Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Management of Myelofibrosis

A CME/MOC-Accredited Virtual Event Held
Adjunct with the 2026 ASCO® Annual Meeting

Tuesday, June 2, 2026
5:00 PM – 6:00 PM ET

Faculty

Professor Claire Harrison
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

MODERATOR
Neil Love, MD
Research To Practice
Miami, 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

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Contributing Clinical Investigators

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

John Mascarenhas, MD
Director, Center of Excellence in Blood Cancers and Myeloid Disorders
Director, Adult Leukemia Program
Leader, Myeloproliferative Disorders Clinical Research Program
Division of Hematology/Oncology
Tisch Cancer Institute
Professor of Medicine
Icahn School of Medicine at Mount Sinai
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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

Abdulraheem Yacoub, MD
Professor of Medicine
Clinical Director of Ambulatory Hematology Clinics
The Division of Hematologic Malignancies and Cellular Therapeutics (HMCT)
Department of Internal Medicine
The University of Kansas Cancer Center
Fairway, Kansas

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Dr Love — Disclosures

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Dr Kuykendall — Disclosures
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Dr Yacoub — Disclosures
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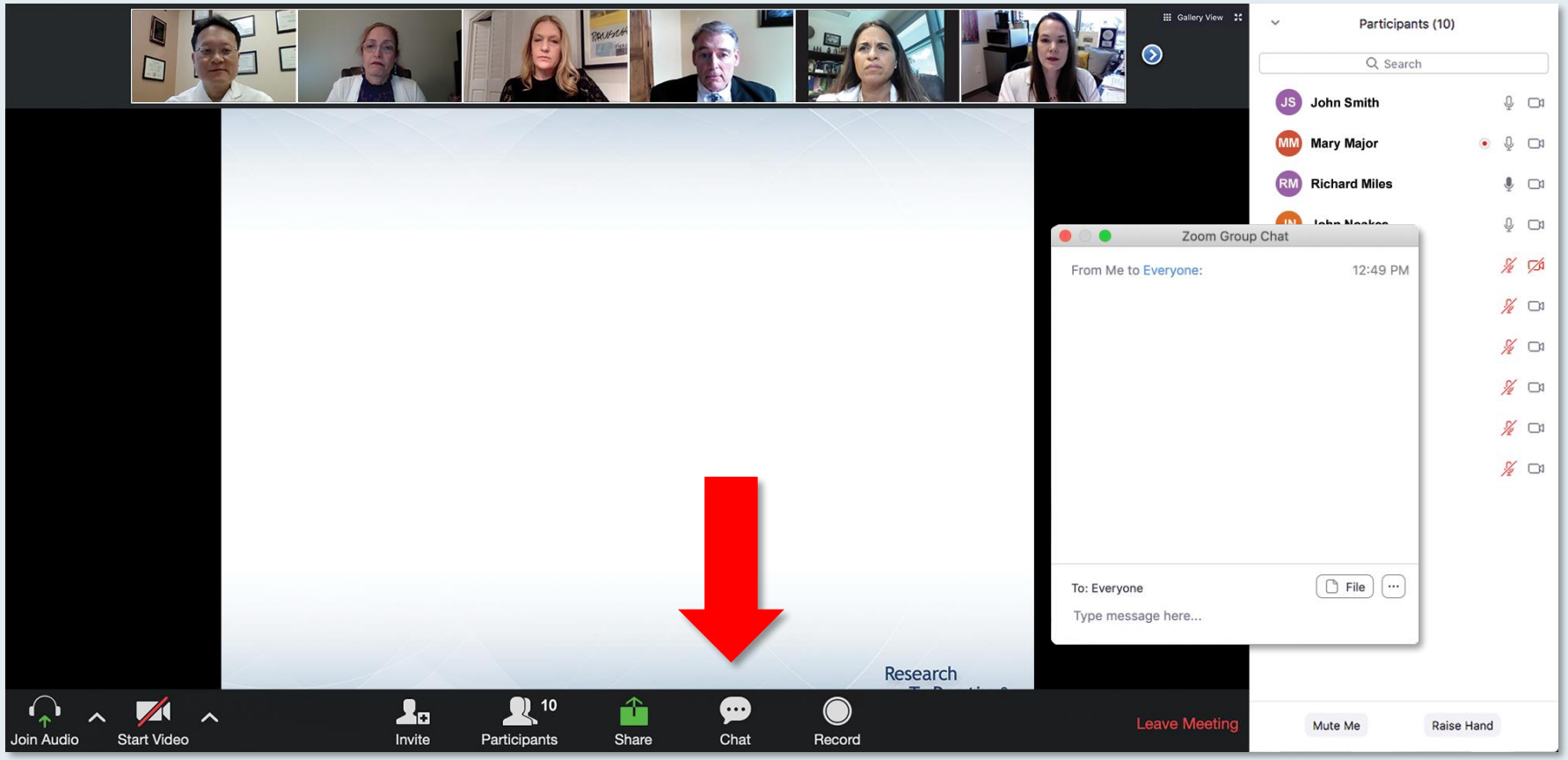

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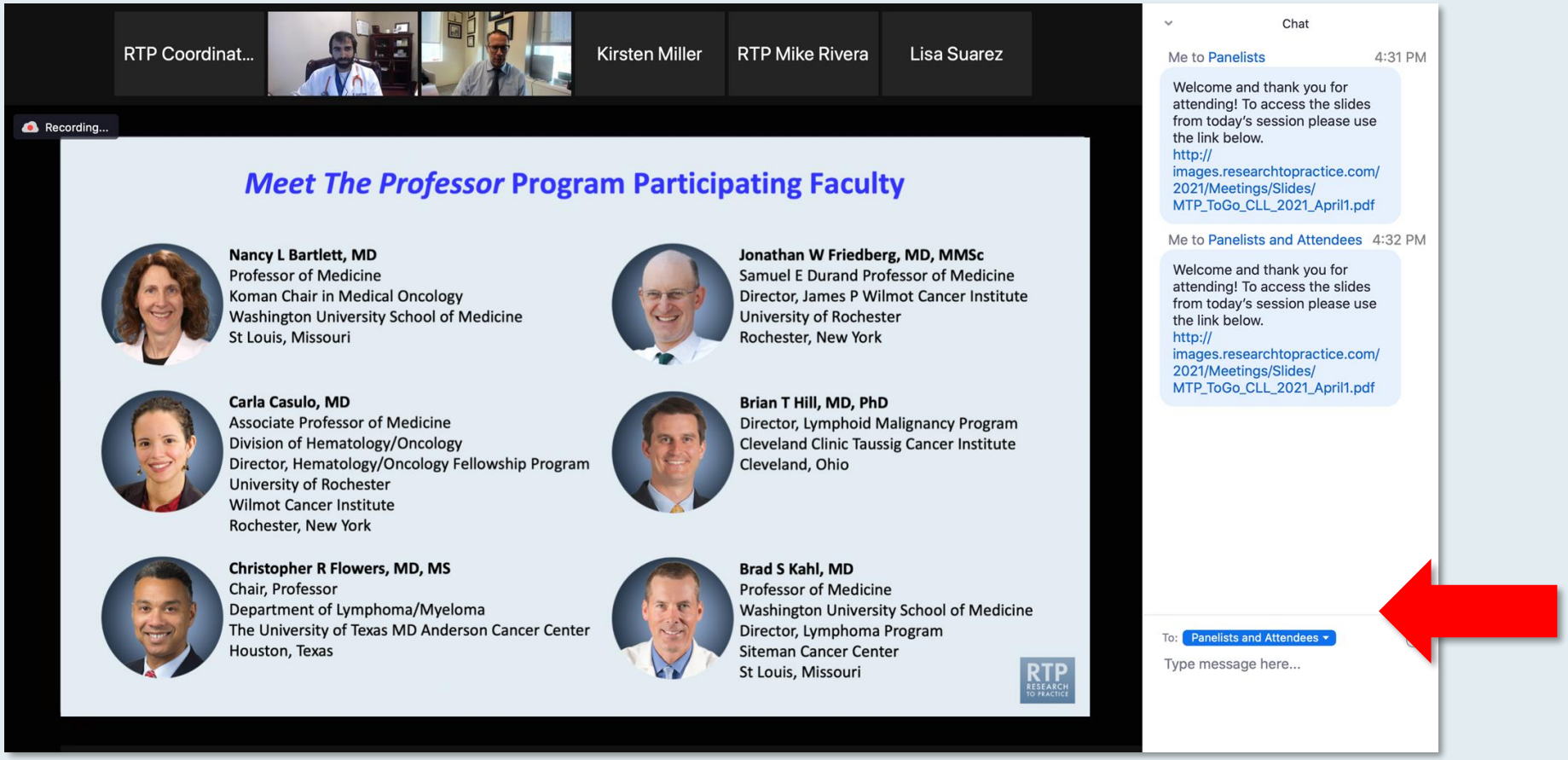

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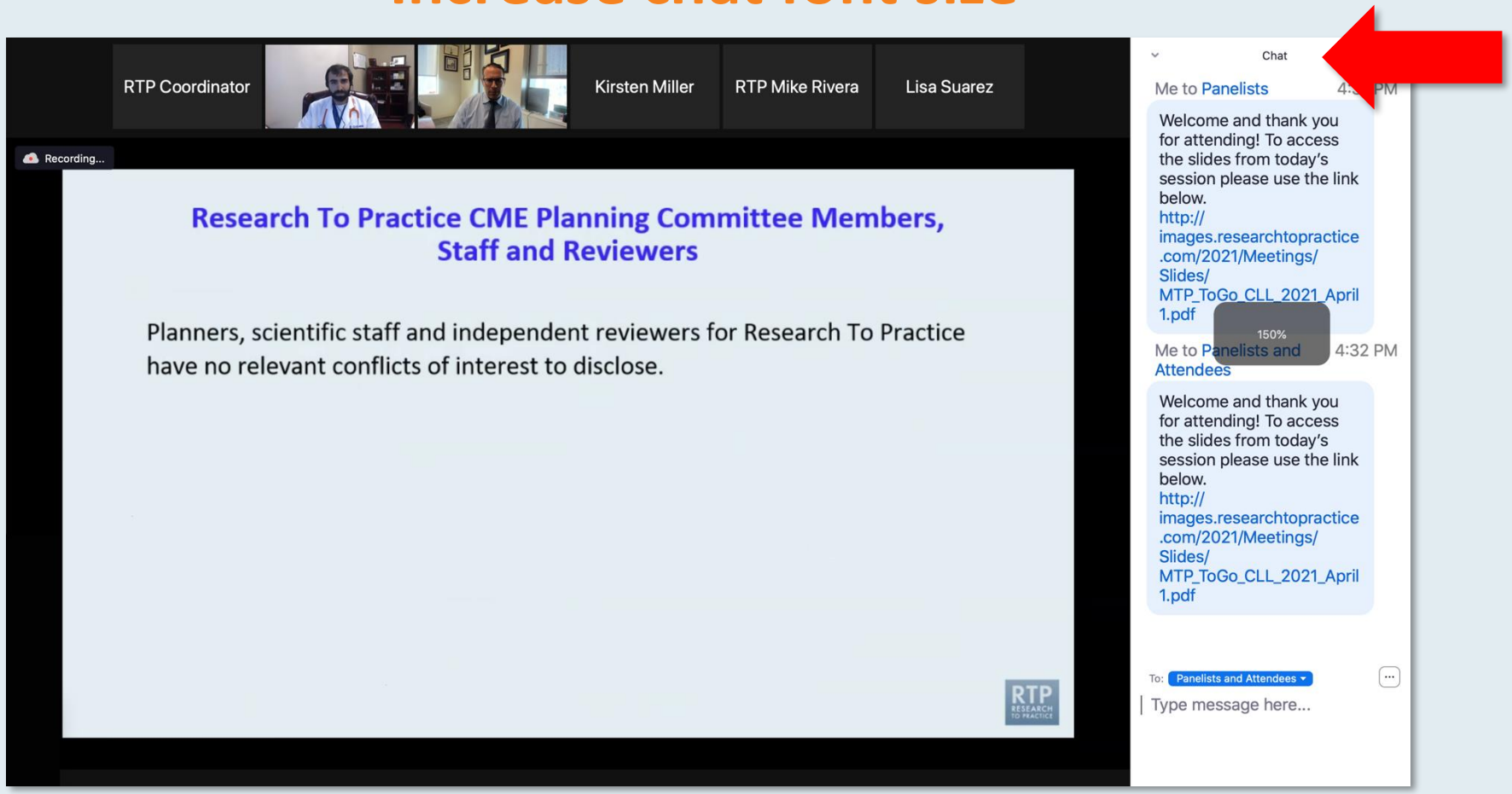

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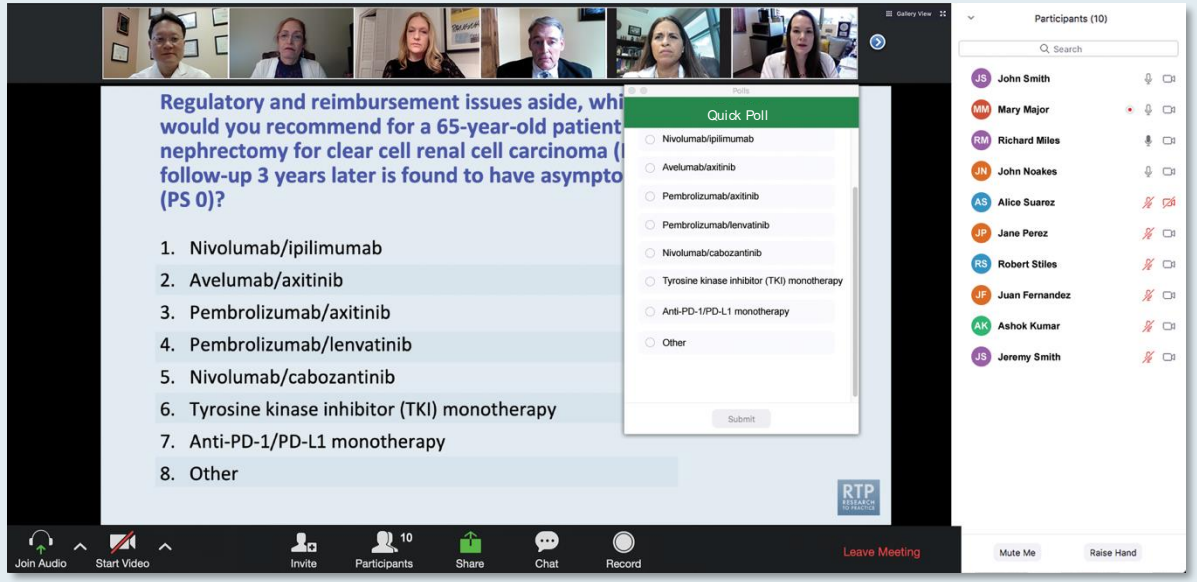

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Expert Second Opinion
Investigators Discuss the Optimal Management of Myelofibrosis and Systemic Mastocytosis

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JEANNE PALMER, MD
MAYO CLINIC SCHOOL OF MEDICINE

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RAAJIT K RAMPAL, MD, PHD
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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Novel Treatment Approaches for Non-Hodgkin Lymphoma

A CME/MOC-Accredited Live Webinar

Wednesday, June 17, 2026

5:00 PM – 6:00 PM ET

Faculty

Matthew Matasar, MD

Sonali M Smith, MD

Moderator

Neil Love, MD

RTP Year in Review 2026

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Gastroesophageal Cancers

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Kohei Shitara, MD

Moderator

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Multiple Myeloma

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Thursday, June 25, 2026
5:00 PM – 6:00 PM ET

Faculty

Amrita Krishnan, MD
Robert Z Orlowski, MD, PhD

Moderator

Neil Love, MD

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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Therapeutic Targets Beyond EGFR for Non-Small Cell Lung Cancer

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John V Heymach, MD, PhD

Maurice Pérol, MD

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Grand Rounds

CME/MOC-Accredited Interactive Series

Regional Activities

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

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Professor, Department of Leukemia
Co-Leader, Section of Myeloproliferative Neoplasms
Division of Cancer Medicine
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Houston, Texas

John Mascarenhas, MD
Director, Center of Excellence in Blood Cancers and Myeloid Disorders
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Professor of Medicine
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Andrew T Kuykendall, MD
Associate Member, Department of Malignant Hematology
Moffitt Cancer Center
Associate Professor, Department of Oncologic Sciences
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Abdulraheem Yacoub, MD
Professor of Medicine
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Department of Internal Medicine
The University of Kansas Cancer Center
Fairway, Kansas

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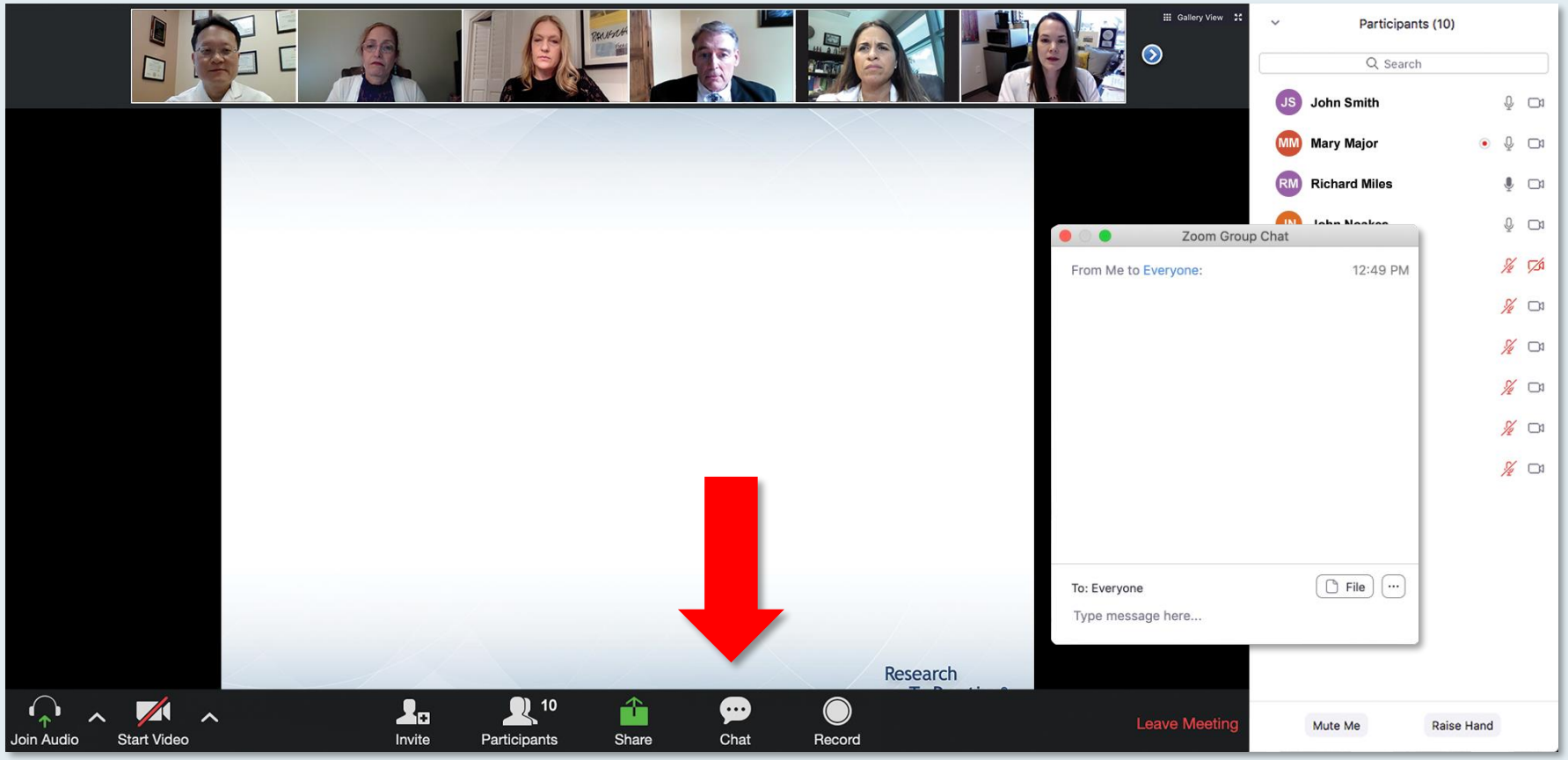

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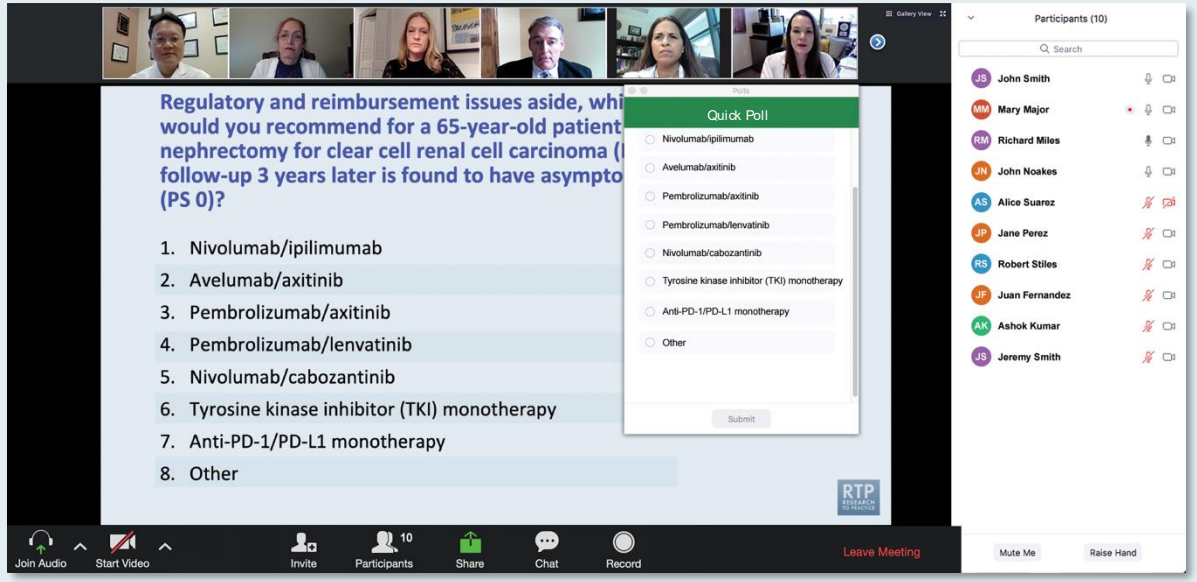

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Investigators Discuss the Optimal Management of Myelofibrosis and Systemic Mastocytosis

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WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

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Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

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Friday May 29	**Gastroesophageal Cancers** 11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Chronic Lymphocytic Leukemia 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Colorectal Cancer 6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)
Saturday May 30	**Ovarian Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Small Cell Lung Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday May 31	**Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Endometrial Cancer 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	CAR T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 1	**ADCs for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Novel Therapies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Relapsed/Refractory Multiple Myeloma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 2	**Myelofibrosis (Webinar)**

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Faculty

Yelena Y Janjigian, MD

Jacob Sands, MD

Jeremy S Abramson, MD, MMSc

Tanios Bekaii-Saab, MD

Kathleen N Moore, MD, MS

Rana R McKay, MD, FASCO

Misty Dawn Shields, MD, PhD

Sara M Tolaney, MD, MPH

Shannon N Westin, MD, MPH, FASCO, FACOG

Hope S Rugo, MD

Brad S Kahl, MD

Sagar Lonial, MD, FACP, FASCO

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Agenda
Management of Myelofibrosis (MF)

Introduction: The Biopathophysiology of MF

Module 1: Current and Future Clinical Decision-Making in the Absence of Severe Cytopenias — Prof Harrison

Module 2: Managing MF for Patients with Anemia and Thrombocytopenia — Dr Rampal

Module 3: Upcoming at EHA 2026

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Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: www.tandfonline.com/journals/ieop20

Targeted treatment of anemia in myelofibrosis and the impact of JAK inhibitors

Iman Al Noumani & Claire Harrison

2026 May 12:1-12.

REVIEW ARTICLE

JAK inhibitor selection in challenging scenarios of myelofibrosis: a review

Pankit Vachhani,[1] Ruben Mesa,[2] John Mascarenhas,[3] Raajit Rampal,[4] Stephen T. Oh,[5] Alessandro Maria Vannucchi,[6] Maria Laura Fox,[7] Francesca Palandri,[8] Francesco Passamonti,[9] Jean-Jacques Kiladjian,[10] Mahshid Azimi,[11] Claire Harrison[12] and Prithviraj Bose[13]

Haematologica 2026;111(4):1179-97.

RTP RESEARCH TO PRACTICE

PATHOPHYSIOLOGY OF MYELOFIBROSIS

Clonal hematopoiesis • Marrow fibrosis • Extramedullary hematopoiesis • Cytopenias

1 CLONAL DRIVER MUTATIONS

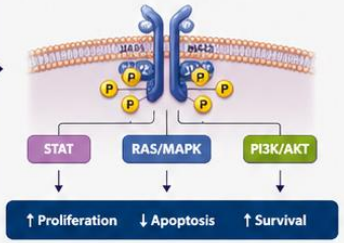
Acquired mutations in hematopoietic stem/progenitor cells lead to constitutive activation of survival and proliferation pathways.

COMMON DRIVER MUTATIONS

- **JAK2** V617F (~50–60%)
- **CALR** (~20–30%)
- **MPL** (~5–10%)
- Triple negative (~10–15%)

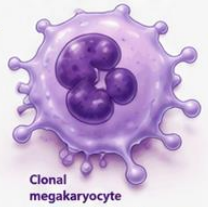
2 CONSTITUTIVE PATHWAY ACTIVATION

Mutant signaling drives cytokine-independent proliferation and resistance to apoptosis.



3 ABERRANT HEMATOPOIESIS AND CYTOKINE RELEASE

Clonal megakaryocytes and other myeloid cells release profibrotic and proinflammatory mediators.

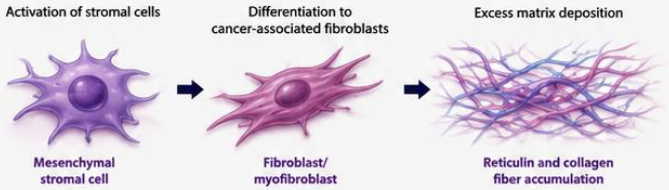


KEY MEDIATORS

- TGF-β1
- PDGF
- CTGF
- VEGF
- bFGF
- IL-1β
- TNF-α

4 MARROW FIBROSIS

Profibrotic mediators activate stromal cells and fibroblasts, leading to excessive deposition of reticulin and collagen fibers.



