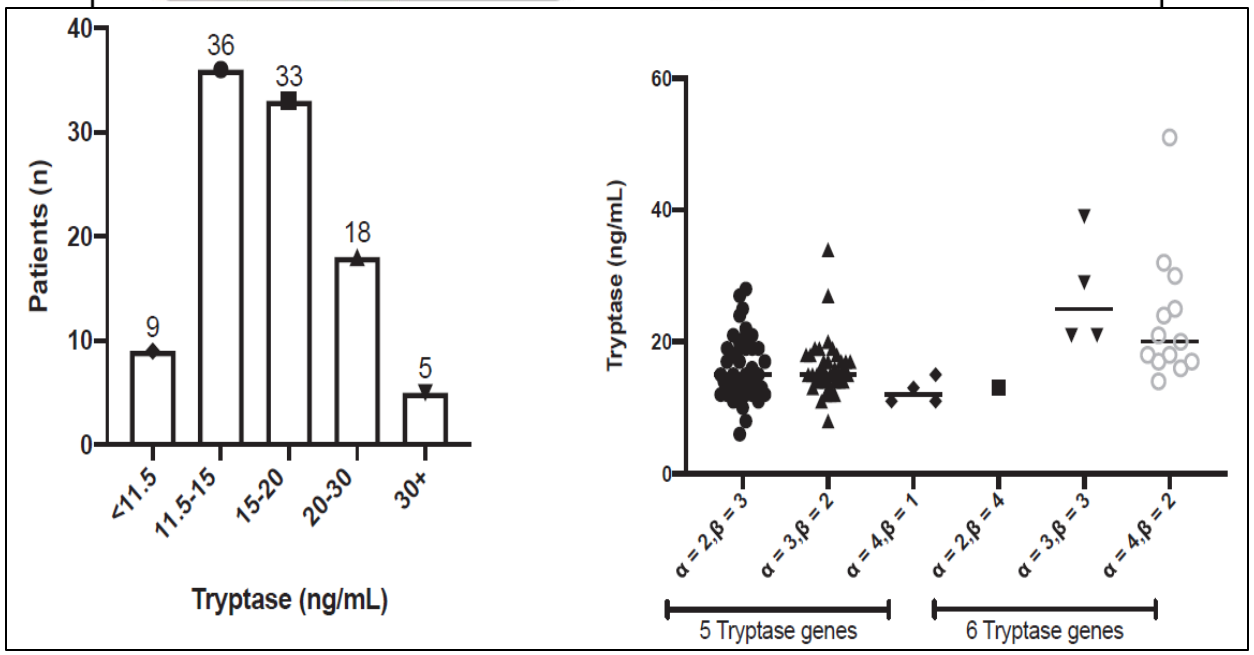
Elevated tryptase is present in anaphylaxis and 2 measurements are required to assess baseline.

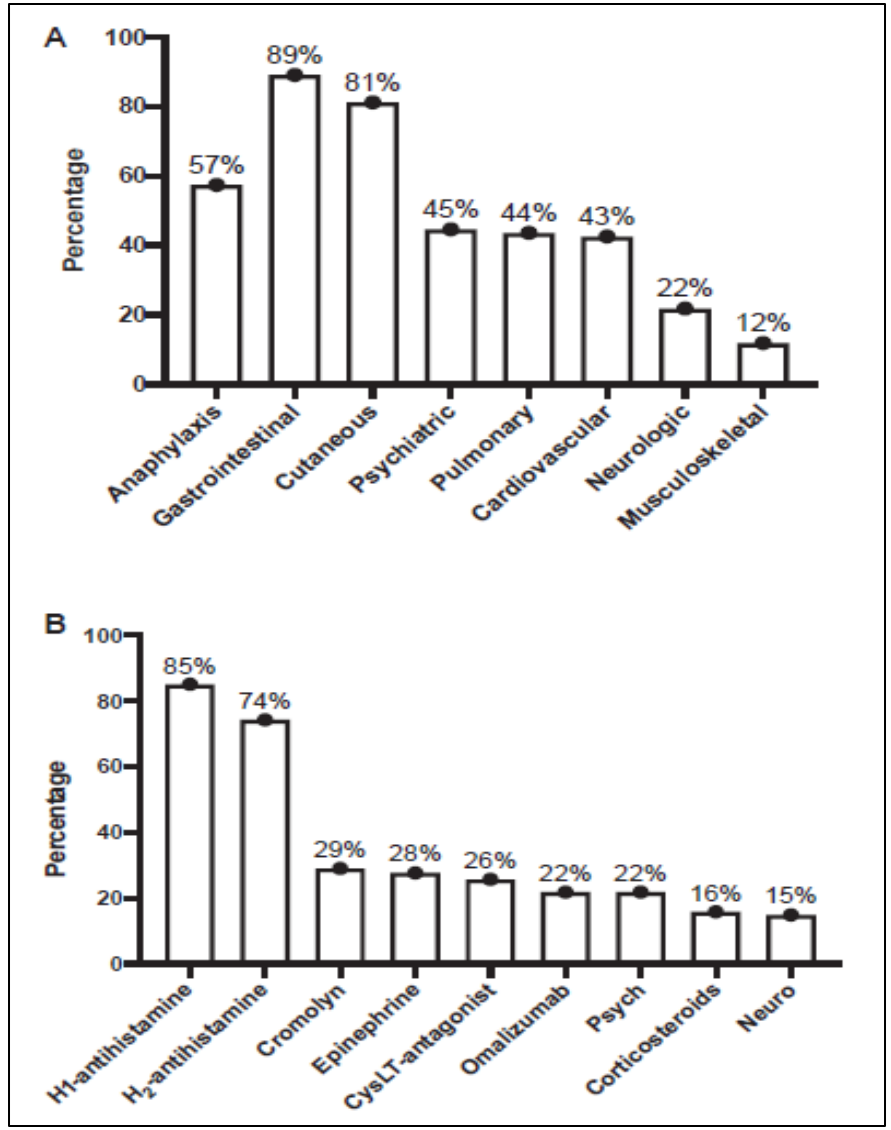


Acute and/or baseline tryptase >8 ng/mL

Schwartz LB, et al. *N Engl J Med*. 1987;316(26):1622-1626. Gaughey GH. *J Allergy Clin Immunol*. 2006;117(6):1411-1414. Alvarez-Twose I, et al. *Allergy*. 2012;67(6):813-821. Schwartz LB. *Immonol Allergy Clin North Am*. 2006;26(3):451-463. Le QT, et al. *J Exp Med*. 2019;216(10):2348-2361.







Giannetti MP, et al. *Ann Allergy Asthma Immunol*. 2021;126(6):655-660. Lyons JJ, et al. *J Allergy Clin Immunol*. 2021;147(2):622-632.

Bone Marrow Morphologic Findings in Patients with ISM and HαT

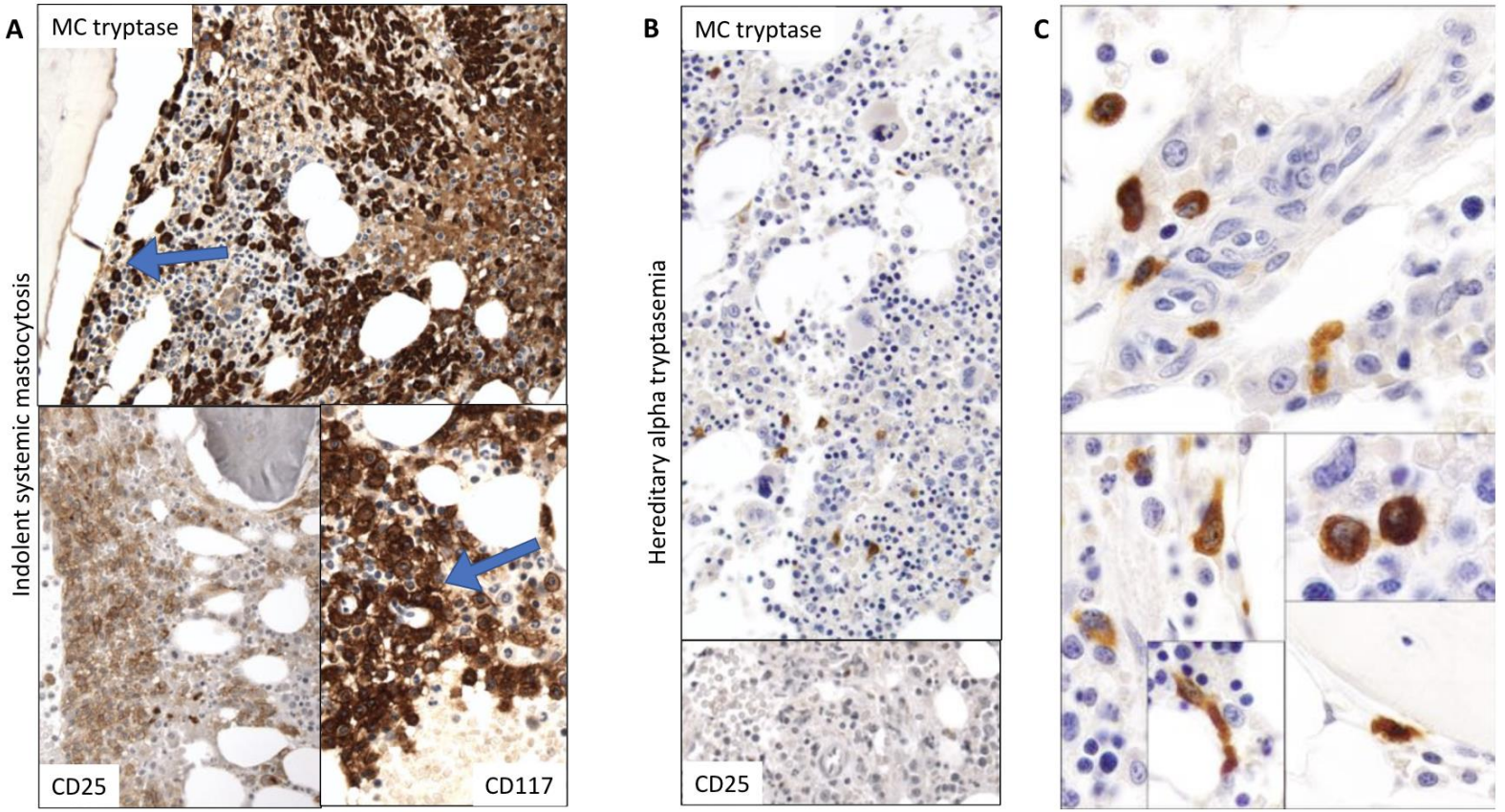
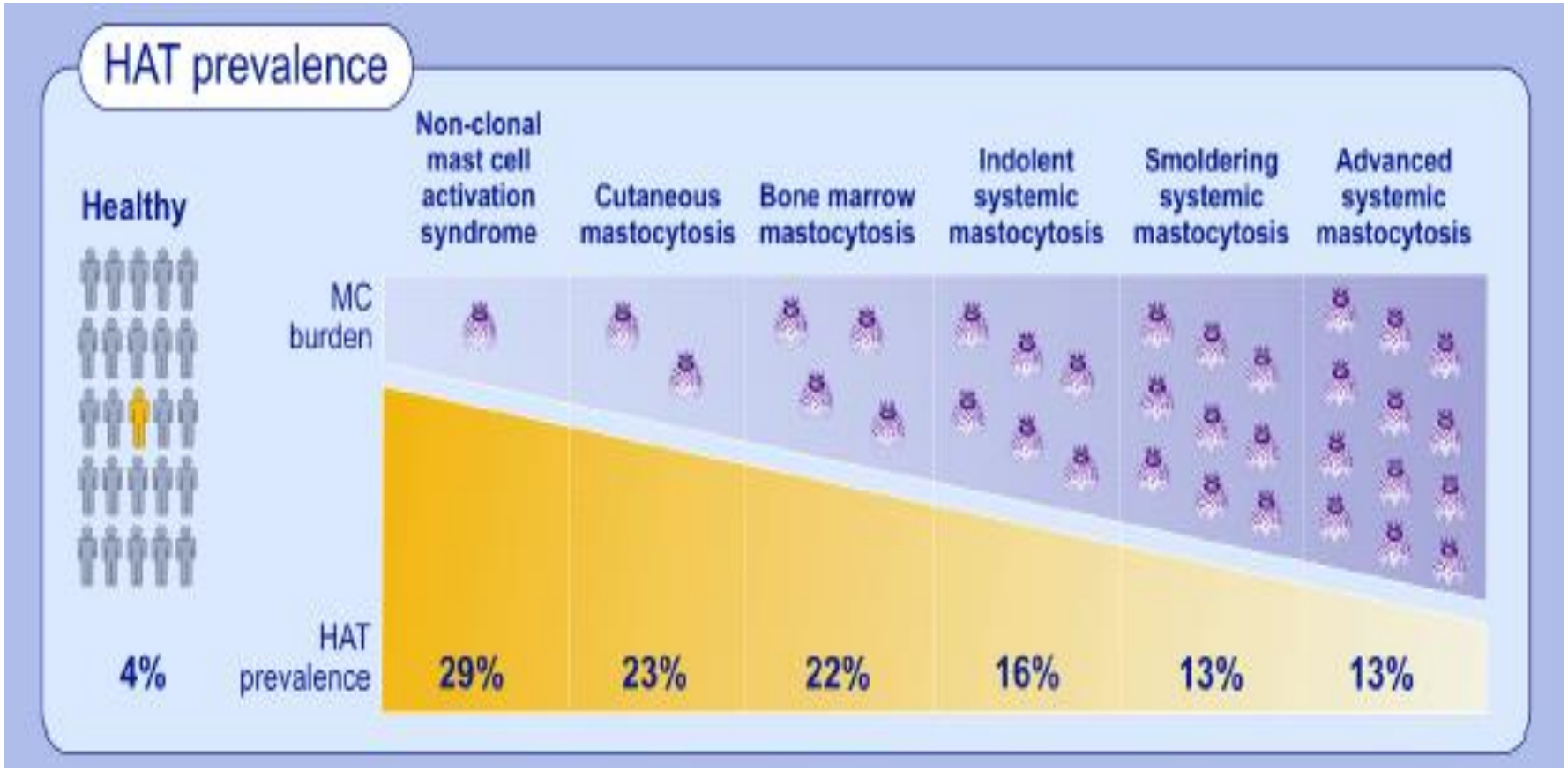


Figure 1

Giannetti MP, et al. *J Allergy Clin Immunol*. 2021;47(4):1497-1501.e1.

Prevalence of HαT in Mast Cell Disorders



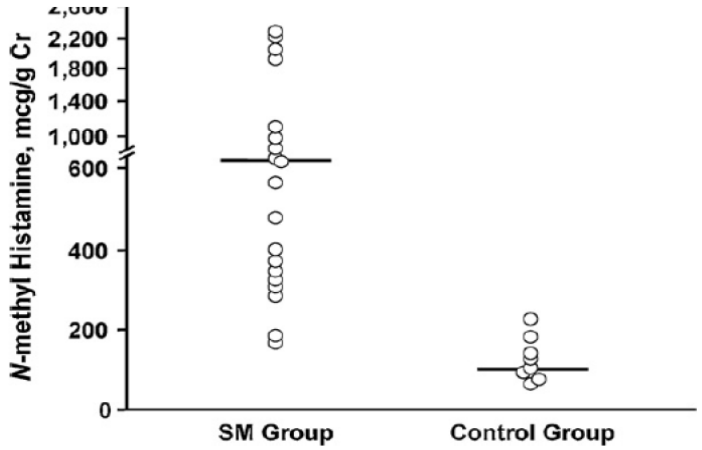
González-de-Olano D, et al. *Allergy*. 2024;79(3):711-723.

Urinary Mast Cell Mediators

Urinary N-methyl histamine (mcg/g creatinine [Cr]) in systemic mastocytosis and controls

Normal value is 30–200 mcg/g Cr.

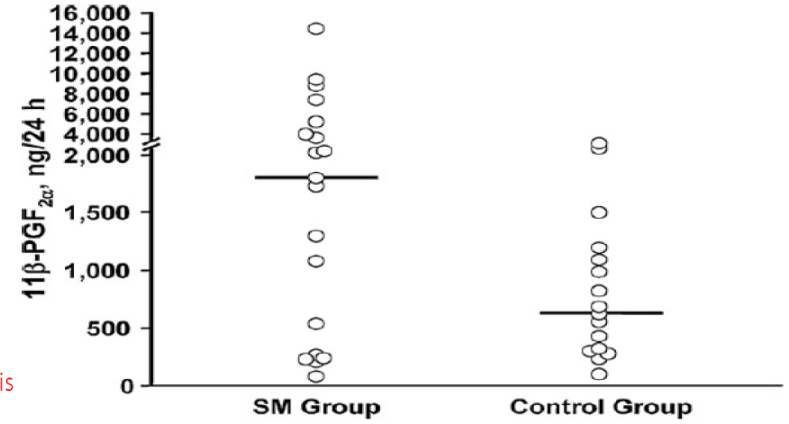
Butterfield 2010



24-h urinary excretion of 11-prostaglandin F2 (11-PGF2) (ng/24 h) in systemic mastocytosis and controls.

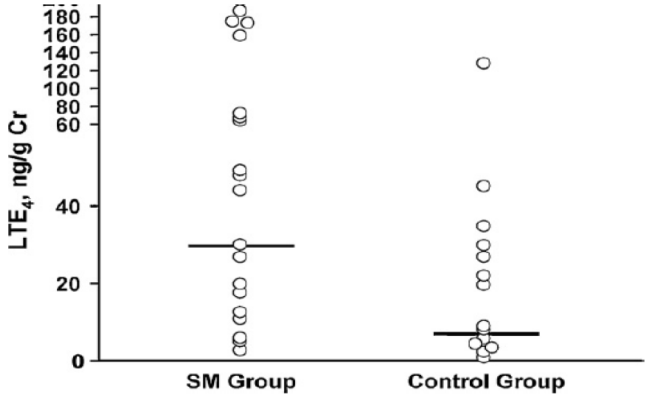
Normal value is <1000 ng/24 h.

Butterfield 2010



Urinary Excretion of LTE4 (ng/g creatinine) in patients with Systemic Mastocytosis and controls

Butterfield 2010

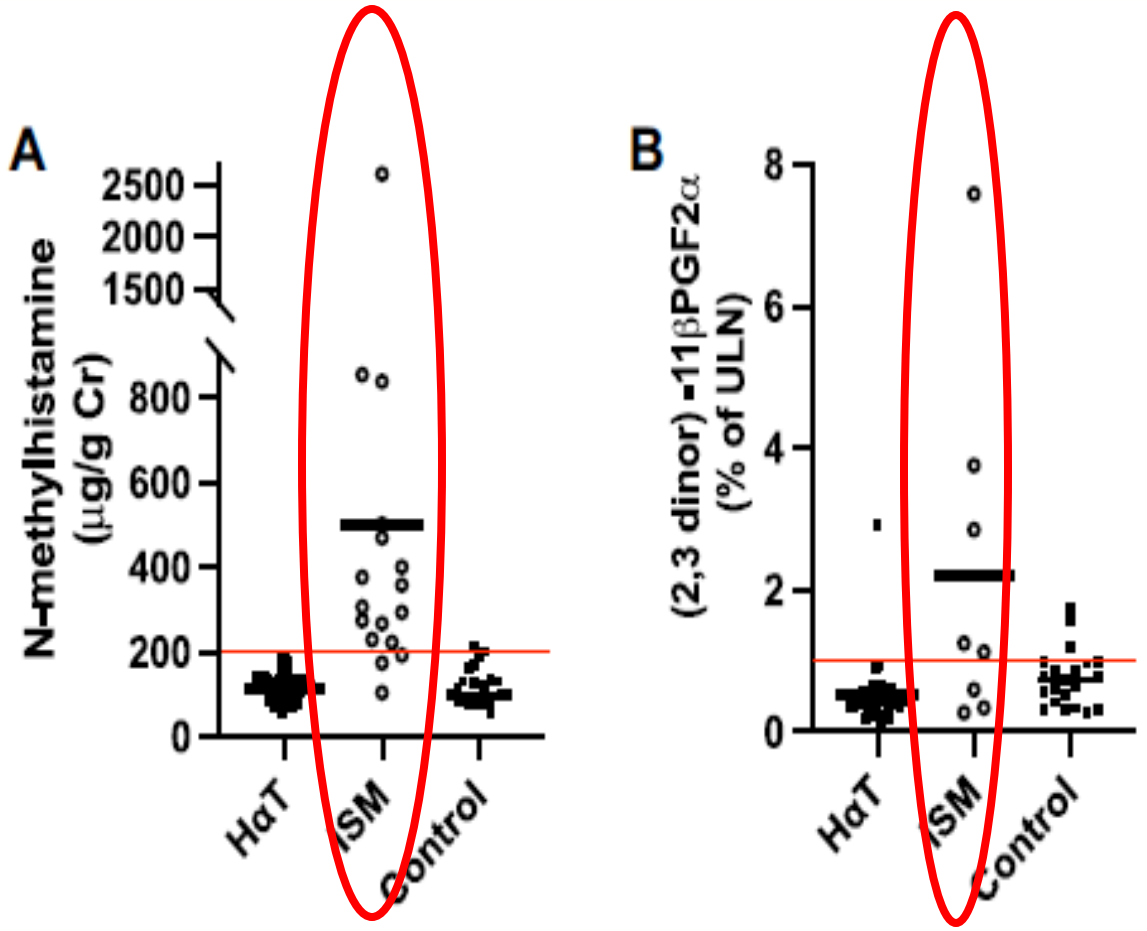


Butterfield JH. *Prostaglandins Other Lipid Mediat*. 2010;92(1-4):73-76.

Differential Mast Cell Mediators in SM and Hereditary α-Tryptasemia

TABLE I. Baseline characteristics of patients with HαT and ISM

Characteristic	HαT cohort	ISM cohort	Controls
Age (y), mean ± SD	53.8 ±13.7	53 ± 12.5	36.2 ± 13.5
Female sex, % (no.)	85.7 (54)	60 (12)	87 (20)
Tryptase (ng/mL)	19.3 ± 8.4	47.5 ± 45.6	4.1± 1.6
α-genes/β-genes	2-4/2-3		
Total IgE level (kUA/L), mean ± SD	256.3 ± 713	122.0 ± 320	64.6± 37.2
Daily symptoms, % (no.)	74.6 (47)	90 (18)	
	n=63	**n=20**	**n=23**

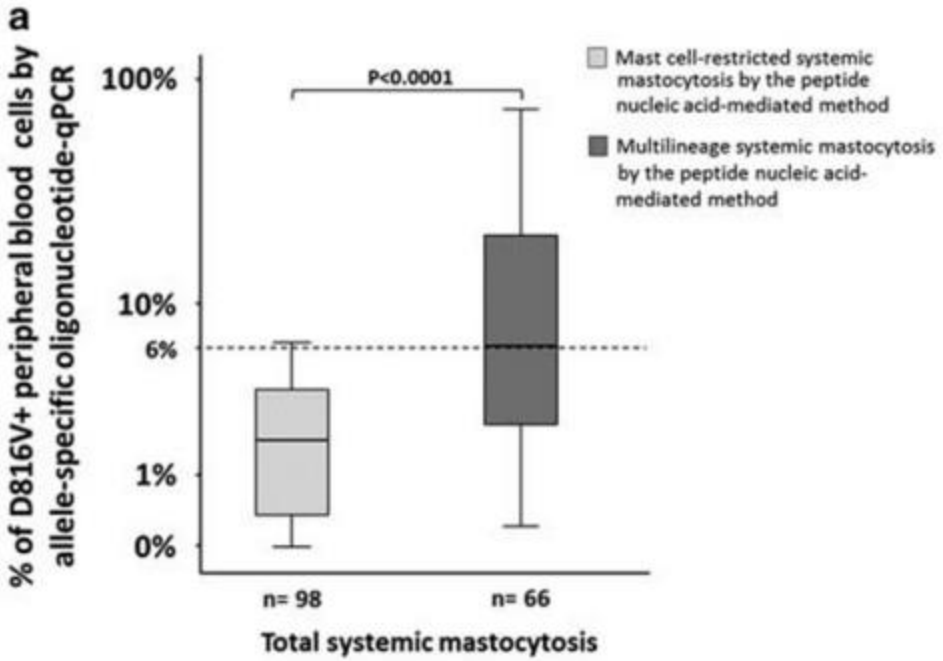


SD = standard deviation; ISM = indolent systemic mastocytosis.
Giannetti MP, et al. *J Allergy Clin Immunol*. 2022;150(5):1225-1227.

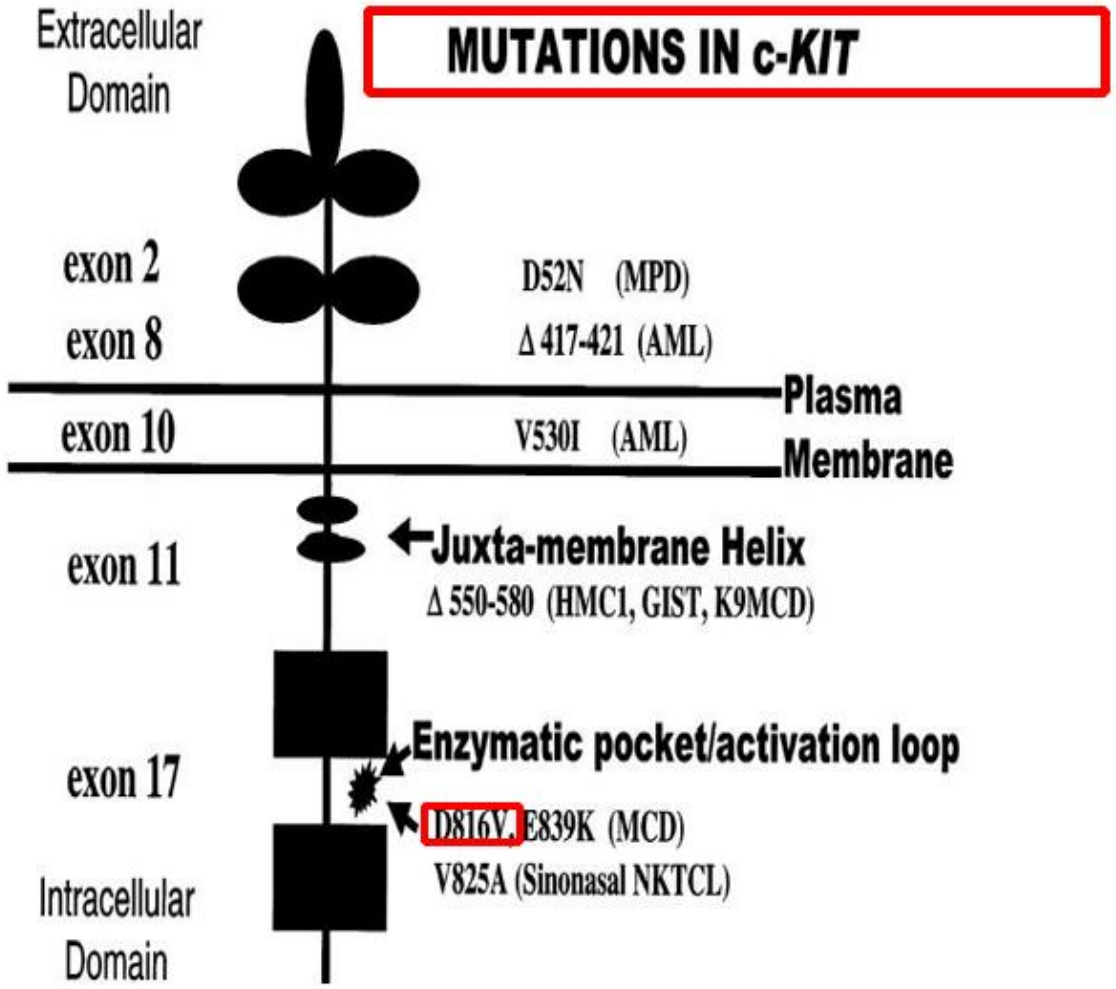
Mutations in *KIT*

Detection of the *KIT* D816V mutation in peripheral blood of systemic mastocytosis: diagnostic implications

Maria Jara-Acevedo[1], Cristina Teodosio[2], Laura Sanchez-Muñoz[3], Ivan Álvarez-Twose[3], Andrea Mayado[1], Carolina Caldas[1], Almudena Matito[3], José M Morgado[3], Javier I Muñoz-González[1], Luis Escribano[1], Andrés C Garcia-Montero[1,4] and Alberto Orfao[1,4]



10% of Mastocytosis are negative for KITD816V



qPCR = quantitative polymerase chain reaction.

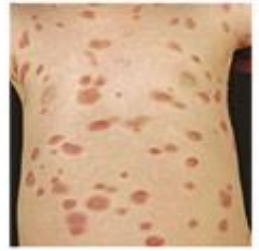
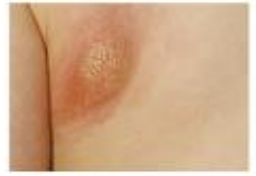
Jara-Acevedo M, et al. *Mod Pathol.* 2015;28(8):1138-1149. Longley BJ, et al. *Leuk Res*. 2001;25(7):571-576.

Cutaneous Manifestations in Mastocytosis

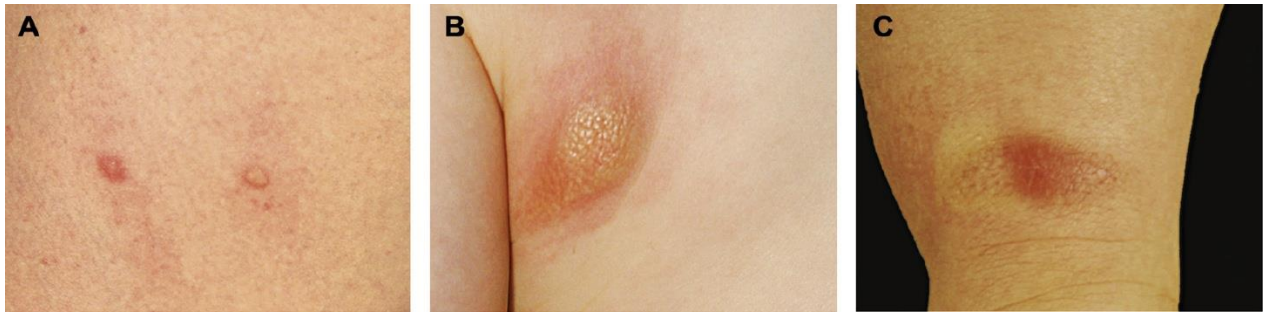
Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology

Karin Hartmann, MD,[a,b] Luis Escribano, MD, PhD,[c] Clive Grattan, MA, MD,[d] Knut Brockow, MD,[e] Melody C. Carter, MD,[f] Ivan Alvarez-Twose, MD,[g] Almudena Matito, MD, PhD,[g] Sigurd Broesby-Olsen, MD,[h] Frank Siebenhaar, MD,[i] Magdalena Lange, MD, PhD,[j] Marek Niedoszytko, MD, PhD,[k] Mariana Castells, MD, PhD,[l] Joanna N. G. Oude Elberink, MD, PhD,[m] Patrizia Bonadonna, MD,[n] Roberta Zanotti, MD,[o] Jason L. Hornick, MD, PhD,[p] Antonio Torrelo, MD,[q] Jürgen Grabbe, MD,[r] Anja Rabenhorst, PhD,[s] Boguslaw Nedoszytko, PhD,[j] Joseph H. Butterfield, MD,[s] Jason Gotlib, MD,[t] Andreas Reiter, MD,[u] Deepti Radia, MD,[v] Olivier Hermine, MD, PhD,[w] Karl Sotlar, MD,[x] Tracy I. George, MD,[y] Thomas K. Kristensen, PhD,[z] Hanneke C. Kluin-Nelemans, MD, PhD,[aa] Selim Yavuz, MD,[bb] Hans Hägglund, MD, PhD,[cc] Wolfgang R. Sperr, MD,[dd] Lawrence B. Schwartz, MD, PhD,[ee] Massimo Triggiani, MD, PhD,[ff] Marcus Maurer, MD,[i] Gunnar Nilsson, PhD,[gg] Hans-Peter Horny, MD,[x] Michel Arock, PharmD, PhD,[hh] Alberto Orfao, MD, PhD,[c] Dean D. Metcalfe, MD,[f] Cem Akin, MD, PhD,[i] and Peter Valent, MD[dd]

Cologne, Luebeck, Munich, Mannheim,

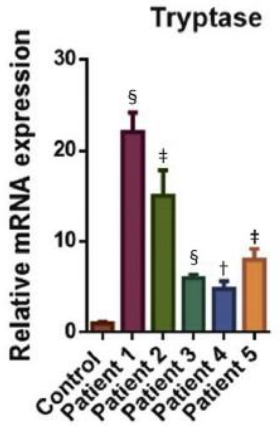
Subforms	Variants	Typical manifestations
Maculopapular cutaneous mastocytosis (syn. urticaria pigmentosa)	Monomorphic	
	Polymorphic	
Diffuse cutaneous mastocytosis		
Cutaneous mastocytoma		

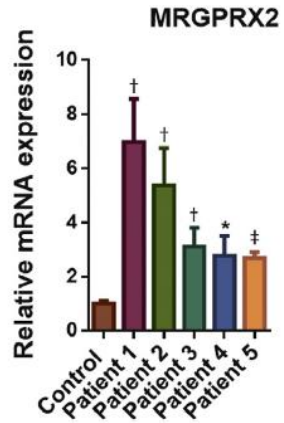
Darier's sign. A wheal-and-flare reaction develops upon stroking of a CM lesion with a tongue spatula. Darier's sign is a highly specific diagnostic feature of CM.

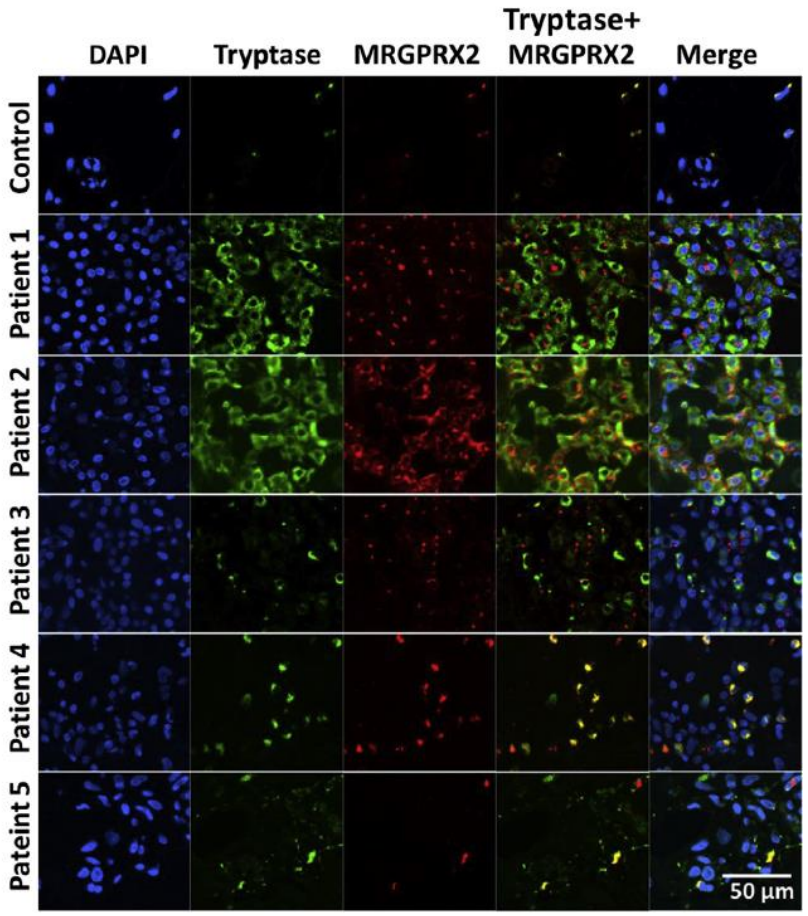


Hartmann K, et al. *J Allergy Clin Immunol*. 2016;137(1):35-45.

Expression of MRGPRX2 in Maculopapular Cutaneous Mastocytosis (MPCM)







Expression of MRGPRX2 in skin mast cells of patients with maculopapular cutaneous mastocytosis

Vishwa Deepak, PhD[a], Hirsh D. Komarow, MD[b], Abdulaziz A. Alblaihess, DDS[a,c], Melody C. Carter, MD[b], Dean D. Metcalfe, MD[b], and Hydar Ali, PhD[a] 2021

Clinical Implications

MRGPRX2 should be considered when evaluating cutaneous reactions in patients with mast cell proliferative disorders. This receptor could be an attractive target for treatment of skin manifestations associated with mastocytosis.

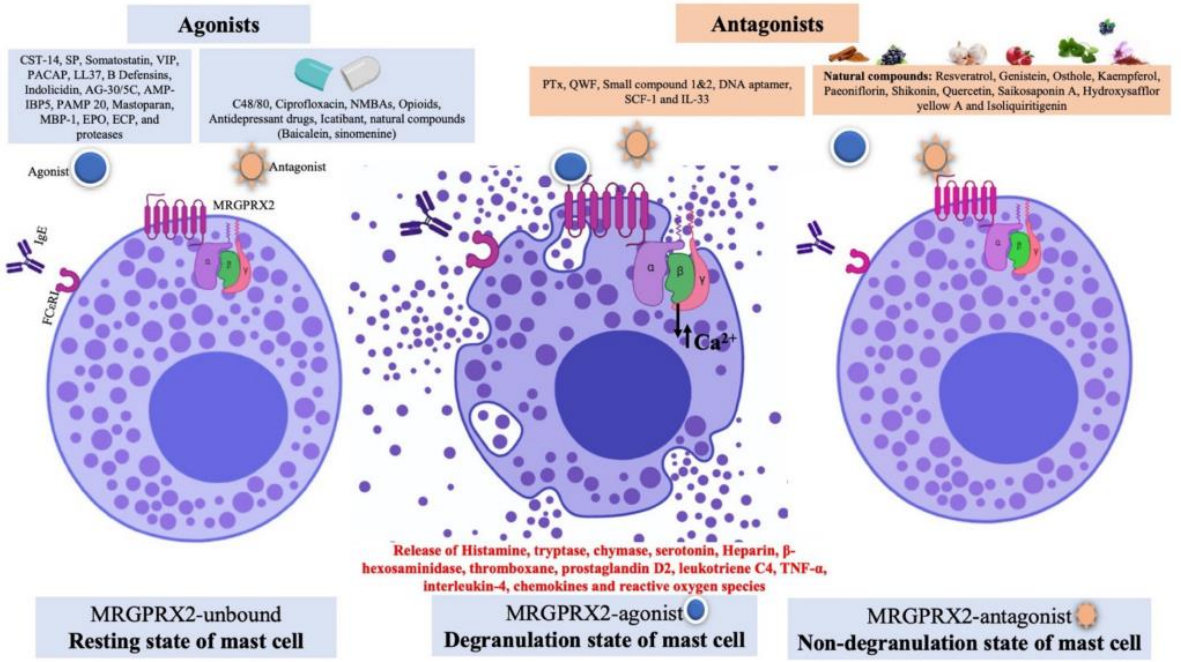
TABLE I. Characteristics of patients with mastocytosis

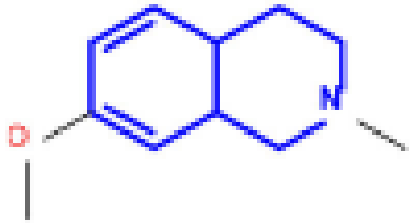
Patient No.	Age at biopsy (y)	Sex	Diagnosis	BM aggregates	Clinical history	Peripheral blood *KIT D816V* (%)	bST
1	8	Female	MPCM	ND	Pediatric onset	Negative	6.7
2	8	Male	MPCM	ND	Pediatric onset	Negative	3.8
3	18	Female	MPCM	None	Pediatric onset	Negative	3.1
4	51	Female	MPCM	None	Adult onset	Negative	7.3
5	60	Male	ISM	Small	Adult onset	3.07	40.2

DAPI = 4',6-diamidino-2-phenylindole.

Deepak V, et al. *J Allergy Clin Immunol Pract.* 2021;9(10):3841-3843.e1.

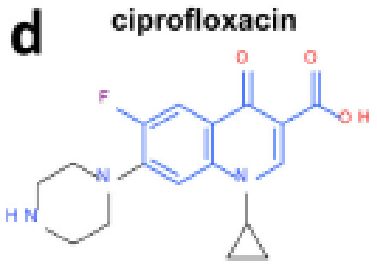
Mast Cells Non-IgE Receptor MRGPRX2 Activation

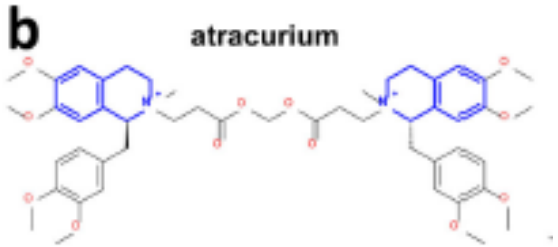


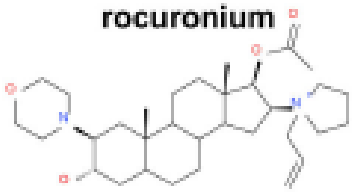


THIQ (tetrahydroisoquinoline) motif

- **Fluoroquinolones**
- **NMBAs (except succinylcholine)**
- **Vancomycin**
- **Icatibant**
- **Leuprolide**
- **Opiods (morphine)**
- **Radiocontrast media**



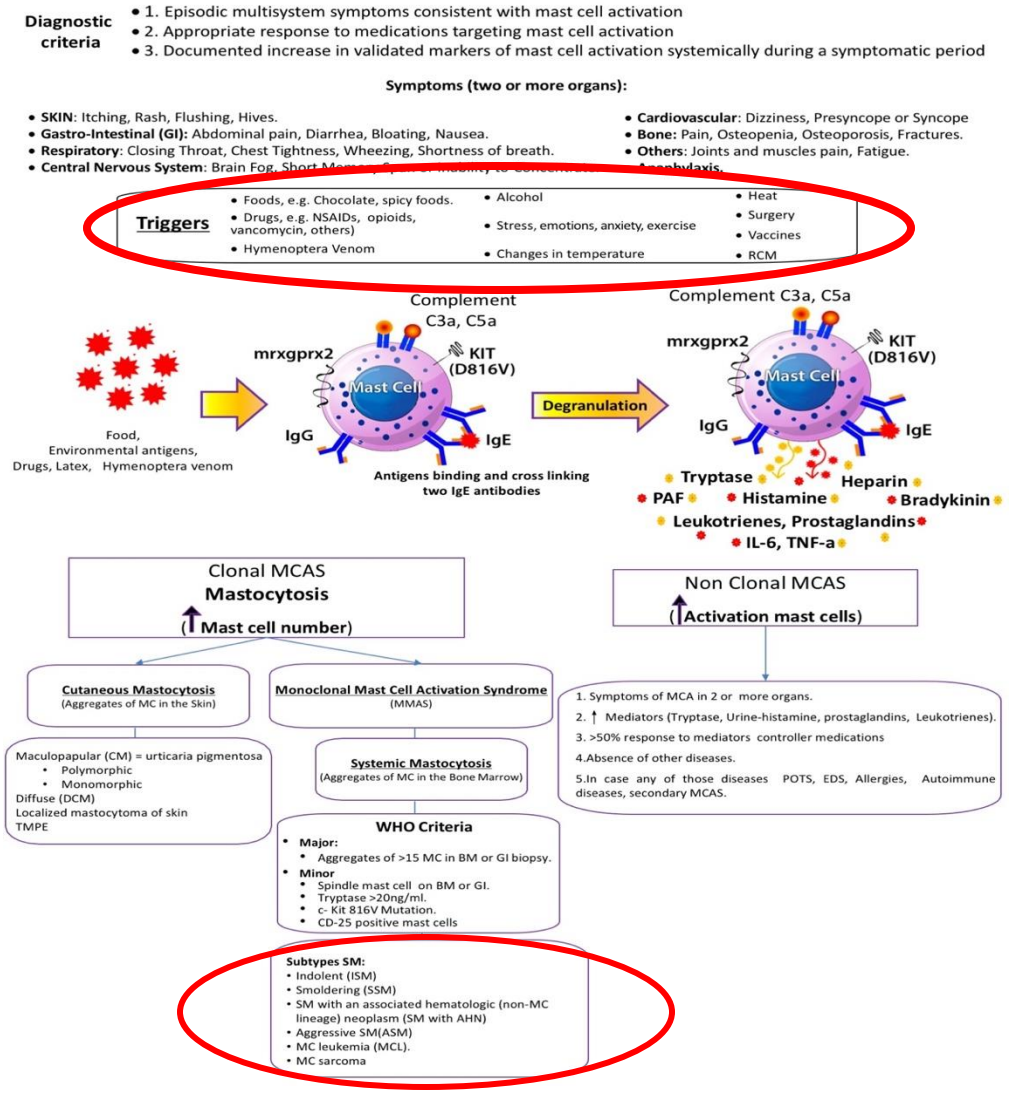




NMBA = neuromuscular blocking agent.

McNeil BD, et al. *Nature*. 2015;519(7542):237-241. Hou Y, et al. *Mol Immunol.* 2019;111:118-127. Kumar M, et al. *Cells*. 2021;10(5):1033.

Mast Cell Activation Disorders



Hereditary Alpha Tryptasemia

Jimenez-Rodriguez TW, et al. *J Asthma Allergy*. 2018;11:121-142.

Differential Diagnoses Mimicking Mast Cell Activation and MCAS

Cardiovascular	Arrythmias
	Myocardial infarction
	Endocarditis/endomyocarditis
	Aortic stenosis with syncope
	Pulmonary embolism
Neuropsychiatric	Seizures
	Stroke
	Multiple sclerosis
	Dysautonomia (eg, postural tachycardia syndrome)
	Vasovagal syncope
	Panic attacks and anxiety conditions
	Somatoform disorders
Immunologic	Vasculitis
	Systemic capillary leak syndrome
	Allergic episodes involving basophils but not mast cells
	Less severe conditions associated with mast cell activation

Valent P, et al. *J Allergy Clin Immunol Pract*. 2019;7(4):1109-1114.

Personalized Medicine: Targeting Mast Cell Mediators and Symptoms

TABLE II. Approach to mast cell mediator–induced symptoms in mastocytosis and MCAS.

A. Avoidance of triggers: patient specific
Specific foods, medications (NSAIDs, vancomycin, quinolones), environmental allergens, and general triggers (stress, lack of sleep, emotions)
Physical triggers (exercise, rubbing, pressure)
Changes in temperature (heat, cold)
Extreme temperatures
Dryness of skin
B. Premedications recommended for surgery, invasive procedures (endoscopy, colonoscopy, others), radiological procedures with contrast dyes, dental procedures, and vaccinations: 12 and 1 h
• Antihistamine receptors H1 and H2
• Leukotriene blocker
• Steroid (0.5-1 mg/kg)
C. Management of cutaneous mastocytosis:
Local care of skin
Skin moisturizer
Water-soluble sodium cromolyn cream/ointment (1% to 4%)
Avoid friction, pressure, and temperature changes
Consider surgical excision for mastocytomas (flexures, soles, palms, scalp)
Steroid creams
PUVA (psoralens)

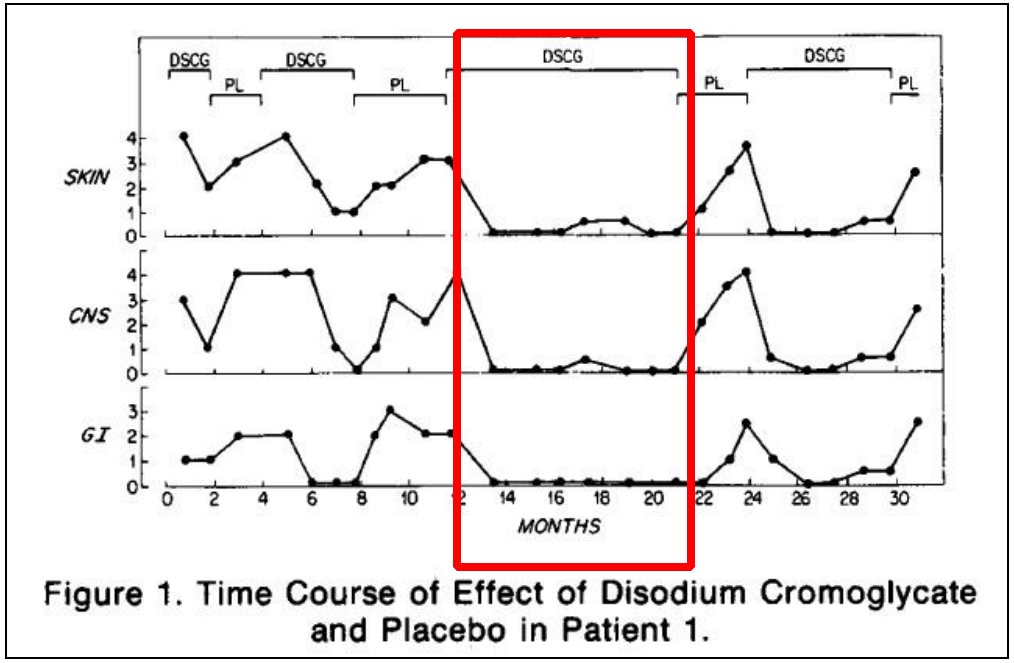


Figure 1. Time Course of Effect of Disodium Cromoglycate and Placebo in Patient 1.

DSCG = disodium cromoglycate; PL = phospholipid.

Castells M, et al. *J Allergy Clin Immunol Pract*. 2019;7(4):1097-1106. Soter NA, et al. *N Engl J Med*. 1979;301(9):465-469.

MCAS and Mastocytosis: Initial Treatment Options and Long-Term Management

TABLE III. Targeted approach for mast cell mediators–related symptoms in mastocytosis and MCAS

Systems and symptoms	Medications targeting mast cell mediators
Skin: pruritus, flushing, urticaria, angioedema, dermatographism	
1	H1-blockers and H2-blockers:
	Cetirizine 10 mg up to QID
	Loratadine 10 mg up to QID
	Fexofenadine 180 mg up to QID
	Hydroxyzine 10-25 mg QID
	Cyproheptadine 4 mg TID
	Doxepin 10-50 mg
	Ranitidine 150-300 mg BID
	Cimetidine 300 mg BID
	Famotidine 20-40 mg dq
2	Leukotriene receptor blockers/ antagonist
	Montelukast 10 mg
	Zileuton 650 mg BID
3	Aspirin 81-650 mg BID
4	Ketotifen 1-2 mg BID
5	4% sodium cromolyn cream/ ointment
Gastrointestinal: diarrhea, abdominal bloating, cramping/ pain, nausea, vomiting, GER	
1	H2-blockers (as per above)
2	Cromolyn sodium 100-200 mg QID
3	Proton pump inhibitors (as per above)
4	Leukotriene receptor blockers/ antagonists (as per above)
5	Ketotifen 1-2 mg BID

QID = four times daily; TID = thrice daily; BID = twice daily; qd = once daily; GER = gastroesophageal reflux.
Castells M, et al. *J Allergy Clin Immunol Pract*. 2019;7(4):1097-1106.

MCAS and Mastocytosis: Initial Treatment Options and Long-Term Management

Neuro/psychiatric: headache, poor concentration, short memory span, brain fog, anxiety, depression		
	1	H1-blockers and H2-blockers (as per above)
	2	Cromolyn sodium (as per above)
	3	Ketotifen (as per above)
		Aspirin (as per above)
Cardiovascular: presyncope, syncope, tachycardia, hypotension, hypertension		
	1	H1-blockers and H2-blockers
	2	Corticosteroids 0.5-1 mg/kg
	3	Epinephrine 0.3-0.5 mg
Pulmonary: wheezing, shortness of breath, throat swelling		
	1	Bronchodilators
		Steroid/bronchodilator combination
	2	H1-blockers and H2-blockers (as per above)
	3	Corticosteroids 0.5-1 mg/kg
	4	

Castells M, et al. *J Allergy Clin Immunol Pract*. 2019;7(4):1097-1106.

MCAS and Mastocytosis: Initial Treatment Options and Long-Term Management

Anaphylaxis	
Acute	Epinephrine IM 0.3-0.5 mg
	Corticosteroids (0.5-1 mg/kg) X1 dose
	IV fluids
	Antihistamine receptors H1 and H2
Prevention	H1-blockers and H2-blockers
	Leukotriene blockers
	Corticosteroids 0.5-1 mg/kg
	Omalizumab 300 mg every 28 days
Hymenoptera-induced	Venom immunotherapy
	Omalizumab 300 mg every 28 days
Naso-ocular: nasal stuffiness, nasal pruritus, conjunctival injection	H1-blockers (as per above)
	Inhaled corticosteroids
	Nasal cromolyn sodium
Bone: osteopenia, osteoporosis, bone fractures	Calcium, Vit D
	Biphosphonates
	Clodronate, pamidornate, alendronate, zolendronate
	Interferon alpha 2a

Castells M, et al. *J Allergy Clin Immunol Pract*. 2019;7(4):1097-1106.

Special Considerations for the Comprehensive Care of Patients with SM

Pregnancy

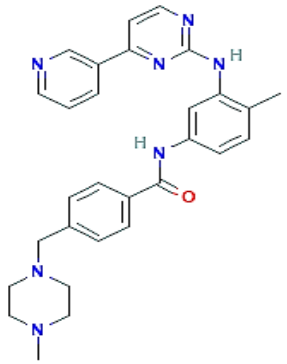
- Based on a paucity of studies, insufficient evidence currently exists regarding whether a diagnosis of SM results in significantly increased rates of adverse maternal or fetal outcomes (eg, spontaneous miscarriage, preterm infants, complications of labor and delivery) compared to the general population
- A diagnosis of SM does not appear to affect fertility
- Pre-conception, pregnancy, and the peripartum period should be managed by a multidisciplinary team, including high-risk obstetrics, anesthesia, and allergy
- Management of SM during pregnancy involves alleviation of symptoms related to mast cell activation and titration of acceptable medications to minimize potential harm to the fetus
- Avoidance of triggers, prophylactic use of antihistamines, as-needed corticosteroids, and epinephrine on demand for anaphylaxis are standard approaches during pregnancy. Please refer to the table for medications used to treat mastocytosis and their potential risks during both pregnancy and lactation
- During pregnancy, for patients with severe SM refractory to conventional therapy, cytoreductive therapy with peginterferon alfa-2a is an option. Use of cladribine or tyrosine kinase inhibitors (eg, imatinib, midostaurin, avapritinib) is not recommended. There are not sufficient data to establish the use of peginterferon alfa-2a (risk category C) in pregnancy. It should be used only if benefits outweigh potential risk to the fetus

National Comprehensive Cancer Center. Accessed September 10, 2024. https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf.

