

Meet The Professor

Current and Future Management of Myelofibrosis

Professor Claire Harrison

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

Commercial Support

This activity is supported by educational grants from CTI BioPharma Corp and Incyte Corporation.

Dr Love — Disclosures

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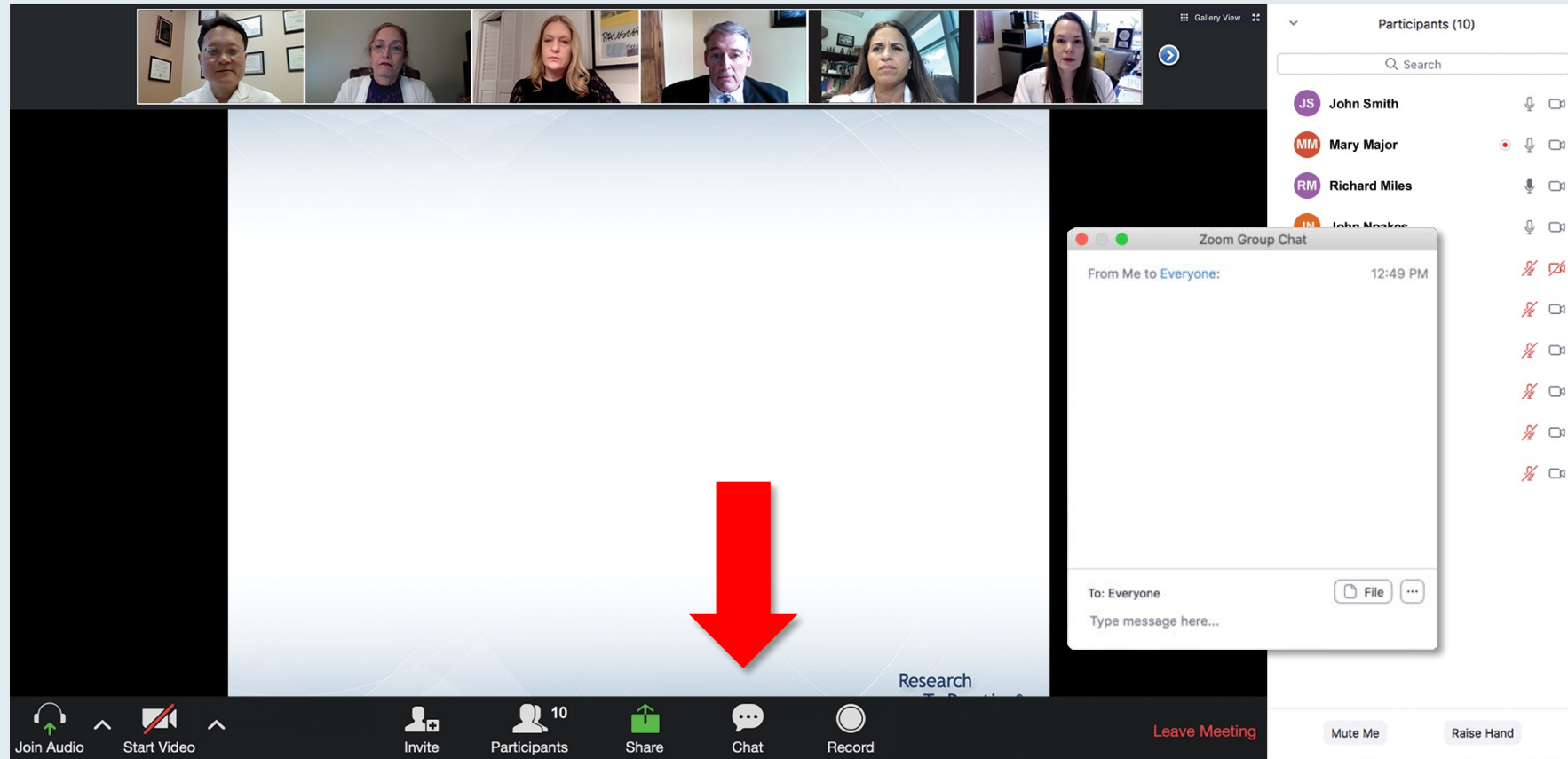
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Prof Harrison — Disclosures

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Expand chat submission box

The screenshot shows a Zoom meeting interface. At the top, there are video thumbnails for participants: RTP Coordinat..., Kirsten Miller, RTP Mike Rivera, and Lisa Suarez. Below the thumbnails is a slide titled "Meet The Professor Program Participating Faculty" with six faculty members listed:

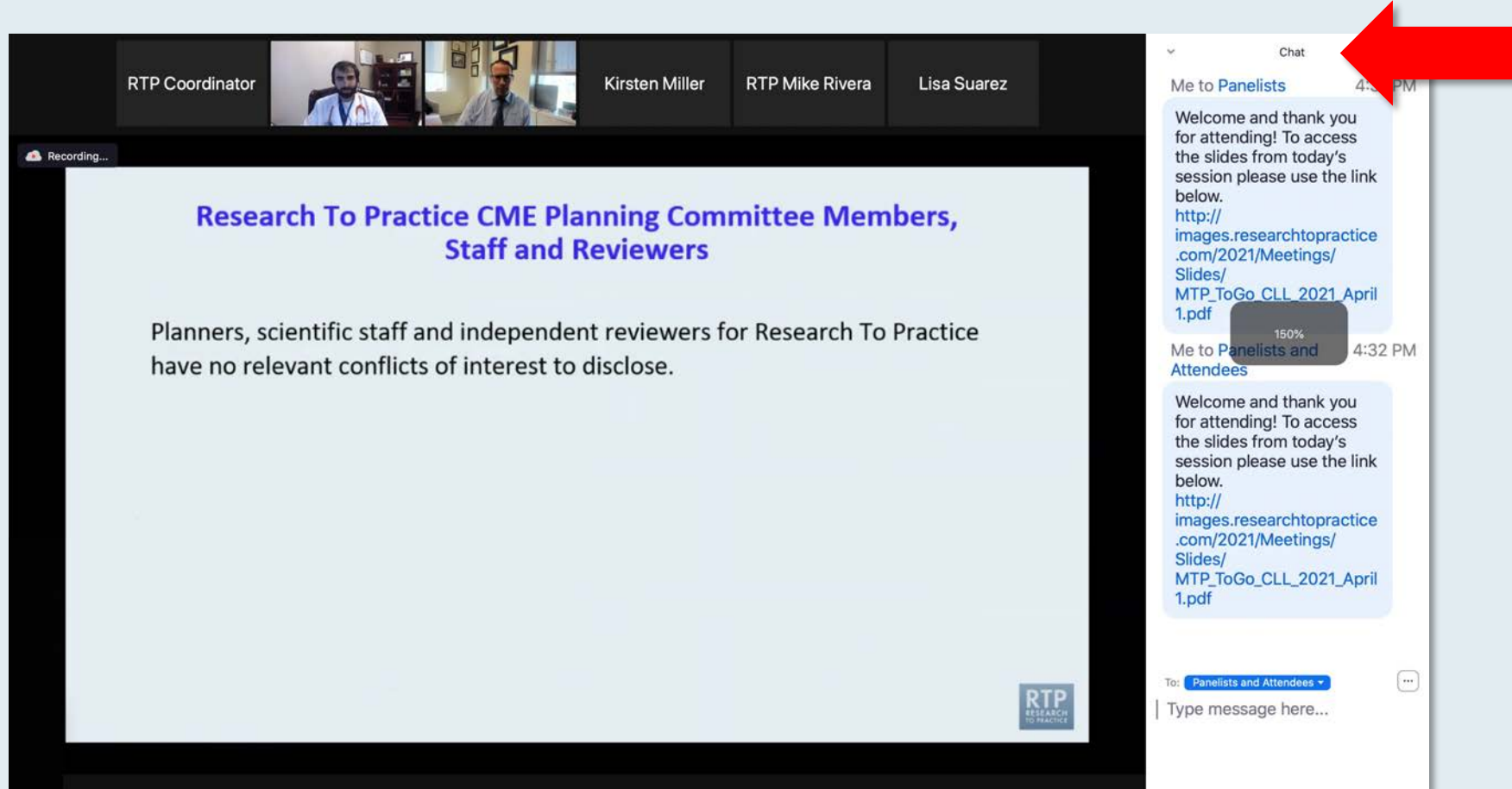
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Director, James P Wilmot Cancer Institute
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University of Rochester
Wilmot Cancer Institute
Rochester, New York
- Brian T Hill, MD, PhD**
Director, Lymphoid Malignancy Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio
- Christopher R Flowers, MD, MS**
Chair, Professor
Department of Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, Texas
- Brad S Kahl, MD**
Professor of Medicine
Washington University School of Medicine
Director, Lymphoma Program
Siteman Cancer Center
St Louis, Missouri

The chat window on the right shows two messages from "Me to Panelists" and "Me to Panelists and Attendees" at 4:31 PM and 4:32 PM respectively. Each message contains a welcome message and a link to a PDF document: http://images.researchtopractice.com/2021/Meetings/Slides/MTP_ToGo_CLL_2021_April1.pdf. A red arrow points to the white line above the "Type message here..." submission box in the chat window.

Drag the white line above the submission box up to create more space for your message.

Familiarizing Yourself with the Zoom Interface

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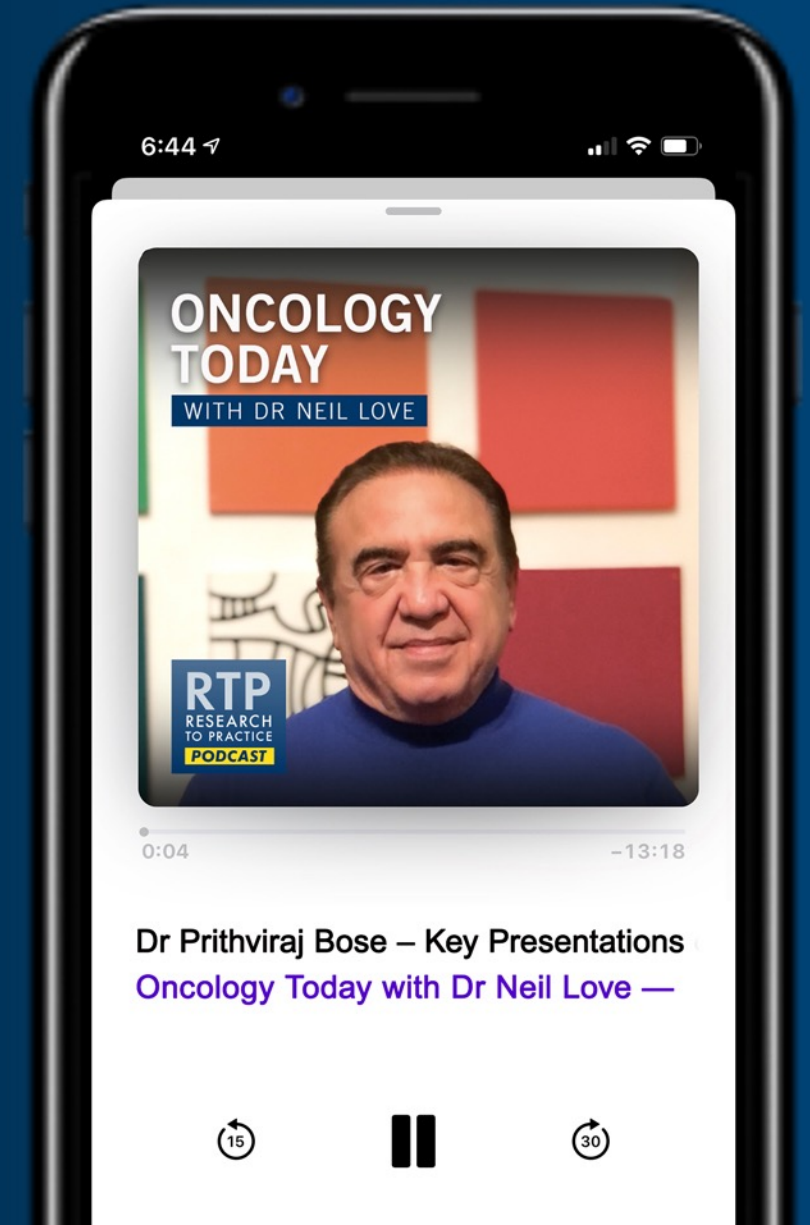
WITH DR NEIL LOVE

Key Presentations on Advances in Myeloproliferative Neoplasms from ASH 2021



DR PRITHVIRAJ BOSE

THE UNIVERSITY OF TEXAS
MD ANDERSON CANCER CENTER



Year in Review: Prostate Cancer

Tuesday, April 12, 2022
5:00 PM – 6:00 PM ET

Faculty

Emmanuel S Antonarakis, MD

Daniel P Petrylak, MD

Special Topics

- ARASENS, PROPEL, MAGNITUDE trials

Year in Review: Hepatobiliary and Pancreatic Cancers

**Wednesday, April 13, 2022
5:00 PM – 6:00 PM ET**

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**Tanios Bekaii-Saab, MD
Philip A Philip, MD, PhD, FRCP**

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Chronic Lymphocytic Leukemia

Thursday, April 14, 2022
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- Pirtobrutinib
- GLOW study

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Non-Small Cell Lung Cancer with an Actionable Target Beyond EGFR

**Monday, April 18, 2022
5:00 PM – 6:00 PM ET**

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Special Topics

- **ALK+ NSCLC: First-line treatment, resistance mutations**

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Prostate Cancer

Thursday, April 28, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Kathy D Burns, RN, MSN, AGACNP-BC, OCN

Robert Dreicer, MD, MS

Sandy Srinivas, MD

Ronald Stein, JD, MSN, NP-C, AOCNP

Non-Small Cell Lung Cancer

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Kelly EH Goodwin, MSN, RN, ANP-BC

Tara Plues, APRN, MSN

Anne S Tsao, MD, MBA

Ovarian Cancer

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Faculty

Jennifer Filipi, MSN, NP

Kathleen N Moore, MD, MS

Krishnansu S Tewari, MD

Deborah Wright, MSN, APRN, AGCNS-BC

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Richard S Finn, MD

Amanda K Wagner, APRN-CNP, AOCNP

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Shilpa Gupta, MD

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Cases from the Community: Urologic Oncology Investigators Provide Perspectives on the Optimal Management of Prostate Cancer

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Fred Saad, MD

Matthew R Smith, MD, PhD

Additional faculty to be announced.

Moderator

To be announced.

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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Srđan Verstovsek, MD, PhD
Professor of Medicine
Director, Hanns A Pielenz Clinical Research
Center for Myeloproliferative Neoplasms
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas

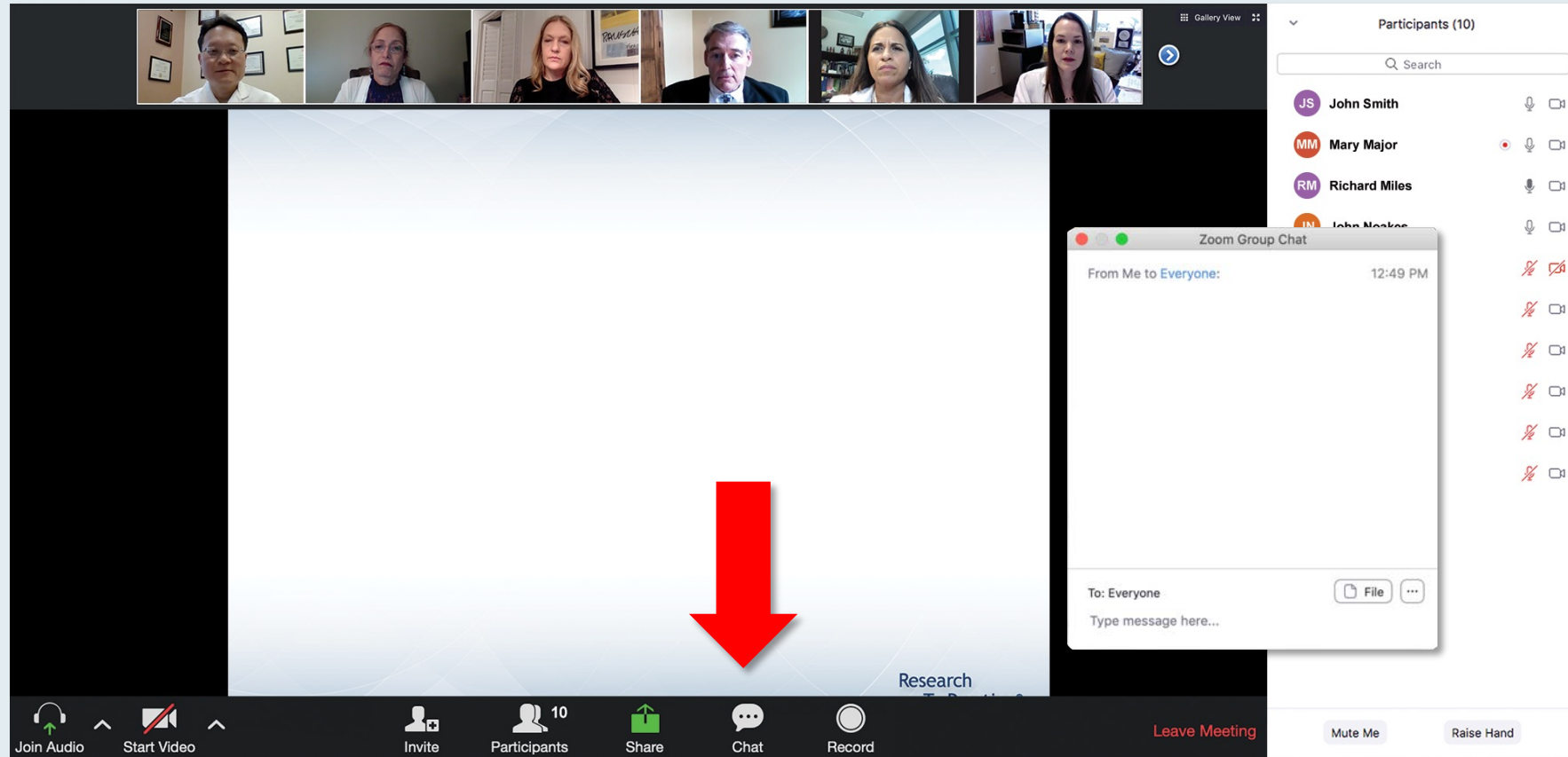


John Mascarenhas, MD
Director, Adult Leukemia Program
Professor of Medicine
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
New York, New York



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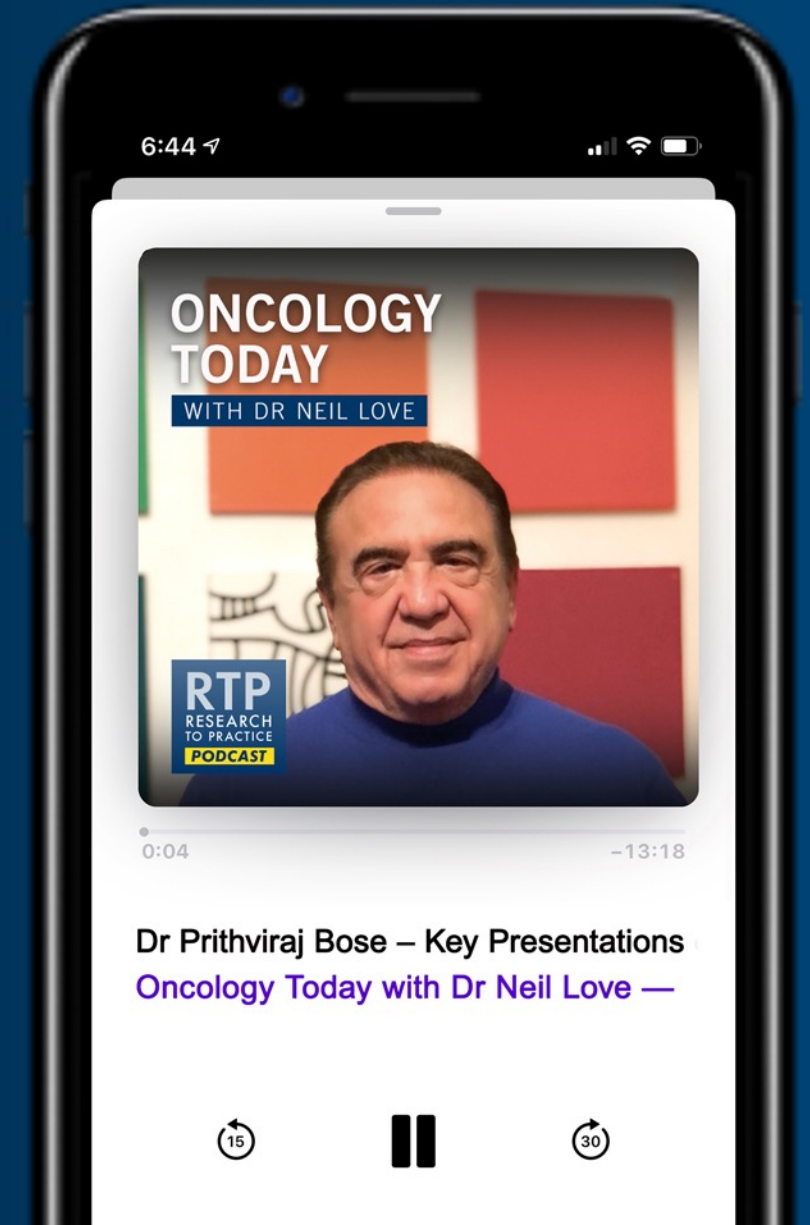
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Bhavana (Tina) Bhatnagar, DO
West Virginia University
Cancer Institute Schiffler Cancer Center
Wheeling, West Virginia



Niyati A Nathwani, MD
Carolina Blood and Cancer Care
Associates
Charlotte, North Carolina



Warren S Brenner, MD
Lynn Cancer Institute
Boca Raton, Florida



Jeanne Palmer, MD
Mayo Clinic in Arizona
Phoenix, Arizona



Susannah Friemel, MD
Iowa Cancer Specialists
Bettendorf, Iowa



Rajni Sinha, MD, MRCP
Piedmont Cancer Institute
Atlanta, Georgia



Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

Meet The Professor with Prof Harrison

Introduction

Module 1: Journal Club with Prof Harrison – Part 1

Module 2: Case Presentations – Part 1

- Dr Brenner: A 70-year-old man with DIPSS low- to intermediate-risk post-essential thrombocythemia myelofibrosis (MF)
- Dr Palmer: A 69-year-old woman with primary MF progressing after 3 years of ruxolitinib
- Dr Morganstein: A 69-year-old woman with disease progression after multiple regimens for post-polycythemia vera MF (post-PV MF)
- Dr Bhatnagar: A 79-year-old woman with post-PV MF with a JAK2 V617F mutation and transfusion dependence

Module 3: Faculty Survey

Module 4: Case Presentations – Part 2

- Dr Nathwani: A 66-year-old man with primary myelofibrosis (MF) with a JAK2 mutation and recurrent herpes zoster reactivation on ruxolitinib
- Dr Friemel: A 71-year-old man with prefibrotic primary MF with a JAK2 mutation and ruxolitinib-associated HPV reactivation
- Dr Sinha: A 23-year-old man with myeloproliferative neoplasm with a JAK2 V617F mutation and thrombocytosis
- Dr Brenner: An 85-year-old woman with primary MF and an MPL mutation

Module 5: Journal Club with Prof Harrison – Part 2

Module 6: Appendix of Key Publications

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Addition of Navitoclax to Ruxolitinib Mediates Responses Suggestive of Disease Modification in Patients with Myelofibrosis Previously Treated with Ruxolitinib Monotherapy

Pemmaraju N et al.

AACR 2022;Abstract LB108.

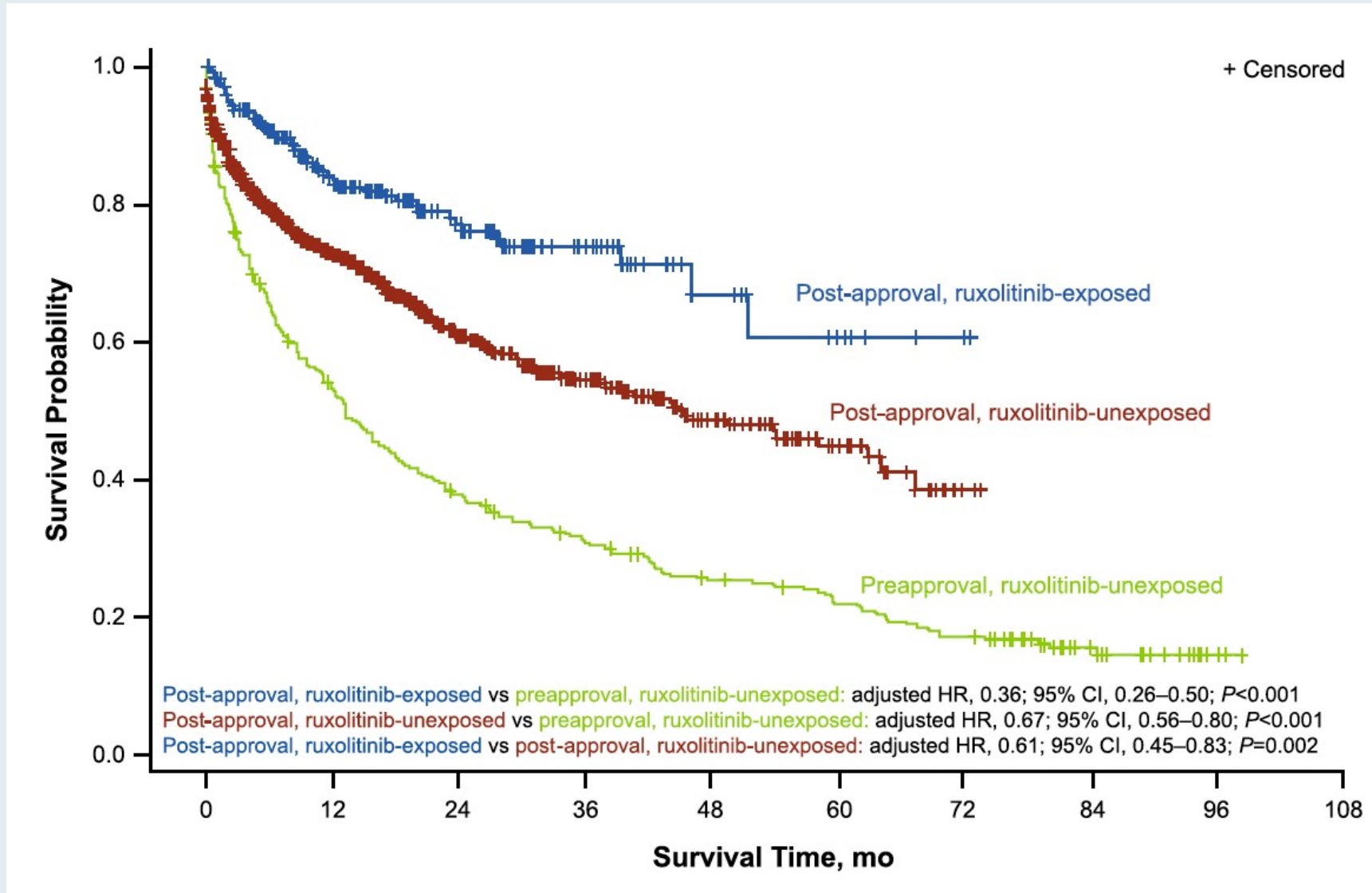
Annals of Hematology (2022) 101:131–137
<https://doi.org/10.1007/s00277-021-04682-x>

ORIGINAL ARTICLE

Real-world survival of US patients with intermediate- to high-risk myelofibrosis: impact of ruxolitinib approval

Srdan Verstovsek¹  · Shreekant Parasuraman² · Jingbo Yu² · Anne Shah³ · Shambhavi Kumar³ · Ann Xi³ · Claire Harrison⁴

Overall Survival for Patients Newly Diagnosed with Intermediate- to High-Risk Myelofibrosis

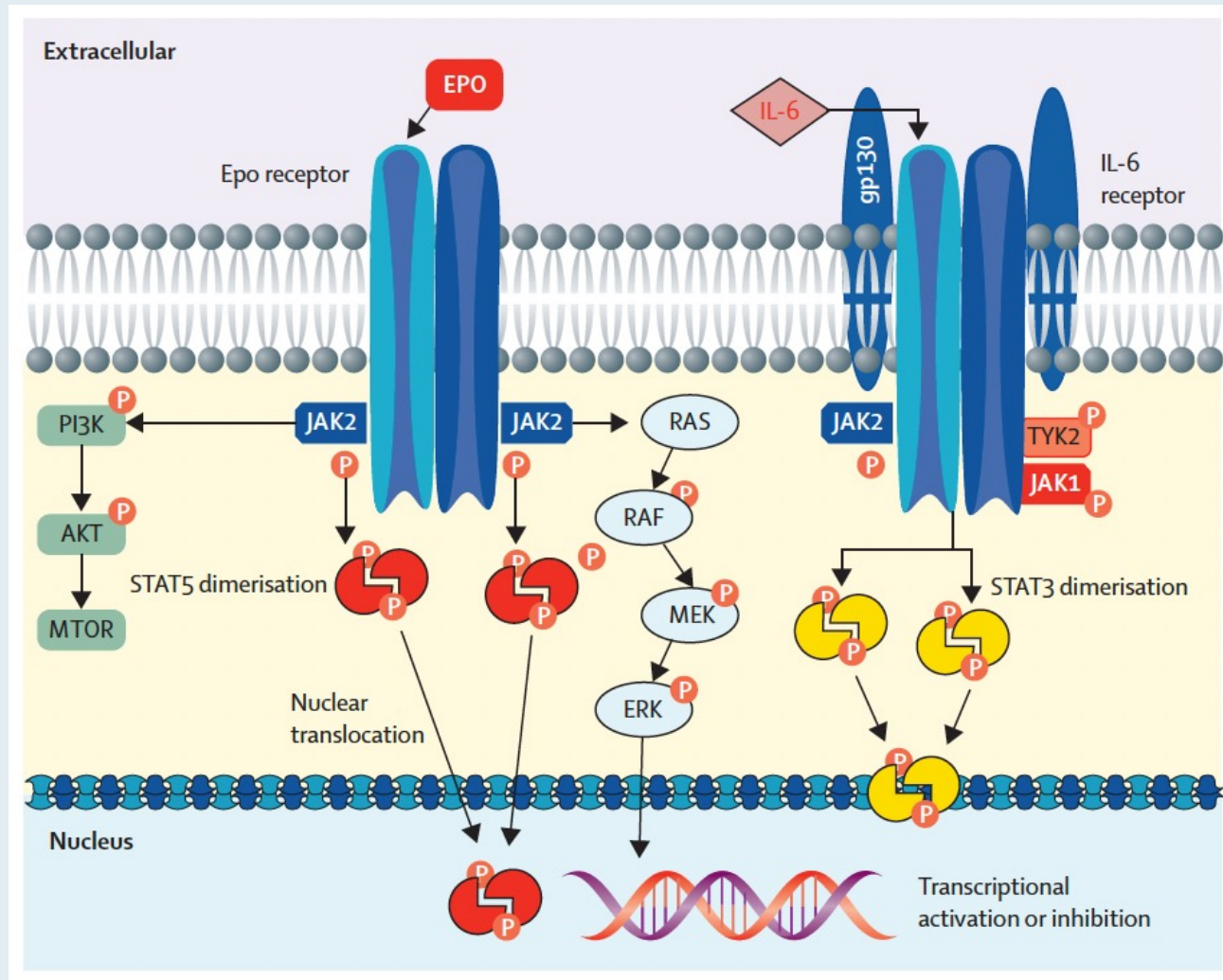


Lancet 2021;398(10302):803-16.