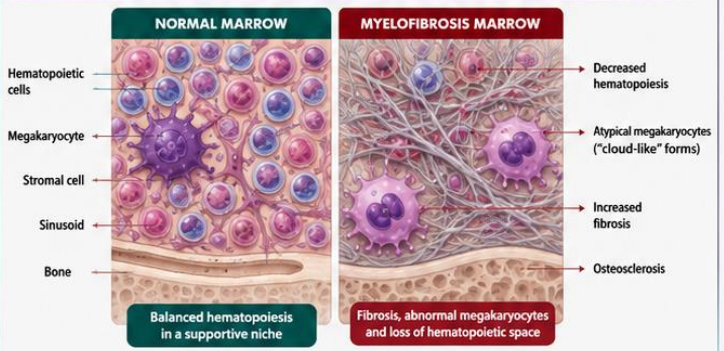
RESULT

Progressive replacement of hematopoietic space with fibrotic tissue

⌄⌄

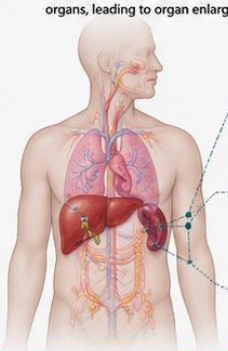
Disrupted hematopoiesis and marrow failure

5 DISRUPTED MARROW MICROENVIRONMENT



6 EXTRAMEDULLARY HEMATOPOIESIS

Hematopoiesis shifts from bone marrow to peripheral organs, leading to organ enlargement and related symptoms.



SPLEEN (most common)
- Site of hematopoiesis
- Splenomegaly
- Pain, early satiety

LIVER
- Hepatomegaly
- Impaired function

LYMPH NODES (less common)
- Lymphadenopathy

7 CLINICAL CONSEQUENCES

CYTOPENIAS
- Anemia (↓ RBCs)
- Leukopenia
- Thrombocytopenia

HYPERSPLENISM

Sequestration and destruction of blood cells in enlarged spleen

CONSTITUTIONAL SYMPTOMS
- Fatigue
- Night sweats
- Weight loss
- Fever

BONE MARROW FAILURE & PROGRESSION
- Progressive cytopenias
- Transfusion dependence
- Increased risk of leukemic transformation

IMPAIRED QUALITY OF LIFE & SHORTENED SURVIVAL

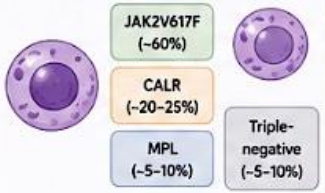
Myelofibrosis is a clonal stem cell disorder in which mutant signaling drives aberrant hematopoiesis, profibrotic inflammation, marrow failure and extramedullary hematopoiesis.

PATHOPHYSIOLOGY OF CYTOPENIAS IN MYELOFIBROSIS

Cytopenias in myelofibrosis result from impaired hematopoiesis, ineffective blood cell production, marrow failure due to fibrosis, and peripheral destruction or sequestration.

OVERVIEW

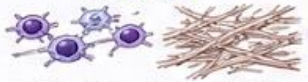
1. DRIVER MUTATIONS in hematopoietic stem cell



2. ABERRANT SIGNALING & INFLAMMATION

- ↑ JAK–STAT signaling
- ↑ TGF-β, PDGF, CTGF
- ↑ IL-1, IL-6, TNF-α
- ↑ Hepcidin, ROS

3. MARROW MICROENVIRONMENT DISRUPTION

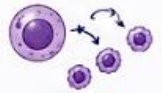


Activation of stromal cells and fibroblasts

Excess deposition of extracellular matrix (collagen I, III, fibronectin)

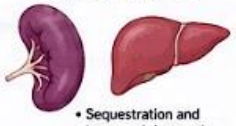
↓ CXCL12, SCF and other niche factors

4. HEMATOPOIETIC FAILURE INEFFECTIVE HEMATOPOIESIS



- Impaired proliferation and differentiation
- Apoptosis of hematopoietic precursors
- Ineffective erythropoiesis

5. EXTRAMEDULLARY HEMATOPOIESIS & HYPERSPLENISM



- Sequestration and increased destruction in enlarged spleen
- Pooling and destruction of cells in liver and other sites

RESULT

Decreased production, increased destruction/ sequestration and redistribution of blood cells lead to **CYTOPENIAS**

MECHANISMS RESPONSIBLE FOR EACH LINEAGE CYTOPENIA

ANEMIA

↓ RED BLOOD CELLS / HEMOGLOBIN

Key Pathophysiologic Mechanisms

Ineffective erythropoiesis

- Abnormal megakaryocytes and inflammatory cytokines (IL-6, TNF-α, IFN-γ) induce apoptosis of erythroid precursors
- Dyserythropoiesis

Marrow fibrosis and niche failure

- Replacement of hematopoietic space by fibrous tissue
- Impaired stem/progenitor cell support

Iron dysregulation

- ↑ Hepcidin (driven by inflammation)
- Iron sequestration in macrophages and reduced iron availability for erythropoiesis

Extramedullary hematopoiesis & hypersplenism

- Sequestration of RBCs in spleen
- Shortened RBC survival

RESULT

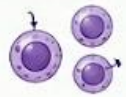
Reduced circulating red blood cells and hemoglobin → **ANEMIA**

NEUTROPENIA

↓ NEUTROPHILS / ANC

Key Pathophysiologic Mechanisms

Impaired myelopoiesis



- Reduced proliferation and differentiation of myeloid precursors
- Increased apoptosis

Marrow fibrosis and niche failure

- Fibrosis limits space and access to supportive signals
- Impaired release of mature neutrophils

Immune-mediated and inflammatory effects

- Cytokines (TNF-α, IFN-γ, IL-1) and immune activation may suppress myelopoiesis
- Autoimmune neutropenia (rare)

Peripheral sequestration / destruction

- Sequestration in hypersplenic state
- Increased peripheral consumption in inflammatory states

RESULT

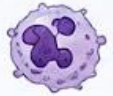
Reduced circulating neutrophils → **NEUTROPENIA** (increased risk of infections)

THROMBOCYTOPENIA

↓ PLATELETS

Key Pathophysiologic Mechanisms

Impaired megakaryopoiesis



- Abnormal megakaryocytes with defective maturation
- Apoptosis of megakaryocyte progenitors

Marrow fibrosis and niche failure

- Reduced megakaryocyte proliferation
- Impaired localization and release of platelets

Hypersplenism

- Sequestration of platelets in enlarged spleen
- Increased destruction

Immune-mediated mechanisms

Immune thrombocytopenia (may coexist)

- Autoantibody-mediated platelet destruction

RESULT

Reduced circulating platelets → **THROMBOCYTOPENIA** (increased risk of bleeding)

CONTRIBUTING SYSTEMIC AND CLINICAL FACTORS THAT WORSEN CYTOPENIAS

Chronic inflammation
Sustained cytokine release suppresses hematopoiesis and iron metabolism

Organomegaly
Extramedullary hematopoiesis and splenomegaly increase sequestration and destruction

Disease progression
Advancing fibrosis and clonal evolution lead to greater marrow failure

Therapy-related
Cytoreductive drugs (e.g., hydroxyurea, ruxolitinib), interferon, chemotherapy

Comorbid conditions
Infections, autoimmune disease, nutritional deficiencies, renal or liver dysfunction

KEY TAKE-HOME MESSAGE

Cytopenias in myelofibrosis are multifactorial—resulting from ineffective hematopoiesis, marrow fibrosis and microenvironmental failure, extramedullary hematopoiesis with hypersplenism, and immune/inflammatory-mediated mechanisms.

Management requires addressing both disease biology and reversible contributing factors.

Abbreviations: ANC, absolute neutrophil count; CTGF, connective tissue growth factor; IFN, interferon; IL, interleukin; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; SCF, stem cell factor; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha.

References: 1. Tefferi A, Barbui T. N Engl J Med. 2019;381:2135-2144. 2. Mesa RA et al. CA Cancer J Clin. 2023;73:119-154. 3. Ginzburg YZ et al. Blood. 2021;137:1861-1871. 4. Leukemia. 2021;35:1051-1069.

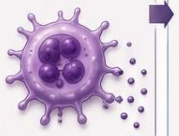
PATHOPHYSIOLOGY OF ANEMIA IN MYELOFIBROSIS

MULTIFACTORIAL, INTERCONNECTED, AND PROGRESSIVE

Anemia in myelofibrosis results from a combination of ineffective erythropoiesis, marrow failure, chronic inflammation, hypersplenism, and increased red cell destruction.

1 CLONAL HEMATOPOIESIS & ABERRANT CYTOKINES

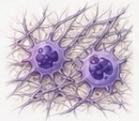
JAK2, CALR, or MPL mutations drive clonal megakaryocyte proliferation and release of profibrotic and inflammatory cytokines.



TGF-β · PDGF · IL-1β · TNF-α · IL-6

2 MARROW FIBROSIS & MICROENVIRONMENTAL DISRUPTION

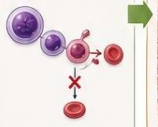
Cytokines activate fibroblasts and promote excessive deposition of reticulin and collagen.



Disrupted niche
Impaired hematopoietic support
Reduced EPO responsiveness

3 INEFFECTIVE ERYTHROPOIESIS

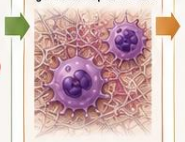
Abnormal marrow microenvironment and cytokines cause apoptosis and maturation arrest of erythroid precursors.



↑ Apoptosis
↓ Colony formation
Poor reticulocyte production

4 MARROW FAILURE (REDUCED PRODUCTION)

Progressive replacement of hematopoietic space by fibrosis and abnormal megakaryocytes leads to global hematopoietic failure.

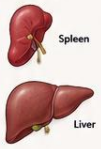


↓ Erythroid precursors
↓ Hematopoietic space
↓ RBC production

5 EXTRAMEDULLARY HEMATOPOIESIS & HYPERSPLENISM

Blood cell production shifts to spleen and liver.

Enlarged spleen sequesters and destroys blood cells.



Cell sequestration
Increased destruction
Reduced circulating RBCs

ANEMIA IN MYELOFIBROSIS

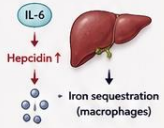
CONSEQUENCES

- Fatigue
- Dyspnea
- Reduced exercise tolerance
- Impaired quality of life

KEY PATHOGENIC MECHANISMS CONTRIBUTING TO ANEMIA

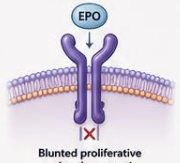
CHRONIC INFLAMMATION (ANEMIA OF CHRONIC DISEASE)

- Elevated IL-6, TNF-α, IL-1β increase hepcidin
- Hepcidin causes iron sequestration and reduced iron availability
- Blunted response to EPO



IMPAIRED ERYTHROPOIETIN SIGNALING

- Fibrotic niche and cytokines reduce EPO sensitivity
- Downregulation of EPO receptor signaling pathways



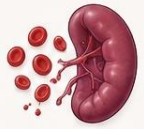
Blunted proliferative and anti-apoptotic signals

NUTRITIONAL AND FUNCTIONAL DEFICIENCIES

- Iron deficiency (absolute or functional)
- Folate and B12 deficiency
- Contribute to impaired erythropoiesis

INCREASED RED CELL DESTRUCTION

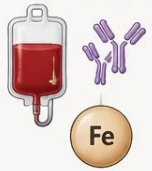
- Hypersplenism leads to sequestration and premature destruction
- Autoimmune hemolysis may occur



Shortened RBC survival

TRANSFUSION-RELATED FACTORS (LATE STAGE)

- Iron overload
- Alloimmunization
- Transfusion dependence worsens symptoms



INTEGRATED MODEL

Clonal mutations (JAK2/CALR/MPL) → Aberrant megakaryocytes & cytokine release → Fibrosis & disrupted marrow niche

Ineffective erythropoiesis	+	Marrow failure (reduced production)	+	Inflammation & iron dysregulation	+	Hypersplenism & hemolysis	=	↓ Circulating RBCs = ANEMIA
↑ Apoptosis ↓ Maturation		↓ Erythroid precursors ↓ Hematopoietic space		↑ Hepcidin ↓ Iron availability		↑ Sequestration ↑ Destruction		

FACTORS ASSOCIATED WITH GREATER ANEMIA SEVERITY

- Higher DIPSS or MIPSS70 risk
- Advanced fibrosis grade (MF-2/3)
- High serum hepcidin and IL-6
- Large spleen volume
- Transfusion dependence
- Fe Iron deficiency
- Older age and comorbidities

CLINICAL IMPLICATION

Anemia in myelofibrosis is not solely due to decreased production but arises from multiple overlapping mechanisms that require a comprehensive, individualized management approach.

THERAPEUTIC TARGETS

- Reduce inflammation (JAK inhibitors, anti-IL-6)
- Improve ineffective erythropoiesis (luspatercept, imetelstat)
- Manage iron dysregulation (hepcidin modulators)
- Treat hypersplenism (ruxolitinib, splenectomy in selected cases)
- Correct deficiencies and minimize transfusion complications

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What is your threshold (in terms of symptom burden, degree of splenomegaly, etc) for initiating active treatment for patients with low-risk MF?

 Prof Harrison	Splenomegaly – symptomatic or progressive >2-3 cm increase, rising WBC and thrombocytosis
 Dr Rampal	Constitutional symptoms +/- symptomatic splenomegaly
 Dr Bose	Any symptoms
 Dr Kuykendall	Significant symptom burden or symptomatic splenomegaly
 Dr Mascarenhas	If MPN-related symptoms are clear and bothersome or spleen >5-10 cm
 Dr Yacoub	Presence of true B symptoms

MPN = myeloproliferative neoplasm

RTP RESEARCH TO PRACTICE

In which situations, if any, will you initiate active treatment for a patient with MF who is asymptomatic?

 Prof Harrison	Increasing splenomegaly, WBC, LDH or blasts, decreasing Hb
 Dr Rampal	Massive splenomegaly
 Dr Bose	Increasing splenomegaly
 Dr Kuykendall	Splenomegaly >20 cm
 Dr Mascarenhas	Splenomegaly >20 cm
 Dr Yacoub	Low risk clinically and high risk by molecular models

If a patient with treatment-naïve MF were to ask you to estimate the likelihood that they would achieve meaningful clinical benefit with ruxolitinib, how would you respond?

 Prof Harrison	If there was an indication to use I would say 97% have an initial reduction in spleen size
 Dr Rampal	>80%
 Dr Bose	90%
 Dr Kuykendall	Most patients treated with ruxolitinib experience benefit in terms of spleen size reduction and improvement in symptoms
 Dr Mascarenhas	Very high
 Dr Yacoub	Patients with good initial response who can tolerate therapy will likely have a longer response

RTP RESEARCH TO PRACTICE

What starting dose and schedule of ruxolitinib would you typically use for the patient below with MF and a platelet count >200,000/µL?

	Otherwise healthy 65-year-old	Frail 80-year-old
 Prof Harrison	20 mg BID	Maybe 10 mg BID (depending on Hb)
 Dr Rampal	20 mg BID	5 mg BID
 Dr Bose	20 mg BID	20 mg BID
 Dr Kuykendall	20 mg BID	15 mg BID
 Dr Mascarenhas	15 mg BID	10 mg BID
 Dr Yacoub	15 mg BID	10 mg BID

What is the highest dose of ruxolitinib you would employ for a patient whose disease is not responding or suboptimally responding?

 Prof Harrison	25 mg BID
 Dr Rampal	25 mg BID
 Dr Bose	25 mg BID
 Dr Kuykendall	25 mg BID
 Dr Mascarenhas	25 mg BID
 Dr Yacoub	25 mg BID

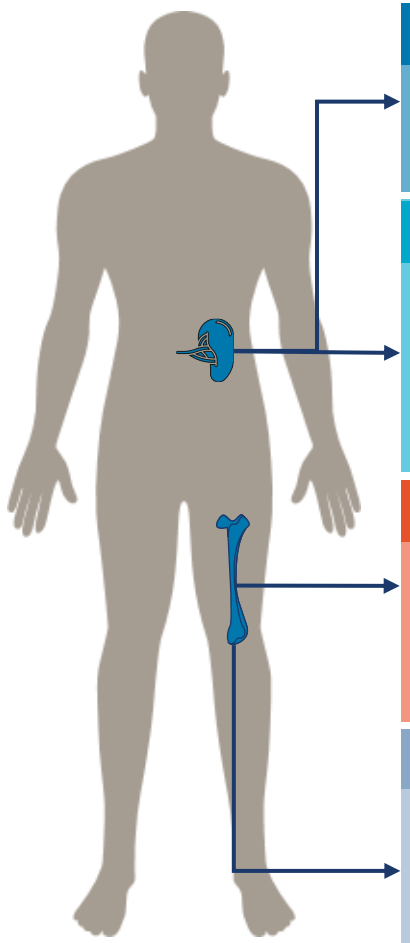
Biology of Myelofibrosis (MF): Current and Future Clinical Decision-Making in the Absence of Severe Cytopenias

Claire.Harrison18@nhs.net

GUY'S INTERNATIONAL CENTRE OF EXCELLENCE IN MYELOID DISORDERS G-ICEMD
MPN • AML • MDS • SM • CML • CEL

MPN voice

MF burden is driven by splenomegaly, bone marrow fibrosis and cytopenias



Splenomegaly[1]

The revised 2022 ICC diagnostic criteria for MF include palpable splenomegaly as a minor criteria

MF-related symptoms[1-3]

Surveys of patients with MF suggest that **>80% were experiencing ≥1 disease-related symptom** at the time of the survey[4]

- **Weight loss**
- **Night sweats**
- **Fever**
- **Fatigue**
- **Itching**
- **Bone pain**

Bone marrow fibrosis[1,5]

Progressive bone marrow fibrosis leads to a myelophthisic phenotype with worsening cytopenias, which can lead to bone pain

Cytopenia[1]

At diagnosis, roughly **40%** of patients have **Hb <10 g/dL, and** over **20%** are already **RBC transfusion-dependent**

- **Anaemia**
- **Thrombocytopenia**

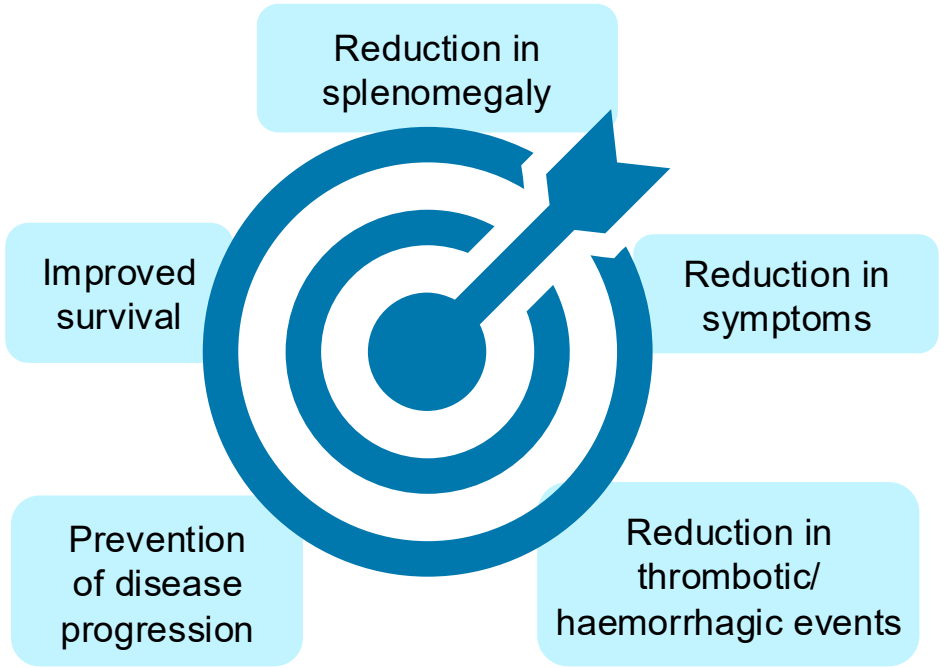
Burdensome symptoms **negatively affect** the **quality of life** of patients[2]

Hb, haemoglobin; ICC, International consensus classification; MF, myelofibrosis; RBC, red blood cell.

1. Tefferi A, et al. *Am J Hematol* 2023;98:801–821; 2. Verstovsek S, et al. *Cancer* 2023;129:1681-1690; 3. Breccia M, et al. *Front Oncol* 2024;14:1382872; 4. Mughal TI, et al. *Int J Gen Med* 2014;7:89–101; 5. O'Sullivan JM, et al. *Clin Adv Hematol Oncol* 2018;16:121–131.

Current treatment goals do not adequately address the underlying MF disease biology

Current MF treatment goals include:[1]



JAKi, the cornerstone of MF therapy, **reduce symptoms and splenomegaly, and modestly improve survival**[2–4]

These treatments do not consistently **resolve pathobiological** features of MF and **may not adequately address the underlying disease biology**[2,5]

An **unmet need** remains due to the **limited depth and durability of clinical response** and frequency of TEAEs with **JAKi monotherapy**[5]

JAKi, Janus kinase inhibitor; MF, myelofibrosis; TEAE, treatment-emergent adverse event.

1. Asher S, et al. Blood Rev 2020;42:100715; 2. Gill H, et al. Hematology Am Soc Hematol Educ Program 2023;2023:667–675; 3. Bose P, Verstovsek S. *Hemasphere* 2020;4:e424; 4. Vainchenker W, et al. *Fac Rev* 2023;12:23; 5. Rampal RK, et al. *Nat Med* 2025;31:1531–1538.

Despite treatment advances for MF, an unmet need remains

JAKi predominantly alleviates splenomegaly and MF-associated symptoms, with modest survival benefit, but has limited impact on disease progression and underlying disease biology

Treatment options remain limited and HSCT, the only curative approach, is available to a minority of patients with high or very high-risk MF

There is a need for novel agents that offer the potential for disease modification to improve clinical outcomes

MF, myelofibrosis.

Addressing the limitations of JAKi monotherapy in MF

MF

MF is a **complex disease**, and current therapies **do not adequately** address the **underlying disease biology**[1,2]

JAKi

JAKi monotherapy is associated with **limited depth** and **durability** of clinical response[2]

Early JAKi initiation for patients with intermediate-2 and high-risk MF **improves clinical outcomes**, including **fewer cytopenias**, **durable SVR** and **prolonged OS**[3]

Early intervention

Novel or **combination first-line strategies** could **improve** the current **treatment paradigm**[4]

New strategies

JAKi, Janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; SVR, spleen volume response.

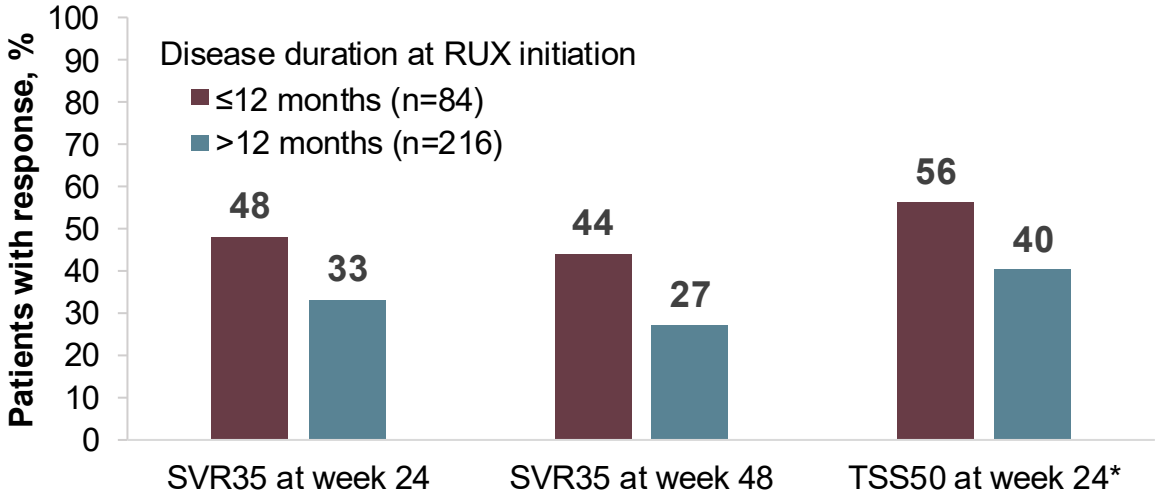
1. Gill H, et al. *Hematology Am Soc Hematol Educ Program* 2023;1:667–675; 2. Rampal RK, et al. *Nat Med* 2025;31:1531–1538; 3. Verstovsek S, et al. *Cancer* 2023;129:1681–1690; 4. Harrison CN, et al. *Cancer* 2024;130:2091–2097.

Early treatment in MF may improve clinical outcomes including prolonged overall survival

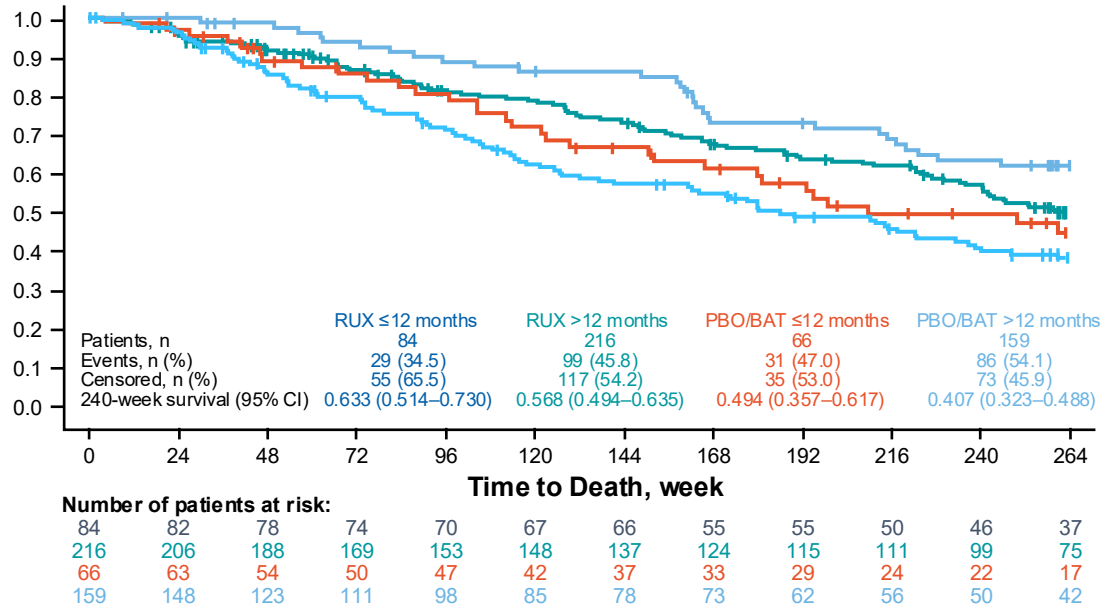
In a pooled analysis of COMFORT-I and COMFORT-II, early RUX initiation within 1 year of diagnosis was associated with improved spleen and symptom responses and prolonged survival

- At RUX initiation, spleen responses were more durable among those with a disease duration ≤12 months vs >12 months

Spleen and symptom responses by disease duration at RUX initiation



OS of patients by disease duration at RUX initiation



BAT, best available therapy; CI, confidence interval; JAKi, Janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; PBO, placebo; RUX, ruxolitinib; SVR35, spleen volume reduction ≥35% from baseline; TSS50, total symptom score reduction ≥50% from baseline.

