Meet The Professor
Current and Future Management of Myelofibrosis

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

Commercial Support

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

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mersana Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Mascarenhas — Disclosures

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Data and Safety Monitoring Board/Committee	Galecto

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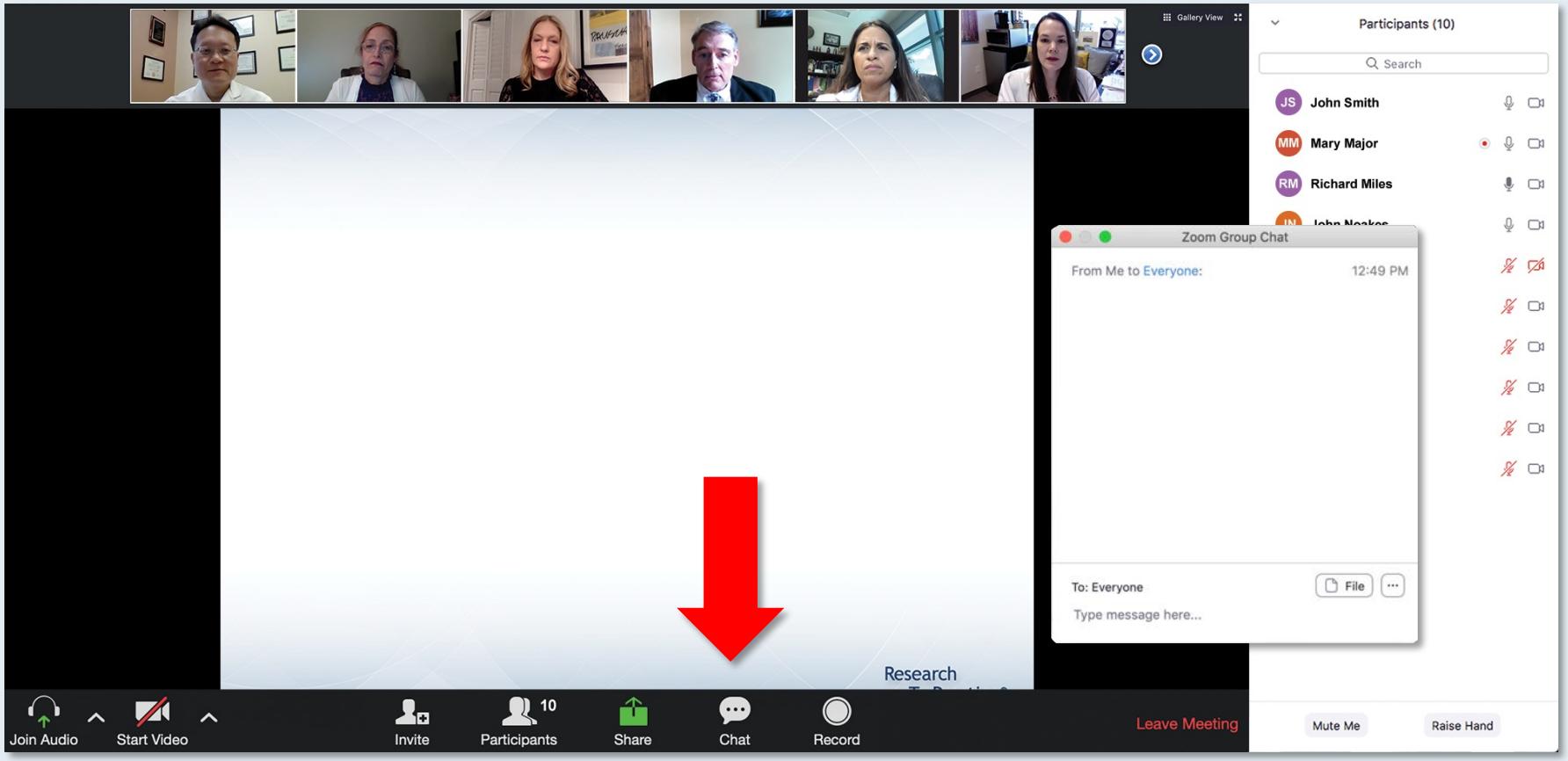

Feel free to submit questions now before the program begins and throughout the program.

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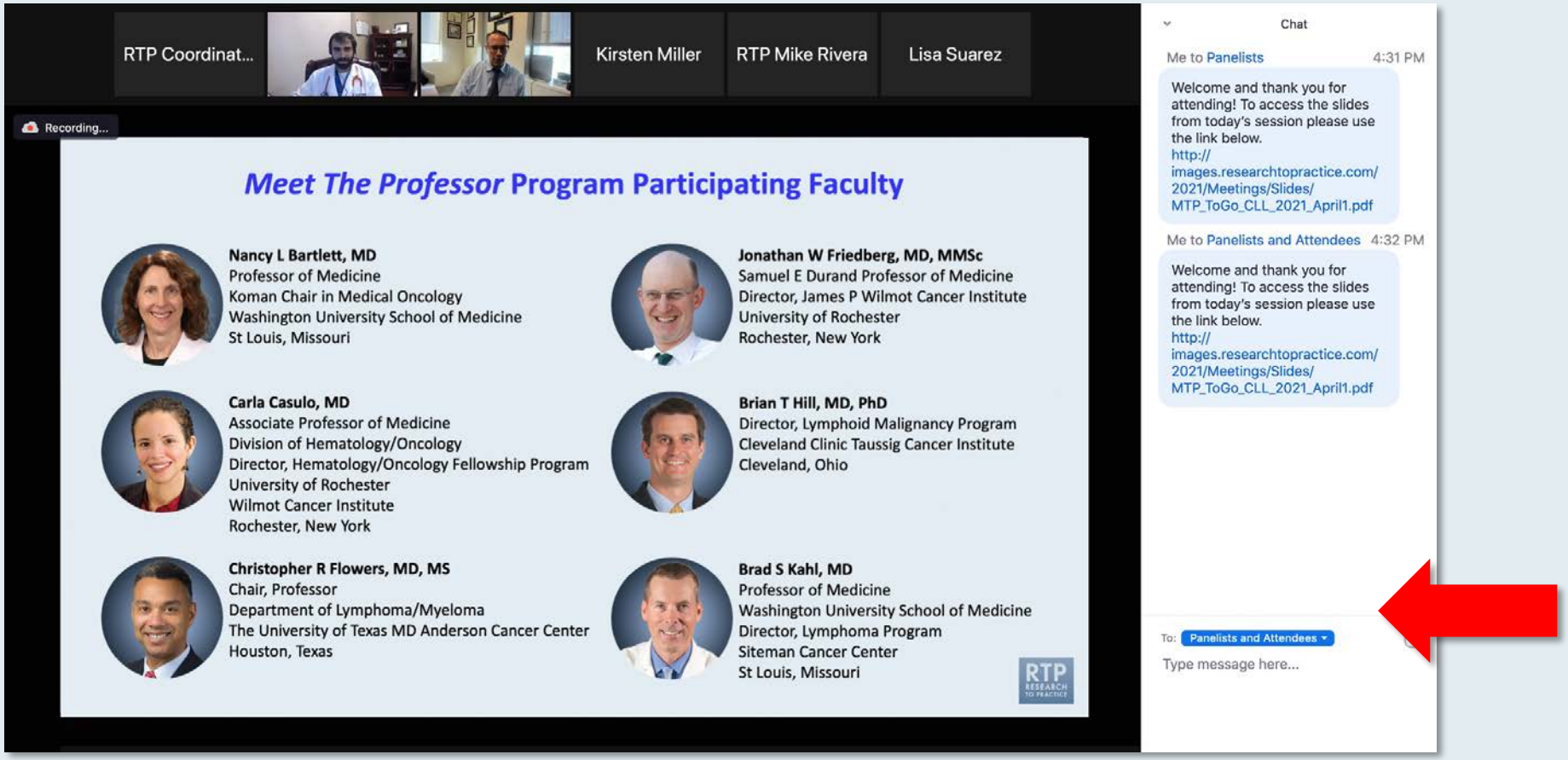

Drag the white line above the submission box up to create more space for your message.

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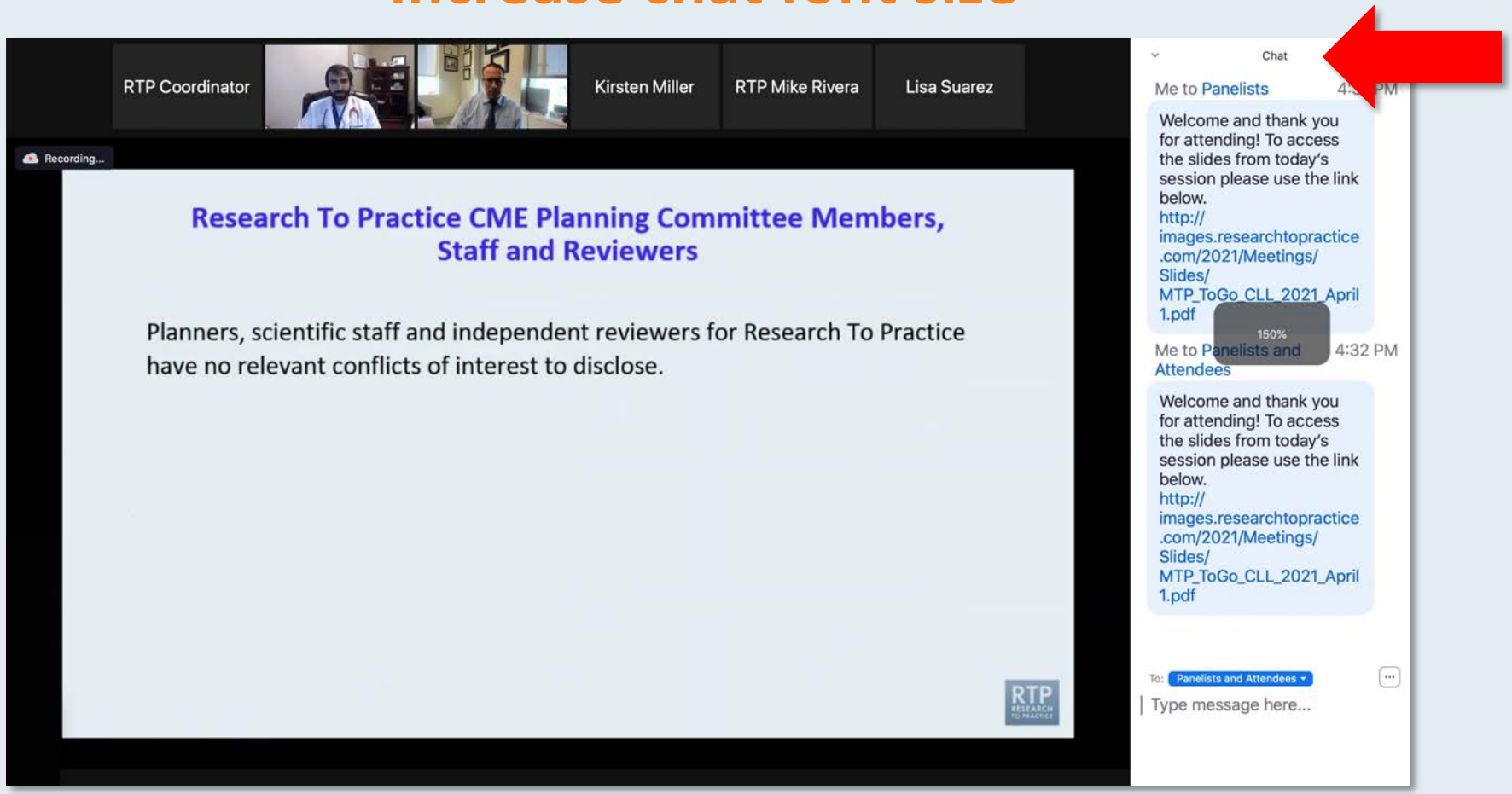

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

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

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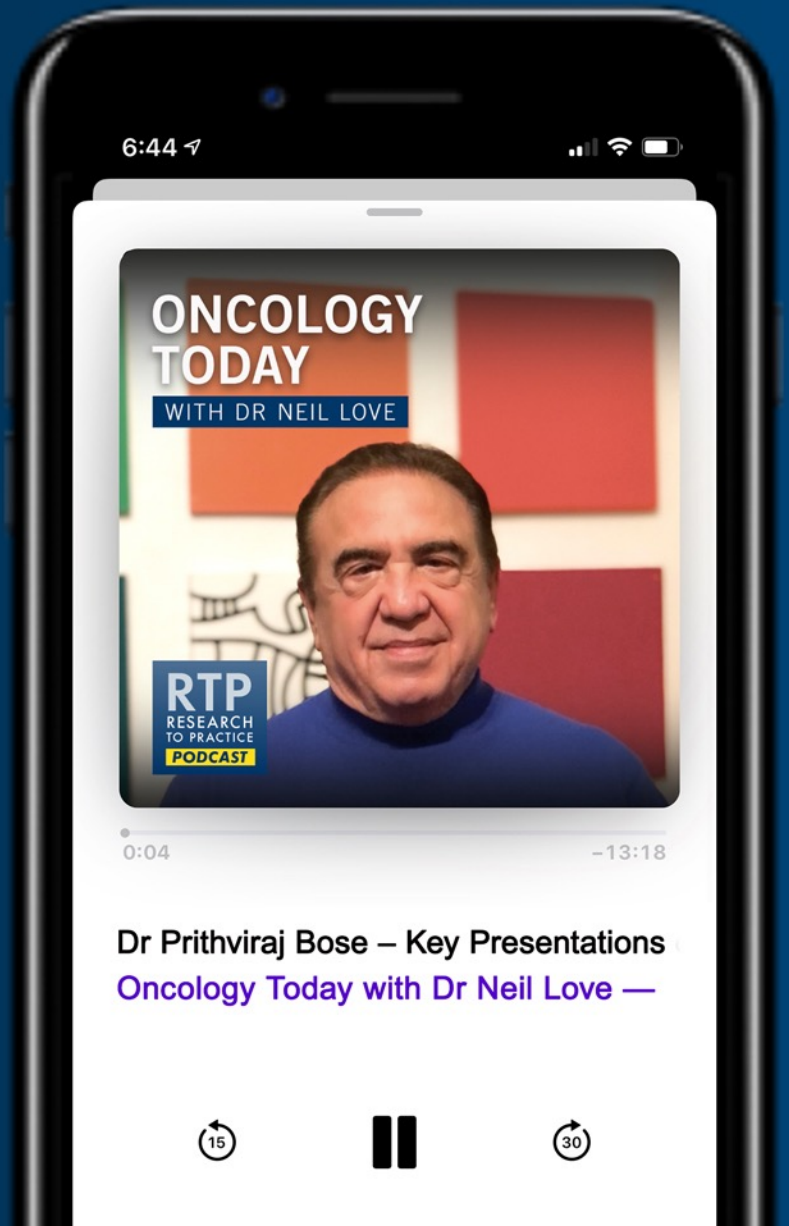

Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Thursday, May 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Harry H Yoon, MD

Moderator

Neil Love, MD

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2022 ASCO Annual Meeting

Acute Myeloid Leukemia and Myelodysplastic Syndromes

Friday, June 3, 2022
11:45 AM – 12:45 PM CT (12:45 PM – 1:45 AM ET)

Faculty
Courtney D DiNardo, MD, MSCE
Michael R Savona, MD
Eunice S Wang, MD

Prostate Cancer

Saturday, June 4, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Andrew J Armstrong, MD, ScM
Alan H Bryce, MD
Alicia K Morgans, MD, MPH

Lung Cancer

Friday, June 3, 2022
6:30 PM – 9:00 PM CT (7:30 PM – 10:00 PM ET)

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Justin F Gainor, MD
Corey J Langer, MD
Luis Paz-Ares, MD, PhD
Heather Wakelee, MD
Jared Weiss, MD
Helena Yu, MD

Gastrointestinal Cancers

Saturday, June 4, 2022
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Faculty
Tanios Bekaii-Saab, MD
Kristen K Ciombor, MD, MSCI
Eileen M O'Reilly, MD
Philip A Philip, MD, PhD, FRCP
John Strickler, MD
Eric Van Cutsem, MD, PhD

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Ovarian Cancer

Sunday, June 5, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty
Antonio González-Martín, MD, PhD
Joyce F Liu, MD, MPH
Kathleen N Moore, MD, MS

Bladder Cancer

Monday, June 6, 2022
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

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Yohann Loriot, MD, PhD
Elizabeth R Plimack, MD, MS
Jonathan E Rosenberg, MD

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Brian T Hill, MD, PhD
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Matthew Lunning, DO
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Elizabeth O'Donnell, MD
Robert Z Orlowski, MD, PhD

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Current and Future Management of Chronic Lymphocytic Leukemia

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Meet The Professor

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

Thursday, June 16, 2022
5:00 PM – 6:00 PM ET

Faculty

Melissa Johnson, MD

Moderator

Neil Love, MD

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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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Professor of Medicine
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
New York, New York

Meet The Professor Program Participating Faculty

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

Srdan 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

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Research To Practice
Miami, Florida

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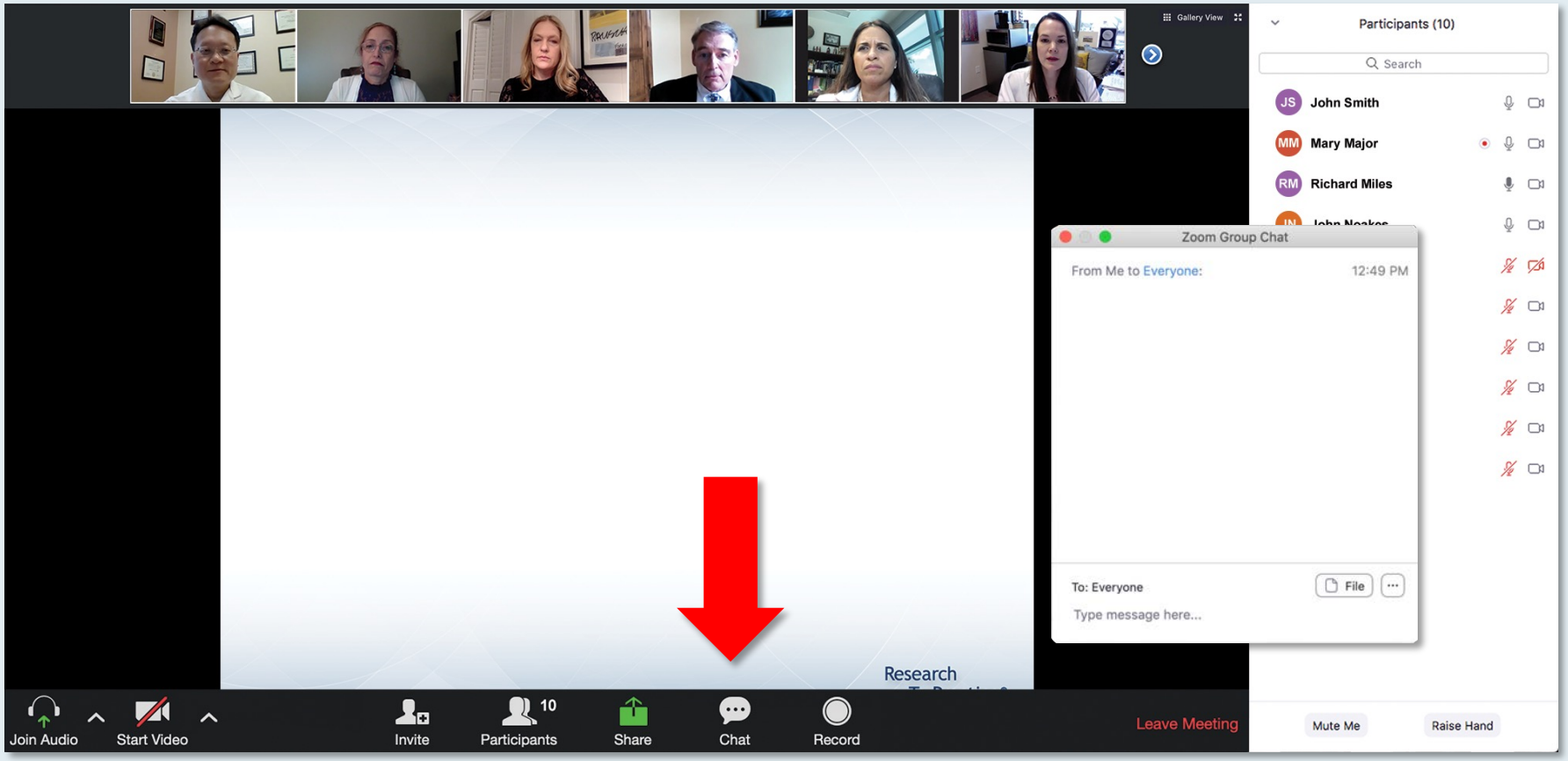

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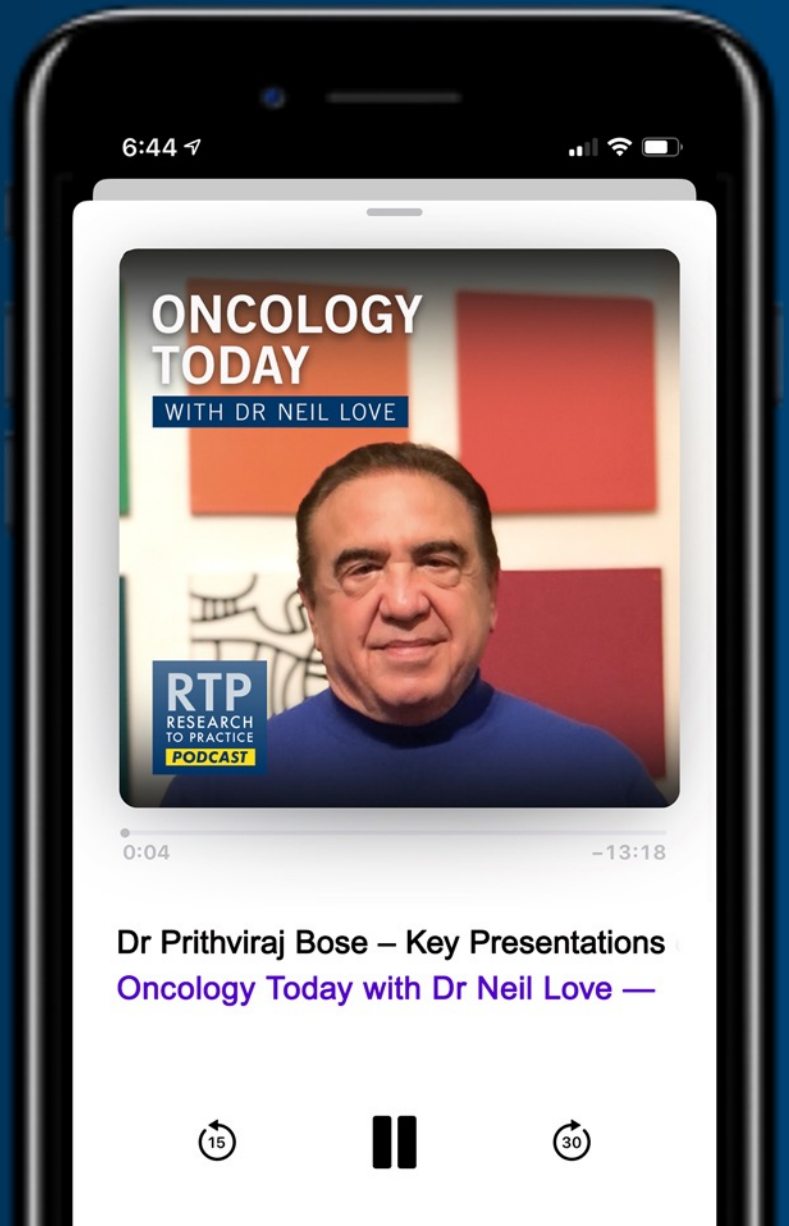

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Data and Safety Monitoring Board/Committee	Galecto

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

Rao Mushtaq, MD
National Jewish Health
Thornton, Colorado

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

Jeanne Palmer, MD
Mayo Clinic in Arizona
Phoenix, Arizona

Paul Markowski, MD
Atlantic Health System
Summit, New Jersey

G Richard Polkinghorn, MD
MaineGeneral Medical Center
Augusta, Maine

Neil Morganstein, MD
Atlantic Health System
Summit, New Jersey

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Meet The Professor with Dr Mascarenhas

Introduction

Module 1: Case Presentations

- Dr Palmer: A 65-year-old man with post-PV MF and ASXL1 and SRSF2 mutations
- Dr Mushtaq: A 70-year-old woman with high-risk primary MF and a CALR mutation
- Dr Bhatnagar: A 76-year-old woman with primary MF with a JAK2 V617F mutation
- Dr Polkinghorn: A 51-year-old woman with secondary MF with a JAK2 mutation
- Dr Brenner: An 85-year-old woman with primary MF and an MPL mutation
- Dr Morganstein: An 86-year-old woman with JAK2 mutation-positive primary MF and ASXL1 and U2F2 mutations with severe anemia
- Dr Markowski: An 84-year-old woman with MF with a JAK2 mutation and severe anemia

Module 2: Faculty Survey

Module 3: Journal Club with Dr Mascarenhas

Module 4: Appendix of Key Publications

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MOMENTUM: Phase 3 Randomized Study of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic and Anemic Myelofibrosis (MF) Patients Previously Treated with a JAK Inhibitor

Mesa RA et al.

ASCO 2022;Abstract 7002.

Session: Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant
June 4, 2022, 9 AM EDT

Rusfertide (PTG-300) Treatment in Phlebotomy-Dependent Polycythemia Vera Patients

Hoffman R et al.

ASCO 2022;Abstract 7003.

Session: Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant
June 4, 2022, 9 AM EDT

Cells 2021;10(5):1034.

cells

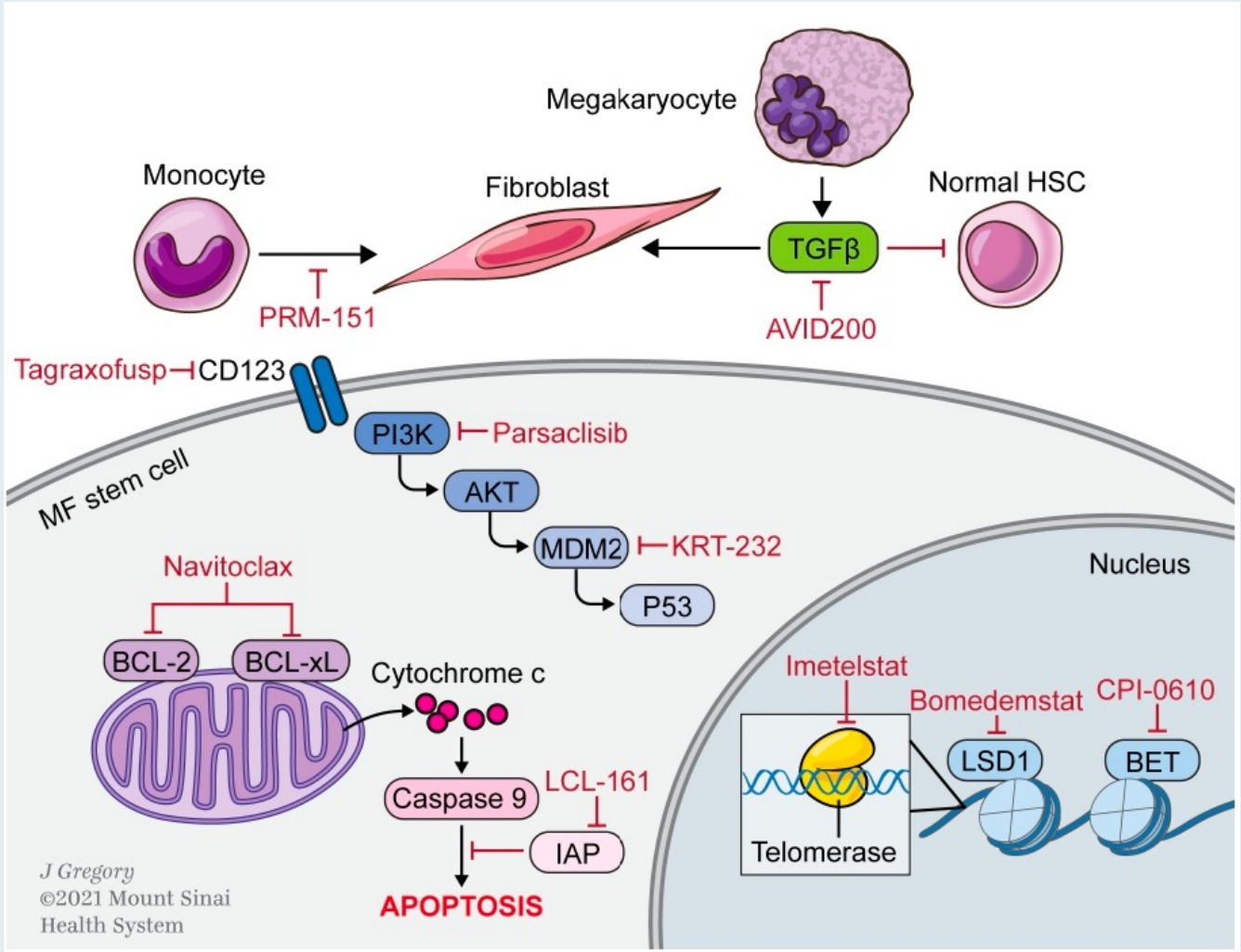
MDPI

Review

Next Generation Therapeutics for the Treatment of Myelofibrosis

Douglas Tremblay and John Mascarenhas *

Targets of Novel Therapeutics in Myelofibrosis for Agents in Clinical Development



Tremblay D, Mascarenhas J. *Cells* 2021;10(5):1034.

Hematol Oncol Clin North Am 2021;35(2):353-73.

Current Clinical Investigations in Myelofibrosis

Sangeetha Venugopal, MD[a,b], John Mascarenhas, MD[c,d,*]

Hematology Oncology Clinics of North America 2021
Volume 35, Issue 2
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Case Presentation: A 65-year-old man with post-PV MF and ASXL1 and SRSF2 mutations

Dr Jeanne Palmer (Phoenix, Arizona)

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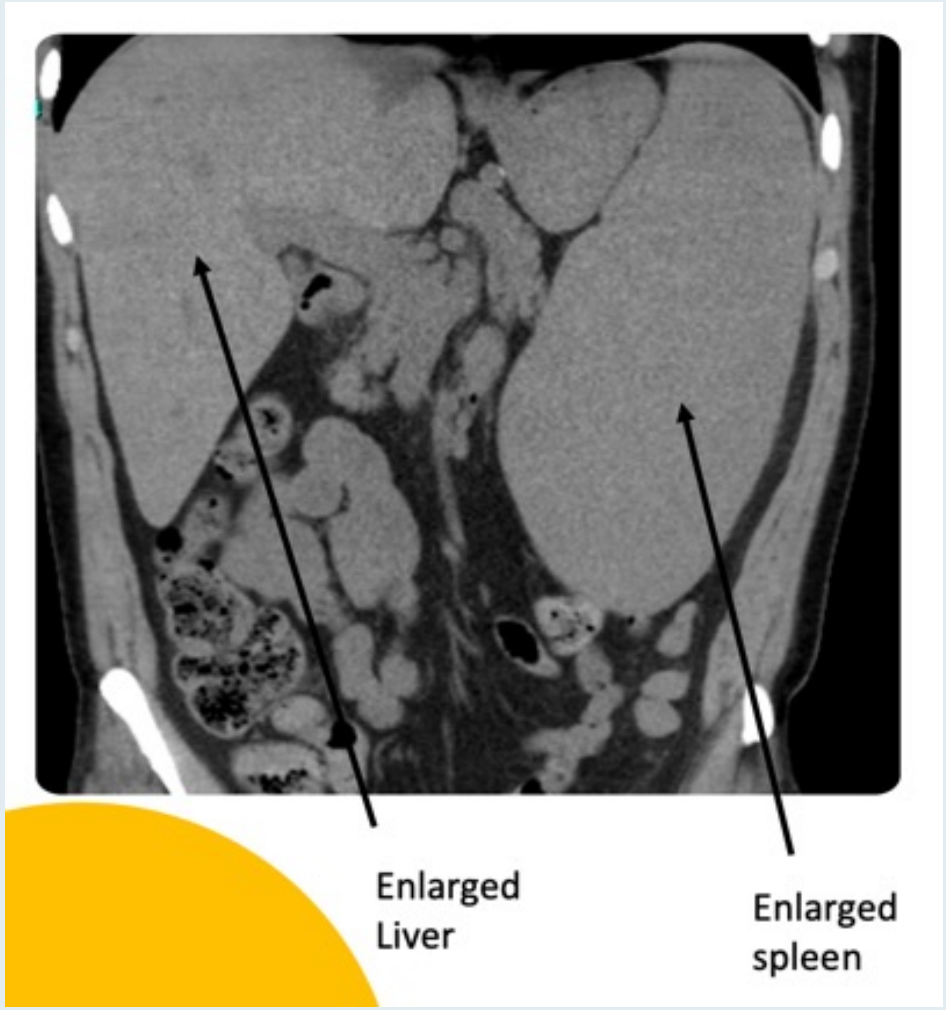
Case Presentation: A 65-year-old man with post-PV MF and ASXL1 and SRSF2 mutations

Dr Jeanne Palmer



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Case Presentation: A 70-year-old woman with high-risk primary MF and a CALR mutation

Dr Rao Mushtaq (Thornton, Colorado)

Case Presentation: A 70-year-old woman with high-risk primary MF and a CALR mutation (continued)

Dr Rao Mushtaq (Thornton, Colorado)

Cancer 2022;[Online ahead of print].

Review Article

The clinical dilemma of JAK inhibitor failure in myelofibrosis: Predictive characteristics and outcomes

John O. Mascarenhas, MD [1]; and Srdan Verstovsek, MD, PhD[2]

Review Article

Thrombocytopenia in Patients With Myelofibrosis: Pathogenesis, Prevalence, Prognostic Impact, and Treatment

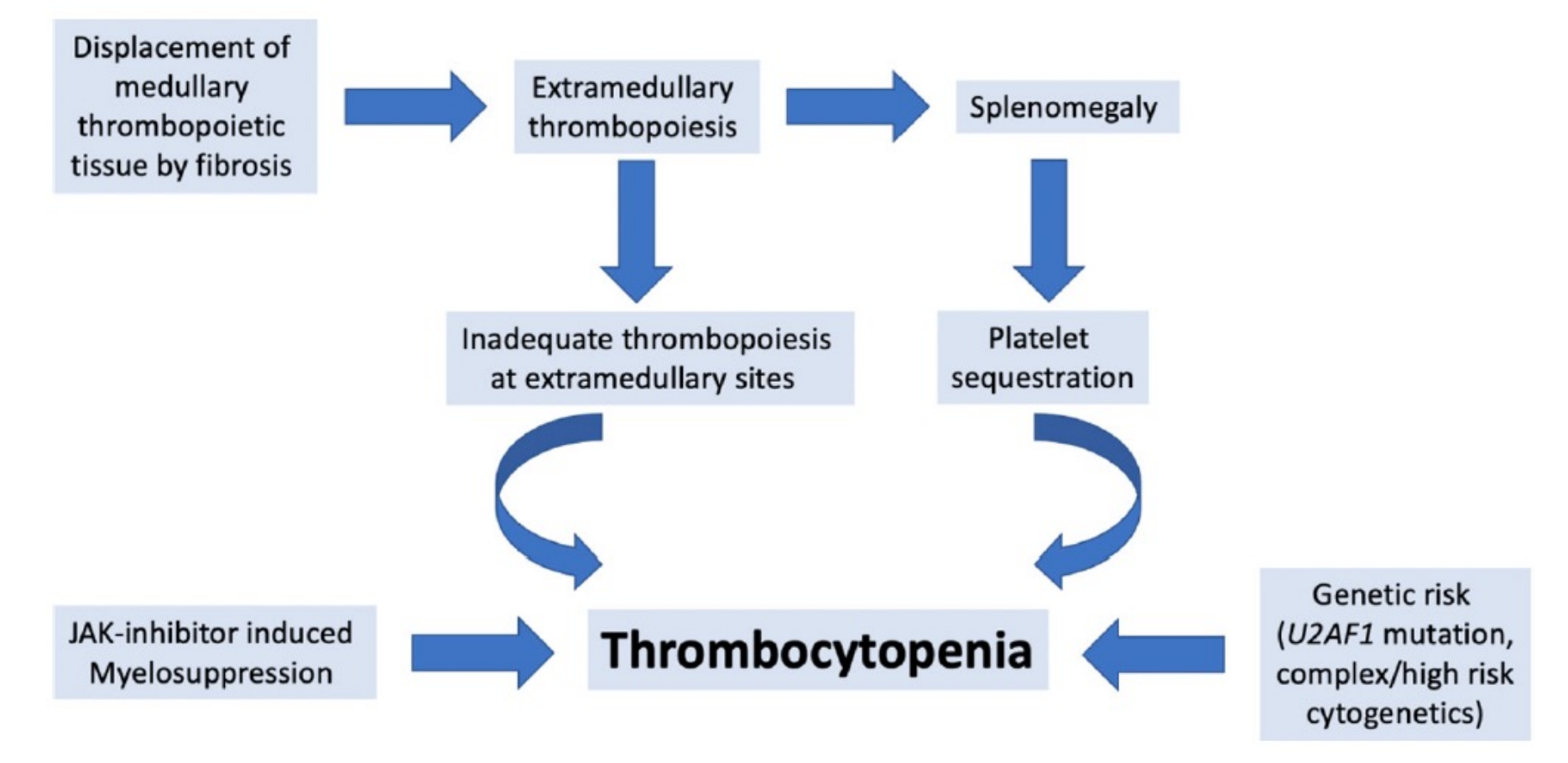
Dahniel Sastow,[1] John Mascarenhas,[2] Douglas Tremblay[2]

Clin Lymphoma Myeloma Leuk 2022;[Online ahead of print].