Current and future status of JAK inhibitors

Donal P McLornan, Janet E Pope, Jason Gotlib, Claire N Harrison

Simplified Overview of JAK–STAT Signalling via EPO Receptor and IL-6 Receptor Activation

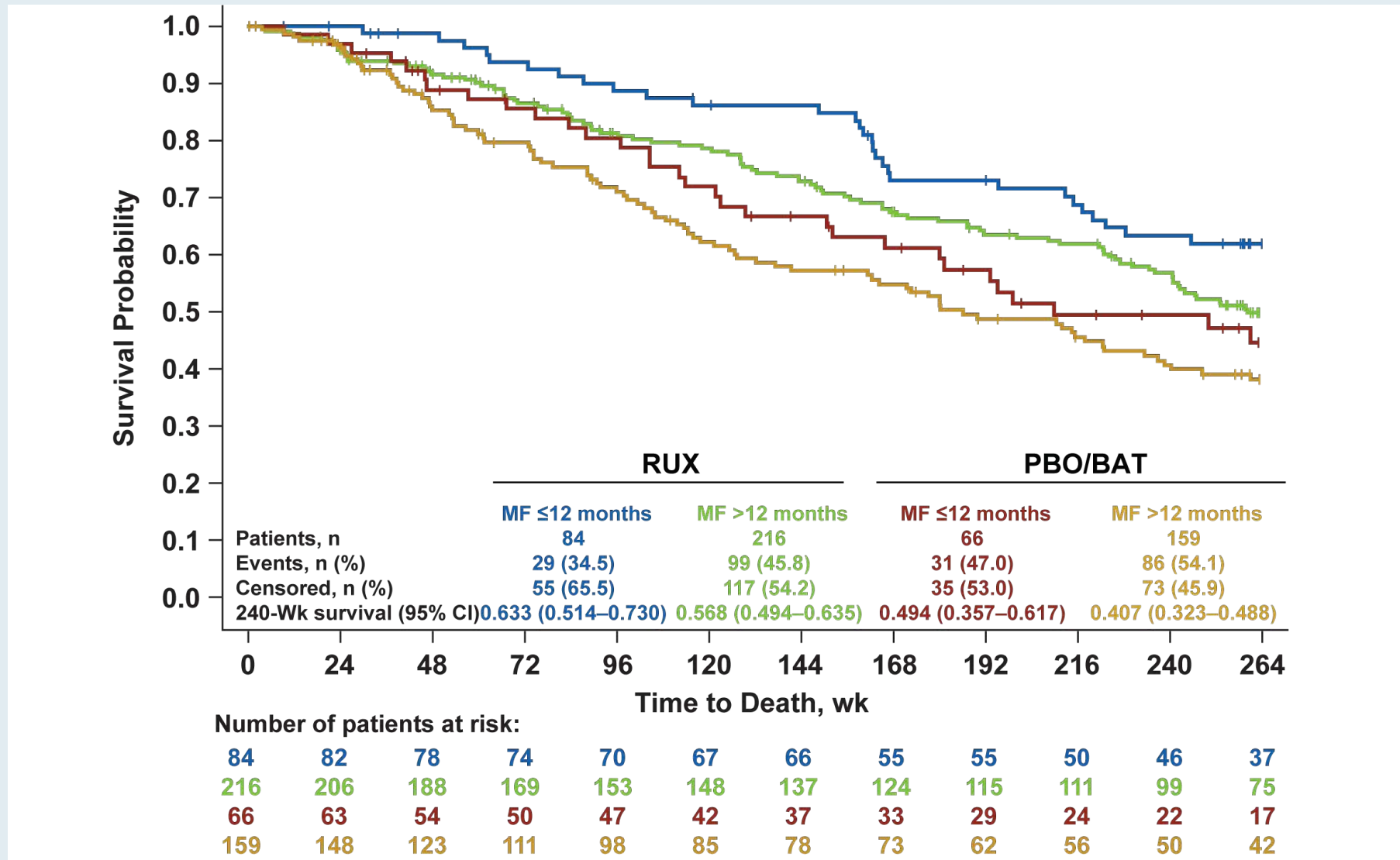


Does Early Intervention in Myelofibrosis Impact Outcomes? A Pooled Analysis of the Comfort I and II Studies

Verstovsek S et al.

ASH 2021;Abstract 1505.

Overall Survival of Patients with MF Stratified by Disease Duration Before Ruxolitinib Initiation



Safety and tolerability of fedratinib, an oral inhibitor of Janus kinase 2, in patients with intermediate- or high-risk myelofibrosis previously treated with ruxolitinib: results from the phase 3b FREEDOM trial

Vikas Gupta¹; Abdulraheem Yacoub²; Srdan Verstovsek³; Ruben Mesa⁴; Claire Harrison⁵; Giovanni Barosi⁶; Jean-Jacques Kiladjian⁷; H. Joachim Deeg⁸; Salman Fazal⁹; Lynda Foltz¹⁰; Ryan Mattison¹¹; Carole Miller¹²; Vinod Parameswaran¹³; Vishwanath Gharpure¹⁴; Christopher Hernandez¹⁴; Jun Zhang¹⁴; and Moshe Talpaz¹⁵

¹Princess Margaret Cancer Centre, Toronto, Canada; ²University of Kansas Medical Center, Kansas City, KS; ³The University of Texas MD Anderson Cancer Center, Houston, TX; ⁴Mays Cancer Center at UT Health San Antonio MD Anderson, San Antonio, TX; ⁵Guy's and St Thomas' Hospital, London, United Kingdom; ⁶Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia, Italy; ⁷Hôpital Saint-Louis; Université de Paris, Inserm, Paris, France; ⁸Fred Hutchinson Cancer Center, Seattle, WA; ⁹Allegheny Health Network Cancer Institute, Pittsburgh, PA; ¹⁰St. Paul's Hospital, University of British Columbia, Vancouver, Canada; ¹¹University of Wisconsin Carbone Comprehensive Cancer Center, Madison, WI; ¹²Ascension Saint Agnes Hospital, Baltimore, MD; ¹³Avera Cancer Institute, Sioux Falls, SD; ¹⁴Bristol Myers Squibb, Princeton, NJ; ¹⁵University of Michigan Comprehensive Cancer Center, Ann Arbor, MI

Publication No. 389

Conclusions

- Fedratinib was generally well tolerated in these older pts with MF, who had all received at least 3 months of prior RUX Tx before study entry
- The frequency and severity of nausea, vomiting, and diarrhea were substantially lower in FREEDOM than in previous clinical trials of fedratinib,^{1,2} suggesting these events can be prevented or mitigated by early implementation of GI prophylaxis
 - GI events were typically low-grade and decreased in frequency after cycle 1
 - Incidence of low-grade constipation in FREEDOM may be related to more frequent use of GI-directed therapies (eg, ondansetron, loperamide)
- Thiamine decreases were uncommon and easily managed with oral supplementation; there were no reported cases of encephalopathy (including WE)
 - Thiamine monitoring is recommended before and periodically during fedratinib Tx
- The open-label, randomized, phase 3 FREEDOM2 trial (NCT03952039)—the first controlled trial to compare fedratinib with other active MF therapies, including RUX—is currently enrolling pts with MF in the European Union, United Kingdom, China, Korea, and Australia

1. Harrison CN, et al. *Am J Hematol* 2020;95(6):594-603. Pardanani A, et al. *Br J Haematol* 2021;195(2):244-248.

Gupta V, et al. ASH 2021 [Abstract #389]



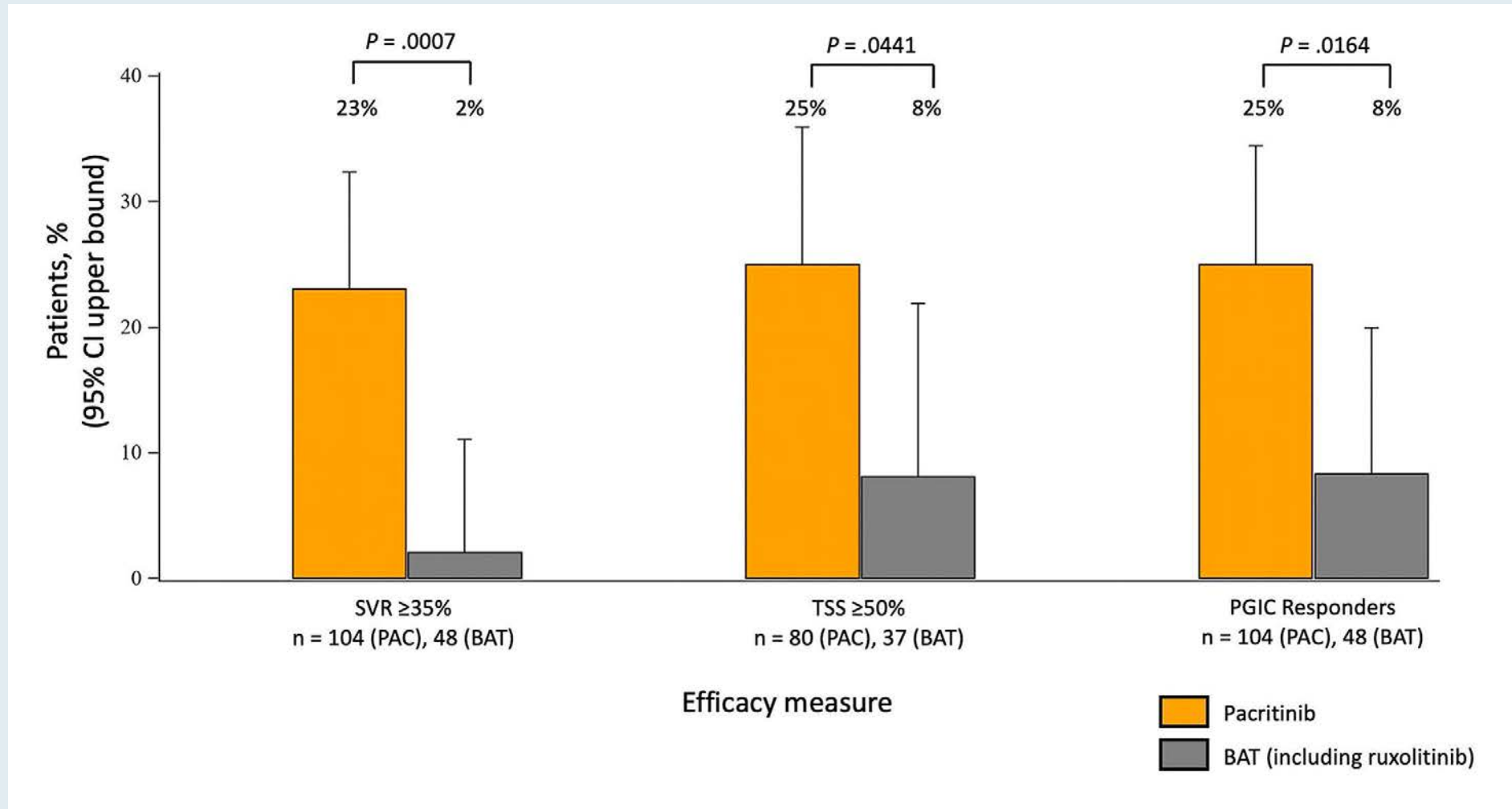
Journal of The Ferrata Storti Foundation

***Haematologica* 2021;[Online ahead of print].**

Retrospective analysis of pacritinib in patients with myelofibrosis and severe thrombocytopenia

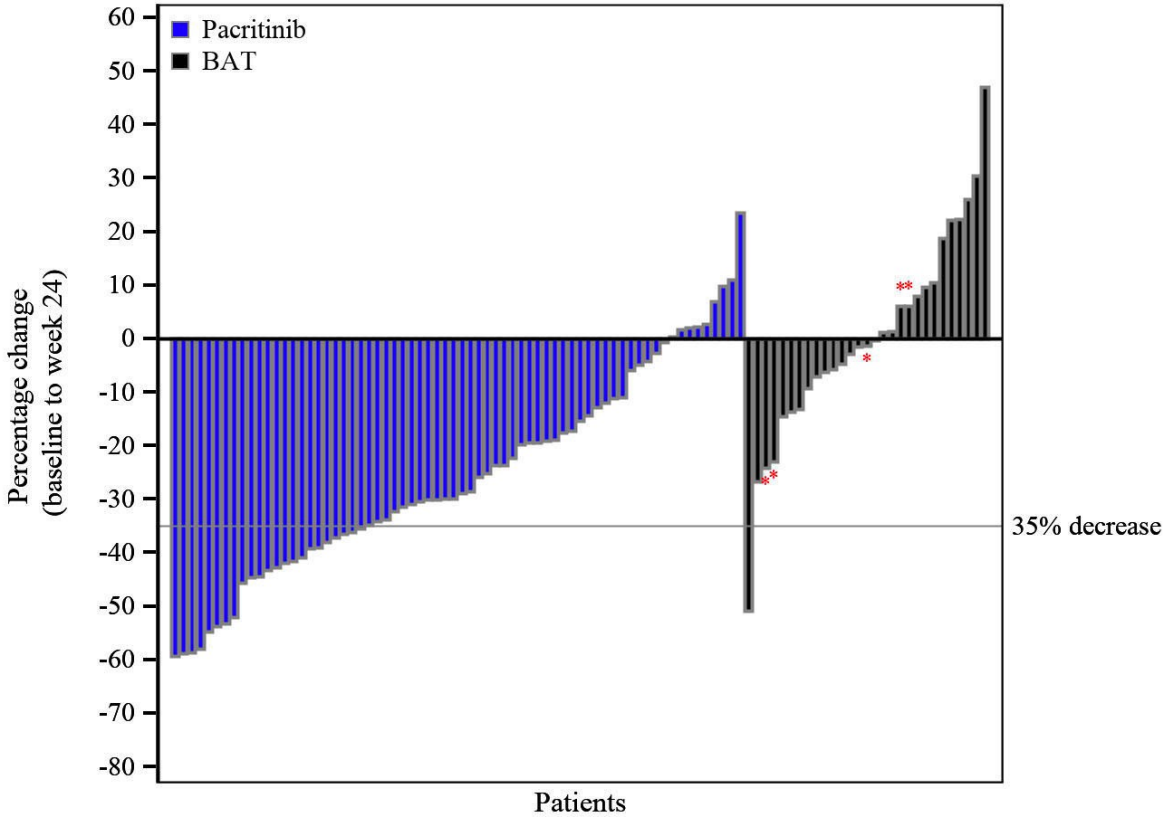
by Srdan Verstovsek, Ruben Mesa, Moshe Talpaz, Jean-Jacques Kiladjian, Claire N. Harrison, Stephen T. Oh, Alessandro M. Vannucchi, Raajit Rampal, Bart L. Scott, Sarah A. Buckley, Adam R. Craig, Karisse Roman-Torres, and John O. Mascarenhas

Efficacy of Pacritinib versus BAT Based on 24-Week Response Rates in Patients with Severe Thrombocytopenia

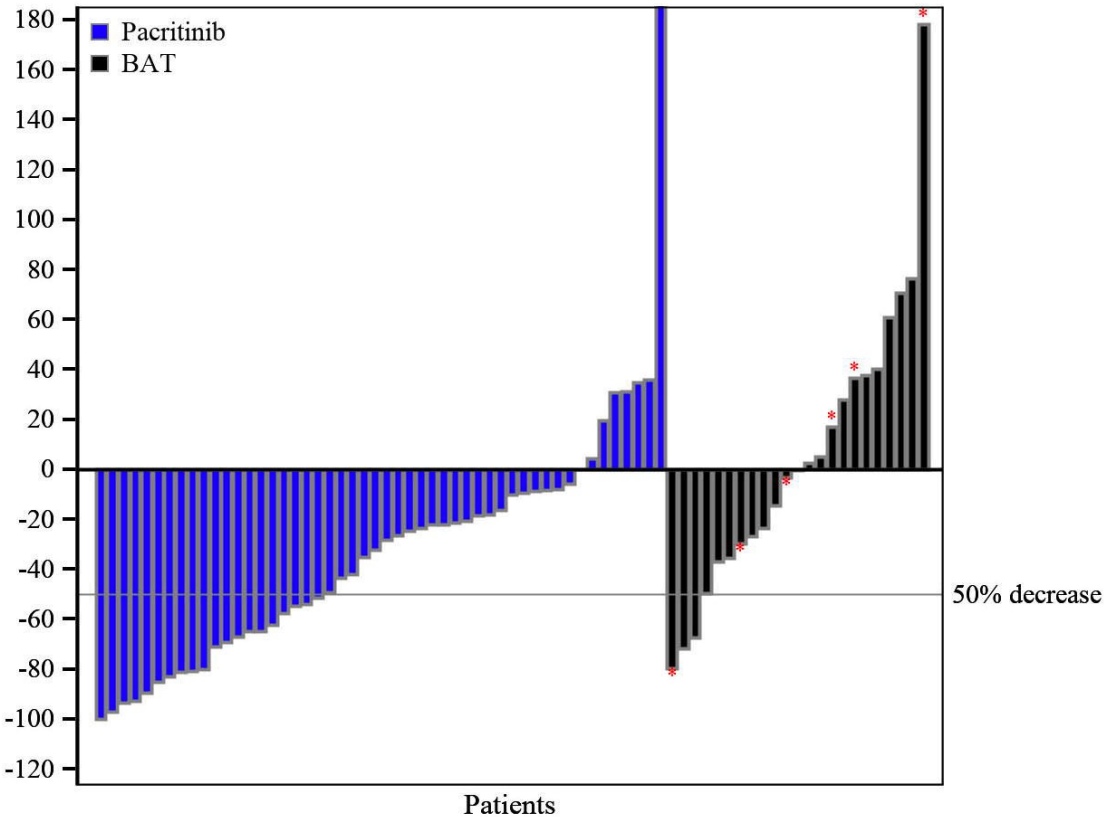


Waterfall Plots of Percent Change from Baseline

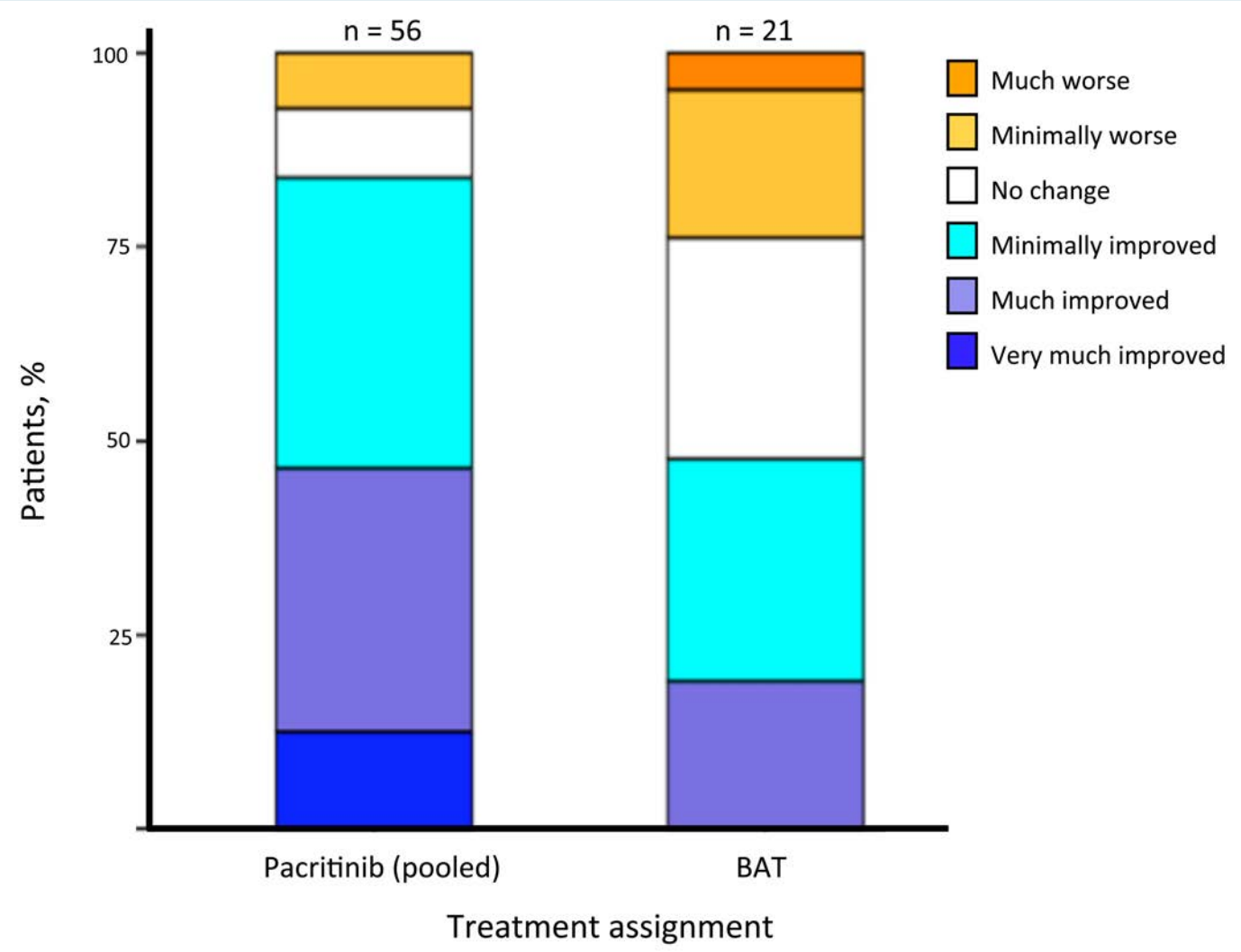
A. Change in Spleen Volume



B. Change in Modified TSS



Self-Reported Symptoms in Patients Who Completed the Patient Global Impression of Change at Week 24 by Treatment Group



Long-Term Treatment with Pacritinib on a Compassionate Use Basis in Patients with Advanced Myelofibrosis

Harrison CN et al.

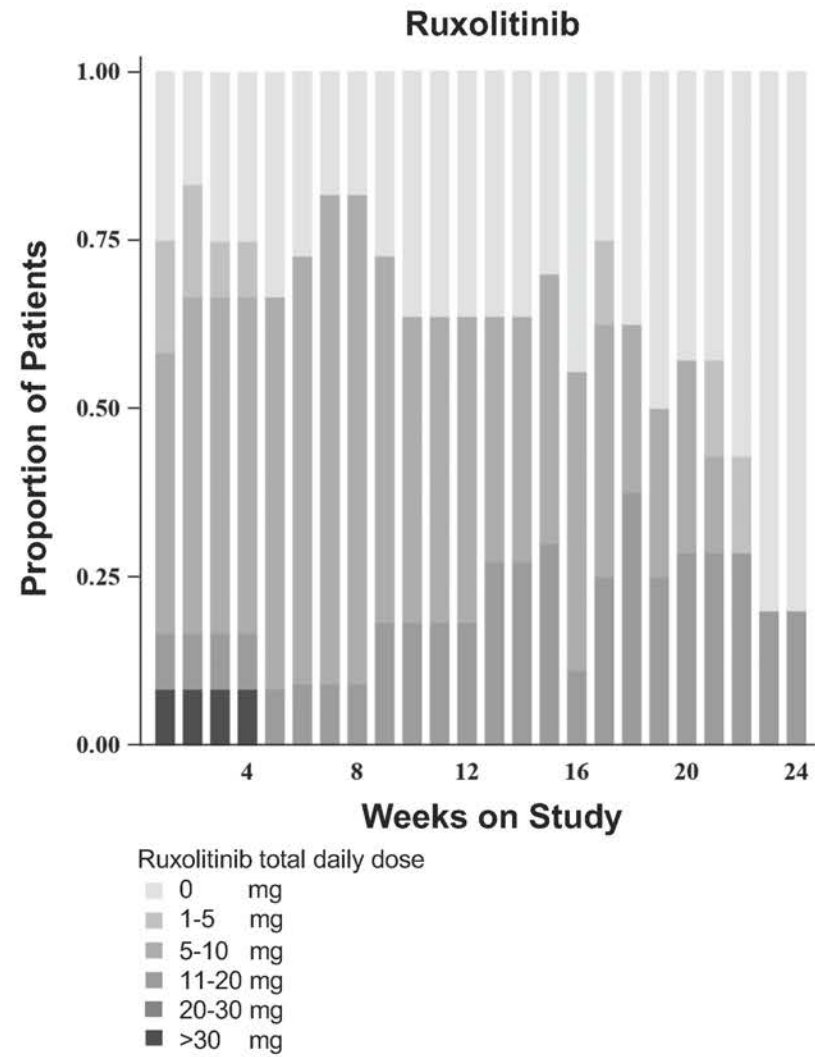
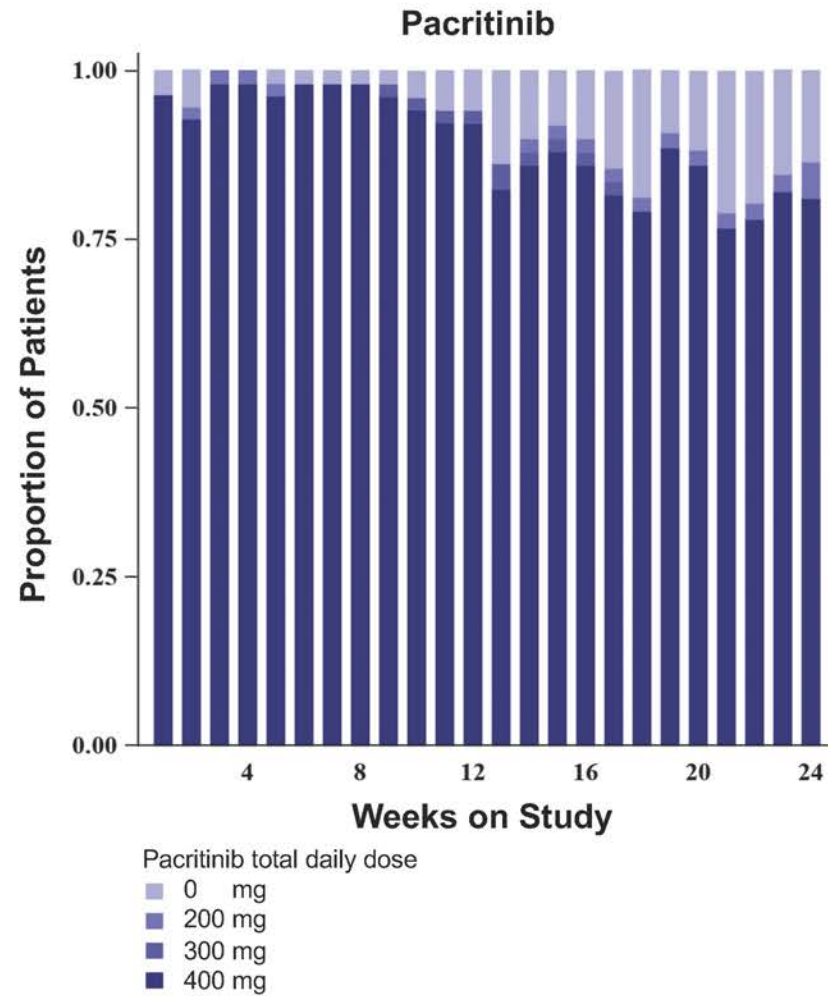
ASH 2021;Abstract 3649.

A Retrospective Head-to-Head Comparison between Pacritinib and Ruxolitinib in Patients with Myelofibrosis and Moderate to Severe Thrombocytopenia

Mascarahenas J et al.

ASH 2021;Abstract 3639.

Dose Intensity on PERSIST-2



Meet The Professor with Prof Harrison

Introduction

Module 1: Journal Club with Prof Harrison – Part 1

Module 2: Case Presentations – Part 1

- Dr Brenner: A 70-year-old man with DIPSS low- to intermediate-risk post-essential thrombocythemia myelofibrosis (MF)
- Dr Palmer: A 69-year-old woman with primary MF progressing after 3 years of ruxolitinib
- Dr Morganstein: A 69-year-old woman with disease progression after multiple regimens for post-polycythemia vera MF (post-PV MF)
- Dr Bhatnagar: A 79-year-old woman with post-PV MF with a JAK2 V617F mutation and transfusion dependence

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- Dr Sinha: A 23-year-old man with myeloproliferative neoplasm with a JAK2 V617F mutation and thrombocytosis
- Dr Brenner: An 85-year-old woman with primary MF and an MPL mutation

Module 5: Journal Club with Prof Harrison – Part 2

Module 6: Appendix of Key Publications

Case Presentation: A 70-year-old man with DIPSS low- to intermediate-risk post-essential thrombocythemia MF



Dr Warren Brenner (Boca Raton, Florida)

Case Presentation: A 69-year-old woman with primary MF progressing after 3 years of ruxolitinib



Dr Jeanne Palmer (Phoenix, Arizona)

Case Presentation: A 69-year-old woman with disease progression after multiple regimens for post-PV MF



Dr Neil Morganstein (Summit, New Jersey)

Case Presentation: A 79-year-old woman with post-PV MF with a JAK2 V617F mutation and transfusion dependence



Dr Bhavana (Tina) Bhatnagar (Wheeling, West Virginia)

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Module 5: Journal Club with Prof Harrison – Part 2

Module 6: Appendix of Key Publications

Which prognostic tool do you typically use for your patients with myelofibrosis (MF)?



For a 65-year-old patient with lower-risk, symptomatic MF, which treatment would you generally recommend?



HU = hydroxyurea

Regulatory and reimbursement issues aside and assuming you could access all these agents, for a 65-year-old patient with higher-risk, symptomatic MF, splenomegaly and a platelet count of 40,000/ μ L, which treatment would you generally recommend (assuming the patient is not a transplant candidate)?



Dr Bhatnagar

Pacritinib



Dr Stein

Pacritinib



Prof Harrison

Ruxolitinib or
pacritinib



Dr Verstovsek

Pacritinib



Dr Mascarenhas

Pacritinib

If treating a patient with higher-risk, symptomatic MF, splenomegaly and a platelet count of 150,000/ μ L with ruxolitinib, what starting dose would you generally use?



Dr Bhatnagar

10 mg BID



Dr Stein

15 mg BID



Prof Harrison

10 mg BID



Dr Verstovsek

15 mg BID



Dr Mascarenhas

10 mg BID

What is the maximum dose of ruxolitinib that you would use for a patient with MF?



Dr Bhatnagar

25 mg BID



Dr Stein

20 mg BID



Prof Harrison

25 mg BID



Dr Verstovsek






25 mg BID



Dr Mascarenhas

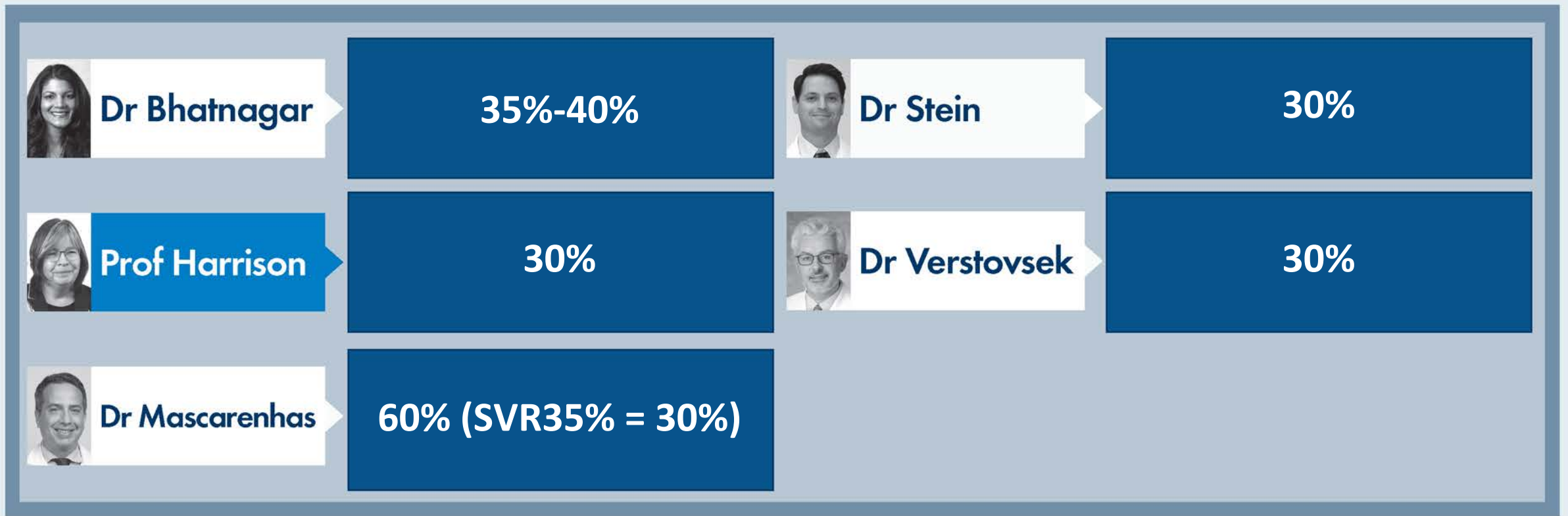
25 mg BID

Regulatory and reimbursement issues aside and assuming you could access all these agents, if a 65-year-old patient with higher-risk, symptomatic MF did not experience reduction in spleen size or improvement in symptoms after 3 months of standard-dose ruxolitinib, which of the following would you most likely attempt (assuming normal renal and hepatic function and a platelet count $>200,000/\mu\text{L}$)?

 Dr Bhatnagar	Switch to fedratinib	 Dr Stein	Switch to fedratinib
 Prof Harrison	Escalate dose of ruxolitinib, consider BMT	 Dr Verstovsek	Escalate dose of ruxolitinib
 Dr Mascarenhas	Switch to fedratinib		

BMT = bone marrow transplant

If you decided to switch to fedratinib for the patient in the previous scenario, what would you estimate is the likelihood that he or she would respond?



SVR = splenic volume reduction

When discontinuing ruxolitinib due to insufficient response, intolerance or progressive disease, do you generally taper off or discontinue immediately?



Dr Bhatnagar

Taper by 5 mg every week until off



Dr Stein

Taper over 2 weeks if possible, by 5-mg increments each several days



Prof Harrison

Taper by 5 mg q3-5 days



Dr Verstovsek

Taper by 10 mg BID weekly



Dr Mascarenhas

Taper over a week unless patient on 5 mg BID and then would taper over 2 days

Based on current clinical trial data and your personal experience, how would you compare the rapidity of splenic response with ruxolitinib to that with fedratinib?



Dr Bhatnagar

About the same



Dr Stein

Ruxolitinib response is more rapid



Prof Harrison

About the same



Dr Verstovsek

About the same



Dr Mascarenhas

About the same

A 65-year-old man with symptomatic, higher-risk MF and splenomegaly (baseline platelet count $110,000/\mu\text{L}$) receives ruxolitinib 15 mg BID and responds with significant clinical improvement. Approximately 3 years later, he presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = $44,000/\mu\text{L}$, Hgb = 11.2 g/dL. Regulatory and reimbursement issues aside, what treatment would you most likely recommend next if the patient is transplant ineligible?



