Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Myelofibrosis

A CME Satellite Symposium During the Society of Hematologic Oncology 2023 Annual Meeting

Thursday, September 7, 2023
6:34 PM – 7:34 PM CT

Faculty

Prithviraj Bose, MD
Andrew T Kuykendall, MD

Moderator

John Mascarenhas, MD

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Faculty

Prithviraj Bose, MD
Professor, Department of Leukemia
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

Moderator

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

Andrew T Kuykendall, MD
Assistant Member
Department of Malignant Hematology
Moffitt Cancer Center
Assistant Professor
Department of Oncologic Sciences
University of South Florida
Tampa, Florida

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Survey Participants

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Associate Professor of Medicine
Hematology and Medical Oncology
Deputy Director for Clinical Research
Cleveland Clinic Taussig Cancer Institute
Medical Director
Case Comprehensive Cancer Center
Clinical Research Office
Cleveland Clinic
Cleveland, Ohio

Ruben A Mesa, MD
President, Enterprise Cancer Service Line
Executive Director, Atrium Health Wake Forest Baptist
Comprehensive Cancer Center
Enterprise Senior Vice President, Atrium Health
Vice Dean for Cancer Programs
Professor of Medicine
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Professor Claire Harrison
Deputy Chief Medical Officer — Research, Data and Analytics
Professor of Myeloproliferative Neoplasms
Guy’s and St Thomas’ NHS Foundation Trust
London, United Kingdom

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Accreditation Information

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Dr Gerds — Disclosures

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Prof Harrison — Disclosures

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Contracted Research	AbbVie Inc, Bristol Myers Squibb, CTI BioPharma Corp, Geron, GSK, Imago BioSciences, Janssen Biotech Inc, Karyopharm Therapeutics, Keros Therapeutics, MorphoSys, Novartis
Data and Safety Monitoring Board/Committee	Keros Therapeutics
Speakers Bureau	AbbVie Inc, AOP Health, Bristol Myers Squibb, CTI BioPharma Corp, GSK, MorphoSys, Novartis
Trustee	Blood Cancer UK

All of the relevant financial relationships of individuals for this activity have been mitigated.

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Dr Kuykendall — Disclosures

Advisory Committee	AbbVie Inc, Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma Corp, Incyte Corporation, PharmaEssentia
Consulting Agreements	AbbVie Inc, GSK, Kartos Therapeutics, MorphoSys, Protagonist Therapeutics
Contracted Research	Bristol Myers Squibb, GSK, Janssen Biotech Inc, MorphoSys, Protagonist Therapeutics
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Dr Mascarenhas (Moderator) — Disclosures

Advisory Committee	CTI BioPharma Corp, Geron, Incyte Corporation, MorphoSys
Consulting Agreements	AbbVie Inc, Bristol Myers Squibb, Celgene Corporation, CTI BioPharma Corp, Geron, Imago BioSciences, Incyte Corporation, Kartos Therapeutics, Karyopharm Therapeutics, Merck, MorphoSys, Novartis, Pfizer Inc
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Dr Mesa — Disclosures

Advisory Committee	AbbVie Inc, Geron, Incyte Corporation, Telios Pharma Inc
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Contracted Research	Blueprint Medicines, Bristol Myers Squibb, Celgene Corporation, CTI BioPharma Corp, Incyte Corporation, Sierra Oncology
Data and Safety Monitoring Board/Committee	Geron, Telios Pharma Inc

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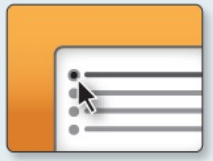
Clinicians in the Meeting Room

Access program slides using the URL included in the program syllabus.



Please take a moment to complete the pre- and postmeeting surveys. Instructions are included in the handout with the syllabus.

To ask a question, please email DrNeilLove@ResearchToPractice.com. We will aim to address as many questions as possible throughout the meeting.

To complete your course evaluation and receive CME credit, please follow the instructions included in the program syllabus.

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Clinicians Attending via Zoom

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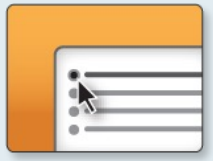

Answer Survey Questions: Complete the pre- and postmeeting surveys.

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Cases from the Community: Investigators Discuss the Application of Available Research in the Care of Patients with Diffuse Large B-Cell Lymphoma

A CME Satellite Symposium During the Society of Hematologic Oncology 2023 Annual Meeting

Friday, September 8, 2023
11:37 AM – 12:37 PM CT

Faculty

Matthew Lunning, DO
Laurie H Sehn, MD, MPH

Moderator

Christopher R Flowers, MD, MS

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Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Myelofibrosis

A CME Satellite Symposium During the Society of Hematologic Oncology 2023 Annual Meeting

Thursday, September 7, 2023
6:34 PM – 7:34 PM CT

Faculty

Prithviraj Bose, MD
Andrew T Kuykendall, MD

Moderator

John Mascarenhas, MD

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Agenda

Module 1 – Clinical Decision-Making for Patients with Myelofibrosis (MF) — Dr Bose

Module 2 – Management of MF in Special Patient Populations — Dr Mascarenhas

Module 3 – Future Directions in the Management of MF — Dr Kuykendall

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Agenda

Module 1 – Clinical Decision-Making for Patients with Myelofibrosis (MF) — Dr Bose

Module 2 – Management of MF in Special Patient Populations — Dr Mascarenhas

Module 3 – Future Directions in the Management of MF — Dr Kuykendall

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

 Dr Bose	MIPSS70-plus version 2.0
 Dr Kuykendall	DIPSS, GIPSS
 Dr Mascarenhas	DIPSS
 Dr Gerds	MIPSS70
 Prof Harrison	DIPSS, DIPSS Plus, MIPSS70, MIPSS70-plus version 2.0, GIPSS
 Dr Mesa	MIPSS70-plus version 2.0

A 75-year-old man presents with fatigue, drenching night sweats, weight loss and abdominal pain and is diagnosed with MF. Platelet count = 110,000/µL, Hgb = 11.1 g/dL, WBC = 18,000/µL with 2% blasts. Regulatory and reimbursement issues aside, which treatment would you most likely recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Ruxolitinib
 Dr Kuykendall	Ruxolitinib
 Dr Mascarenhas	Ruxolitinib
 Dr Gerds	Ruxolitinib
 Prof Harrison	Ruxolitinib
 Dr Mesa	Ruxolitinib

If administering ruxolitinib to a patient with higher-risk, symptomatic MF, splenomegaly and a platelet count of 150,000/µL, which doses would you generally use?