*Data only available for COMFORT-1.

Verstovsek S, et al. ASH 2021. Abstract 1505. Reproduced with permission from Incyte Corporation; Verstovsek S, et al. *Cancer* 2023;129:1681–1690.

Many patients experience inadequate response with JAKi monotherapy

1L 'failure' and its subcategories

Primary resistance	
Primary refractory	Absence of onset of any clinical response within 28 days of starting treatment
Lack of response	Failure to achieve a >CI (e.g., spleen or symptom response) within 12 weeks of starting
“Mixed response”	AEs (e.g., cytopenias) complicate CI or better clinical response
Secondary resistance	
Relapse/loss of response	<CI after reaching CI/PR/CR or loss of anaemia or spleen responses persisting for ≥1 month (IWG-MRT/ELN)
and/or disease progression	e.g., worsening leukocytosis, thrombocytopenia, anaemia, increase in circulating blasts
Intolerance	
Patients have dose reductions or interruptions due to development or exacerbation of cytopenias	

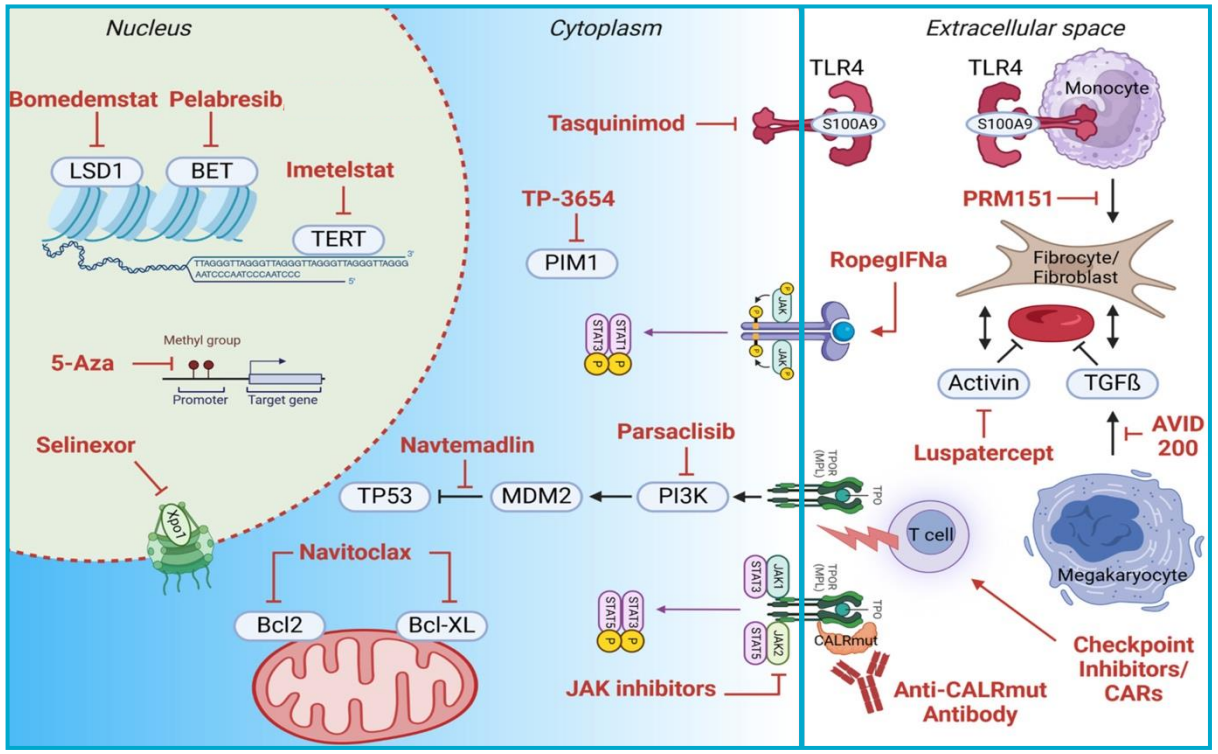
1L, first-line; AE, adverse events; CI, clinical improvement; CR, complete response; ELN, European LeukemiaNet; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; PR, partial response; RUX, ruxolitinib.

Harrison CN, et al. *Ann Hematol* 2020;99:1177–1191.

New targets beyond JAK-STAT could enable opportunities for combination strategies

- Resistance may occur due to the activation of non-JAK-STAT pathways[1,2]
- Targets of novel therapeutics in MF in clinical development include:[2]
  - Epigenetics
  - Apoptosis
  - Telomerase
  - Intracellular signaling pathways

Targets beyond the JAK-STAT pathway[3]



Bcl-2, B-cell lymphoma-2; Bcl-XL, B-cell lymphoma-extra large; BET, bromodomain and extra-terminal domain; CALR, calreticulin; CARs, chimeric antigen receptor T cells; CD123, interleukin-3 receptor subunit alpha; JAK, Janus kinase; JAK-STAT, JAK signal transducer and activator of transcription; LSD1, lysine-specific demethylase 1; MDM2, murine double minute 2 homolog; MF, myelofibrosis; PI3K, phosphoinositide 3-kinase; PIM, proviral insertion site in Moloney murine leukaemia virus kinase; TERT, telomerase reverse transcriptase; TGFβ, transforming growth factor beta; TLR4, Toll-like receptor 4; TP53, tumour protein 53; TPOR, thrombopoietin receptor; XPO1, exportin 1.

1. Thaw K, et al. Curr Hematol Malig Rep 2024;19:264-275; 2. Tremblay D and Mascarenhas J. *Cells* 2021;10:1034; 3. Koschmieder S. *HemaSphere* 2024;8:e70056.

JAKi combination approaches are being explored to address unmet needs – Phase 3 trials

Drug	Trials	Mechanism of action	Latest phase in MF	Line of treatment	Active Phase 3 MF clinical trials,* n
Therapies in development for MF					
Pelabresib[1,2]	MANIFEST (Phase 2) MANIFEST-2 (Phase 3)	BET inhibitor	Phase 3	JAKi-naive, in combination with RUX	1
Imetelstat[3,4]	IMproveMF (Phase 1/1b) IMbark (Phase 2) IMpactMF (Phase 3)	Telomerase inhibitor	Phase 3	Relapsed/refractory to JAKi treatment	1
Luspatercept[5-7]	ACE-536-MF-001 (Phase 2) INDEPENDENCE (Phase 3)	TGF-β inhibitor	Phase 3	Patients with anaemia and require red blood cell transfusions on concomitant JAKi treatment	1
Navtemadlin[8,9]	KRT-232-109 (Phase 1/2) POEISIS (Phase 3) BOREAS (Phase 2/3)	MDM2 inhibitor	Phase 3	JAKi-naive with suboptimal response to RUX, as add-on to RUX Relapsed/refractory to JAKi	2
Selinexor[10]	SENTRY-2 (Phase 2) SENTRY (Phase 3)	XPO1 inhibitor	Phase 3	JAKi-naive, in combination with RUX	1

BET, bromodomain and extra-terminal domain; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MDM2, murine double minute 2 homolog; MF, myelofibrosis; RUX, ruxolitinib; TGF-β, transforming growth factor beta; XPO1, exportin 1.
*Phase 3 trials active as of December 18, 2024.

1. ClinicalTrials.gov. NCT0460349. Available at: https://clinicaltrials.gov/study/NCT04603495. Accessed April 2026; 2. Rampal RK, et al. Nat Med 2025;31:1531-1538; 3. ClinicalTrials.gov. NCT04576156. Available at: https://clinicaltrials.gov/study/NCT04576156. Accessed April 2026; 4. Mascarenhas J, et al. Future Oncol 2022;18:2393–2402; 5. ClinicalTrials.gov. NCT04717414. Available at: https://clinicaltrials.gov/study/NCT04717414. Accessed April 2026; 6. Gerds AT, et al. Blood Adv 2024;8:4511–4522; 7. ClinicalTrials.gov. NCT04717414. Available at: https://clinicaltrials.gov/study/NCT04717414. Accessed April 2026; 8. ClinicalTrials.gov. NCT03662126. Available at: https://clinicaltrials.gov/study/NCT03662126. Accessed April 2026; 9. ClinicalTrials.gov. NCT06479135. Available at: https://clinicaltrials.gov/study/NCT06479135. Accessed April 2026; 10. ClinicalTrials.gov. NCT04562389. Available at: https://clinicaltrials.gov/study/NCT04562389. Accessed April 2026.

Phase 3 MANIFEST-2 study evaluates pelabresib + RUX in patients who are JAKi-naïve

Global, randomized, double-blind, active-controlled, Phase 3 trial[1,2]

Study population[1]

JAKi-naive patients with myelofibrosis (N=430)
(primary or post-ET/PV)

- DIPSS Int-1 risk or higher
- Spleen volume (≥450 cm^3)
- Platelet count ≥100 × $10^9/L^2$
- TSS ≥10 (≥3 for two symptoms, MFSAF v4.0)
- Peripheral blast count <5%
- ECOG PS ≤2

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

Double-blind randomization[1] (1:1)

Treatment arms[1]

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

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

Primary endpoint[1]
- SVR35 response at week 24

Key secondary endpoints[1]
- Absolute change in TSS from baseline at week 24
- TSS50 response at week 24

Safety[1]
- AEs of all grades and serious AEs

AE, adverse event; BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythaemia; Int, intermediate; JAKi, Janus kinase inhibitor; MFSAF, Myelofibrosis Symptom Assessment Form; PO, orally; PV, polycythaemia vera; QD, once daily; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline.

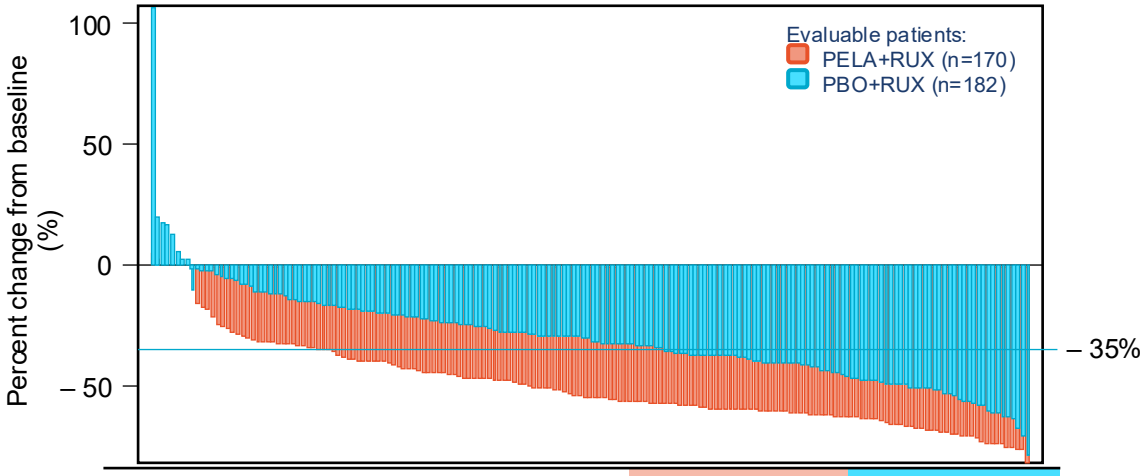
*The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD. †RUX was started at 10 mg BID (baseline platelet count 100-200 × 109/L) or 15 mg BID (baseline platelet count >200 ×109/L) with a mandatory dose increase by 5 mg BID after 1 cycle and a maximum dose of 25 mg BID as per the label.

1. Rampal RK, et al. Nat Med 2025;31:1531–1538; 2. Harrison CN et al. *Future Oncol* 2022;18:2987–2997

Significant reduction in spleen volume was demonstrated in MANIFEST-2 at week 24 and sustained at week 96

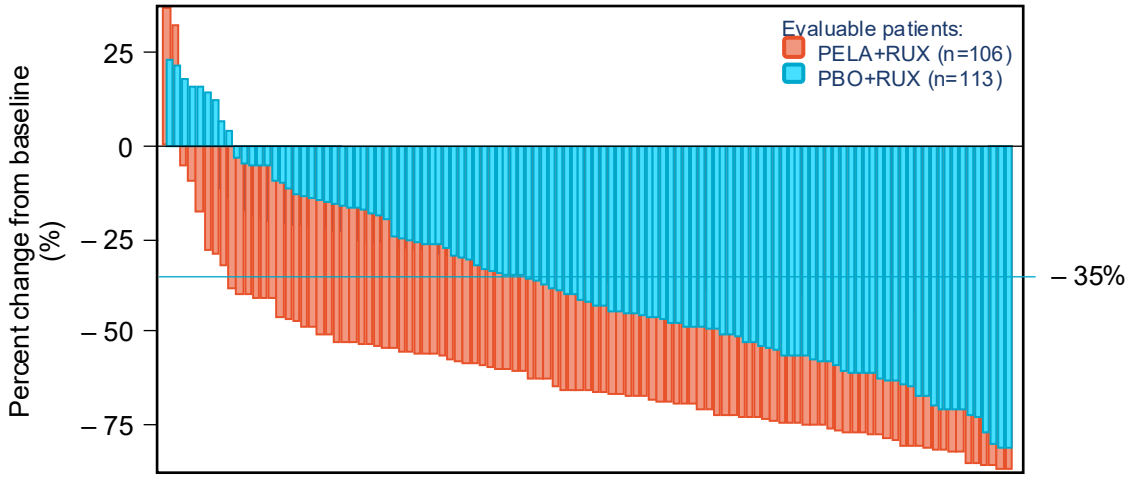
Phase 3 MANIFEST-2 primary endpoint

Week 24



	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at week 24 in **evaluable patients**	82.9% (141/170)	41.8% (76/182)
Difference	41.1%	
SVR35 response at week 24 in **ITT population**	65.9% (141/214)	35.2% (76/216)
Difference	30.4% (21.6-39.3)	

Week 96



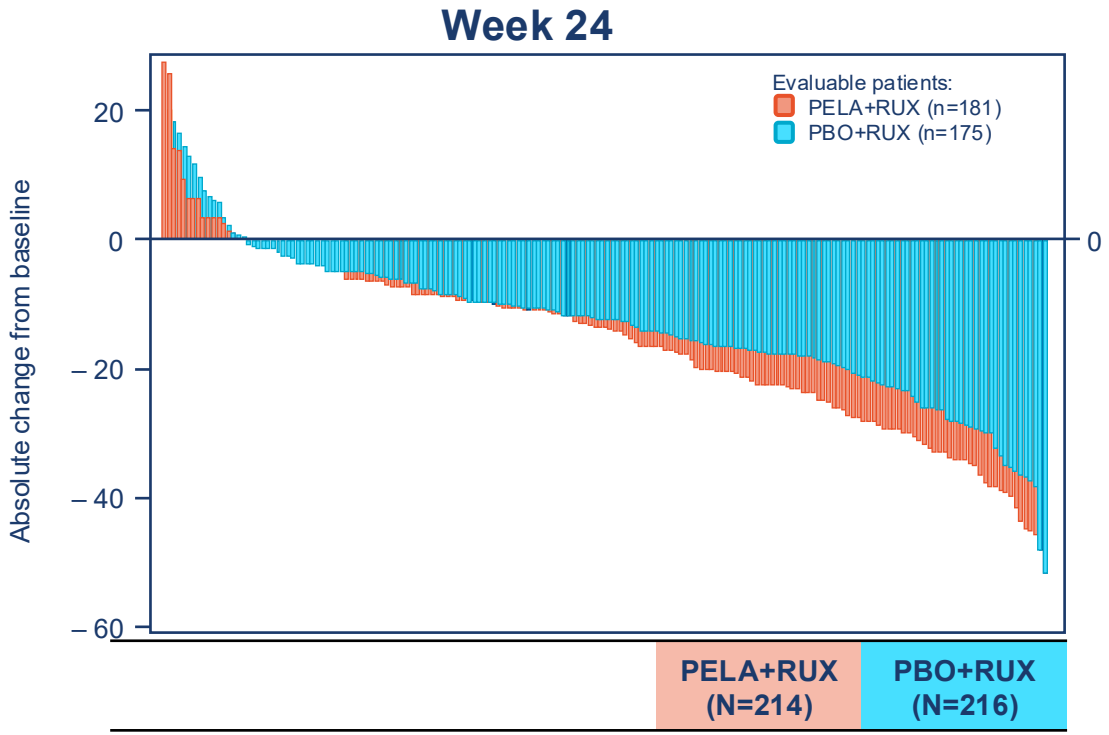
	PELA+RUX (N=214)	PBO+RUX (N=216)
SVR35 response at week 96 in **evaluable patients**	91.5% (97/106)	57.5% (65/113)
Difference	34.0%	
SVR35 response at week 96 in **ITT population**	45.3% (97/214)	30.1% (65/216)
Difference	14.9% (6.1-23.8)	

Data cutoff date: March 2, 2025.
Spleen volume assessed by central read.

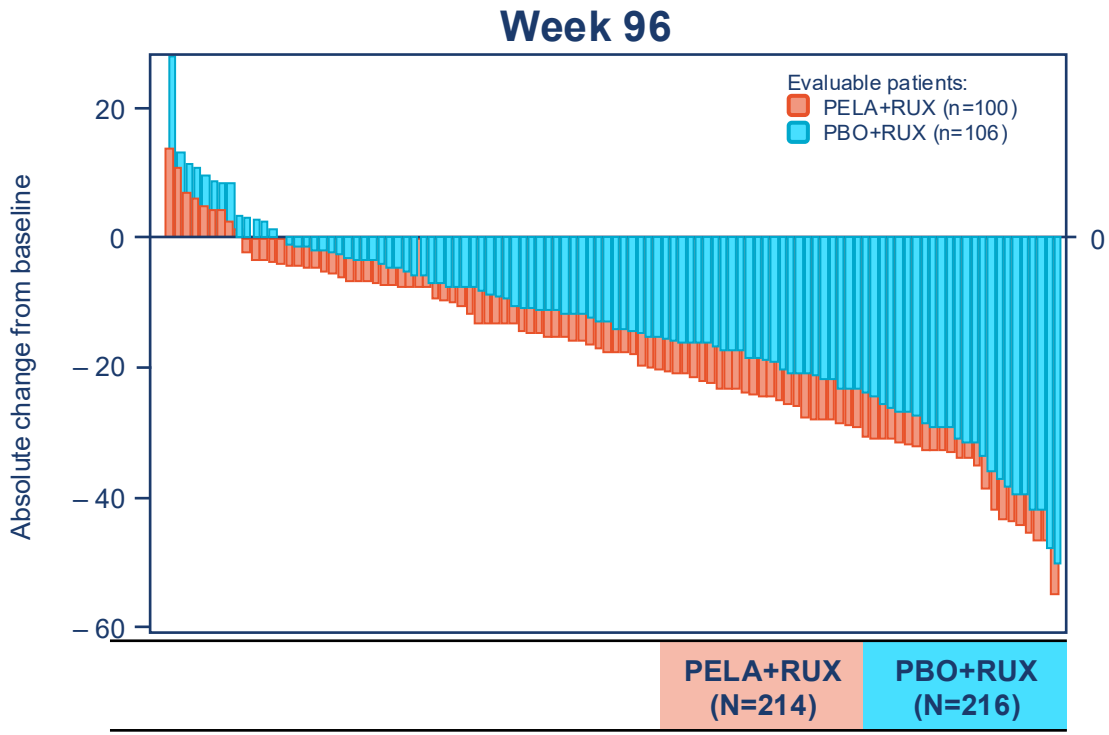
Waterfall plots represent evaluable patients who have baseline and week 24 or week 96 data. * Calculated by stratified Cochran–Mantel–Haenszel test.
CI, confidence interval; ITT, intent-to-treat; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; SVR35, ≥35% reduction in spleen volume from baseline.

Rampal R, et al. Presented at: ASH 2025 Congress; December 6–9, 2025; Orlando, Florida. Oral 910.

In MANIFEST-2, improvements in absolute TSS at week 24 were sustained through week 96



	PELA+RUX (N=214)	PBO+RUX (N=216)
TSS change from baseline at Week 24 in the **ITT population,** LSM	-15.08	-13.12
Difference (95% CI)	-1.96 (-4.11, 0.18)	



	PELA+RUX (N=214)	PBO+RUX (N=216)
TSS change from baseline at Week 96 in the **ITT population,** LSM	-15.07	-12.48
Difference (95% CI)	-2.59 (-5.23, 0.05)	

Data cutoff date: March 02, 2025.

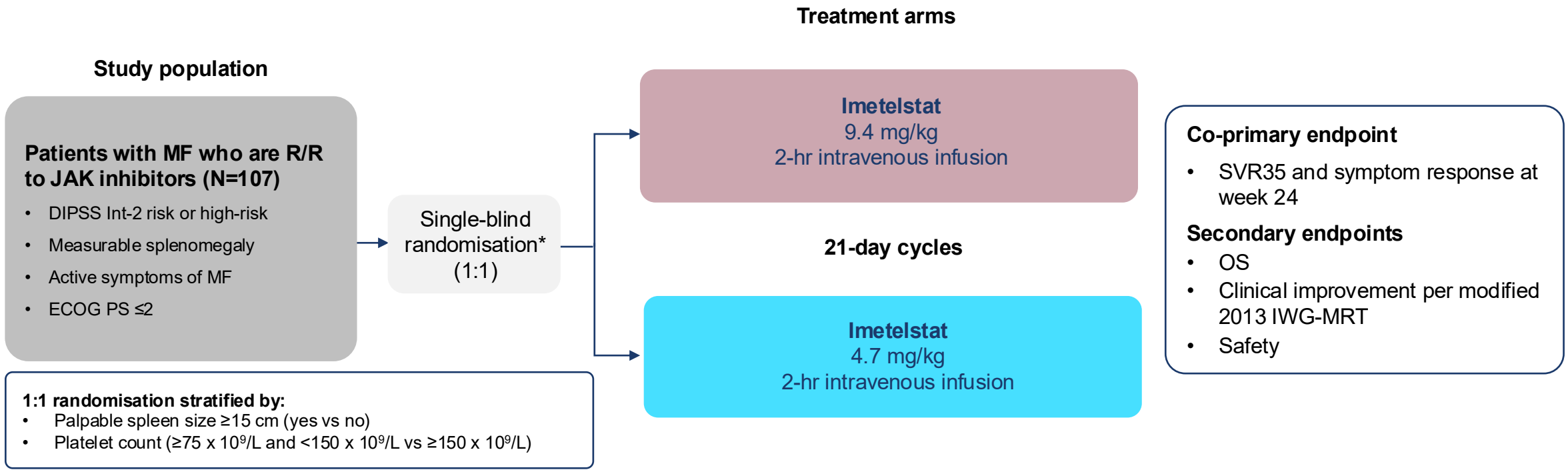
Waterfall plots represent evaluable patients who have baseline and Week 24 or Week 96 data. TSS assessed by MFSAF v4.0 and using an MMRM analysis of absolute change from baseline TSS.

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.

Rampal R, et al. Presented at: ASH 2025 Congress; December 6–9, 2025; Orlando, Florida. Oral 910.

Phase 2 IMbark study evaluates imetelstat in patients with R/R MF

Single-blind, randomised study to assess the efficacy and safety of two doses of imetelstat



The Phase 3 study of imetelstat is ongoing

*Patients were blinded to treatment dose.
DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; Int, intermediate; IWG-MRT, International Working Group-Myeloproliferative Neoplasm Research and Treatment; JAK, Janus kinase; MF, myelofibrosis; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; SVR35, ≥35% reduction in spleen volume from baseline.
Mascarenhas J, et al. *J Clin Oncol* 2021;39:2881–2892.

Greater spleen and symptom responses were seen with a higher dose of imetelstat in the IMbark study

Phase 2 IMbark co-primary endpoints

Spleen response (SVR) at week 24

Spleen response	4.7 mg/kg (n=48)	9.4 mg/kg (n=59)
≥10% SVR, n (%)	4 (8.3)	22 (37.3)
≥20% SVR, n (%)	1 (2.1)	13 (22)
≥30% SVR, n (%)	0	6 (10.2)

Symptom response (TSS50) at week 24

Symptom response	4.7 mg/kg (n=48)	9.4 mg/kg (n=59)
≥50% TSS reduction, n (%)	3 (6.3)	19 (32.2)

An imetelstat dose of 9.4 mg/kg demonstrated clinical benefit in patients with MF who are R/R to JAKi treatment

JAKi, Janus kinase inhibitor; MF, myelofibrosis; R/R, relapse/refractory; SVR, spleen volume reduction; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score.

