Expert Second Opinion
Investigators Discuss the Optimal Management of Myelofibrosis and Systemic Mastocytosis

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

3:15 PM – 5:15 PM ET

Faculty

Professor Claire Harrison
Andrew T Kuykendall, MD
Stephen T Oh, MD, PhD
Jeanne Palmer, MD
Raajit K Rampal, MD, PhD

Moderator

Neil Love, MD

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Faculty

Professor Claire Harrison
Professor of Myeloproliferative Neoplasms
Guy's and St Thomas' NHS Foundation Trust
London, United Kingdom

Jeanne Palmer, MD
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Mayo Clinic in Arizona
Phoenix, Arizona

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Associate Member, Department of Malignant Hematology
Moffitt Cancer Center
Associate Professor, Department of Oncologic Sciences
University of South Florida
Tampa, Florida

Raajit K Rampal, MD, PhD
Associate Member, Director
MPN and Rare Hematologic Malignancies Program
Director, Center for Hematologic Malignancies
Memorial Sloan Kettering Cancer Center
New York, New York

Stephen T Oh, MD, PhD
Associate Professor of Medicine
Co-Chief, Division of Hematology
Washington University School of Medicine
St Louis, Missouri

Moderator

Neil Love, MD
Research To Practice
Miami, Florida

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Prof Harrison — Disclosures
Faculty

Advisory Committees	Galecto Inc, Geron Corporation, GSK, Incyte Corporation, Karyopharm Therapeutics, Keros Therapeutics, Novartis, Silence Therapeutics, Sobi
Consulting Agreements	Galecto Inc, Geron Corporation, GSK, Incyte Corporation, Karyopharm Therapeutics, Keros Therapeutics, Novartis, Silence Therapeutics, Sobi, Takeda Pharmaceutical Company Limited
Contracted Research	Galecto Inc, Geron Corporation, GSK, Incyte Corporation, Karyopharm Therapeutics, Novartis, Silence Therapeutics, Sobi
Data and Safety Monitoring Boards/Committees	Galecto Inc, Incyte Corporation, Novartis, Silence Therapeutics
Speakers Bureaus	AOP Health, GSK, Incyte Corporation, Novartis

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Dr Kuykendall — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Incyte Corporation, Karyopharm Therapeutics, PharmaEssentia
Consulting Agreements	AbbVie Inc, Karyopharm Therapeutics, MorphoSys
Contracted Research	Blueprint Medicines, Bristol Myers Squibb, Geron Corporation, Janssen Biotech Inc, MorphoSys, Protagonist Therapeutics
Data and Safety Monitoring Boards/Committees	Geron Corporation

Dr Oh — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Geron Corporation, GSK, Incyte Corporation, Morphic Therapeutic, a wholly owned subsidiary of Lilly, MorphoSys, Protagonist Therapeutics
Stock Options — Private Companies	Harmonic Discovery, Phoenix Molecular Designs

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Dr Palmer — Disclosures
Faculty

Presentation (Money to Institution — Not Speakers Bureau)	CTI BioPharma, a Sobi Company

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Dr Rampal — Disclosures
Faculty

Advisory Committees	AbbVie Inc, Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Disc Medicine, Galecto Inc, GSK, Incyte Corporation, Jazz Pharmaceuticals Inc, Kartos Therapeutics, Karyopharm Therapeutics, MorphoSys, Novartis, Opna Bio, PharmaEssentia, Roche Laboratories Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Zentalis Pharmaceuticals
Contracted Research	BioMed Valley Discoveries, Incyte Corporation, MorphoSys, Ryvu Therapeutics, Stemline Therapeutics Inc, Zentalis Pharmaceuticals
Data and Safety Monitoring Boards/Committees	Merck

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Dr Love — Disclosures

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Expert Second Opinion
Investigators Discuss the Role of Novel Treatment Approaches in the Care of Patients with Follicular Lymphoma and Diffuse Large B-Cell Lymphoma

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

7:00 PM – 9:00 PM ET

Faculty

Nancy L Bartlett, MD
John P Leonard, MD
Matthew Matasar, MD
Loretta J Nastoupil, MD
Professor Pier Luigi Zinzani

Moderator

Neil Love, MD

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CASES FROM THE COMMUNITY
Investigators Discuss the Role of Antibody-Drug Conjugates in the Management of Triple-Negative and HR-Positive Metastatic Breast Cancer

Part 1 of a 3-Part CME Satellite Symposium Series

Tuesday, December 9, 2025

7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)

Faculty

Javier Cortés, MD, PhD

Professor Peter Schmid, FRCP, MD, PhD

Rita Nanda, MD

Priyanka Sharma, MD

Moderator

Neil Love, MD

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RESEARCH TO PRACTICE

CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Management of HER2-Positive Breast Cancer

Part 2 of a 3-Part CME Satellite Symposium Series

Wednesday, December 10, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Professor Giuseppe Curigliano, MD, PhD
Nadia Harbeck, MD, PhD
Ian E Krop, MD, PhD
Nancy U Lin, MD
Joyce O'Shaughnessy, MD

Moderator

Neil Love, MD

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CASES FROM THE COMMUNITY
Investigators Discuss the Optimal Role of Endocrine-Based and Other Strategies in the Management of HR-Positive Breast Cancer

Part 3 of a 3-Part CME Satellite Symposium Series

Thursday, December 11, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Angela DeMichele, MD, MSCE
Komal Jhaveri, MD, FACP, FASCO
Erica Mayer, MD, MPH, FASCO
Hope S Rugo, MD
Seth Wander, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss Available Research Guiding the Management of Relapsed/Refractory Multiple Myeloma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Monday, December 15, 2025

5:00 PM – 6:00 PM ET

Faculty

Sagar Lonial, MD, FACP, FASCO

María-Victoria Mateos, MD, PhD

Moderator

Neil Love, MD

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Practical Perspectives on the Current and Future Management of Immune Thrombocytopenia — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Tuesday, December 16, 2025

5:00 PM – 6:30 PM ET

Faculty

Hanny Al-Samkari, MD

Francesco Zaja, MD

Additional faculty to be announced

Moderator

Neil Love, MD

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Practical Perspectives on the Current Role of Bispecific Antibodies in the Management of Lymphoma — What Happened at ASH 2025?

A CME/MOC-Accredited Live Webinar

Wednesday, December 17, 2025
5:00 PM – 6:00 PM ET

Faculty

Michael Dickinson, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

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Grand Rounds

CME/MOC-Accredited Interactive Series

Through April 2026

Three Series

Optimizing Treatment for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia

Optimizing the Use of Novel Therapies for Patients with Diffuse Large B-Cell Lymphoma

Optimizing Therapy for Patients with Hormone Receptor-Positive Localized Breast Cancer

Host a 1-hour session at your institution:
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or call (800) 233-6153

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Save The Date

Fifth Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, NCPD- and ACPE-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

Friday to Sunday, April 24 to 26, 2026

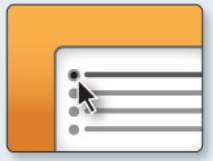
The Ritz-Carlton Orlando, Grande Lakes | Orlando, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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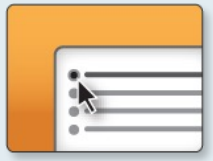
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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RTP Playlist with Neil Love, MD

BREAST CANCER

Dr Hope Rugo: Interview (28 min)

SMALL CELL LUNG CANCER

Drs Stephen Liu and Charles Rudin: Cases (58 min)

GASTROESOPHAGEAL CANCER

Drs Geoffrey Ku and Zev Wainberg: Cases (61 min)

PROSTATE CANCER

Drs Emmanuel Antonarakis and Karim Fizazi: Year in Review (60 min)

ENDOMETRIAL AND OVARIAN CANCER

Dr Shannon Westin: Interview (52 min)

NEUROENDOCRINE TUMORS

Drs Simron Singh and Jonathan Strosberg: Meeting (50 min)

NON-HODGKIN LYMPHOMA

Drs Jeremy Abramson, Joshua Brody, Christopher Flowers, Ann LaCasce and Tycel Phillips: Meeting, cases (59 min)

CHRONIC LYMPHOCYTIC LEUKEMIA

Drs Jennifer Brown and Paolo Ghia: Year in Review (59 min)

ACUTE MYELOID LEUKEMIA

Dr Jorge Cortes: Interview (43 min)

MULTIPLE MYELOMA

Drs Natalie Callander and Sagar Lonial: Patient videos (59 min)

IMMUNE THROMBOCYTOPENIA

Drs Hanny Al-Samkari, James Bussel and Nichola Cooper: Think Tank (117 min)

OCULAR TOXICITES IN ONCOLOGY

Dr Neel Pasricha: Interview (54 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

RTP Playlist with Neil Love, MD

Webinar for patients and families on relapsed multiple myeloma with Drs Natalie Callander and Sagar Lonial.

Relapsed Multiple Myeloma: Where We Were, Where We Are (4 min)

Common Questions from the Beginning (5 min)

Choosing Treatment Options (4 min)

Clinical Research Trials (6 min)

Neuropathy (5 min)

Chimeric Antigen Receptor (CAR) T-Cell Therapy (6 min)

Bispecific Antibodies (8 min)

Antibody-Drug Conjugates: Belantamab Mafadotin (8 min)

Interacting with the Oncology Team (5 min)

Other Questions (4 min)

Recording of Entire Webinar (62 min)

Feedback (Please!)
DrNeilLove@ResearchToPractice.com

ASH and SABCS RTP Video Participants

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Expert Second Opinion
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Raajit K Rampal, MD, PhD

Moderator

Neil Love, MD

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Consulting Faculty

Prithviraj Bose, MD
Professor, Department of Leukemia
Co-Leader, Section of
Myeloproliferative Neoplasms
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Laura C Michaelis, MD
Armand J Quick Professor of Medicine
Chief, Division of Hematology and Oncology
Department of Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin

John Mascarenhas, MD
Director, Center of Excellence in
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Director, Adult Leukemia Program
Leader, Myeloproliferative Disorders
Clinical Research Program
Division of Hematology/Oncology
Tisch Cancer Institute
New York, New York

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Agenda

Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Palmer

Module 2: Managing MF in Patients with Anemia — Dr Oh

Module 3: Managing MF in Patients with Thrombocytopenia — Dr Rampal

Module 4: Promising Novel Agents Under Investigation for MF — Prof Harrison

Module 5: Current and Future Management of Systemic Mastocytosis — Dr Kuykendall

Agenda

Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Palmer

Module 2: Managing MF in Patients with Anemia — Dr Oh

Module 3: Managing MF in Patients with Thrombocytopenia — Dr Rampal

Module 4: Promising Novel Agents Under Investigation for MF — Prof Harrison

Module 5: Current and Future Management of Systemic Mastocytosis — Dr Kuykendall

Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias

Jeanne Palmer, MD

Mayo Clinic Arizona

Case Presentation

Patient is a 51 year old female recently diagnosed with myelofibrosis when she presented with a mild anemia and leukocytosis.

-Hgb 11.2

-WBC 15.2, leukoerythroblastic picture

- Plt 190
- Spleen- 5cm below LCM
- *JAK2v617f* present, no other mutations
- Patient reports night sweats and a 15 lb weight loss

HIPAA Compliant Stock photo- not a real patient

NCCN Guidelines: Approach to MF Management

Initial assessment: PASS

- **P**rognosis (prognostic scoring systems)
- **A**nemia / Thrombocytopenia (CBC, EPO)
- **S**ystemic Symptoms (MPN-SAF TSS)
- **S**pleen size (exam, US) and related symptoms (MPN-SAF TSS)

Lower Risk
MIPSS-70: ≤3
MIPSS-70+ Version 2.0: ≤3
DIPSS-Plus: ≤1
DIPSS: ≤2
MYSEC-PM: <14

- Asymptomatic → Observation or clinical trial
- Symptomatic → Clinical trial, ruxolitinib, PEG-IFNA2a, hydroxyurea[1], pacritinib[2], or momelotinib (category 2B)

Higher Risk
MIPSS-70: ≥4
MIPSS-70+ Version 2.0: ≥4
DIPSS-Plus: >1
DIPSS: >2
MYSEC-PM: ≥14

- Platelets < 50 x 10^9/L
  - Transplant Candidate (No) → Clinical trial, or pacritinib (preferred, category 1), or momelotinib (category 2B)
  - Transplant Candidate (Yes) → Allogeneic HSCT
- Platelets ≥ 50 x 10^9/L
  - Transplant Candidate (Yes) → Allogeneic HSCT
  - Transplant Candidate (No) → Clinical trial, or ruxolitinib (category 1), fedratinib (category 1), momelotinib[3], or pacritinib (category 2B)

[1]If cytoreduction would help symptoms; [2]If platelets < 50 x 10^9/L; [3]Recommended for MF-related anemia with splenomegaly and uncontrolled symptoms

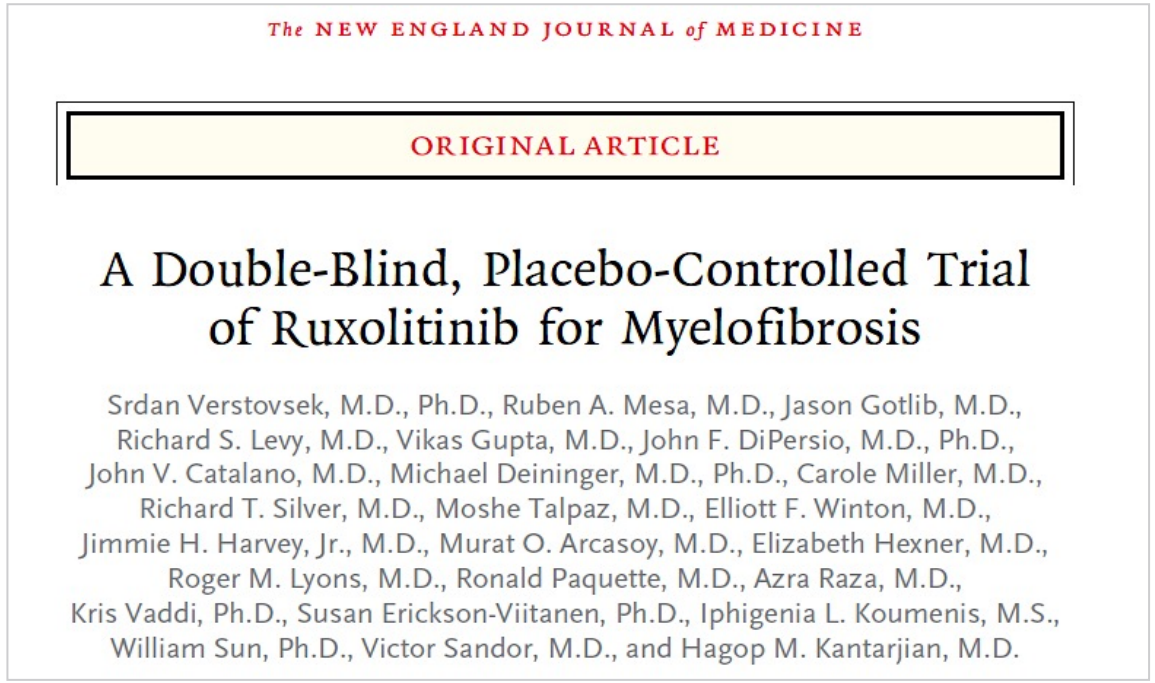
SAF = Symptom Assessment Form; TSS = Total Symptom Score; HSCT = Hematopoietic Stem Cell Transplant; PEG-IFNA2a = Peginterferon alfa-2a

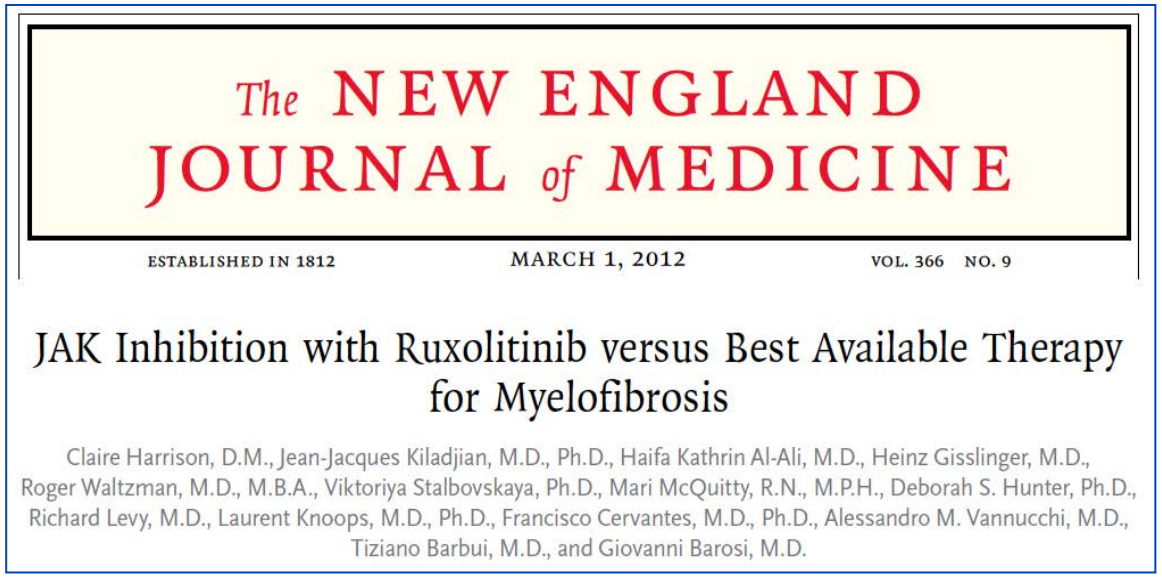
NCCN. Clinical Practice Guidelines: Myeloproliferative Neoplasms. Version 2.2025. www.nccn.org. Accessed 12/2025.

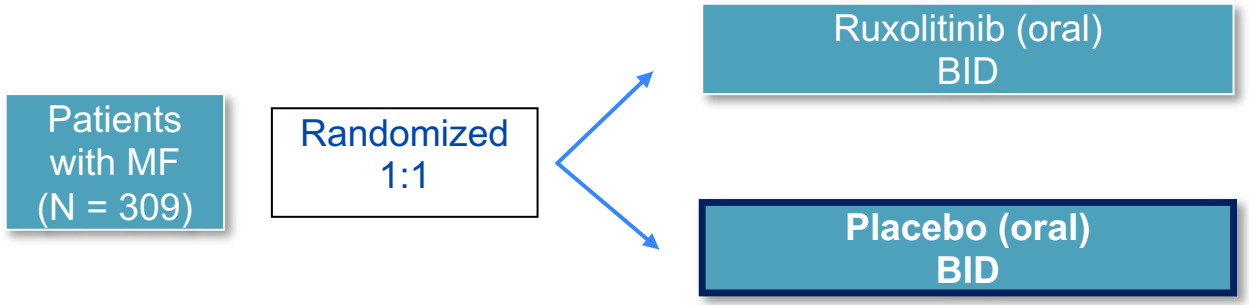
To treat or not to treat?

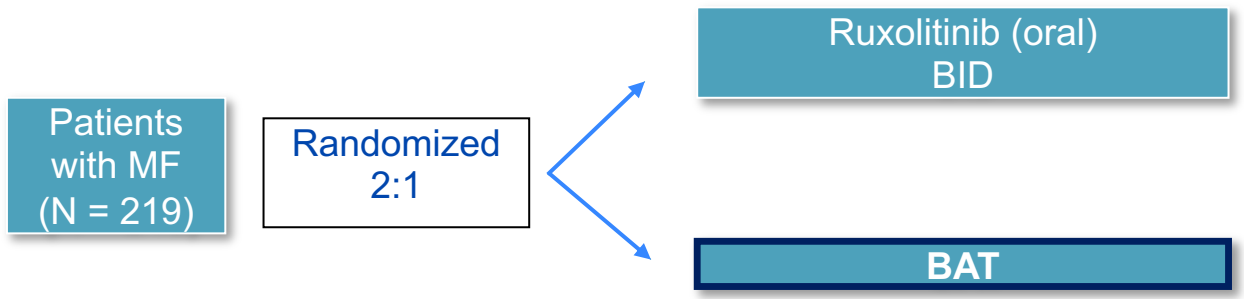
- Symptoms and enlarged spleen

			Symptom	Score Range	Score
◆	◆	◆	Fatigue	0 (Absent) ---------- 10 (Worst Imaginable)	
	◆		Early satiety	0 (Absent) ---------- 10 (Worst Imaginable)	
	◆		Abdominal discomfort	0 (Absent) ---------- 10 (Worst Imaginable)	
	◆	◆	Inactivity	0 (Absent) ---------- 10 (Worst Imaginable)	
◆		◆	Problems with concentration	0 (Absent) ---------- 10 (Worst Imaginable)	
◆			Night sweats	0 (Absent) ---------- 10 (Worst Imaginable)	
◆			Itching	0 (Absent) ---------- 10 (Worst Imaginable)	
◆			Bone pain	0 (Absent) ---------- 10 (Worst Imaginable)	
◆			Fever	0 (Absent) ---------- 10 (Daily)	
◆	◆		Unintentional weight loss*	0 (Absent) ---------- 10 (Worst Imaginable)	
				Total Score	(0 to 100)


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis
Srdan Verstovsek, M.D., Ph.D., Ruben A. Mesa, M.D., Jason Gotlib, M.D., Richard S. Levy, M.D., Vikas Gupta, M.D., John F. DiPersio, M.D., Ph.D., John V. Catalano, M.D., Michael Deininger, M.D., Ph.D., Carole Miller, M.D., Richard T. Silver, M.D., Moshe Talpaz, M.D., Elliott F. Winton, M.D., Jimmie H. Harvey, Jr., M.D., Murat O. Arcasoy, M.D., Elizabeth Hexner, M.D., Roger M. Lyons, M.D., Ronald Paquette, M.D., Azra Raza, M.D., Kris Vaddi, Ph.D., Susan Erickson-Viitanen, Ph.D., Iphigenia L. Koumenis, M.S., William Sun, Ph.D., Victor Sandor, M.D., and Hagop M. Kantarjian, M.D.

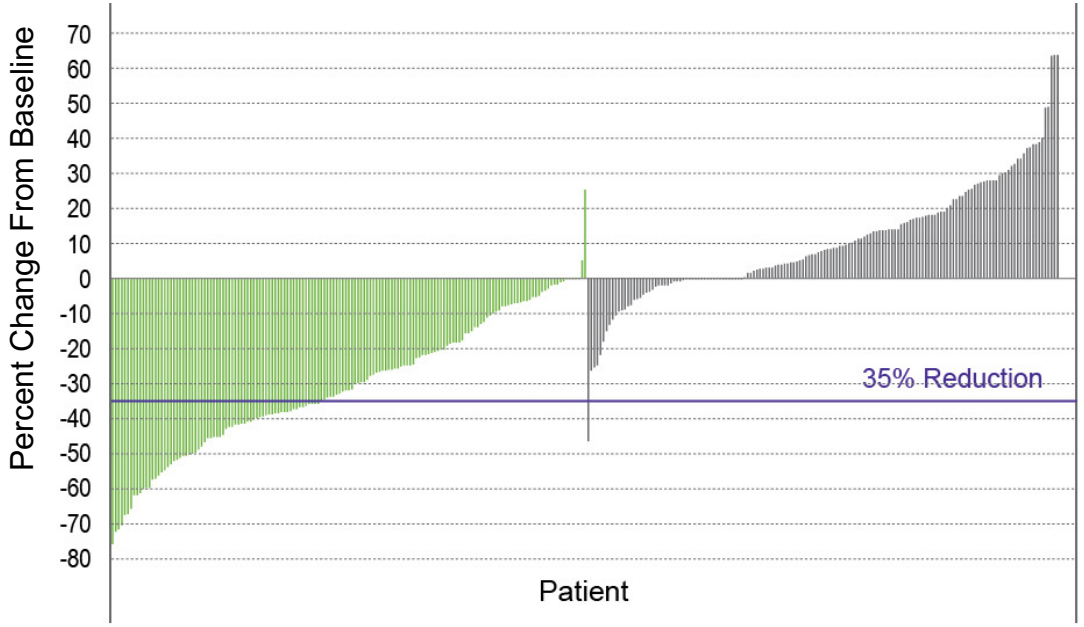

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812
MARCH 1, 2012
VOL. 366 NO. 9
JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis
Claire Harrison, D.M., Jean-Jacques Kiladjian, M.D., Ph.D., Haifa Kathrin Al-Ali, M.D., Heinz Gisslinger, M.D., Roger Waltzman, M.D., M.B.A., Viktoriya Stalbovskaya, Ph.D., Mari McQuitty, R.N., M.P.H., Deborah S. Hunter, Ph.D., Richard Levy, M.D., Laurent Knoops, M.D., Ph.D., Francisco Cervantes, M.D., Ph.D., Alessandro M. Vannucchi, M.D., Tiziano Barbui, M.D., and Giovanni Barosi, M.D.


Patients with MF (N = 309)
Randomized 1:1
Ruxolitinib (oral) BID
Placebo (oral) BID


Patients with MF (N = 219)
Randomized 2:1
Ruxolitinib (oral) BID
BAT

COMFORT-I: Key Efficacy Endpoints

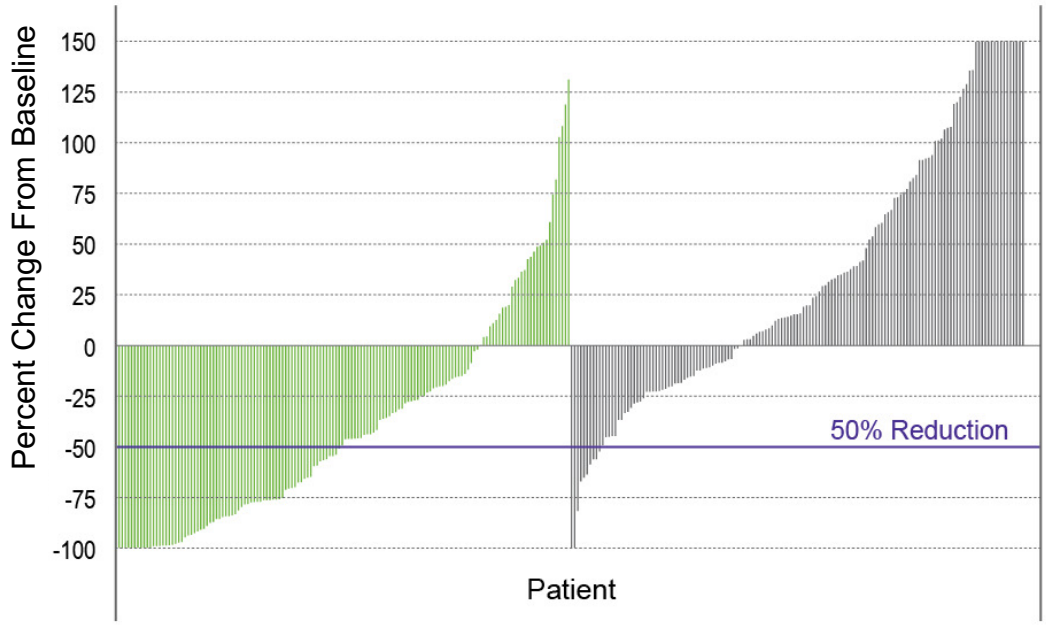
Ruxolitinib (n=155) | **SVR at 24 Weeks** | **Placebo (n=153)**



41.9% ruxolitinib vs 0.7% placebo achieved SVR35[a]; *P*<0.001

OR, 134.4 (95% CI: 18, 1004.9); *P*<0.001

Ruxolitinib (n=145) | **TSS at 24 Weeks** | **Placebo (n=145)**

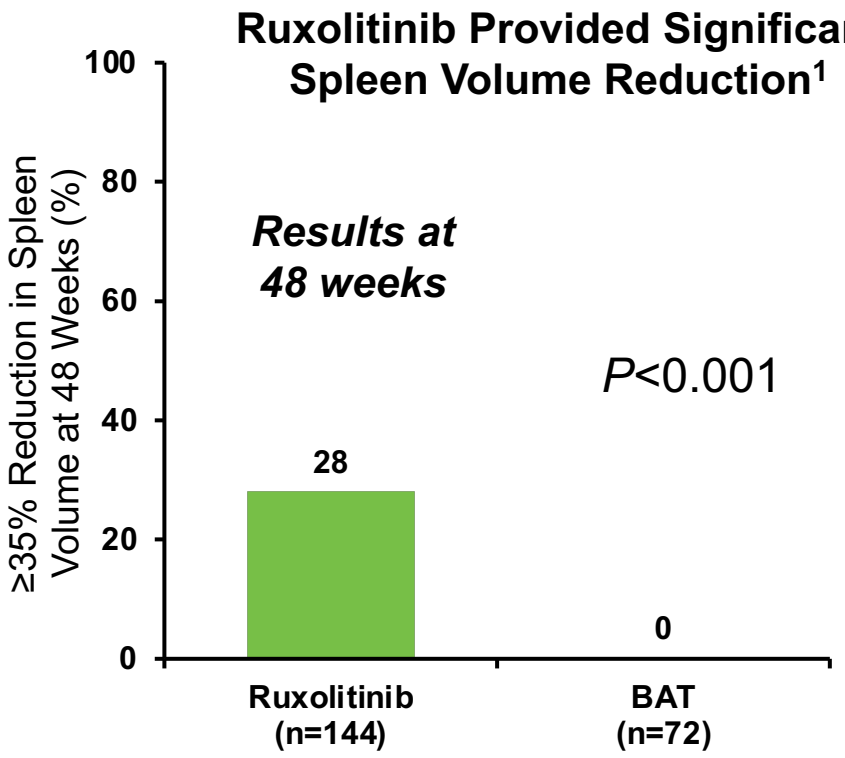


OR, 15.3 (95% CI: 6.9-33.7); *P*<0.001

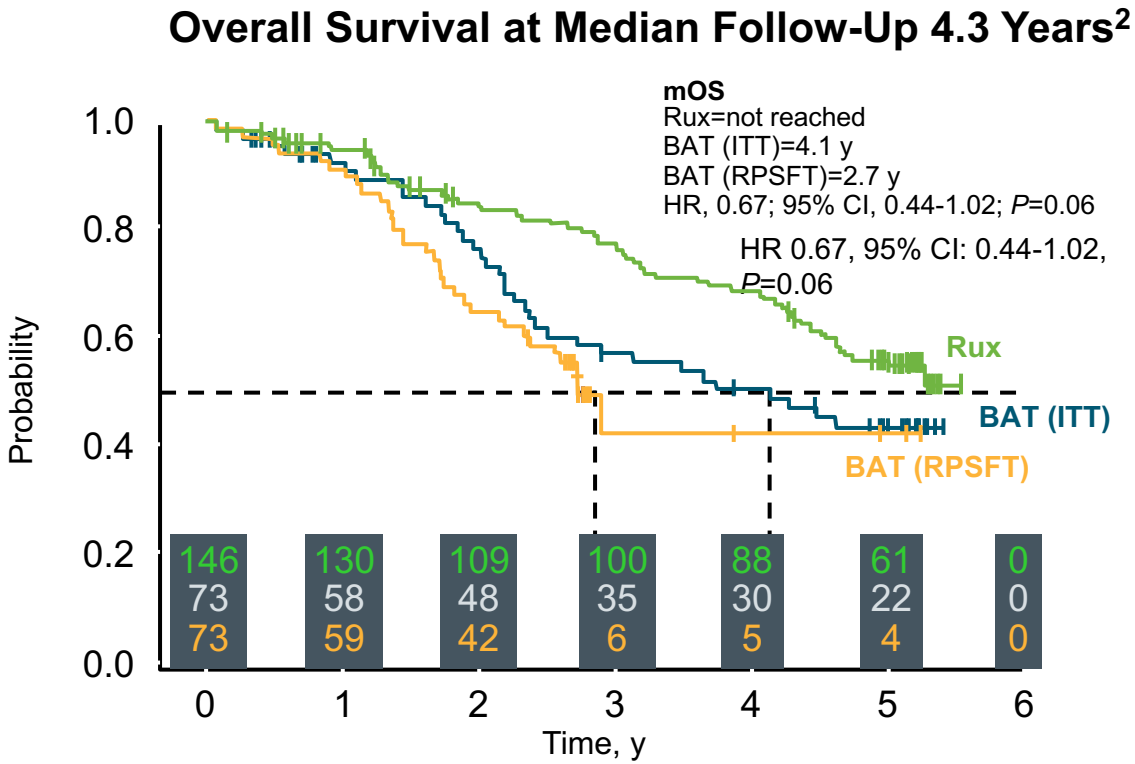
[a]Changes in palpable spleen length in the ruxolitinib and placebo groups mirrored the changes in spleen volume

Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807.

COMFORT-II: Efficacy Results



- Median time to response was 12 weeks[1]



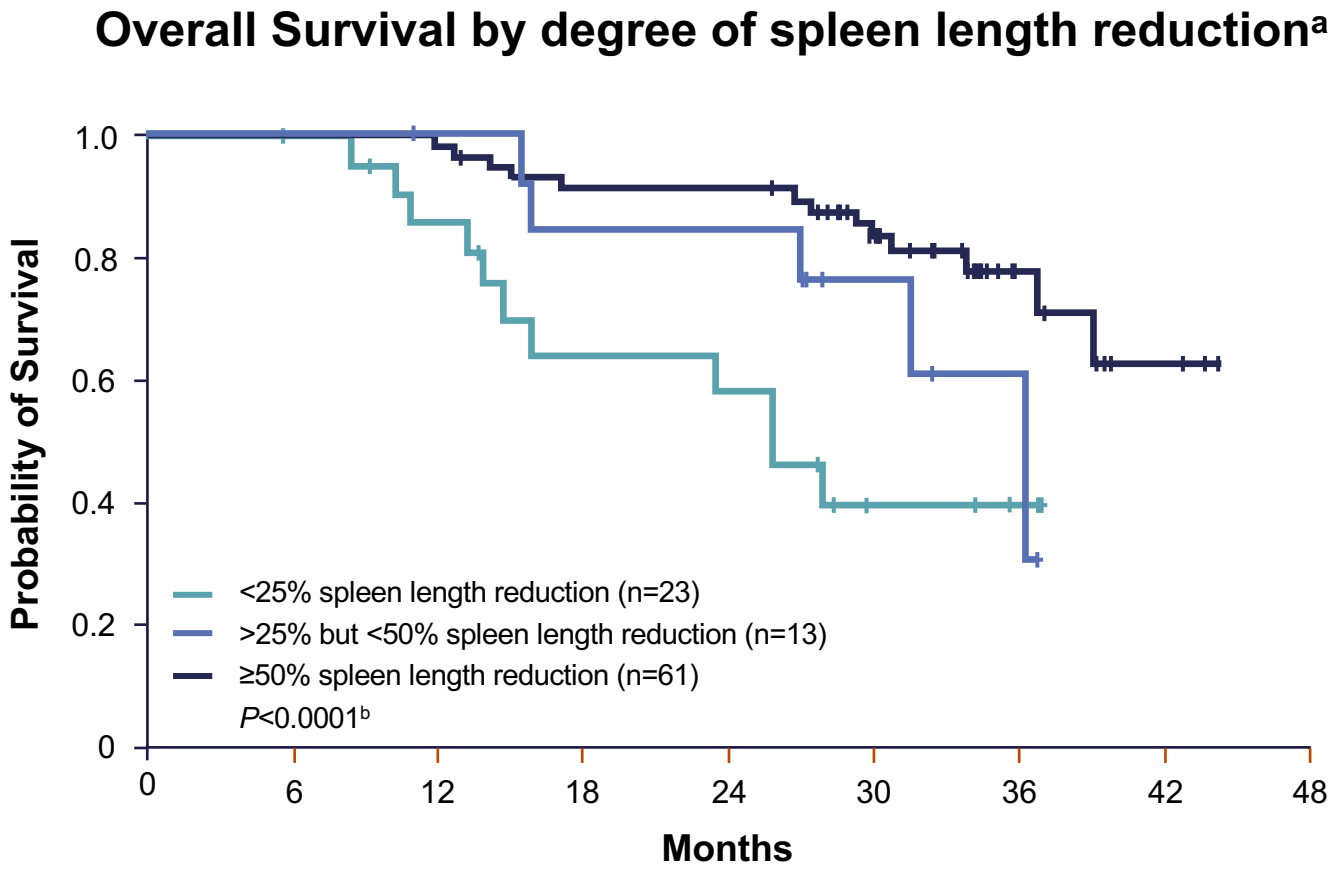
- 33% reduced risk of death among patients treated with ruxolitinib vs those treated with BAT[2]
  - Most patients in the BAT arm crossed over to receive ruxolitinib

RPSFT, rank-preserving structural failure time

[1]Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798. 2. Harrison CN, et al. *Leukemia.* 2016;30(8);1701-1707.

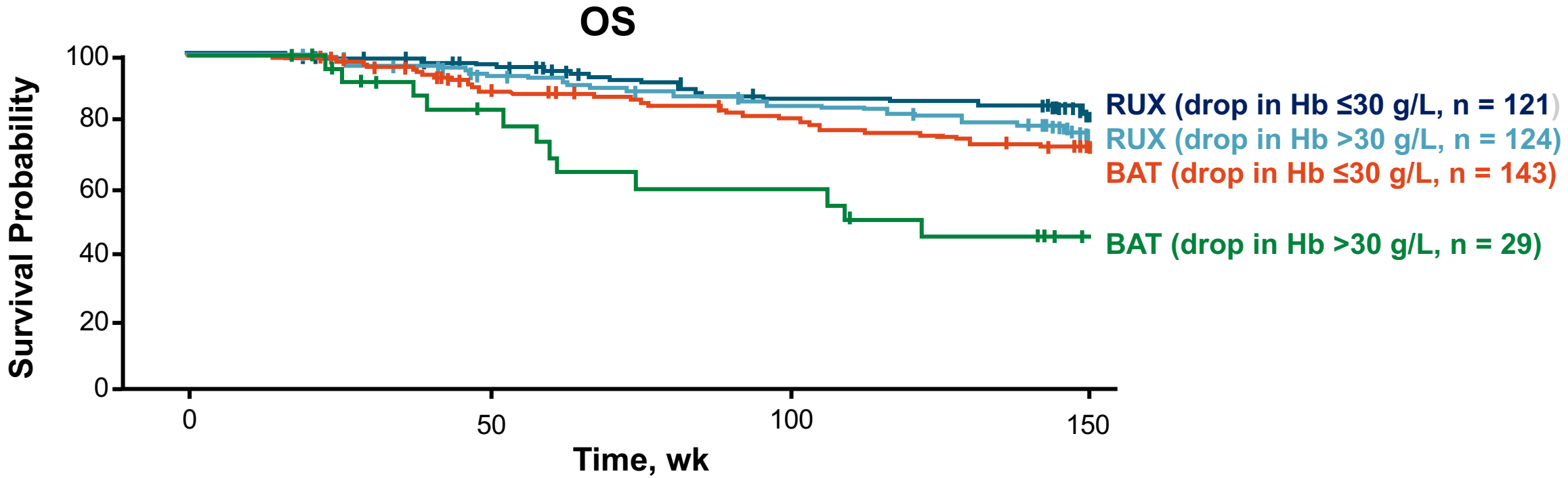
Achieving a Spleen Response is Associated With Improved Overall Survival

- Achieving ≥50% reduction in palpable spleen length was associated with longer survival compared with <25% reduction



[a] 97 patients with myelofibrosis enrolled at the Mayo Clinic Rochester on a study INCB18424-251 of ruxolitinib.
[b] Comparison of <25% reduction with ≥50% reduction, hazard ratio=0.22, 95% CI, 0.10-0.51.
Verstovsek S, et al. *Blood.* 2012;120:1202-1209.

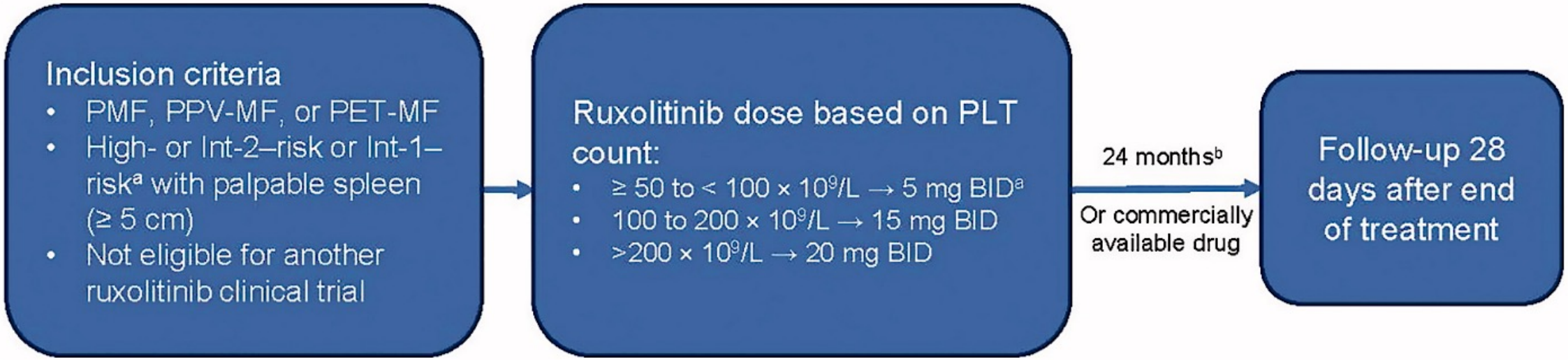
COMFORT Studies: Ruxolitinib Overcomes Adverse Prognostic Effect of Anemia in MF



- Anemia is not a contraindication for ruxolitinib use
- Hb changes on ruxolitinib treatment do not bear the same prognostic implications as Hb changes that occur as a consequence of MF pathology

Al-Ali HK, et al. *Leuk Lymph*. 2016;57:2464-2467.; Gupta V, et al. *Haematologica.* 2016;101:e482-e484.

JAK Inhibitor Ruxolitinib in Myelofibrosis Patients; NCT01493414 — JUMP study



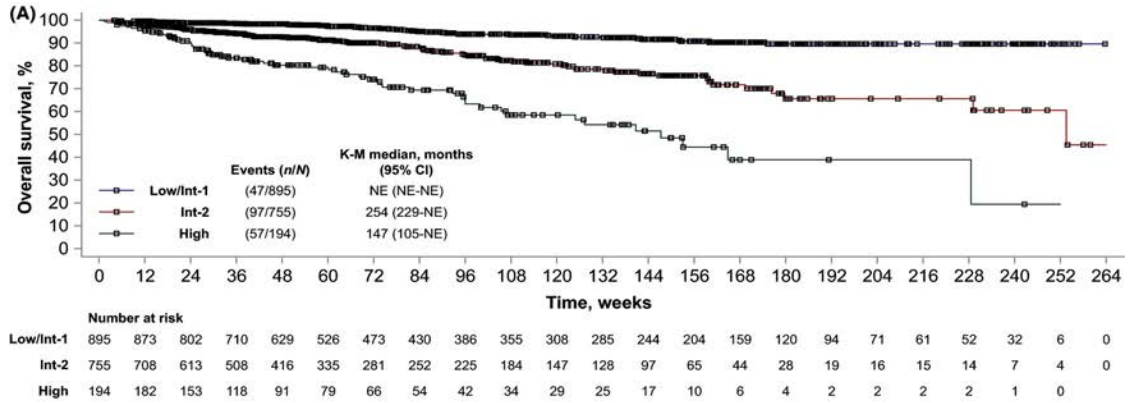
A phase 3b expanded-access study in MF in countries without access to ruxolitinib outside a clinical trial
Primary endpoint: safety
Secondary endpoint: # of patients who achieved SVR of 50%, and reduction in PRO

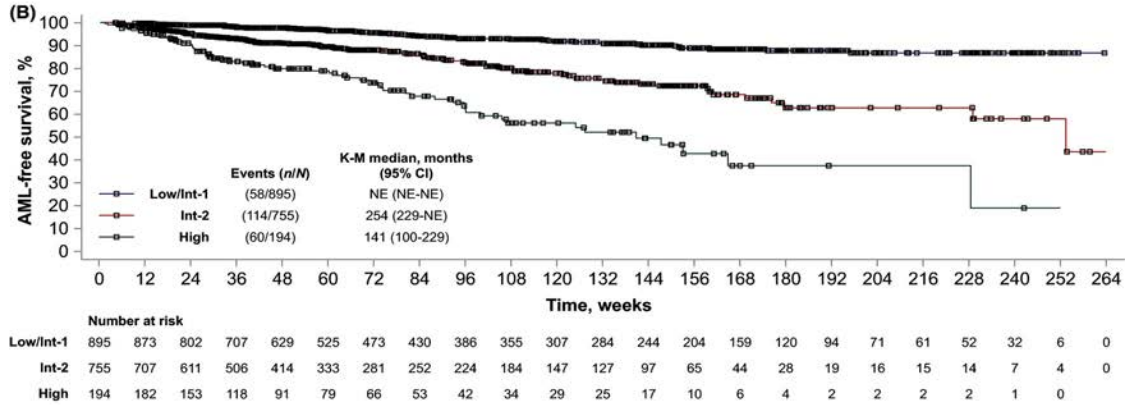
Br J Haematol, Volume: 189, Issue: 5, Pages: 888-903, First published: 04 February 2020, DOI: (10.1111/bjh.16462)

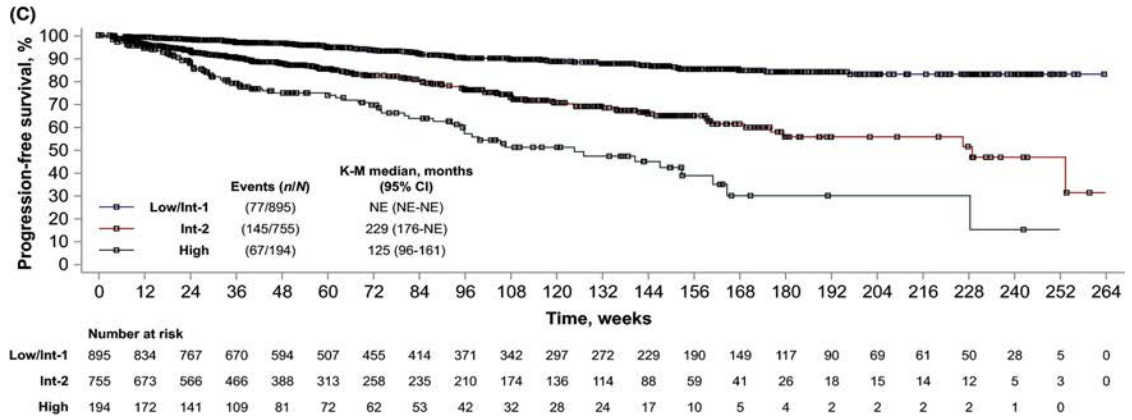
JUMP study

DIPSS	N (%)
Low/Int-1 risk	895 (40.1)
Int-2 risk	755 (33.8)
High Risk	194 (8.7)
Missing	389 (17.4)

Platelet count	N (%)
50- 75	28 (1.3)
75-100	109 (4.9)
100-200	689 (30.9)
>200	1398 (62.6)

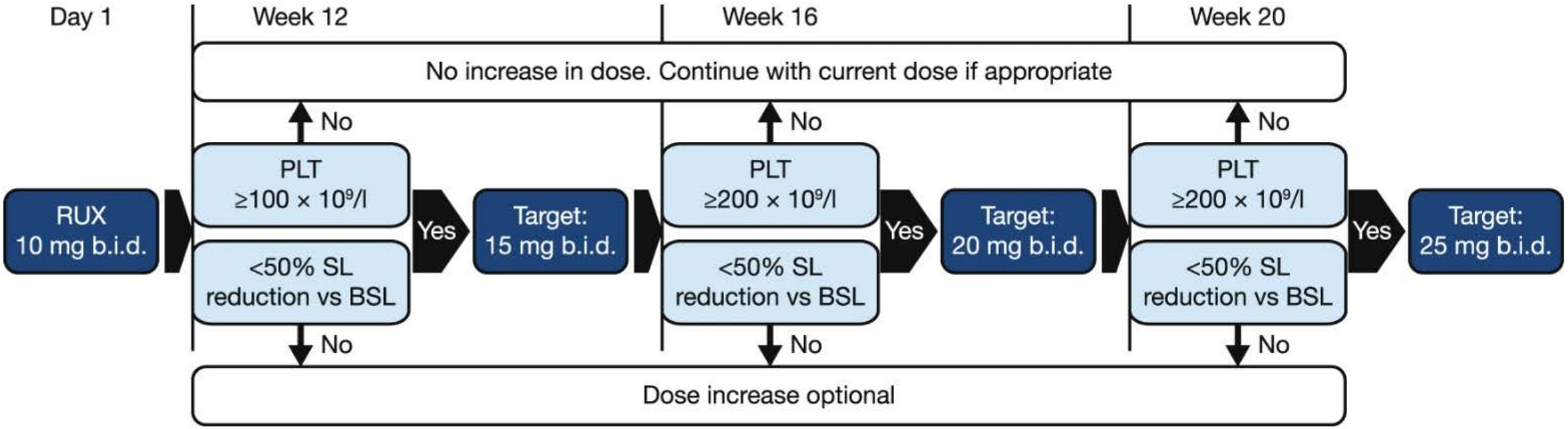






Br J Haematol, Volume: 189, Issue: 5, Pages: 888-903, First published: 04 February 2020, DOI: (10.1111/bjh.16462)

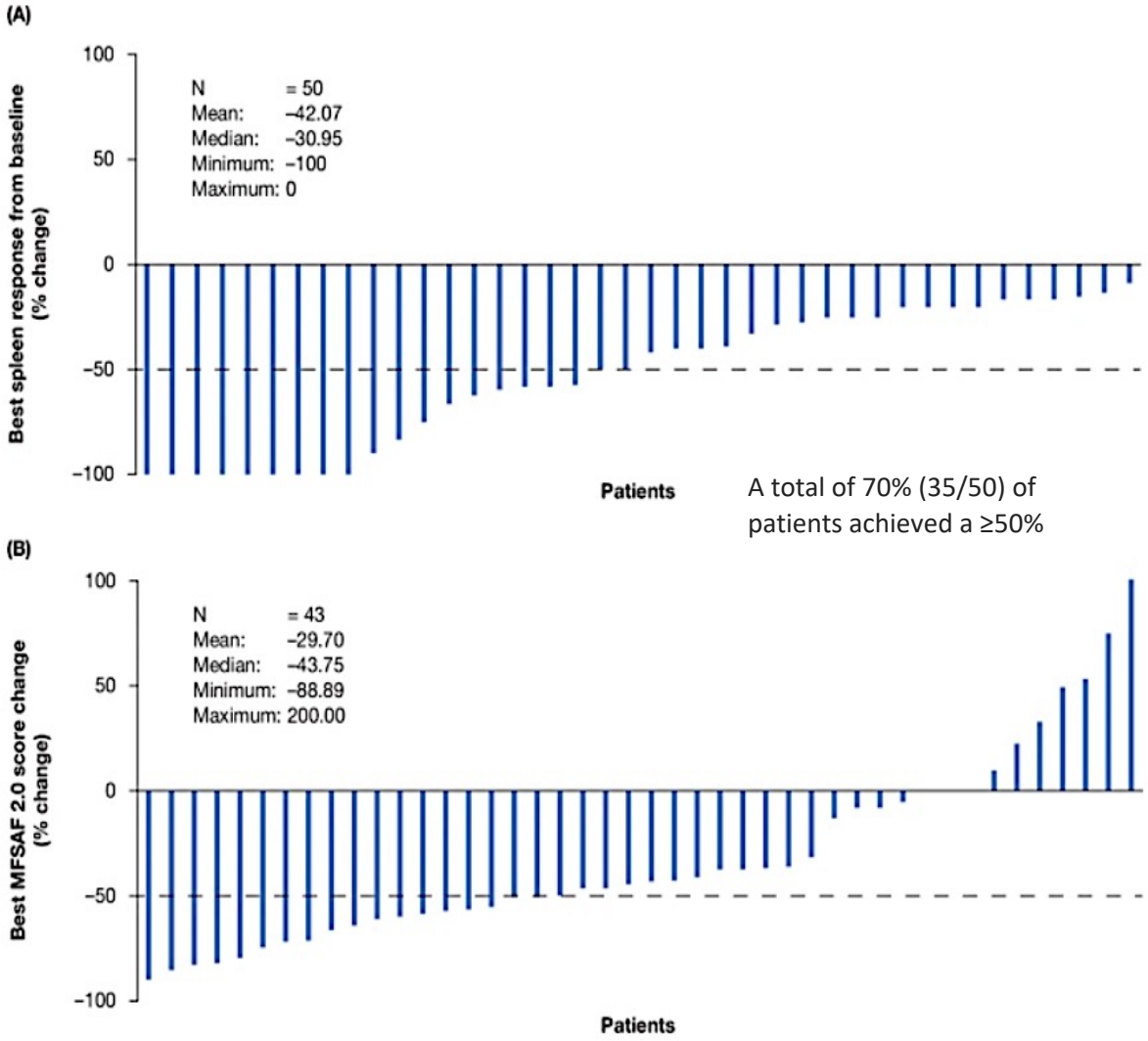
Dosing Ruxolitinib in anemia — REALISE study



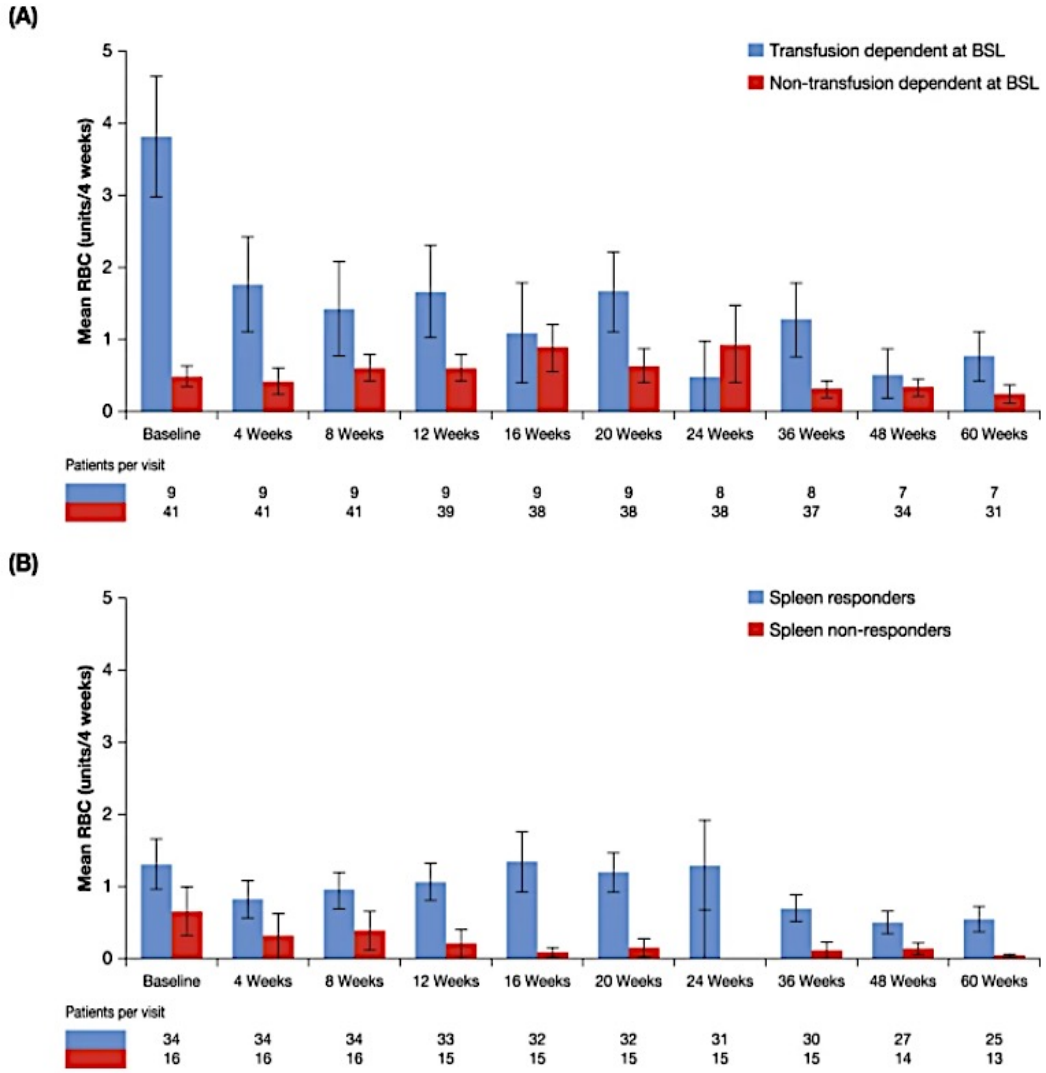
b.i.d. twice daily, BSL baseline spleen length, PLT platelets, RUX ruxolitinib, SL spleen length.