	Starting dose	Maximum dose
 Dr Bose	15 mg BID	25 mg BID
 Dr Kuykendall	15 mg BID	25 mg BID
 Dr Mascarenhas	10 mg BID	25 mg BID
 Dr Gerds	20 mg BID	20 mg BID
 Prof Harrison	10 mg BID	25 mg BID
 Dr Mesa	15 mg BID	25 mg BID

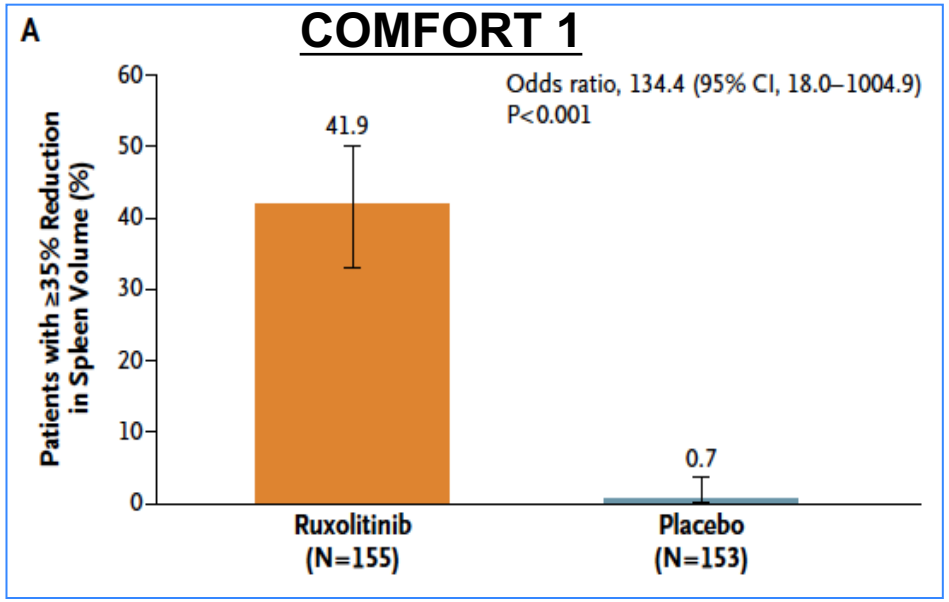
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

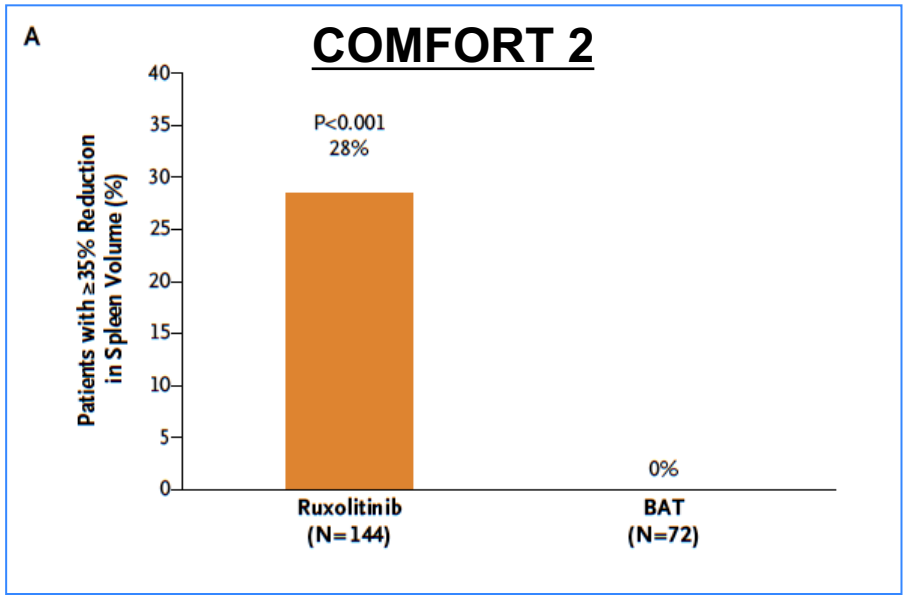
Optimizing Clinical Decision-Making for Patients with MF

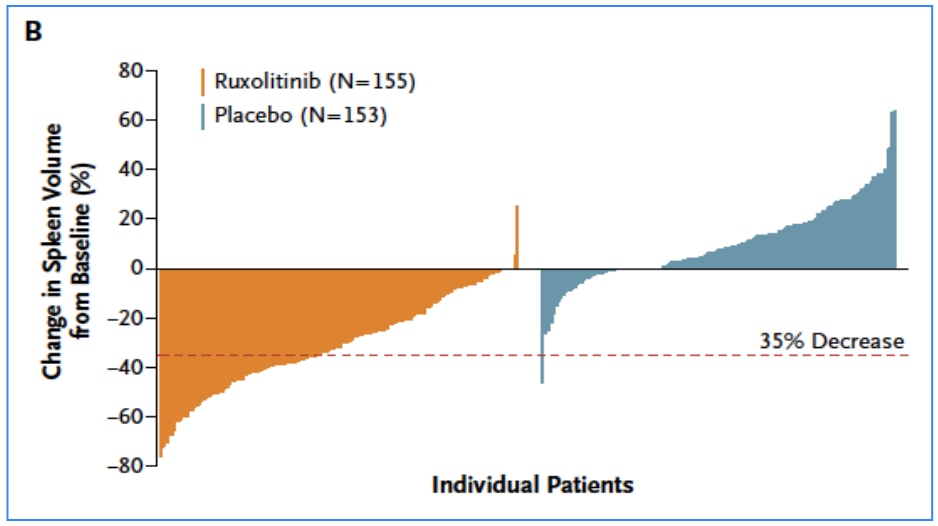
Prithviraj Bose, M.D.
Professor, Department of Leukemia