Clinical Strategies in Systemic Mastocytosis

KIT-Targeting TKIs: Status 2024

Imatinib

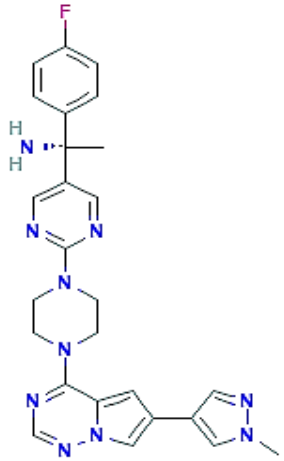


Approved in 2006 for ASM **lacking *KIT* D816V** mutation or with **unknown *KIT* mutation status**

Midostaurin

FDA and EMA approved in 2017 for 1L+ in AdvSM

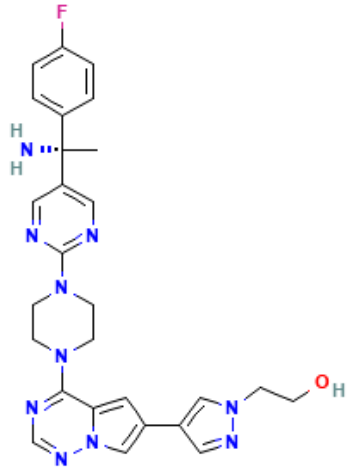
Avapritinib



FDA-approved for 1L+ in AdvSM (2021); EMA in 2022 – 2L+

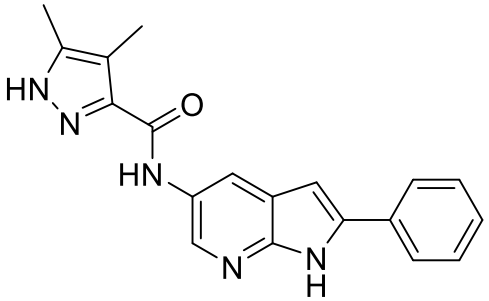
FDA-approved ISM 2022 EMA in 2023

Elenestinib



BLU-263
Phase II study advSM
***AZURE* (NCT05609942)**
Phase II ISM Trial
***HARBOR* (NCT04910685)**

Bezuclastinib

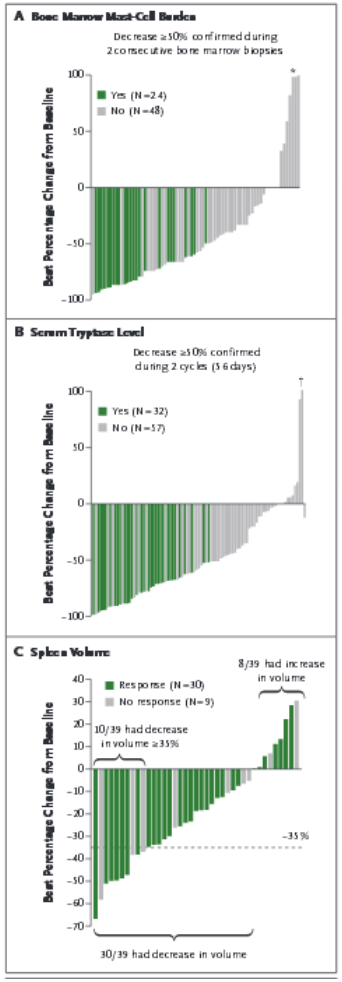


Phase II study in advanced SM
Apex
(NCT04996875)

ISM/SSM trial
Summit
(NCT05186753)

FDA. Accessed November 19, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021588s024lbl.pdf; 2017/207997s000lbl.pdf; 2021/212608s007lbl.pdf. European Medicines Agency. Accessed November 19, 2024. https://ec.europa.eu/health/documents/community-register/html/h1473.htm; https://www.ema.europa.eu/en/medicines/human/EPAR/rydapt. NIH. Accessed November 19, 2024. https://clinicaltrials.gov/study/NCT05609942; NCT04910685; NCT04996875; NCT05186753.

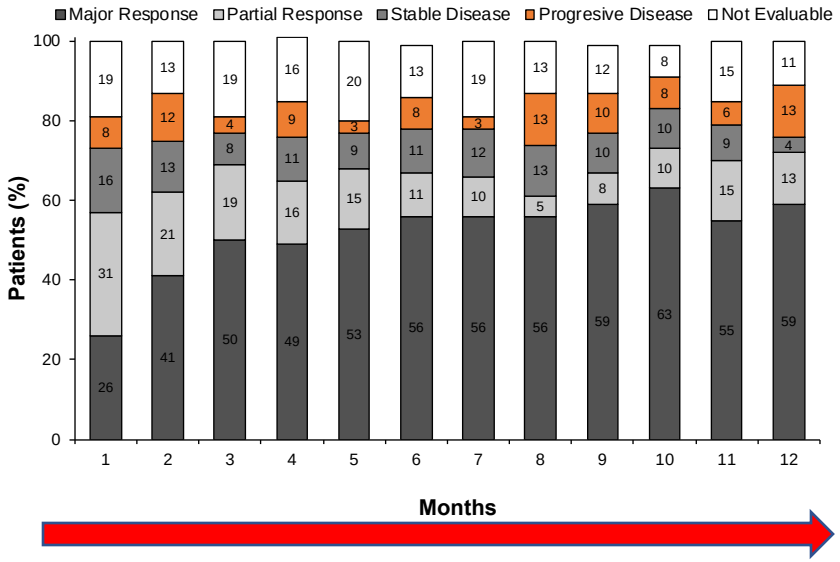
Midostaurin in Advanced SM



Bone marrow MC

Tryptase levels

Spleen volume

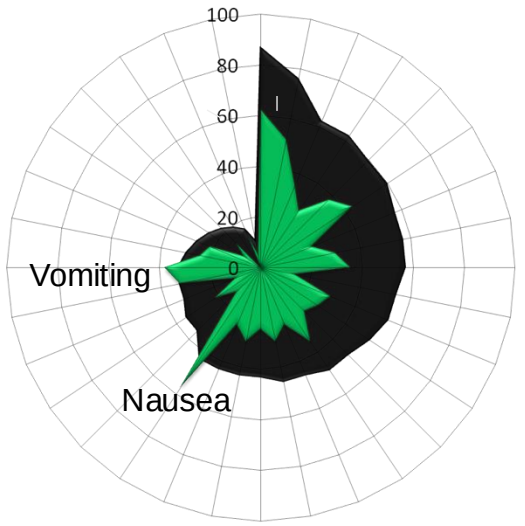


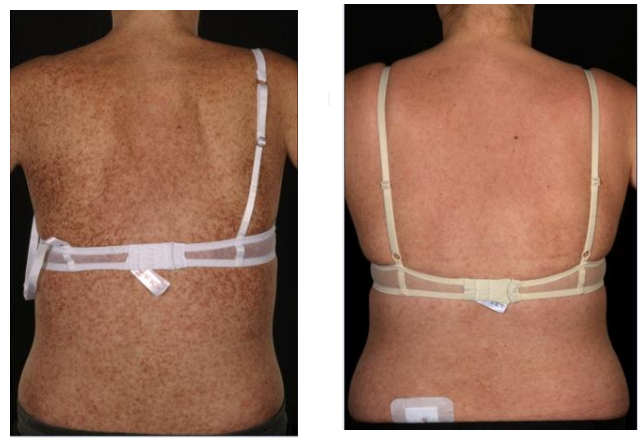
Continued depth of response over time

Midostaurin ORR: 60% per modified Valent and Cheson criteria; 45% MR

Median DOT: 11.4 months (0.3-51.5)
Median DOR: 24.1 months
Median PFS: 14.1 months
Median OS: 28.7 months

22% AEs – dose reduction in 56% & re-escalation in 32%



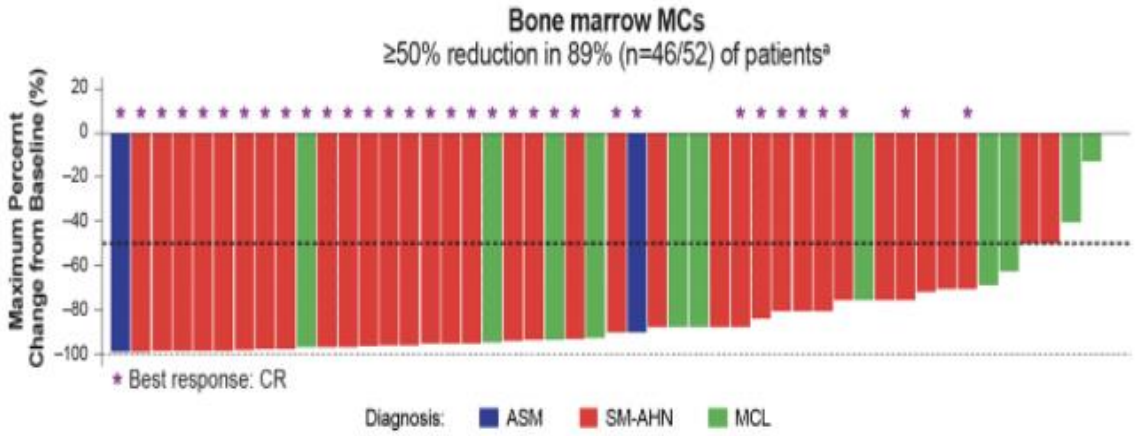


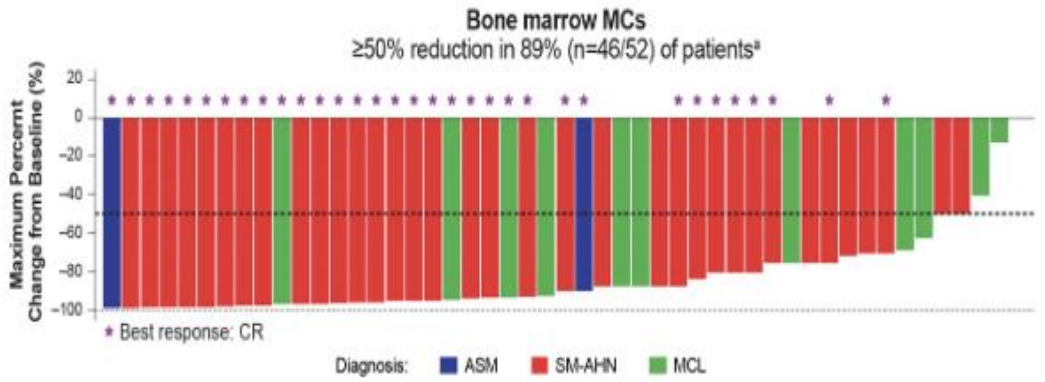
Baseline and 3 years on Midostaurin 100mg bid*

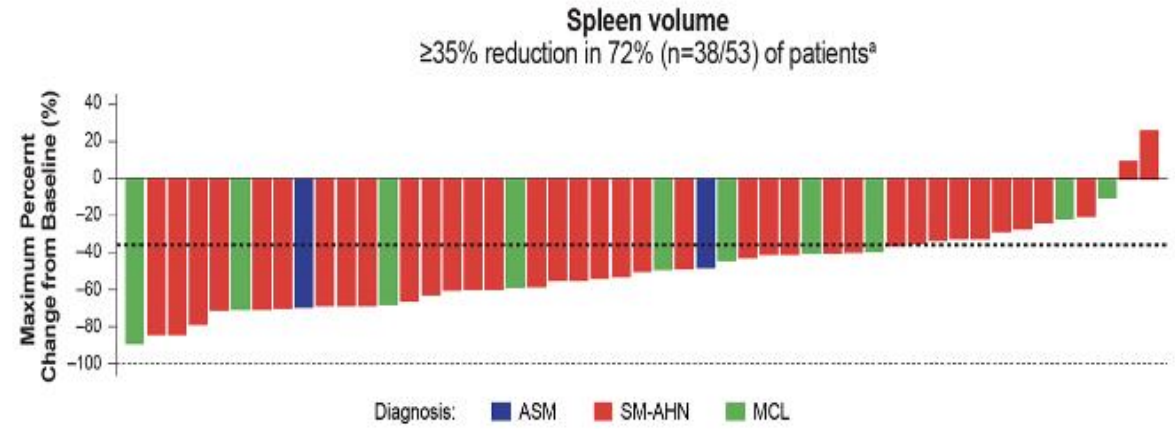
***Photos used for educational purposes with consent.**
ORR = overall response rate; MR = major response; DOT = duration of treatment; DOR = duration of response; PFS = progression-free survival; OS = overall survival; AE = adverse event.
Gotlib J, et al. *N Engl J Med*. 2016;374(26):2530-2541.

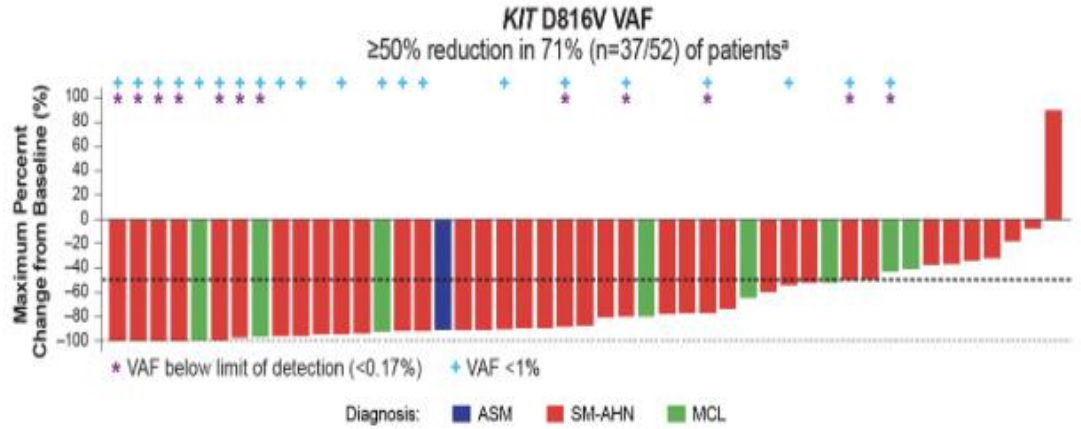
EXPLORER: Overall Response Rate By

30% molecular remission of *KIT* D816V using ddPCR with LOD of 0.17%









[a]Partial hematologic recovery: ANC >0.5 × 10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) and platelet count >50 × 10^9/L and Hgb level >8.0 g/dL; [b]Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks). Data cut-off: May 27, 2020.
ANC = absolute neutrophil count.
DeAngelo D, et al. *Nat Med*. 2021;27(12):2183-2191.

Responses in All Subtypes of AdvSM Regardless of Prior Therapy

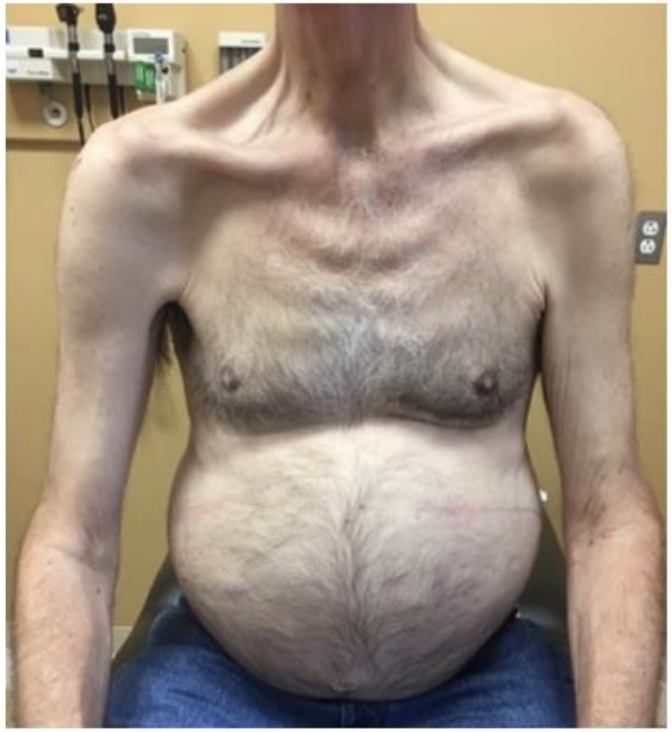
Best Confirmed Response, n (%)	All AdvSM (n=32)[c]	AdvSM Subtype			Any Prior Therapy	
		ASM (n=2)	SM-AHN (n=26)	MCL (n=4)	Yes (n=23)	No (n=9)
Overall Response Rate (CR + CRh + PR + CI)	**24 (75)**	2 (100)	21 (81)	1 (25)	17 (74)	7 (78)
CR + CRh[a] + PR	**16 (50)**	2 (100)	13 (50)	1 (25)	10 (43)	6 (67)
CR or CRh[a]	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Complete Remission (CR)	0	0	0	0	0	0
CR with partial hematologic recovery (CRh)[a]	6 (19)	1 (50)	5 (19)	0	3 (13)	3 (33)
Partial Remission (PR)[b]	10 (31)	1 (50)	8 (31)	1 (25)	7 (30)	3 (33)
Clinical Improvement (CI)	8 (25)	0	8 (31)	0	7 (30)	1 (11)
Stable Disease (SD)	4 (13)	0	2 (8)	2 (50)	2 (9)	2 (22)
Progressive Disease (PD)	1 (3)	0	0	1 (25)	1 (4)	0
Not Evaluable (NE)	3 (9)[d]	0	3 (12)	0	3 (13)	0

[a]CRh (mIWG-MRT-ECNM) requires full resolution of all evaluable C-findings, elimination of BM MC aggregates, serum tryptase <20 ng/mL, resolution of palpable hepatosplenomegaly, and partial hematologic recovery (defined as ANC >0.5 × 10^9/L with normal differential, platelet count >50 × 10^9/L, and Hgb level >8.0 g/dL); [b]PR requires full resolution of ≥1 evaluable C-findings and ≥50% reduction in both BM MCs and serum tryptase; [c]One patient in the evaluable population started at 100 mg QD; [d]Three (9%) patients were in the interim analysis efficacy population but were assessed as "not evaluable" for response due to early withdrawal from study before a confirmed response could be determined (13 weeks). Data cut-off: June 23, 2020.

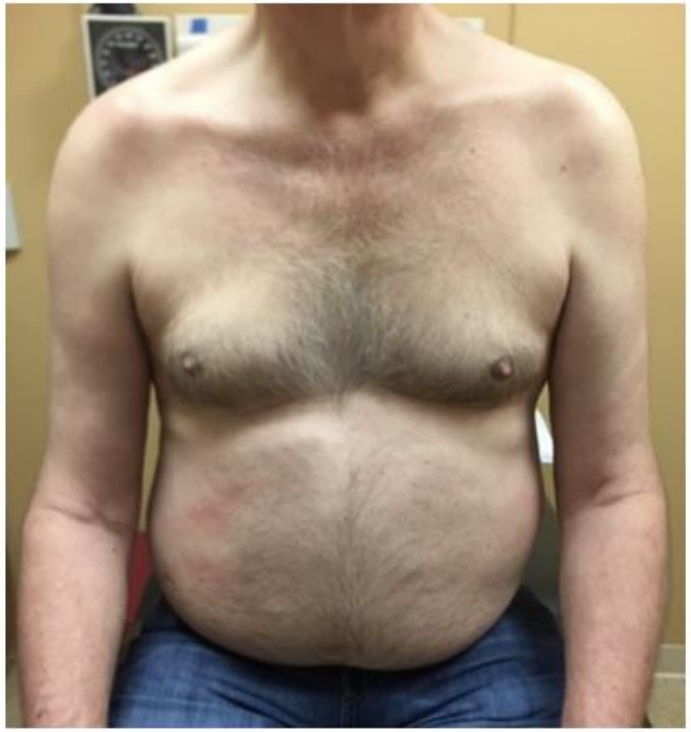
Gotlib J, et al. *Nat Med*. 2021;27(12):2192-2199.

PATHFINDER:
Rapid and Durable Reduction in SM Symptoms

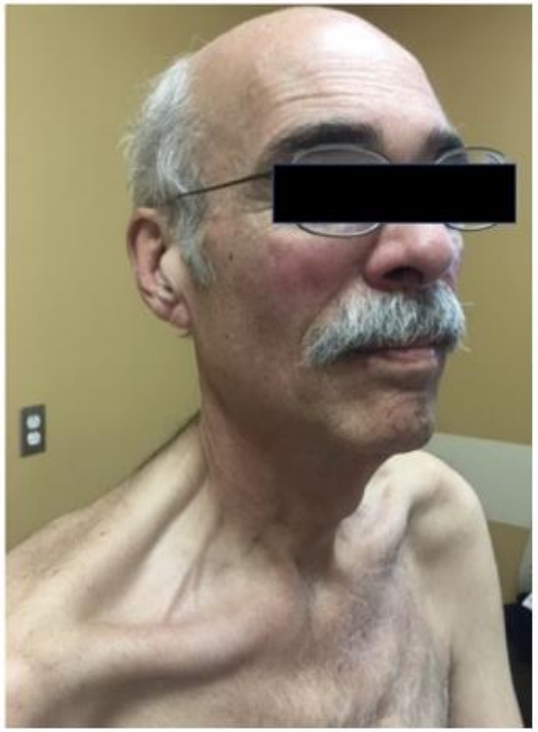
Advanced Systemic Mastocytosis-Symptom Assessment Form (AdvSM-SAF): Validated patient-reported outcome tool in AdvSM



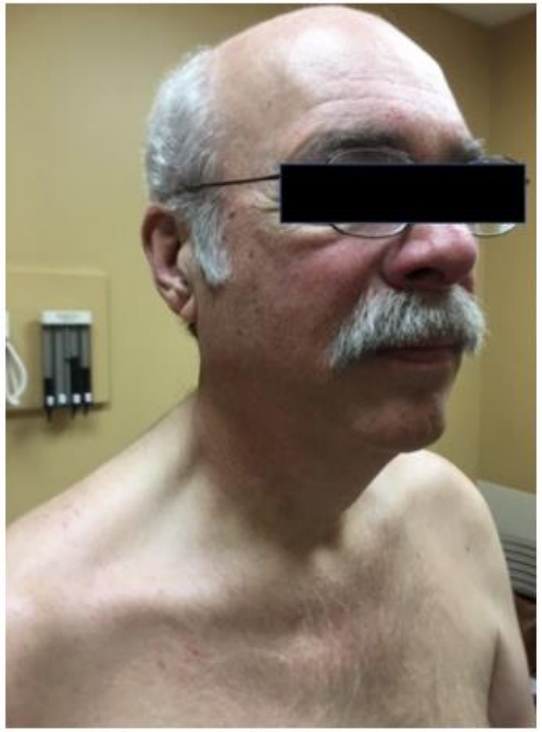
Baseline



Cycle 6 day 1



Baseline



Cycle 6 day 1

Gotlib J, et al. *Nat Med*. 2021;27(12):2192-2199. Taylor F, et al. Presented at: International Society for Pharmacoeconomics and Outcomes Research Europe Conference; November 2-6, 2019; Copenhagen, Denmark. Abstract PRO143.

Adverse Events

Safety population, n=62

Adverse Events (AEs) in ≥15%	Any-cause AEs	
Non-hematologic, n (%)	Any Grade	Grade 3/4
Peripheral ed		
Periorbital ed		
Diarrhea		
Nausea		
Vomiting		
Fatigue	9 (15)	2 (3)
Hematologic, n (%)		
Thrombocytopenia	28 (45)	10 (16)
Anemia	20 (32)	10 (16)
Neutropenia	15 (24)	15 (24)[a]

AE table includes pooled similar AE terms for periorbital edema, thrombocytopenia, anemia, and neutropenia.

- Avapritinib – risk of ICH reduced with Plt threshold to be maintained >50 x 10^9/L
- Caution with anti-platelets/dual APT and anticoagulation
- Cognitive impairment – subtle mostly, dose dependent
- Myelosuppression

Support with G-CSF, ESAs and TPO agonists if needed to facilitate delivery of the TKI.
50 mg od minimum dose—most patients "settle" on 100 mg od and maintain response if achieved.

- 52 (84%) remain on treatment
- 3 (5%) discontinued due to treatment-related AE

to an AE, (19%)

ed

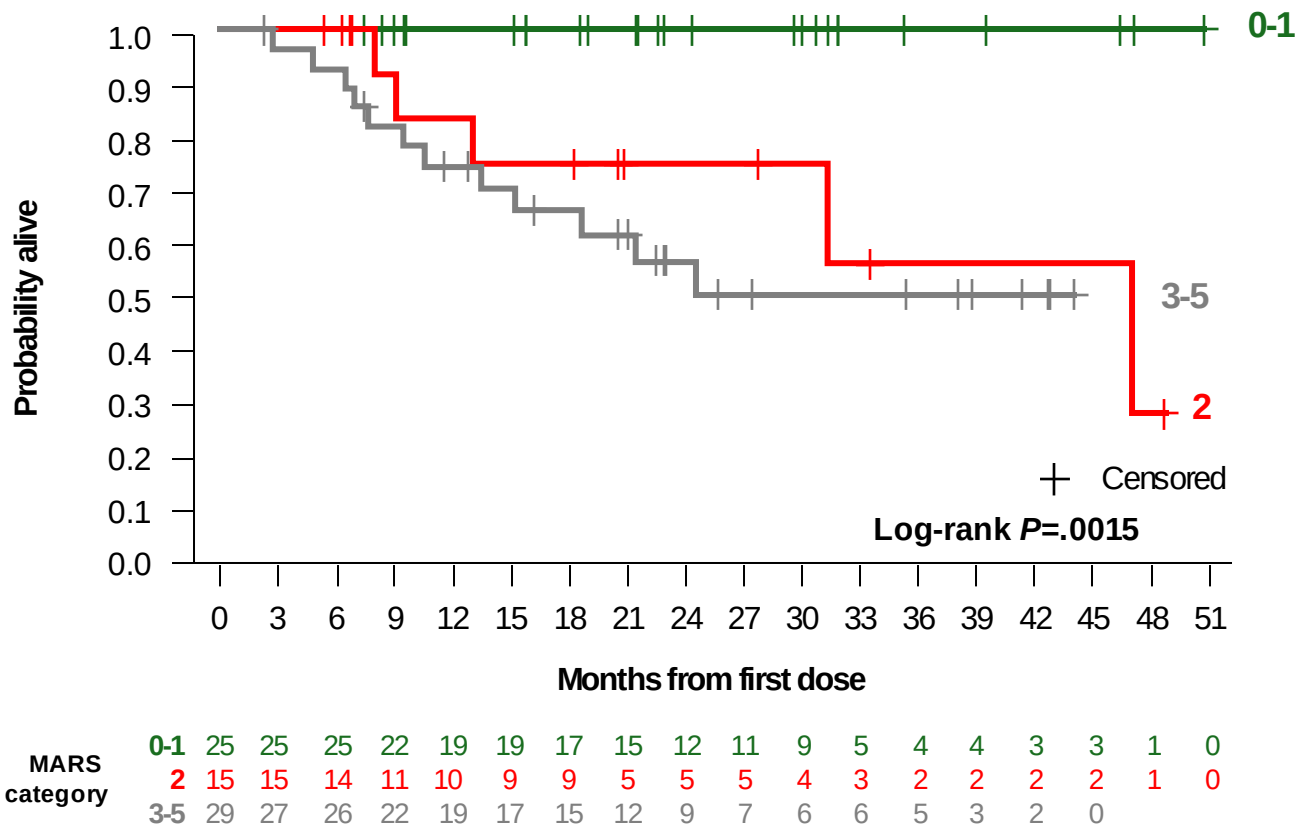
Gr 2

re-existing severe thrombocytopenia (<50×10^9/L), prior to exclusion of such patients

  - Protocol subsequently amended to exclude patients with baseline platelets <50,000/µL, increase complete blood count (CBC) monitoring, and modify dose guidance[c]

[a]Five (8%) patients had Grade 4 neutropenia; [b]Confusional state (n=3), memory impairment (n=3), and cognitive disorder (n=1); [c]CBC monitored every 2 weeks for the first 4 weeks, then at least every 4 weeks, or every 2 weeks if platelets <75 × 10^9/L. If platelets <50 × 10^9/L, interrupt avapritinib and resume at lower dose when ≥50 × 10^9/L. Avapritinib treatment with platelet growth factor support or recurrent platelet transfusions was allowed with Sponsor approval.
ICH = intercranial hemorrhage; APT = anti-platelet therapy; G-CSF = granulocyte colony-stimulating factor; ESAs = erythropoiesis-stimulating agents; TPO = thrombopoietin.
Gotlib J, et al. *Nat Med*. 2021;27(12):2192-2199.

Overall Survival Is More Favorable in Patients with a Low Baseline Mutation-Adjusted Risk Score

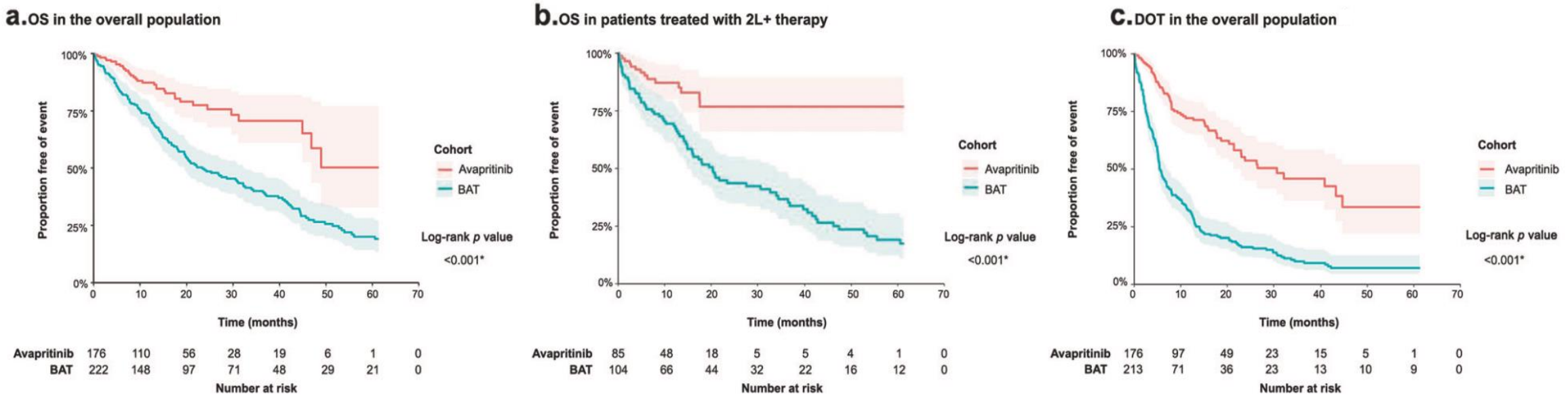


Mutation-Adjusted Risk Score (MARS) is a validated, WHO-independent prognostic score based on 5 parameters

1) >60 years of age
2) Anemia (Hgb <10 g/dL)
3) Thrombocytopenia (Plts <100×10^9/L)
4) 1 *S*/*A*/*R* mutation
5) ≥2 *S*/*A*/*R* mutations

Jawhar M, et al. *J Clin Oncol.* 2019;37(31):2846-2856. Deininger MW, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 11-14, 2021; Atlanta, Georgia. Abstract 307.

Efficacy of Avapritinib vs Best Available Therapy in the Treatment of Advanced SM



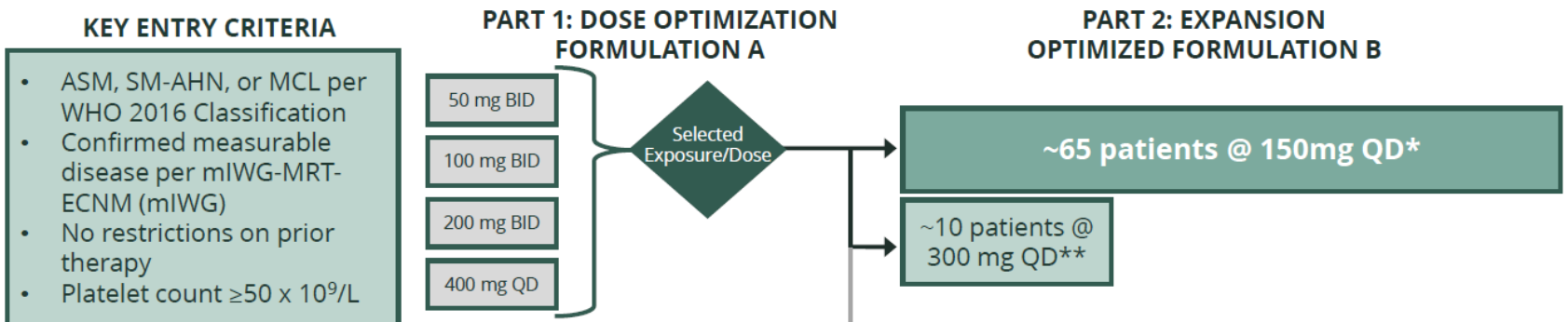
This study (NCT04695431) compared clinical outcomes between patients with AdvSM treated with avapritinib in the Phase 1 EXPLORER (NCT0256198) and Phase 2 PATHFINDER (NCT03580655) trials (n=176) and patients treated with best available therapy (BAT; n=141).

A multi-center, observational, retrospective chart review study was conducted at six study sites (four European, two American) to collect data from patients with AdvSM who received BAT; these data were pooled with data from EXPLORER and PATHFINDER.

Reiter A, et al. *Leukemia*. 2022;36:2108-2120. NIH. Accessed November 19, 2024. https://clinicaltrials.gov/study/NCT04695431.

Apex Trial

A Phase 2, Open-Label, Multi-Center Clinical Study of Bezuclastinib in Patients with Advanced SM



Primary Endpoint

- **Part 1:** Incidence of AEs/SAEs, laboratory changes, PK, biomarkers, ORR
- **Part 2:** ORR (confirmed CR, CRh, PR and CI) per mIWG-MRT-ECNM and assessed by Central Response Review Committee

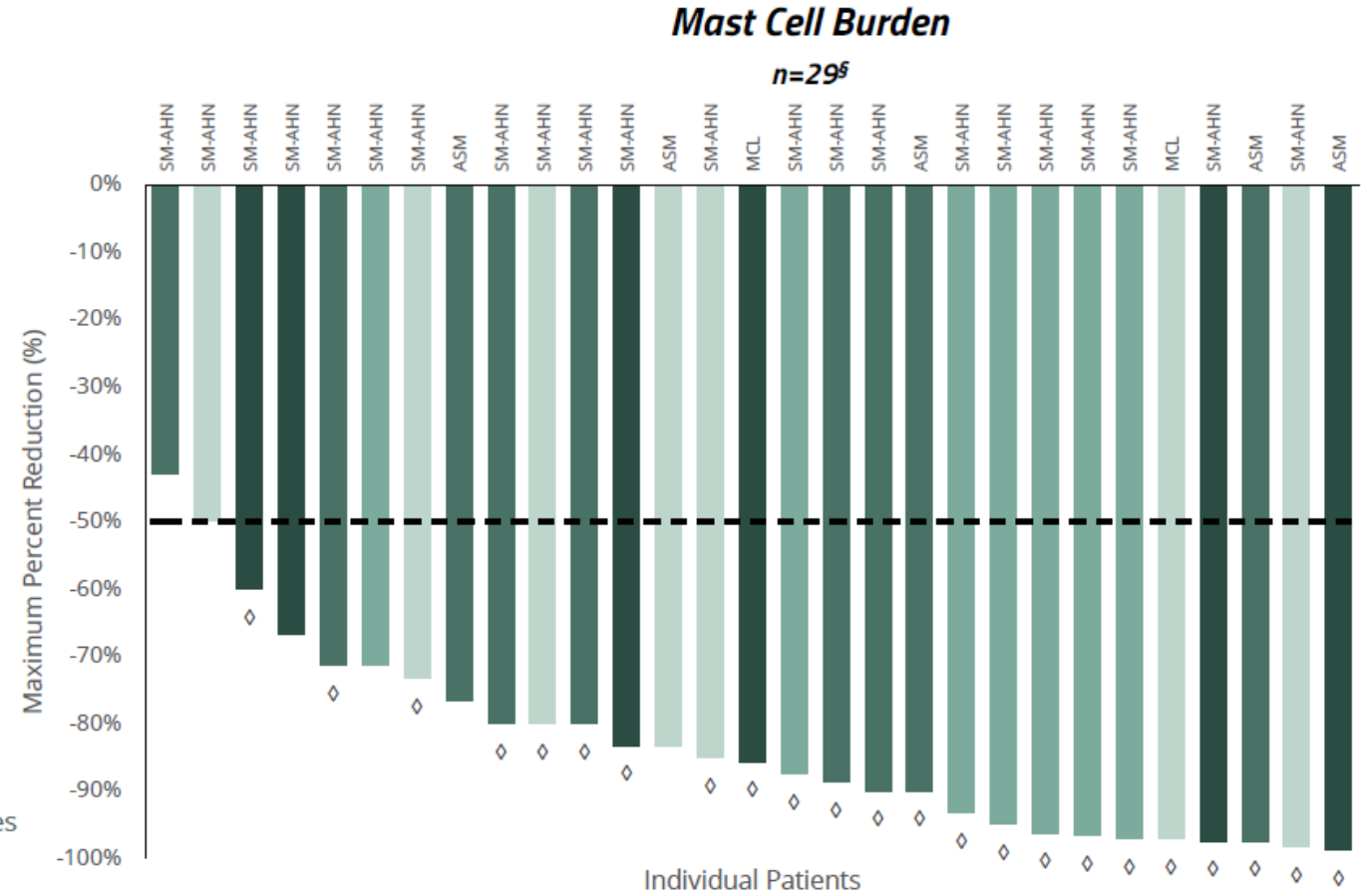
Other Endpoints

- Safety/Tolerability: Incidence of AEs leading to dose modification, changes in Patient Reported Outcomes (PROs)
- Efficacy: DOR, TTR, PFS, OS, pure pathologic response
- PK/PD: plasma concentration of bezuclastinib, serum tryptase, KIT D816V burden, BM mast cells

***Part 2 specifics subject to regulatory authority feedback; **Designed to explore the effect of exceeding IC90 *KIT* D816V engagement in AdvSM patients.**
mIWG-MRT-ECNM = (modified) International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; SAE = serious adverse event; PK/PD = pharmacokinetics/pharmacodynamics; IC90 = concentration required for 90% inhibition.
Vachhani P, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 11, 2023; San Diego, California. Abstract 4567. NIH. Accessed November 19, 2024. https://clinicaltrials.gov/study/NCT04996875.

Bezuclastinib Demonstrates Deep Reductions in Markers of Mast Cell Burden

- Bone Marrow MC Burden
  - 97% (28/29) of patients with baseline and at least 1 post-baseline assessment achieved a ≥ 50% reduction
  - 79% (23/28) achieved complete clearance of mast cell aggregates by central review
  - Median time to first clearance of mast cell aggregates was 9.0 weeks (range: 7.3-34.3)



§ Four patients without post-baseline data were excluded.

Vachhani P, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 11, 2023; San Diego, California. Abstract 4567.

Safety and Tolerability of Bezuclastinib

- The majority of adverse events were of low grade and reversible
- No related cognitive impairment or bleeding events reported
- The majority of hematological adverse events were of low grade, reversible and did not require dose reduction
- Related SAEs reported in 4 patients including Gr4 Thrombocytopenia, Gr3 DILI, Gr3 Hypersensitivity (mediator flare), and Gr3 Leishmaniasis
  - SAE of DILI presented with late onset (day 488) and mixed cholestatic pattern of injury and subject was subsequently found to have biliary outflow tract obstruction.
- 9/32 patients required dose reduction due to adverse events, 6 of whom were at 400 mg/day; 3/32 patients discontinued due to adverse events.

Treatment Related Adverse Events in > 10% Patients

	Total *(n=32)* n (%)		50 mg BID *(n=8)* n (%)	100 mg BID *(n=7)* n (%)	200 mg BID *(n=8)* n (%)	400 mg QD *(n=9)* n (%)
Preferred Term	All grade	Grade ≥3	All grade	All grade	All grade	All grade
Hair color changes	11 (34)	0	0	4 (57)	3 (38)	4 (44)
*Thrombocytopenia**	7 (22)	2 (6)	0	4 (57)	1 (13)	2 (22)
*Neutropenia**	6 (19)	3 (9)	1 (13)	2 (29)	1 (13)	2 (22)
*Taste disorder**	6 (19)	0	1 (13)	1 (14)	1 (13)	3 (33)
ALT increased	5 (16)	0	1 (13)	2 (29)	1 (13)	1 (11)
Oedema peripheral	4 (13)	0	0	1 (14)	1 (13)	2 (22)
Periorbital oedema	4 (13)	1 (3)	0	0	3 (38)	1 (11)

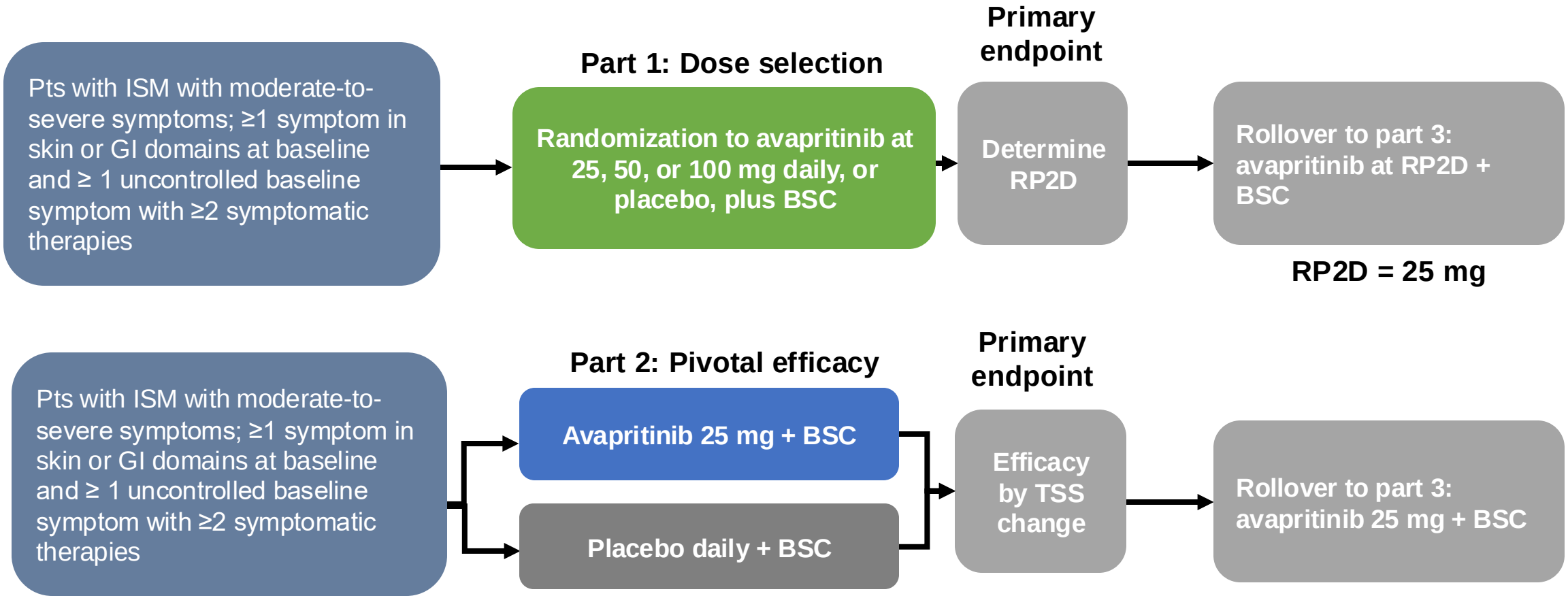
***Includes pooled preferred terms.**

Vachhani P, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 11, 2023; San Diego, California. Abstract 4567.

Indolent SM

PIONEER Trial

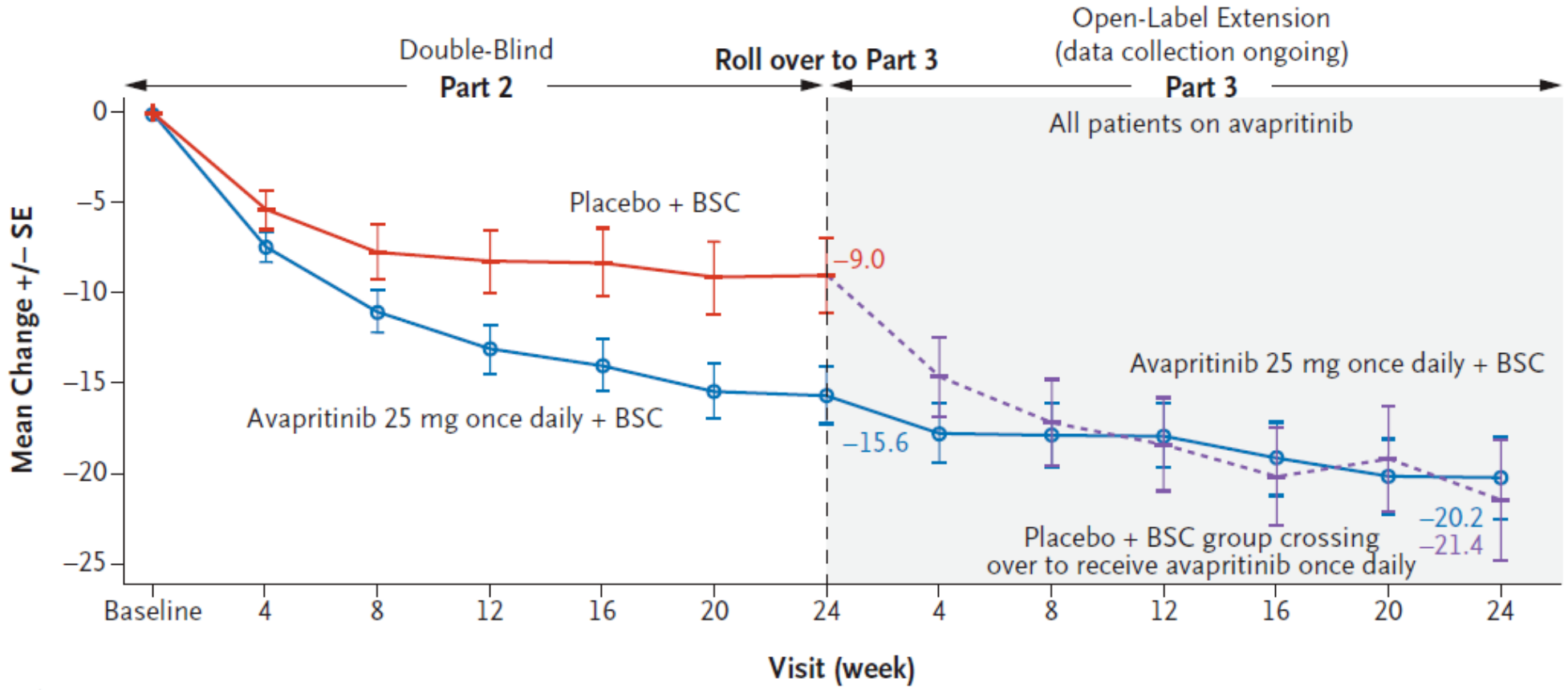
Phase 2 Trial of Avapritinib in Patients with Indolent SM



GI = gastrointestinal; RP2D = dose level producing around 20% of dose-limiting toxicity; BSC = best supportive care.

Akin C, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 7-10, 2019; Orlando, Florida. Abstract 2950. Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

SM Symptom Score over Time: Avapritinib vs Placebo

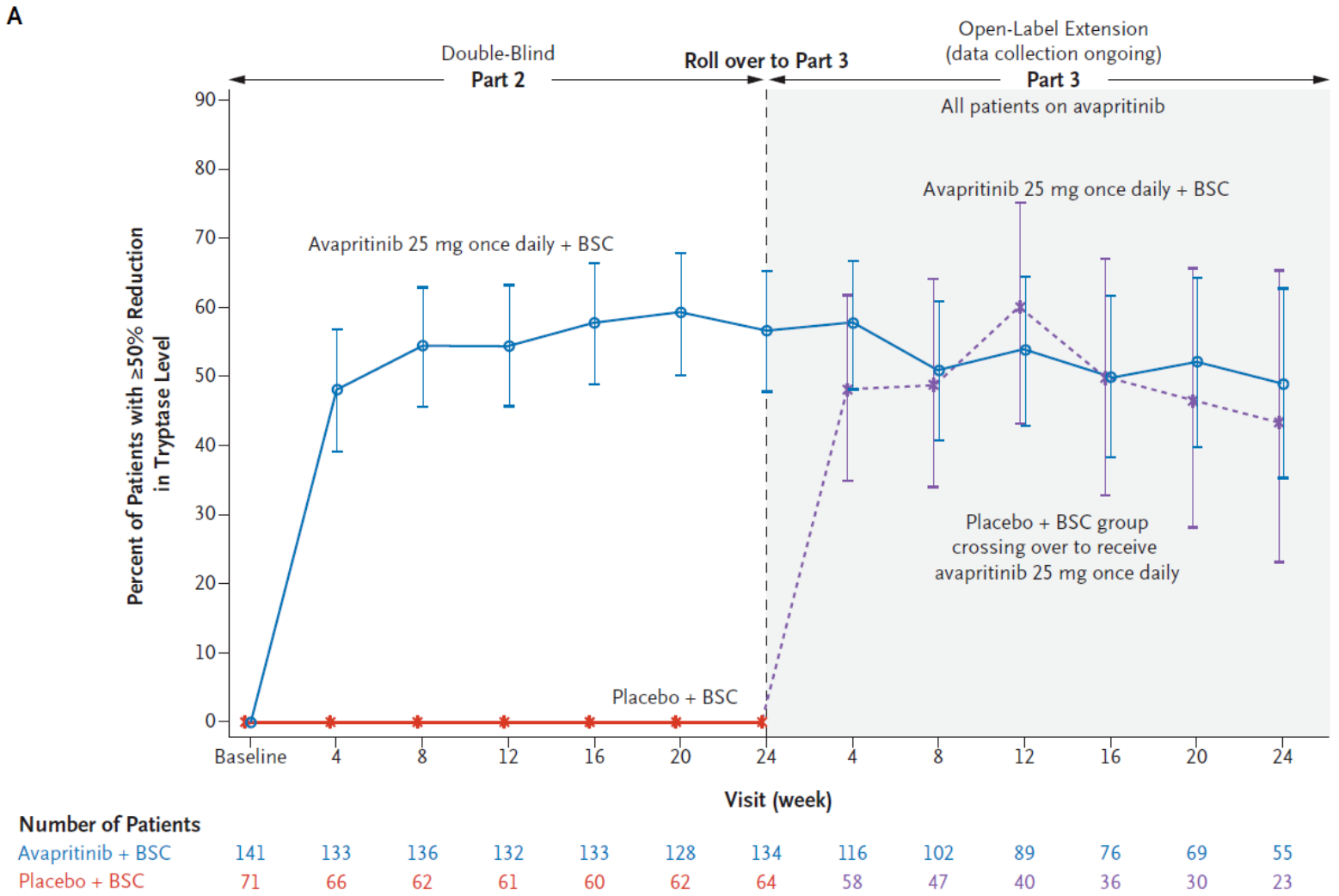


Number of Patients

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

Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

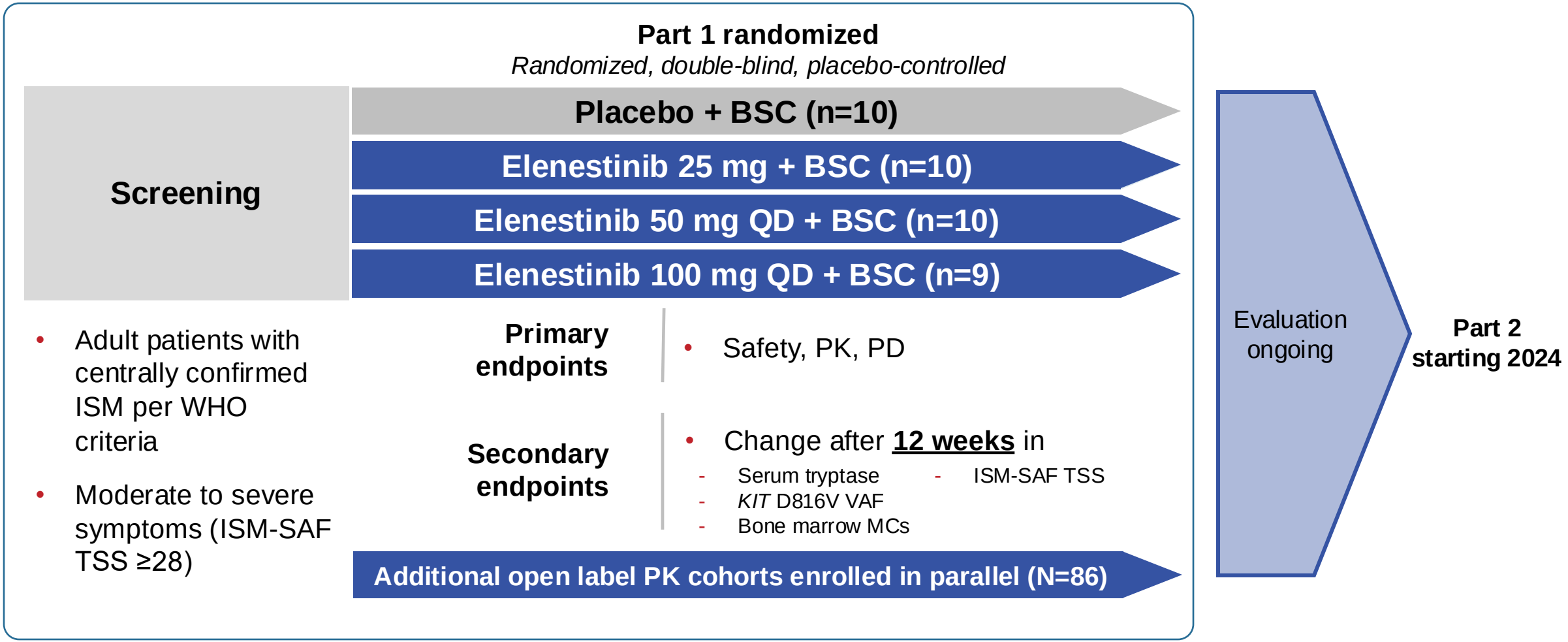
Reduction in Serum Tryptase Levels over Time



Gotlib J, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200339.

HARBOR Part 1

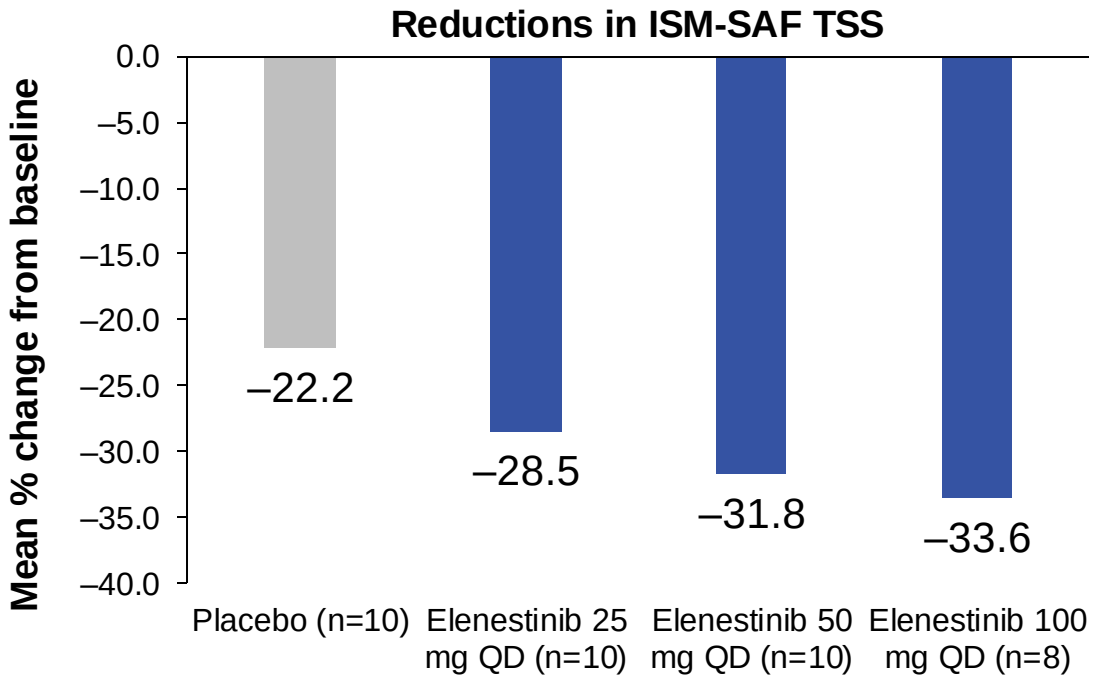
A Randomized, Double-Blind, Placebo-Controlled Dose Finding Part of Elenestinib



Tashi T, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9, 2023; San Diego, California. Abstract 76. NIH. Accessed November 19, 2024. https://clinicaltrials.gov/study/NCT04910685.