Cervantes et al. Leukemia **volume 35**, pages3455–3465 (2021)

Results



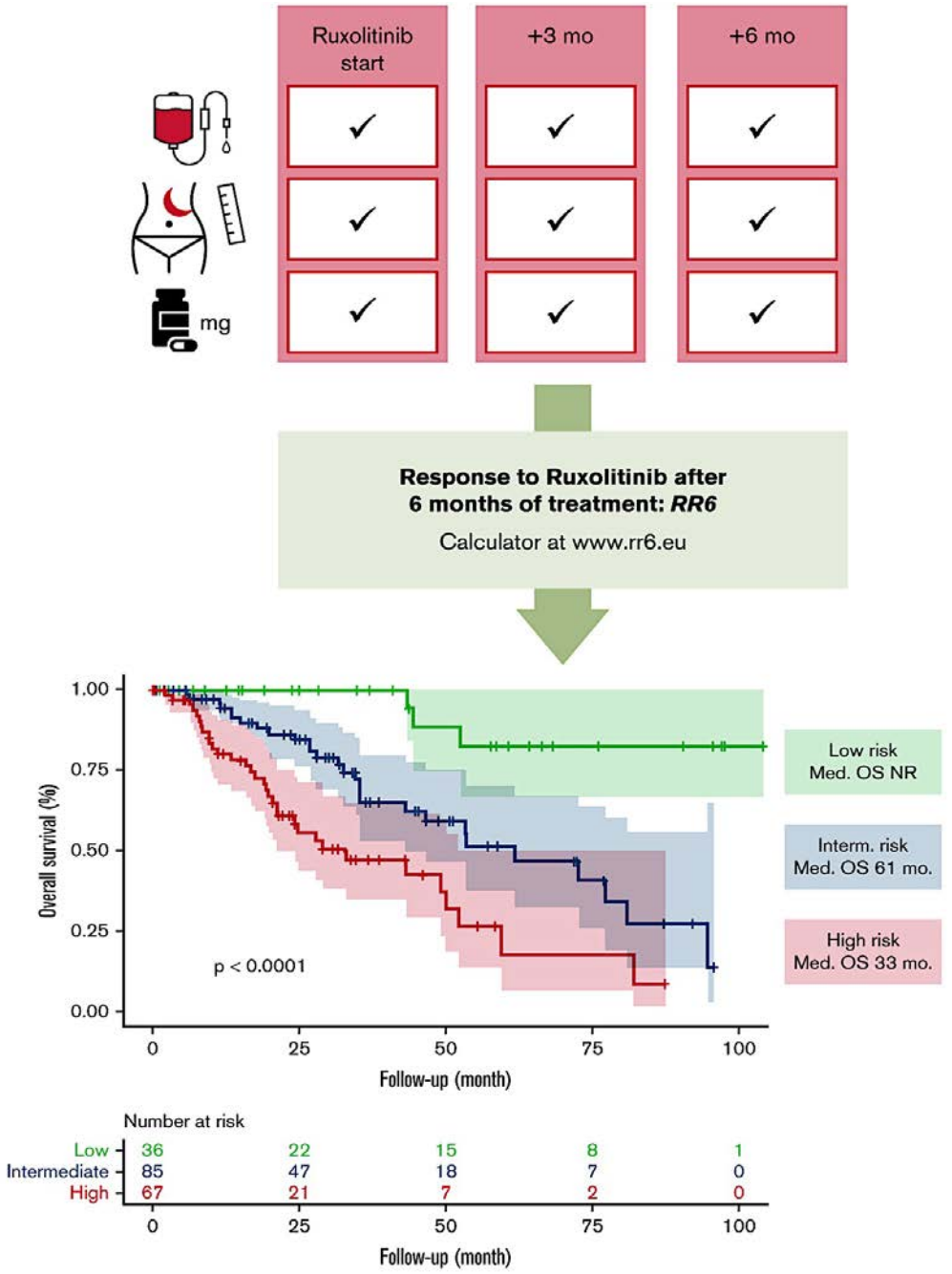
A total of 70% (35/50) of patients achieved a ≥50%



- Cervantes et al. Leukemia **volume 35**, pages3455–3465 (2021)

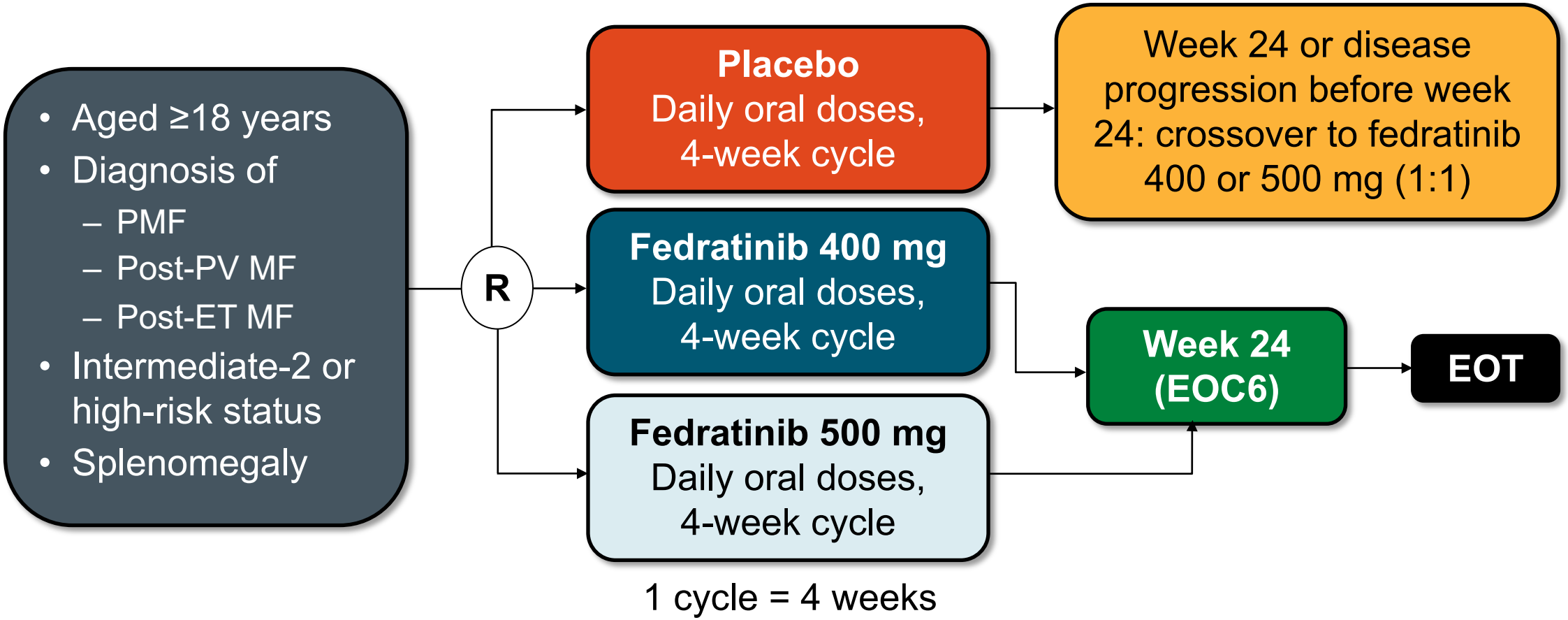
A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis

- **209 RUX-treated MF patients entered the analysis**
- 1 point
  - Receiving RUX at a dose <20mg twice daily at all time points
  - RBC transfusion requirement at 3 and/or 6 months
- 1.5 points were assigned to
  - Obtaining a palpable spleen length reduction ≤30% with respect to baseline at months 3 and 6
  - Needing RBC transfusions at all time points



Maffioli et al. Blood Adv (2022) 6 (6): 1855–1864

JAKARTA: Phase 3 Study Design



Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.; Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-e324.

JAKARTA-1: Baseline Characteristics

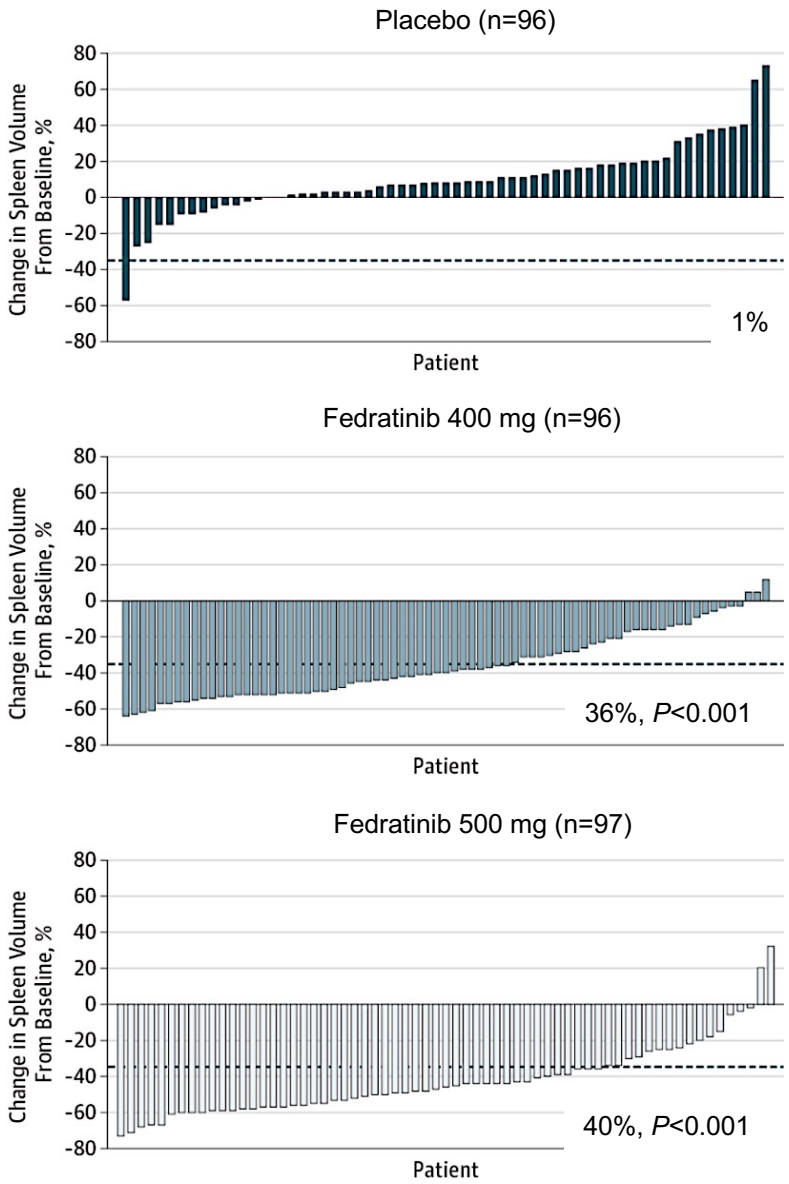
Key Baseline Characteristics	JAKARTA-1	
	Fedratinib 400/500 (n=96/n=97)	Placebo n=154
Median age, years	63/65	66
Male, %	56/63	57
MF diagnosis: PMF, PPV-MF, PET-MF, %	65/65, 25/26, 10/9	60, 28, 11.5
IPSS risk status: Int-2, High, %	59.0/48.5, 41.0/51.5	48, 52
Median palpable length, cm	16/14	17
Median volume, cm	2652/2366	2660
Median platelet count, $x10^9$/L <$100x10^9$/L , % ≥$100x10^9$/L, %	221/241 15/15 85/85	187 20 80
Median hemoglobin, g/dL	10.7/9.8	10.1

Int, intermediate; IPSS, International Prognostic Scoring System; MF, myelofibrosis; NR, not reached; PET-MF, postessential thrombocythemia MF; PMF, primary MF; PPV-MF, postpolycythemia vera MF.

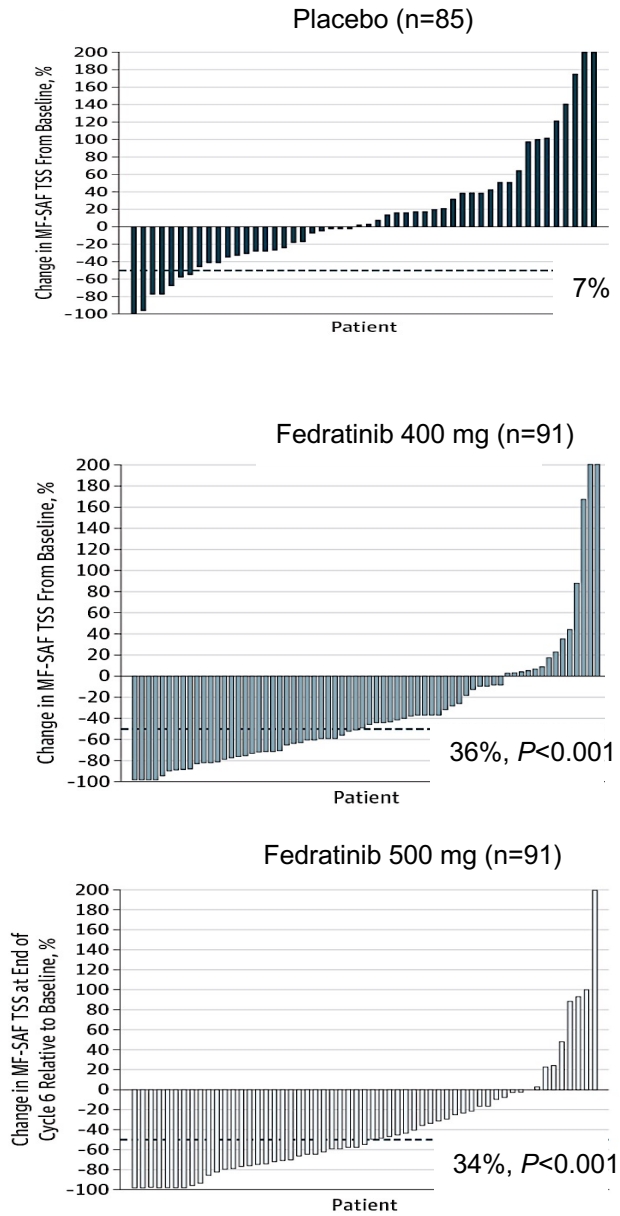
Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.; Harrison CN, et al. *Lancet Haematol.* 2017;4:e317-e324.

JAKARTA-1: Key Efficacy Endpoints

≥35% SVR at 24 Weeks



≥50% Reduction in TSS at 24 Weeks



SVR, spleen volume reduction;
TSS, total symptom score.

Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.

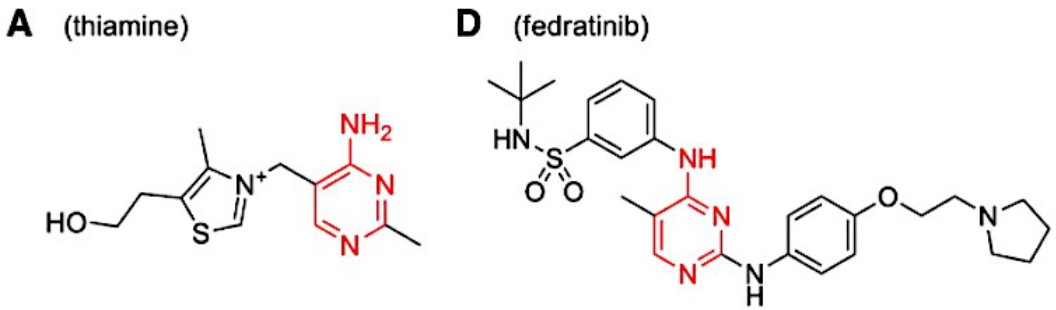
JAKARTA-1: Hematologic/Nonhematologic Adverse Reactions

Hematologic Adverse Reactions[a]	Fedratinib 400/500 (n=96/n=97)		Placebo n=95	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Thrombocytopenia	63/57	17/27	51	9
Anemia	99/98	43/60	91	25
Neutropenia	28/44	8/18	15	4
Nonhematologic Adverse Reactions	Fedratinib 400/500		Placebo	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Diarrhea	66/56	5/5	16	0
Vomiting	42/55	3/9	5	0
Nausea	64/51	0/6	15	0
Constipation	10/18	2/0	7	0
Asthenia	9/16	2/4	6	1
Abdominal pain	15/12	0/1	16	1
Fatigue	16/10	6/5	10	0
Dyspnea	8/10	0/1	6	2
Weight decrease	4/10	0/0	5	0

[a] *Presented values are worst grade values regardless of baseline (NCI Common Terminology Criteria for AEs, version 3.0).*
FDA places clinical hold on fedratinib in November 2013 because of WE (n=7 patients)

Pardanani A, et al. *JAMA Oncol*. 2015;1:643-651.; Scott BL, et al. *JAMA Oncol*. 2015;1:651-652.

Fedratinib Considerations



Black Box Warning!

Wernike's encephalopathy (WE) (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

Expert review:

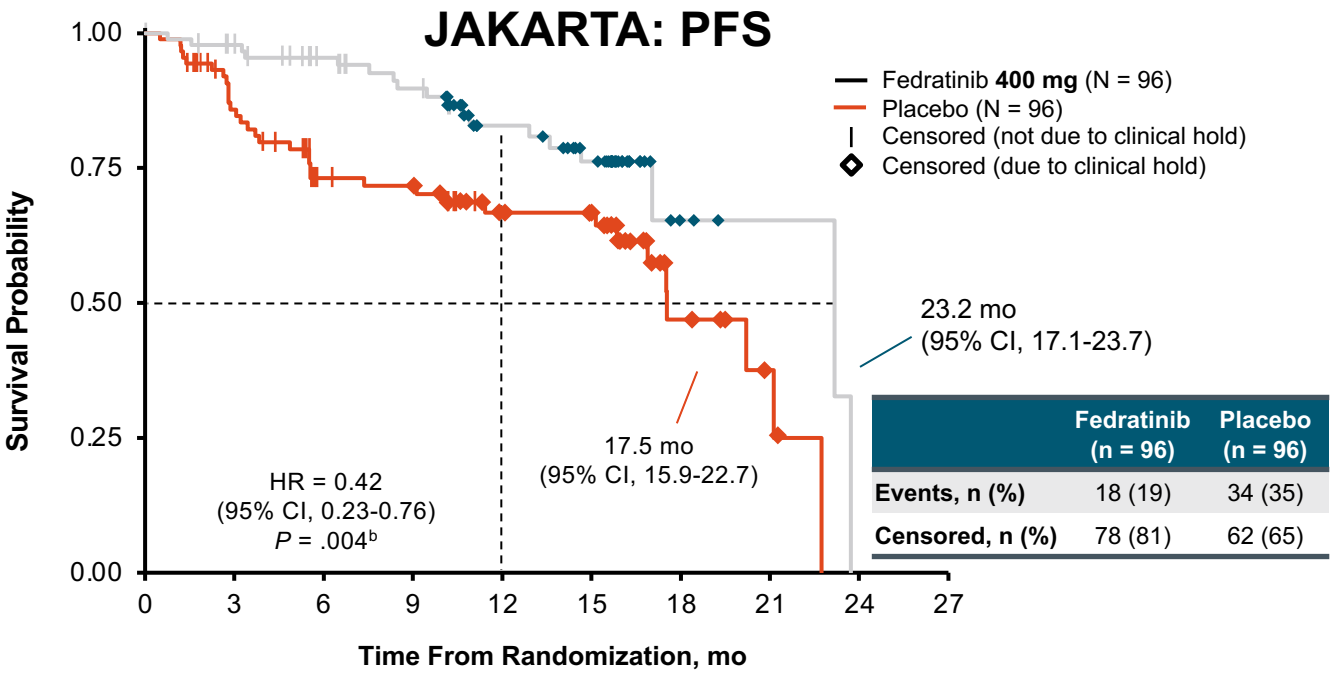
- 3 cases weren't WE
- 1 cases confirmed WE based on MRI in patient with significant GI toxicity
- 2 cases confirmed WE resolved without holding fedratinib
- 2 cases indeterminate

- Check thiamine when starting fedratinib and periodically during treatment
- If patient experiences neurologic symptoms consistent with WE, hold fedratinib and give IV thiamine
- Do not start fedratinib in patients with thiamine deficiency; replete thiamin prior to treatment initiation

Zhang Q, et al. *Drug Metab Dispos.* 2014;42(10):1656-1662.
Harrison C, et al. *Blood*. 2017;130 (Supplement 1):4197.

JAKARTA: Progression-Free Survival

- Fedratinib significantly reduced the risk of disease progression vs placebo (*P* = .004)
  - Median PFS was 5.7 mo longer with fedratinib vs placebo (23.2 vs 17.5 mo, respectively)
  - 1-year PFS: fedratinib 83%, placebo 67%
- 80 patients (42%) were still being followed for PFS at the time of clinical hold
  - Median follow-up: fedratinib 10.6 mo; placebo, 9.1 mo
- AML transformation reported in 3 patients (3%) who received fedratinib and 2 patients (2%) in the placebo arm[a]

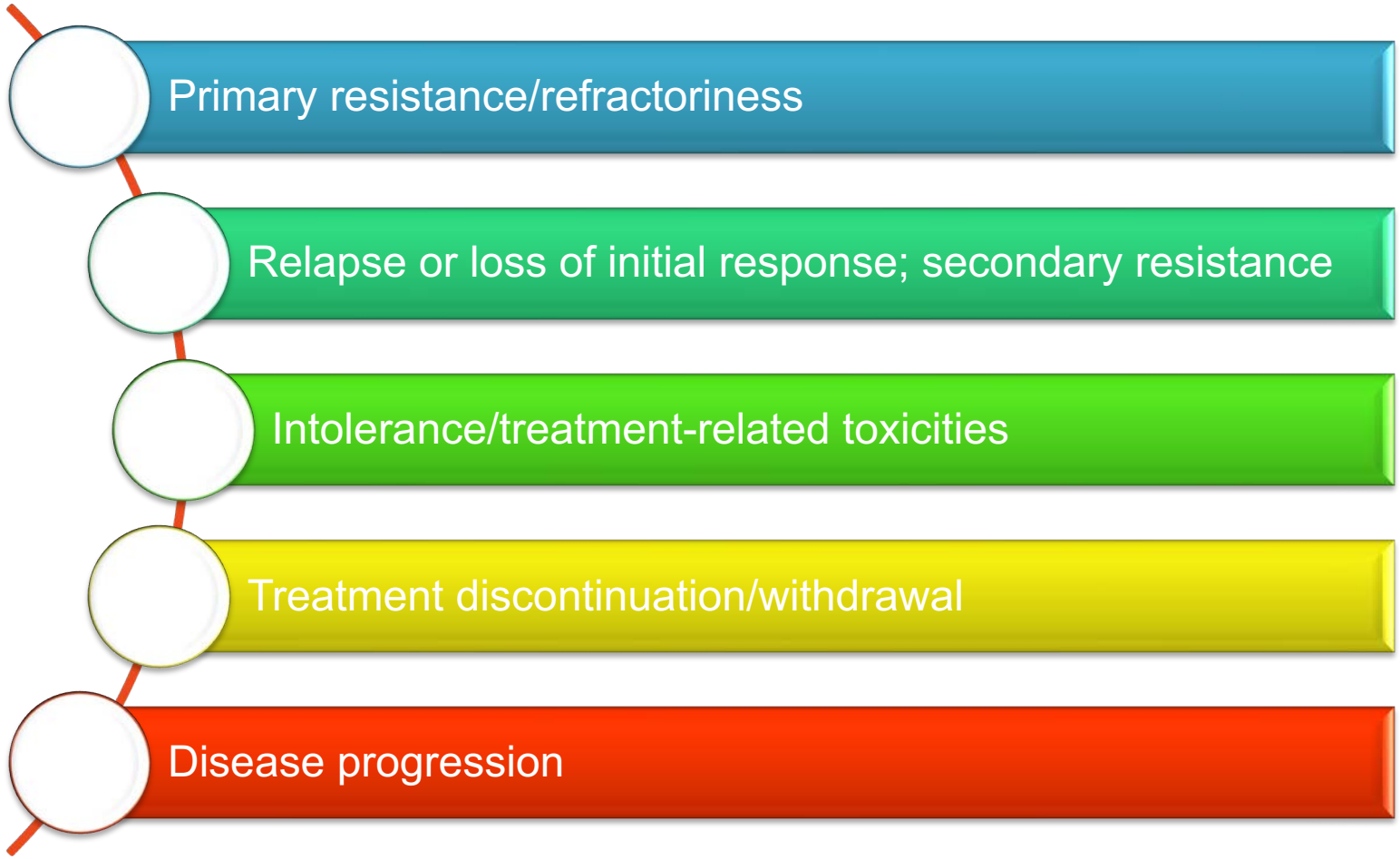


	Fedratinib (n = 96)	Placebo (n = 96)
Events, n (%)	18 (19)	34 (35)
Censored, n (%)	78 (81)	62 (65)

[a] AML transformation was based on AE reporting, including the preferred terms of "acute myeloid leukemia," "acute leukemia," and "transformation to acute myeloid leukemia." [b] *P* value from log-rank test.

Harrison C, et al. EHA 2021. Abstract S203.

Defining Treatment Failure in Clinical Practice



No change in spleen size or reduction in symptoms

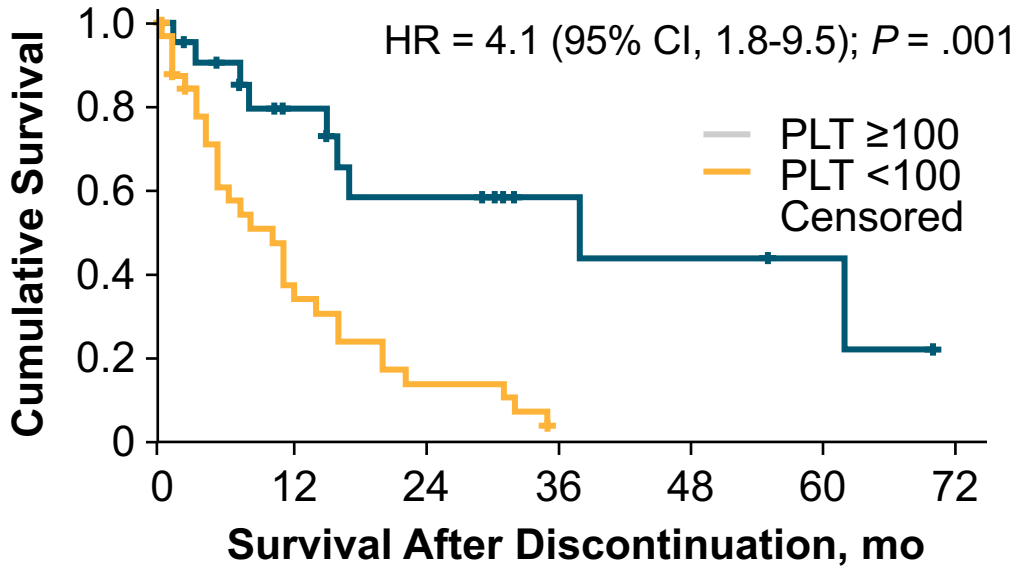
At dose reduction or on stable dose; symptom & spleen return to baseline

Myelosuppression, early-onset cytopenias (including increase in transfusion requirements), bleeding, infections

Accelerated-phase disease, leukemic transformation (increase in blast percentage), late-onset cytopenias

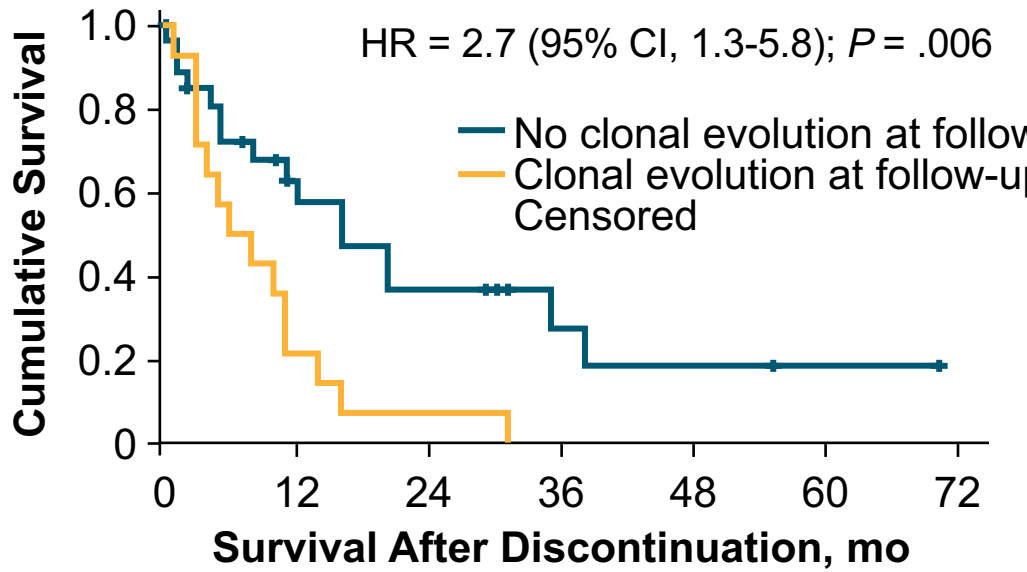
Harrison CN, et al. *Ann Hematol.* 2020;99:1177-1191; Pardanani A, et al. *Blood Cancer J.* 2014;4:e268; McLoman DP, et al. *Blood Adv.* 2024;4:607-610.

Prognosis After Ruxolitinib Discontinuation[1]



PLTs <100 median survival: 11/12

No. at Risk							
PLT ≥100	23	12	7	4	3	1	0
PLT <100	33	10	4	0			



Clonal evolution median survival: 6/12

No. at Risk							
No clonal evolution	28	16	4	4	2	1	0
Clonal evolution	14	3	3	1	0		

- Survival after ruxolitinib discontinuation is poor[1-3]
- Salvage therapy or rechallenge with ruxolitinib can provide responses after discontinuation[4]
- This continues to be an area of unmet clinical need in MF

1. Newberry KJ et al. *Blood.* 2017;130:1125-1131. 2. Kuykendall AT et al. *Ann Hematol.* 2018;97:435-441. 3. Palandri F et al. *Cancer.* 2020;126:1243-1252.
4. Gerds A et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:e463-e468.

JAKARTA-2 Reanalysis Confirmed the Benefit of Post-Ruxolitinib Therapy with Fedratinib[1]

- In original JAKARTA-2 analysis, fedratinib demonstrated a 55% rate of SVR_{35} in patients resistant/intolerant to RUX on per protocol analysis
  - Reanalysis employed a more stringent definition of RUX failure

	ITT Population (N = 97)		RUX Failure Cohort (n = 79)		Sensitivity Cohort (n = 66)	
	N	Patients, % (95% CI)	N	Patients, % (95% CI)	N	Patients, % (95% CI)
SVRR	97	31 (22%-41%)	79	30 (21%-42%)	66	36 (25%-49%)
Symptom RR	90	27 (18%-37%)	74	27 (17%-39%)	62	32 (21%-45%)

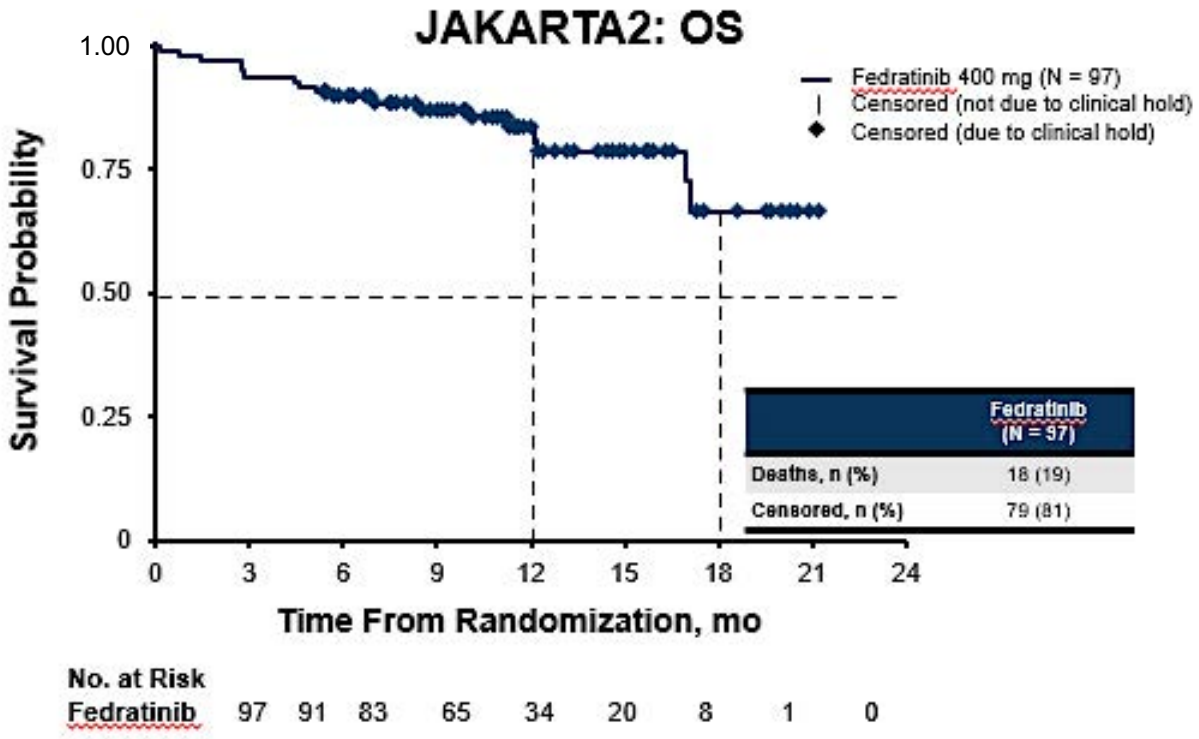
- **Main findings**
  - 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%)
- **Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria**
  - SVRR: 30%
  - Symptom RR: 27%
  - Safety consistent with prior reports

1. Harrison CN et al. *Am J Hematol* 2020;95(6):594-603.

JAKARTA-2: Fedratinib Is an Effective Option in Patients With MF Progressing on Ruxolitinib[1]

97 patients with int-1 with symptoms, int-2 or high-risk PMF, pos-PV MF, or post-ET MF

- Median OS was NR (95% CI, 17.1-NR)
  - 1-year and 18-mo OS rates were 84% and 67%, respectively
- 79 patients (81%) were censored for OS at the time of clinical hold
  - Median follow-up: 10.8 mo



1. Harrison C et al. EHA 2021. Abstract S203.

Conclusions and future directions

- Ruxolitinib remains the frontline agent for treatment of myelofibrosis
  - Progression on ruxolitinib is associated with a poor prognosis
- Fedratinib is a good second line choice for those with adequate blood counts and has shown efficacy in ruxolitinib failures
- Future therapies that focus on improving duration of response disease modification are needed

Case Presentation: 75-year-old woman presents with symptomatic JAK2 V617F-mutant primary MF with mild anemia (Hgb 9.9) and normal platelet count

Dr John Mascarenhas (New York, New York)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What is the optimal initial JAK inhibitor for this symptomatic patient with DIPPS high-risk, JAK2-mutated primary MF?

In your experience, how likely are patients with treatment-naïve MF to respond to ruxolitinib and/or achieve meaningful clinical benefit? Do you still consider ruxolitinib to be the "best-in-class" JAK inhibitor?

What have you observed in terms of quality-of-life side effects with ruxolitinib, such as bruising, dizziness and headaches?

Asymptomatic patients with MF; re-reads of pathology reports; “triple-negative” MF, secondary causes

Dr Laura Michaelis (Milwaukee, Wisconsin)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What is your threshold for initiating active treatment for patients with intermediate-1-, intermediate-2- and high-risk MF, respectively? In what situations, if any, will you recommend a JAK inhibitor to an asymptomatic patient with MF? What about for a patient with low-risk disease? Is there an advantage to early intervention versus observation for certain patients?

When do you obtain re-reads of pathology reports for your patients with MF, and how often does this result in a change in treatment recommendations?

What secondary causes of MF should be looked for in "triple-negative" disease?

Ruxolitinib-associated dermatologic cancers, weight gain

Dr Prithviraj Bose (Houston, Texas)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What is known about MF-associated second cancers, including pathogenesis?

What is your experience with ruxolitinib-associated dermatologic cancers? What would you recommend for patients whose disease is well controlled with ruxolitinib but who are frequently developing nonmelanoma skin cancers?

What is your experience with ruxolitinib-associated weight gain?

QUESTIONS FOR THE FACULTY

What is your threshold for recommending a change in treatment for patients receiving fedratinib? In which situations are you prioritizing the use of fedratinib for patients with newly diagnosed MF and for those with ruxolitinib-resistant or intolerant disease?

Agenda

Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Palmer

Module 2: Managing MF in Patients with Anemia — Dr Oh

Module 3: Managing MF in Patients with Thrombocytopenia — Dr Rampal

Module 4: Promising Novel Agents Under Investigation for MF — Prof Harrison

Module 5: Current and Future Management of Systemic Mastocytosis — Dr Kuykendall

Managing Myelofibrosis in Patients with Anemia

Stephen Oh, M.D., Ph.D.
Professor of Medicine
Co-Chief, Division of Hematology
Washington University School of Medicine

WashU Medicine

SITEMAN CANCER CENTER
A NATIONAL CANCER INSTITUTE COMPREHENSIVE CANCER CENTER

Anemia in Myelofibrosis – Defining the Scope of the Problem

- Anemia is a defining feature of MF
  - Virtually all MF patients develop anemia at some point in their disease course
  - Nearly 40% of MF patients have Hgb < 10g/dL at diagnosis
  - Nearly 25% already transfusion-dependent at diagnosis
- Anemia has a detrimental impact on quality of life for MF patients
  - Amelioration of anemia has been associated with improved QOL
- Anemia has been consistently associated with poor prognosis in MF
- Anemia remains an important unmet need for MF patients

TABLE 1. Clinical and Laboratory Features of 1000 Patients With Primary Myelofibrosis at Time of Referral to Mayo Clinic[a]

Variable	No. evaluable	All patients (N=1000)	Patients seen at time of diagnosis (n=340), Group A	Patients seen within 1 y of diagnosis (n=274), Group B	Patients seen more than 1 y after diagnosis (n=386), Group C	*P* value[b] for groups A vs B	*P* value[b] for groups B vs C
Hemoglobin <10 g/dL, No.	1000	535 (54)	130 (38)	158 (58)	247 (64)	**<.001**	.10
Transfusion requiring, No.	1000	383 (38)	83 (24)	126 (46)	174 (45)	**<.001**	.82

Tefferi et al, Mayo Clinic Proc 2012

Anemia in Myelofibrosis – Defining the Scope of the Problem

RISK STRATIFICATION FOR PATIENTS WITH PMF

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[1]

Prognostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

Online calculator for DIPSS score can be found at https://qxmd.com/calculate/calculator_187/dipss-prognosis-in-myelofibrosis

DIPSS-PLUS[2]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

Online calculator for DIPSS-PLUS score can be found at https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

[1]Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010;115:1703-1708.

[2]Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol 2011;29:392-397.

Anemia in Myelofibrosis – Defining the Scope of the Problem

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION AND KARYOTYPE-ENHANCED IPSS (MIPSS-70+ VERSION 2.0) FOR PATIENTS WITH PMF[4,5]

Prognostic Variable	Points
Severe anemia (Hemoglobin <8 g/dL in women and <9 g/dL in men)	2
Moderate anemia (Hemoglobin 8–9.9 g/dL in women and 9–10.9 g/dL in men)	1
Circulating blasts ≥2%	1
Constitutional symptoms	2
CALR type-1 unmutated genotype	2
HMR mutations[a]	2
≥2 HMR mutations	3
Complex karyotype[b]	3
Very-high-risk (VHR) karyotype[c]	4

Risk Group	Points
Very low	0
Low	1–2
Intermediate	3–4
High	5–8
Very high	≥9

Online calculator for MIPSS-70+ Version 2.0 can be found at http://www.mipss70score.it/.

Footnotes

[a]Presence of a mutation in any of the following genes: *ASXL1*, *EZH2*, *SRSF2*, *U2AF1*, or *IDH1/2*.

[b]Complex karyotype or sole or two abnormalities of +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p− or 11q23 rearrangement, (+21, +19).

[c]VHR karyotype: single/multiple abnormalities of −7, i(17q), inv(3)/3q21, 12p−/12p11.2, 11q−/11q23, or other autosomal trisomies not including + 8/+9 (eg, +21, +19).

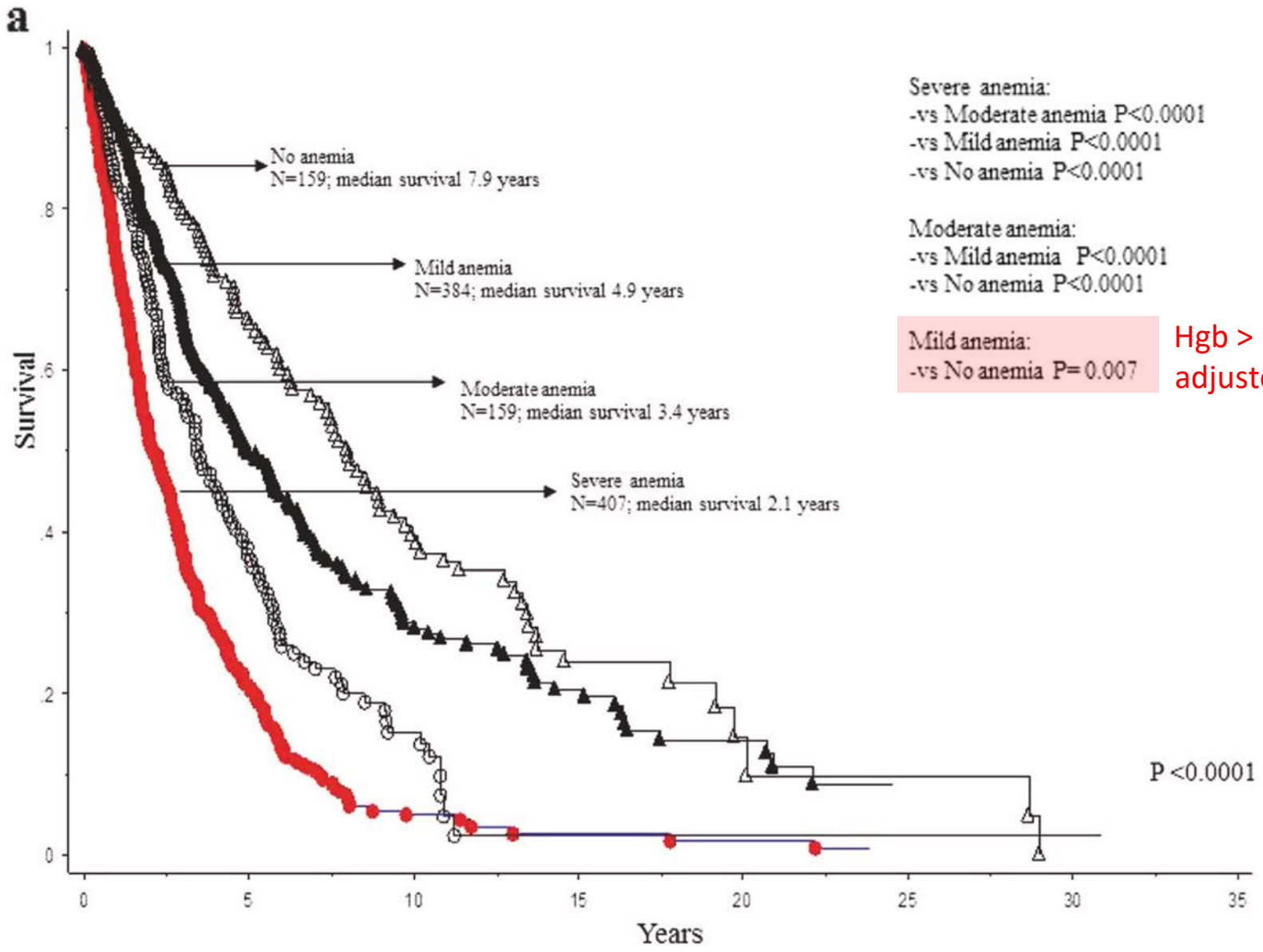
References

[4]Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70 + Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. J Clin Oncol 2018,36:1769-1770.

[5]Tefferi A, Nicolosi M, Mudireddy M, et al. Revised cytogenetic risk stratification in primary myelofibrosis: analysis based on 1002 informative patents. Leukemia 2018;32:1189-199.