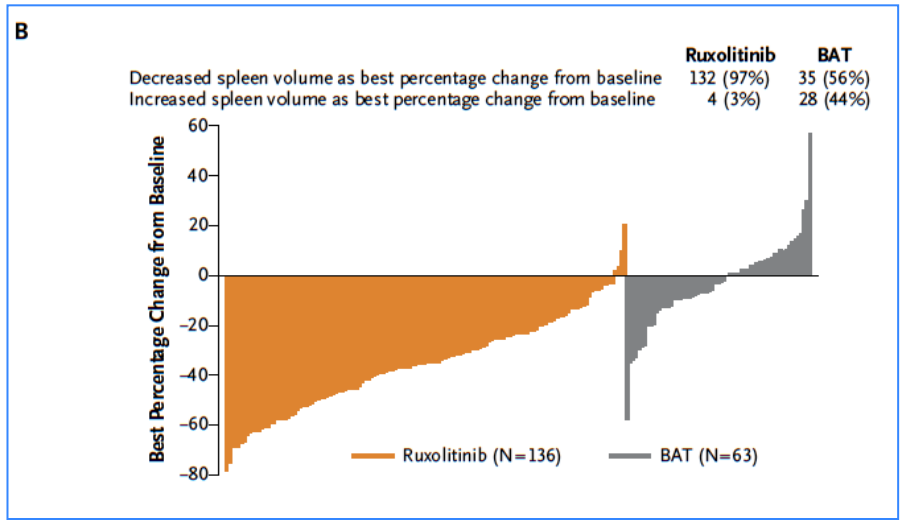
Research To Practice Symposium, SOHO 11th Annual Meeting
September 7th, 2023

Ruxolitinib Phase III Trials (COMFORT I & II – Spleen Response)







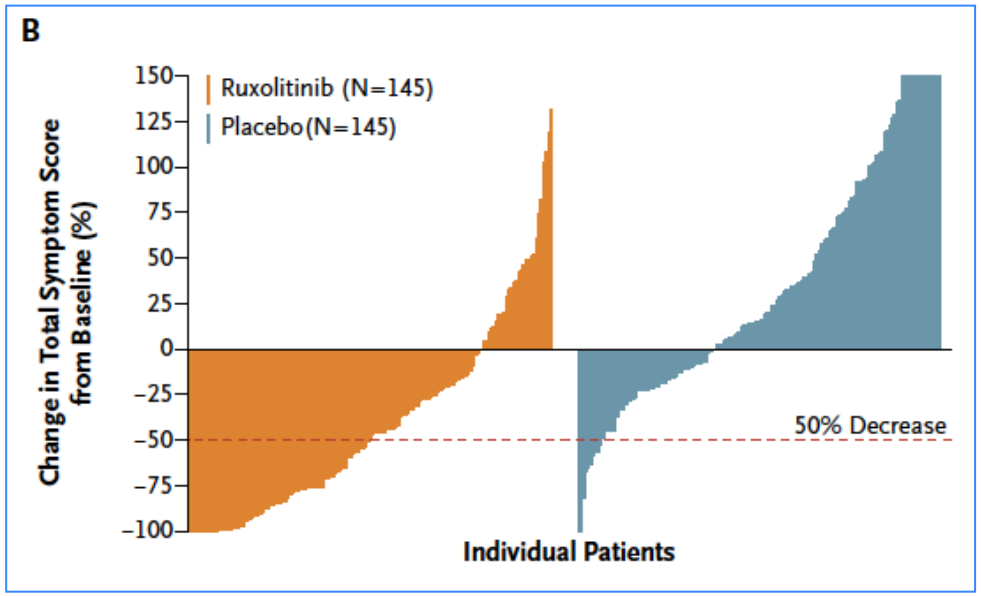


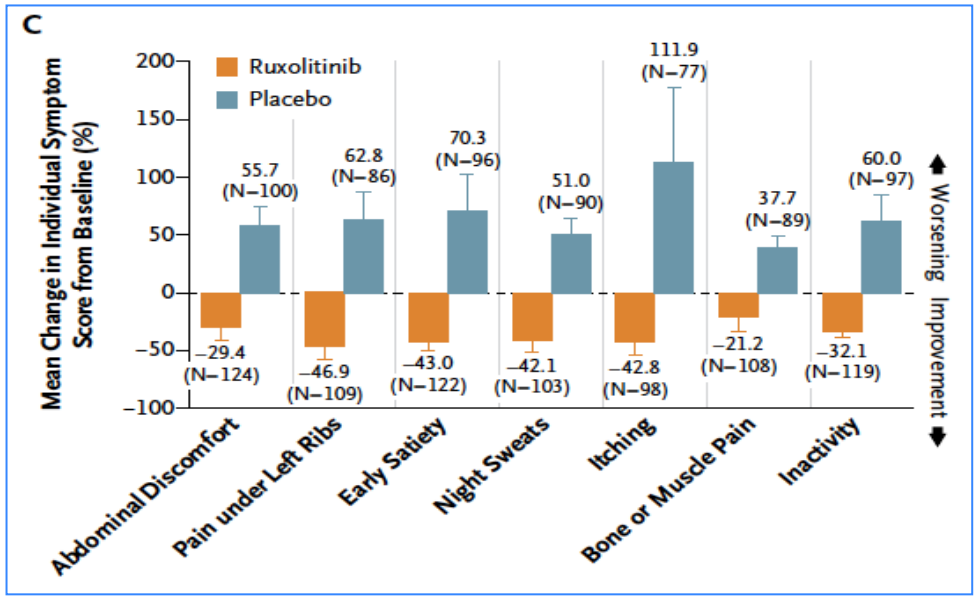
Reductions in spleen volume w/ RUX seen across all patient subgroups, including
Sex, MF subtype, and prognostic category (all prespecified analyses)