After 12 Weeks of Elenestinib: Symptom Improvement Was Observed for All Dose Cohorts

- All elenestinib dose cohorts demonstrated clinically meaningful changes in symptoms without clear dose dependence
- Percentage change of symptom reduction in TSS was greater for patients on elenestinib vs placebo in the blinded portion of Part 1
- Elenestinib has high selectivity and potency for *KIT* D816V and limited central nervous system penetration, which may reduce the risks of cognitive toxicities and intracranial bleeding

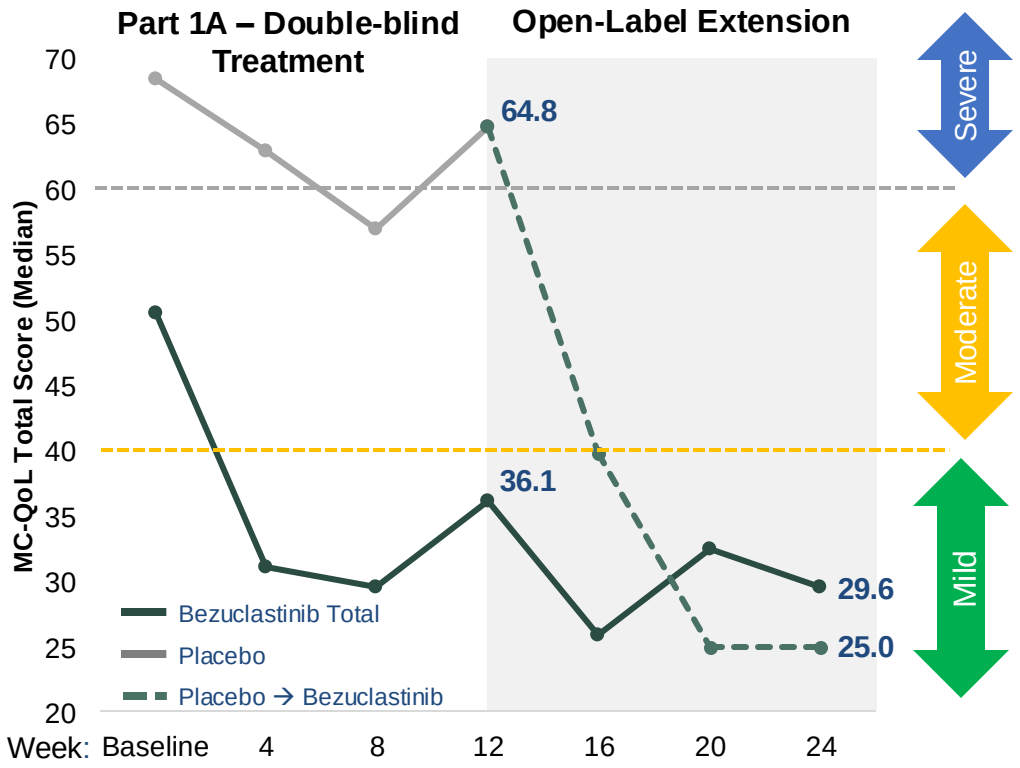


Tashi T, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9, 2023; San Diego, California. Abstract 76.

Encouraging Signs of Rapid Improvement in Symptom Severity and Quality of Life

- **Best percent improvement in patients treated with bezuclastinib (n=8) was 38% in Part 1a and 56% in OLE**
- **After placebo crossover to bezuclastinib in OLE (n=5), the best percent improvement was 63%**

Quality-of-Life Assessed by MC-QoL



Symptom Severity Assessed by MAS

Mastocytosis Activity Score (MAS) % change from baseline at week 12[a]		
	Total Bezuclastinib (n=8)	**Placebo (n=4)**
Median	-35.53	-27.76
Min, Max	-60.1, -5.0	-73.1, 3.3

- 49% median decrease in MAS for patients treated with 100 mg QD dose level

[a]Not collected in OLE. Data cut-off: October 25, 2023.
MC-QoL = Mastocytosis Quality of Life Questionnaire; OLE = open label extension.
Bose P, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9, 2023; San Diego, California. Abstract 77.

Key Learning Points

- Systemic mastocytosis is a clinicopathologic entity
- Clinical subtypes have been revised and correlate with prognosis (WHO 2022)
  - In 2022, WHO updated the major and minor diagnostic criteria; serum total tryptase >20 ng/mL is considered a minor criterion
- B- and C-findings are used to aid in the classification of non-advanced and advanced SM
  - Organomegaly without impaired organ function is considered a B-finding
- *KIT* D816V is the most common pathognomonic mutation
- *KIT* mutation is a late event → phenotypic modification towards mast cells
- Avapritinib, a potent and selective type I TKI of activation loop mutants, is a safe and effective targeted therapy for advanced SM and indolent SM
  - New therapeutic options being explored with bezuclastinib and elenestinib
  - Elenestinib demonstrated high selectivity and potency for *KIT* D816V with limited CNS penetration—reducing the risk of cognitive toxicities and intracranial bleeding

Looking Forward

- Do KIT inhibitors (eg, avapritinib or bezuclastinib) modify SM natural history and does this correlate with depth of *KIT* D816V molecular response?
  - *Concept of negative MRD in AdvSM?*
- SM-AHN: How do we sequence KIT inhibitors with AHN-directed therapy?
  - *Treat AHN or SM component first? Tolerance of combination therapy?*
- What is the role of KIT inhibition pre- and post-transplant?
  - *Do we need to rethink who we take to transplant and when?*

Non-Advanced Mastocytosis

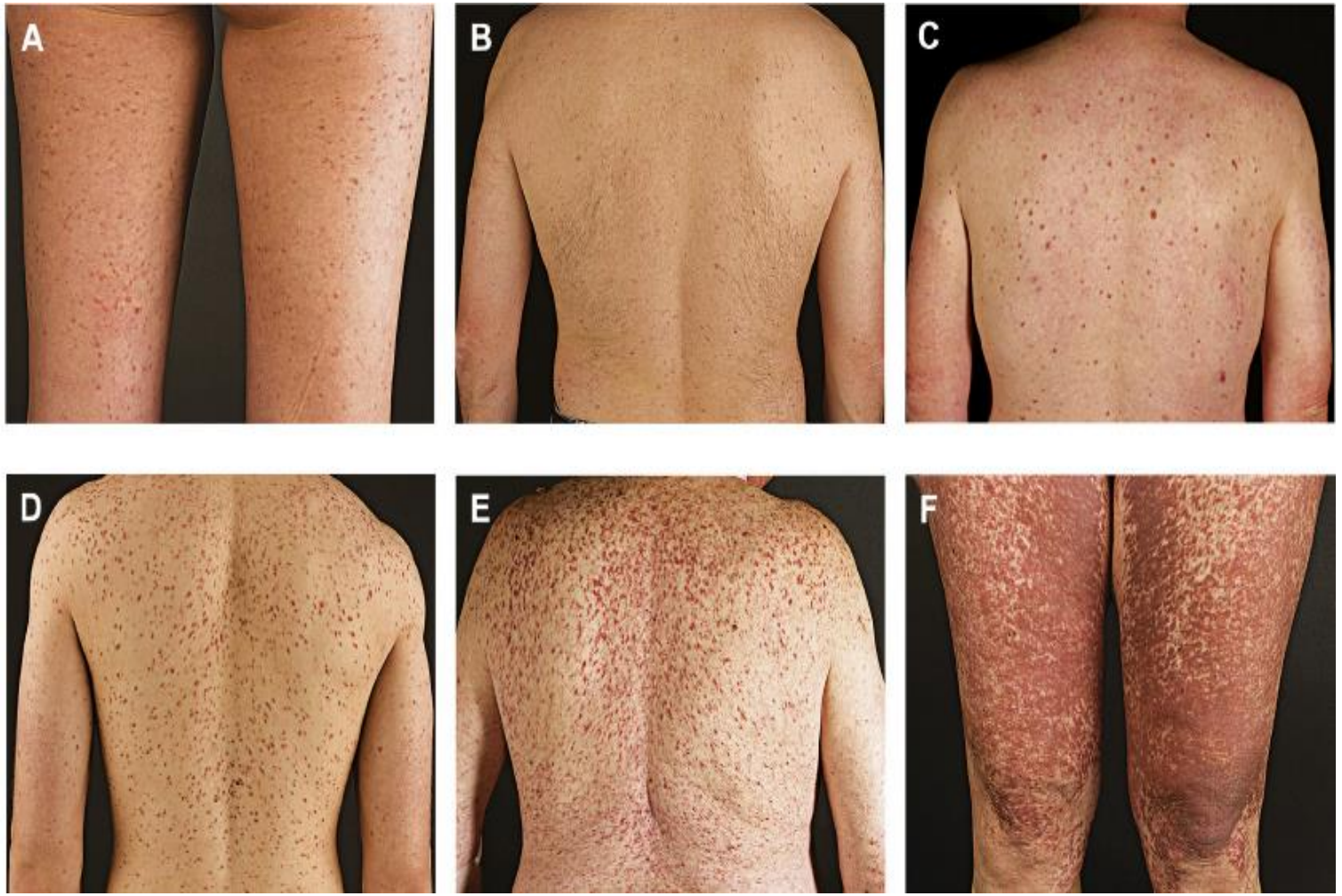
Indolent Systemic Mastocytosis Case Study

Case Presentation – NonAdvSM

- 44-year-old truck driver slipped and fell on his back on ice and developed lower back and calf muscle pain exacerbated by walking and standing
- MRI revelated vertebral body T3 compression fracture and lumbar spine fracture 10 years prior after heavy lifting
- Found to have osteoporosis in spine and osteopenia in hip
- Baseline serum tryptase: 41.9 ng/mL
- Additional history
  - Urticaria pigmentosa for over 20 years, spots increasing over time
  - GER, R sided abdominal pain, cramping, loose stools/diarrhea with greasy foods, heat, stress and alcohol use
  - Anaphylaxis with loss of consciousness after 2 hornet stings, the 2nd requiring 3 doses of epinephrine
  - Brain fog, depression, difficulty concentrating, short memory span

MRI = magnetic resonance imaging.
Hamilton MJ, et al. *Front Allergy.* 2024;5:1401187.

MPCM in Patients with Adulthood-Onset Mastocytosis



Parameter	Adulthood-onset mastocytosis	Childhood-onset mastocytosis
Most frequent category of mastocytosis	ISM	Cutaneous mastocytosis
Typical course of the disease	Chronic	Temporary
Frequency of anaphylaxis (%)	50	<10
Typical tryptase level (μg/L)	>20	<20
Typical location of *KIT* mutation	Exon 17, most frequently *KIT* D816V	Exon 8, 9, 11, or 17 or absent
Most frequent type of cutaneous lesions	Maculopapular	Maculopapular
Typical morphology of maculopapular lesions	Monomorphic	Polymorphic
Typical size of maculopapular lesions	Small	Large
Typical distribution of maculopapular lesions	Thigh, trunk	Trunk, head, extremities

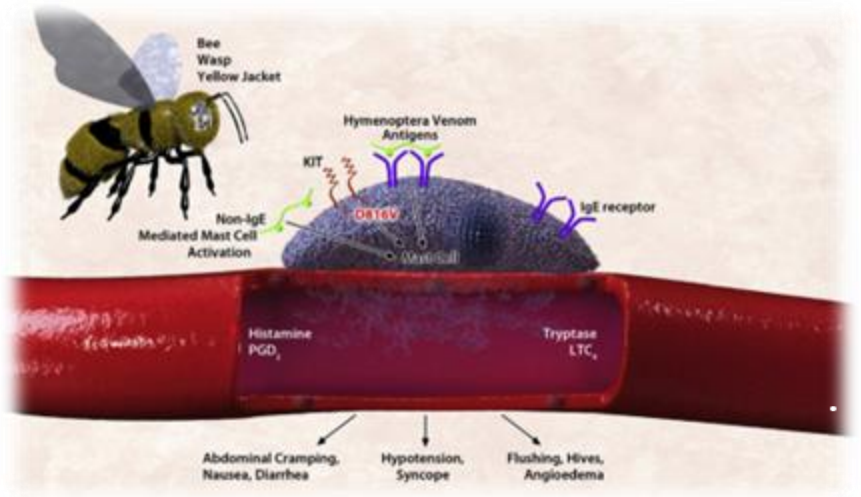
Hartmann K, et al. *J Allergy Clin Immunol*. 2016;137(1):35-45.

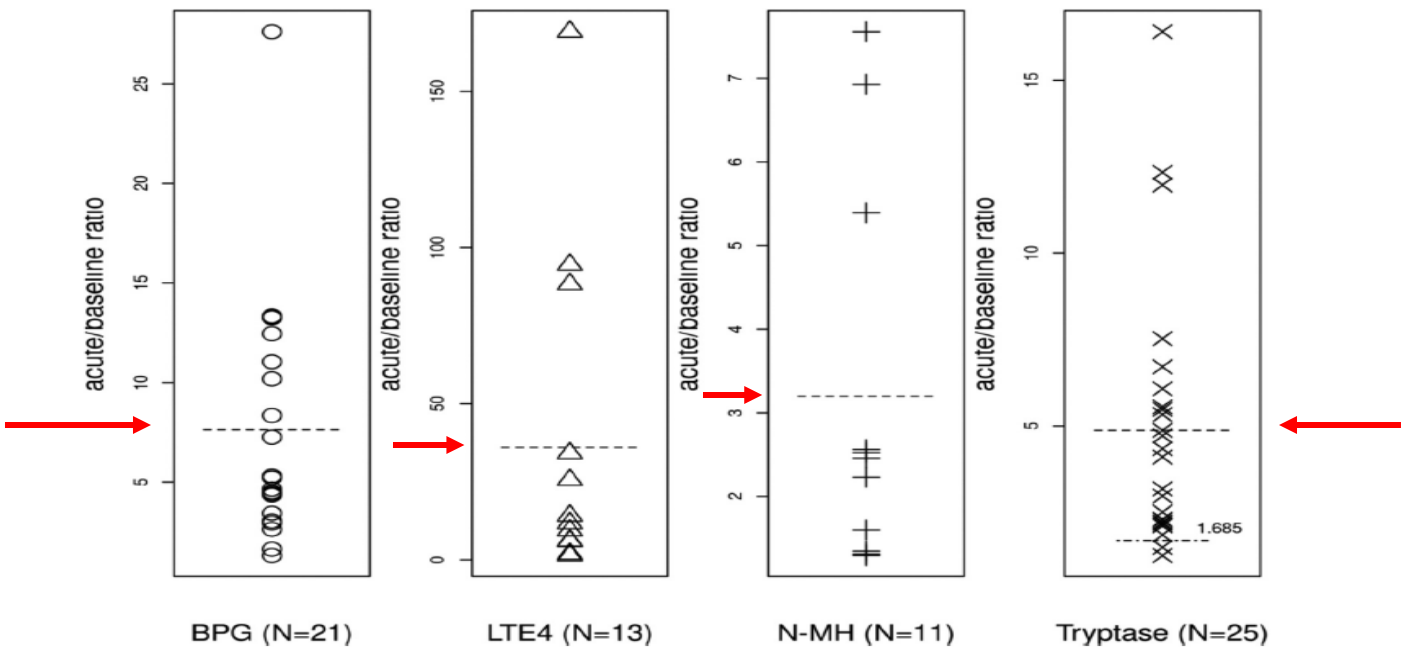
Diagnostic Evaluation

- CBC with differential
- Liver function tests, including serum albumin, serum LDH, and serum ALP
- DEXA bone density scan
- Serum tryptase
- Urine mediators: N-methyl histamine, prostaglandin D2, leukotriene E4
- Skin biopsy
- Bone marrow or other extracutaneous organ biopsy
  - Tryptase
  - CD117, CD25, CD30, and/or CD2
- Molecular testing
  - High sensitivity c-KIT D816V (eg, PCR) and other *KIT* exon mutations
  - Myeloid mutation panel for possible additional mutations
  - FIPIL1-PDGFRA fusion if eosinophilia present
- Evaluation of B- and C-findings and organ involvement
- CT/MRI or ultrasound of the abdomen/pelvis
- Metastatic skeletal survey to evaluate for osteolytic lesions
- Organ-directed biopsy

LDH = lactate dehydrogenase; ALP = alkaline phosphatase.
Hartmann K, et al. *J Allergy Clin Immunol*. 2016;137(1):35-45.

Further testing showed normal blood counts without eosinophilia (0.07 K/μl) and normal liver and kidney function tests. Abdominal CT scan revealed cholelithiasis, nonobstructing renal calculi in the left kidney, and "haziness" of the mesentery in the left upper quadrant with associated lymphadenopathy (largest lymph node, 16 × 13 mm). Upper endoscopy revealed no evidence of erosive esophagitis, Barrett's esophagus, or peptic ulcer disease. Blood tests showed elevated immunoglobulin E (IgE) level of 234 kU/L (upper limit, 100 kU/L) and negative serum-specific IgE against Hymenoptera venom antigens (test performed 5 years after last venom-induced anaphylaxis). Intradermal skin testing was positive to white-faced hornet and bee venoms. Repeat BST was 38.5 ng/ml, and 24-hour urine collection revealed elevated prostaglandin F2-α at 14,858 pg/mg (normal, <5,205 pg/mg) and N-methylhistamine at 1,905 mg/dl (normal, <1,800 mg/dl). He tested positive for *KIT* D816V mutation in peripheral blood (low level detected by droplet digital PCR (ddPCR), fractional abundance 0.08%). Due to the elevated prostaglandin and history of flushing, he began full-strength aspirin daily and was educated on the use of epinephrine. He was also prescribed daily oral cromolyn sodium and a nonsedating H1 antihistamine.

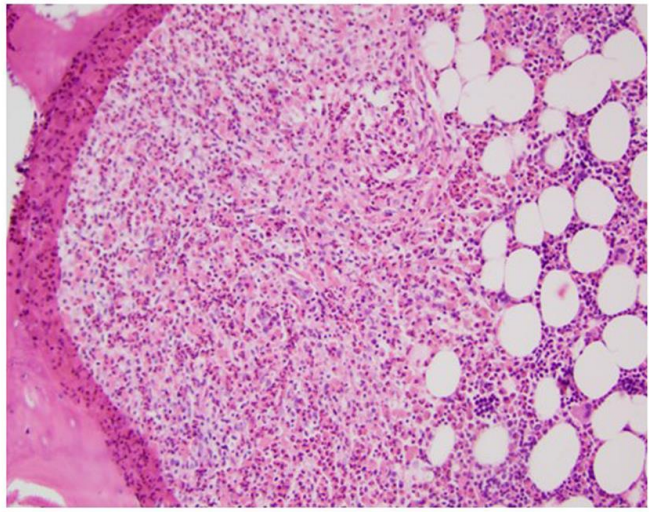




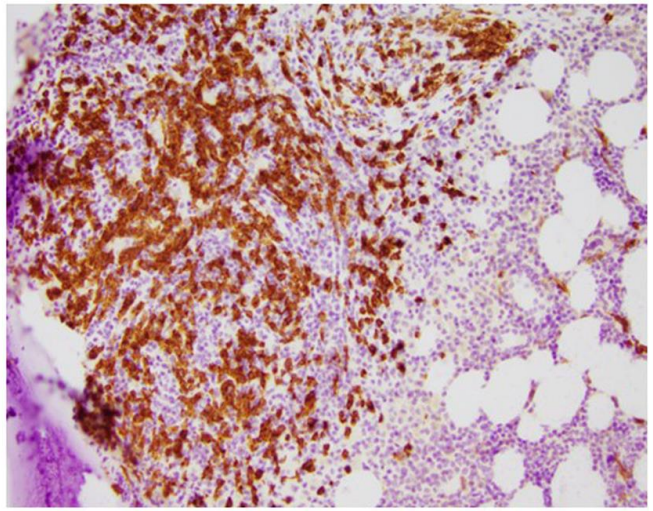
Hartmann K, et al. *J Allergy Clin Immunol*. 2016;137(1):35-45. Butterfield JH. *JACI Pract.* 2023;11(8):2542-2546.

Bone Marrow Biology Histology

A

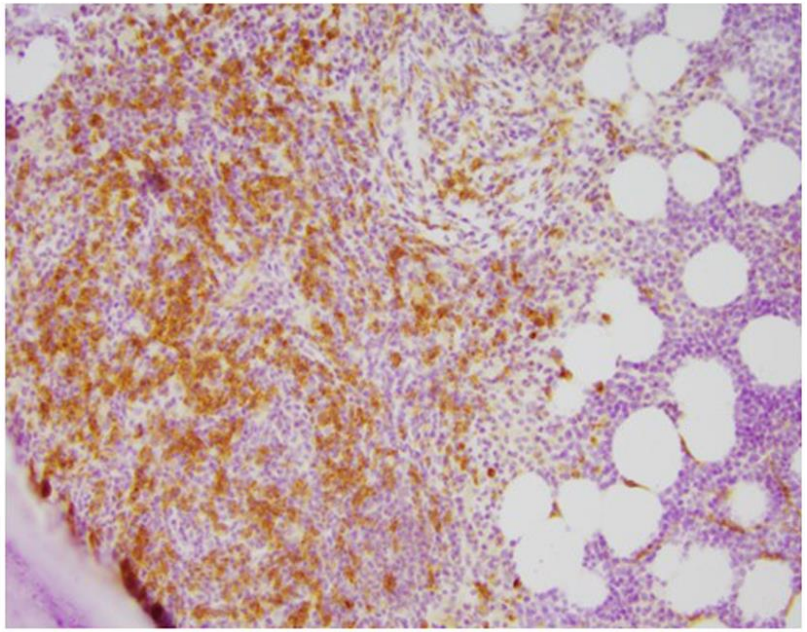


B



Tryptase
***KIT* CD117**
CD25/CD2/CD30

C



Hamilton MJ, et al. *Front Allergy.* 2024;5:1401187.

Multi-Disciplinary Approach to Mastocytosis

Problem/symptom	Intervention/test	Specialist involved	Treatment/outcome
Osteoporosis	Bone density, baseline serum tryptase test	Endocrinologist	Bisphosphonates
Hymenoptera allergy	Serum Hymenoptera venom-specific IgE skin testing	Allergist/Immunologist	Specific allergen immunotherapy desensitization
MC mediator symptoms	24-hour urine test for MC mediator metabolites N-methylhistamine and 11β-prostaglandin F2α	Allergist/Immunologist	Medications to target MC mediators (e.g., antihistamines, cromolyn)
Anaphylaxis	Education about characteristic symptoms and proper use of epinephrine	Allergist/Immunologist	Epinephrine prescribed to all patients with SM, consider omalizumab
Cutaneous lesions	Skin biopsy	Dermatologist Dermatopathologist	Antihistamines, topical corticosteroids, phototherapy, omalizumab
Depression	Assess for commonly comorbid anxiety and depression	Psychiatrist	Medical therapies, counseling
Gastroesophageal reflux disease, peptic ulcer disease	Recognize high incidence, consider endoscopy to assess for erosive disease	Gastroenterologist	Endoscopy, use of proton pump inhibitors—caution with chronic use in patients with osteopenia/osteoporosis
Hepatosplenomegaly, lymphadenopathy	Cross-section abdominal imaging	Gastroenterologist, Allergist/ Immunologist, Hematologist	Document presence to characterize mastocytosis (B-findings)
Diagnosis of systemic mastocytosis	Bone marrow biopsy	Pathologist with experience in assessment of SM	Use of appropriate immunostaining for tryptase, CD25, and CD30, flow cytometry, test for *KIT* D816V and other associated mutations

Hamilton MJ, et al. *Front Allergy.* 2024;5:1401187.

Treatment Options: Systemic Mastocytosis

Symptoms/therapy	ISM and AdvSM treatment	ISM-only treatment	AdvSM-only treatment
MC mediator and other SM-specific symptoms	Antihistamines, oral cromolyn sodium, antileukotriene, ketotifen, PPI		
Prevention of complications	Anaphylaxis—omalizumab, desensitization Osteoporosis—bisphosphonates, anti-RANKL		
Refractory symptoms (investigational)		Avapritinib, (bezuclastinib, elenestinib)	
Conventional therapy to reduce clonal MC			Cladribine, interferon-α, hydroxyurea
Targeted tyrosine kinase therapy	*KIT* D816V present—avapritinib		*KIT* D816V present—midostaurin Mutation absent or well-differentiated SM—imatinib
Investigational targeted therapy	Bezuclastinib, elenestinib	Masitinib, TL-895	

PPI = proton pump inhibitor.
Hamilton MJ, et al. *Front Allergy.* 2024;5:1401187.

Advanced Systemic Mastocytosis

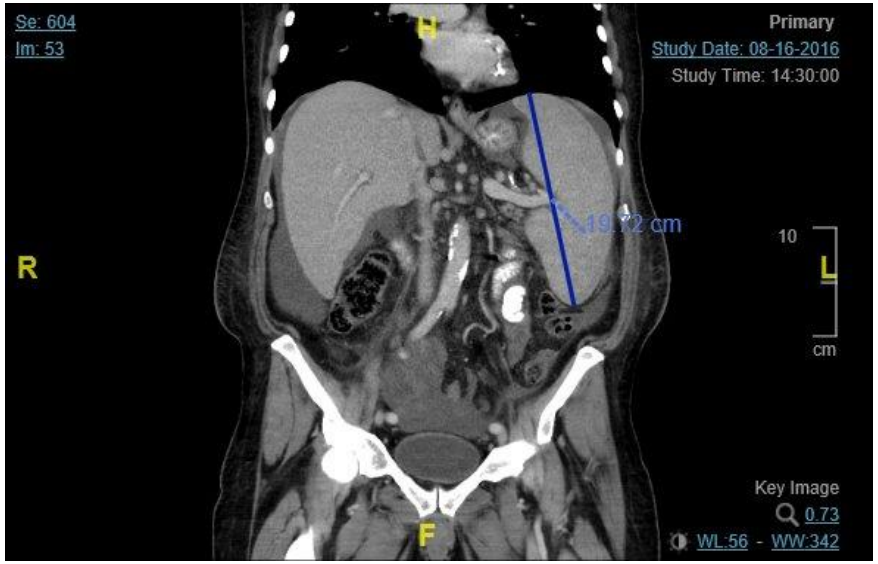
Case Study

Case Presentation – AdvSM #1

- 75-year-old man with 3-month history of fatigue, abdominal distention, and lower extremity edema
- WBC: 27 x 10^9/L; Hgb: 8.2 g/dL; Platelet count: 64 x 10^9/L; differential showed 76% polys, 9% bands, 8% lymphs 3% monos, and 1 NRBC
- CT scan showed diffuse LAN 2-3 cm, small pleural effusion, ascites and splenomegaly

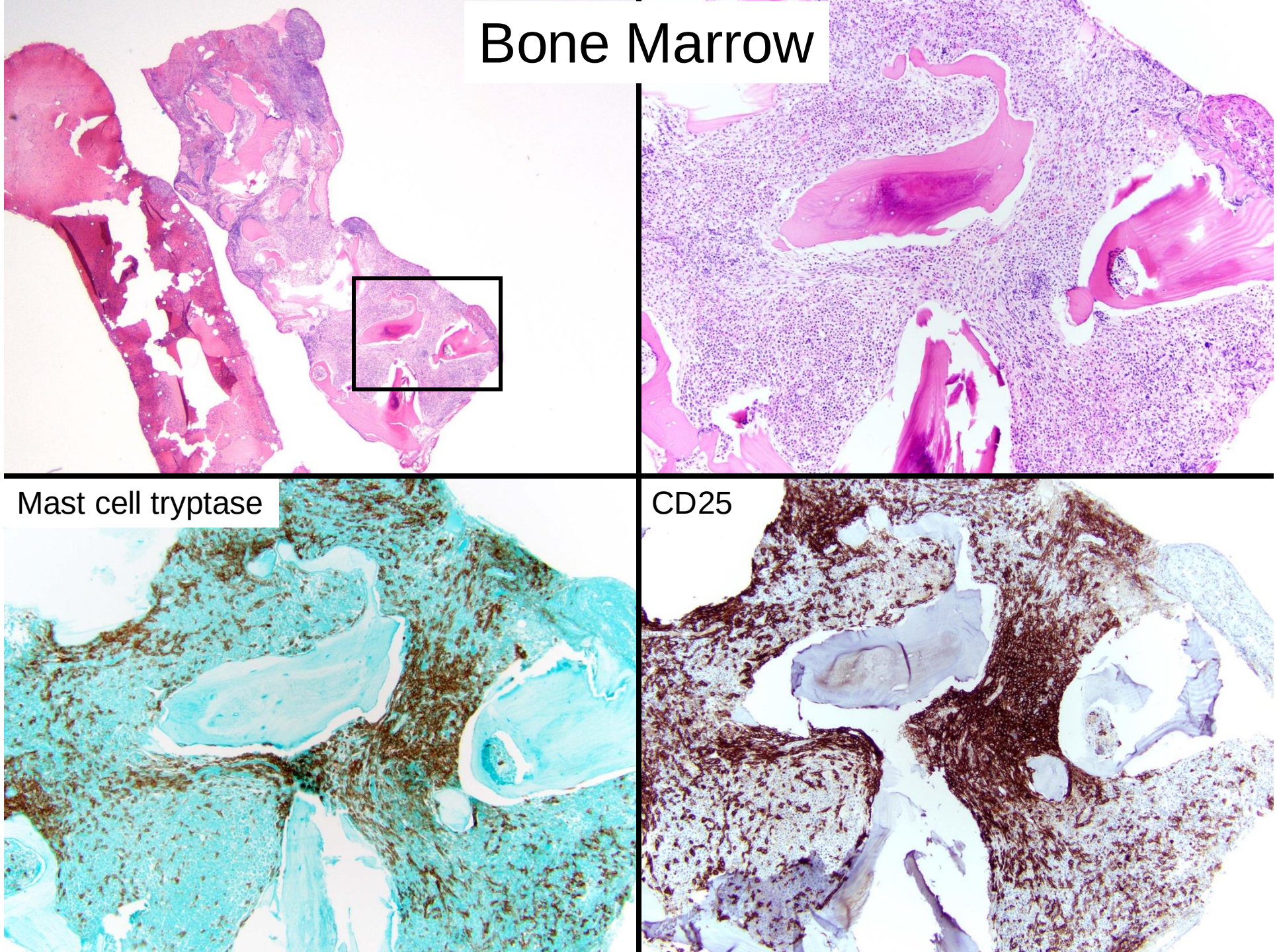
What is the next step?

- Tryptase 187
- BM exam showed hypercellular marrow with 40% mast cells
  - Flow: mast cells expressing CD117 and aberrant CD2 and CD25
  - Cytogenetics: 46 XY
  - RHP: KIT D816V and SRSF2, TET2 and CUX1 mutations



What is the diagnosis?

WBC = white blood cell; NRBC = nucleated red blood cell


Bone Marrow
Mast cell tryptase
CD25

==== RAPID HEME PANEL ====
RESULT:

Average coverage: 1356X >200X coverage: 88.7% <50X coverage: 4.4%
(A high quality sample/run has >90% of the amplicons with >200X coverage)

Pathogenic Single Nucleotide Variants and Small Insertions/Deletions:

SRSF2 NM_001195427 c.284C>A p.P95H - in 58.1% of 129 reads
CUX1 NM_181552 c.1197_1198insC p.A410fs* - in 48.8% of 121 reads
KIT NM_000222 c.2447A>T p.D816V - in 35.1% of 390 reads
TET2 NM_001127208 c.4132T>C p.C1378R - in 82.3% of 368 reads

Read count analysis shows no significant copy number alteration in the regions
tested.

FLT3-ITD is not detected.

Case Presentation – AdvSM #2

- 46-year-old woman who presented in 2006 with chronic diarrhea, weight loss, and abdominal distension
- Labs: elevated tryptase of 774, with elevated histamine level of 4777
- CT scan showed diffuse LAN <2 cm, ascites, and hepatosplenomegaly
- EGD
  - Esophageal varices, gastric erythema, and a duodenal nodule
- Colonoscopy
  - Pan-colonic edema (cecum, ascending, transverse, and descending)
- Transjugular liver biopsy
  - Elevated hepatic pressure gradient
- Bone marrow
  - >30% of the cellularity mast cells

Gastrointestinal Symptoms of Mast Cell Disease*

Symptom	Presumed etiology
Abdominal pain	Altered gut motility-mediators
Diarrhea	Altered gut motility-mediators
Nausea	↑ H+ secretion, delayed stomach emptying
Vomiting	Delayed stomach emptying
Peptic Ulcer disease	Histamine induced H+ secretion
GI Bleeding	Histamine induced acid secretion, heparin
Weight loss, malnutrition	Mast cell infiltration

*May occur without involvement of other organs.

Back to Our Cases

Case #1

- Started **avapritinib** at 200 mg daily
- Ascites resolved; hepato-splenomegaly resolved
- Entered a CR with BM in remission from SM and tryptase level 6 (nL, <11.5)
- His AHN transformed to AML; SM was still in remission
  - Started AML-directed therapy

Case #2

- Was on TPN
- Started **midostaurin** at 100 mg twice daily and completed 12 years
- Weaned off TPN after 3 months on midostaurin; GI symptoms resolved
- SM progressed on midostaurin to mast cell leukemia
- Transitioned to **avapritinib** at 200 mg daily; remains in remission now 5+ years on therapy

TPN = total parenteral nutrition.

Thank You!

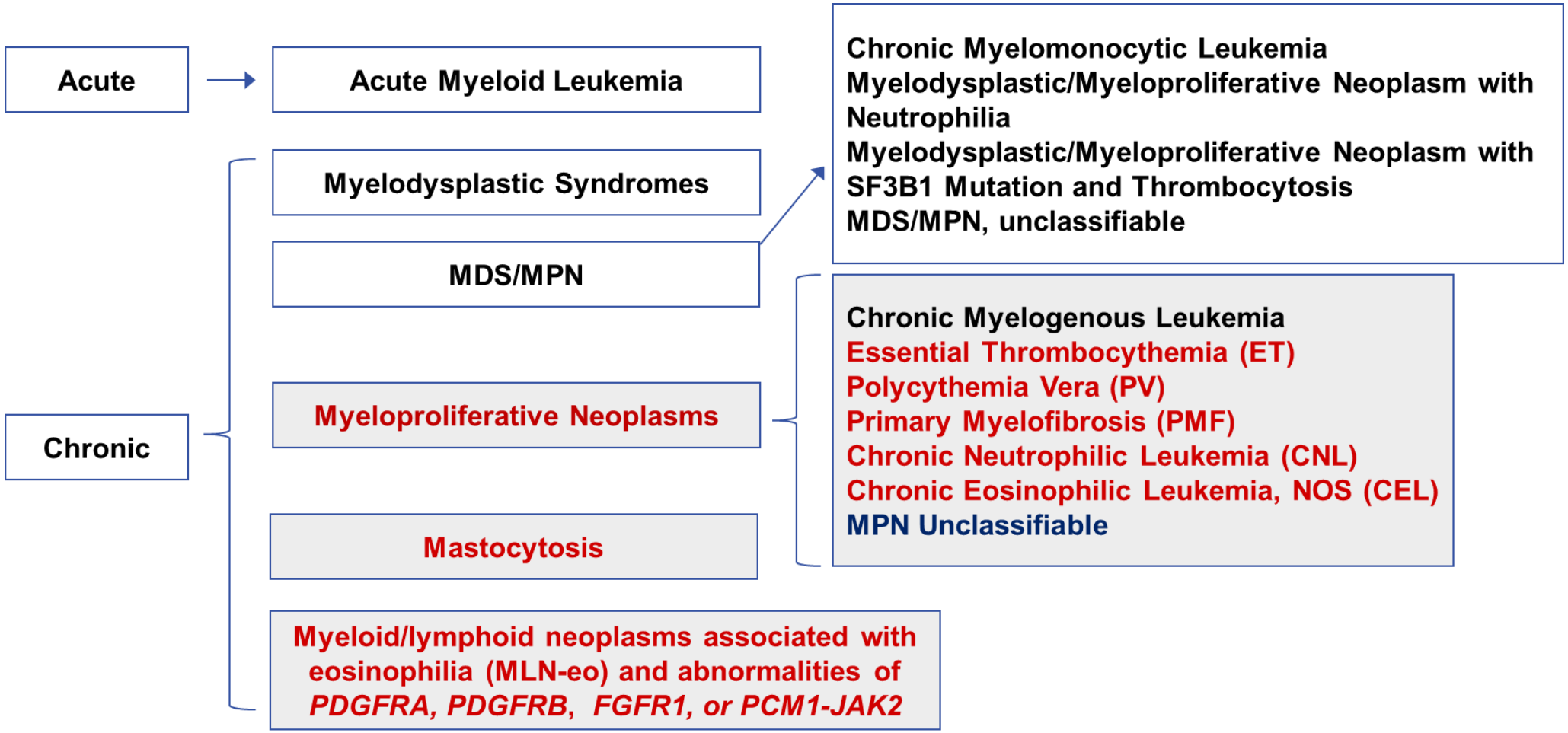
Submit Your Questions and Post-Event Surveys

- Scan the QR Code to submit your questions
- Scan the QR Code to complete the Post-Event Surveys and be entered to win a $100 Amazon Gift Card!

Myeloproliferative Neoplasms

Raajit Rampal, MD, PhD, and John Mascarenhas, MD, PhD

2022 Revised WHO Classification Scheme for Myeloid Neoplasms



Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719. Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Classic MPNs: An Overview of Disease Features

Polycythemia Vera (PV)

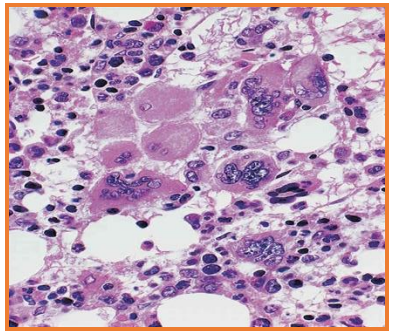
- Overproduction of red blood cells (erythrocytosis), often with increased white blood cells and platelets
- Patients may have splenomegaly and symptoms (pruritus, fatigue, shortness of breath, dizziness, headache, paresthesia, night sweats, blurred vision)
- Cardiovascular complications due to thrombosis (**main cause of death**) or hemorrhage
- Typical age at diagnosis: 60+ years old, with median survival of 15-20 years
- Potential for progression to MF (20-25%) or AML (5-10%)

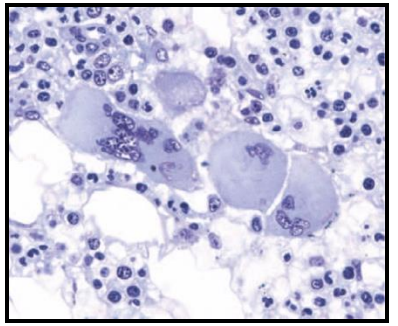
Essential Thrombocythemia (ET)

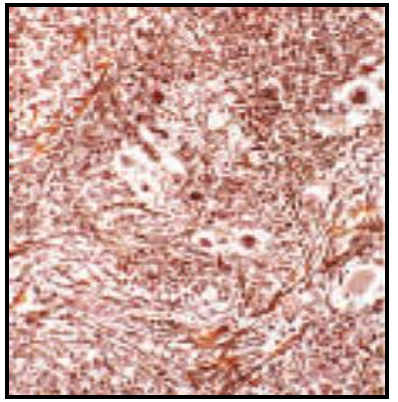
- Overproduction of platelets
- Similar to PV but less clinically problematic; normal life expectancy (20+ years)
- Potential for progression to PV (5%), MF (10-15%) or AML (2-5%)

Myelofibrosis (MF): Prefibrotic and Overt Fibrotic

- Variable clinical features (ie, cytopenias, splenomegaly, constitutional symptoms)
- Typical age at diagnosis: 60+ years old; may significantly reduce life expectancy
- Arises de novo (primary MF) or following PV or ET (post-PV MF or post-ET MF)
- Potential for progression to AML (20-25%)



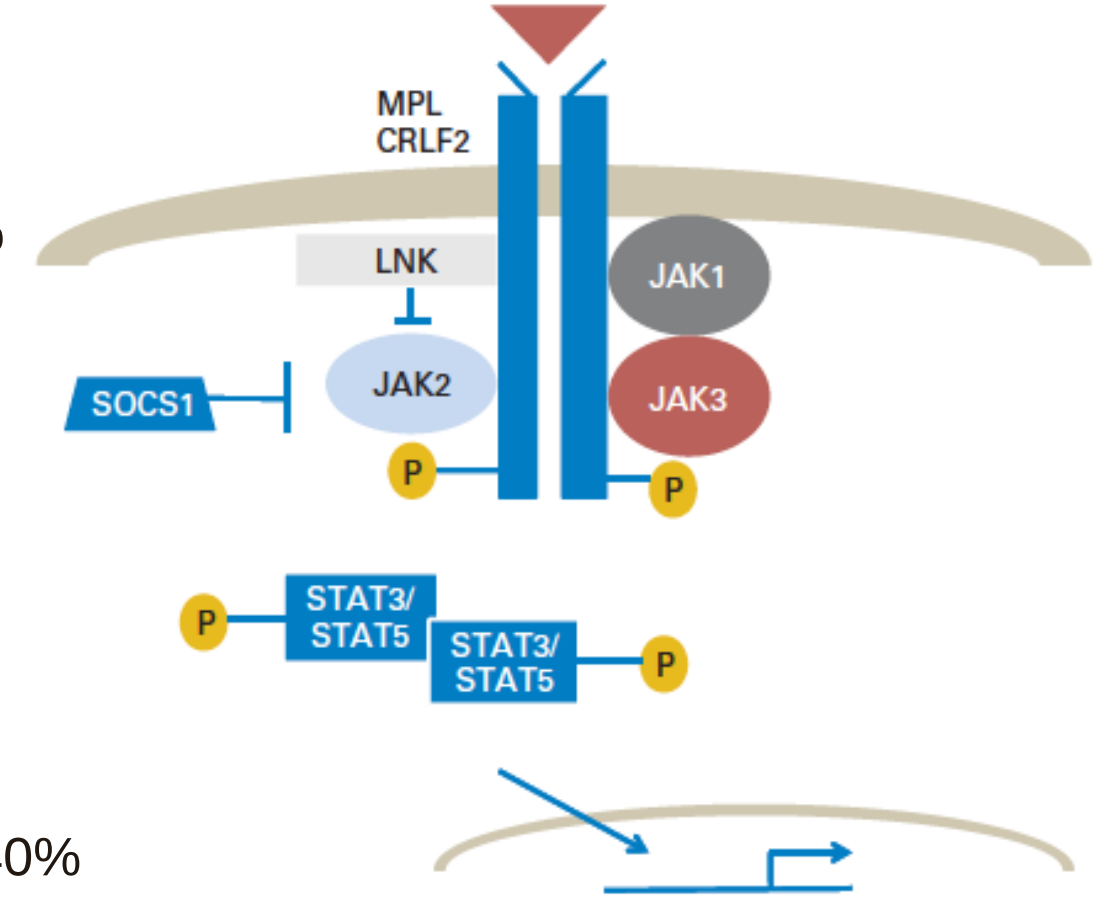




Spivak JL. *N Engl J Med*. 2017;376(22):2168-2181. Rumi E, et al. *Blood*. 2017;129(6):680-692. Verstovsek S, et al. *The MD Anderson Manual of Medical Oncology.* 3rd Edition. McGraw-Hill Education; 2016.

JAK-STAT Activation Is the Hallmark of MPNs

LNK
- ET/MF: <5%



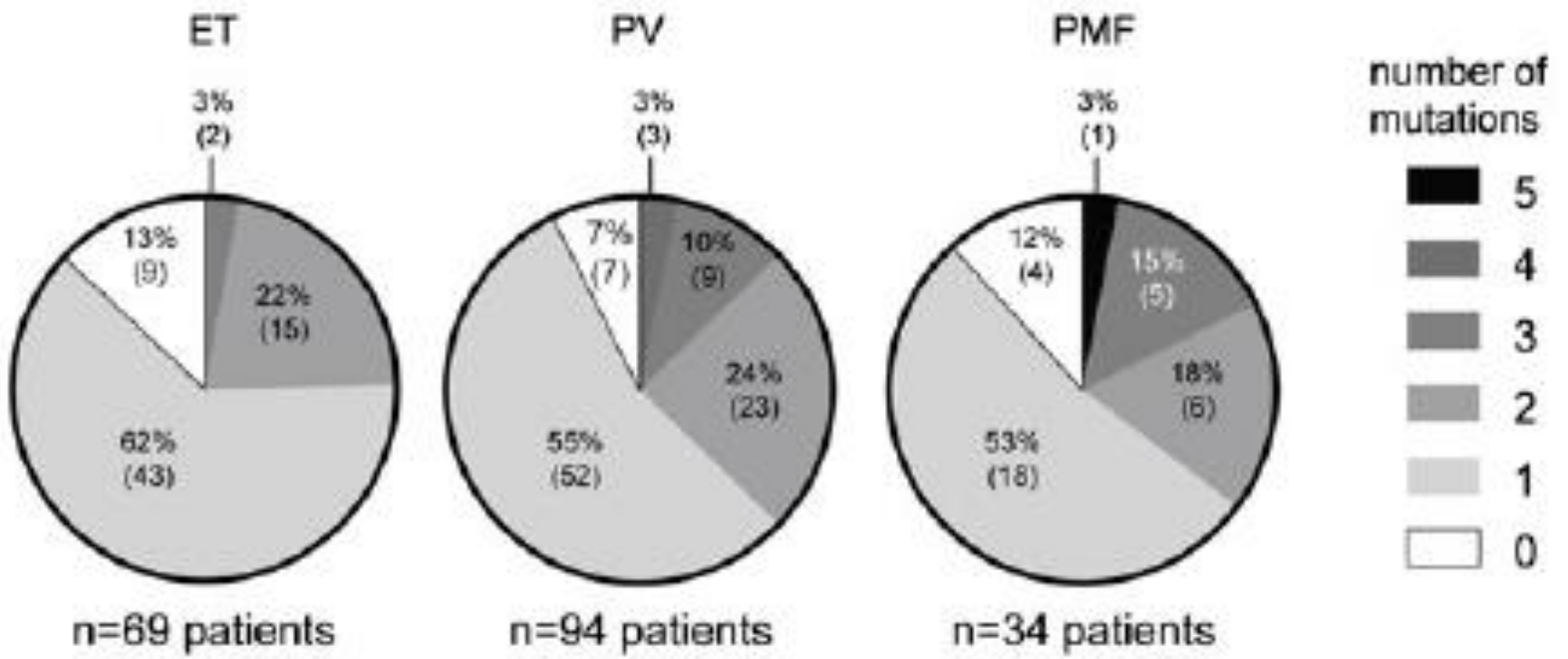
CALR
- ET/MF: 30-40%

MPL
- ET/MF: 10%

JAK2
- **PV: 96%**
- ET: 45-50%
- MF: 45-50%

Rampal R, et al. *J Clin Oncol.* 2013;31(15):1885-1892.

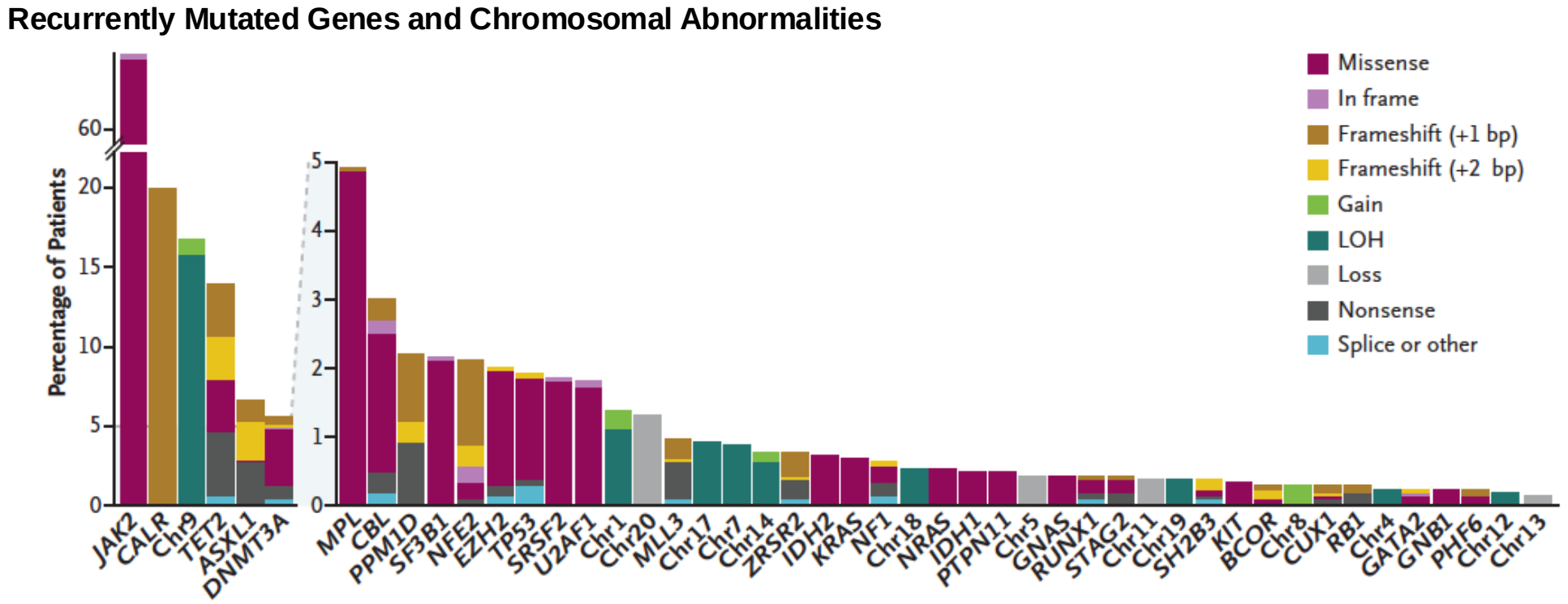
Additional Genetic Events Occur in MPNs



PMF = primary myelofibrosis.

Lundberg P, et al. *Blood*. 2014;123(14):2220-2228.

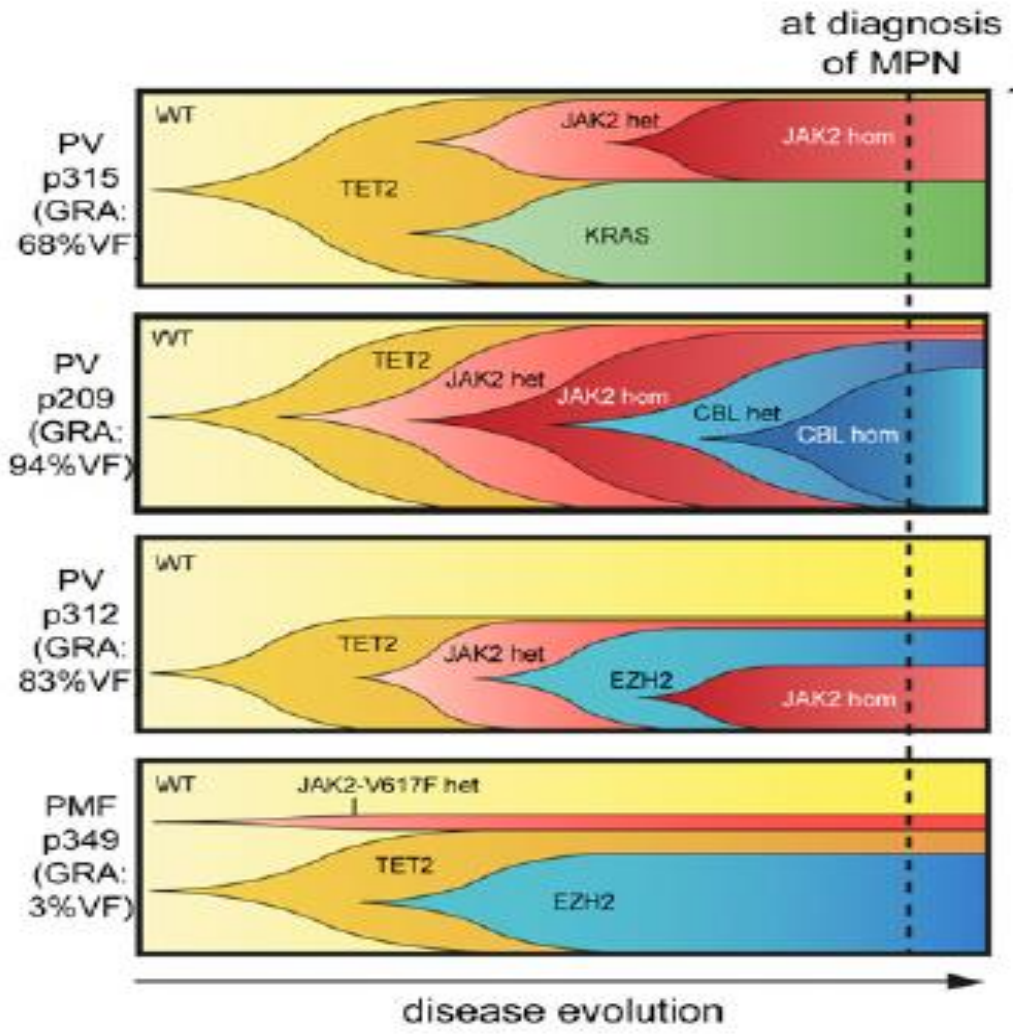
The Mutation Profile of Chronic-Phase MPNs



bp = base pair; LOH = loss of heterozygosity.

Grinfeld J, et al. *N Engl J Med*. 2018;379(15):1416-1430.

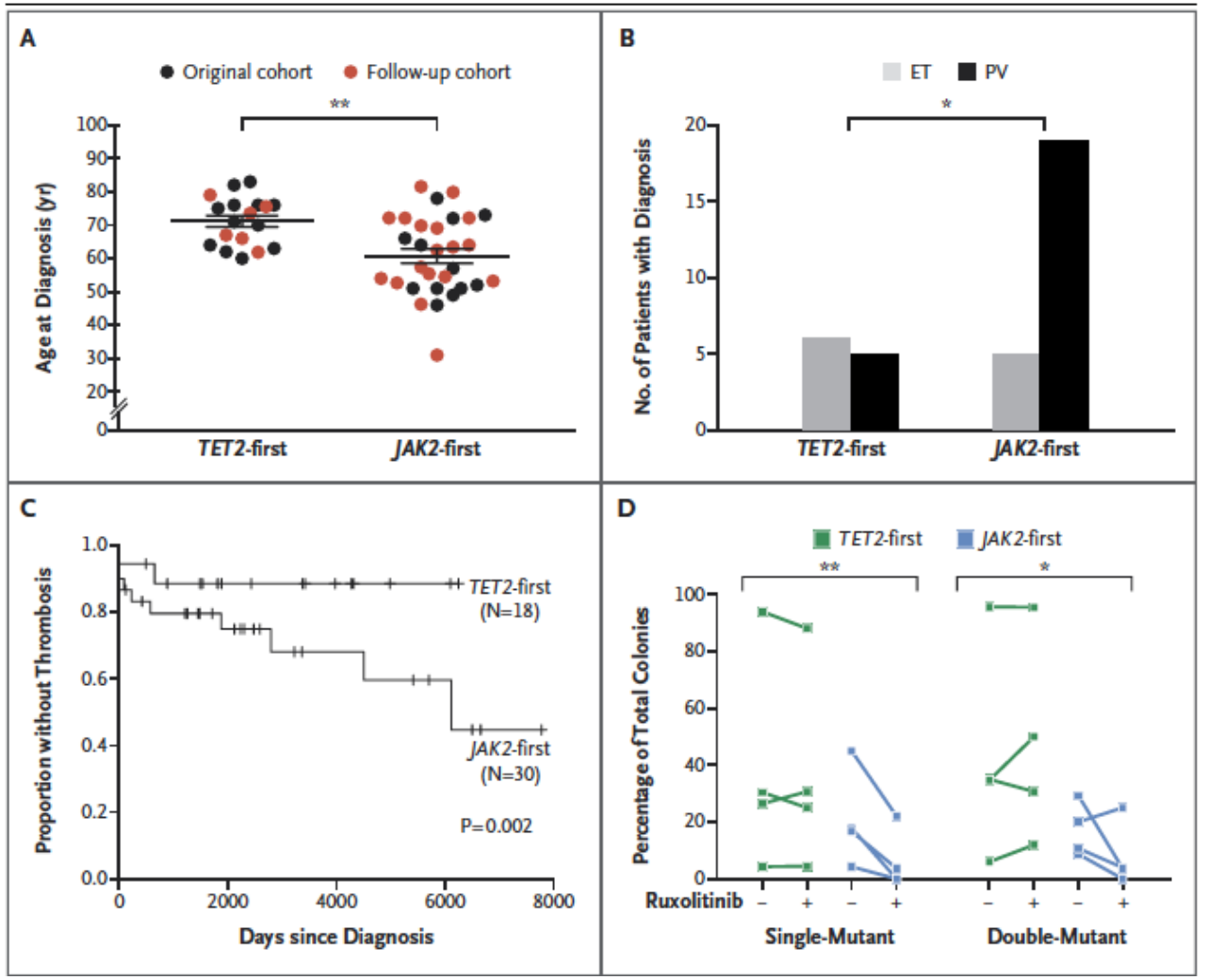
Mutations May Evolve Over Time



GRA = granulocyte; %VF = JAK2-V617F mutant allele burden in purified granulocytes from peripheral blood.