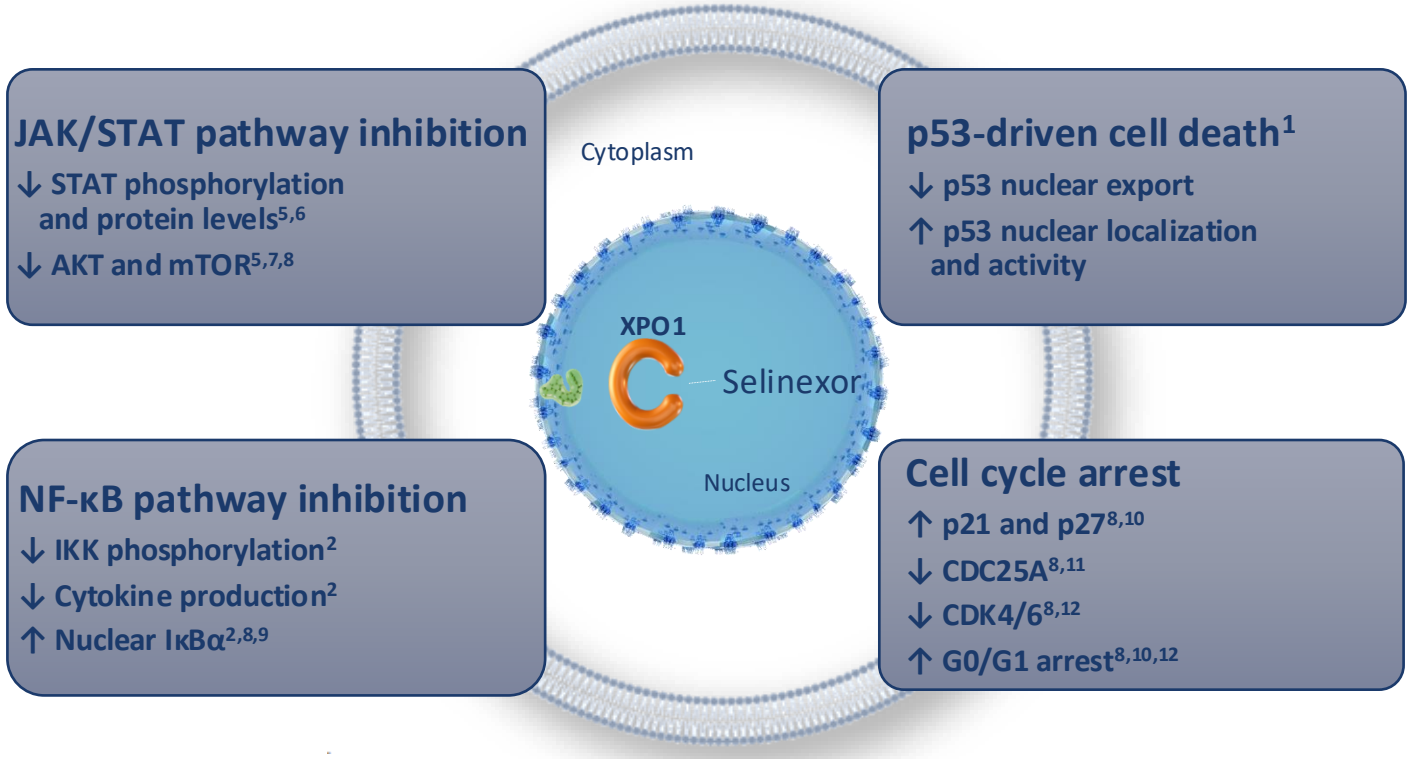
Mascarenhas J, et al. *J Clin Oncol* 2021;39:2881–2892.

Selinexor is an investigational, targeted, oral XPO1 inhibitor

Selinexor inhibits XPO1-mediated nuclear cargo protein export that may lead to:

- Increased malignant cell death[1]
- Reduced inflammation[2]
- Apoptosis of *JAK2*-mutated MF CD34+ cells but not healthy donor cells[3]
- Synergism with ruxolitinib and other therapeutic agents in cell lines with or without *JAK2*^{V617F} and *TP53* mutations[4]

XPO1 inhibition is a fundamental mechanism of action that may target both JAK/STAT and non-JAK/STAT pathways in MF



IκBα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKK, IκB kinase complex; JAK 2, janus kinase 2; JAK/STAT, janus kinase/signal transducer and activator of transcription; MF, myelofibrosis; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; STAT, signal transducer and activator of transcription; XPO1, exportin 1.

1. Yan D, et al. Clin Cancer Res 2019;25:2323–35; 2. Kashyap T, et al. Oncotarget 2016;7:78883–895; 3. Lu M, et al. Abstract #1792; poster at ASH 2023; San Diego, CA. 4. Maloof M, et al. Poster presented at: 15th International Congress for Myeloproliferative Neoplasms (MPN); November 2–3, 2023; Brooklyn, NY; 5. Walker CJ, et al. Blood 2013;122:3034–44; 6. Cheng Y, et al. Mol Cancer Ther 2014;13:675–86; 7. Argueta C, et al. Oncotarget. 2018;9;25529–44; 8. Gandhi UH, et al. Clin Lymphoma Myeloma Leuk 2018;18:335–45; 9. Turner JG, et al. Oncotarget 2016;7:78896–909; 10. Gravina GL, et al. BMC Cancer 2015;15:941; 11. Garg M, et al. Oncotarget 2017;8:7521–32; 12. Tan M, et al. Am J Physiol Renal Physiol 2014;307:F1179–86.

ASCO 2026;Abstract LBA6500

Selinexor plus ruxolitinib in JAK inhibitor–naïve myelofibrosis: Phase 3 SENTRY trial

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Selinexor Plus Ruxolitinib in JAK Inhibitor–Naïve Myelofibrosis: Phase 3 SENTRY Trial

Authors: Prithviraj Bose, MD , Haris Ali, MD , Haifa Kathrin Al-Ali, MD, PhD, Valentin Garcia-Gutierrez, MD, PhD, Sebastian Grosicki, MD, PhD , Zhanet Grudeva-Popova, MD, PhD, MHM , Claire Harrison, DM, FRCP, PRCPath , ... SHOW ALL ... , for the SENTRY Trial Investigators | AUTHORS INFO & AFFILIATIONS

J Clin Oncol • Just Accepted

Phase 3 SENTRY study evaluates selinexor + RUX in patients who are JAKi-naïve

Double-blind, placebo-controlled, randomised study to assess the efficacy and safety of selinexor + RUX vs placebo + RUX[1,2]

Study population[1,2]

Adults with JAKi-naive MF (N=353)[1,2]

- DIPSS Int-1 with symptoms, Int-2 or high-risk[1]
- Measurable splenomegaly[1]
- Active symptoms of MF[1]
- ECOG PS ≤2[1]

Stratified by:[1]
- DIPSS: Int-1 vs Int-2 or high risk
- Spleen volume: <1800 cm^3 vs >1800 cm
- Baseline platelet counts: 100–200 x 10^9/L vs >200 x10^9/L

Double-blind randomisation (2:1) with stratification[1]

Treatment arms[1,2]

Selinexor 60 mg oral tablet QW days 1, 8, 15, 22 + **RUX** 15 or 20 mg BID starting dose based on baseline platelet count

28-day cycles

Placebo 60 mg oral tablet QW days 1, 8, 15, 22 + **RUX** 15 or 20 mg BID starting dose based on baseline platelet count

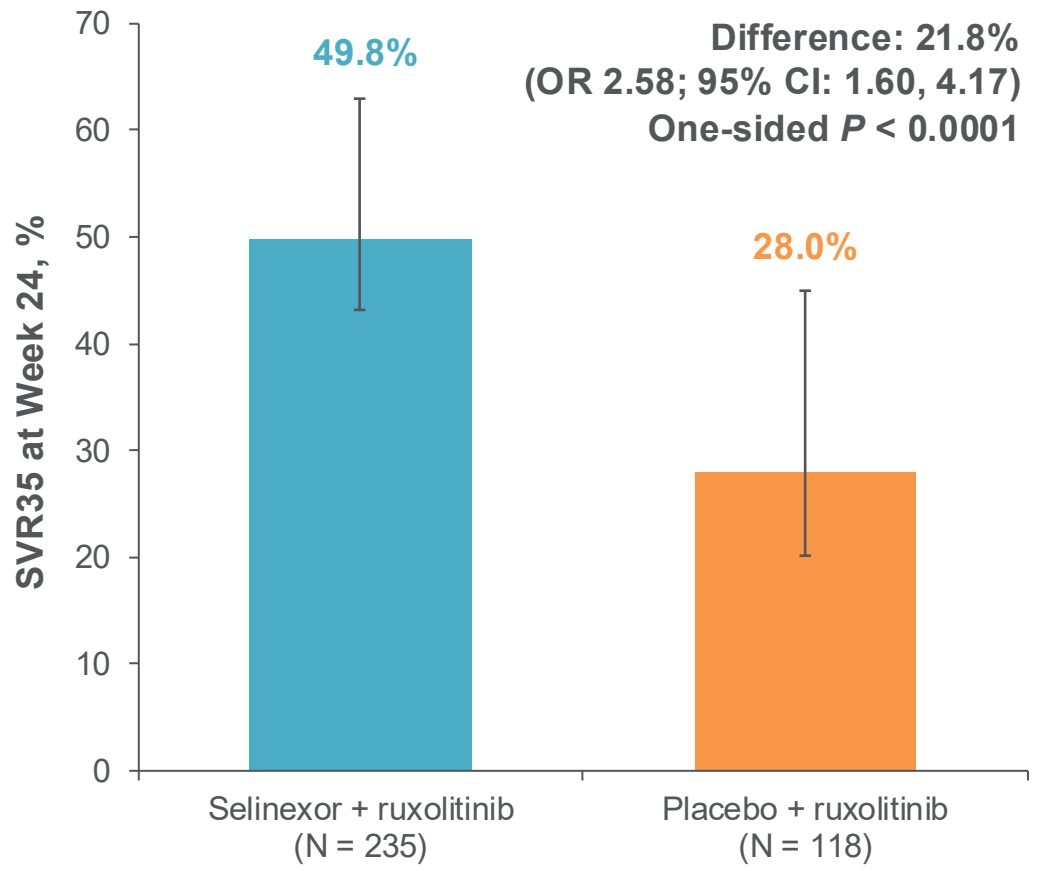
Co-primary endpoint[1,2]
- SVR35 and absolute mean change in TSS at week 24

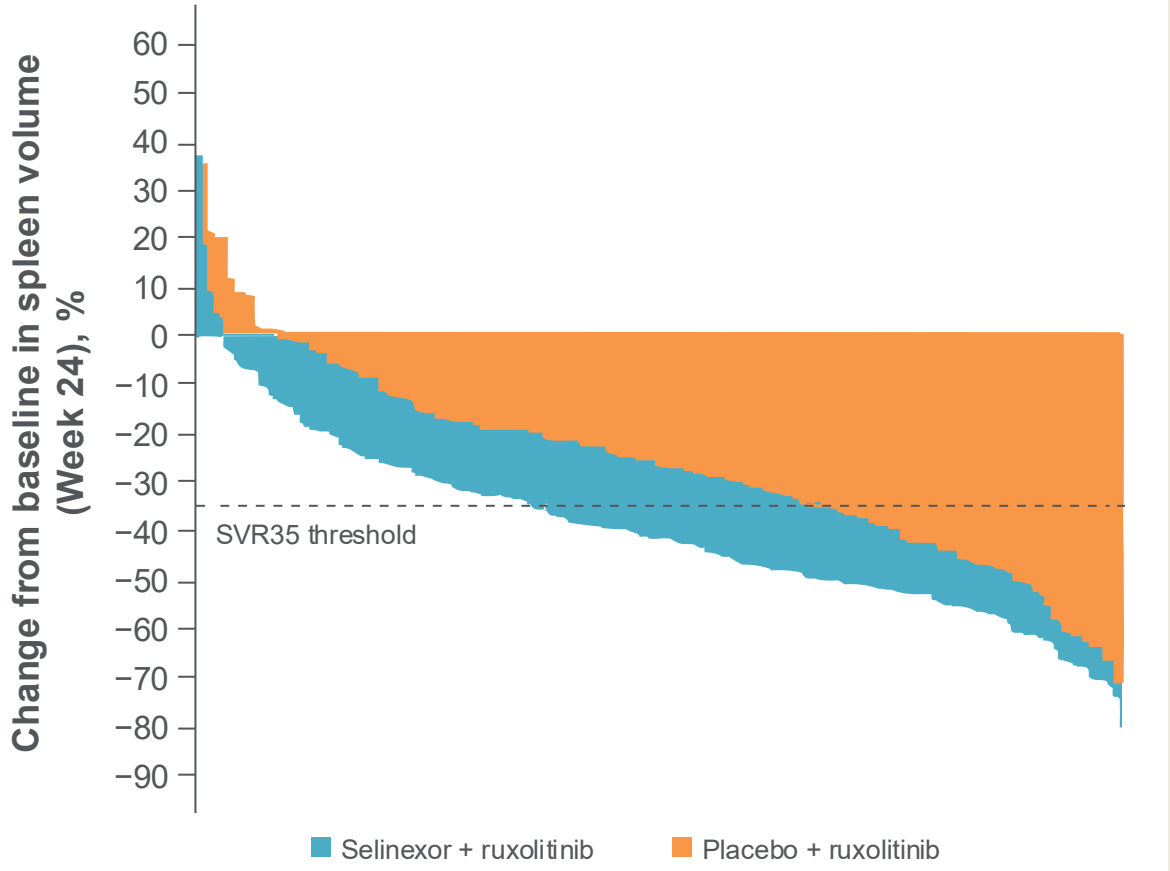
Secondary endpoints[1,2]
- Safety and tolerability[1]
- OS and PFS[1,2]
- SVR35 and absolute mean change in TSS at week 48 and anytime[1]
- Duration of SVR response[1]
- Pharmacokinetics[1]

BID, twice a day; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; Int, intermediate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; PFS, progression-free survival; QW, once weekly; RUX, ruxolitinib; SVR, spleen volume reduction; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score;

1. Mascarenhas J, et al. *Future Oncol* 2025;21:807–813; 2. Clinicaltrial.gov. NCT04562389. Available at: https://clinicaltrials.gov/study/NCT04562389. Accessed April 2026.

Significantly higher SVR35 at Week 24 with selinexor + ruxolitinib vs ruxolitinib alone





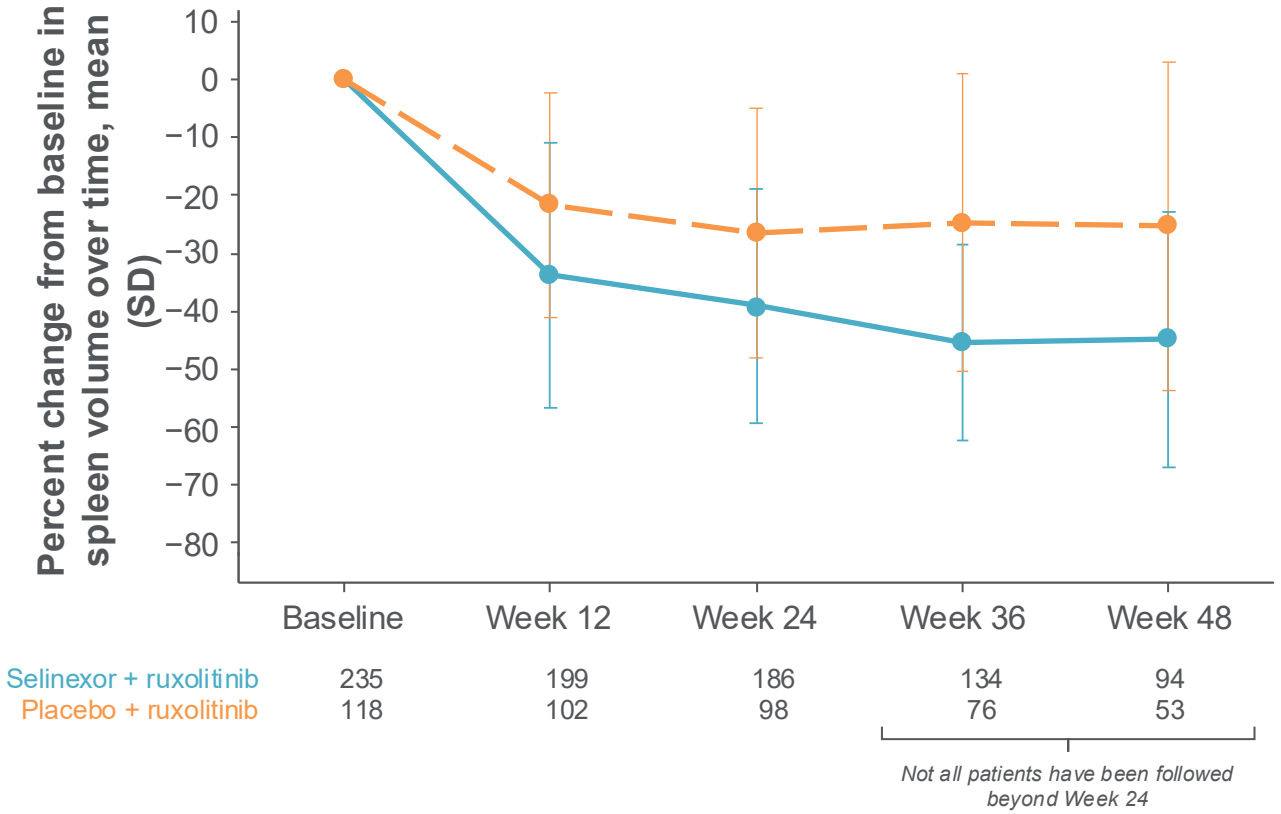
Data cut off: February 20, 2026.
*Cochran-Mantel-Haenszel test stratified by randomization factors.
Placebo arm scaled 2:1 to compensate for randomization ratio.
CI: confidence interval; OR: odds ratio; SD: standard deviation; SVR35: spleen volume reduction of at least 35% from baseline.

Presented by: John Mascarenhas, MD

ASCO 2026;Abstract LBA6500.

Rapid, deep, and sustained spleen volume reduction with selinexor + ruxolitinib vs ruxolitinib alone

Percent change from baseline in spleen volume over time



SVR35 rates over time

SVR35*	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Week 12, n (%)	116 (49.4)	24 (20.3)
Week 24, n (%)	117 (49.8)	33 (28.0)
Week 36, n/n1† (%)	97/207 (46.9)	23/100 (23.0)
At any time, n (%)	159 (67.7)	53 (44.9)
	OR 2.59 (95% CI: 1.64, 4.10) **Nominal *P* < 0.0001**	

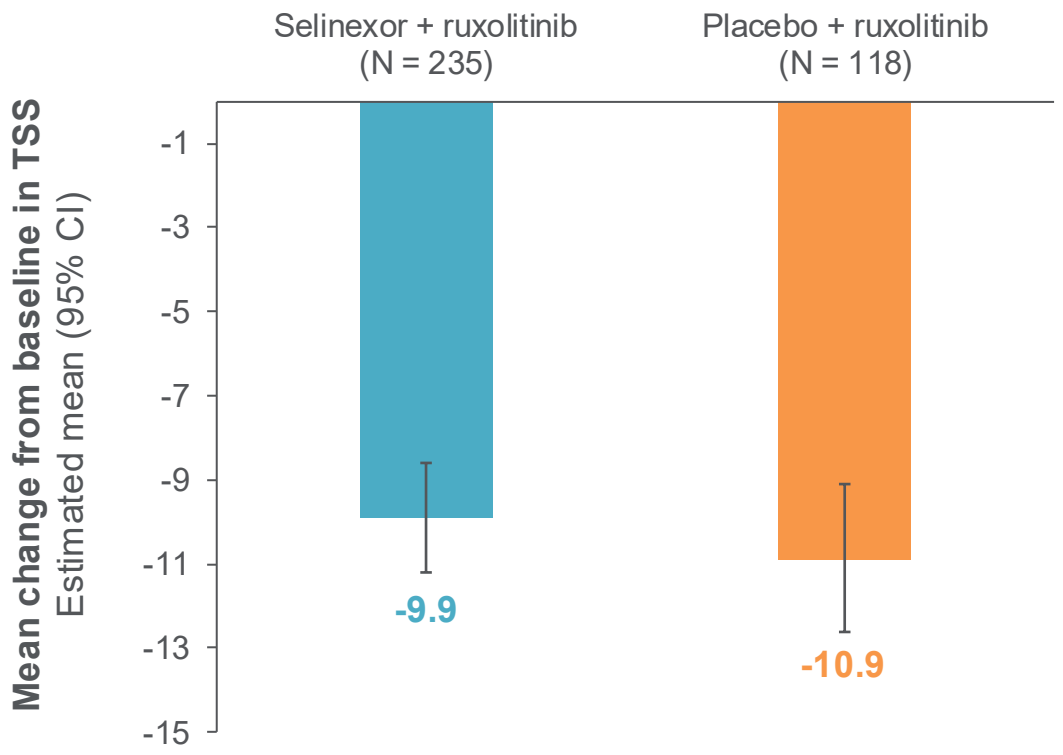
Data cut off: February 20, 2026.
*SVR35 at any time defined as proportion of patients with SVR35 to any post-baseline assessment regardless of visit window before any new anti-MF therapy or disease progression.
†n1 = number of patients who completed spleen assessment or discontinued the study prior to the specific timepoint.
CI: confidence interval; MF: myelofibrosis; OR: odds ratio; SD: standard deviation; SVR35: spleen volume reduction of at least 35% from baseline.

Presented by: John Mascarenhas, MD

ASCO 2026;Abstract LBA6500.

No difference in AbsTSS between treatment arms at Week 24

Both arms demonstrated similar improvement in symptoms



TSS	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Change in absolute TSS at Week 24 Estimated mean (95% CI)	-9.9 (-11.2, -8.6)	-10.9 (-12.6, -9.1)
Adjusted mean difference (95% CI)	0.97 (-1.07, 3.02); one-sided *P* = 0.825	

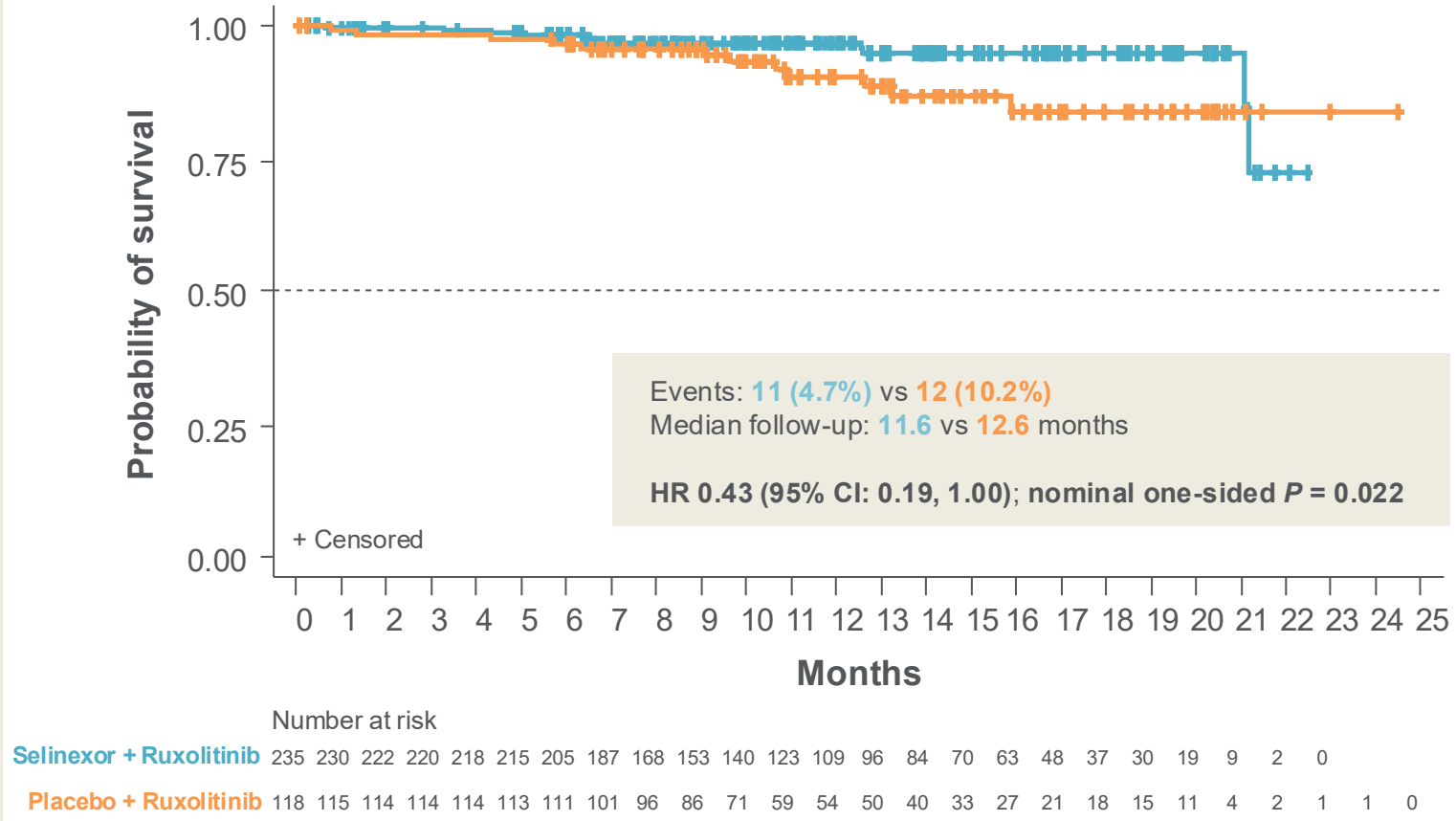
Reductions in TSS were consistent across symptom domains

Data cut off: February 20, 2026.
Adjusted absolute mean change from baseline, adjusted mean difference, 95% CI, and one-sided P-value are based on mixed-effects model for repeated measures adjusted for randomization stratification factors and baseline TSS.
AbsTSS; absolute total symptom score; CI: confidence interval; TSS: total symptom score.

Presented by: John Mascarenhas, MD

ASCO 2026;Abstract LBA6500.