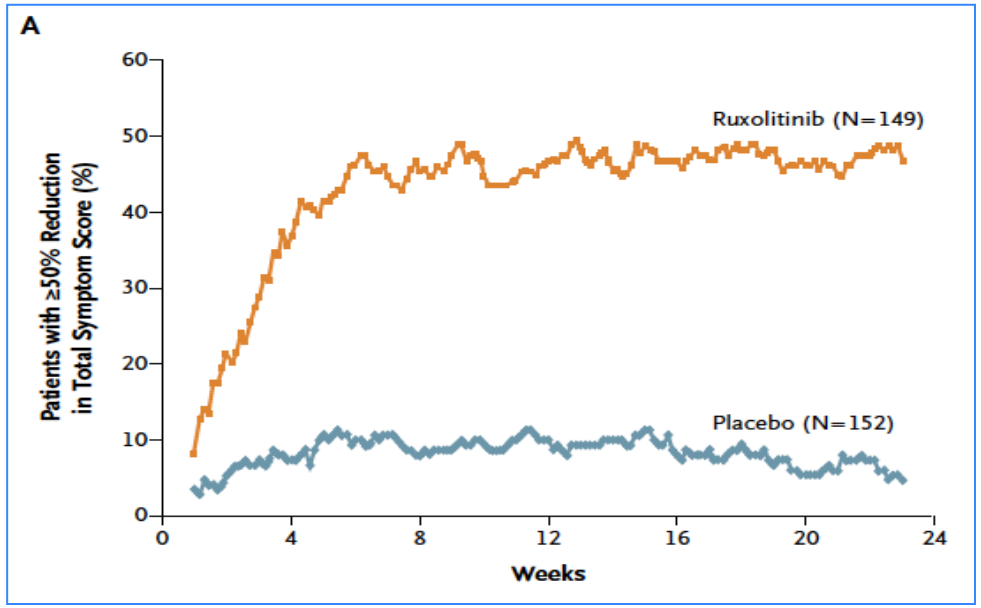
JAK2 V617F mutation status (post hoc analyses)

Verstovsek, et. al. *N Engl J Med*. 2012;366:799-807; Harrison, et al. *N Engl J Med*. 2012;366:787-798

Ruxolitinib Phase III Trials (COMFORT I – Symptom Response)