Dr Bhatnagar

Pacritinib



Dr Stein

Pacritinib



Prof Harrison

Pacritinib



Dr Verstovsek

Pacritinib



Dr Mascarenhas

Pacritinib

Do you believe pacritinib has real pharmacologic advantages over other available JAK inhibitors that make it a preferable treatment option for patients with MF and low platelet counts?



Dr Bhatnagar

Yes



Dr Stein

Yes



Prof Harrison

Yes



Dr Verstovsek

Yes



Dr Mascarenhas

Yes

Do you believe that the risk of bleeding and/or cardiovascular toxicities is a significant concern for patients with MF receiving pacritinib?



Dr Bhatnagar

No



Dr Stein

No



Prof Harrison

Yes



Dr Verstovsek

No



Dr Mascarenhas

No

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Module 5: Journal Club with Prof Harrison – Part 2

Module 6: Appendix of Key Publications

Case Presentation: A 66-year-old man with primary MF with a JAK2 mutation and recurrent herpes zoster reactivation on ruxolitinib



Dr Niyati Nathwani (Charlotte, North Carolina)

Case Presentation: A 71-year-old man with prefibrotic primary MF with a JAK2 mutation and ruxolitinib-associated HPV reactivation



Dr Susannah Friemel (Bettendorf, Iowa)

Case Presentation: A 23-year-old man with myeloproliferative neoplasm with a JAK2 V617F mutation and thrombocytosis



Dr Rajni Sinha (Atlanta, Georgia)

Case Presentation: An 85-year-old woman with primary MF and an MPL mutation



Dr Warren Brenner (Boca Raton, Florida)

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Module 5: Journal Club with Prof Harrison – Part 2

Module 6: Appendix of Key Publications

Safety Analysis of Pacritinib in Patients with Myelofibrosis and Severe Thrombocytopenia

Mascarahenas J et al.

ASH 2021;Abstract 3640.

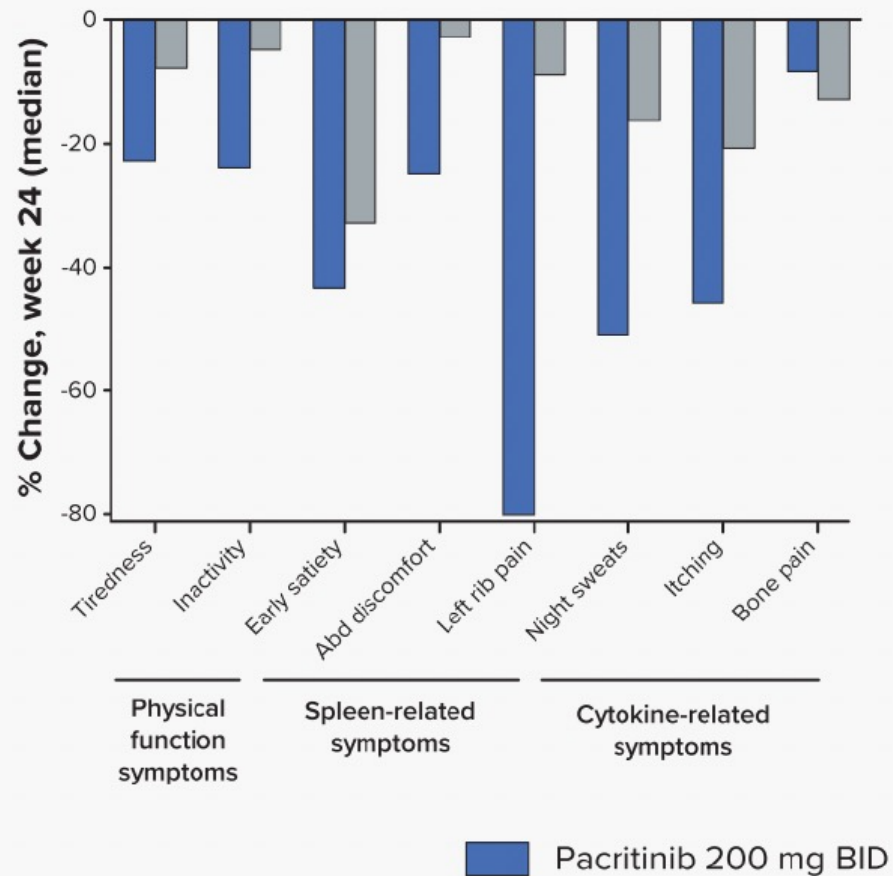
The Impact of Pacritinib on Myelofibrosis Symptoms in Patients with Moderate and Severe Thrombocytopenia: A Retrospective Analysis of Patients in the Persist-2 Study

Palmer JM et al.

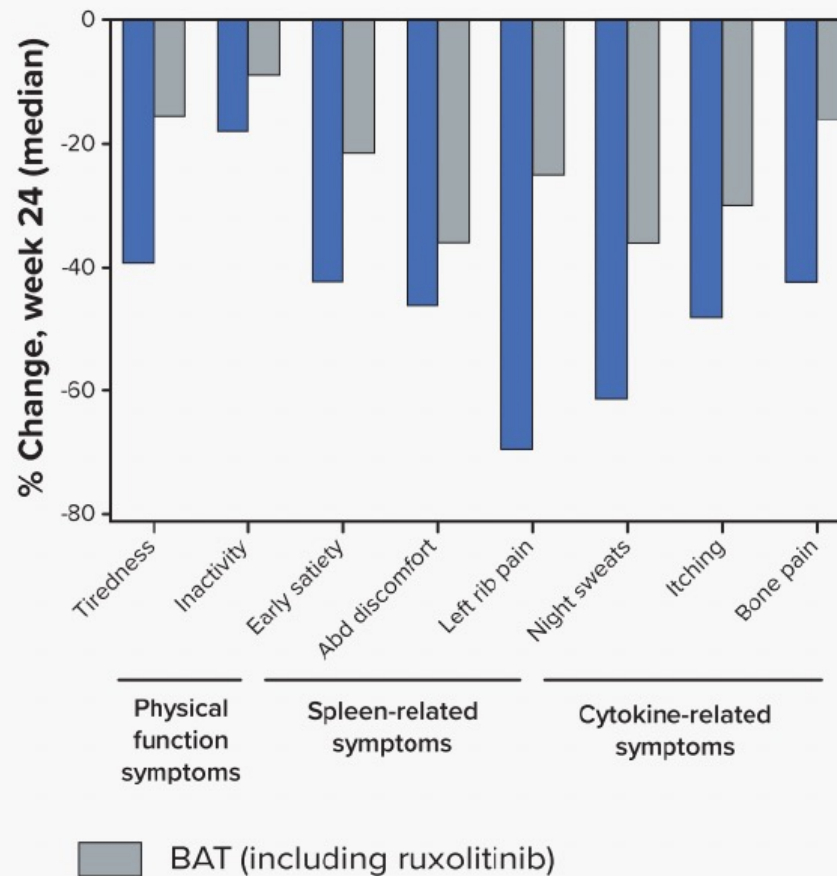
ASH 2021;Abstract 3628.

Percent Change in Individual Symptom Score

A. Individuals with Baseline Platelet Count <math><50 \times 10^9/L</math>



B. Individuals with Baseline Platelet Count $\geq 50 \times 10^9/L$



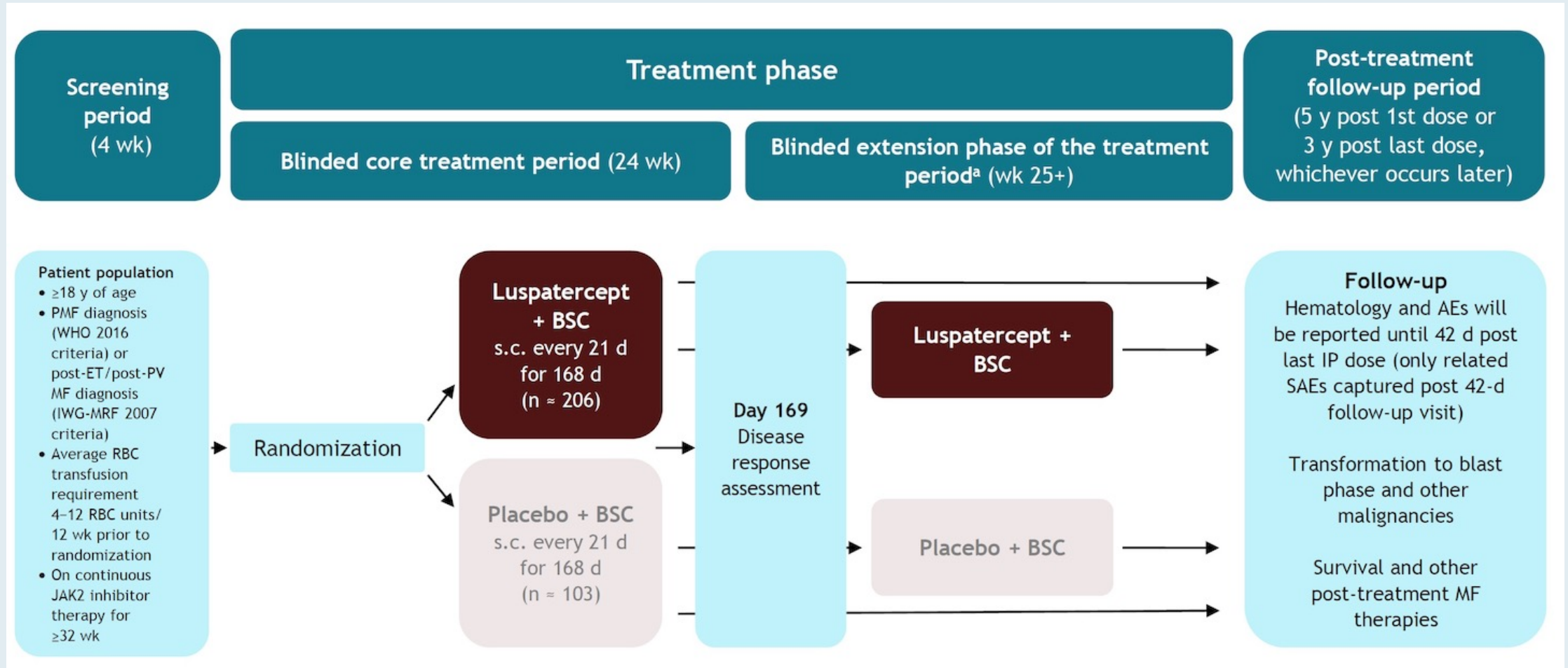
BAT=best available therapy; BID=twice daily.

INDEPENDENCE: A Phase 3 Study of Efficacy and Safety of Luspatercept versus Placebo in Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis on JAK2 Inhibitor Therapy and Requiring Red Blood Cell Transfusions

Mesa RA et al.

ASH 2021;Abstract 1490.

INDEPENDENCE Trial Design



REVIEW

Br J Haematol 2022;[Online ahead of print].



How I manage myeloproliferative neoplasm-unclassifiable: Practical approaches for 2022 and beyond

Donal P. McLornan^{1,2}  | Rupen Hargreaves² | Juan Carlos Hernández-Boluda³  |
Claire N. Harrison¹ 

How I manage myeloproliferative neoplasm unclassifiable (MPN-U): Practical approaches for 2022 and beyond

- Case 1: Obstetric management for MPN-U
- Case 2: Thrombotic complications in MPN-U
- Case 3: Role of intensified therapy and allogeneic stem cell transplantation for MPN-U
- Case 4: To cytoreduce or not in MPN-U?

Curr Res Transl Med 2022;[Online ahead of print].



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Original article

Diagnostic and management strategies for Myeloproliferative Neoplasm- Unclassifiable (MPN-U): An international survey of contemporary practice

Rupen Hargreaves^a, Claire N Harrison^b, Donal P McLornan^{a,b,*}

Low-dose Splenic Irradiation in Conjunction With Ruxolitinib to Provide Symptomatic Relief in Heavily Treated, Advanced Stage Myelofibrosis: A Case Series From a UK Tertiary Referral Center

Alesia Khan^{1,2}, Claire Woodley¹, Deepti Radia¹, George N. Mikhaeel³, Jessica Brady³, Natalia Curto Garcia¹, Patrick Harrington¹, Jennifer O'Sullivan¹, Shahram Kordasti^{1,4}, Yvonne Francis¹, Susan Asirvatham¹, Sahra Ali¹, Priya Sriskandarajah¹, Jamie Saunders¹, Hugues de Lavallade¹, Donal P. McLornan¹, Claire N. Harrison¹

© original reports

Addition of Navitoclax to Ongoing Ruxolitinib Therapy for Patients With Myelofibrosis With Progression or Suboptimal Response: Phase II Safety and Efficacy

Claire N. Harrison, MD¹; Jacqueline S. Garcia, MD²; Tim C. P. Somerville, MBBS, PhD^{3,4}; James M. Foran, MD⁵; Srdan Verstovsek, MD, PhD⁶; Catriona Jamieson, MD, PhD⁷; Ruben Mesa, MD⁸; Ellen K. Ritchie, MD⁹; Srinivas K. Tantravahi, MBBS¹⁰; Pankit Vachhani, MD¹¹; Casey L. O'Connell, MD¹²; Rami S. Komrokji, MD¹³; Jason Harb, PhD¹⁴; Jessica E. Hutti, PhD¹⁴; Leanne Holes, MBA¹⁴; Abdullah A. Masud, MS, PhD¹⁴; Silpa Nuthalapati, PhD¹⁴; Jalaja Potluri, MD¹⁴; and Naveen Pemmaraju, MD⁶

J Clin Oncol 2022;[Online ahead of print].

Adore: A Randomized, Open-Label, Phase 1/2 Open-Platform Study Evaluating Safety and Efficacy of Novel Ruxolitinib Combinations in Patients with Myelofibrosis

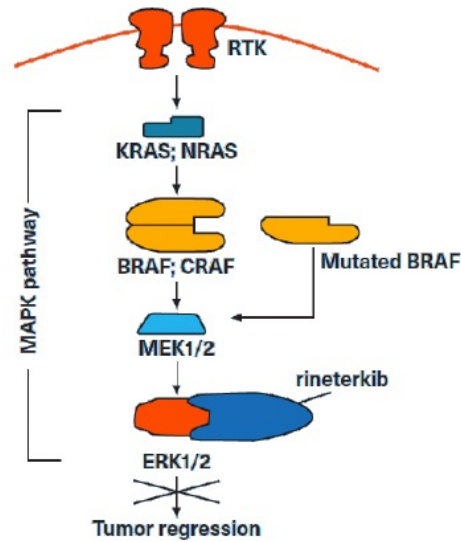
Ross DM et al.

ASH 2021;Abstract 1489.

Study Compounds

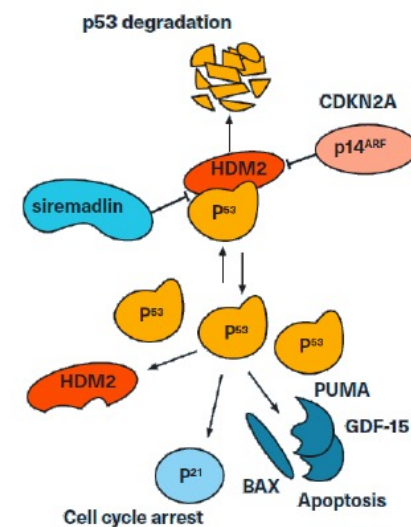
RUX + rineterkib

- Constitutive JAK2 signaling results in activation of MEK/ERK signaling, which may limit the efficacy of JAK2 inhibition¹
- Rineterkib is a small molecule inhibitor of ERK1/2²



RUX + siremadlin

- JAK2 mutations are thought to induce the expression of HDM2, which acts to degrade p53^{3,4}
- Siremadlin is a small molecule inhibitor of the p53/HDM2 interaction, protecting p53 from degradation⁵



RUX + crizanlizumab

- In patients with MF, impaired megakaryocytes express high levels of P selectin, which leads to increased TGF- β release and disease progression⁶
- Crizanlizumab is a mAb that binds to and inhibits P-selectin⁷

RUX + sabatolimab

- Sabatolimab is a mAb that blocks the binding of TIM-3 to its ligand PtdSer⁸
- TIM-3 blockade restores activity of exhausted T cells, and may diminish suppressor activity of regulatory T cells⁹

RUX + NIS793

- TGF- β is a pro-inflammatory cytokine that promotes bone marrow fibrosis^{10,11}
- NIS793 is a mAb that binds to TGF- β 1 and TGF- β 2 and displays TGF- β 1- and TGF- β 2-neutralizing activity¹²

1. Stivala S, et al. *J Clin Invest*. 2019;129(4):1596–1611. 2. Janku F, et al. *Journa of Clinical Oncology*. 38(15_suppl):3640-3640. 3. Saha MN, et al. *J Hematol Onco*. 2013;6:23. 4. Nakatake M, et al. *Oncogene*. 2012;31:1323–1333. 5. Stachyra-Valat T, et al. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, LA. Philadelphia (PA): AACR; Cancer Res 2016;76(14 Suppl):Abstract nr 1239. 6. Spangrude GJ, et al. *Stem Cells*. 2016;34:67–82. 7. Ataga KI, et al. *N Engl J Med*. 2017;376:429–439. 8. Sabatos-Peyton CA, et al. Poster presented at the European School of Hematology (ESH), 2021. 9. Sakuishi K, et al. *Trends Immunol*. 2011;32(8):345–349. 10. Zingariello M, et al. *Blood*. 2013;121:3345–3363. 11. Agarwal A, et al. *Stem Cell Investig*. 2016;3:5. 12. Derynck R, et al. *Nat Rev Clin Oncol*. 2021;18(1):9–34.

Poster presented at the American Society of Hematology (ASH) Annual Meeting & Exposition, held in-person in Atlanta, GA, USA, and virtually, December 11-14, 2021.



Contents lists available at [ScienceDirect](#)

Blood Reviews
Blood Rev 2022;[Online ahead of print].
journal homepage: www.elsevier.com/locate/issn/0268960X

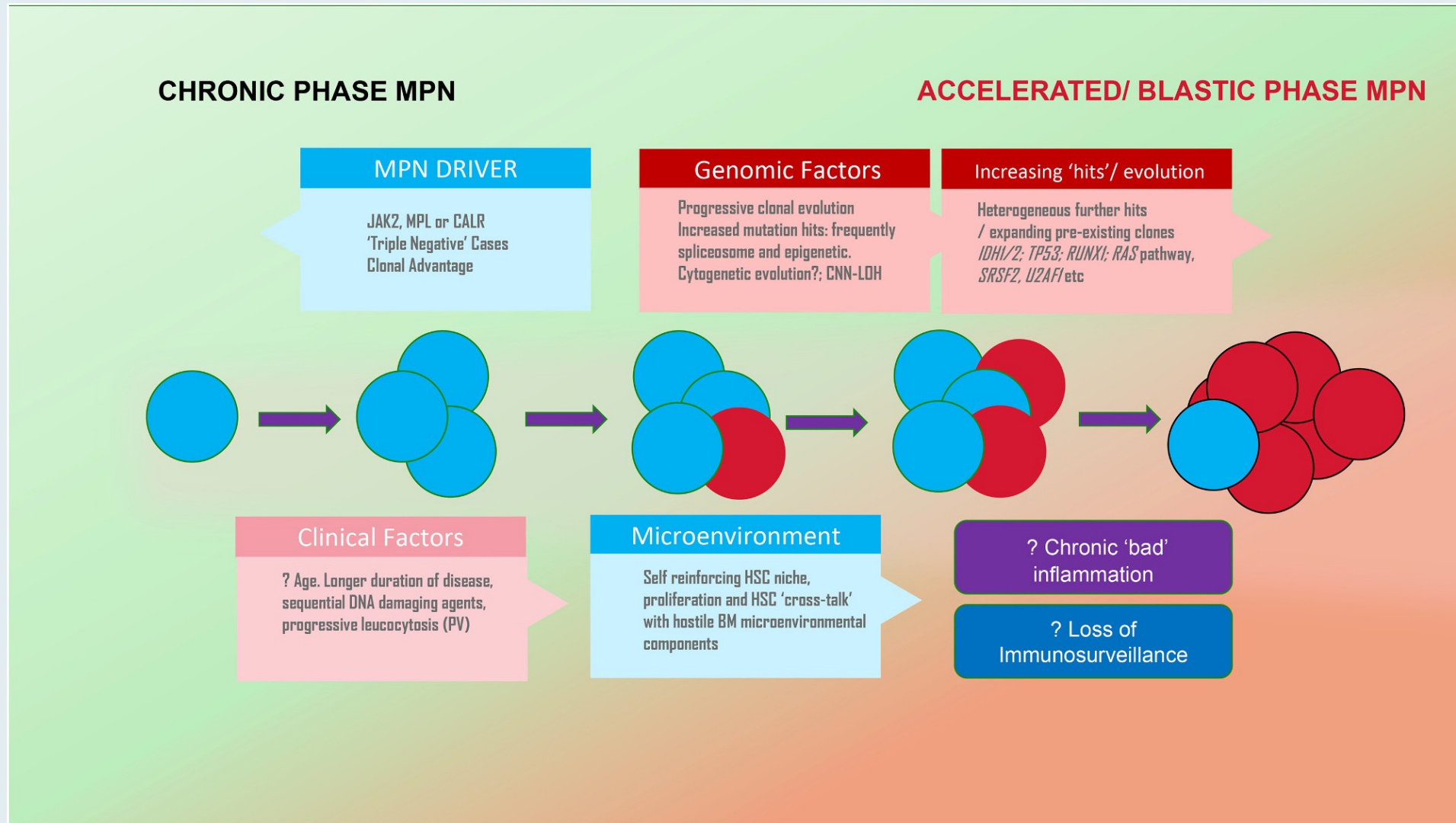


Review

Addressing the challenges of accelerated and blast phase myeloproliferative neoplasms in 2022 and beyond

Chandan Saha^{a,1}, Luke Attwell^{b,1}, Claire N. Harrison^a, Donal P. McLornan^{a,c,*}

Underlying Pathogenetic Features Promoting Disease Progression



CORRESPONDENCE

CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Second versus first wave of COVID-19 in patients with MPN

Barbui T et al. *Leukemia* 2022;36(3):897-900.

Letter

Repeated vaccination against SARS-CoV-2 elicits robust polyfunctional T cell response in allogeneic stem cell transplantation recipients

Patrick Harrington,^{1,2} Katie J. Doores,³ Chandan Saha,¹ Jamie Saunders,¹ Fiona Child,¹ Richard Dillon,^{1,4} Sukran Saglam,¹ Kavita Raj,¹ Donal McLornan,¹ Daniele Avenoso,⁵ Shahram Kordasti,^{1,2} Amy O'Reilly,¹ Andreas Espehana,¹ Thomas Lechmere,³ Hataf Khan,³ Michael H. Malim,³ Claire Harrison,^{1,2} Varun Mehra,⁵ and Hugues de Lavallade^{1,2,*}

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Module 5: Journal Club with Prof Harrison – Part 2

Module 6: Appendix of Key Publications

Disease Modification in Myelofibrosis: An Elusive Goal?

Pankit Vachhani, MD¹; Srdan Verstovsek, MD, PhD²; and Prithviraj Bose, MD²

J Clin Oncol 2022;40(11):1147-55.

***N Engl J Med* 2012;366:799-807**

The NEW ENGLAND JOURNAL of MEDICINE

COMFORT-I

ORIGINAL ARTICLE

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis

Srdan Verstovsek, M.D., Ph.D., Ruben A. Mesa, M.D., Jason Gotlib, M.D.,
Vikas Gupta, M.D., John F. DiPersio, M.D., Ph.D.,
Michael Deining, M.D., Ph.D., Carole Miller, M.D.,
Moshe Talpaz, M.D., Elliott F. Winton, M.D.,
Murat O. Arcasoy, M.D., Elizabeth Hexner, M.D.,
Ronald Paquette, M.D., Azra Raza, M.D.,
Erickson-Viitanen, Ph.D., Iphigenia L. Koumenis, M.S.,
Victor Sandor, M.D., and Hagop M. Kantarjian, M.D.

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

MARCH 1, 2012

VOL. 366 NO. 9

COMFORT-II

JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis

Claire Harrison, D.M., Jean-Jacques Kiladjan, M.D., Ph.D., Haifa Kathrin Al-Ali, M.D., Heinz Gisslinger, M.D.,
Roger Waltzman, M.D., M.B.A., Viktoriya Stalbovskaya, Ph.D., Mari McQuitty, R.N., M.P.H., Deborah S. Hunter, Ph.D.,
Richard Levy, M.D., Laurent Knoops, M.D., Ph.D., Francisco Cervantes, M.D., Ph.D., Alessandro M. Vannucchi, M.D.,
Tiziano Barbui, M.D., and Giovanni Barosi, M.D.

COMFORT-I and COMFORT-II: Ruxolitinib for Intermediate-2- or High-Risk MF

- Randomized Phase III studies in which patients with intermediate 2- or high-risk MF received ruxolitinib (15 or 20 mg BID) versus placebo (COMFORT-I, N = 309) or best available therapy (COMFORT-II, N = 149)

Efficacy outcomes	COMFORT-I, Wk 24 ¹		p-value	COMFORT-II, Wk 48 ²		p-value
	Ruxolitinib (n = 155)	Placebo (n = 154)		Ruxolitinib (n = 144)	BAT (n = 72)	
Spleen volume reduction ≥35%	41.9%	0.7%	< 0.001	28%	0	< 0.001
≥50% reduction in MF-SAF TSS	45.9%	5.3%	< 0.001	NR	NR	NR
Safety outcomes						
Discontinued due to AEs	11.0%	10.6%	NR	8%	5%	NR
Grade 3/4 anemia	45%	19%		NR	NR	
Grade 3/4 thrombocytopenia	13%	1%		NR	NR	
Grade 3/4 neutropenia	7%	2%		NR	NR	

1. Verstovsek. *NEJM* 2012;366:799. 2. Harrison. *NEJM* 2012;366:787.

RESEARCH

Open Access

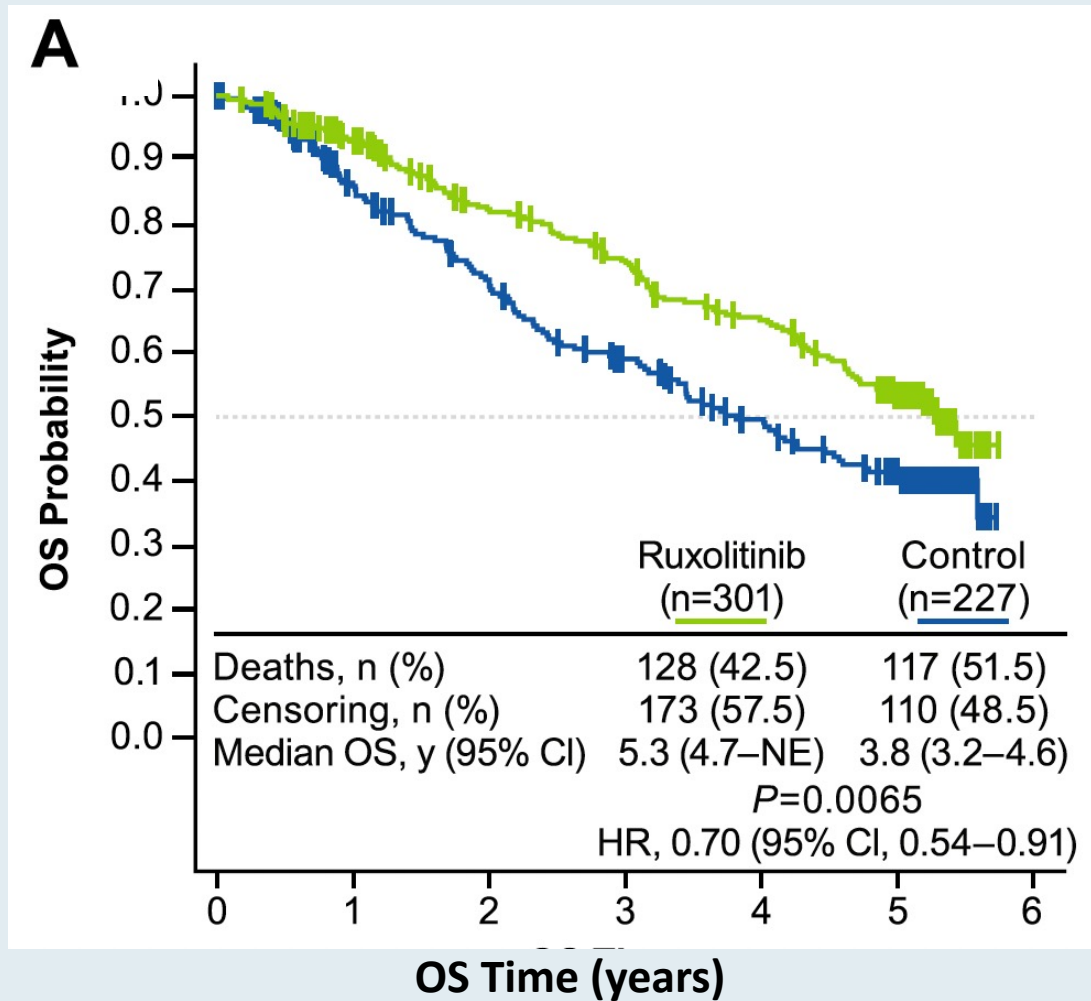


Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses

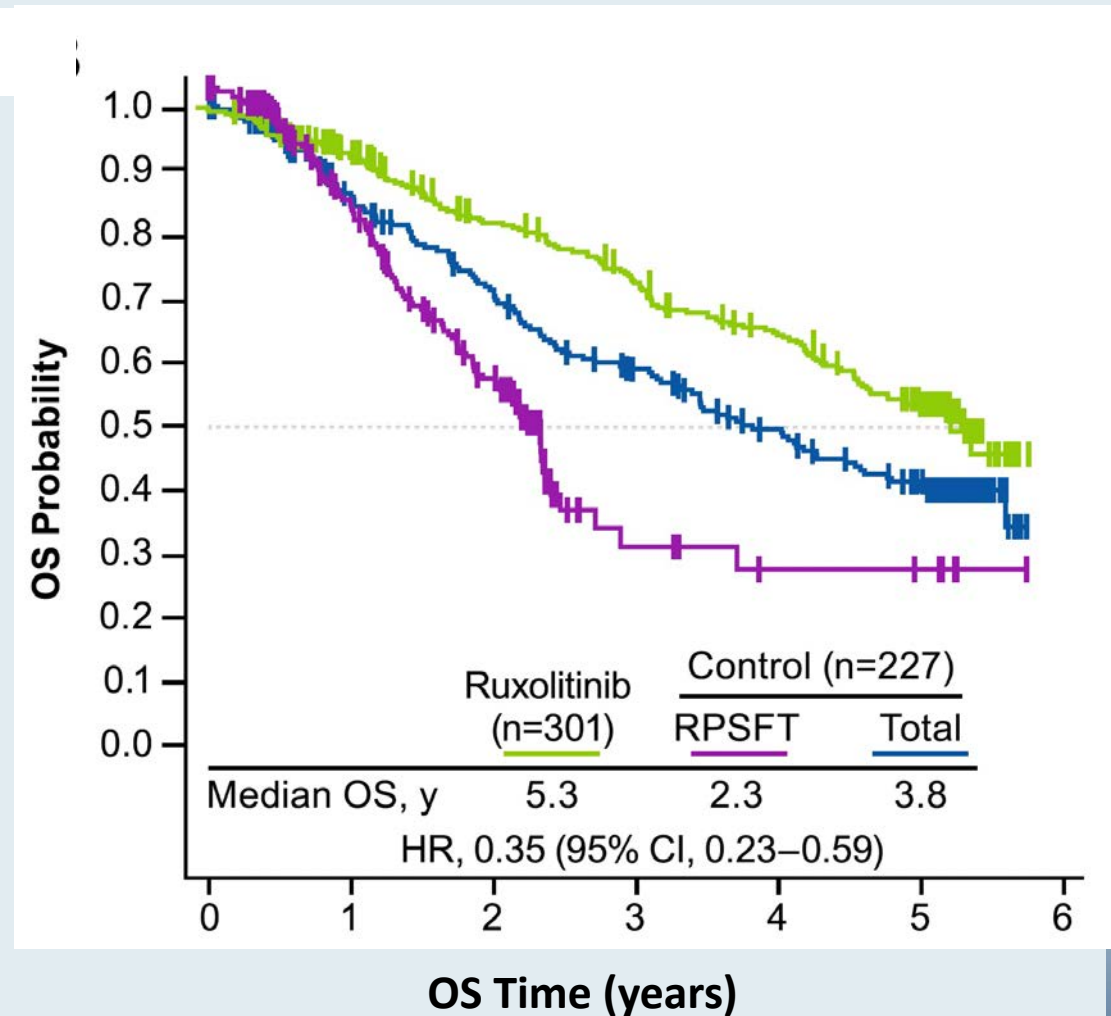
Srdan Verstovsek^{1*}, Jason Gotlib², Ruben A. Mesa³, Alessandro M. Vannucchi⁴, Jean-Jacques Kiladjian⁵, Francisco Cervantes⁶, Claire N. Harrison⁷, Ronald Paquette⁸, William Sun⁹, Ahmad Naim⁹, Peter Langmuir⁹, Tuochuan Dong¹⁰, Prashanth Gopalakrishna¹¹ and Vikas Gupta¹²