Meaningful overall survival with selinexor + ruxolitinib vs ruxolitinib alone



Deaths	Selinexor + ruxolitinib (N = 235)	Placebo + ruxolitinib (N = 118)
Primary cause of death, n (%)		
Disease progression	3 (1.3)	3 (2.5)
Adverse event	3 (1.3)	5 (4.2)
Other	5 (2.1)	1 (0.8)
Unknown	0	3 (2.5)

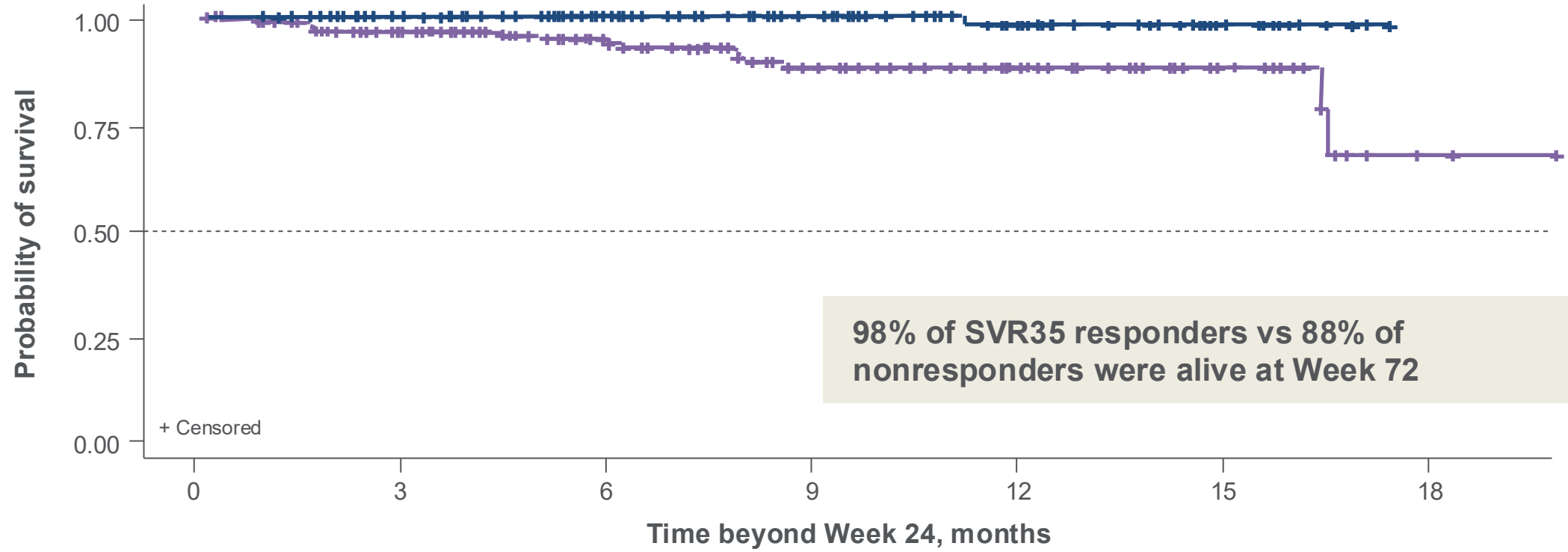
Data cut off: February 20, 2026.
OS is defined as the duration from date of randomization to date of death due to any cause. Follow-up time based on reverse Kaplan-Meier method by swapping the censoring status. OS analysis stratified by the randomization stratification factors. Hazard ratio based on Cox Proportional Hazard model with Efron's method of handling ties.
CI: confidence interval; HR: hazard ratio; OS: overall survival.

Presented by: John Mascarenhas, MD

ASCO 2026;Abstract LBA6500.

SVR35 at Week 24 predicted overall survival irrespective of treatment

Landmark analysis at Week 24



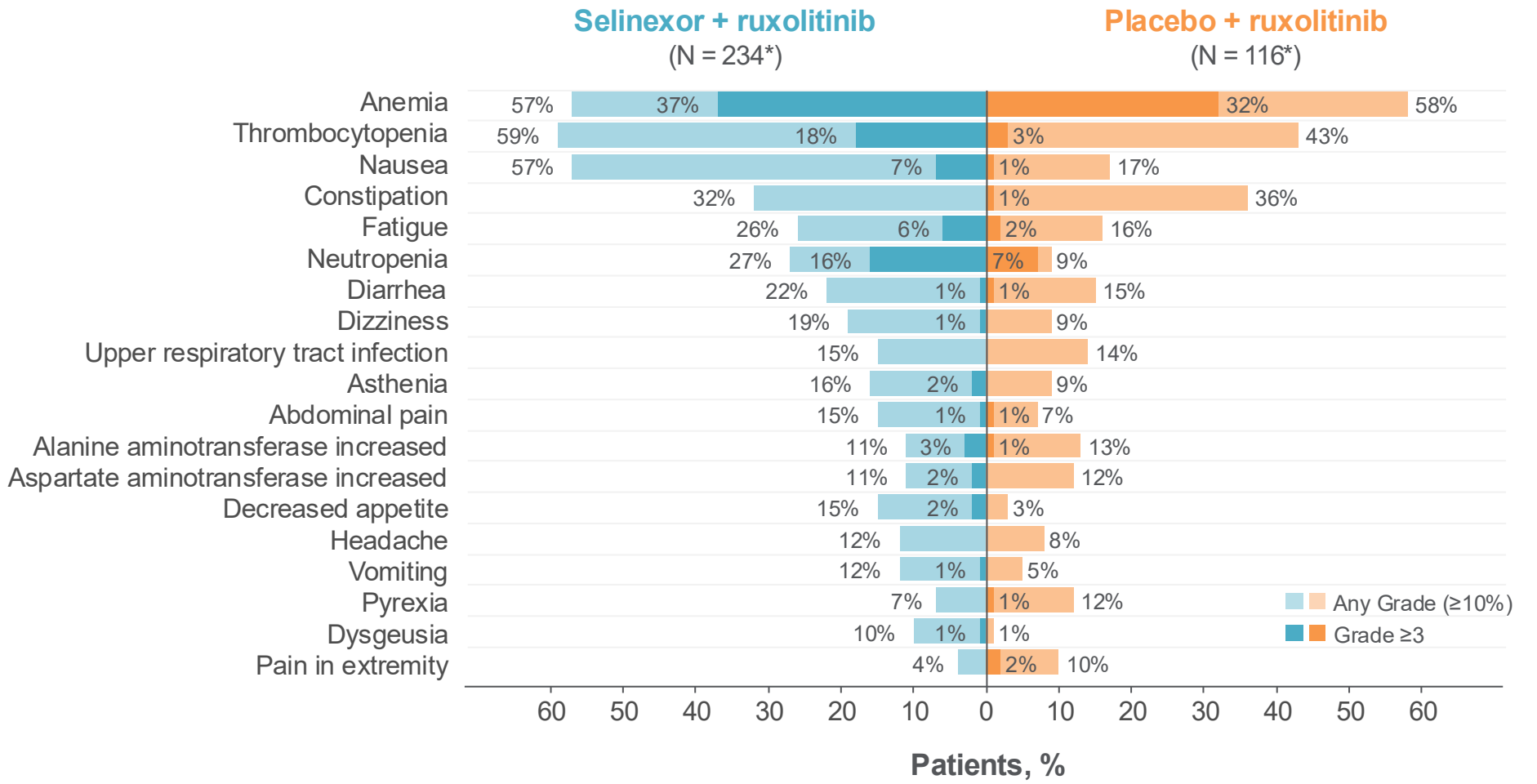
	Number at risk						
SVR35 at Week 24	150	126	89	68	37	12	0
No SVR35 at Week 24	180	141	99	62	35	18	2

Data cut off: February 20, 2026.
SVR35: spleen volume reduction of at least 35% from baseline.

Presented by: John Mascarenhas, MD

ASCO 2026;Abstract LBA6500.

Treatment-emergent adverse events



Transformation to acute myeloid leukemia was rare and equivalent between arms (1.7% each)

% of selinexor + ruxolitinib patients who experienced nausea drops from 35% at Wks 1-4 to 5% at Wks 21-24

Data cut off: February 20, 2026.
*Three patients total did not receive treatment (n = 1, selinexor; n = 2, placebo) and were excluded from this analysis.

Presented by: John Mascarenhas, MD

ASCO 2026;Abstract LBA6500.

Phase 3 BOREAS study evaluates navtemadlin vs BAT* in patients with R/R MF

Randomised, controlled, open-label study to assess the efficacy and safety of navtemadlin vs BAT[1,2]

Study population[1-3]

Adults with *TP53*^{WT} MF who are R/R to JAKi (N=282)[1]

- Confirmed diagnosis of PMF, post-PV or post-ET MF[1-3]
- Failure of prior JAKi treatment[1-3]
- DIPSS Int-1, Int-2 or high-risk[2]
- ECOG PS ≤2[1,2]

Stratified by:[1]

- MF type (primary vs secondary [post-PV or post-ET])
- Baseline TSS (≤10 v <10)

Double-blind randomisation (2:1) with stratification[1]

Treatment arms[1-3]

Navtemadlin (n=188)[1]
240 mg oral QD
7 days on, 21 days off

28-day cycles

BAT* (n=94)[1]
7 days on, 21 days off

Primary endpoint[1-3]

- SVR35 at week 24

Key secondary endpoints[1-3]

- TSS50 at week 24[1-3]
- OS and PFS[1-3]
- Overall SVR35 any time[1-3]
- Duration of SVR response[1,3]
- RBC transfusion independence at week 24[1,3]
- Safety[1,3]

*BAT includes monotherapy or combinations: hydroxyurea, chemotherapy, and supportive care; JAKi were excluded.[1-3]

BAT, best available treatment; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythaemia; Int, intermediate; JAK, Janus kinase; JAKi, Janus kinase inhibitor; MF, myelofibrosis; OS, overall survival; PFS, progression-free survival; PV, polycythaemia vera; QD, once daily; RBC, red blood cell; R/R, relapsed/refractory; SVR, spleen volume reduction; SVR35, ≥35% reduction in spleen volume from baseline; TP53, tumour protein 53; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score; WT, wild type.

1. Verstovsek S, et al. *Future Oncol* 2022;18:4059-4069; 2. Clinicaltrials.gov. NCT03662126. Available at: https://clinicaltrials.gov/study/NCT03662126. Accessed April 2026; 3. Mascarenhas JO, et al. *Blood* 2024;144:1000.

Navtemadlin monotherapy led to a greater spleen response compared with BAT* at week 24 in BOREAS

Phase 3 BOREAS study primary endpoint

Spleen response at week 24 (ITT population)

Response	Navtemadlin (n=123)	BAT* (n=60)
Patients achieving SVR35, no (%)	18 (15)	3 (5)

Navtemadlin being tested in the on-going POEISIS trial

*BAT entails monotherapy or combinations: hydroxyurea, chemotherapy, and supportive care; JAKi were excluded.
BAT, best available treatment; ITT, intent-to-treat; MF, myelofibrosis; SVR35, ≥35% reduction in spleen volume from baseline.
Mascarenhas J et al. Oral presented at: ASH Annual Meeting & Exposition; December 7-10, 2024; San Diego, CA. Oral 1000

Emerging therapies and combinations are shaping the future of MF treatment

- Early intervention may improve clinical outcomes, including survival; however, some patients may still experience inadequate response
- Combination strategies with JAKi and emerging agents such as pelabresib, imetelstat, luspatercept, navtemadlin and selinexor are being explored in Phase 3 studies
- Mutation targeted therapies are also of great interest in the management of MF

MF, myelofibrosis.

Emerging Therapies

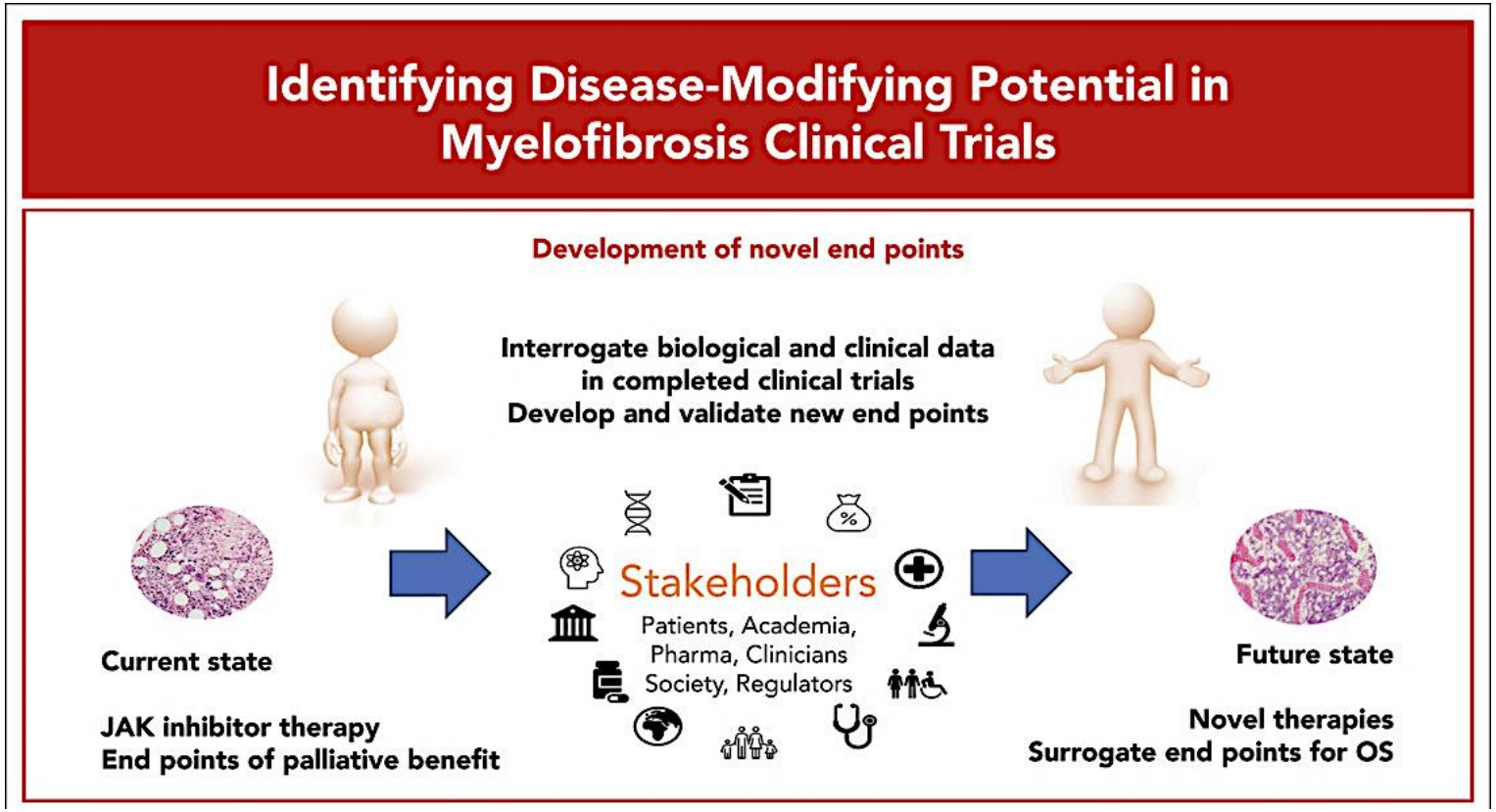
Gotlib 2026

Endpoints

- Overall Survival
- Progression
- Molecular
- Biological
- Treatment independence

- Symptoms

……..Require redefinition



What is your threshold for recommending a change in treatment for patients with MF receiving first-line ruxolitinib or fedratinib?

 Prof Harrison	Lack of response or progression
 Dr Rampal	Lack of any spleen response
 Dr Bose	Usually a multifactorial decision taking into account cytopenias, spleen, symptoms, any transfusion requirements
 Dr Kuykendall	If persistent symptoms/splenomegaly at optimal doses, I would consider clinical trials
 Dr Mascarenhas	PLT <50-75K, new transfusion dependence that persists after initial 3 months of therapy, enlarging spleen, return of symptoms or TKI-specific toxicity
 Dr Yacoub	The patient should have true disease progression and complete loss of benefit

PLT = platelet count; TKI = tyrosine kinase inhibitor

RTP RESEARCH TO PRACTICE

An 80-year-old patient receiving ruxolitinib 15 mg BID for intermediate-risk MF for 10 months is found to have increasing asymptomatic splenomegaly, a platelet count of 150,000/µL and Hgb of 13.8 g/dL. Regulatory and reimbursement issues aside, what would you most likely recommend?

 Prof Harrison	Continue ruxolitinib and add luspatercept
 Dr Rampal	Continue ruxolitinib at a higher dose
 Dr Bose	Switch to momelotinib
 Dr Kuykendall	Continue ruxolitinib and add luspatercept
 Dr Mascarenhas	Continue ruxolitinib and add luspatercept
 Dr Yacoub	Continue ruxolitinib at a higher dose

Hgb = hemoglobin

RTP RESEARCH TO PRACTICE

An 80-year-old patient has been receiving ruxolitinib 15 mg BID for intermediate-risk MF for 2 years, and his Hgb has dropped from a baseline of 10.0 g/dL to 7.0 g/dL. Spleen volume and symptoms remain well controlled. Regulatory and reimbursement issues aside, what would you most likely recommend?

 Prof Harrison	Continue ruxolitinib at a higher dose
 Dr Rampal	Continue ruxolitinib and add luspatercept
 Dr Bose	Switch to fedratinib
 Dr Kuykendall	Continue ruxolitinib at a higher dose
 Dr Mascarenhas	Continue ruxolitinib at a higher dose
 Dr Yacoub	Continue ruxolitinib and add luspatercept

RTP RESEARCH TO PRACTICE

By what increments and over what period of time do you decrease the dose of ruxolitinib for a patient you are tapering off therapy?

 Prof Harrison	5 mg every 3 to 4 days
 Dr Rampal	1 to 2 weeks by 10 mg a week
 Dr Bose	Usually by 5 mg BID every 2 weeks
 Dr Kuykendall	Ideally by 5 mg BID increments
 Dr Mascarenhas	Typically by 5 to 10 mg daily for 2 to 3 days each drop
 Dr Yacoub	If 10 mg BID or less would stop with no taper, 15 mg BID or higher, drop the dose to 10 mg

RTP
RESEARCH TO PRACTICE

Are there any scenarios in which you feel it is appropriate to discontinue therapy with ruxolitinib without tapering and, if so, which ones?

 Prof Harrison	No
 Dr Rampal	Yes, if patient is receiving low-dose ruxolitinib (5 mg BID)
 Dr Bose	Only when switching to momelotinib
 Dr Kuykendall	If patient is on 5 mg BID OR has recently started treatment and is experiencing nonhematologic intolerance
 Dr Mascarenhas	At low doses if patient has developed an evolving serious infectious complication but rarely do I stop abruptly if I can avoid it
 Dr Yacoub	Yes, if 10 mg BID or lower, would not taper

RTP RESEARCH TO PRACTICE

Based on currently available evidence, do you believe the results from the Phase III SENTRY trial will support the clinical use of or the FDA approval of selinexor in combination with ruxolitinib as first-line treatment for MF?

	Clinical use of selinexor/ruxolitinib	FDA approval of selinexor/ruxolitinib
 Prof Harrison	Yes	Yes
 Dr Rampal	Yes	No
 Dr Bose	Yes	Unsure
 Dr Kuykendall	No	No
 Dr Mascarenhas	Yes	Yes
 Dr Yacoub	No	No

Based on currently available evidence, would you like to have access to selinexor today for any of your patients with MF?

 Prof Harrison	Yes
 Dr Rampal	No
 Dr Bose	Yes, especially for those with resistant splenomegaly
 Dr Kuykendall	Yes
 Dr Mascarenhas	Yes
 Dr Yacoub	No

RTP RESEARCH TO PRACTICE

If selinexor were to become clinically available, for which patients with MF would you prioritize its use?

 Prof Harrison	Patients who have int-2/high-risk disease and a large spleen
 Dr Rampal	Patients with massive splenomegaly that are planned to go to transplant
 Dr Bose	Large spleen, possibly HMR disease, higher blasts
 Dr Kuykendall	Suboptimal response to ruxolitinib as a single agent; persistent splenomegaly affecting QOL
 Dr Mascarenhas	Very advanced disease with massive splenomegaly, TP53 mutation, other high-risk mutations that predict less response to rux alone
 Dr Yacoub	If FDA approved, I will offer it to appropriate patients

RTP RESEARCH TO PRACTICE

How would you characterize the incidence and severity of gastrointestinal side effects among patients with MF receiving selinexor?

 Prof Harrison	Common need for prophylaxis supposed to settle over time; manageable with recommended treatment
 Dr Rampal	High incidence with variable severity
 Dr Bose	The nausea is real but manageable
 Dr Kuykendall	Challenging but expected
 Dr Mascarenhas	Occurs in 2/3 and most pronounced in the first several cycles, manageable with prophylaxis and diet modifications
 Dr Yacoub	Sounds manageable based on available data

What premedication(s), if any, would you generally recommend for a patient who is about to begin treatment with selinexor?

 Prof Harrison	Dual antiemetics
 Dr Rampal	At least one antiemetic and one antidiarrheal
 Dr Bose	Dual antiemetics
 Dr Kuykendall	Likely ondansetron with PRN prochlorperazine with consideration of olanzapine if that was not effective
 Dr Mascarenhas	Ondansetron and dexamethasone
 Dr Yacoub	Dual antiemetics

RTP RESEARCH TO PRACTICE

Agenda
Management of Myelofibrosis (MF)

Introduction: The Biopathophysiology of MF

Module 1: Current and Future Clinical Decision-Making in the Absence of Severe Cytopenias — Prof Harrison

Module 2: Managing MF for Patients with Anemia and Thrombocytopenia — Dr Rampal

Module 3: Upcoming at EHA 2026

Management of Anemic and Thrombocytopenic Myelofibrosis Patients

Raajit K. Rampal M.D. Ph.D.
Director, MPN and Rare Hematologic Malignancy Program
Director, Center for Hematologic Malignancies

Memorial Sloan Kettering
Cancer Center

Cytopenic Myelofibrosis

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

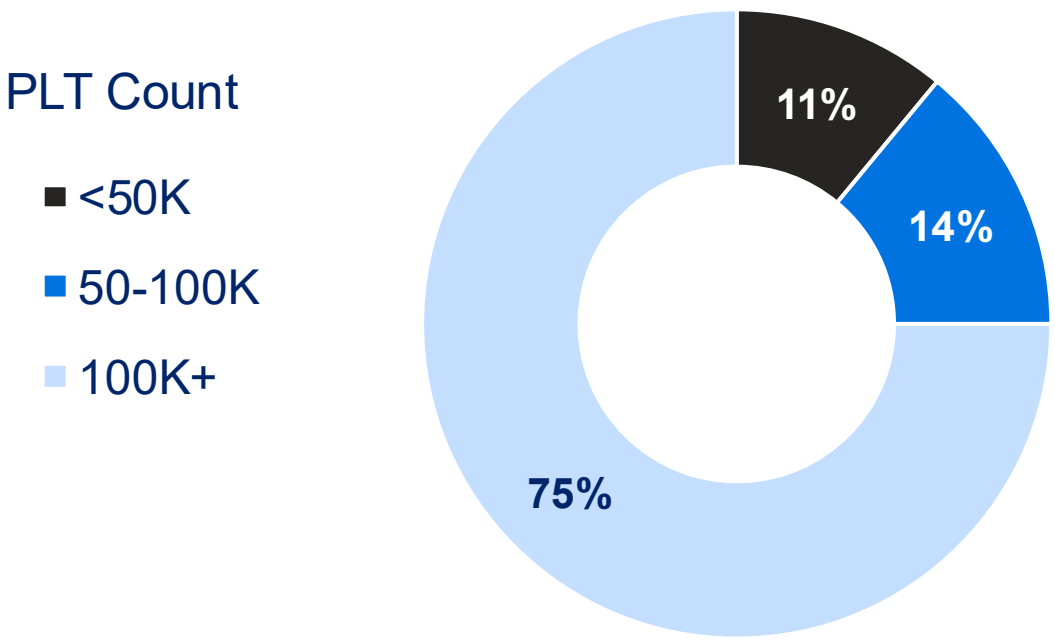
- Exam: Splenomegaly (12 cm below costal margin)
- **CBC: WBC 3.3k (1% blasts), Hb 7.5 g/dL, platelets 44k**
- Bone marrow biopsy: 90% cellular marrow with myeloid expansion, dysplastic megakaryocytes in clusters, and MF-3 fibrosis with 5% myeloid blasts
- Cytogenetics: Normal Karyotype
- Myeloid NGS panel: JAK2 V617F+, ASXL1mut+

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

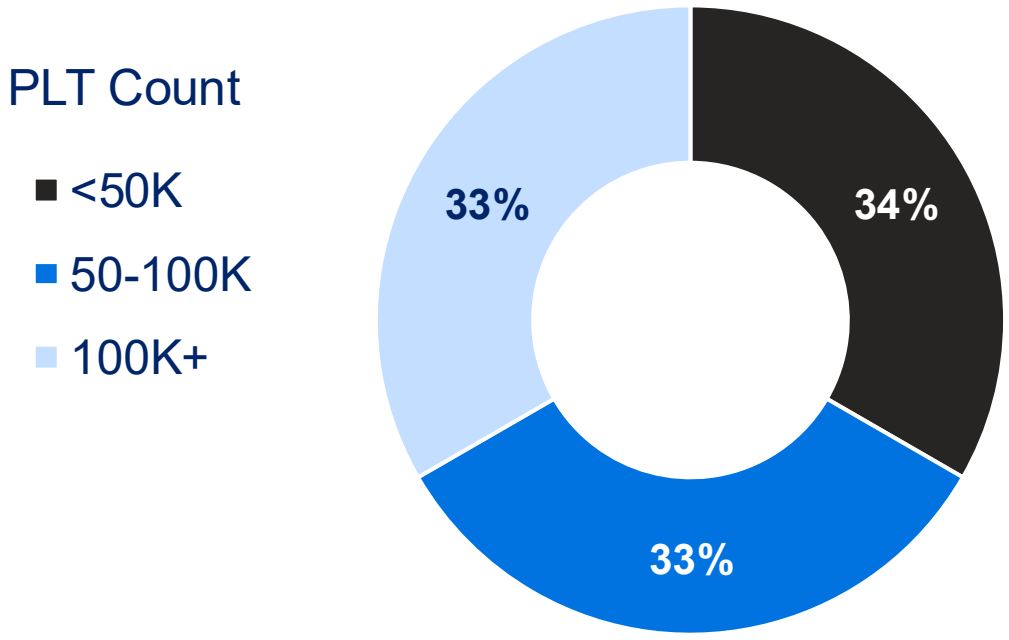
How can we manage cytopenic MF ?