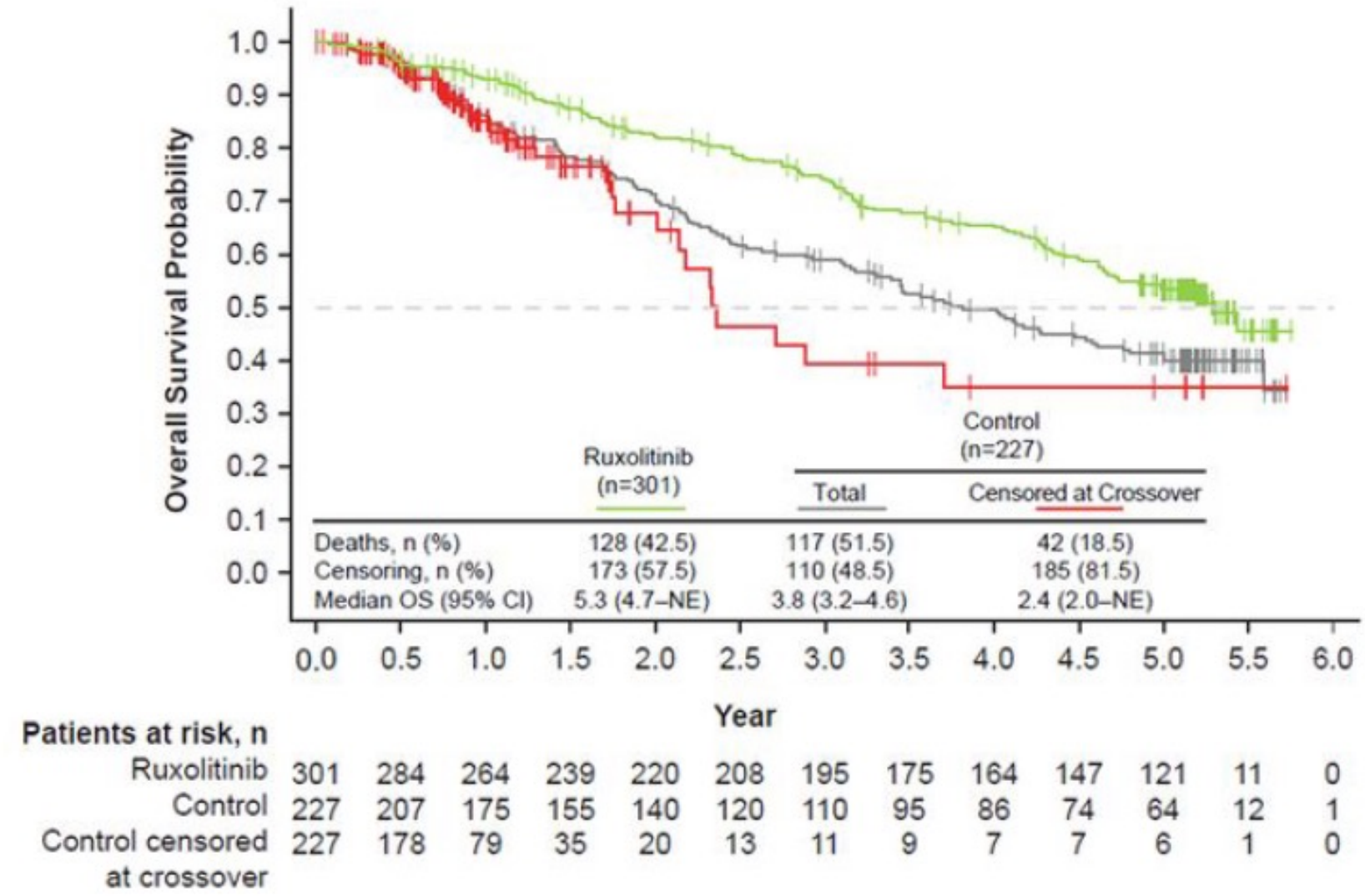






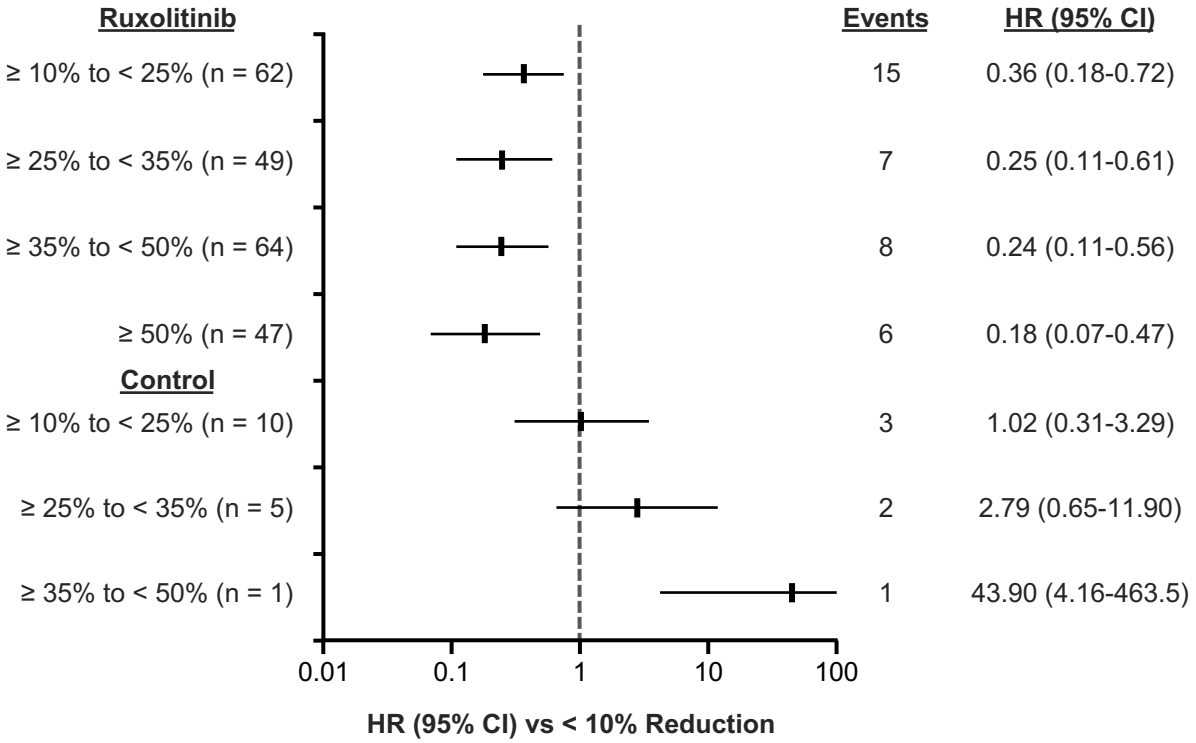
Verstovsek, et. al. *N Engl J Med*. 2012;366:799-807.

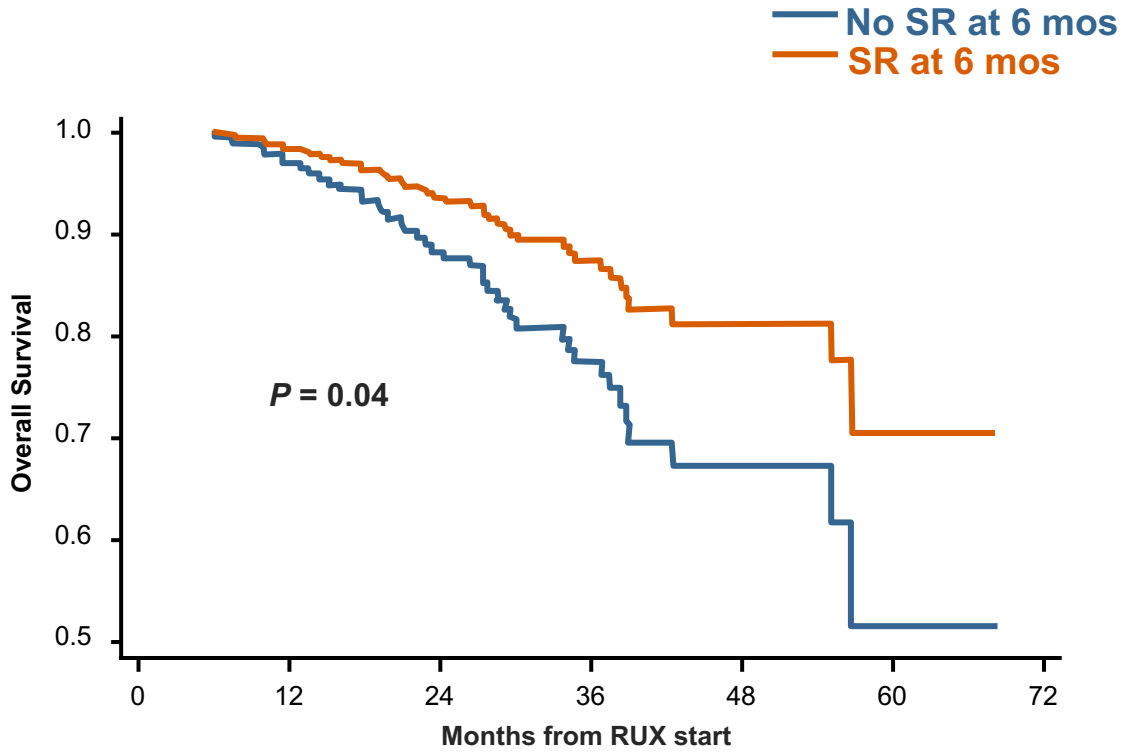
COMFORT Trials Five-Year OS Pooled Analysis



Verstovsek S et al ASH 2016; Verstovsek S et al. J Hem Onc 2017;10:156.