COMFORT-I and COMFORT-II Pooled Analyses: Long-Term Survival with Ruxolitinib

OS (5-Year ITT Population)



OS (Corrected for Crossover)



OPEN

Leukemia (2016) **30**, 1701–1707

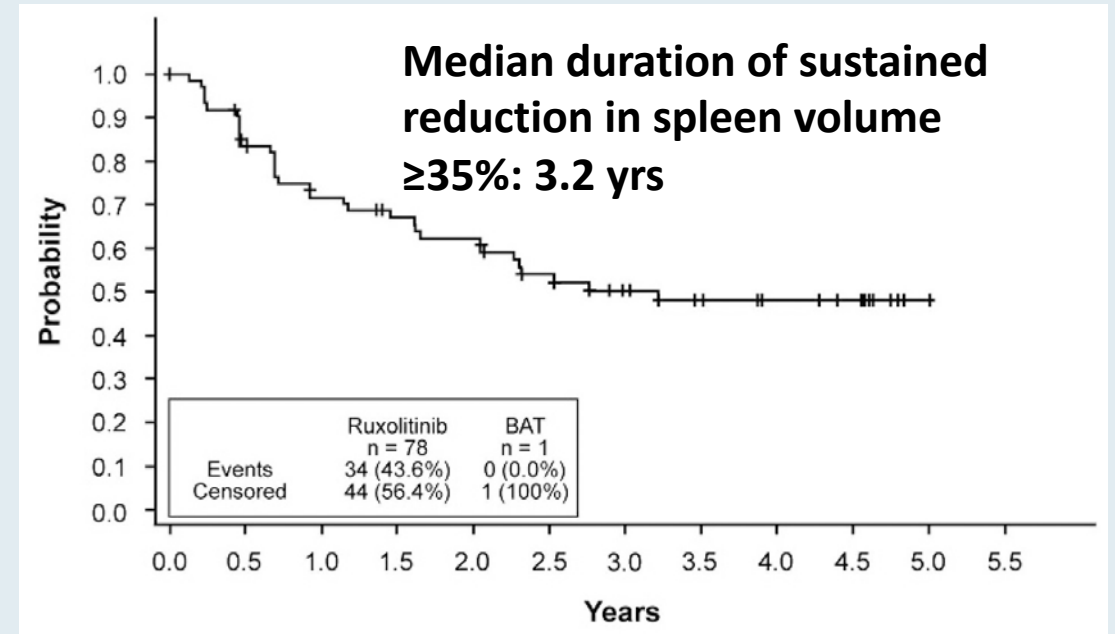
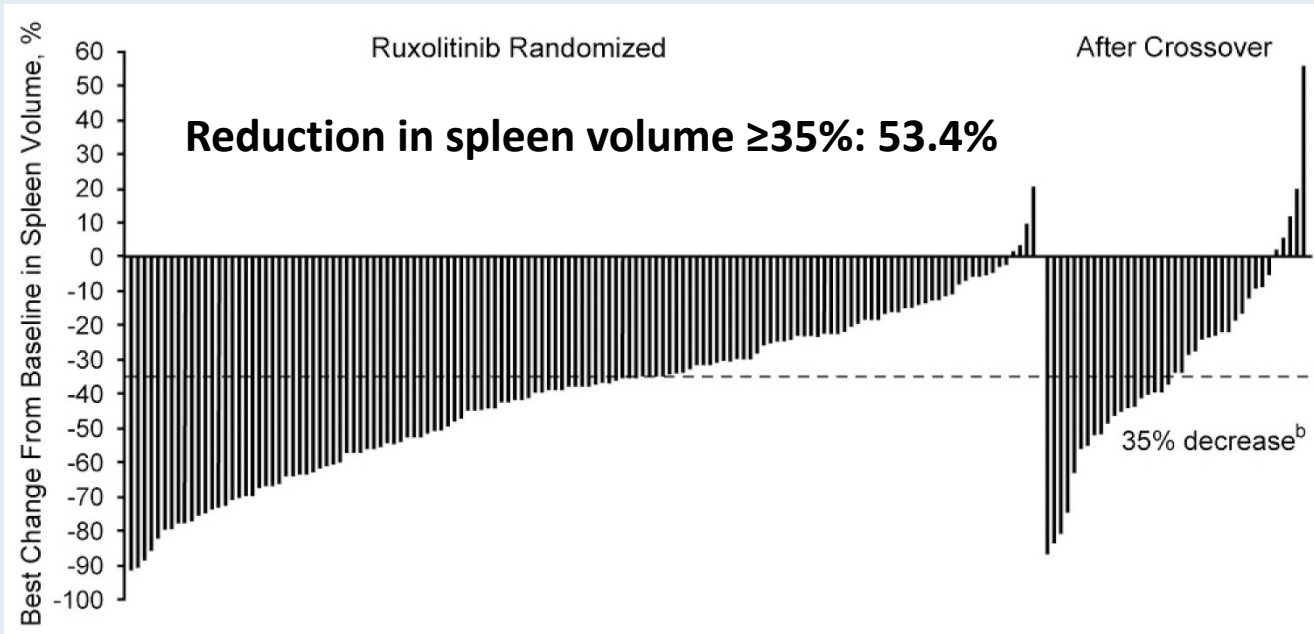
www.nature.com/leu

ORIGINAL ARTICLE

Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis

CN Harrison¹, AM Vannucchi², J-J Kiladjian³, HK Al-Ali⁴, H Gisslinger⁵, L Knoops⁶, F Cervantes⁷, MM Jones⁸, K Sun⁸, M McQuitty⁹, V Stalbovskaya⁹, P Gopalakrishna⁹ and T Barbui¹⁰ on behalf of the COMFORT-II Investigators¹¹

COMFORT-II Final 5-Year Analysis: Rates and Duration of Splenic Reduction



COMFORT-II Final 5-Year Analysis: Exposure-Adjusted Rates of Grade 3/4 Adverse Events

	BAT (n = 73)	Ruxolitinib (n = 191)
Any AE	36%	275
Anemia	8%	9%
Thrombocytopenia	6%	6%
Pneumonia	6%	2%
General physical health deterioration	5%	2%
Acute renal failure	0	1%

Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts

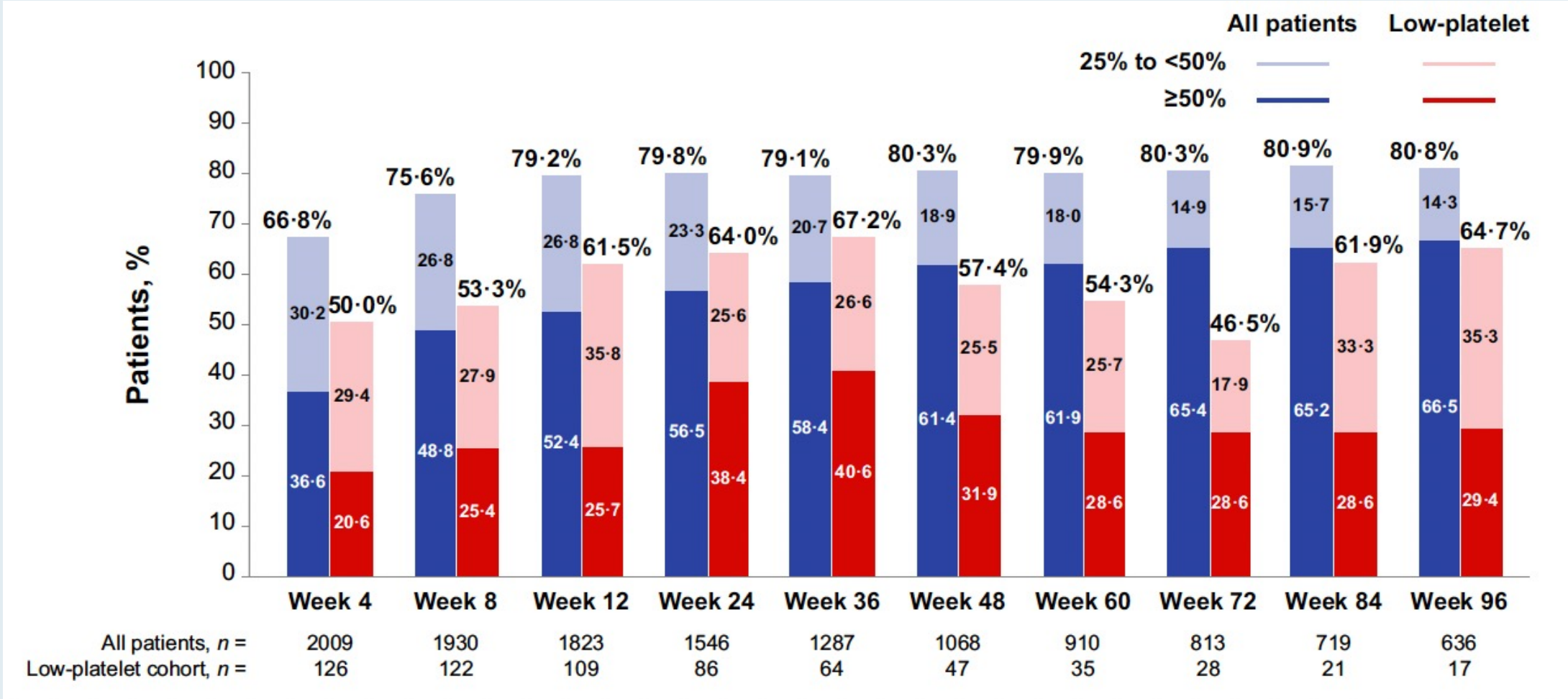
Haifa Kathrin Al-Ali,^{1,†}  Martin Griesshammer,^{2,†}  Lynda Foltz,³ Giuseppe A. Palumbo,⁴ Bruno Martino,⁵ Francesca Palandri,⁶ Anna Marina Liberati,⁷ Philipp le Coutre,⁸ Carmen García-Hernández,⁹ Andrey Zaritskey,¹⁰ Renato Tavares,¹¹ Vikas Gupta,¹² Pia Raanani,¹³ Pilar Giraldo,¹⁴ Mathias Hänel,¹⁵ Daniela Damiani,¹⁶  Tomasz Sacha,¹⁷  Catherine Bouard,¹⁸ Carole Paley,¹⁹ Ranjan Tiwari,²⁰ Francesco Mannelli²¹ and Alessandro M. Vannucchi²¹

Br J Haematol 2020;189(5):888-903

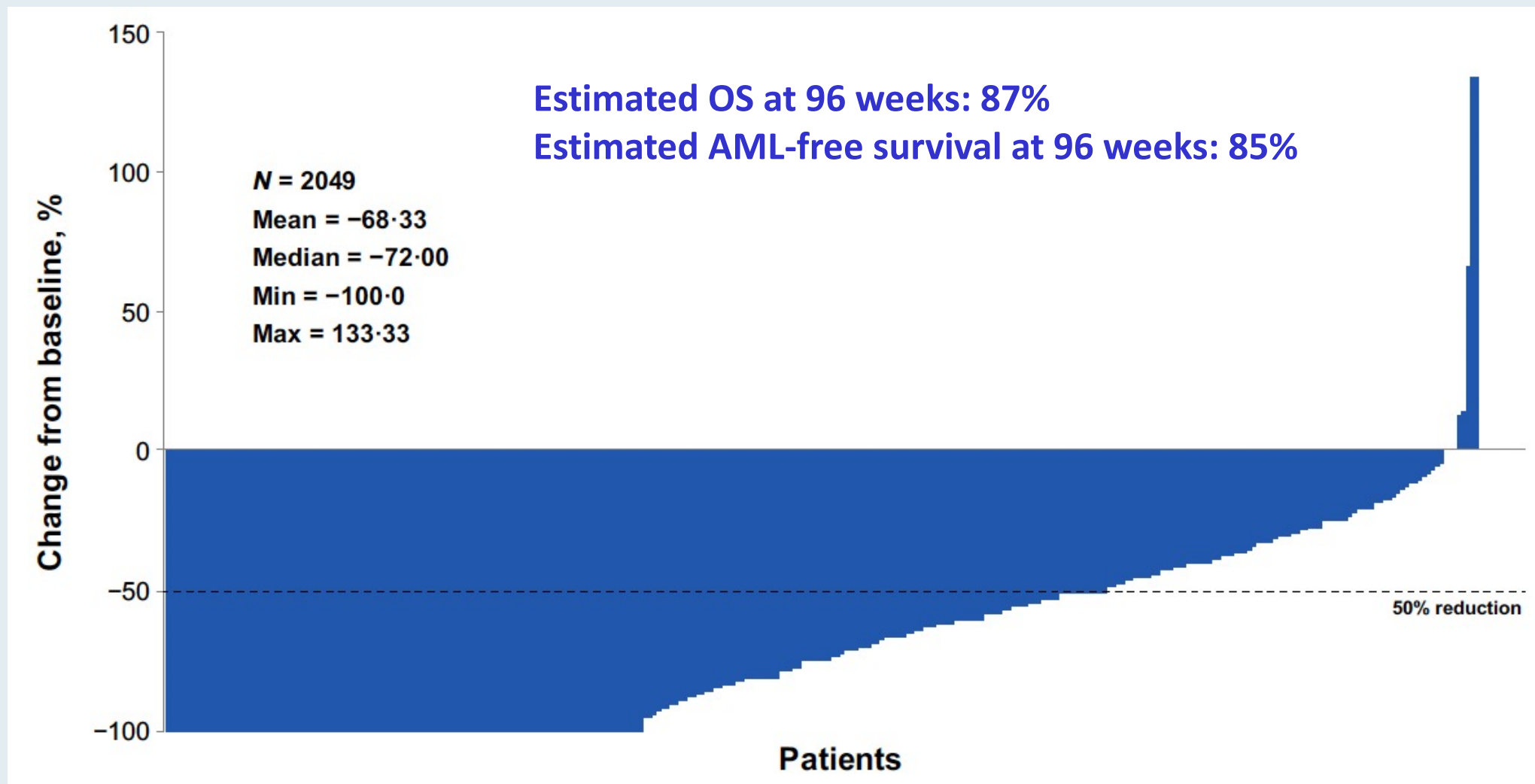
JUMP: Baseline Characteristics

Parameter	All patients (N = 2,233)	Plt count (<100 x 10 ⁹ /l) (n = 138)	Plt count (≥100 x 10 ⁹ /l) (n = 2,087)
Median age	67.0	67.5	67.0
Time since initial diagnosis	25.8 mo	36.1 mo	25.1 mo
DIPSS risk status			
Low	2.7%	0	2.9%
Intermediate-1	37.4%	23.9%	38.4%
Intermediate-2	33.8%	43.5%	33.3%
High	8.7%	8.7%	8.7%
Platelet count, x 10 ⁹ /l			
<50	<0.1%	0.7%	0
≥50 to <75	1.3%	20.3%	0
≥100 to <200	4.9%	79.0%	0
≥200	62.6%	0	67.0%

JUMP: Patients with a $\geq 25\%$ and a $\geq 50\%$ Decrease from Baseline in Spleen Length



JUMP: Best Percent Change from Baseline in Palpable Spleen Length at Any Time in the Overall Patient Population

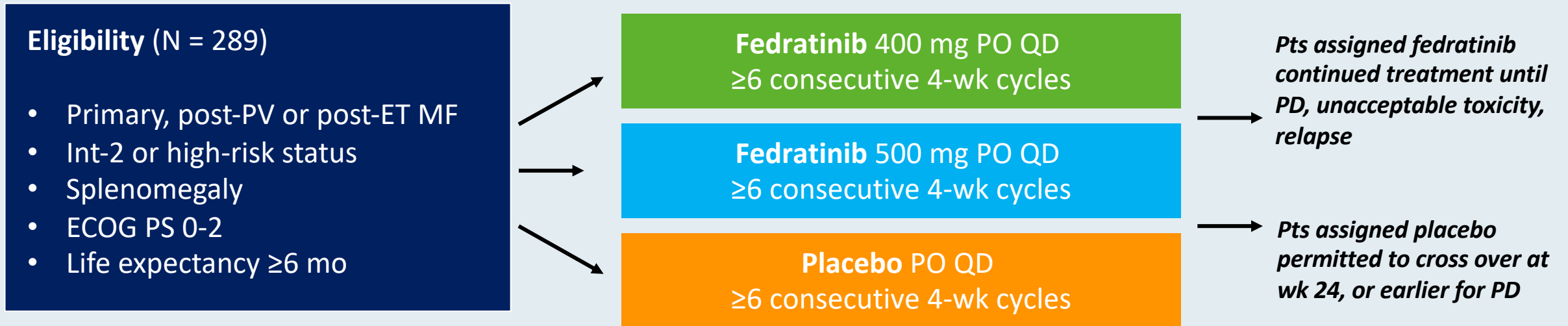


Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis

Animesh Pardanani,¹ 
Ayalew Tefferi,¹  Tamás Masszi,²
Elena Mishchenko,³ Mark Drummond,⁴
Eric Jourdan,⁵ Alessandro Vannucchi,⁶
Mindaugas Jurgutis,⁷ Vincent Ribrag,⁸
Alessandro Rambaldi,^{9,10}
Liang Piu Koh,¹¹ Shelonitda Rose,¹²
Jun Zhang¹² and Claire Harrison¹³

Br J Haematol 2021;195:244-8.

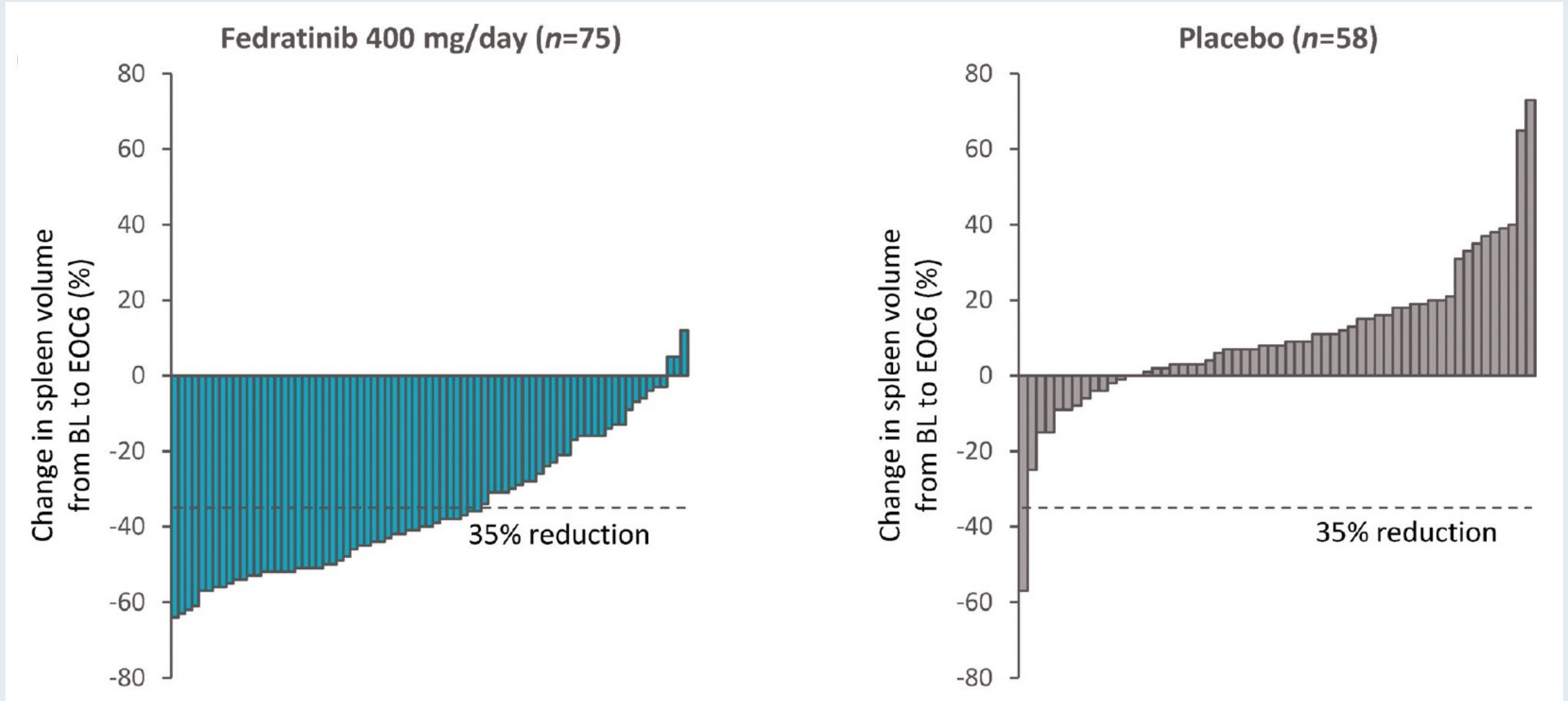
JAKARTA Phase III Study Design



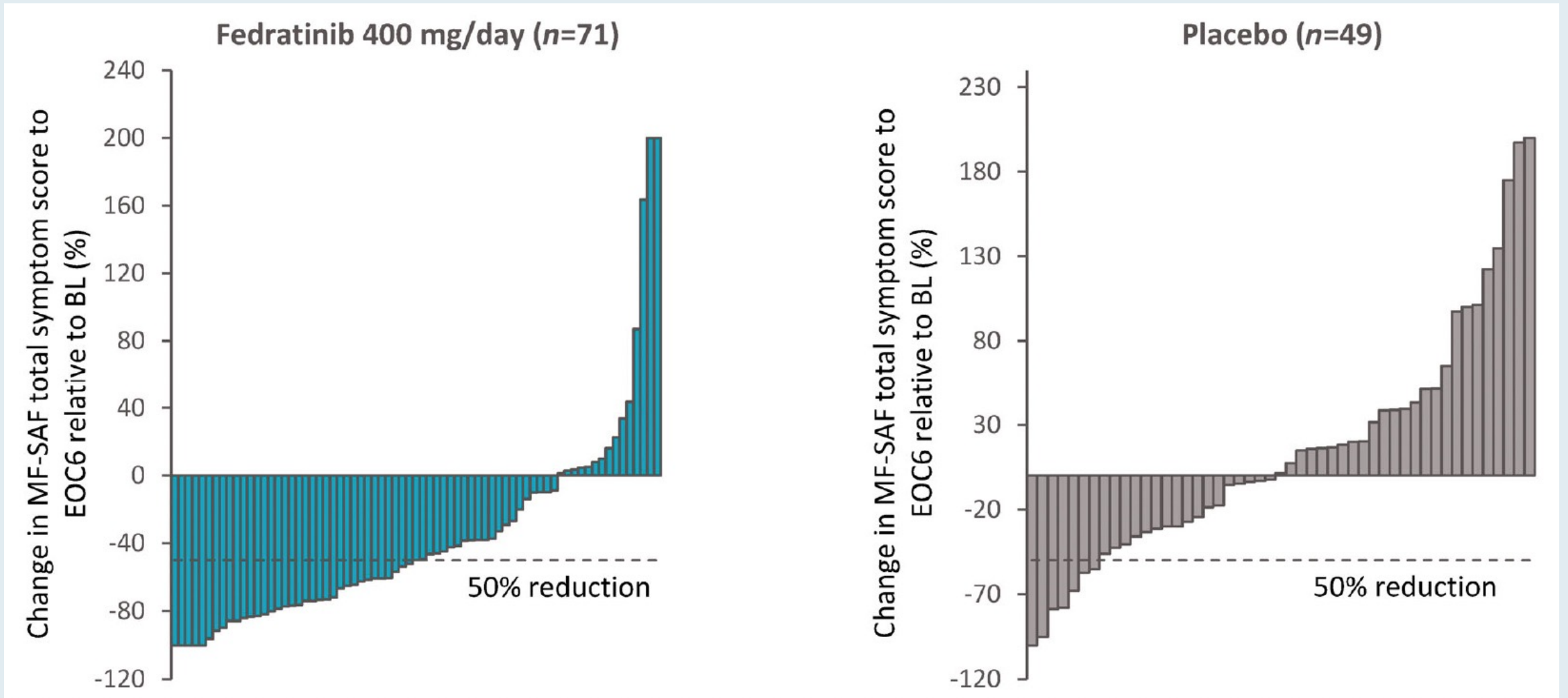
Primary endpoint: Spleen response ($\geq 35\%$ reduction in spleen volume vs BL) at Wk 24, and confirmed 4 wks later

Secondary endpoints: Symptom response ($\geq 50\%$ reduction in TSS), safety

JAKARTA: Change in Spleen Volume from Baseline to End of Cycle 6



JAKARTA: Change in Total Symptom Scores from Baseline to End of Cycle 6



JAKARTA: Selected Adverse Events

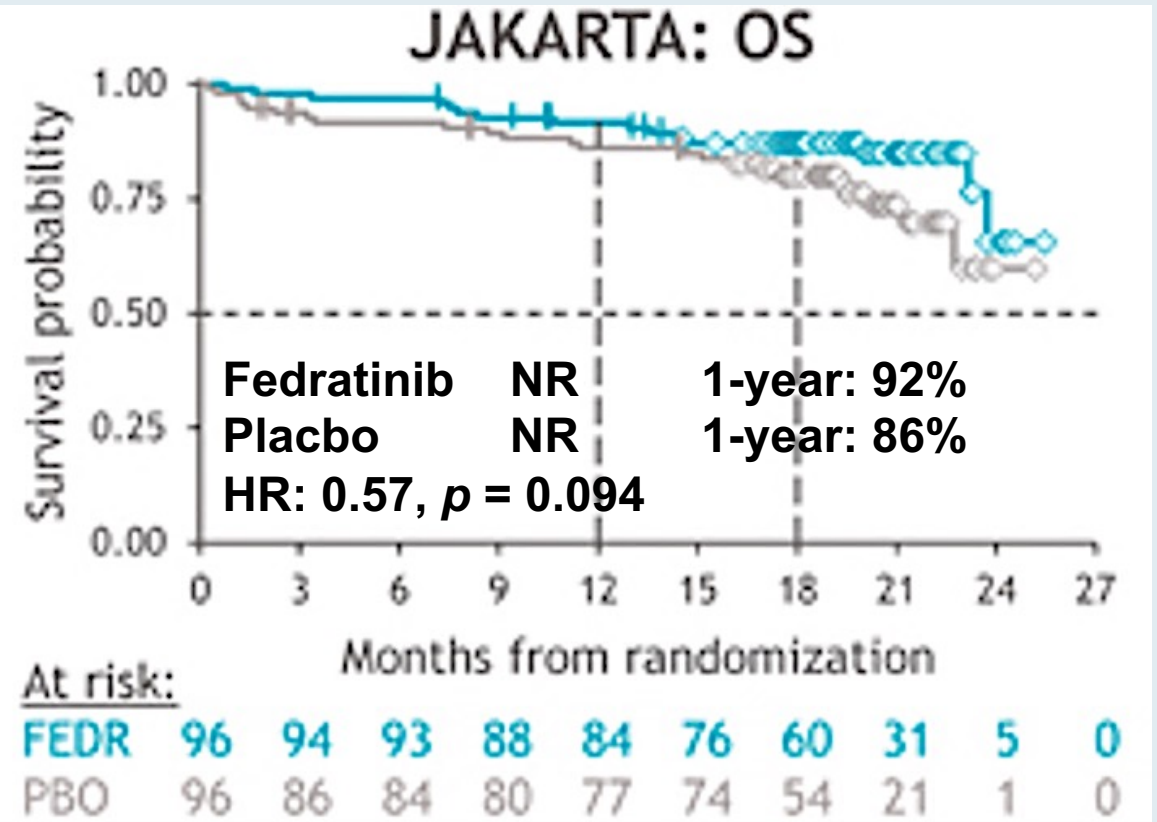
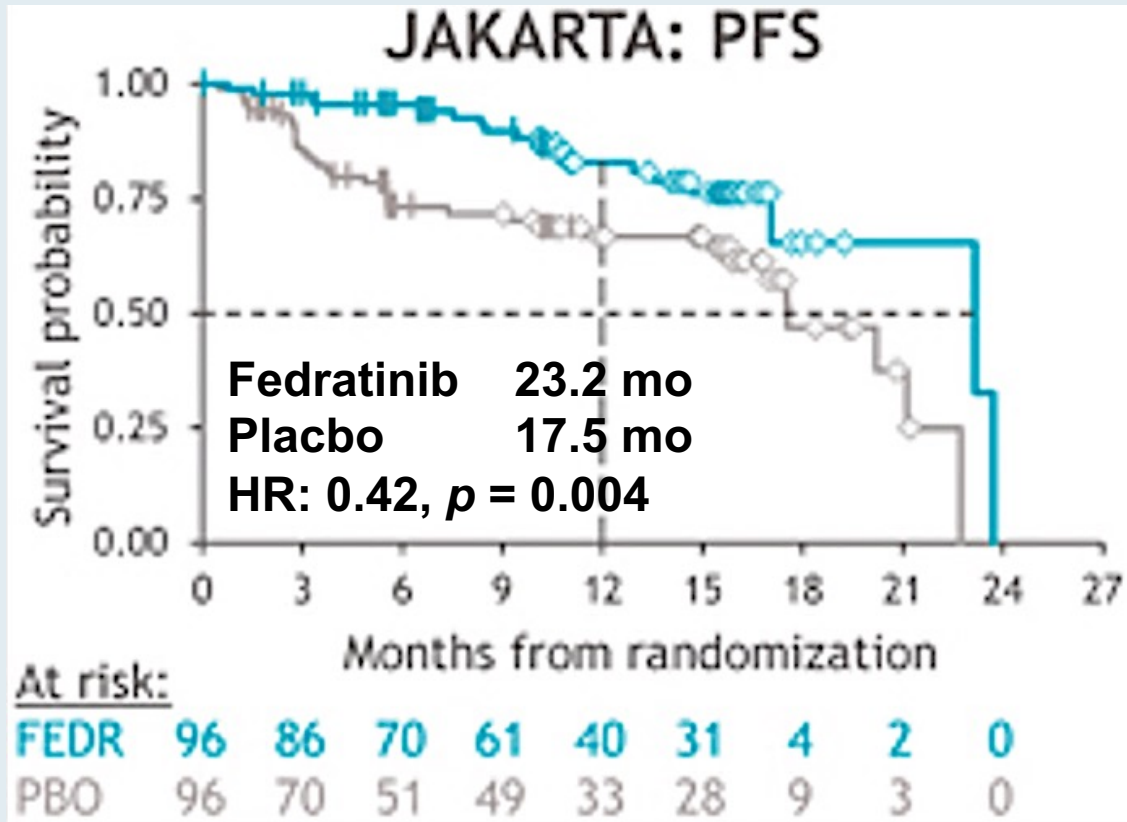
Adverse events	Fedratinib 400 mg (n = 96)		Placebo (n = 95)	
	All grades	Grade ≥3	All grades	Grade ≥3
Diarrhea	66%	5%	16%	0
Nausea	62%	0	15%	0
Anemia	40%	30%	14%	7%
Vomiting	39%	3.1%	5%	0
Fatigue	19%	5%	16%	1.1%
Laboratory parameters				
Anemia	74%	34%	32%	10%
Thrombocytopenia	47%	12%	26%	10%
Neutropenia	23%	5%	13%	3.3%
Biochemistry				
Lipase increased	35%	10%	7%	2.2%

Overall and Progression-Free Survival in Patients Treated with Fedratinib as First-Line Myelofibrosis (MF) Therapy and After Prior Ruxolitinib (RUX): Results from the JAKARTA and JAKARTA2 Trials

Harrison C et al.

EHA 2021;Abstract S203.

JAKARTA: Survival Analysis



New Option for the Management of MF in Patients with Thrombocytopenia: Pacritinib

Pacritinib Granted Accelerated Approval for MF with Severe Thrombocytopenia

Press Release: February 28, 2022

“Pacritinib received accelerated approval from the FDA at a twice daily, 200-mg dose for patients with intermediate- or high-risk primary or secondary myelofibrosis who are experiencing severe thrombocytopenia with a platelet count below $50 \times 10^9/L$. The agency’s decision comes from results of the phase 3 PERSIST-2 study (NCT02055781).

Treatment with pacritinib at 200 mg resulted in a reduction in spleen volume of at least 35% for 29% of patients, vs 3% of patients who received the best available therapy, including ruxolitinib (Jakafi). As part of the post-approval plans for pacritinib, the phase 3 PACIFICA trial (NCT03165734) will be completed with results estimated in 2025.

The PERSIST-2 study, which assessed the use of pacritinib compared with best available therapy in patients with myelofibrosis and thrombocytopenia, enrolled 311 patients. Those who enrolled were randomized into 1 of 3 treatment regimens, including pacritinib once daily (n = 104), pacritinib twice daily (n = 107), or a best alternative treatment (n = 100). Best alternative treatments included ruxolitinib (45%), hydroxyurea (19%), and prednisone and/or prednisolone (13%).”

https://www.cancernetwork.com/view/pacritinib-granted-accelerated-approval-for-use-in-myelofibrosis-with-severe-thrombocytopenia?utm_source=sfmc&utm_medium=email&utm_campaign=3.01.22_CN_Breaking_B&eKey=cmthZGVybWFuQHJlc2VhcmNodG9wcmFjdGljZS5jb20=

Phase III PERSIST-1 and PERSIST-2 Study Designs

PERSIST-1

Key Eligibility

- Primary or secondary MF
- Any platelet count
- No prior treatment with JAK2 inhibitors

Randomization

- 2:1 pacritinib vs. BAT
- N=327

Pacritinib
400mg QD

BAT
(excluding ruxolitinib)

Primary Endpoint

- $\geq 35\%$ SVR at Week 24

PERSIST-2

Key Eligibility

- Primary or secondary MF
- Platelet count $< 100,000/\mu\text{L}$
- Prior JAK2 inhibitor therapy allowed

Randomization

- 1:1:1 pacritinib vs. pacritinib vs. BAT
- N=311 (211 completed 24 weeks on study)

Pacritinib
400mg QD

Pacritinib
200mg BID

BAT
(including ruxolitinib)

Co-Primary Endpoints*

- $\geq 35\%$ SVR at Week 24
- $\geq 50\%$ TSS reduction at Week 24

BAT, best available therapy; **SVR**, spleen volume response; **TSS**, total symptom score

* Primary analysis compared pooled pacritinib (400mg QD and 200mg BID) vs. BAT

Research

JAMA Oncol 2018;4(5):652-9.