Thrombocytopenia
Incidence and Prevalence

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



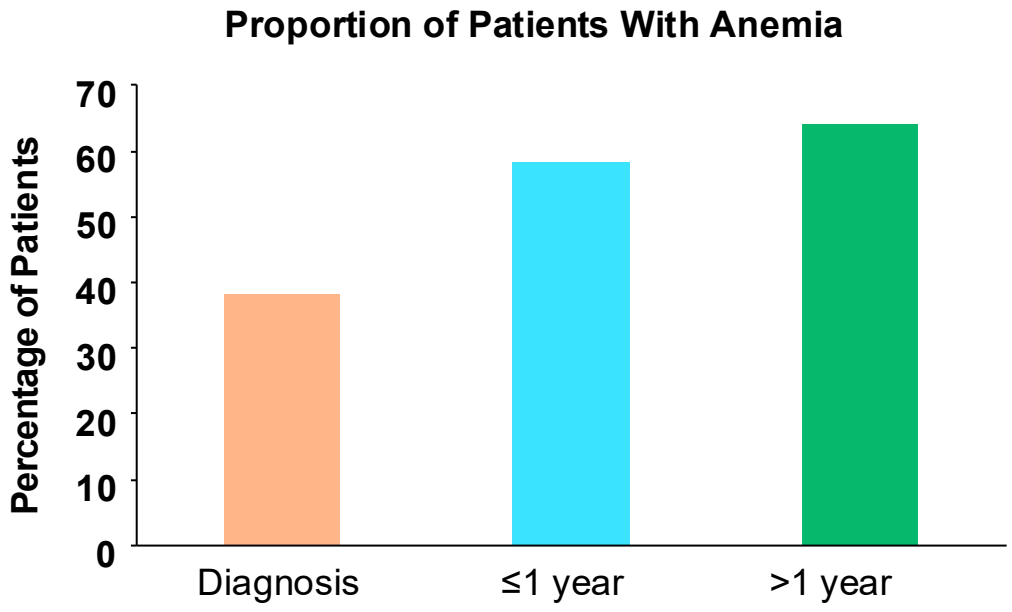
The prevalence of thrombocytopenia (PLT < 100 × 10^9/L) is approximately 68% in all patients diagnosed with MF[2]

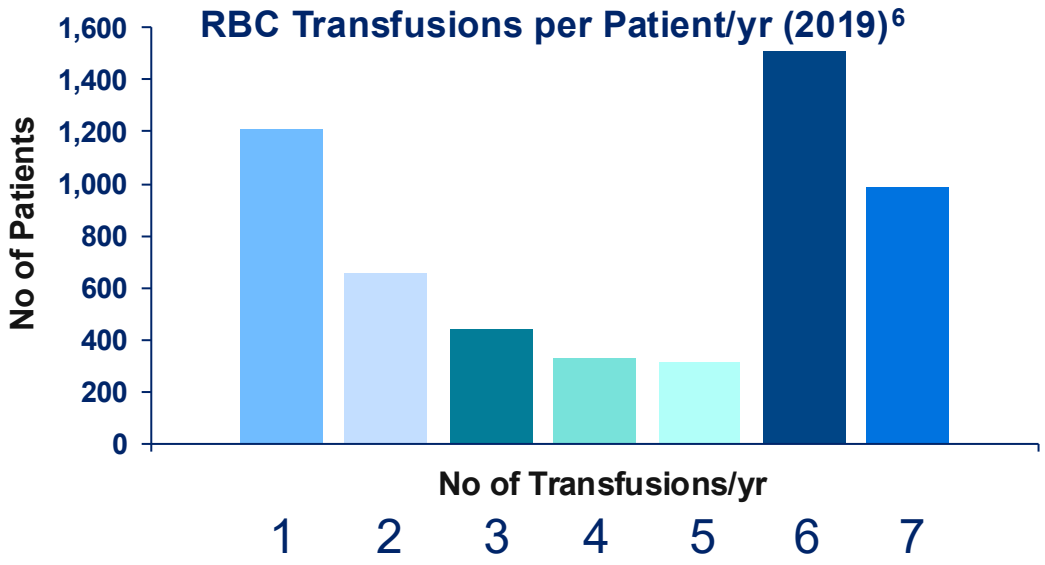


1. Masarova L, et al. Eur J Haematol. 2018;100:257-263; 2. Masarova L, et al. Leuk Res. 2020;91:106338.

Anemia In Myelofibrosis

- Anemia presents in 35% to 54% of patients at diagnosis[1]
- ~50% of patients with MF require ≥6 RBC transfusions/year
- Independent prognostic risk factor for leukemic transformation[2,3]
- Up to 46% of patients become dependent on RBC transfusions within 1 year of diagnosis[4,5]





JAKi, JAK inhibitor; RBC, red blood cell.

1. Tefferi A, et al. *Blood.* 2013;122:1395-1398; 2. Rago A, et al. *Leuk Res.* 2015:3:314-317; 3. Curto-Garcia N, et al. *Future Oncol.* 2018;14:137-150; 4. Harrison CN, et al. *Leukemia.* 2016;30:1701-1707; 5. Tefferi A, et al. *Mayo Clin Proc.* 2012;87:25-33.

Dynamic International Prognostic Scoring System (DIPSS): Survival by risk group

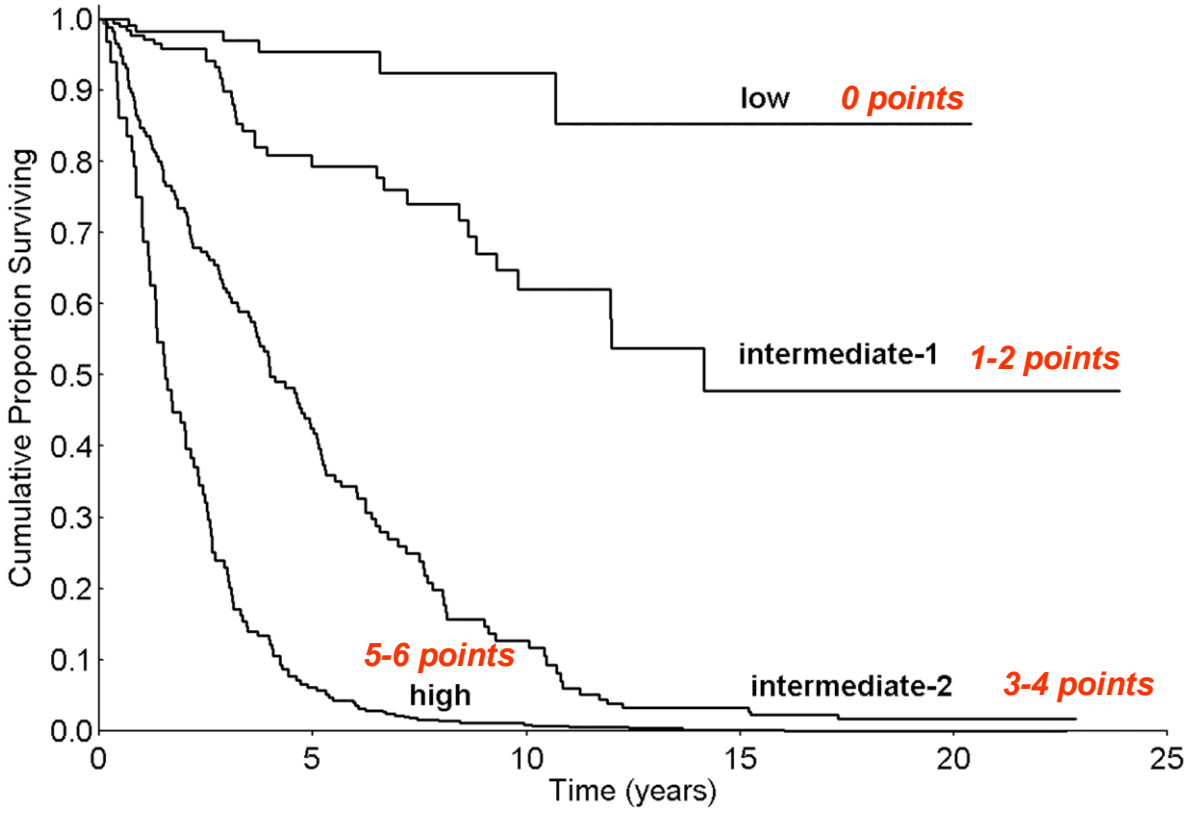


Table 3. DIPSS for survival in primary myelofibrosis

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

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

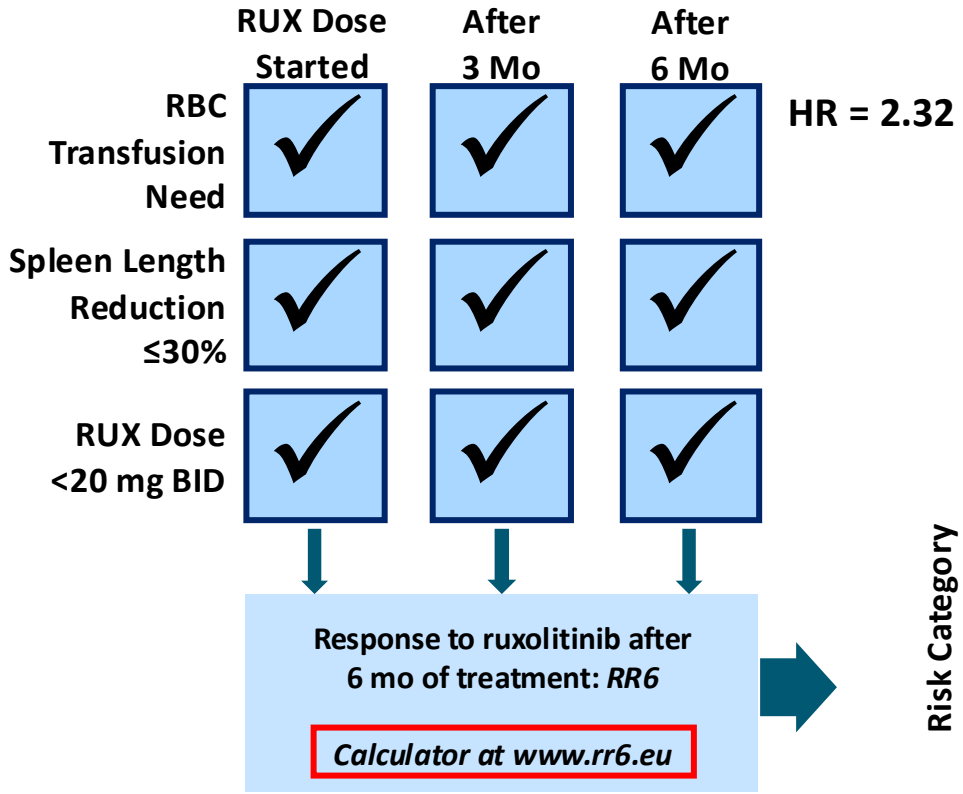
DIPSS indicates Dynamic International Prognostic Scoring System.

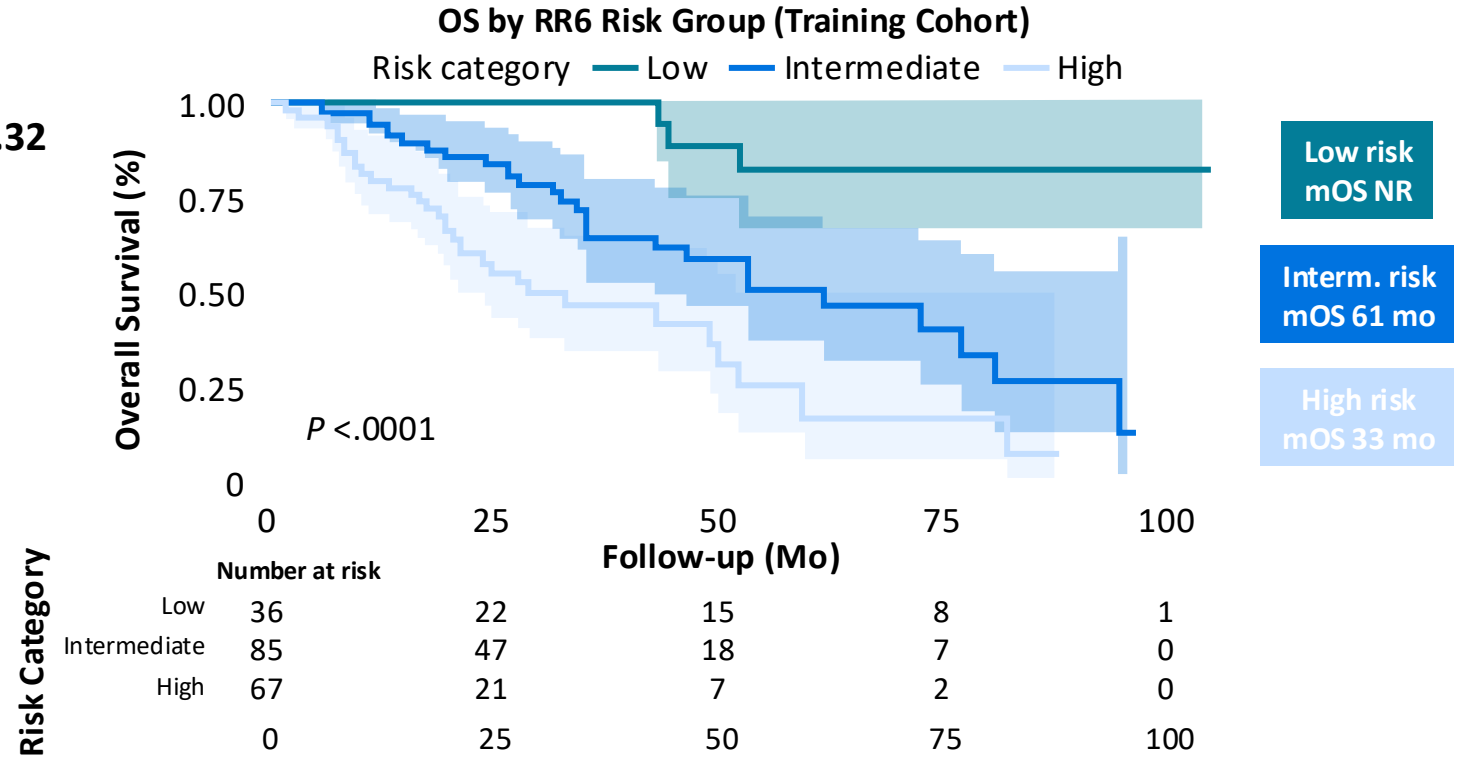
- Dynamic International Prognostic Scoring System-PLUS (DIPSS-PLUS): Takes into account transfusion requirements, platelet count, and karyotype (Gangat et al. JCO 2011)

Passamonti *et al., Blood* 2010

RR6: 3 Factors Predict Survival Benefit With Ruxolitinib in Patients With MF

Assessment of potential predictors of survival in patients with intermediate-1 risk or higher MF who had been treated with ruxolitinib for ≥6 mo in an observational study





- The RR6 model was validated in another cohort of patients (n = 40; *P* = .0276) treated with ruxolitinib at Moffitt Cancer Center

Maffioli. Blood Adv. 2022;6:1855.

Treatment Approaches to Myelofibrosis

Clinical Issue	Treatments	
Anemia	▪ ESAs ▪ Danazol ▪ Corticosteroids	▪ Thalidomide, lenalidomide (IMiDs)
Symptomatic splenomegaly	▪ Ruxolitinib ▪ Fedratinib ▪ Pacritinib ▪ Momelotinib ▪ Hydroxyurea	▪ Cladribine, IMiDs ▪ Splenectomy ▪ HMAs
Constitutional symptoms/QoL	▪ Ruxolitinib ▪ Fedratinib ▪ Pacritinib ▪ Corticosteroids	
Thrombocytopenia	▪ Thalidomide, danazol	

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): *Management of MF-Associated Anemia*[1]

Assess for and treat alternative causes of anemia (ie, bleeding, nutritional deficiencies, hemolysis)

Ongoing symptomatic splenomegaly and/or constitutional symptoms

Preferred regimens:
- Clinical trial
- **Momelotinib**

Other recommended regimens:
- **Pacritinib**
- **Ruxolitinib** combination:
  - **Luspatercept-aamt**
  - **ESAs** (if serum EPO < 500 mU/mL)
  - **Danazol**

No splenomegaly or constitutional symptoms

Preferred regimen:
- Clinical trial

Other recommended regimens:
- **ESAs** (if serum EPO < 500 mU/mL)
- **Luspatercept-aamt**
- **Danazol**
- **Pacritinib**
- **Momelotinib**

Useful in certain circumstances:
- Lenalidomide + prednisone for del(5q)

Splenomegaly and constitutional symptoms well-controlled on current JAK inhibitor

Preferred regimen:
- Clinical trial

Other recommended regimens:
- **JAK inhibitor** combination:
  - **ESAs** (if serum EPO < 500 mU/mL)
  - **Luspatercept-aamt**
  - **Danazol**

Useful in certain circumstances:
- Switch to **pacritinib**
- Switch to **momelotinib**

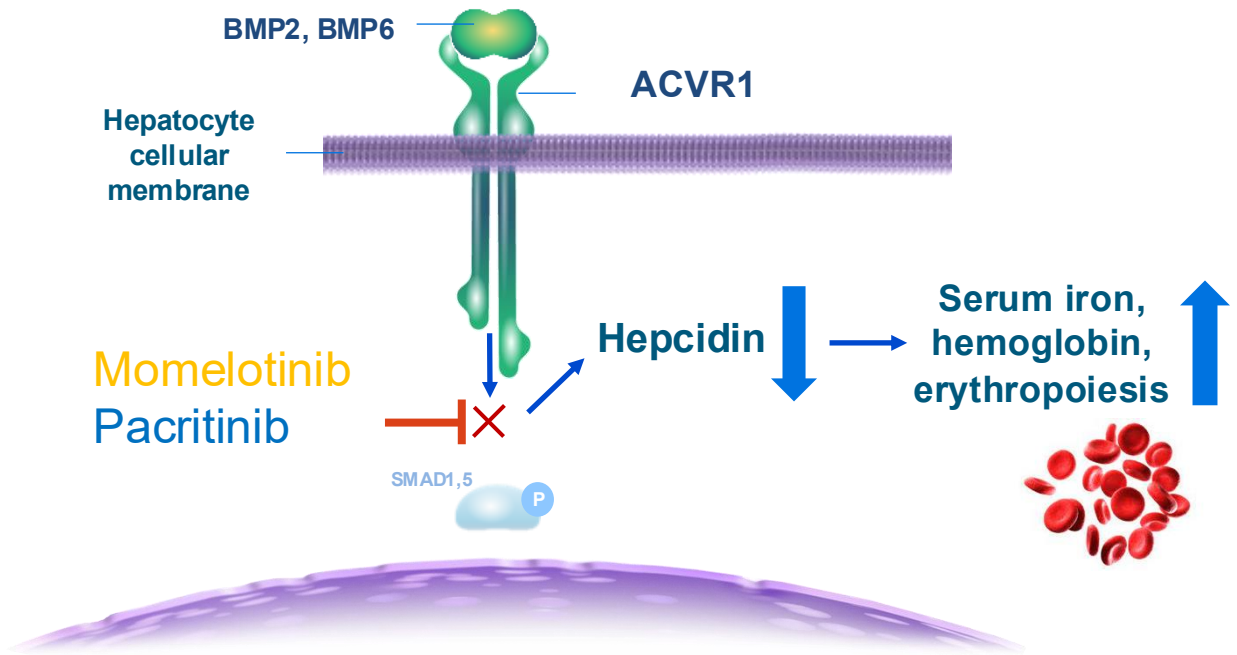
del, deletion; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; JAK, Janus kinase.

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, Pardananni et al. JAMA Oncology 2015, Mascarenhaas et al. JAMA Oncology 2018, Verstovsek et al Lancet 2023

Momelotinib and Pacritinib Inhibit ACVR1



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

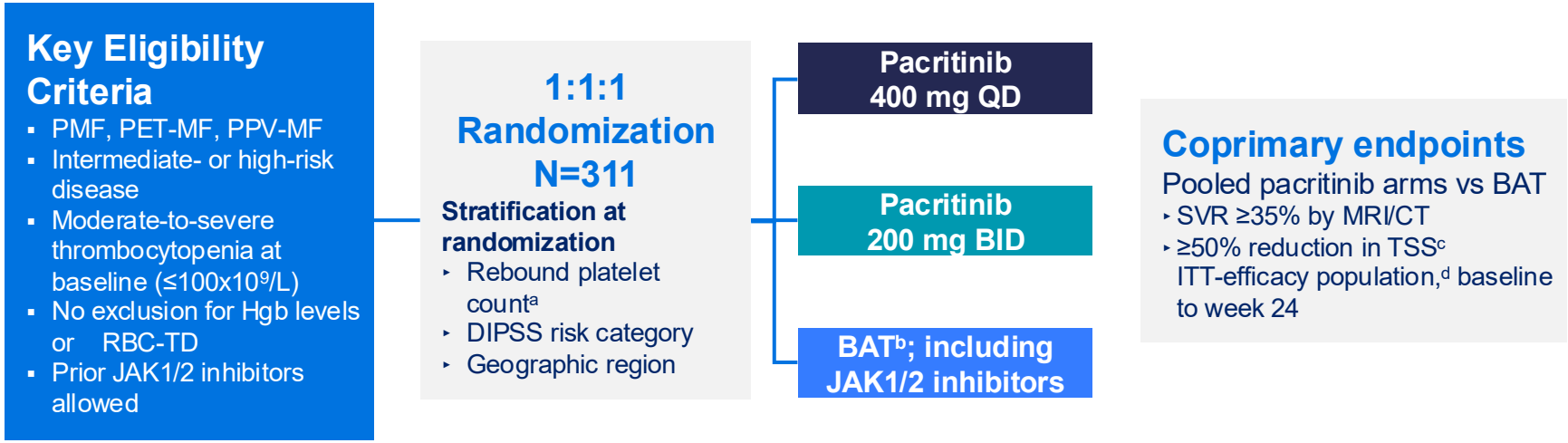
ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

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

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]

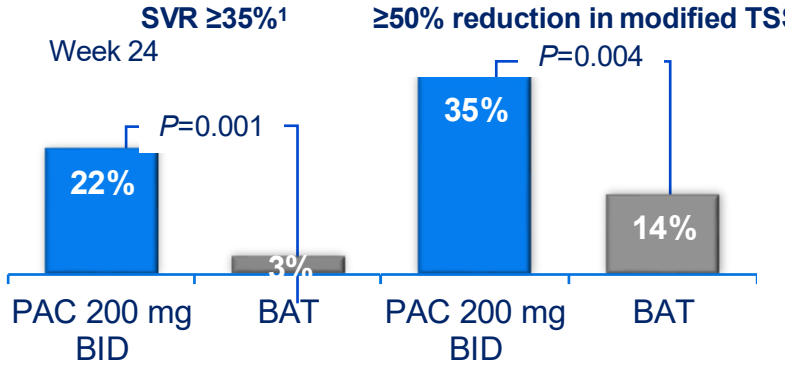


~40% of patients had baseline PLT < 50K

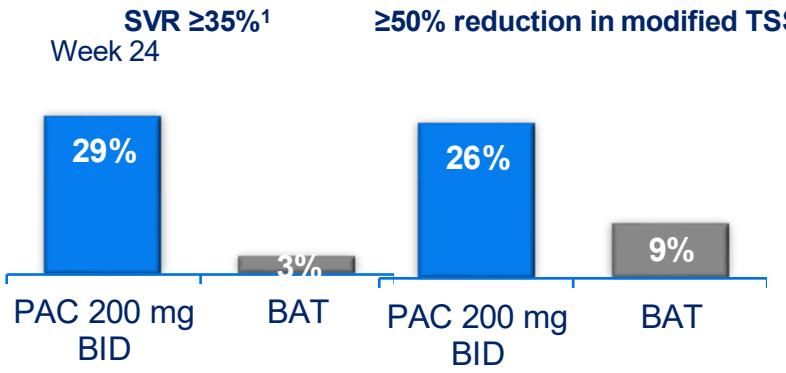
1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. 2. Al-Fayoumi S, et al. *Blood*. 2013;122;4080.

PERSIST-2: 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

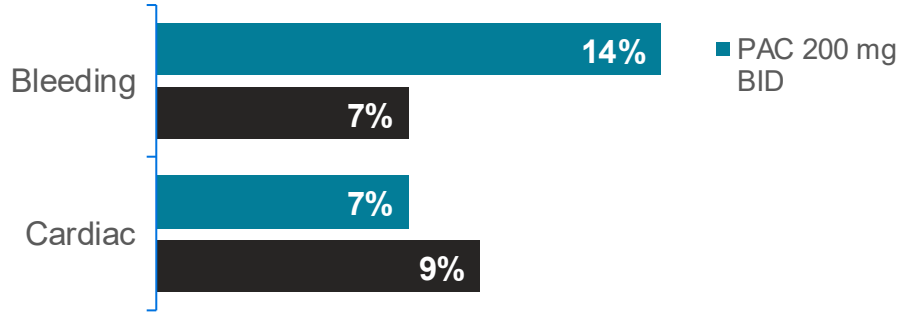
[a] Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.
1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. 2. Data on File. CTI Biopharma Corp. Pacritinib Clinical Overview.