NCCN guidelines for MPNs v2.2025

Anemia in Myelofibrosis – Defining the Scope of the Problem



Severe anemia:
-vs Moderate anemia P<0.0001
-vs Mild anemia P<0.0001
-vs No anemia P<0.0001

Moderate anemia:
-vs Mild anemia P<0.0001
-vs No anemia P<0.0001

Mild anemia:
-vs No anemia P= 0.007

Hgb > 10 g/dL but below sex-adjusted lower limit of normal

Nicolosi et al, Leukemia 2018

Anemia in Myelofibrosis - Pathogenesis

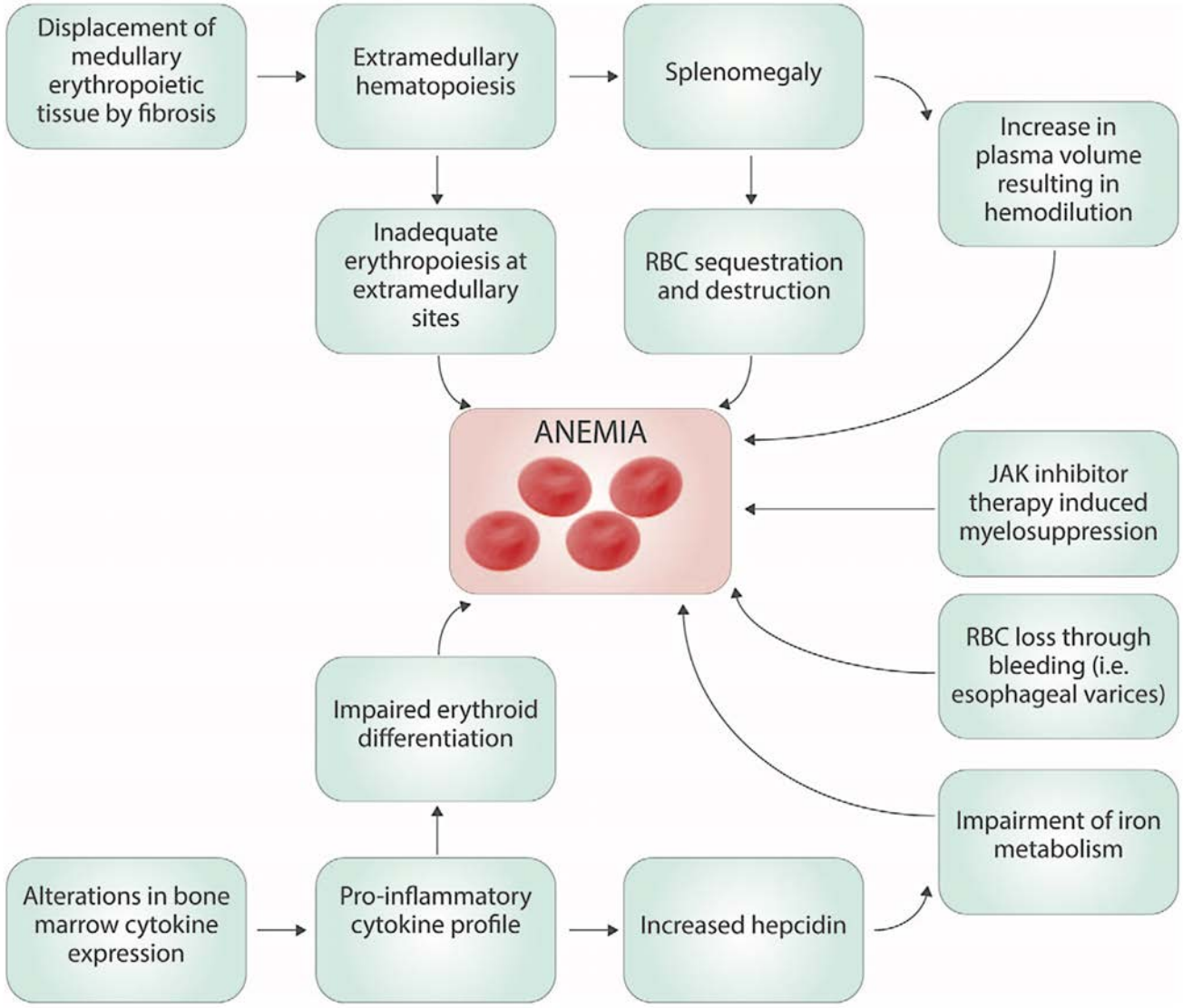
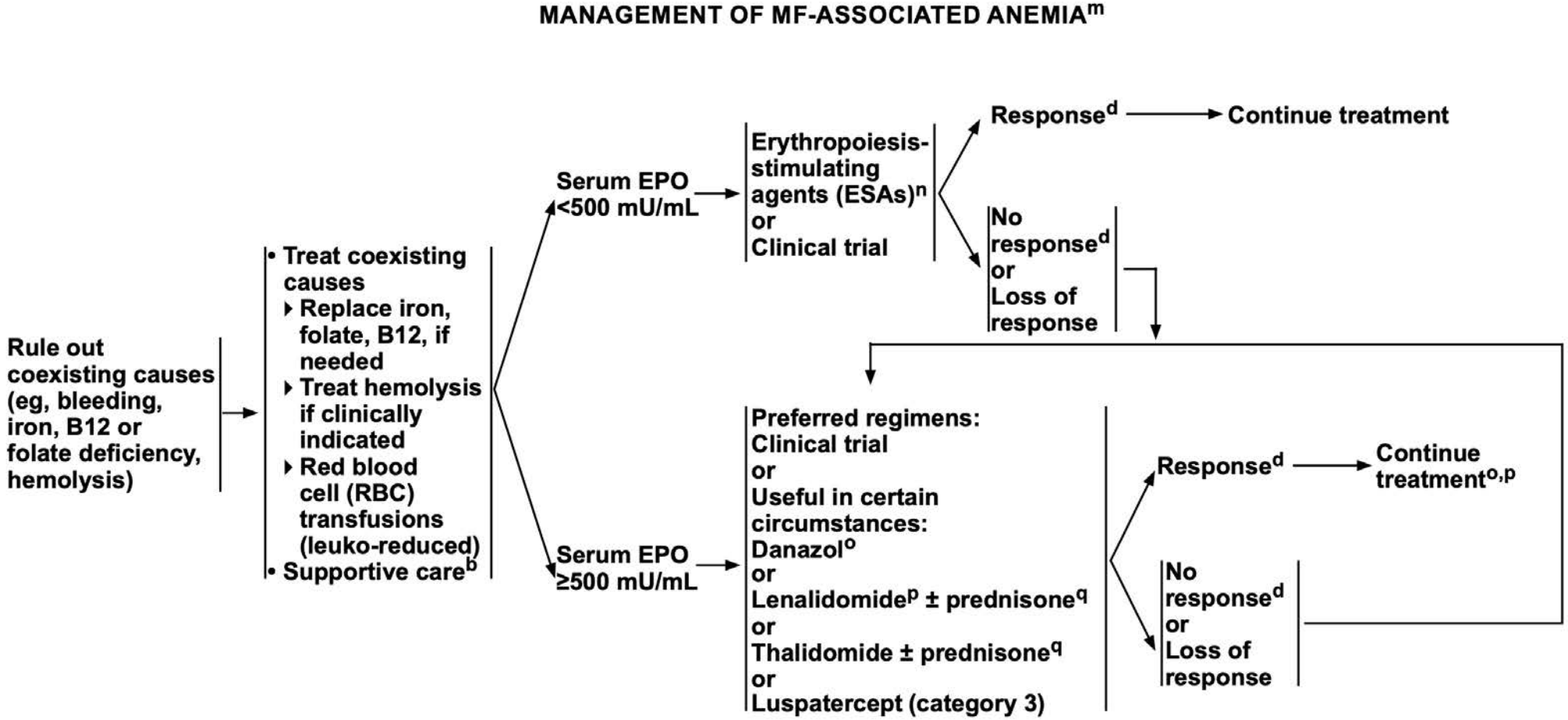


Figure 1. The pathogenesis of anemia in myelofibrosis is the result of a multifactorial process, which is only partially understood. The relative contributions of each of the above etiologies vary from patient to patient, and this variability in pathogenesis may explain the variability in responses to different therepeutic modalities. RBC = red blood cell.

Naymagon & Mascarenhas, HemaSphere 2017

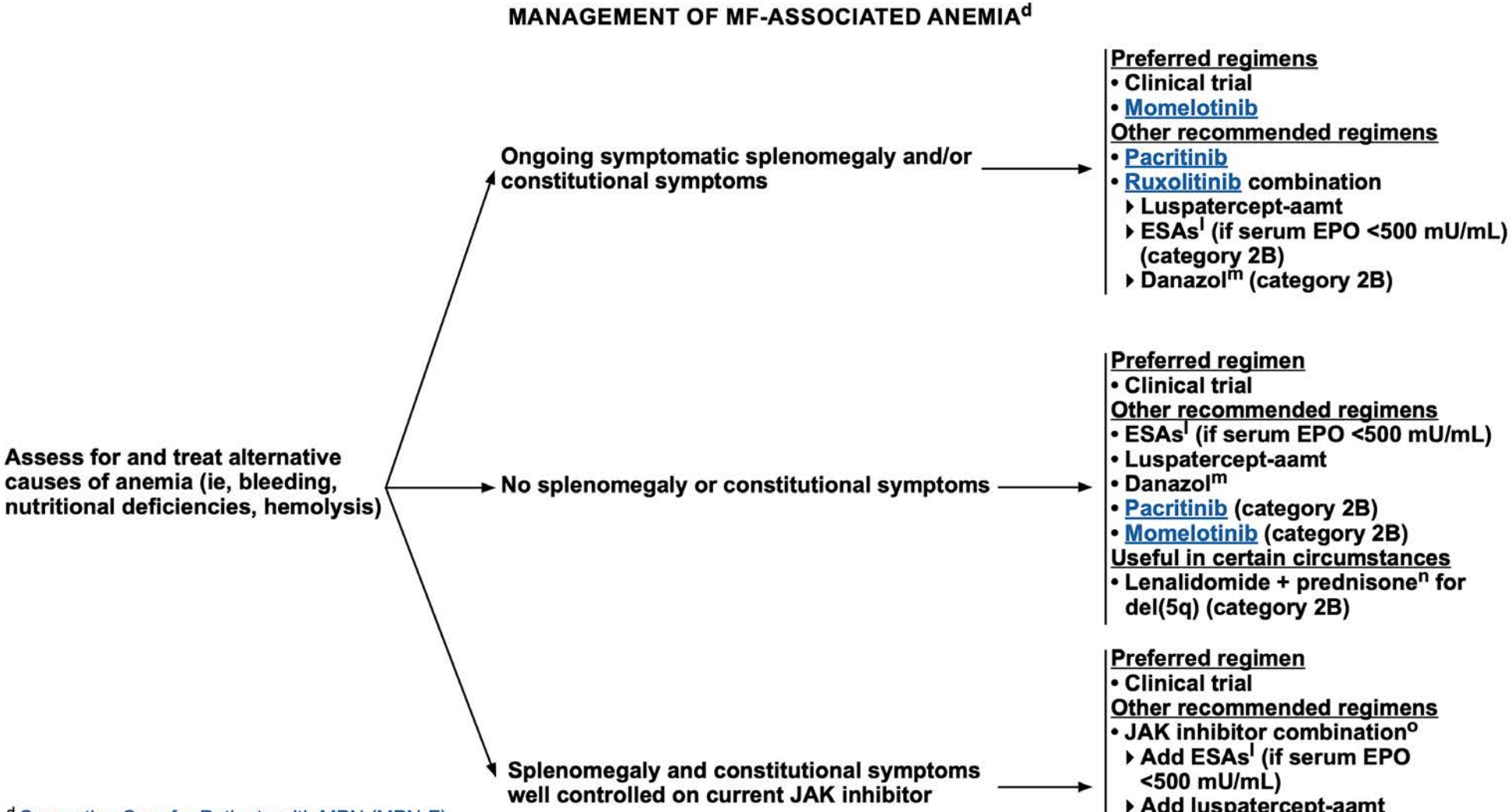
Anemia in Myelofibrosis – NCCN Guidelines



[b] Supportive Care for Patients with MPN (MPN-G).
[d] 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.
[m] JAK inhibitors may be continued for the improvement of splenomegaly and other disease-related symptoms.
[n] ESAs include epoetin alfa and darbepoetin alfa. An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.
[o] Prostate cancer screening and monitoring of LFTs as well as the use of concomitant medications such as statins are recommended over concerns for increased risk of rhabdomyolysis.
[p] Presence of del(5q) is associated with better response rates with lenalidomide.
[q] Start as a combination followed by tapering of prednisone over 3 months.

NCCN guidelines for MPNs v2.2023

Anemia in Myelofibrosis – NCCN Guidelines

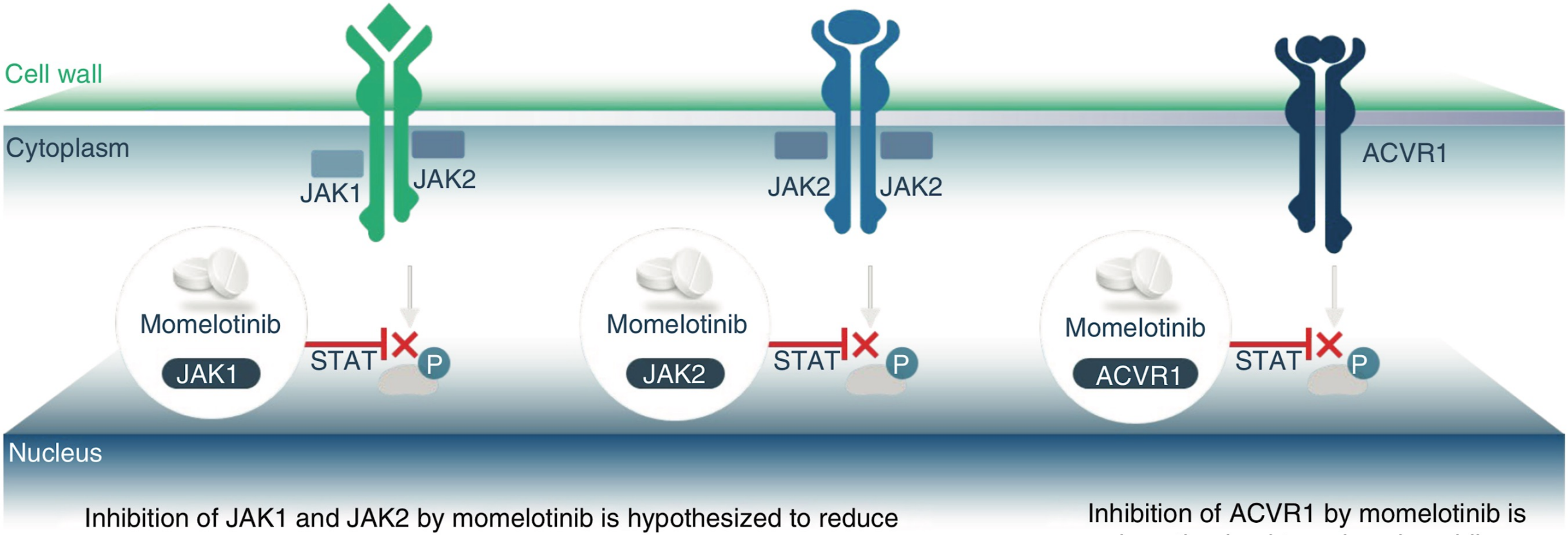


[d] Supportive Care for Patients with MPN (MPN-F).
[l] ESAs include epoetin alfa and darbepoetin alfa. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[m] Prostate cancer screening and monitoring of LFTs as well as the use of concomitant medications such as statins are recommended over concerns for increased risk of rhabdomyolysis.
[n] Start as a combination followed by tapering of prednisone over 3 months.
[o] JAK inhibitors may be continued for the improvement of splenomegaly and other disease-related symptoms.

Note: All recommendations are category 2A unless otherwise indicated.

NCCN guidelines for MPNs v2.2025

Anemia in Myelofibrosis – Momelotinib



Inhibition of JAK1 and JAK2 by momelotinib is hypothesized to reduce inflammation, aberrant cytokine signaling, extramedullary hematopoiesis, constitutional symptoms and splenomegaly

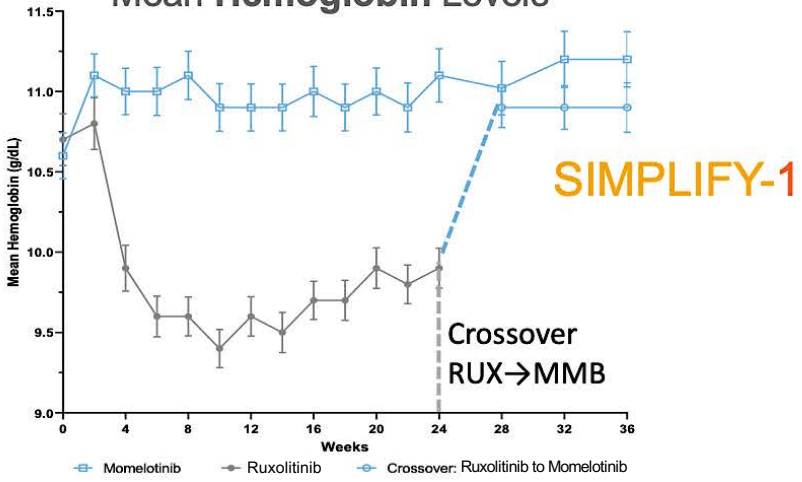
Inhibition of ACVR1 by momelotinib is hypothesized to reduce hepcidin transcription, restore iron homeostasis and increase hemoglobin

Verstovsek et al, Future Oncol 2021

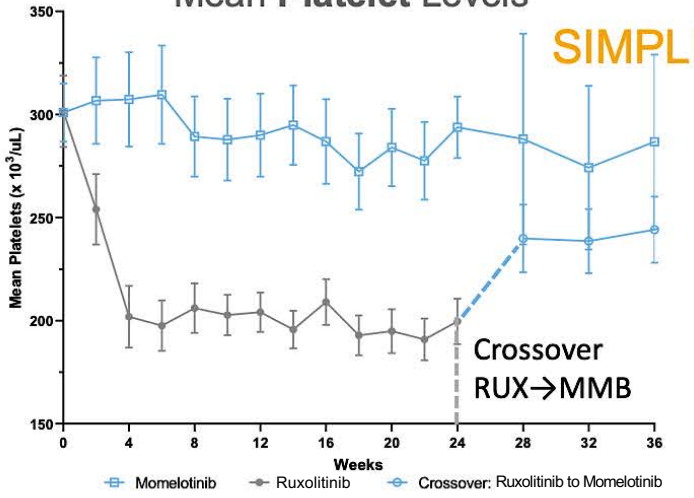
Anemia in Myelofibrosis – Momelotinib

Momelotinib:
Differentiated Heme Profile Allows High Dose Intensity

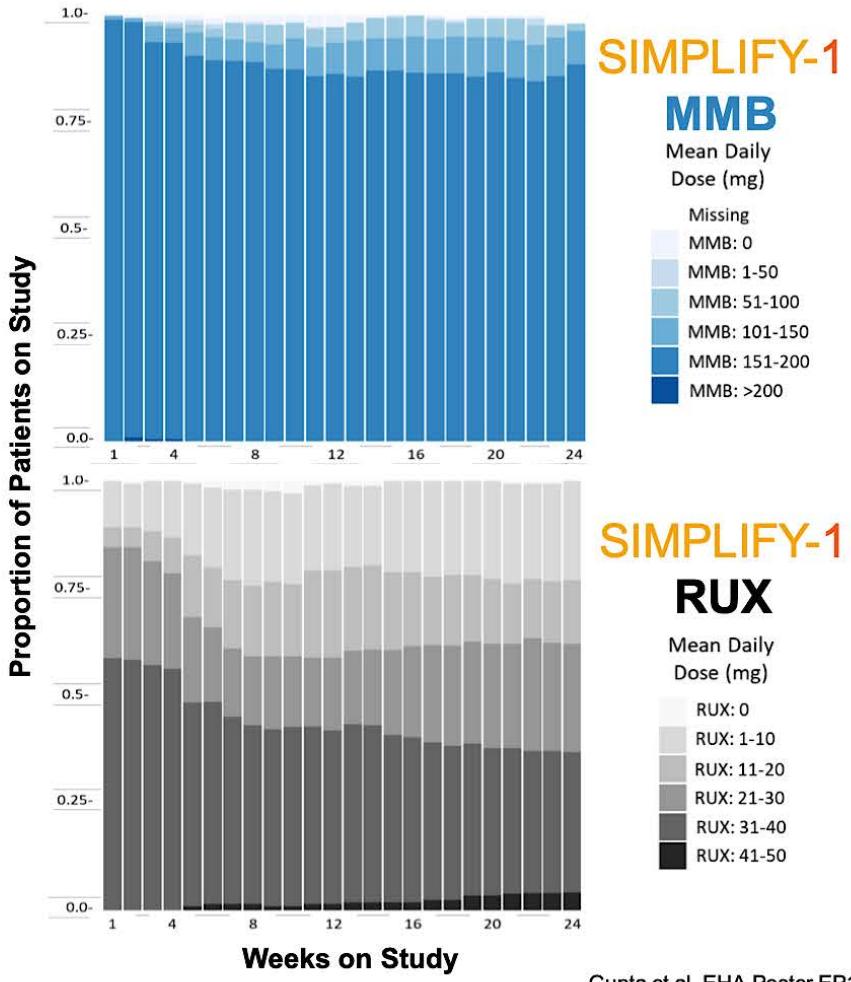
Mean **Hemoglobin** Levels



Mean **Platelet** Levels



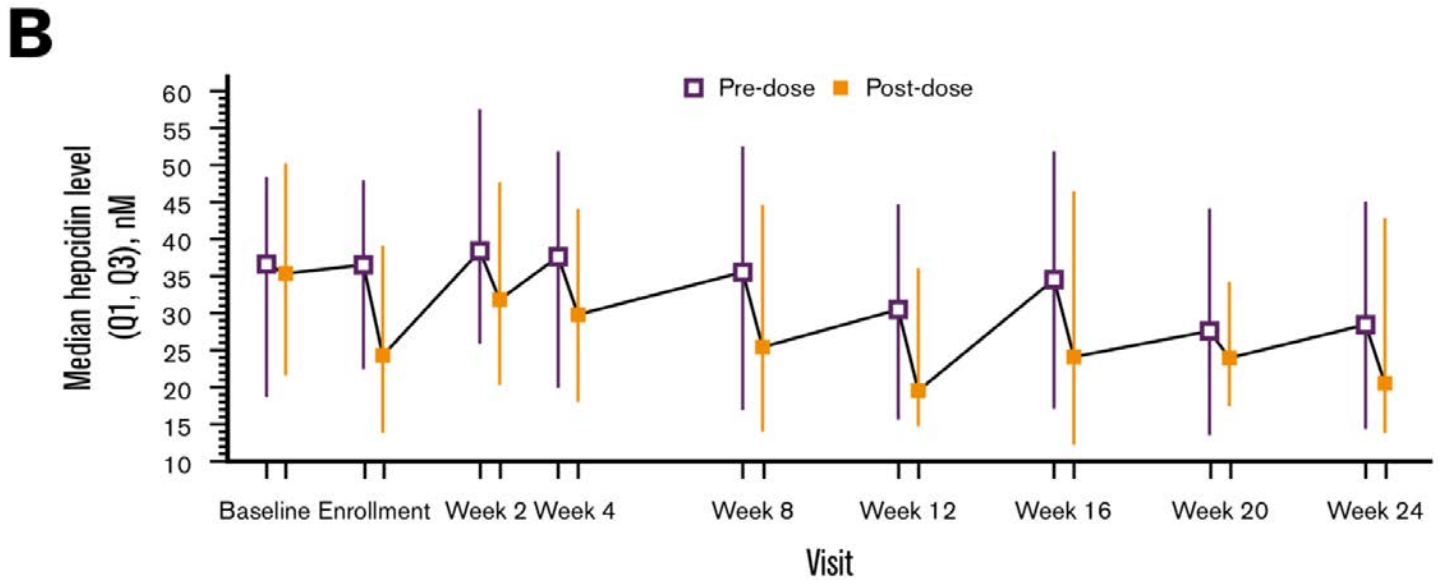
Average **Dose Intensity** by Week

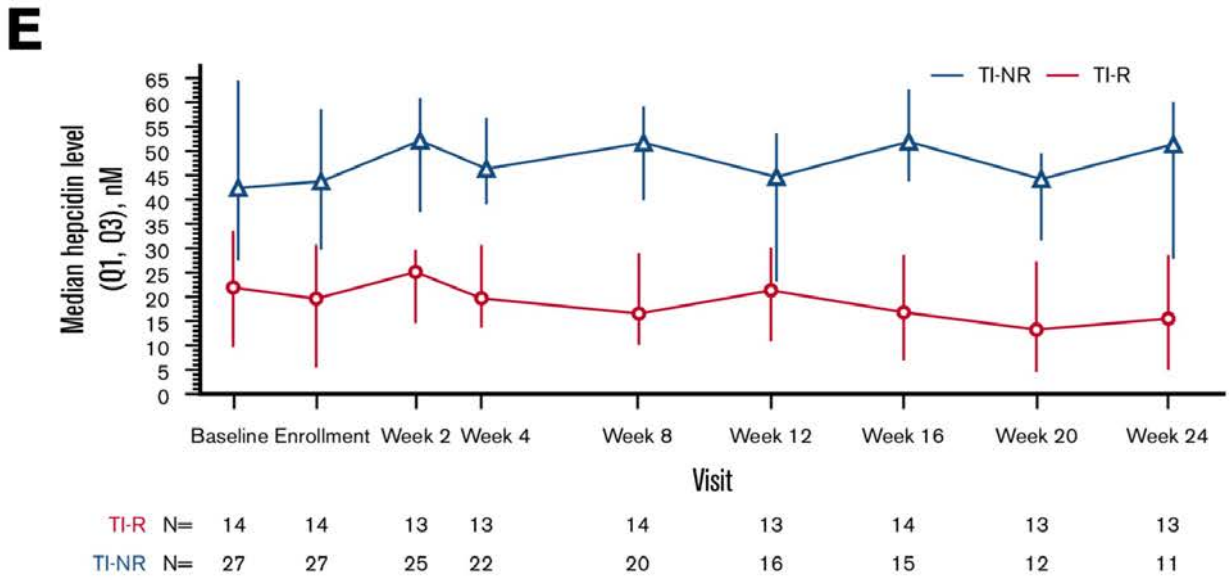


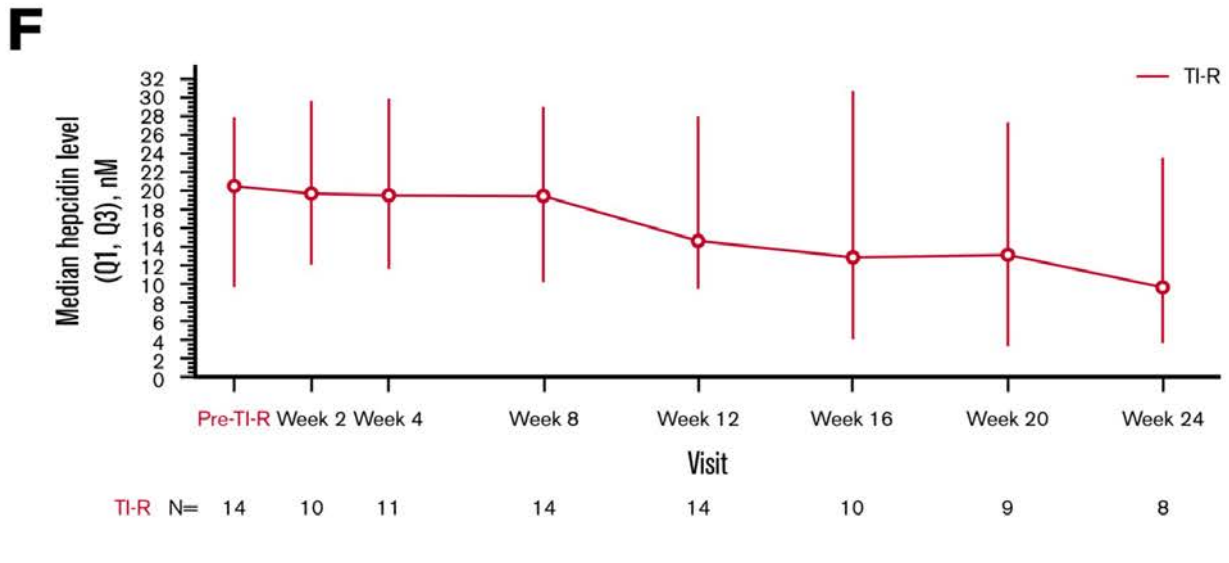
Gupta et al. EHA Poster EP1103. 2020.

Verstovsek et al, ASH 2020

Anemia in Myelofibrosis – Momelotinib







Oh et al, Blood Advances 2020

MOMENTUM Phase III Study of Momelotinib vs Danazol in Symptomatic Patients with Myelofibrosis and Anemia

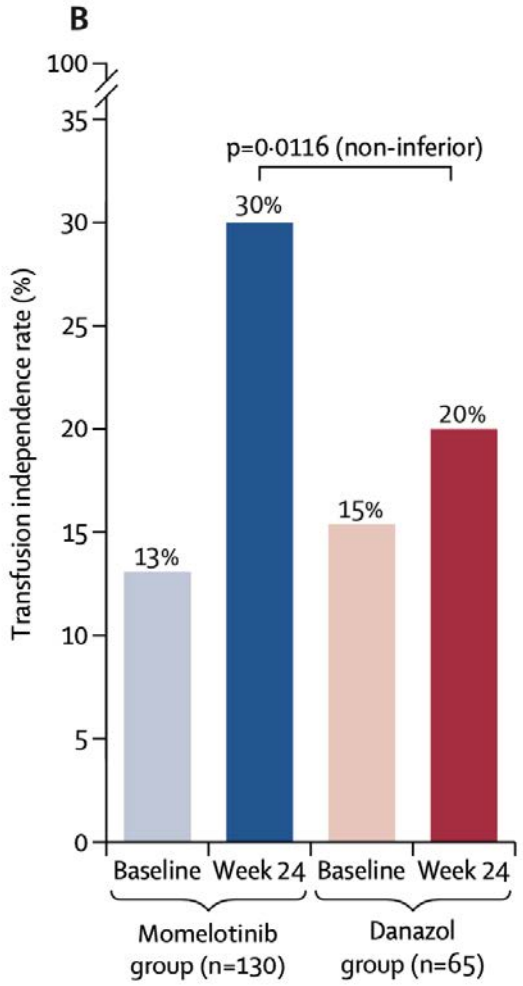
Total Symptom Score Response Rate at Week 24

	MFSAF TSS Response Rate at Week 24 no. (%) [95% CI]	*P* Value
Momelotinib (n = 130)	32 (25) [17, 33]	.0095
Danazol (n = 65)	6 (9) [4, 19]	

Spleen Response Rate at Week 24

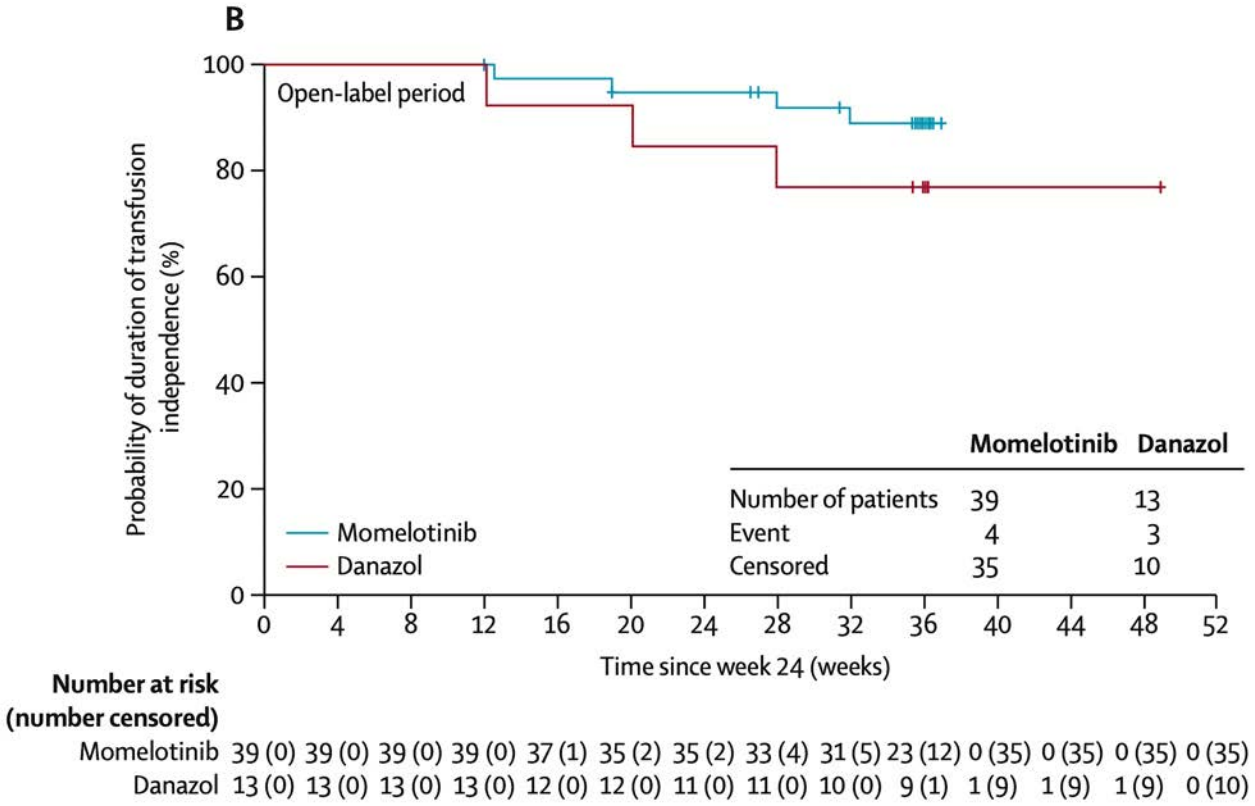
	SRR at Week 24, n (%) [95% CI]	
	25% reduction	**35% reduction**
Momelotinib (n = 130)	52 (40) [32, 49]	30 (23) [16, 31]
Danazol (n = 65)	4 (6) [2, 15]	2 (3) [1, 11]
	P < .0001	*P* = .0006

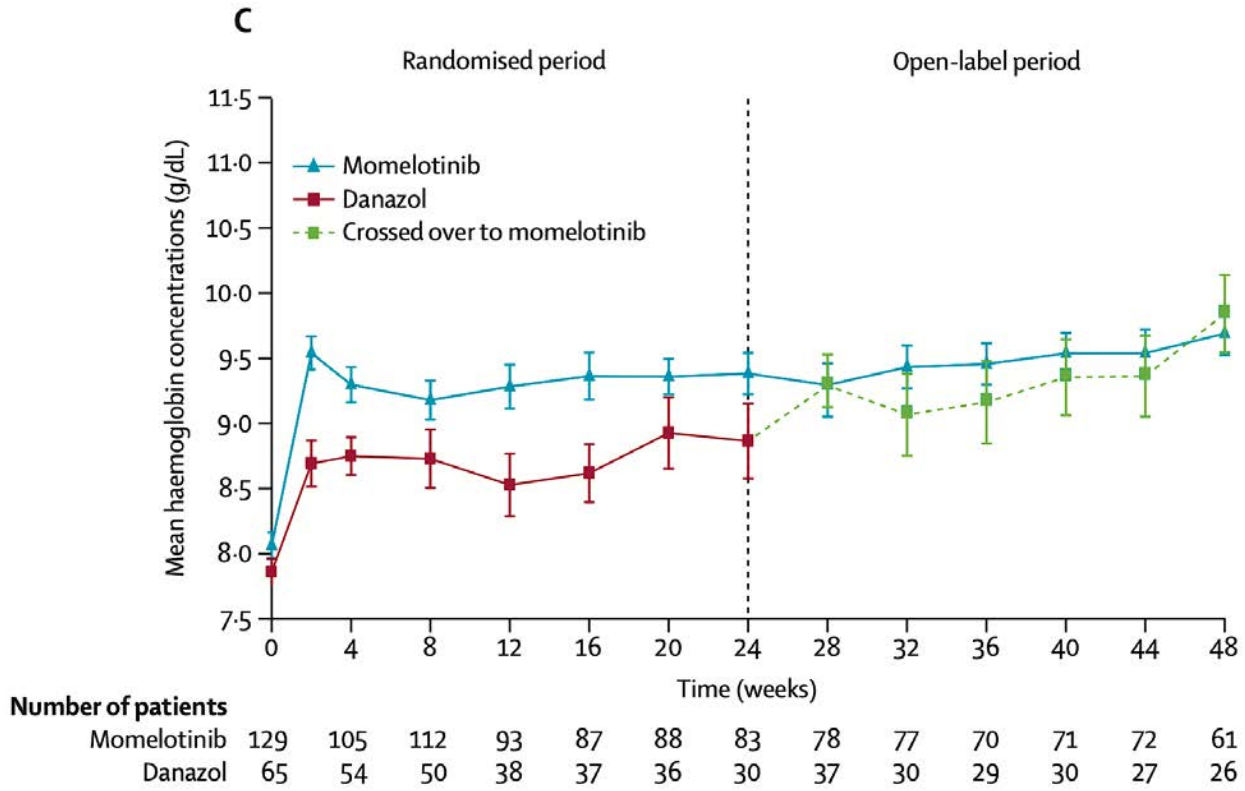
Transfusion Independence at Week 24



Verstovsek et al. Lancet 2023

MOMENTUM: Week 24 TI Responses Sustained Through Week 48





Week 24 TI response was maintained in 35 of 39 (90%) MMB->MMB and 10 of 13 (77%) DAN->MMB patients

Gerds et al, Lancet Haematology 2023

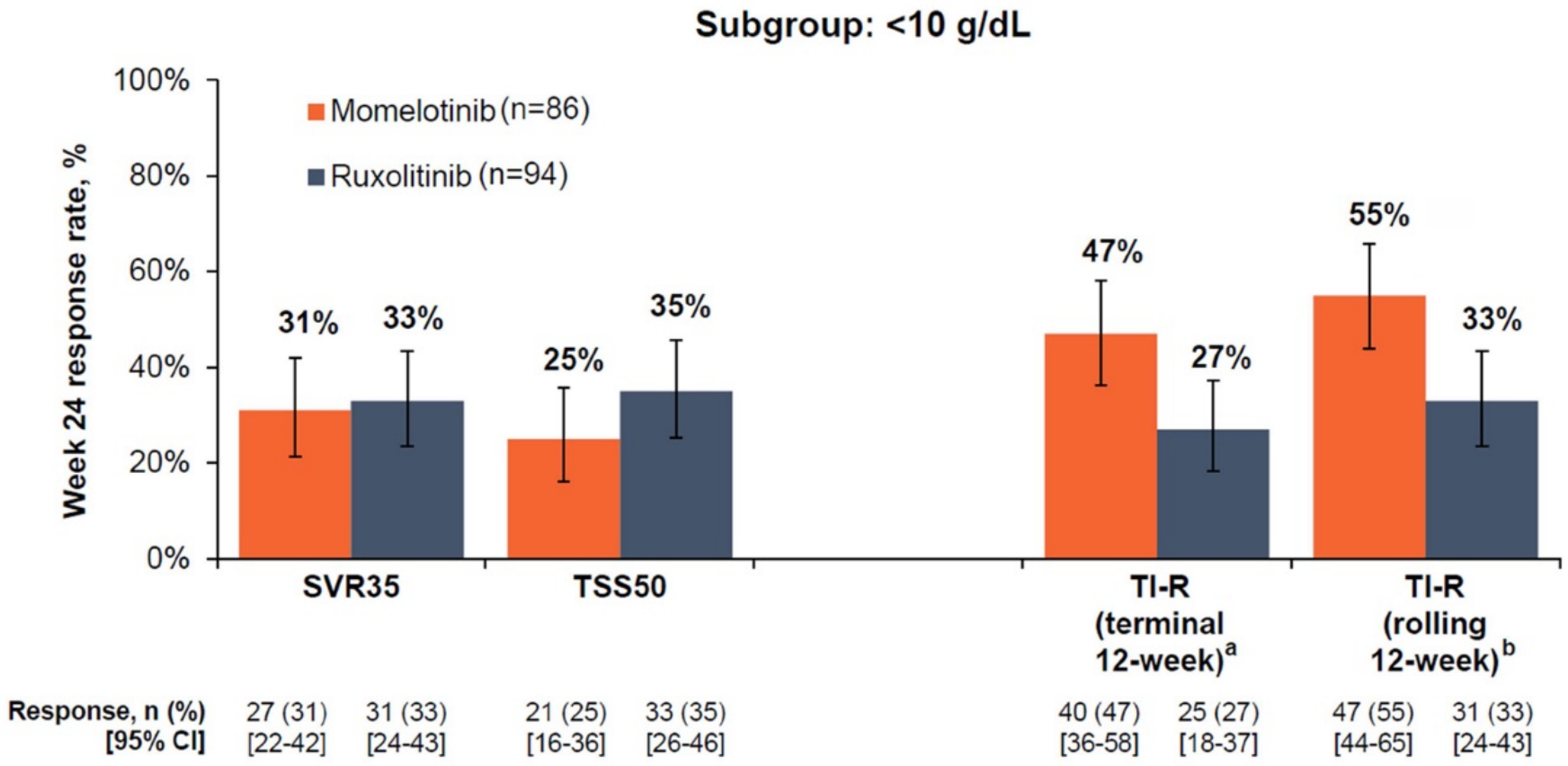
MOMENTUM: Treatment-Emergent Adverse Events (TEAEs, ≥10% of Patients)

	Momelotinib group (n=130)		Danazol group (n=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological abnormalities (preferred term)				
Diarrhoea	29 (22%)	0	6 (9%)	1 (2%)
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Asthenia	17 (13%)	1 (1%)	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Weight decreased	14 (11%)	0	4 (6%)	0
Blood creatinine increased	10 (8%)	1 (1%)	10 (15%)	2 (3%)
Dyspnoea	10 (8%)	3 (2%)	9 (14%)	1 (2%)
Peripheral oedema	10 (8%)	2 (2%)	9 (14%)	0
Fatigue	8 (6%)	1 (1%)	7 (11%)	2 (3%)
Acute kidney injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)
Haematological abnormalities*				
Anaemia	129 (99%)	79 (61%)	65 (100%)	49 (75%)
Thrombocytopenia	99 (76%)	36 (28%)	40 (62%)	17 (26%)
Neutropenia	38 (29%)	16 (12%)	17 (26%)	6 (9%)

Data are n (%). *Haematological abnormalities are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase of the study, regardless of whether this grade was a change from baseline.

Verstovsek et al. Lancet 2023

SIMPLIFY-1: Week 24 Efficacy Endpoints With Momelotinib in Subgroup of Patients with MF and Moderate/Severe Baseline Anemia



Gupta et al. Leuk Lymphoma 2024.

SIMPLIFY-1: Most Common TEAEs in Overall Safety Population and Moderate/Severe Baseline Anemia Subgroup

	Overall safety population [30]				Hb <10 g/dL			
n (%)	Momelotinib (*n* = 214)		Ruxolitinib (*n* = 216)		Momelotinib (*n* = 86)		Ruxolitinib (*n* = 94)	
Grade:	Any	≥3	Any	≥3	Any	≥3	Any	≥3
Any TEAE	198 (93)	77 (36)	206 (95)	94 (44)	81 (94)	42 (49)	91 (97)	52 (55)
Hematologic TEAEs occurring in >5% of patients in a momelotinib arm								
Thrombocytopenia	40 (19)	15 (7)	63 (29)	10 (5)	19 (22)	9 (10)	32 (34)	6 (6)
Anemia	31 (14)	13 (6)	81 (38)	49 (23)	14 (16)	10 (12)	36 (38)	26 (28)
Neutropenia	9 (4)	6 (3)	14 (6)	10 (5)	4 (5)	3 (3)	9 (10)	7 (7)
Nonhematologic TEAEs occurring in >10% of patients in a momelotinib arm								
Diarrhea	39 (18)	6 (3)	43 (20)	3 (1)	19 (22)	2 (2)	19 (20)	1 (1)
Nausea	34 (16)	2 (1)	8 (4)	1 (<1)	19 (22)	1 (1)	3 (3)	1 (1)
Dizziness	34 (16)	0	25 (12)	1 (<1)	15 (17)	0	10 (11)	1 (1)
Fatigue	31 (14)	1 (<1)	26 (12)	2 (1)	13 (15)	0	11 (12)	0
Hypotension	19 (9)	3 (1)	1 (<1)	0	12 (14)	2 (2)	0	0
Cough	18 (8)	0	17 (8)	0	12 (14)	0	9 (10)	0
Dyspnea	19 (9)	0	17 (8)	1 (<1)	11 (13)	0	8 (9)	1 (1)
Abdominal pain	22 (10)	3 (1)	25 (12)	1 (<1)	11 (13)	2 (2)	11 (12)	1 (1)
Constipation	21 (10)	0	15 (7)	0	11 (13)	0	6 (6)	0
Peripheral sensory neuropathy	20 (9)	0	12 (6)	1 (<1)	10 (12)	0	5 (5)	0
Pyrexia	14 (7)	1 (<1)	17 (8)	0	10 (12)	1 (1)	10 (11)	0
Headache	38 (18)	1 (<1)	43 (20)	0	10 (12)	0	15 (16)	0
Pain in extremity	14 (7)	0	18 (8)	0	9 (10)	0	5 (5)	0
Abdominal pain upper	10 (5)	0	10 (5)	0	3 (3)	0	2 (2)	0
Hypertension	9 (4)	6 (3)	20 (9)	9 (4)	1 (1)	1 (1)	7 (7)	4 (4)

Gupta et al. Leuk Lymphoma 2024.

Anemia in Myelofibrosis – Momelotinib

PRESENTATION ID 2023
OCCC - West Halls B3-B4
Saturday, December 6
05:30 PM - 07:30 PM EST

Dual transfusion independence and spleen volume reduction is associated with overall survival in patients with myelofibrosis treated with momelotinib: Post hoc analyses of SIMPLIFY-1 and MOMENTUM

Stephen Oh, MD, PhD

PRESENTATION ID 2025
OCCC - West Halls B3-B4
Saturday, December 6
05:30 PM - 07:30 PM EST

Transfusion independence with momelotinib regardless of baseline erythropoietin levels in the Phase 3 SIMPLIFY-1 trial

Stephen Oh, MD, PhD

PRESENTATION ID 5581
OCCC - West Halls B3-B4
Monday, December 8
06:00 PM - 08:00 PM EST

Impact of hemoglobin improvement with momelotinib on survival in patients with myelofibrosis and anemia: Post hoc analyses of the simplify-1 and momentum trials

Francesca Palandri

ASH 2025

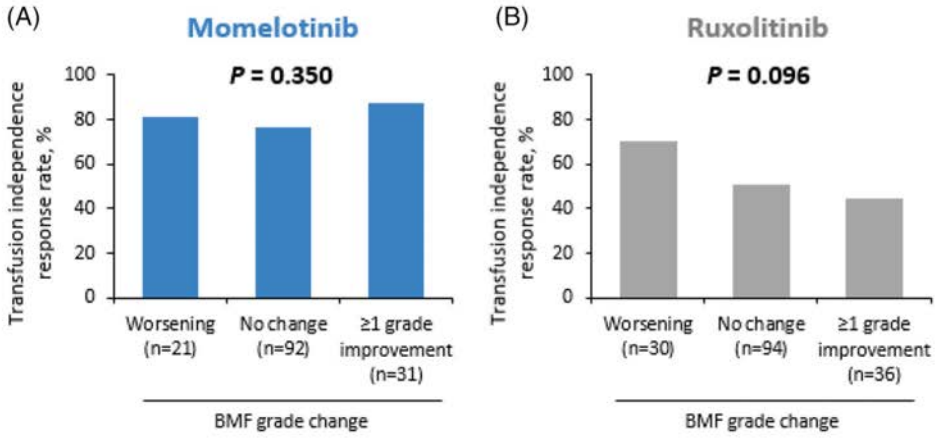
Anemia in Myelofibrosis – Momelotinib

Changes in bone marrow fibrosis during momelotinib or ruxolitinib therapy do not correlate with efficacy outcomes in patients with myelofibrosis

Stephen T. Oh[1] | Srdan Verstovsek[2] | Vikas Gupta[3] | Uwe Platzbecker[4] | Timothy Devos[5] | Jean-Jacques Kiladjian[6] | Donal P. McLornan[7] | Andrew Perkins[8] | Maria Laura Fox[9] | Mary Frances McMullin[10] | Adam J. Mead[11] | Miklos Egyed[12] | Jiri Mayer[13] | Tomasz Sacha[14] | Jun Kawashima[15] | Mei Huang[15] | Bryan Strouse[15] | Ruben Mesa[16]

- Anemia response with momelotinib in SIMPLIFY-1 study occurred regardless of improvement or worsening in BM fibrosis

Transfusion independence response and BMF grade changes at week 24



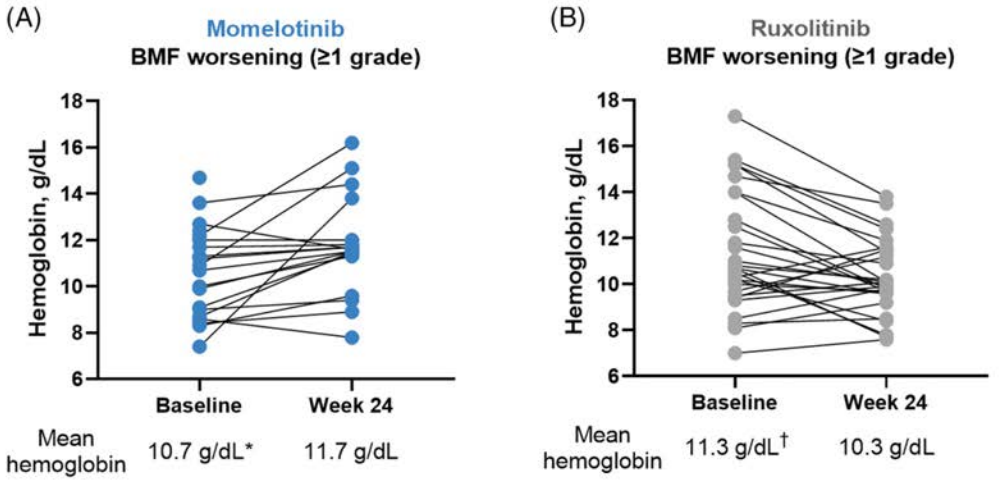


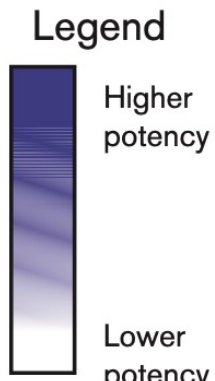
FIGURE 5 Proportion of JAK inhibitor–naive patients in SIMPLIFY-1 who achieved transfusion independence response by change in BMF grade from baseline to week 24. (A) Patients treated with momelotinib. (B) Patients treated with ruxolitinib. Transfusion independence response was defined as the absence of red blood cell transfusions and no hemoglobin levels < 8 g/dL in the 12 weeks before week 24. The *p*-value was calculated using a χ^2-test. BMF, bone marrow fibrosis; JAK, Janus kinase.