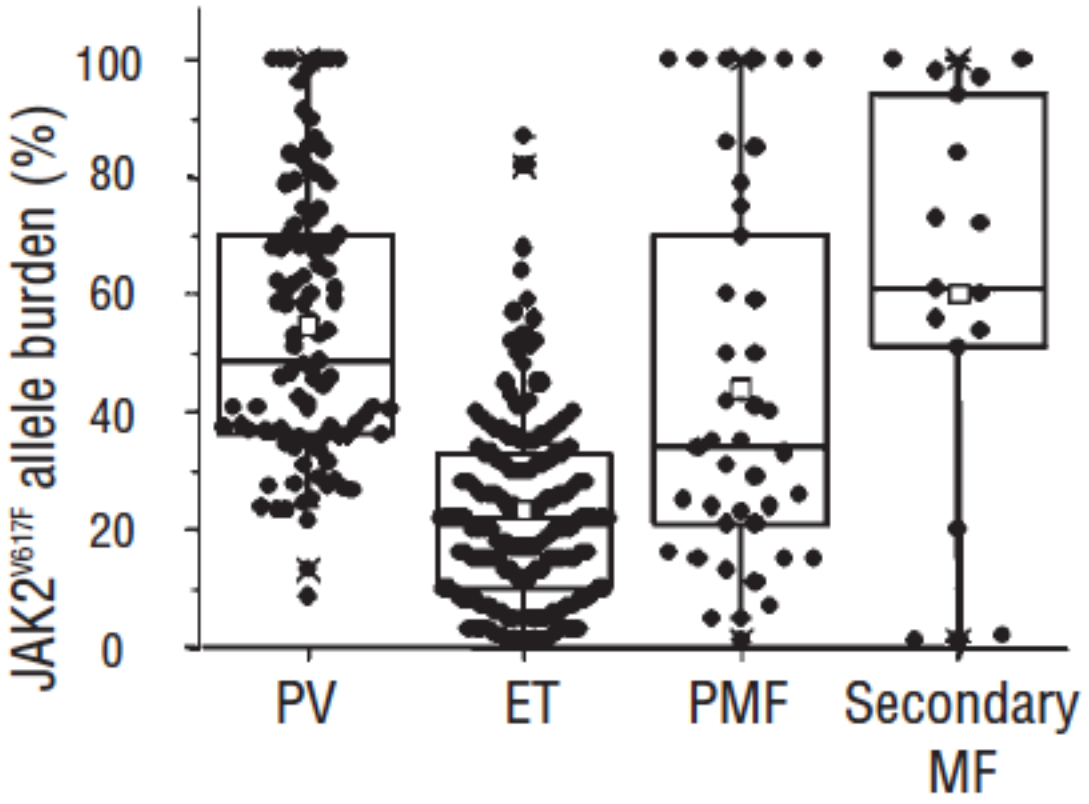
Lundberg P, et al. *Blood*. 2014;123(14):2220-2228.

Mutation Order May Impact Clinical Phenotype



Ortmann CA, et al. *N Engl J Med*. 2015;372(7):601-612.

MPN Disease Phenotype and *JAK2* V617F VAF



Antonioli E, et al. *Haematologica*. 2008;93(1):41-48.

Polycythemia Vera

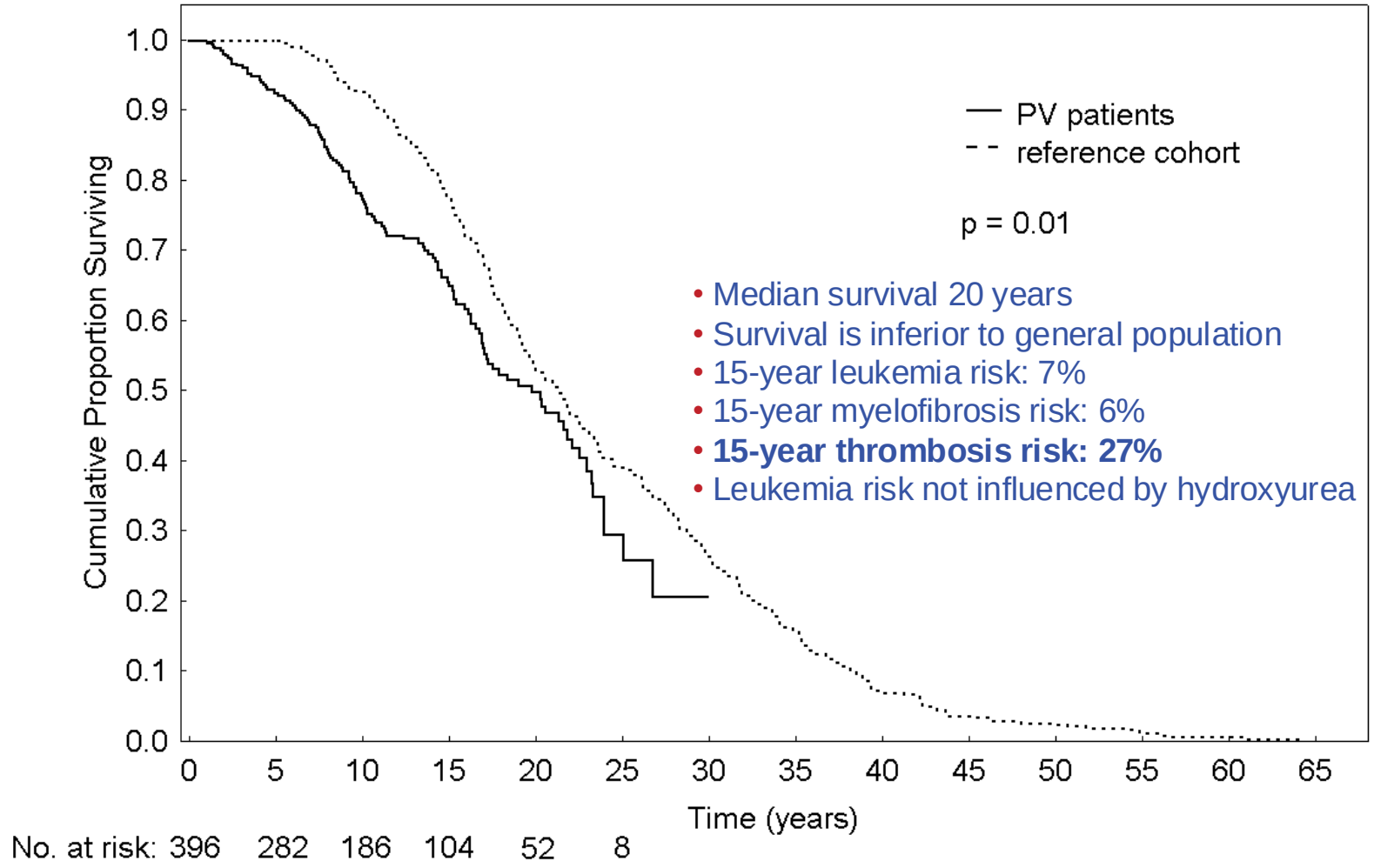
Evolution of WHO PV Diagnostic Criteria

2008 WHO	2016 WHO
Requirement for diagnosis	
• 2 major and 1 minor criteria OR 1 major and 2 minor criteria	• All 3 major criteria OR first 2 major criteria and the minor criterion
Major criteria	
1. Hb >18.5 g/dL (men); >16.5 g/dL (women) 2. *JAK2* V617F mutation or similar (*JAK2* exon 12)	1. Hb >16.5 g/dL or HCT >49% (men); or Hb >16.0 g/dL or HCT >48% (women); or increased red cell mass 2. BM biopsy showing hypercellularity, trilineage growth (panmyelosis) with erythroid, granulocytic, and pleomorphic, mature megakaryocytic proliferation 3. *JAK2* V617F or *JAK2* exon 12 mutation
Minor criteria	
1. Subnormal serum EPO level 2. BM trilineage proliferation 3. Endogenous erythroid colony growth	1. Subnormal serum EPO level

HCT = hematocrit; EPO = erythropoietin.

Thiele J, et al. *Curr Hematol Malig Rep*. 2009;4:33-40. Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Modern Natural History of PV



Passamonti F, et al. *Am J Med*. 2004;117(10):755-761.

Therapy and Goals in PV

- Goals of therapy
  - Reduce symptoms burden
  - Decrease risk of thrombotic events
- Therapeutic modalities
  - Therapeutic phlebotomy
  - Cytoreductive therapies: hydroxycarbamide (HU), interferon
  - JAK inhibitors: ruxolitinib
  - Antithrombotic modalities: aspirin, lifestyle modification

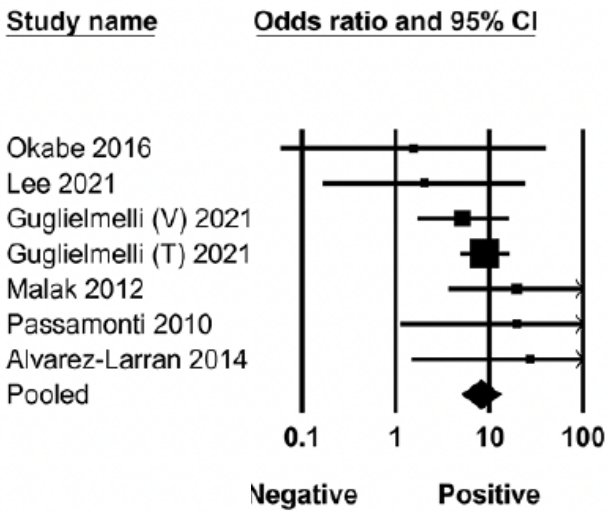
Stratification for Thrombohemorrhagic Complications in ET and PV

	Low-risk	**Age <60 years *and* No history of thrombosis *and* Platelet count <1.5 million *and* No cardiovascular risk factors**	**Thrombosis risk is not significantly increased compared to controls**
	High-risk	**Age ≥60 years *or* Previous thrombosis**	**Thrombosis risk is significantly increased**
	Indeterminate risk	**Neither low nor high risk**	**Thrombosis risk is not well studied**

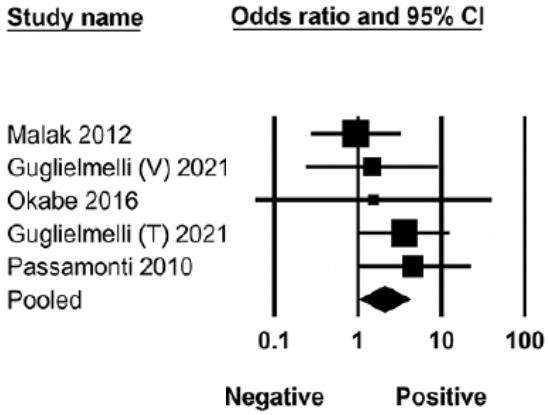
Finazzi G, et al. *Leukemia*. 2008;22(8):1494-1502.

Higher JAK2 VAF in PV Is Linked to Disease Progression

Myelofibrosis
n=1522, OR ~8

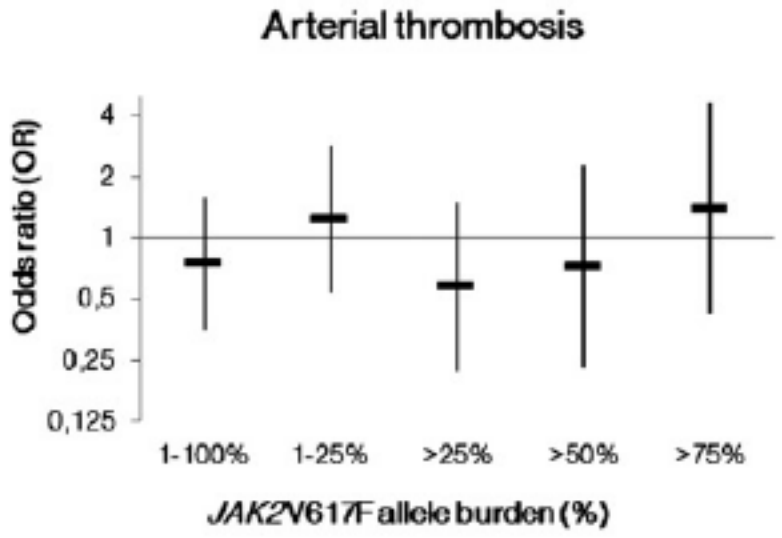


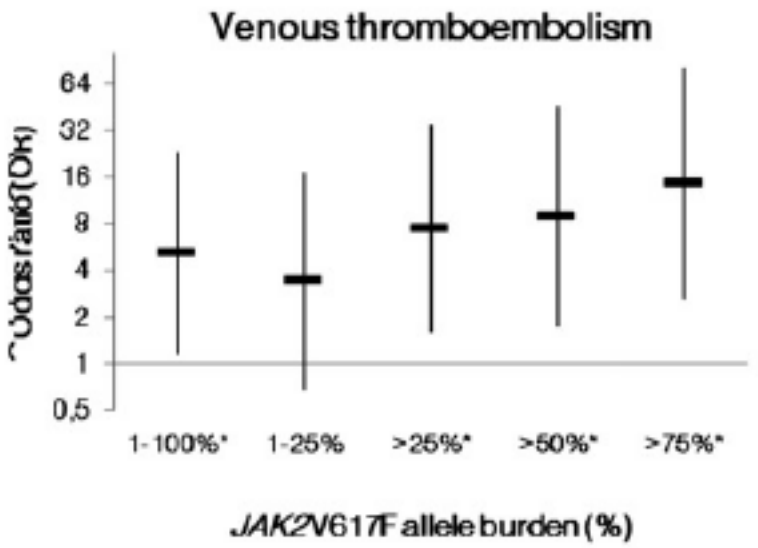
AML
n=1318, OR ~2

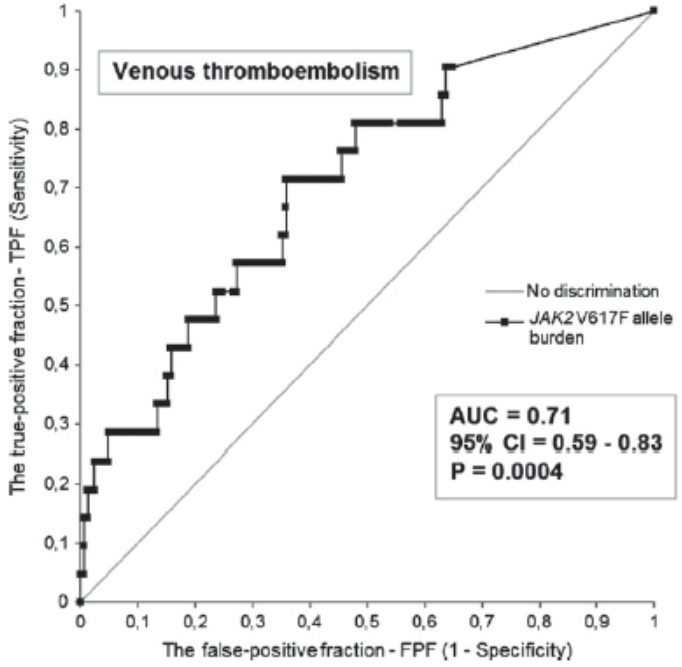


OR = odds ratio; CI = confidence interval.
Chen CC, et al. *Ann Hematol*. 2024;103(6):1947-1965.

Association of *JAK2* V617F Allele Burden and Thrombosis Risk







AUC = area under the curve.

Borowczyk M, et al. *Thromb Res.* 2015;135(2):272-280.

Thrombosis in PV: Contribution of WBC

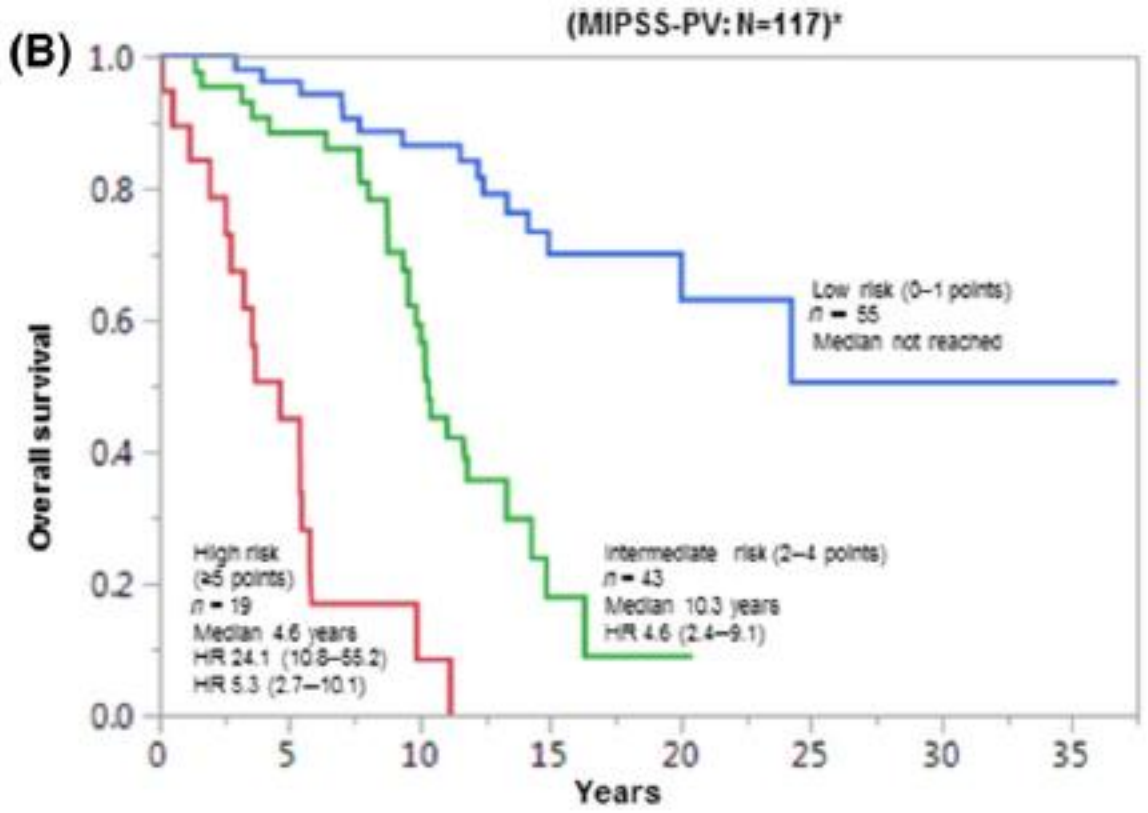
Table 3. Multivariate analysis using patients' characteristics at baseline on the relative risk of major thrombosis, arterial thrombosis, venous thrombosis, myocardial infarction, stroke plus TIA, and peripheral arterial thrombosis among men and women with polycythemia vera; n = 1638

	No. patients	10.1 to 15.0 × 10^9/L white blood cells*†		More than 15.0 × 10^9/L white blood cells*‡	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Major thrombosis	169	1.05 (0.69-1.61)	.811	1.24 (0.78-1.96)	.370
Arterial thrombosis	121	1.07 (0.65-1.76)	.802	1.21 (0.69-2.11)	.508
Venous thrombosis	51	1.02 (0.47-2.21)	.963	1.28 (0.56-2.92)	.554
Myocardial infarction	41	0.82 (0.31-2.16)	.683	2.27 (1.00-5.15)	.049
Stroke/TIA	54	1.32 (0.64-2.70)	.450	0.69 (0.26-1.86)	.464
Peripheral arterial thrombosis	21	1.44 (0.44-4.74)	.549	1.12 (0.21-6.02)	.892

Multivariable model adjusted for information colleted at baseline, including white blood cells (3 categories), age (2 categories), sex, time from PV diagnosis to recruitment (2 categories), thrombotic or hemorrhagic events prior to recruitment (yes/no), smoking (yes/no), history of diabetes (yes/no), hypertension (yes/no), intermittent claudication (yes/no), erythromelalgia (yes/no), splenomegaly (yes/no), circulating immature cells (yes/no), hematocrit (tertiles), platelet count (tertiles), total blood cholesterol (2 categories), phlebotomy use (yes/no), interferon use (yes/no), hydroxyurea use (yes/no), antiplatelet use (yes/no), anticoagulant use (yes/no), ^{32}P use (yes/no), busulfan use (yes/no), chlorambucil use (yes/no), and pipobroman use (yes/no).

***Reference category: ≤10.0 x 10^9/L (n=990 [62.0%]); †n=365 (22.9%); ‡n=241 (15.1%).**
Landolfi R, et al. *Blood*. 2007;109(6):2446-2452.

SRSF2 Mutations in Polycythemia Vera (MIPSS-PV)



- *SRSF2* mutation
- Abnormal karyotype
- Age >67 years old
- Leukocyte count ≥15 x10^9/L

Tefferi A, et al. *Br J Haematol*. 2020;189(2):291-302.

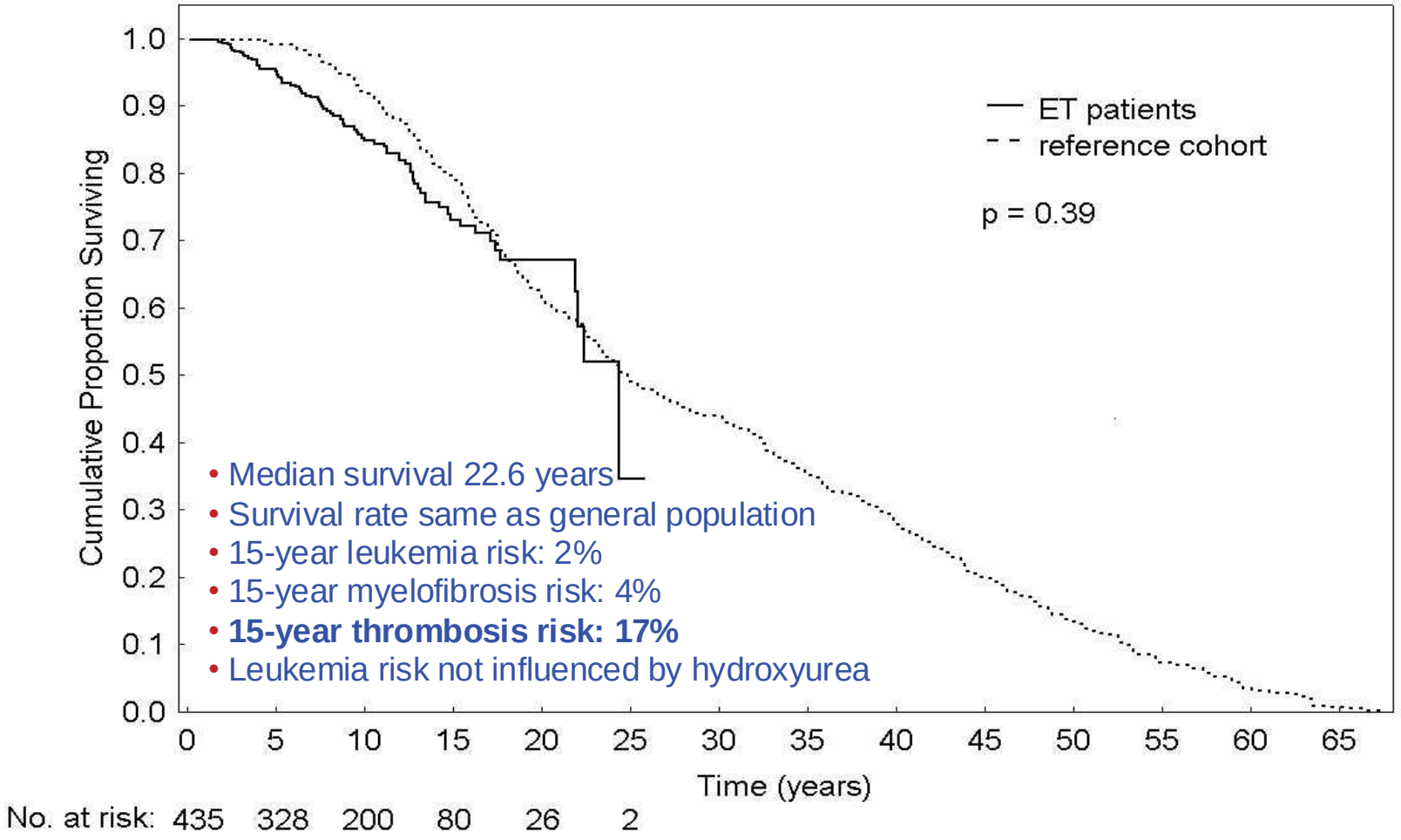
Essential Thrombocythemia

WHO 2016 Criteria for ET

WHO ET criteria
Major criteria
1. Platelet count ≥450 × 10^9/L
2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4. Presence of *JAK2*, *CALR*, or *MPL* mutation
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis
Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Modern Natural History of ET



Passamonti F, et al. *Am J Med*. 2004;117(10):755-761.

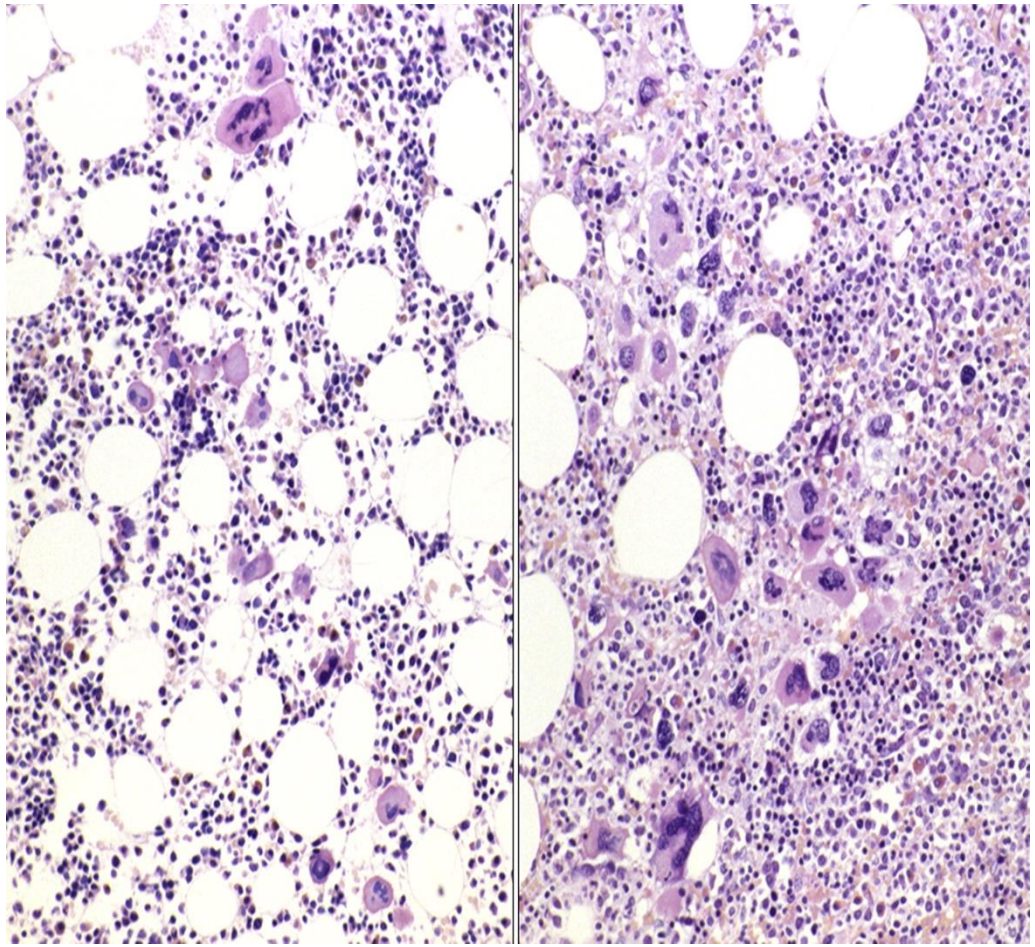
Essential Thrombocythemia vs Prefibrotic MF: Diagnosis

Parameter	ET	Prefibrotic MF
Blood counts	Sustained thrombocytosis (≥450 x 10^9/L)	Sustained thrombocytosis plus ≥1 of: **anemia, leukocytosis >11 x 10^9/L, palpable splenomegaly, or ↑LDH**
Bone marrow	**↑enlarged, mature megakaryocytes with hyperlobulated nuclei**	**Atypical megakaryocyte proliferation with no reticulin fibrosis >grade 1; ↑BM cellularity, granulocytic proliferation, and often ↓erythropoiesis**
Mutations	*JAK2, CALR, MPL* (~90%) or another clonal marker	*JAK2, CALR, MPL* (~90%) or another clonal marker
Overt MF at 15 yrs, %	**9.3**	**16.9**
Cumulative AML at 15 yrs, %	**2.1**	**11.7**
15-yr survival, %	**80**	**59**

Barbui T, et al. *J Clin Oncol*. 2011;29(23):3179-3184. Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Essential Thrombocythemia vs Prefibrotic MF: Histopathology

Essential Thrombocytosis



Prefibrotic MF

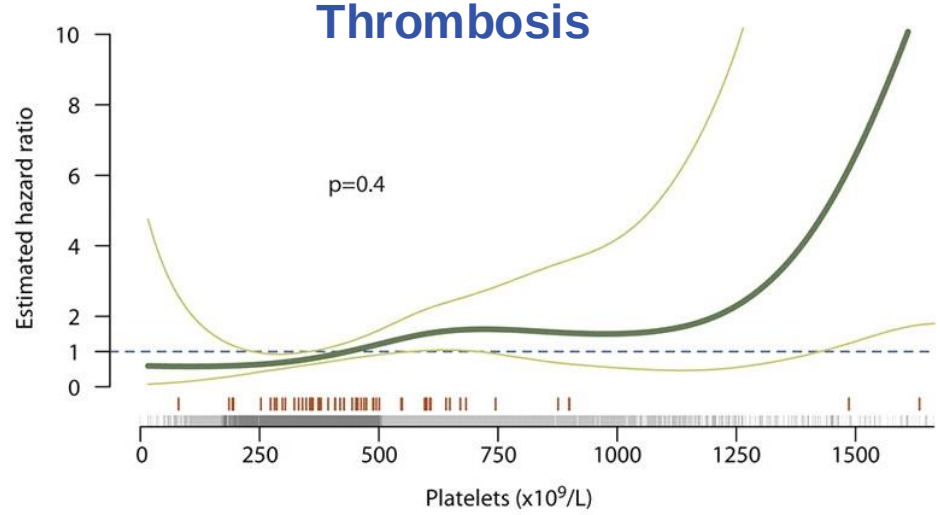
Barosi G. *Best Pract Res Clin Haematol*. 2014;27(2):129-140.

Therapy and Goals in PV and ET

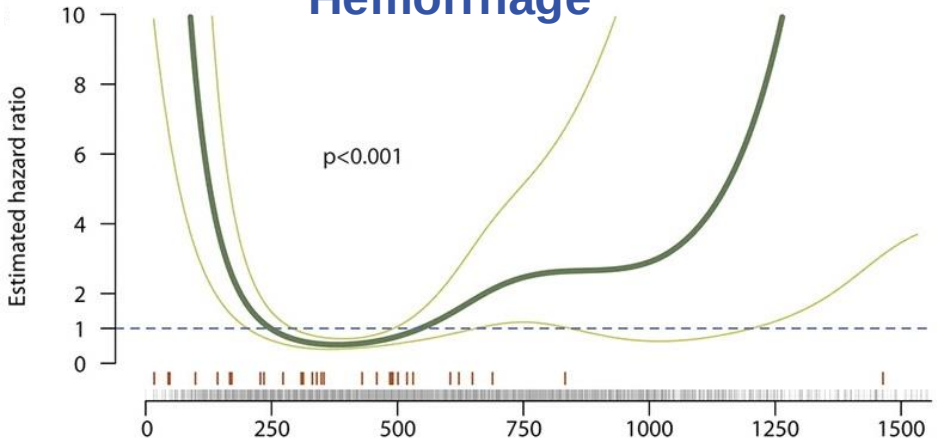
- Goals of therapy
  - Reduce symptoms burden
  - Decrease risk of thrombotic events
- Therapeutic modalities
  - Therapeutic phlebotomy (PV)
  - Cytoreductive therapies: hydroxyurea, interferon, **anagrelide (ET)**
  - JAK inhibitors: ruxolitinib
  - Antithrombotic modalities: aspirin, lifestyle modification

Platelet Count Is NOT a Risk Factor for Thrombosis

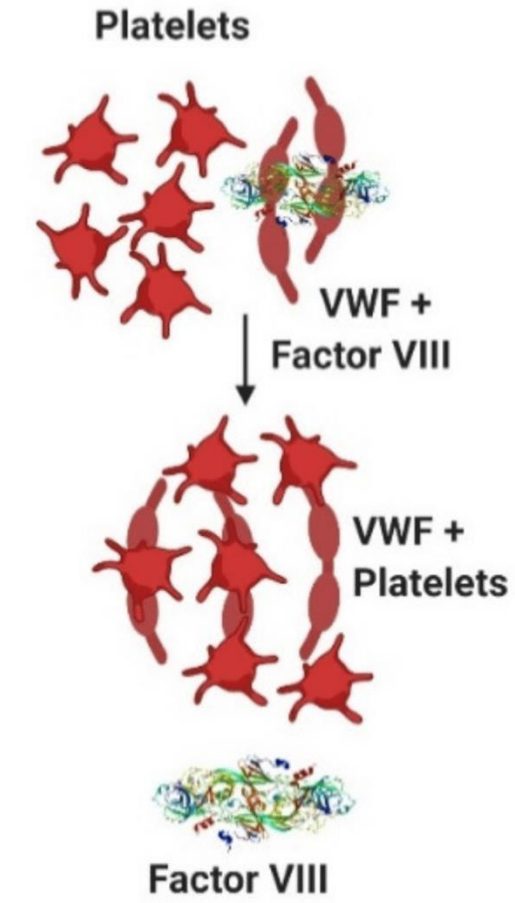
Thrombosis



Hemorrhage



Acquired von Willebrand disease

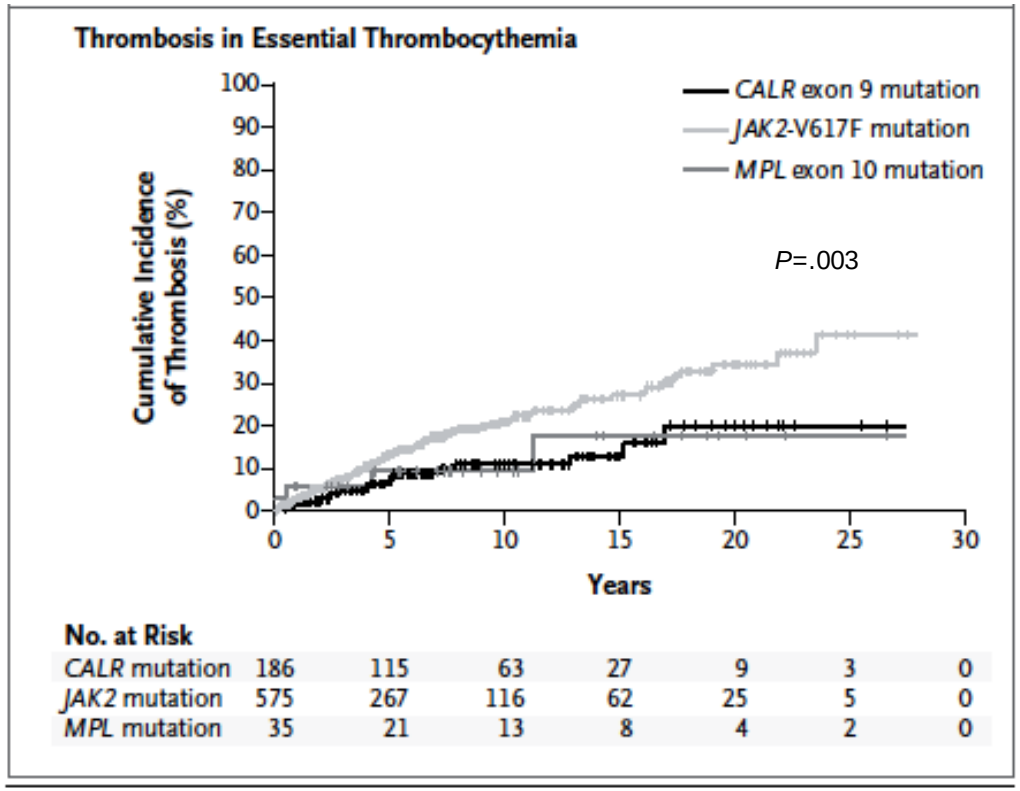


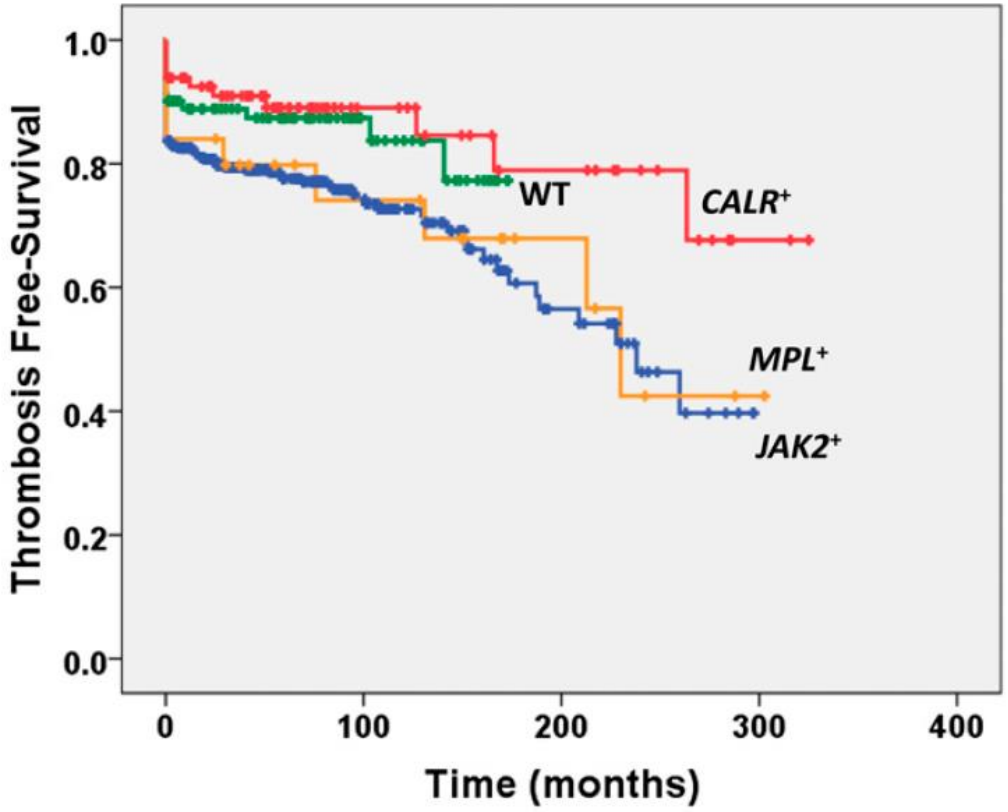
↓VWF:Rco/VWF:Ag
Loss of HMW multimers

VWF = von Willebrand factor; Rco = ristocetin cofactor; Ag = VWF antigen; HMW = high molecular weight.

Campbell PJ, et al. *Blood.* 2012;120(7):1409-11. Awada H, et al. *Cancers (Basel).* 2020;12(7):1746.

Influence of Genetic Alterations on Thrombosis Risk





WT = wild-type.

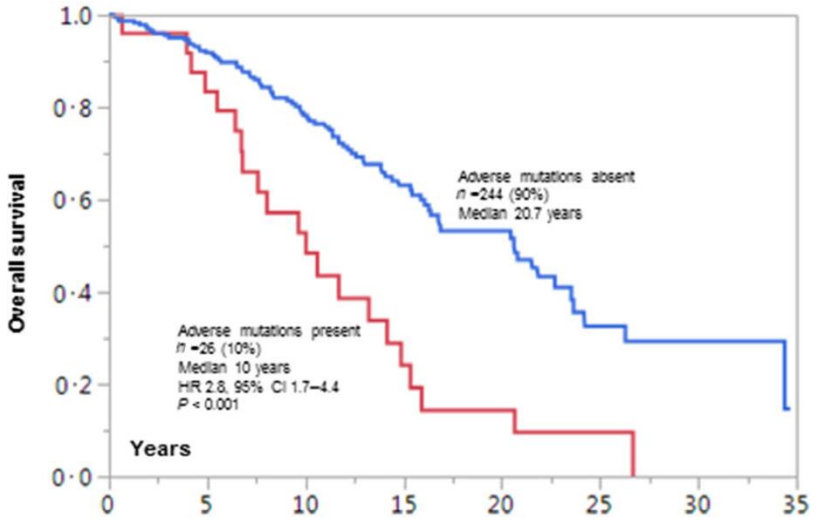
Klampfl T, et al. *N Engl J Med*. 2013;369(25):2379-2390. Rotunno G, et al. *Blood*. 2014;123(10):1552-1555.

Clinical Decision Making

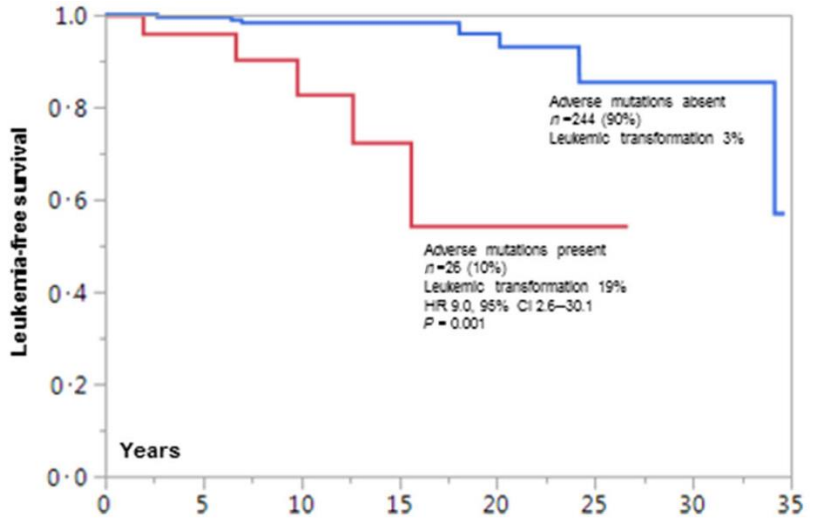
	Revised IPSET-Thrombosis
Very low risk	No prior thrombosis history and Age <61 years old and Negativity for the *JAK2* V617F mutation
Low risk	No prior thrombosis history and Age <61 years old and Positivity for the *JAK2* V617F mutation
Intermediate risk	No prior thrombosis history and Age >60 years old and Negativity for the *JAK2* V617F mutation
High risk	Prior history of thrombosis or Age >60 years old and Positivity for the *JAK2* V617F mutation

Prognostication – Disease Progression in ET

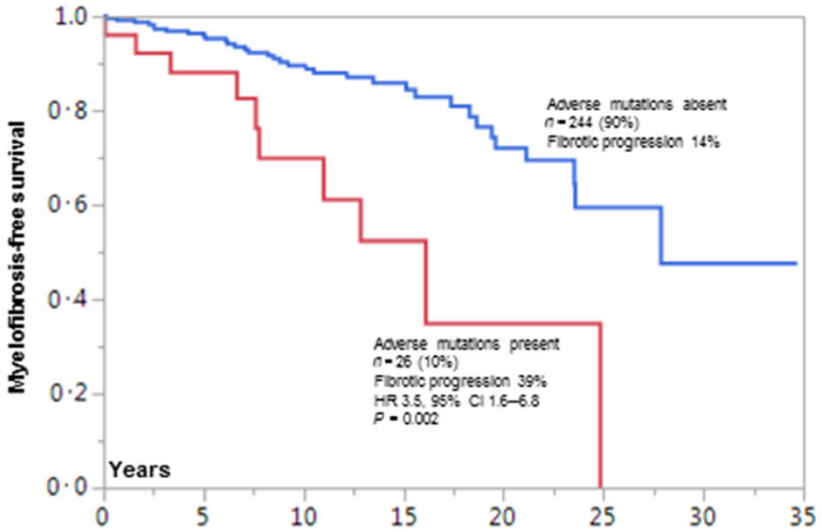
OS



LFS



MF



- *SRSF2* mutation
- *SF3B1* mutation
- *U2AF1* mutation
- *TP53* mutation

Tefferi A, et al. *Br J Haematol*. 2020;189(2):291-302.

Myelofibrosis

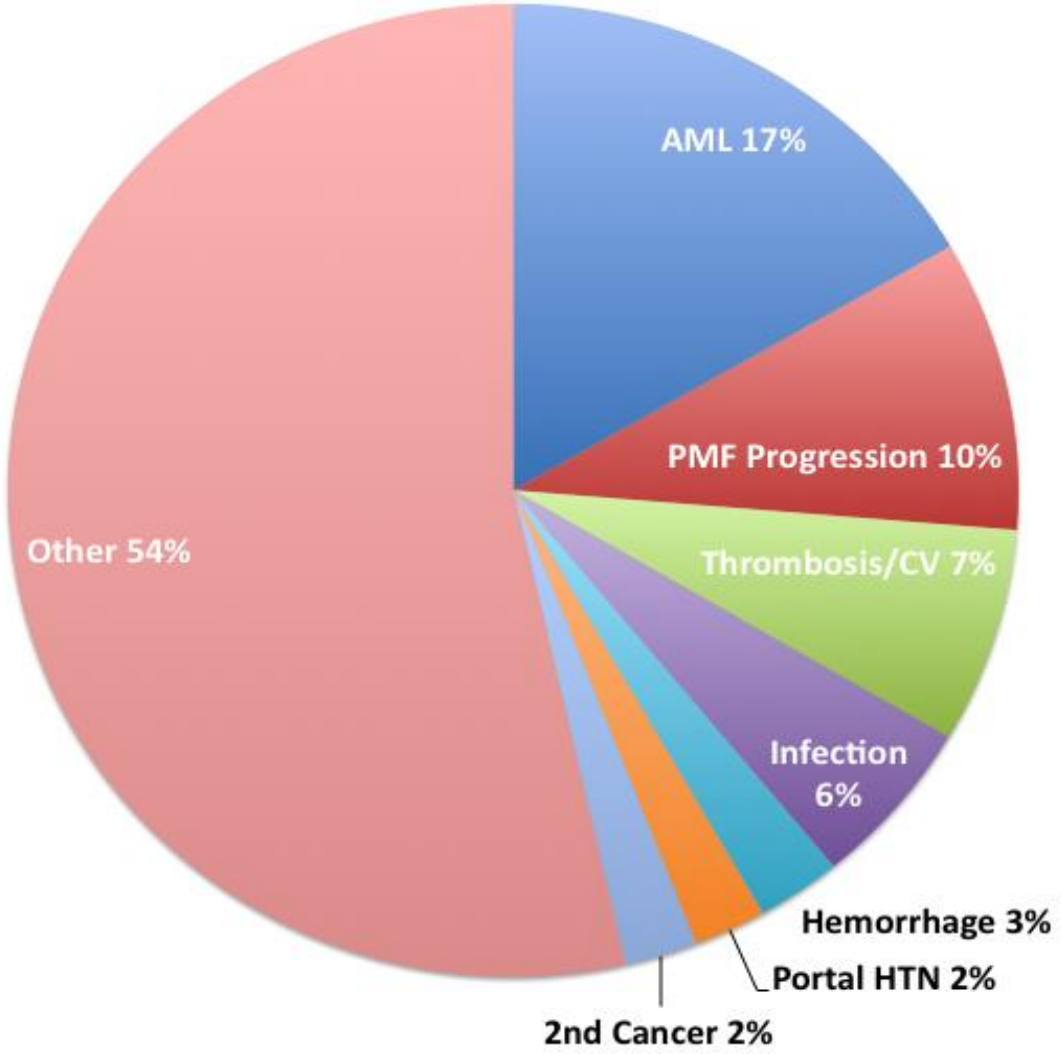
WHO Diagnostic Criteria: MF

Primary Overt MF Diagnosis	
Requirement for diagnosis	
• All 3 major criteria AND ≥1 minor criteria	
Major criteria	
1. Megakaryocytic proliferation and atypia **with reticulin and/or collagen fibrosis grade 2/3** 2. *JAK2, CALR*, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF 3. Not meeting WHO criteria for other myeloid malignancies	
Minor criteria	
1. Anemia not attributed to a comorbid condition 2. Leukocytosis ≥ 11 x 10^9/L	3. Palpable splenomegaly 4. LDH increased above ULN **5. Leukoerythroblastosis**

***eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1.**
ULN = upper limit of normal.
Arber DA, et al. *Blood*. 2016;127(20):2391-2405.

Mortality in PMF

- Median survival: 69 months (517/1001 died)



Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.

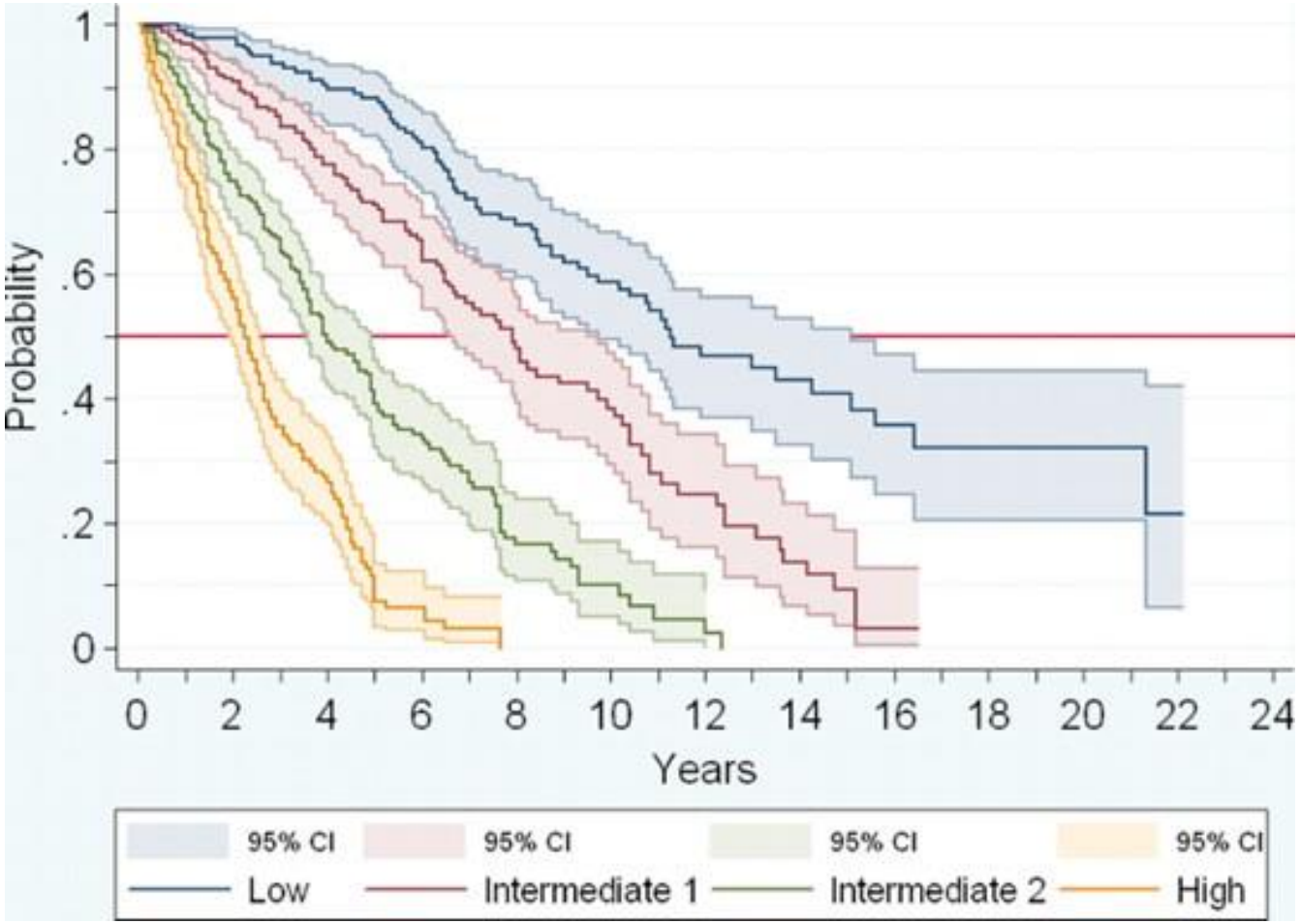
International Prognostic Scoring System (IPSS)

Prognostic Factors

- Age >65 years
- Constitutional symptoms
- Hb <10 g/dL
- Leukocytes >25 x 10^9/L
- Blood blasts ≥1%

Risk Groups

Low	0
Intermediate-1	1
Intermediate-2	2
High	≥3



Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.