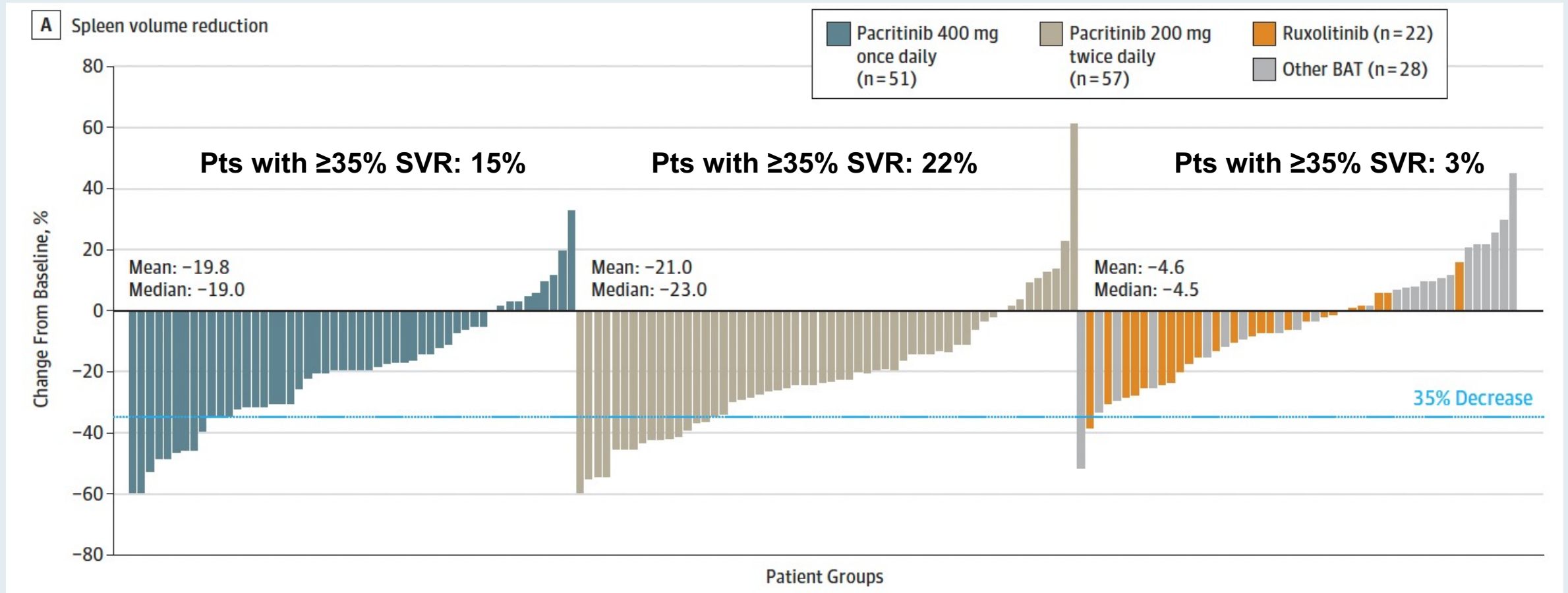
JAMA Oncology | **Original Investigation**

Pacritinib vs Best Available Therapy, Including Ruxolitinib, in Patients With Myelofibrosis

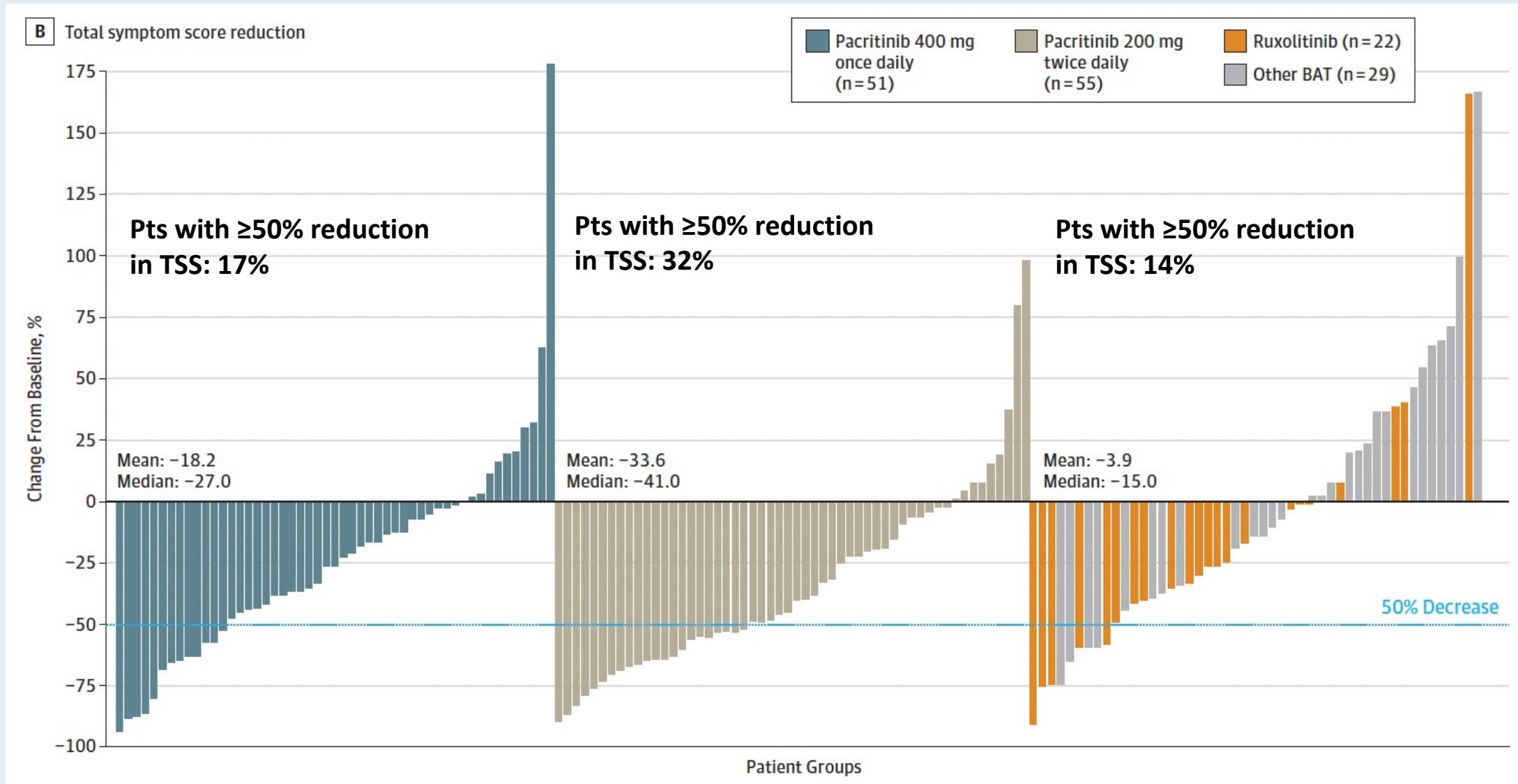
A Randomized Clinical Trial

John Mascarenhas, MD; Ronald Hoffman, MD; Moshe Talpaz, MD; Aaron T. Gerds, MD; Brady Stein, MD; Vikas Gupta, MD, FRCP, FRCPath;
Anita Szoke, MD; Mark Drummond, MBChB, PhD, FRCPath; Alexander Pristupa, MD; Tanya Granston, PhD; Robert Daly, PhD;
Suliman Al-Fayoumi, PhD; Jennifer A. Callahan, MS; Jack W. Singer, MD; Jason Gotlib, MD; Catriona Jamieson, MD, PhD;
Claire Harrison, MD, DM, FRCP, FRCPath; Ruben Mesa, MD, FACP; Srdan Verstovsek, MD, PhD

PERSIST-2: Spleen Volume Reduction



PERSIST-2: Reduction in Total Symptom Score

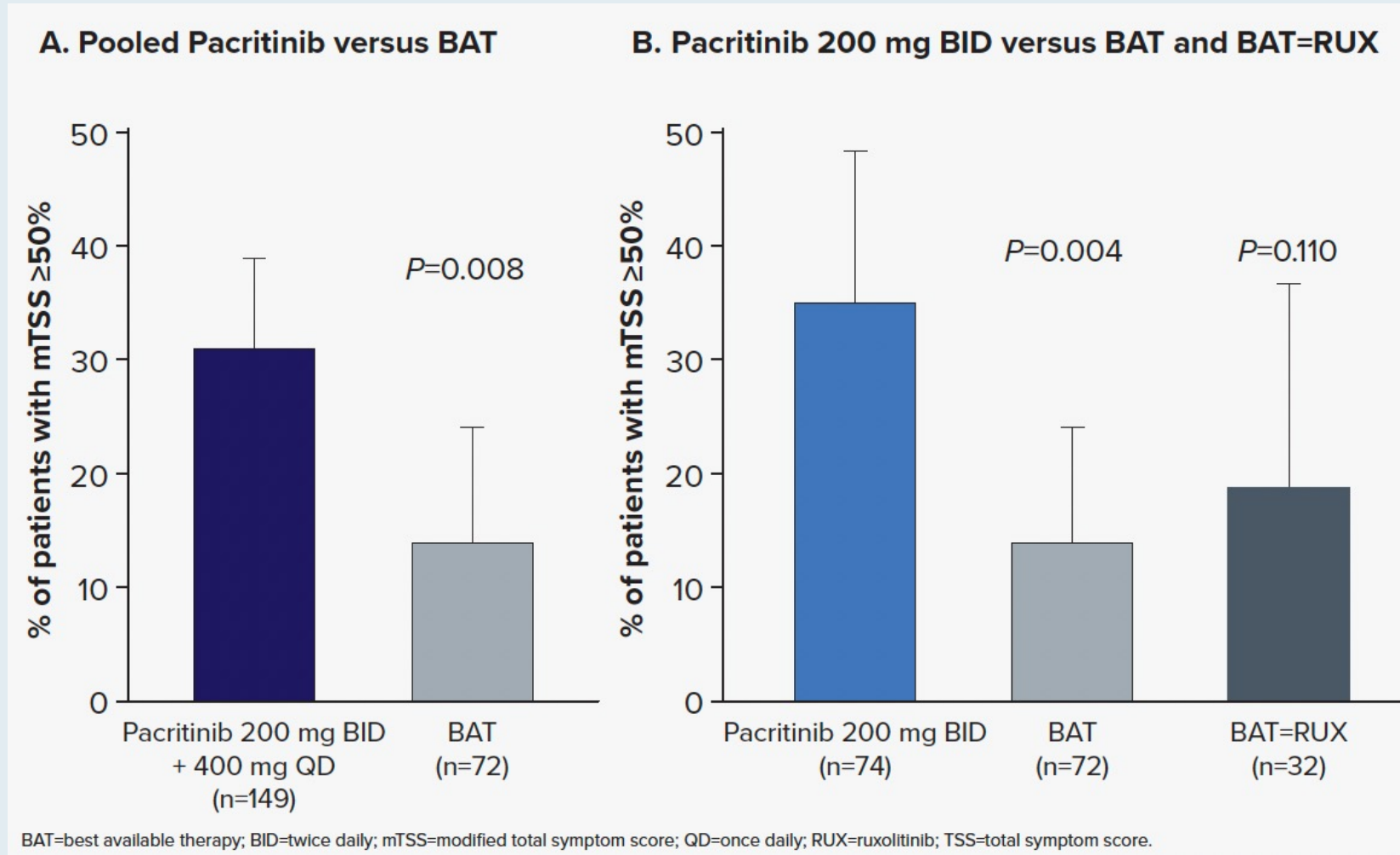


The Impact of Pacritinib on Myelofibrosis Symptoms

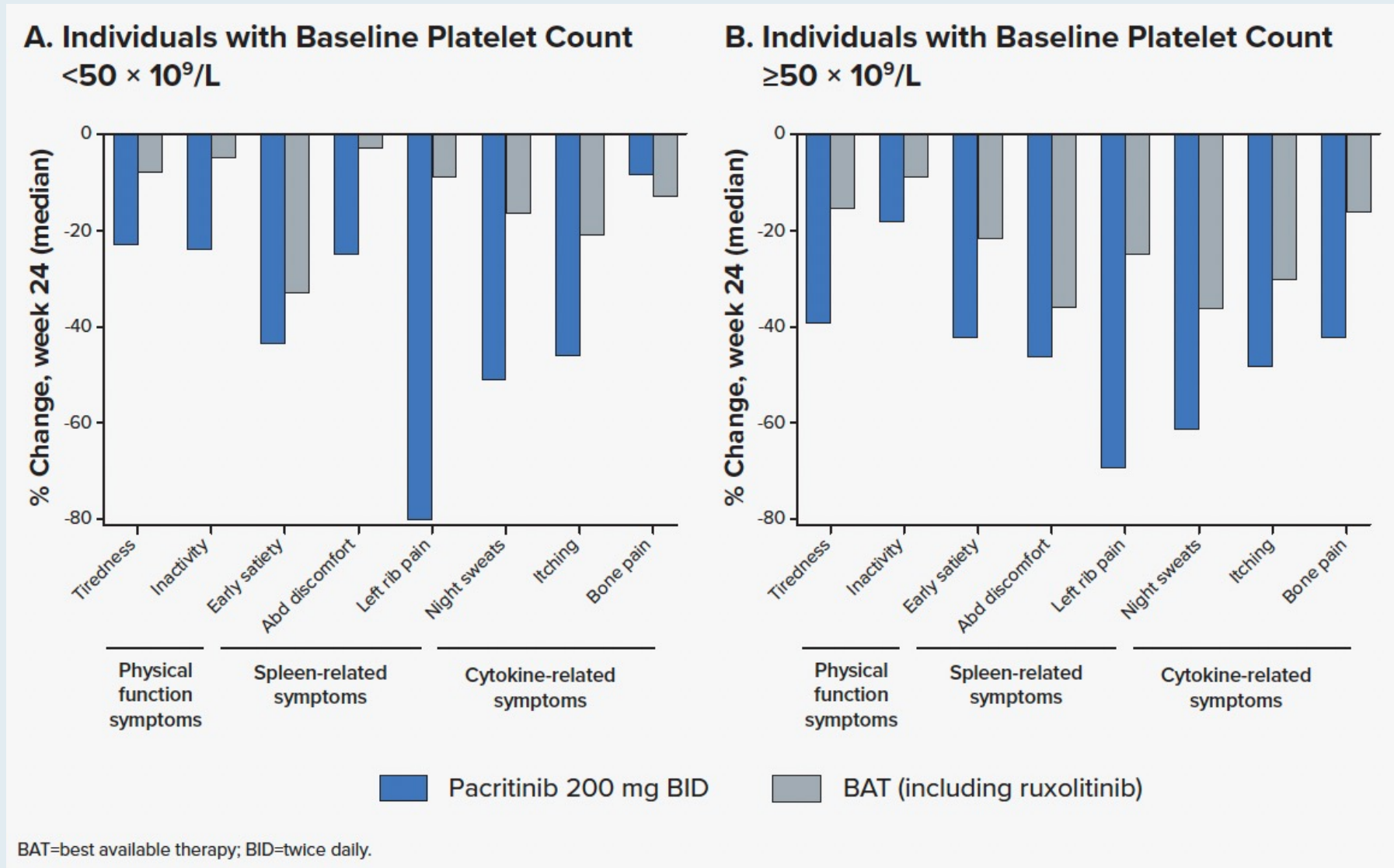
Palmer J et al.

ASH 2021;Abstract 3628.

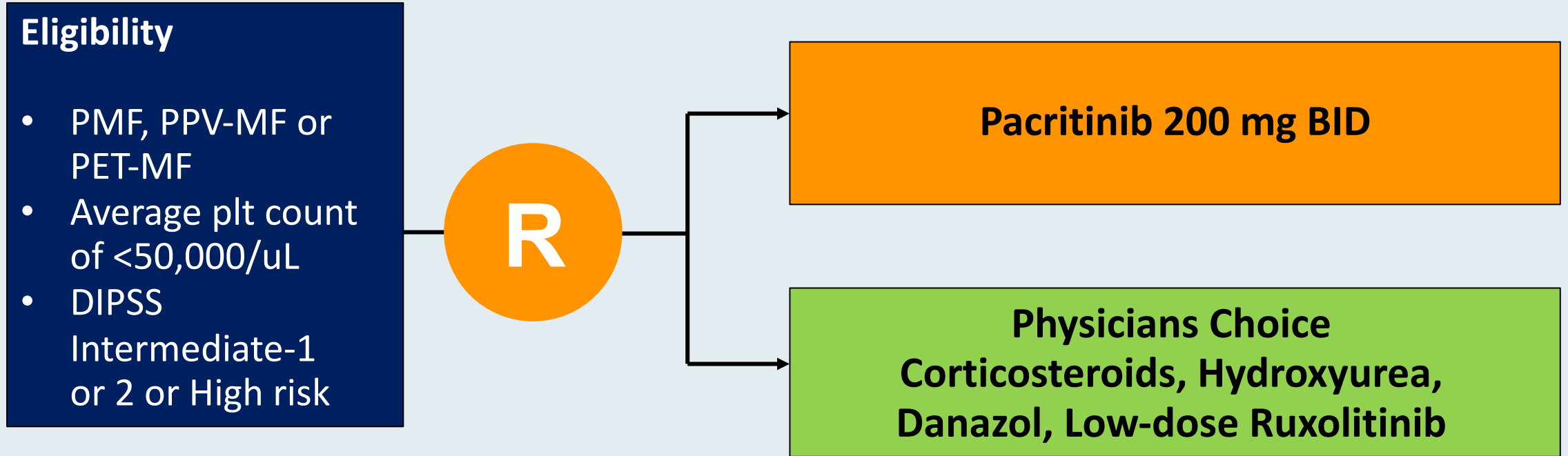
Modified TSS Response Rates (Week 24) in PERSIST-2



Percent Change in Individual Symptom Scores in PERSIST-2



PACIFICA (PAC303) Study Design



Primary Endpoint: Spleen volume

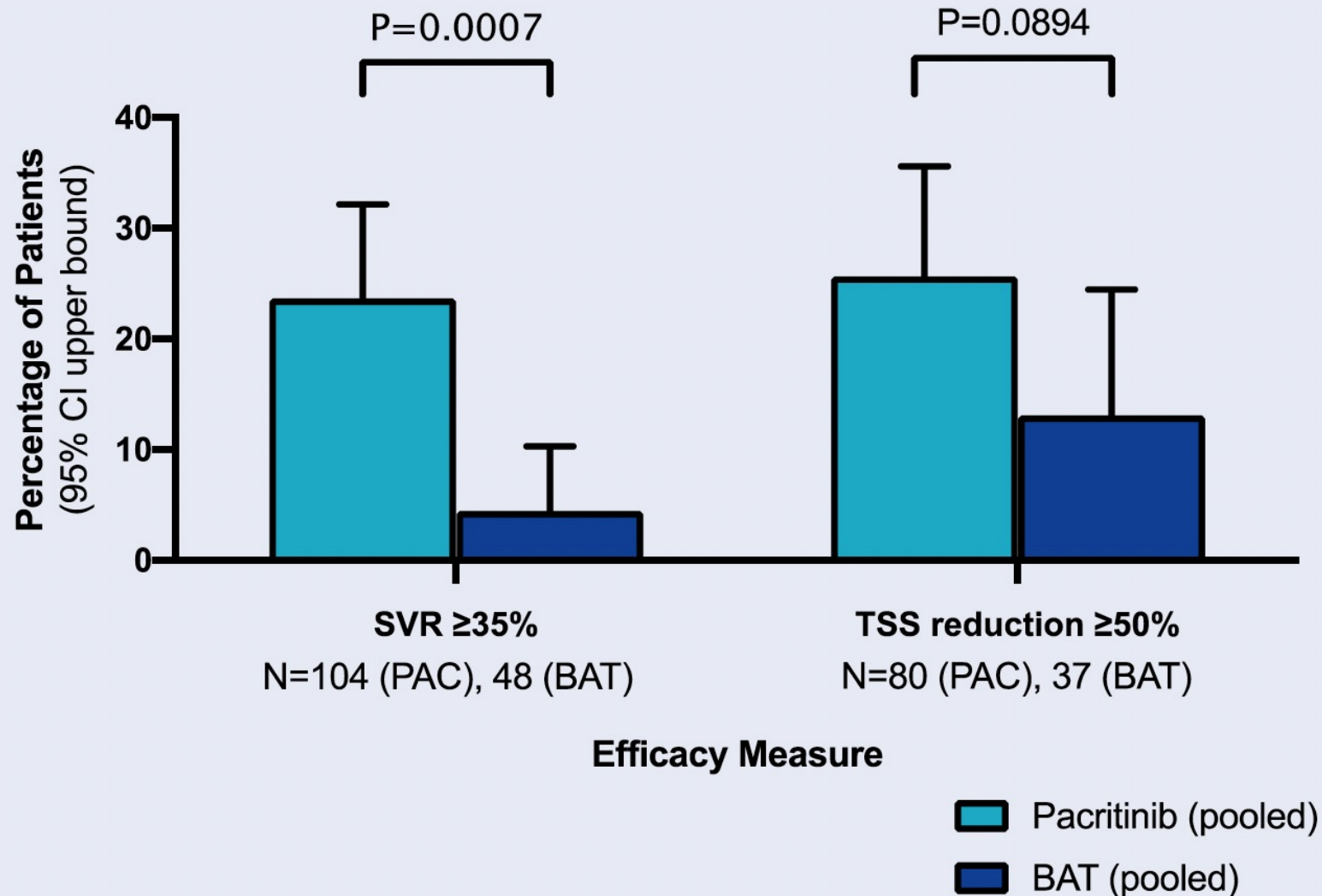
Secondary Endpoints: Total Symptom Score, OS, Patient Global Impression of Change

Pacritinib Demonstrates Efficacy Versus Best Available Therapy in Myelofibrosis Patients with Severe Thrombocytopenia in Two Phase 3 Studies

Mesa RA et al.

ASH 2019;Abstract 4195.

PERSIST-1 and PERSIST-2: Pacritinib versus BAT Efficacy Outcomes (Week 24) in Patients with Baseline Platelet Counts <math><50,000/\mu\text{L}</math>

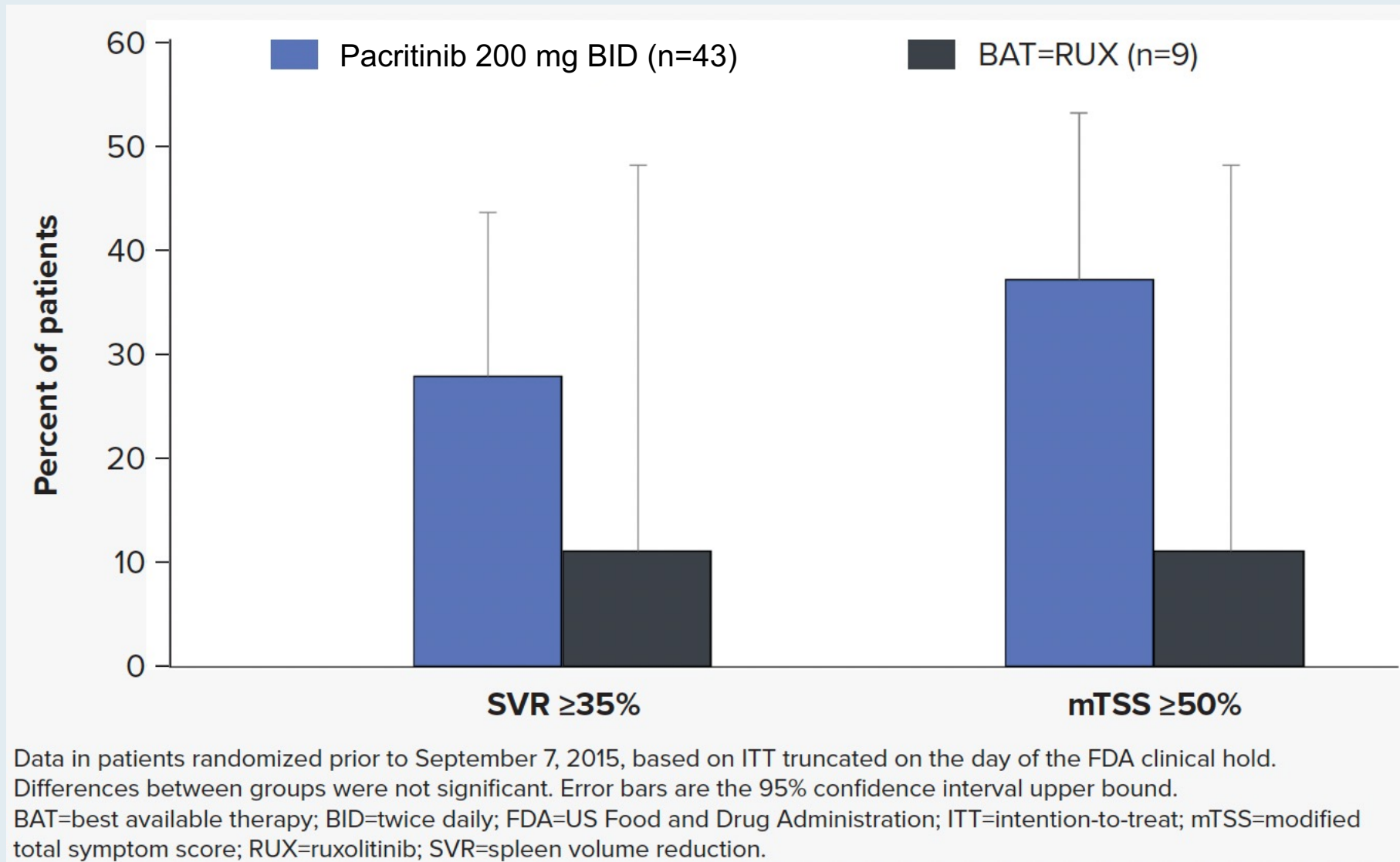


A Retrospective Head-to-Head Comparison Between Pacritinib and Ruxolitinib in Patients with Myelofibrosis and Moderate-to-Severe Thrombocytopenia

Mascarenhas J et al.

ASH 2021;Abstract 3639.

Proportion of Patients Meeting SVR and Modified TSS Thresholds in a Retrospective Analysis of PERSIST-2



Safety Analysis of Pacritinib in Patients with Myelofibrosis and Severe Thrombocytopenia

Mascarenhas J et al.

ASH 2021;Abstract 3640.

Overview of Adverse Events in the Target Population in PERSIST-2 and PAC203

AE, n (%)	PERSIST-2		PAC203	Total (pooled)
	Pacritinib 200 mg BID (n=47)	BAT ^a (n=42)	pacritinib 200 mg BID (n=24)	pacritinib 200 mg BID (N=71)
TEAE (all grades)	46 (98)	38 (91)	24 (100)	70 (99)
Grade ≥3 TEAE	39 (83)	26 (62)	23 (96)	62 (87)
Treatment-emergent serious AE	28 (60)	16 (38)	16 (67)	44 (62)
Grade ≥3 treatment-emergent serious AE	25 (53)	15 (36)	14 (58)	39 (55)
TEAE leading to study drug discontinuation	10 (21)	7 (17)	4 (17)	14 (20)
TEAE with an outcome of death	6 (13)	8 (19)	3 (13)	9 (13)

^aThe most common BAT was ruxolitinib (40%) and watch and wait (31%).

AE=adverse event; BAT=best available therapy; BID=twice daily; TEAE=treatment-emergent adverse event.

Summary of Hemorrhage AEs, Cardiac AEs and MACE in the Target Population in PERSIST-2 and PAC203

AE, n (%)	PERSIST-2		PAC203 pacritinib 200 mg BID (n=24)	Total (pooled) pacritinib 200 mg BID (N=71)
	Pacritinib 200 mg BID (n=47)	BAT ^a (n=42)		
Treatment-emergent hemorrhage AEs (SMQ)^b				
Any-grade bleeding AEs	23 (49)	26 (62)	18 (75)	41 (58)
Serious bleeding AEs	6 (13)	4 (10)	2 (8)	8 (11)
Grade ≥3 bleeding AEs	8 (17)	5 (12)	3 (13)	11 (16)
Treatment-emergent cardiac AEs (SMQ)^b				
Any-grade cardiac AEs	16 (34)	19 (45)	13 (54)	29 (41)
Serious cardiac AEs	4 (9)	9 (21)	3 (13)	7 (10)
Grade ≥3 cardiac AEs	4 (9)	8 (19)	2 (8)	6 (9)
MACE category^c				
MACE	0 (0)	2 (5)	0 (0)	0 (0)
MACE death (Grade 5)	0 (0)	1 (2)	0 (0)	0 (0)

^aThe most common BAT agents were ruxolitinib and watch and wait. ^bBleeding and cardiac events defined by SMQ include the preferred terms in hemorrhage and cardiac arrhythmias, cardiac failure, ischemic heart disease, and embolic and thrombotic events, respectively.

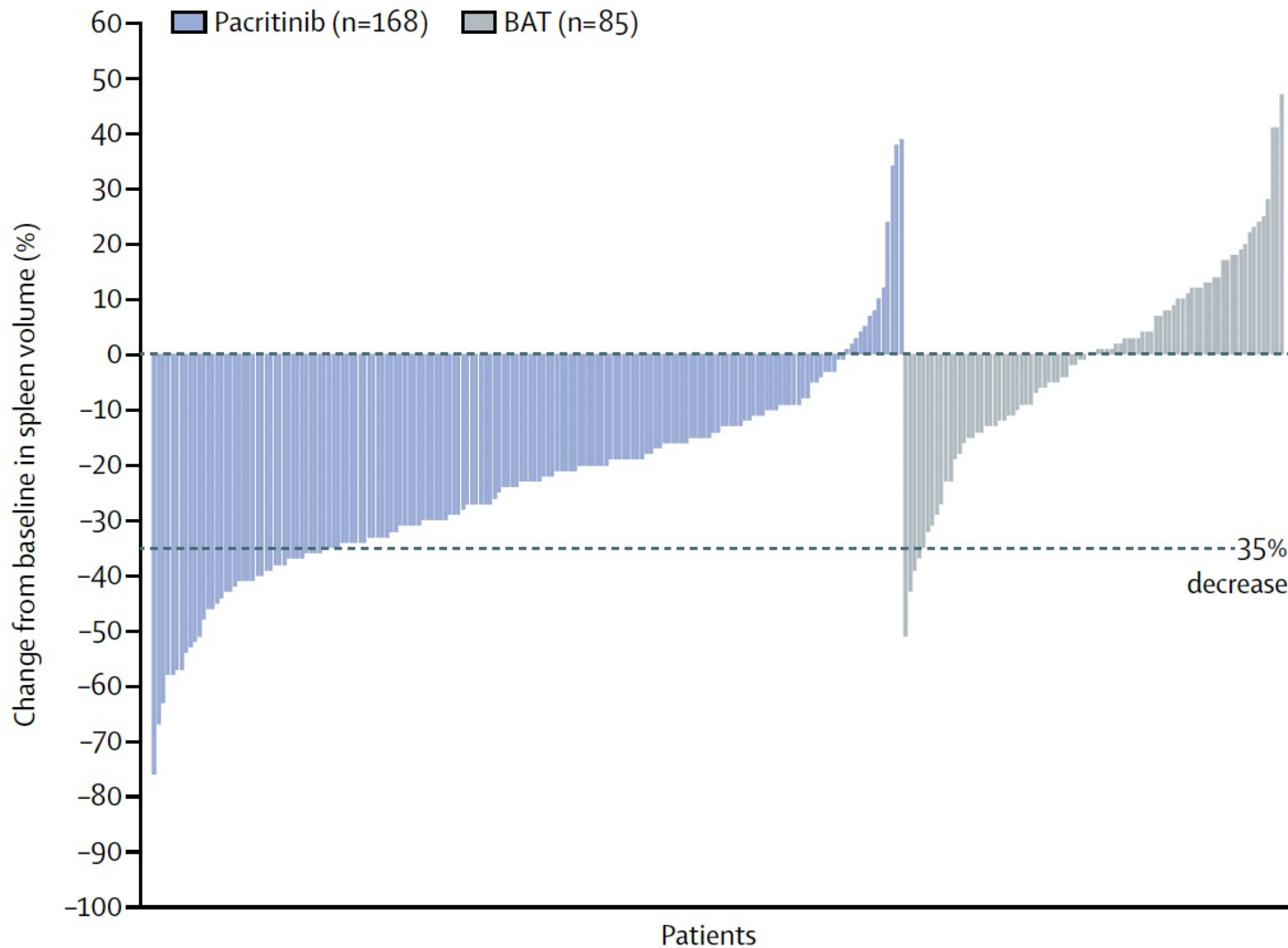
Lancet Haematol 2017;4:e225-36

Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial



Ruben A Mesa, Alessandro M Vannucchi, Adam Mead, Miklos Egyed, Anita Szoke, Aleksandr Suvorov, Janos Jakucs, Andrew Perkins, Ritam Prasad, Jiri Mayer, Judit Demeter, Peter Ganly, Jack W Singer, Huafeng Zhou, James P Dean, Peter A te Boekhorst, Jyoti Nangalia, Jean-Jacques Kiladjian, Claire N Harrison

PERSIST-1: Reduction in Spleen Volume at Week 24



≥35% reduction in spleen volume at week 24 in evaluable patients

	Pacritinib (N = 168)	BAT (n = 85)	p-value
Overall	25%	6%	0.0001
Plts <100,000/uL	24%	0	0.0072
Plts <50,000/uL	33%	0	0.037

PERSIST-1: Patients Achieving $\geq 50\%$ Reduction in Total Symptom Score 2.0 at weeks 24 and 48

	Week 24			Week 48		
	Pacritinib	BAT	p value	Pacritinib	BAT	p value
Overall	19/100 (19%)	5/48 (10%)	0.24	15/100 (15%)	0/48	0.0027
Platelets						
<100 000/ μL	7/28 (25%)	1/13 (8%)	0.40	3/28 (11%)	0/13	0.54
<50 000/ μL	3/11 (27%)	0/5	0.51	2/11 (18%)	0/5	1.0

Data are n/N (%).