FIGURE 6 Hemoglobin levels at baseline and week 24 in JAK inhibitor–naive patients in SIMPLIFY-1 with worsening BMF grade from baseline to week 24. (A) Patients treated with momelotinib. (B) Patients treated with ruxolitinib. *A total of 3/21 patients were missing week 24 hemoglobin measurement. †A total of 2/30 patients were missing week 24 hemoglobin measurement. BMF, bone marrow fibrosis; JAK, Janus kinase.

Oh et al, eJHaem 2024

Anemia in Myelofibrosis –Pacritinib

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

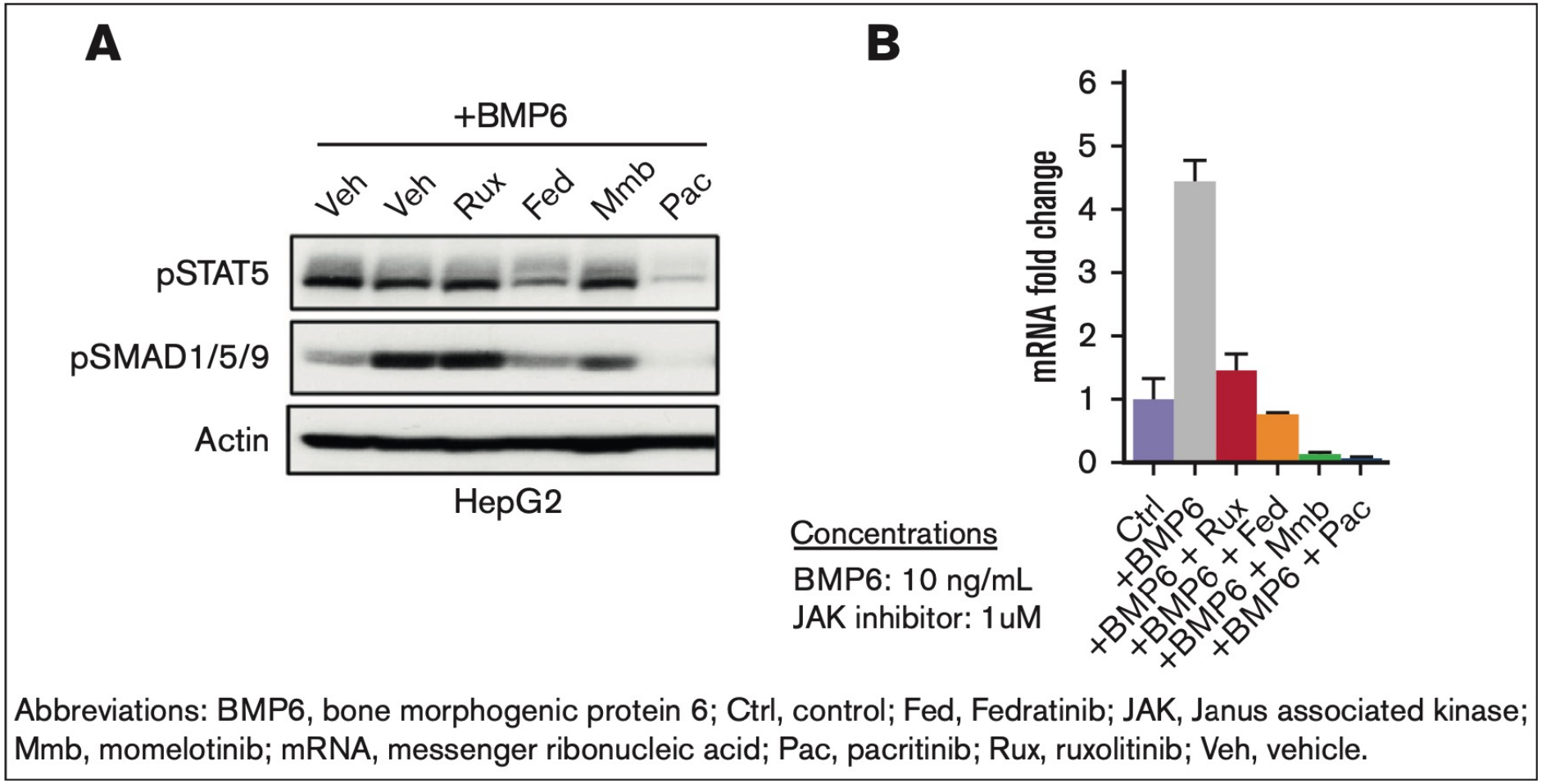


C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.
Darker blue indicates higher potency (lower IC_{50}).

- **Pacritinib inhibits ACVR1 activity**

Oh et al, Blood Advances 2024

Anemia in Myelofibrosis –Pacritinib



Abbreviations: BMP6, bone morphogenic protein 6; Ctrl, control; Fed, Fedratinib; JAK, Janus associated kinase; Mmb, momelotinib; mRNA, messenger ribonucleic acid; Pac, pacritinib; Rux, ruxolitinib; Veh, vehicle.

- **Pacritinib decreases hepcidin expression *in vitro***

Oh et al, Blood Advances 2023

Anemia in Myelofibrosis –Pacritinib

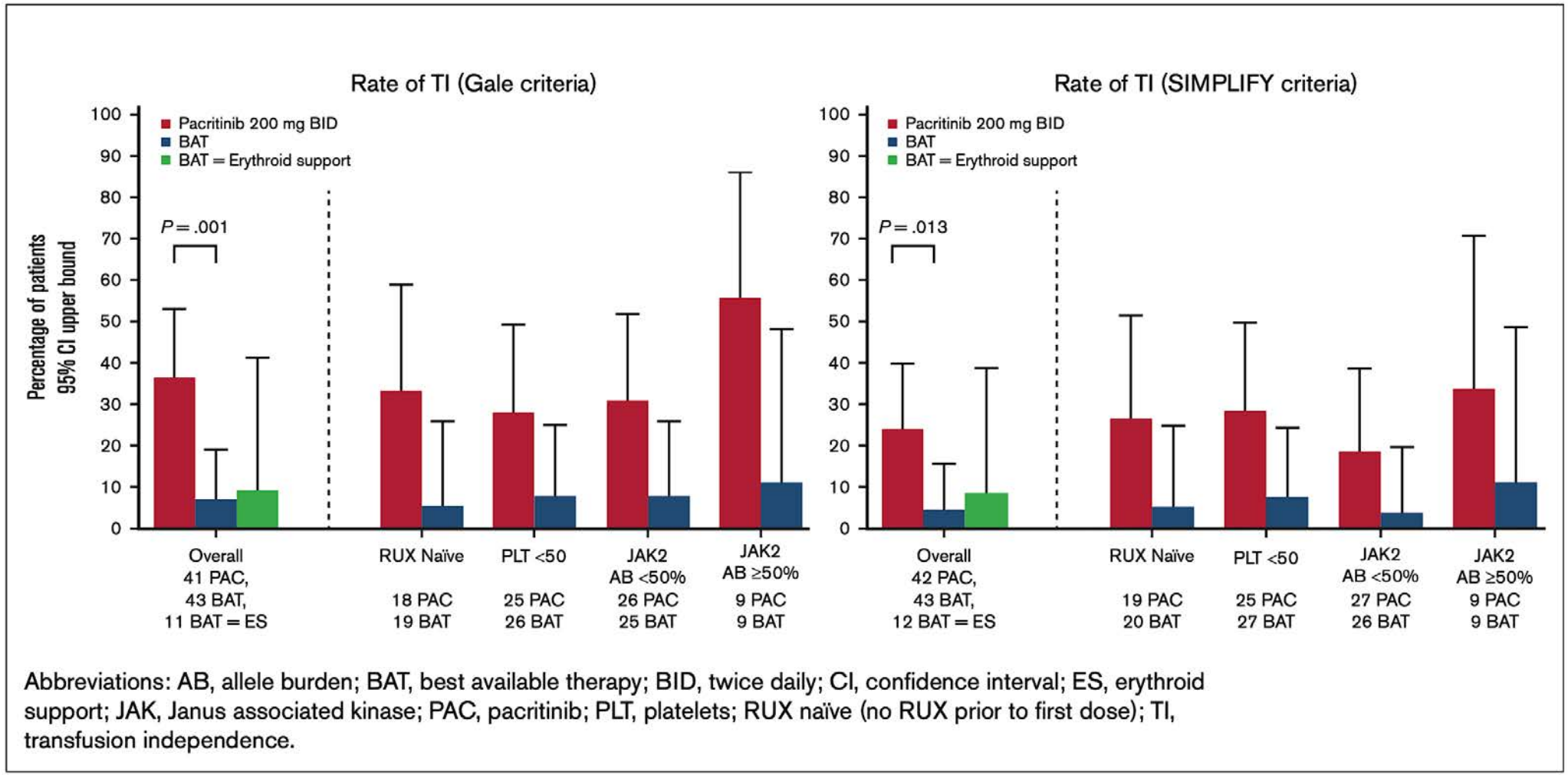


Figure 3. Rate of transfusion independence. Percentage of patients achieving transfusion independence over any 12 weeks through week 24 among patients who **were not** TI at baseline based on Gale criteria (left) and SIMPLIFY criteria (right) over any 12-week interval. Data shown in overall population (including statistical testing), as well as in subgroups.

- **In PERSIST-2 more pacritinib patients achieved transfusion independence**

Oh et al, Blood Advances 2023

Anemia in Myelofibrosis –Pacritinib

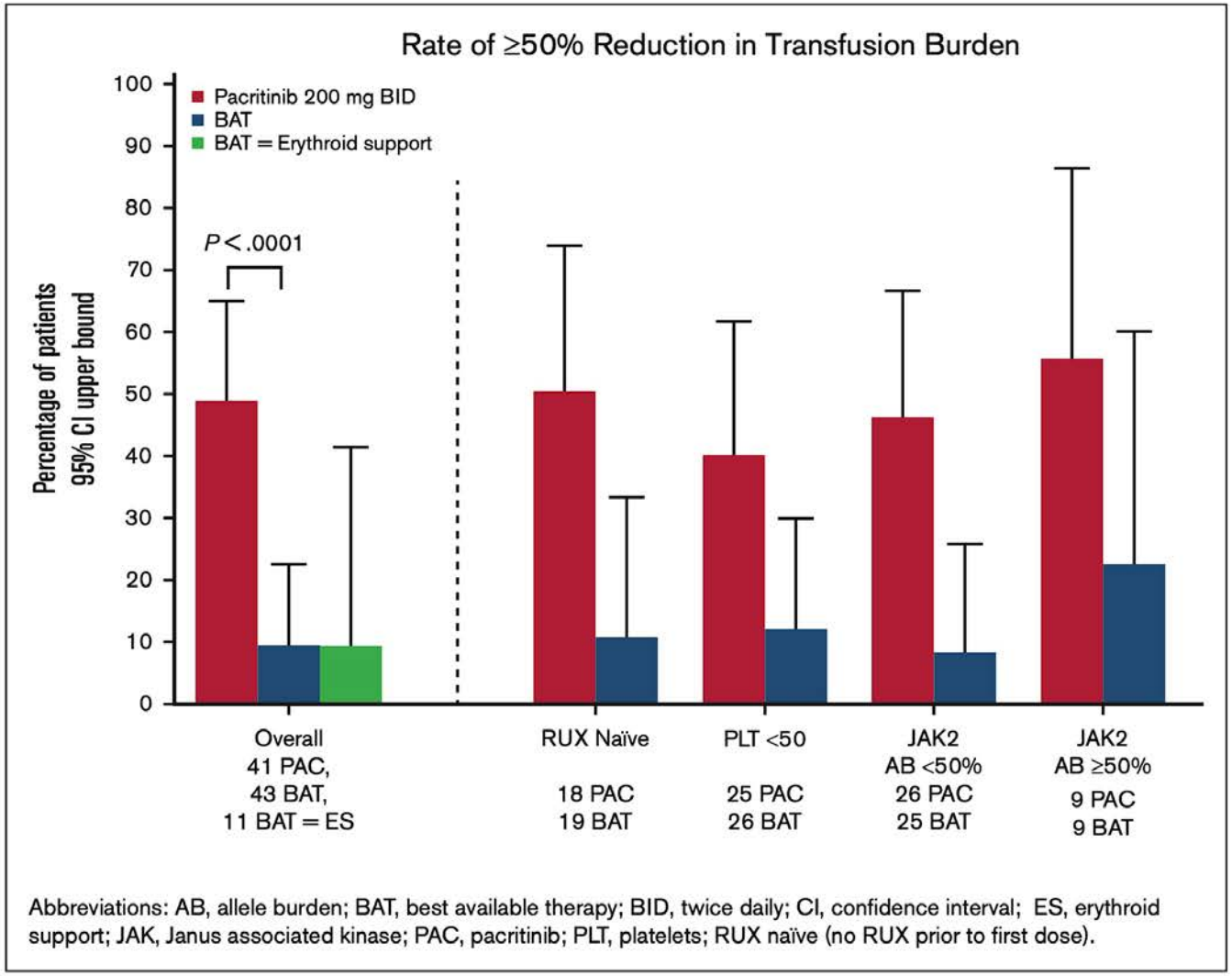


Figure 5. Percentage of patients achieving ≥50% reduction in transfusion burden over any 12 weeks through week 24. Data shown in overall population of patients requiring RBC transfusions at baseline (including statistical testing), as well as in subgroups.

- **More pacritinib patients had ≥ 50% reduction in transfusion burden**

Oh et al, Blood Advances 2023

Anemia in Myelofibrosis –Pacritinib

PRESENTATION ID 2019
OCCC - West Halls B3-B4
Pacritinib in patients with high-risk myelofibrosis: Outcomes from post-hoc analyses of two Phase 3 studies
Pankit Vachhani, MD, PhD

Saturday, December 6
05:30 PM - 07:30 PM EST

PRESENTATION ID 725
OCCC - W414CD
Real-world treatment patterns and outcomes in patients with myelofibrosis who presented with thrombocytopenia and anemia at initiation of pacritinib treatment
Naveen Pemmaraju, MD

Sunday, December 7
04:30 PM - 06:00 PM EST

PRESENTATION ID 4607
OCCC - West Halls B3-B4
Real-world treatment patterns and clinical outcomes in patients with myelofibrosis treated with pacritinib (PAC): Results from the my-PAC study
Douglas Tremblay, MD

Sunday, December 7
06:00 PM - 08:00 PM EST

PRESENTATION ID 5577
OCCC - West Halls B3-B4
Treatment patterns and outcomes in patients with myelofibrosis treated with pacritinib following a switch from ruxolitinib: The my-PAC study
Douglas Tremblay, MD

Monday, December 8
06:00 PM - 08:00 PM EST

PRESENTATION ID 5600
OCCC - West Halls B3-B4
An independent, multi-center analysis of the post-approval utilization and efficacy of pacritinib and momelotinib in patients with myelofibrosis
Andrew Kuykendall, MD

Monday, December 8
06:00 PM - 08:00 PM EST

ASH 2025

Case Presentation: 72-year-old man with splenomegaly and mild fatigue is diagnosed with JAK2 V617F-mutant primary MF and receives momelotinib

Dr Laura Michaelis (Milwaukee, Wisconsin)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

How do you select a JAK inhibitor for patients with primary MF and anemia? Are you now preferentially employing momelotinib for all patients with higher-risk MF who present with anemia?

Are there any circumstances in which you would consider momelotinib over other JAK inhibitors for a broader population, such as for patients who do not have clinically significant anemia but are refractory to initial JAK inhibitor therapy?

What leads you to include luspatercept for your patients with MF-associated anemia?

Post-hoc analysis from SIMPLIFY-1 (EHA)

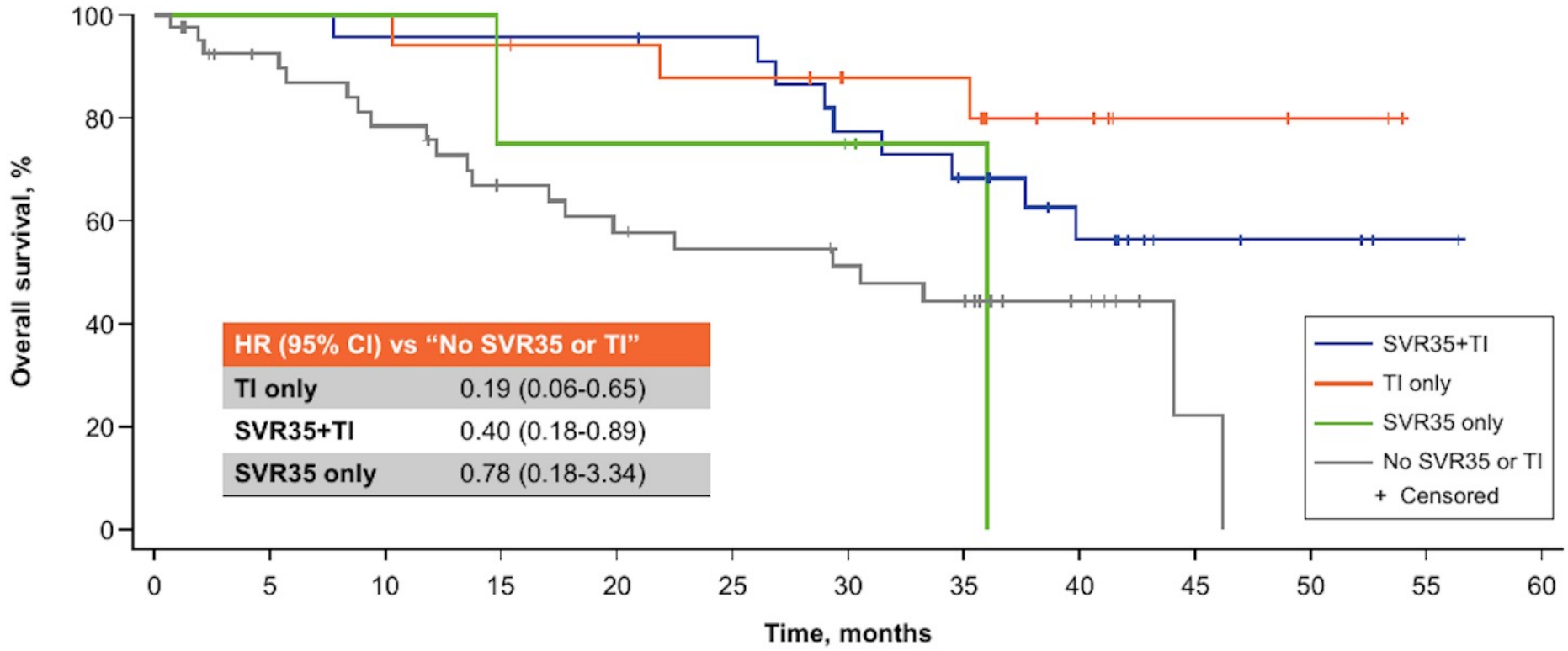
Dr Prithviraj Bose (Houston, Texas)

RTP
RESEARCH
TO PRACTICE

Impact of dual spleen response and transfusion independence on survival in JAK inhibitor–naive patients with myelofibrosis and anemia treated with momelotinib: a subgroup analysis of SIMPLIFY-1

Francesca Palandri,[1] Nicolaas P.M. Schaap,[2] Jerome Rey,[3] Nikolas von Bubnoff,[4] Andreas Reiter,[5] Juan Carlos Hernandez-Boluda,[6] Timothy Devos,[7] Lars Nilsson,[8] Bethan Psaila,[9] Donal P. McLornan,[10] Bryan Strouse,[11] Bharat Patel,[11] Dwaipayan Patnaik,[12] Stephen T. Oh[13]

Figure 4: **OS From Treatment Initiation Based on Week 24 TI and/or SVR35 Response in Momelotinib-Randomized, JAK Inhibitor–Naive Patients With Baseline Hb <10 g/dL**



Palandri F et al.
EHA 2025;Abstract S1829

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What were your thoughts about the post-hoc analysis from SIMPLIFY-1 presented at EHA?

What is your experience with nonhematologic toxicities of momelotinib, including hypotension and neuropathy?

In what situations will you recommend momelotinib to a patient with preexisting peripheral neuropathy?

Agenda

Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Palmer

Module 2: Managing MF in Patients with Anemia — Dr Oh

Module 3: Managing MF in Patients with Thrombocytopenia — Dr Rampal

Module 4: Promising Novel Agents Under Investigation for MF — Prof Harrison

Module 5: Current and Future Management of Systemic Mastocytosis — Dr Kuykendall

Management of Patients with Myelofibrosis and Thrombocytopenia

Raajit Rampal M.D. Ph.D.
Director, Center for Hematologic Malignancies
Director, Myeloproliferative Neoplasm Program

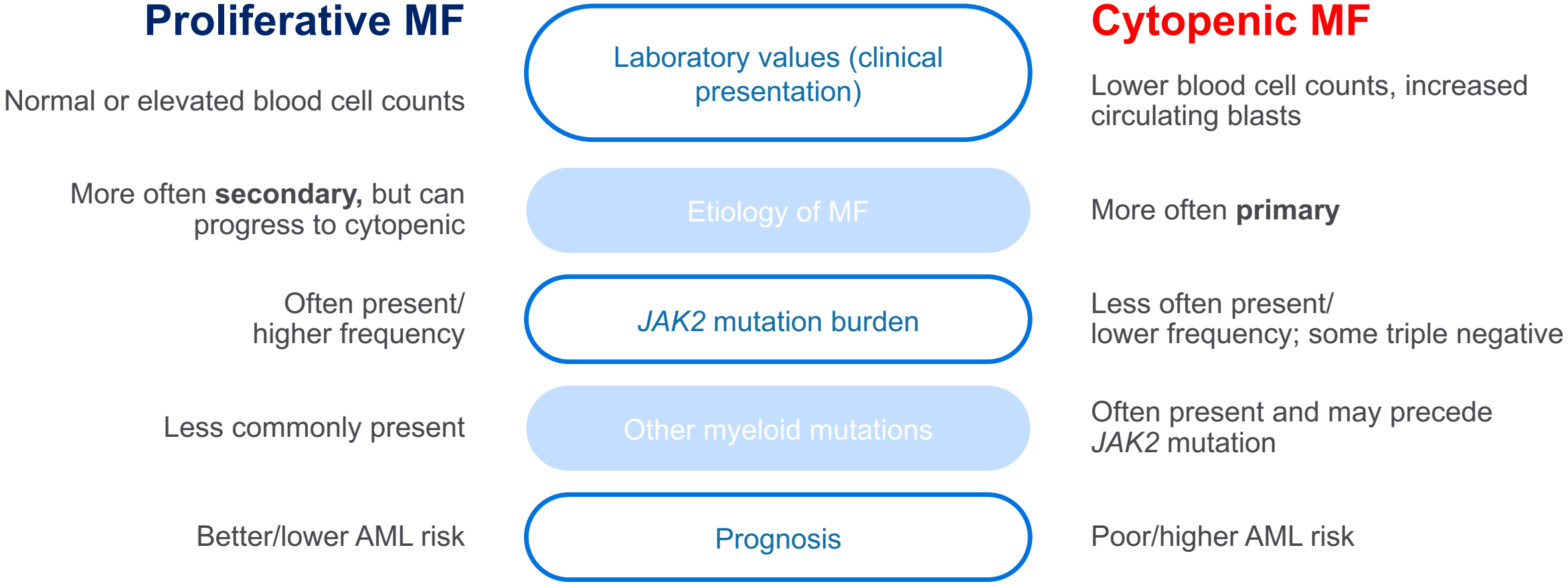
Memorial Sloan Kettering Cancer Center

Case Presentation

67-year-old male presents with fatigue and abdominal fullness

- Endorses early satiety
- Exam: Splenomegaly (14 cm below costal margin); volume 3500cm
- **CBC: WBC 8.3** x 10^9/L **(1% blasts), Hb 8.0 g/dL, platelets 41** x 10^9/L
- Bone marrow biopsy: 90% cellular marrow with myeloid expansion, dysplastic megakaryocytes in clusters, and MF-3 fibrosis with 2% myeloid blasts
- Cytogenetics: Del 7q
- Myeloid NGS panel: *JAK2* V617F+, *U2AF1*+
- A MUD has been identified, however transplant is felt to be too high risk due to massive splenomegaly

The Spectrum of Myelofibrosis Phenotypes

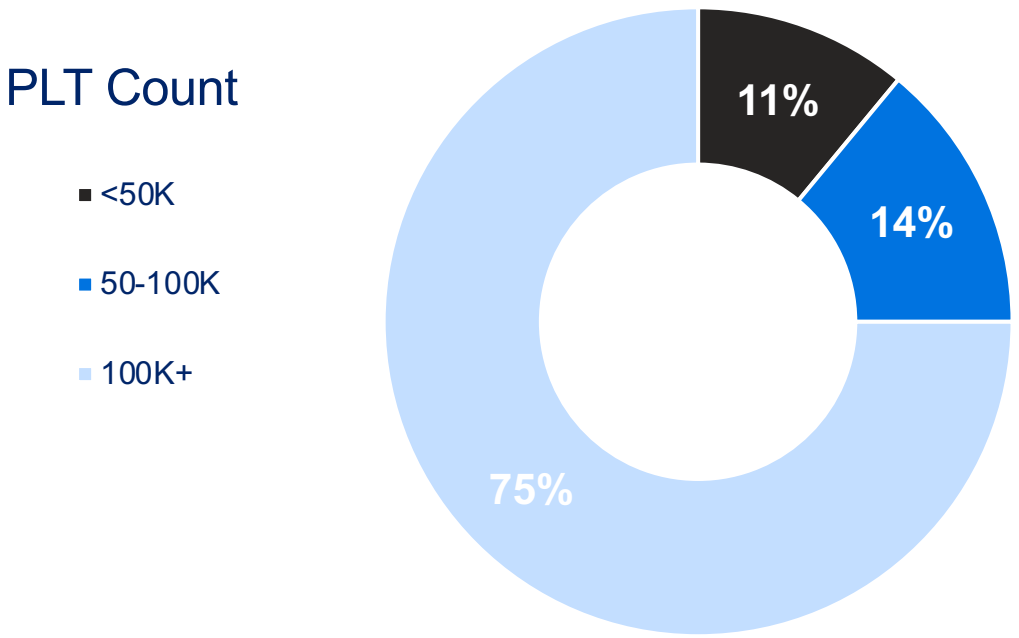


AML, acute myeloid leukemia.

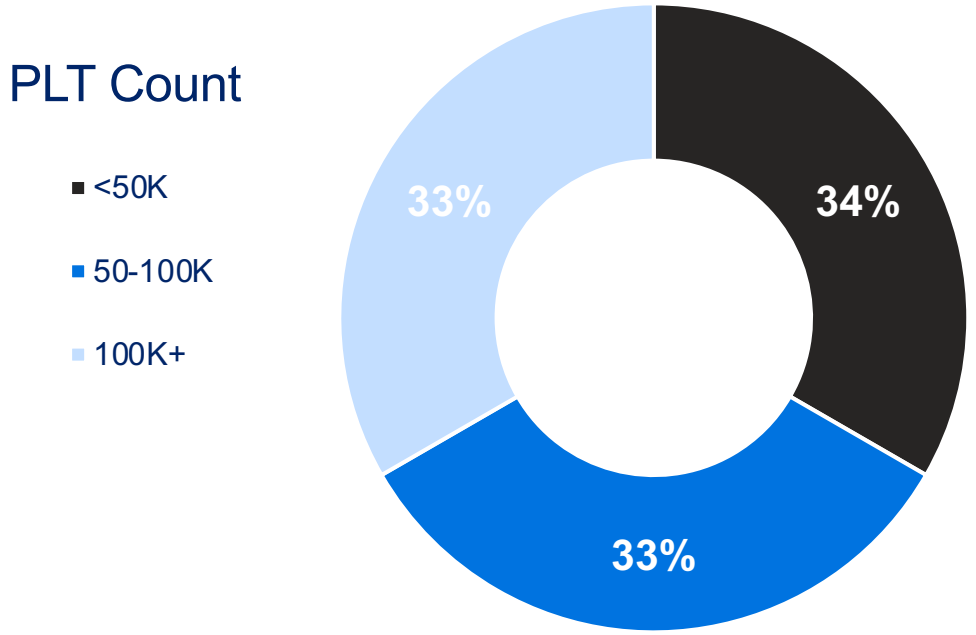
Marcellino BK, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:415-421.

Thrombocytopenia: Incidence and Prevalence

The incidence of thrombocytopenia (PLT < 100 × 10^9/L) is approximately 25% in patients newly diagnosed with MF[1]



The prevalence of thrombocytopenia (PLT < 100 × 10^9/L) is approximately 68% in all patients diagnosed with MF[2]



1. Masarova L, et al. Eur J Haematol. 2018;100:257-263; 2. Masarova L, et al. Leuk Res. 2020;91:106338.

Thrombocytopenia is Prognostic of Inferior Outcomes

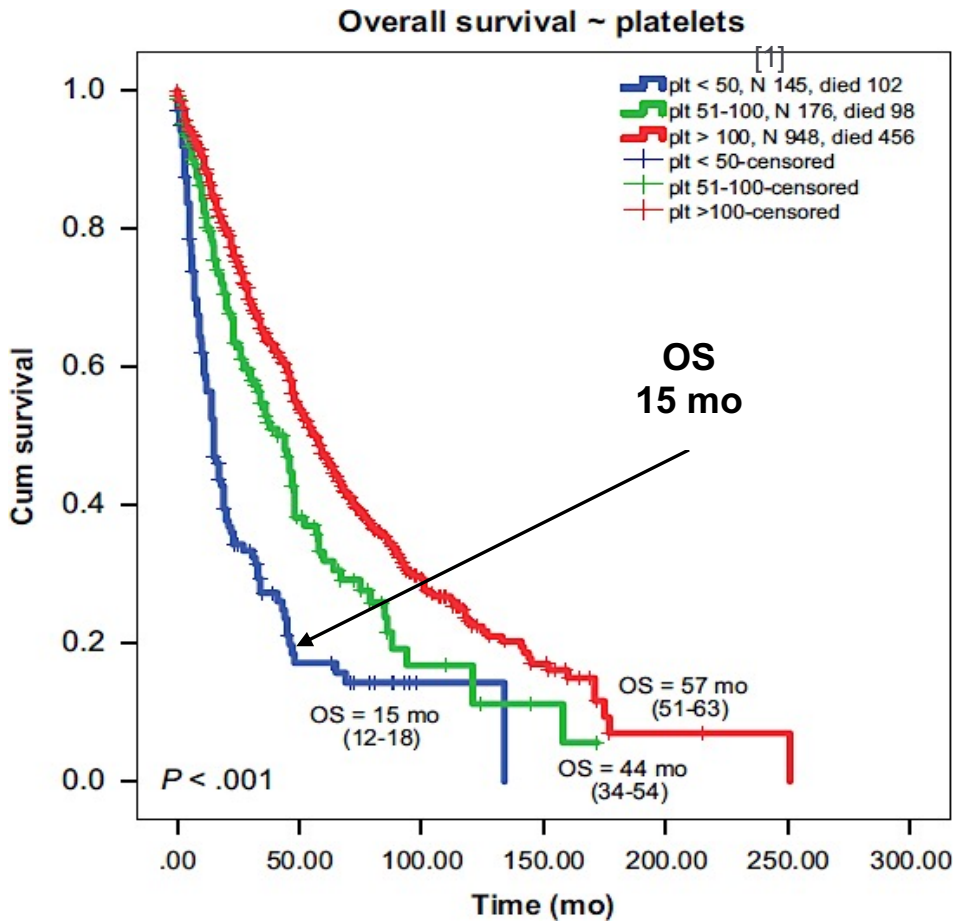
- **OS of patients with PLT < 100 × 10^9/L is worse than those with PLT > 100 × 10^9/L[1]**

PLT (× 10^9/L)	< 100	> 100	*P* value
Median OS (mo)	26	57	< .001

- **In patients with PLT < 50 × 10^9/L**
  - 2× higher risk of leukemia[1]
  - High-grade marrow fibrosis[2]
  - More anemia and leukopenia[2]

Typical Characteristics of Patients with PLT < 50 × 10^9/L:[3]

- Older
- Anemic
- Transfusion-dependent
- Leukopenic
- PB blasts
- Adverse karyotype
- BMF score = 3
- Primarily PMF; less PET/PPV MF



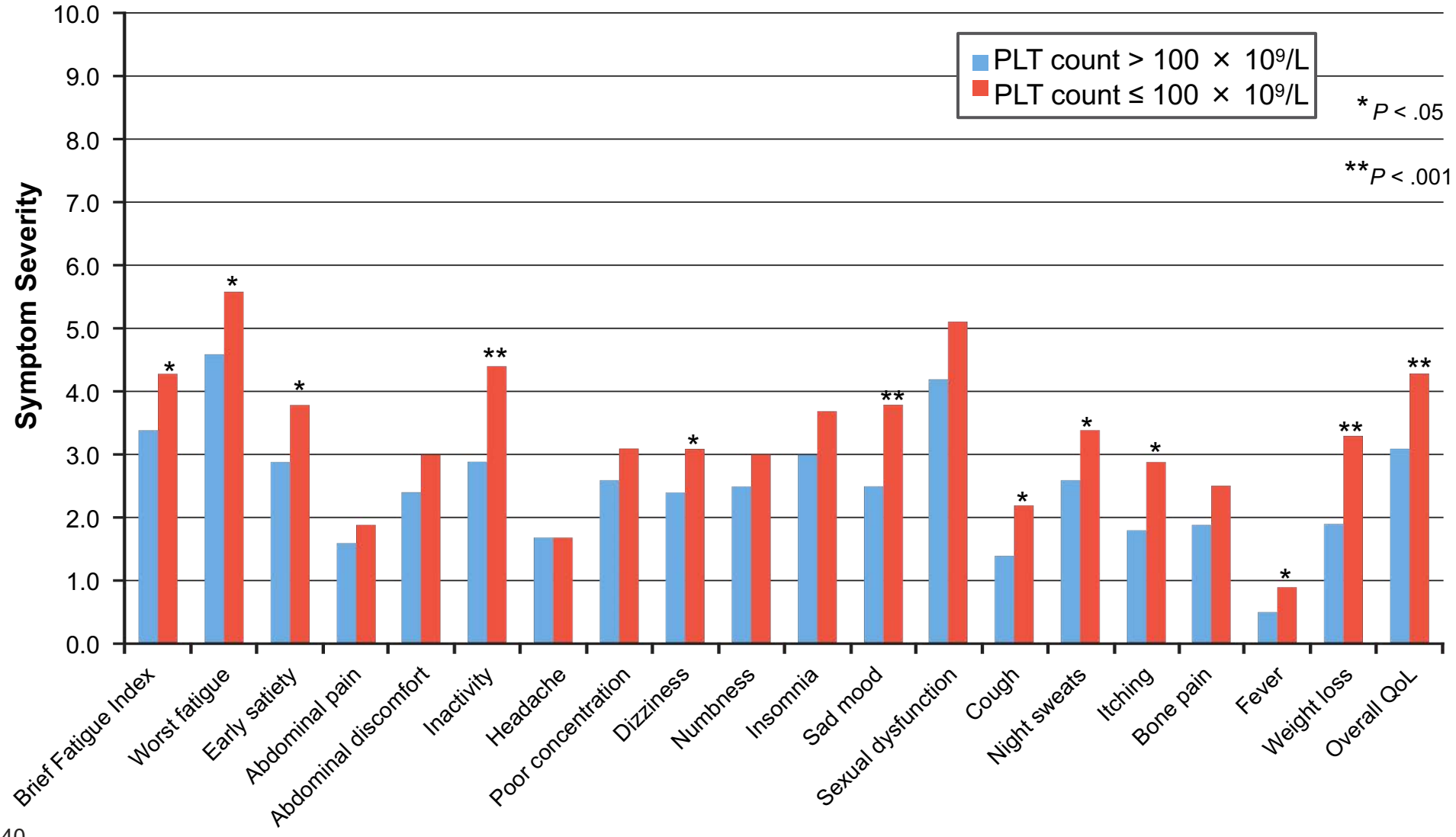
BMF, bone marrow fibrosis; PB, peripheral blood.

1. Masarova L, et al. Eur J Haematol. 2018;100:257-263; 2. Masarova L, et al. Leuk Res. 2020;91:106338; 3. Alhuraiji A, et al. J Clin Oncol. 2016;34(suppl 15):7068.

Thrombocytopenia is Associated with Worse Symptom Burden

Significant:

- Brief Fatigue Index
- Worst fatigue
- Early satiety
- Inactivity
- Dizziness
- Sad mood
- Cough
- Night sweats
- Itching
- Fever
- Weight loss
- Overall QoL



QoL, quality of life.

Scotch AH, et al. Leuk Res. 2017;63:34-40.

Thrombocytopenia and Anemia Often Co-Occur

Variable	PLT < 50 × 10^9/L, % (n = 57)	PLT > 50 × 10^9/L, % (n = 834)	*P* Value
Age > 65 y	75	60	.019
Bleeding manifestations	19	6	< .001
Constitutional symptoms	40	34	.31
Hgb < 80 g/L	35	8	< .001
WBC count < 4 × 10^9/L	26	10	< .001
WBC count > 25 × 10^9/L	14	11	.47
Blasts ≥ 1%	57	45	.069
Blasts ≥ 3%	21	11	.022
Grade 3 BMF	24	11	.008
Unfavorable cytogenetics	17	11	.35
JAK2 mutated	50	64	.057
Int-2/high-risk IPSS	86	60	< .001
Int-2/high-risk DIPSS+	100	59	< .001

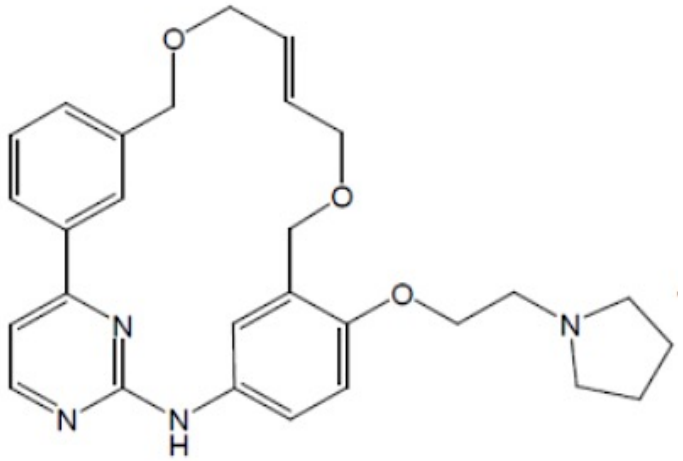
WBC, white blood cell
Modified from Hernandez-Boluda JC, et al. Brit J Haem. 2018;181:397-400.

Current JAK Inhibitor Landscape

JAKi	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Targets	JAK1, JAK2	JAK2, JAK1 (less), FLT3, TYK2, many others	JAK2, IRAK1, FLT3, ACVR1	JAK1, JAK2, ACVR1
Indication	Intermed or high-risk MF with platelets ≥50k	Intermed-2 or high-risk MF with platelets ≥50k	Intermed or high-risk MF with **platelets <50k**	Approved for MF patients with Anemia
Clinical practice points	Hematologic toxicities	Hematologic toxicities GI toxicities Monitor thiamine	Less cytopenia-inducing GI toxicities Monitor QTc Monitor for bleeding	Less cytopenia-inducing Rare peripheral neuropathy

Verstovsek et al NEJM 2012, Pardanani et al. JAMA Oncology 2015, Mascarenhas et al. JAMA Oncology 2018, Verstovsek et al Lancet 2023

Pacritinib



Pacritinib

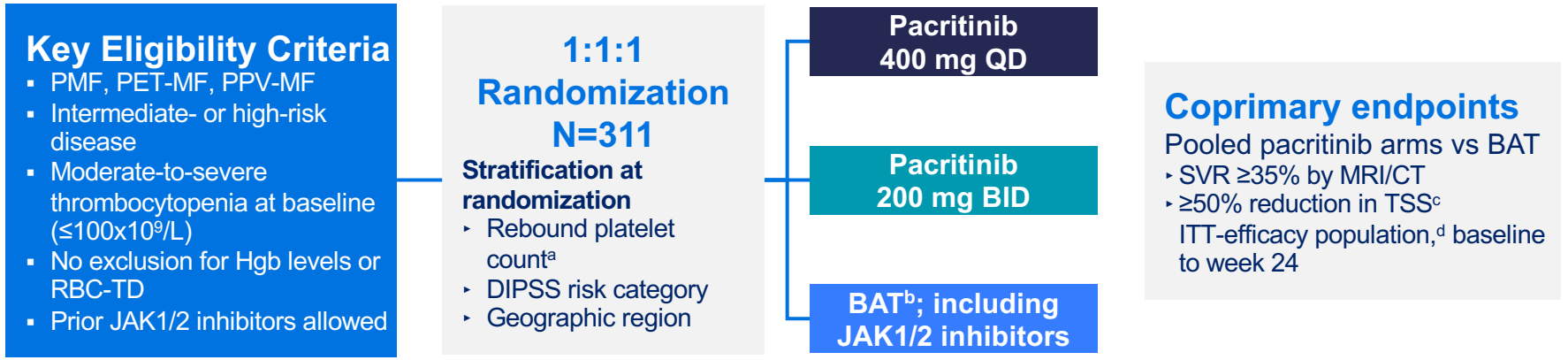
- Pacritinib is an oral kinase inhibitor approved in 2022 for intermediate-risk or high-risk PMF or secondary MF with PLT < 50 × 10^9/L
- Pacritinib does not inhibit JAK1 and has higher inhibitory activity for JAK2 than JAK3/TYK2, which minimizes exacerbation of thrombocytopenia
- Most frequent nonhematologic AEs: diarrhea, nausea, and peripheral edema

1. Pacritinib [PI]. Approved 2022. Revised August 2023; 2. Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236; 3. Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659; 4. Singer JW, et al. J Exp Pharmacol. 2016;8:11-19.

Pacritinib: Phase 3 Trial PERSIST-2

Pacritinib 400 mg QD or 200 mg BID vs BAT (Including JAK1/2 Inhibitors) in MF[1]

- In this phase 3 trial, 200 mg BID was also tested for potentially improved tolerability, given PK modeling data demonstrating increased daily systemic exposure with lower maximum concentration vs 400 mg QD[2]



~40% of patients had baseline PLT < 50K

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. 2. Al-Fayoumi S, et al. *Blood*. 2013;122;4080.

PERSIST-2: Baseline Characteristics and BAT Received

Key Baseline Characteristics in ITT-Efficacy Population[1,2]	PAC 200 mg BID (n = 74)	BAT (n = 72)
Median age, years ≥65 years, %	67 62	69 71
Male, %	65	54
MF diagnosis: PMF, PPV-MF, PET-MF, %	74, 19, 7	60, 22, 18
DIPSS score[a]: Int-1, Int-2, High, %	19, 51, 30	18, 51, 31
Median spleen length, cm[a]	15	13
JAK2^{V617F} positive, %	80	71
JAK2^{V617F} allele burden, median	30	25
Platelet count <50 × 10^9/L, %	42	44
Hemoglobin <10 g/dL, %	59	57
RBC transfusion dependence[b]: dependent, independent, indeterminate, %	19, 50, 30	19, 51, 29
Prior JAK1/2 inhibitors, % Prior ruxolitinib	45 42	47 46

- Of the BAT patients who received ruxolitinib, 93% began treatment at ≤10 mg BID, including 64% at ≤5 mg BID[3]

BAT Received in >2 Patients, %[1]	BAT (n = 98)
Ruxolitinib[c]	45
Hydroxyurea	19
Watch-and-wait only	19
Prednisone/prednisolone	13
Danazol	5
Thalidomide	3

Note: While allowed on the BAT arm, patients who received pacritinib could not receive corticosteroids or erythropoietic agents.[2]

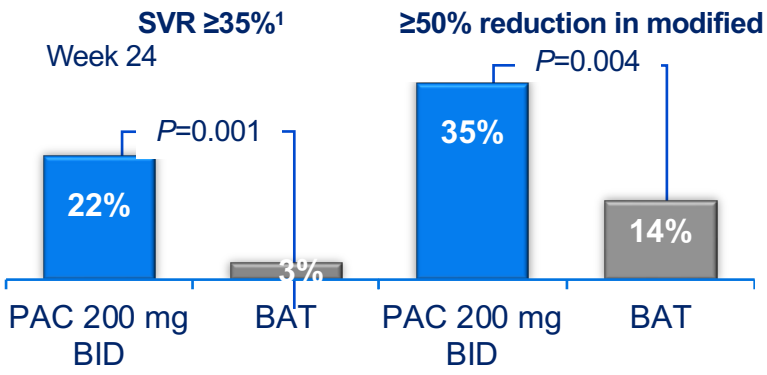
[a]By physician examination. [b]Defined according to Gale criteria; missing for 1 PAC patient. [c]Seventeen (39%) had baseline platelet counts <50 × 10^9/L and would not have been candidates for ruxolitinib by approved indication (or PERSIST-2 study protocol).

BAT, best available therapy; BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; ITT, intention-to-treat; JAK, Janus kinase; MF, myelofibrosis; PAC, pacritinib; PET-MF, postessential thrombocythemia MF; PMF, primary MF; PPV-MF, postpolycythemia vera MF; RBC, red blood cell.

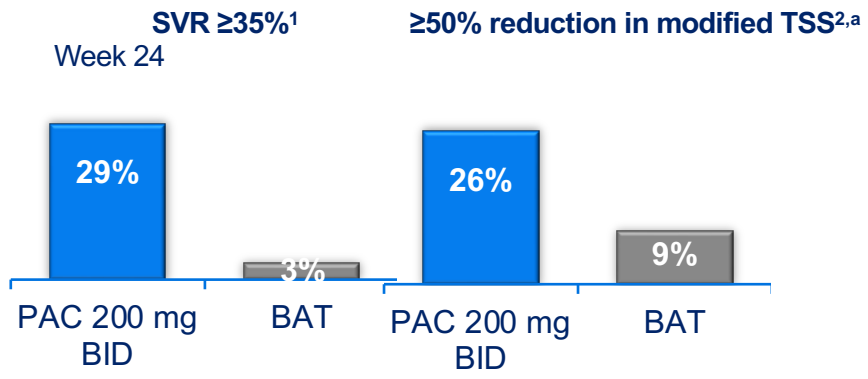
1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659; 2. Data on File. CTI Biopharma Corp. PERSIST-2 CSR; 3. Harrison C, et al. EHA 2017. Abstract P701.

PERSIST-2: Spleen/Symptom Response

ITT Population



Patients With Platelets <50x10⁹/L



- The proportions of patients with much improved or very much improved scores were 57% with pacritinib 200 mg BID versus 28% with BAT

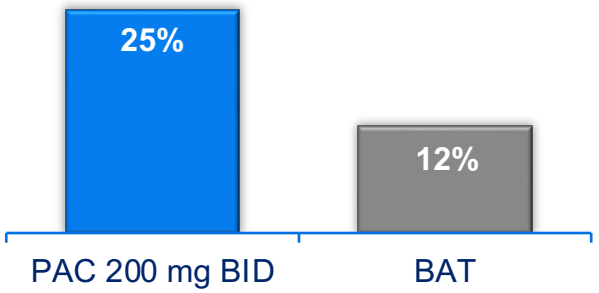
[a] Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. 2. Data on File. CTI Biopharma Corp. Pacritinib Clinical Overview.

PERSIST-2: Hematologic Stability

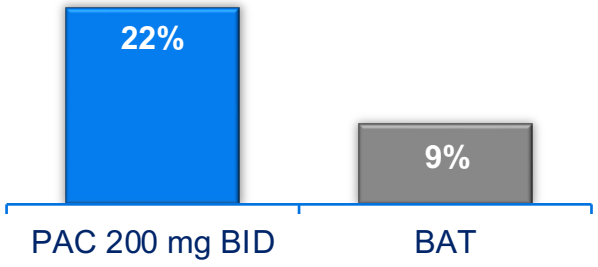
Clinical Improvement in Hemoglobin Levels in Patients With Baseline Anemia[a]

Baseline to week 24



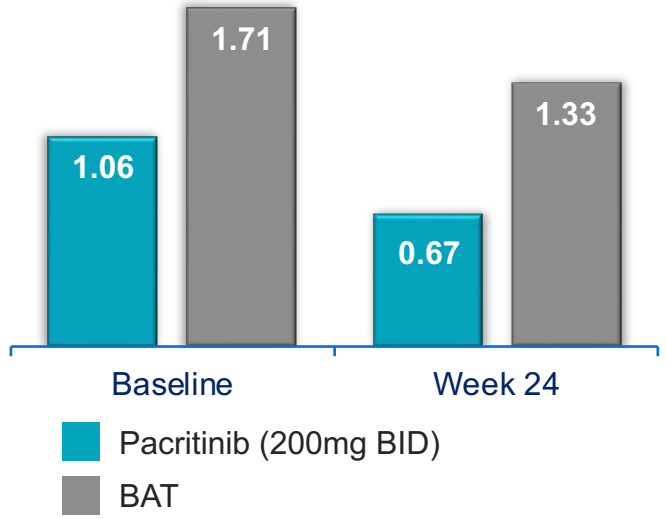
Pacritinib Reduced Transfusion Burden in Patients Not TI at Baseline

Baseline to week 24



Transfusion Burden in Patients Who Received ≥1 RBC Transfusion on Study

Units per month



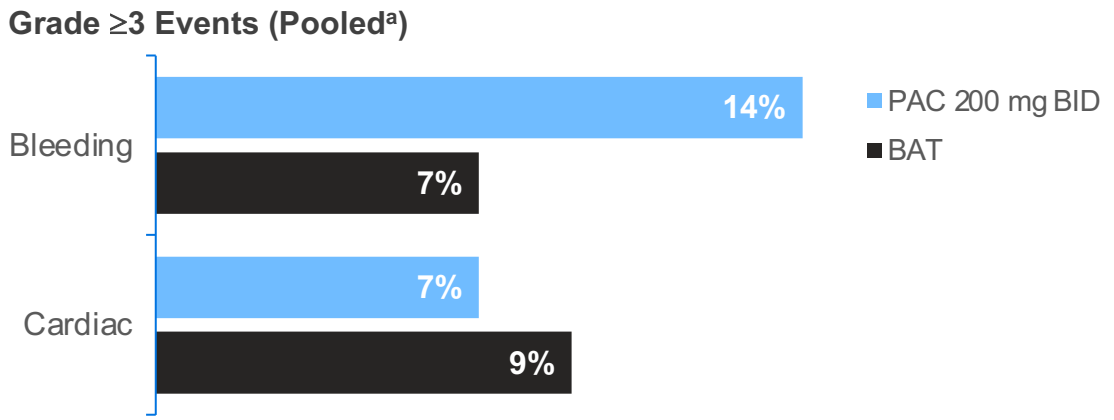
TI defined according to Gale criteria (0 units over the course of 12 weeks).
[a]International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL.

BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; PAC, pacritinib; RBC, red blood cell.
Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

PERSIST-2: Adverse Event Profile

Adverse Reactions	PAC 200 mg BID (n = 106)	BAT (n = 98)
Any-grade AEs in >15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	24
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
- Neurologic AEs and opportunistic infections rarely reported with pacritinib



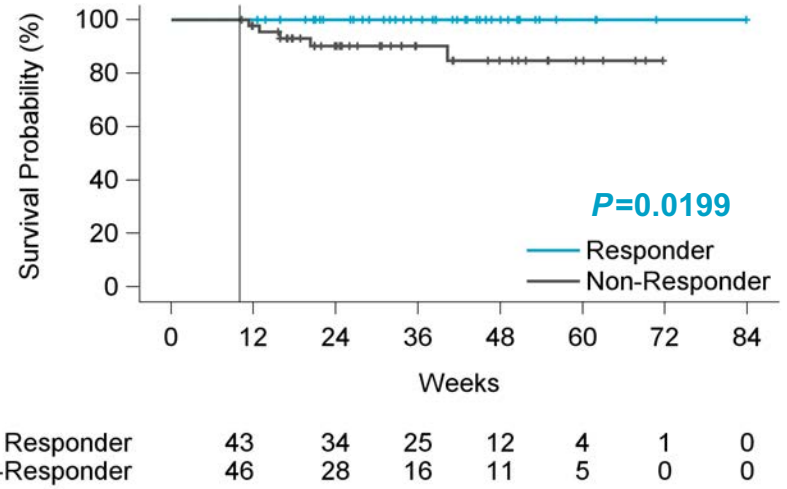
- **Safety outcomes with pacritinib were similar for those with <50 × 10^9/L vs 50–100 × 10^9/L platelets at baseline**

[a]Pooled, per standardized MedDRA queries.
AE, adverse event; BAT, best available therapy; BID, twice daily; PAC, pacritinib.
Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

Response to Pacritinib is Associated with an Overall Survival Benefit

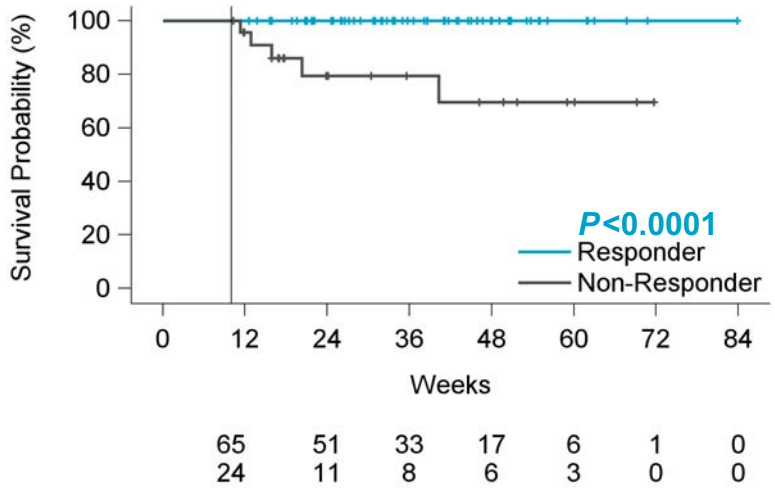
PAC 200 mg BID: survival stratified by SVR

OS stratified by **≥20% SVR**



Responder	43	34	25	12	4	1	0
Non-Responder	46	28	16	11	5	0	0

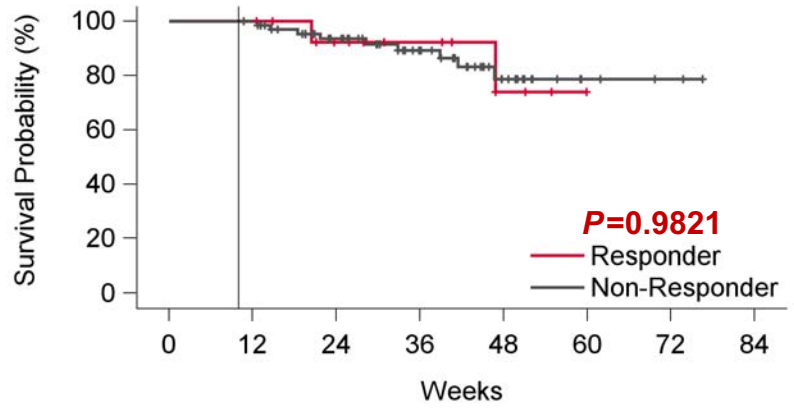
OS stratified by **≥10% SVR**



Responder	65	51	33	17	6	1	0
Non-Responder	24	11	8	6	3	0	0

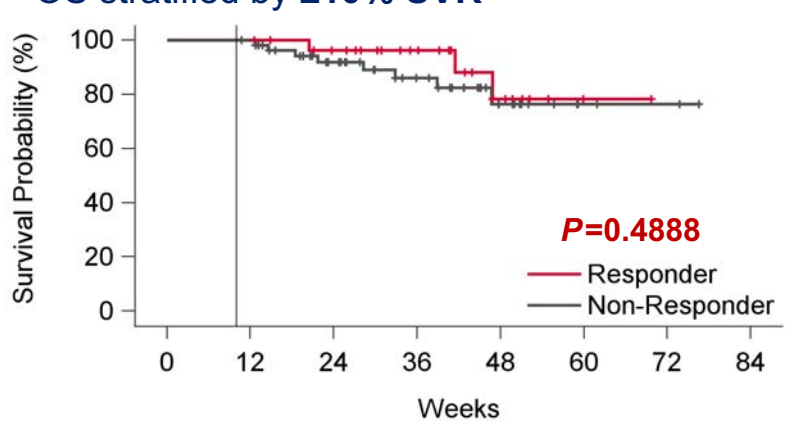
BAT: survival stratified by SVR

OS stratified by **≥20% SVR**



Responder	15	10	7	3	0	0	0
Non-Responder	69	50	34	15	4	2	0

OS stratified by **≥10% SVR**



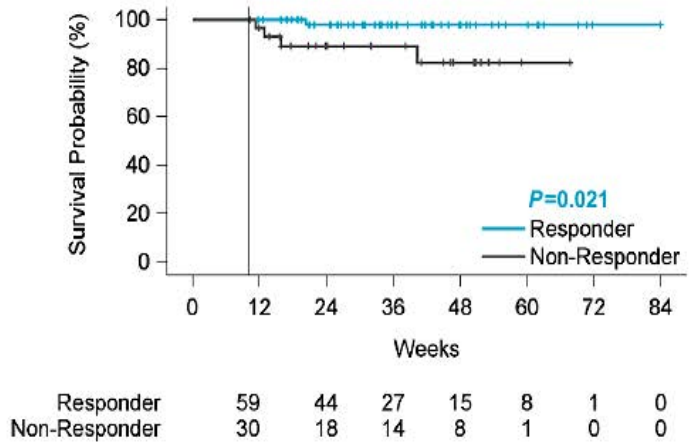
Responder	28	23	16	7	1	0	0
Non-Responder	56	37	25	11	3	2	0

Ajufo, et al. *European Journal of Haematology* 2024

Response to Pacritinib is Associated with an Overall Survival Benefit

Pacritinib

(A) OS stratified by **≥10% TSS**



Best Available Therapy (including RUX)

(B) OS stratified by **≥10% TSS**

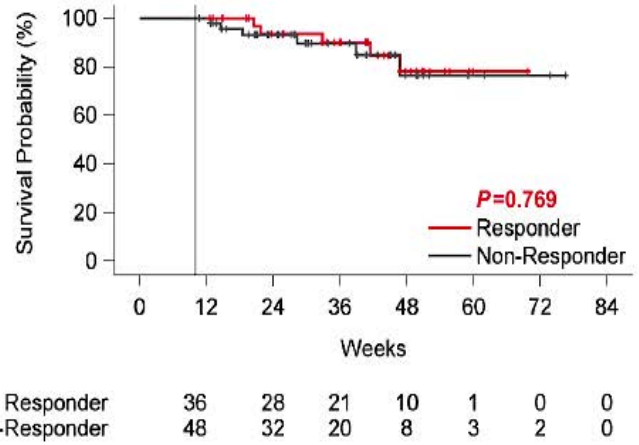


Table 2. Hazard for mortality in PAC-treated patients based on ≥20% reduction in TSS domains, HR compares responders vs. non-responders

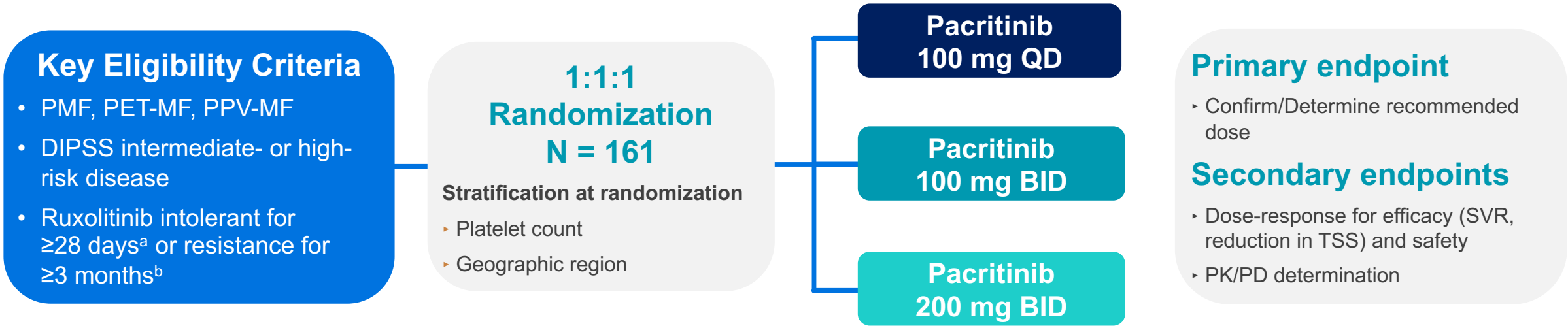
Domain	R deaths	N-R deaths	Hazard ratio
Physical function symptoms	2.9% (1/35)	5.9% (2/34)	0.60 [0.05, 6.74], *P*=0.6792
Spleen-related symptoms	2.5% (1/40)	10.5% (2/19)	0.26 [0.02, 2.93], *P*=0.2435
Cytokine-related symptoms	0% (0/35)	13.3% (2/15)	0.00 [0.00, 0.71], *P*=0.0325

HR, hazard ratio; N-R, non-responder; PAC, pacritinib; R, responder; TSS, total symptom score.

Ajufo, et al. *European Journal of Haematology* 2024

Pacritinib: Phase II Dose-Finding Study PAC203 in Patients With MF Intolerant of or Resistant to Ruxolitinib

PAC203 incorporated risk-mitigation factors put in place to address findings from the thorough clinical review of PERSIST data, including enhanced eligibility criteria, patient monitoring, and dose modifications



[a]Complicated by red blood cell transfusion, grade ≥3 anemia, thrombocytopenia, hematoma, and/or hemorrhage while treated with a dosage of <20 mg twice daily.
[b]Less than 10% SVR or <30% decrease in spleen length or regrowth of these parameters.
BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PET-MF, postessential thrombocythemia MF; PK/PD, pharmacokinetic/pharmacodynamic; PMF, primary MF; PPV-MF, postpolycythemia vera MF; QD, once daily; SVR, spleen volume reduction; TSS, total symptom score.
Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

PAC203: Baseline Characteristics

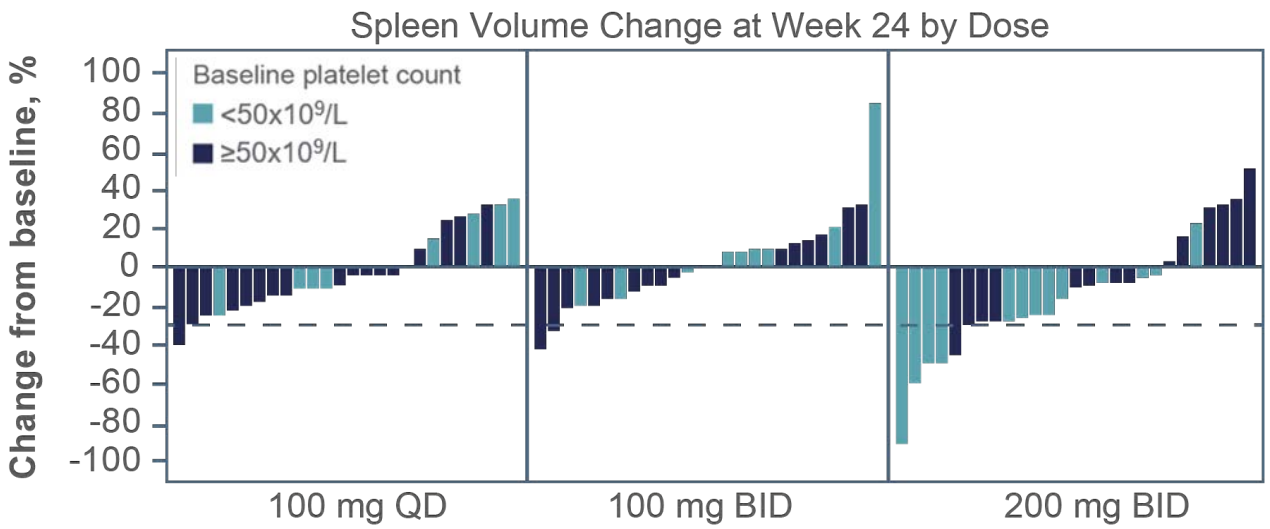
Key Baseline Characteristics	PAC 100 mg QD (n = 52)	PAC 100 mg BID (n = 55)	PAC 200 mg BID (n = 54)
Median age, years	69.5	69.0	68.5
Male, %	60	53	59
MF diagnosis: PMF, PPV-MF, PET-MF, %	54, 31, 15	51, 33, 16	69, 19, 13
DIPSS score: Int-1, Int-2, High, %	17, 48, 35	26, 49, 26	22, 52, 26
Median spleen length, cm	12	15	14
Median platelet count, × 10^9/L <50 × 10^9/L, %	59 44	53 44	59 44
Platelet transfusion-dependent,[a] %	12	9	11
Hemoglobin <10 g/dL, %	67	69	76
RBC transfusion dependence[b]: dependent, independent, indeterminate, %	29, 46, 25	27, 42, 29	39, 37, 24
Prior ruxolitinib: resistant, intolerant, both, %	77, 73, 50	75, 75, 51	78, 70, 48
Median duration of prior ruxolitinib, years	1.7	1.8	1.6

Of note, patients were required to taper ruxolitinib to ≤10 mg BID during screening, but no treatment washout was required

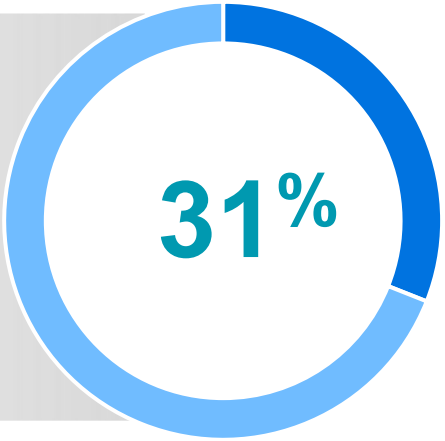
- Baseline analyses of spleen size and symptoms may have occurred while patients were still receiving ruxolitinib
- Potential impact on reductions measured on study

[a]Defined by any platelet transfusion required during the past month. [b] Defined by Gale criteria.
BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; MF, myelofibrosis; PET-MF, postessential thrombocythemia MF; PMF, primary MF; PPV-MF, postpolycythemia vera MF; QD, once daily; PAC, pacritinib; RBC, red blood cell.
Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

PAC203: Spleen Response Across Doses (Evaluable Population, Week 24)



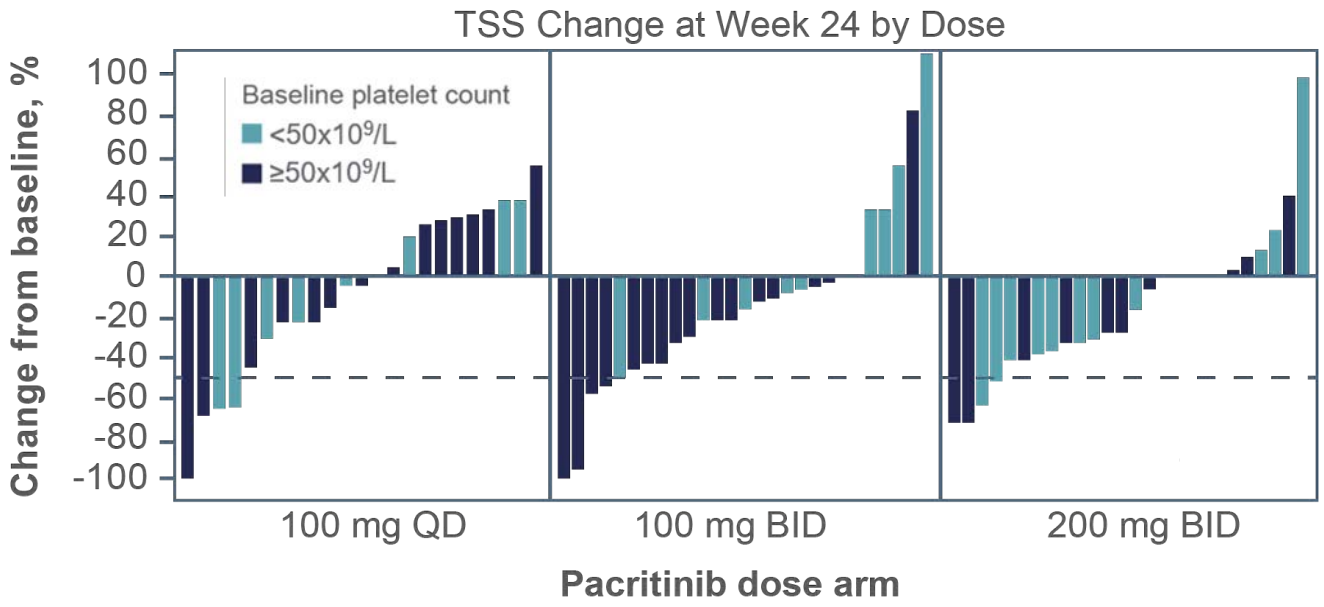
Evaluable SVR in patients with severe thrombocytopenia (<50 × 10^9/L) at baseline treated with 200 mg BID



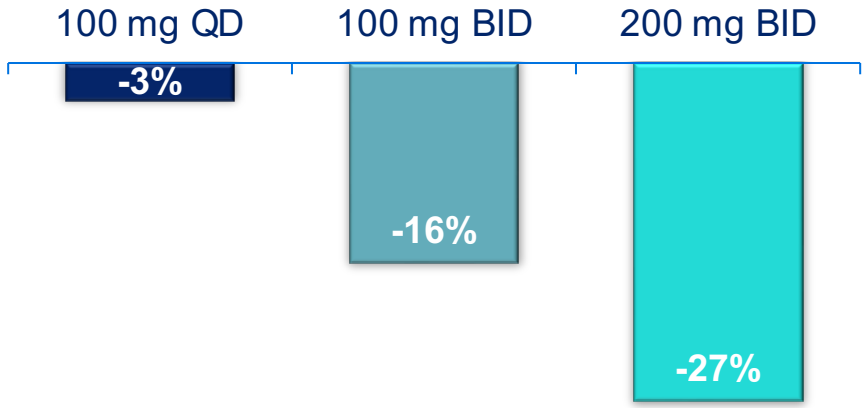
BID, twice daily; QD, once daily; SVR, spleen volume reduction.

Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

PAC203: Symptom Responses Across Doses (Evaluable Population, Week 24)



TSS analyzed as a continuous variable:
Deeper reductions with 200 mg BID

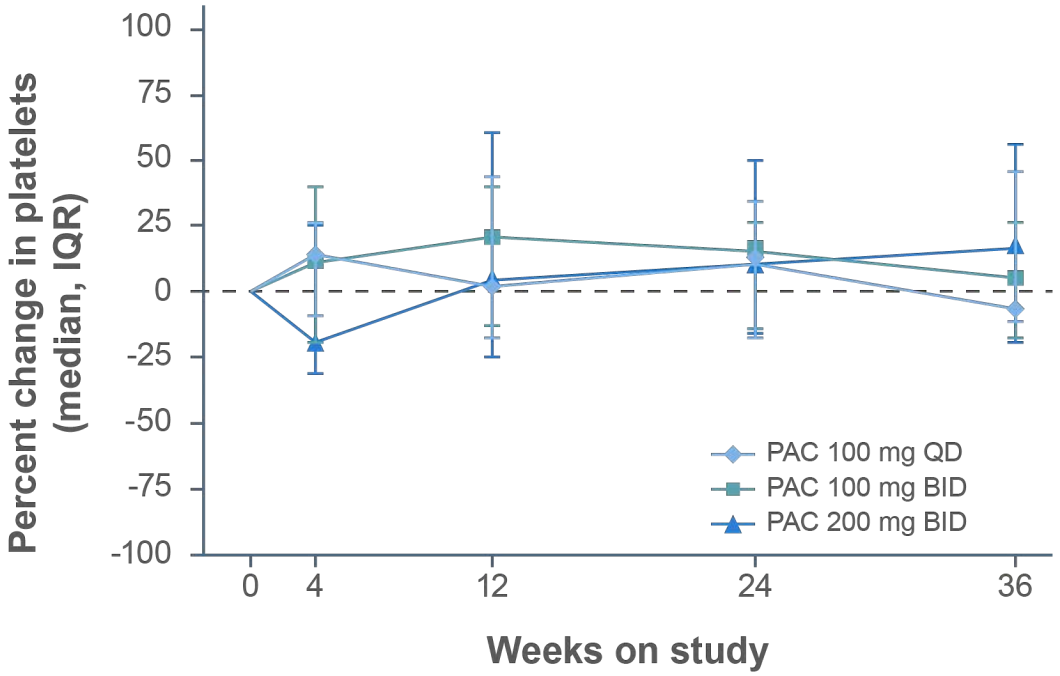


Note: One patient with 302% increase from baseline TSS score represented by truncated bar to fit to scale (far right bar in 100 mg BID).
BID, twice daily; QD, once daily; TSS, total symptom score.
Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

PAC203: Hematologic Stability

- Platelet counts were stable for most patients on study, including those with severe thrombocytopenia

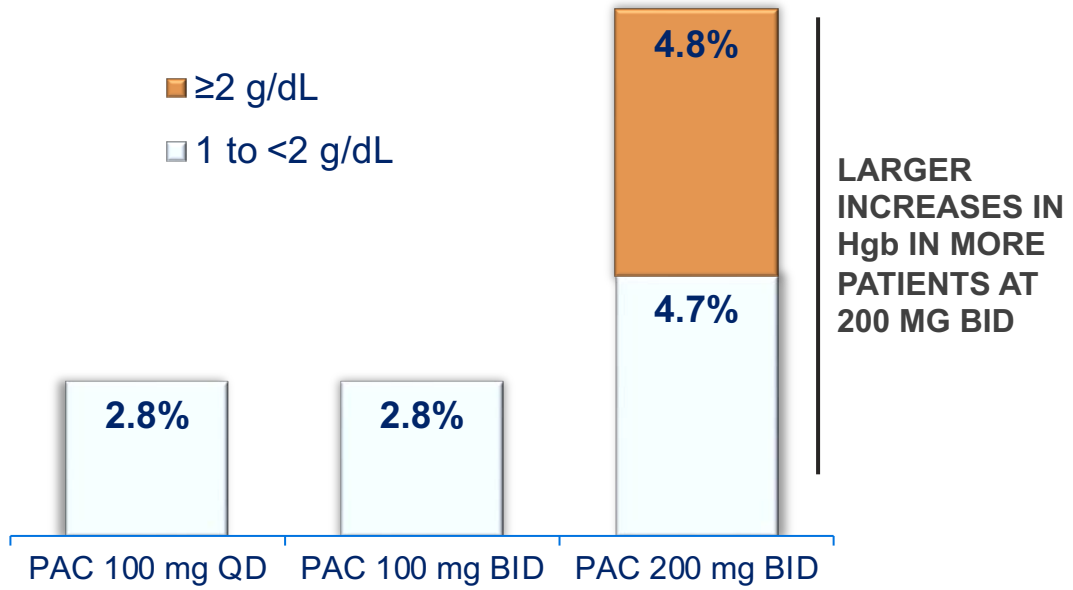
Percentage Change in Platelet Count From Baseline



Number of Patients					
PAC 100 mg QD	52	44	37	22	11
PAC 100 mg BID	55	49	42	24	16
PAC 200 mg BID	53	49	38	26	14

- Reductions in transfusion burden and achievement of transfusion independence occurred in patients in all arms

Hgb Increases in Patients With Baseline Anemia (Hgb ≤10 g/dL)



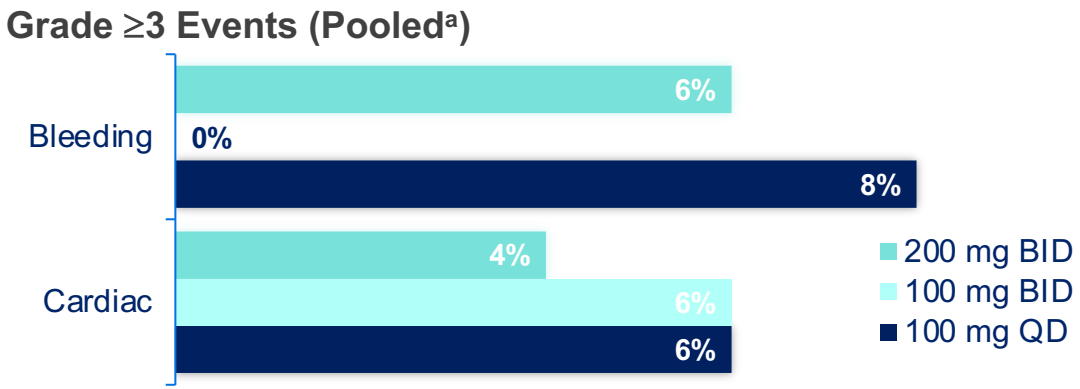
Baseline to week 24

BID, twice daily; Hgb, hemoglobin; IQR, interquartile range; PAC, pacritinib; QD, once daily.

Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

PAC203: Adverse Event Profile

Adverse Reactions	PAC 100 mg QD (n = 52)	PAC 100 mg BID (n = 55)	PAC 200 mg BID (n = 54)
Grade ≥3 AEs in >5% of patients in any arm, %			
Thrombocytopenia	19	22	33
Anemia	10	7	20
Pneumonia	4	4	9
Neutropenia	6	6	6
Diarrhea	2	4	6
Fatigue	6	4	4
Abdominal pain	0	4	6
Hyperuricemia	2	2	6
Hyponatremia	0	6	4
Dehydration	0	6	2
Hypertension	0	6	2



- Two deaths due to bleeding events, subdural hemorrhages, at 100 mg BID and 200 mg BID
- One death due to cardiac event, heart failure in the setting of progressive hyperleukocytosis, at 100 mg BID
- No patient had QTc >500 msec

Rates of bleeding and cardiac events were generally lower than those reported in PERSIST-2,[2] likely due to enhanced patient selection, patient monitoring, and dose-modification guidelines

[a]Pooled, per standardized MedDRA queries.
AE, adverse event; BID, twice daily; PAC, pacritinib; QD, once daily.
1. Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835; 2. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

ASH 2023

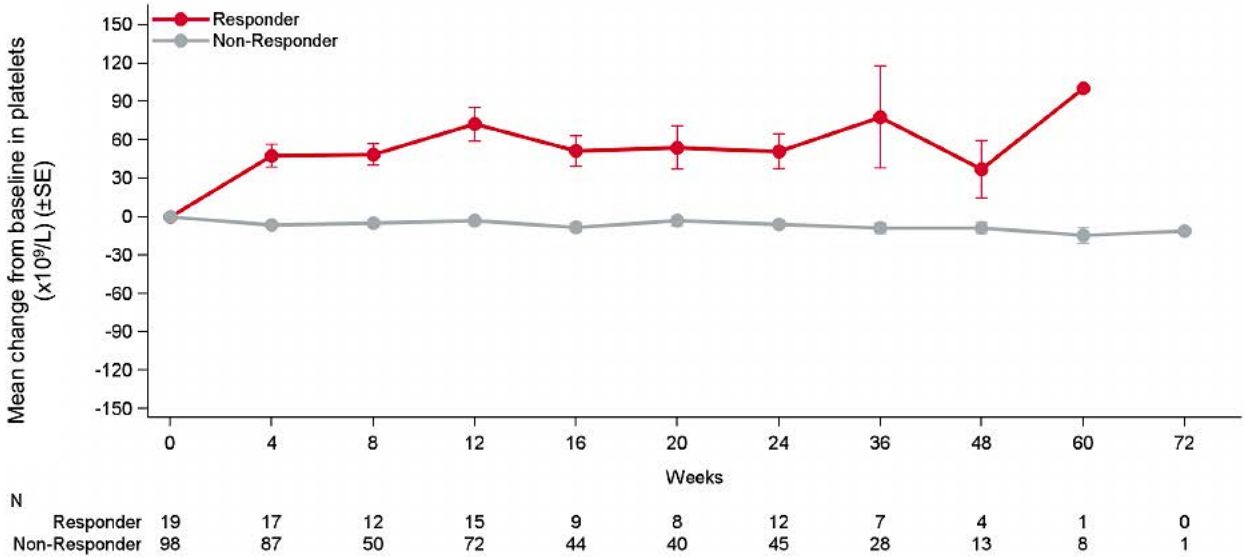
P4554

Platelet Response in Pacritinib-Treated Patients with Cytopenic Myelofibrosis: a Retrospective Analysis of PERSIST-2 and PAC203 Studies

Pankit Vachhani,[1] Abdulraheem Yacoub,[2] Elie Traer,[3] Lina Benajiba,[4,5] Francesco Passamonti,[6] Ashwin Kishtagari,[7] Mojtaba Akhtari,[8] James McCloskey,[9] Sarah Buckley,[10] Purvi Suthar,[10] Karisse Roman-Torres,[10] John Mascarenhas[11]

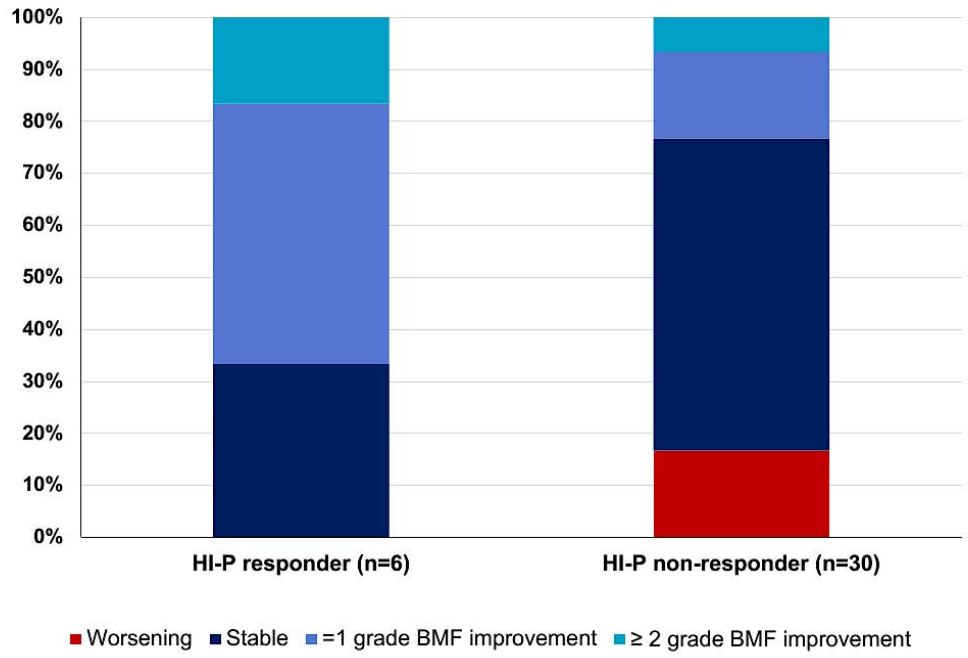
[1]O' Neal Comprehensive Cancer Center, University of Alabama, Birmingham, AL; [2]The University of Kansas Clinical Cancer Research Center, Leawood, KS; [3]Oregon Health & Science University, Portland, OR; [4]Centre d'Investigations Cliniques, INSERM CIC 1427, Université Paris Cité, APHP, Hôpital Saint-Louis, Paris, France; [5]INSERM UMR 944, Institut de Recherche Saint-Louis, Paris, France; [6]Università degli Studi di Milano; Fondazione I.R.C.C.S. Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; [7]Division of Hematology & Oncology, Vanderbilt Ingram Cancer Center, Nashville, TN; [8]Loma Linda University Cancer Center, Loma Linda, CA; [9]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [10]CTI BioPharma Corp., a Sobi company, Seattle, WA; [11]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Figure 1. Mean change in platelet count from baseline over time on pacritinib 200 mg BID among HI-P responders vs non-responders, PERSIST-2 & PAC203



Please note: assessment every 12 weeks after week 24.

Figure 3. Change in bone marrow fibrosis in HI-P responders vs non-responders, PERSIST-2 & PAC203, pacritinib 200 mg BID



19% of pacritinib treated patients on PAC203 and PERSIST-2 trials experienced an improvement in platelet counts

PACIFICA: A Randomized, Controlled Phase 3 Study of Pacritinib Versus Physician's Choice in Patients with Primary or Secondary Myelofibrosis and Severe Thrombocytopenia

Key Eligibility Criteria:

- PMF, PET-MF, PPV-MF
- DIPSS Intermediate- or high-risk disease
- Severe thrombocytopenia at baseline ($<50 \times 10^9$/L)
- JAK2 inhibitor-naïve or limited duration of prior JAK2 inhibitor

2:1 Randomization N=399

Stratification at randomization:

- Prior JAK2 inhibitor therapy
- Physician's choice selected prior to randomization

Pacritinib 200 mg BID

Physician's Choice

- Low-dose ruxolitinib (5 mg QD or BID)
- Hydroxyurea
- Danazol
- Corticosteroids

Co-primary endpoints at 24 weeks:

- Reduction in SVR ≥35%
- Reduction in mTSS ≥50%

Key secondary endpoints

- PGIC at 24 weeks
- Overall survival
- Safety

- Investigators can select an individual P/C agent but cannot combine agents or give them sequentially.
- Patients are treated until disease progression, intolerable adverse events, or withdrawal of consent.
- All patients are followed for survival until 2.5 years after randomization.

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

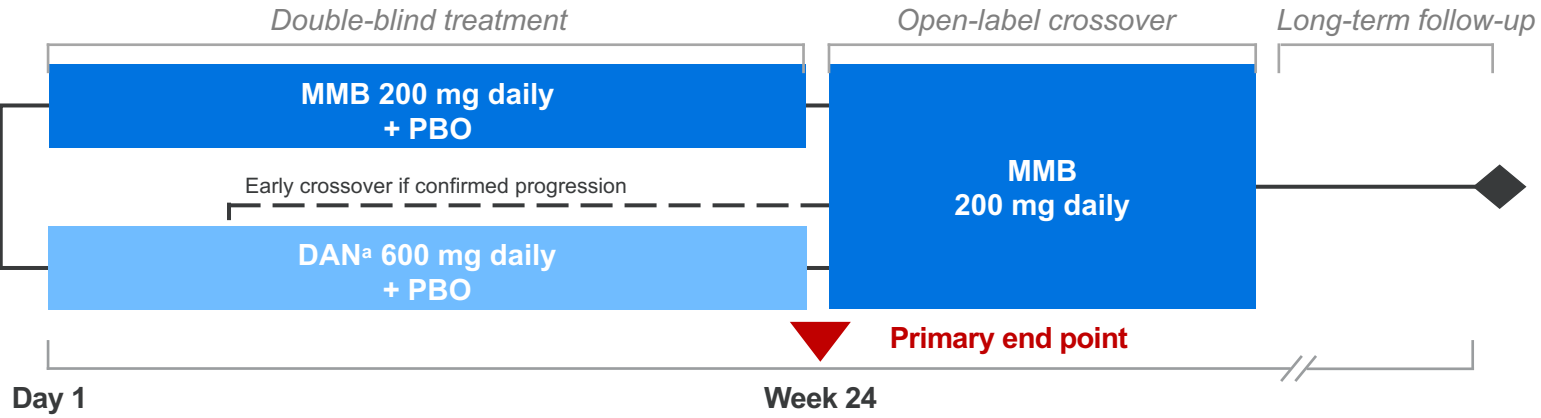
Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥25 × 10^9/L

Stratification:
- TSS
- Palpable spleen length
- Transfused units in prior 8 weeks
- Study site

Patients
N=195

2:1 randomization
JAKi taper/washout ≥21 days

Planned enrollment: 180
FPE Apr 2020
LPE Jun 2021
Database lock Dec 2021



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

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

Summary

- Myelofibrosis associated with cytopenias represent a significant clinical challenge
- Pacritinib can be used without platelet count restrictions in patients with thrombocytopenia
- Anemia, which often co-occurs with thrombocytopenia, can improve with pacritinib
- Common side effects include: diarrhea (often transient), nausea, anemia, thrombocytopenia.
- Momelotinib can be used in patients with a platelet count as low as 25K

Dr Laura Michaelis
(Milwaukee, Wisconsin)

Management of MF with moderate thrombocytopenia (75,000)

Dr John Mascarenhas
(New York, New York)

Case Presentation: 65-year-old man with primary MF and anemia (Hgb 8.2g/dL), thrombocytopenia (platelets 55,000) and splenomegaly and low JAK2 V617F allele frequency

QUESTIONS FOR THE FACULTY

What is your usual up-front JAK inhibitor for a patient with a platelet count of 75,000 without anemia?

Would you likely have administered pacritinib to Dr Mascarenhas's patient?

Agenda

Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Palmer

Module 2: Managing MF in Patients with Anemia — Dr Oh

Module 3: Managing MF in Patients with Thrombocytopenia — Dr Rampal

Module 4: Promising Novel Agents Under Investigation for MF — Prof Harrison

Module 5: Current and Future Management of Systemic Mastocytosis — Dr Kuykendall

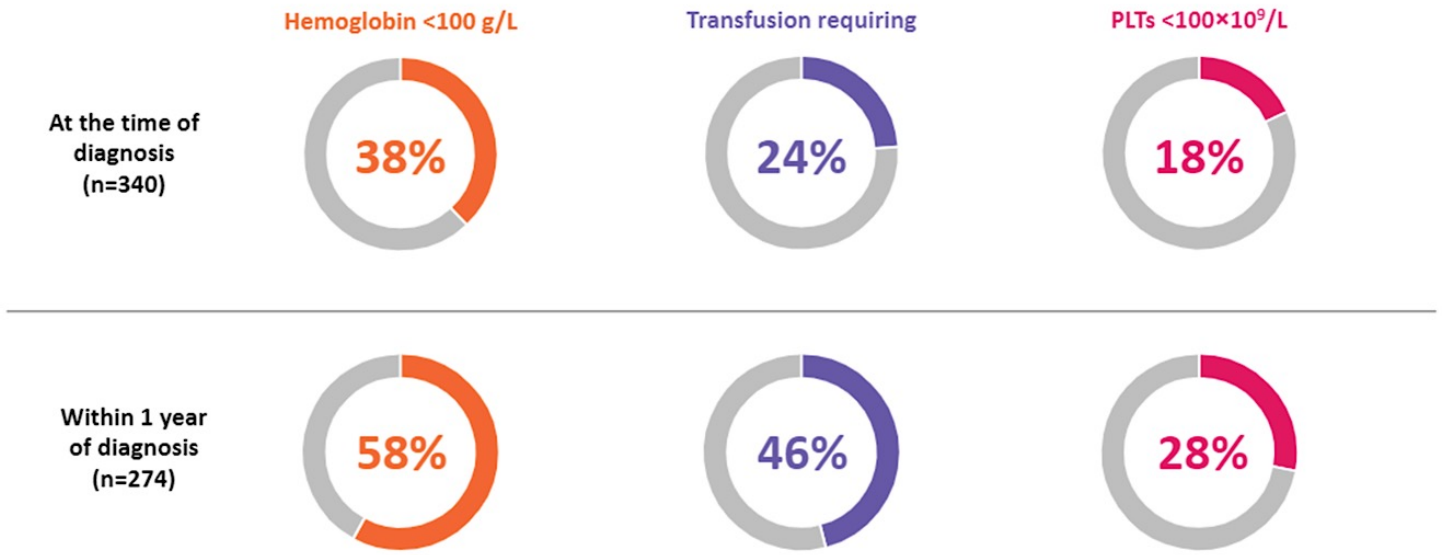
Promising Novel Agents Under Investigation for MF

Professor Claire Harrison

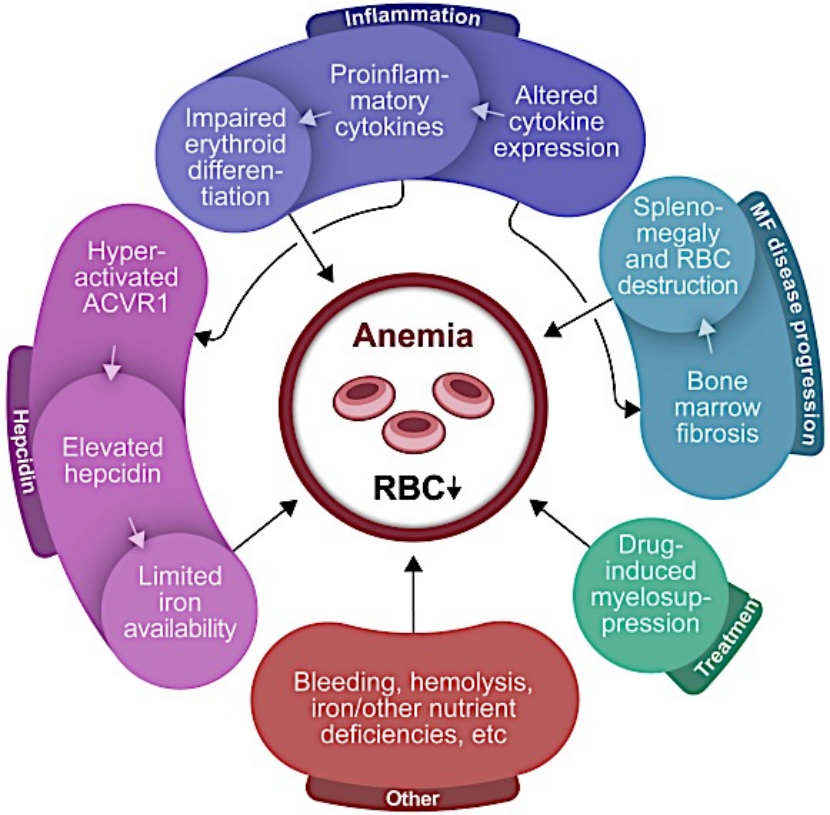
Anemia in myelofibrosis

- Is an ongoing area of unmet need
- And often multifactorial

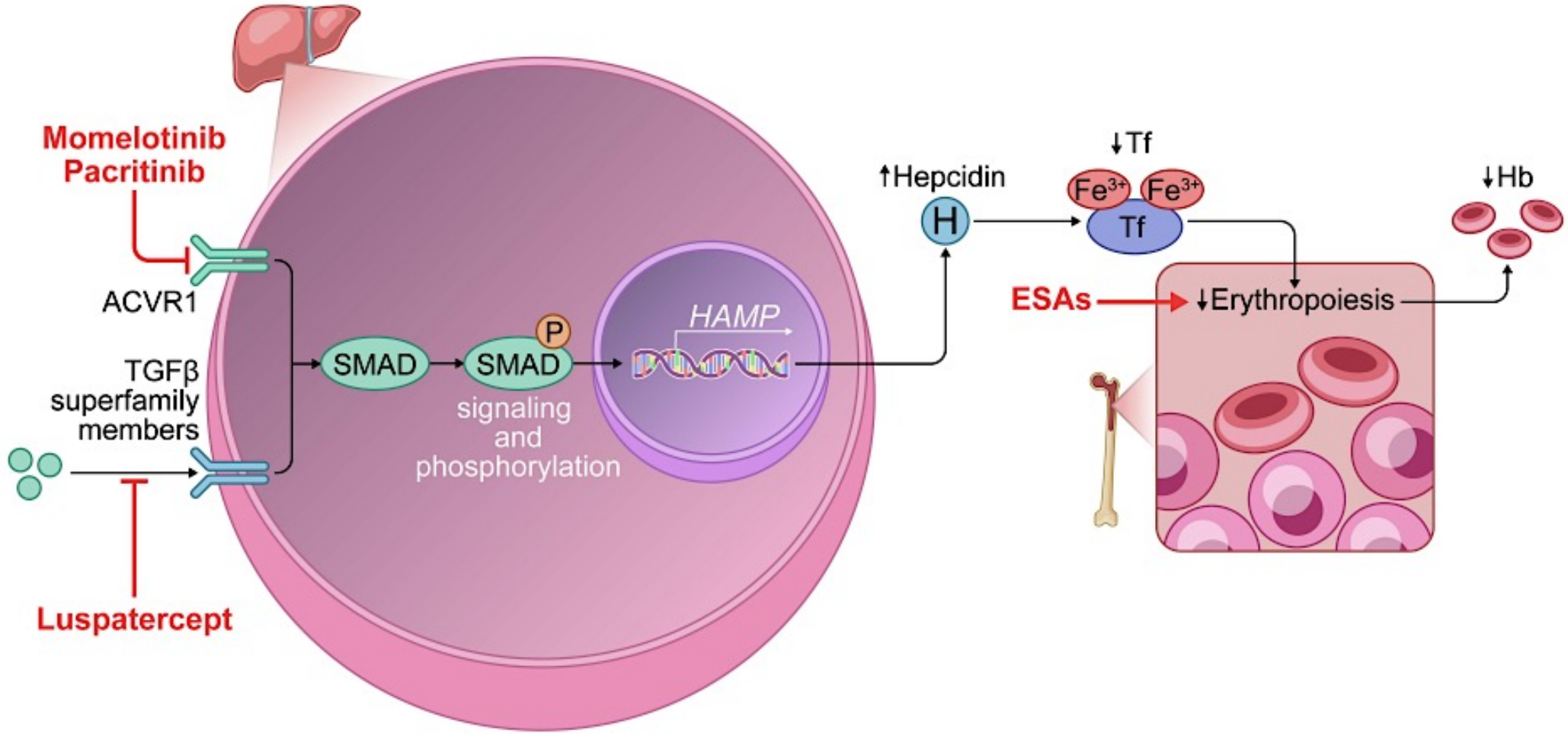
Rates of Anemia and Thrombocytopenia Increase Over Time in Patients With Primary Myelofibrosis



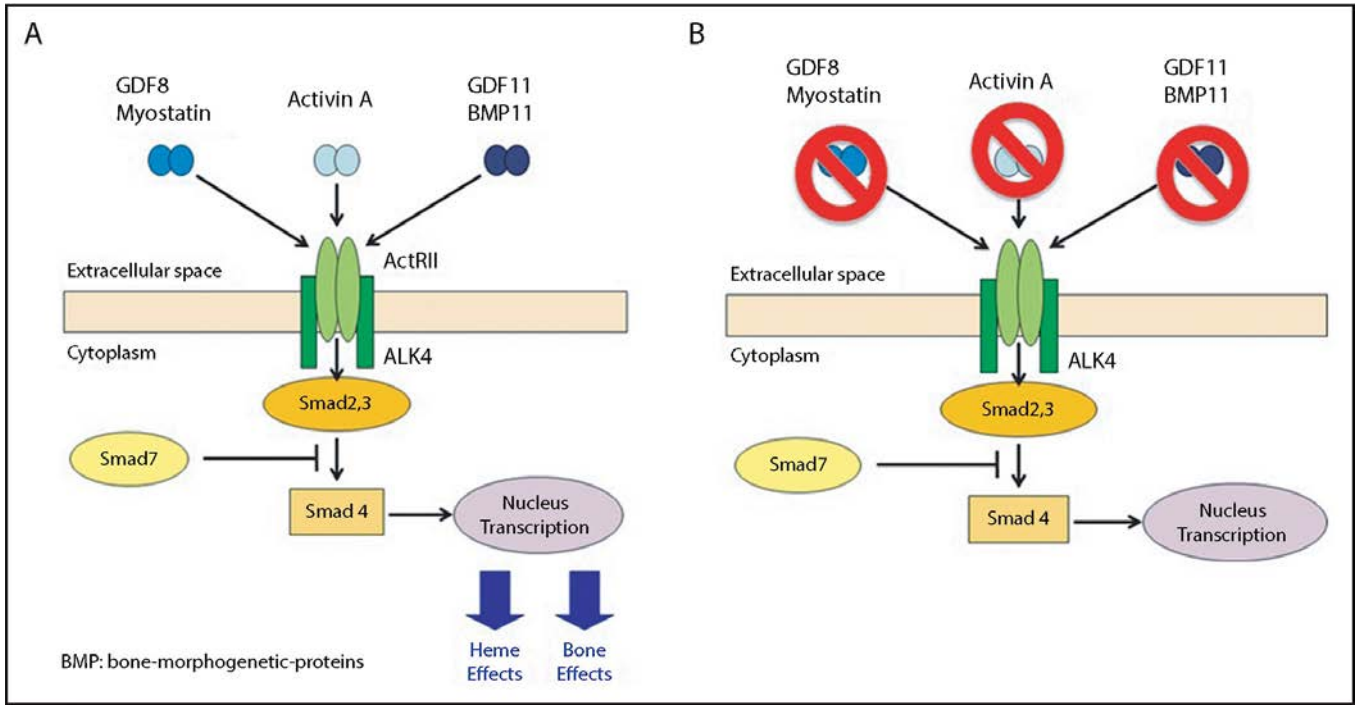
The data shown are based on patients with primary myelofibrosis seen at the Mayo Clinic between November 4, 1977, and September 1, 2011.
PLT, platelet.
Tefferi A, et al. *Mayo Clin Proc*. 2012;87(1):25-33.