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

Multifactorial Pathogenesis of Thrombocytopenia in Myelofibrosis

(Patients with MF presenting with thrombocytopenia may have variable contributions of all or some of the following mechanisms)



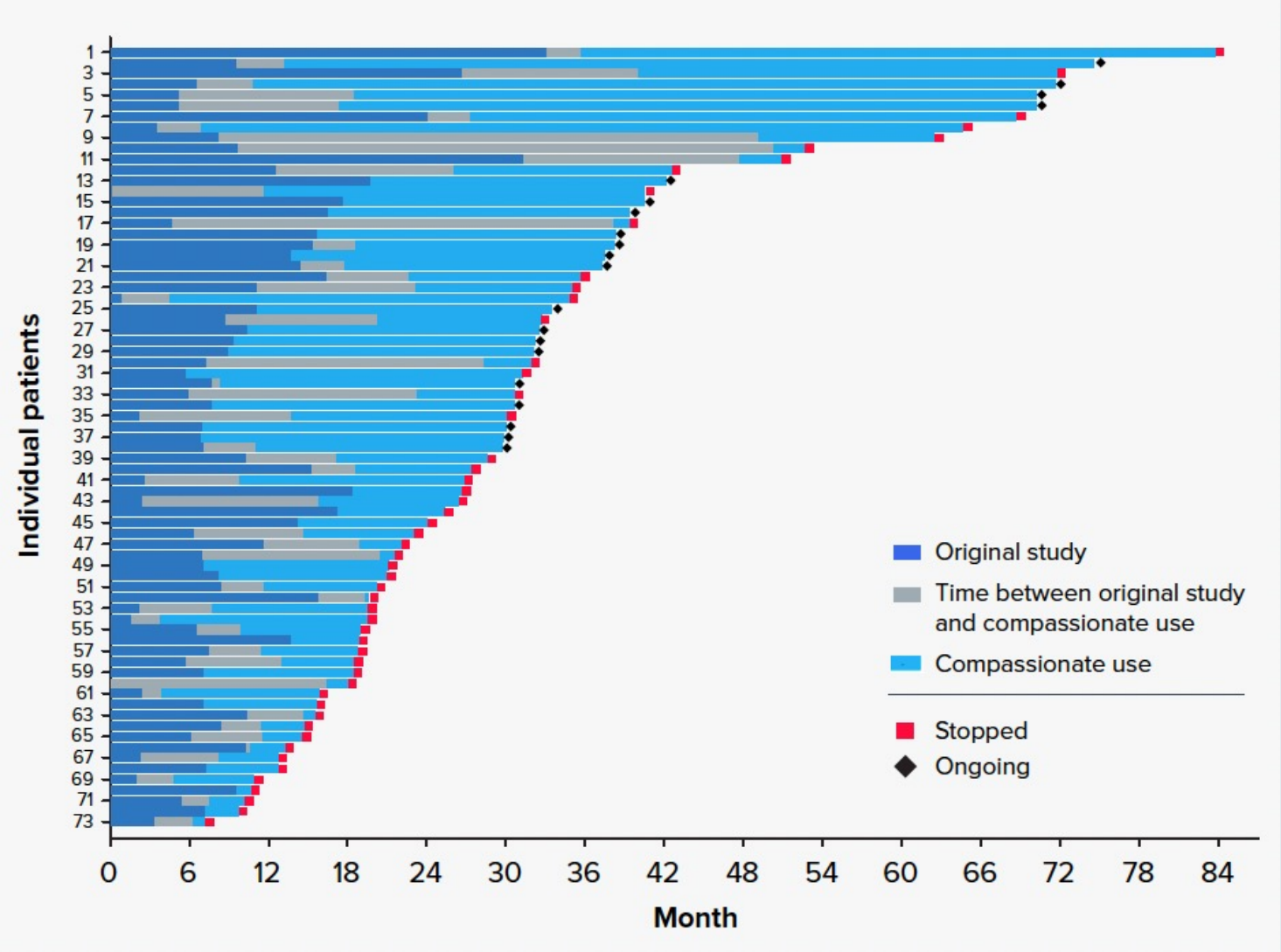
Sastow D et al. *Clin Lymphoma Myeloma Leuk* 2022;[Online ahead of print].

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

Harrison CN et al.

ASH 2021;Abstract 3649.

Time on Pacritinib in Compassionate Use Population



Harrison CN et al. ASH 2021;Abstract 3649.

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American Society *of* Hematology

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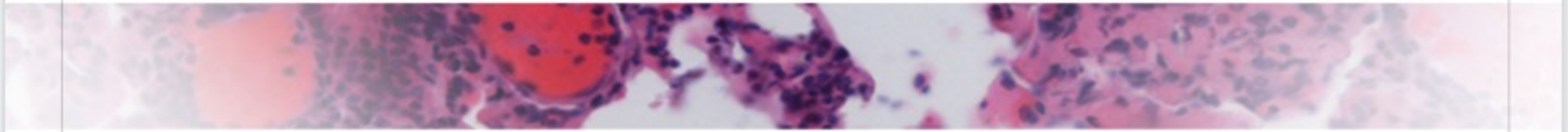


Retrospective Head-to-Head Comparison Between Pacritinib and Ruxolitinib in Patients With Myelofibrosis and Moderate-to-Severe Thrombocytopenia

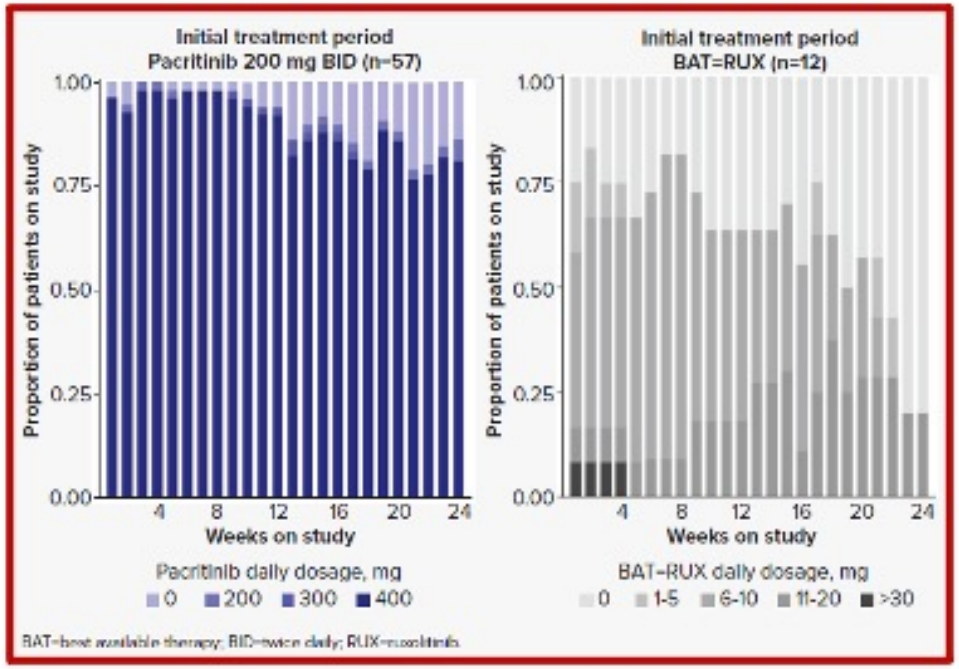
Session 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Poster III

Dec 13, 2021, #3639

Mascarenhas J et al. ASH 2021;Abstract 3639.

Results

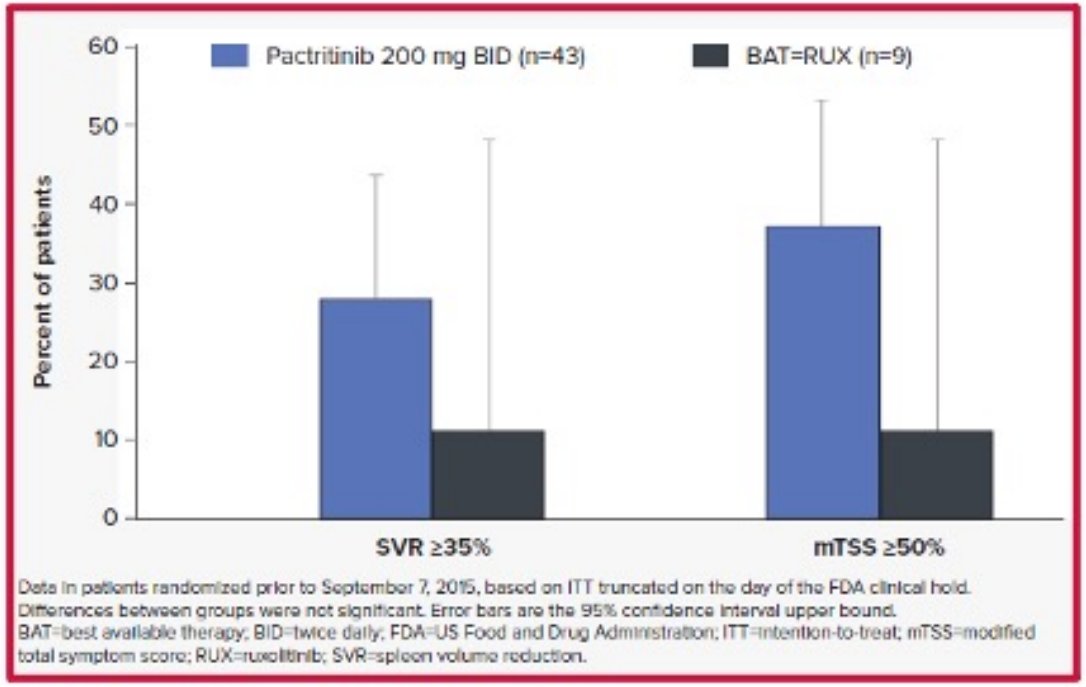
- The majority of patients treated with pacritinib were able to maintain full doses over time at weeks 12 and 24
  - (median dose = 400 mg/day)
- By contrast, patients on ruxolitinib received:
  - a median starting dose of 10 mg (interquartile range [IQR] 10-10 mg) daily at baseline
  - 10 mg (IQR, 0-10 mg) daily at week 12
  - 10 mg (IQR, 0-20 mg) daily at week 24



Mascarenhas J et al. ASH 2021;Abstract 3639.

Results

- Patients treated with pacritinib had numerically higher rates of SVR (28% vs 11%) and mTSS response (37% vs 11%) compared with patients treated with ruxolitinib.

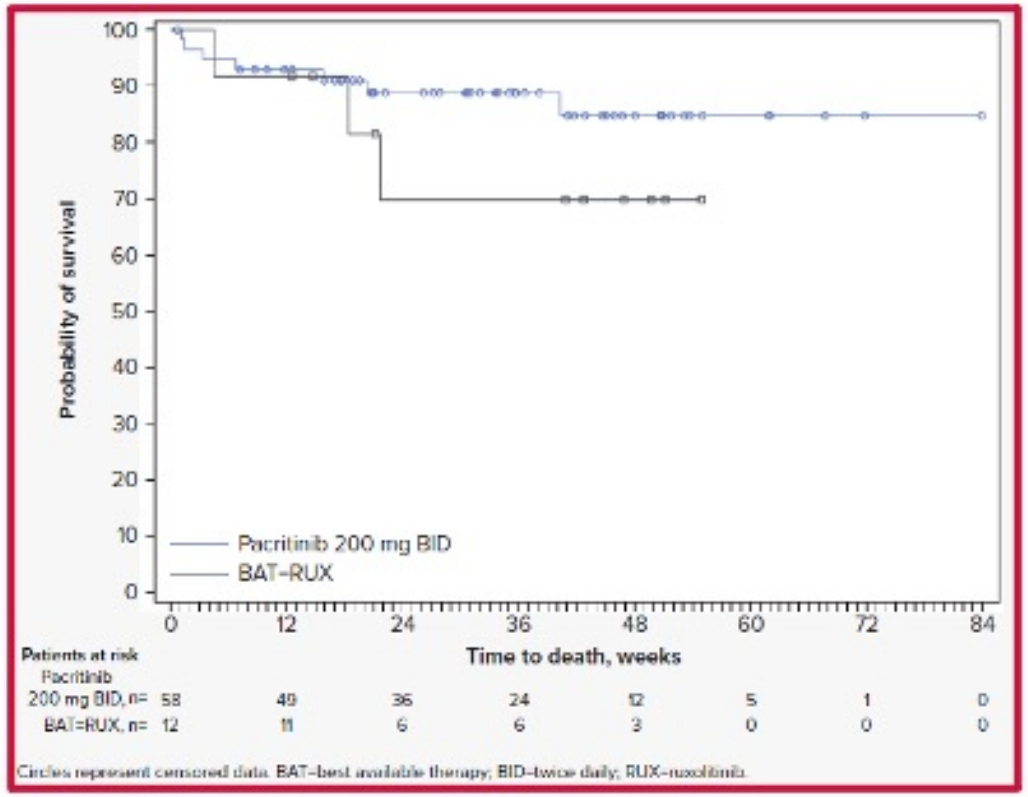


Data in patients randomized prior to September 7, 2015, based on ITT truncated on the day of the FDA clinical hold. Differences between groups were not significant. Error bars are the 95% confidence interval upper bound.
BAT=best available therapy; BID=twice daily; FDA=US Food and Drug Administration; ITT=intention-to-treat; mTSS=modified total symptom score; RUX=ruxolitinib; SVR=spleen volume reduction.

Mascarenhas J et al. ASH 2021;Abstract 3639.

Results

- The hazard ratio for overall survival for pacritinib versus ruxolitinib was 0.49 (95% confidence interval, 0.13-1.92).
  - There was no diminution of treatment effect observed for SVR, TSS, or survival after adjusting for baseline Dynamic International Prognostic Scoring System high risk, platelet count, and primary versus secondary MF.



Mascarenhas J et al. ASH 2021;Abstract 3639.

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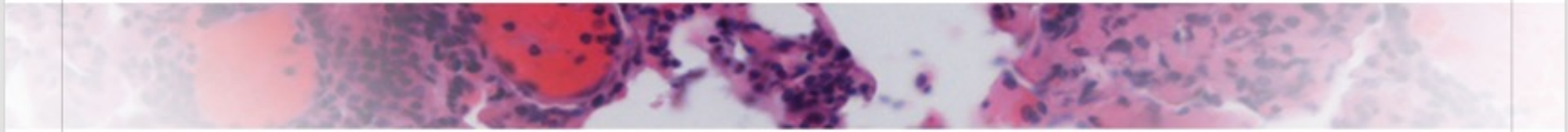


Safety Analysis of Pacritinib in Patients With Myelofibrosis and Severe Thrombocytopenia

Mascarenhas J et al.

Session 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Poster III

Dec 13, 2021, #3640

Conclusion

- In this analysis of patients with cytopenic MF, including those who have severe thrombocytopenia, the safety profile of pacritinib 200 mg BID was comparable to BAT, which included supportive care and watch and wait.
- This analysis suggests that pacritinib 200 mg BID may represent the first fully dosed therapeutic option for patients with cytopenic MF, including severe thrombocytopenia.

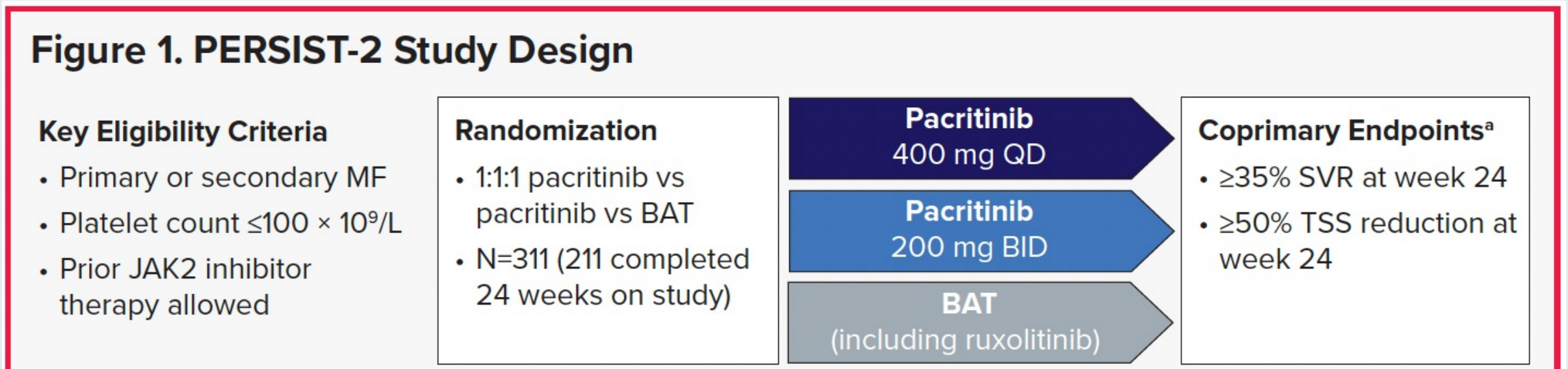
Mascarenhas J et al. ASH 2021;Abstract 3639.

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.

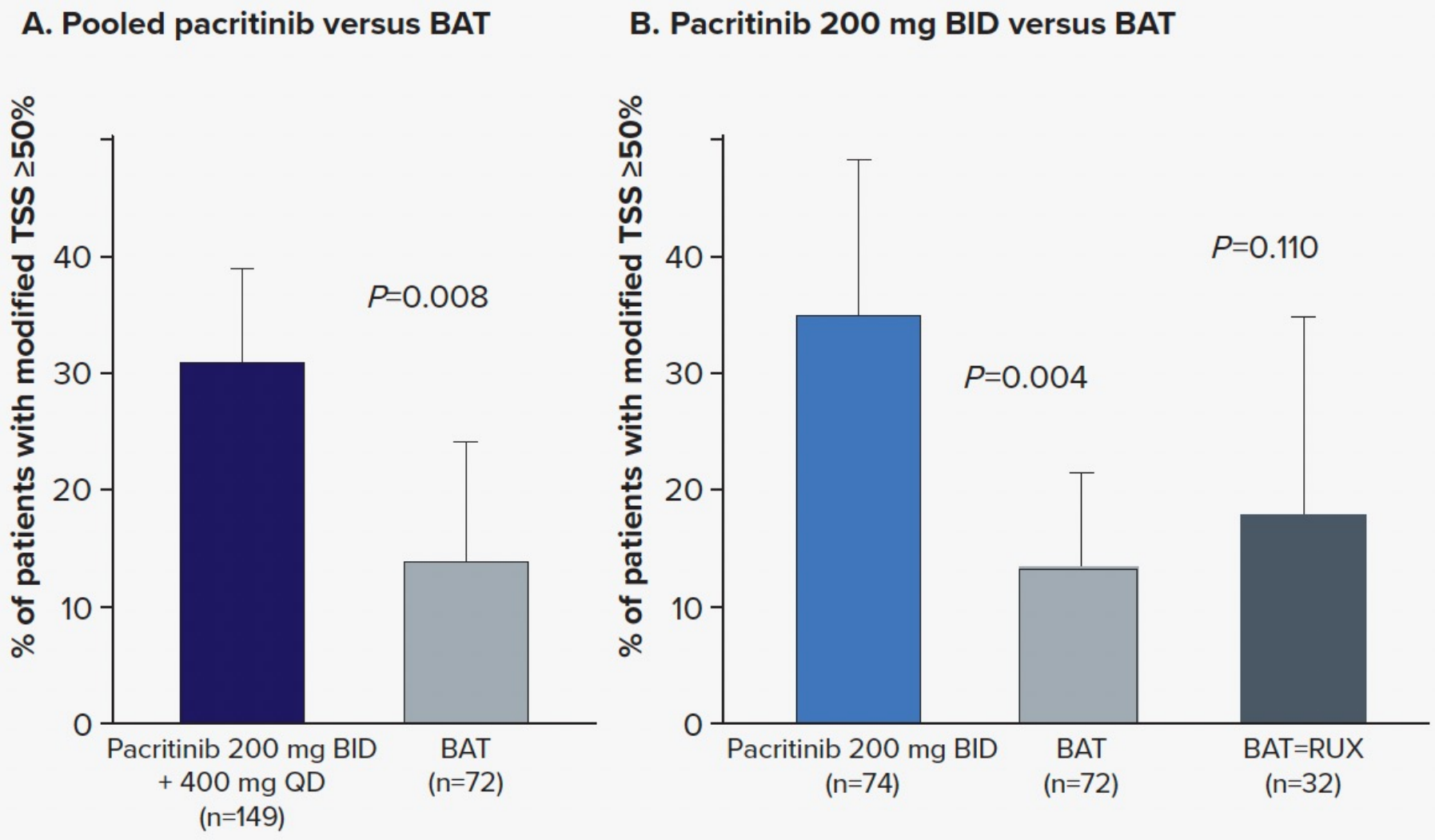
Figure 1. PERSIST-2 Study Design



[a]The primary analysis compared pooled pacritinib (400 mg QD and 200 mg BID) versus BAT. BAT=best available therapy; BID=twice daily; MF=myelofibrosis; QD=once daily; SVR=spleen volume response; TSS=total symptom score.

Palmer JM et al. ASH 2021;Abstract 3628.

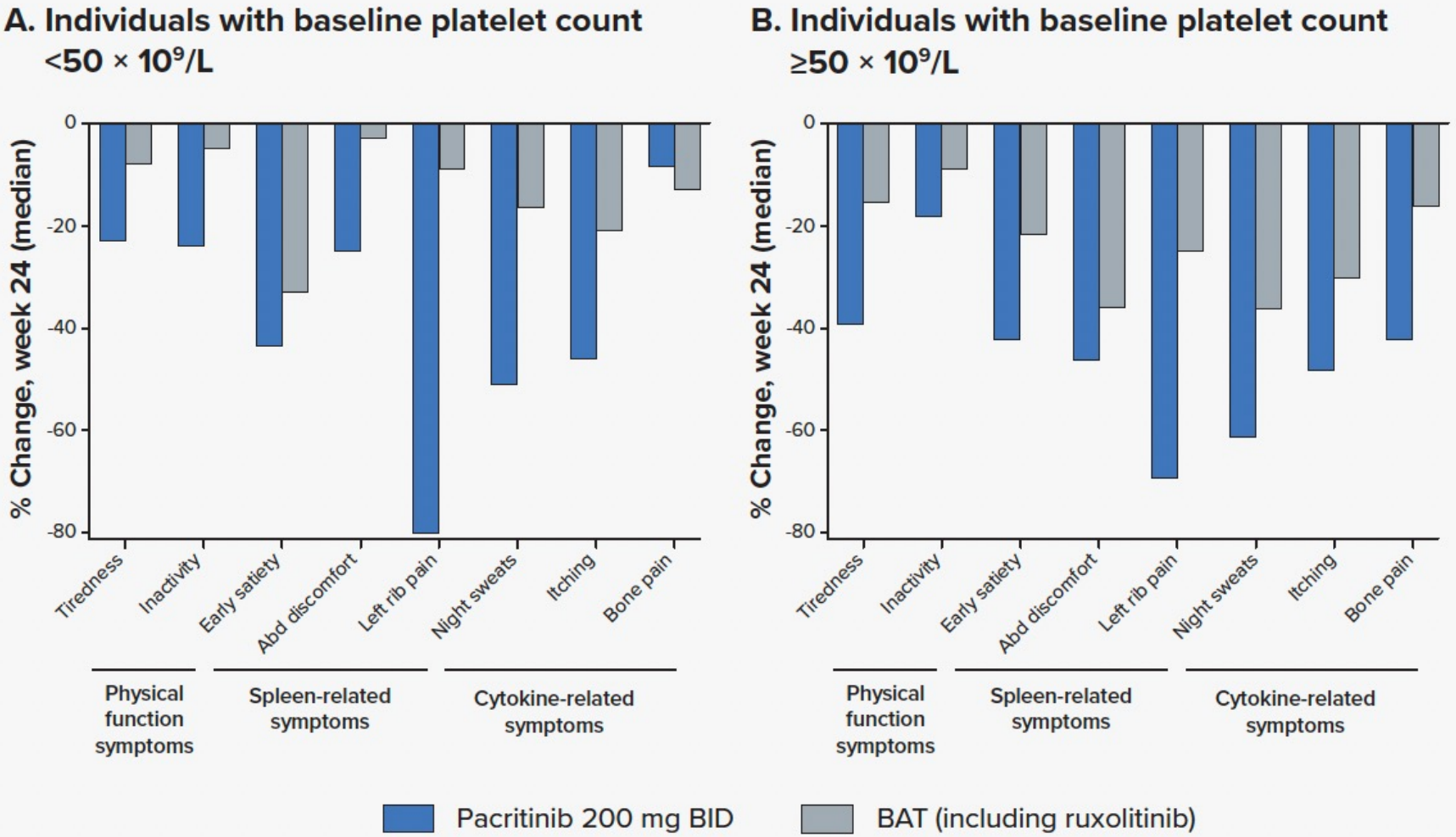
Figure 2. Modified TSS Response Rates (Week 24)



BAT=best available therapy; BID=twice daily; QD=once daily; RUX=ruxolitinib; TSS=total symptom score.

Palmer JM et al. ASH 2021;Abstract 3628.

Figure 3. Percent Change in Individual Symptom Scores



BAT=best available therapy; BID=twice daily.

Palmer JM et al. ASH 2021;Abstract 3628.

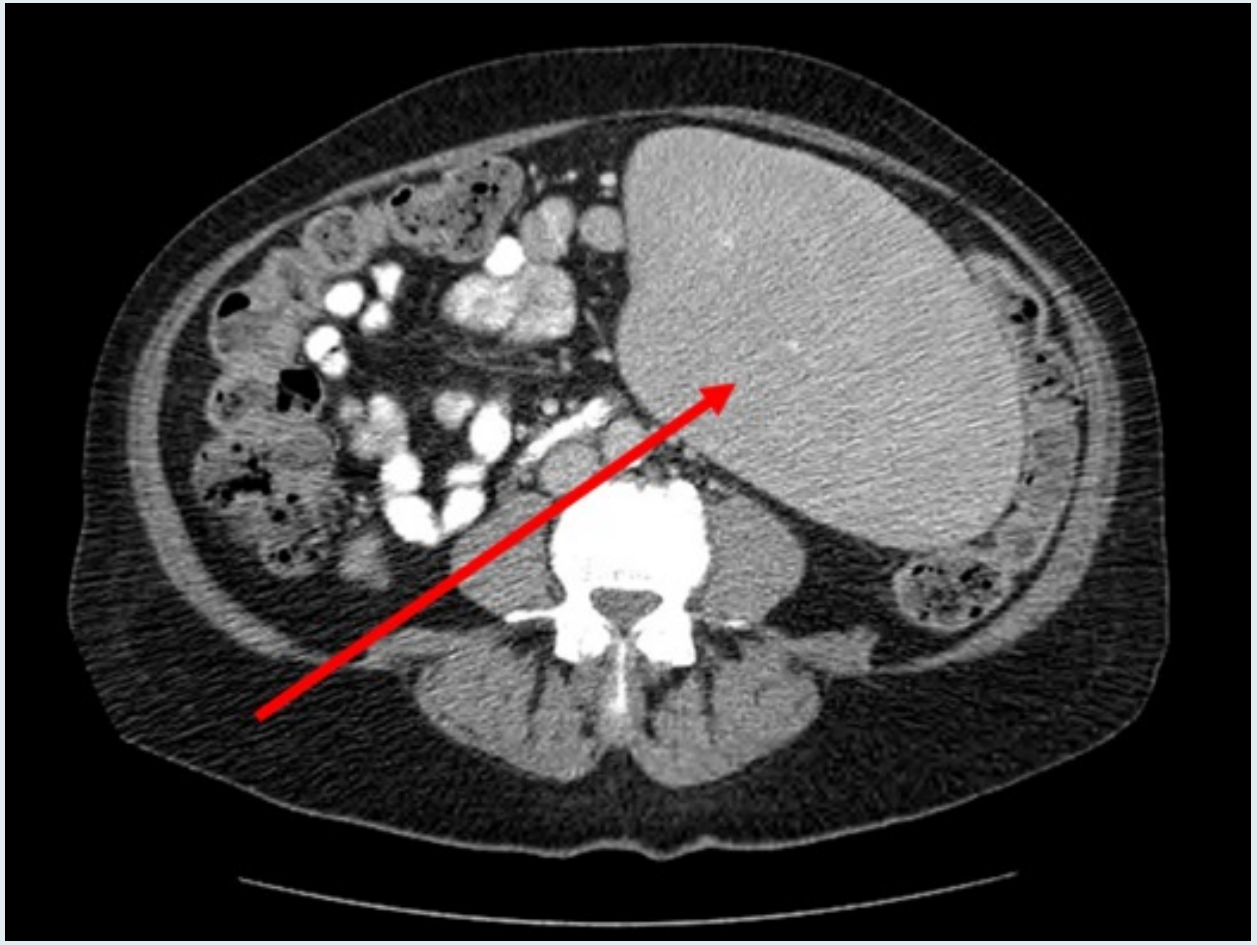
Case Presentation: A 76-year-old woman with primary MF with a JAK2 V617F mutation

Dr Tina Bhatnagar (Wheeling, West Virginia)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 76-year-old woman with primary MF with a JAK2 V617F mutation

Dr Tina Bhatnagar



RTP
RESEARCH
TO PRACTICE

Case Presentation: A 51-year-old woman with secondary MF with a JAK2 mutation

Dr Richard Polkinghorn (Augusta, Maine)

RTP
RESEARCH
TO PRACTICE

ASH 2021;Abstract 3059

Real-World Utilization of Fedratinib for Myelofibrosis Post-Ruxolitinib: Patient Characteristics, Treatment Patterns, and Characterization of Ruxolitinib Failure

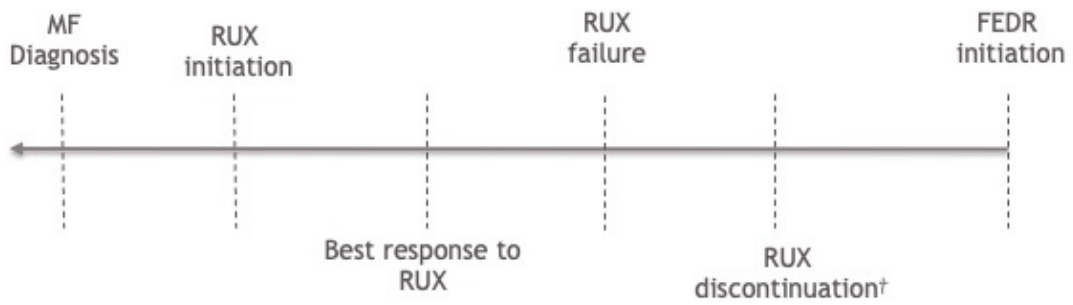
Claire Harrison,[1] John Mascarenhas,[2] Pranav Abraham,[3] Arianna Kee,[3] Jose A. Nadal,[3] Alexandrina Balanean,[4] Ali McBride,[3] Jonathan K. Kish,[4] Djibril Liassou,[4] Bruce A. Feinberg,[4] Aaron T. Gerds[5]

[1]Guy's and St Thomas' NHS Foundation Trust, London, UK; [2]The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Bristol Myers Squibb, Princeton, NJ, USA; [4]Cardinal Health Specialty Solutions, Dublin, OH, USA; [5]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

Presentation 3059

Study Period

Figure 2. Time points during the patient journey for data abstraction

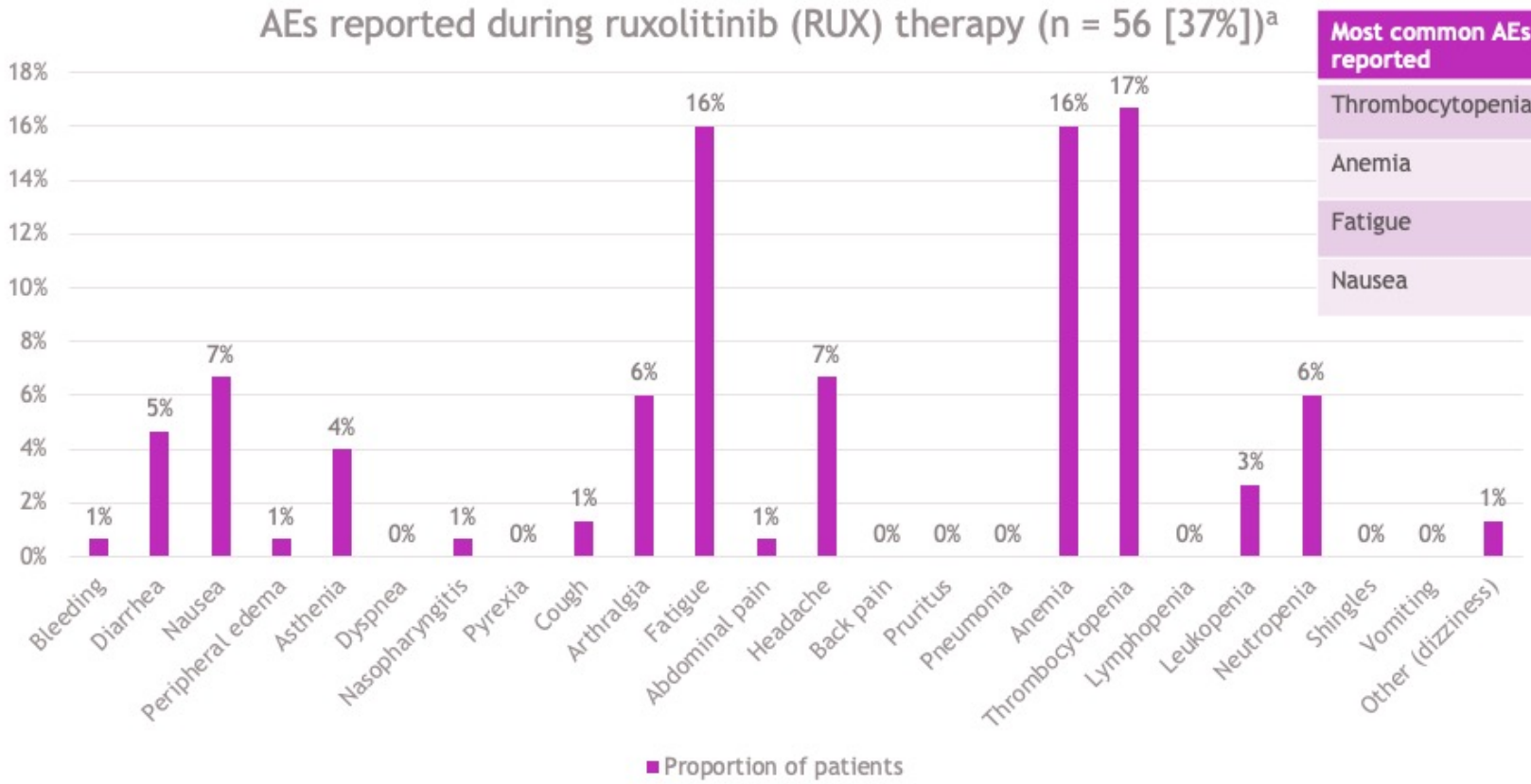


- Data were captured only at certain time points during RUX treatment prior to FEDR initiation
  - Physicians identified the time of best response and failure on RUX
- Spleen, blood counts, and MF-related symptoms were charted at each visit as shown during RUX treatment and at initiation of FEDR

Harrison C et al. ASH 2021;Abstract 3059.