Dynamic International Prognostic Scoring System (DIPSS): Survival by Risk Group

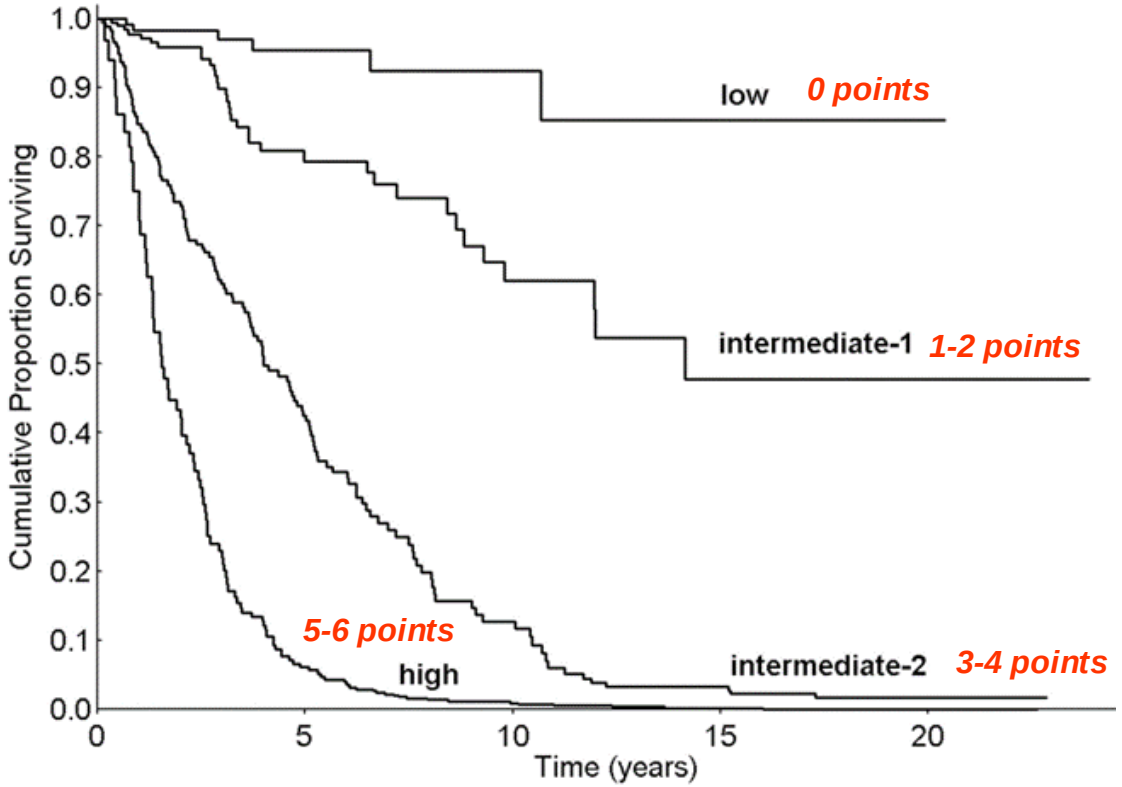


Table 3. DIPSS for survival in primary myelofibrosis

	Value		
Prognostic variable	**0**	**1**	**2**
Age, y	≤ 65	> 65	
White blood cell count, $\times 10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

The risk category is obtained adding up the values of each prognostic variable. Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

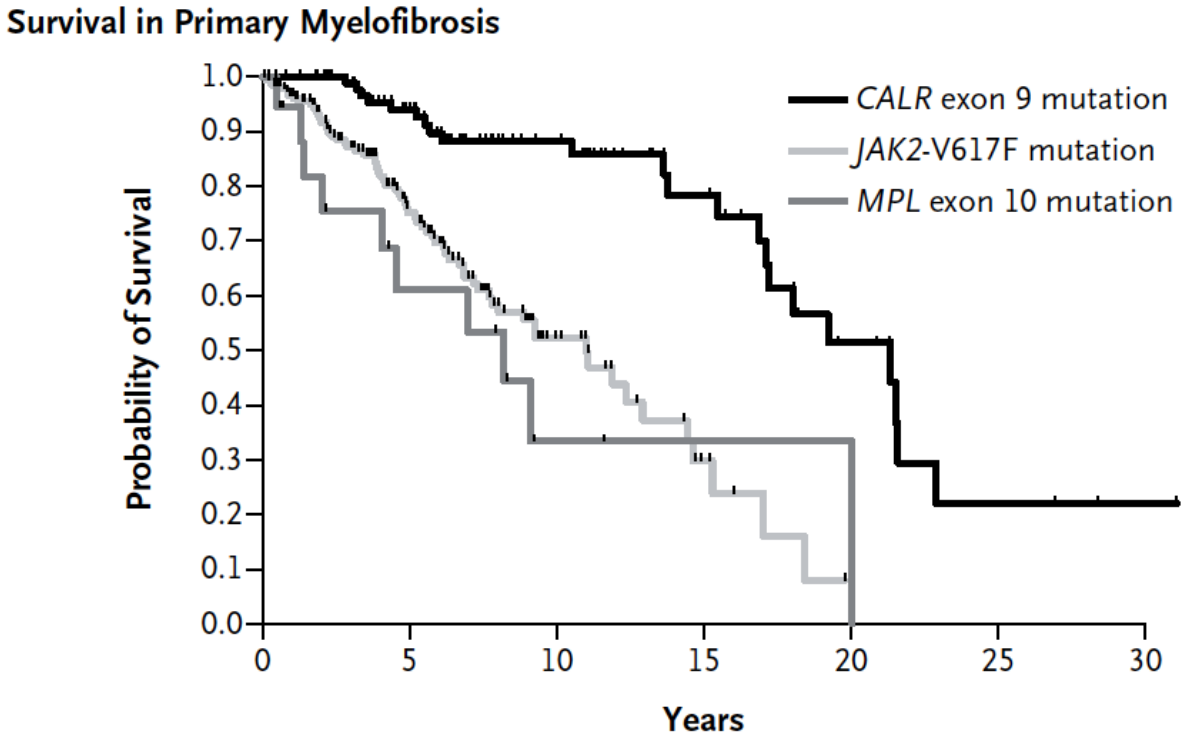
- Dynamic International Prognostic Scoring System-PLUS (DIPSS-PLUS) takes into account transfusion requirements, platelet count, and karyotype

Passamonti F, et al. *Blood*. 2010;115(9):1703-1708.

Gangat N, et al. *J Clin Oncol*. 2011;29(4):392-397.

Prognostication – Disease Progression in Myelofibrosis

Implications of *JAK2*, *MPL*, and *CALR* Mutations

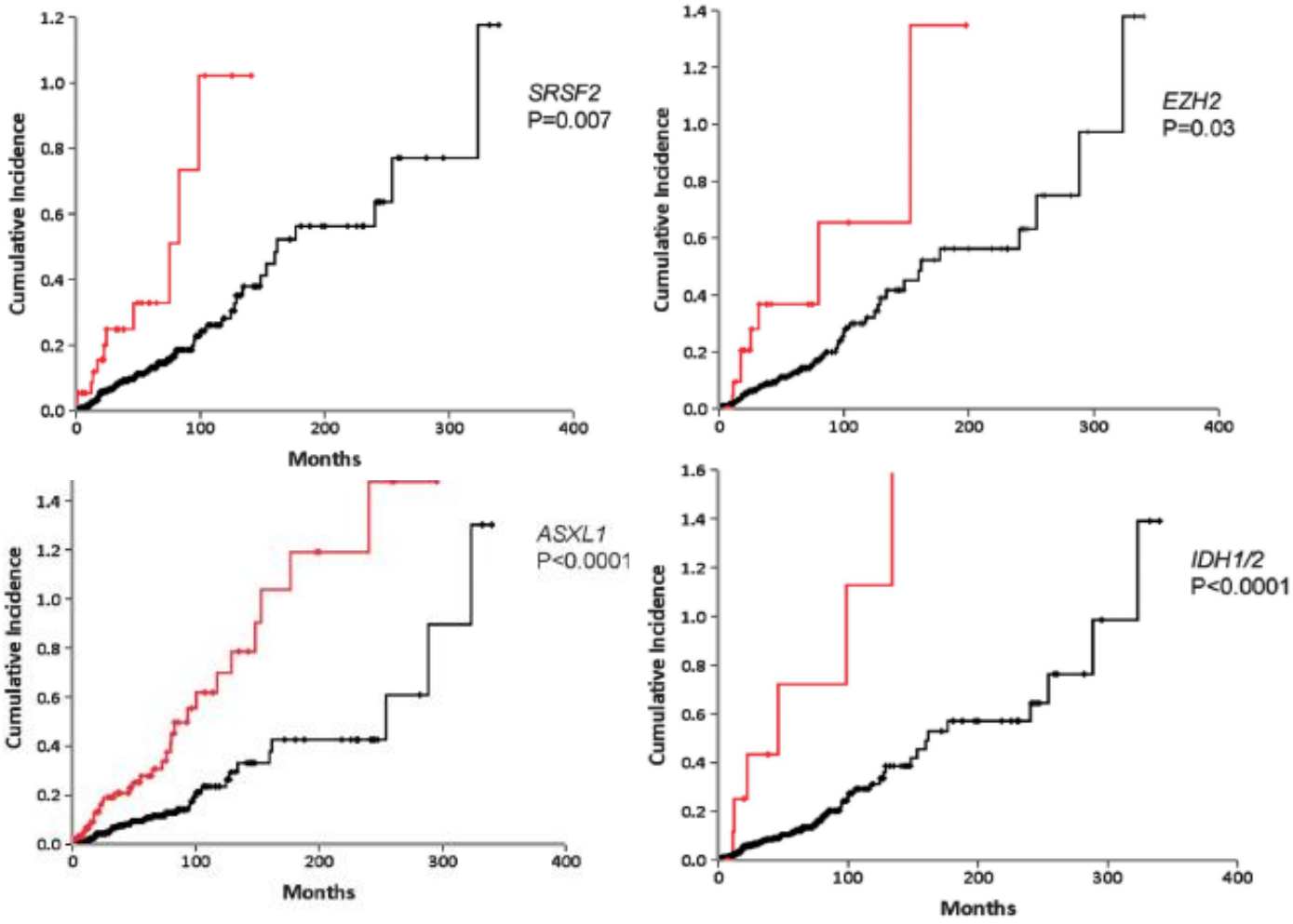


No. at Risk							
CALR mutation	98	69	38	21	9	3	1
JAK2 mutation	189	85	24	6	0	0	0
MPL mutation	18	8	2	1	1	0	0

Klampfl T, et al. *N Engl J Med*. 2013;369(25):2379-2390.

Prognostication – Disease Progression in Myelofibrosis

Genetic Risk Factors for Leukemic Transformation



Vannucchi AM, et al. *Leukemia.* 2013;27(9):1861-1869.

MIPSS70-Plus Risk Score

Variables Associated with Reduced OS

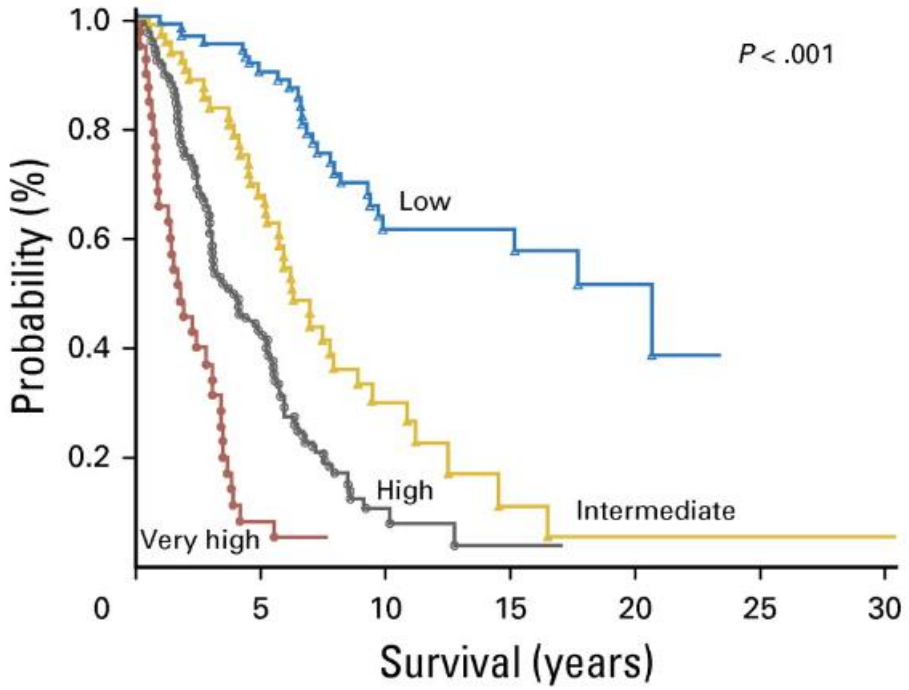
Variables	HR (95% CI)	P	Weighted Value
Hb <100g/L	1.5 (1.1-2.0)	.005	**1**
PB blasts ≥2%	1.6 (1.2-2.3)	.002	**1**
Constitutional Symptoms	1.9 (1.4-2.5)	<0.001	**1**
Absence CALR Type1	2.4 (1.7-3.5)	<.001	**2**
HMR*	1.8 (1.3-2.5)	<.001	**1**
≥2 HMR mutations	2.4 (1.4-4.0)	<0.001	**2**
Unfavorable karyotype**	3.1 (2.3-4.3)	<.001	**3**

***Any mutation in: *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*; **Any abnormal karyotype other than normal karyotype or sole abnormalities of 20q-, 13q-, +9, chr. 1 translocation/duplication, -Y, or sex chromosome abnormality other than -Y.**

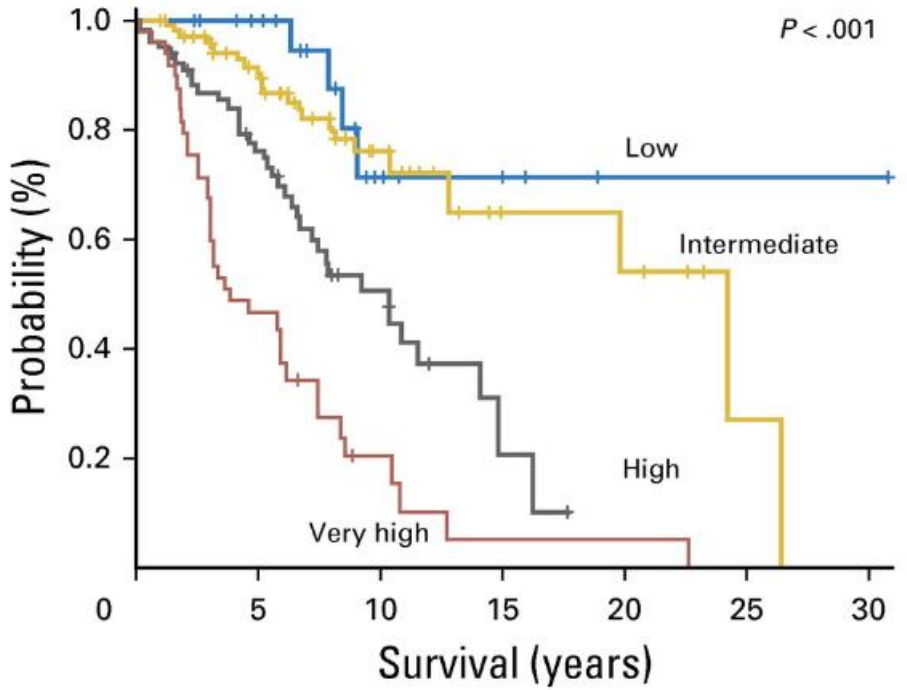
HR = hazard ratio; PB = peripheral blood; CALR = calreticulin; HMR = high molecular risk.

Guglielmelli P, et al. *J Clin Oncol*. 2018;36(4):310-318.

MIPSS70-Plus Risk Score



At risk time					
Low	86	67	28	17	4
Intermediate	63	38	10	12	1
High	127	43	4	1	0
Very high	39	3	0	0	0



At risk time					
Low	25	20	6	3	1
Intermediate	108	74	24	7	0
High	79	50	18	2	0
Very high	49	18	4	1	0

Guglielmelli P, et al. *J Clin Oncol*. 2018;36(4):310-318.

MIPSS70 Risk Score

MIPSS70 score Home Credits

#	Question	Answer
1	Anemia (hemoglobin <100g/L)	(•) Yes ( ) No
2	Leucocytosis >25x10^9/L	( ) Yes (•) No
3	Thrombocytopenia (platelet count <100x10^9/L)	( ) Yes (•) No
4	Peripheral blood blast count ≥2%	(•) Yes ( ) No
5	Bone marrow fibrosis grade ≥2	(•) Yes ( ) No
6	Constitutional symptoms	(•) Yes ( ) No
7	Absence of CALR type 1/like mutation	(•) Yes ( ) No
8	HMR* category	(•) Yes ( ) No
9	≥2 HMR mutated genes	(•) Yes ( ) No
10	Unfavorable karyotype**	(•) Yes ( ) No ( ) Not available

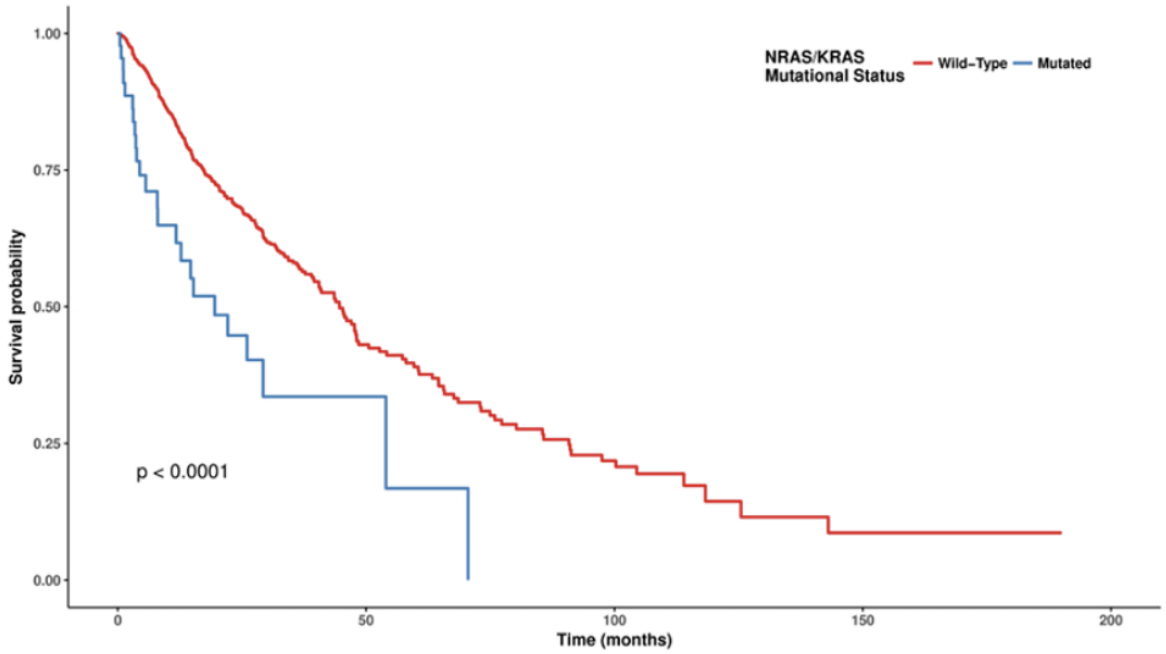
Score	Result
MIPSS70	HIGH RISK [5-year OS= 34%]
MIPSS70-plus	VERY HIGH RISK [5-year OS= 46%]

MIPSS70score. Accessed November 20, 2024. http://www.mipss70score.it/.

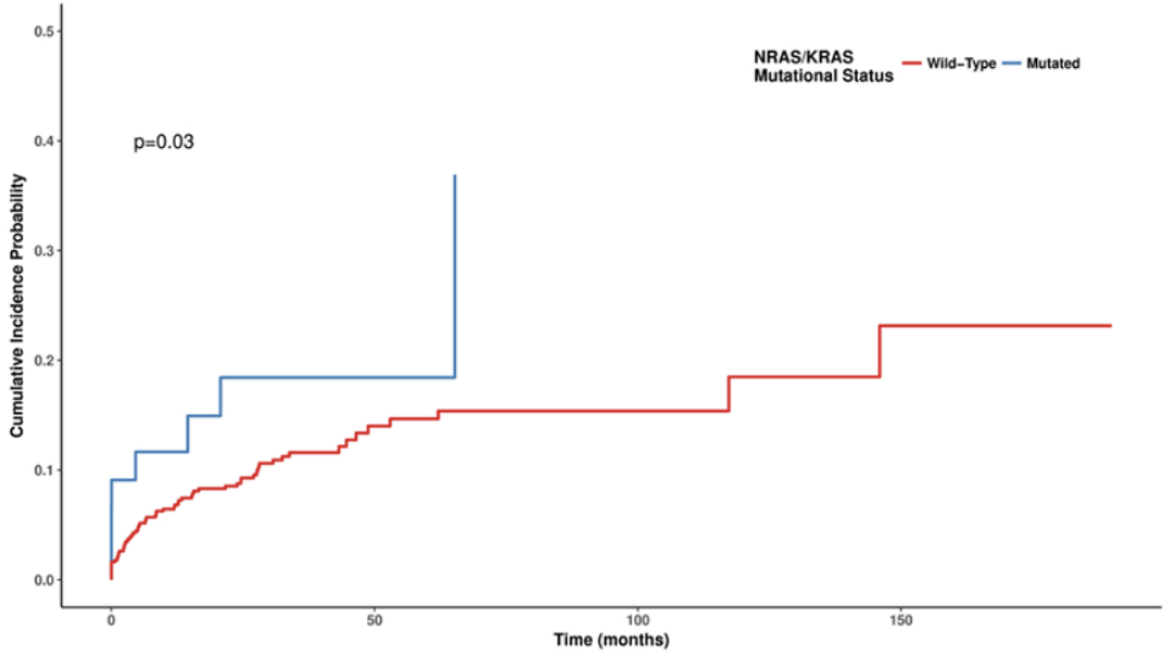
Prognostication – Disease Progression in Myelofibrosis

Impact of *NRAS* and *KRAS* Mutations

Overall Survial

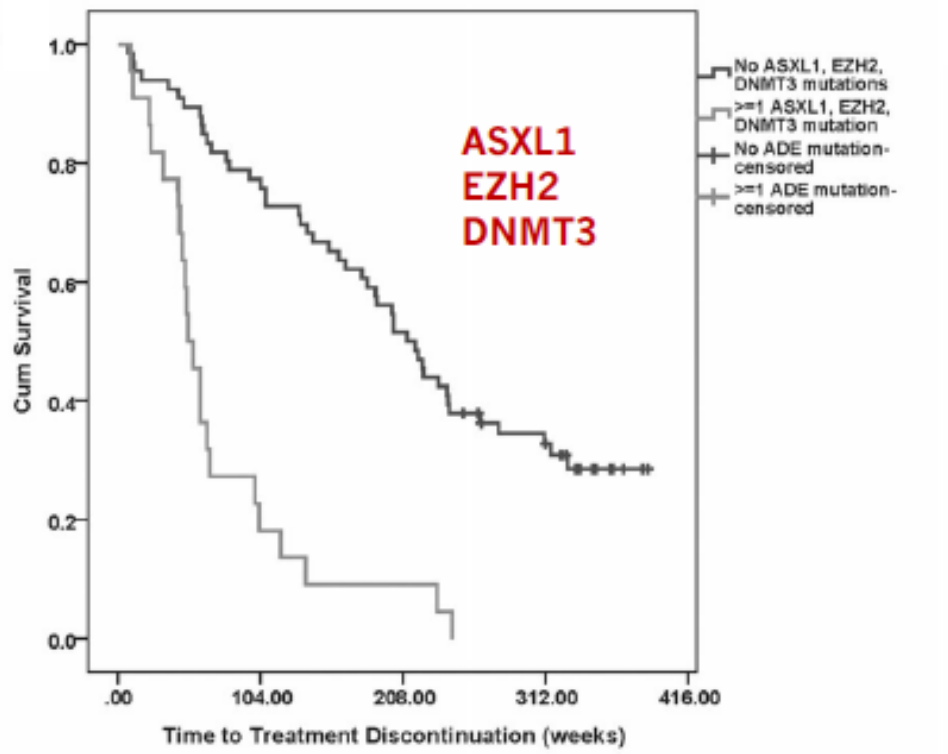


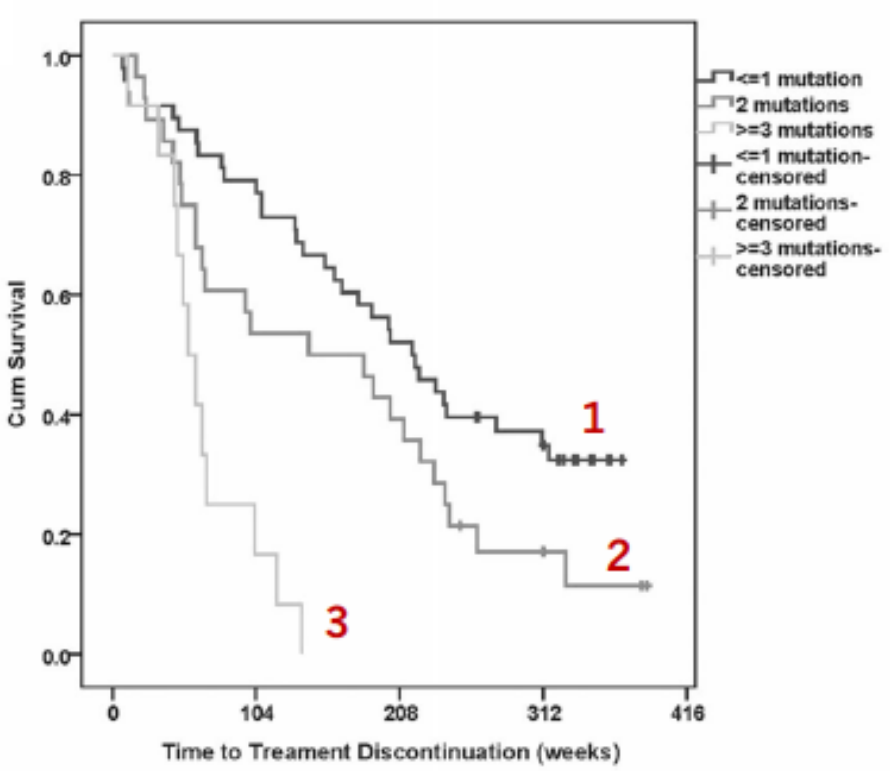
Leukemic Transforamtion



Santos FPS, et al. *Leukemia.* 2020;34(3):799-810.

Type and Number of Mutations Predict Ruxolitinib Response Duration

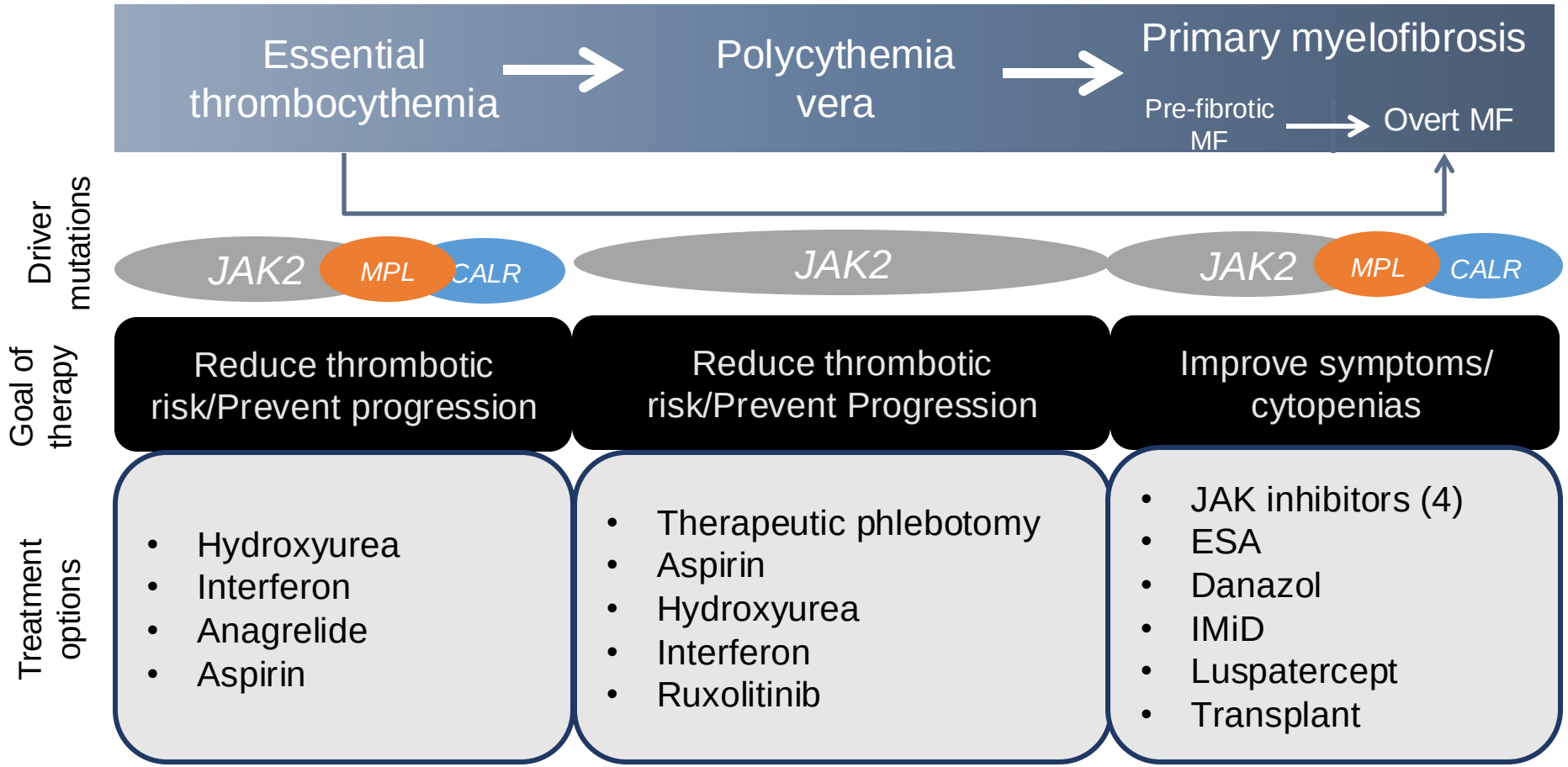




Patel KP, et al. *Blood.* 2015;126(6):790-797.

Management of MPNs – ET and PV

Conventional Treatment Approach and Options for MPNs



IMiD = immunomodulatory drug.
Courtesy of Dr. Andrew Kuykendall.

Revised IPSET-Thrombosis Prognostic Score (Endorsed by NCCN Guidelines)

Risk Factors	
Age ≥ 60 years	
Previous thrombosis	
JAK2V617F mutation positive	
Risk Categories	
Very low-risk: No risk factors	NO aspirin?
Low-risk: *JAK2V617F only*	aspirin
Intermediate-risk: Age > 60 years only	aspirin, NO cytoreduction?
High-risk: Previous thrombosis, OR > 60 years and *JAK2V617F*	aspirin and cytoreduction

"OLD" low risk

"OLD" high risk

IPSET = International Prognostic Score of thrombosis in Essential Thrombocythemia.

Barbui T, et al. *Blood Cancer*. 2015;5(11):e369. Haider M, et al. *Am J Hematol*. 2016;91(4):390-394.

Randomized Controlled Trials: Hydroxyurea vs Anagrelide

UK MRC PT1 Study (2005)

- 809 high-risk ET patients randomized
- 2661 patient-years of follow up
- All patients were on ASA
- Anagrelide had a higher risk of
  - Arterial or venous thrombosis, serious hemorrhage, or death from vascular cause (OR 1.6, 95% CI 1.0-2.4)
  - Rate of transformation into myelofibrosis at five years (7% versus 2%, OR 2.9, 95% CI 1.2-6.9)

ANAHYDRET Study (2013)

- 259 high-risk ET patients randomized
- 730 patient-years of follow up
- Only 28% of patients across arms received ASA
- Anagrelide was non-inferior for platelet counts and ET-related thombo-hemmorhagic events (HR 0.92, 95% CI 0.57-1.46)
- No comments were made concerning the long-term risk of myelofibrosis or acute leukemia

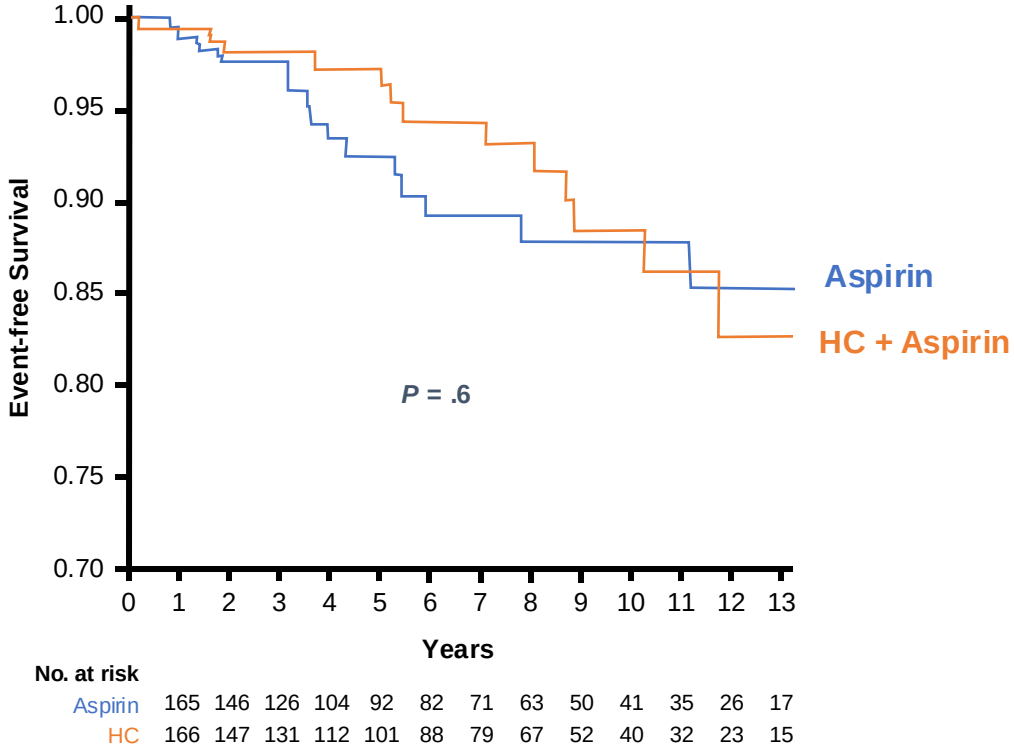
ASA = acetylsalicylic acid (aspirin).

Harrison CN, et al. *N Engl J Med*. 2005;353(1):33-45. Gisslinger H, et al. *Blood*. 2013;121(10):1720-1728.

Hydroxyurea + Aspirin vs Aspirin Alone in "early" ET

- Preemptive addition of HU to aspirin did not reduce the risk of vascular events, myelofibrotic progression, or leukemic transformation in this patient subset
- Patients aged **40 to 59 years** without other indications for treatment (ie, previous thrombosis or hemorrhage) and platelet count <1500 x 10^9/L should **not** receive cytoreductive therapy

Composite end point: any major disease-related complication (arterial thrombosis, venous thromboembolism, major hemorrhage, transformation to AML, MDS, MF, or death from any of these causes).

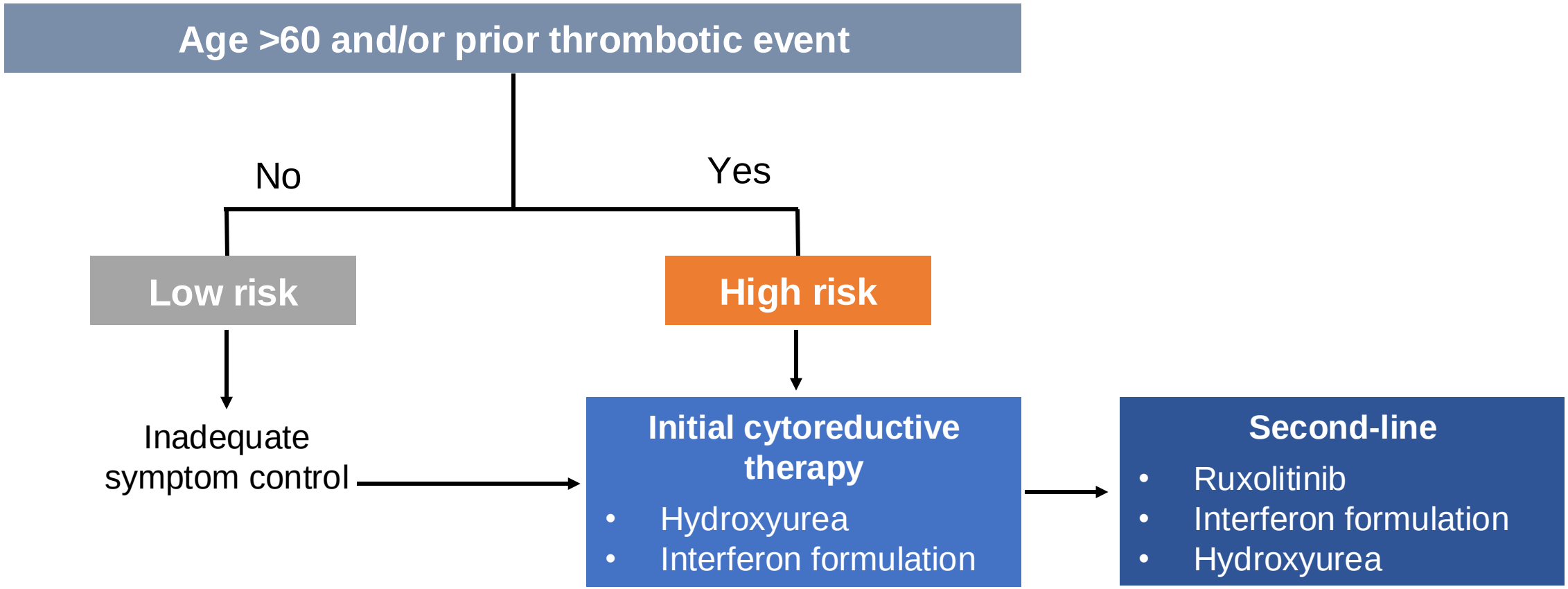


HC = hydroxycarbamide.

Godfrey AL, et al. *J Clin Oncol*. 2018;36(34):3361-3369.

Treatment of PV: Conventional Risk Model

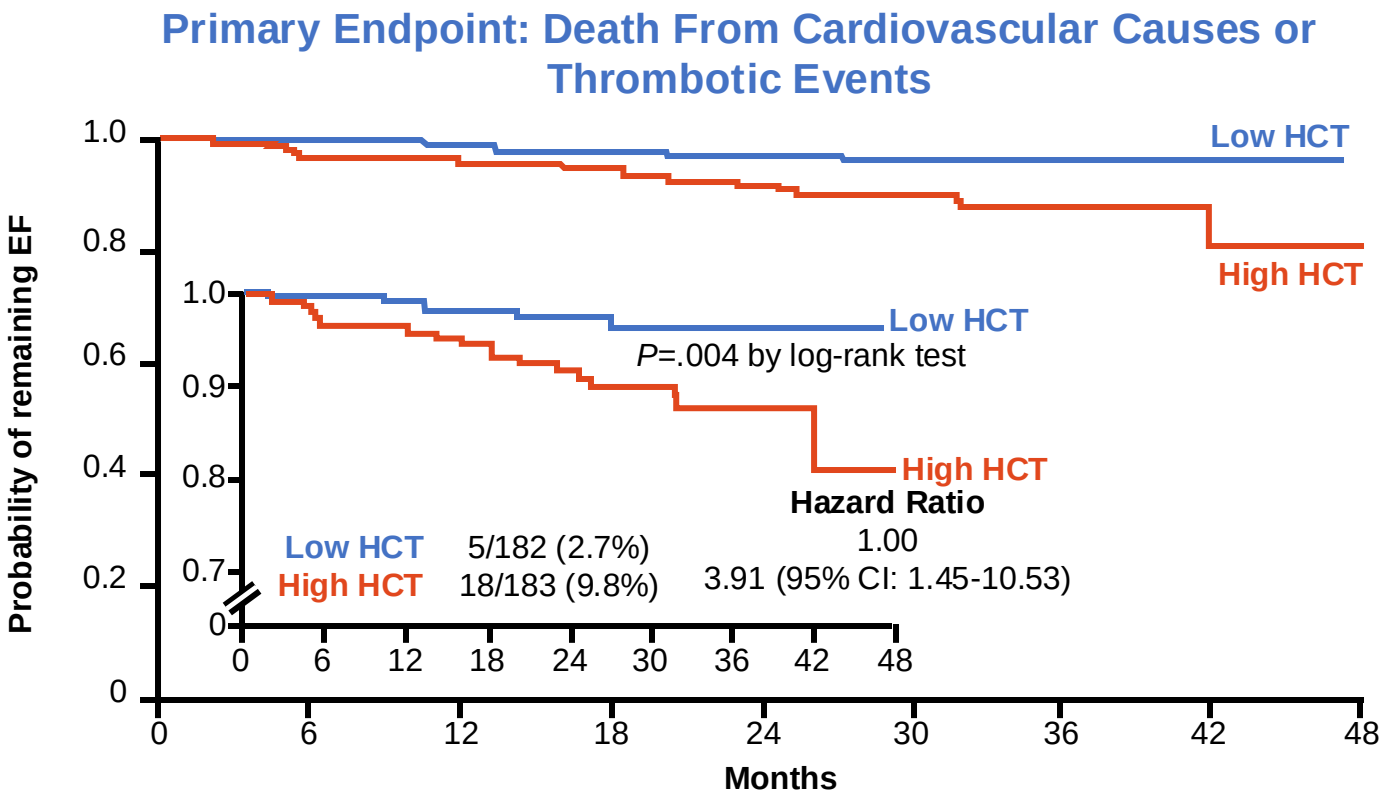
ASA + phlebotomy to keep hematocrit <45%

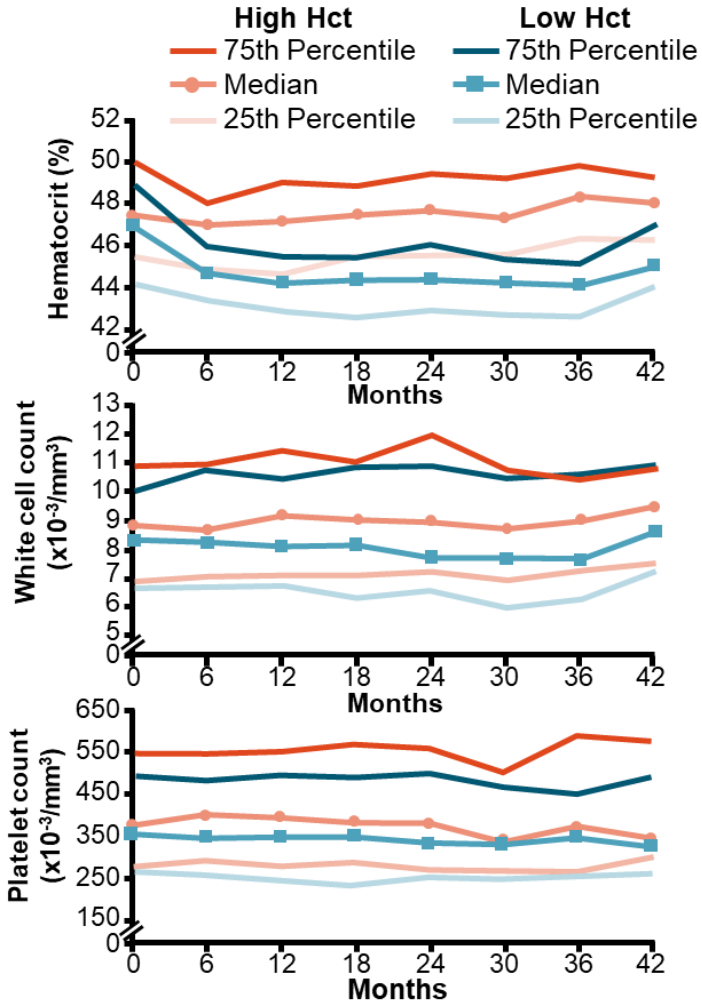


NCCN. Accessed November 5, 2024. https://www.nccn.org/patients/guidelines/content/PDF/mpn-patient.pdf.

Strict Hematocrit Control Is Associated With Decreased Risk of Cardiovascular Events

365 patients with PV randomized to target hematocrit <45% or 45%-50%



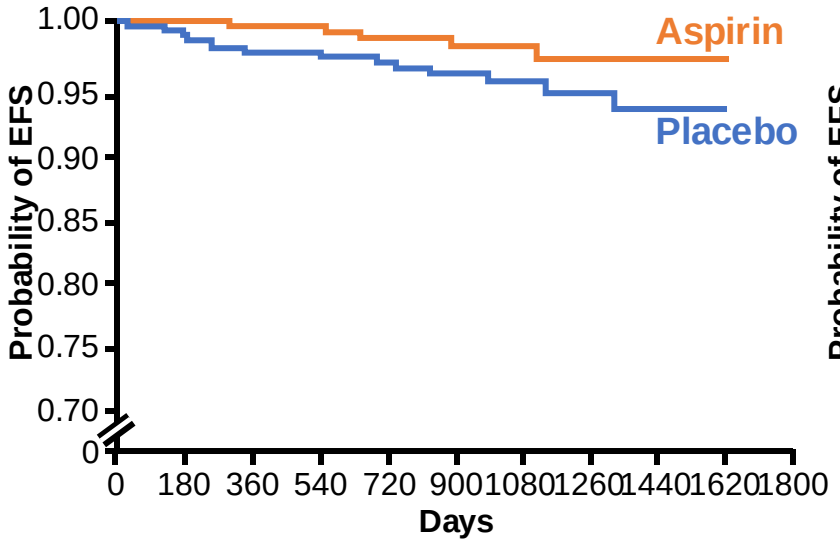


Marchioli R, et al. *N Engl J Med*. 2013;368(1):22-33.

Low-Dose Aspirin Is Associated With Decreased Risk of Cardiovascular Events in Patients With PV

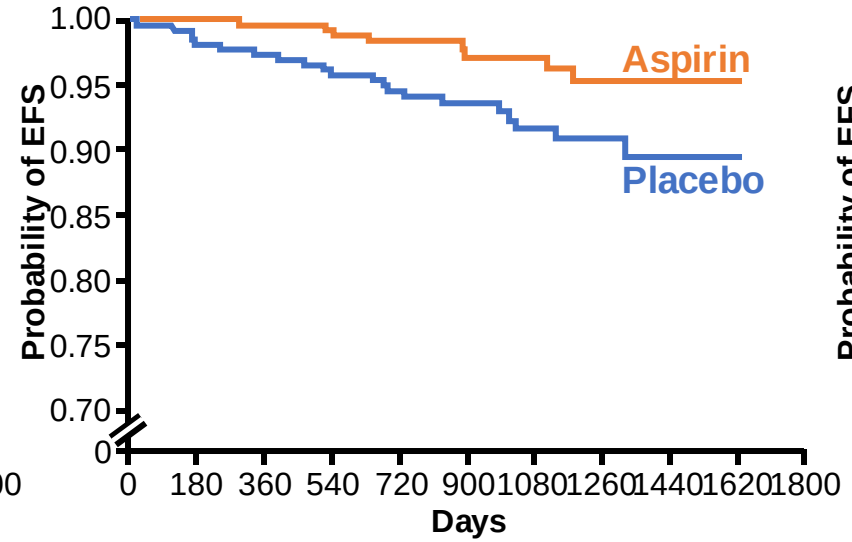
Double-blind, randomized trial of patients with PV with no clear indication for aspirin (N=518)

Survival Free of MI, CVA, and Death From CV Causes



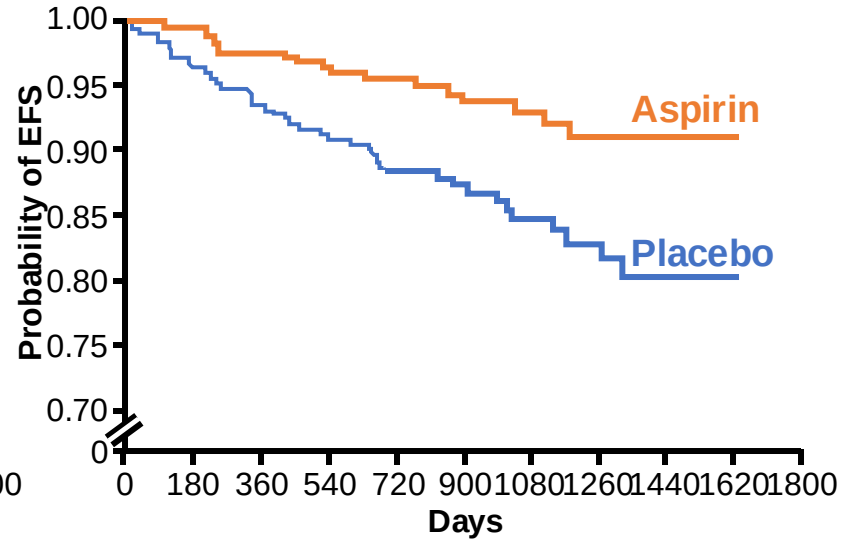
Not significant

Survival Free of MI, CVA, Death From CV Causes, PE, and DVT



P=.03

Thrombosis-Free Survival



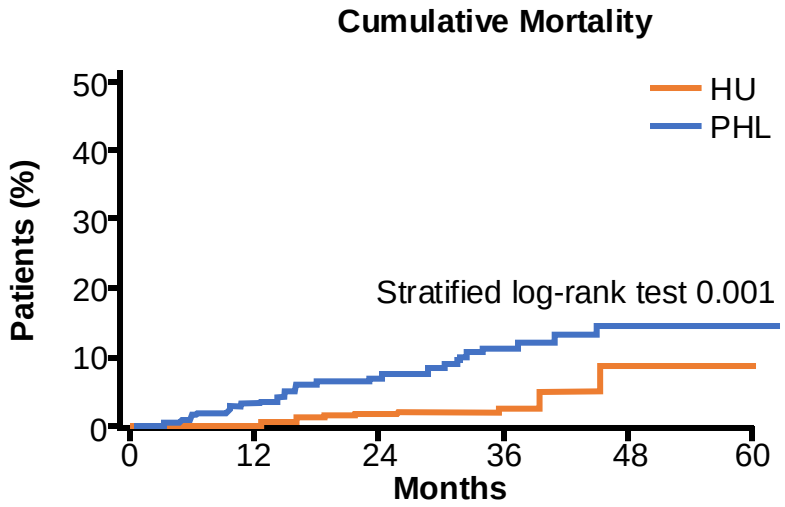
P=.003

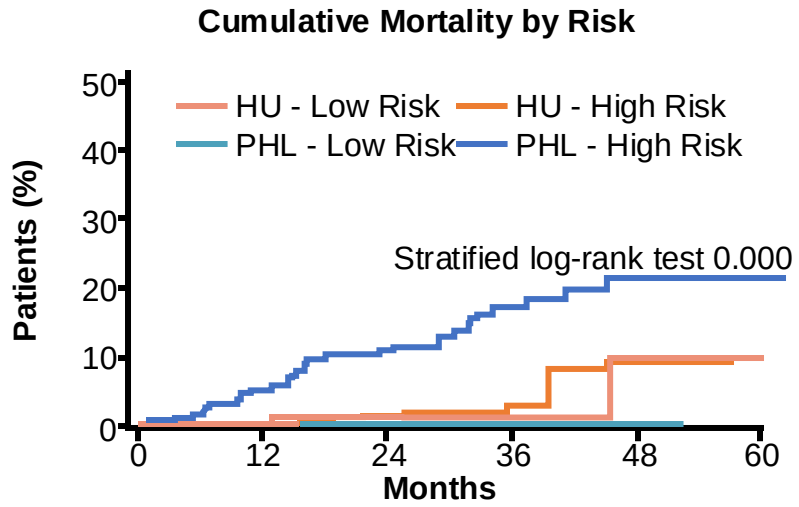
EFS = event-free survival; MI = myocardial infarction; CVA = cerebrovascular accident; CV = cerebrovascular; PE = pulmonary embolism; DVT = deep vein thrombosis.

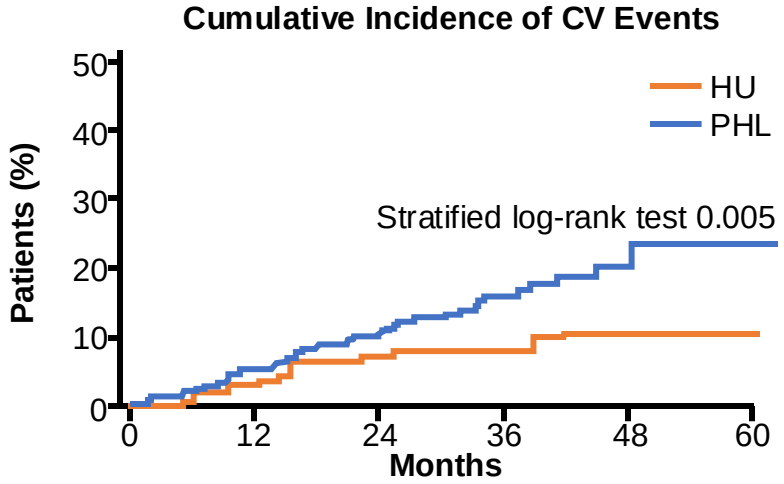
Landolfi R, et al. *N Engl J Med*. 2014;350(2):114-124.

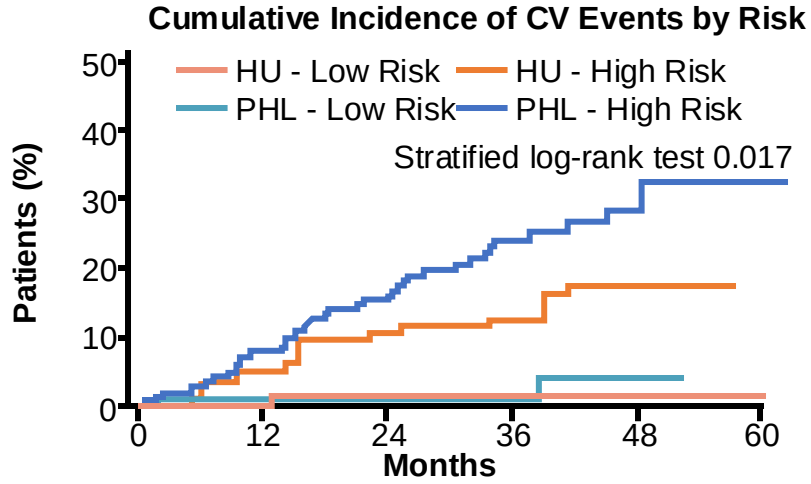
HU Is Associated With Thrombotic and Survival Benefit in Patients With High-Risk PV

- Retrospective analysis of 1042 patients with PV treated with HU or phlebotomy within ECLAP prospective observational study
- Treatment of physician's choice, required maintenance of hematocrit <45% and platelet count <400 x 10^9/L









ECLAP = European collaborative low-dose aspirin; PHL = phlebotomy.
Barbui T, et al. *Am J Hematol*. 2017;92(11):1131-1136.

Hydroxyurea Resistance and Intolerance: ELN Criteria

- Need for phlebotomy to maintain HCT <45%
- Platelets >400 x 10^9/L and WBC >10 x 10^9/L
- No reduction of massive splenomegaly by >50%
- No reduction of spleen symptoms

After >3 mo at MTD or 2 g/day

- Cytopenias (any)
  - ANC <1.0 x 10^9/L
  - Hemoglobin <100 g/L
  - Platelets <100 x 10^9/L

At lowest dose to achieve either a PR or CR

- GI toxicity
- Fevers
- Mucocutaneous toxicity
- Skin cancers

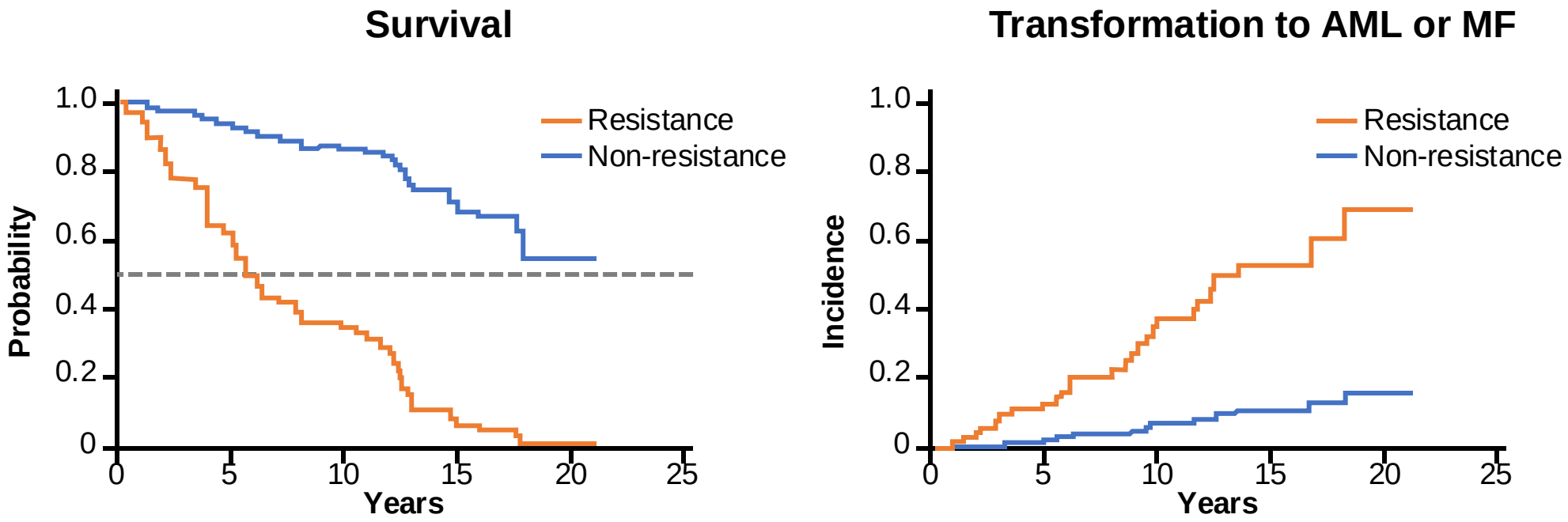
At any dose

- Prevalence of HU resistance/intolerance: up to 25%
- Uncontrolled PV symptoms can be a trigger to reevaluate therapeutic strategy

ELN = European LeukemiaNet; MTD = maximum tolerated dose; PR = partial response; CR = complete response.