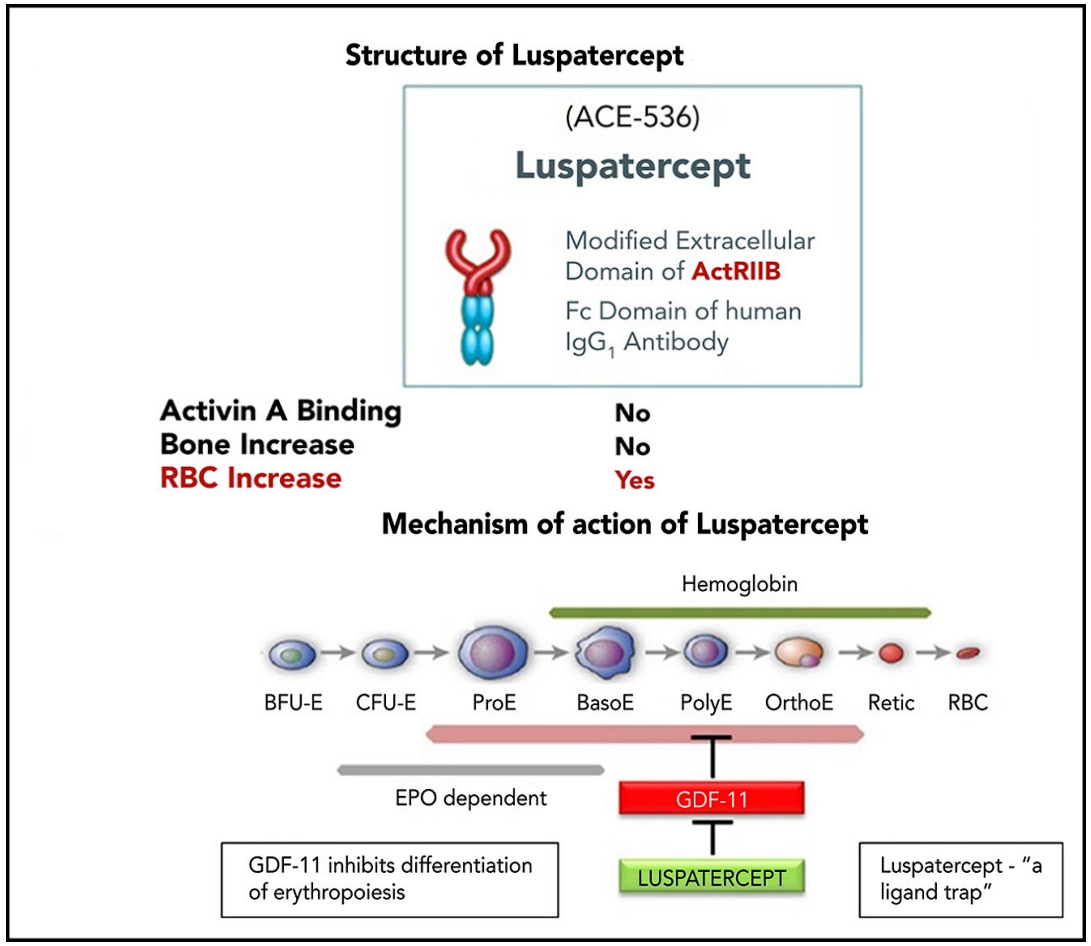


Targets of interest for anemia in MF



Luspatercept

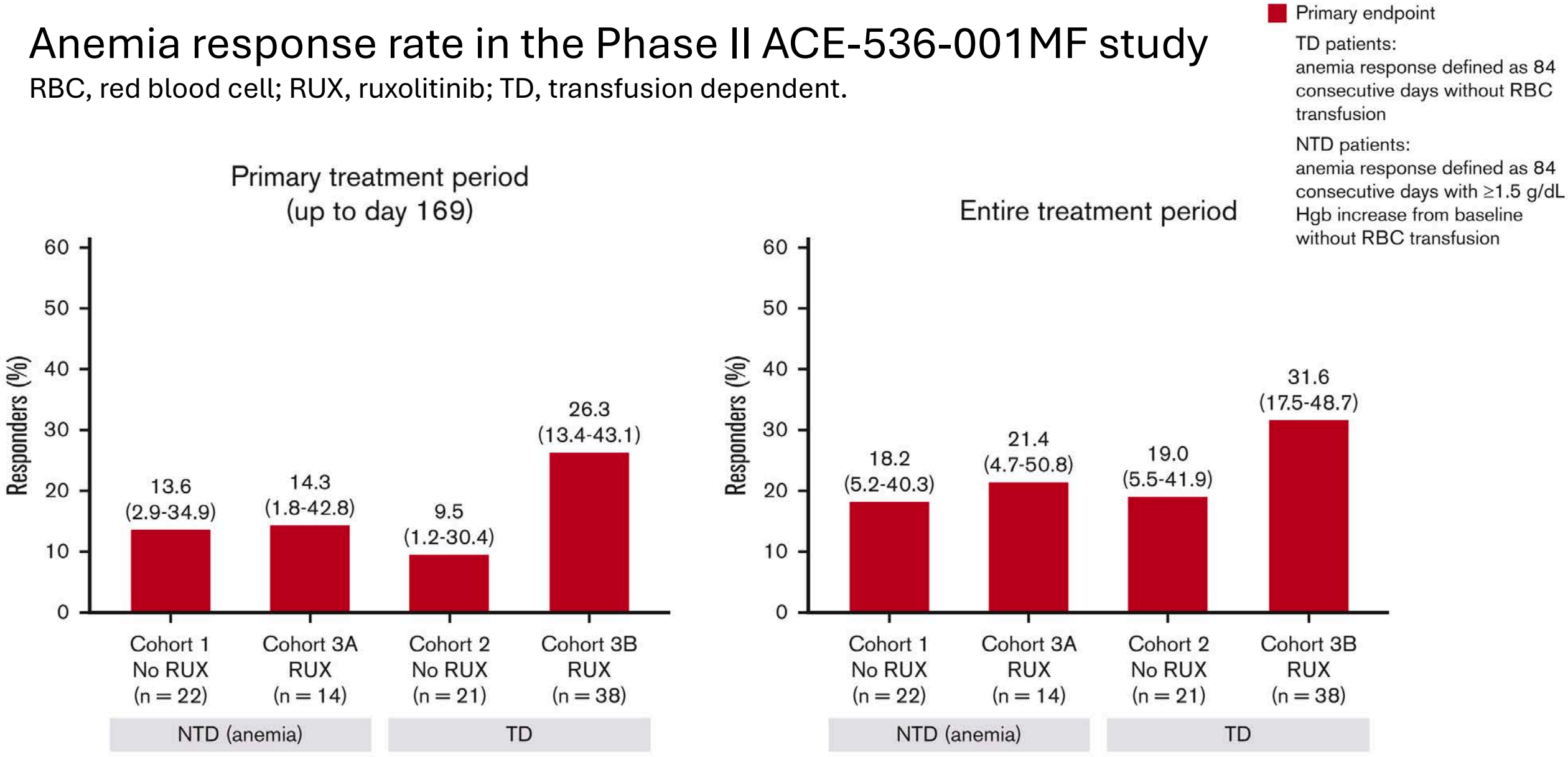




Modified from Fenaux P et al. Blood. 2019 Feb 21;133(8):790-794.

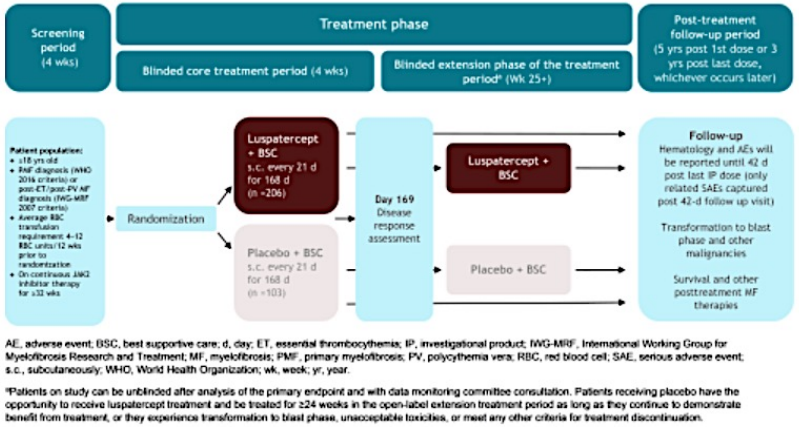
Anemia response rate in the Phase II ACE-536-001MF study

RBC, red blood cell; RUX, ruxolitinib; TD, transfusion dependent.



Adapted from Gerds, *et al Blood Adv*. 2024;8(17):4511-4522.

Emerging outcomes from and potential implications of the Phase III INDEPENDENCE study evaluating luspatercept with concomitant JAK inhibitor therapy



Topline Results from Phase 3 INDEPENDENCE Trial for Luspatercept-aamt in Adult Patients with Myelofibrosis-Associated Anemia

PRINCETON, N.J.--(BUSINESS WIRE)-- July 18, 2025: [The manufacturer] announced the Phase 3 INDEPENDENCE trial evaluating luspatercept with concomitant janus kinase inhibitor (JAKi) therapy in adult patients with myelofibrosis-associated anemia receiving red blood cell (RBC) transfusions did not meet its primary endpoint of RBC transfusion independence during any consecutive 12-week period, starting within the first 24 weeks of treatment, compared to placebo (p=0.0674). Patients saw a numerical and clinically meaningful improvement in RBC transfusion independence favoring luspatercept, in line with previous results from the Phase 2 trial (NCT03194542).

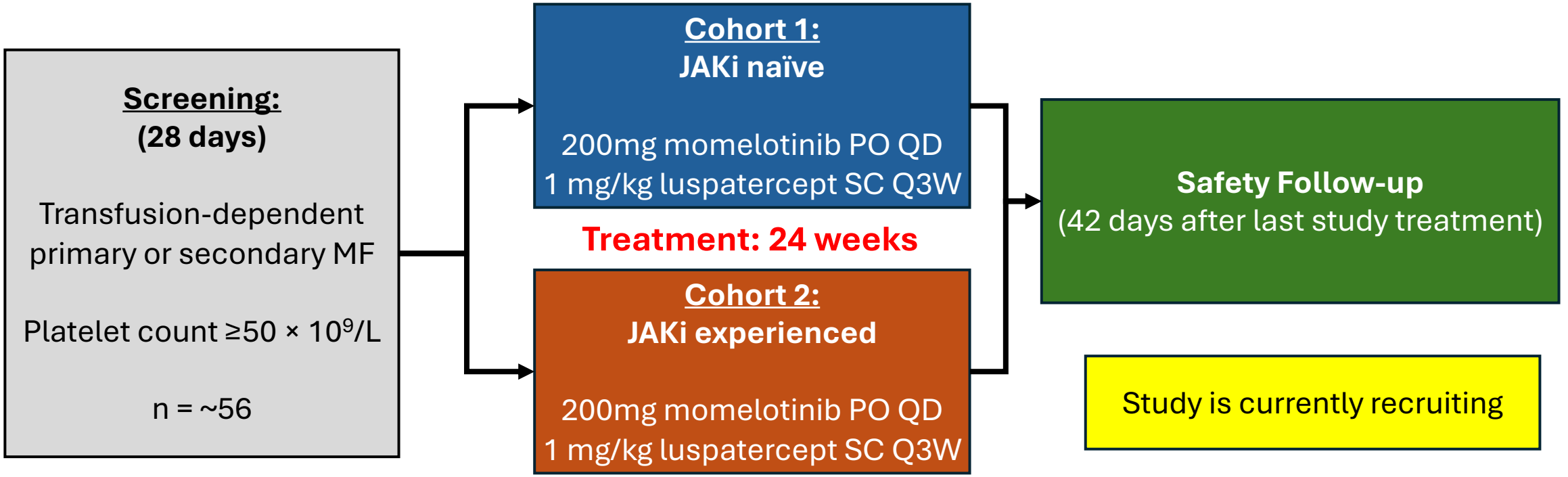
Several important secondary measures also showed a clinically meaningful benefit favoring luspatercept, which included a higher number of patients who achieved at least a 50% reduction (and by at least 4 RBC units) in RBC transfusion burden, as well as a higher number of patients achieving a hemoglobin (Hb) level increase by at least 1 g/dL while remaining transfusion independent for at least 12 consecutive weeks.

Frequently observed treatment emergent adverse events were consistent with the known safety profile of luspatercept previously reported across indications.

The company is encouraged by the clinically meaningful results of the study and will engage with the FDA and EMA to discuss the submission of marketing applications.

Momelotinib and luspatercept have a complementary mechanism of action, which may improve anemia by promoting both early- and late-stage erythropoiesis, suggesting a potential additive and possibly synergistic benefit.

The phase II ODYSSEY trial (NCT06517875) assesses this.



Preliminary experience from the ODYSSEY trial: Efficacy and safety of momelotinib in combination with luspatercept in patients with transfusion-dependent myelofibrosis
Bose P et al. ASH 2025;Abstract 3803

Bose P et al. ASH 2024;Abstract 3191.2.

A retrospective study to assess real-world treatment patterns and outcomes in luspatercept-treated patients with myelofibrosis-associated anemia who required red blood cell transfusion in the United States

Hobbs G et al. ASH 2025;Abstract 2825

RESULTS:

At the end of data availability (Dec 31, 2024), 99 patients who received luspatercept were identified, of whom 19 also received overlapping JAKi treatment. The median (range) age was 77 years (55–87), 54.6% were male, and 41.4% had primary MF. The majority (74.7%) of patients were White, 14.1% were Black, 3.0% were Asian, and 8.1% were classified as other races. The median (IQR) time between MF diagnosis and index date was 1.2 years (0.4–3.7) and median (IQR) follow-up time post-index was 12.3 months (6.7–20.7). Thirty-one (31.3%) patients were treated with JAKi at any time post-MF diagnosis and 54 (54.6%) patients were deceased by the end of data availability. Median (IQR) number of RBCT events was 3 (2–5) and 77 (77.8%) patients were considered transfusion dependent (TD: ≥ 2 RBCT events) at baseline.

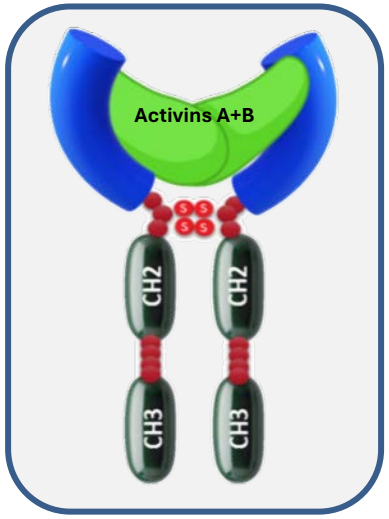
The median time to treatment discontinuation per Kaplan–Meier estimate was 33.6 weeks (95% CI 25.1– 51.7). The probability of remaining on treatment was 55.7% at 6 months and 35.8% at 12 months.

The proportion of patients who achieved RBC-TI 12 and RBC-TI 16 after luspatercept initiation was 38.4% (n = 38) and 33.3% (n = 33). The median (95% CI) duration of both RBC-TI 12 and RBC-TI 16 was 37.4 weeks (30.4–NR). Sixty-six (66.7%) patients achieved ≥ 50% RBCT reduction by 24 weeks.

CONCLUSION:

In this RW study, **MF patients who required RBCT treated with luspatercept showed clinically meaningful benefits: nearly 40% achieved 12-week RBC-TI and two-thirds experienced ≥ 50% RBCT reduction within 24 weeks of luspatercept initiation**. The findings of this RW study generally corroborate and supplement previous clinical trial results, indicating that luspatercept can be effective in increasing RBC-TI and reducing transfusion burden in this population.

Elritercept (KER-050) is Designed to Target Disorders of Ineffective Hematopoiesis Including MF



Elritercept

Designed to inhibit select TGF-beta superfamily ligands, including **activin A,** which has been associated with **ineffective hematopoiesis, inflammation, disease pathogenesis, and progression**[1,2,3]

Preclinical data showed that the research form of **elritercept** (RKER-050):

- induced erythropoiesis in mouse model of MF[4]
- reversed ruxolitinib-associated reductions in hemoglobin, hematocrit, and red blood cell (RBC) count[5]
- increased platelet counts[6]

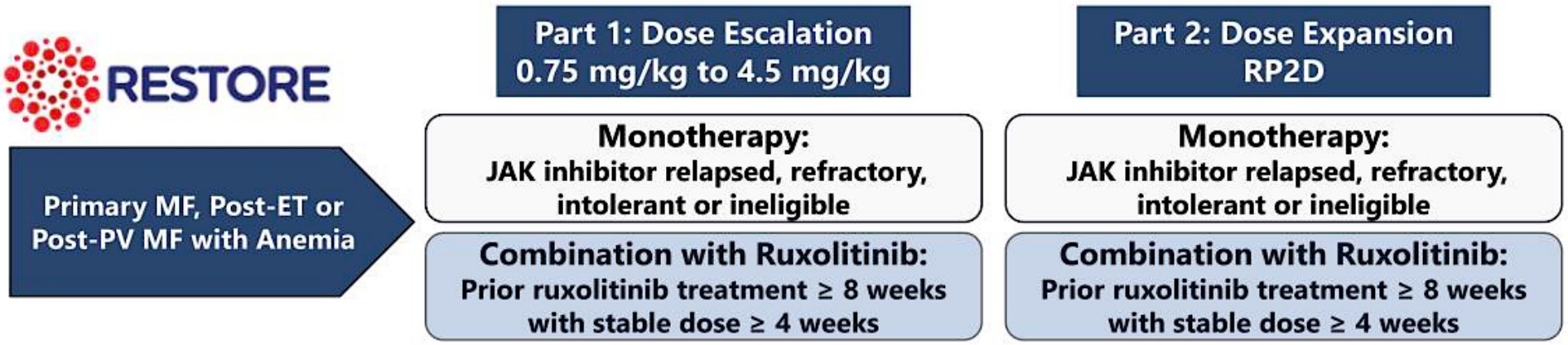
Updated results from the ongoing open-label Phase 2 RESTORE trial evaluating elritercept in participants with MF and anemia

In mono and combo spleen symptoms and anemia responses were seen

[1]Verma A, et al. *J Clin Inv*. 2020; [2]Portale F, et al. *Haematologica*. 2019; [3]Phillips D, et al. *Cytokine Growth Factor Rev*. 2009; [4]Moses B, et al. *EHA*. 2023; [5]Nathan R, et al. *ASH*. 2021; [6]Moses B, et al. *GRC: Cell Biology of Megakaryocytes and Platelets*. 2023.
TGF-β = transforming growth factor-β.

Phase II RESTORE Study Design

Hematological and clinical improvements with elritercept (KER-050, TAK-226) at the recommended Phase 2 dose (RP2D) in patients with myelofibrosis (MF) receiving ruxolitinib: Updated results from the Phase 2 RESTORE trial
Rinaldi C et al. ASH 2025;Abstract 909.



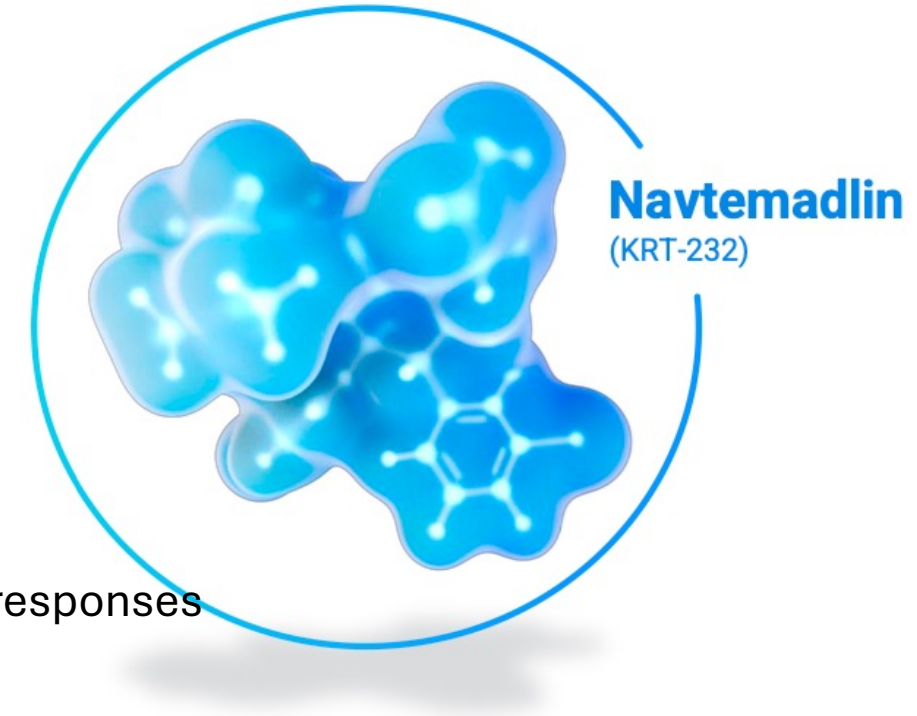
Key Eligibility	Objectives and Endpoints	Trial Status
• Transfusion dependent (TD): average of ≥6 RBC units/12 weeks with ≥1 transfusion within 28 days prior to treatment • Non-transfusion dependent (Non-TD): baseline hemoglobin < 10 g/dL, with or without transfusions • Baseline platelet count ≥ 25 x 10^9/L	• Primary: To evaluate safety and tolerability of elritercept as monotherapy or in combination with ruxolitinib in patients with MF • Secondary/Exploratory: To evaluate effects of elritercept with or without ruxolitinib on: ○ Anemia, spleen volume, symptom score, exploratory biomarkers	• Data presented as of a data cut-off date of April 3, 2024 • Dose escalation complete • RP2D identified as 3.75 mg/kg with option to up-titrate to 5 mg/kg Q4W • Part 2 Dose Expansion open and enrolling • Total of 54 patients enrolled

Post-ET = post-essential thrombocythemia; Post-PV= post polycythemia vera

Navtemadlin is a Novel p53 Potentiating Anticancer Agent

Navtemadlin is a potent, selective, orally available best-in-class inhibitor of MDM2[1,2] that restores p53 function:

- Binding affinity = 0.045 nM[2]
- IC_{50} = 9.1 nM[2]
- Constant oral clearance across doses[3]
- Rapid absorption (1-3 hour T_{max})[3]
- $T_{1/2}$ = 17 hours[3]



Spleen symptoms and biological – mutation VAF, BM fibrosis responses
In the monotherapy second line BOREAS study

NO APPARENT selection of p53 clones
? The NEXT approved therapy

[1]Canon J, et al. *Mol Cancer Ther*. 2015. [2]Sun D, et al. *J Med Chem*. [3]Ma SC, et al. *Blood*. 2019.
Abbreviations: IC_{50}, half maximal inhibitory concentration; MDM2, mouse double minute 2; MPN, myeloproliferative neoplasms; nM, nanomolar; $T_{1/2}$, half-life; T_{max}, time to maximum concentration.

Mascarenhas et al. ASH 2024;Abstract 1000

A Randomized, Open-Label, Global Phase 3 Study of Navtemadlin in *TP53*^{WT} Patients With Myelofibrosis Who Are Relapsed or Refractory to JAK Inhibitor Treatment

BOREAS
Blocking MDM2 to reactivate p53 in myelofibrosis

Stratification Factors:
- Primary MF vs Secondary MF
- Baseline TSS (≤10 vs >10)

Physician's Choice (BAT):
- Hydroxyurea
- Peginterferon
- IMiDs
- Supportive care

Patients With JAKi R/R Myelofibrosis
183 Patients

2:1

Navtemadlin 240 mg QD
Days 1-7 / 28-Day Cycle
123 Patients

Best Available Therapy
60 Patients

Crossover Permitted*

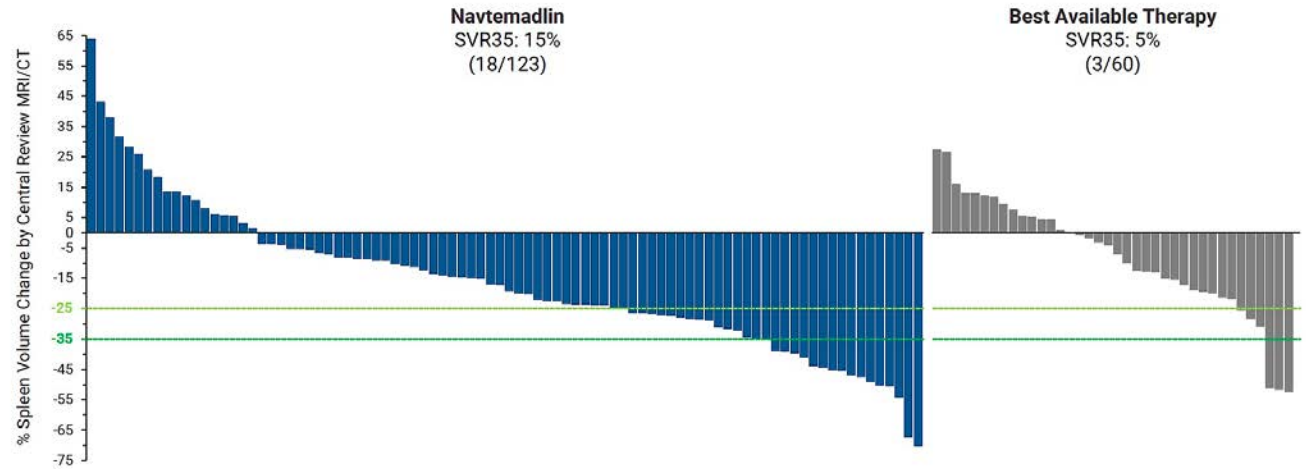
1 Cycle = 28 Days

PRIMARY ENDPOINT	KEY SECONDARY ENDPOINT	KEY PHASE 3 STUDY NOTES
• SVR35 Week 24 by MRI/CT Central Review	• TSS50 Week 24 by MFSAF v4.0	• 28-day JAKi wash-out prior to C1D1 • JAKi excluded in BAT arm • C1D1 occurred within 7-days of baseline MRI/CT • Diarrhea prophylaxis for first two cycles

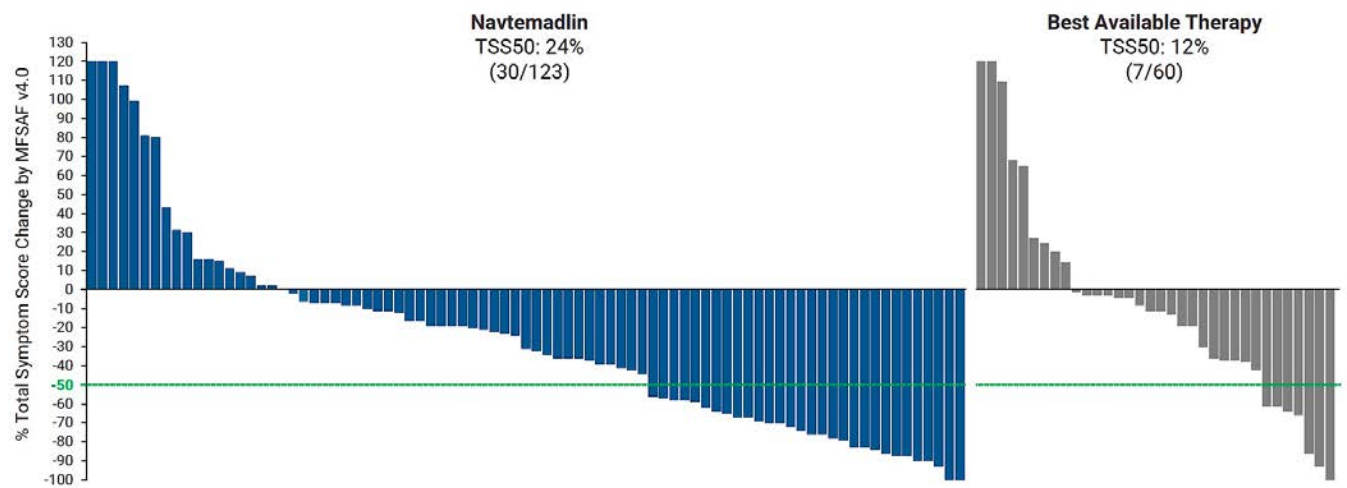
	Navtemadlin n = 123[1]	Best Available Therapy n = 60[1,2]
Randomized Not Treated	–	3 (5)
On Treatment	37 (30)	3 (5)
Discontinued	86 (70)	54 (90)
Withdrawal of Consent	30 (24)	7 (12)
Adverse Event	14 (11)	4 (7)
Disease Progression	11 (9)	6 (10)
Death	9 (7)	4 (7)
Investigator Decision	18 (15)	17 (28)
Other*	4 (3)	16 (27)

Median time on study, months (range): Navtemadlin 15.6 (0.23, 39.9); BAT 6.5 (0.03, 30.5)

Spleen Volume Reduction by Central Review MRI/CT – Baseline to Week 24

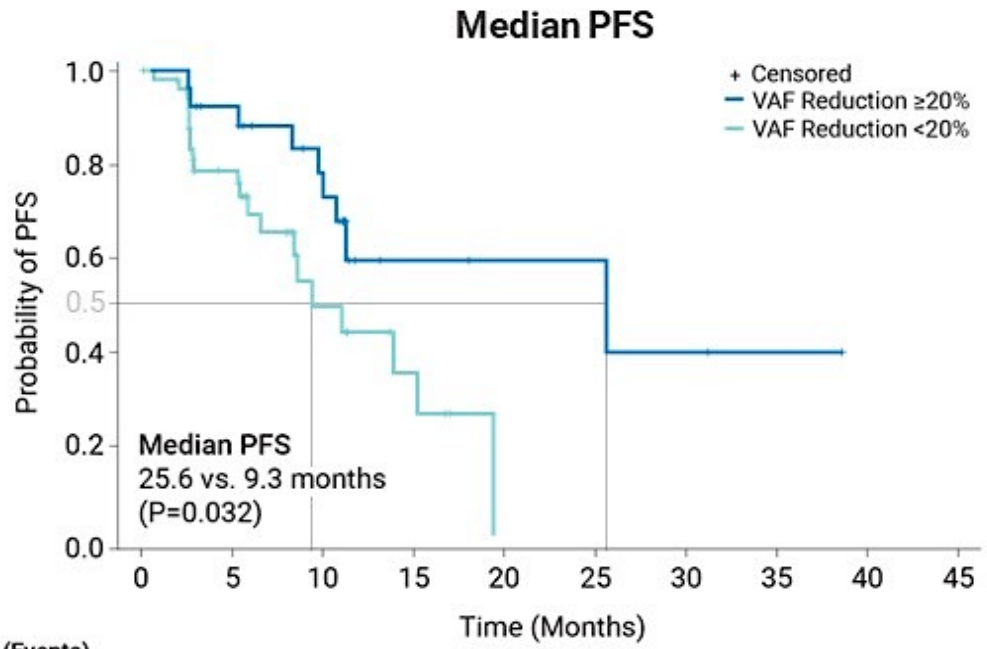


Total Symptom Score Reduction by MFSAF v4.0 – Baseline to Week 24

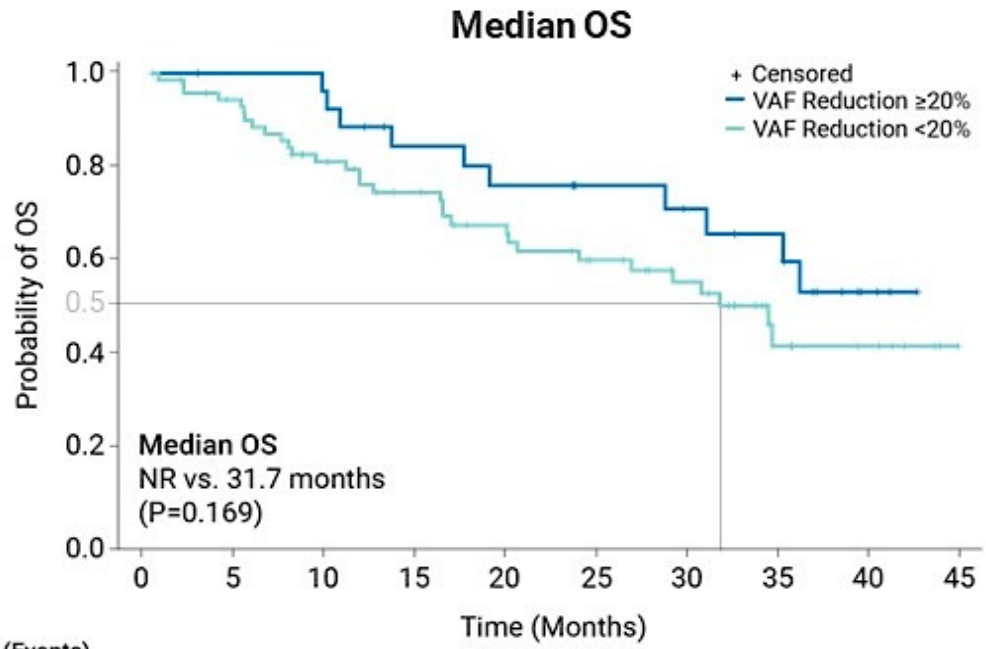


Navtemadlin in JAKi R/R MF some key biological results...
Driver Gene VAF Reduction Correlates with PFS and OS in All Cohorts

Driver Gene VAF Reduction*, ≥20% or <20%



# at risk (Events)										
VAF Reduction ≥20%	27 (0)	22 (2)	14 (6)	4 (8)	3 (8)	3 (8)	2 (9)	1 (9)	0 (0)	
VAF Reduction <20%	72 (0)	29 (10)	9 (17)	4 (19)	0 (21)					



# at risk (Events)										
VAF Reduction ≥20%	27 (0)	26 (0)	24 (2)	20 (4)	18 (6)	15 (6)	13 (7)	11 (8)	3 (10)	0 (10)
VAF Reduction <20%	72 (0)	63 (5)	50 (13)	43 (17)	35 (22)	28 (25)	22 (27)	9 (31)	6 (31)	0 (31)

n=99

Data cut-off: 06 Jan 2023.
All Cohorts, four dose schedules at either 120 mg QD or 240 mg QD.
*Patients with paired samples (baseline, week 12, week 24) n=99. Progression free survival defined as time from start of navtemadlin treatment until progression of disease by spleen progression, transformation to accelerated phase or leukemia, or death due to any cause.
Abbreviations: OS, Overall Survival; PFS, progression free survival; VAF, variant allele frequency.

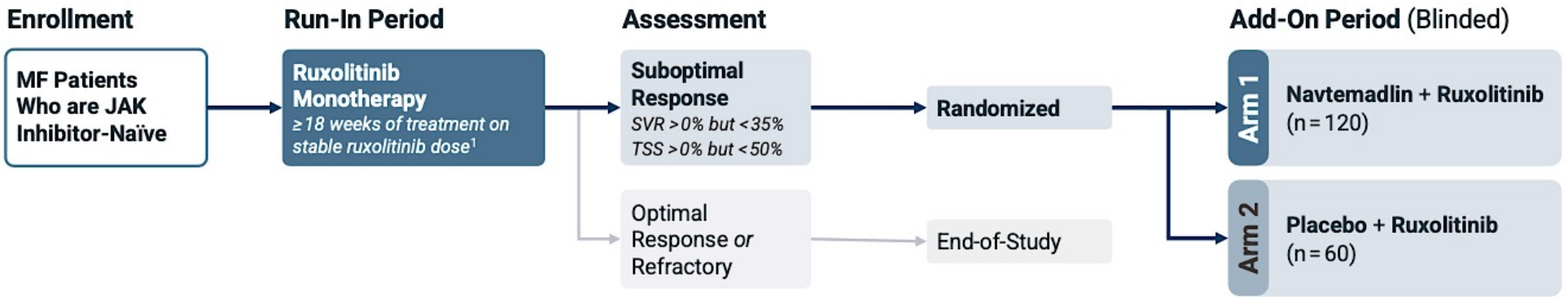
Vachhani P, et al. EHA 2023.

Currently open first line study:

Navtemadlin in Suboptimal Responders to Ruxolitinib

poiesis

A Phase 3 Randomized, Double-Blind, Add-On Study Evaluating the Safety and Efficacy of Navtemadlin and Ruxolitinib vs Placebo and Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis Who Have a Suboptimal Response to Ruxolitinib Treatment



Run-In Period (N = 600)

Key Inclusion Criteria

- Primary or secondary MF by WHO criteria
- Int-1, Int-2, or High-risk disease by IPSS
- Spleen volume ≥450 cm^3
- Platelet count ≥100 x 10^9/L

Add-On Period (N = 180)

Key Inclusion Criteria

- *TP53*^{WT} by central testing
- Treatment with a stable dose of ruxolitinib
- Suboptimal response to ruxolitinib run-in

Endpoints

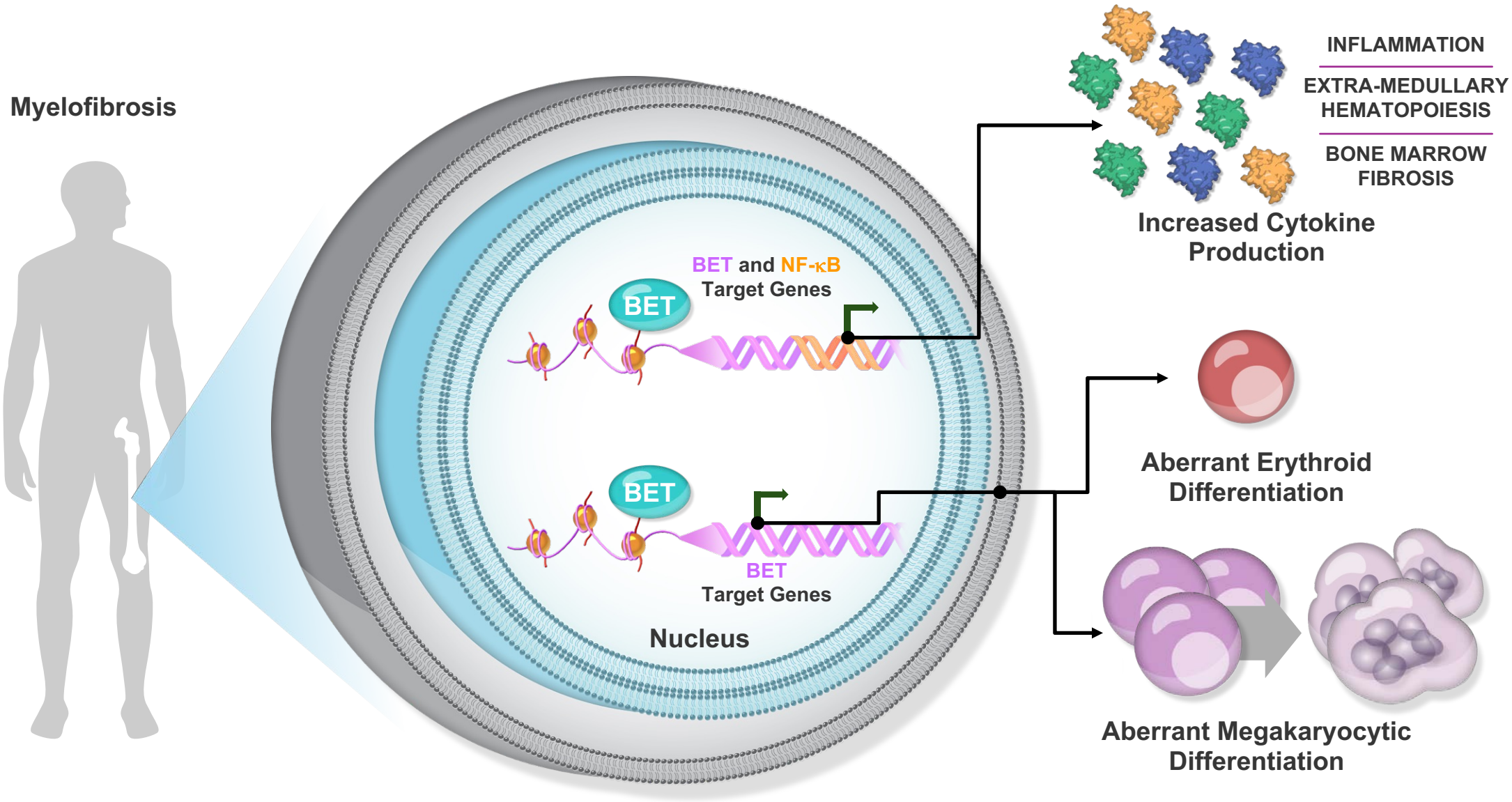
Co-Primary Endpoints

- Targeted SVR and TSS reduction 24 weeks after randomization

Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). Target enrollment from 220 sites across 19 countries.
[1]Stable ruxolitinib is ≥5 mg BID that does not require treatment hold or dose adjustment during the eight weeks prior to add-on navtemadlin or placebo.
Abbreviations: BID, twice daily; Int, intermediate; IPSS, International Prognostic Scoring System; JAK, Janus kinase; MF, myelofibrosis; TSS, total symptom score; WHO, World Health Organization; WT, wild-type.

Mascarenhas et al. ASH 2024;Abstract 1000

BET Proteins Promote Myelofibrosis



Pelabresib in combination with ruxolitinib for Janus kinase inhibitor-naive patients with myelofibrosis: 72-week follow-up with long-term efficacy outcomes of the Phase III MANIFEST-2 study

Alessandro M. Vannucchi,* Raajit K. Rampal, Dominik Chraniuk, Sebastian Grosicki, Elisabetta Abruzzese, Sung-Eun Lee, Alessandro Lucchesi, Aaron Gerds, Stephen T. Oh, Andrea Patriarca, Alberto Álvarez-Larrán, David Lavie, Vikas Gupta, Andrew T. Kuykendall, Prithviraj Bose, Moshe Talpaz, Francesca Palandri, Ruben Mesa, Jean-Jacques Kiladjian, Monika Wroclawska, Qing Li, Harald Maier, John Mascarenhas, Claire Harrison

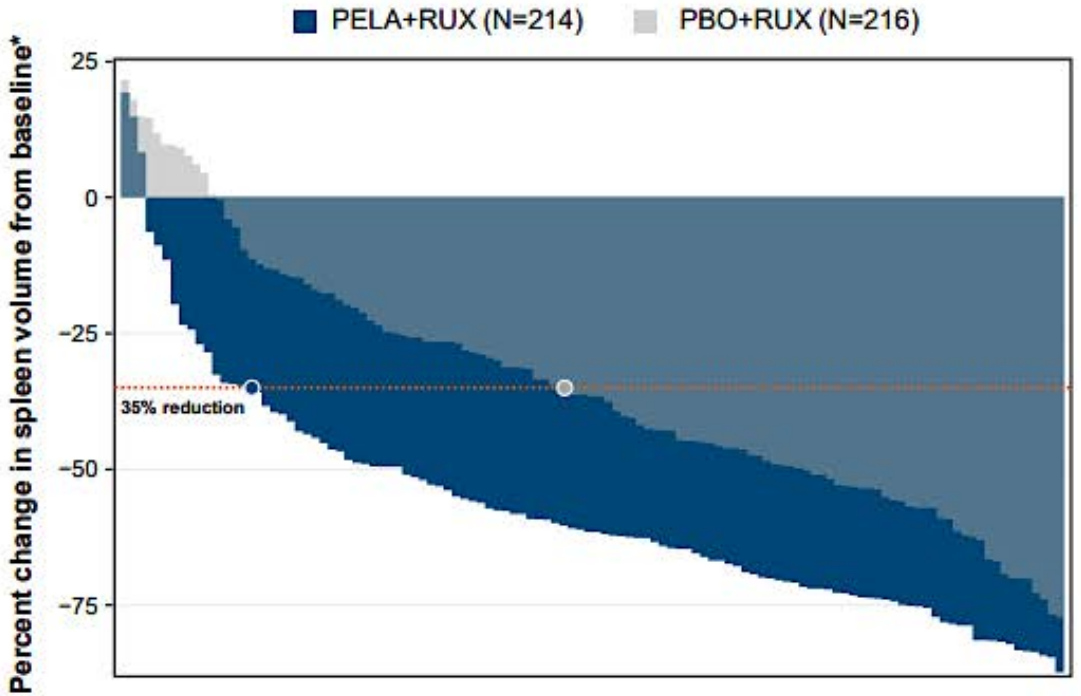
Durable efficacy and long-term safety with pelabresib plus ruxolitinib in JAK Inhibitor– Naive myelofibrosis: 96-week Results from the Phase III MANIFEST-2 study

Rampal R et al. ASH 2025;Abstract 910

As presented at EHA 2025;Abstract S223, **update at ASH 2025**

Splenic response rates continued to be greater at Week 72 with PELA+RUX versus PBO+RUX

Sustained improvements in spleen volume with PELA+RUX versus PBO+RUX at Week 72



ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at Week 72	46.3	29.2
Difference† (95% CI)	16.7 (7.9-25.4)	

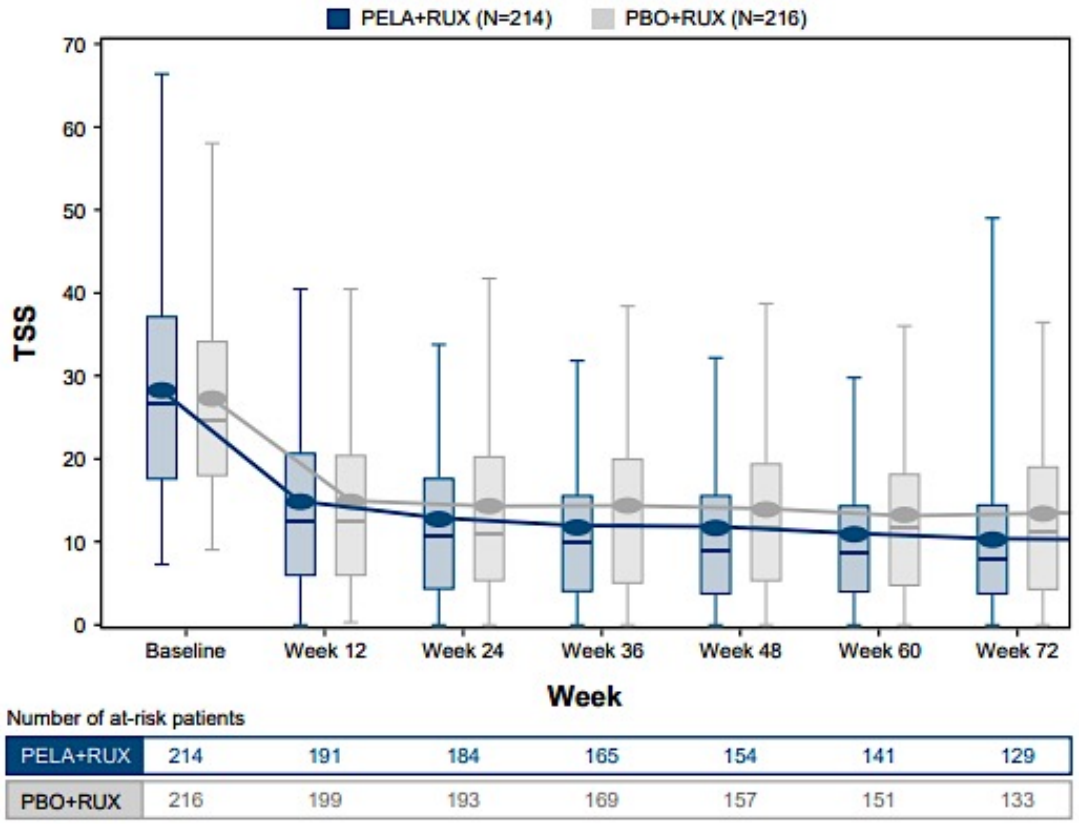
Mean % change in spleen volume at Week 72‡	−57.2 (n=114)	−34.9 (n=119)
95% CI	−61.0, −53.3	−39.0, −30.7

Data cutoff date: August 30, 2024.
Spleen volume assessed by central read.
*Waterfall plots represent patients who have baseline and Week 72 data. †Calculated by stratified Cochran-Mantel-Haenszel test. ‡Patients without Week 72 assessment are considered non-responders.
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline.

Oral S223 presented at: European Hematology Association (EHA) Annual Congress; June 12-15, 2025; Milan, Italy

Numerically greater improvements in TSS at Week 72 were observed in patients treated with PELA+RUX versus PBO+RUX

Sustained improvements in TSS with PELA+RUX versus PBO+RUX at Week 72



Number of at-risk patients

PELA+RUX	214	191	184	165	154	141	129
PBO+RUX	216	199	193	169	157	151	133

ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Absolute change in TSS* at Week 72, LSM	−15.42	−13.19
LSM difference (95% CI) at Week 72	−2.23 (−4.73, 0.27)	
TSS50 response at Week 72, %	42.1	35.2
Difference† (95% CI) at Week 72	6.3 (−2.6, 15.3)	

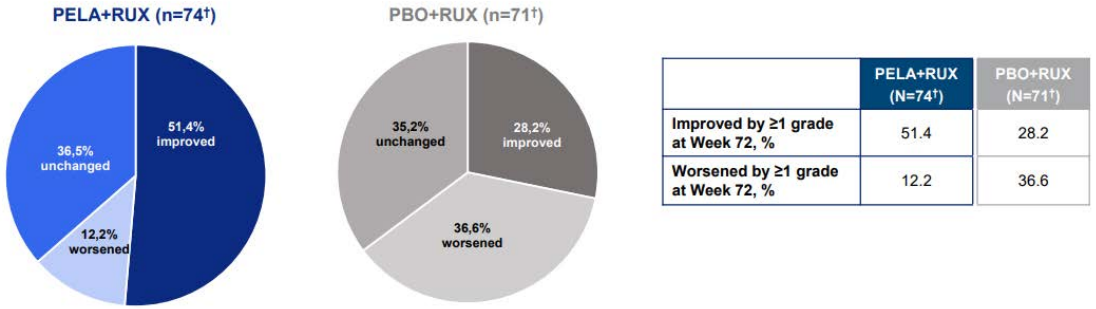
Data cutoff date: August 30, 2024.
Spleen volume assessed by central read.
*TSS assessed by MFSAF v4.0 and using an MMRM analysis of absolute change from baseline in TSS. †Difference in treatment groups analyzed by stratified Cochran-Mantel-Haenszel test (weighted 95% CI adjusted across strata).
CI, confidence interval; ITT, intent-to-treat; LSM, least squares mean; MFSAF, Myelofibrosis Symptom Assessment Form; MMRM, mixed model for repeated measures; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

Oral S223 presented at: European Hematology Association (EHA) Annual Congress; June 12-15, 2025; Milan, Italy

Other benefits

A greater proportion of patients had improvements in bone marrow fibrosis at Week 72 with PELA+RUX versus PBO+RUX

Improvement of reticulin fibrosis grade* with PELA+RUX versus PBO+RUX at Week 72

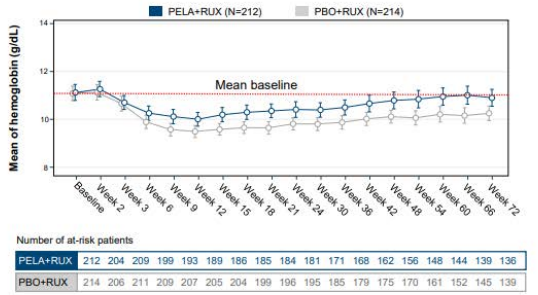


	PELA+RUX (N=74†)	PBO+RUX (N=71†)
Improved by ≥1 grade at Week 72, %	51.4	28.2
Worsened by ≥1 grade at Week 72, %	12.2	36.6

- BMF improvement of ≥1 grade in evaluable patients was reported in 51.4% versus 28.2% of patients in the PELA+RUX versus PBO+RUX arms, respectively, at Week 72 (difference: 25.33%; 95% CI: 9.77-40.88)

A numerically greater proportion of patients had a hemoglobin response, and fewer patients required RBC transfusions with PELA+RUX versus PBO+RUX

Hemoglobin levels in the PELA+RUX arm continued to rise, approaching baseline levels at Week 72 (safety population*)



ITT population

	PELA+RUX (N=214)	PBO+RUX (N=216)
Hemoglobin response,†‡ % (n/N) (95% CI)	**16.4** (35/214) (11.4-21.31)	**9.3** (20/216) (5.39-13.12)
Hemoglobin response,†‡ in patients with anemia (baseline <10 g/dL), % (n/n) (95% CI)	**20.9** (14/67) (11.16-30.63)	**16.9** (12/71) (8.18-25.62)

Fewer patients in the PELA+RUX arm versus the PBO+RUX arm required RBC transfusions§ over 72 weeks:

- Weeks 0 to 24: 24.1% (35/145) versus 36.4% (59/162)
- Weeks 25 to 48: 19.3% (28/145) versus 30.9% (50/162)
- Weeks 49 to 72: 19.3% (28/145) versus 25.3% (41/162)

Data cutoff date: August 30, 2024. *Safety population received ≥1 dose of study drug. †Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the prior 12 weeks in the ITT population. ‡Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. §RBC transfusions refer to number of patients who received any RBC transfusion during the first 24 weeks after Cycle 1 Day 1; during the 25-48 weeks after Cycle 1 Day 1 or during the 49-72 weeks after Cycle 1 Day.
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RBC, red blood cell; RUX, ruxolitinib.