Adverse Events

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
- Neurological AEs and opportunistic infections rarely reported with pacritinib

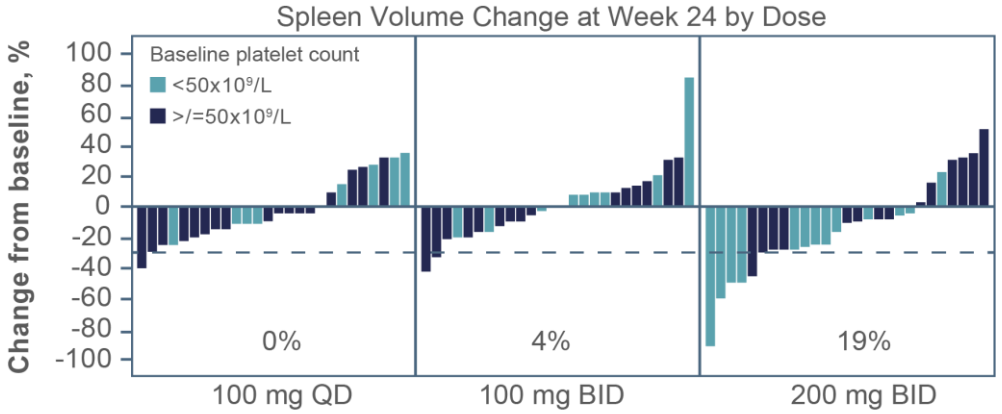
Grade ≥3 Events (Pooled[a])



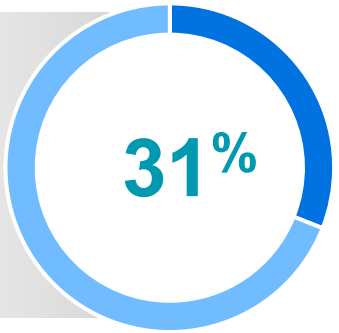
- **Safety outcomes with pacritinib were similar for those with <50x10^9/L vs 50-100x10^9/L platelets at baseline**

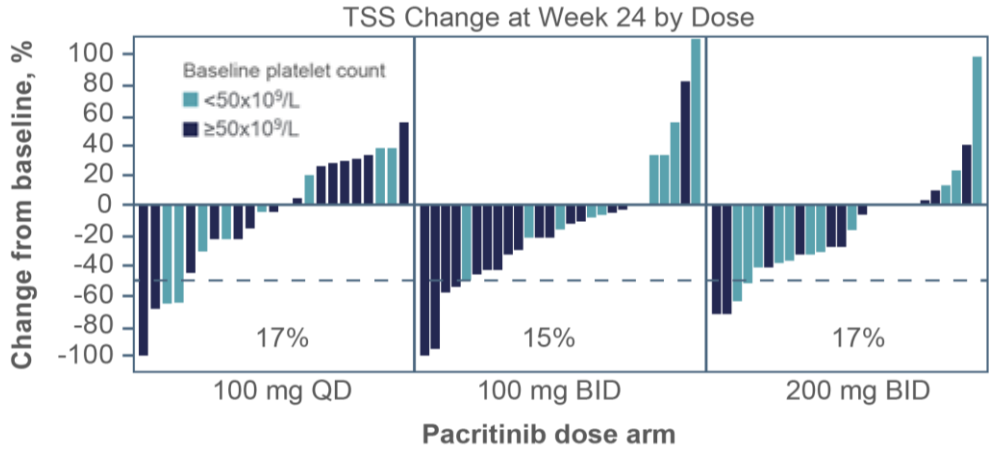
Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

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

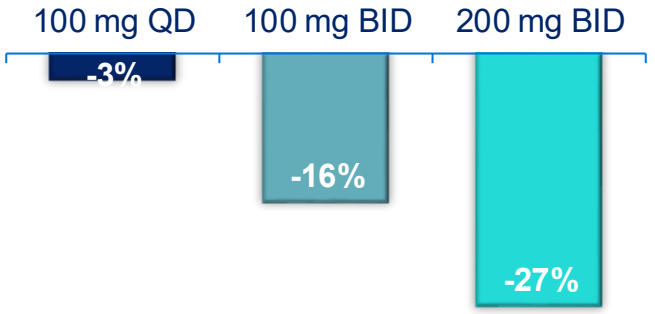


Evaluable SVR in patients with severe thrombocytopenia (<50x10^9/L) at baseline treated with 200 mg BID





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



BID, twice daily; QD, once daily; SVR, spleen volume reduction.
Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

Transfusion Independence (TI): Analysis of PERSIST-2

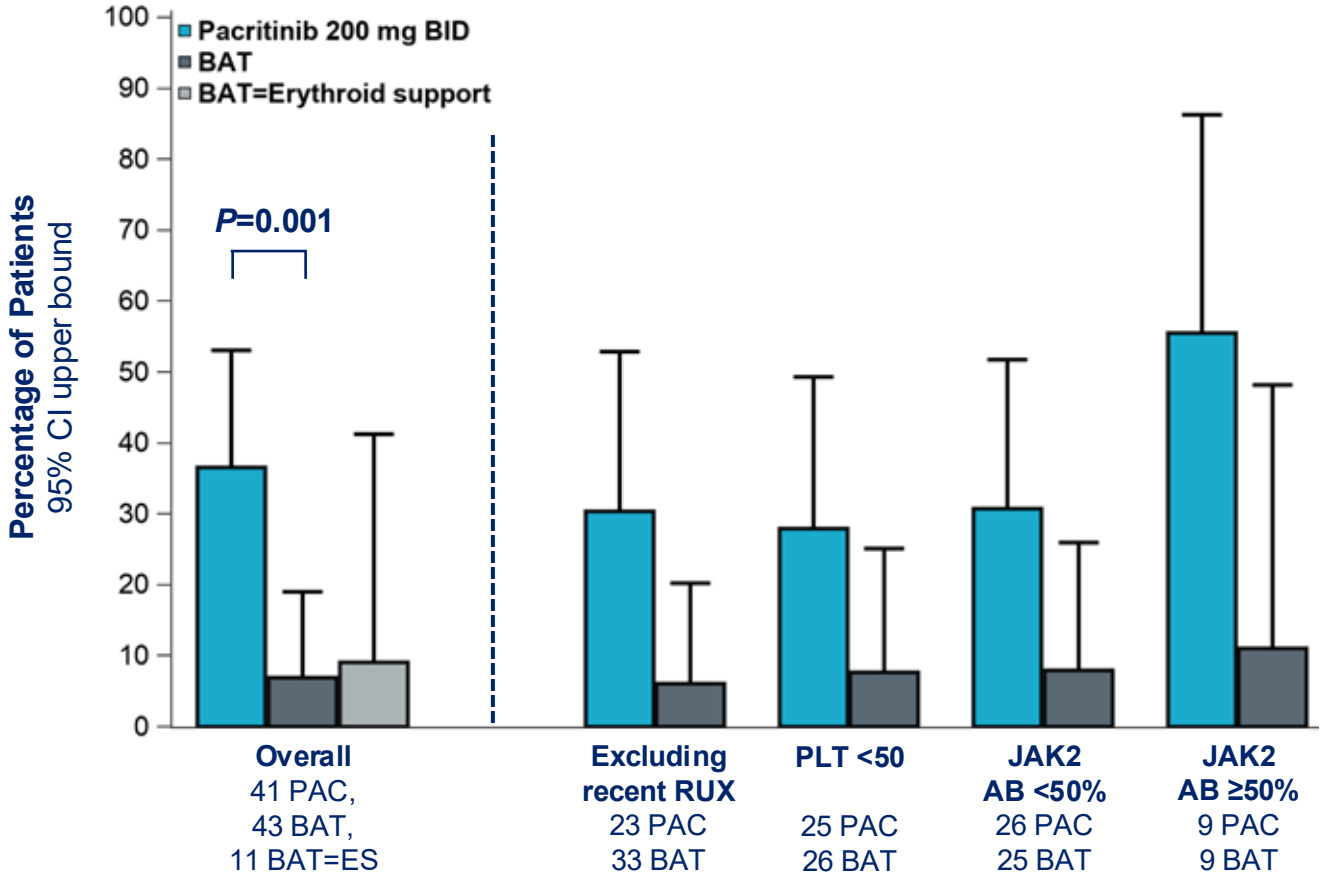
TI Conversion Rate

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

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

- Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



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

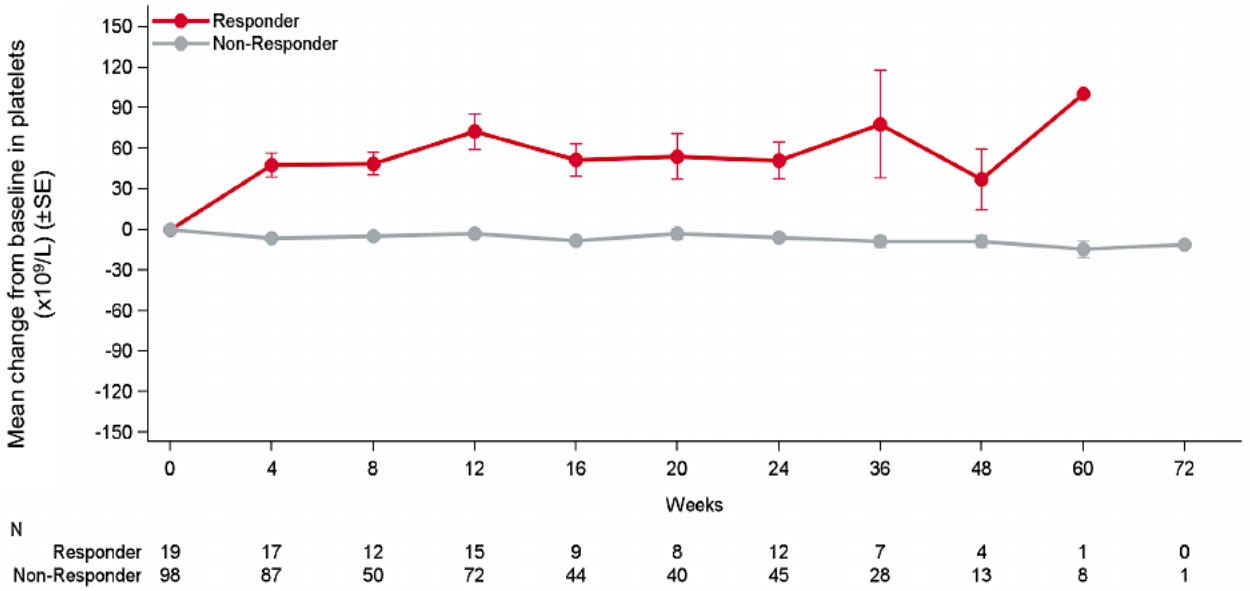
Oh ASH 2022

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]

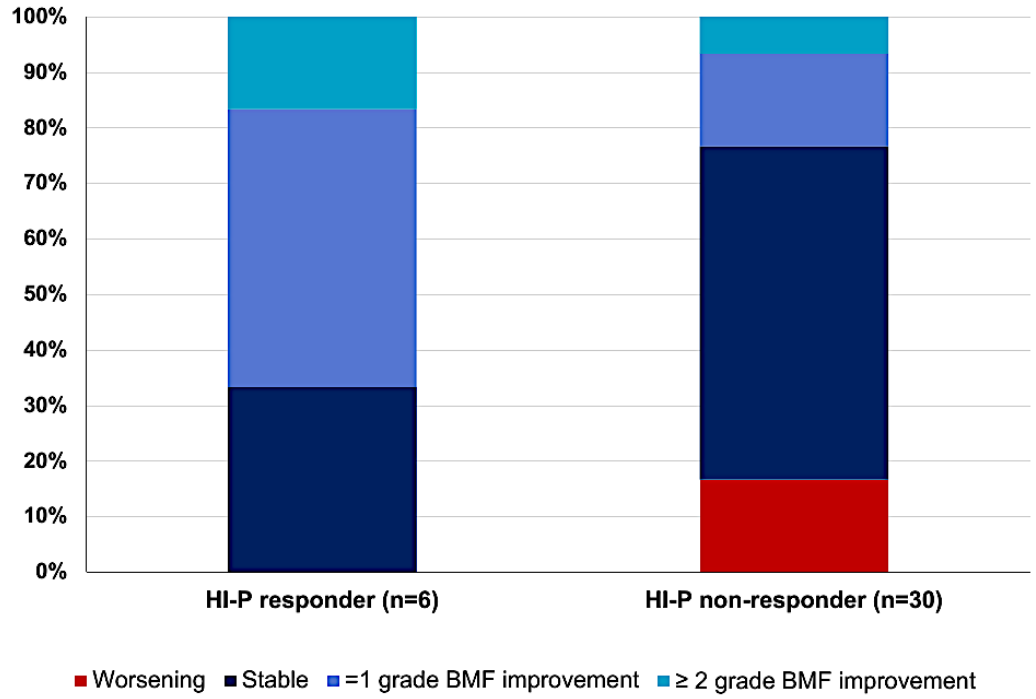
[1]O' Neal Comprehensive Cancer Center, University of Alabama, Birmingham, AL; [2]The University of Kansas Clinical Cancer Research Center, Leawood, KS; [3]Oregon Health & Science University, Portland, OR; [4]Centre d'Investigations Cliniques, INSERM CIC 1427, Université Paris Cité, APHP, Hôpital Saint-Louis, 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-responder, PERSIST-2 & PAC203, pacritinib 200 mg BID



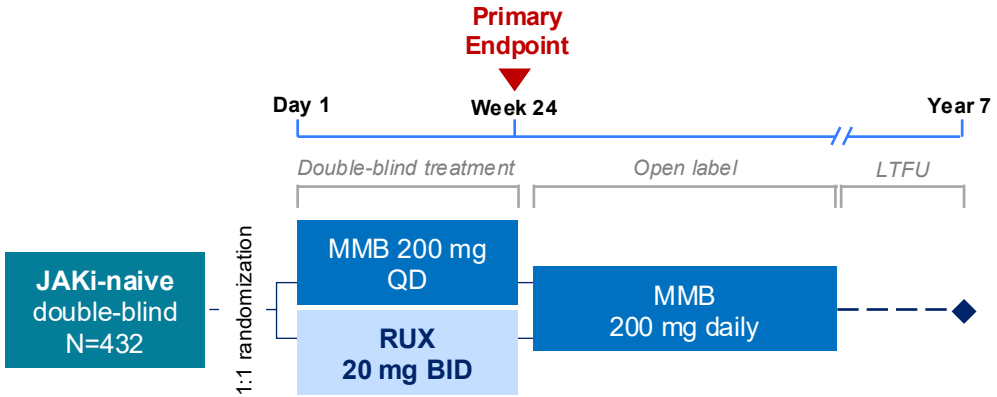
19% of pacritinib treated patients on PAC203 and PERSIST-2 trials experience an improvement in platelet counts

Vachhani P et al. ASH 2023;Abstract 4554

Momelotinib: SIMPLIFY-1 and 2

SIMPLIFY-1: First-Line Population

JAKi naive[1]



Goal: Noninferiority

Momelotinib 200 mg QD: n=215

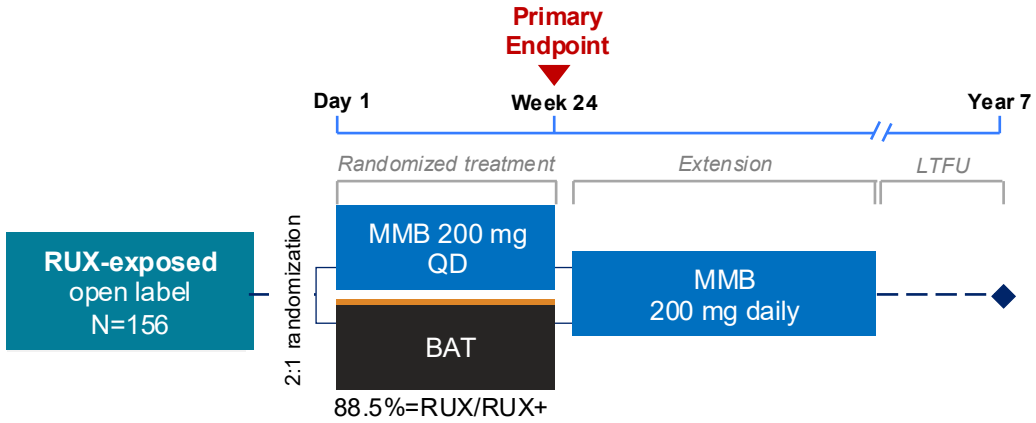
Ruxolitinib 20 mg BID: n=217

Primary Endpoint: SRR

Secondary Endpoints:
- TSS
- TI rate

SIMPLIFY-2: Second-Line Population

Prior ruxolitinib with anemia, thrombocytopenia, or grade ≥3 bleeding[2]



Goal: Superiority

Momelotinib 200 mg QD: n=104

Best Available Treatment: n=52

Primary Endpoint: SRR

Secondary Endpoints:
- TSS
- TI rate

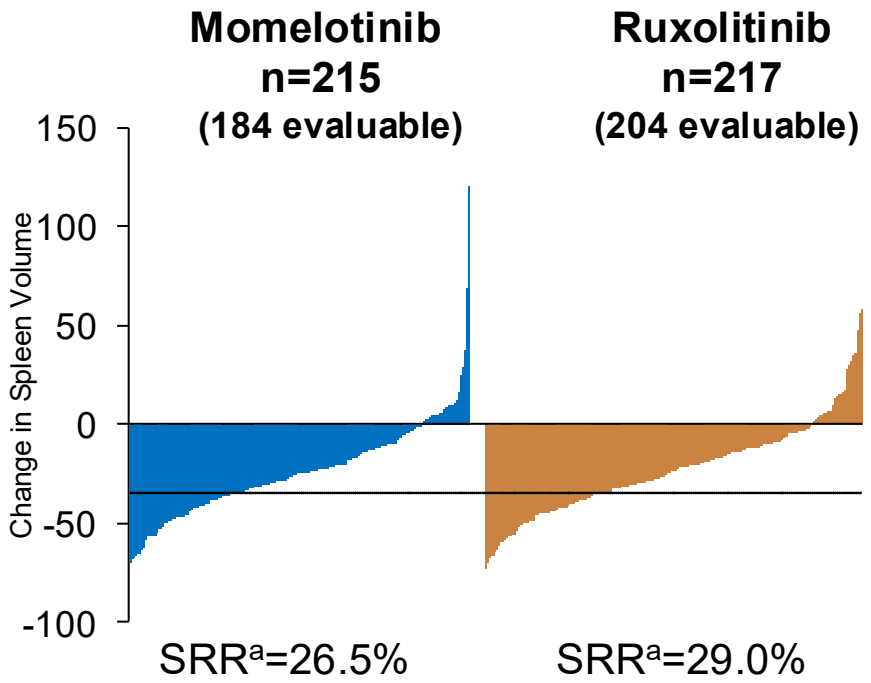
TI defined as absence of RBC transfusions and no Hb <8 g/dL in the prior 12 weeks[1,2].

BAT, best available therapy; BID, twice daily; Hb, hemoglobin; JAKi, Janus kinase inhibitor; LTFU, long-term follow-up; MMB, momelotinib; QD, once daily; RBC, red blood cells; RUX, ruxolitinib; SRR, splenic response rate; TI, transfusion independence; TSS, total symptom score.

1. Mesa RA, et al. *J Clin Oncol*. 2017;35:3844-3850; 2. Harrison CN, et al. *Lancet Haematol*. 2018;5:e73-e81.

SIMPLIFY-1

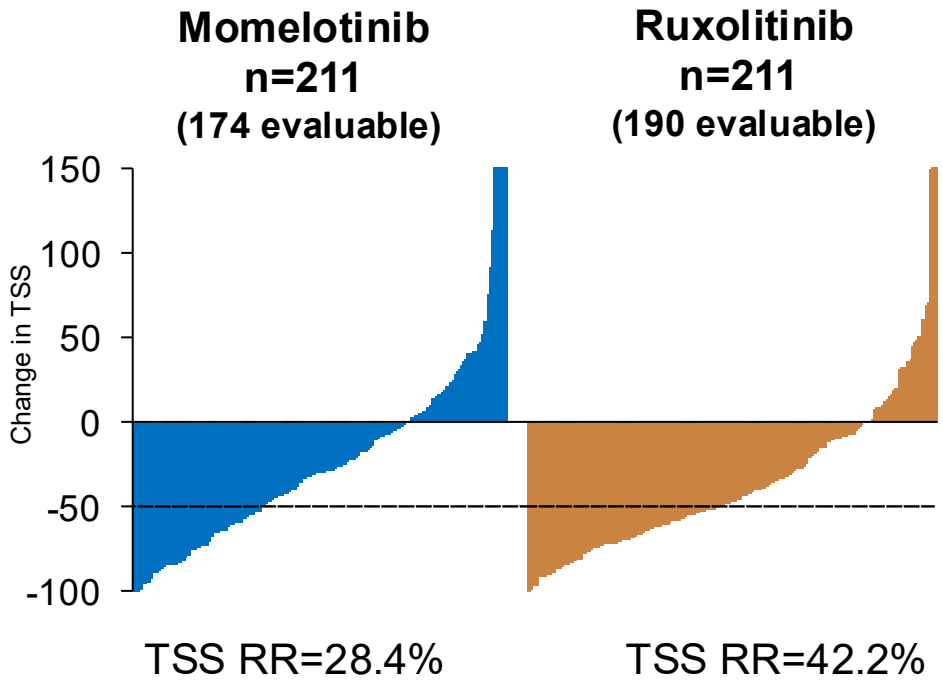
Primary Endpoint: SRR



P=0.011

Momelotinib is noninferior to ruxolitinib

Secondary Endpoint: TSS RR



P=0.98

Momelotinib is inferior to ruxolitinib

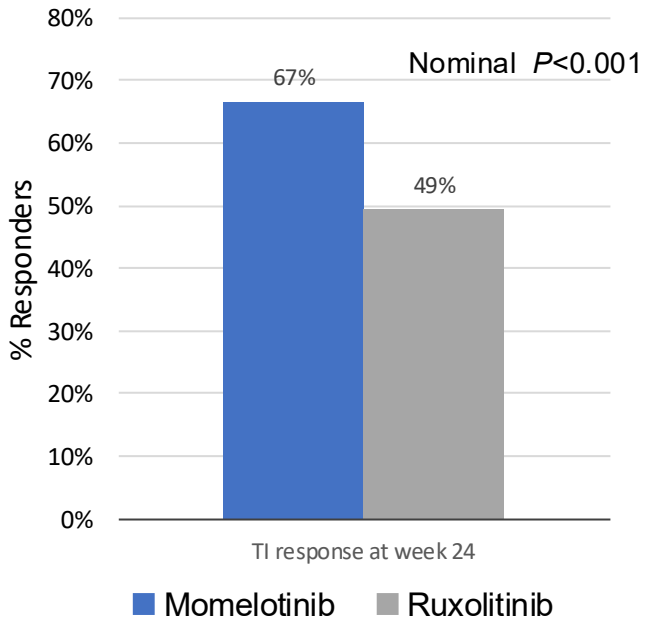
[a] Patients with missing baseline or week 24 spleen volume assessments were considered nonresponders.
SRR, splenic response rate; TSS RR, total symptom score response rate.
Mesa RA, et al. *J Clin Oncol*. 2017;35:3844-3850.

SIMPLIFY-1: TI and Duration of TI

- Median duration of TI was not reached[2]
- Follow-up >3 y

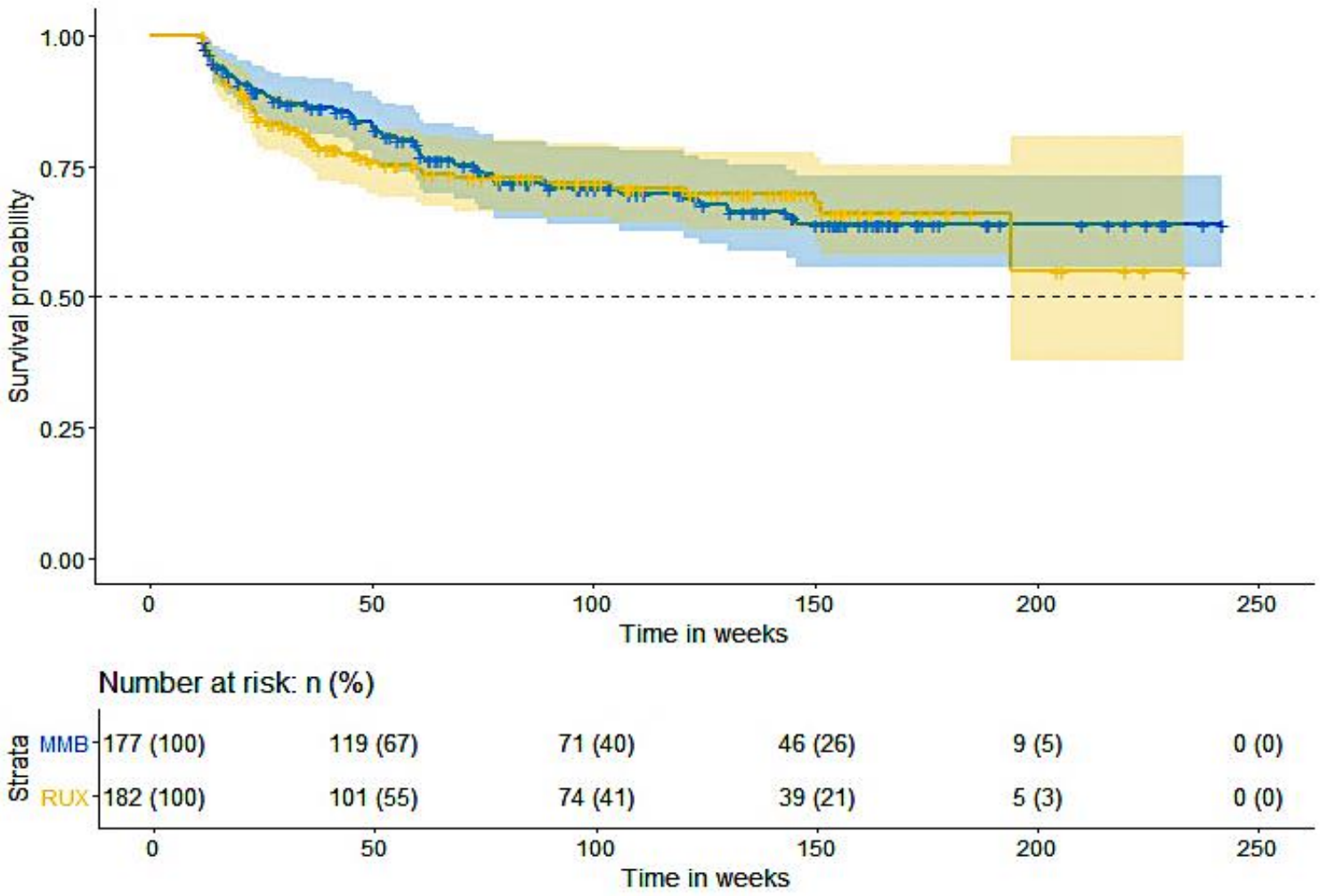
- Baseline TI rate was maintained with momelotinib[1]

Landmark Week 24 TI Rate[1,2]



Baseline TI rate[1]:

- Momelotinib 68%
- Ruxolitinib 70%



MMB, momelotinib; RUX, ruxolitinib; TI, transfusion independence.