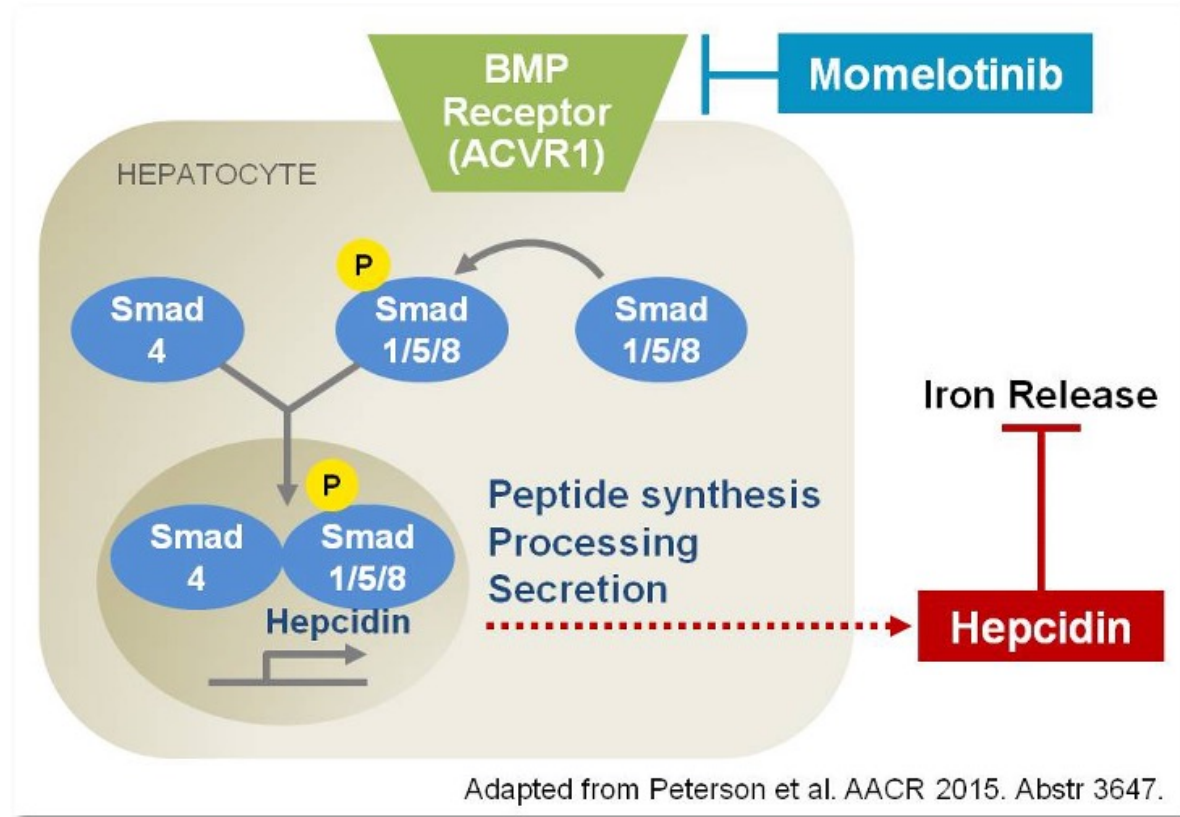
PERSIST-1: Select Adverse Events

	Pacritinib (N = 220)		BAT (N = 106)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	55%	5%	10%	0
Nausea	27%	1%	7%	0
Anemia	24%	17%	20%	15%
Thrombocytopenia	17%	11%	14%	11%
Vomiting	16%	1%	6%	0
Fatigue	10%	2%	9%	1%

**Potential Front-Line Option for Patients
with MF and Significant Anemia and/or
Transfusion Dependence: Momelotinib**

Momelotinib Mechanism of Action

- ◆ MMB also inhibits activin A receptor, Type 1 (ACVR1)
- ◆ ACVR1 activation leads to increased hepcidin gene expression¹
- ◆ Hepcidin decreases plasma iron and hepcidin is elevated in MF²
- ◆ MMB ameliorates anemia in a rodent ACD model¹



1. Asshoff M, et al. Blood 2017;129:1823-30; 2. Pardanani A, et al. Am J Hematology 2013;88:312-6.
ACVR1: Activin A Receptor, Type 1; BMP, bone morphogenic protein.

VOLUME 35 · NUMBER 34 · DECEMBER 1, 2017

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

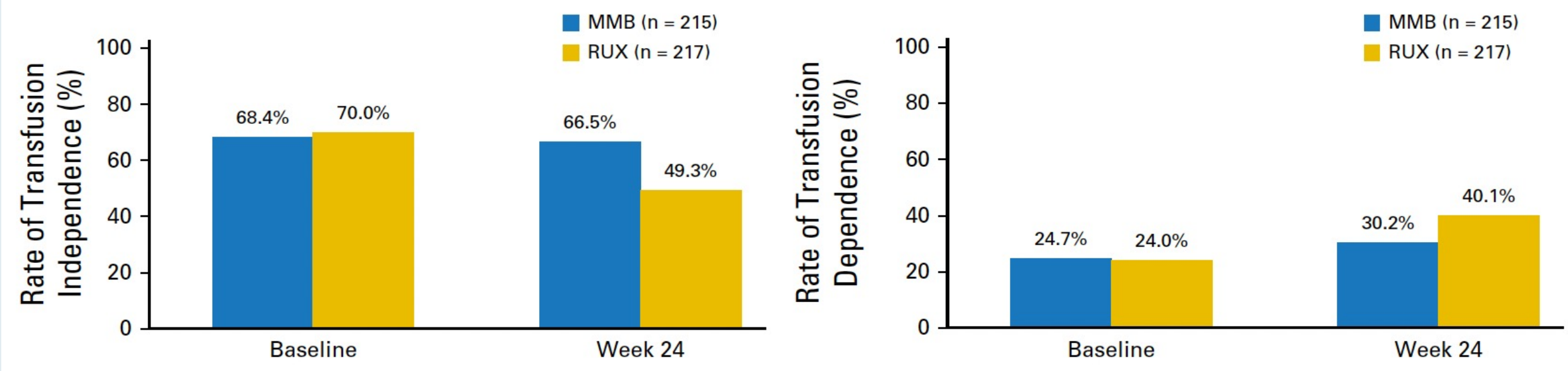
SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis

Ruben A. Mesa, Jean-Jacques Kiladjian, John V. Catalano, Timothy Devos, Miklos Egyed, Andrzej Hellmann, Donal McLornan, Kazuya Shimoda, Elliott F. Winton, Wei Deng, Ronald L. Dubowy, Julia D. Maltzman, Francisco Cervantes, and Jason Gotlib

SIMPLIFY-1 Trial of Momelotinib (MMB) in Patients with Treatment-Naïve MF

Efficacy outcomes	SIMPLIFY-1, Wk 24 ¹		p-value
	MMB (n = 215)	RUX (n = 217)	
Spleen volume reduction \geq 35%	26.5%	29.0%	0.011
\geq 50% reduction in MF-SAF TSS	28.4%	42.2%	0.98
Transfusion independence at week 24	66.5%	49.3%	<0.001
Safety outcomes			
Discontinued due to AEs	13.1%	5.6%	NR
Grade 3/4 anemia	5.6%	23.1%	
Grade 3/4 thrombocytopenia	7.0%	4.6%	
Grade 3/4 neutropenia	2.8%	4.6%	

SIMPLIFY-1: Momelotinib versus Ruxolitinib Effects on Transfusion Requirements at Week 24



Evolving Therapeutic Landscape for Individuals with MF Progressing on or Intolerant to Initial JAK Inhibitor Therapy

- JAKARTA-2: Fedratinib in patients with intermediate- or high-risk MF resistant or intolerant to ruxolitinib
- Ongoing FREEDOM and FREEDOM2 trials of fedratinib after ruxolitinib
- SIMPLIFY-2: Momelotinib

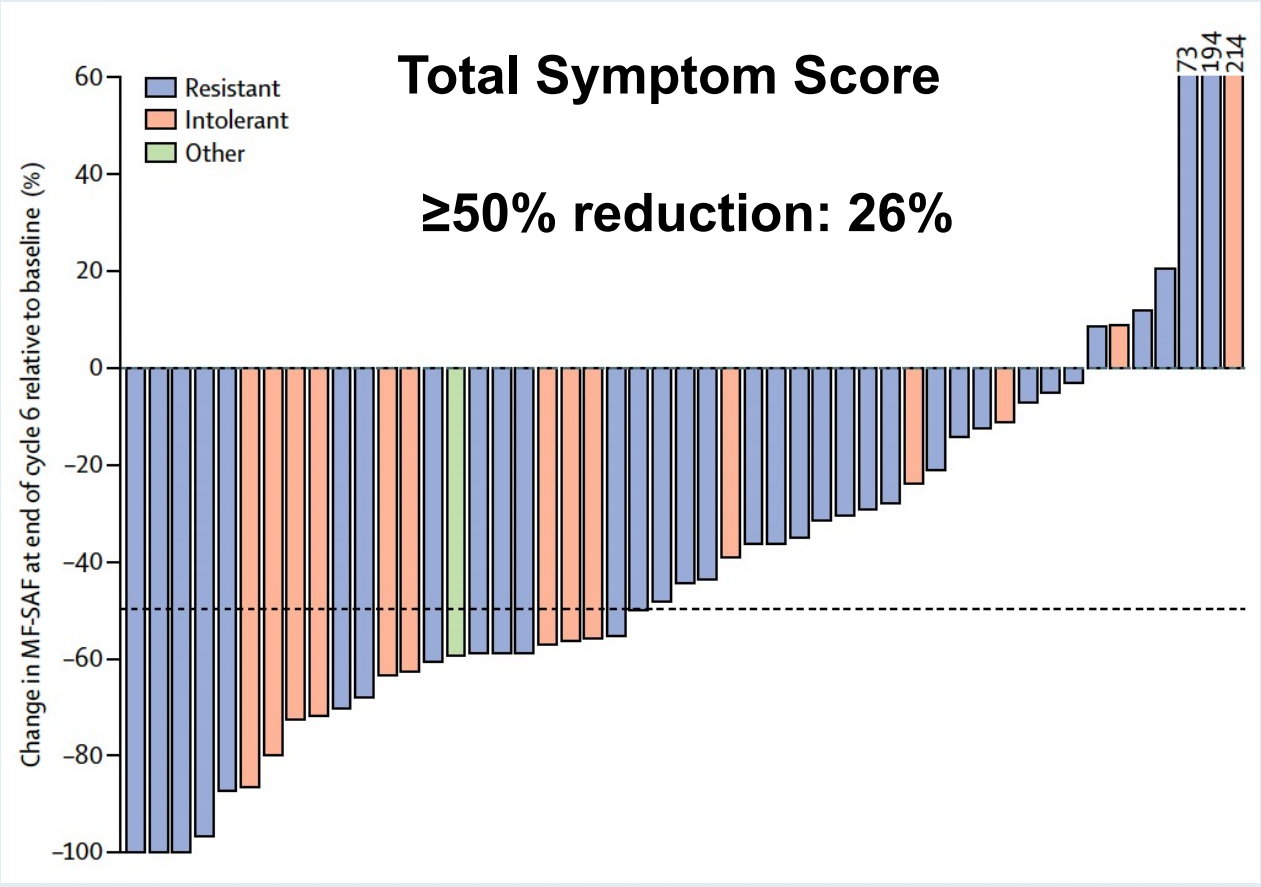
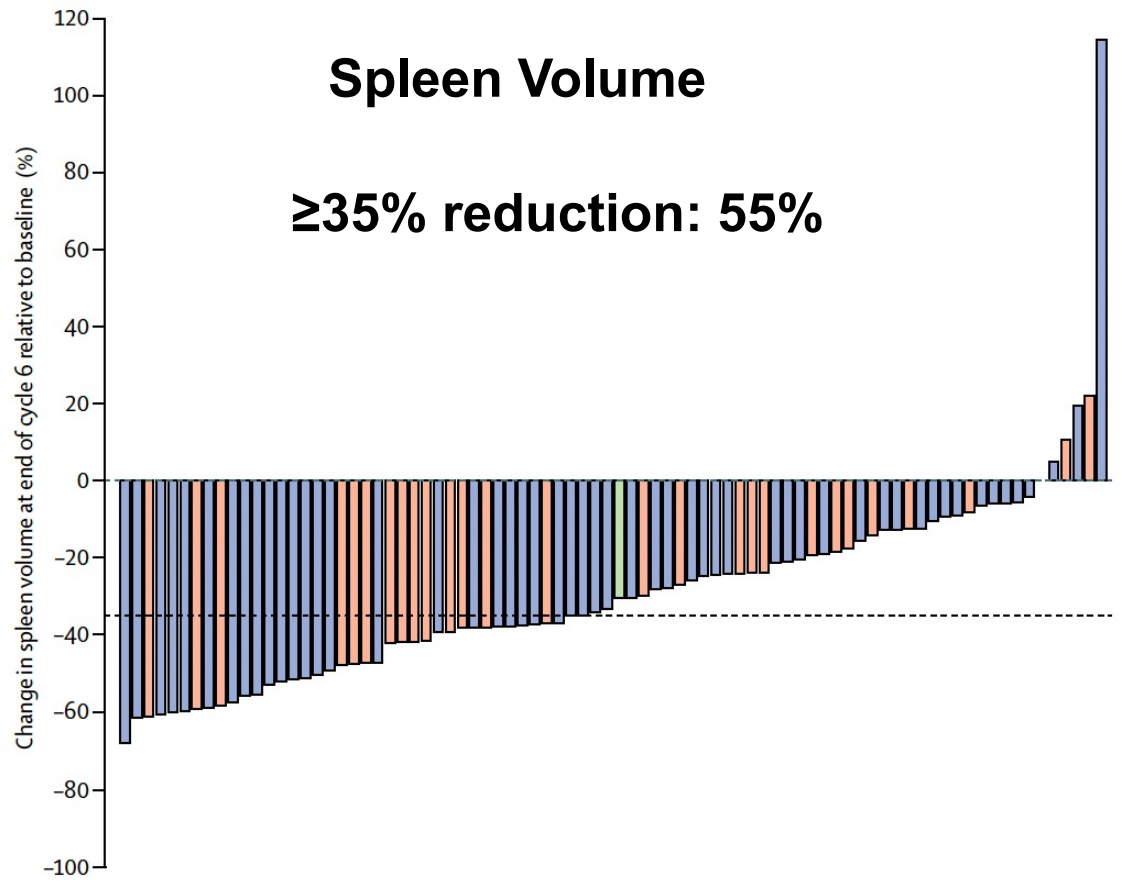
Lancet Haematol 2017;4:e317-24.

Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study



Claire N Harrison, Nicolaas Schaap, Alessandro M Vannucchi, Jean-Jacques Kiladjian, Ramon V Tiu, Pierre Zachee, Eric Jourdan, Elliott Winton, Richard T Silver, Harry C Schouten, Francesco Passamonti, Sonja Zweegman, Moshe Talpaz, Joanne Lager, Zhenming Shun, Ruben A Mesa

JAKARTA-2: Change in Total Symptom Score and Spleen Volume from Baseline to End of Cycle 6



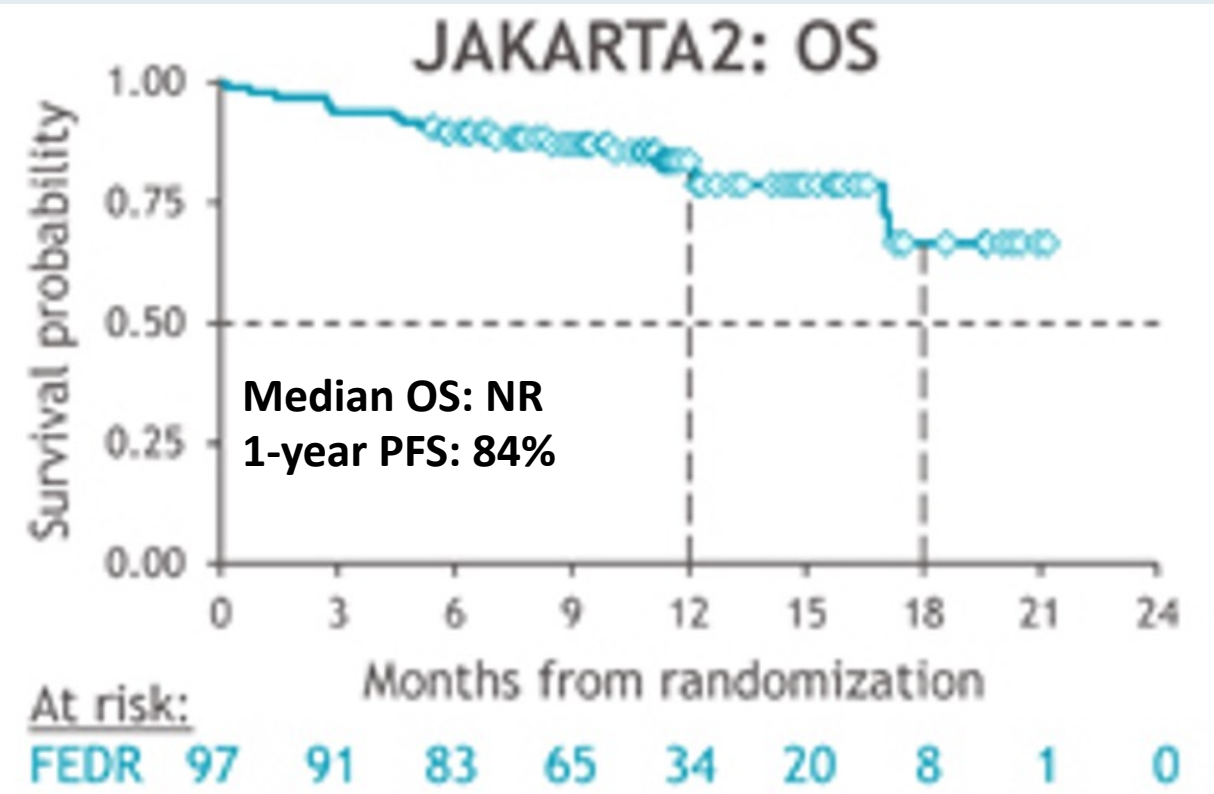
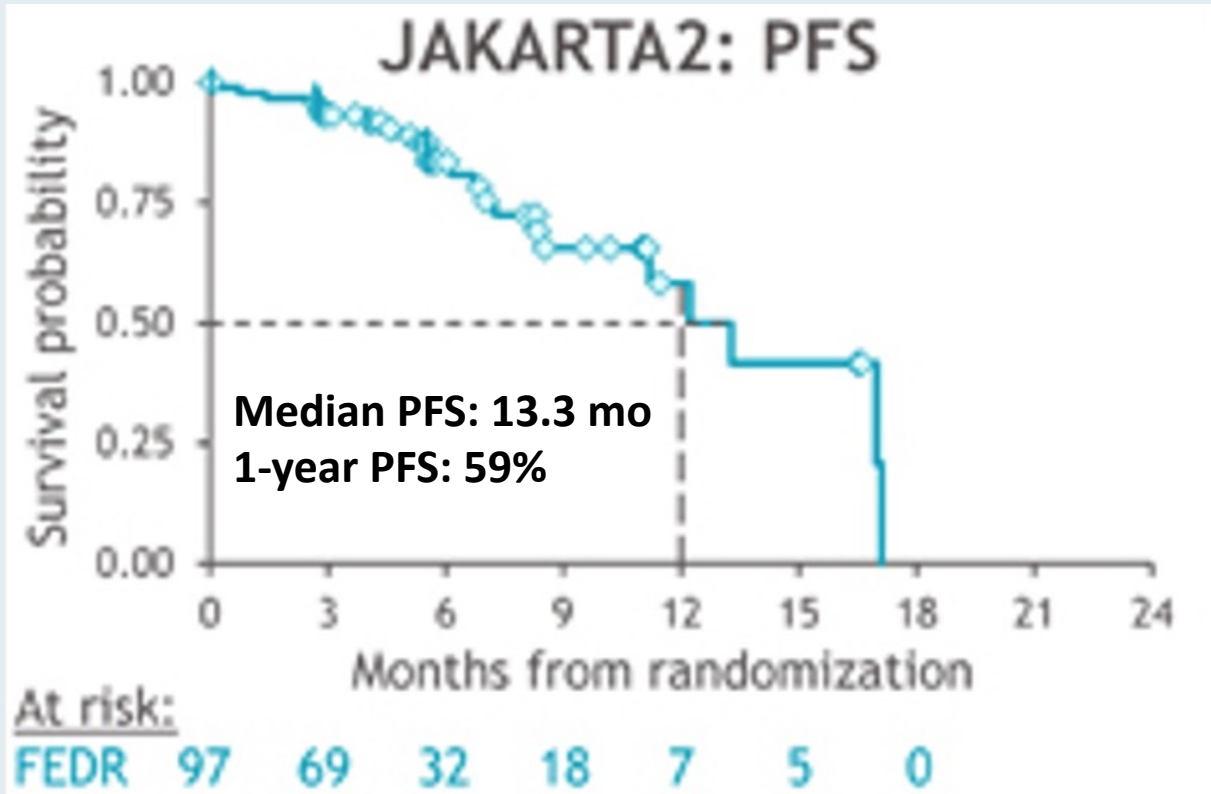
Harrison CN et al. *Lancet Haematol* 2017;4:e317-24.

Overall and Progression-Free Survival in Patients Treated with Fedratinib as First-Line Myelofibrosis (MF) Therapy and After Prior Ruxolitinib (RUX): Results from the JAKARTA and JAKARTA2 Trials

Harrison C et al.

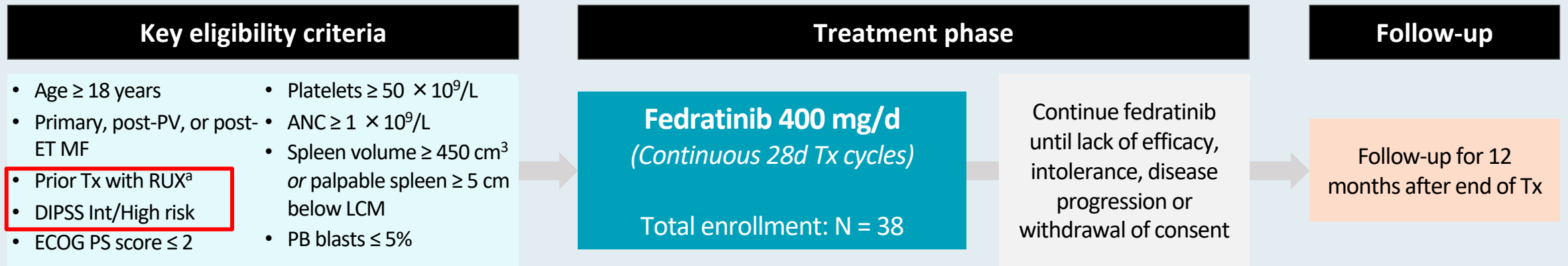
EHA 2021;Abstract S203.

JAKARTA2: Survival Analysis



FREEDOM: Trial Design and Key Eligibility Criteria

International, single-arm, open-label, phase 3b trial (NCT03755518)



Primary endpoint:

- SVRR at EOC6: Proportion of pts with \geq 35% spleen volume reduction from baseline (BL)

Key secondary endpoints:

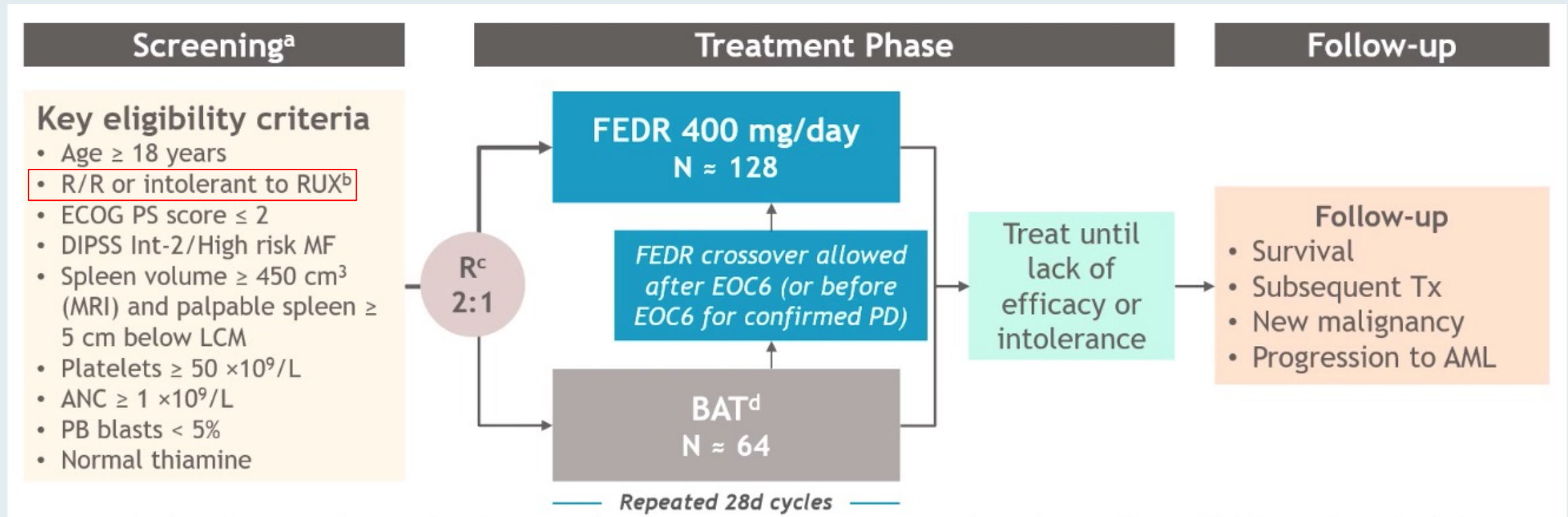
- Symptom RR at EOC6: Proportion of pts with \geq 50% improvement in MFSAF TSS from BL
- Safety; assess risk mitigation for GI AEs and potential WE
- Spleen response by palpation
- Durability of spleen and symptom responses

AE mitigation strategies:

- Prophylactic/symptomatic use of anti-emetic/vomiting and anti-diarrheal Tx
- Administration of fedratinib with food
- Fedratinib dosing modifications
- Thiamine supplementation

^aPts must have received RUX for \geq 3 mo, or for \geq 28 d with development of RBC transfusion requirement (\geq 2 units/mo for 2 mo) or Grade \geq 3 thrombocytopenia, anemia, hematoma or hemorrhage.

FREEDOM2 Phase III Study Design



Momelotinib Yields Statistically Significant Improvement in Symptoms for Myelofibrosis

Press Release: January 27, 2022

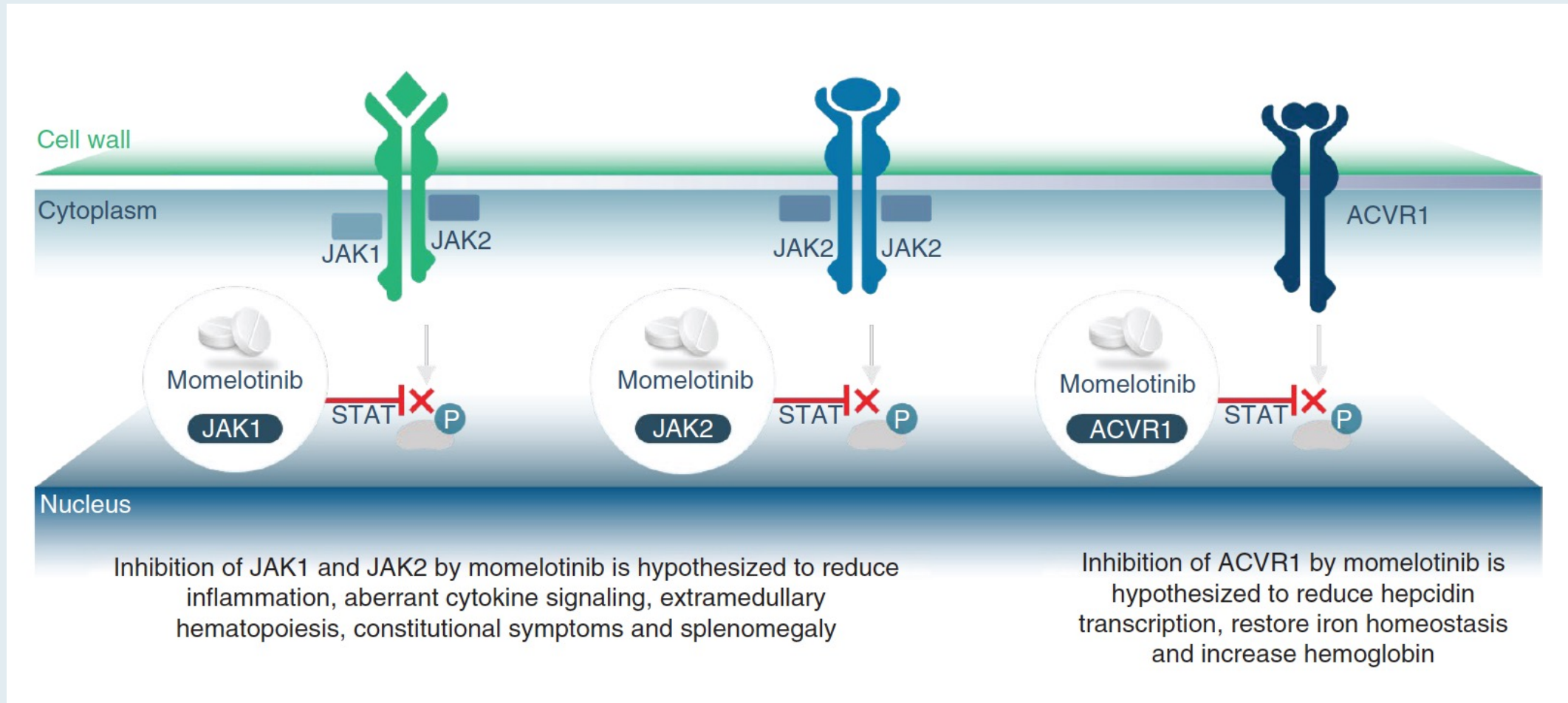
“Topline findings from the phase 3 MOMENTUM study indicated that patients with myelofibrosis experienced a statistically significant reduction in symptoms following treatment with momelotinib.

Treatment with momelotinib resulted in a statistically significant reduction in symptoms for patients with myelofibrosis, according to a press release of the topline findings from the pivotal phase 3 MOMENTUM trial (NCT04173494).

In a population of 195 patients, specifically 130 who received momelotinib and 65 who received danazol, 25% and 9% of patients, respectively, had a total symptom score of more than 50% ($P = .0095$). Additionally, 31% of patients in the momelotinib arm and 20% in the control arm were transfusion independent following treatment (one-sided $P = .0064$), indicating non-inferiority. Investigators also reported a splenic response rate of over 35% in 23% of patients in the experimental arm compared with 3% of patients in the control arm ($P = .0006$).

The full data are set to be presented at an upcoming medical meeting and plans have been put in place to submit a new drug application for the agent in the second quarter of 2022.”

Momelotinib Therapy May Decrease Inflammation, Improve Splenomegaly and Normalize Hemoglobin



Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial



Claire N Harrison, Alessandro M Vannucchi, Uwe Platzbecker, Francisco Cervantes, Vikas Gupta, David Lavie, Francesco Passamonti, Elliott F Winton, Hua Dong, Jun Kawashima, Julia D Maltzman, Jean-Jacques Kiladjian, Srdan Verstovsek

Lancet Haematol 2018;5(2):e73-81.