Oral S223 presented at: European Hematology Association (EHA) Annual Congress; June 12-15, 2025; Milan, Italy

Updates on accelerated phase and leukemia

Leukemic transformation

Accelerated- and blast-phase progression*

	PELA+RUX			PBO+RUX		
	Accelerated and blast phase*	Accelerated phase	Blast phase	Accelerated and blast phase*	Accelerated phase	Blast phase
As of March 29, 2024, (Week 48) data cutoff, % (n/N)†,‡	**6.1** (13/213)	**0.9** (2/213)	**5.2** (11/213)	**2.3** (5/214)	**1.4** (3/214)	**0.9** (2/214)
As of August 30, 2024, (Week 72) data cutoff, % (n/N)§,¶	**6.1** (13/214)	**0.9** (2/214)	**5.1** (11/214)	**4.2** (9/214)	**1.4** (3/214)	**2.8** (6/214)

- As of August 30, 2024, accelerated- and blast-phase progression, adjudicated independently by external experts, was reported in 6.1% (13/214) of patients on PELA+RUX and in 4.2% (9/214) of patients on PBO+RUX

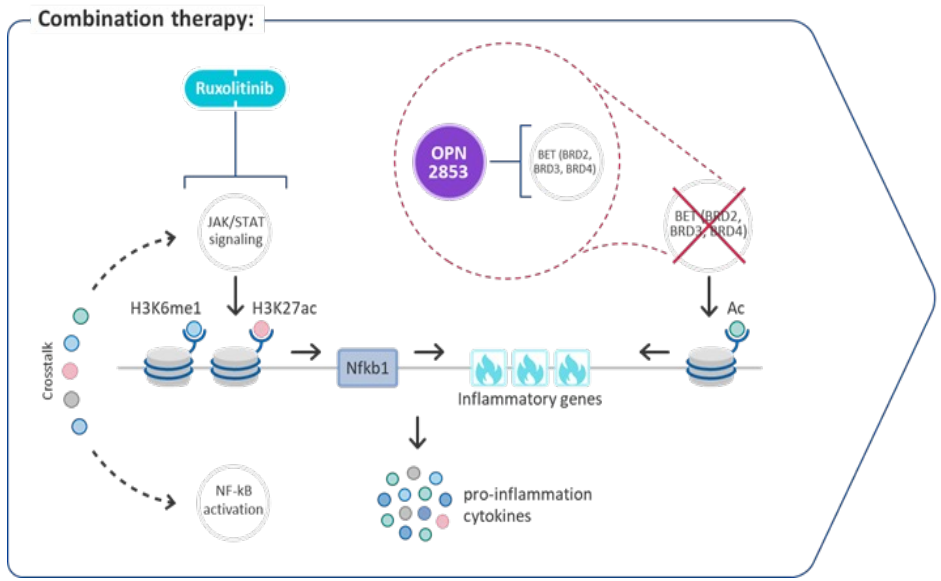
- An early imbalance in cases of leukemic transformation was observed with PELA+RUX compared with PBO+RUX. Over time, the imbalance in proportion of patients with transformation to blast phase decreased. Overall, the observed frequency was in line with what is typically seen in MF

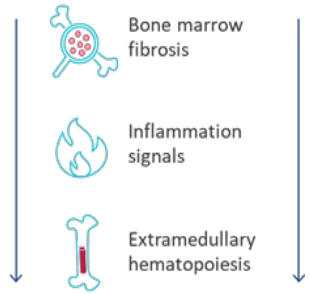
*Assessment based on local laboratory results, adverse events, and documented disease progression. Leukemic transformation confirmed by a bone marrow blast count of ≥20% or a peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10^9/L that lasts for at least 2 weeks. †Minimum of 48 weeks of leukemia-free survival follow-up; median follow-up 17.1 months. ‡The denominator of 213 includes 1 patient who crossed over from placebo + ruxolitinib. §Minimum of 72 weeks of leukemia-free survival follow-up. The last adjudication in March 2025, with the cutoff as of August 30, 2024, showed a ratio of 11:6. ¶The denominator of 214 for PELA+RUX includes 2 patients who crossed over from PBO+RUX. MF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib.

Oral S223 presented at: European Hematology Association (EHA) Annual Congress; June 12-15, 2025; Milan, Italy

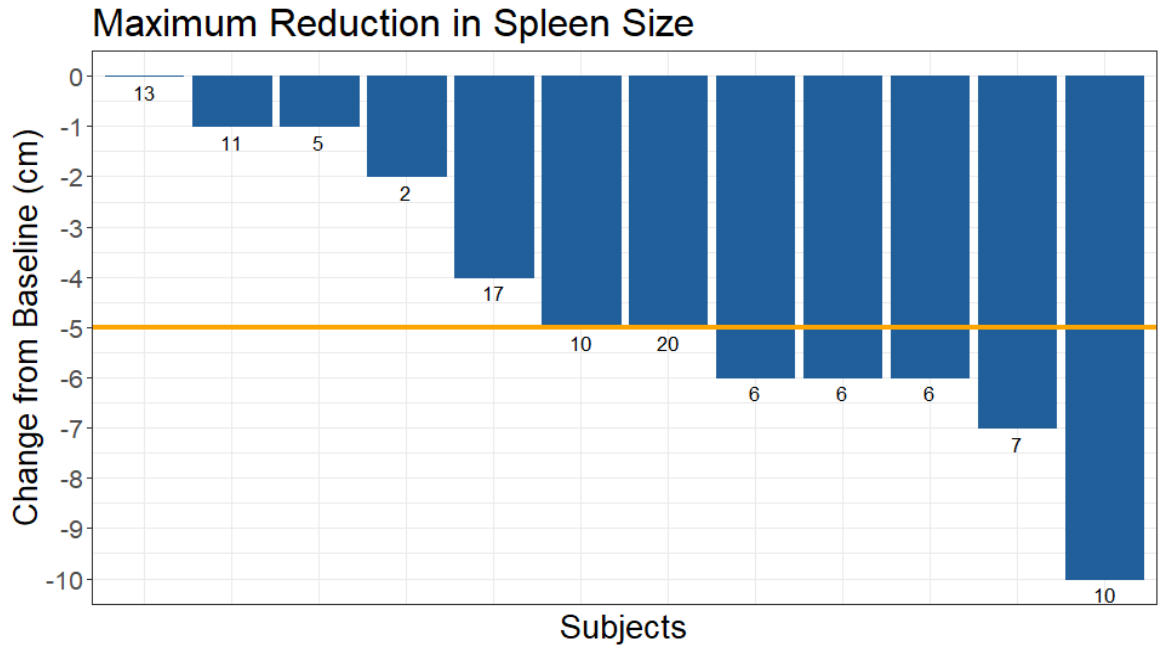
BET Inhibitor OPN-2853: Phase I PROMise Study

OPN-2853 Mechanism of Action





Spleen Length Reduction



*Numbers on the bar indicate patients' spleen size at baseline.

Interim analysis of PROMise, a clinical study combining the BET inhibitor OPN-2853 with ruxolitinib in patients with advanced myelofibrosis experiencing an inadequate response to ruxolitinib
Mead A et al. ASH 2025;Abstract 3794

Mead A et al. ASH 2024;Abstract 3186

Mutant targeted therapies currently being tested:

Vaccine study
mutCALR and JAK2V617F neoepitopes
(negative and closed)

Incyte inhibitory mut-CALR antibody
(ASH/ICML 2023)

Anti-mutCALR bispecific antibodies

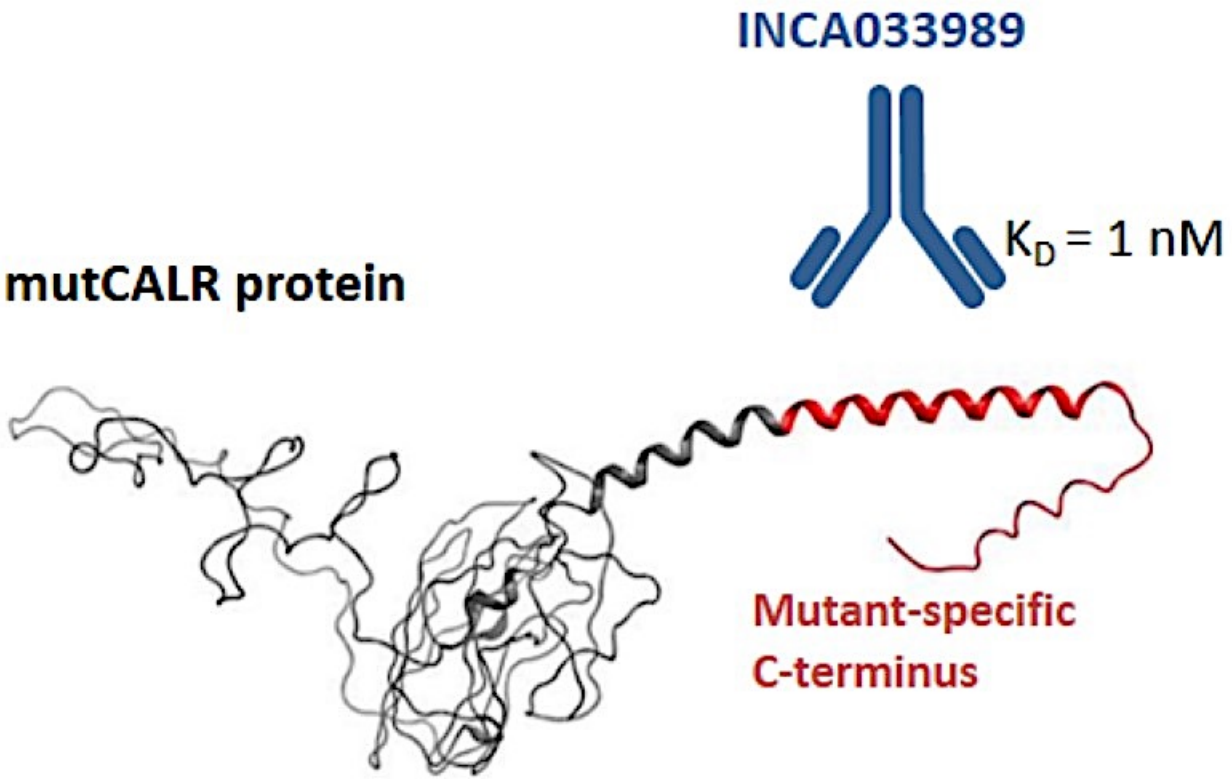
Mut CALR targeting CAR-T
(presented at EHA 2024 (Rampotas et al) not yet in active trials)

Mutant-specific C-terminus

***JAK2* V617F specific kinase inhibition also entered clinical testing in 2024**

INCA033989: a mutCALR-specific monoclonal antibody

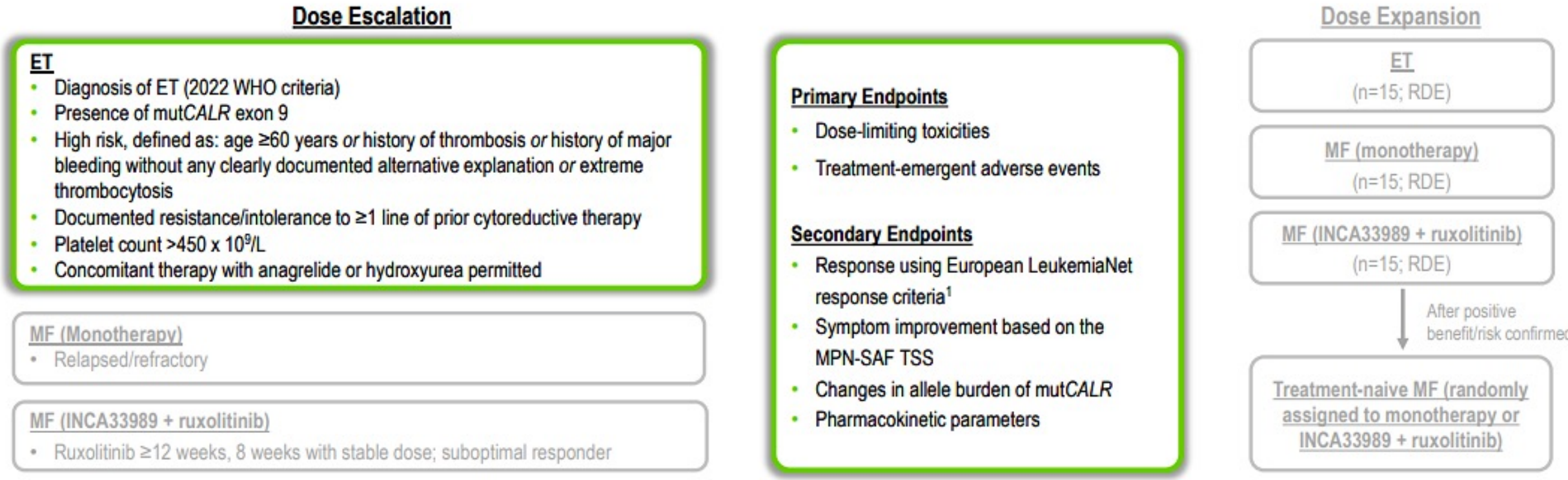
- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function



Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).

IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

Study Design: INCA33989-101 and INCA33989-102



- **INCA33989-101** (NCT05936359; outside the US) and **INCA33989-102** (NCT06034002; US only) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA33989 in patients harboring a *CALR* exon-9 mutation with high-risk ET or MF (as monotherapy or in combination with ruxolitinib)
- INCA33989 is administered intravenously every 2 weeks

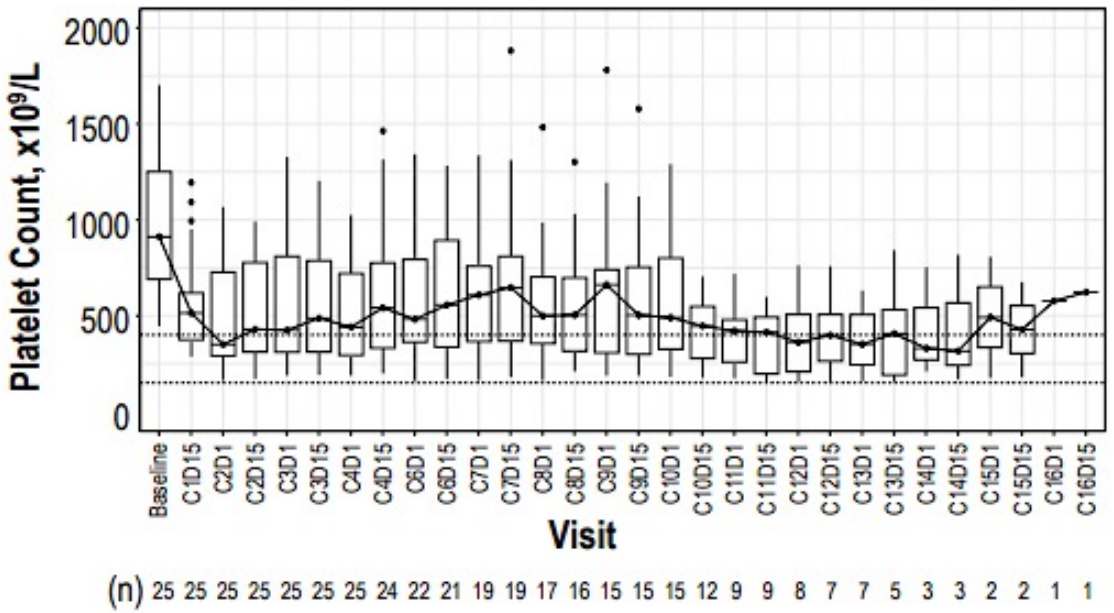
1. Barosi et al. *Blood*. 2013;23:4778-4781.

CALR, calreticulin; ET, essential thrombocythemia; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mut*CALR*, mutations of calreticulin; RDE, recommended dose for expansion; TSS, total symptom score.

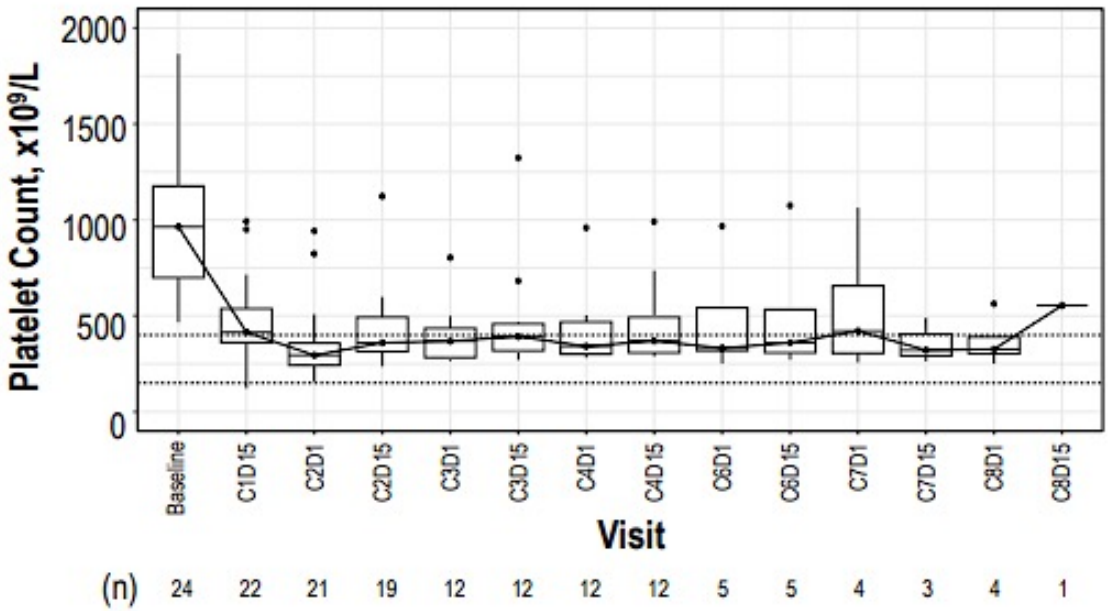
Mascarenhas J et al. EHA 2025;Abstract LBA4002

Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

Doses 24-250 mg*



Doses 400-2500 mg†



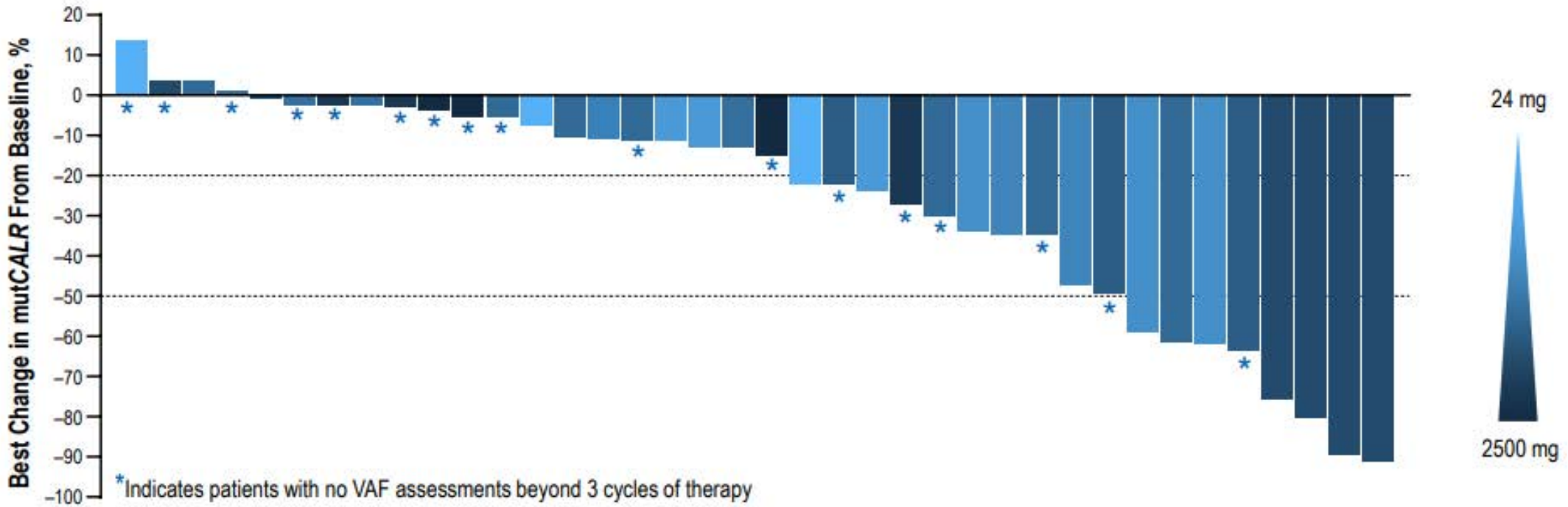
- Of the 31 patients that enrolled with concomitant cytoreductive therapy (hydroxyurea or anagrelide), 20 (65%) discontinued it and remained on study
- Thrombocytopenia was not observed in any patient
- Doses of ≥400 mg produced higher frequency of platelet count normalization

Dotted lines indicate upper and lower limit of normal. Boxes denote the first and third quartiles, lines represent the median. Number of patients with available data at each visit is noted below the x axis.
*24 mg (n=3), 50 mg (n=3), 70 mg (n=3), 100 mg (n=3), 200 mg (n=5), 250 mg (n=8). †400 mg (n=5), 750 mg (n=9), 1500 mg (n=6), 2500 mg (n=4). C, cycle; D, day.

Mascarenhas J et al. EHA 2025;Abstract LBA4002

Molecular Responses Are Rapid and Frequent

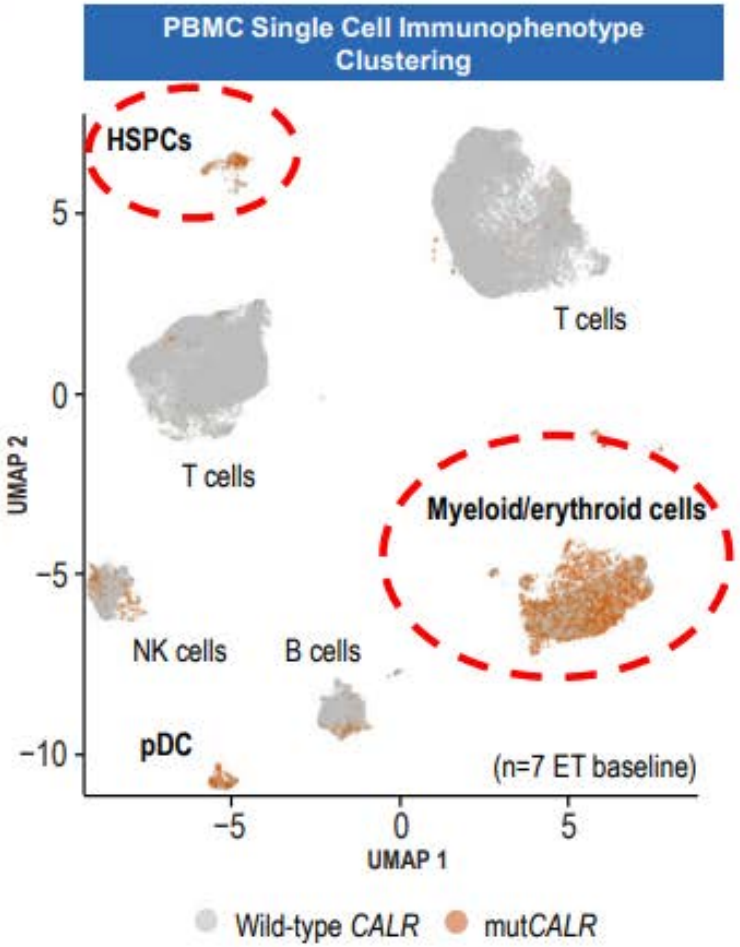
- A reduction in mut*CALR* VAF from baseline occurred in 34/38 (89%) evaluable patients
  - 18/38 (47%) achieved >20% best reduction in VAF
  - 8/38 (21%) achieved >50% best reduction in VAF
- A reduction of ≥20% VAF occurred within 6 cycles of therapy for all 18 responders
- All 18 molecular responders achieved a hematological response of CR or PR

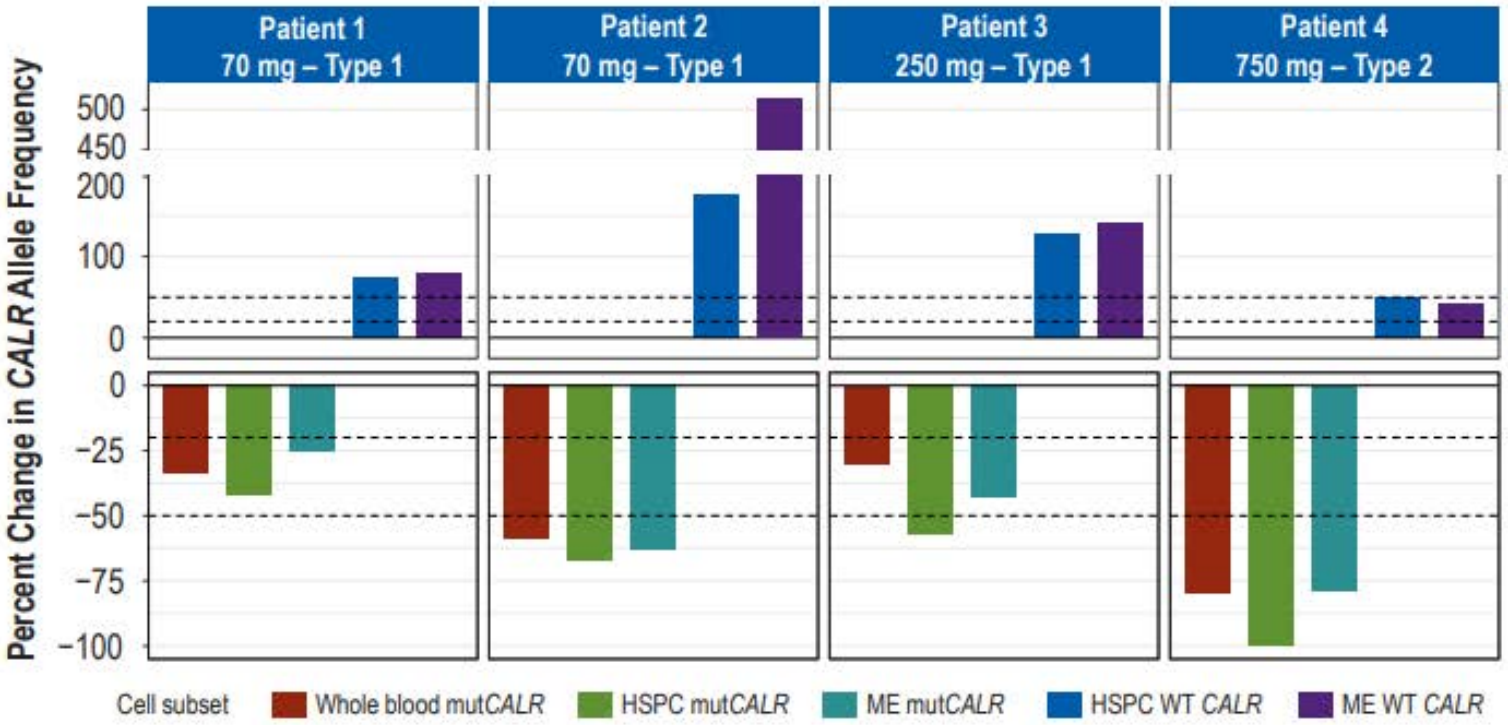


Dotted lines represent 20% and 50% VAF thresholds. 1 cycle = 28 days or 2 doses. CR, complete response; mut*CALR*, mutations in calreticulin; PR, partial response; VAF, variant allele frequency.

Mascarenhas J et al. EHA 2025;Abstract LBA4002

Reduction of mut*CALR*$^{+}$ HSPCs and Myeloid/Erythroid Cells in Clinical Responders



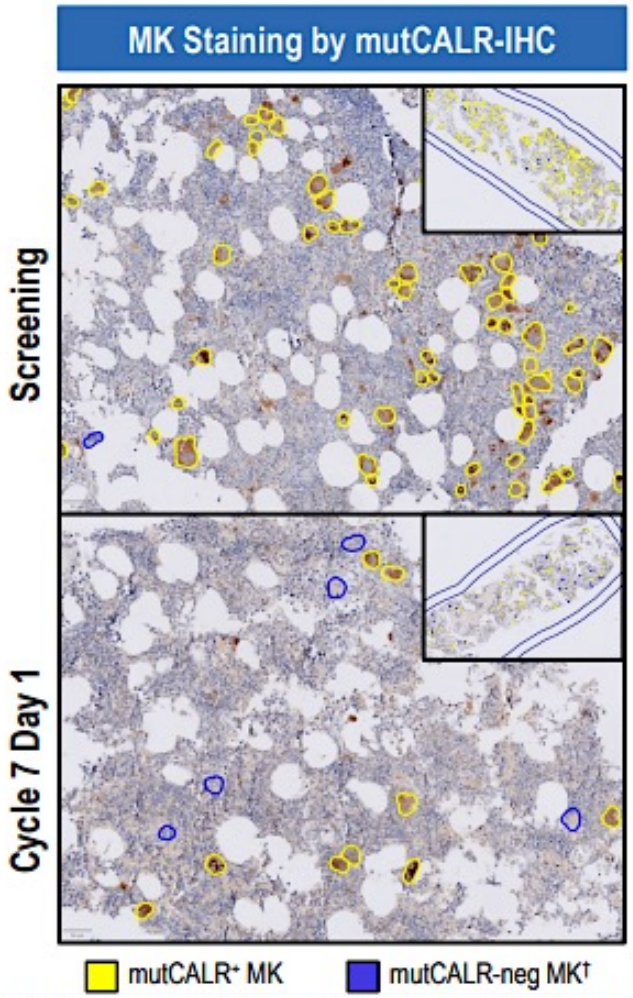


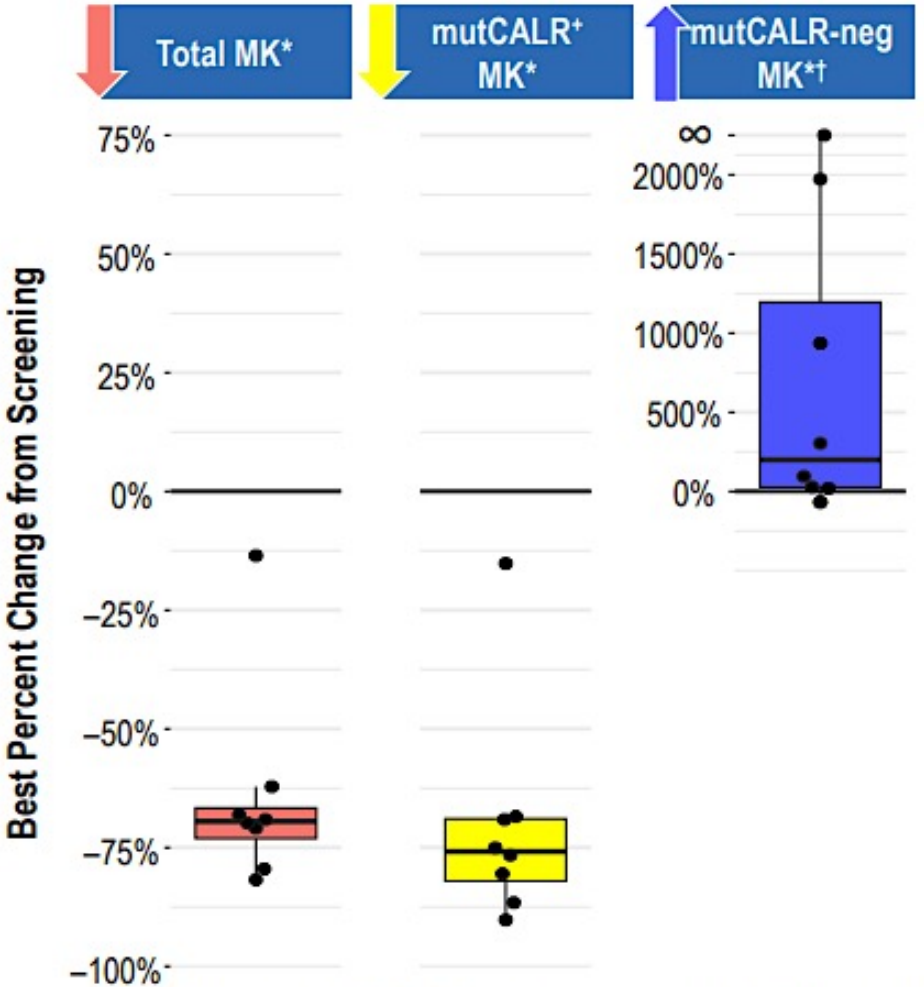
- Reduction of mut*CALR* VAF in HSPCs is deeper than in whole blood VAF
- Reduction of mutant populations (HSPC and ME) is accompanied by significant increases in *CALR* WT cell fractions indicating a shift to normal hematopoiesis

Single-cell sequencing (Tapestri™) conducted on PBMCs collected at C1D1 and C4D1. Cells were clustered and visualized using a UMAP based on cell surface expression of 46 proteins.
CALR, calreticulin; ET, essential thrombocythemia; HSPCs, hematopoietic stem/progenitor cells; ME, myeloid/erythroid; mut*CALR*, mutations in calreticulin; NK, natural killer; PBMC, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cells; scDNA, single-cell deoxyribonucleic acid; UMAP, Uniform Manifold Approximation and Projection; WT, wild-type; VAF, variant allele frequency.

Mascarenhas J et al. EHA 2025;Abstract LBA4002

Reduction in mutCALR⁺ Megakaryocytes in the Bone Marrow of Clinical Responders





In 8 patients with hematologic response after 6 cycles of treatment:

- Total number of megakaryocytes (MK) decreased
- Fraction of mutCALR⁺ MKs decreased
- Fraction of mutCALR negative MKs increased

*Best % change in total, mutCALR⁺, or mutCALR-neg MKs in hematologic responders with available data (n=8), dose range 24 mg-250 mg. †Undetectable mutCALR protein by IHC. Bone marrow biopsies stained for mutCALR using mutant-specific IHC. MKs quantified by semi-automated pathology scoring. CALR, calreticulin; IHC, immunohistochemistry; MK, megakaryocytes; mutCALR, mutations in

Mascarenhas J et al. EHA 2025;Abstract LBA4002

JAK2V617F-selective and Type II JAK2 Inhibitors

	INCB160058	AJ1-10502 / AJ1-11095
Inhibitor type	**JAK2V617F-selective inhibitor**	**Type II JAK2 Inhibitor**
Binding mechanism	Binds to the pseudokinase domain, inhibiting TPOR dimerization[1]	Binds to the ATP-binding pocket of kinase domains in inactive conformation[2]
Selectivity	Selective to JAK2V617F[1,3]	Type II JAK2-selective[4]
Preclinical data	• Inhibited JAK2V617F-induced TPOR dimerization[1] • Selectively reduced human JAK2V617F cell engraftment • Normalized pathogenic cytokine levels	• Reduced blood counts, splenomegaly, and mutant allele burden[4] • Type II JAK2i CHZ868 reversed Type I JAKi persistence in vitro[5]
Clinical trial status	Phase 1, recruiting[6]	Phase 1, not yet recruiting[7] (AJ1-11095)

? In phase 1 trials but

No clinical data in the public domain

Binding Locations of JAK2 Inhibitors

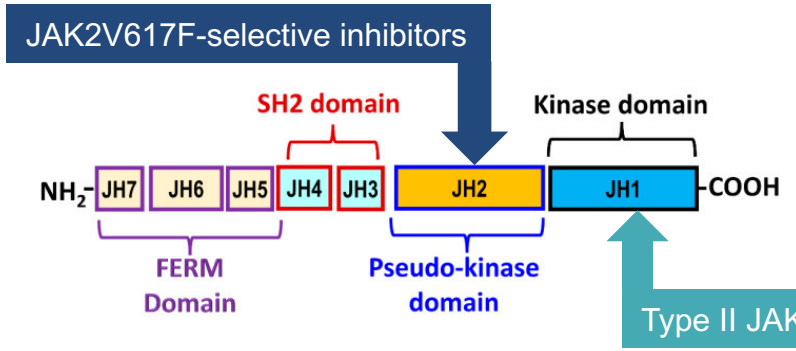


Image adapted from Shwaky AM et al. *Pharmaceutics*. 2022;14:1001.

1. Stubbs MC, et al. ASH 2023. Oral Presentation 860. 2. Shwaky AM et al. *Pharmaceutics*. 2022;14:1001. 3. Nair PC et al. *Blood Cancer Discov*. 2023; 4:352-64.
4. Rai S, et al. ASH2022. Poster Presentation 2992. 5. Meyer, et al. *Cancer Cell.* 2015;28:15-28. 6. ClinicalTrials.gov. Accessed Jul 2024. https://clinicaltrials.gov/study/NCT06313593.
7. ClinicalTrials.gov. Accessed Jul 2024. https://clinicaltrials.gov/study/NCT06343805.

Abstracts at ASH 2025 to watch out for…

AJ1-11095, a potent and highly selective type-II JAK2 inhibitor, shows enhanced therapeutic efficacy as compared with type-I JAK2 inhibitor ruxolitinib in models of myeloproliferative neoplasms (MPNs)
Dunbar A et al. ASH 2025;Abstract 1983

A multicenter, open-label phase 1 study of INCB160058, a first-in-class JAK2V617F mutant– selective inhibitor, in patients with myelofibrosis, polycythemia vera, or essential thrombocythemia
Gotlib J et al. ASH 2025;Abstract 2051

Safety and efficacy of the mutant calreticulin-specific monoclonal antibody INCA033989 as monotherapy or in combination with ruxolitinib in patients (pts) with myelofibrosis (MF): Preliminary results from dose escalation of two global Phase 1 studies
Mascarenhas J et al. ASH 2025;Abstract 484

Molecular characterization of patients (pts) with myeloproliferative neoplasms treated with INCA033989 demonstrates selective targeting of CALR mutant hematopoietic cells
Psaila B et al. ASH 2025;Abstract 71

Dr Laura Michaelis
(Milwaukee, Wisconsin)

Case Presentation: 78-year-old woman with primary MF (CALR1 and SF3B1 mutations) and anemia receives luspatercept

Dr Prithviraj Bose
(Houston,Texas)

Current role of luspatercept for patients with MF-associated anemia

QUESTIONS FOR THE FACULTY

How would you likely have managed this patient's care?

In what situations, if any, do you combine a JAK inhibitor with luspatercept?

How do you dose-escalate luspatercept for patients with MF? When do you discontinue treatment?

What are your thoughts about the emerging results from the Phase III INDEPENDENCE trial?

Promising novel therapies under development for MF

Dr John Mascarenhas (New York, New York)

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

What are your thoughts about the future role of the following in MF?

- **Pelabresib**
- **Selinexor**
- **Navtemadlin**
- **Imetelstat**
- **Mutant CALR-directed monoclonal and bispecific antibodies**

Agenda

Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Palmer

Module 2: Managing MF in Patients with Anemia — Dr Oh

Module 3: Managing MF in Patients with Thrombocytopenia — Dr Rampal

Module 4: Promising Novel Agents Under Investigation for MF — Prof Harrison

Module 5: Current and Future Management of Systemic Mastocytosis — Dr Kuykendall

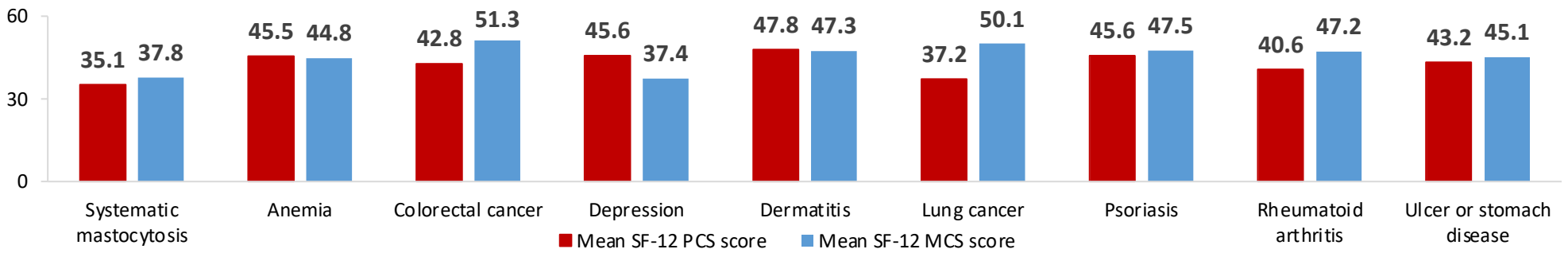
Current and Future Management of Systemic Mastocytosis

Andrew Kuykendall, MD
Associate Member
Moffitt Cancer Center
Tampa, Florida

Systemic Mastocytosis: Challenges and Opportunities

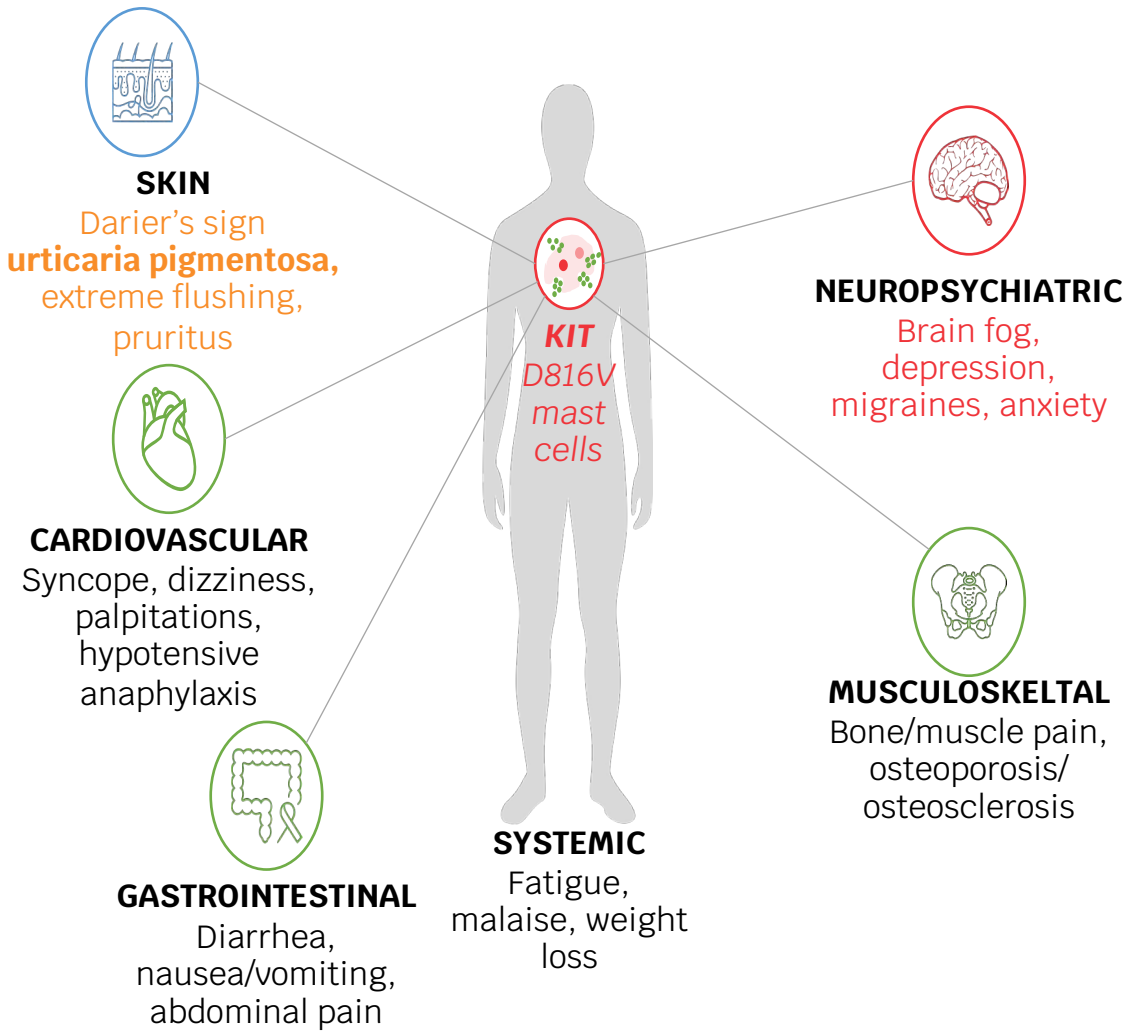
- The diagnosis of SM is often **delayed** due to non-specific symptoms, protracted time-course from initial symptom evaluation to referral to hematology/oncology.
- **Misdiagnosis and incorrect classification** is common
- Often complicated by **co-existing Hematologic neoplasms**
- Patients have a **high symptom burden** with **poor quality of life and shortened survival**
- **~ 95% of patients** have a gain of function mutation in KIT, a receptor tyrosine kinase, stem cell factor
  FDA approved targeted therapy is available

QOL by SF-12 in SM comparatively[2]



1. Mukherjee et. al. Evaluation of Survival Among Patients With Indolent Systemic Mastocytosis: A Population-Level Retrospective Cohort Analysis Using Healthcare Claims Dataset. ASH 2023 Oral Presentation;Abstract 75.
2. Mesa et. al. Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey. Cancer. 2022 Oct;128(20):3691-3699. doi: 10.1002/cncr.34420. Epub 2022 Aug 23.

Presentation and Diagnosis



Diagnosis of SM by WHO criteria requires **major and ≥1 minor criterion OR ≥3 minor criteria**

MAJOR CRITERION

- Multifocal dense mast cell infiltrates (≥15 mast cells in aggregates) are detected in sections of bone marrow and/or sections of other extracutaneous organ(s)

MINOR CRITERIA

- In bone marrow biopsy sections or biopsy sections from other extracutaneous organs, >25% of the mast cells in the infiltrate appear spindle-shaped or have atypical morphologic features; or >25% of all mast cells in bone marrow aspirate smears are immature or have atypical features
- Presence of an activating point mutation in *KIT* at codon 816 in bone marrow, blood, or another extracutaneous organ (any detectable level is significant)
- Mast cells in bone marrow, blood, or other extracutaneous organs express CD25 ± expression of CD2 in addition to normal mast cell markers*
- Serum total tryptase persistently >20 ng/mL (if the patient has an associated myeloid neoplasm, this parameter is not valid)

*CD25 is the more sensitive marker by flow cytometry or immunohistochemistry.

CD, cluster of differentiation; KIT, KIT proto-oncogene, receptor tyrosine kinase; WHO, World Health Organization. Pardanani A. Am J Hematol. 2019;94(3):363-377.

Castellas M et al. AAAAI 2023

How could people possibly get confused?

Variants and subvariants (abbreviations)	Classification proposed by			
	EU/US 2021	WHO 2021	ICC 2021	H-2024 *
Cutaneous mastocytosis (CM)	CM	CM	CM	CM
Nonadvanced systemic mastocytosis (non-AdvSM)				
Bone marrow mastocytosis (BMM)	BMM	BMM	— †	BMM
Indolent SM (ISM)	ISM	ISM	ISM (BMM) †	ISM
Smoldering SM (SSM)	SSM	SSM	SSM	SSM
Advanced SM (AdvSM)				
Aggressive SM (ASM)	ASM	ASM	ASM	ASM
SM with an associated hematologic (myeloid or lymphoid) neoplasm (SM-AHN)	SM-AHN	SM-AHN	SM-AMN	SM-AHN: SM-AMN SM-ALN
Mast cell leukemia (MCL)	MCL	MCL	MCL	MCL
Mast cell sarcoma (MCS)	MCS	MCS	MCS	MCS
Extracutaneous mastocytoma (ECM) ‡	—	—	—	ECM

Valent et al. Harmonization of Diagnostic Criteria in Mastocytosis for Use in Clinical Practice: WHO vs ICC vs AIM/ECNM, JACI In Practice, 2024.

How could people possibly get confused (continued)?

Variants and subvariants (abbreviations)	Classification proposed by			
	EU/US 2021	WHO 2021	ICC 2021	H-2024 *
Cutaneous mastocytosis (CM)	CM	CM	CM	CM
Nonadvanced systemic mastocytosis (non-AdvSM)				
Bone marrow mastocytosis (BMM)	BMM	BMM	— †	BMM
Indolent SM (ISM)	ISM	ISM	ISM (BMM) †	ISM
Smoldering SM (SSM)	SSM	SSM	SSM	SSM
Advanced SM (AdvSM)				
Aggressive SM (ASM)	ASM	ASM	ASM	ASM
SM with an associated hematologic (myeloid or lymphoid) neoplasm (SM-AHN)	SM-AHN	SM-AHN	SM-AMN	SM-AHN: SM-AMN SM-ALN
Mast cell leukemia (MCL)	MCL	MCL	MCL	MCL
Mast cell sarcoma (MCS)	MCS	MCS	MCS	MCS
Extracutaneous mastocytoma (ECM) ‡	—	—	—	ECM

Variants and subvariants of CM (abbreviations)	Classification proposed by			
	EU/US 2021	WHO 2021	ICC 2021	H-2024
Cutaneous mastocytosis (CM)	CM	CM	CM	CM
Maculopapular CM (MPCM)	MPCM	MPCM	MPCM	MPCM
Monomorphic MPCM (MPCM-m) *	MPCM-m	MPCM-m	—	MPCM-m
Polymporphic MPCM (MPCM-p) *	MPCM-p	MPCM-p	—	MPCM-p
Diffuse CM (DCM)	DCM	DCM	DCM	DCM
Cutaneous mastocytoma (CUTM)	+	+	—	CUTM †
Isolated (cutaneous) mastocytoma	+	+	—	CUTM1 †
Multilocalized (cutaneous) mastocytoma	+	+	—	CUTM2/3 †

Variant	Definition of variant
SM-AMN	SM criteria by WHO and/or ICC are fulfilled
	WHO or ICC criteria for an AMN-type disease are fulfilled
	Confirming observation *: The SM cells and the AMN cells express the same somatic lesion(s)
SM-ALN	SM criteria by WHO and/or ICC are fulfilled
	WHO or ICC criteria for an ALN-type disease are fulfilled
	Confirming observation *: The SM cells and the ALN cells express the same somatic lesion(s)

Valent et al. Harmonization of Diagnostic Criteria in Mastocytosis for Use in Clinical Practice: WHO vs ICC vs AIM/ECNM, JACI In Practice, 2024.