AEs During RUX Therapy

Figure 4. AEs reported during RUX therapy, overall and most common



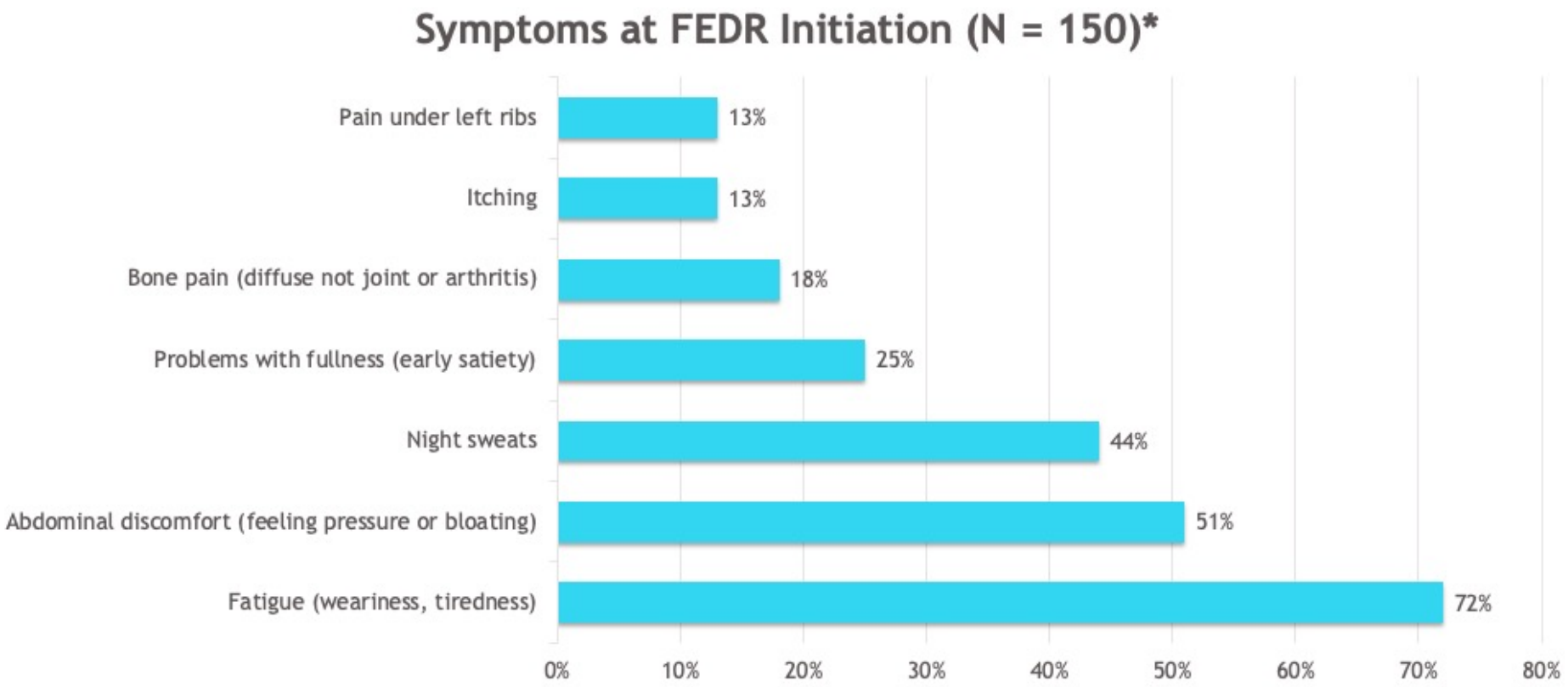
Most common AEs reported	Number reported	Grade ≥ 3
Thrombocytopenia	25	4
Anemia	24	3
Fatigue	24	1
Nausea	10	1

aTotals include reported AEs that led to dosage reduction, treatment interruption, or diagnosis of intolerance to RUX; not mutually exclusive and do not include AEs previously reported as part of dosage modifications.

Harrison C et al. ASH 2021;Abstract 3059.

Symptoms at Initiation of FEDR

Figure 5. Symptoms reported at initiation of FEDR therapy



*Not mutually exclusive.
International Prognostic Scoring System (IPSS), Dynamic IPSS (DIPSS), DIPSS Plus, Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM), Mutation-Enhanced IPSS (MIPSS 70), Mutation-Enhanced IPSS (MIPSS) 70+ v2.

Harrison C et al. ASH 2021;Abstract 3059.

Clin Lymphoma Myeloma Leuk 2022;[Online ahead of print].

Editorial

Douglas Tremblay
Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY
Lara Cavalli
Oumar Sy
Shelonitda Rose
Bristol Myers Squibb, Princeton, NJ
John Mascarenhas
Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY

The Effect of Fedratinib, A Selective Inhibitor of Janus Kinase 2, on Weight and Metabolic Parameters in Patients with Intermediate- or High-risk Myelofibrosis

Onco Targets Ther 2021;14:4509-21.

OncoTargets and Therapy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Clinical Utility of Fedratinib in Myelofibrosis

Julian A Waksal, Douglas Tremblay, John Mascarenhas

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

Dr Warren Brenner (Boca Raton, Florida)

Case Presentation: An 86-year-old woman with JAK2 mutation-positive primary MF and ASXL1 and U2F2 mutations with severe anemia

Dr Neil Morganstein (Summit, New Jersey)

Case Presentation: An 84-year-old woman with MF with a JAK2 mutation and severe anemia

Dr Paul Markowski (Summit, New Jersey)

Leukemia

Leukemia 2021;35(12):3361-3.

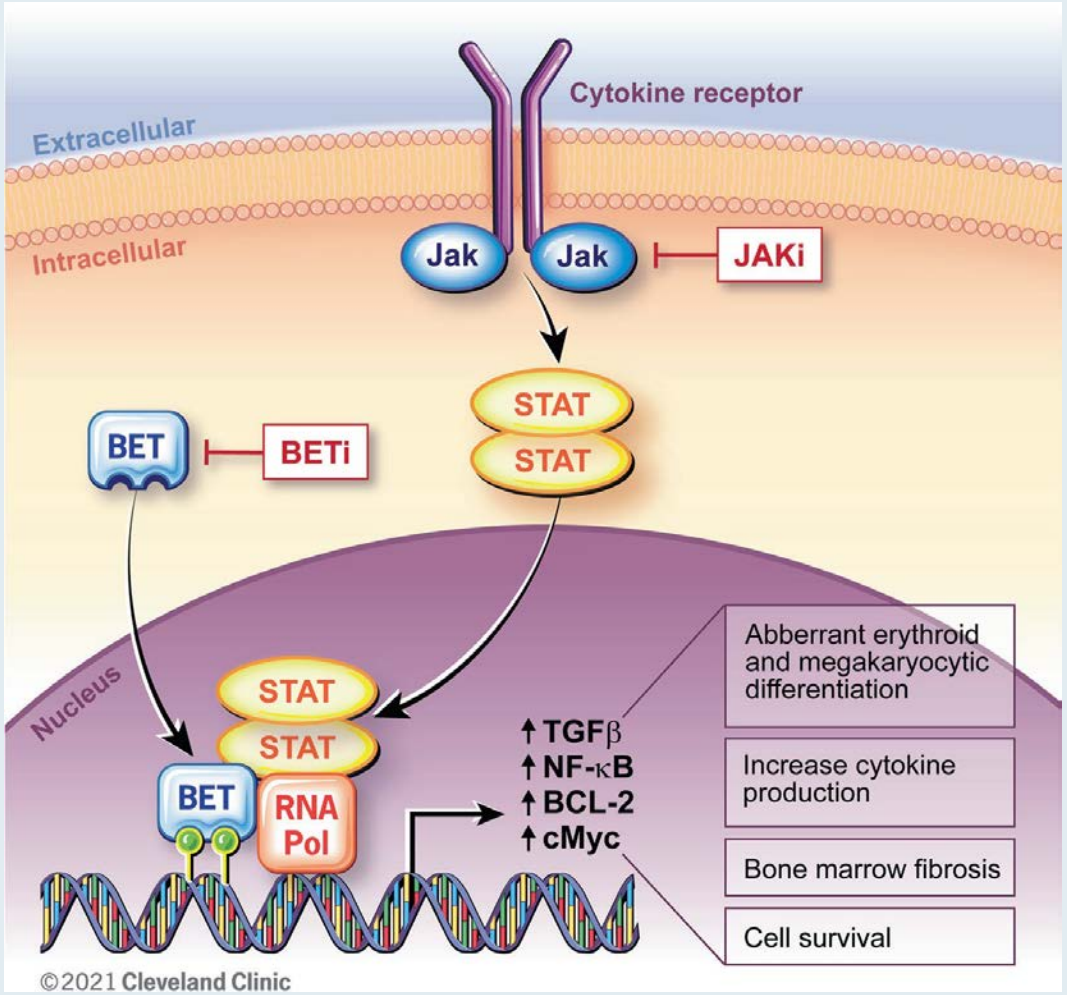
www.nature.com/leu

PERSPECTIVE OPEN

Paradigm shift: combination BET and JAK inhibition in myelofibrosis

John Mascarenhas[1]✉, Aaron Gerds[2] and Srdan Verstovsek[3]

Inhibitors Targeting JAK2 and BET Proteins Cooperate to Downregulate NFκB Activity and Expression of Target Genes That Contribute to the Underlying Pathologic Features of Myelofibrosis



Mascarenhas J et al. *Leukemia* 2021;35(12):3361-3.

Meet The Professor with Dr Mascarenhas

Introduction

Module 1: Case Presentations

- Dr Palmer: A 65-year-old man with post-PV MF and ASXL1 and SRSF2 mutations
- Dr Mushtaq: A 70-year-old woman with high-risk primary MF and a CALR mutation
- Dr Bhatnagar: A 76-year-old woman with primary MF with a JAK2 V617F mutation
- Dr Polkinghorn: A 51-year-old woman with secondary MF with a JAK2 mutation
- Dr Brenner: An 85-year-old woman with primary MF and an MPL mutation
- Dr Morganstein: An 86-year-old woman with JAK2 mutation-positive primary MF and ASXL1 and U2F2 mutations with severe anemia
- Dr Markowski: An 84-year-old woman with MF with a JAK2 mutation and severe anemia

Module 2: Faculty Survey

Module 3: Journal Club with Dr Mascarenhas

Module 4: Appendix of Key Publications

RTP RESEARCH TO PRACTICE

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

 Dr Bhatnagar	DIPSS	 Dr Mascarenhas	DIPSS
 Dr Gerds	MIPSS70	 Dr Stein	MIPSS70 plus version 2.0
 Prof Harrison	Multiple tools, but don't tend to use GIPSS	 Dr Verstovsek	DIPSS

RTP RESEARCH TO PRACTICE

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/µL, which treatment would you generally recommend (assuming the patient is not a transplant candidate)?

 Dr Bhatnagar	Pacritinib	 Dr Mascarenhas	Pacritinib
 Dr Gerds	Pacritinib	 Dr Stein	Pacritinib
 Prof Harrison	Ruxolitinib or pacritinib	 Dr Verstovsek	Pacritinib

RTP RESEARCH TO PRACTICE

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

 Dr Bhatnagar	10 mg BID	 Dr Mascarenhas	10 mg BID
 Dr Gerds	20 mg BID	 Dr Stein	15 mg BID
 Prof Harrison	10 mg BID	 Dr Verstovsek	15 mg BID

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

 Dr Bhatnagar	25 mg BID	 Dr Mascarenhas	25 mg BID
 Dr Gerds	20 mg BID	 Dr Stein	20 mg BID
 Prof Harrison	25 mg BID	 Dr Verstovsek	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/µL)?

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

BMT = bone marrow transplant

RTP RESEARCH TO PRACTICE

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 Mascarenhas	Taper over a week unless patient on 5 mg BID and then would taper over 2 days
 Dr Gerds	Taper by reducing dose by 50% x 1 week, then stop	 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

RTP RESEARCH TO PRACTICE

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 Mascarenhas	About the same
 Dr Gerds	Ruxolitinib response is more rapid	 Dr Stein	Ruxolitinib response is more rapid
 Prof Harrison	About the same	 Dr Verstovsek	About the same

Meet The Professor with Dr Mascarenhas

Introduction

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RTP
RESEARCH
TO PRACTICE

Leuk Lymphoma 2021;2:1-14.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.2010068

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REVIEW

Novel therapeutics and targets in myelofibrosis

Julian A. Waksal[a], Claire N. Harrison[b] and John O. Mascarenhas[a]

Blood Adv 2021;5(23):5086-97.

REGULAR ARTICLE

blood advances

PD-1 inhibition in advanced myeloproliferative neoplasms

Gabriela Hobbs,[1,*] Cansu Cimen Bozkus,[2,*] Erin Moshier,[2] Mikaela Dougherty,[2] Michal Bar-Natan,[2] Lonette Sandy,[2] Kathryn Johnson,[2] Julia Elise Foster,[1] Tina Som,[1] Molly Macrae,[1] Hetal Marble,[1] Mohamed Salama,[3] Siraj M. El Jamal,[4] Nicole Zubizarreta,[2] Martha Wadleigh,[5] Richard Stone,[5] Nina Bhardwaj,[2] Camelia Iancu-Rubin,[2,4,†] and John Mascarenhas[2,†]

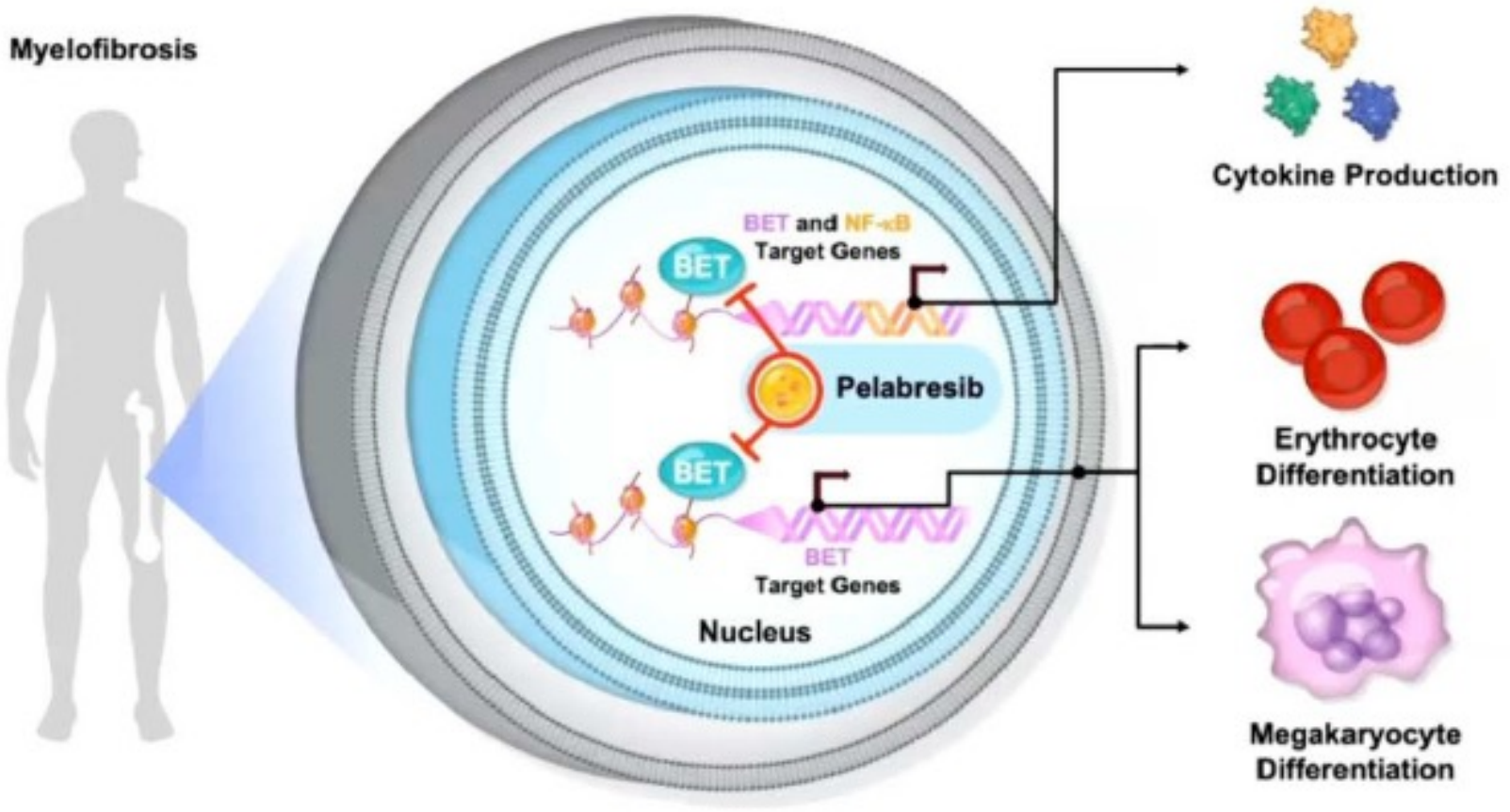
ASH 2021;Abstract 141

Pelabresib (CPI-0610) Monotherapy in Patients with Myelofibrosis – Update of Clinical and Translational Data from the Ongoing MANIFEST Trial

Marina Kremyanskaya, MD, PhD[1], John Mascarenhas, MD[1], Francesca Palandri, MD,PhD[2], Alessandro Vannucchi, MD[3], Srdan Verstovsek[4], Claire Harrison, MD, FRCPath[5], Prithviraj Bose, MD , Gary J. Schiller, MD[7], Raajit Rampal, MD, PhD[8], Mark W. Drummond,PhD, FRCPath[9], Vikas Gupta, MD, FRCP, FRCPath[10], Andrea Patriarca, MD[11], Nikki Granacher, MD[12], Joseph Scandura, MD, PhD[13], Witold Prejzner, MD, PhD[14], Lino L.Teichmann[15], Natalia Curto-Garcia, MD[16], Ronald Hoffman, MD[17], Gozde Colak, PhD[18], Zheng Ren[18], Suresh Bobba, MD[19], Jike Cui, PhD[19], Sergey Efuni, MD[19], and Moshe Talpaz, MD[20]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [2]IRCCSAzienda Ospedaliero-Universitaria S. Orsola-Malpighi, BOLOGNA, Italy; [3]Az. Ospedaliero-Universitaria Careggi, Firenze, Italy; [4]The University of Texas MD Anderson Cancer Center,Houston, TX; [5]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [6]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston,TX; [7]David Geffen School of Medicine, UCLA, Los Angeles; [8]Memorial Sloan KetteringCancer Center, New York, NY; [9]Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom; [10]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [11]Azienda Ospedaliero Universitaria Maggiore della Carità di Novara SCDU Ematologia,Novara, Italy; [12]Ziekenhuis Netwerk Antwerpen, Antwerp, Belgium; [13]Richard T. Silver, M.D. Myeloproliferative Neoplasms (MPN) Center, Weill Cornell Medicine, New York, NY; [14]Department of Hematology and Transplantology, Medical University of Gdansk, Gdansk,Poland; [15]Universitätsklinikum Bonn, Bonn, DEU; [16]Department of Haematology, Guy's andSt Thomas' NHS Foundation Trust, London, United Kingdom; [17]Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, NewYork, NY; [18, 19]Constellation Pharmaceuticals a MorphoSys Company, Cambridge, MA; [20]Department ofInternal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI

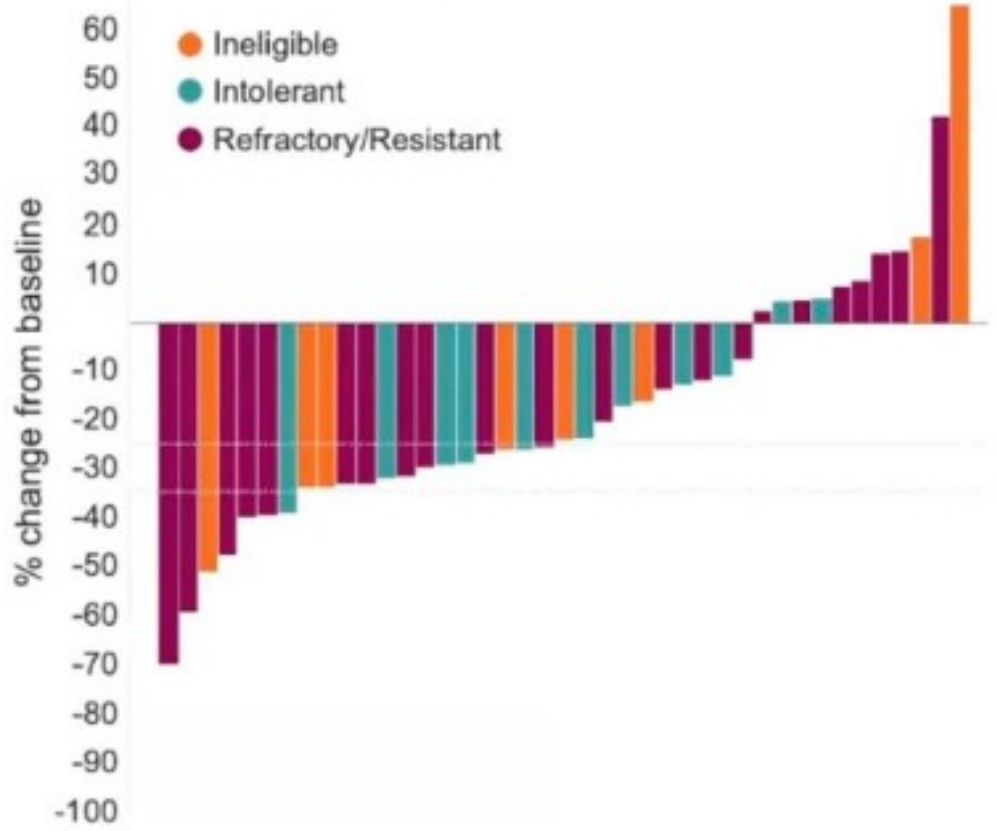
Pelabresib, an investigational oral small molecule inhibitor of BD1 and BD2 of BET proteins[1]



[1]Albrecht et al. *J Med Chem*. 2016;59:1330−1339

Kremyanskaya M et al. ASH 2021;Abstract 141.

Pelabresib in myelofibrosis, MANIFEST Arm 1: Spleen volume percent change at week 24



Arm 1B Non-TD cohort primary endpoint:
SVR35 at week 24
18% (7/38)

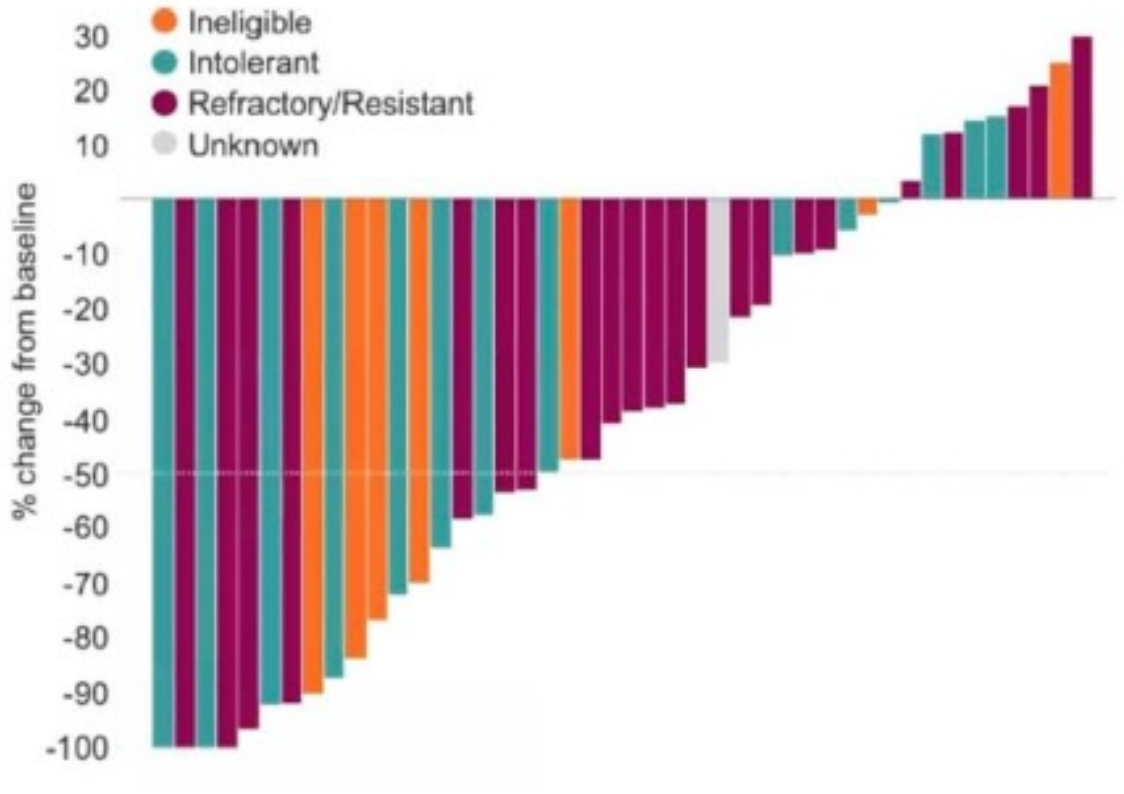
	Arm 1 (TD and Non-TD) N=64
SVR35	11% (7/64)
SVR25	31% (20/64)
Median spleen volume % change	-24%
Mean spleen volume % change	-17%

SVR: Spleen volume reduction per local radiology review; SVR25: ≥25% reduction in spleen volume from baseline; SVR35: ≥35% reduction in spleen volume from baseline
Patients evaluable if non-missing baseline and week 24 spleen assessment or discontinued at any time without wk 24 spleen assessment
22 patients non-evaluable: 4 pts due to missing baseline and 18 ongoing pts without wk 24 assessment. 23 pts discontinued without having wk 24 assessment included as non-responders
Patients evaluable for SVR at wk 24: JAKi ineligible (n=10); JAKi intolerant (n=15); JAKi refractory/resistant (n=38); 1 patient with unknown subgroup

Data cut-off 10 Sep 21 ASH 2021 Abstract 141 Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority 11

Kremyanskaya M et al. ASH 2021;Abstract 141.

Pelabresib in myelofibrosis, MANIFEST Arm 1
TSS percent change at week 24



	Arm 1 (TD and Non-TD) N=64
TSS50	28% (18/64)
Median TSS % change	-40%
Mean TSS % change	-40%

TSS: Total Symptom Score; TSS50: ≥50% reduction in total symptom score from baseline
Patients evaluable if non-missing baseline and week 24 TSS assessment or discontinued at any time without wk 24 TSS assessment
22 patients non-evaluable: 7 pts due to missing baseline and 15 ongoing pts did not reach wk 24 as of data cut-off. 20 patients discontinued without wk 24 assessment are included as non-responders
Patients evaluable for TSS at wk 24: JAKi ineligible (n=8); JAKi intolerant (n=18); JAKi refractory/resistant (n=37); UNK: 1 patient with unknown subgroup

Data cut-off 10 Sep 21 ASH 2021 Abstract 141 Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority 12

Kremyanskaya M et al. ASH 2021;Abstract 141.

Pelabresib in myelofibrosis, MANIFEST Arm 1: Conclusions

Pelabresib monotherapy in advanced myelofibrosis patients evaluated to date that are refractory/resistant, ineligible or intolerant to JAKi treatment:

- Clinical activity observed based on preliminary results of spleen volume reduction, symptom reduction, hemoglobin benefit and warrants further investigation
- Exploratory analysis showed bone marrow fibrosis improvement in a subset of patients and plasma cytokines involved in myelofibrosis pathogenesis were reduced during treatment with pelabresib
- Majority of the most common treatment-emergent adverse events were low grade
- Additional clinical and translational updates from MANIFEST Arm 3 (JAKi naïve 1st line MF pts) and Arm 2 (2nd line MF pts with suboptimal response to rux) are presented at Poster # 2568
- MANIFEST-2, a Phase 3 randomized double-blind trial of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAKi naïve MF patient population, has been initiated and is open for enrollment (NCT04603495; https://www.manifestclinicaltrials.com)

Kremyanskaya M et al. ASH 2021;Abstract 141.

Annals of Hematology (2022) 101:139–146
https://doi.org/10.1007/s00277-021-04683-w

ORIGINAL ARTICLE

Favorable overall survival with imetelstat in relapsed/refractory myelofibrosis patients compared with real-world data

Andrew T. Kuykendall[1] · Libo Sun[2] · John Mascarenhas[3] · Jean-Jacques Kiladjian[4] · Alessandro M. Vannucchi[5] · Julia Wang[6] · Qi Xia[6] · Eugene Zhu[6] · Faye Feller[2] · Aleksandra Rizo[2] · Jacqueline Bussolari[6] · Ying Wan[2] · Rami Komrokji[1]

2021

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Trial in Progress
Abstract #1503

IMpactMF

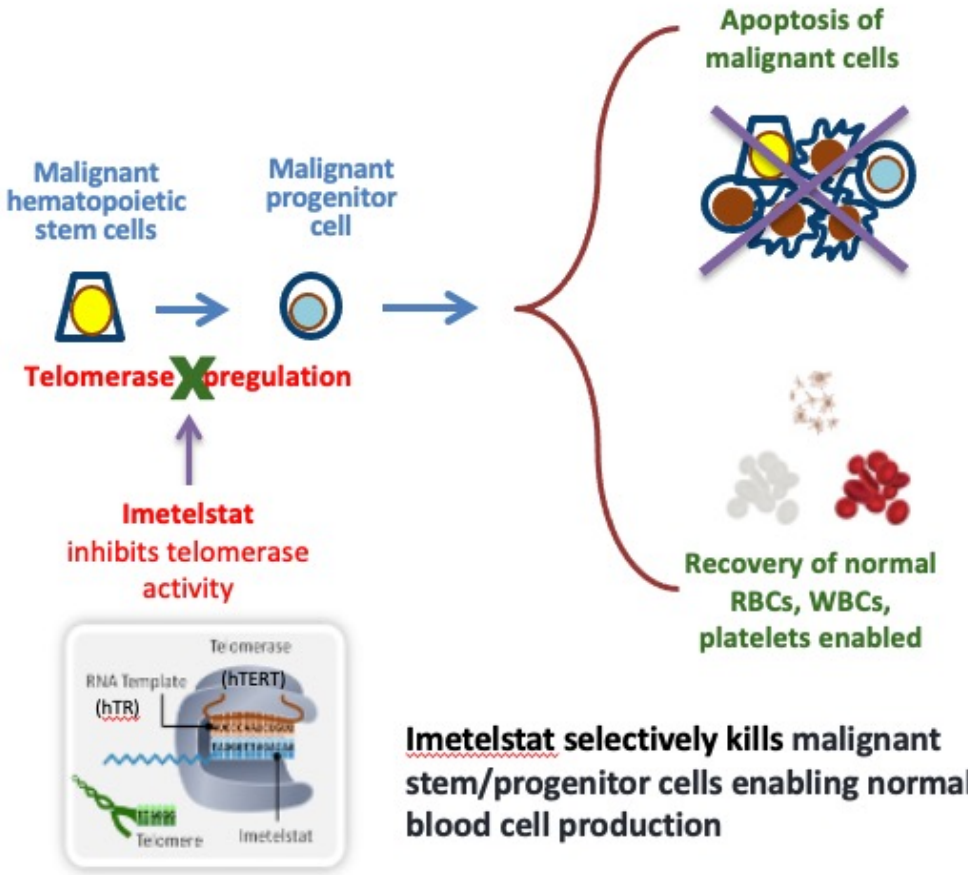
A Randomized Open Label, Phase 3 Study to Evaluate Imetelstat Versus Best Available Therapy (BAT) in Patients with Intermediate-2 or High- risk Myelofibrosis (MF) Refractory to Janus Kinase Inhibitor (JAKi)

John Mascarenhas[1]; Claire N. Harrison[2]; Jean-Jacques Kiladjian[3]; Rami S. Komrokji[4]; Steffen Koschmieder[5]; Alessandro M. Vannucchi[6]; Tymara Berry[7], Laurie Sherman[7]; Souria Dougherty[7]; Libo Sun[7]; Fei Huang[7]; Ying Wan[7]; Faye M. Feller[7]; Aleksandra Rizo[7]; Srdan Verstovsek[8]

[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, United States; [2]Guy's and St Thomas' Hospital, London, United Kingdom; [3]Hôpital Saint-Louis, Université Paris, Paris, France; [4]H Lee Moffitt Cancer Center, Tampa, FL, United States; [5]Faculty of Medicine, RWTH Aachen University, Aachen, Germany; [6]AOU Careggi, University of Florence, Florence, Italy; [7]Geron Corporation, Parsippany, NJ, United States; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, United States

JC JOURNAL CLUB
RTP RESEARCH TO PRACTICE

Imetelstat: First-in-Class Telomerase Inhibitor with Disease-Modifying Potential



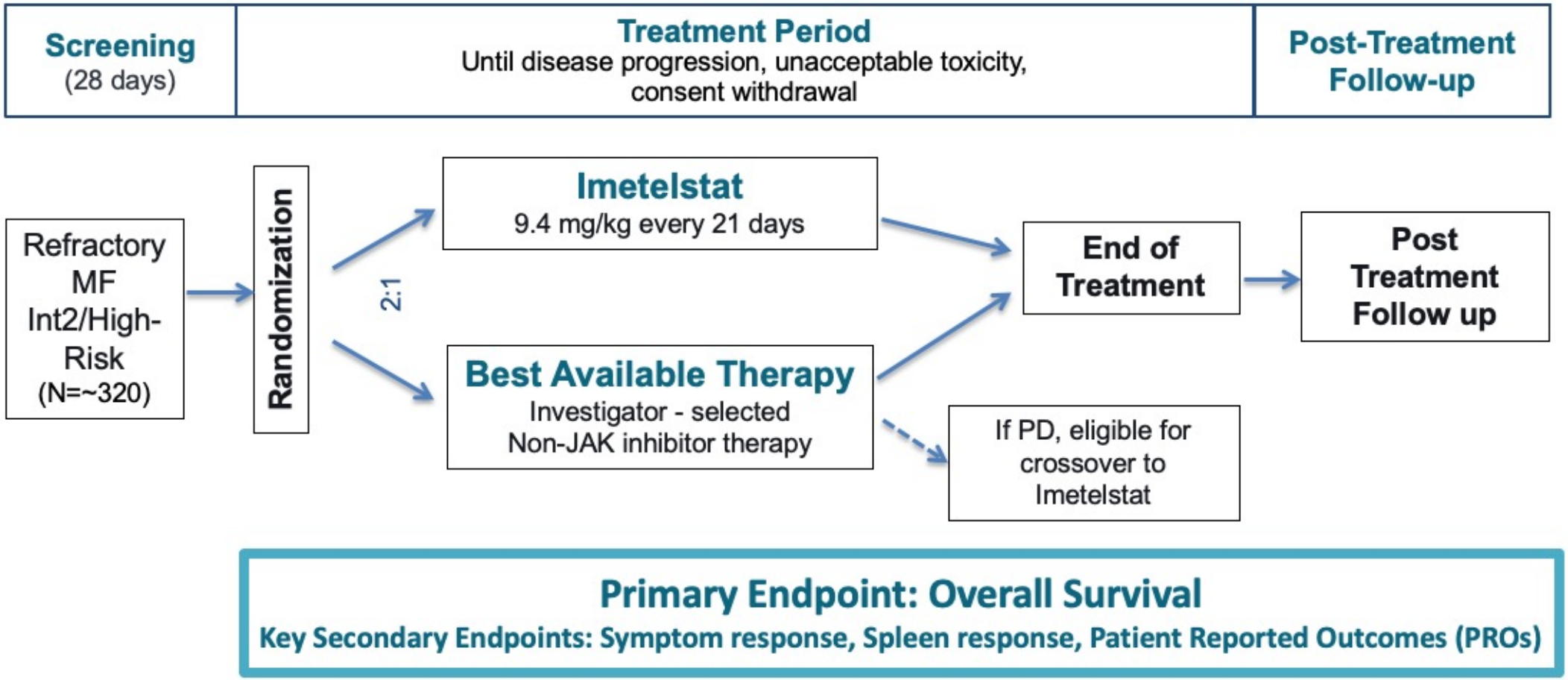
Imetelstat selectively kills malignant stem/progenitor cells enabling normal blood cell production

- Imetelstat is a 13-mer lipid-conjugated oligonucleotide that specifically targets the RNA template of human telomerase and is a potent, first-in-class competitive inhibitor of telomerase enzymatic activity.[1,2]
- Imetelstat has shown meaningful clinical improvement in symptom response and improved OS in IMbark, a Phase 2 study in patients with intermediate-2 or high-risk MF who have relapsed after or are refractory to JAK inhibitors.[3,4,5]
- Imetelstat demonstrated disease-modifying activity by targeting malignant clones, improvement in bone marrow fibrosis and overall survival.[5,6]

1. Asai A, et al, Cancer Res 2003; 63(14):3931–3939.
2. Herbert BS, et al, Oncogene 2005; 24(33):5262–5268.
3. Mascarenhas et al; Blood. 2018;132:68.5.
4. Kuykendall et al; EHA 2019 #PS1456
5. Mascarenhas et al; JCO 2021; 39(26):2881-2892
6. Mascarenhas et al; ASH 2020 #346

Mascarenhas J et al. ASH 2021;Abstract 1503.