Spleen Response (SR) Correlates With Survival





In the pooled COMFORT 1 and 2 analysis, reductions in spleen size with ruxolitinib treatment correlated with longer survival

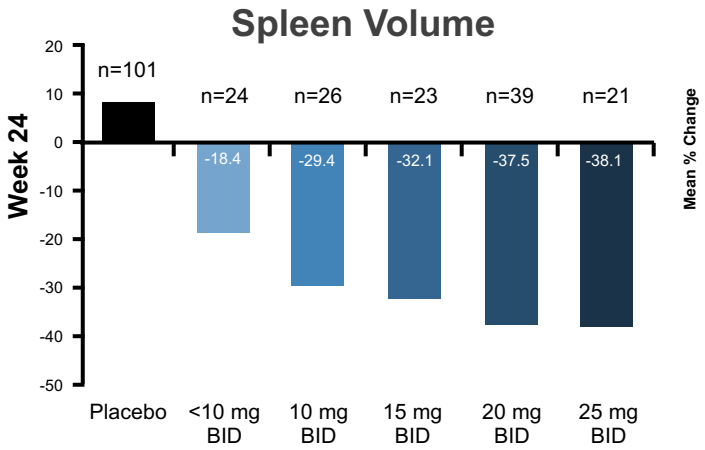
In a retrospective study of 284 patients treated with ruxolitinib for ≥ 1 year, spleen response at 6 months correlated with longer survival

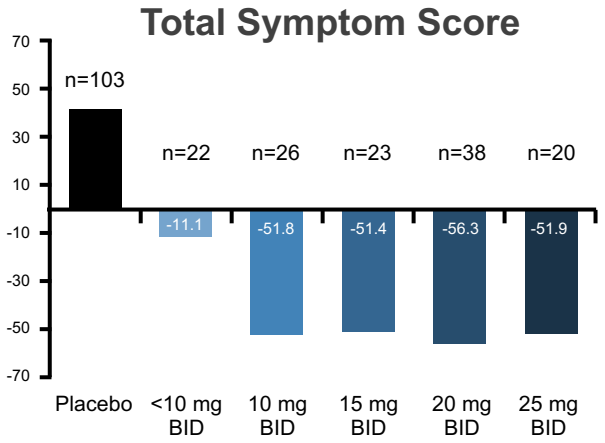
HR, hazard ratio; SR, spleen response.

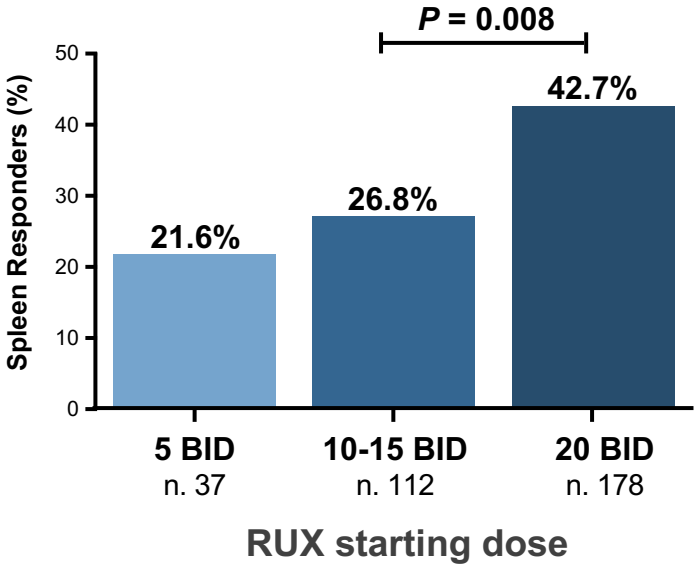
Vannucchi AM, et al. *Haematologica.* 2015;100; Palandri F, et al. *Leuk Res.* 2018;74:86–8.

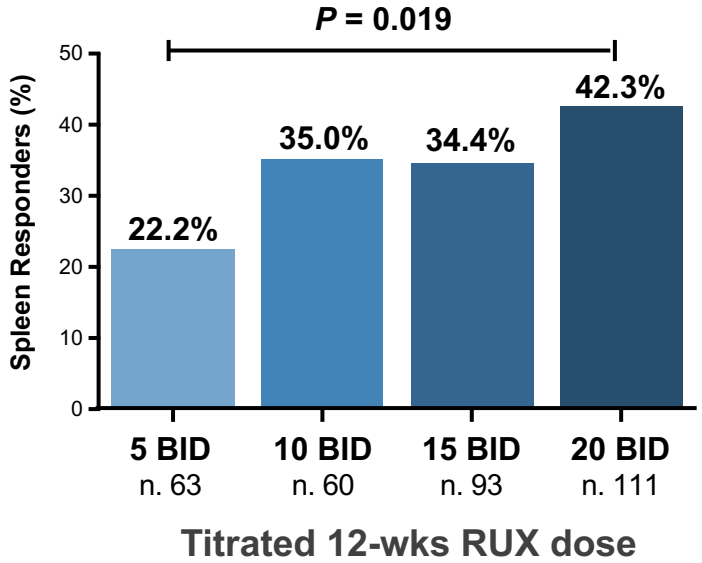
Ruxolitinib Efficacy by Titrated Dose

COMFORT-I & Real-World Evidence









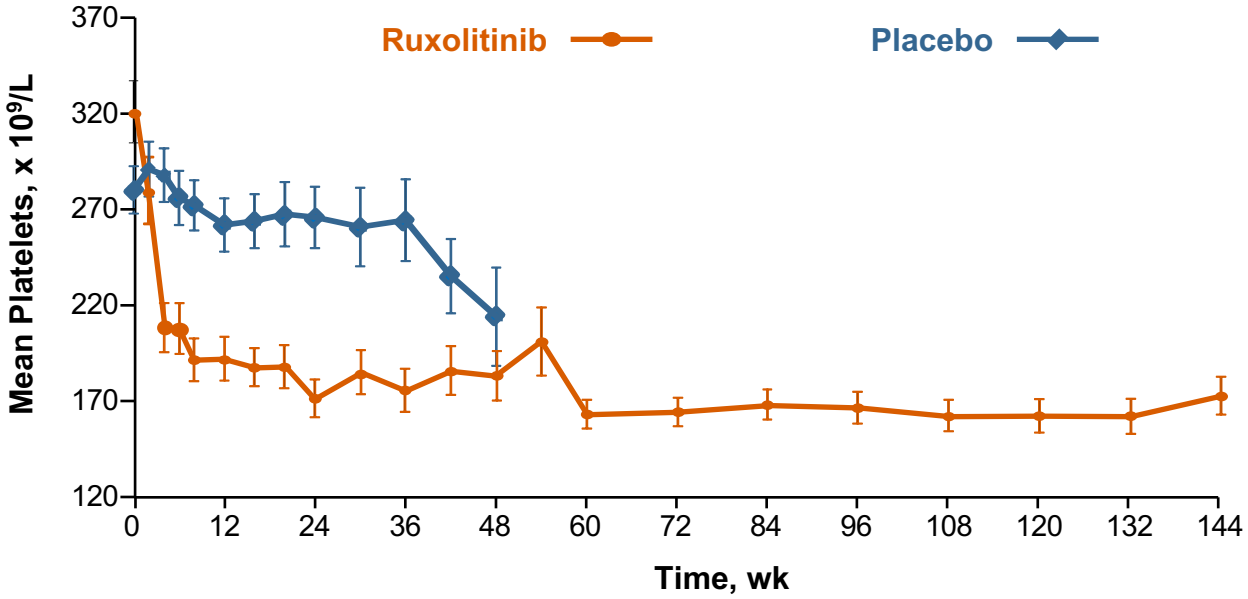
- Phase 2 study and real-world data showed that doses less than 10mg BID are not effective long term
- If starting low, ESCALATE quickly to maximum safe dose