How could people possibly get confused (continued)?

Proposed Harmonized B Findings

High burden of MCs:
Infiltration grade of MCs in BM sections is ≥30% and/or
Serum tryptase ≥200 ng/mL * and/or
KIT D816V VAF is ≥10% in BM or PB leukocytes
Signs of myeloproliferation and/or myelodysplasia † :
Hypercellular BM with loss of fat cells and prominent myelopoiesis and/or
Myelodysplasia in <10% of cells (neutrophils, erythrocytes, megakaryocytes) and/or
Cytosis or cytopenia neither meeting criteria of an AHN nor criteria of C-Findings
Organomegaly:
Persistent hepatomegaly that is palpable or imaging-based (ULS or CT) without ascites or other signs of organ damage or/and
Persistent splenomegaly that is palpable or imaging-based (ULS or CT) without hypersplenism and without weight loss or/and
Persistent lymphadenopathy that is palpable or shows clearly enlarged lymph nodes in ULS or CT studies (>2 cm) or shows multiple (>3) enlarged lymph nodes (>1 cm).
These lymph nodes should be described as pathologic (SM-related) and not reactive by either ULS/CT or by histopathologic assessment of lymph nodes

Proposed Harmonized C Findings

PB cytopenia(s):
ANC < 1×10^9 /L
Hb < 10 g/dL
PLT < 100×10^9 /L
(1 or more found)
Hepatopathy:
Elevated liver enzymes and/or ascites †
± hepatomegaly or cirrhotic liver
± portal hypertension
Spleen:
Palpable splenomegaly with hypersplenism
± weight loss
± hypoalbuminemia
GI tract:
Malabsorption with hypoalbuminemia
± weight loss
Bone:
Large-sized osteolysis (≥2 cm)
with pathologic fracture or a high risk to develop such fracture
± bone pain

Valent et al. Harmonization of Diagnostic Criteria in Mastocytosis for Use in Clinical Practice: WHO vs ICC vs AIM/ECNM, JACI In Practice, 2024.

Systemic Mastocytosis is Driven by the KIT D816V Mutation

The KIT D816V mutation is present in ~95% of patients with systemic mastocytosis and is an underlying driver of disease[1]

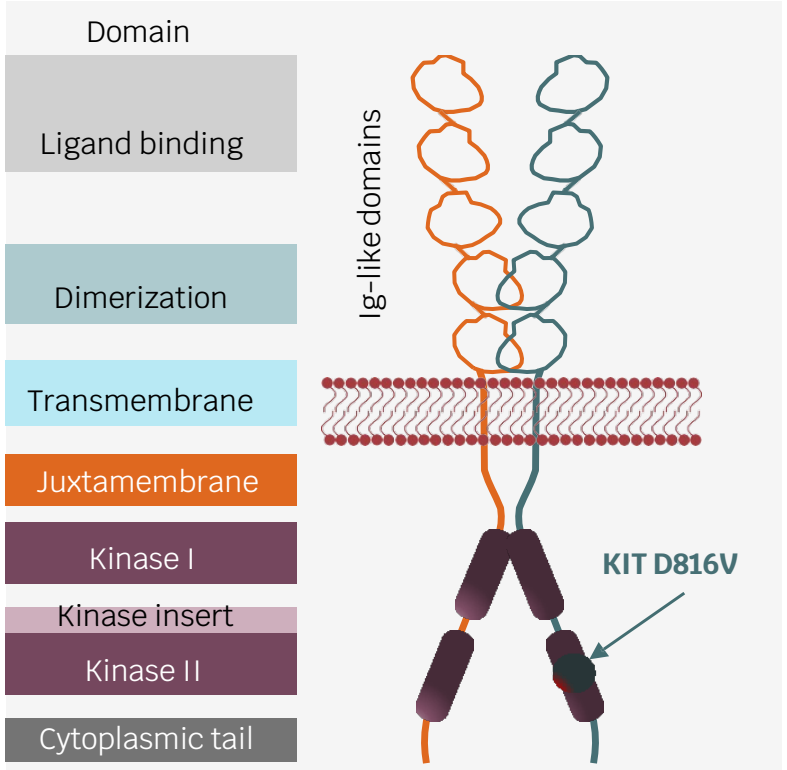
The D816V mutation causes structural changes that result in constitutive activation of the transmembrane tyrosine kinase KIT[2]

Multiple additional mutations are often present and may negatively impact prognosis

Mast cells harboring the KIT D816V mutation have constitutive KIT activation/signaling resulting in uncontrolled mast cell proliferation and activation[3,4]

The mutation is inconsistently present in the cells comprising the AHN component

Position of D816V mutation[3]



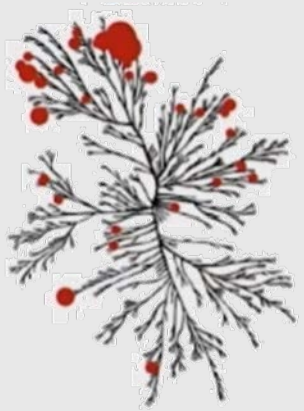
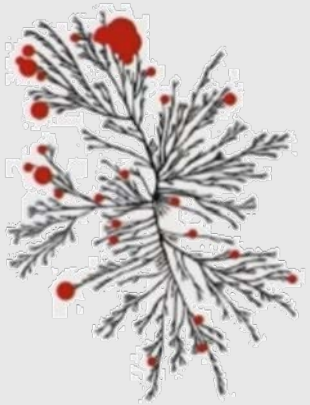
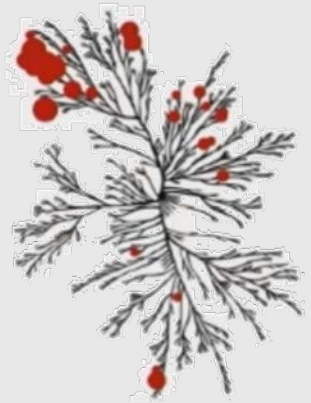
High-sensitivity KIT testing is critical in diagnosing Systemic Mastocytosis

Ig, immunoglobulin; KIT, KIT proto-oncogene, receptor tyrosine kinase.

1. Garcia-Manero AC et al. Blood. 2006;108(7):2366-2372. 2.Laine E et al. PLoS Comput Biol. 2011;6:e1002068. 3. Cruse G et al. Immunol Allergy Clin North Am. 2014;34(2):219-237.
4. Theoharides TC et al. N Engl J Med. 2015;373(2):163-172.

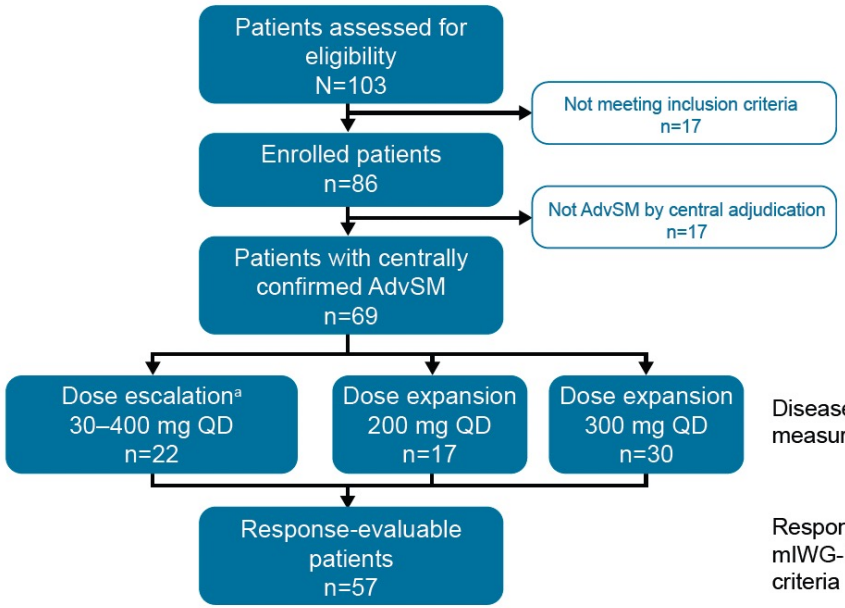
Available and Upcoming Therapies for Systemic Mastocytosis

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

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

Tashi et al. *Elenestinib, an Investigational, Next Generation KIT D816V Inhibitor, Reduces Mast Cell Burden, Improves Symptoms, and Has a Favorable Safety Profile in Patients with Indolent Systemic Mastocytosis: Analysis of the HARBOR Trial. ASH 2023;Abstract 76.*

Avapritinib for Patients with Systemic Mastocytosis: Phase I EXPLORER



[a]Patients in the dose escalation group received 30 mg (n=3), 60 mg (n=4), 100 mg (n=1), 130 mg (n=1), 200 mg (n=3), 300 mg (n=4), or 400 mg (n=6).
AdvSM, advanced systemic mastocytosis; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis; OS, overall survival; QD, once-daily.

Outcome, n (%)	All patients[a] (n=57)	ASM (n=4)	SM-AHN (n=40)	MCL (n=13)	Treament-naïve (n=22)	≥1 prior systemic therapy (n=35)
ORR,[b] n (%) [95% CI]	44 (77) [64–87]	4 (100) [40–100]	29 (73) [56–85]	11 (85) [55–98]	18 (82) [60–95]	26 (74) [57–88]
CR	12 (21)	2 (50)	6 (15)	4 (31)	5 (23)	7 (20)
CRh	11 (19)	1 (25)	9 (23)	1 (8)	6 (27)	5 (14)
PR	19 (33)	1 (25)	14 (35)	4 (31)	6 (27)	13 (37)
CI	2 (4)	0	0	2 (15)	1 (5)	1 (3)
SD	12 (21)	0	10 (25)	2 (15)	4 (18)	8 (23)
PD	0	0	0	0	0	0
NE	1 (2)	0	1 (3)	0	0	1 (3)

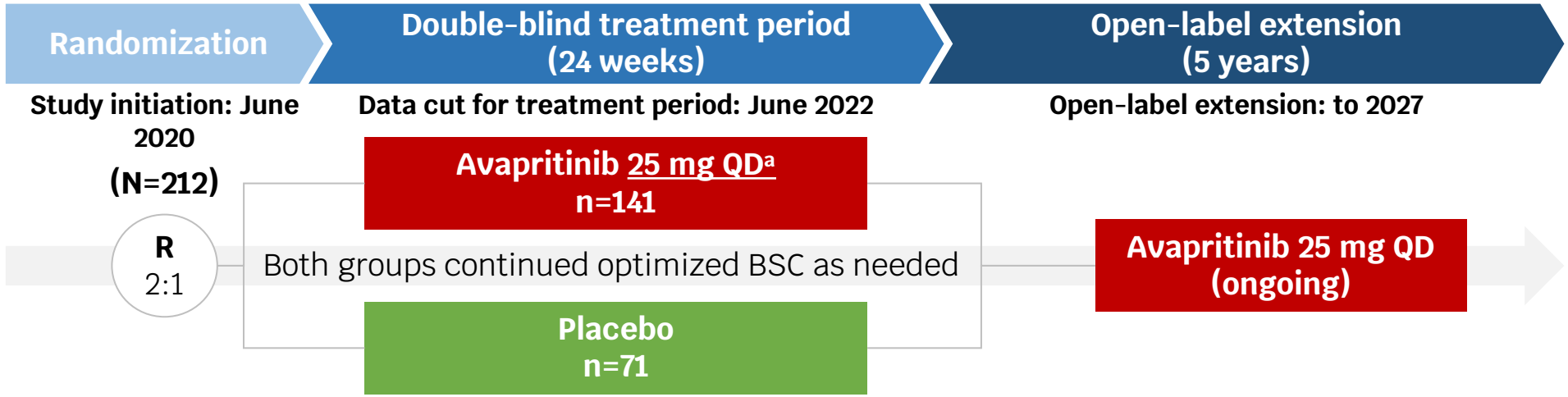
[a]57 patients with a confirmed diagnosis of AdvSM, and ORR evaluable per mIWG-MRT-ECNM criteria at baseline.
[b]CR + CRh + PR + CI
95% CI, 95% confidence interval; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematologic recovery; MCL, mast cell leukemia; NE, not evaluable for response; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

DeAngelo DJ et al. ASH 2022;Abstract 1710.

PIONEER: Randomized, double-blind, placebo-controlled study in patients with Indolent Systemic Mastocytosis

Screening period

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



Symptoms

Primary endpoint

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

Biomarkers of mast cell burden

Key secondary endpoints

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

Quality of life

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

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

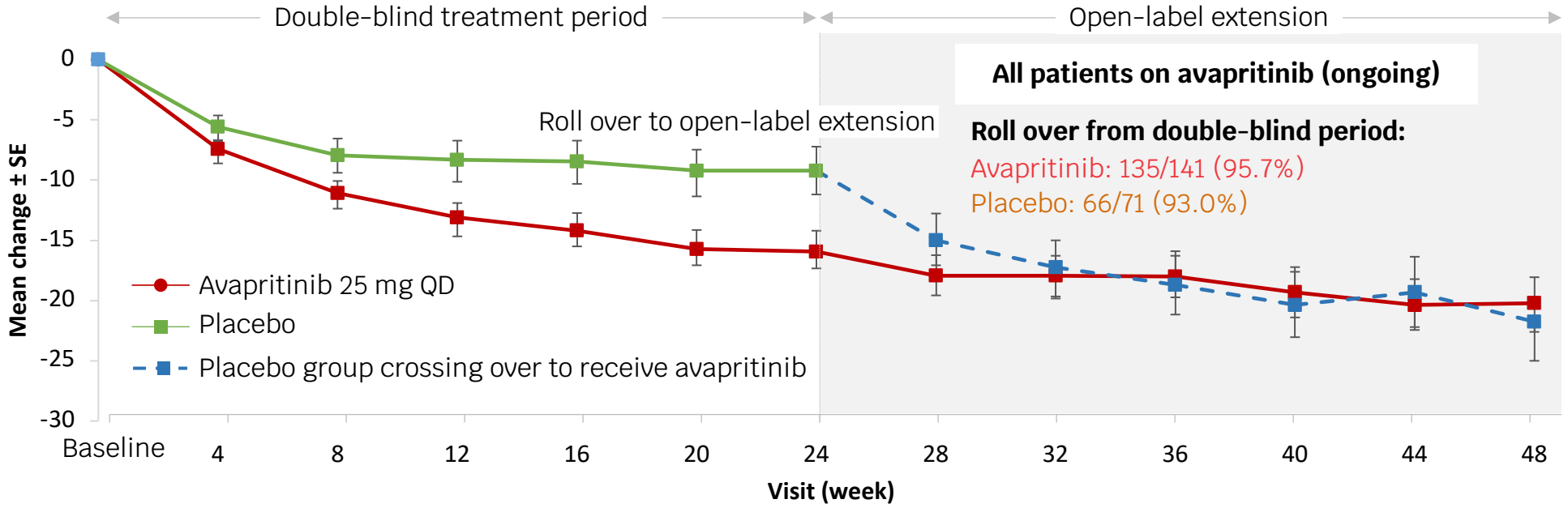
Castells et al. Presented at AAAAI Annual Meeting, February 2023.

PIONEER: Primary Endpoint—TSS by ISM-SAF*

TSS over time

Worse symptoms

Improved symptoms



Number of patients

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

Primary endpoint

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

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

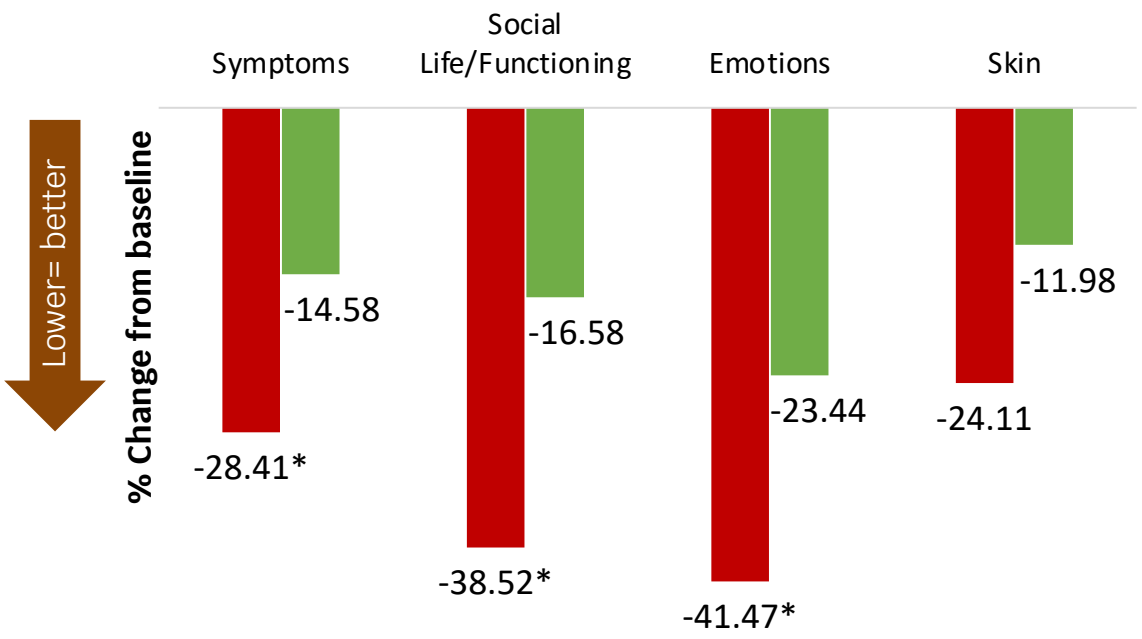
SE, standard error of the mean.

Castells et al. Presented at AAAAI Annual Meeting, February 2023.

*ISM-SAF: Validated symptom assessment tool specifically developed for evaluation of ISM symptomology based on severity of 11 ISM symptoms

PIONEER: Impact of Reduction in TSS on QoL

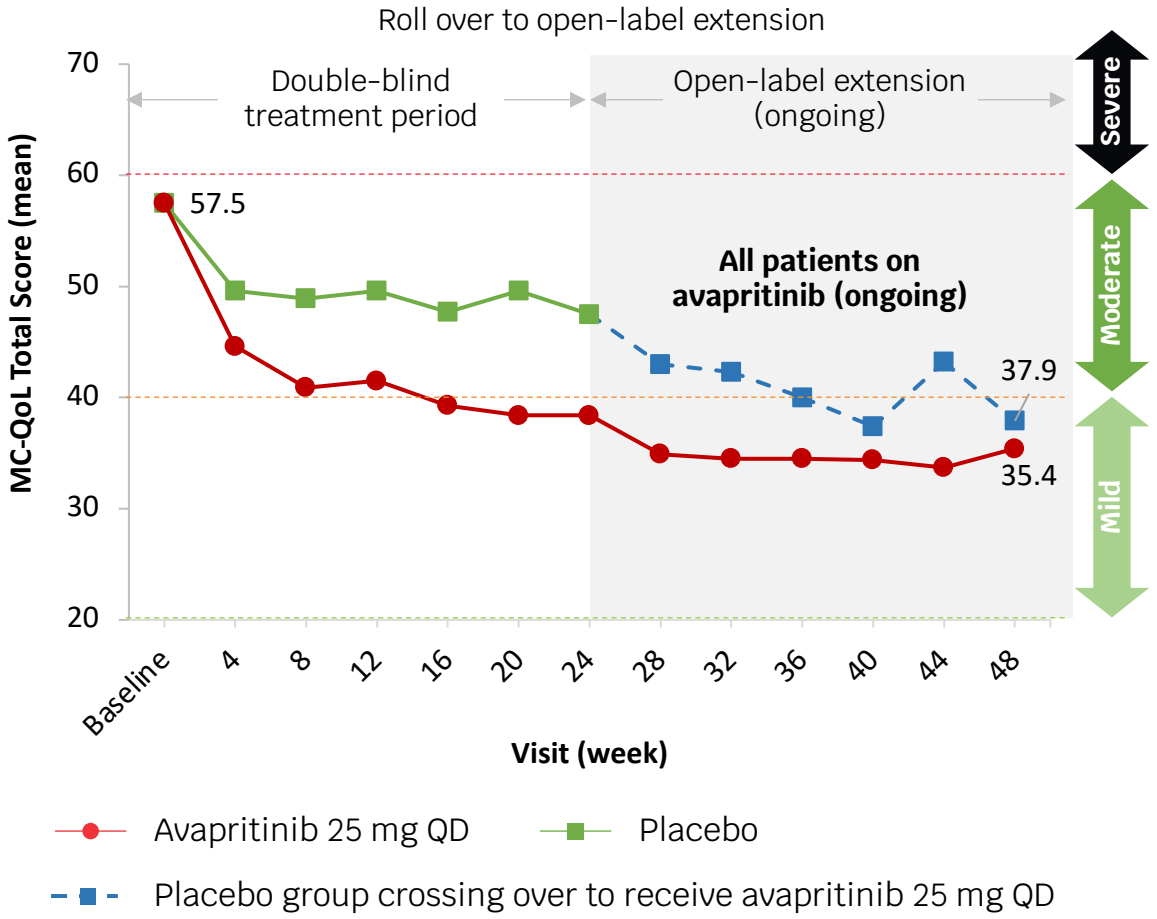
Change in mean MC-QoL component score from baseline to Week 24 in the ITT population



At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Mean % change MC-QoL (95% CI)	-34.3% (-39.9, -28.7)	-17.9% (-25.1, -10.8)	0.001

ITT, intent-to-treat. *p≤0.05.

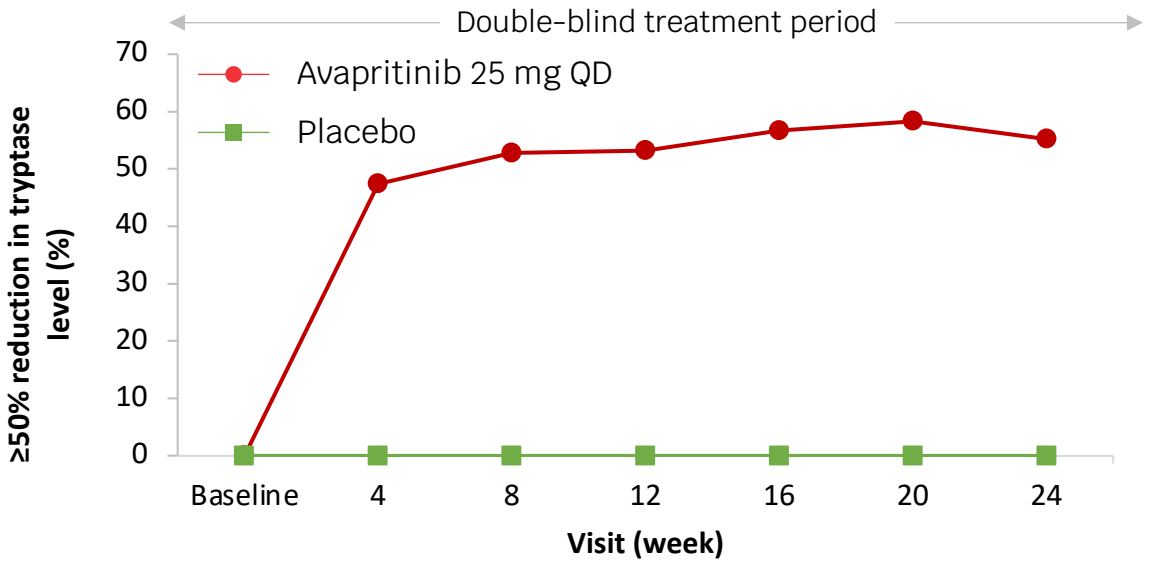
MC-QoL total score (mean) ITT Patients Part 2 and Part 3



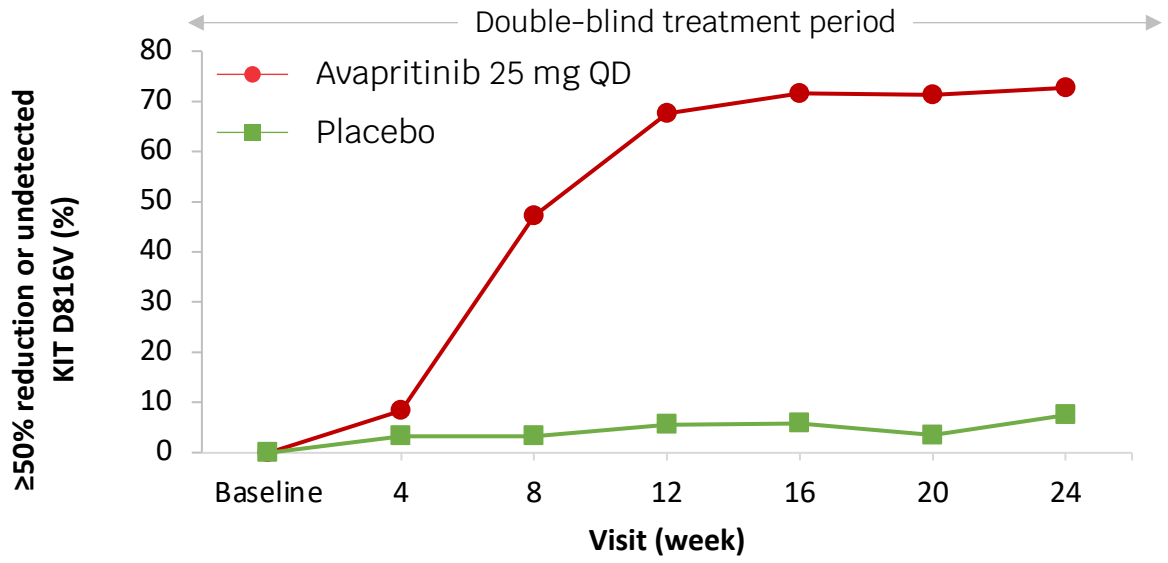
Castells et al. Presented at AAAAI Annual Meeting, February 2023.

PIONEER: Key Secondary Endpoints

Patients with **≥50% reduction in serum tryptase**



Patients with **≥50% reduction in peripheral blood *KIT* D816V VAF**



Number of patients

Avapritinib	141	133	136	132	133	128	134
Placebo	71	66	62	61	60	62	64

Avapritinib	118	110	113	109	107	104	109
Placebo	63	57	54	52	51	53	54

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Proportion of patients with **≥50% reduction in serum tryptase (95% CI)**	53.9% (45.3 – 62.3)	0.0% (0.0 -5.1)	<0.0001

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Proportion of patients with **≥50% reduction in *KIT* D816V VAF** (95% CI)	67.8% (58.6-76.1)	6.3% (1.8-15.5)	<0.0001

At Week 24	Avapritinib 25 mg QD (n=141)	Placebo (n=71)	P-value
Proportion of patients with **≥50% reduction in BM mast cell aggregates (95% CI)**	52.8% (42.9-62.6)	22.8% (12.7-35.8)	<0.0001

BM, bone marrow; CI, confidence interval

Castells et al. Presented at AAAAI Annual Meeting, February 2023.

PIONEER: Safety

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

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

[a]AEs refer to treatment-emergent AEs (TEAEs), defined as any AE that occurred between day 1 or Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not cross over, then through 30 days after the last dose of study drug
[b]There were too few events (≤5 per group) to assess the impact of avapritinib on anaphylaxis
AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related adverse events

Castells et al. Presented at AAAAI Annual Meeting, February 2023.

PATHFINDER: Avapritinib in Advanced Systemic Mastocytosis

AdvSM includes three subtypes: ASM, SM-AHN, and MCL,3,4 all with high disease burden and limited treatment options – SM-AHN is the most prevalent (~70%), subtypes include CMML, MDS/MPN-U, MDS and CE. The majority of patients in this trial had SM-AHN.

Outcome, % (n)	All[a] (n = 25)	ASM (n = 4)	SM–AHN (n = 19)	MCL (n = 2)
ORR, [b]	**84 (n =21)**	**75 (n = 3)**	**95 (n = 18)**	–
CR or CRh	32 (n = 8)	25 (n = 1)	37 (n = 7)	–
Complete Remission	8 (n = 2)	-	11 (n = 2)	–
CR with partial Hematologic Recovery[C]	24 (n = 6)	25 (n =1)	26 (n = 5)	–
Partial Remission[d]	48 (n = 12)	50 (n = 2)	53 (n = 10)	–
Clinical Improvement	4 (n = 1)	-	5 (n = 1)	–
Stable Disease	16 (n = 4)	25 (n = 1)	5 (n = 1)	100 (n = 2)
Progressive Disease	-	-	-	–
Not Evaluable	-	-	-	–
Median time to response (range), months	2.0 (0.3 – 12.2)	1.9 (0.3 – 2.1)	2.2 (0.5 - 12.2)	–
Median time to CR/CRh (range), months	5.8 (2.0 – 12.2)	2.1 (2.1 – .2.1)	6.1 (2.0 – 12.2)	–
Median duration of response (95% CI), months	NR	NR	NR	NE

32% of patients in the ORR-evaluable population experienced complete remission(CR or CRh)

Radia et. al. Presented at ASH 2022 Annual Meeting

PATHFINDER Safety

	Any-cause AEs		Treatment-related AEs	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE, *n* (%)	62 (100)	42 (68)	57 (92)	32 (52)
Nonhematologic AEs[a], *n* (%)				
Peripheral edema	31 (50)	2 (3)	26 (42)	1 (2)
Periorbital edema[b]	30 (48)	2 (3)	28 (45)	2 (3)
Diarrhea	14 (23)	1 (2)	7 (11)	1 (2)
Nausea	11 (18)	1 (2)	5 (8)	0
Vomiting	11 (18)	1 (2)	6 (10)	1 (2)
Fatigue	9 (15)	2 (3)	6 (10)	2 (3)
Increased blood alkaline phosphatase	7 (11)	3 (5)	2 (3)	1 (2)
Hematologic AEs[a], *n* (%)				
Thrombocytopenia[b]	28 (45)	10 (16)	25 (40)	9 (15)
Anemia[b]	20 (32)	10 (16)	12 (19)	5 (8)
Neutropenia[b]	15 (24)	15 (24)[c]	14 (23)	14 (23)[c]
Leukopenia[b]	7 (11)	3 (5)	7 (11)	3 (5)
AEs of special interest, *n* (%)				
Cognitive effects	7 (11)	0	–	–
Confusional state	3 (5)	0	–	–
Memory impairment	3 (5)	0	–	–
Cognitive disorder	2 (3)	0	–	–
Intracranial bleeding	1 (2)	1 (2)[d]	–	–
Subdural hematoma	1 (2)	1 (2)[d]	–	–

Gotlib et al., Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021

PATHFINDER: Updates at ASH 2025 – Key Findings

PRESENTATION ID 1022
OCCC - West Hall D2
Avapritinib treatment of patients with advanced systemic mastocytosis: 4-year safety, effect on bone and first-line efficacy results of the pathfinder clinical study
Andreas Reiter

Monday, December 8
04:30 PM - 06:00 PM EST

- Best confirmed overall response rate was 87% (95% CI, 69-96), including 43% complete response/complete response with partial hematologic recovery and 43% partial response. Median time to response was 3 months.
- Median duration of response was not reached (95% CI, 37-not evaluable [NE]) regardless of subtype.
- Median PFS was not reached in the first-line population (39-NE), aggressive systemic mastocytosis or mast cell leukemia subtypes, and was 48 months (25-NE) in systemic mastocytosis with an associated hematological neoplasm; PFS rate at 48 months was 67% (95% CI, 49-85).
- Median overall survival (OS) was not reached (95% CI, NE-NE) regardless of subtype, and OS rate at 48 months was 79% (95% CI, 64-93).

Reiter A et al. ASH 2025;Abstract 1022.

Summit: Phase 2 Clinical Study Evaluating Bezuclastinib in NonAdv SM

PART 1: DOSE OPTIMIZATION (fully enrolled)

Primary objective: Determine the recommended dose of bezuclastinib

Eligibility

ISM or SSM based on 2016 WHO classification

Moderate – severe symptoms on ≥2 anti-mediator therapies

BSC: Best supportive care

Screening Enrollment

Double-blind Treatment Period (12 weeks)

PART 1a: Formulation A

N=20

R

1:1:1[a]

- Bezuclastinib 100 mg QD + BSC
- Bezuclastinib 200 mg QD + BSC
- Placebo + BSC

PART 1b: Formulation B[b]

N=34

R

1:1:1

- Bezuclastinib 100 mg QD + BSC
- Bezuclastinib 150 mg QD + BSC
- Placebo + BSC

[a] Prior to amendment, Part 1a included a bezuclastinib 400mg QD + BSC cohort with randomization of 1:1:1:1

[b] Formulation B is an optimized formulation with improved bioavailability

Selected Dose

Part 1 Endpoints

Safety

PK

Biomarkers

Symptom improvement based on PRO measures

PART 2: EXPANSION

Primary objective: Determine the efficacy of bezuclastinib

Double-blind Treatment Period (24 weeks)

N=TBD[c]

R

2:1

- Bezuclastinib (Formulation B) Selected Dose + BSC
- Placebo + BSC

[c] Part 2 will be sized based on Part 1 results and regulatory discussions

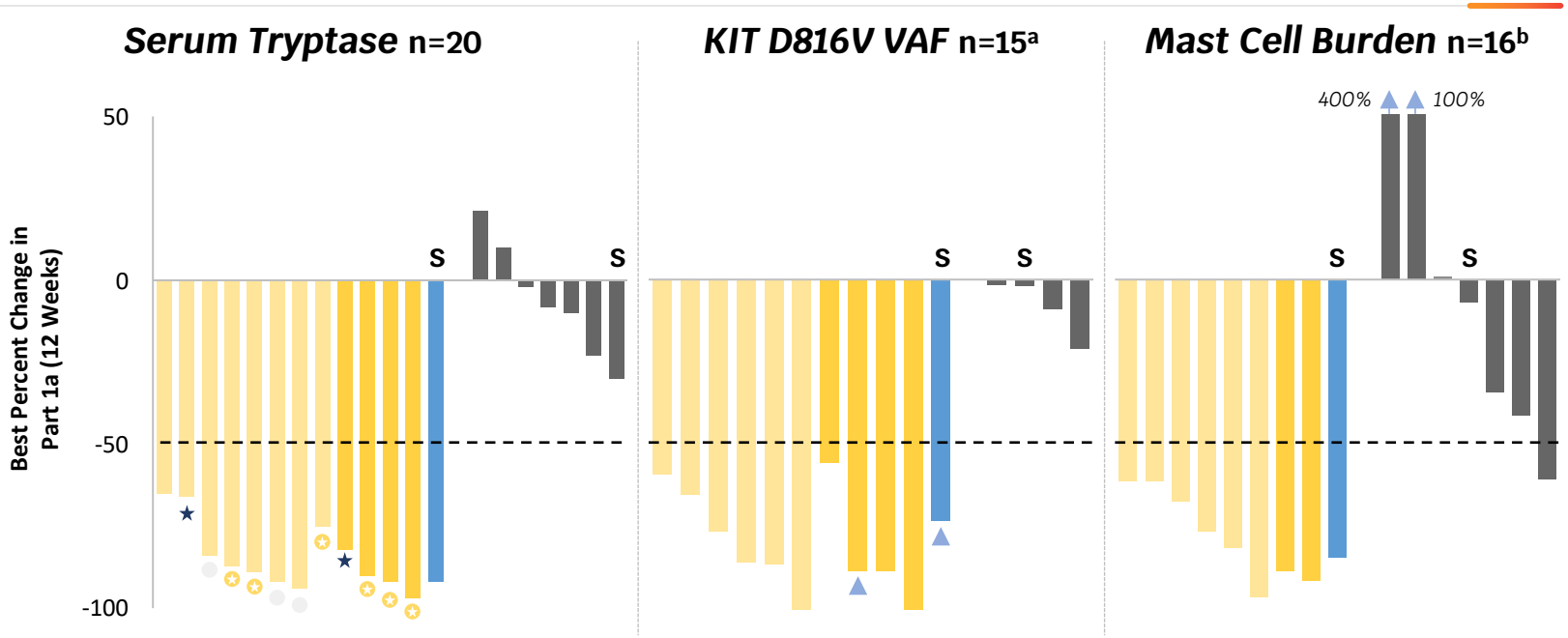
OPEN-LABEL EXTENSION (OLE)

Primary Objective: Characterize safety and tolerability of bezuclastinib

Prithviraj Bose, Stephen T. Oh, Brian Modena, Anthony M. Hunter, Cem Akin, Mariana Castells, Michael Manning, Richard Herrscher, Frank Siebenhaar, Daniel J. DeAngelo, Tracy I. George, Benjamin Exter, Jenna Zhang, Amanda Pilla, Hina Jolin, Rachael Easton, Lindsay A.M Rein; Initial Results from Summit: An Ongoing, 3-Part, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of Bezuclastinib in Adult Patients with Nonadvanced Systemic Mastocytosis (NonAdvSM). *ASH 2023;Abstract 77*

Summit: Efficacy and Safety

Within 12 Weeks, 100% of Bezuclastinib Treated Patients Achieved >50% Reduction in Markers of Mast Cell Burden



- 90% (9/10) of patients with baseline serum tryptase 220ng/mL achieved <20ng/mL after 12 weeks of bezuclastinib
- 67% (8/12) of patients with baseline serum tryptase 211.4ng/mL achieved <11.4ng/mL after 12 weeks of bezuclastinib

Dose
- 100 mg QD bezuclastinib
- 200 mg QD bezuclastinib
- 400 mg QD bezuclastinib
- Placebo

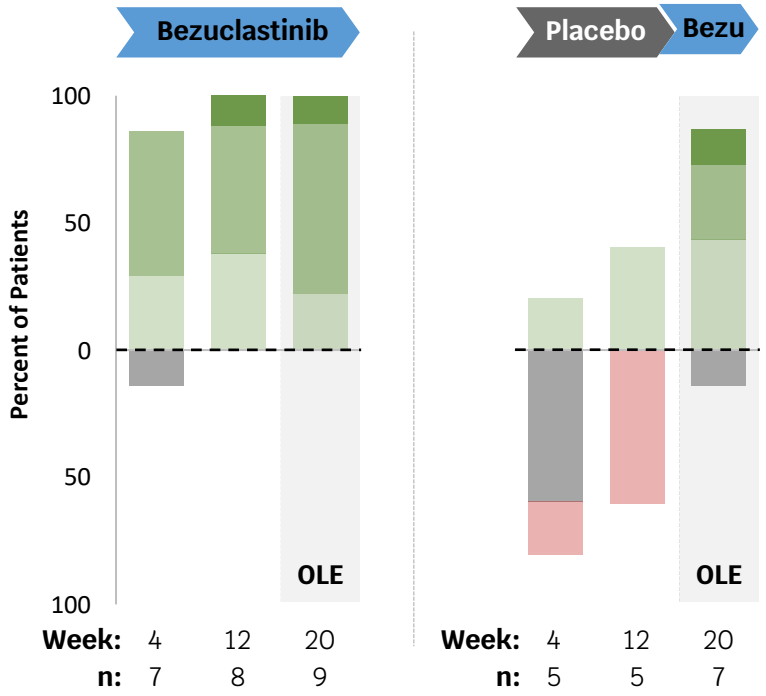
Serum Tryptase Outcomes
- Achieved <20ng/mLμ
- ★ Achieved <11.4ng/mLμ
- Achieved bothμ

***KIT* D816V VAF Outcomes**
- ▲ Achieved <0.03% (LLD)

S SSM

μ In Order to achieve, serum tryptase must have been above the threshold at baseline LLD, lower limit of detection

Overall Symptoms



Patient Global Impression of Change (PGIC)

Improving
- Very much better
- Much better
- A little better

No Change or Worsening
- No change
- A little worse
- Much worse
- Very much worse

[a] Patients with undetectable peripheral blood *KIT* mutant excluded; [b] Sample inevaluable in 4 patients; As of Data Cut-off of 25-Oct-2023.

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POSITIVE TOP-LINE RESULTS ACHIEVING STATISTICAL SIGNIFICANCE ACROSS ALL PRIMARY AND KEY SECONDARY ENDPOINTS FROM THE SUMMIT TRIAL OF BEZUCLASTINIB IN PATIENTS WITH NON-ADVANCED SYSTEMIC MASTOCYTOSIS

July 7, 2025

PDF Version

-- Patients treated with bezuclastinib showed a superior mean change in total symptom score at 24 weeks (-24.3 points vs. -15.4 points, -8.91 point placebo-adjusted difference; p=0.0002), compared to patients treated with placebo, establishing new benchmarks for placebo-adjusted and absolute symptomatic improvement for this patient population --

-- Bezuclastinib demonstrated a powerful effect on mast cell burden, with 87.4% of patients treated with bezuclastinib achieving at least 50% reduction in serum tryptase compared to 0% of patients treated with placebo --

-- Bezuclastinib demonstrated a favorable safety and tolerability profile supporting chronic use in this patient population --

https://investors.cogentbio.com/news-releases/news-release-details/cogent-biosciences-announces-positive-top-line-results-achieving

ASH 2025 – Bezuclastinib

PRESENTATION ID 80
OCCC - W414CD
Efficacy and safety results from the primary analysis of the pivotal summit trial: Bezuclastinib in adults with non-advanced systemic mastocytosis
Lindsay Rein, MD

Saturday, December 6
09:30 AM - 11:00 AM EST

As of May 22, 2025, 179 patients were enrolled in Part 2: 119 were randomized to receive bezuclastinib and 60 to placebo.

Bezuclastinib demonstrated statistically significant superiority to placebo on all primary and key secondary endpoints.

At Week 24, bezuclastinib led to significantly greater symptom improvement vs placebo (LS mean [95% CI] MS2D2 TSS change: –24.3 [–27.6 to –21.1] vs –15.4 [–19.6 to –11.2]; placebo-adjusted difference: –8.9 points; P=0.0002). A ≥50% reduction in serum tryptase was achieved in 87.4% of bezuclastinib-treated patients vs 0% on placebo (P<0.0001).

Significantly more patients receiving bezuclastinib achieved ≥50% reductions in KIT D816V VAF, serum tryptase, BM MCs (P<0.0001), MS2D2 TSS (P=0.01), and ≥30% reduction in MS2D2 TSS (P=0.0004).

Rein L et al. ASH 2025;Abstract 80.

Elenestinib (BLU-263)

- Potent KIT inhibitor with minimal penetration through blood brain barrier
  - Potential reduction in intracranial hemorrhage risk.
  - Potential reduction in impact on cognitive function.
- HARBOR study: evaluating elenestinib in symptomatic indolent SM
- AZURE: evaluating elenestinib in advanced SM (terminated)

Chifotides and Bose, SOHO State of the Art Update and Next Questions: Current and Emerging Therapies for Systemic Mastocytosis. Clin Lymphoma Myeloma Leuk. 2025 Jan;25(1):1-12.

Comparison of Potent KIT Inhibitors in Advanced SM

Table 3 Efficacy of KIT Inhibitors in Clinical Trials in AdvSM

	Midostaurin[51,52]	Avapritinib[55]	Avapritinib[56,58]	Bezuclastinib[69]
Disease	AdvSM	AdvSM	AdvSM	AdvSM
FDA approval date	April 28, 2017	June 16, 2021		–
EMA approval date	September 18, 2017	March 25, 2022		–
Target	Wild type KIT and KIT D816V	KIT D816V		KIT D816V
IC_{50} (KIT D816V), nM	2.9[54]	0.27[54] 13[66]		14[66]
Clinical trial NCT number	CPKC412D2201 NCT00782067	EXPLORER NCT02561988	PATHFINDER NCT03580655	APEX NCT04996875
Phase	2	1	2	2 (Part 1)
Approved or recommended dose	100 mg twice daily	200 mg daily		150 mg daily (optimized formulation B)
Response criteria	Modified Valent[a]/Cheson criteria IWG-MRT-ECNM (IWG) criteria[b]	mIWG-MRT-ECNM criteria[b]	mIWG-MRT-ECNM criteria[b]	mIWG-MRT-ECNM criteria[b]
ORR, %	ORR = 60 (MR [45] + PR [15]) with modified Valent criteria 17 (CR [2] + PR [15])[c] 28 (CR [1] + PR [15] + CI [12])[d] with IWG criteria	75 (CR + CRh + PR + CI)	73 (CR + CRh + PR + CI)	56 (confirmed and unconfirmed responses)[e] 44 (confirmed responses)[e] (CR + CRh + PR + CI)[f]
CR, %	0	15	13	18
CRh, %	NR	21	13	4
ORR by AdvSM subtype, %	ASM: 75 SM-AHN: 58 MCL: 50 with modified Valent criteria ASM: 60 SM-AHN: 21 MCL: 33 with IWG-MRT-ECNM criteria	ASM: 100 SM-AHN: 76 MCL: 69 (CR + CRh + PR + CI)	ASM: 77 SM-AHN: 75 MCL: 67 (CR + CRh + PR + CI)	ASM: 100[e] SM-AHN: 58[e] MCL: 50[e] (CR + CRh + PR + CI)
≥ 50% decrease in serum tryptase level, % patients	60	99	92	94
≥ 50% decrease in *KIT* D816V VAF, % patients	46	80	81	93
≥ 50% decrease in BM MC burden, % patients	57	92	88	97
SVR35, % patients	26	82	70	NR
Median DOR	24.1 mo (modified Valent criteria) Not reached (IWG criteria)	38 mo	Not reached	NR Duration on study: 34.7 mo
Median TTR	NR (modified Valent criteria) Not reached (IWG criteria)	2 mo	2.3 mo	2 mo

Chifotides and Bose, SOHO State of the Art Update and Next Questions: Current and Emerging Therapies for Systemic Mastocytosis. Clin Lymphoma Myeloma Leuk. 2025 Jan;25(1):1-12.

Comparison of Potent KIT Inhibitors in Non-Advanced SM

Table 4 Efficacy of KIT Inhibitors in Clinical Trials in NonAdvSM

	Avapritinib[64]	Bezuclastinib[70,72]	Elenestinib[74]
Disease	Symptomatic ISM	Symptomatic ISM, SSM	Symptomatic ISM
FDA approval date	May 22, 2023	–	–
EMA approval date	December 15, 2023	–	–
Target	KIT D816V	KIT D816V	KIT D816V
IC_{50} (KIT D816V), nM	13[66]	14[66]	6[66]
Clinical trial name NCT number	PIONEER NCT03731260	SUMMIT NCT05186753	HARBOR NCT04910685
Phase	2 (Part 2)	2 (Part 1)	2/3 (Part 1)
Approved or recommended dose	25 mg daily	100 mg daily (optimized formulation B)	25, 50, or 100 mg daily
Assessments of disease-related symptoms	Mean ISM-SAF TSS decrease: 15.6 points at W24	Mean MS2D2 TSS decrease: 51% at W12 Mean MAS decrease: 41% at W12 (100 mg daily)	Mean ISM-SAF TSS decrease at W12: 28.5% (25 mg daily) 31.8% (50 mg daily) 33.6% (100 mg daily)
Symptom improvements, % patients	≥ 50% decrease in ISM-SAF TSS: 25% at W24 ≥ 30% decrease in ISM-SAF TSS: 45% at W24	≥ 50% decrease in MS2D2 TSS: 70% at W12 ≥ 50% decrease in MAS: 50% at W12 (100 mg daily)	N/A
≥ 50% decrease in serum tryptase level, % patients[a]	54% at W24	91% at W12 (100 mg daily)	Decrease in mean tryptase level at W12: 15.4% (25 mg daily) 50.9% (50 mg daily) 68.4% (100 mg daily)
≥ 50% decrease in *KIT* D816V VAF, % patients[a]	68% at W24	100% at W12 (100 mg daily)	Decrease in mean *KIT* D816V VAF at W12: 37.5% (25 mg daily) 70.3% (50 mg daily) 77.0% (100 mg daily)
≥ 50% decrease in BM MC burden, % patients[a]	53% at W24	86% at W12 (100 mg daily)	Decrease in mean BM MC burden at W12: 22.6% (25 mg daily) 28.1% (50 mg daily) 57.9%% (100 mg daily)
QoL improvement	Mean MC-QoL score decrease: 34% at W24	Mean MC-QoL score decrease: 49% at W12 (100 mg daily)	N/A

Chifotides and Bose, SOHO State of the Art Update and Next Questions: Current and Emerging Therapies for Systemic Mastocytosis. Clin Lymphoma Myeloma Leuk. 2025 Jan;25(1):1-12.

Future Directions

- Combination Therapy:
  - APEX (combo subset),
  - NCT06327685 (Decitabine + Avapritinib IIT)
  - Abstract 3763: Investigating the clonal and biological underpinnings of systemic mastocytosis with an associated hematological neoplasm
- BTK Inhibition (TL-895)
  - BTK involved in IgE mediated mast cell activation and degranulation.
  - Acalabrutinib and ibrutinib have showed preclinical activity
  - TL-895 is currently being evaluated in a randomized phase 2 study (NCT04655118)

Initial assessment of patients diagnosed with systemic mastocytosis; avapritinib dosing

Dr Prithviraj Bose (Houston, Texas)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What are key issues for general medical oncologists to understand about SM?

How is SM subclassified, and how does this affect treatment selection?

What is your threshold for initiating avapritinib for patients with indolent SM? What about advanced SM?

What is your usual starting dose of avapritinib for advanced SM? What are the common side effects/toxicities of avapritinib based on dose, and how can these be ameliorated?

Systemic mastocytosis with associated hematologic neoplasm

Dr Prithviraj Bose (Houston, Texas)

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QUESTIONS FOR THE FACULTY

How do you approach the management of SM with an associated hematologic neoplasm, particularly when both components or the SM component are indolent?

Are you administering KIT D816V inhibitors to all of your patients with SM with an associated hematologic neoplasm or only those for whom the SM is more problematic?

Potential clinical role of bezuclastinib in therapy for systemic mastocytosis

Dr Prithviraj Bose (Houston, Texas)

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

What are your thoughts about bezuclastinib? If this agent is approved, in what situations will you use it?

What other novel KIT D816V inhibitors look promising in SM?
In your opinion, what potential advantages, if any, does elenestinib offer over avapritinib? Do you anticipate that elenestinib will eventually reach the clinic, and if so, how do you see yourself using it?

Expert Second Opinion
Investigators Discuss the Role of Novel Treatment Approaches in the Care of Patients with Follicular Lymphoma and Diffuse Large B-Cell Lymphoma

A CME-Accredited Friday Satellite Symposium Preceding the 67th ASH Annual Meeting

Friday, December 5, 2025

7:00 PM – 9:00 PM ET

Faculty

Nancy L Bartlett, MD
John P Leonard, MD
Matthew Matasar, MD
Loretta J Nastoupil, MD
Professor Pier Luigi Zinzani

Moderator

Neil Love, MD

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