Phase 3 Study Design



American Society of Hematology

Mascarenhas J et al. ASH 2021;Abstract 1503.

original reports

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

John Mascarenhas, MD[1]; Rami S. Komrokji, MD[2]; Francesca Palandri, MD[3]; Bruno Martino, MD[4]; Dietger Niederwieser, MD, PhD[5]; Andreas Reiter, MD[6]; Bart L. Scott, MD[7]; Maria R. Baer, MD[8]; Ronald Hoffman, MD[1]; Olatoyosi Odenike, MD[9]; Alessandro M. Vannucchi, MD[10]; Jacqueline Bussolari, PhD[11]; Eugene Zhu, PhD[11]; Esther Rose, MD[11]; Laurie Sherman, BSN[12]; Souria Dougherty, BS, MBA[12]; Libo Sun, PhD[12]; Fei Huang, PhD[12]; Ying Wan, PhD[12]; Faye M. Feller, MD[12]; Aleksandra Rizo, MD, PhD[12]; and Jean-Jacques Kiladjian, MD, PhD[13]

J Clin Oncol 2021;39(26):2881-92.

JCI insight

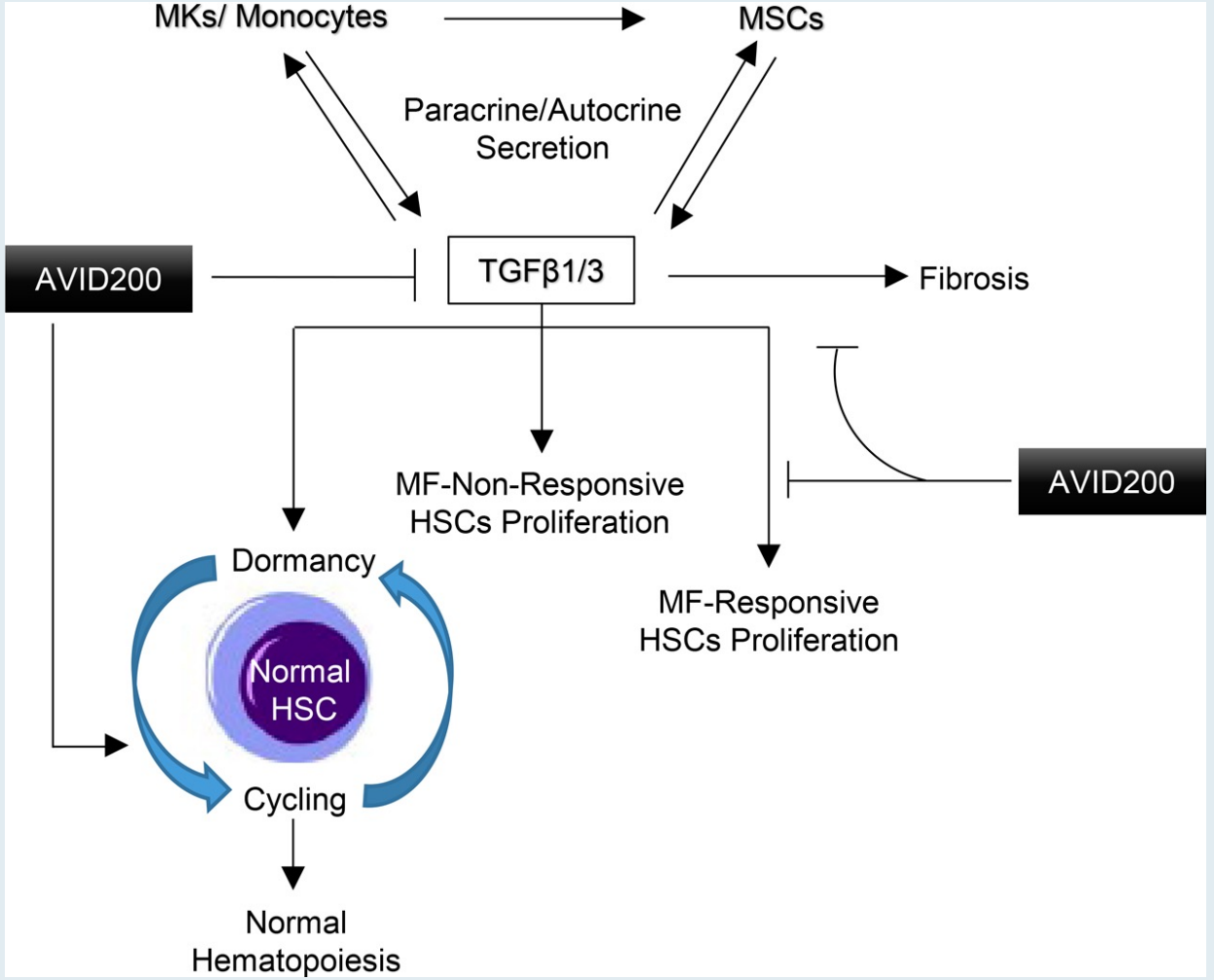
JCI Insight 2021;6(18):e145651

RESEARCH ARTICLE

TGF-β1 protein trap AVID200 beneficially affects hematopoiesis and bone marrow fibrosis in myelofibrosis

Lilian Varricchio,[1] Camelia Iancu-Rubin,[1,2] Bhaskar Upadhyaya,[3] Maria Zingariello,[4] Fabrizio Martelli,[5] Paola Verachi,[6] Cara Clementelli,[1] Jean-Francois Denis,[7] Adeeb H. Rahman,[3] Gilles Tremblay,[7] John Mascarenhas,[1] Ruben A. Mesa,[8] Maureen O'Connor-McCourt,[7] Anna Rita Migliaccio,[6] and Ronald Hoffman[1]

Schematic Model Showing the Molecular Mechanisms Underlying the Effects of AVID200 on TGF-β Signaling in MF and ND Cells



Varricchio L et al. *JCI Insight* 2021;6(18):e145651.

Rationale for and Results of a Phase I study of the TGF-β 1/3 inhibitor AVID200 in Subjects with Myelofibrosis

Myeloproliferative Neoplasms Research Consortium (MPN-RC) 118 Study

NCT03895112

John Mascarenhas, Heidi Kosiorek, Rupali Bhave, Jeanne Palmer, Andrew Kuykendall, Ruben Mesa, Raajit Rampal, Aaron Gerds, Abdulraheem Yacoub, Kristen Pettit, Moshe Talpaz, Rami Komrokji, Marina Kremyanskaya, Agapito Gonzalez, Frank Fabris, Lonette Sandy, Kathryn Johnson, Mikaela Dougherty, Erin McGovern, Juan Arango Ossa, Dylan Domenico, Noushin Farnoud, Anna Rita Migliaccio, Mohammad Salama, Rona Weinberg, Amy Kong, Vesna Najfeld, Carolyn Mead-Harvey, Amylou Dueck, Lilian Varricchio, Ronald Hoffman

ASH 2021;Abstract 142

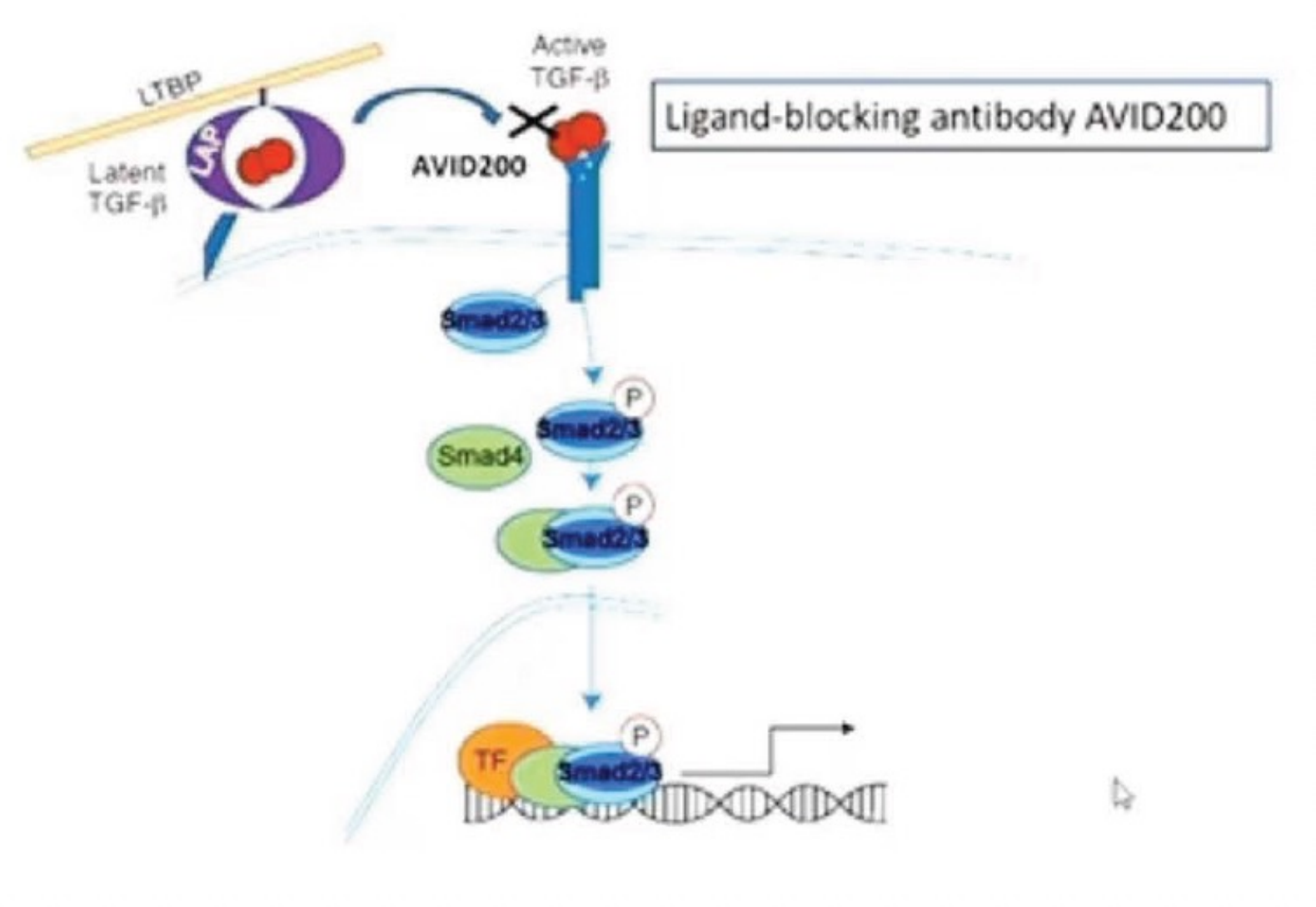
Mount Sinai *The Tisch Cancer Institute*

NIH NATIONAL CANCER INSTITUTE

MPN - RC

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

AVID200 Is a Novel TGFB Trap with Antibody-Like Properties and a Highly Specific TGFB1 and TGFB3 Inhibitor



Mascarenhas J et al. ASH 2021;Abstract 142.

BOREAS: A Global Phase 3 Study of KRT-232, a First-in-Class Murine Double Minute 2 (MDM2) Inhibitor in TP53WT Relapsed/Refractory (R/R) Myelofibrosis (MF)

Verstovsek S et al.

ASCO 2021;Abstract TPS7057.

Annals of Hematology (2022) 101:935–951
https://doi.org/10.1007/s00277-022-04826-7

REVIEW ARTICLE

Low-risk polycythemia vera and essential thrombocythemia: management considerations and future directions

Hannah Goulart[1] · John Mascarenhas[2] · Douglas Tremblay[2]

Leukemia Research 115 (2022) 106820

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Myelodysplastic syndrome/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis: Ringing in a new future

Daniel I. Nathan [a], Jonathan Feld [a], Siraj M. El Jamal [b], John Mascarenhas [a], Douglas Tremblay [a,*]

Novel Machine Learning Algorithm Predicts Disease Progression in Polycythemia Vera (PV) with Readily-Available Baseline Characteristics

Srisuwananukorn A et al.

ASH 2021;Abstract 2583.

RESEARCH ARTICLE

eJHaem

British Society for Haematology

EJHaem 2021;6:10.1002/jha2.167

Mild anemia as a single independent predictor of mortality in patients with COVID-19

Douglas Tremblay[1] | Joseph L. Rapp[2] | Naomi Alpert[2] | Wil Lieberman-Cribbin[2] | John Mascarenhas[1,3] | Emanuela Taioli[2,3] | Saghi Ghaffari[3,4]

Leukemia Research 109 (2021) 106629

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Ruxolitinib discontinuation in polycythemia vera: Patient characteristics, outcomes, and salvage strategies from a large multi-institutional database

Douglas Tremblay [a], Lukas Ronner [b], Nikolai Podoltsev [c], Jason Gotlib [d], Mark Heaney [e], Andrew Kuykendall [f], Casey O'Connell [g], Jamile M. Shammo [h], Angela Fleischman [i], Ruben Mesa [j], Abdulraheem Yacoub [k], Ronald Hoffman [a], Erin Moshier [l], Nicole Zubizarreta [l], John Mascarenhas [a,*]

Blood Reviews 46 (2021) 100735

Contents lists available at ScienceDirect

Blood Reviews

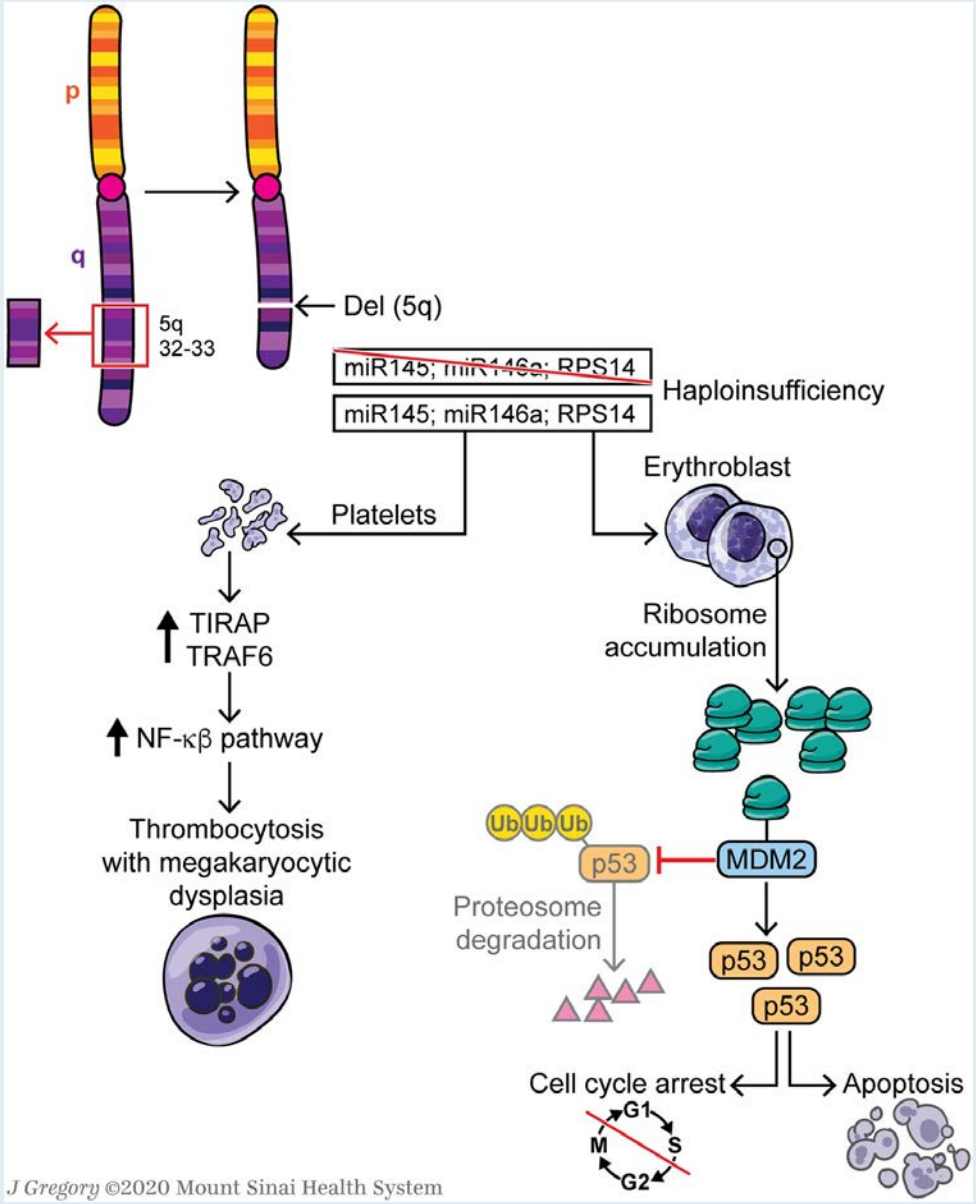
journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Loss of 5q in myeloid malignancies – A gain in understanding of biological and clinical consequences

Sangeetha Venugopal [a,1], John Mascarenhas [a,*], David P. Steensma [b,2]

Schematic Representation of the Pathophysiology of Del(5q) Myelodysplastic Syndromes



Venugopal S et al. *Blood Rev* 2021;46:100735.

Acta Haematol. 2021 ; 144(1): 48–57.

Clinical benefit derived from decitabine therapy for advanced phases of myeloproliferative neoplasms

Selena Zhou[1,^], Douglas Tremblay[2,^], Ronald Hoffman[2], Marina Kremyanskaya[2], Vesna Najfeld[2,3], Lihua Li[4], Erin Moshier[4], John Mascarenhas[2]

Meet The Professor with Dr Mascarenhas

Introduction

Module 1: Case Presentations

- Dr Palmer: A 65-year-old man with post-PV MF and ASXL1 and SRSF2 mutations
- Dr Mushtaq: A 70-year-old woman with high-risk primary MF and a CALR mutation
- Dr Bhatnagar: A 76-year-old woman with primary MF with a JAK2 V617F mutation
- Dr Polkinghorn: A 51-year-old woman with secondary MF with a JAK2 mutation
- Dr Brenner: An 85-year-old woman with primary MF and an MPL mutation
- Dr Morganstein: An 86-year-old woman with JAK2 mutation-positive primary MF and ASXL1 and U2F2 mutations with severe anemia
- Dr Markowski: An 84-year-old woman with MF with a JAK2 mutation and severe anemia

Module 2: Faculty Survey

Module 3: Journal Club with Dr Mascarenhas

Module 4: Appendix of Key Publications

RTP
RESEARCH TO PRACTICE

comments and controversies

Disease Modification in Myelofibrosis: An Elusive Goal?

Pankit Vachhani, MD[1]; Srdan Verstovsek, MD, PhD[2]; and Prithviraj Bose, MD[2]

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

RTP RESEARCH TO PRACTICE

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 Deininger, M.D., Ph.D., Carole Miller, M.D.,
M.D., Moshe Talpaz, M.D., Elliott F. Winton, M.D.,
M.D., Murat O. Arcasoy, M.D., Elizabeth Hexner, M.D.,
, M.D., Ronald Paquette, M.D., Azra Raza, M.D.,
n 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 Kiladjian, M.D., Ph.D., Haifa Kathrin Al-Ali, M.D., Heinz Gisslinger, M.D., Roger Waltzman, M.D., M.B.A., Viktoriya Stalbovskaya, Ph.D., Mari McQuitty, R.N., M.P.H., Deborah S. Hunter, Ph.D., Richard Levy, M.D., Laurent Knoops, M.D., Ph.D., Francisco Cervantes, M.D., Ph.D., Alessandro M. Vannucchi, M.D., Tiziano Barbui, M.D., and Giovanni Barosi, M.D.

RTP RESEARCH TO PRACTICE

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]			COMFORT-II, Wk 48[2]		
	Ruxolitinib (n = 155)	Placebo (n = 154)	*p*-value	Ruxolitinib (n = 144)	BAT (n = 72)	*p*-value
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.

Verstovsek *et al. Journal of Hematology & Oncology* (2017) 10:156
DOI 10.1186/s13045-017-0527-7

Journal of Hematology & Oncology

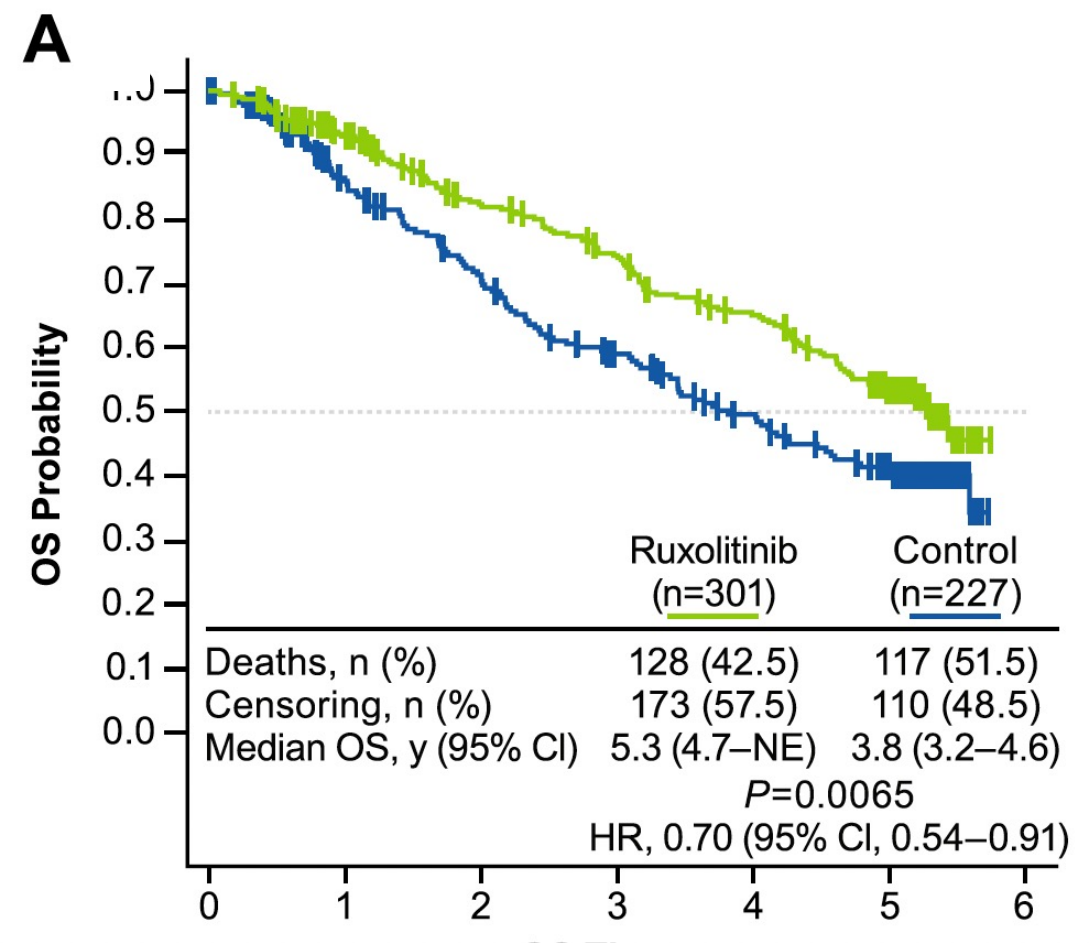
RESEARCH Open Access

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

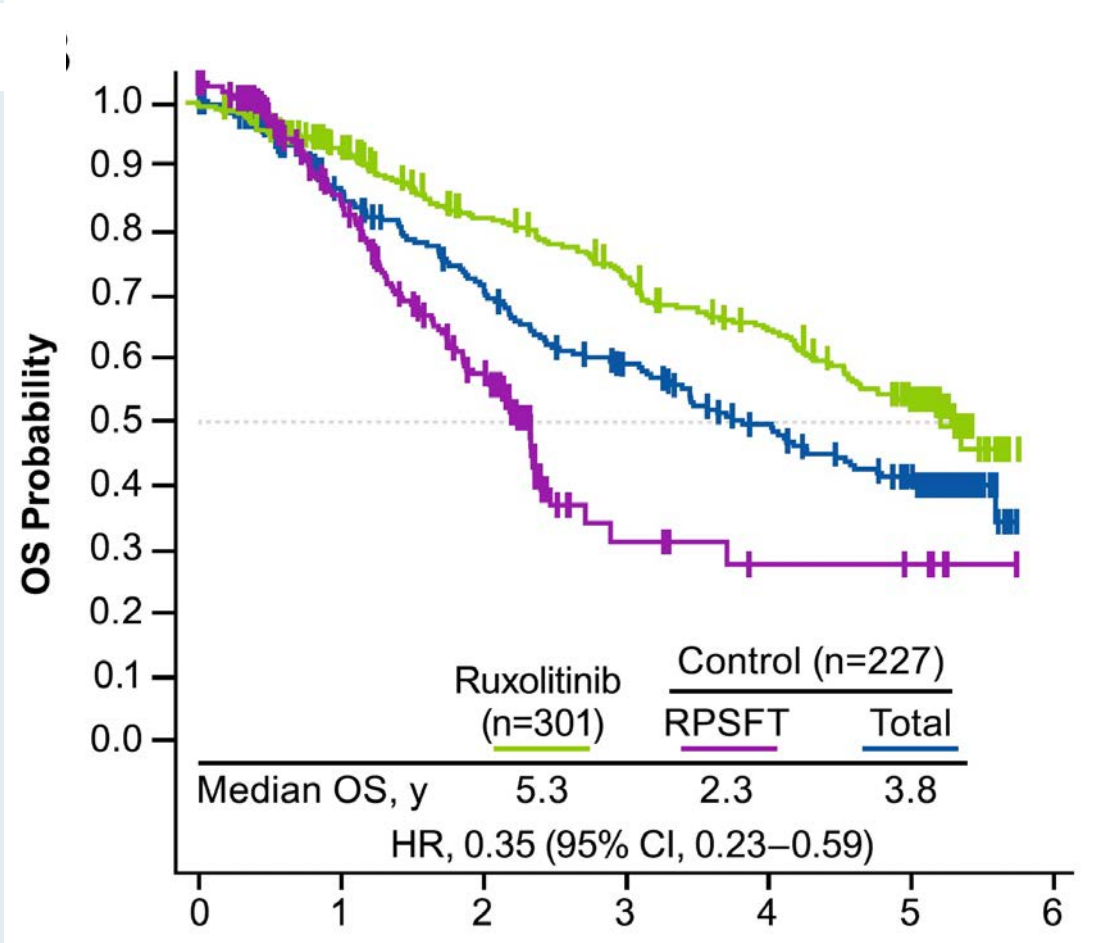
Srdan Verstovsek[1*], Jason Gotlib[2], Ruben A. Mesa[3], Alessandro M. Vannucchi[4], Jean-Jacques Kiladjian[5], Francisco Cervantes[6], Claire N. Harrison[7], Ronald Paquette[8], William Sun[9], Ahmad Naim[9], Peter Langmuir[9], Tuochuan Dong[10], Prashanth Gopalakrishna[11] and Vikas Gupta[12]

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

OS (5-Year ITT Population)



OS (Corrected for Crossover)



Verstovsek S et al. *J Hem Onc* 2017;10:156.

RTP RESEARCH TO PRACTICE

OPEN

Leukemia (2016) **30**, 1701–1707

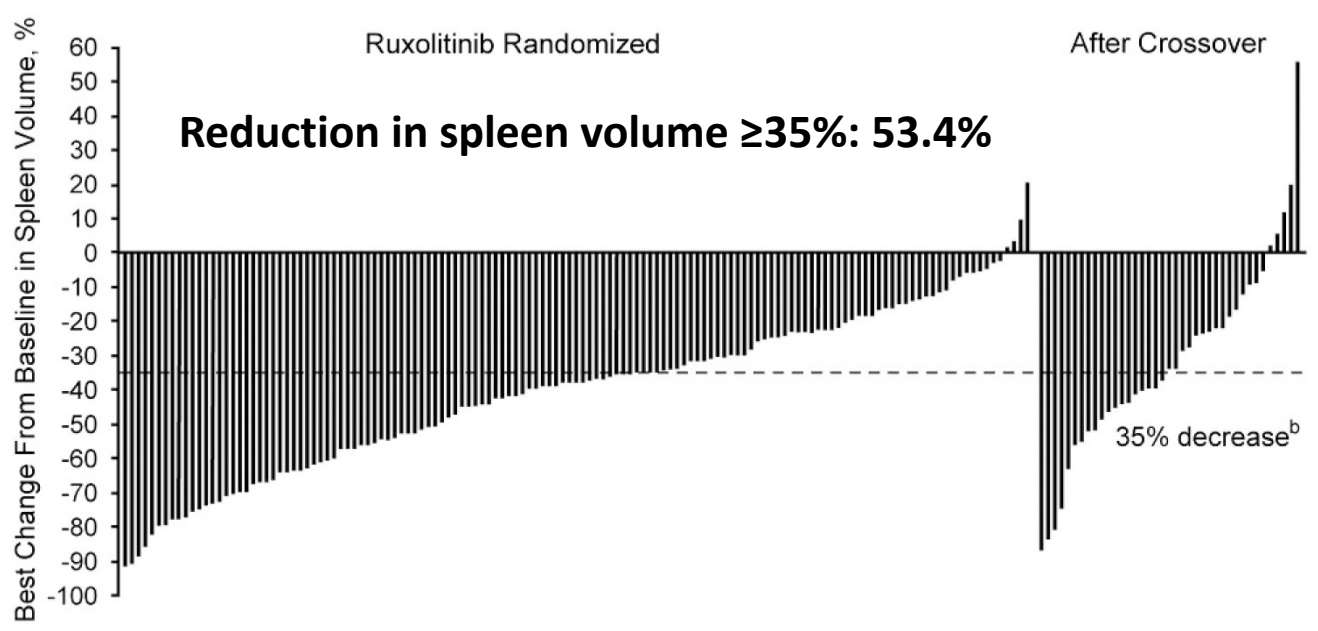
www.nature.com/leu

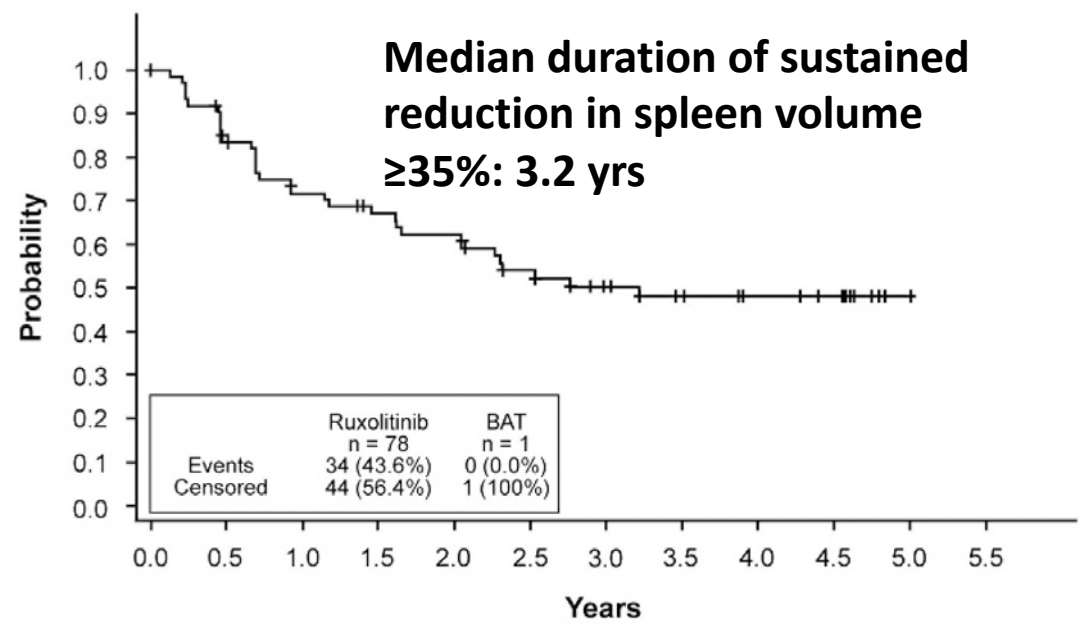
ORIGINAL ARTICLE

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

CN Harrison[1], AM Vannucchi[2], J-J Kiladjian[3], HK Al-Ali[4], H Gisslinger[5], L Knoops[6], F Cervantes[7], MM Jones[8], K Sun[8], M McQuitty[9], V Stalbovskaya[9], P Gopalakrishna[9] and T Barbui[10] on behalf of the COMFORT-II Investigators[11]

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





Harrison CN et al. *Leukemia* 2016;30:1701-7.

RTP RESEARCH TO PRACTICE

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%

Harrison CN et al. *Leukemia* 2016;30:1701-7.

bjh research paper

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 Mannelli[21] and Alessandro M. Vannucchi[21]

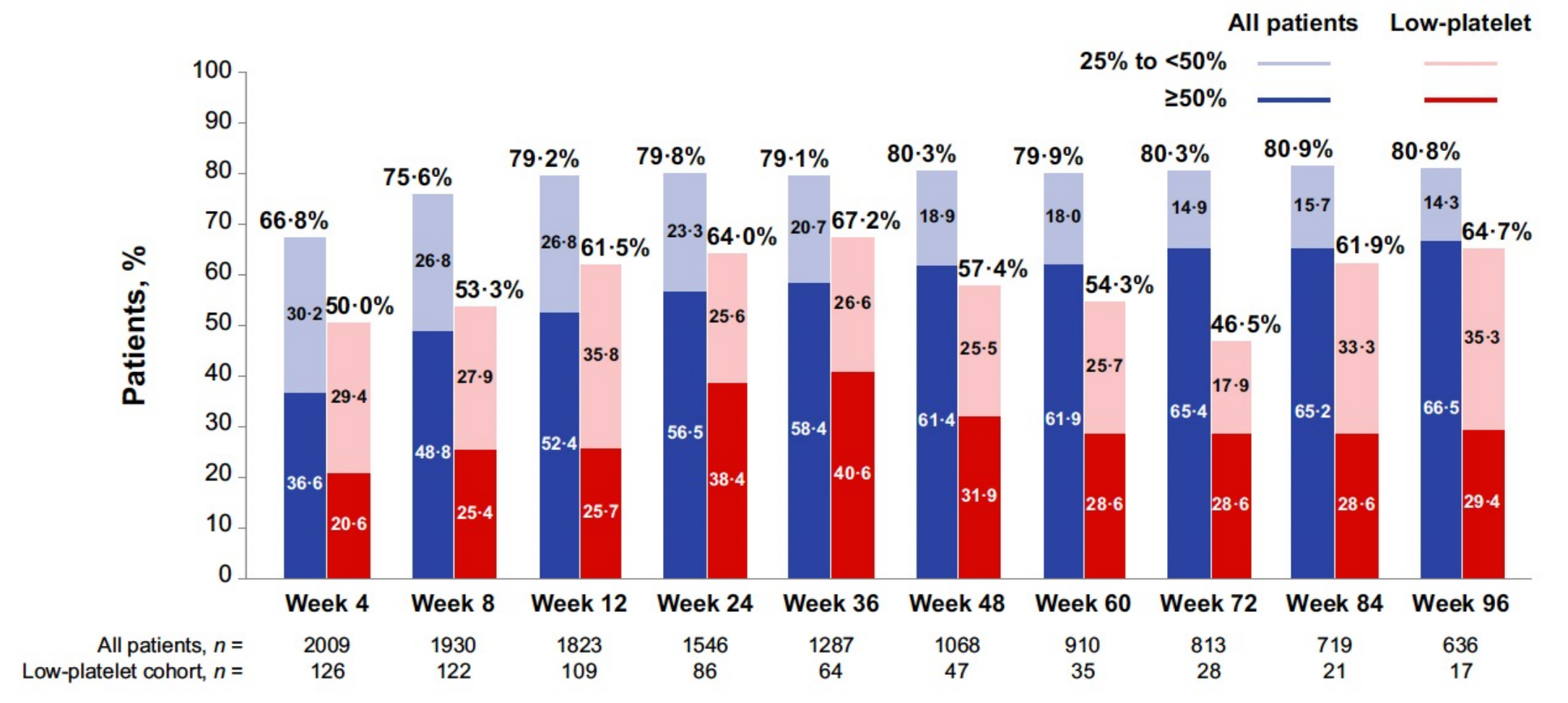
Br J Haematol 2020;189(5):888-903

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%

Al-Ali HK et al. *Br J Haematol* 2020;189(5):888-903.