Palandri F, et al. *Oncotarget*. 2017;8:79073-86; Verstovsek S, et al. *Onco Targets and Therapy*. 2014;7:13-21.

Mean Platelet Count and Hemoglobin Over Time

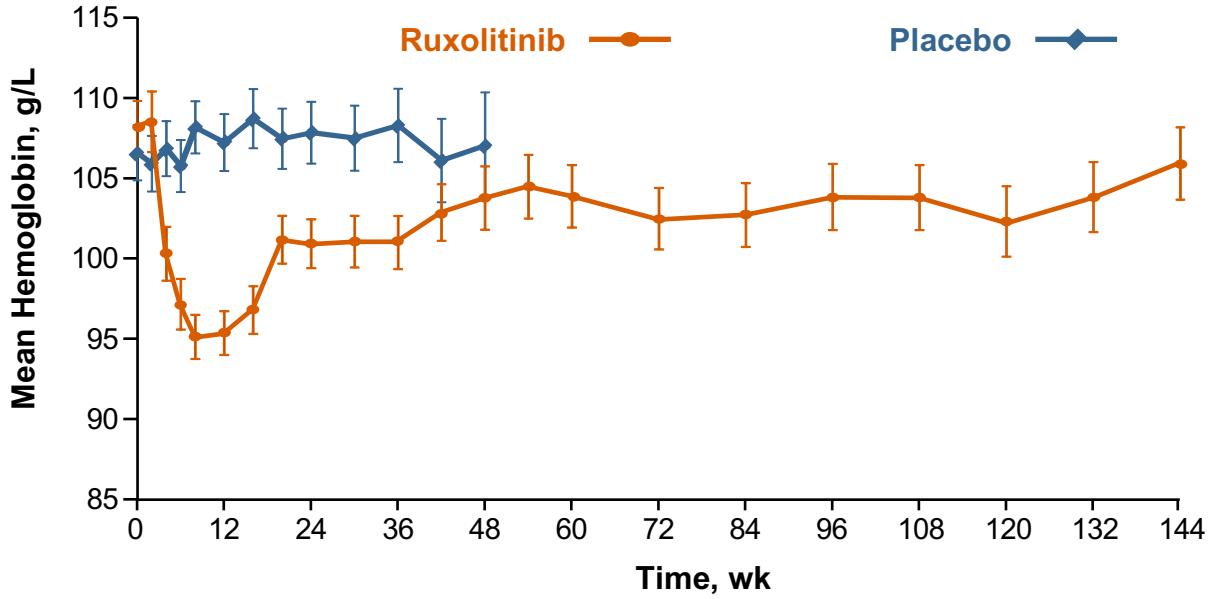
COMFORT-I

Platelet Count



No. of Patients													
RUX	155	144	143	136	124	112	110	107	104	100	94	88	79
Placebo	151	128	112	82	37								

Hemoglobin



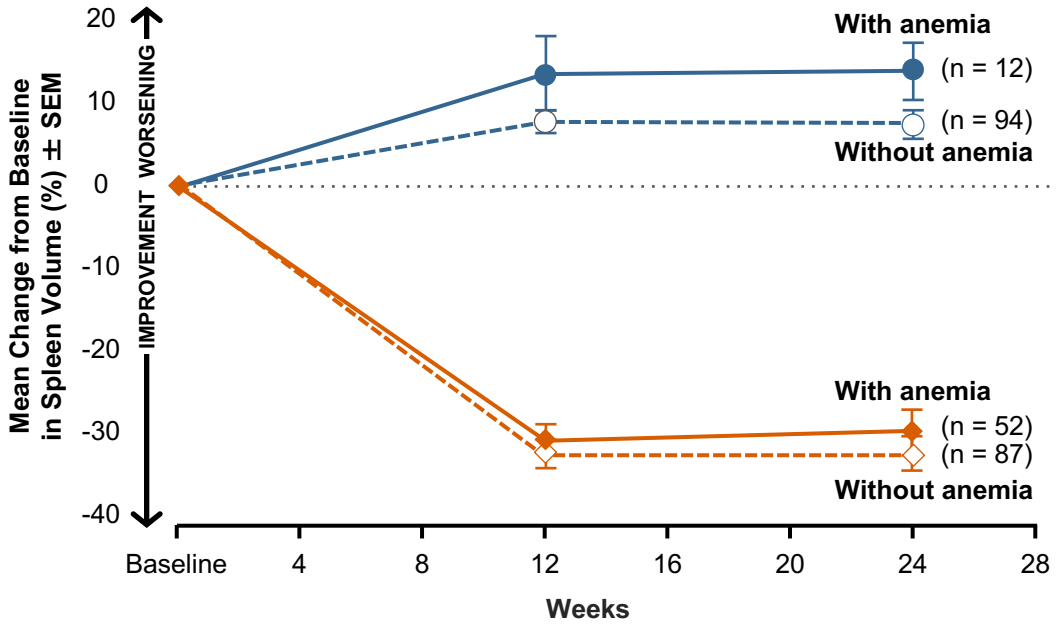
No. of Patients													
155	145	143	136	124	113	110	107	104	100	94	88	79
151	132	113	83	37								