SIMPLIFY-2 Trial of Momelotinib (MMB) in Patients with MF Previously Treated with Ruxolitinib

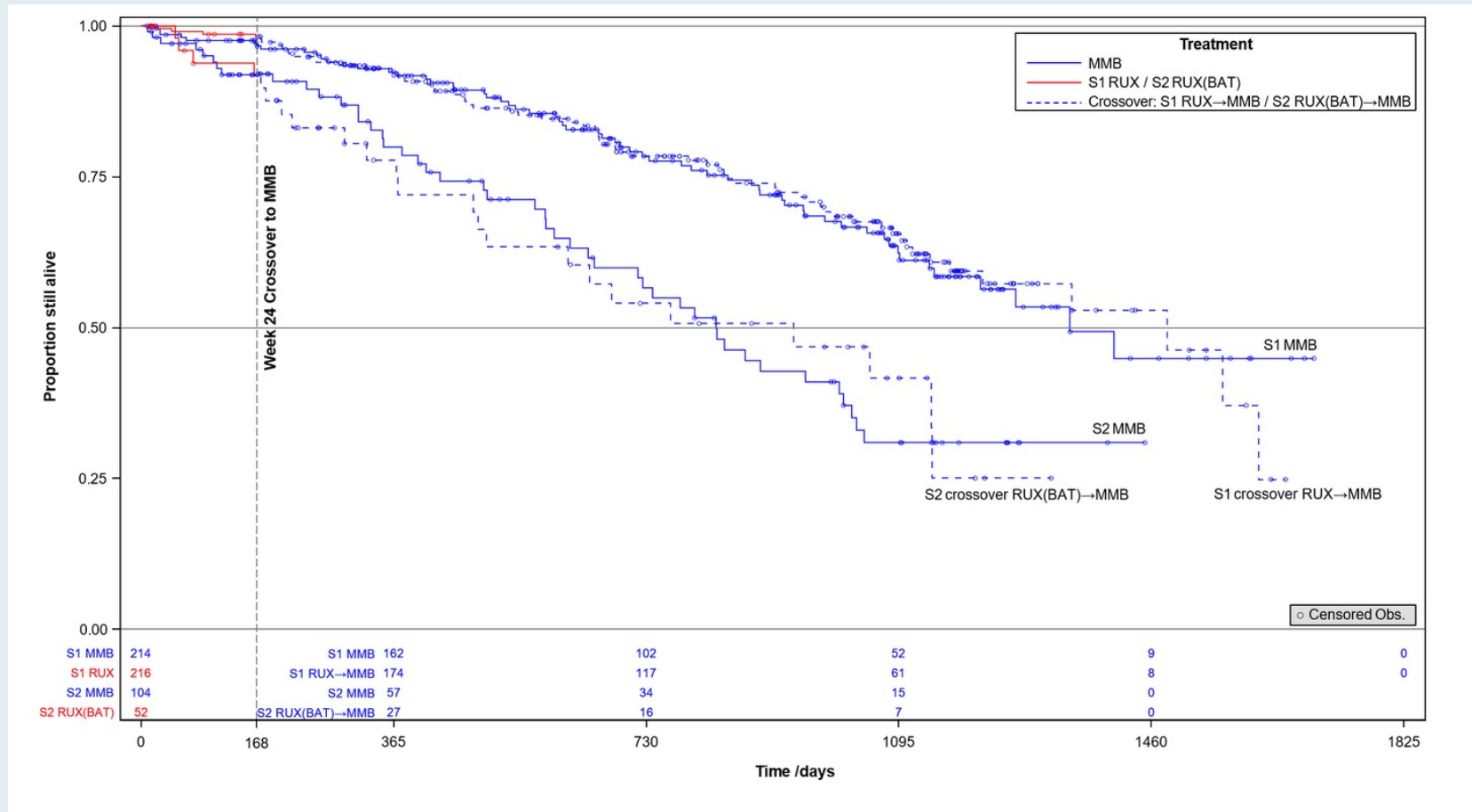
Efficacy outcomes	SIMPLIFY-2, Wk 24		p-value
	MMB (n = 104)	BAT (n = 52)	
Spleen volume reduction $\geq 35\%$	7%	6%	0.90
$\geq 50\%$ reduction in MF-SAF TSS	26%	6%	0.0006
Transfusion independence	43%	26%	0.0012
Safety outcomes			
Discontinued due to AEs	21%	16%	NR
Grade 3/4 anemia	14%	14%	
Grade 3/4 thrombocytopenia	7%	6%	
Grade 3/4 neutropenia	NR	NR	

**Robust Overall Survival and Sustained Efficacy Outcomes
during Long Term Exposure to Momelotinib in JAK Inhibitor
Naïve and Previously JAK Inhibitor Treated
Intermediate/High Risk Myelofibrosis Patients**

Verstovsek S et al.

ASH 2020;Abstract 54.

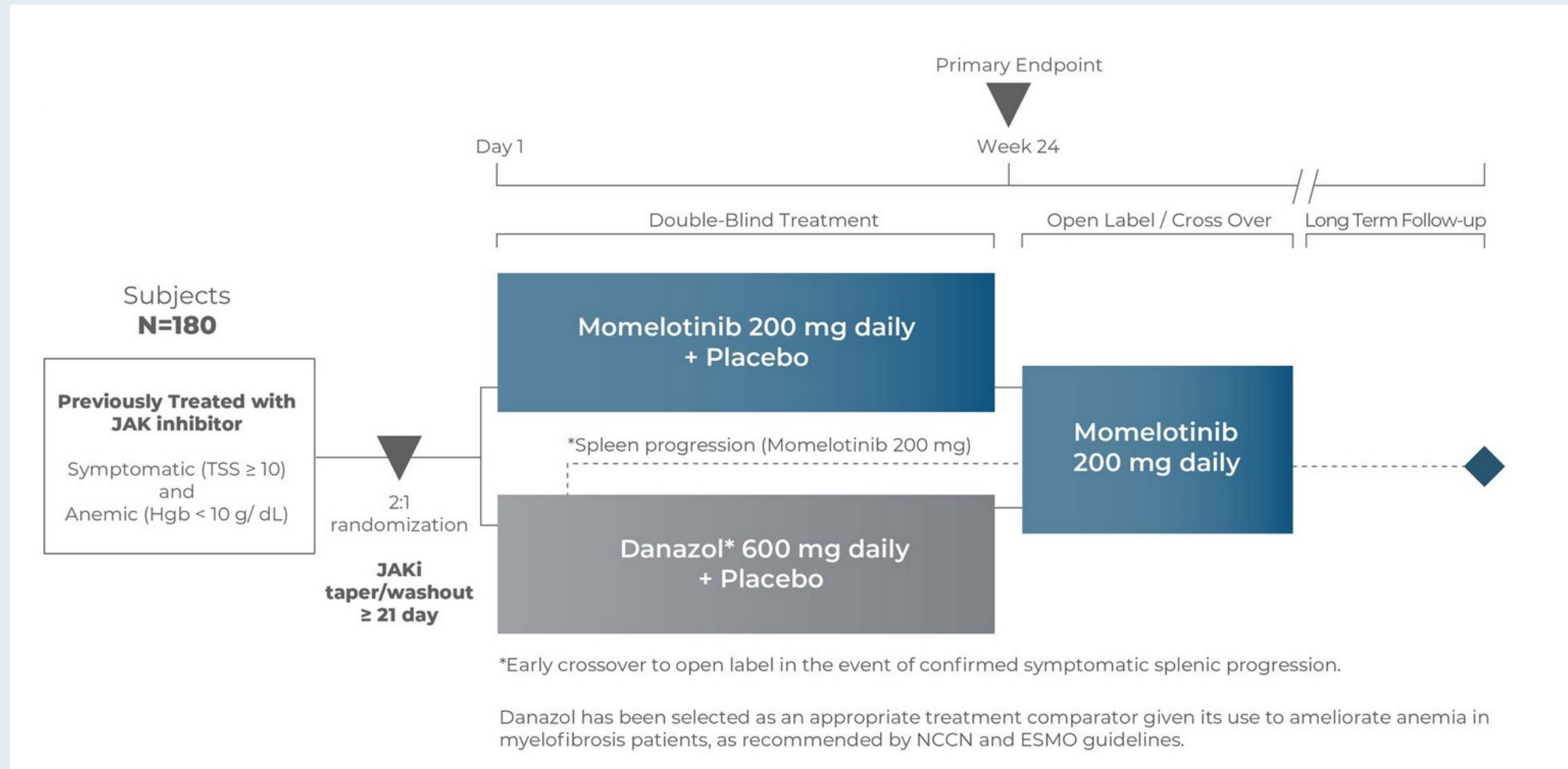
SIMPLIFY-1 (S1) and SIMPLIFY-2 (S2): Long-Term Outcomes with MMB



- S1 reduction in spleen volume of $\geq 35\%$ from baseline at week 24 (MMB vs RUX): 26.5% vs 29.5%
- S1 transfusion independence at week 24 (MMB vs RUX): 70% vs 54%
- S2 transfusion independence at week 24 (MMB vs BAT/RUX): 44% vs 27%

MOMENTUM: Phase III Trial Schema of Mometotinib in MF

Trial Identifier: NCT04173494 (Closed)



Novel Agents and Strategies Beyond JAK Inhibitors Under Investigation in MF

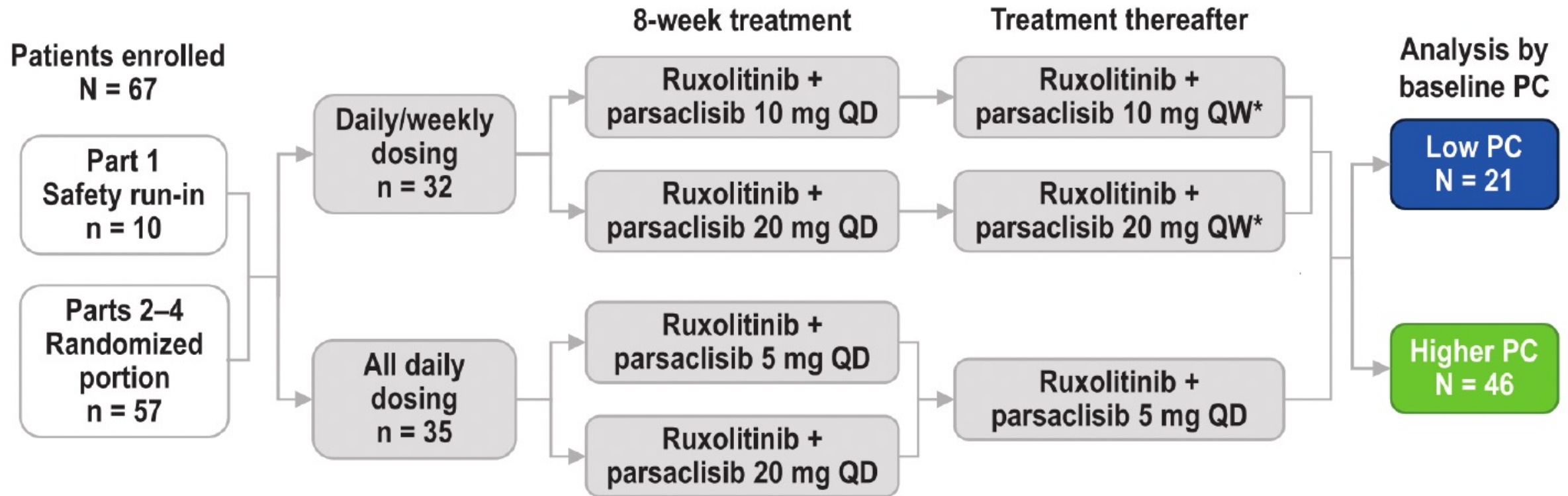
Subgroup Analysis From a Phase 2 Study of the Efficacy and Safety of Parsaclisib, a Selective PI3K δ Inhibitor, in Combination With Ruxolitinib in Patients With Myelofibrosis

Abdulraheem Yacoub,¹ Uma Borate,² Raajit Rampal,³ Haris Ali,⁴ Eunice Wang,⁵ Aaron Gerds,⁶ Gabriela Hobbs,⁷ Marina Kremyanskaya,⁸ Elliott Winton,⁹ Casey O'Connell,¹⁰ Swati Goel,¹¹ Stephen Oh,¹² Gary Schiller,¹³ Albert Assad,¹⁴ Sue Erickson-Viitanen,¹⁴ Feng Zhou,¹⁴ Naval Daver¹⁵

¹University of Kansas Cancer Center, Westwood, KS, USA; ²Oregon Health & Science University, Portland, OR, USA; ³Memorial Sloan Kettering Cancer Center, New York, NY, USA; ⁴City of Hope National Medical Center, Duarte, CA, USA; ⁵Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; ⁶Cleveland Clinic, Cleveland, OH, USA; ⁷Massachusetts General Hospital, Boston, MA, USA; ⁸Icahn School of Medicine at Mount Sinai, New York, NY, USA; ⁹Emory University, Atlanta, GA, USA; ¹⁰University of Southern California, Los Angeles, CA, USA; ¹¹Montefiore Medical Center, Bronx, NY, USA; ¹²Washington University School of Medicine, St. Louis, MO, USA; ¹³David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; ¹⁴Incyte Corporation, Wilmington, DE, USA; ¹⁵University of Texas MD Anderson Cancer Center, Houston, TX, USA

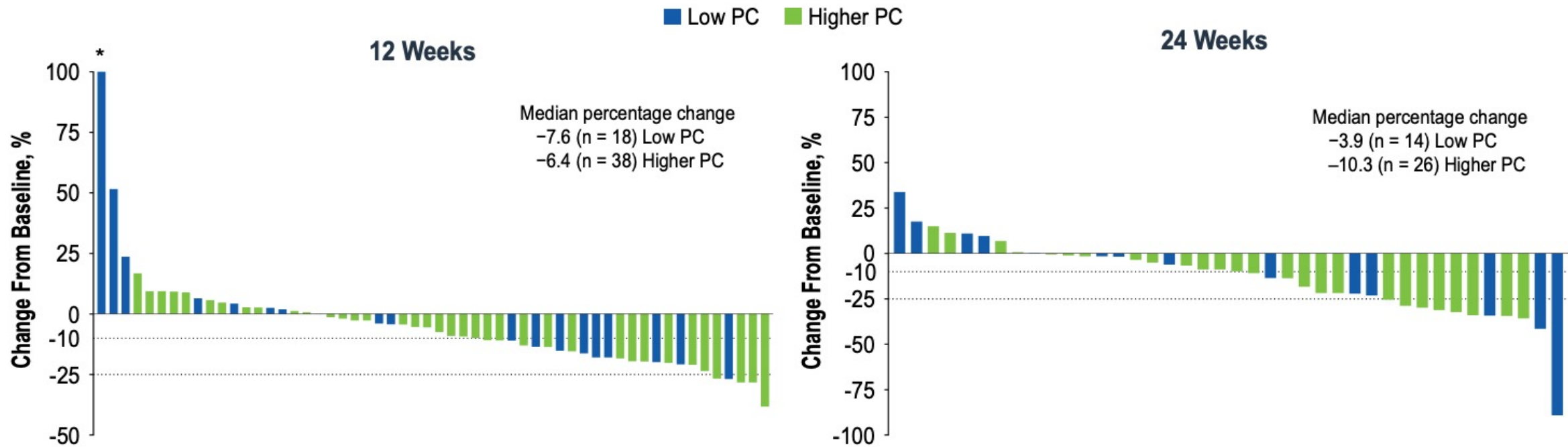
ASH 2021;Abstract 3647.

Phase II INCB 50465-201 Study of Adding Parsaclisib to Ruxolitinib



*Options for QD dosing were made available to patients once daily dosing regimens were added to the protocol.
PC, platelet counts; QD, once daily; QW, once weekly.

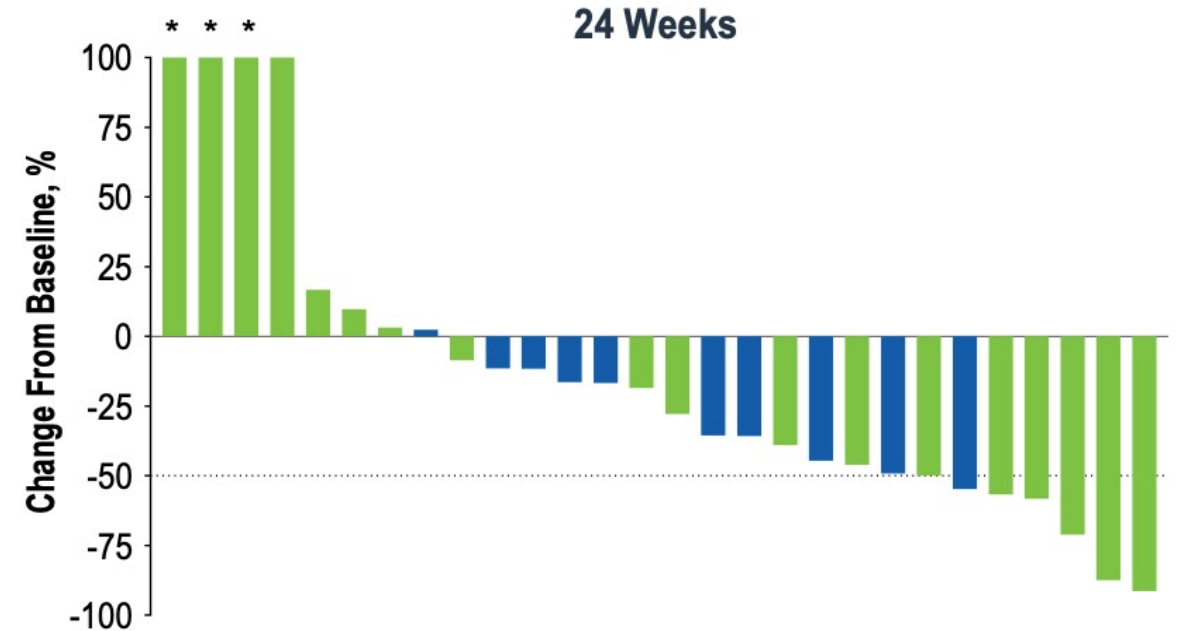
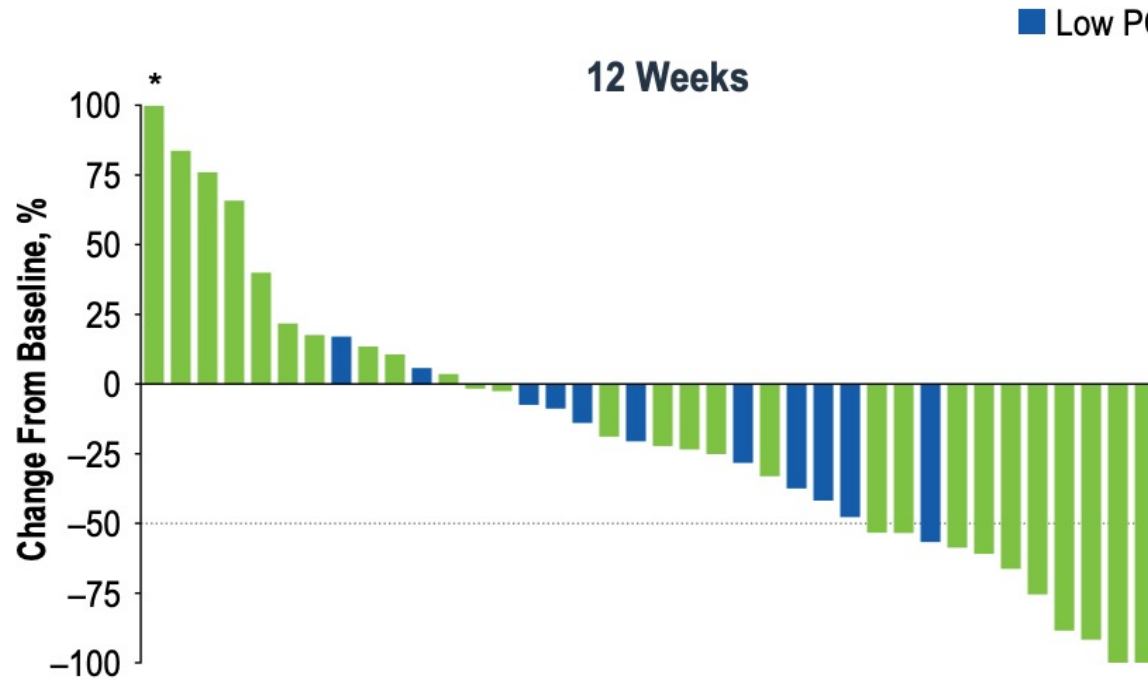
Phase II INCB 50465-201: Percent Change in Spleen Volume



Response Category, n (%)	Low PC	Higher PC
Week 12	n = 18	n = 38
≥10% reduction	9 (50)	15 (39)
≥25% reduction	1 (6)	4 (11)
≥35% reduction	0	1 (3)

Response Category, n (%)	Low PC	Higher PC
Week 24	n = 17	n = 35
≥10% reduction	6 (35)	13 (37)
≥25% reduction	3 (18)	8 (23)
≥35% reduction	2 (12)	1 (3)

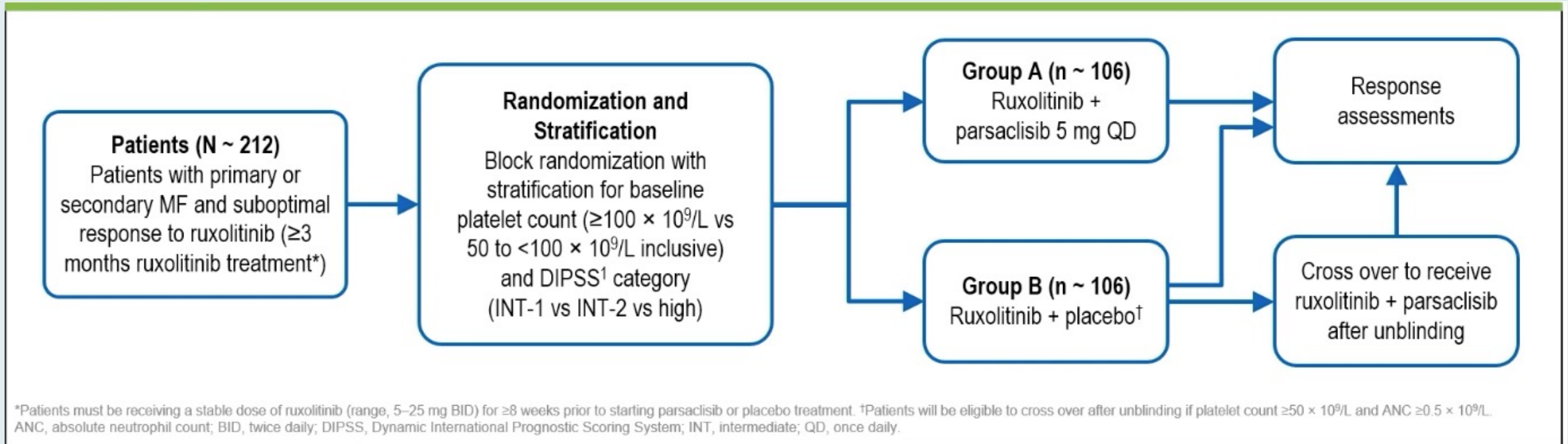
Phase II INCB 50465-201: Percent Change in MFSAF-TSS



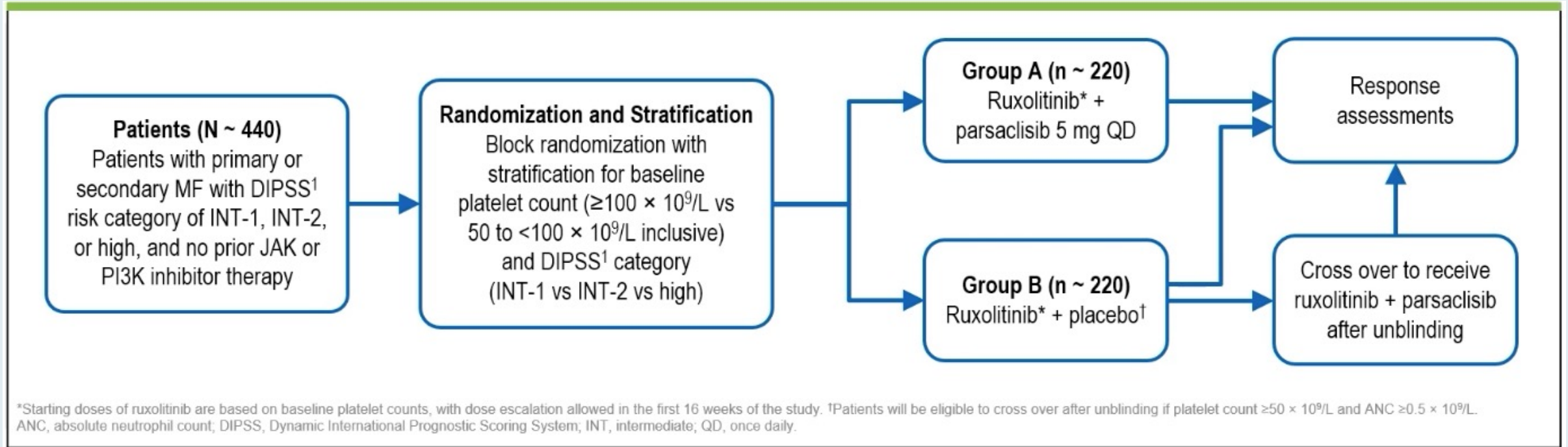
Median change in MFSAF-TSS at 12 Weeks	n	% Change (Range)
Low PC	11	-20.5 (-56.6 to 17.1)
Higher PC	27	-22.2 (-100.0 to 500.0)

Median change in MFSAF-TSS at 24 Weeks	n	% Change (Range)
Low PC	10	-26.1 (-54.7 to 2.4)
Higher PC	18	-23.1 (-91.3 to 222.5)

LIMBER-304 Phase III Study Design



LIMBER-313 Phase III First-Line Study Design



A Phase 2 Study of the LSD1 Inhibitor Img-7289 (Bomedemstat) for the Treatment of Advanced Myelofibrosis

Gill H et al.

ASH 2021;Abstract 139.

Phase I/II Trial of Bomedemstat for Advanced MF

Primary Endpoints

- Safety and tolerability
- Pharmacokinetics in first 15 patients
- Spleen volume reduction

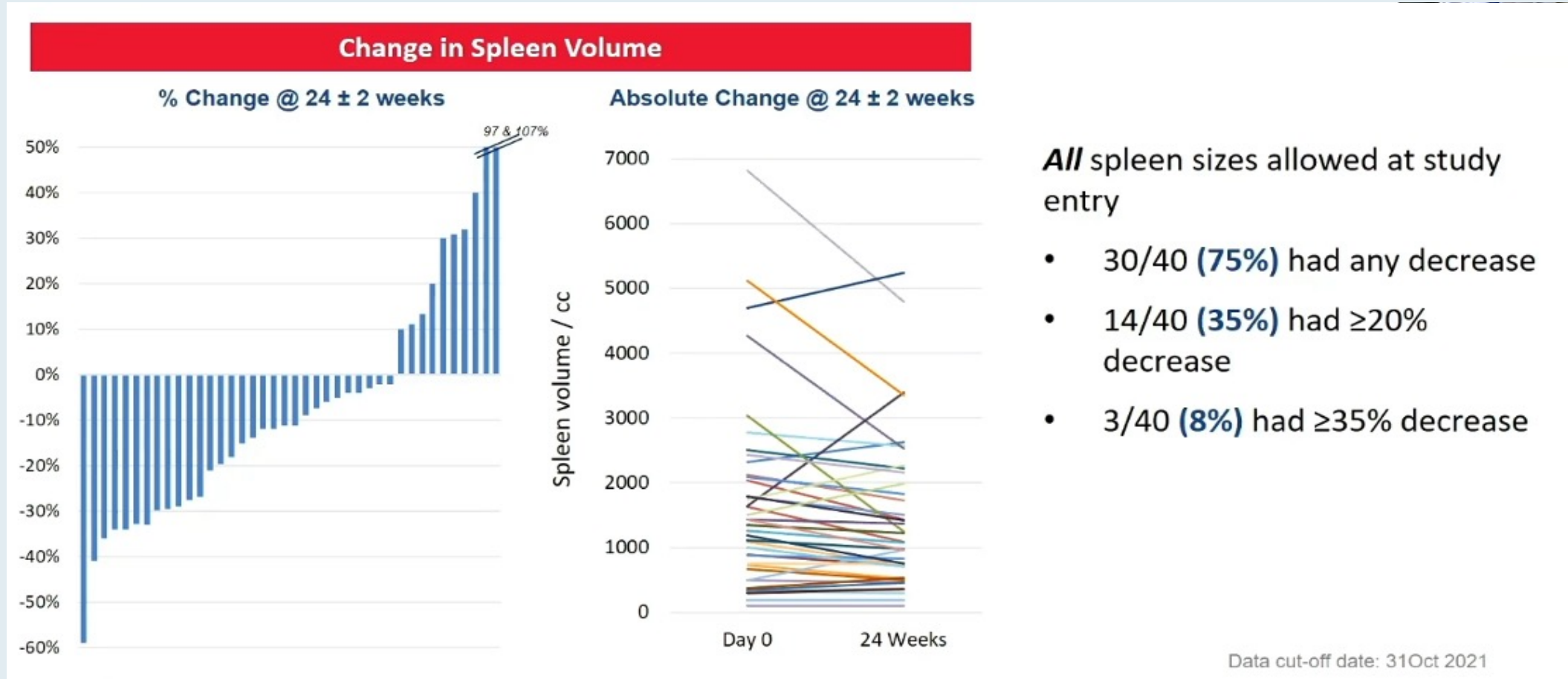
Secondary Endpoints

- Symptom reduction (MPN-SAF TSS)
- Changes in cytokine profiles
- Changes in mutant allele frequencies (MAF)
- Changes in bone marrow (BM) fibrosis

Key Eligibility Criteria

- Dx of PMF, PET-MF, or PPV-MF
- Refractory or resistant to, intolerant of, inadequate control by, or ineligible for, available approved therapies
- IPSS Intermediate-1, -2 or High-risk disease
- **Platelets $\geq 100 \times 10^9/L$**
- Peripheral blasts $\leq 10\%$
- Spleen of **any size**
- ECOG PS ≤ 2

Spleen Volume Reduction and Total Symptom Score at 24 Weeks with Bomedemstat



- 17/23 patients (74%) had a decrease in TSS and 6/23 patients (26%) had a decrease of $\geq 50\%$.