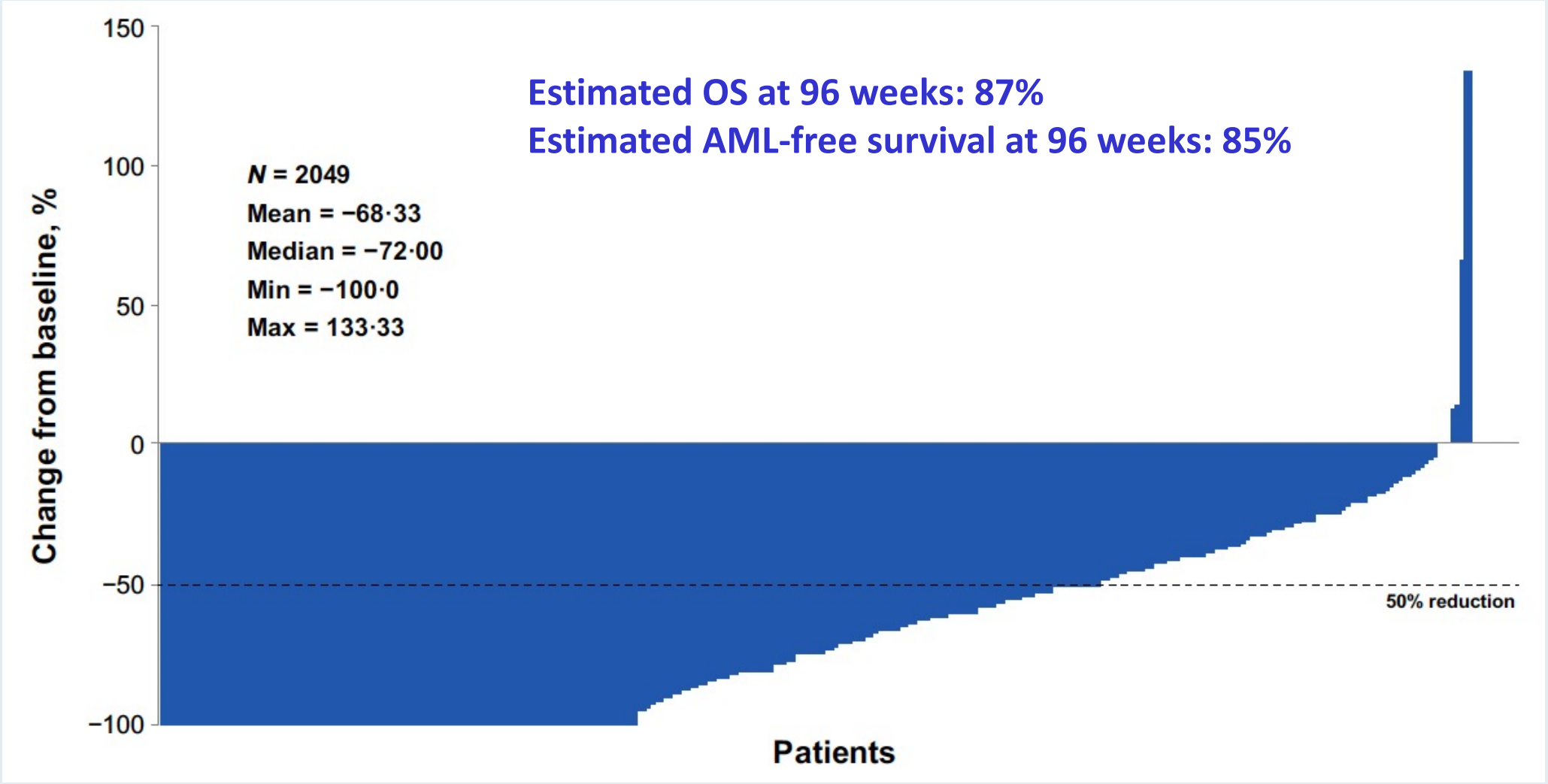
JUMP: Patients with a ≥25% and a ≥50% Decrease from Baseline in Spleen Length



Al-Ali HK et al. *Br J Haematol* 2020;189(5):888-903.

RTP RESEARCH TO PRACTICE

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



Al-Ali HK et al. *Br J Haematol* 2020;189(5):888-903.

RTP RESEARCH TO PRACTICE

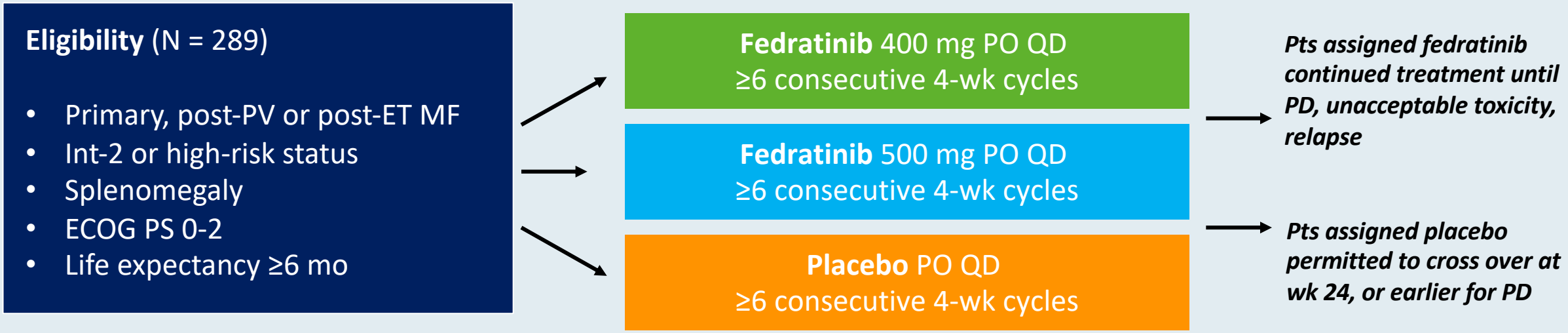
bjh short report

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 Zhang[12] and Claire Harrison[13]

Br J Haematol 2021;195:244-8.

JAKARTA Phase III Study Design

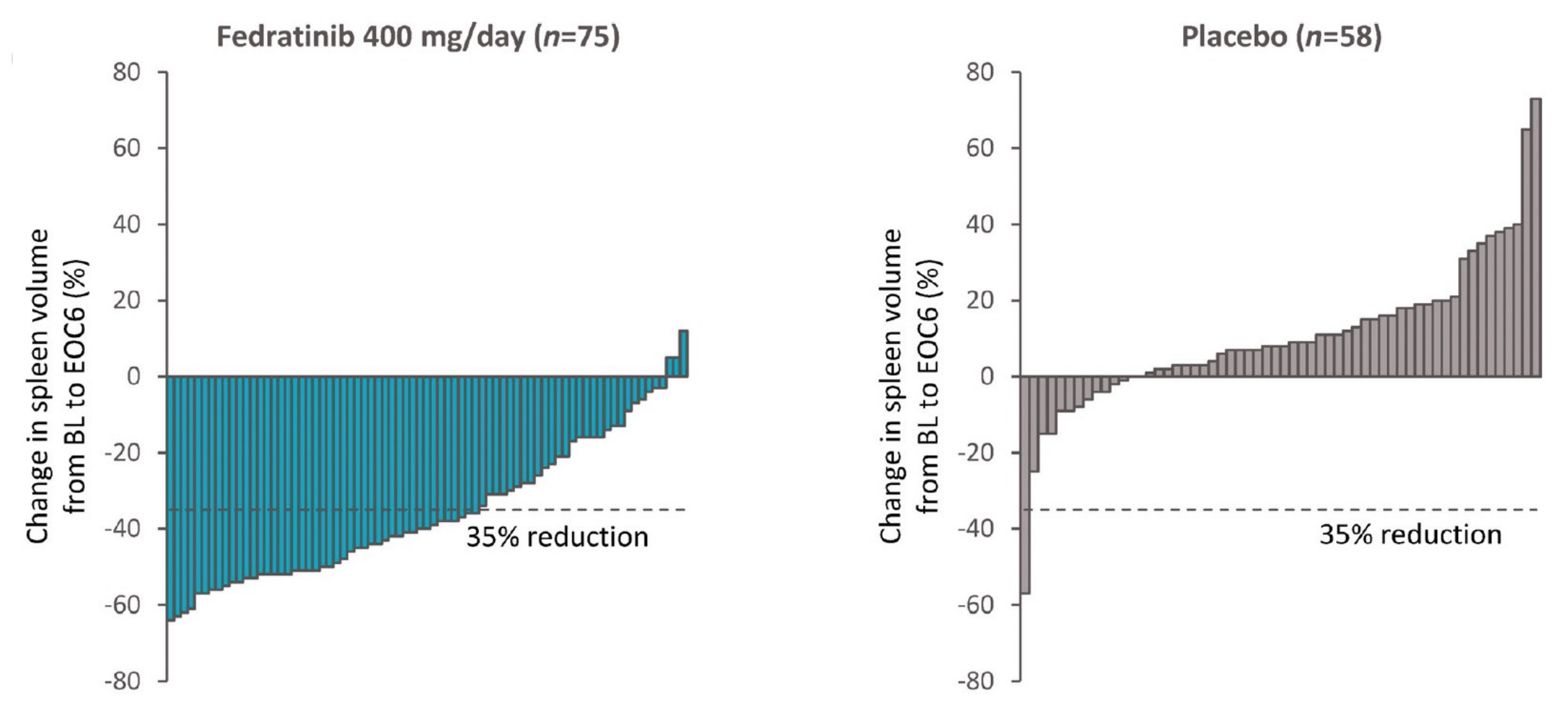


Primary endpoint: Spleen response (≥35% reduction in spleen volume vs BL) at Wk 24, and confirmed 4 wks later

Secondary endpoints: Symptom response (≥50% reduction in TSS), safety

Pardanani A et al. *JAMA Oncol* 2015;1:643-51.

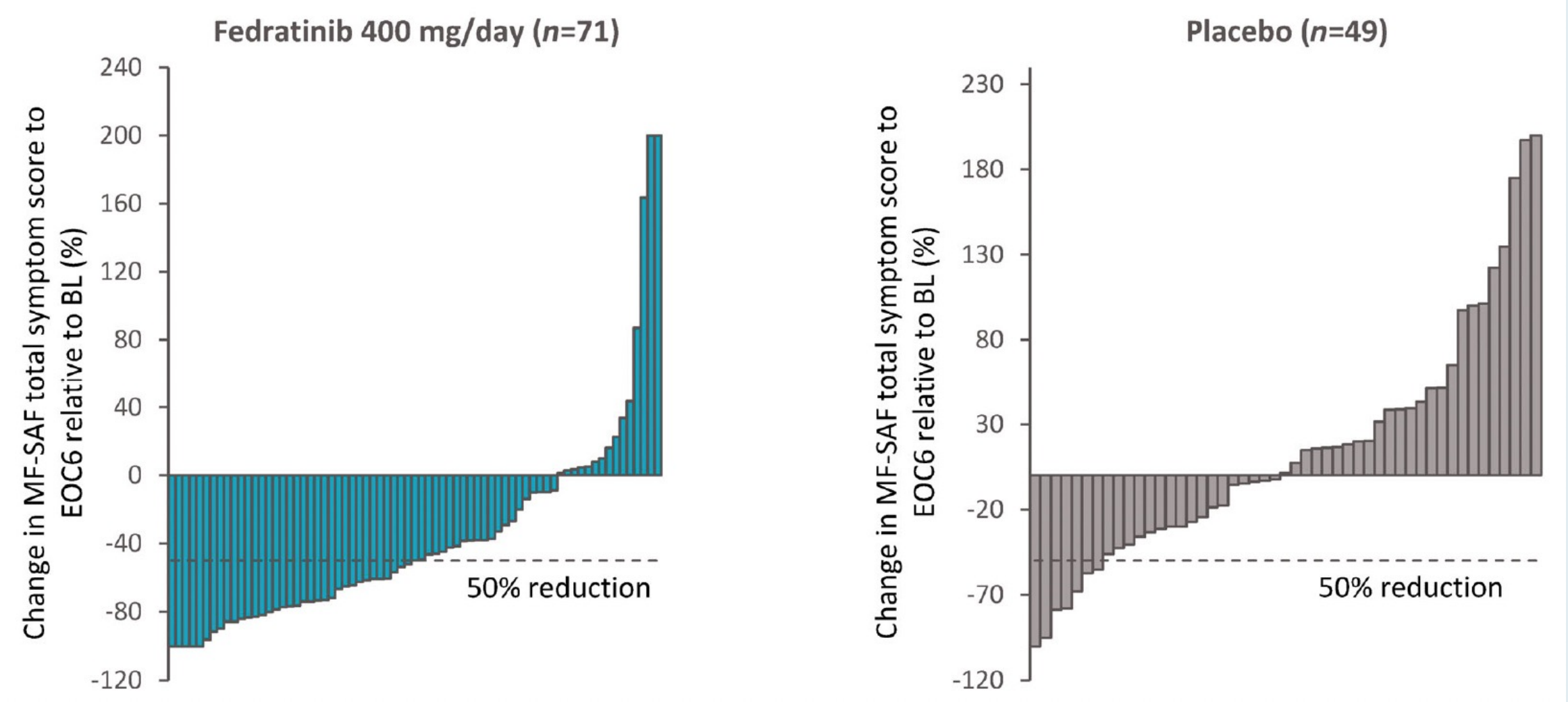
JAKARTA: Change in Spleen Volume from Baseline to End of Cycle 6



Pardanani A et al. *Br J Haematol* 2021;195:244-8.

RTP RESEARCH TO PRACTICE

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



Pardanani A et al. *Br J Haematol* 2021;195:244-8.

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%

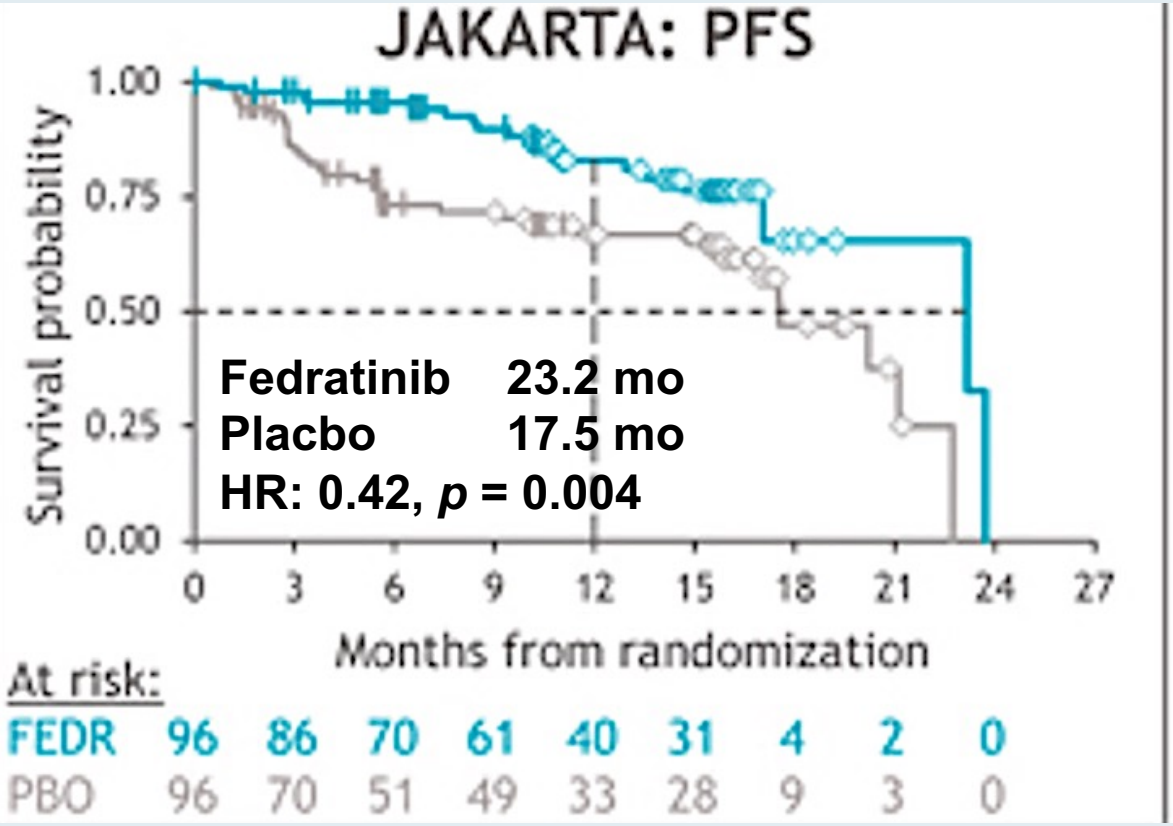
Pardanani A et al. *Br J Haematol* 2021;195:244-8.

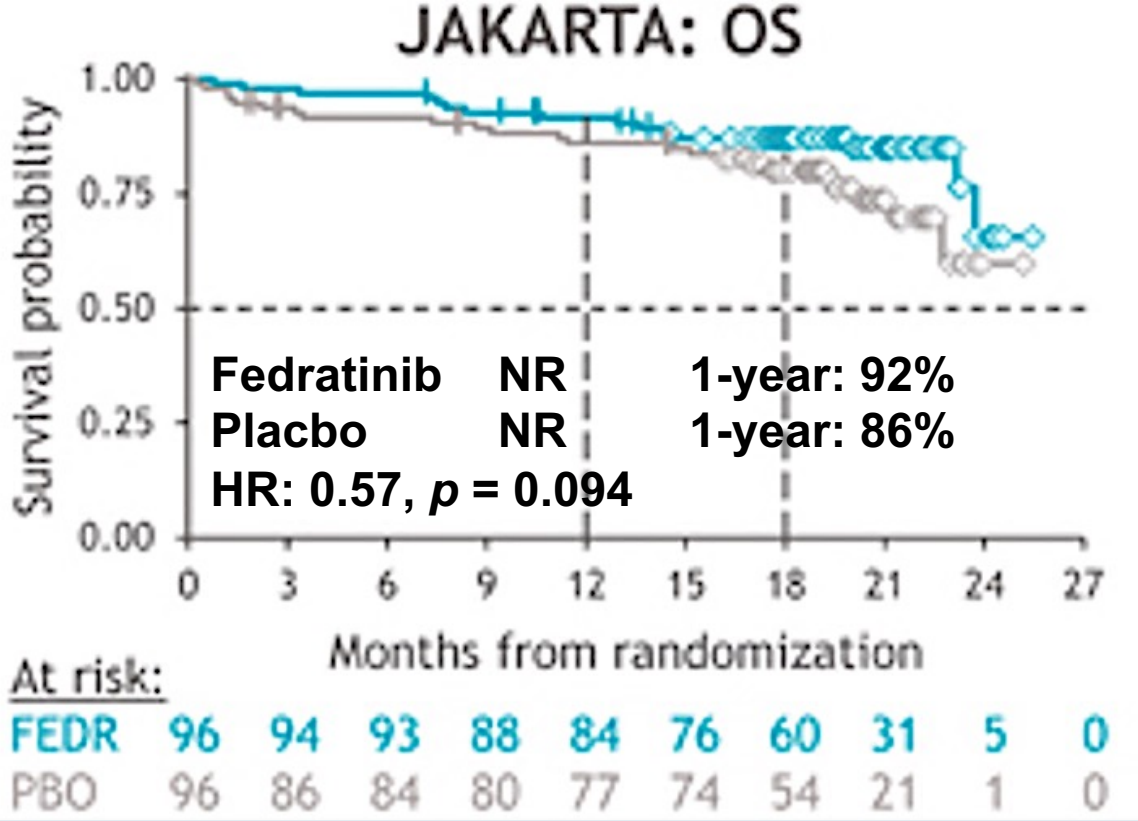
Overall and Progression-Free Survival in Patients Treated with Fedratinib as First-Line Myelofibrosis (MF) Therapy and After Prior Ruxoltinib (RUX): Results from the JAKARTA and JAKARTA2 Trials

Harrison C et al.

EHA 2021;Abstract S203.

JAKARTA: Survival Analysis





Harrison C et al. EHA 2021;Abstract S203.

RTP RESEARCH TO PRACTICE

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

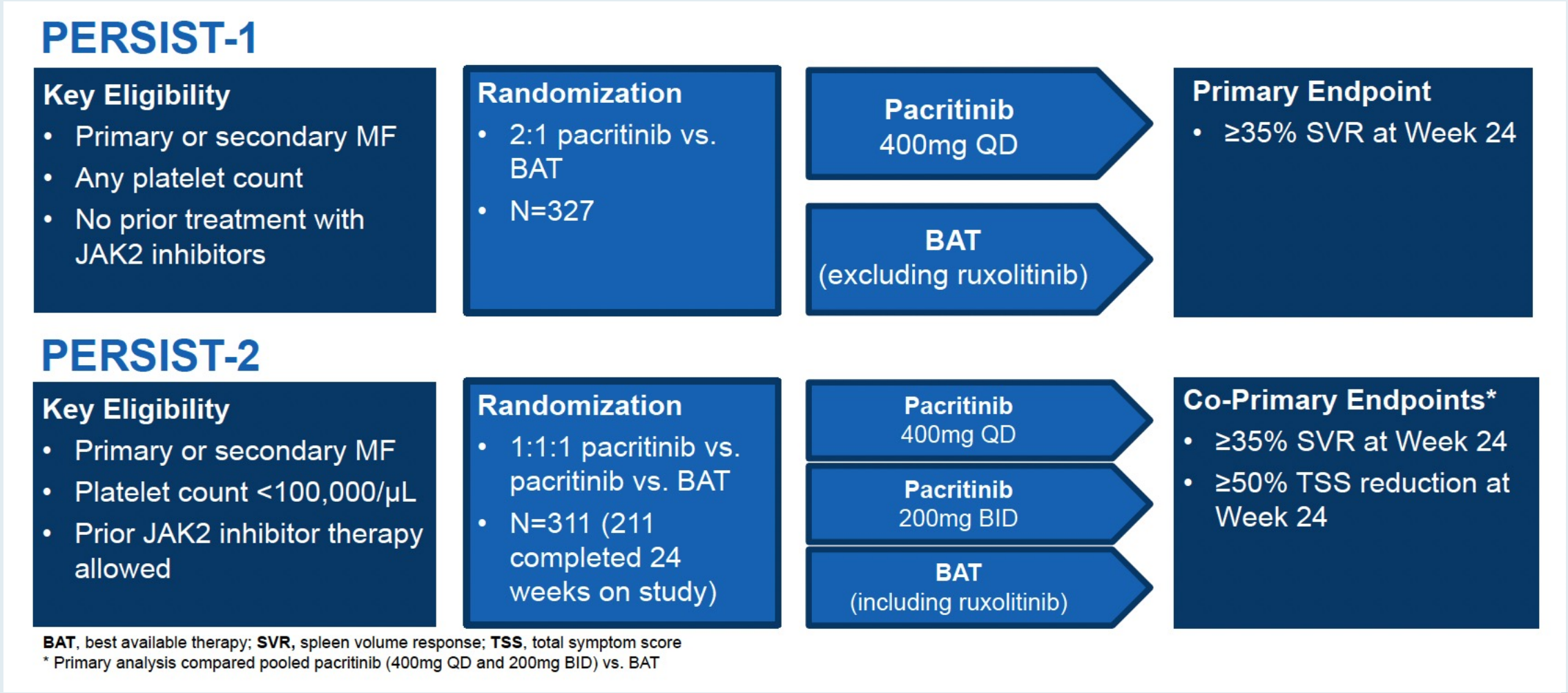
"Pacritinib received accelerated approval from the FDA at a twice daily, 200-mg dose for patients with intermediate- or high-risk primary or secondary myelofibrosis who are experiencing severe thrombocytopenia with a platelet count below 50 × 10^9/L. The agency's decision comes from results of the phase 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



BAT, best available therapy; **SVR**, spleen volume response; **TSS**, total symptom score
* Primary analysis compared pooled pacritinib (400mg QD and 200mg BID) vs. BAT

Mesa RA et al. ASH 2019;Ab 4195.

Research

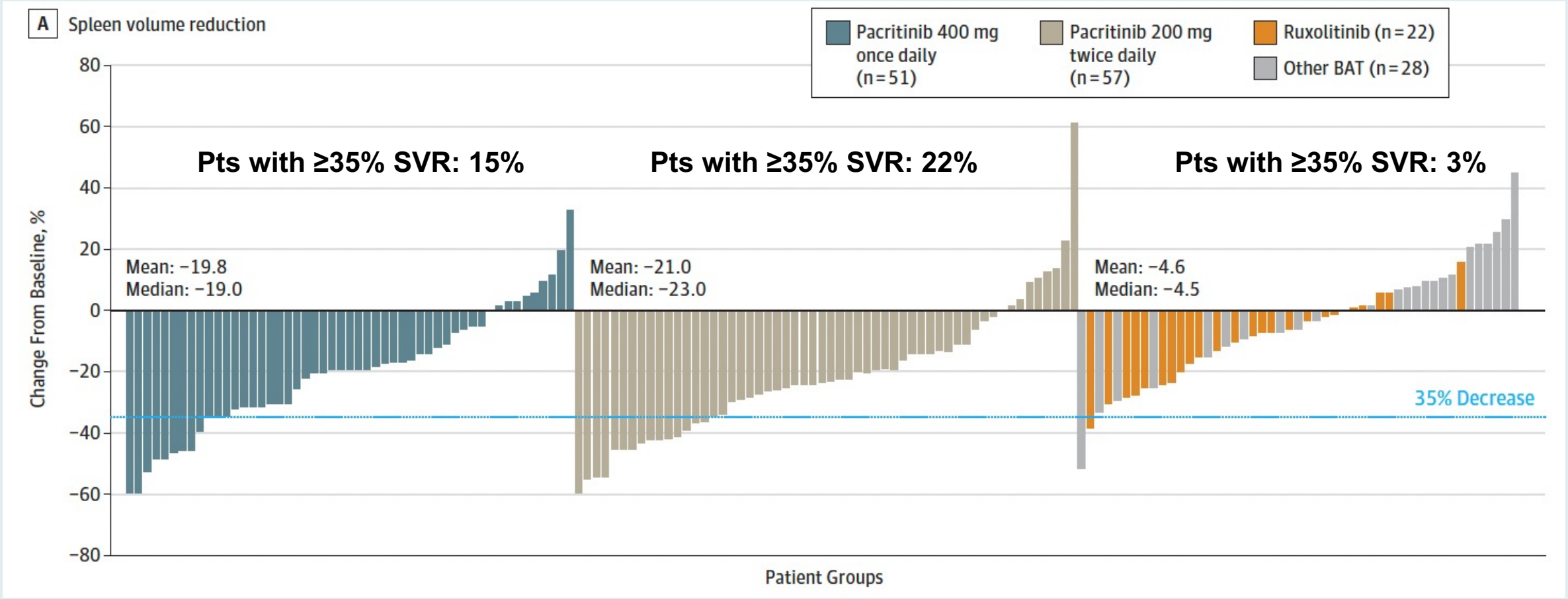
JAMA Oncol 2018;4(5):652-9.

JAMA Oncology | Original Investigation

Pacritinib vs Best Available Therapy, Including Ruxolitinib, in Patients With Myelofibrosis
A Randomized Clinical Trial

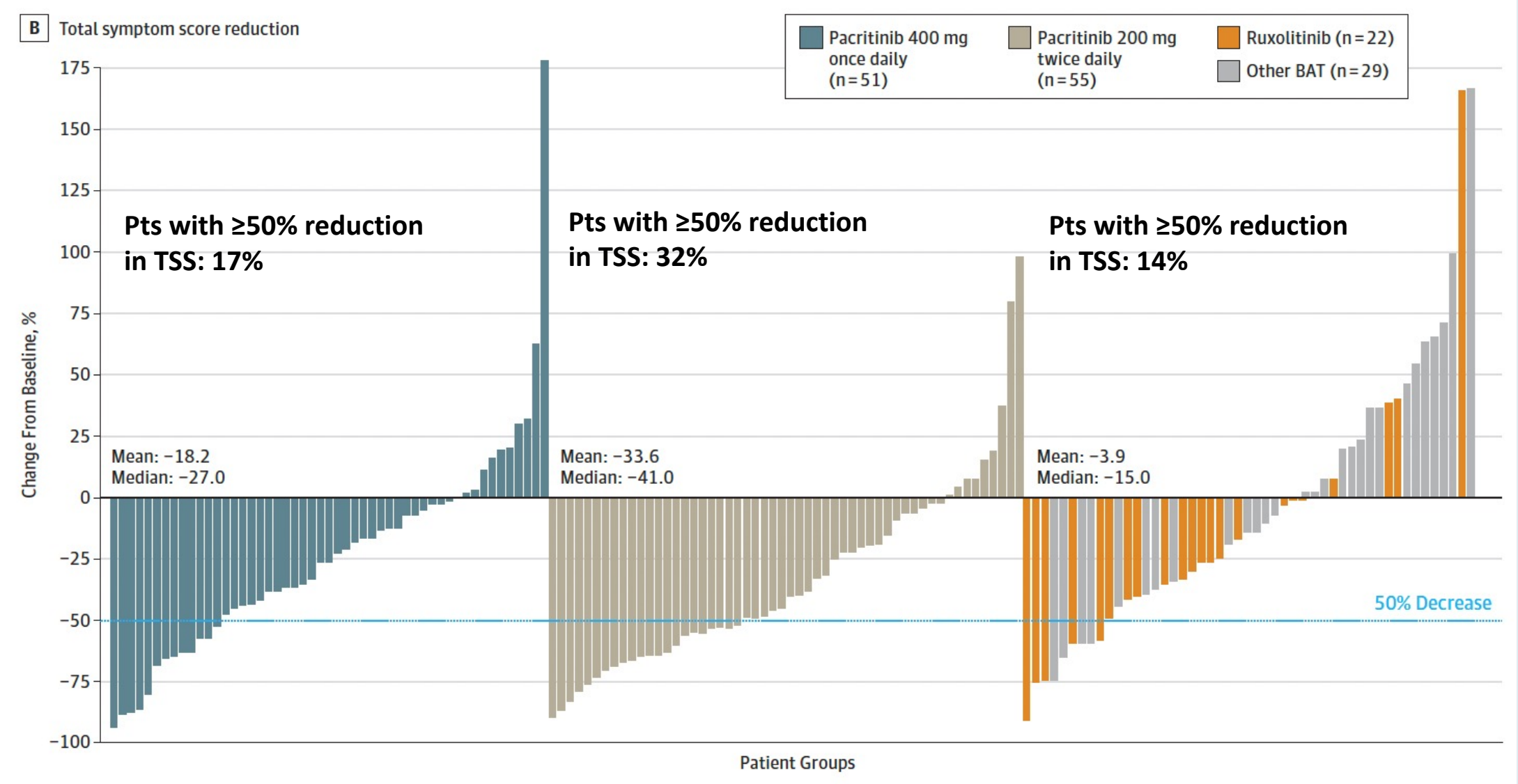
John Mascarenhas, MD; Ronald Hoffman, MD; Moshe Talpaz, MD; Aaron T. Gerds, MD; Brady Stein, MD; Vikas Gupta, MD, FRCP, FRCPath; Anita Szoke, MD; Mark Drummond, MBChB, PhD, FRCPath; Alexander Pristupa, MD; Tanya Granston, PhD; Robert Daly, PhD; Suliman Al-Fayoumi, PhD; Jennifer A. Callahan, MS; Jack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

PERSIST-2: Spleen Volume Reduction



Mascarenhas J et al. *JAMA Oncol* 2018;4(5):652-9.

PERSIST-2: Reduction in Total Symptom Score



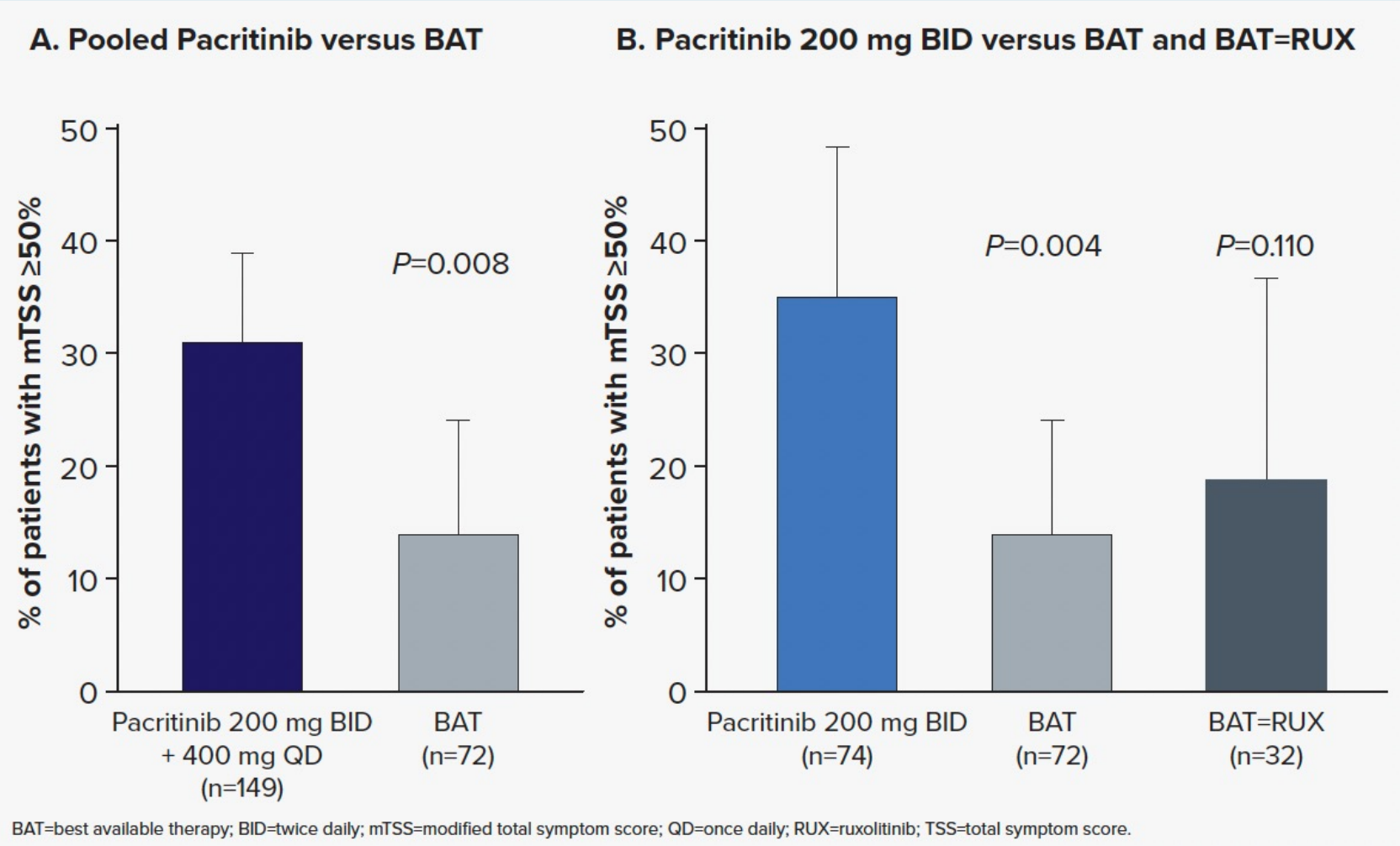
Mascarenhas J et al. *JAMA Oncol* 2018;4(5):652-9.

The Impact of Pacritinib on Myelofibrosis Symptoms

Palmer J et al.

ASH 2021;Abstract 3628.