1. Mesa RA, et al. *J Clin Oncol*. 2017;35:3844-3850; 2. Verstovsek S, et al. ASH 2020. Abstract 54.

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

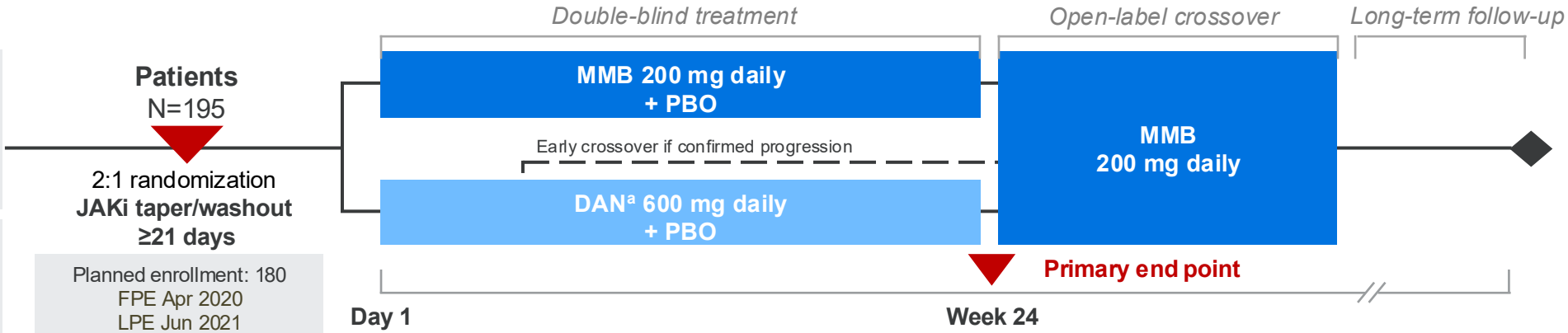
Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥25 × 10^9/L

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]

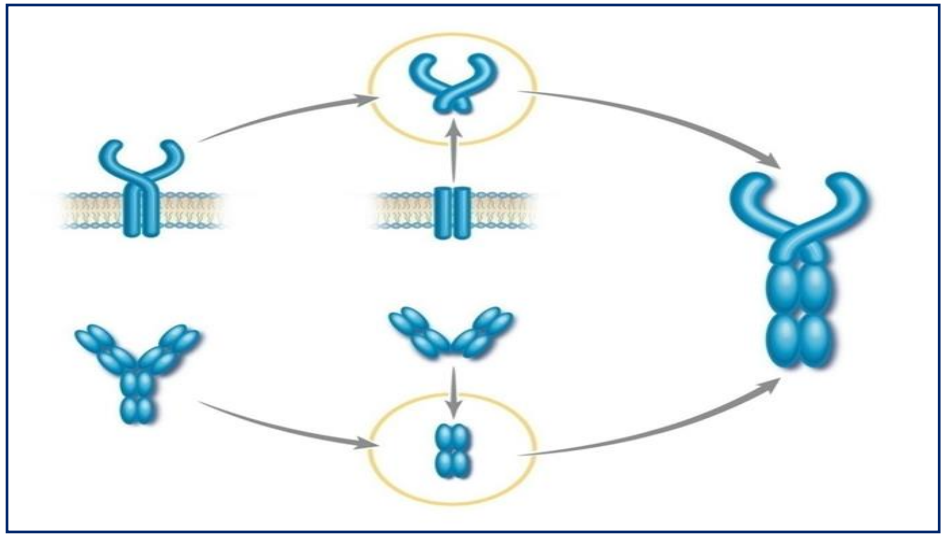
	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

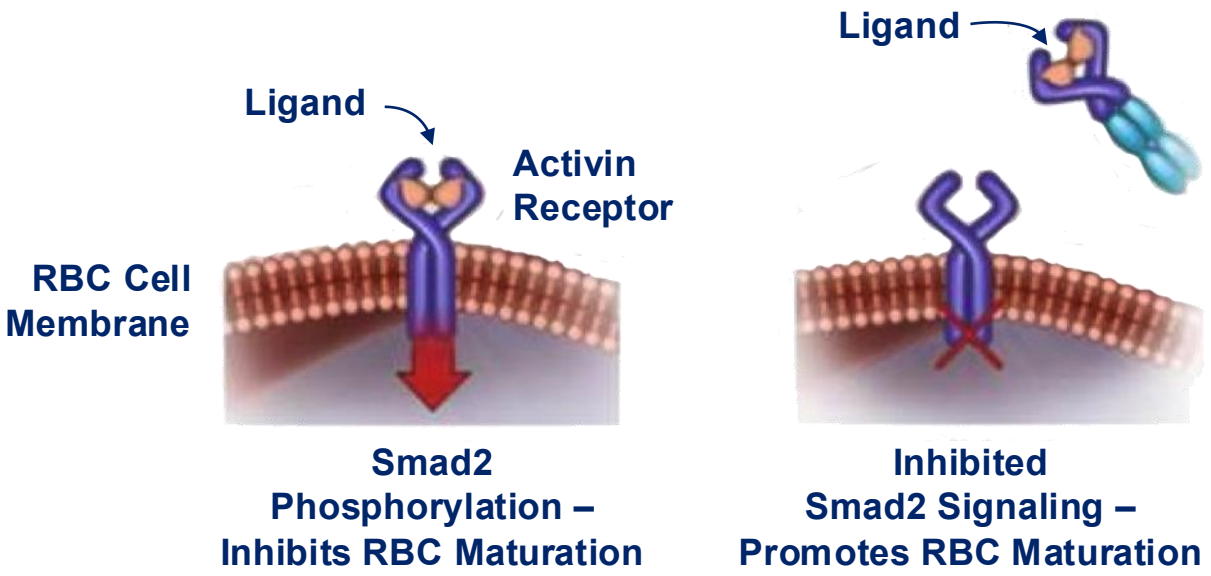
Anemia Therapy in Combination With a JAK Inhibitor

Luspatercept

Fusion protein that acts as activin receptor ligand trap

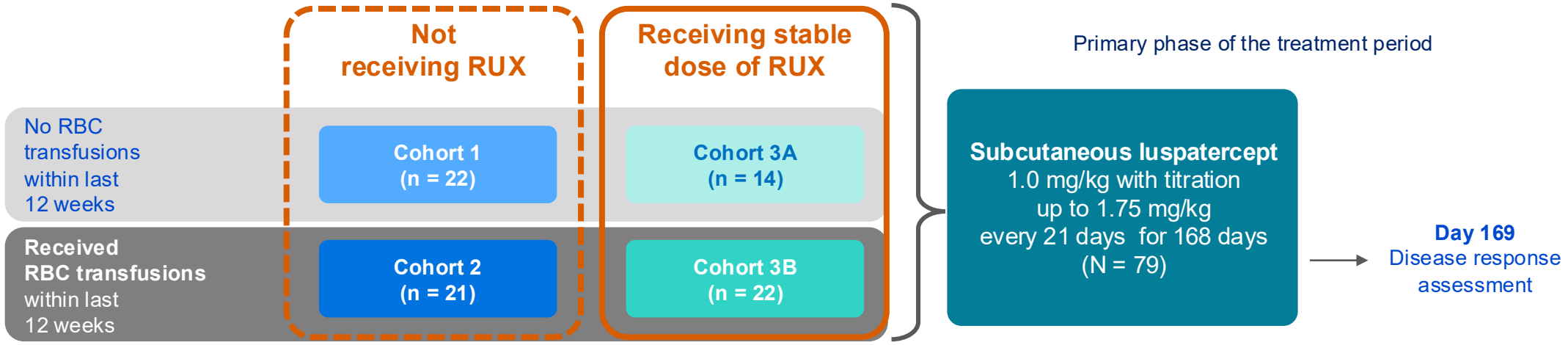
Sequester ligands of TGFß superfamily, (eg, GDF11) secreted by BM stroma, that inhibit terminal erythropoiesis





Iancu-Rubin C et al. *Exp Hematol*. 2013;41(2):155-166; Carrancio S et al. *Br J Haematol*. 2014;165:870-882.

Luspatercept in MF and Anemia: Phase 2 study



Parameter	RBC Transfusion Dependent	
	No RUX (Cohort 2; n = 21)	RUX (Cohort 3B; n = 19)
RBC transfusion free ≥12 consecutive wk, n (%)*	2 (10)	6 (27)
▪ Median duration of response, wk (range)	49 (16-82)	42 (12-111)
≥50% reduction in RBC transfusion burden from BL, n (%)	8 (37)	10 (46)

Hgb Increase ≥1.5 g/dL From BL for ≥12 Consecutive Wk‡	No RBC Transfusions	
	No RUX (Cohort 1; n = 22)	RUX (Cohort 3A; n = 14)
Hgb increase ≥1.5 g/dL at every assessment, n (%)	3 (14)	3 (21)
Mean Hgb increase ≥1.5 g/dL, n (%)	4 (18)	9 (64)

Gerds A, et al. 2020 ASH Annual Meeting. Abstract 2992.

July 18, 2025

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

The manufacturer today announced the Phase 3 INDEPENDENCE trial evaluating luspatercept-aamt 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.

2026 ASCO ANNUAL MEETING

Abstract 6501

RALLY-MF: Initial efficacy of a Phase 2 study of DISC-0974, an anti-hemojuvelin antibody, to treat anemia in myelofibrosis

Naseema Gangat[1*], Ayalew Tefferi[1*], Prithviraj Bose[2^], Elizabeth Hexner[3^], Laura Michaelis[4^], Aaron Gerds[5#], Akriti Jain[5#], Prioty Islam[6#], Raajit Rampal[6#], Ronan Swords[7#], Moshe Talpaz[8#], Kristen Pettit[8#], Anthony Hunter[9], Andrew Kuykendall[10], Sima Bhatt[11], William Savage[11], Anna Halpern[12]

[1]Mayo Clinic, Rochester, MN; [2]MD Anderson Cancer Center, Houston, TX; [3]University of Pennsylvania, Philadelphia, PA; [4]Medical College of Wisconsin, Milwaukee, WI; [5]Cleveland Clinic, Cleveland, OH ; [6]Memorial Sloan Kettering Cancer Center, New York, NY; [7]Oregon Health and Science University, Portland, OR; [8]University of Michigan, Ann Arbor, MI; [9]Emory Winship Cancer Institute, Atlanta, GA; [10]Moffitt Cancer Center, Tampa, FL; [11]Disc Medicine, Watertown, MA; [12]University of Washington, Seattle, WA

*, ^, # indicate equal contribution

DISC-0974 is an investigational first-in-class mAb that blocks the co-receptor hemojuvelin and decreases hepcidin expression

- ↓ HJV-dependent BMP signaling in the liver
- ↓ Hepcidin production
- ↑ Mobilization of stored iron into circulation
- ↑ Iron absorption
- ↑ Hemoglobin (Hgb) levels

Source: Novikov et al, Blood, 2022;140(Suppl 1):5339-5340. Abbreviations: ALK = activin receptor-like kinase; BMP = bone morphogenetic protein; HAMP = hepcidin antimicrobial peptide; HJV = hemojuvelin; mAb = monoclonal antibody; SMAD = small mothers against decapentaplegic.

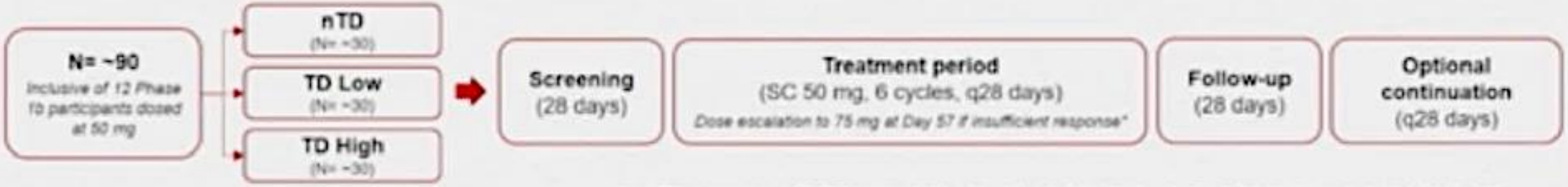
Naseema Gangat, MBBS, Professor of Medicine, Mayo Clinic, on behalf of RALLY-MF Investigators

RALLY-MF Phase 2: study design and eligibility

Study population

- Age ≥18 years, with **primary**, **post-essential thrombocythemia**, or **post-polycythemia vera MF**
- **Anemia**, defined as:
  - **Non-transfusion dependence (nTD):** baseline **Hgb <10 g/dL** on ≥3 assessments over 84 days prior to Screening, **without RBC transfusion**
  - **Low transfusion dependence (TD Low):** RBC transfusion requirement of **1 to 2 PRBC units over the 84 days** immediately prior to Screening
  - **High transfusion dependence (TD High):** RBC transfusion requirement of **3 to 12 PRBC units over the 84 days** immediately prior to Screening
- **Concomitant** stable **JAK inhibitor** or hydroxyurea use is **allowed**
- Participants with anemia due to infection, bleeding, or iron or vitamin B12 deficiency are excluded

Study design



Study is ongoing. N=61 per data cut of 27 Apr 2026 including data through 20 Mar 2026 visit.

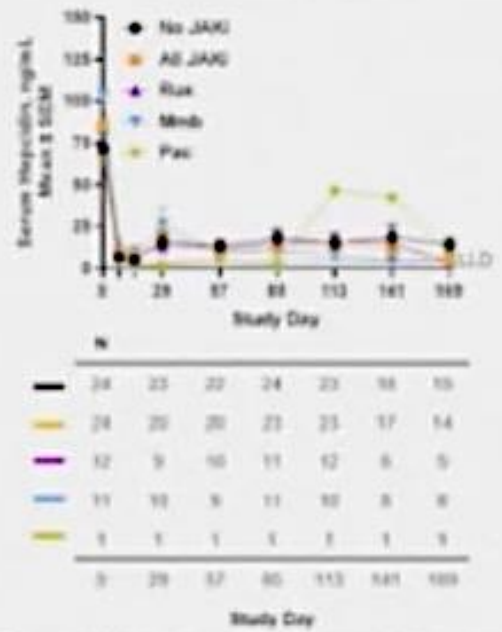
*Insufficient response: nTD/TD Low = no Hgb values ≥1 g/dL from baseline by Day 57 (excluding values within 14 days of transfusion); TD High = continued average monthly transfusion rate at Day 57 equal or > than in the 84 days prior to Screening. Full eligibility criteria available at NCT05320198.

Presented by: Naseema Gangat, MBBS, Professor of Medicine, Mayo Clinic, on behalf of RALLY-MF Investigators

DISC-0974 leads to hepcidin reduction, iron mobilization, and hematologic response regardless of concomitant JAKi use

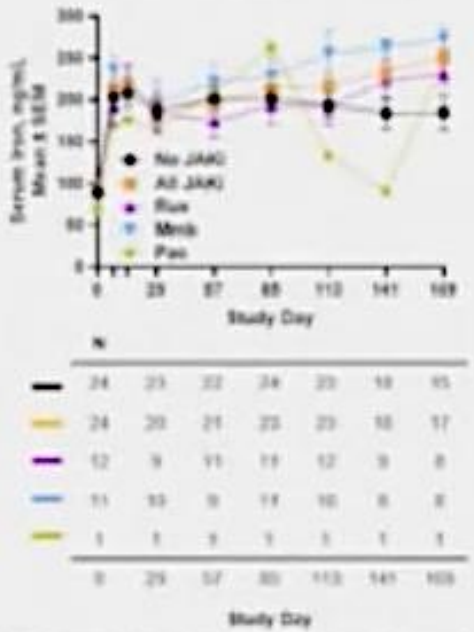
(A) Hepcidin by JAKi

Evaluable participants (n=50)



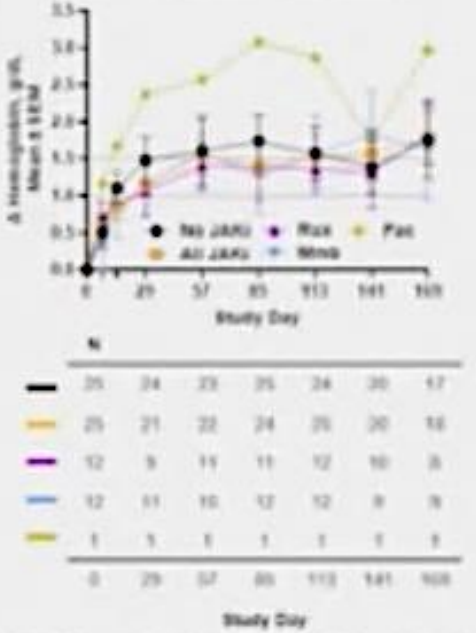
(B) Iron by JAKi

Evaluable participants (n=50)



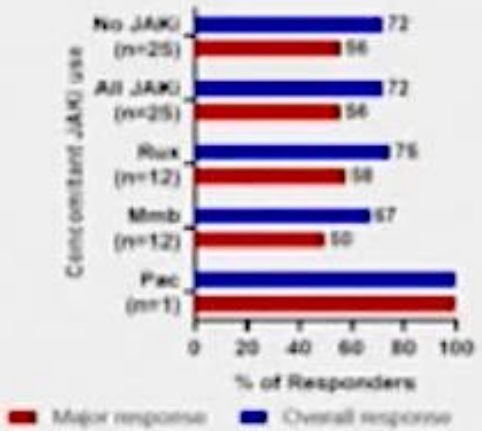
(C) Hemoglobin by JAKi

Evaluable participants (n=50)



(D) Hematologic Response by JAKi

Evaluable participants (n=50)



Mean (SEM) absolute serum hepcidin (A), serum iron (B), mean change from baseline in hemoglobin (C) and hematologic response (D) by concomitant JAKi use in participants with follow-up through visit Day 113 (evaluable participant). Abbreviations: JAKi = JAK inhibitor; LLD = limit of detection; Mmb = momelotinib; Pac = pacritinib; Rux = ruxolitinib; TD = transfusion dependent. Analyses exclude values within 7 days of transfusion receipt. Participant on concomitant pacritinib had study drug dose held on Days 85 and 113 due to Hgb ≥12 g/dL.

Naseema Gangat, MBBS, Professor of Medicine, Mayo Clinic, on behalf of RALLY-MF Investigators

Conclusions

- DISC-0974 was safe and generally well tolerated
- DISC-0974 resulted in sustained ↓hepcidin and ↑serum iron in participants regardless of concomitant JAKi therapy or baseline transfusion requirement
- DISC-0974 resulted in meaningful hematologic responses across cohorts:
  - ✓ 55% of nTD participants achieved mean Hgb increases of ≥1.5 g/dL for ≥12 weeks
  - ✓ 64% of TD Low participants achieved TI-16 weeks
  - ✓ 50% of TD High participants achieved TI-12 weeks
  - ✓ Major responses were achieved regardless of baseline JAKi therapy
    - ✓ 56% of participants receiving concomitant JAKi (n=25) achieved a major response
    - ✓ 56% of participants not receiving concomitant JAKi (n=25) achieved a major response
- Increase in Hgb after DISC-0974 dosing was correlated with improvement in patient-reported outcomes

Approximately what proportion of your patients with MF present with severe anemia at initial diagnosis? Approximately what proportion of your patients with MF develop anemia at a later point in the disease course?

	Severe anemia at diagnosis	Anemia at later point in disease course
 Prof Harrison	10%	50%
 Dr Rampal	30%	60%
 Dr Bose	10%	100%
 Dr Kuykendall	25%	90%
 Dr Mascarenhas	15%	90%
 Dr Yacoub	15%	50%

Approximately what proportion of your patients with MF present with severe thrombocytopenia (platelet count <50,000/µL) at initial diagnosis? Approximately what proportion of your patients with MF develop thrombocytopenia at a later point in the disease course?

	Severe thrombocytopenia at diagnosis	Thrombocytopenia at later point in disease course
 Prof Harrison	5%	40%
 Dr Rampal	10%	40%
 Dr Bose	10%	67%
 Dr Kuykendall	10%	60%
 Dr Mascarenhas	10%	70%
 Dr Yacoub	10%	30%

What initial treatment would you generally recommend for an otherwise healthy 65-year-old patient with severe anemia (eg, baseline Hgb 7 g/dL) requiring transfusions? If the patient had severe anemia (eg, baseline Hgb 7 g/dL) requiring transfusions and a baseline platelet count of 44,000/µL?

	Severe anemia requiring transfusions	Severe anemia requiring transfusions and baseline platelets 44,000/µL
 Prof Harrison	Momelotinib	Momelotinib
 Dr Rampal	Momelotinib	Pacritinib
 Dr Bose	Momelotinib	Pacritinib
 Dr Kuykendall	Momelotinib	Momelotinib
 Dr Mascarenhas	Depends on platelet count	Pacritinib
 Dr Yacoub	Momelotinib	Momelotinib

A 65-year-old man with symptomatic, high-risk MF and splenomegaly (baseline platelet count 110,000/µL) receives ruxolitinib 15 mg BID to which he has a limited response and 6 months later presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 110,000/µL, Hgb = 8.2 g/dL. Which treatment would you most likely recommend next?

 Prof Harrison	Momelotinib
 Dr Rampal	Fedratinib
 Dr Bose	Momelotinib
 Dr Kuykendall	Fedratinib
 Dr Mascarenhas	Momelotinib
 Dr Yacoub	Fedratinib

RTP RESEARCH TO PRACTICE

A 65-year-old man with symptomatic, high-risk MF and splenomegaly (baseline platelet count 110,000/µL) receives ruxolitinib 15 mg BID and experiences significant symptom improvement and a decrease in spleen size. Three years later, he presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 44,000/µL, Hgb = 11.2 g/dL. Which treatment would you most likely recommend next?

 Prof Harrison	Momelotinib
 Dr Rampal	Pacritinib
 Dr Bose	Pacritinib
 Dr Kuykendall	Pacritinib
 Dr Mascarenhas	Pacritinib
 Dr Yacoub	Momelotinib

A 65-year-old man with symptomatic, high-risk MF and splenomegaly (baseline platelet count 110,000/µL) receives ruxolitinib 15 mg BID to which he has a limited response and 6 months later presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 44,000/µL, Hgb of 8.2 g/dL. Which treatment would you most likely recommend next?

 Prof Harrison	Momelotinib
 Dr Rampal	Momelotinib
 Dr Bose	Pacritinib
 Dr Kuykendall	Momelotinib
 Dr Mascarenhas	Pacritinib
 Dr Yacoub	Momelotinib

RTP RESEARCH TO PRACTICE

A 65-year-old man with symptomatic, high-risk MF and splenomegaly (baseline platelet count 110,000/µL) receives ruxolitinib 15 mg BID and experiences significant symptom improvement and a decrease in spleen size. Three years later, he presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 44,000/µL, Hgb = 8.2 g/dL. Which treatment would you most likely recommend next?

 Prof Harrison	Momelotinib
 Dr Rampal	Momelotinib
 Dr Bose	Pacritinib
 Dr Kuykendall	Momelotinib
 Dr Mascarenhas	Pacritinib
 Dr Yacoub	Momelotinib

RTP RESEARCH TO PRACTICE

Agenda
Management of Myelofibrosis (MF)

Introduction: The Biopathophysiology of MF

Module 1: Current and Future Clinical Decision-Making in the Absence of Severe Cytopenias — Prof Harrison

Module 2: Managing MF for Patients with Anemia and Thrombocytopenia — Dr Rampal

Module 3: Upcoming at EHA 2026

Efficacy and Safety of Luspatercept in Patients with Myelofibrosis on Janus Kinase Inhibitors Who Require Red Blood Cell Transfusions: Primary Analysis of the Phase 3 Independence Trial

Passamonti F et al.

EHA 2026;Abstract S215.

Myeloproliferative Neoplasms – Clinical

SATURDAY JUNE 13, 2026

A2-3 Hall

17:15 – 17:30 CEST.

Results of AJX-101, A Phase 1 Clinical Trial Of The Type II JAK2 Inhibitor AJ1-11095, in Patients with Myelofibrosis Who Have Been Failed by a Type I JAK2 Inhibitor

Mascarenhas J et al.

EHA 2026;Abstract S218.

Myeloproliferative Neoplasms – Clinical

SATURDAY JUNE 13, 2026

A2-3 Hall

18:00 – 18:15 CEST.

Mutant Calreticulin–Specific Monoclonal Antibody, INCA033989, is Well Tolerated and Achieves Robust Spleen, Anemia, and Molecular Responses in Patients (Pts) with Myelofibrosis (MF)

Harrison C et al.

EHA 2026;Abstract S216.

Myeloproliferative Neoplasms – Clinical

SATURDAY JUNE 13, 2026

A2-3 Hall

17:30 – 17:45 CEST.

Transcriptional Subtypes of Myelofibrosis Are Independent of Driver Mutations and Capture Distinct Biology, Outcomes, and Disease Trajectories

Zeng A et al.

EHA 2026;Abstract S214.

Myeloproliferative Neoplasms – Biology & Translational Research

FRIDAY JUNE 12, 2026

A5 Hall

18:00 – 18:15 CEST.

Characterization of Symptoms After Immediate Transition from Ruxolitinib to Momelotinib in Patients with Myelofibrosis: Post Hoc Analyses of the Phase 3 SIMPLIFY-1 and SIMPLIFY-2 Trials

Vachhani P et al.

EHA 2026;Abstract PS2001.

Poster Session: Myeloproliferative Neoplasms – Clinical

SATURDAY JUNE 13, 2026

Hall A

18:45 CEST.

SENTRY-2—A Phase II Study Evaluating Selinexor Monotherapy in Patients with JAKi-Naïve Myelofibrosis and Moderate Thrombocytopenia

Scandura JM et al.

EHA 2026;Abstract PB3546 (Publication Only).

Clinical Outcomes of Momelotinib in a Real-World Cohort of Patients with Myelofibrosis

Ortega Vida E et al.

EHA 2026;Abstract PB3537 (Publication Only).

Real-World Hematologic Outcomes with Momelotinib in Patients with Myelofibrosis and Anemia: A German Retrospective Chart Review

Al-Ali HK et al.

EHA 2026;Abstract PB3455 (Publication Only).

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Datasets and Advances in Oncology

Novel Treatment Approaches for Non-Hodgkin Lymphoma

A CME/MOC-Accredited Live Webinar

Wednesday, June 17, 2026

5:00 PM – 6:00 PM ET

Faculty

Matthew Matasar, MD

Sonali M Smith, MD

Moderator

Neil Love, MD

RTP Year in Review 2026

Thank you for joining us!

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Information on how to obtain CME and ABIM MOC credit is provided in the Zoom chat room. Attendees will also receive an email in 1 to 3 business days with these instructions.

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