Barosi G, et al. *Br J Haematol*. 2010;148(6):961-963.

Impact of Hydroxyurea Resistance on Survival and Disease Progression in PV



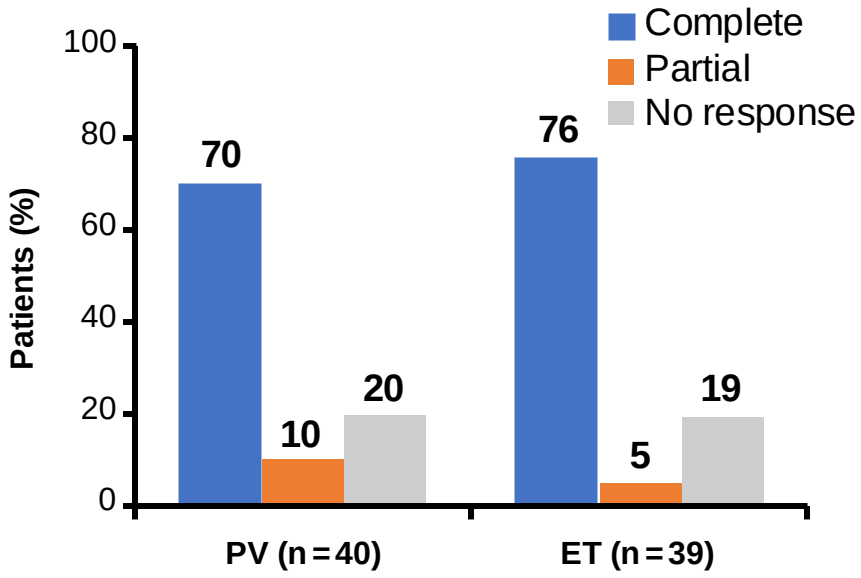
- Spanish chart review of patients with PV treated with HU (n=261)
  - Resistance and intolerance to hydroxyurea occurred in 11% and 13%, respectively
  - Resistance implied 5.6-fold increase in risk of death and 6.8-fold increase in risk of transformation to AML or MF

Alvarez-Larran A, et al. *Blood*. 2012;119(6):1363-1369.

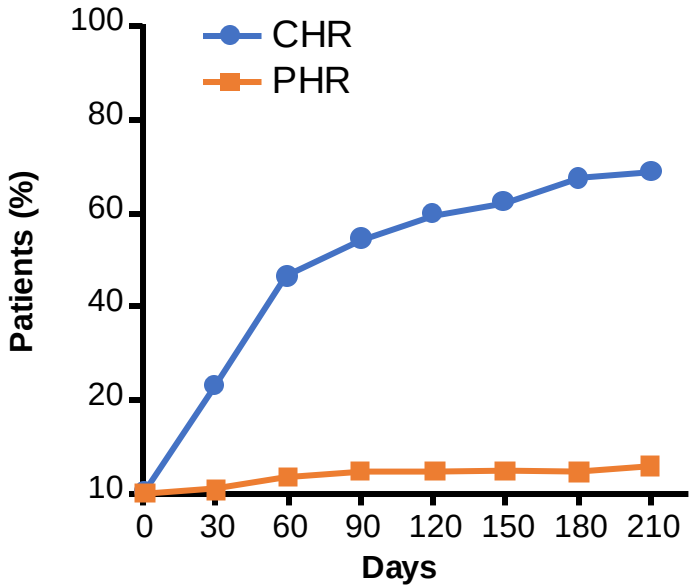
Pegylated Interferon α-2a Effectively Controls Blood Counts in PV

Prospective, single-center (UT M.D. Anderson Cancer Center) phase 2 study of peg-IFN α-2a in patients with PV* or ET** (N=79)

Hematologic Response

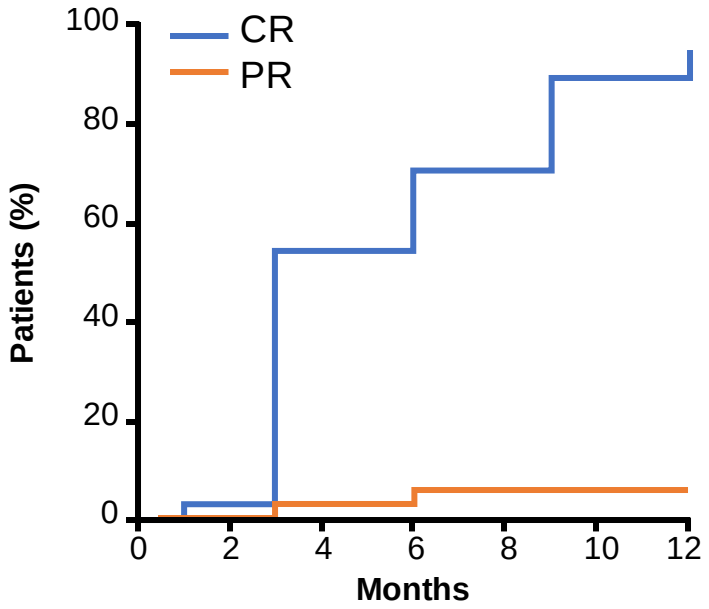


Cumulative Hematologic Response



Prospective, multi-center (France) phase 2 study of peg-IFN α-2a in patients with PV (N=40)

Cumulative Hematologic Response

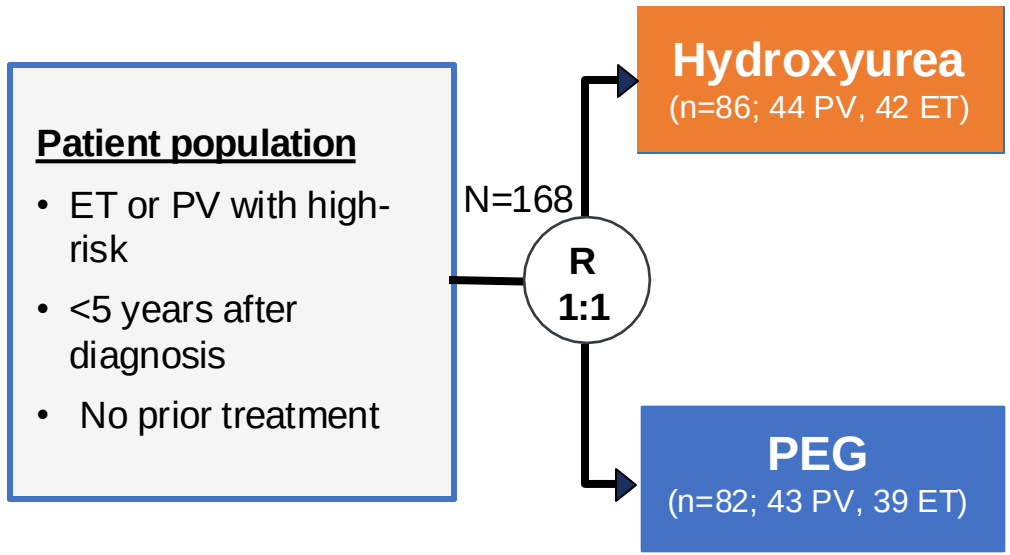


*PV: CR is hematocrit <45% (males) or <42% (females), normalized WBC and platelet counts, and normalized spleen size, without use of phlebotomies, hydroxyurea, or anagrelide and absence of thromboembolic events, PR is ≥50% reduction in phlebotomy requirement or spleen size; **ET: CR is platelet count ≤400 × 10^9/L without use of hydroxyurea or anagrelide and absence of thromboembolic events, PR is ≥50% reduction in platelet count.

IFN = interferon; CHR = complete hematologic response; PHR = partial hematologic response.

Quintas-Cardama A, et al. *J Clin Oncol.* 2009;27(32):5418-5424. Kiladjian JJ, et al. *Blood.* 2008;112(8):3065-3072.

Phase 3 MPD-RC 112 Trial: Peg-IFN α-2a and Hydroxyurea Produce Similar Rates of CR at 12mo



Primary Endpoint

CR at 12 months

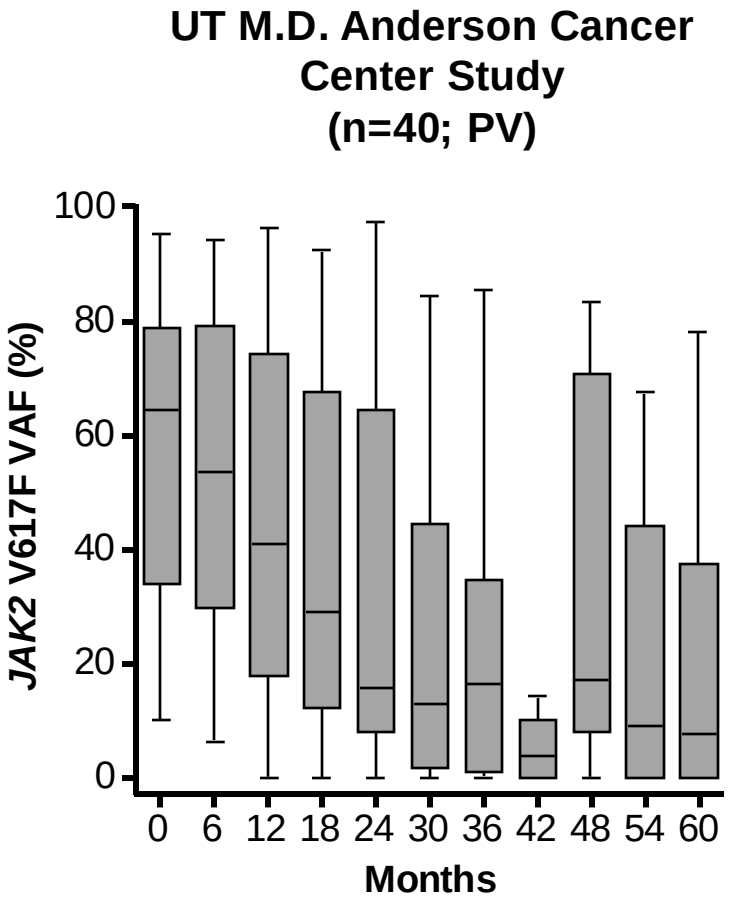
High-risk defined as 1 of the following:
- Age >60 years
- History of thrombosis
- History of bleeding (ET only)
- Platelet count >1500 × 10^9/L (ET) or >1000 × 10^9/L (PV)
- Vasomotor symptoms
- Significant/symptomatic splenomegaly
- Diabetes or hypertension requiring pharmacologic intervention

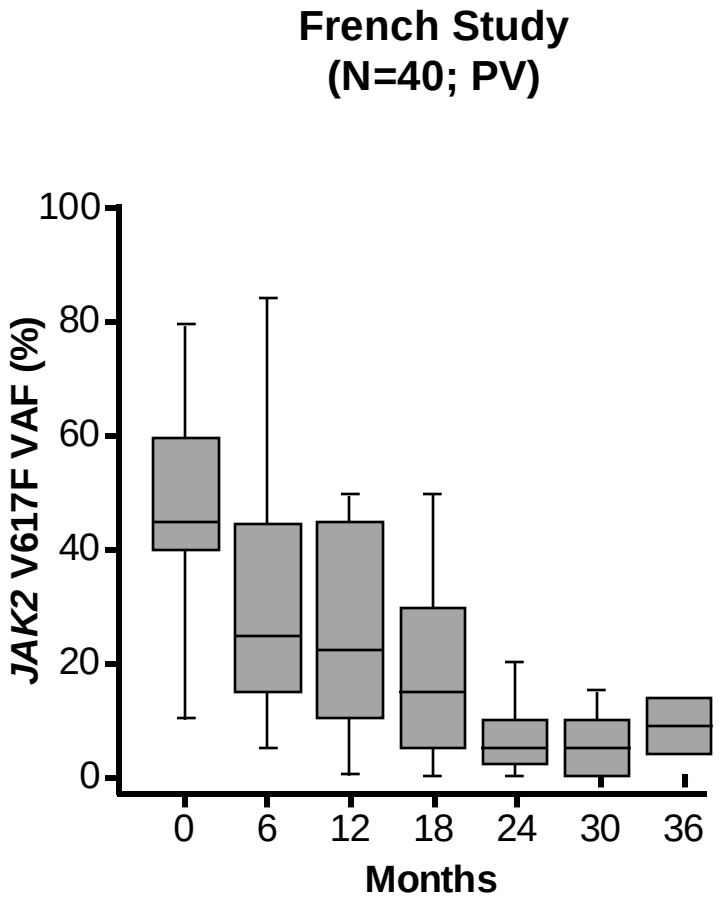
Response	HU	PEG	Rate, PEG - HU (95% CI)	Rate Ratio (95% CI)
12 mo	**(n=86)**	**(n=82)**		
CR	32 (37)	29 (35)	-2 (-16 to 13)	0.95 (0.64-1.42)
• ET	19 (45)	17 (44)		
• PV	13 (30)	12 (28)		
OR	60 (70)	64 (78)	8 (-5 to 21)	1.12 (0.93-1.34)
• ET	30 (71)	27 (69)		
• PV	30 (68)	37 (86)		
24 mo	**(n=54)**	**(n=52)**		
CR	11 (20)	15 (29)	9 (-9 to 26)	1.42 (0.72-2.79)
• ET	6 (25)	9 (38)		
• PV	5 (17)	7 (25)		
OR	22 (41)	31 (60)	19 (1 to 37)	1.46 (1.00-2.16)
• ET	8 (33)	14 (58)		
• PV	14 (47)	17 (61)		
36 mo	**(n=30)**	**(n=27)**		
CR	5 (17)	9 (33)	17 (-8 to 40)	2.00 (0.76-5.23)
• ET	2 (17)	4 (40)		
• PV	3 (17)	5 (29)		
OR	14 (47)	16 (59)	13 (-15 to 38)	1.27 (0.77-2.08)
• ET	4 (33)	6 (60)		
• PV	10 (56)	10 (59)		

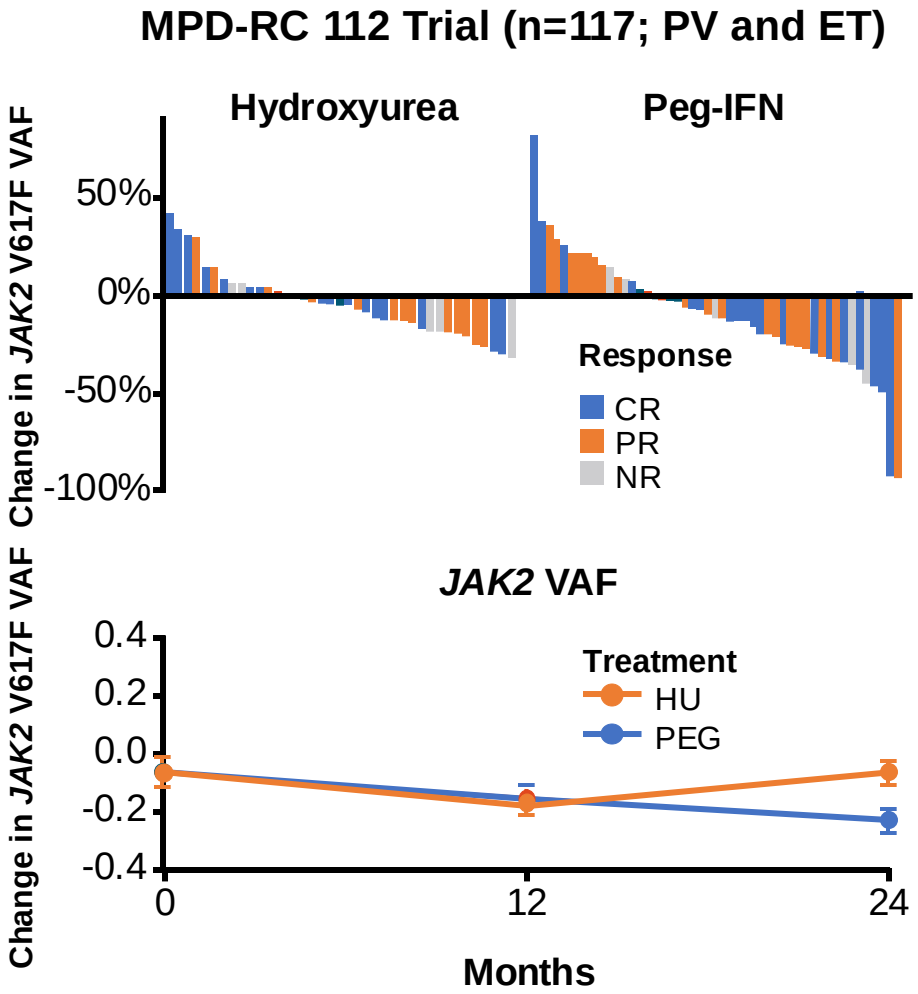
PEG = pegylated IFNα.

Mascarenhas J, et al. *Blood*. 2022;139(19):2931-2941. NIH. Accessed November 5, 2024. https://clinicaltrials.gov/study/NCT01259856.

Peg-IFN α-2a Has Been Associated With Decrease in Variant Allele Fractions With Prolonged Administration





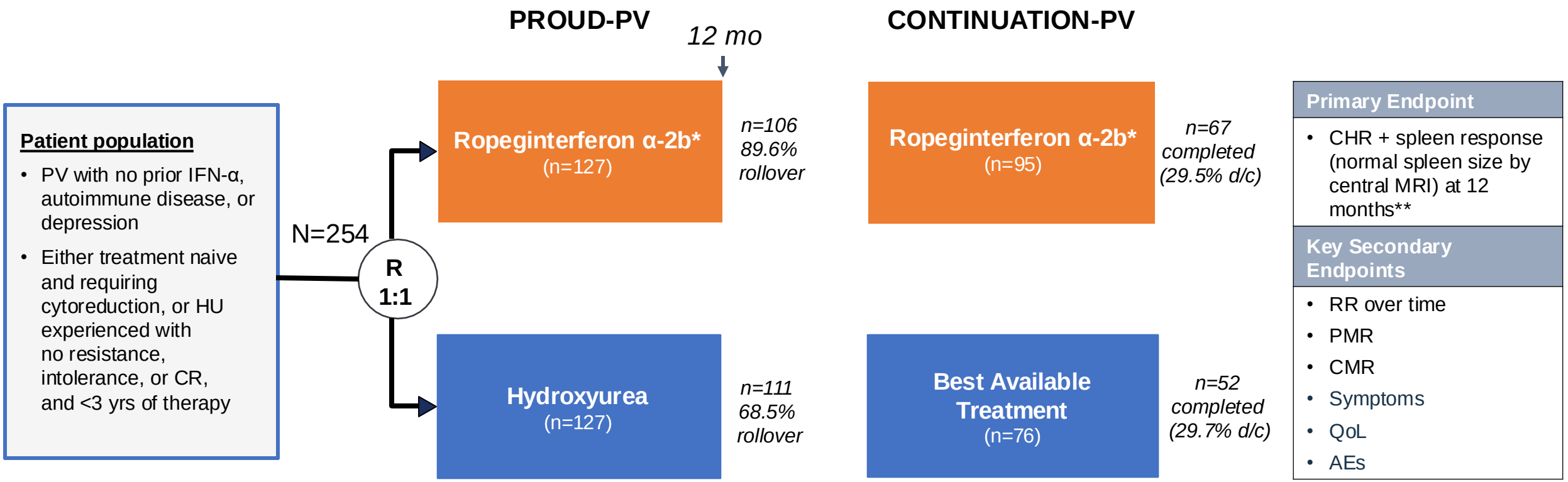


NR = no response.

Kiladjian JJ, et al. *Blood*. 2008;112(8):3065-3072. Quintas-Cardama A, et al. *Blood*. 2013;122(6):893-901. Mascarenhas J, et al. *Blood*. 2022;139(19):2931-2941.

Phase 3 PROUD-PV/CONTINUATION-PV

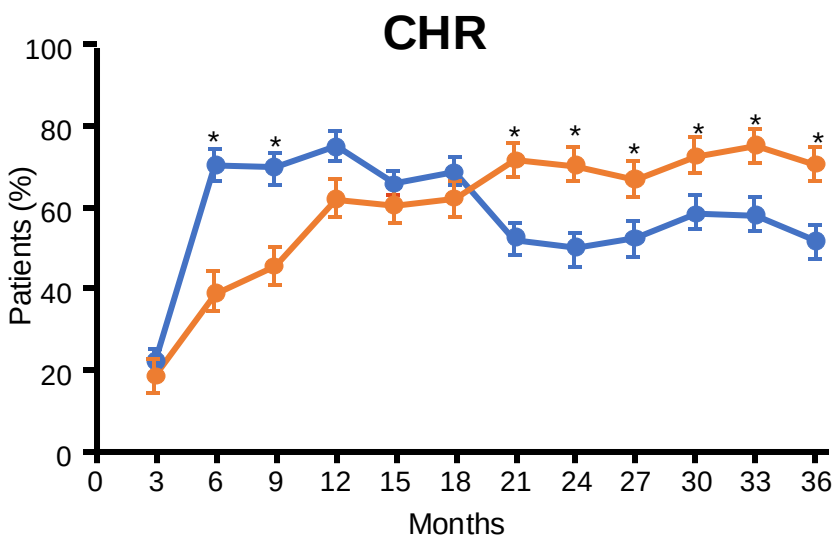
An open-label, active-controlled, randomized, noninferiority trial in Europe

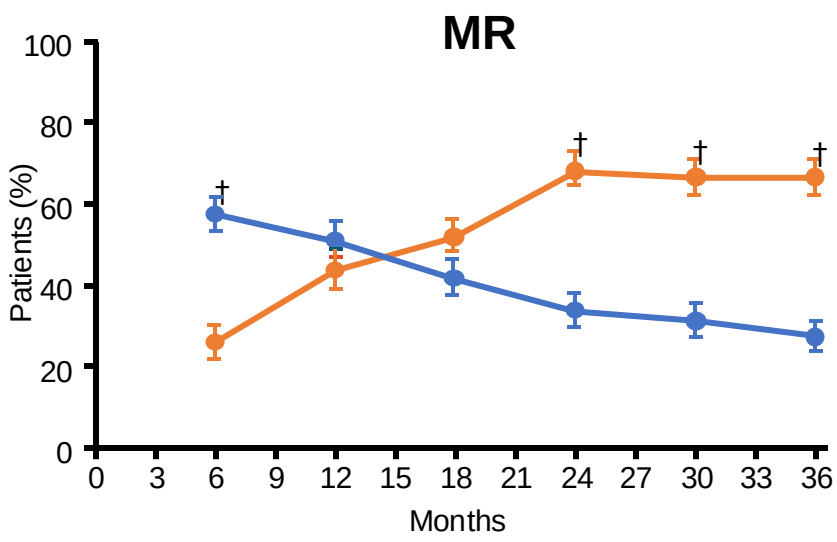


After 6 years of treatment, ropeginterferon alfa-2b resulted in diminished *JAK2*V617F allele burden, significantly higher complete hematologic response (CHR), and an established positive safety profile.

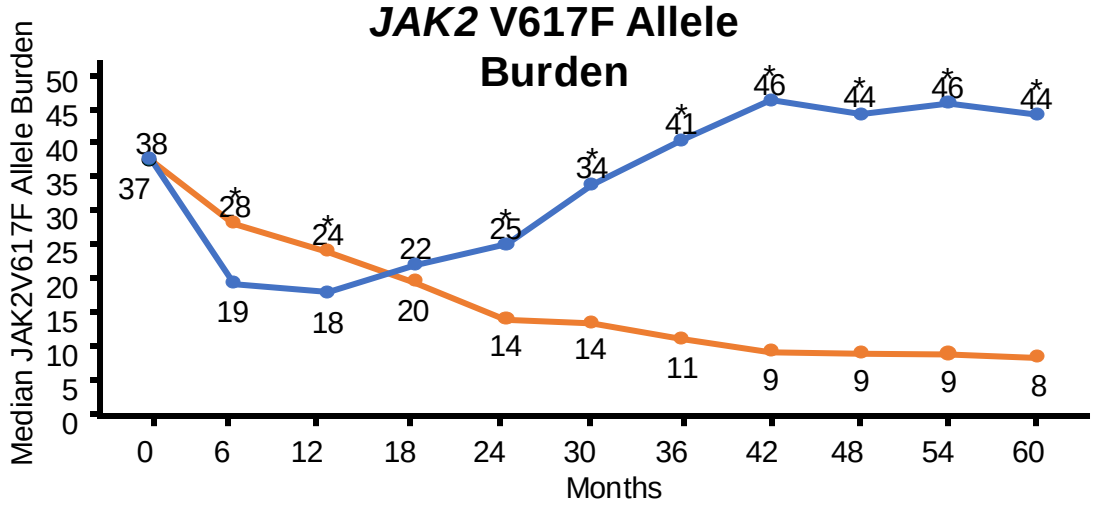
***Response-driven dosing in both arms, up to 10 dose levels (50-500 µg ropeginterferon α-2b every other week or 250-3000 mg HU daily); **CHR defined as hematocrit <45% without phlebotomy in previous 3 months, leukocyte count <10 x 10^9/L, and platelet count <400 x 10^9/L.**
d/c = discontinued; CMR = complete molecular response; PMR = partial molecular response; RR = response rate.
Gisslinger H, et al. *Lancet Haematol*. 202;7(3):e196-e208. NIH. Accessed November 5, 2024. https://clinicaltrials.gov/study/NCT01949805; NCT02218047.

CONTINUATION-PV: Response in the Extension Period





Ropeginterferon α-2b
Hydroxyurea



*P<.05; †P<.01.
MR = molecular response.
Gisslinger H, et al. *Lancet Haematol*. 202;7(3):e196-e208; Kiladjian JJ, et al. *Leukemia*. 2022;36(5):1408-1411.

PROUD-PV/CONTINUATION-PV: TRAEs of Special Interest at 36 Months

AE, n (%)	Ropeg-IFN α-2b (n=127)	HU/BAT (n=127)
Endocrine		
• Any AE	8 (6)	2 (2)
• Any TRAE	6 (5)	0
Psychiatric		
• Any AE	5 (4)	6 (5)
• Any TRAE	2 (2)	1 (1)
Musculoskeletal and connective tissue		
• Any AE	2 (2)	0
• Any TRAE	2 (2)	0
Major cardiovascular and thromboembolic		
• Any major cardiovascular AE	13 (10); 16 events	8 (6); 25 events
• Major thromboembolic AE	4 (3); 6 events	4 (3); 4 events
Neoplasms benign, malignancy, and unspecified		
• Any neoplasm	9 (7); 11 events	10 (8); 12 events
• Leukemic transformation	0	2 (2); 2 events
• TR phase skin cancer (basal cell carcinoma and melanoma)	0	3 (2); 3 events

Gisslinger H, et al. *Lancet Haematol*. 202;7(3):e196-e208.

Low-PV: Ropeg-IFN-α2b for Patients With Low-Risk PV

Patient population

- Low-risk: <60 yrs and no history of thrombotic event

N=127

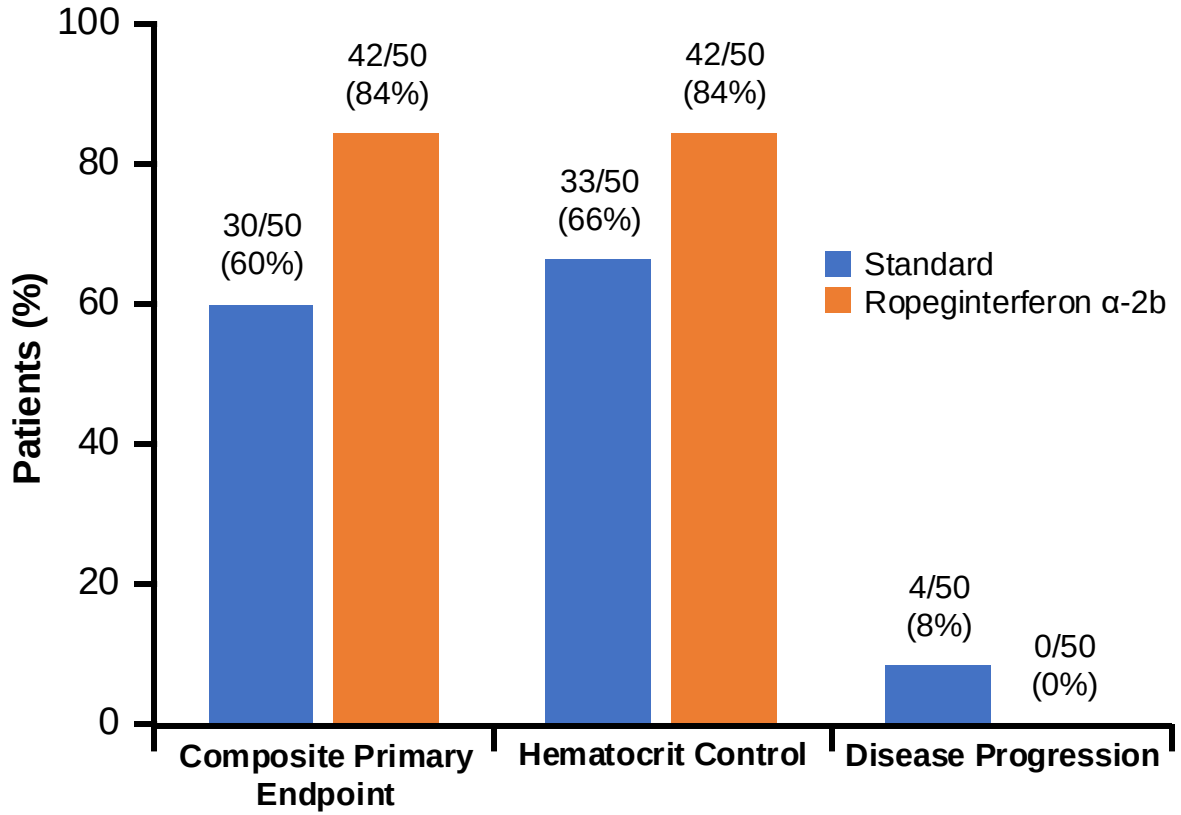
R
1:1

Ropeginterferon α-2b
(n=64)
Fixed dose, 100 µg Q2W + standard treatment

Standard
(n=63)
Phlebotomy + low-dose aspirin

Composite Primary Endpoint

- Hematocrit control <45%
- Lack of disease progression: Thrombocytosis, leukocytosis, or major vascular/bleeding complications



Disease progression events in control arm (n=4): 3 symptomatic thrombocytosis, 1 splenic vein thrombosis.

Q2W = every 2 weeks.

Barbui T, et al. *Lancet Haematol*. 2021;8(3):e175-e184. NIH. Accessed November 5, 2024. https://clinicaltrials.gov/study/NCT06290765.

Ropeginterferon α-2b Dosing Strategies in PV

Recommended starting dose
If on HU: 100 µg SC Q2W
If not on HU: 50 µg SC Q2W

Perform CBC every 2 weeks during titration
If on HU, gradually taper by 20% to 40% of every total 2-week dose during weeks 3-12 and discontinue by week 13

Decrease dose for AE

If	Dose adjustment
Liver enzymes >20 x ULN or any elevation with bilirubin elevation or hepatic decompensation	Interrupt dose until recovery
Liver enzymes >5 and ≤20 x ULN	Decrease dose by 50 µg every Q2W until improved
Urgent/life-threatening anemia OR platelets <25,000/mm^3 OR WBC <1000/mm^3	Interrupt dose until recovery
Moderate or persistent depression	Consider psychiatric consultation
Severe depression or suicidal ideation	Discontinue

Increase dose for insufficient response

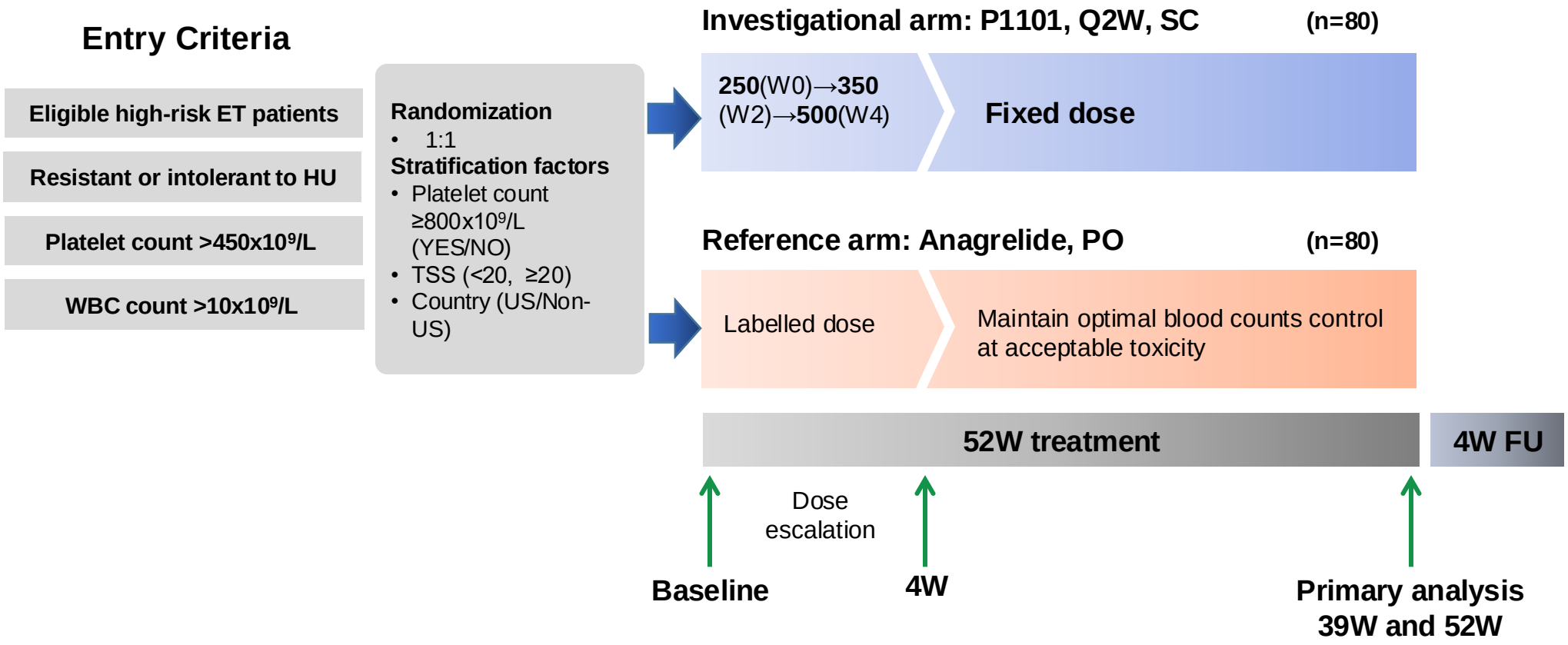
Until stabilized with	Dose adjustment
If transitioning from HU • Hct <45%, AND • Platelets <400 x 10^9/L, AND • Leukocytes <10 x 10^9/L	Increase by 50 µg Q2W to maximum 500 µg Q2W
If not transitioning from HU • Hct <45%, AND • Leukocytes <10 x 10^9/L	

Phase 3 trial of accelerated dosing in PV: estimated completion 2024

SC = subcutaneous.

FDA. Last updated November 2021. Accessed November 5, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761166s000lbl.pdf.

SURPASS ET Study (P1101 ET)



PO = by mouth; FU = follow-up.

Verstovsek S, et al. *Future Oncol.* 2022;18(27):2999-3009. NIH. Accessed November 20, 2024. https://clinicaltrials.gov/study/NCT04285086.

Significant Symptom Burden with Polycythemia Vera

	Swedish PV Cohort (N=53)		International PV Cohort (N=538)	
MPN-SAF Symptom	**Severity*, mean (95% CI)**	**Prevalence, %**	**Severity*, mean (SD)**	**Prevalence, %**
Fatigue	**3.0 (2.4-3.6)**	**87**	**4.4 (2.9)**	**88**
Early satiety	**2.3 (1.5-3.1)**	**66**	**2.5 (2.7)**	**64**
Abdominal pain	1.2 (0.6-1.9)	38	—	—
Abdominal discomfort	1.5 (0.8-2.2)	42	1.6 (2.3)	51
Inactivity	1.8 (1.2-2.5)	60	2.4 (2.7)	61
Headache	1.2 (0.7-1.6)	38	—	—
Concentration problem	1.9 (1.3-2.5)	60	2.7 (2.9)	65
Dizziness	1.8 (1.1-2.5)	51	—	—
Numbness	2.5 (1.7-3.4)	65	—	—
Insomnia	3.0 (2.2-3.8)	70	—	—
Sad mood	2.0 (1.4-2.6)	68	—	—
Sexual problems	2.5 (1.5-3.5)	50	—	—
Cough	1.4 (0.9-2.0)	48	—	—
Night sweats	**2.7 (1.8-3.5)**	**64**	**2.1 (2.8)**	**52**
Itching	**1.9 (1.2-2.6)**	**57**	**2.8 (3.2)**	**62**
Bone pain	1.7 (0.9-2.4)	44	2.0 (2.7)	50
Fever	0.3 (0.1-0.4)	19	0.4 (1.1)	18
Weight loss	1.2 (0.6-1.8)	63	1.0 (2.1)	31
Quality of life	**2.5 (2.0-3.1)**	**88**	**—**	**—**

***Symptom severity was rated on a 0 (absent/as good as it can be) to 10 (worst-imaginable/as bad as it can be) scale. Myeloproliferative Neoplasm Symptom Assessment Form total symptom score has a possible range of 0 to 100 with 100 representing the highest level of symptom severity.**

MPN-SAF = myeloproliferative neoplasm symptom assessment form; SD = standard deviation.

Emanuel R, et al. *J Clin Oncol*. 2012;30(33):4098-4103. Johansson P, et al. *Leuk Lymphoma*. 2012;53(3):441-444.

Phase 3 RESPONSE Study: Ruxolitinib vs Standard Therapy in Patients with PV and HU Resistance Intolerance

Patient population

- PV requiring phlebotomy
- **HU resistance/ intolerance**
- Spleen volume ≥450 cm^3
- No JAK inhibitor experience
- HCT 40%-45% before randomization*

Stratification

- HU status (resistance vs intolerance)

N=222

R 1:1

Ruxolitinib: JAK 1/2 inhibitor

Ruxolitinib
Initial 10 mg BID; dose titrated to maintain HCT
(n=110)

Crossover at PD or week 32 if primary endpoint not met

Standard Therapy
selected by investigator†
(n=112)

Week 32

Primary analysis data cutoff at week 48 or treatment discontinuation

All patients received low-dose ASA.

Primary Endpoint

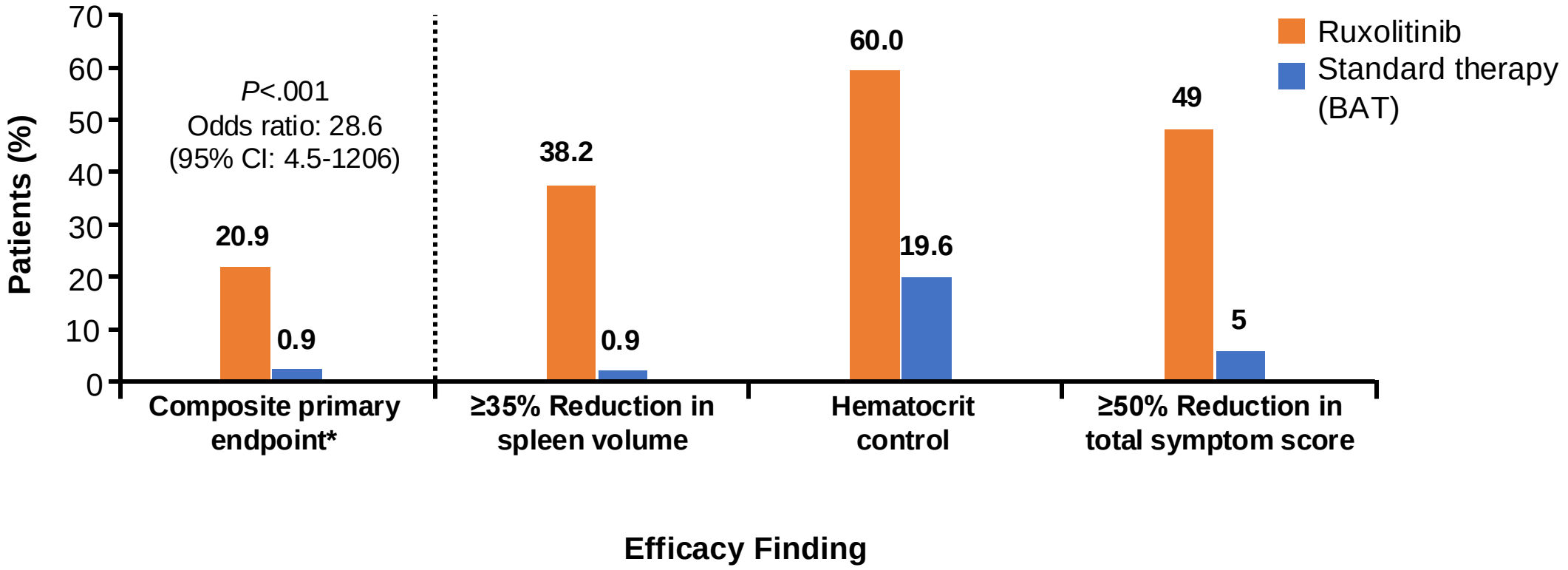
- HCT control and ≥35% reduction in spleen volume

Key Secondary Endpoints

- Primary response at week 32
- CHR
- Duration of response
- Symptom reduction
- Safety

***Patients with HCT <40% or >50% entered HCT control period prior to randomization; †Excluding ^{32}P, busulfan, and chlorambucil.**
BID = twice daily; PD = progressive disease.
Vannucchi A, et al. *N Engl J Med*. 2015;372(5):426-435. NIH. Accessed November 6, 2024. https://clinicaltrials.gov/study/NCT05421104.

RESPONSE: Key Efficacy Findings at Week 32



*Proportion with HCT control + spleen volume reduction ≥35%.

Vannuchi A, et al. *N Engl J Med*. 2015;372(5):426-435.

RESONSE: 80-Week Follow-Up Outcomes

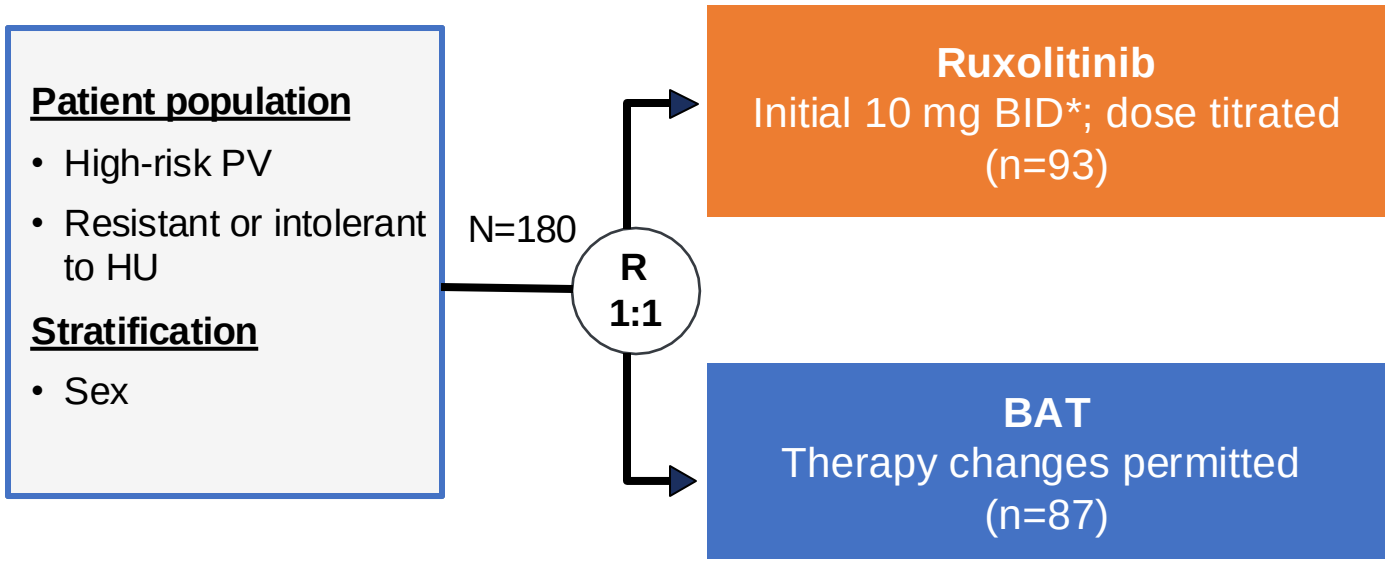
- For patients randomized to **ruxolitinib** (n=110)
  - Median exposure: 111 weeks
  - Remained on treatment: 83%
  - For patients achieving response at 32 weeks, likelihood of maintaining response for ≥80 weeks:
    - Primary endpoint*: 92%
    - HCT control: 89%
    - Spleen reduction: 97%
  - Allele burden decrease: 22%

Events per 100 Patient Years	Ruxolitinib (n=110)	BAT (n=111)
Thromboembolic events	1.8	8.2
MF progression	1.3	1.4
AML progression	0.4	0
Grade 3/4 thrombocytopenia	2.6	5.4
Zoster	5.3	0
Skin cancer	4.4	2.7
Increased weight	7.5	1.4

***Proportion with HCT control + spleen volume reduction ≥35%.**
Tx = therapy.
Verstovsek S, et al. *Haematologica*. 2016;101(7):821-829.

Phase 2 MAJIC-PV Study

A multi-center, open-label, randomized study in the UK



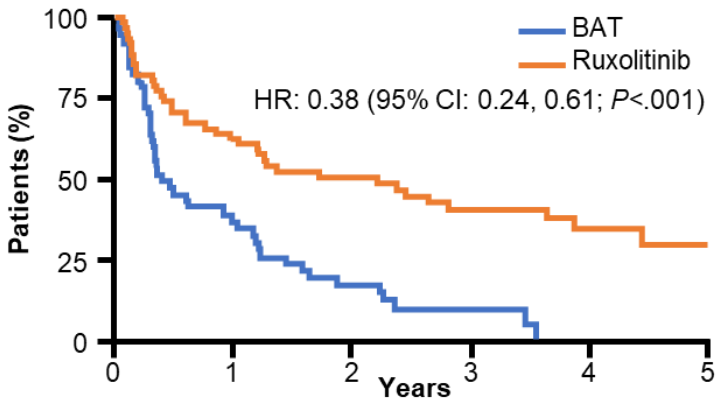
Primary Endpoint
• CR rate per ELN (WBC ≤10, HCT ≤0.45, Plt ≤400) within 1 year
Key Secondary Endpoints
• PR rate • Duration • Safety • Histologic and molecular response • QoL • PFS • OS • EFS

***5 mg BID if baseline platelets are 100-200 x 10^9/L.**

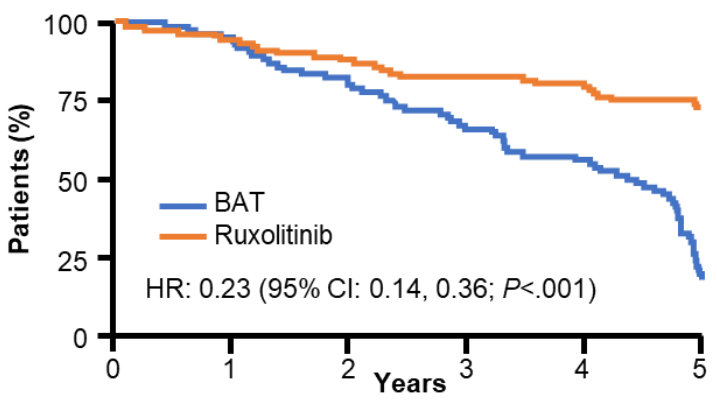
Harrison C, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

MAJIC-PV: Outcomes

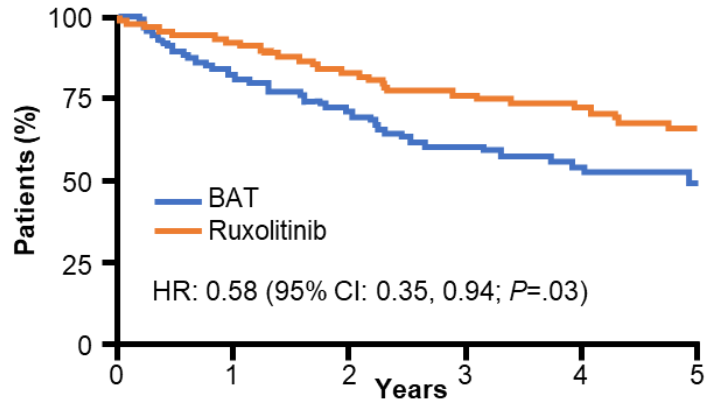
Duration of CR



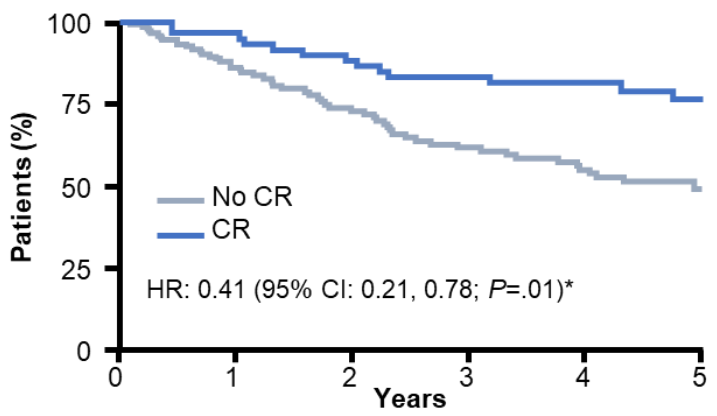
Time to Discontinuation of First Treatment



EFS



EFS by Attainment of CR Within 12 Months



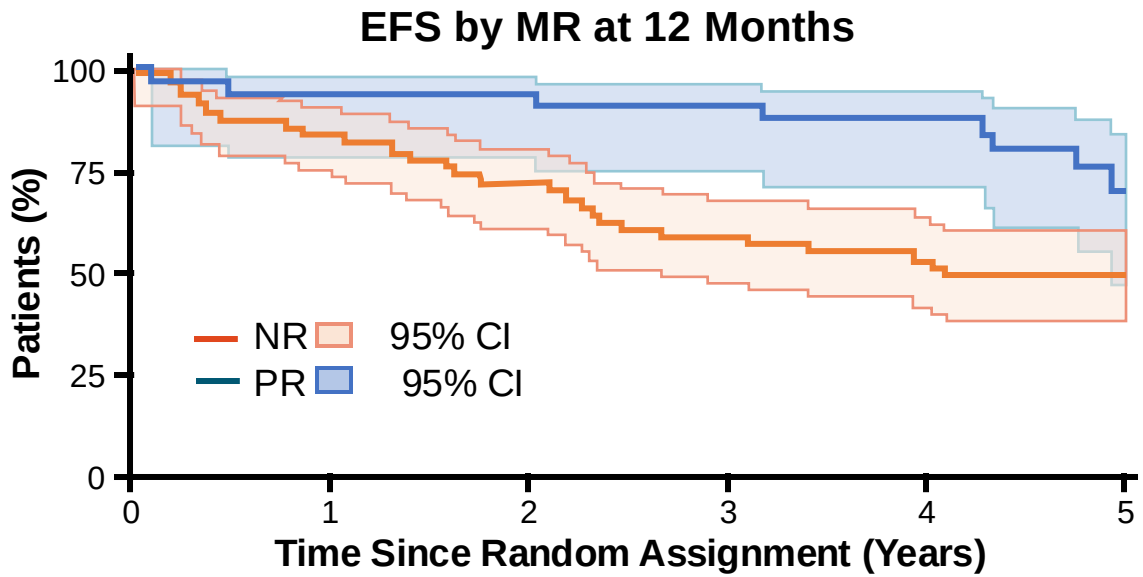
Endpoint	Rux (n=93)	BAT (n=87)
CR within 12 mo, n (%)	40 (43)	23 (26)
OR (90% CI), adjusted for sex (stratification factor)	2.12 (1.25-3.60) *P*=.02	
OR (90% CI), adjusted for sex, treatment arm, and baseline characteristics**	2.03 (1.09-3.78) *P*=.06	
Thrombolic EFS, HR (95% CI)	0.56 (0.32-1.00) *P*=.05	
Hemorrhagic EFS, HR (95% CI)	0.66 (0.34-1.28) *P*=.22	
3-year PFS, % (95% CI)	84 (74-90)	75 (63-83)
3-year OS, % (95% CI)	88 (79-93)	87 (77-93)

***Also adjusted for treatment; **HGB, number of prior therapies, history of thrombosis, resistance or intolerance to HU, and splenomegaly.**

Harrison C, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

MAJIC-PV: Association of MR with Clinical Endpoints

- Molecular response at 1 year correlated with superior EFS
- Those with durable MR at last time point had significant improvements in EFS, PFS, and OS regardless of treatment arm
  - Correlation of clinical improvement with MR was driven by the ruxolitinib arm

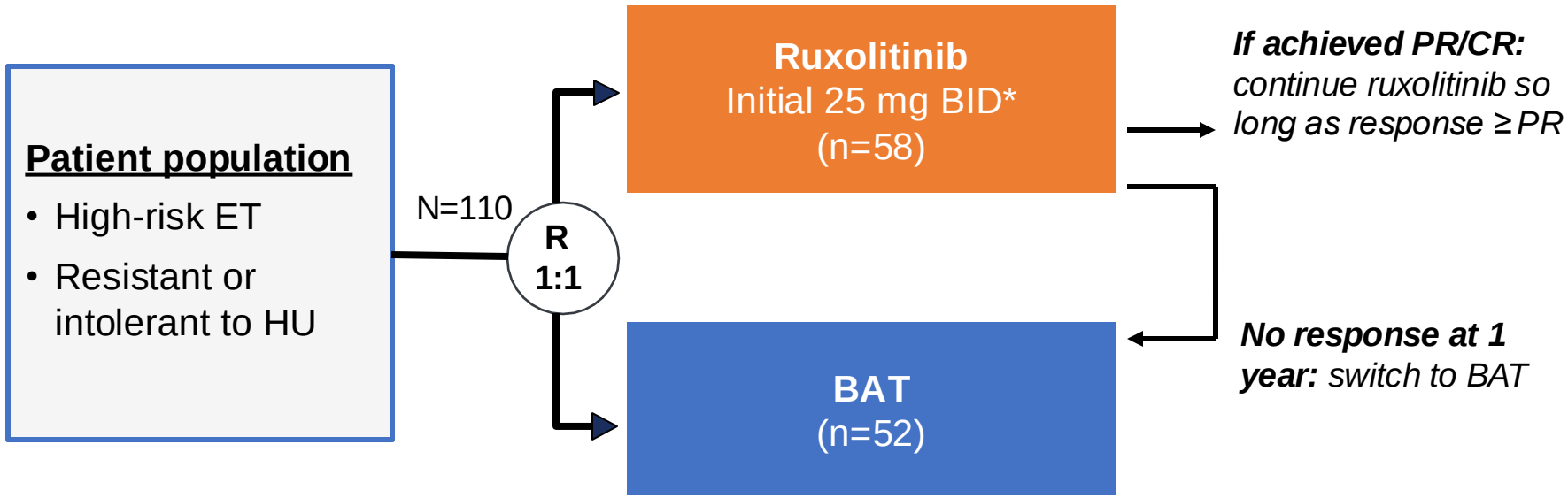


Event, n (%)	All Treatments				Ruxolitinib			BAT		
	All patients (n=127)	NMR (n=74)	PMR (n=53)	*P* value	NMR (n=31)	PMR (n=39)	*P* value	NMR (n=43)	PMR (n=14)	*P* value
Thromboembolic event	38 (30)	28 (38)	10 (19)	0.02	10 (32)	7 (18)	0.17	18 (42)	3 (21)	0.17
Hemorrhagic event	28 (22)	23 (31)	5 (9)	0.004	9 (29)	4 (10)	0.04	14 (33)	1 (7)	0.06
PFS	35 (28)	29 (39)	6 (11)	0.001	13 (42)	3 (8)	0.001	16 (37)	3 (21)	0.28
EFS	53 (42)	40 (54)	13 (25)	0.001	16 (52)	8 (21)	0.006	24 (56)	5 (36)	0.19
OS	22 (17)	18 (24)	4 (8)	0.01	8 (26)	3 (8)	0.04	10 (23)	1 (7)	0.18

Harrison C, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

Phase 2 MAJIC-ET Study

A randomized, open-label study of ruxolitinib vs BAT in patients with ET-resistant or intolerant to HU



Baseline: resistant to HU, 48.2%; intolerant to HU, 51.8%; both, 22.7%

This regimen is not approved by the FDA.