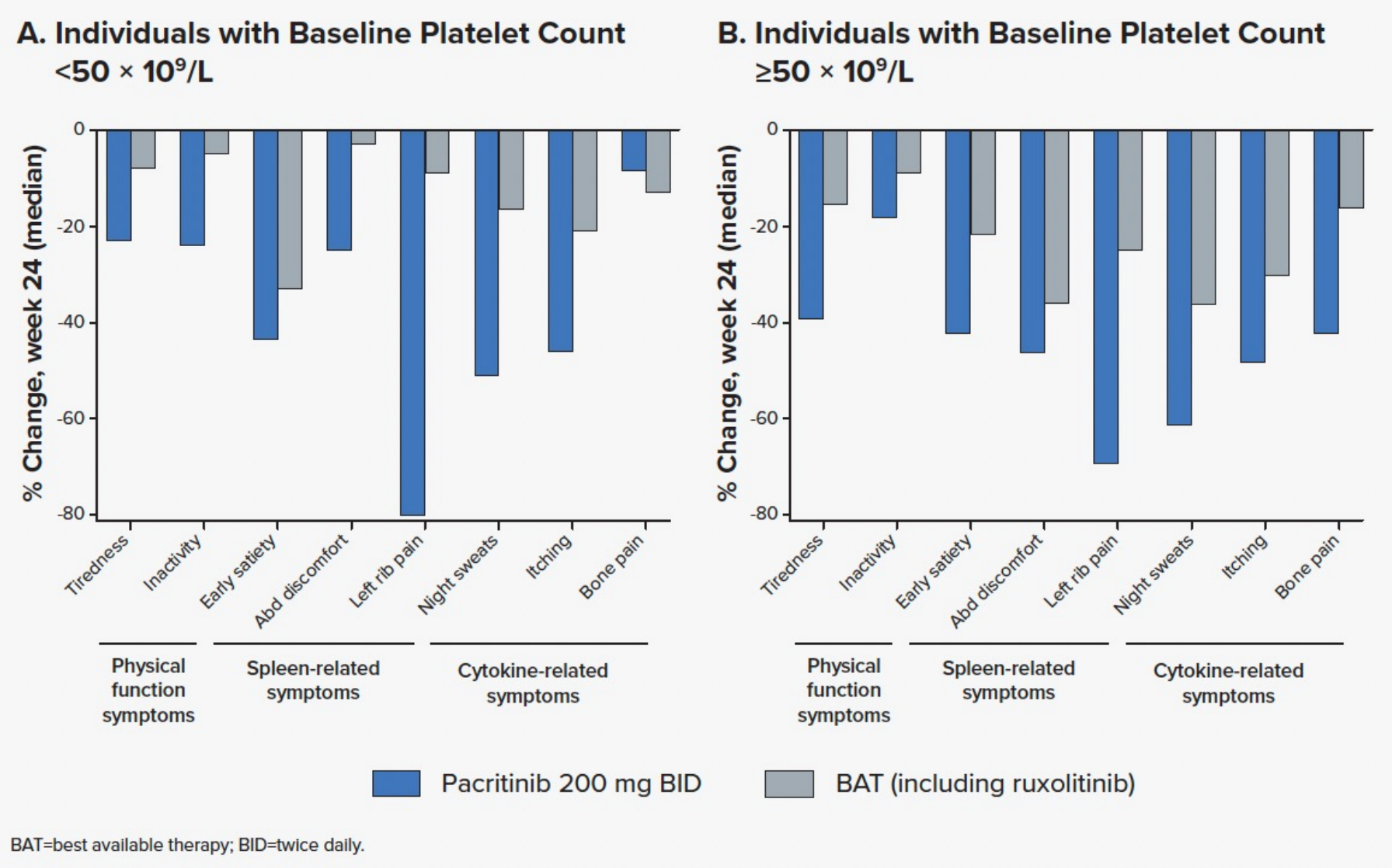
Modified TSS Response Rates (Week 24) in PERSIST-2



BAT=best available therapy; BID=twice daily; mTSS=modified total symptom score; QD=once daily; RUX=ruxolitinib; TSS=total symptom score.

Palmer J et al. ASH 2021;Abstract 3628.

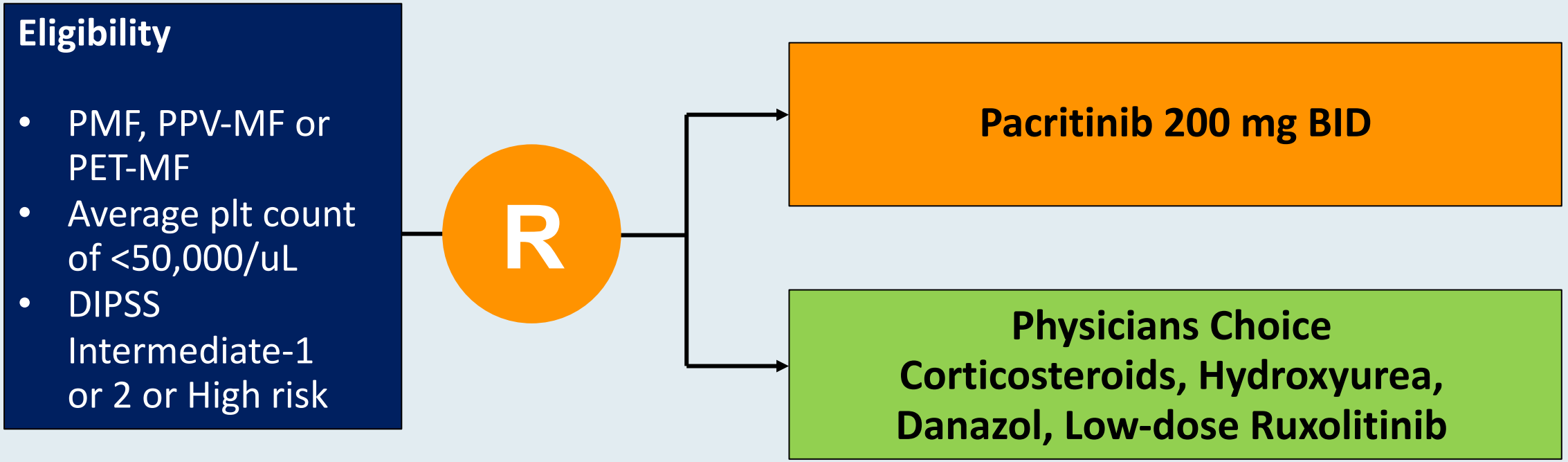
Percent Change in Individual Symptom Scores in PERSIST-2



BAT=best available therapy; BID=twice daily.

Palmer J et al. ASH 2021;Abstract 3628.

PACIFICA (PAC303) Study Design



Primary Endpoint: Spleen volume
Secondary Endpoints: Total Symptom Score, OS, Patient Global Impression of Change

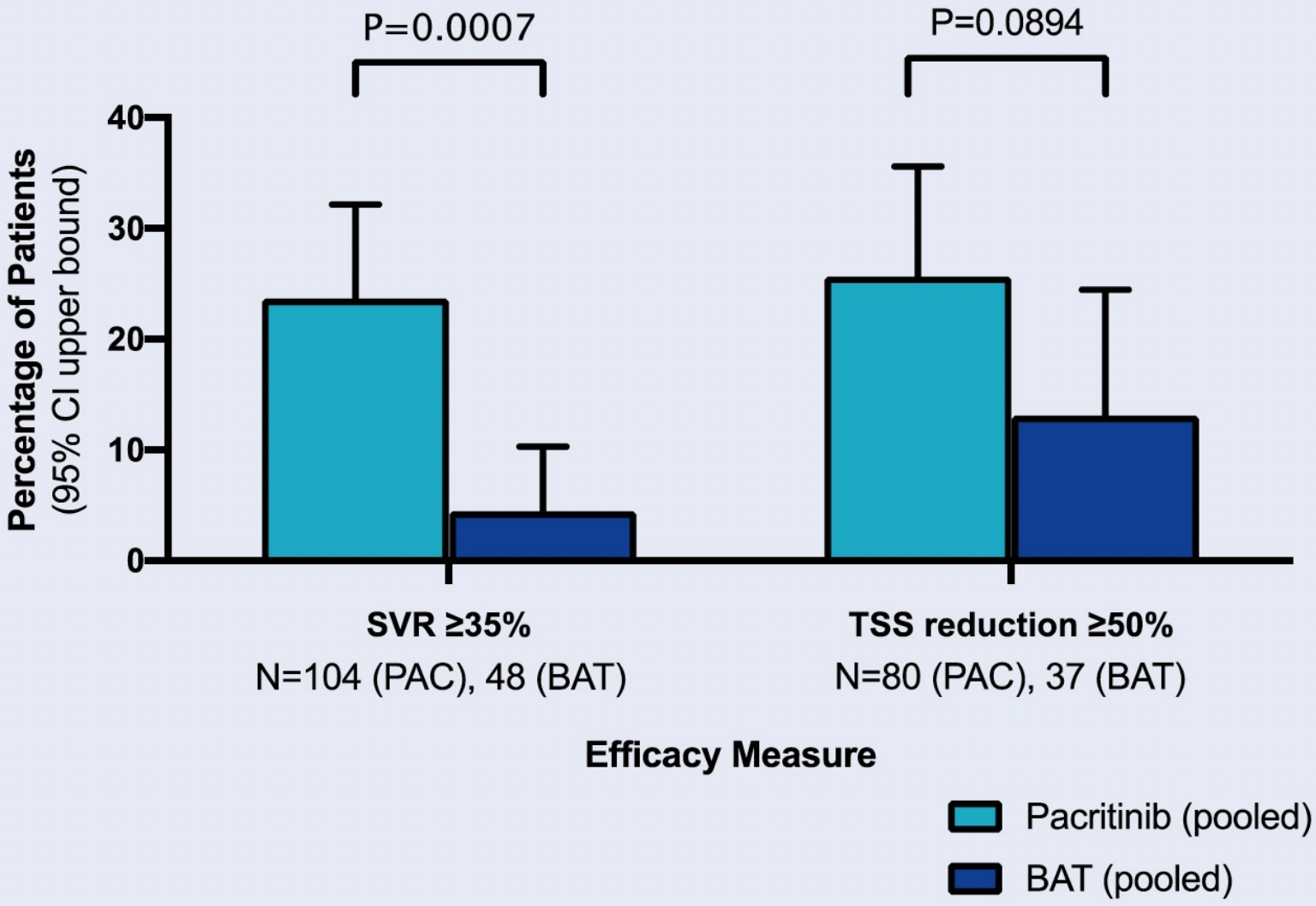
https://clinicaltrials.gov/ct2/show/NCT03165734

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 <50,000/µL



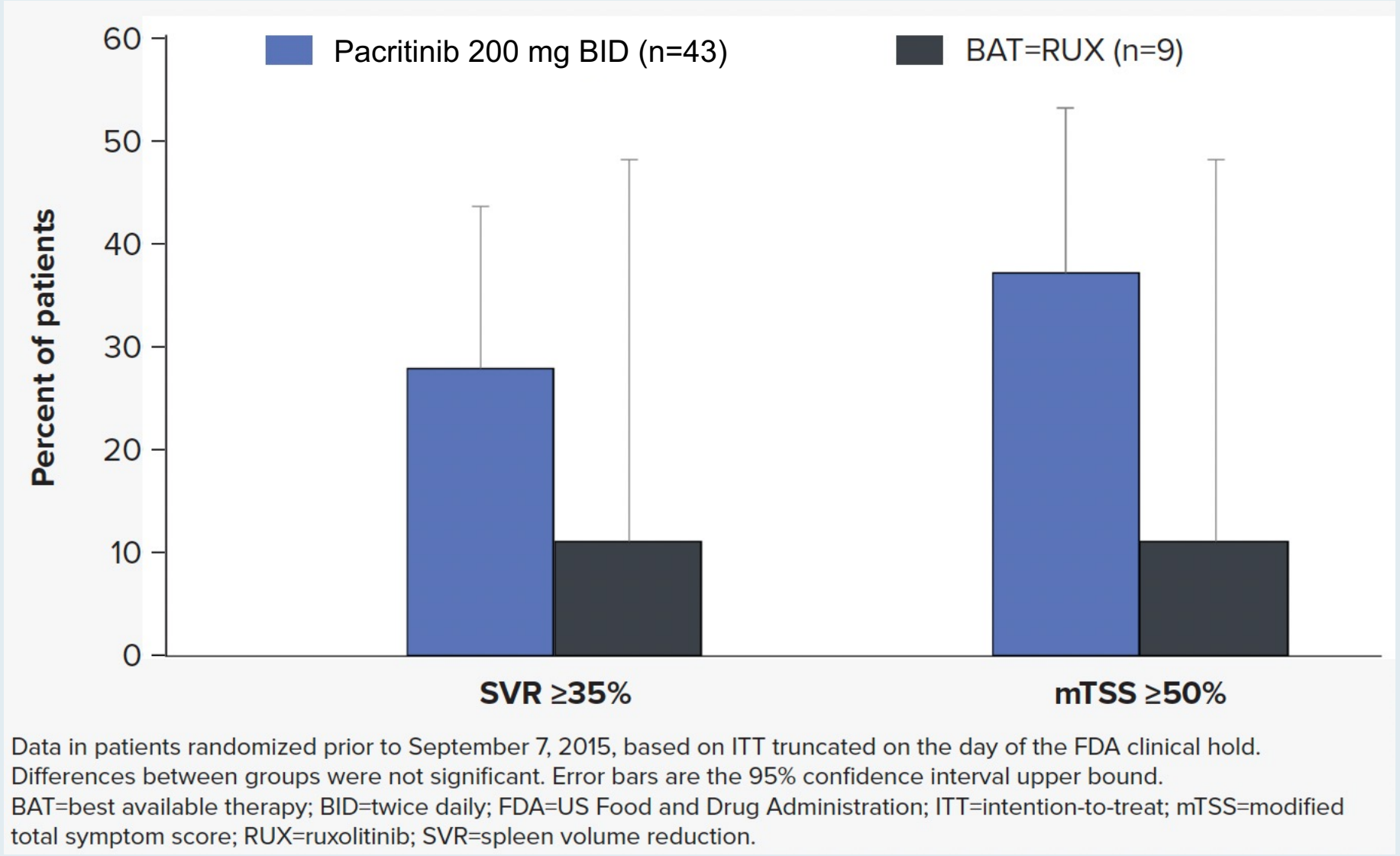
Mesa RA et al. ASH 2019;Abstract 4195.

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



Data in patients randomized prior to September 7, 2015, based on ITT truncated on the day of the FDA clinical hold. Differences between groups were not significant. Error bars are the 95% confidence interval upper bound.
BAT=best available therapy; BID=twice daily; FDA=US Food and Drug Administration; ITT=intention-to-treat; mTSS=modified total symptom score; RUX=ruxolitinib; SVR=spleen volume reduction.

Mascarenhas J et al. ASH 2021;Abstract 3639.

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)

[a]The 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.

Mascarenhas J et al. ASH 2021;Abstract 3640.

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

AE, n (%)	PERSIST-2 Pacritinib 200 mg BID (n=47)	PERSIST-2 BAT[a] (n=42)	PAC203 pacritinib 200 mg BID (n=24)	Total (pooled) pacritinib 200 mg BID (N=71)
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)

[a]The most common BAT agents were ruxolitinib and watch and wait. [b]Bleeding 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.

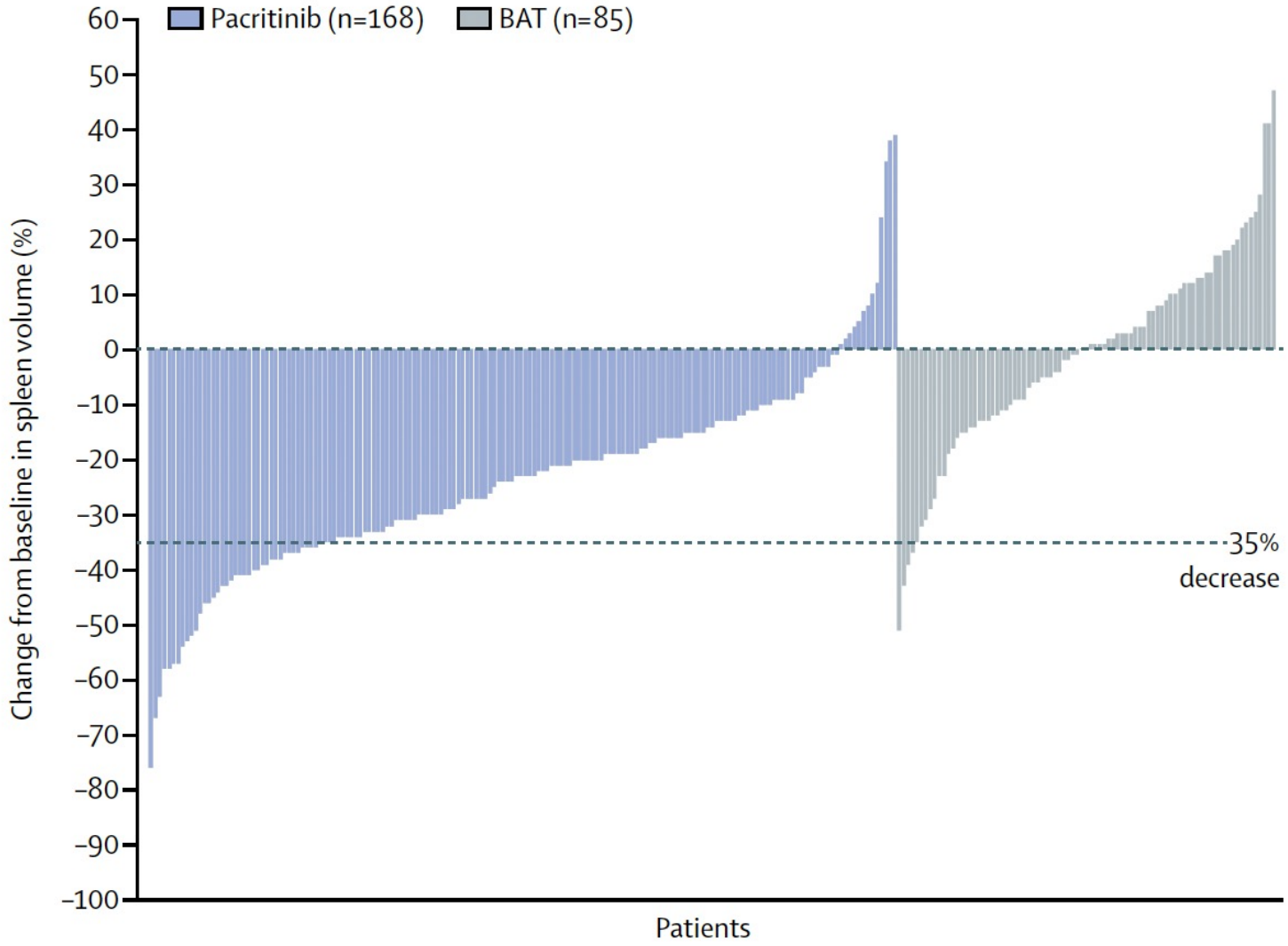
Mascarenhas J et al. ASH 2021;Abstract 3640.

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

Mesa RA et al. *Lancet Haematol* 2017;4:e225-36.

PERSIST-1: Patients Achieving ≥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 (%).

Mesa RA et al. *Lancet Haematol* 2017;4:e225-36.

PERSIST-1: Select Adverse Events

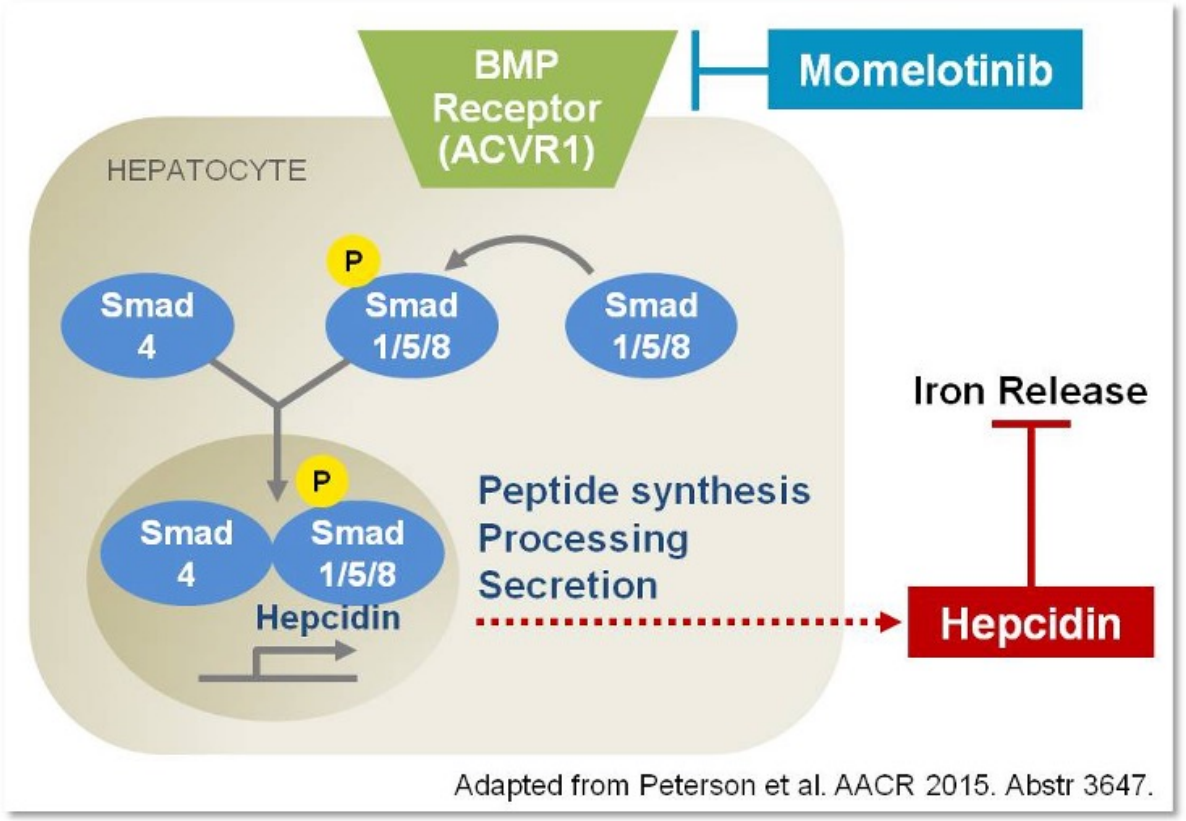
	Pacritinib (N = 220)		BAT (N = 106)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Diarrhea	55%	5%	10%	0
Nausea	27%	1%	7%	0
Anemia	24%	17%	20%	15%
Thrombocytopenia	17%	11%	14%	11%
Vomiting	16%	1%	6%	0
Fatigue	10%	2%	9%	1%

Mesa RA et al. *Lancet Haematol* 2017;4:e225-36.

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 expression[1]
- Hepcidin decreases plasma iron and hepcidin is elevated in MF[2]
- MMB ameliorates anemia in a rodent ACD model[1]



Adapted from Peterson et al. AACR 2015. Abstr 3647.

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.

Harrison CN et al. ASCO 2017;Abstract 7001.

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

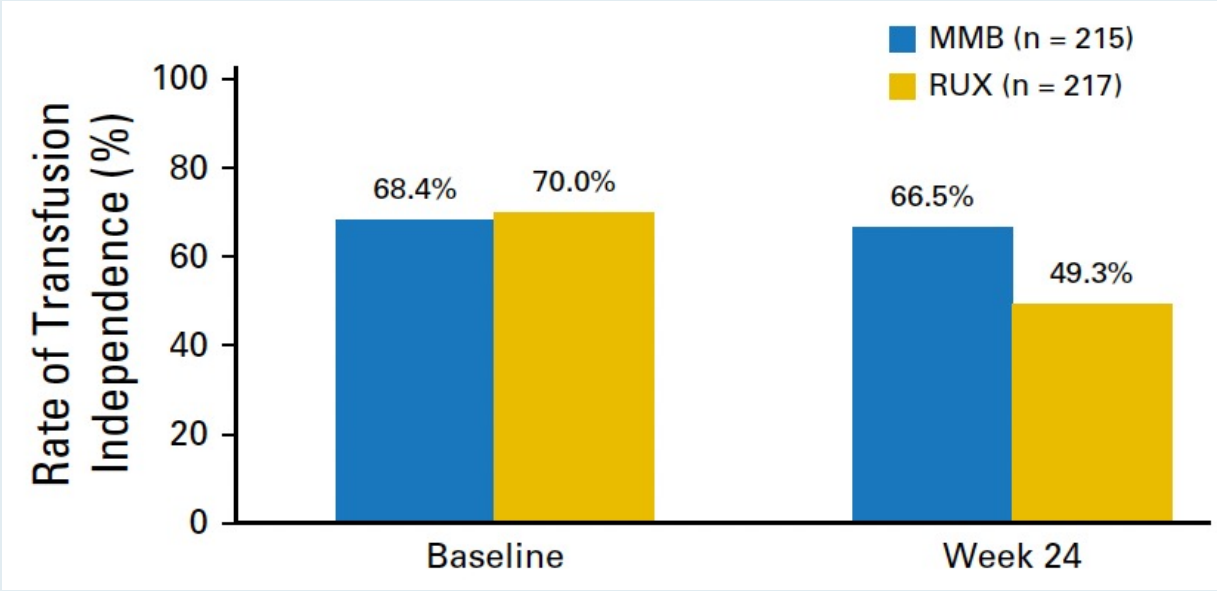
Ruben A. Mesa, Jean-Jacques Kiladjian, John V. Catalano, Timothy Devos, Miklos Egyed, Andrzei Hellmann, Donal McLornan, Kazuya Shimoda, Elliott F. Winton, Wei Deng, Ronald L. Dubowy, Julia D. Maltzman, Francisco Cervantes, and Jason Gotlib

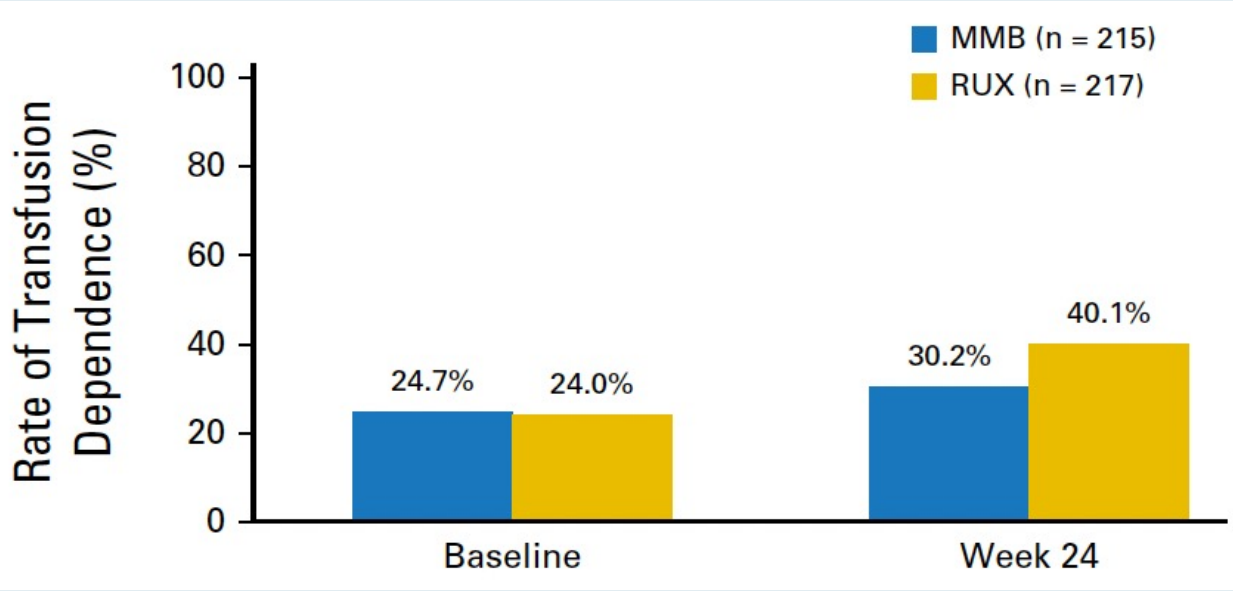
SIMPLIFY-1 Trial of Momelotinib (MMB) in Patients with Treatment-Naïve MF

Efficacy outcomes	SIMPLIFY-1, Wk 24[1]		*p*-value
	MMB (n = 215)	RUX (n = 217)	
Spleen volume reduction ≥ 35%	26.5%	29.0%	0.011
≥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%	

Mesa RA et al. *J Clin Oncol* 2017;35(34):3844-50.

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





Mesa RA et al. *J Clin Oncol* 2017;35(34):3844-50.

RTP RESEARCH TO PRACTICE

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

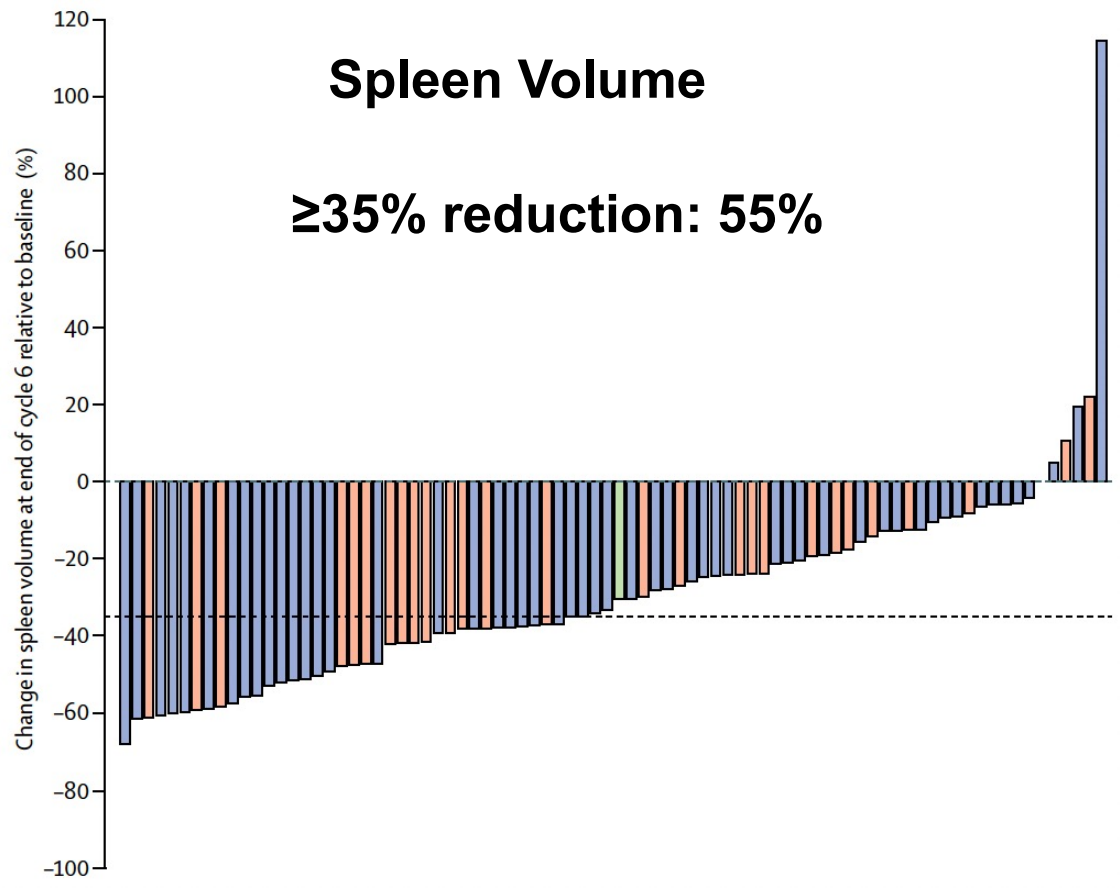
- JAKARTA-2: Fedratinib in patients with intermediate- or high-risk MF resistant or intolerant to ruxolitinib
- Ongoing FREEDOM and FREEDOM2 trials of fedratinib after ruxolitinib
- SIMPLIFY-2: Momelotinib

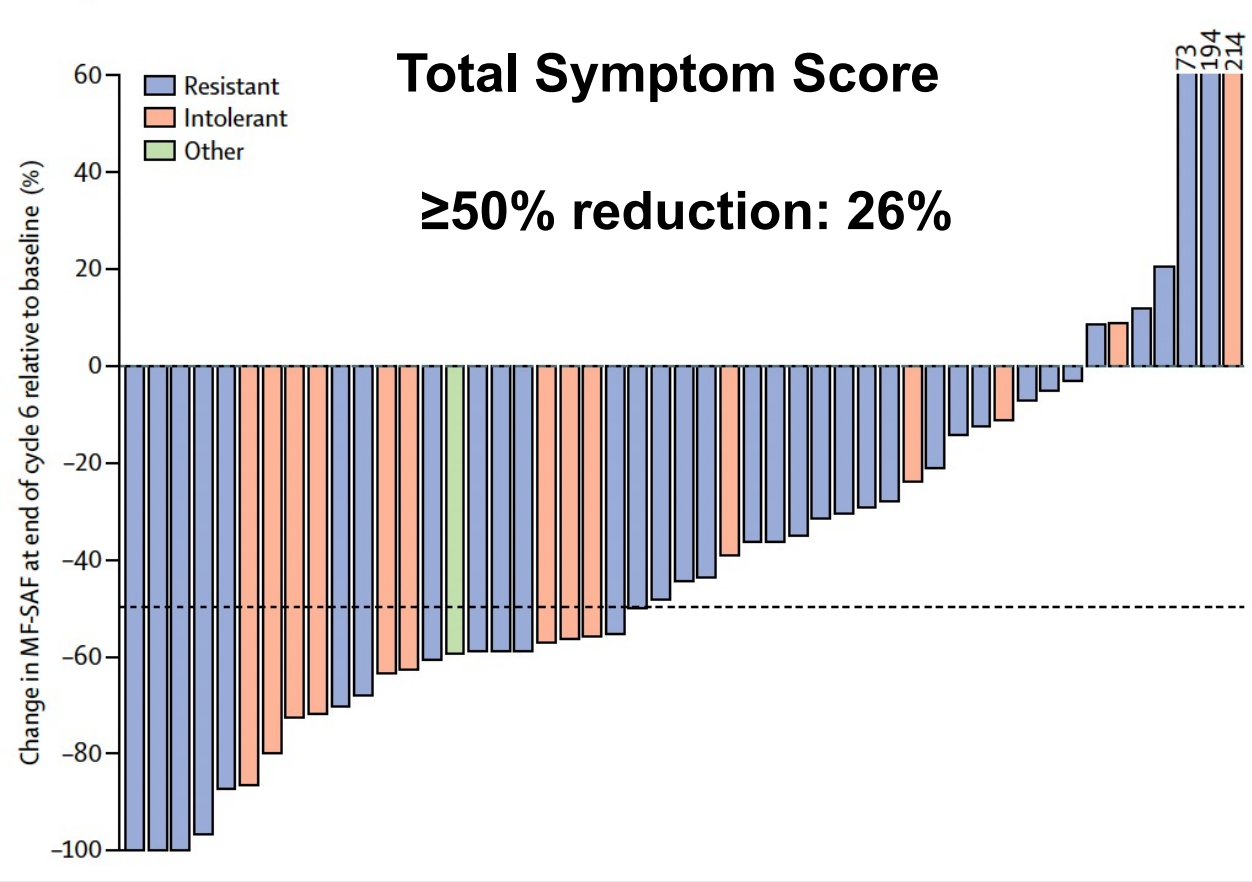
Lancet Haematol 2017;4:e317-24.

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.