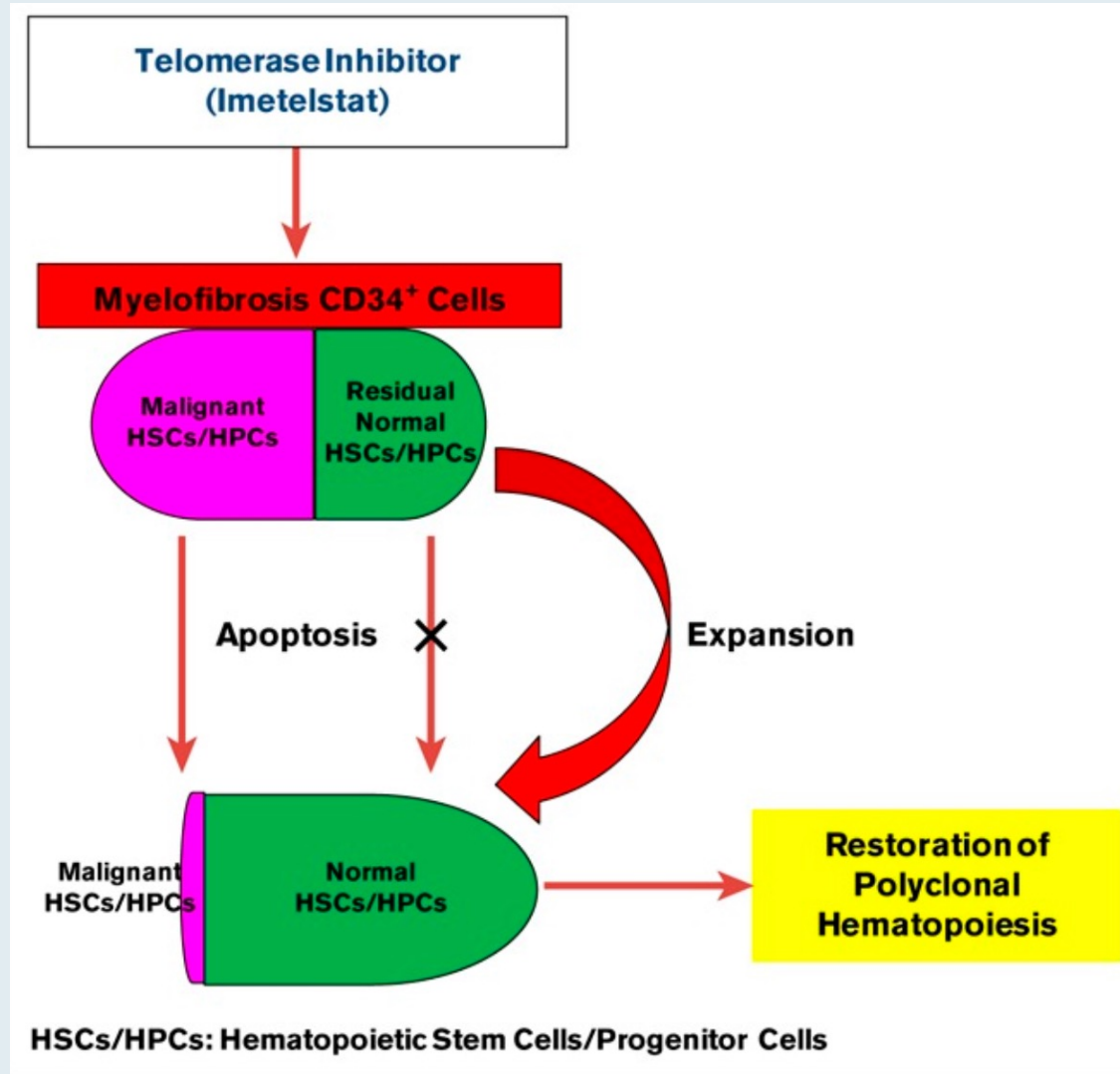
Safety and Tolerability of Bomedemstat

Preferred Term (N=90)	Any Grade AEs	Grade 3/4 AEs
Thrombocytopenia	42 (47%)	35 (39%)
Dysgeusia	29 (32%)	0
Anaemia	29 (32%)	20 (22%)
Diarrhoea	27 (30%)	0
Nausea	25 (28%)	2 (2%)
Fatigue	22 (24%)	4 (4%)
Constipation	21 (23%)	1 (1%)
Oedema peripheral	18 (20%)	1 (1%)
Arthralgia	16 (18%)	0
Abdominal pain	15 (17%)	1 (1%)
Decreased appetite	14 (16%)	2 (2%)
Pruritus	14 (16%)	2 (2%)

- Bomedemstat is generally well tolerated
- Most common hematologic AE, thrombocytopenia, is anticipated because dose titration rules target Grade 2 ($50-75 \times 10^9/L$)
- The most common non-hematologic AE **related** to bomedemstat was dysgeusia (n=27, 30% of patients) with 1 patient who discontinued

Any grade of AE occurring at a frequency of >15% included regardless of relatedness; total number of events = 1443

Telomerase Inhibitor Imetelstat: Mechanism of Action

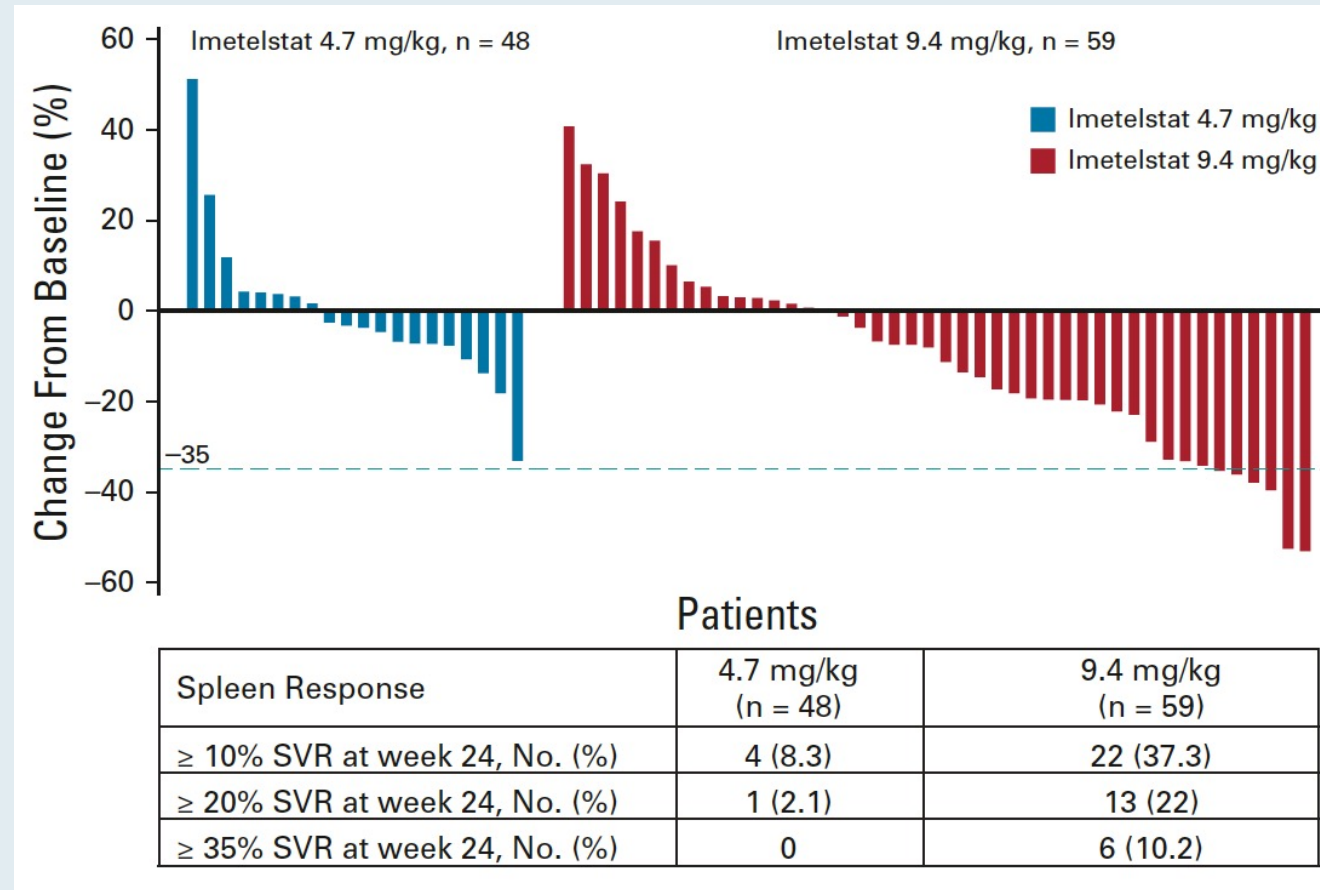


Randomized, Single-Blind, Multicenter Phase II Study of Two Doses of Imetelstat in Relapsed or Refractory Myelofibrosis

John Mascarenhas, MD¹; Rami S. Komrokji, MD²; Francesca Palandri, MD³; Bruno Martino, MD⁴; Dietger Niederwieser, MD, PhD⁵; Andreas Reiter, MD⁶; Bart L. Scott, MD⁷; Maria R. Baer, MD⁸; Ronald Hoffman, MD¹; Olatoyosi Odenike, MD⁹; Alessandro M. Vannucchi, MD¹⁰; Jacqueline Bussolari, PhD¹¹; Eugene Zhu, PhD¹¹; Esther Rose, MD¹¹; Laurie Sherman, BSN¹²; Souria Dougherty, BS, MBA¹²; Libo Sun, PhD¹²; Fei Huang, PhD¹²; Ying Wan, PhD¹²; Faye M. Feller, MD¹²; Aleksandra Rizo, MD, PhD¹²; and Jean-Jacques Kiladjian, MD, PhD¹³

J Clin Oncol 2021;39:2881-92.

Phase II Trial of Imetelstat in Relapsed/Refractory Myelofibrosis



- At week 24, symptom response rates were 32.2% in the 9.4-mg/kg arm and 6.3% in the 4.7-mg/kg arm.
- Most common adverse events on both arms were grade 3 or 4 reversible cytopenias.

A Randomized Open-Label, Phase 3 Study to Evaluate Imetelstat versus Best Available Therapy (BAT) in Patients with Intermediate-2 (Int-2) or High-Risk Myelofibrosis (MF) Refractory to Janus Kinase Inhibitor (JAKi)

Mascarenhas J et al.

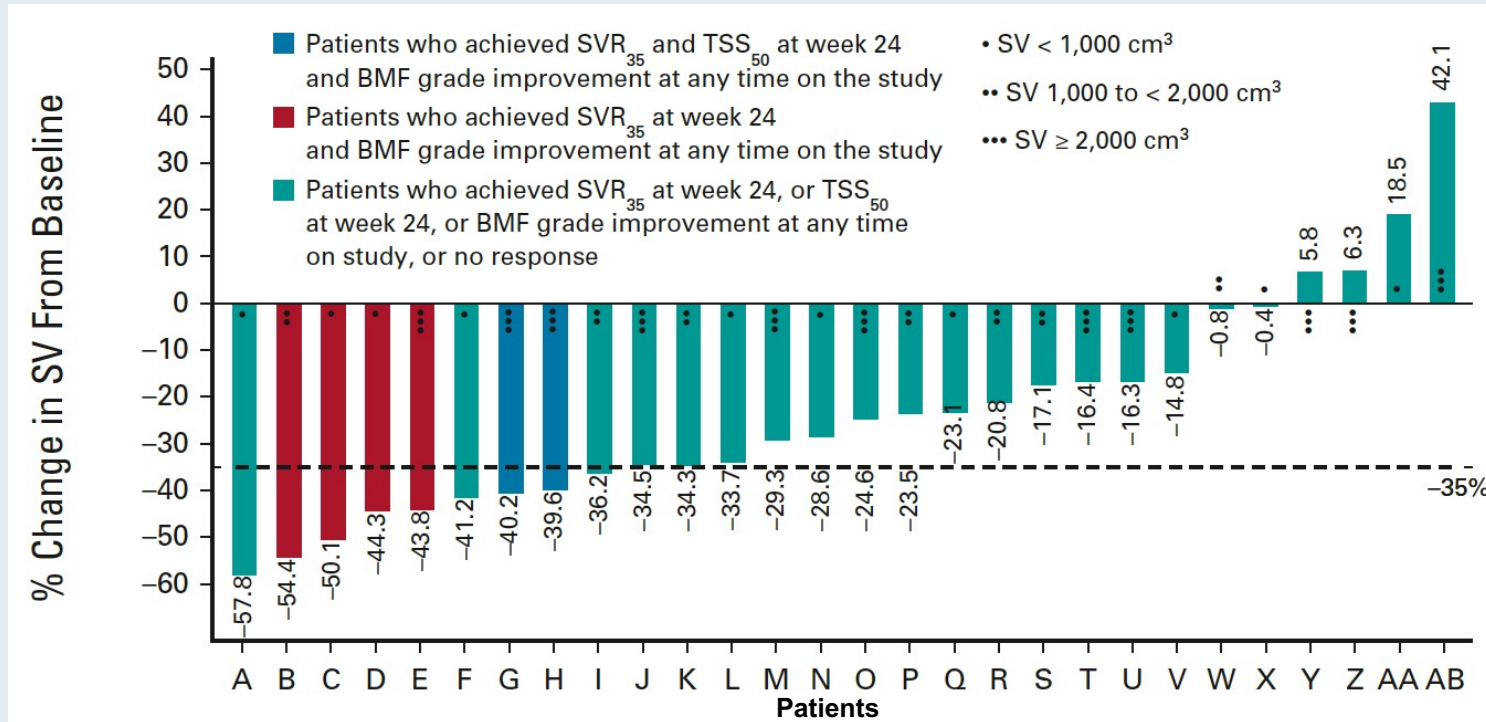
ASH 2021;Abstract 1503.

Addition of Navitoclax to Ongoing Ruxolitinib Therapy for Patients With Myelofibrosis With Progression or Suboptimal Response: Phase II Safety and Efficacy

Claire N. Harrison, MD¹; Jacqueline S. Garcia, MD²; Tim C. P. Somerville, MBBS, PhD^{3,4}; James M. Foran, MD⁵; Srdan Verstovsek, MD, PhD⁶; Catriona Jamieson, MD, PhD⁷; Ruben Mesa, MD⁸; Ellen K. Ritchie, MD⁹; Srinivas K. Tantravahi, MBBS¹⁰; Pankit Vachhani, MD¹¹; Casey L. O'Connell, MD¹²; Rami S. Komrokji, MD¹³; Jason Harb, PhD¹⁴; Jessica E. Hutti, PhD¹⁴; Leanne Holes, MBA¹⁴; Abdullah A. Masud, MS, PhD¹⁴; Silpa Nuthalapati, PhD¹⁴; Jalaja Potluri, MD¹⁴; and Naveen Pemmaraju, MD⁶

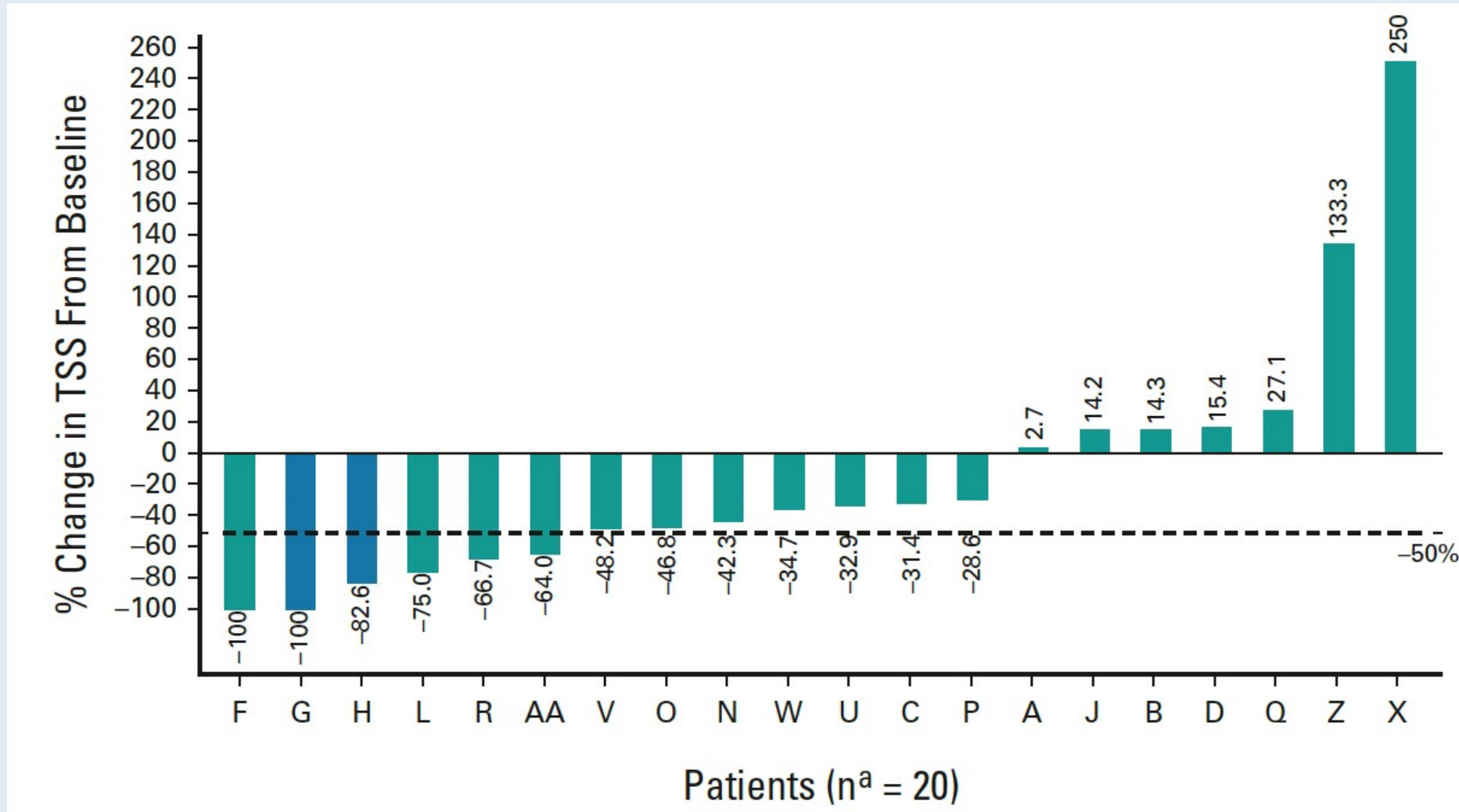
J Clin Oncol 2022;[Online ahead of print].

Phase II Trial of Adding the Bcl-XL/Bcl-2 Inhibitor Navitoclax to Ruxolitinib for Patients with MF and Disease Progression or a Suboptimal Response



- $\geq 50\%$ reduction in total symptom score (TSS50) was achieved by 30% (6 of 20) of patients at week 24, and bone marrow fibrosis improved by 1-2 grades.
- Reversible thrombocytopenia without clinically significant bleeding was the most common adverse event (88%) but was manageable with dose reductions and interruptions.

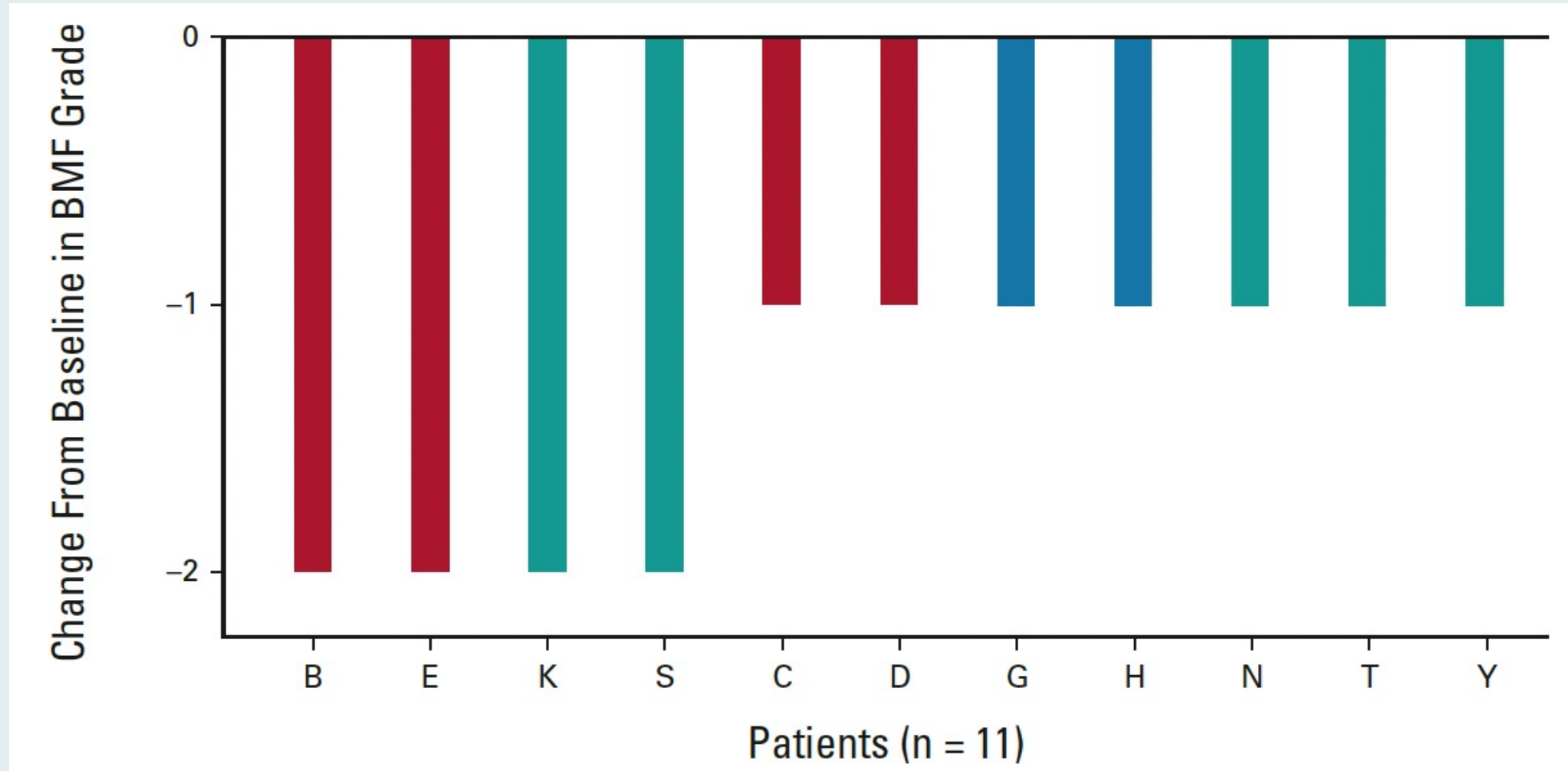
Percent Change in TSS from Baseline at Week 24



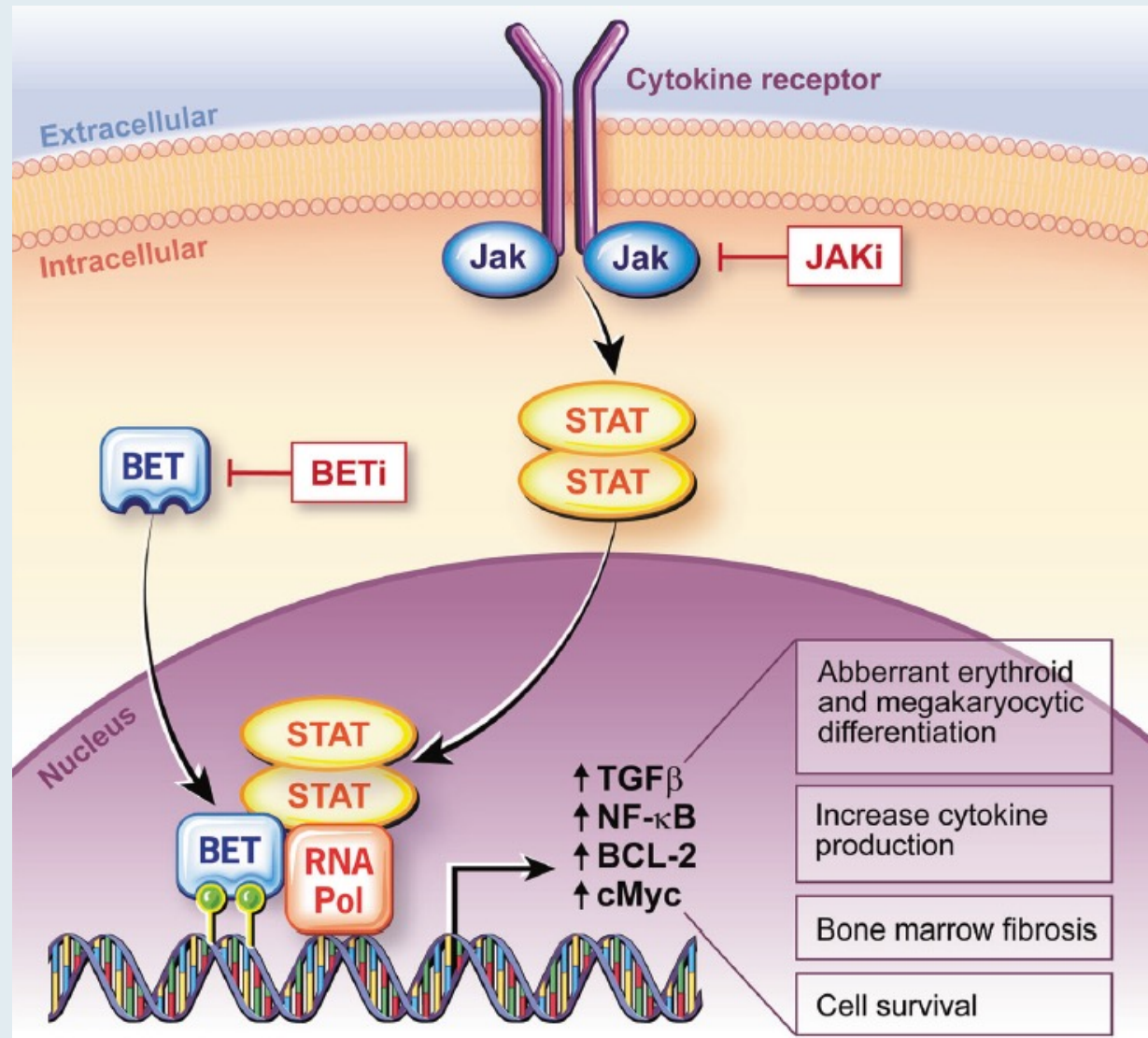
TSS = total symptom score

Harrison CN et al. *J Clin Oncol* 2022;[Online ahead of print].

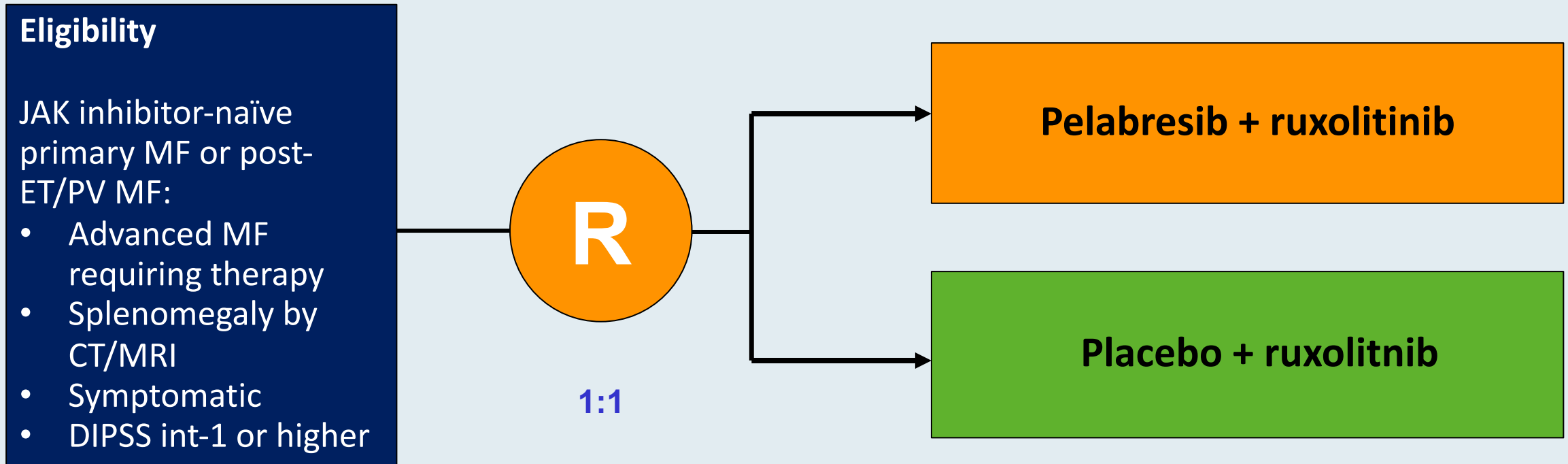
Percent Change in Bone Marrow Fibrosis (BMF) from Baseline



Mechanism of Action of BET Inhibitor Pelabresib



MANIFEST-2: Phase III Trial Design



Primary Endpoint: SVR35 at 24 weeks

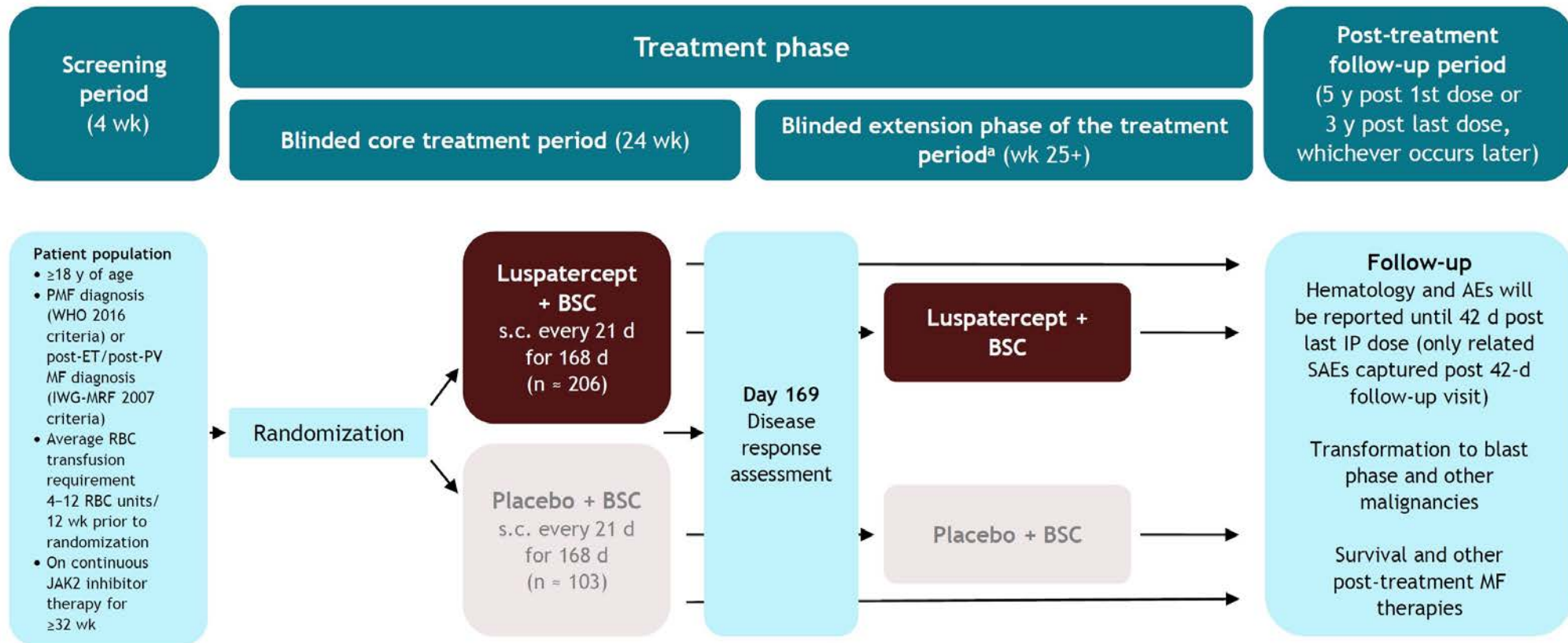
Key Secondary Endpoint: TSS50 by at 24 weeks

INDEPENDENCE: A Phase 3 Study of Efficacy and Safety of Luspatercept versus Placebo in Patients with Myeloproliferative Neoplasm-Associated Myelofibrosis on JAK2 Inhibitor Therapy and Requiring Red Blood Cell Transfusions

Mesa RA et al.

ASH 2021;Abstract 1490.

Figure. The INDEPENDENCE trial design



^aPatients on study can be unblinded after analysis of the primary endpoint and with data monitoring committee consultation. Patients receiving placebo have the opportunity to receive luspatercept treatment and be treated for ≥ 24 wk in the open-label extension treatment period as long as they continue to demonstrate benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.

AE, adverse event; BSC, best supportive care; d, day; ET, essential thrombocythemia; IP, investigational product; IWG-MRF, International Working Group for Myelofibrosis Research and Treatment; MF, myelofibrosis; PMF, primary myelofibrosis; PV, polycythemia vera; RBC, red blood cell; SAE, serious adverse event; s.c., subcutaneously; WHO, World Health Organization; wk, week; y, year.

Year in Review: Prostate Cancer

**Tuesday, April 12, 2022
5:00 PM – 6:00 PM ET**

Faculty

Emmanuel S Antonarakis, MD

Daniel P Petrylak, MD

Special Topics

- **ARASENS, PROPEL, MAGNITUDE trials**

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Prostate Cancer

Thursday, April 28, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Kathy D Burns, RN, MSN, AGACNP-BC, OCN

Robert Dreicer, MD, MS

Sandy Srinivas, MD

Ronald Stein, JD, MSN, NP-C, AOCNP

Non-Small Cell Lung Cancer

Thursday, April 28, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Edward B Garon, MD, MS

Kelly EH Goodwin, MSN, RN, ANP-BC

Tara Plues, APRN, MSN

Anne S Tsao, MD, MBA

Ovarian Cancer

Thursday, April 28, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Jennifer Filipi, MSN, NP

Kathleen N Moore, MD, MS

Krishnansu S Tewari, MD

Deborah Wright, MSN, APRN, AGCNS-BC

Hepatobiliary Cancers

Thursday, April 28, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Richard S Finn, MD

Amanda K Wagner, APRN-CNP, AOCNP

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Small Cell Lung Cancer

Friday, April 29, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Marianne J Davies, DNP, MSN, RN, APRN

Matthew Gubens, MD, MS

Lowell L Hart, MD

Chaely J Medley, MSN, AGNP

Breast Cancer

Friday, April 29, 2022

6:00 PM – 8:00 PM PT (9:00 PM – 11:00 PM ET)

Faculty

Jamie Carroll, APRN, MSN, CNP

Sara A Hurvitz, MD

Kelly Leonard, MSN, FNP-BC

Hope S Rugo, MD

Chronic Lymphocytic Leukemia

Friday, April 29, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Lesley Camille Ballance, MSN, FNP-BC

Amy Goodrich, CRNP

Anthony R Mato, MD, MSCE

Susan O'Brien, MD

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, April 29, 2022

8:20 PM – 9:20 PM PT (11:20 PM – 12:20 AM ET)

Faculty

Faculty to be announced

What I Tell My Patients: Expert Insights into Patient Education on New Treatments and Clinical Trial Participation

A Complimentary NCPD Hybrid Symposium Series Held During the 47th Annual ONS Congress

Cervical and Endometrial Cancer

Saturday, April 30, 2022

6:00 AM – 7:30 AM PT (9:00 AM – 10:30 AM ET)

Faculty

Paula J Anastasia, MN, RN, AOCN

Robert L Coleman, MD

David M O'Malley, MD

Jaclyn Shaver, MS, APRN, CNP, WHNP

Bladder Cancer

Saturday, April 30, 2022

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Monica Averia, MSN, AOCNP, NP-C

Shilpa Gupta, MD

Brenda Martone, MSN, NP-BC, AOCNP

Sumanta Kumar Pal, MD

Thank you for joining us!

***CME and MOC credit information will be emailed
to each participant within 5 business days.***