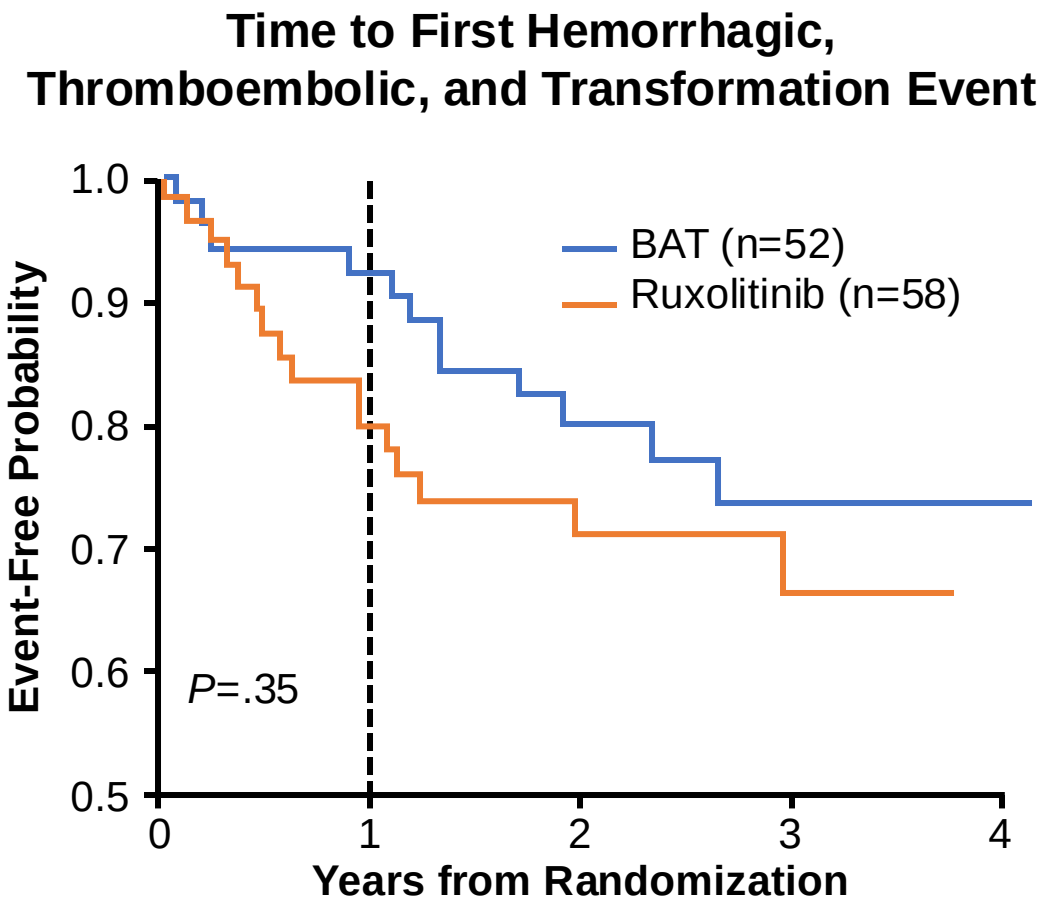
Primary Endpoint
• CR within 1 yr of treatment (ELN criteria)
Key Secondary Endpoints
• PR rate within 1 yr of treatment • DoR • ORR • Histologic response • Molecular response • Hemorrhagic and thromboembolic events • Disease transformation • OS • PFS • QoL • Disease symptom burden • Safety

***If platelets are 100-200 x 10^9/L, ruxolitinib is dosed at 20 mg BID.**

Harrison C, et al. *Blood.* 2017;130(17):1889-1897.

MAJIC-ET: Similar Outcomes with Ruxolitinib vs BAT in ET

- No difference in CR, PR within first yr of treatment
  - CR: ruxolitinib, 46.6%; BAT, 44.2% (*P*=.40)
- Rates of thrombosis, hemorrhage, or transformation not different between arms at 2 years
- More grade 3/4 anemia, thrombocytopenia, and grade 3 infections with ruxolitinib vs BAT
- More d/c with ruxolitinib vs BAT (60% vs 19%)
- Some molecular responses in ruxolitinib-treated patients with *JAK2* V617F or *CALR* positivity
- Better improvement of some disease-related symptoms with ruxolitinib



This regimen is not approved by the FDA.

Harrison C, et al. *Blood.* 2017;130(17):1889-1897.

Ruxolitinib Dosing Strategies in PV

Recommended starting dose: 10 mg PO BID

Perform CBC every 2 to 4 weeks during titration

Decrease dose for AE

If	Dose adjustment
HGB ≥12 g/dL AND platelets ≥100 x 10^9/L	No change
HGB 10 to <12 g/dL AND platelets 75 to <100 x 10^9/L	Consider dose reduction with the goal of avoiding interruption
HGB 8 to <10 g/dL OR platelets 50 to <75 x 10^9/L	Reduce by 5 mg BID If 5 mg BID, reduce to 5 mg daily
HGB <8 g/dL OR platelets <50 x 10^9/L	Interrupt dosing

Increase dose for insufficient response

If all 4 conditions are met	Dose adjustment
1. Inadequate efficacy (≥1 of below) • Continued need for TP • WBC > ULN • Platelets > ULN • Palpable spleen reduced <25% from baseline	Increase by 5 mg BID to maximum 25 mg BID Do not increase during first 4 weeks or more frequently than every 2 weeks
2. Platelets ≥140 x 10^9/L	
3. HGB ≥12 g/dL	
4. ANC ≥1.5 x 10^9/L	

TP = treatment plan.

FDA. Last updated November 2011. Accessed November 6, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf.

Pearls: Notable Treatment-Related AEs

INTERFERONS

Contraindications
- Severe psychiatric disorders, especially depression or suicidal ideation
- Hepatic impairment
- History of serious or untreated autoimmune disease

Ophthalmologic toxicities (eg, retinopathy)
- Occurred in 23% of patients
- Patients with diabetes or hypertension more susceptible
- Advise regular eye examinations

Liver function
- Regular monitoring; manage with dose adjustments

HYDROXYUREA

Leg or mouth ulcers
- Occurred in ~9% of patients
- Will not respond to conventional therapy while continuing HU treatment

RUXOLITINIB

Weight gain
- Due to on-target effect on leptin signaling
- Inform patients and provide diet/exercise counseling

Risk of nonmelanoma skin cancer
- Perform regular skin examination

Risk of infection
- Active surveillance and prophylactic antibiotics
- Consider zoster vaccination

FDA. Last updated March 2016. Accessed November 5, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/016295Orig1s047,s048Lbl.pdf. FDA. Last updated November 2021. Accessed November 5, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761166s000lbl.pdf. FDA. Accessed November 5, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202192lbl.pdf. Badawi M, et al. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2015;120(6):e232-e234. Geyer H, et al. *J Clin Oncol*. 2016;34(2):151-159. Mesa R, et al. *Cancer*. 2017;123(3):449-458. Molle N, et al. *Blood*. 2020;135(13):1062-1066.

ET/PV Treatment Landscape: Examples of Ongoing Trials in the US

Agent	MOA	Trial/Phase	Population
RoPEG	Interferon	NCT05481151 (ECLIPSE-PV) Phase 3b	PV; no restrictions regarding phlebotomies or prior treatments
Rusfertide vs placebo	Peptide hepcidin–mimetic	NCT05210790 (VERIFY) Phase 3	Phlebotomy-dependent PV with/without concurrent cytoreductive therapy to control hematocrit
Givinostat	HDAC inhibitor	NCT06093672 (GIV-IN PV) Phase 3	JAK2 V617F-positive, high-risk PV
Ruxolitinib + HU or IFN-α vs BAT	JAK 1/2 inhibitor	NCT04116502 (MITHRIDATE) Phase 3	High-risk PV patients with leukocytosis
Ruxolitinib	JAK 1/2 inhibitor	NCT04644211 Phase 2	Low-risk, symptomatic PV patients
Ruxolitinib + Umbralisib	JAK 1/2 inhibitor; PI3Kδ inhibitor	NCT02493530 Phase 1	PV patients refractory/intolerant of HU
Bomedemstat	LSD1 inhibitor	NCT04262141 Phase 2	ET and PV patients who require platelet, WBC,or RBC control, and failed ≥1 therapy
Sapablursen	TMPRSS6 ligand-conjugated antisense oligonucleotide	NCT05143957 Phase 2	Phlebotomy-dependent PV patients
SLN124	TMPRSS6 ligand-conjugated antisense oligonucleotide	NCT05499013 Phase 1/2	All PV patients

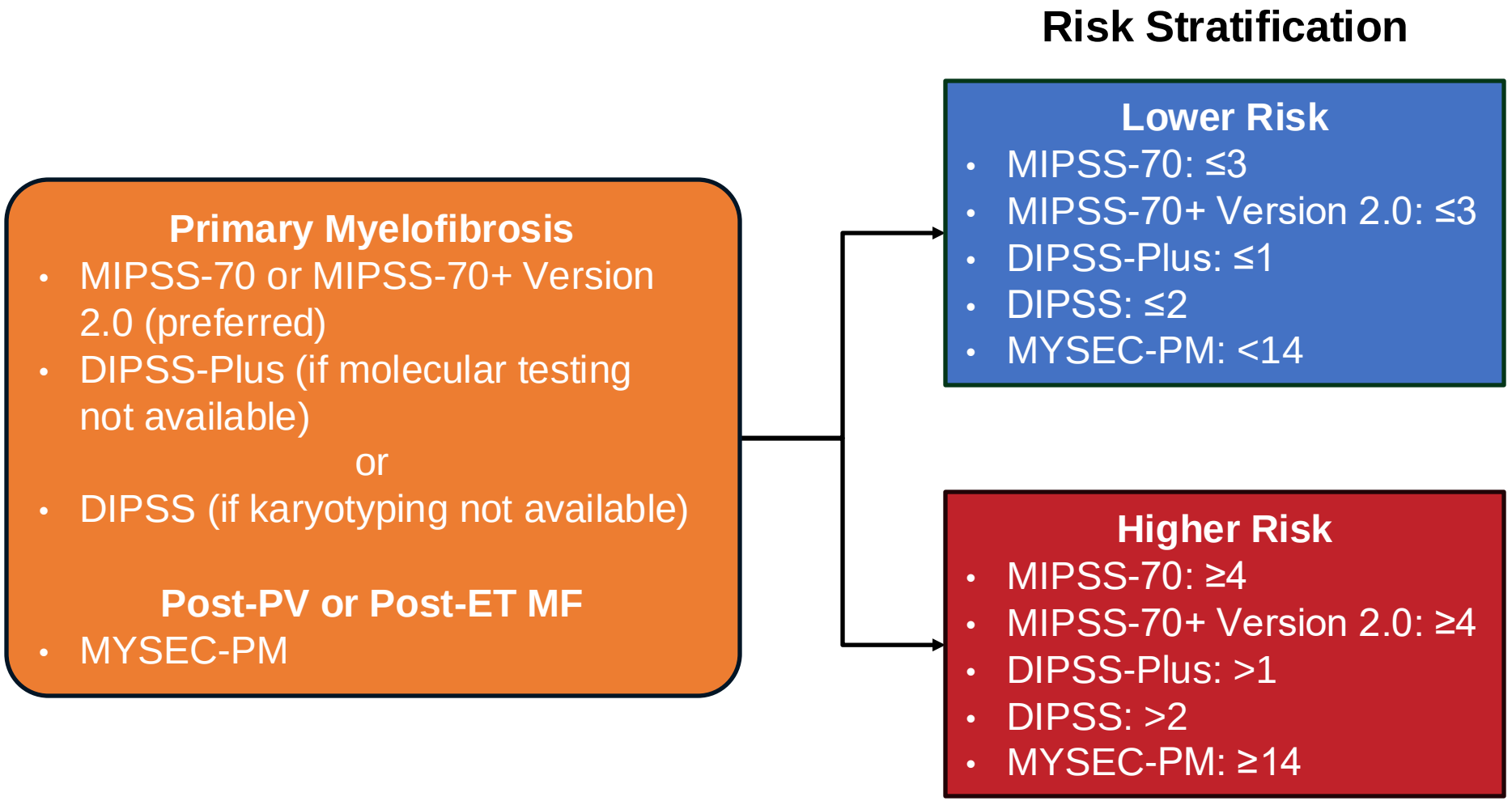
These regimens are not approved by the FDA.

RBC = red blood cell.

Adapted from Masarova L, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24(3):141-148. NIH. Accessed November 6, 2024. https://clinicaltrials.gov/study/NCT05481151; NCT05210790; NCT06093672; NCT04116502; NCT04644211; NCT02493530; NCT04262141; NCT05143957; NCT05499013.

Management of MPNs – MF

Risk Stratification Has Become a Critical Aspect of Planning for Appropriate Therapy



MIPSS = Mutation-enhanced International Prognostic Scoring System; DIPSS = Dynamic International Prognostic Scoring System; MYSEC-PM = Myelofibrosis Secondary to PV and ET-Prognostic Model.

National Comprehensive Cancer Network. Accessed November 6, 2024. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Characterizing Established JAKi Platforms

Ruxolitinib (*JAK1/2*)

- Approved for intermediate-/high-risk MF based in part on COMFORT trials

Fedratinib (*JAK2/FLT3*)

- Approved for INT-2/high-risk MF; validated by JAKARTA and long-term safety evidence (where no cases of WE were reported)

Pacritinib (*JAK2/FLT3/ACVR1/IRAK1*)

- Approved for adults with adults with intermediate- or high-risk MF, and especially at risk for developing cytopenias, with platelets <50 x 10^9/L
- Validated by PERSIST trials

Momelotinib (*JAK1/JAK2/ACVR1*)

- Approved for intermediate- or high-risk MF patients with anemia
- Validated by MOMENTUM study and subpopulation from the SIMPLIFY-1 trial

JAKi = JAK protein inhibitor.

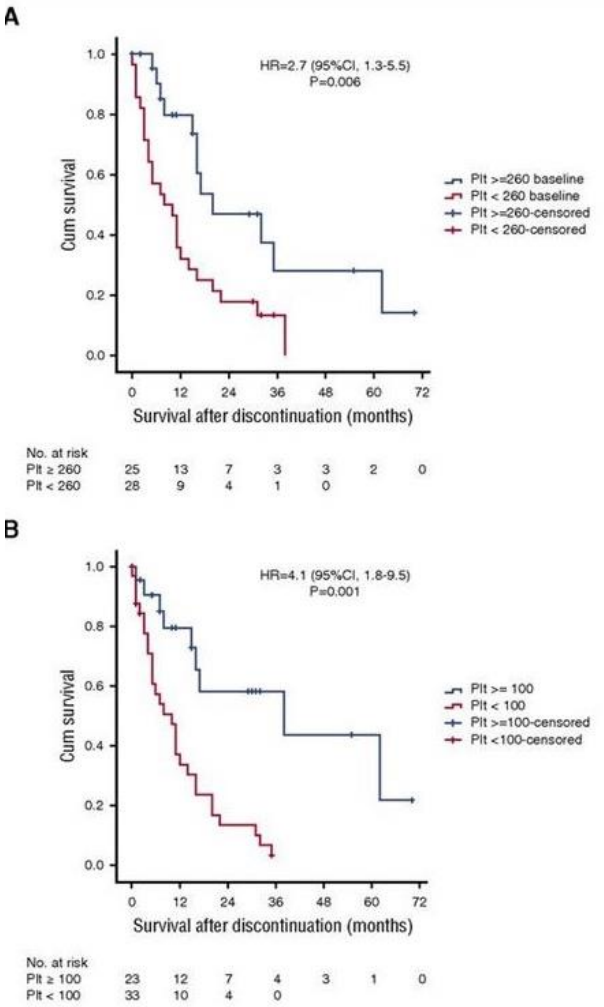
Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798. Pardanani A, et al. *Br J Haematol*. 2021;195(2):244-248. Pardanani A, et al. Presented at: American Hematology Society Annual Meeting and Exposition; December 5-8, 2020; Virtual. Abstract 3006. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. NIH. Accessed November 6, 2024. https://clinicaltrials.gov/study/NCT04173494; NCT01969838.

Challenges in Optimizing Care with JAKi Platforms

METER: Real-world study exploring treatment patterns, effectiveness, and healthcare resource use in MF

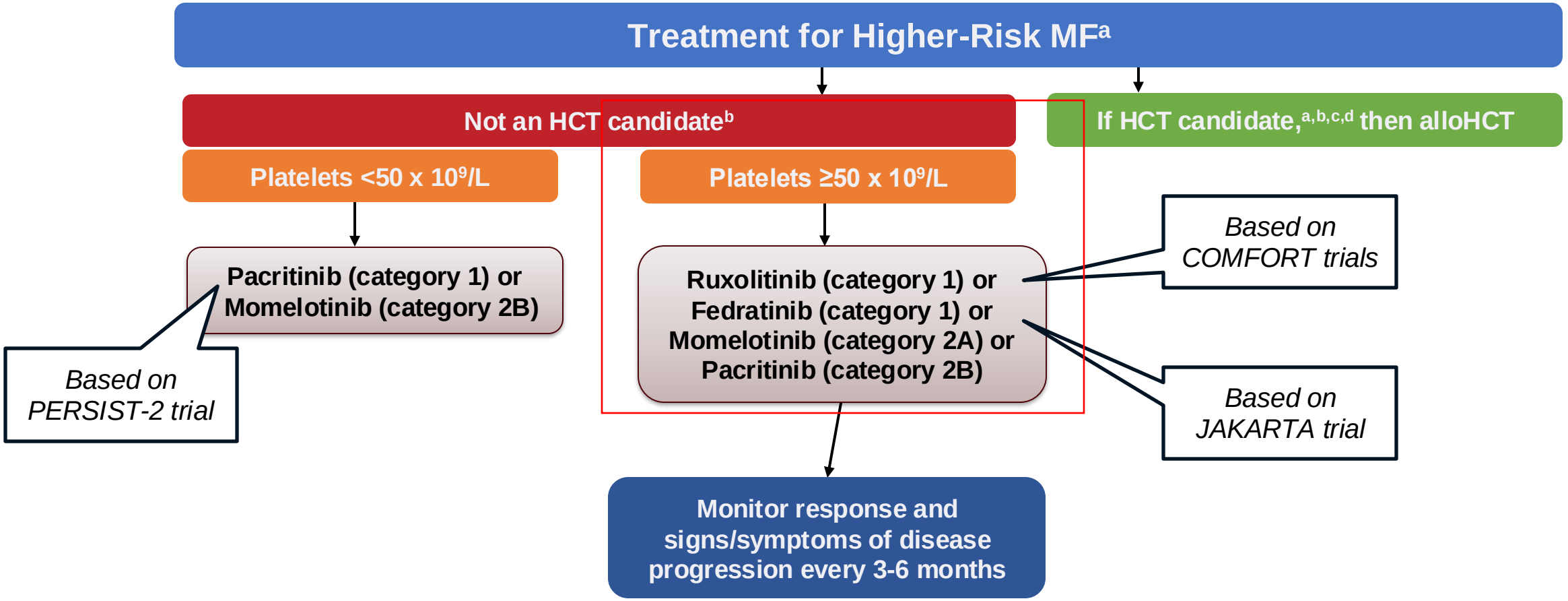
- Average interval from MF diagnosis to start of initial treatment was ~8.5 months
- Gaps in care transition: most patients remained on 1L therapy through week 24; however, 2L treatment was not initiated until week 156

- Survival in MF patients after ruxolitinib discontinuation is poor (mOS = 14 months)
- Low platelets at the start or end of therapy or clonal evolution while on therapy was associated with an even worse prognosis



Gupta V, et al. *Blood*. 2023;142(Suppl 1):3205. Newberry KJ, et al. *Blood*. 2017;130(9):1125-1131. NIH. Accessed November 6, 2024. https://clinicaltrials.gov/study/NCT05444972.

NCCN Guidelines: JAKi Therapy Is Well Established as an Effective Option in Higher-Risk Disease



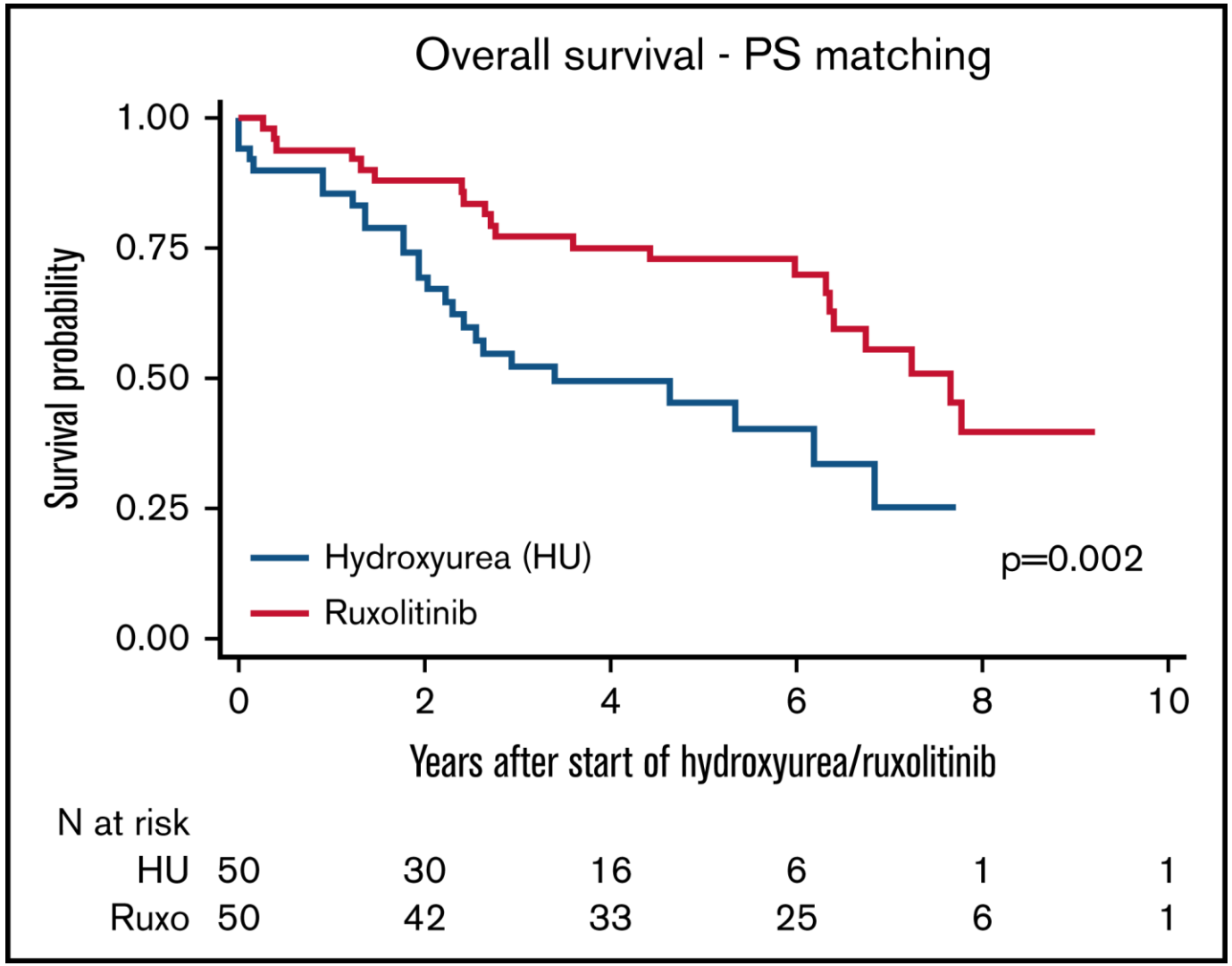
[a]Evaluation for alloHCT is recommended for all patients. Identification of "higher-risk" mutations can be helpful for decision-making; [b]The selection of patients for alloHCT should be based on age, PS, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Early referral recommended for planning purposes. Bridging therapy can be used to decrease marrow blasts prior to HCT; [c]JAK inhibitors may be continued near to the start of conditioning to improve splenomegaly and other disease-related symptoms; [d]Donor selection and conditioning should be evaluated on a case-by-case basis.

NCCN. Accessed November 6, 2024. https://www.nccn.org/patients/guidelines/content/PDF/mpn-patient.pdf.

ERNEST: What Is the Real-World Impact of Ruxolitinib in MF?

Analysis of the impact of ruxolitinib for OS by using real-world data (n=1010)

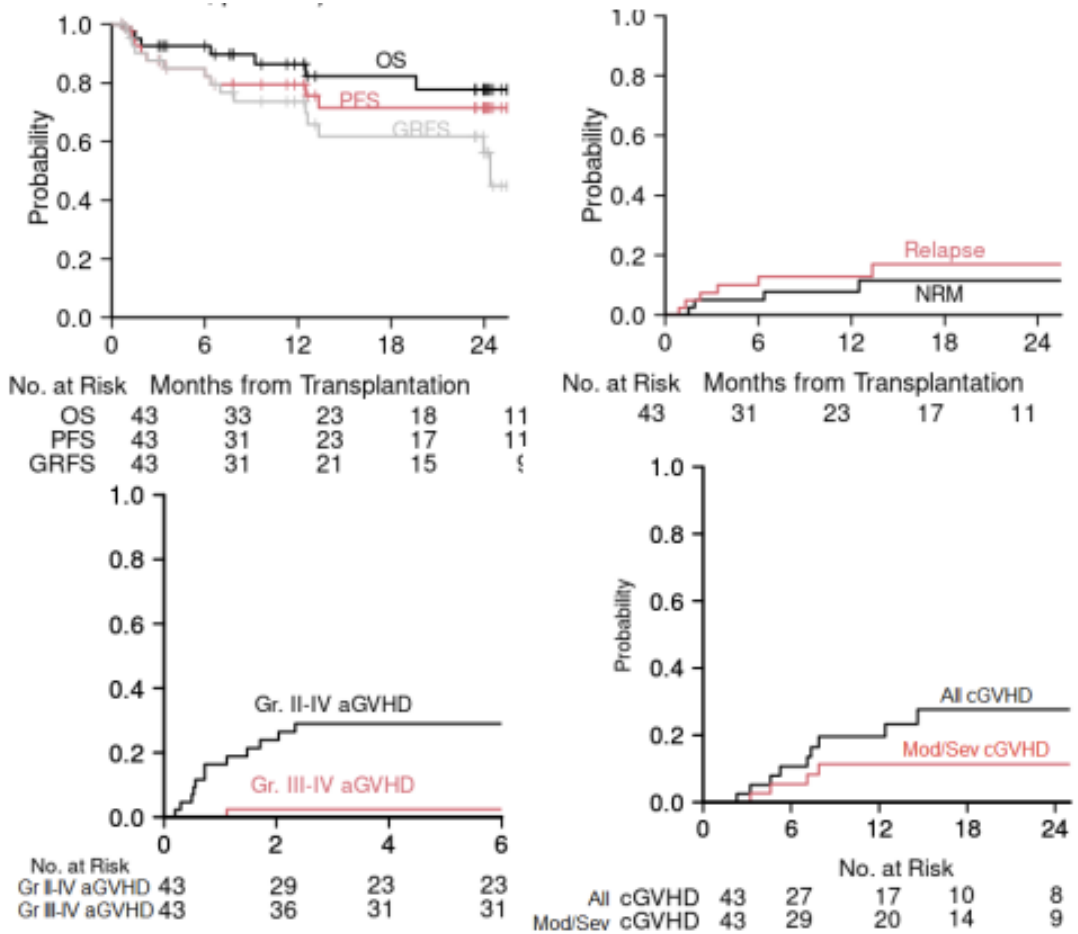
- 10-year OS after start of HU and ruxolitinib in PS-matched groups
- Compared with HU, ruxolitinib was associated with a significant benefit in terms of OS
- Benefit was also seen in PS analysis within small sample sizes



Guglielmelli P, et al. *Blood Adv*. 2022;6(2):373-375.

Updates on Ruxolitinib In the Peri- and Post-Transplant Setting

- 1-year GRFS: 74%
- OS, PFS, and cumulative incidence of NRM and disease relapse were 86%, 79%, 10%, and 10%, respectively
- Most common grade 3/4 AEs were anemia, thrombocytopenia, neutropenia, and hypertriglyceridemia

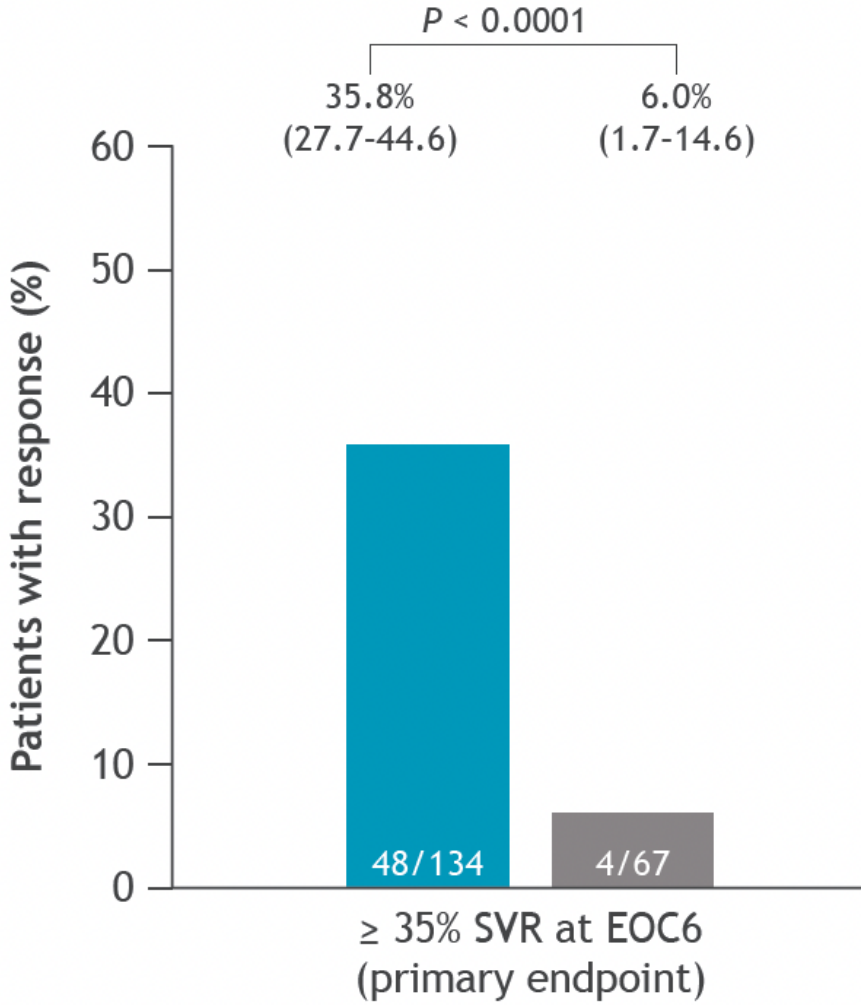


GRFS = graft-versus-host disease-free, relapse-free survival; NRM = non-relapse mortality; GVHD = graft-versus-host disease; a = acute; c = chronic.

Hobbs GS, et al. Presented at: 65th American Society of Hematology Annual Meeting and Exposition; December 9, 2023; San Diego, California. Abstract 2103.

Fedratinib as a Sequential Option in MF Patients Previously Treated with Ruxolitinib

- **FREEDOM2**: Patients with MF previously treated with ruxolitinib had superior SVR and symptom response when treated with fedratinib compared with BAT
- The primary endpoint of SVR35 at EOC6 was met by 35.8% of patients in the fedratinib arm compared with 6.0% of patients in the BAT arm
- Most patients treated with fedratinib showed a reduction in spleen volume from baseline at EOC6



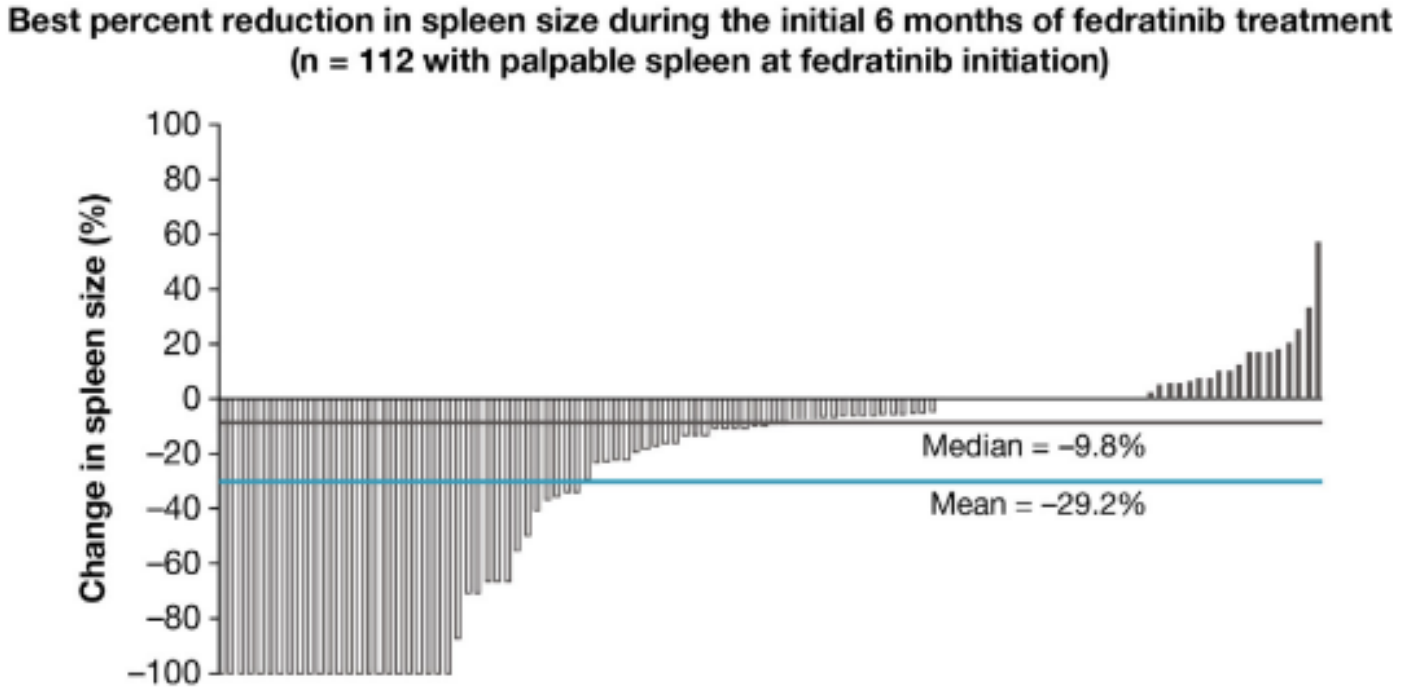
SVR = spleen volume reduction; EOC = end of cycle.

Harrison CN, et al. Presented at: 65th American Society of Hematology Annual Meeting and Exposition; December 10, 2023; San Diego, California. Abstract 3204.

RWE Shows Benefits of Sequential Therapy with Fedratinib

Retrospective patient chart review in adults with MF who initiated fedratinib after discontinuing ruxolitinib (N=150 eligible patients).

- At month 3 of fedratinib treatment, spleen size decreased by 19.4% to 13.2 cm (*P*=.0001)
- At month 6, spleen size decreased by 53.4% to 7.2 cm (*P*=.01)
- 26.8% of patients had achieved ≥50% spleen reduction by month 6



RWE = real-world evidence.

Mascarenhas J, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24(2):122-132.

Practical Guidance on Delivering Therapy with JAKi Platforms: Ruxolitinib

Starting dose by baseline platelet count

- >200 x 10^9/L: 20 mg BID
- 100 to 200 x 10^9/L: 15 mg BID
- 50 to >100 x 10^9/L: 5 mg BID

Safety considerations

- Thrombocytopenia, anemia, and neutropenia: Manage by dose reduction, interruption, or transfusion
- Assess patients for signs and symptoms of infection and initiate appropriate treatment promptly
- Serious infections should have resolved before starting therapy

Practical Guidance on Delivering Therapy with JAKi Platforms: Fedratinib

Recommended dosage

- 400 mg orally once daily with or without food

Safety considerations

- Frequency and severity of GI AEs can be reduced via early implementation of GI prophylaxis (eg, antiemetics)
- Monitoring thiamine levels before fedratinib initiation and periodically during therapy is recommended (thiamine supplements can be useful)

2024 NCCN Guidelines Updates for MF-Associated Anemia

Presence of symptomatic splenomegaly and/or constitutional symptoms

No symptomatic splenomegaly and/or constitutional symptoms

Controlled on a JAKi

Preferred	Other Recommended Regimens	Useful in Certain Circumstances
• Clinical trial	• Ruxolitinib combination - Add luspatercept - Add ESA (if serum EPO <500 mU/mL) - Danazol (category 2B)	• Change to momelotinib • Change to pacritinib

Not controlled

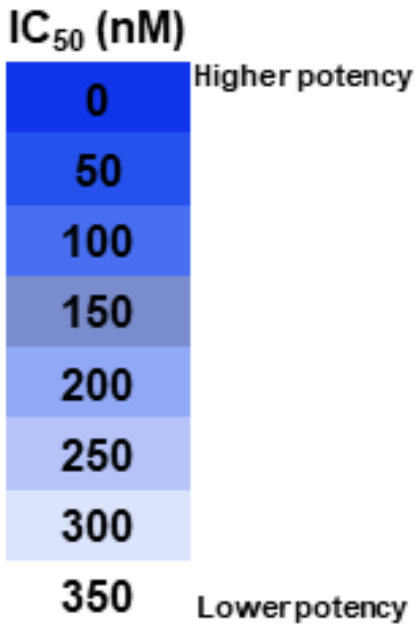
Preferred	Other Recommended Regimens
• Clinical trial • Momelotinib	• Pacritinib • Ruxolitinib combination - Luspatercept - ESAs (if serum EPO <500 mU/mL) - Danazol (category 2B)

NCCN. Accessed November 6, 2024. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Pacritinib Is a Potent ACVR1 Inhibitor

	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
ACVR1 IC_{50} (nM) **Replicate 1**	22.6	70.2	312	>1000
ACVR1 IC_{50} (nM) **Replicate 2**	10.8	34.9	235	>1000
ACVR1 IC_{50} (nM) **Mean**	16.7	52.5	273	>1000
Potency (C_{max}:IC_{50})[a]	12.7	3.2	1	<0.01

[a]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.



Pacritinib is ~4x more potent than momelotinib against ACVR1

C_{max} = maximum concentration; FED = fedratinib; MMB = momelotinib.

Oh ST, et al. *Blood*. 2022;140(suppl 1):1518-1521.

PERSIST-2
Study Design

Status: reached agreement with FDA on SPA October 2013

Sites: North America, Europe, Russia, and Oceania

Anticipated patient accrual: ~ 300

Principal investigator: Srdan Verstovsek

[a] Crossover from BAT allowed after progression or assessment of the primary endpoint.

[b] BAT may include ruxolitinib at the approved dose for platelet count

CT, computed tomography; JAK, Janus kinase; MRI, magnetic resonance imaging; TSS, total symptom score.

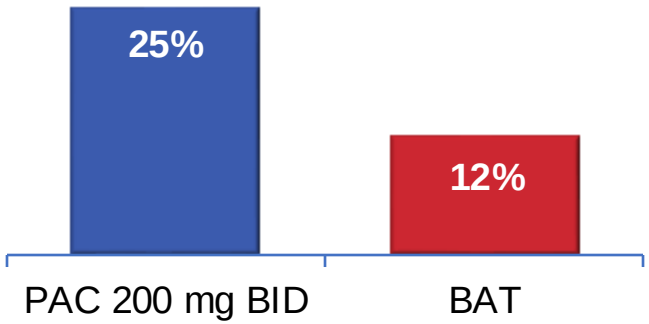
[a]International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL; [b]TI defined according to Gale criteria (0 units over the course of 12 weeks).

Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

PERSIST-2: Hematologic Study

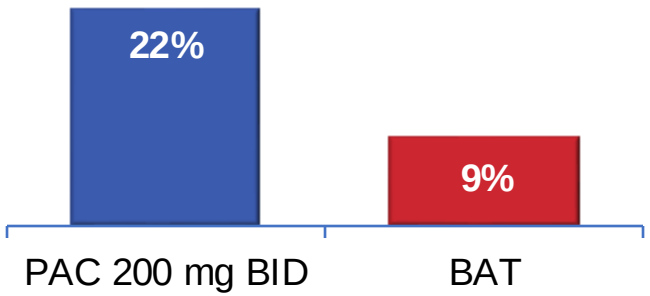
Clinical improvement in hemoglobin levels in patients with baseline anemia[a]

Baseline to week 24



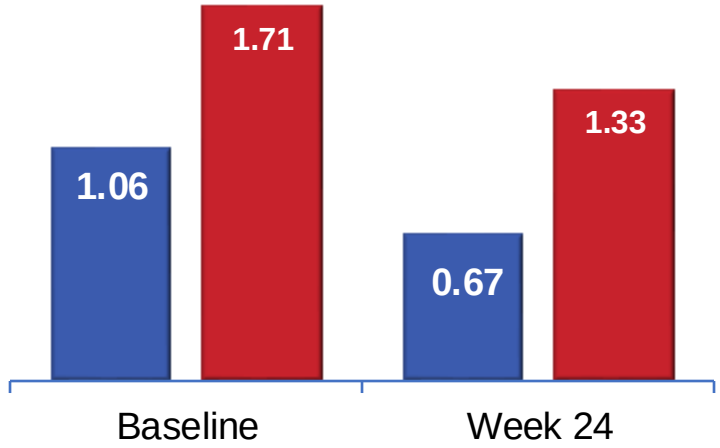
Pacritinib reduced transfusion burden in patients not TI[b] at baseline

Baseline to week 24



Transfusion burden in patients who received ≥1 RBC transfusion on study

Units per month



In MF patients especially at risk for developing worsened cytopenias with a platelet count of <50 x 10^9/L, pacrinitib may be used in first- and second-line treatment.

[a]International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL; [b]TI defined according to Gale criteria (0 units over the course of 12 weeks).

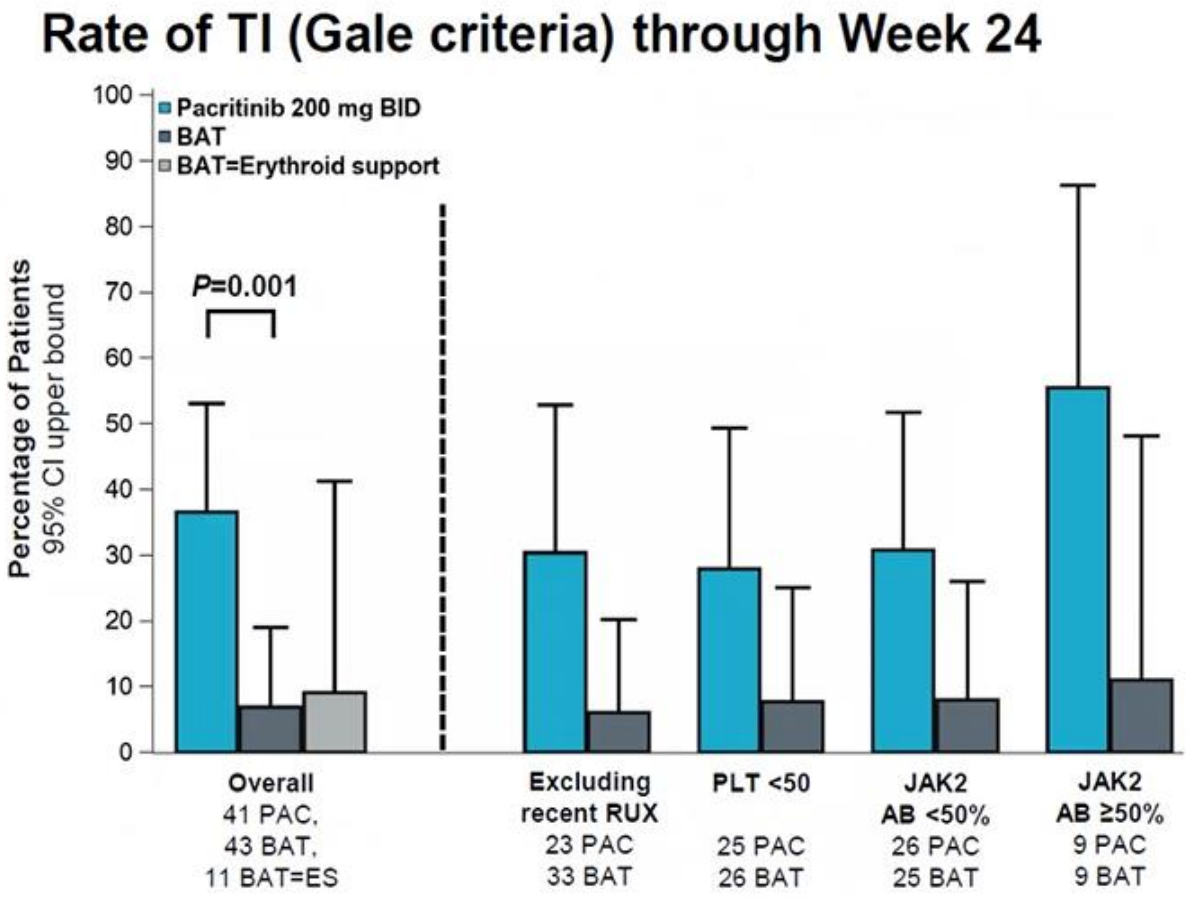
Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

More Pacritinib Patients Had TI (Gale Criteria)

TI Conversion Rate

Pacritinib n=41	BAT n=43	P Value
37%	7%	.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



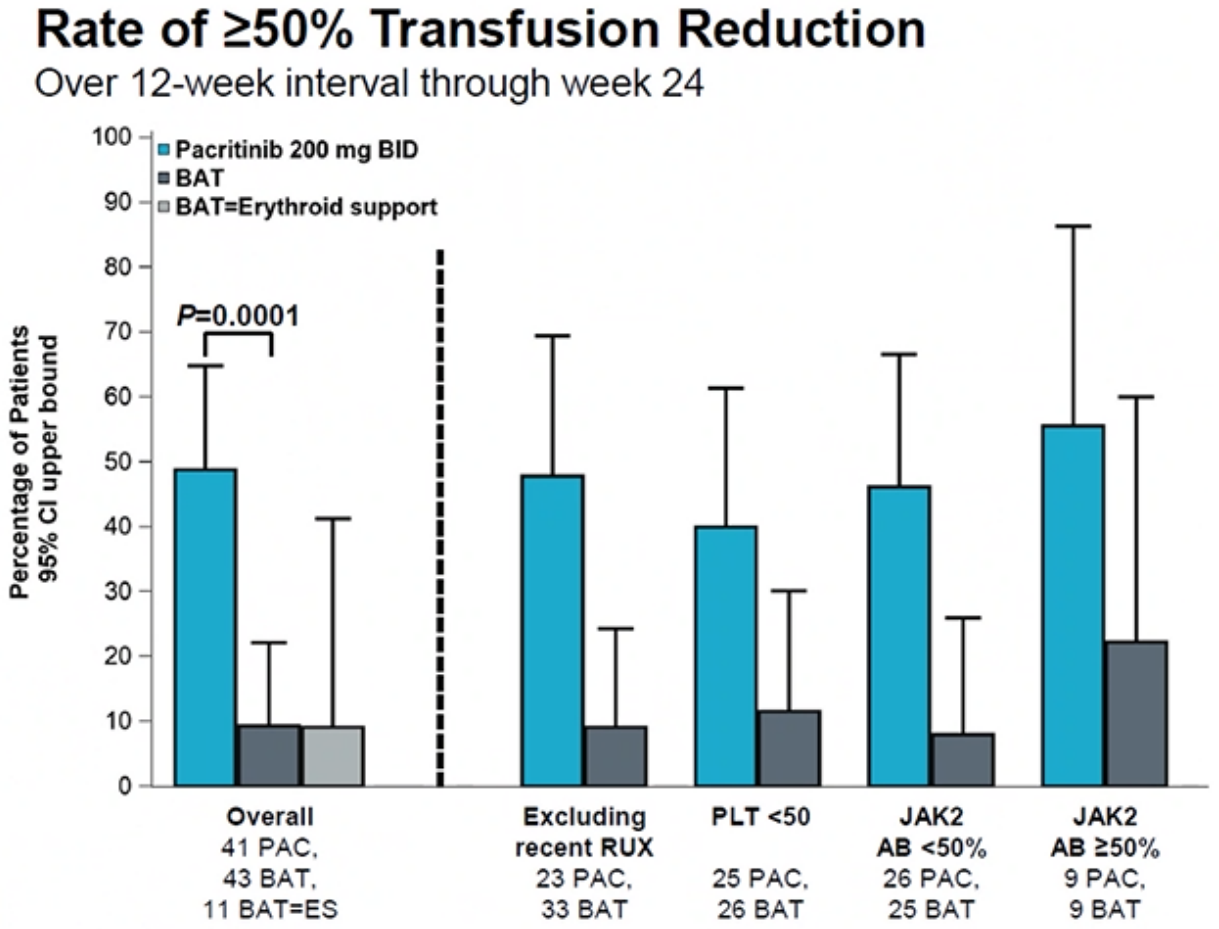
Oh ST, et al. *Blood*. 2022;140(suppl 1):1518-1521.

More Pacritinib Patients Had ≥50% Transfusion Reduction

Transfusion Reduction

Pacritinib n=41	BAT n=43	P Value
49%	9%	.0001

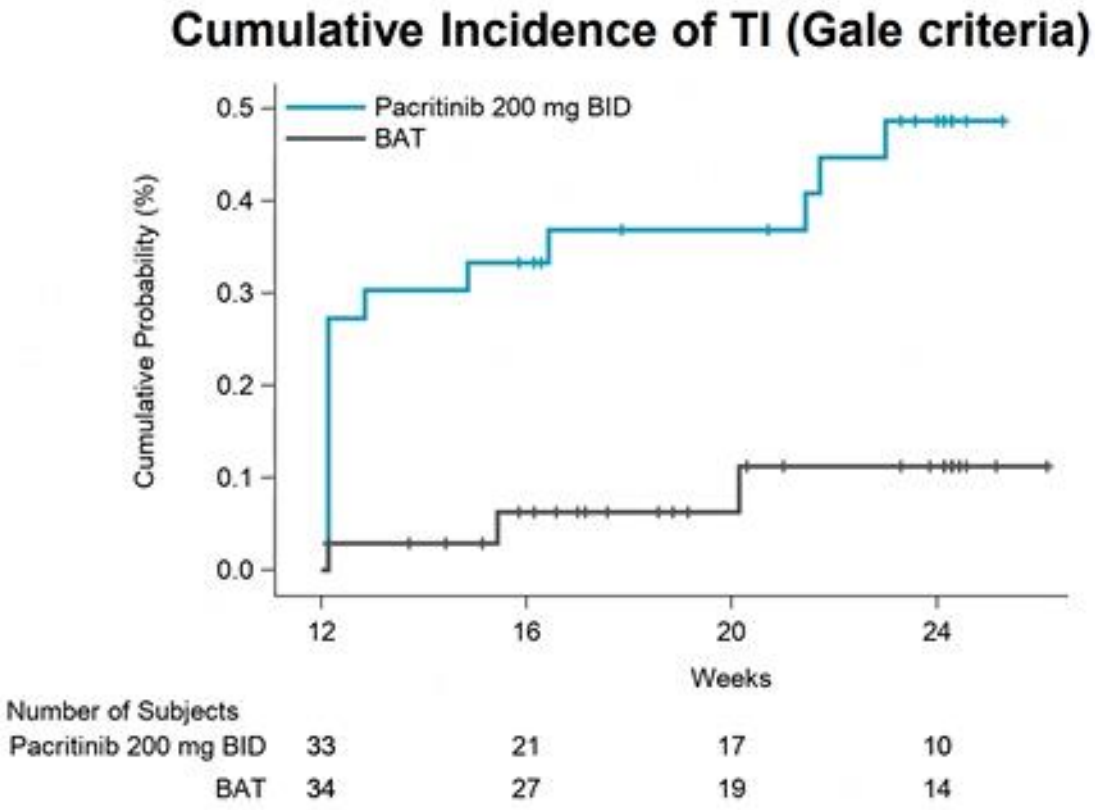
- Clinically significant reduction in transfusion burden more common on pacritinib



Oh ST, et al. *Blood*. 2022;140(suppl 1):1518-1521.

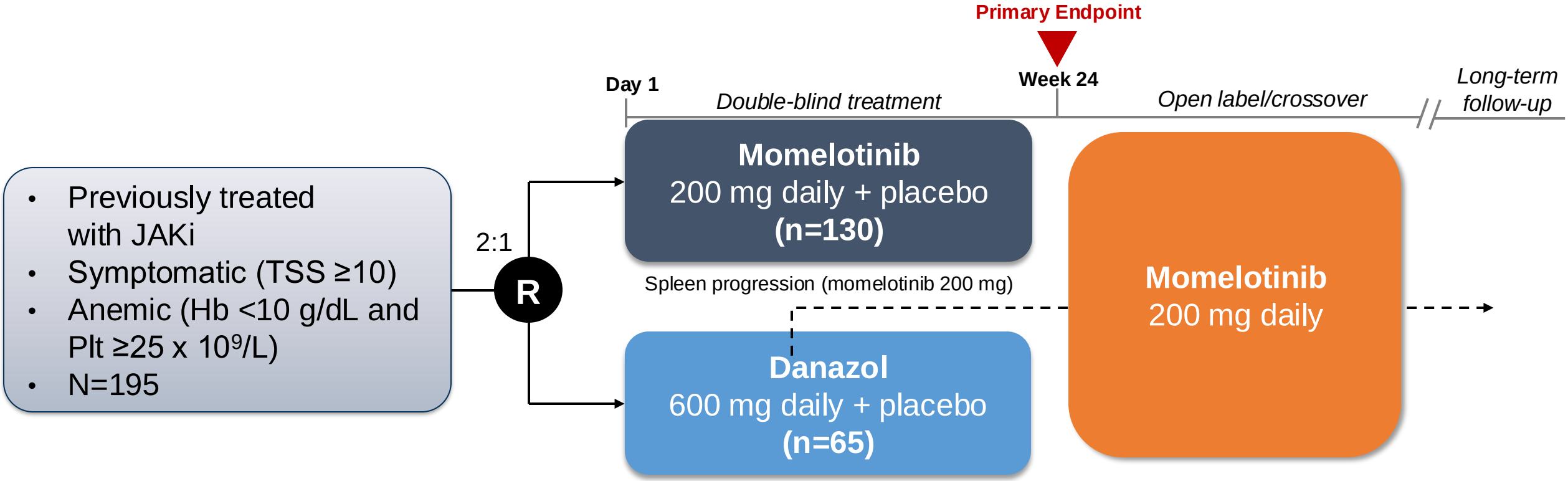
TI Conversion Can Occur Late in Treatment

- Many responses occurred early during treatment
- Some responses occurred after several months on treatment



Oh ST, et al. *Blood*. 2022;140(suppl 1):1518-1521.