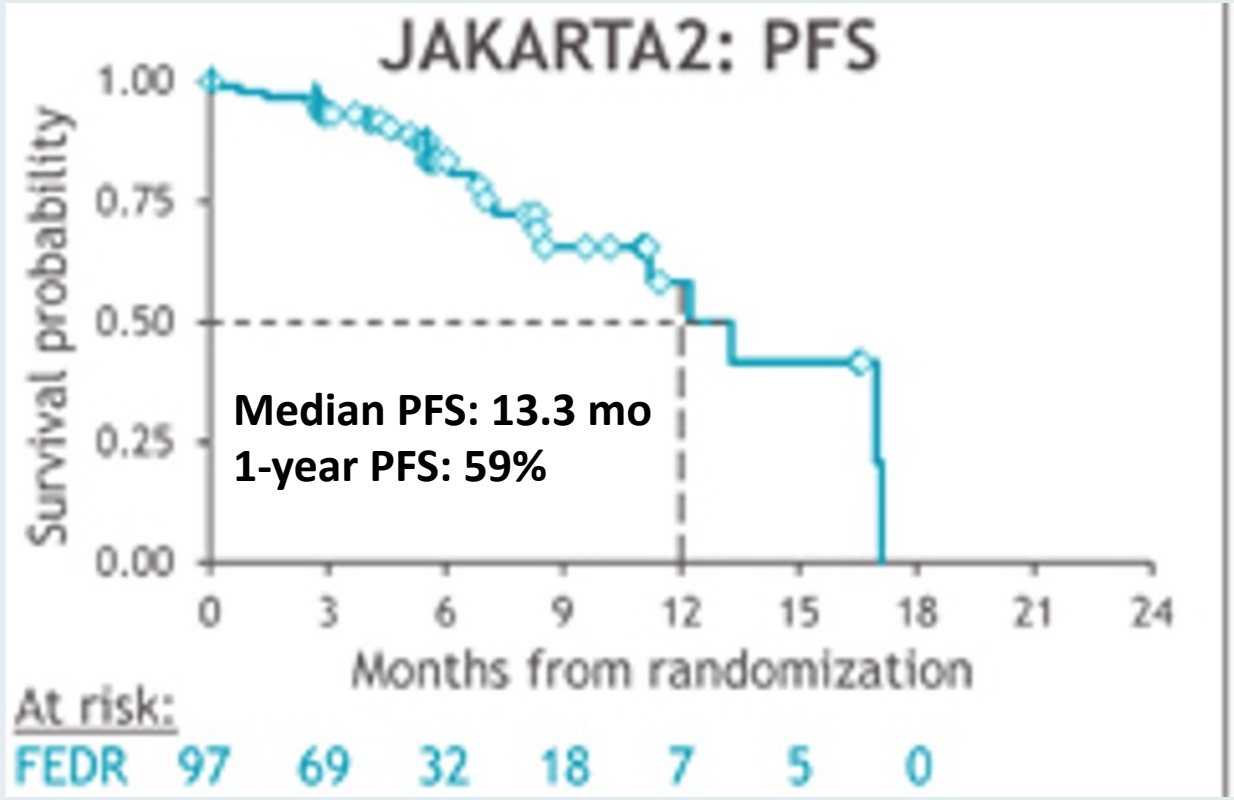
RTP RESEARCH TO PRACTICE

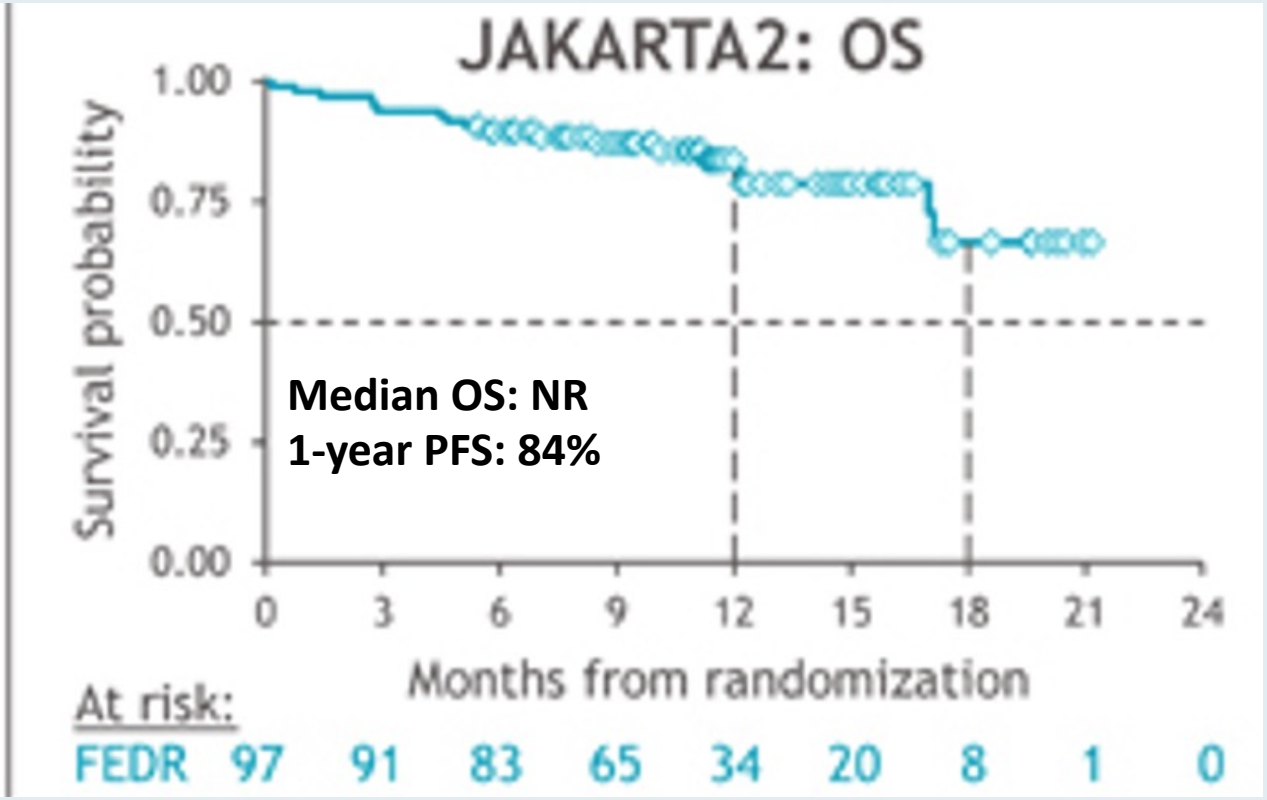
Overall and Progression-Free Survival in Patients Treated with Fedratinib as First-Line Myelofibrosis (MF) Therapy and After Prior Ruxoltinib (RUX): Results from the JAKARTA and JAKARTA2 Trials

Harrison C et al.

EHA 2021;Abstract S203.

JAKARTA2: Survival Analysis





Harrison C et al. EHA 2021;Abstract S203.

RTP RESEARCH TO PRACTICE

FREEDOM: Trial Design and Key Eligibility Criteria

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

Key eligibility criteria

- Age ≥ 18 years
- Primary, post-PV, or post-ET MF
- Prior Tx with RUX[a]
- DIPSS Int/High risk
- ECOG PS score ≤ 2
- Platelets ≥ 50 × 10^9/L
- ANC ≥ 1 × 10^9/L
- Spleen volume ≥ 450 cm^3 *or* palpable spleen ≥ 5 cm below LCM
- PB blasts ≤ 5%

Treatment phase

Fedratinib 400 mg/d
(Continuous 28d Tx cycles)

Total enrollment: N = 38

Continue fedratinib until lack of efficacy, intolerance, disease progression or withdrawal of consent

Follow-up

Follow-up for 12 months after end of Tx

Primary endpoint:

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

Key secondary endpoints:

- Symptom RR at EOC6: Proportion of pts with ≥ 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

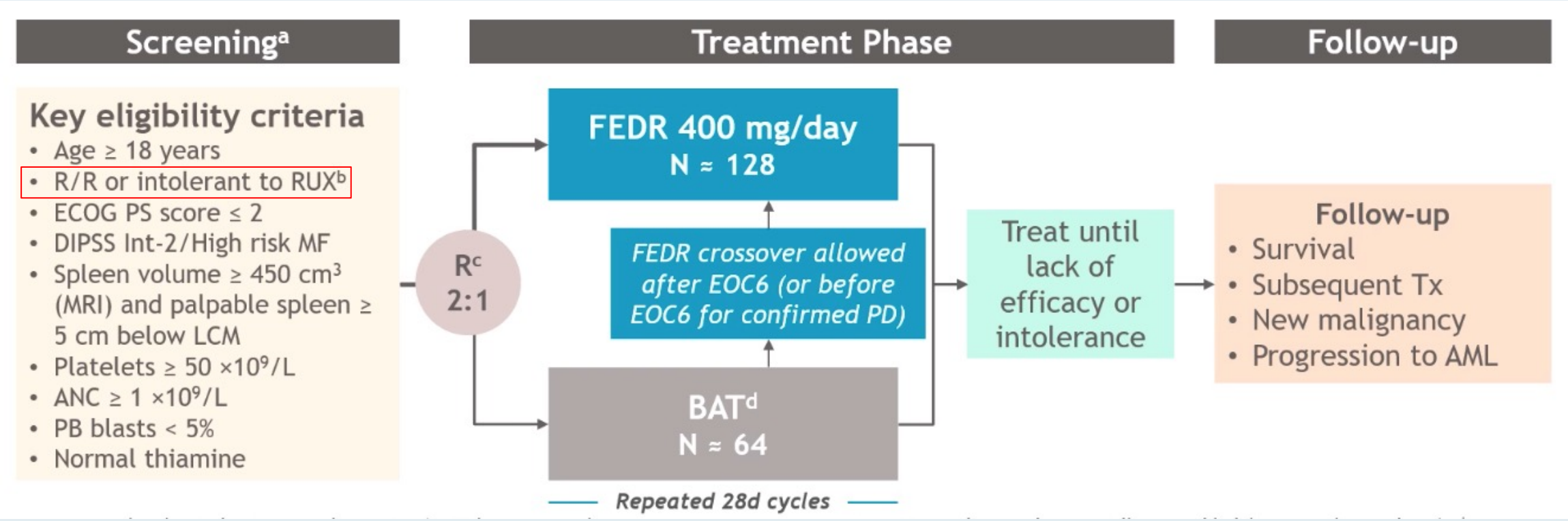
AE mitigation strategies:

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

[a]Pts must have received RUX for ≥3 mo, or for ≥28 d with development of RBC transfusion requirement (≥2 units/mo for 2 mo) or Grade ≥3 thrombocytopenia, anemia, hematoma or hemorrhage.

Gupta V et al. ASH 2021;Abstract 389.

FREEDOM2 Phase III Study Design



Vianelli N et al. ASH 2021;Abstract 3643.

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.

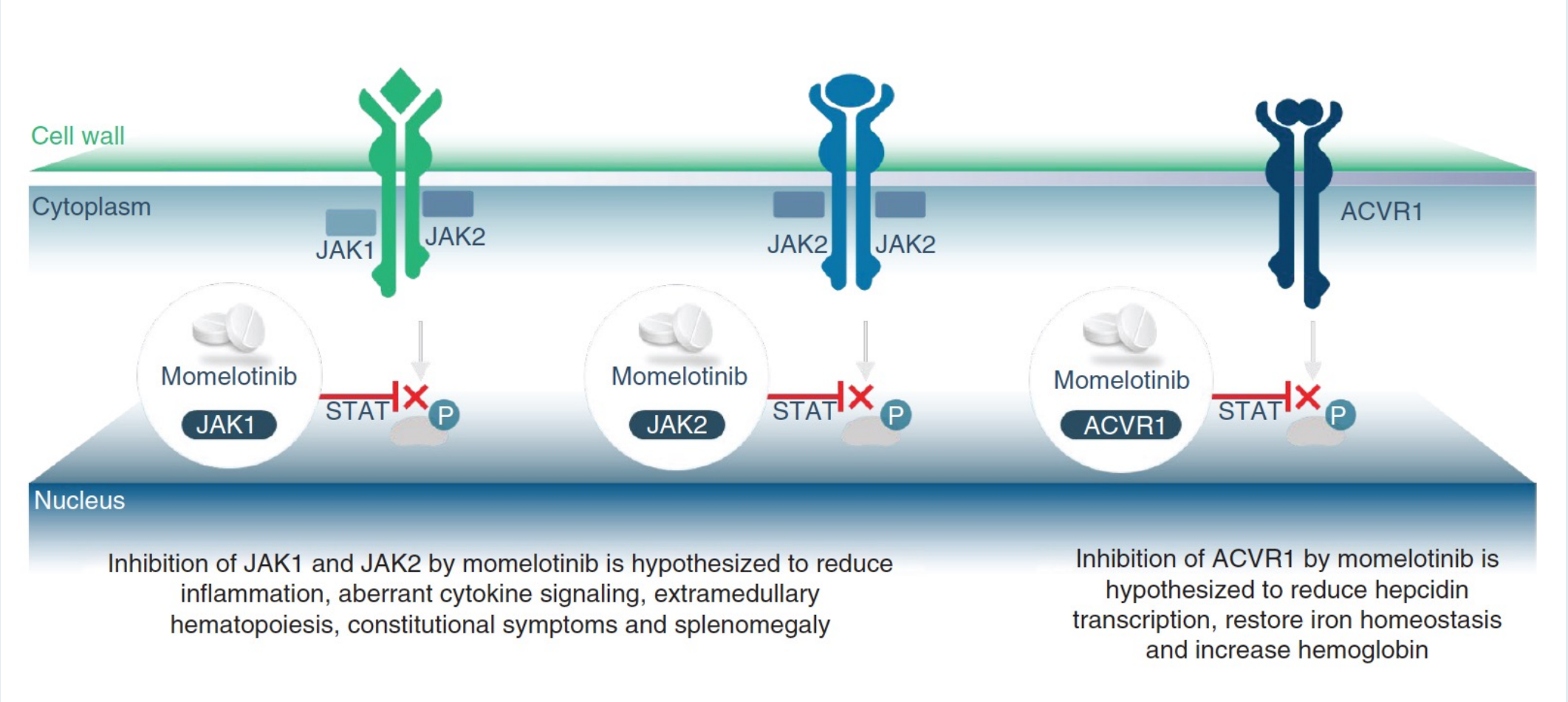
Treatment with momelotinib resulted in a statistically significant reduction in symptoms for patients with myelofibrosis, according to a press release of the topline findings from the pivotal phase 3 MOMENTUM trial (NCT04173494).

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."

https://www.cancernetwork.com/view/momelotinib-yields-statistically-significant-improvement-in-symptoms-for-myelofibrosis

Momelotinib Therapy May Decrease Inflammation, Improve Splenomegaly and Normalize Hemoglobin



Verstovsek S et al. *Future Oncol* 2021;17(12):1449-58.

Articles

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 ≥35%	7%	6%	0.90
≥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	

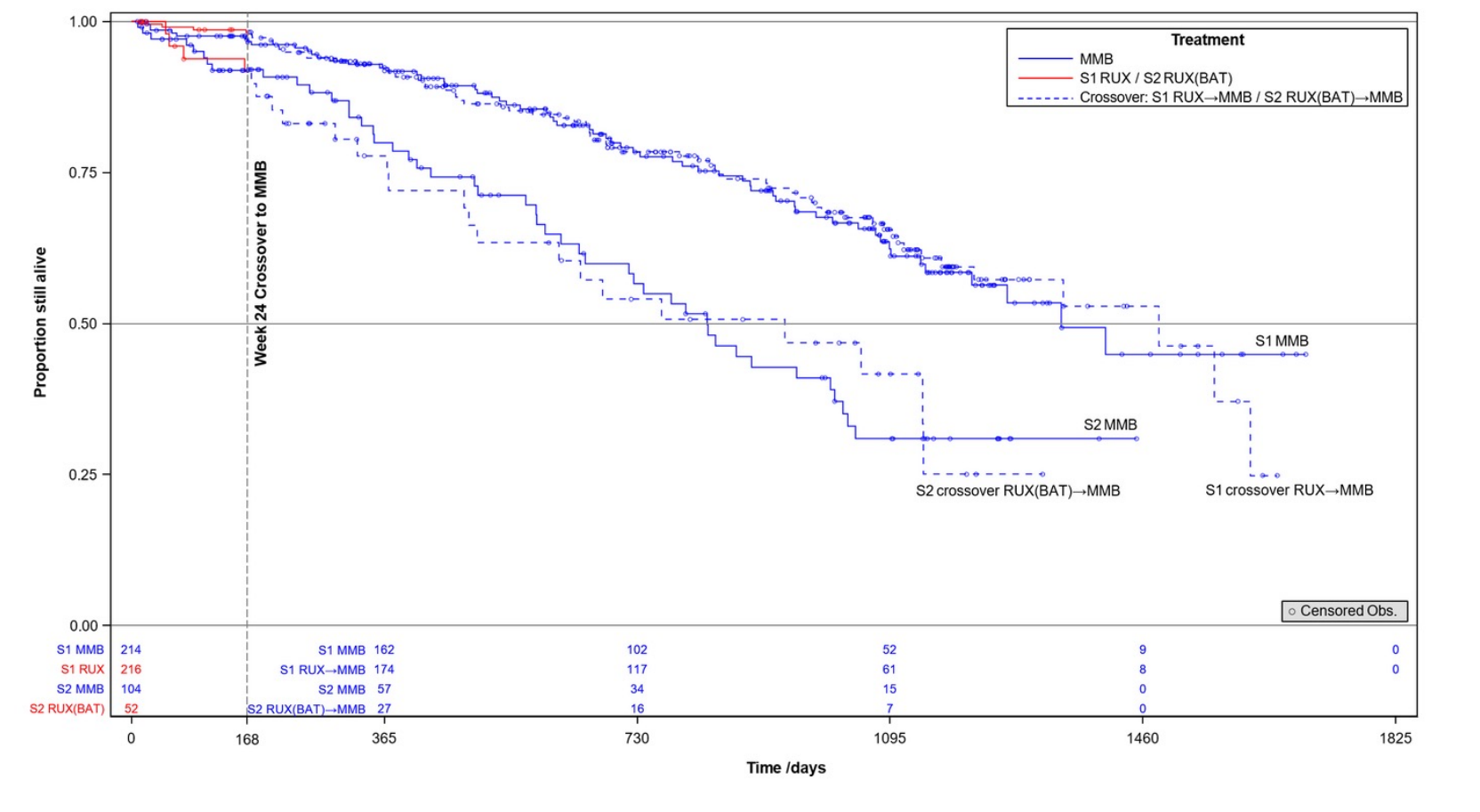
Harrison CN et al. *Lancet Haematol* 2018;5(2):e73-81.

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



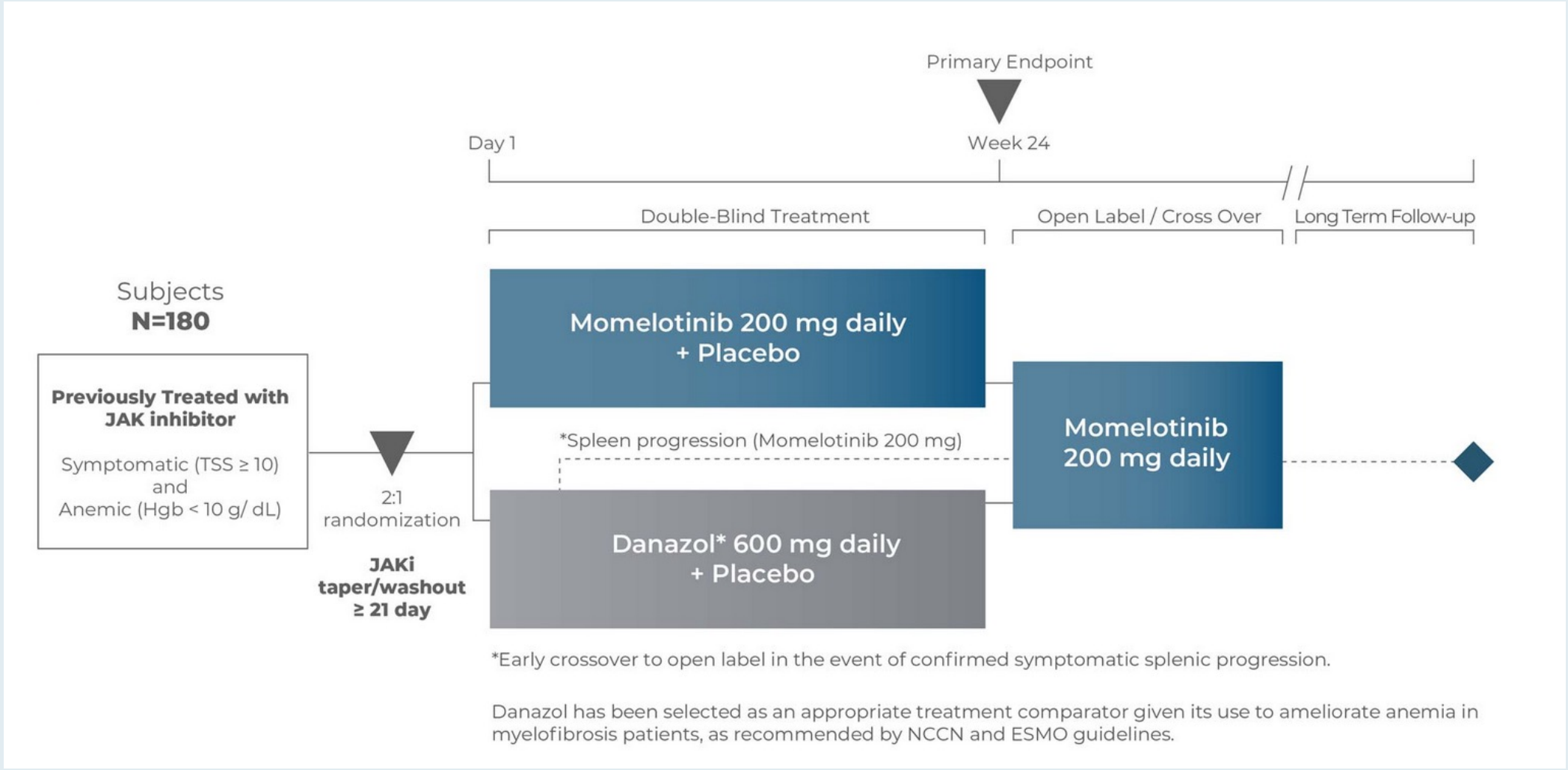
- S1 reduction in spleen volume of ≥35% from baseline at week 24 (MMB vs RUX): 26.5% vs 29.5%
- S1 transfusion independence at week 24 (MMB vs RUX): 70% vs 54%
- S2 transfusion independence at week 24 (MMB vs BAT/RUX): 44% vs 27%

Verstovsek S et al. ASH 2020;Abstract 54.

RTP RESEARCH TO PRACTICE

MOMENTUM: Phase III Trial Schema of Momelotinib in MF

Trial Identifier: NCT04173494 (Closed)



Verstovsek S et al. *Future Oncology* 2021;17(12):1449-58.

RTP RESEARCH TO PRACTICE

Novel Agents and Strategies Beyond JAK Inhibitors Under Investigation in MF

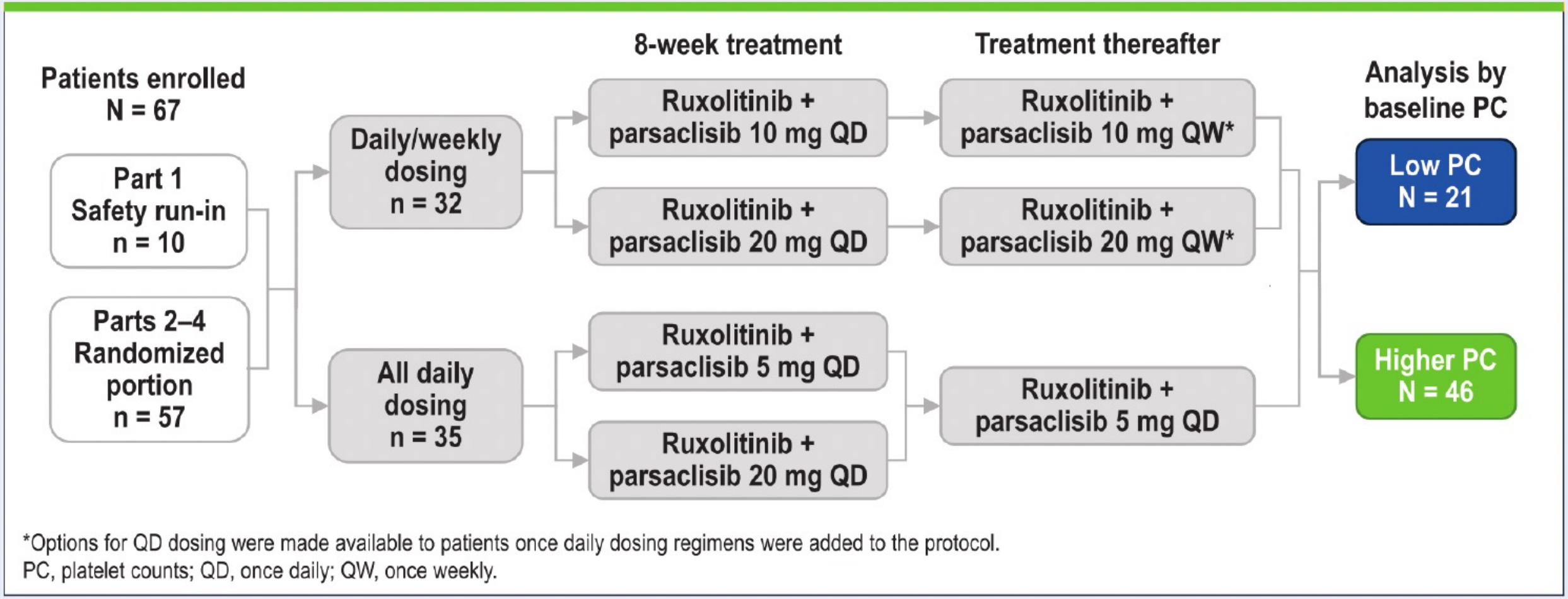
Subgroup Analysis From a Phase 2 Study of the Efficacy and Safety of Parsaclisib, a Selective PI3Kδ Inhibitor, in Combination With Ruxolitinib in Patients With Myelofibrosis

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 Daver[15]

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

ASH 2021;Abstract 3647.

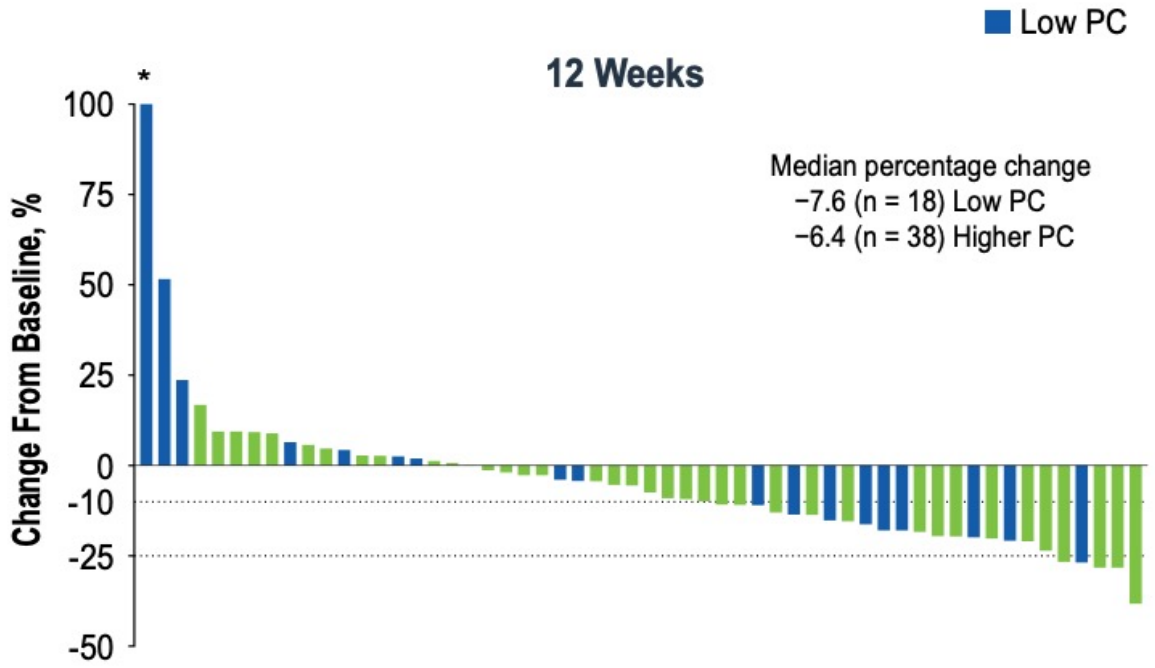
Phase II INCB 50465-201 Study of Adding Parsaclisib to Ruxolitinib

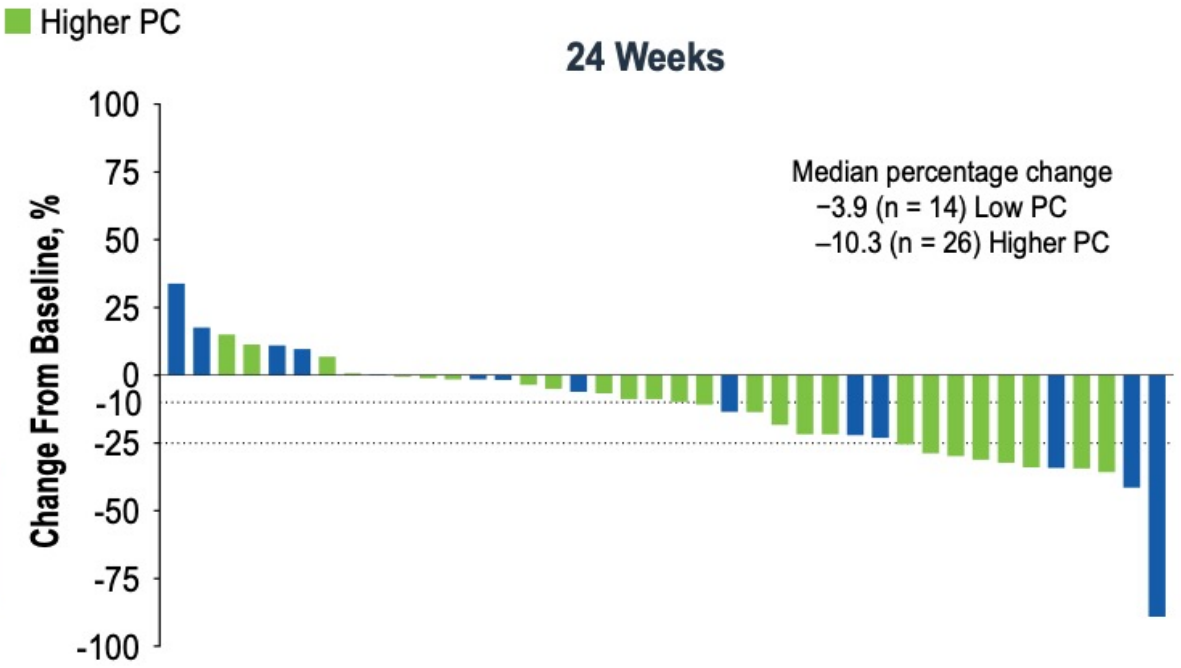


*Options for QD dosing were made available to patients once daily dosing regimens were added to the protocol.
PC, platelet counts; QD, once daily; QW, once weekly.

Yacoub A et al. ASH 2021;Abstract 3647.

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



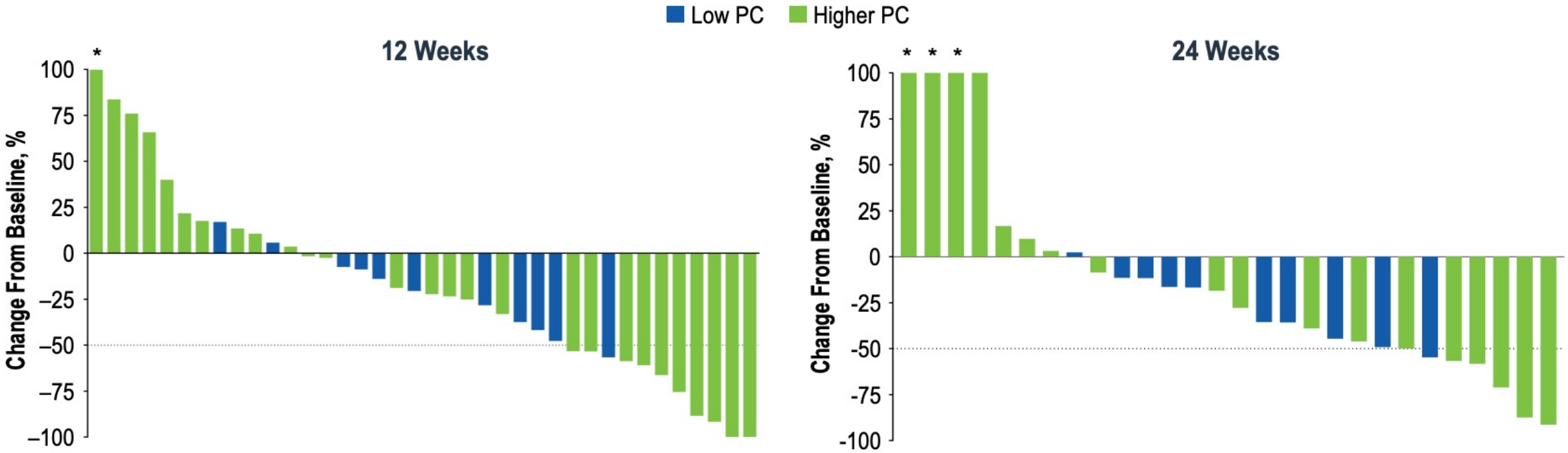


Response Category, n (%)	Low PC	Higher PC
Week 12	n = 18	n = 38
≥10% reduction	9 (50)	15 (39)
≥25% reduction	1 (6)	4 (11)
≥35% reduction	0	1 (3)

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)

Yacoub A et al. ASH 2021;Abstract 3647.

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

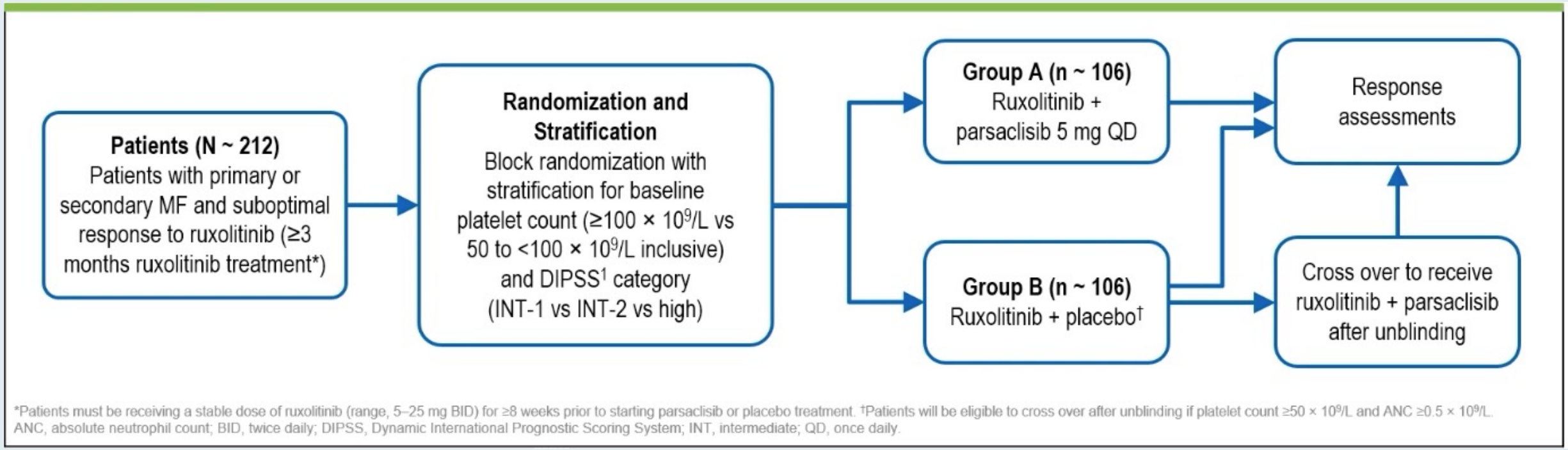


Median change in MFSAF-TSS at 12 Weeks	n	% Change (Range)
Low PC	11	−20.5 (−56.6 to 17.1)
Higher PC	27	−22.2 (−100.0 to 500.0)

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)

Yacoub A et al. ASH 2021;Abstract 3647.