Phase 3 MOMENTUM Trial Assessed Momelotinib in the Post-JAKi Setting in MF



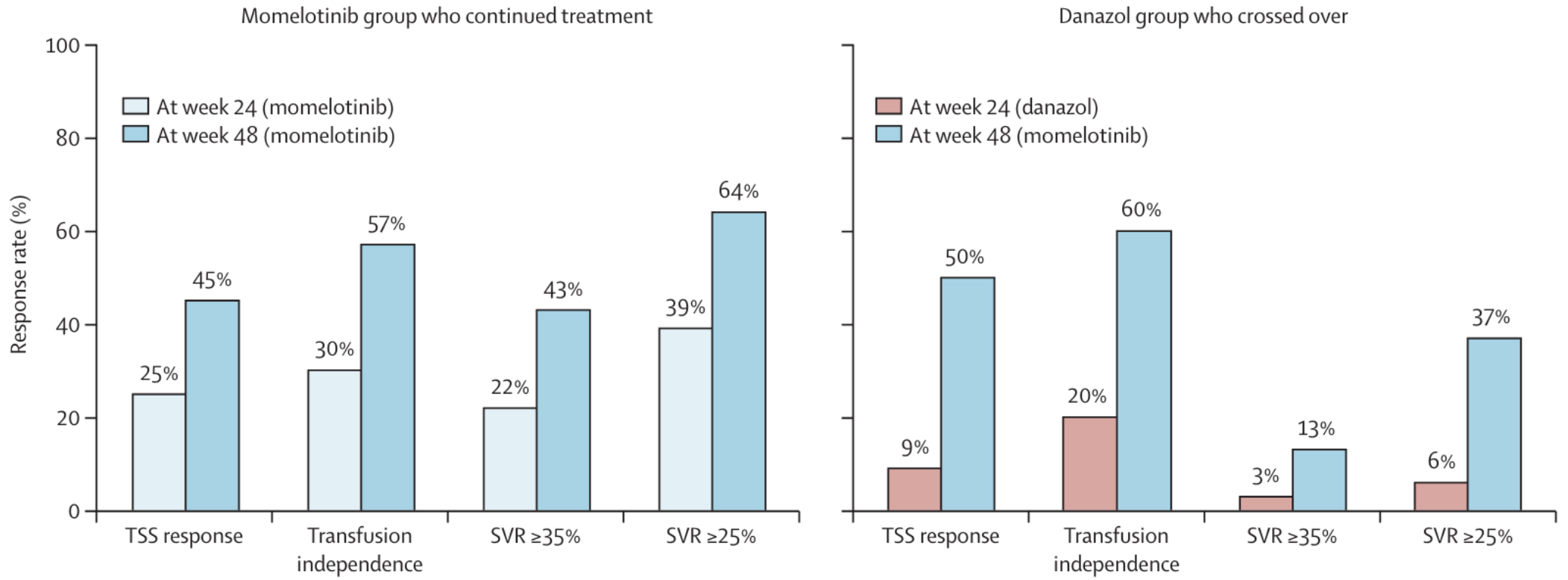
- **Primary endpoint:** TSS response rate at week 24
- **Secondary endpoints:** TI rate at week 24, splenic response rate (SRR) at week 24

All primary and key secondary endpoints met

Hb = hemoglobin; TI = transfusion independence.

NIH. Accessed November 13, 2024. https://clinicaltrials.gov/study/NCT04173494. Verstovsek S, et al. *Lancet*. 2023;401(10373):269-280. Mesa R, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, Illinois. Abstract 7002.

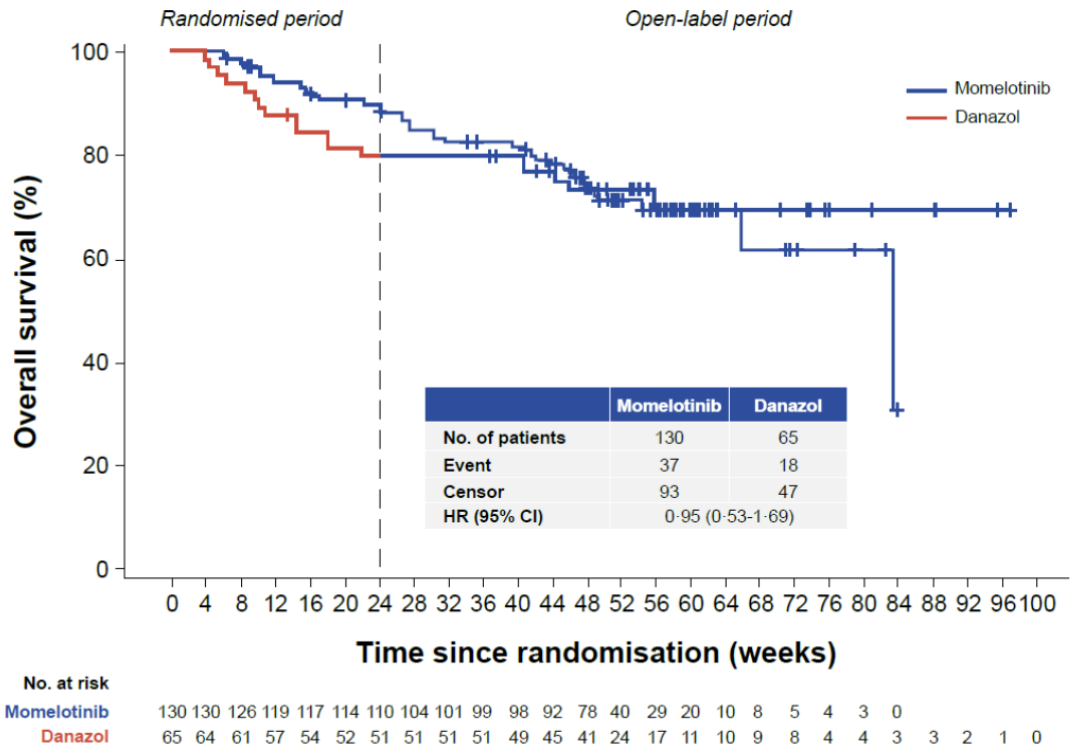
MOMEMTUM: Week 24 Responses Were Sustained through Week 48



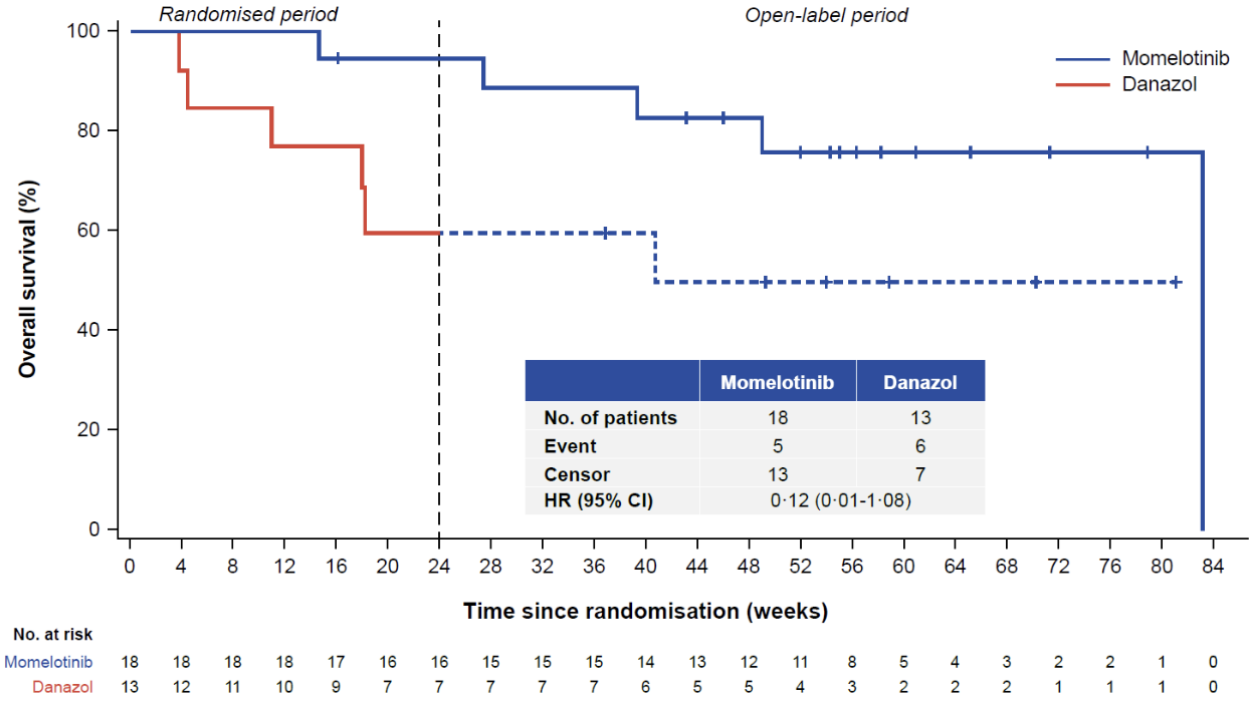
- Week 24 TSS response was 25% in the MMB group and 9% in the DAN group
- No new safety signals emerged with long-term follow-up

Gerds AT, et al. *Lancet Haematol.* 2023;10(9):e735-e746.

MOMEMTUM: Survival Analysis and Updates



	Momelotinib	Danazol
No. of patients	130	65
Event	37	18
Censor	93	47
HR (95% CI)	0·95 (0·53-1·69)	



	Momelotinib	Danazol
No. of patients	18	13
Event	5	6
Censor	13	7
HR (95% CI)	0·12 (0·01-1·08)	

2024 ASCO Annual Meeting - Poster Session

Long-term survival adjusted for treatment crossover in patients (pts) with myelofibrosis (MF) treated with momelotinib (MMB) vs danazol (DAN) in the MOMENTUM trial.

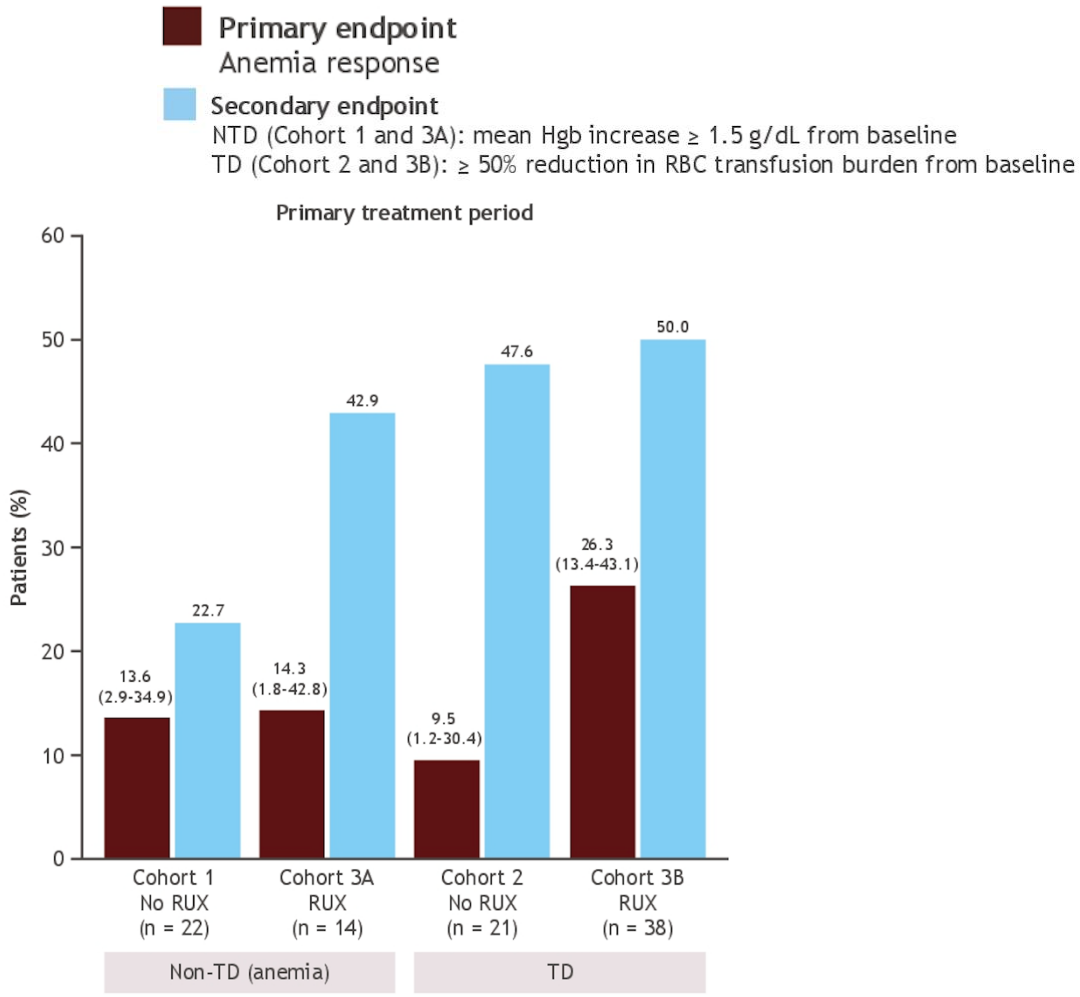
Abstract: 6571 | Poster Bd #: 130

Gerds AT, et al. *Lancet Haematol.* 2023;10(9):e735-e746.

Luspatercept Shows Efficacy in the Setting of MF-Induced Anemia

- Phase 2 trial assessing erythroid maturation agent luspatercept in patients with MF associated anemia ± TD
- Safety profile of luspatercept consistent with previous studies
- Treatment with luspatercept induced improvements in anemia and transfusion burden in all cohorts

Use of luspatercept for MF-induced anemia in patients with TD on JAK2i therapy is being assessed in the phase 3 INDEPENDENCE study.

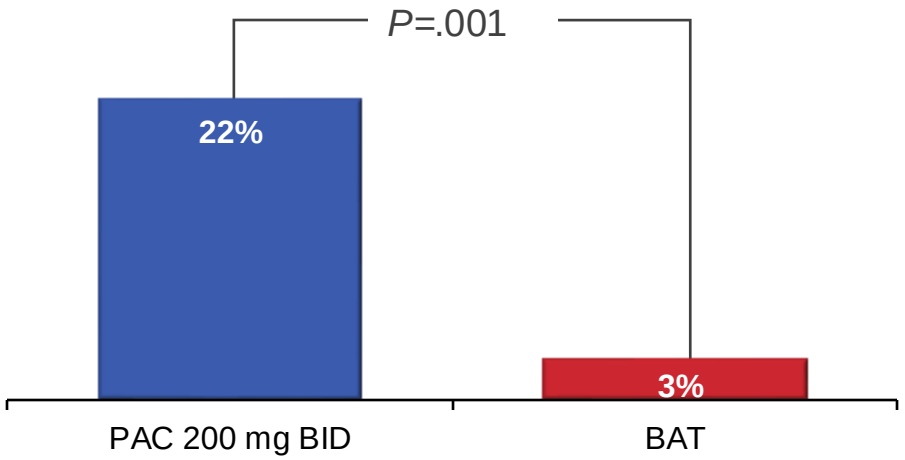


NTD = non-transfusion-dependent; RUX = ruxolitinib.

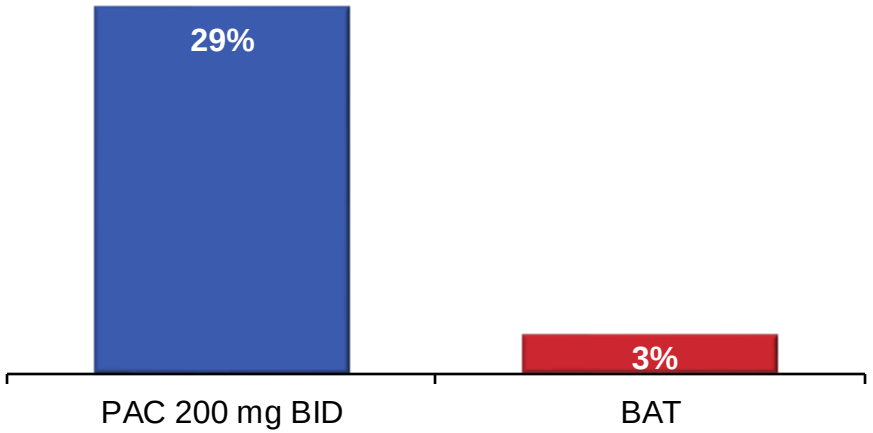
Gerds AT, et al. Presented at: American Society of Clinical Oncology Annual Meeting; June 2-6, 2023; Chicago, Illinois. Abstract 7016. NIH. Accessed November 13, 2024. https://clinicaltrials.gov/study/NCT04717414.

PERSIST-2: Spleen Volume Responses ≥35% at Week 24

ITT population



Patients with platelets <50 × 10^9/L



Additional subgroup analyses demonstrated patients receiving pacritinib had SVR ≥35% regardless of subgroup (eg, sex, age, *JAK2* V617F mutation status, prior treatment with JAK2 inhibitors, and baseline cytopenias).

ITT = intent-to-treat; PAC = pacritinib.

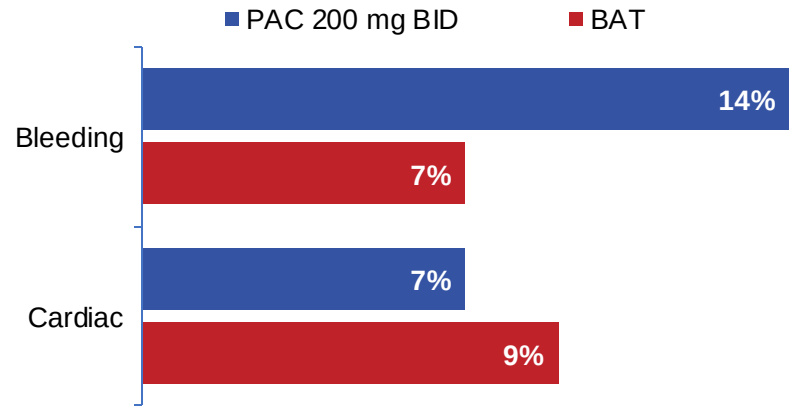
Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. NIH. Accessed December 2, 2024. https://clinicaltrials.gov/study/NCT02055781.

PERSIST-2: Adverse Event Profile

	PAC 200 mg BID (n=106)	BAT (n=98)
Any-grade AEs in >15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	23
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16
Grade ≥3 AEs in >5% of patients in either arm, %		
Thrombocytopenia	32	18
Anemia	22	14
Neutropenia	7	5
Pneumonia	7	3
Serious AEs in >3% of patients in either arm, %		
Anemia	8	3
Thrombocytopenia	6	2
Pneumonia	6	4
Congestive heart failure	4	2

- Diarrhea with pacritinib most often occurred during weeks 1-8, was manageable, and resolved within 1-2 weeks
- Neurological AEs and opportunistic infections rarely reported with pacritinib

Grade ≥3 Events (Pooled[a])



Safety outcomes with pacritinib were similar for those with <50 x 10^9/L vs 50 to 100 x 10^9/L platelets at baseline.

PROs best help facilitate follow-up care visits with clinicians by assessing response to therapy and symptom control.

[a]Pooled, per standardized MedDRA queries.
PRO = patient-reported outcome.
Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

Practical Guidance on Delivering Therapy with JAKi Platforms: Pacritinib

Recommended dosage

- 200 mg orally twice daily

Safety considerations

- Avoid in patients with active bleeding; hold prior to surgical procedures
- For significant diarrhea: antidiarrheals, dose reduction, or dose interruption
- Thrombocytopenia: manage by dose reduction or interruption
- Avoid use in patients with baseline QTc >480 ms
- Interrupt and reduce dosage in patients who have a QTcF >500 ms

QTc = Q-Tc interval on an electrocardiogram; QTcF = Q-Tc interval corrected by the Fridericia method.

Momelotinib in MF: Practical Considerations

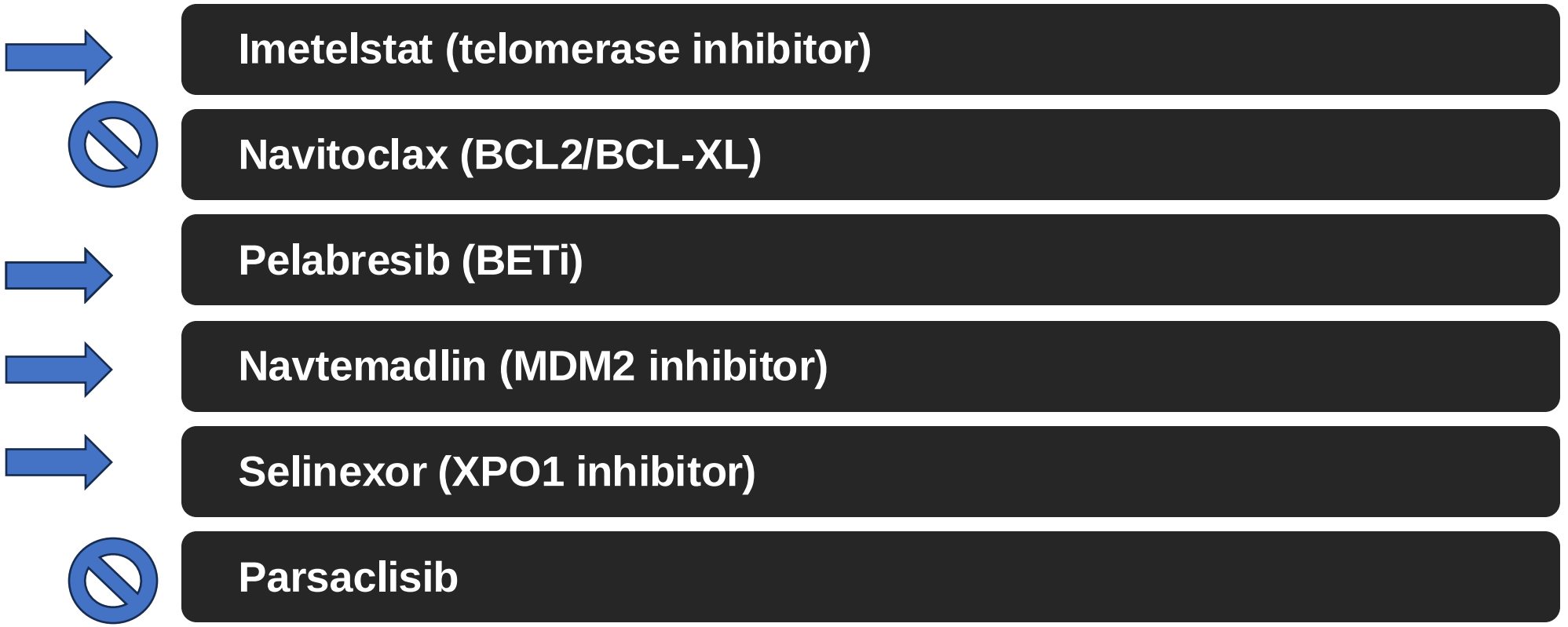
Dosing

- 200 mg orally once daily with or without food

Safety considerations

- The most common AEs reported in studies to date are thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea
- Monitor for signs and symptoms of infection
- Thrombocytopenia and neutropenia: manage by dose reduction or interruption
- Hepatotoxicity: obtain liver tests before therapy initiation and periodically throughout treatment

Other Novel MOAs with Applications in MF Are Being Rapidly Developed



MANIFEST-2 Global, Randomized, Double-Blind, Active-Control Phase 3 Study

Study population

JAKi-naïve patients with MF (N=430)
(primary or post-ET/PV)

- DIPSS Int-1 or higher
- Splenomegaly (≥450 cm^3) by CT/MRI
- TSS ≥10 (≥3 for two symptoms, MFSAF v4.0)

Double-blind randomization (1:1)

Treatment arm

Pelabresib 125 mg* PO QD Day 1-14 + **Ruxolitinib** Per label with a 5-mg BID lower starting dose† Day 1-21

21-day cycles

Placebo PO QD Day 1-14 + **Ruxolitinib** Per label with a 5-mg BID lower starting dose† Day 1-21

1:1 randomization stratified by:

- DIPSS risk category: Int-1 vs Int-2 vs high
- Platelet count: >200 × 10^9/L vs 100–200 × 10^9/L
- Spleen volume: ≥1800 cm^3 vs <1800 cm^3

Primary endpoint

- SVR35 at Week 24

Key secondary endpoints

- Absolute change in TSS from baseline at Week 24
- TSS50 at Week 24

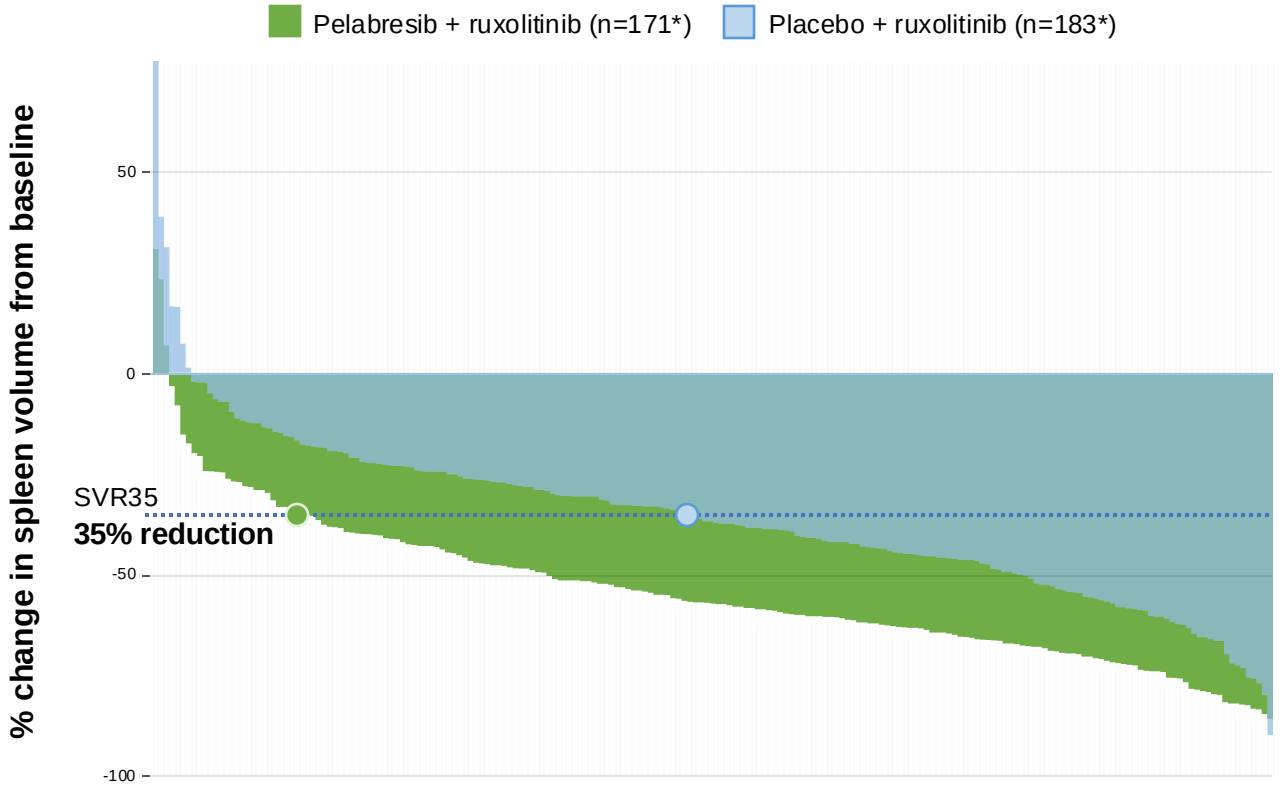
Safety

- AEs of all grades and serious AEs

***The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD;**
†Ruxolitinib was started at 10 mg BID (baseline platelet count 100–200 × 10^9/L) or 15 mg BID (baseline platelet count >200 × 10^9/L) with a mandatory dose increase by 5 mg BID after one cycle and a maximum dose of 25 mg BID per label.
MFSAF = Myelofibrosis Symptom Assessment Form.
Harrison CN, et al. *Future Oncol*. 2022;18(27):2987-2997. Rampal R, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California. Abstract 628.

MANIFEST-2 Study
Met its Primary Endpoint SVR35 at Week 24

There was a significantly greater response in patients treated with pelabresib + ruxolitinib vs placebo + ruxolitinib.



ITT population

	Pelabresib + ruxolitinib (n=214)	Placebo + ruxolitinib (n=216)	p-value
SVR35 at Week 24	65.9%	35.2%	
Difference† (95% CI)	30.4 (21.6, 39.3)		<0.001

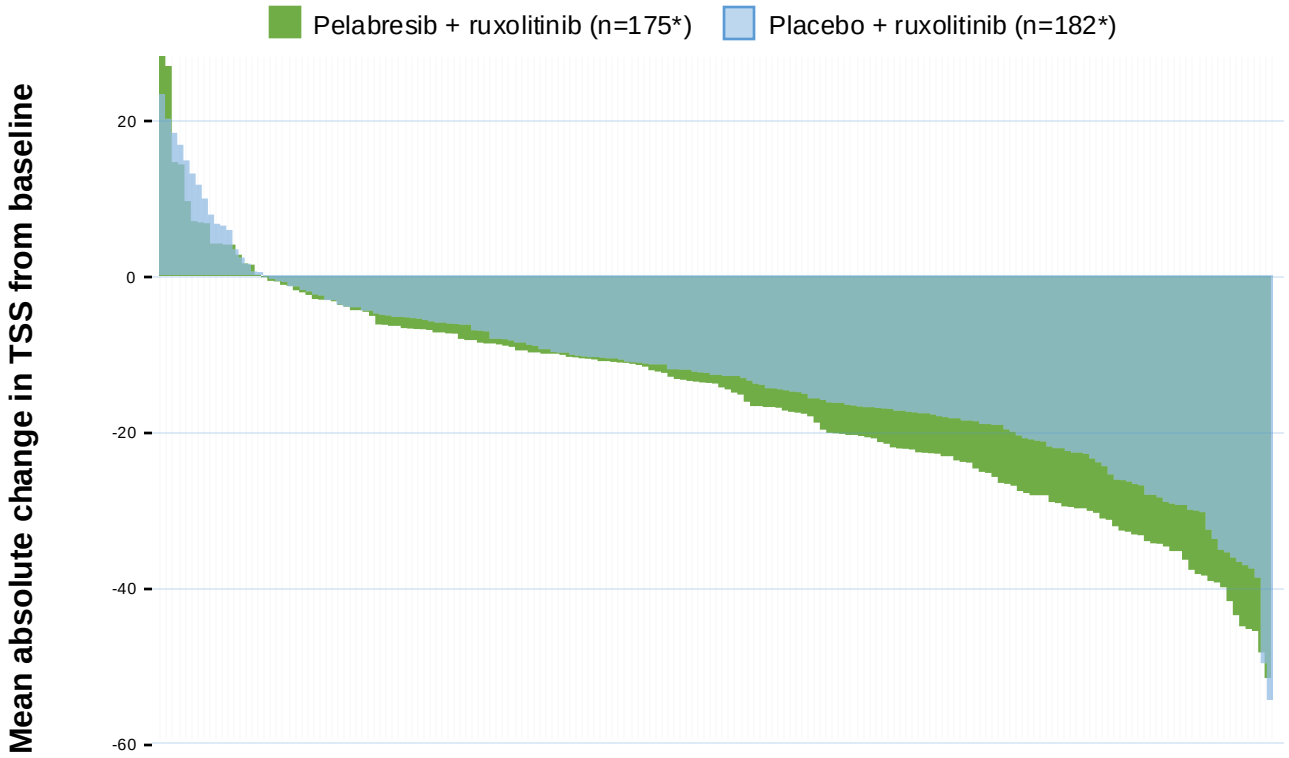
Mean % change in spleen volume at Week 24‡	-50.6 (n=171)	-30.6 (n=183)	
95% CI	-53.2, -48	-33.7, -27.5	

Data cut off: August 31, 2023. Spleen volume assessed by central read.

***Waterfall plots represent patients who have baseline and Week 24 data; †Calculated by stratified Cochran-Mantel-Haenszel test; ‡Patients without Week 24 assessment are considered non-responders.**
ITT = intent-to-treat.
Rampal R, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California. Abstract 628.

Absolute Change in TSS at Week 24

Strong numerical improvements for patients treated with pelabresib + ruxolitinib vs placebo + ruxolitinib.



ITT population

	Pelabresib + ruxolitinib (n=214)	Placebo + ruxolitinib (n=216)	p-value
TSS change† from baseline at Week 24	-15.99	-14.05	
Mean difference‡ (95% CI)	-1.94 (-3.92, 0.04)		0.0545

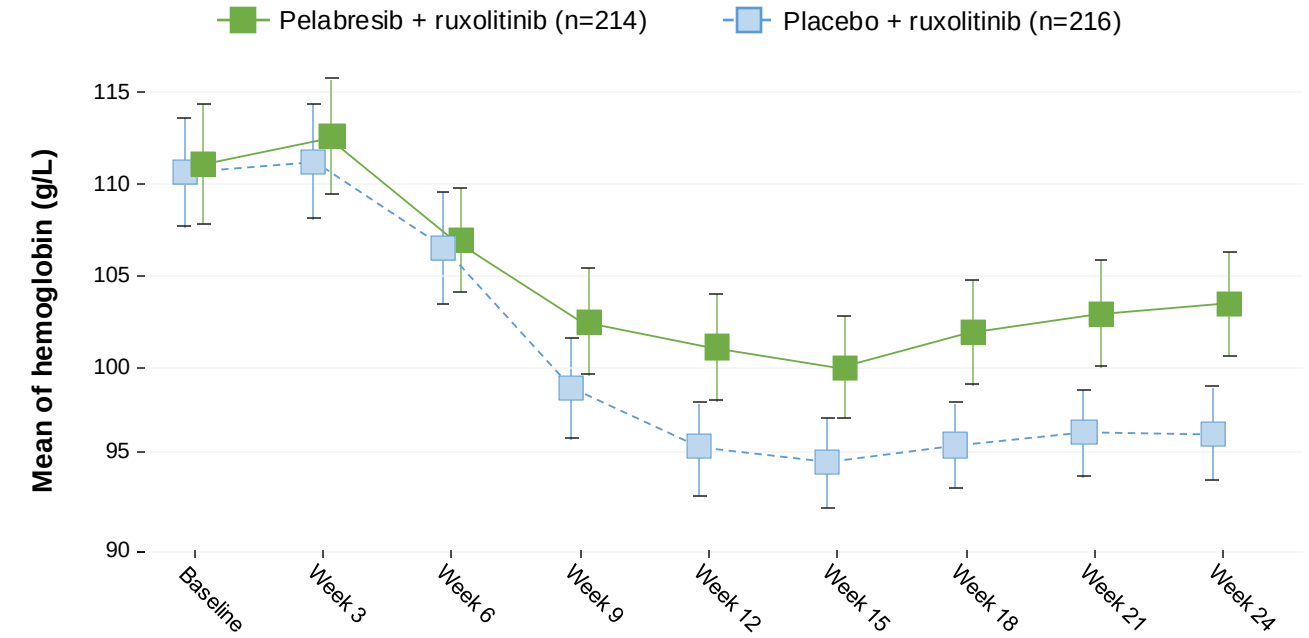
Data cut off: August 31, 2023.

- **Absolute change in TSS is a continuous endpoint** that estimates magnitude of symptom burden reduction with enhanced precision

***Waterfall plots represent patients who have baseline and Week 24 data; †Change from baseline determined by ANCOVA model using multiple imputation; ‡Least squares mean difference from ANCOVA model using baseline DIPSS score, baseline platelet count, and baseline spleen volume as factors, and baseline TSS as covariate.**
ANCOVA = analysis of covariance.
Rampal R, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California. Abstract 628.

Hemoglobin Response

A numerically greater proportion of patients had a hemoglobin response with pelabresib + ruxolitinib vs placebo + ruxolitinib.



Number of patients

Pelabresib + ruxolitinib	212	204	209	199	193	189	186	185	184
Placebo + ruxolitinib	214	206	211	209	207	205	204	199	196

ITT population

	Pelabresib + ruxolitinib (n=214)	Placebo + ruxolitinib (n=216)
Hemoglobin response* ≥1.5 g/dL mean increase (95% CI)	10.7% (6.60, 14.90)	6.0% (2.85, 9.19)
Patients requiring RBC transfusion during screening, n (%)	35 (16.4)	25 (11.6)
Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)	66 (30.8)	86 (39.8)

Preliminary analyses; data cut off: August 31, 2023.

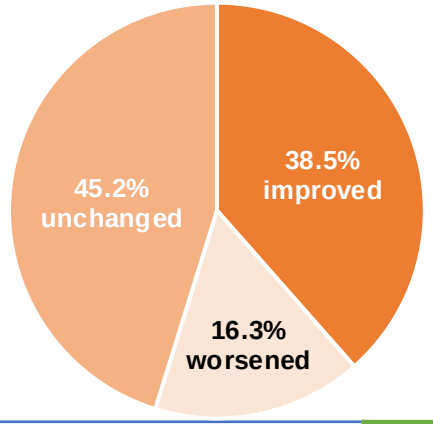
***Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the previous 12 weeks. Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. A similar effect was observed across DIPSS categories.**

Rampal R, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California. Abstract 628.

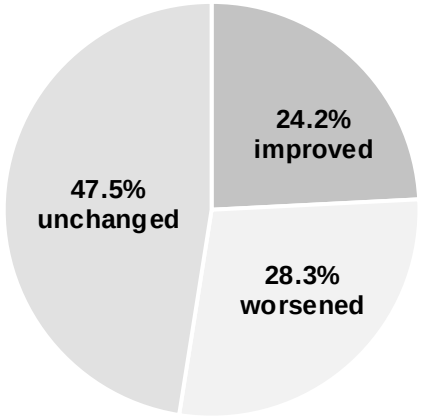
Reduction in Bone Marrow Fibrosis and Inflammatory Cytokines

Improvement of reticulin fibrosis grade in central read by Week 24

Pelabresib + ruxolitinib (n=104*)



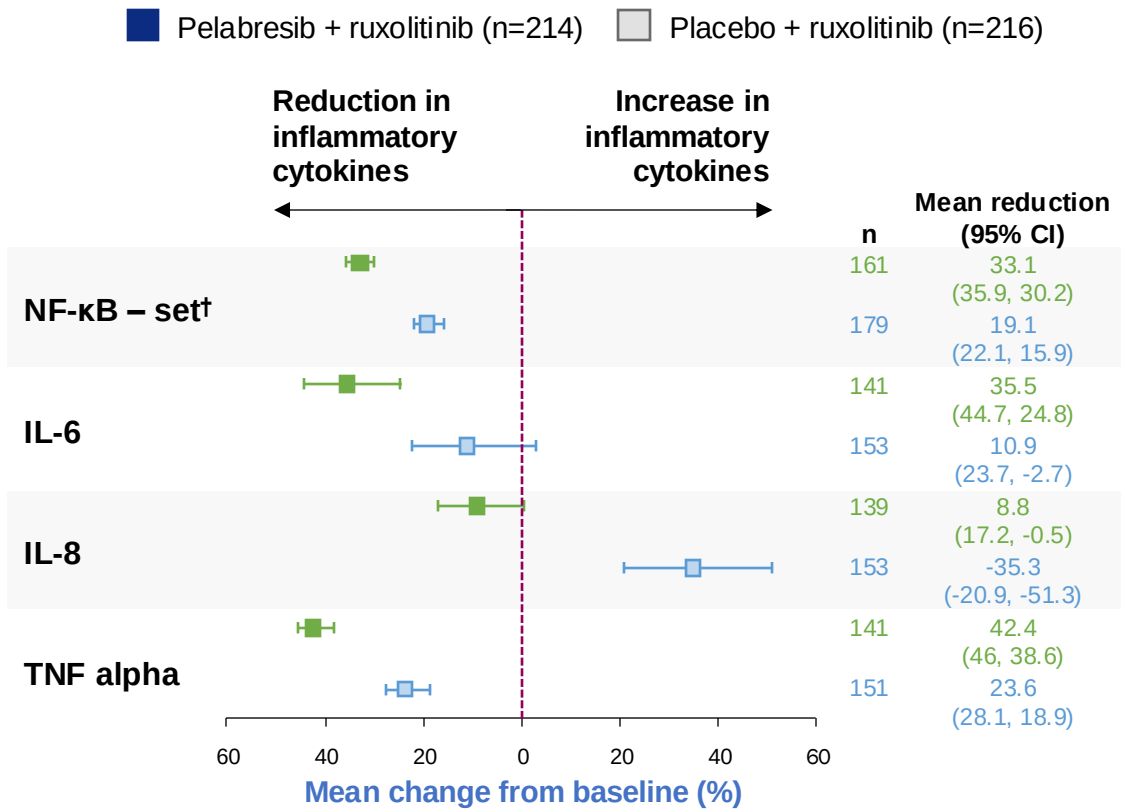
Placebo + ruxolitinib (n=99*)



	Pelabresib + ruxolitinib	Placebo + ruxolitinib	Odds ratio
Worsened ≥1 grade (%)	16.3	28.3	0.47 (0.23, 0.92)
Improved ≥1 grade (%)	38.5	24.2	2.09 (1.14, 3.93)

Preliminary analyses; data cut off: August 31, 2023.

Reduction of inflammatory cytokines by Week 24

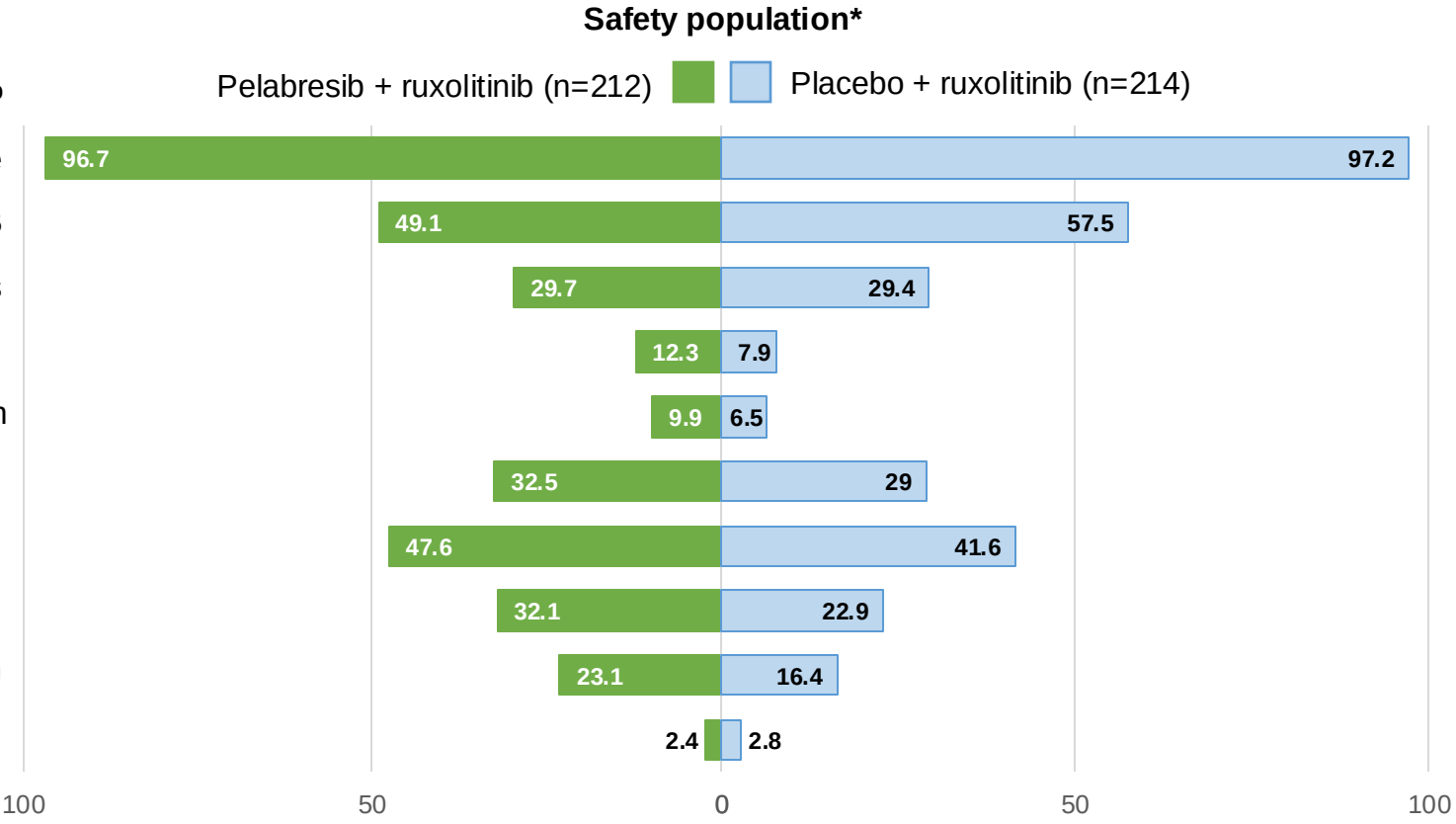


*n=203 evaluable patients (baseline and Cycle 9 Day 1). †NF-κB set includes: B2M, CRP, CD40-L, hepcidin, IL-6, IL-12p40, MIP-1 beta, MPIF-1, RANTES, TNFR2, TNF alpha, VCAM-1.
B2M = beta-2 microglobulin; CD = cluster of differentiation; CRP = C-reactive protein; MIP = macrophage inflammatory protein; MPIF = myeloid progenitor inhibitory factor; NF-κB = nuclear factor kappa B; RANTES = regulated upon activation, normal T cell expressed and secreted; TNFR = TNF receptor; VCAM = vascular cell adhesion protein.

Rampal R, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California. Abstract 628.

Summary of Safety

The pelabresib + ruxolitinib safety profile at 24 weeks was generally comparable to the established safety profile of ruxolitinib.



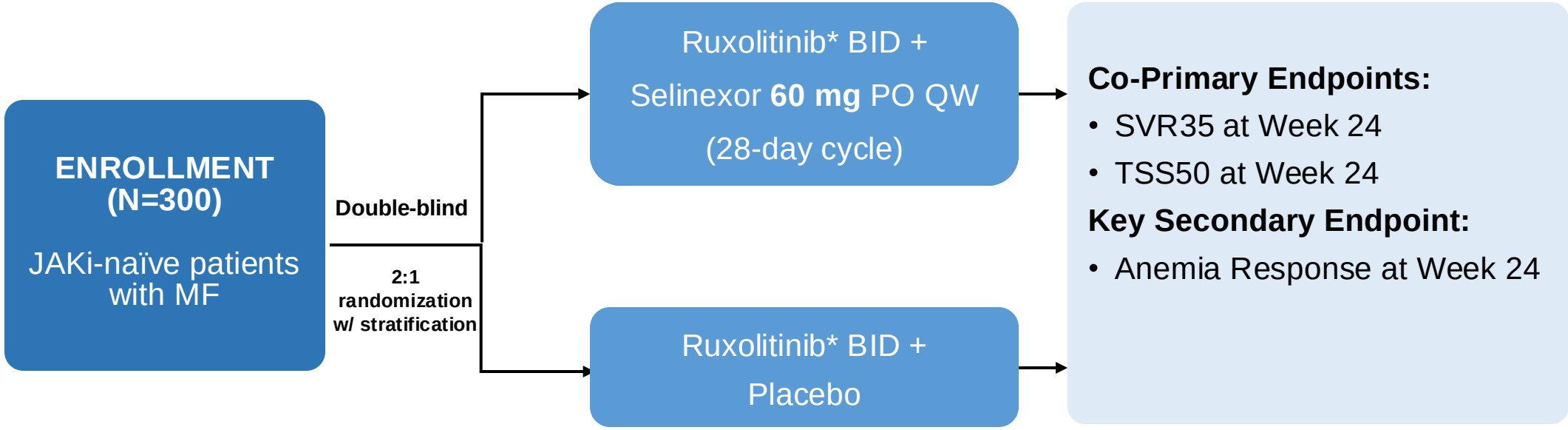
Preliminary analyses; data cut off: August 31, 2023.

***Safety population: received at least one dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blinded treatment period is defined as an adverse event that has a start date on or after the first dose of the pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first.**

TEAE = treatment-emergent adverse event.

Rampal R, et al. Presented at: American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California. Abstract 628.

XPORT-MF-034 Phase 3 Trial Design
Selinexor in Treatment-Naïve Myelofibrosis



Randomization stratified by

- Dynamic International Prognostic Scoring System (DIPSS) risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 cm^3 vs >1800 cm^3 by MRI/CT scan
- Baseline platelet counts 100-200 x 10^9/ L vs >200 x 10^9/L

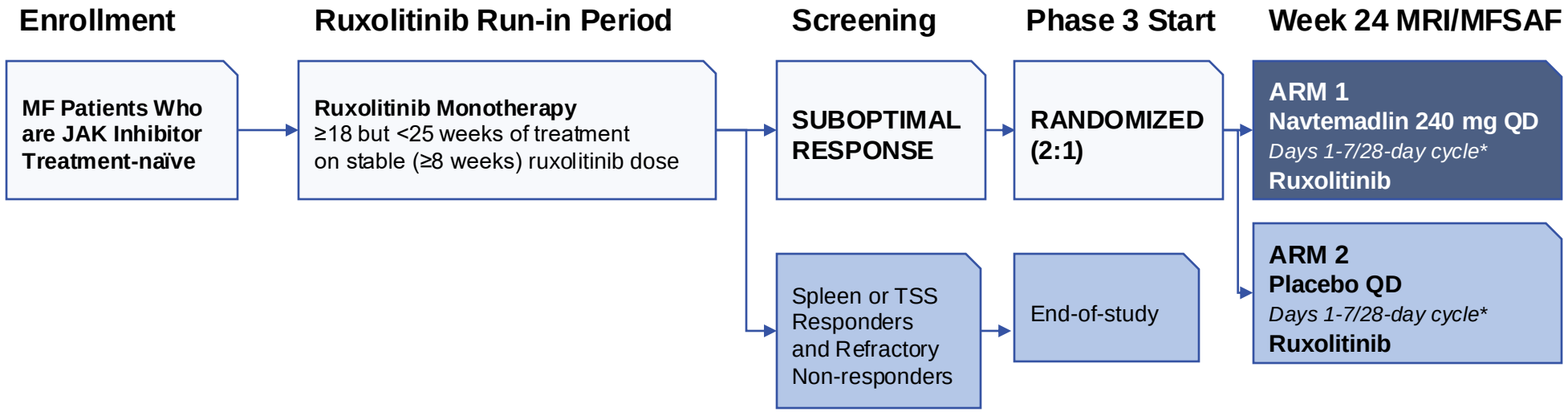
***Ruxolitinib dose based on platelet count per prescribing information.**
QW = once weekly.
NIH. Accessed November 13, 2024. https://clinicaltrials.gov/study/NCT04562389.

POIESIS: Phase 3 Study Design

Phase 3 randomized, double-blind, placebo-controlled study of navtemadlin added to ruxolitinib in JAK inhibitor-naïve patients with myelofibrosis who have suboptimal response to ruxolitinib.

Suboptimal Response to Ruxolitinib

- SVR >0% but <35% and
- TSS reduction >0% but <50%



Co-primary endpoints

- Spleen volume reduction and TSS improvement rate at Week 24 after start of navtemadlin
- SVR35 by central review MRI/CT
- TSS50 improvement by MFSAF v4.0

Secondary endpoints

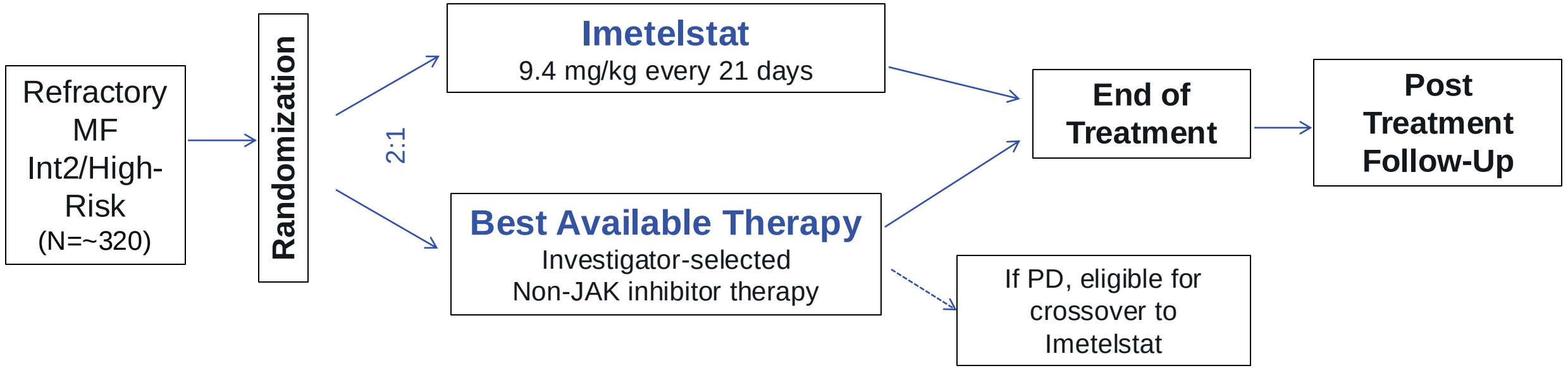
- Best spleen and TSS response at any time
- Spleen response duration
- RBC transfusion usage and dependent to independent
- Overall survival

***Cycle is 28 days, stable dose defined as ruxolitinib dose without dose increase.**

NIH. Accessed November 13, 2024. https://clinicaltrials.gov/study/NCT06479135.

IMpactMF: Phase 3 Study Design

Screening (28 days)	Treatment Period: Until disease progression, unacceptable toxicity, consent withdrawal	Post-Treatment Follow-Up



Primary endpoint: overall survival

Key secondary endpoints: symptom response, spleen response, patient reported outcomes (PROs)

NIH. Accessed November 13, 2024. https://clinicaltrials.gov/study/NCT04576156.

Key Learning Points

- ET and PV are MPNs with inherent risk of thrombohemorrhagic complications, reduction in quality of life, and progression of disease
- *JAK2* V617F is most prevalent in PV and linked to risk of thrombosis and progression
- Therapeutic interventions in ET/PV are mainly focused on thrombotic risk reduction
- Emerging data supports the potential for disease course modification with JAKi and IFN in Pv
- MF is an inflammatory disease with significant symptom burden and 4 approved JAKi fill therapeutic niches and provide options for sequencing
- Pacritinib can be used as a first- and second-line treatment in MF patients at risk for developing worsening cytopenias with a platelet count of $<50 \times 10^9/L$
- Anemia is an adverse MF prognostic variable and can be ameliorated with certain JAKi and TGF ligand traps
- Many novel drugs with relevant MOAs are in MPN clinical development, including combination strategies and approaches to improve OS

Submit Your Questions and Post-Event Surveys

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