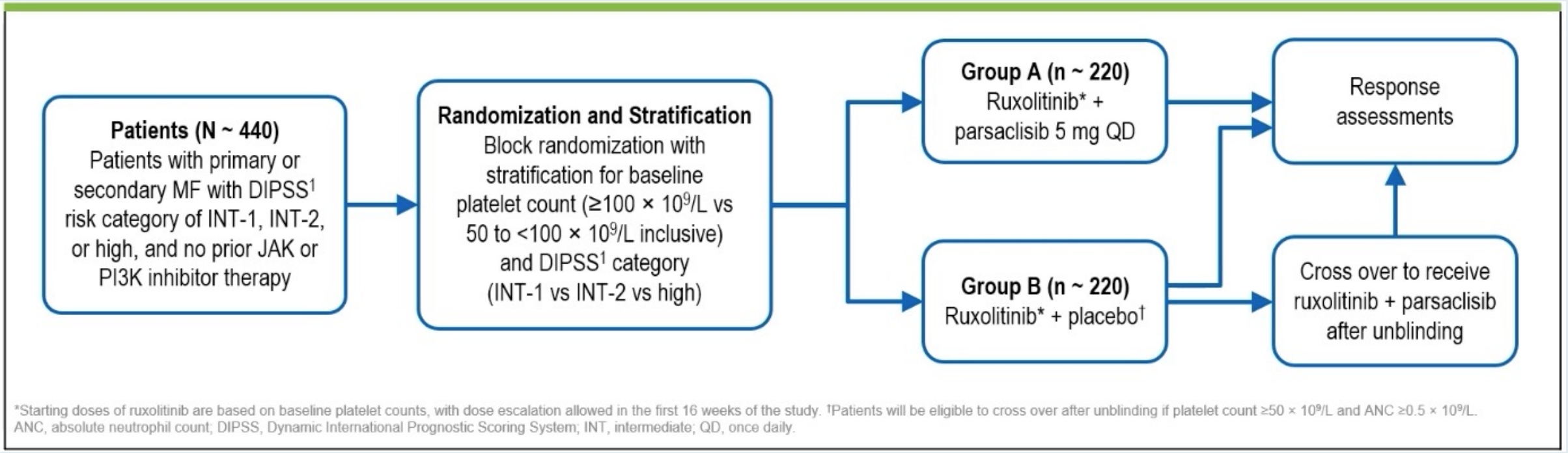
LIMBER-304 Phase III Study Design



*Patients must be receiving a stable dose of ruxolitinib (range, 5–25 mg BID) for ≥8 weeks prior to starting parsaclisib or placebo treatment. †Patients will be eligible to cross over after unblinding if platelet count ≥50 × 10^9/L and ANC ≥0.5 × 10^9/L.
ANC, absolute neutrophil count; BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; INT, intermediate; QD, once daily.

Yacoub A et al. ASH 2021;Abstract 1502.

LIMBER-313 Phase III First-Line Study Design



*Starting doses of ruxolitinib are based on baseline platelet counts, with dose escalation allowed in the first 16 weeks of the study. †Patients will be eligible to cross over after unblinding if platelet count ≥50 × 10⁹/L and ANC ≥0.5 × 10⁹/L.
ANC, absolute neutrophil count; DIPSS, Dynamic International Prognostic Scoring System; INT, intermediate; QD, once daily.

Yacoub A et al. ASH 2021;Abstract 2579.

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

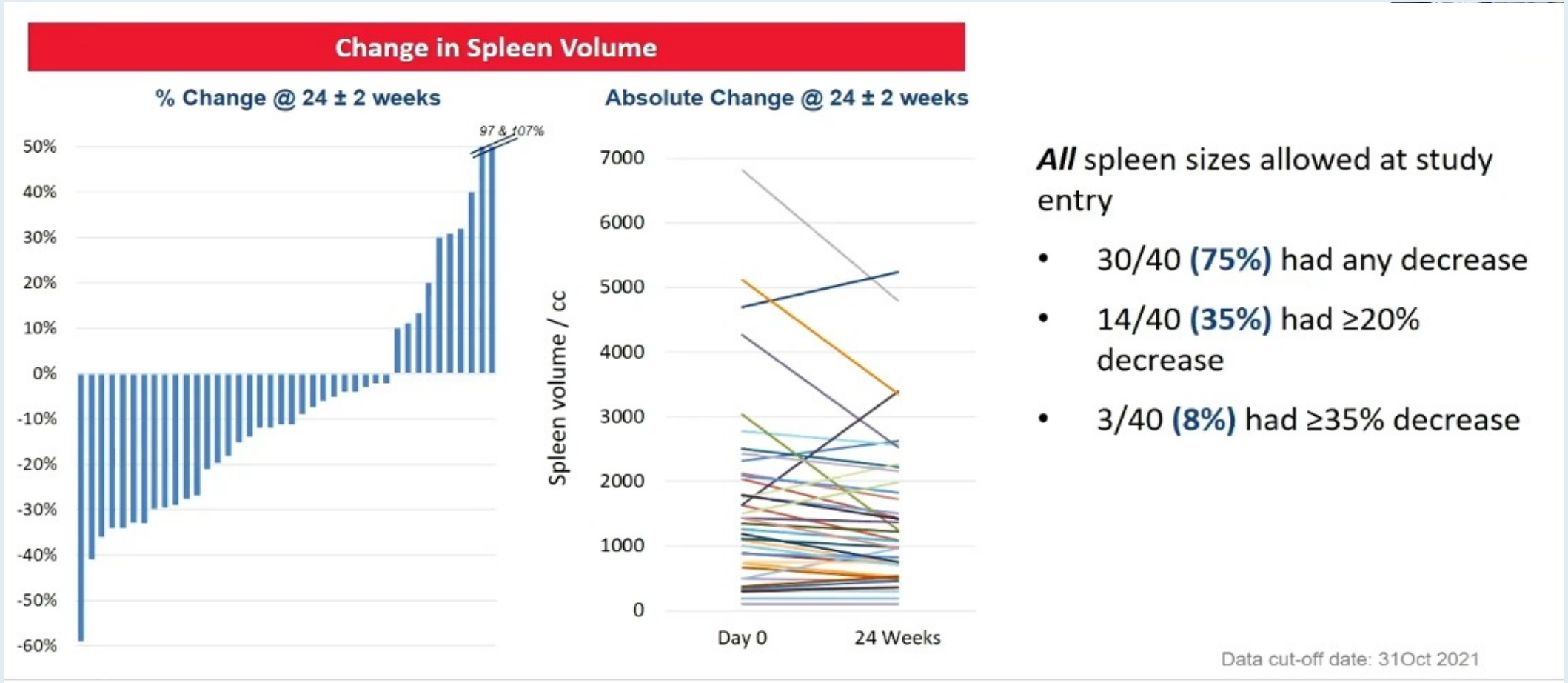
- Symptom reduction (MPN-SAF TSS)
- Changes in cytokine profiles
- Changes in mutant allele frequencies (MAF)
- Changes in bone marrow (BM) fibrosis

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 ≥100 x10^9/L**
- Peripheral blasts ≤10%
- Spleen of ***any size***
- ECOG PS ≤2

Gill H et al. ASH 2021;Abstract 139.

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 ≥50%.

Gill H et al. ASH 2021;Abstract 139.

RTP RESEARCH TO PRACTICE

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%)

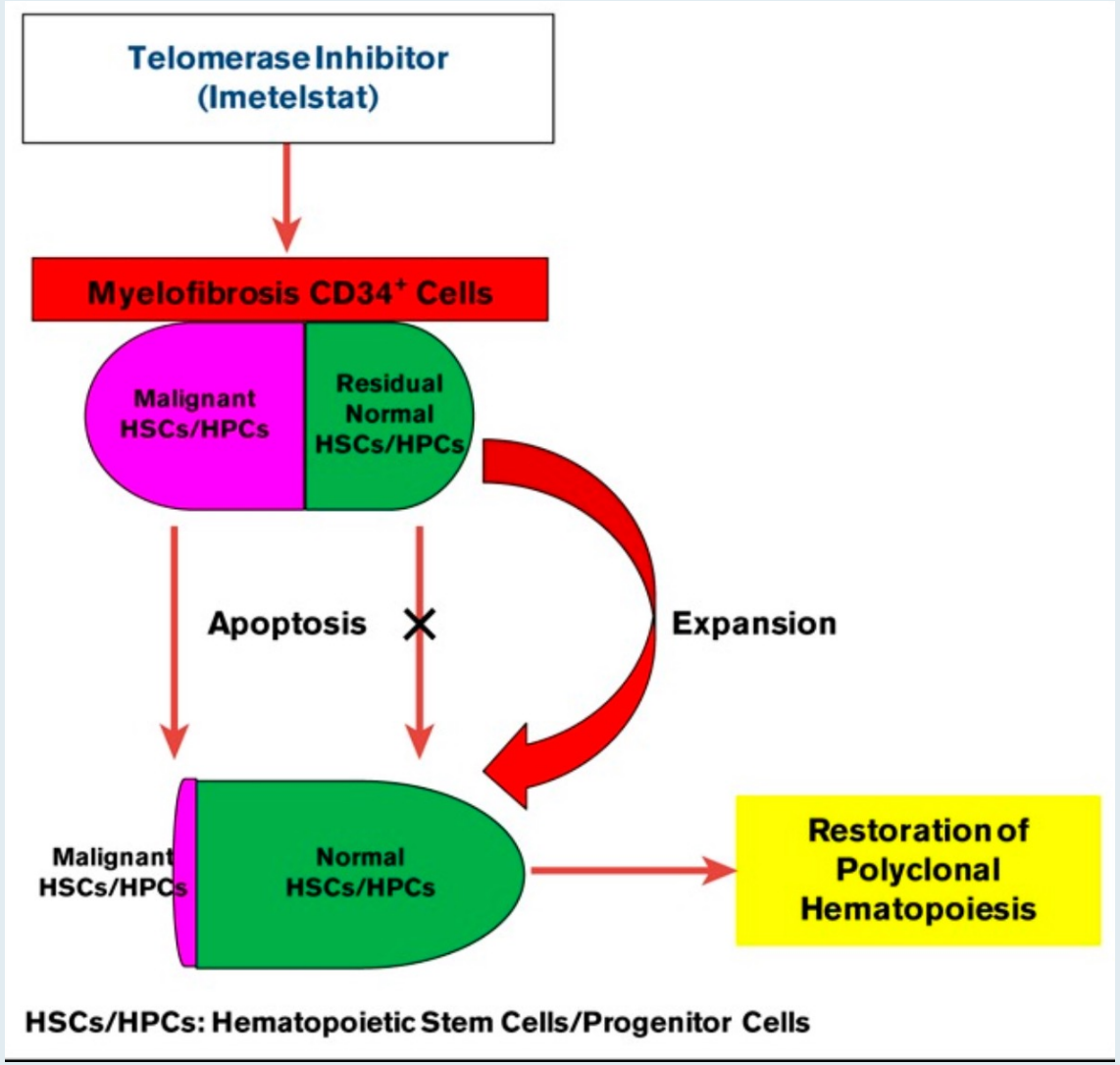
Any grade of AE occurring at a frequency of >15% included regardless of relatedness; total number of events = 1443

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

Gill H et al. ASH 2021;Abstract 139.

RTP RESEARCH TO PRACTICE

Telomerase Inhibitor Imetelstat: Mechanism of Action



Wang X et al. *Blood Advances* 2018;2(18):2378-88.

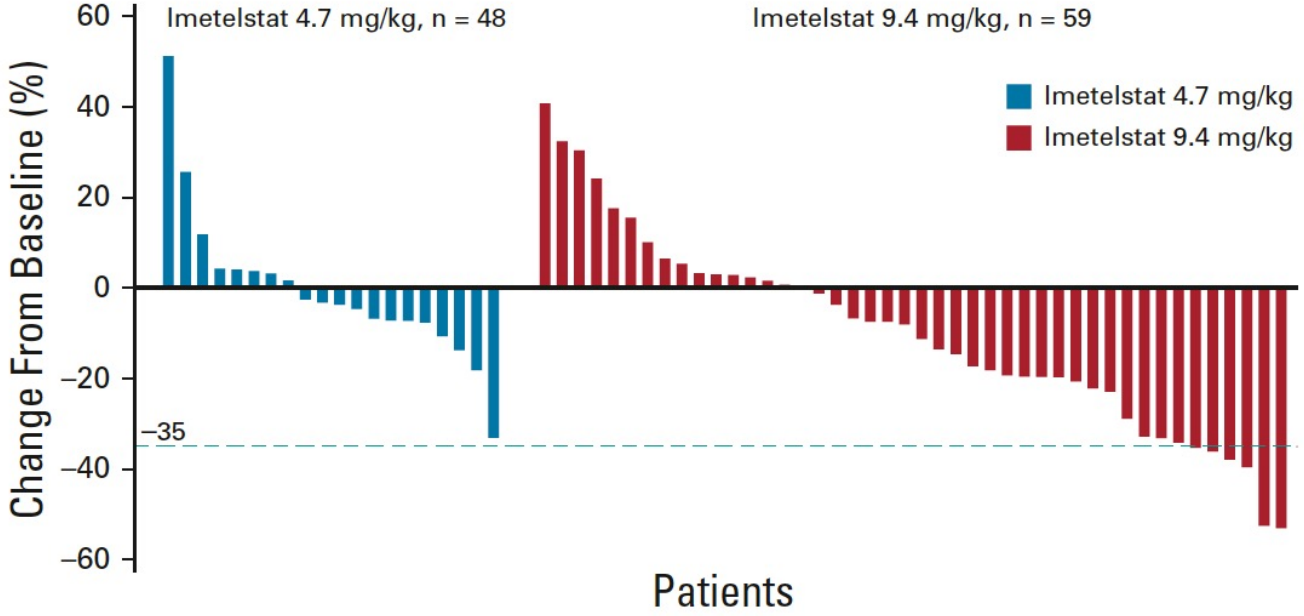
original reports

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

John Mascarenhas, MD[1]; Rami S. Komrokji, MD[2]; Francesca Palandri, MD[3]; Bruno Martino, MD[4]; Dietger Niederwieser, MD, PhD[5]; Andreas Reiter, MD[6]; Bart L. Scott, MD[7]; Maria R. Baer, MD[8]; Ronald Hoffman, MD[1]; Olatoyosi Odenike, MD[9]; Alessandro M. Vannucchi, MD[10]; Jacqueline Bussolari, PhD[11]; Eugene Zhu, PhD[11]; Esther Rose, MD[11]; Laurie Sherman, BSN[12]; Souria Dougherty, BS, MBA[12]; Libo Sun, PhD[12]; Fei Huang, PhD[12]; Ying Wan, PhD[12]; Faye M. Feller, MD[12]; Aleksandra Rizo, MD, PhD[12]; and Jean-Jacques Kiladjian, MD, PhD[13]

J Clin Oncol 2021;39:2881-92.

Phase II Trial of Imetelstat in Relapsed/Refractory Myelofibrosis



Spleen Response	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)
≥ 10% SVR at week 24, No. (%)	4 (8.3)	22 (37.3)
≥ 20% SVR at week 24, No. (%)	1 (2.1)	13 (22)
≥ 35% SVR at week 24, No. (%)	0	6 (10.2)

- 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.

Mascarenhas J et al. *J Clin Oncol* 2021;39:2881-92.

RTP RESEARCH TO PRACTICE

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.

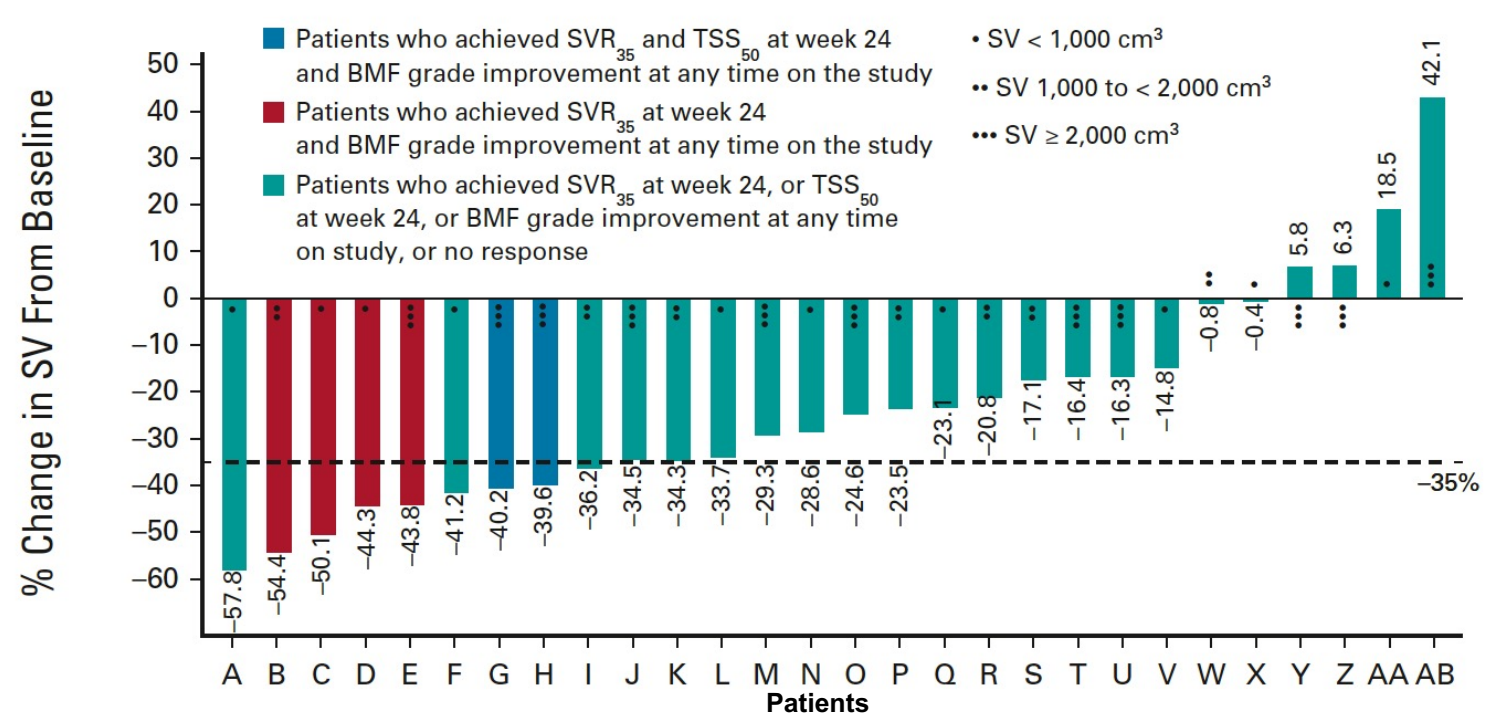
original reports

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

Claire N. Harrison, MD[1]; Jacqueline S. Garcia, MD[2]; Tim C. P. Somervaille, MBBS, PhD[3,4]; James M. Foran, MD[5]; Srdan Verstovsek, MD, PhD[6]; Catriona Jamieson, MD, PhD[7]; Ruben Mesa, MD[8]; Ellen K. Ritchie, MD[9]; Srinivas K. Tantravahi, MBBS[10]; Pankit Vachhani, MD[11]; Casey L. O'Connell, MD[12]; Rami S. Komrokji, MD[13]; Jason Harb, PhD[14]; Jessica E. Hutti, PhD[14]; Leanne Holes, MBA[14]; Abdullah A. Masud, MS, PhD[14]; Silpa Nuthalapati, PhD[14]; Jalaja Potluri, MD[14]; and Naveen Pemmaraju, MD[6]

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

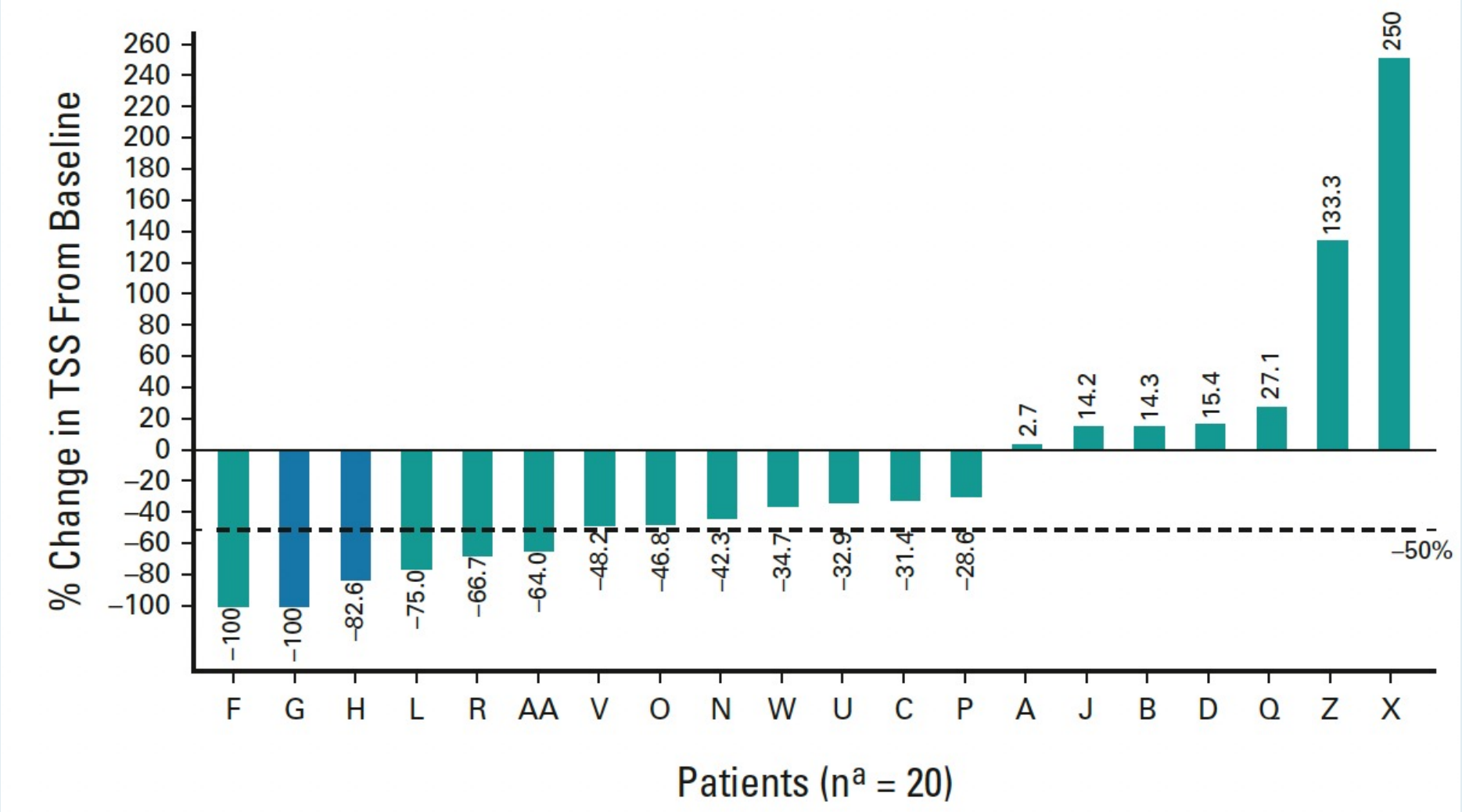
Phase II Trial of Adding the Bcl-XL/Bcl-2 Inhibitor Navitoclax to Ruxolitinib for Patients with MF and Disease Progression or a Suboptimal Response



- ≥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.

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

Percent Change in TSS from Baseline at Week 24

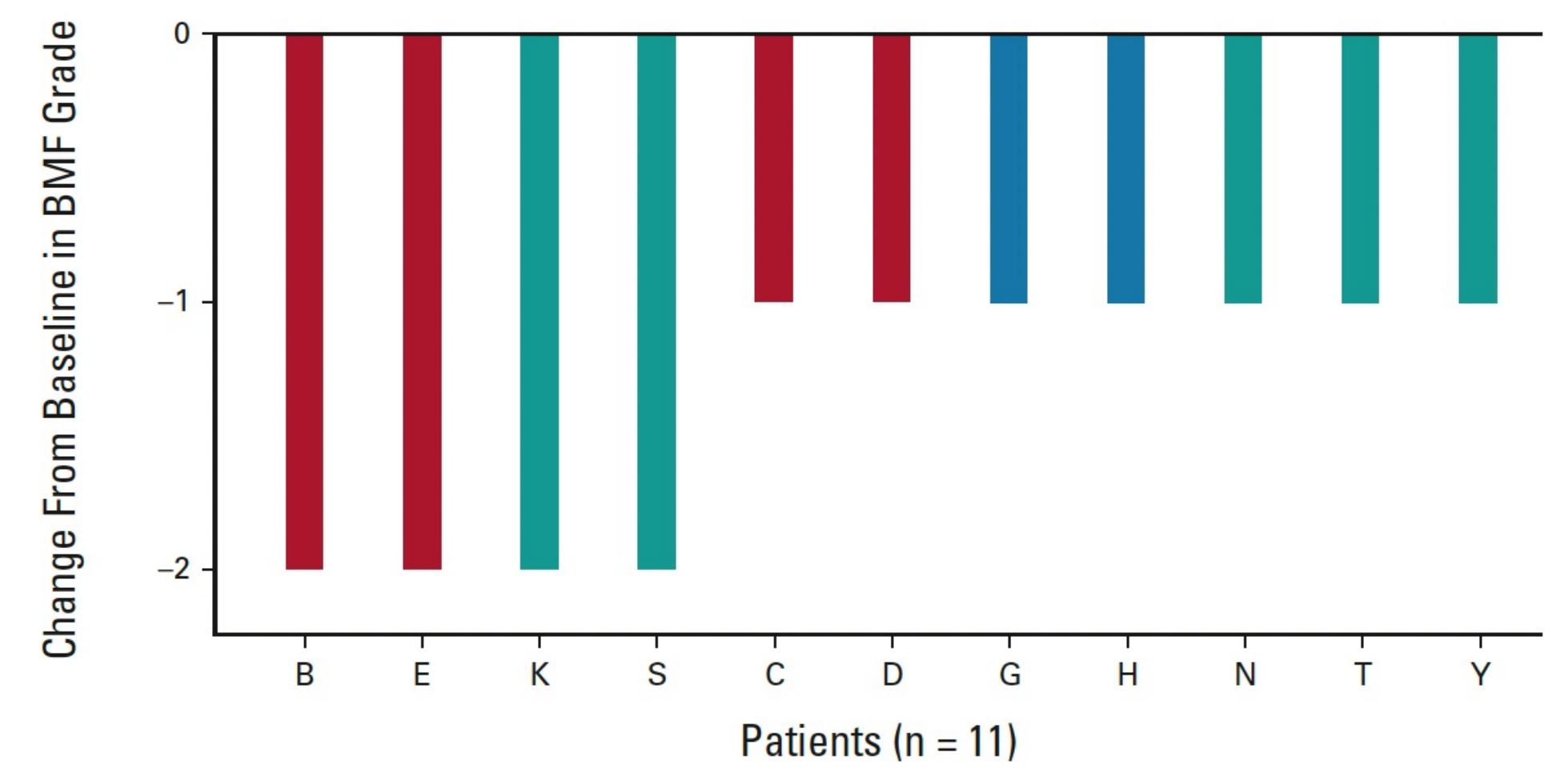


TSS = total symptom score

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

RTP RESEARCH TO PRACTICE

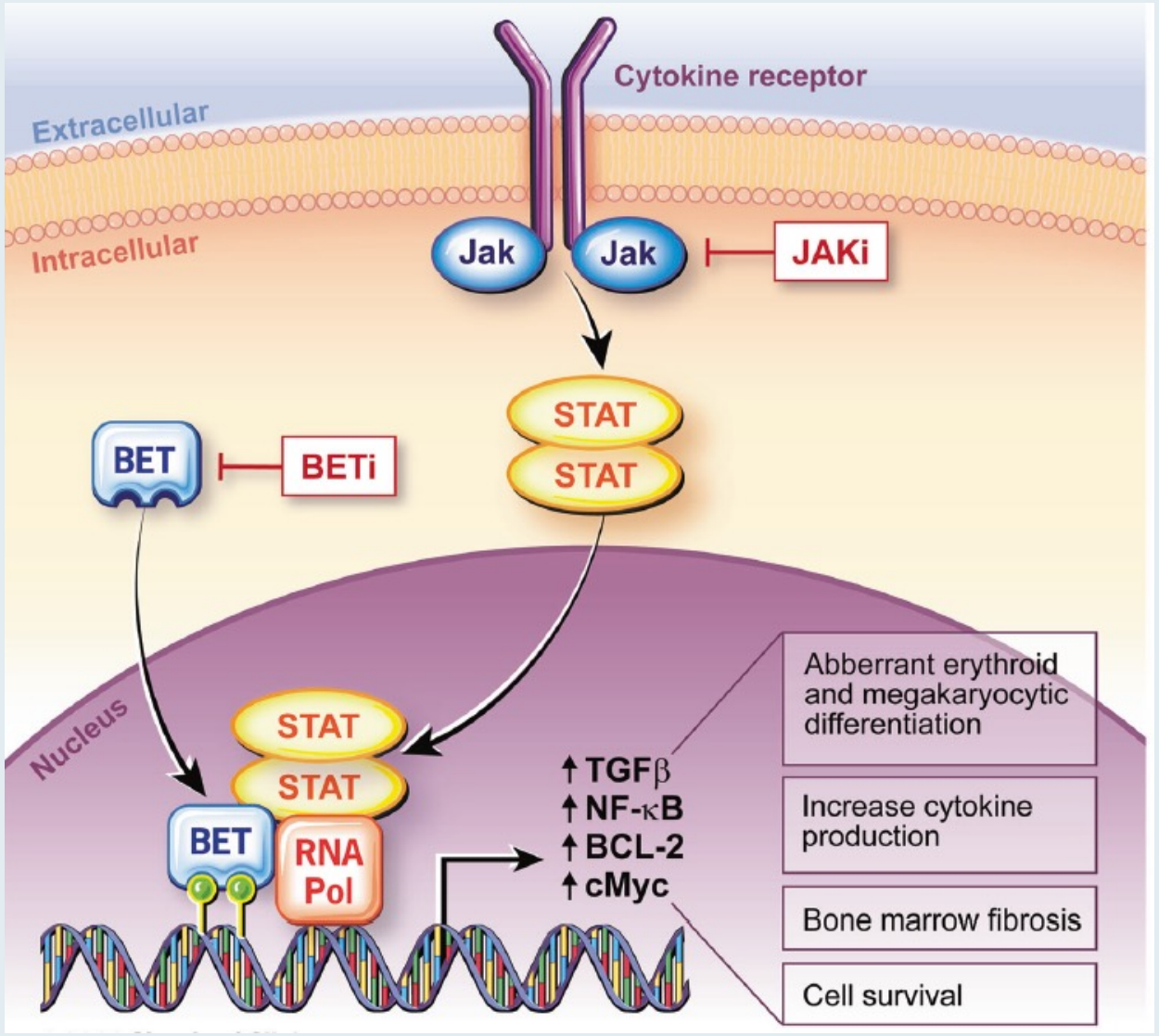
Percent Change in Bone Marrow Fibrosis (BMF) from Baseline



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

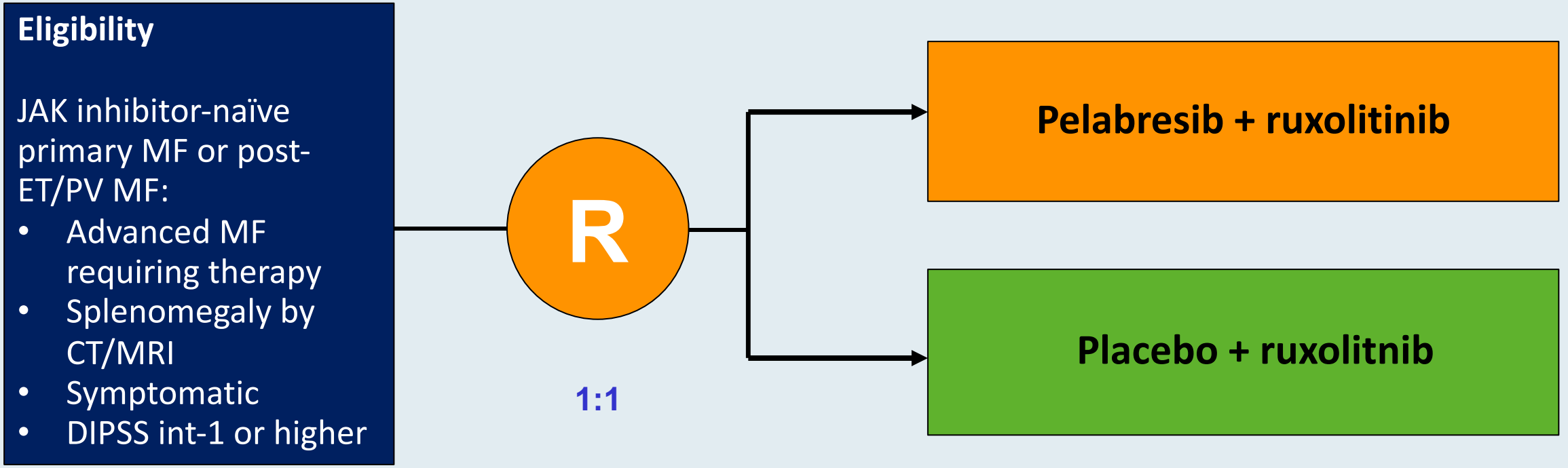
RTP RESEARCH TO PRACTICE

Mechanism of Action of BET Inhibitor Pelabresib



Mascarenhas J et al. *Leukemia* 2021;35(12):3361-3.

MANIFEST-2: Phase III Trial Design



Primary Endpoint: SVR35 at 24 weeks
Key Secondary Endpoint: TSS50 by at 24 weeks

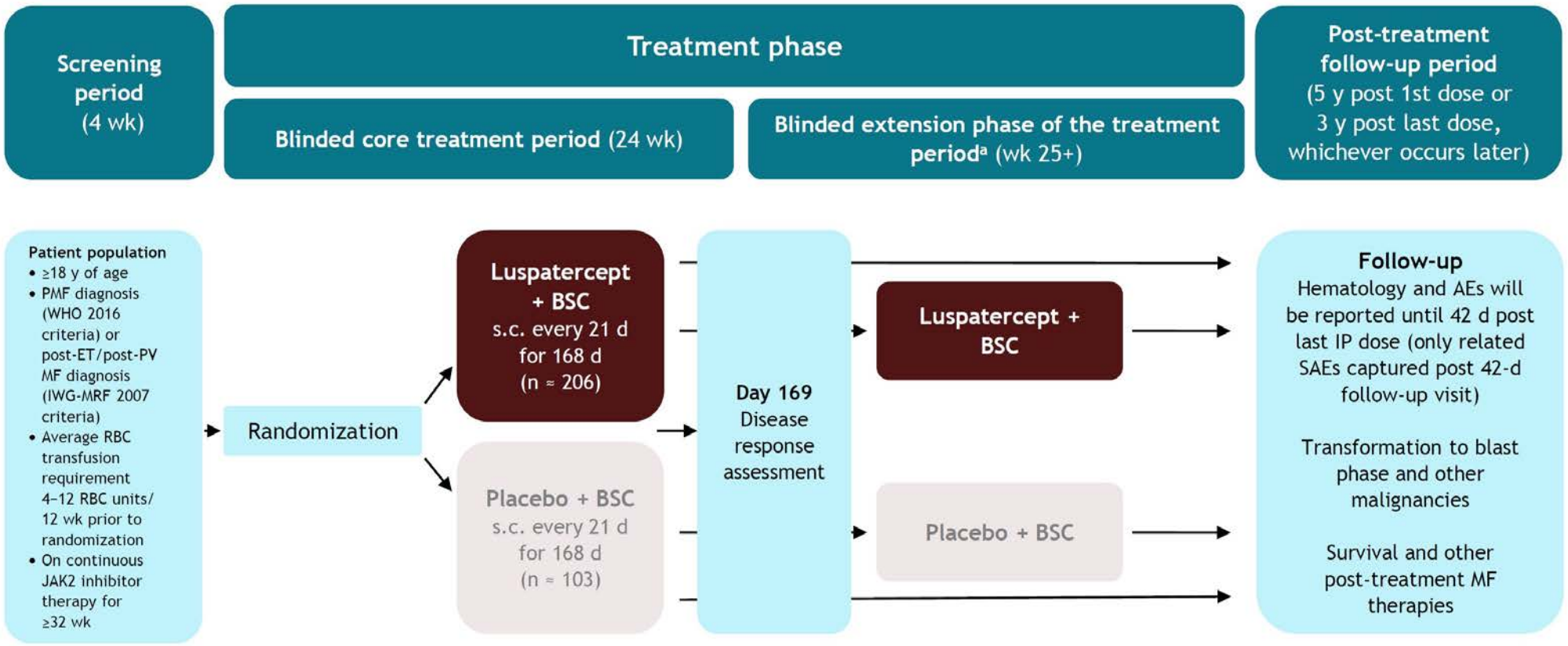
Kremyanskaya M et al. ASH 2021;Abstract 141.

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



[a]Patients 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.

Mesa RA et al. ASH 2021;Abstract 1490.

Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Thursday, May 26, 2022
5:00 PM – 6:00 PM ET

Faculty

Harry H Yoon, MD

Moderator

Neil Love, MD

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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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