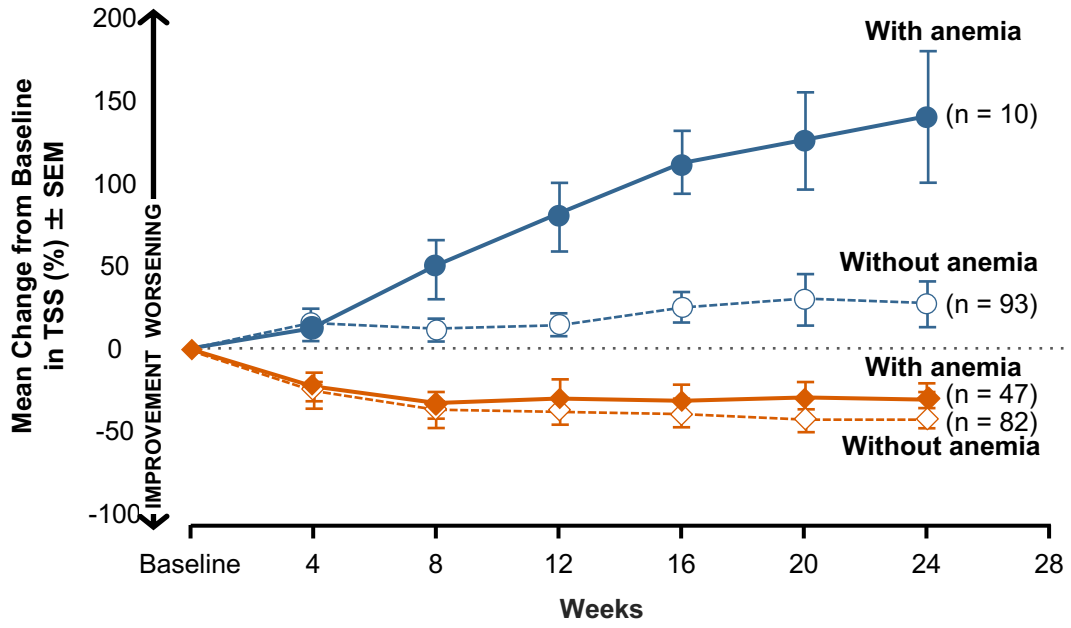
Verstovsek S, et al. *Haematologica*. 2015;100:479-488.

Development of Anemia Does Not Affect Response to Ruxolitinib Treatment

COMFORT-I

Baseline anemia is not a contra-indication for ruxolitinib use





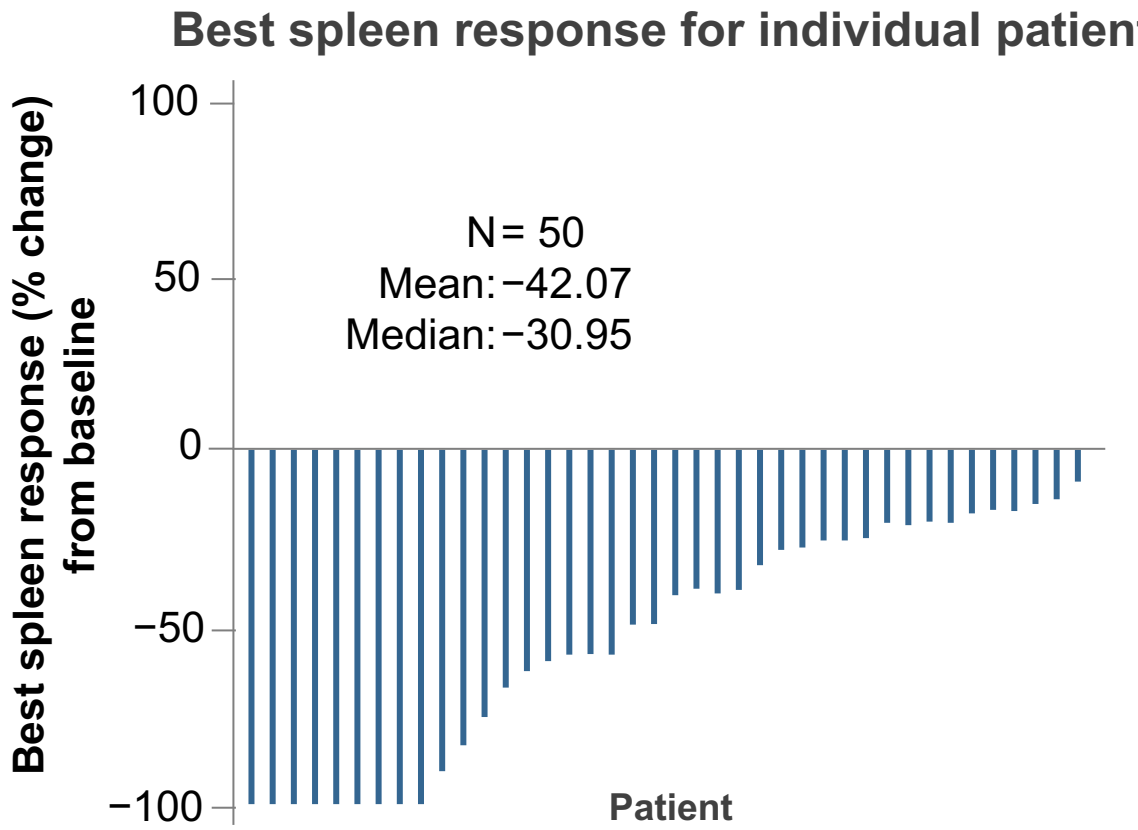
Placebo Ruxolitinib

Figures adapted from Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807, supplementary appendix.

Alternative Ruxolitinib Dosing in Patients with MF and Anemia (Hb < 10 g/dL)

REALISE Study

Alternative ruxolitinib dosing regimen **starting at 10 mg BID for 12 weeks followed by upwards titration** in the phase 2 study



≥ 50% spleen length reduction	Week 24	Any time
Patients	**56%**	70%

Week 24 spleen response was seen in both transfusion-dependent and non-transfusion-dependent patients

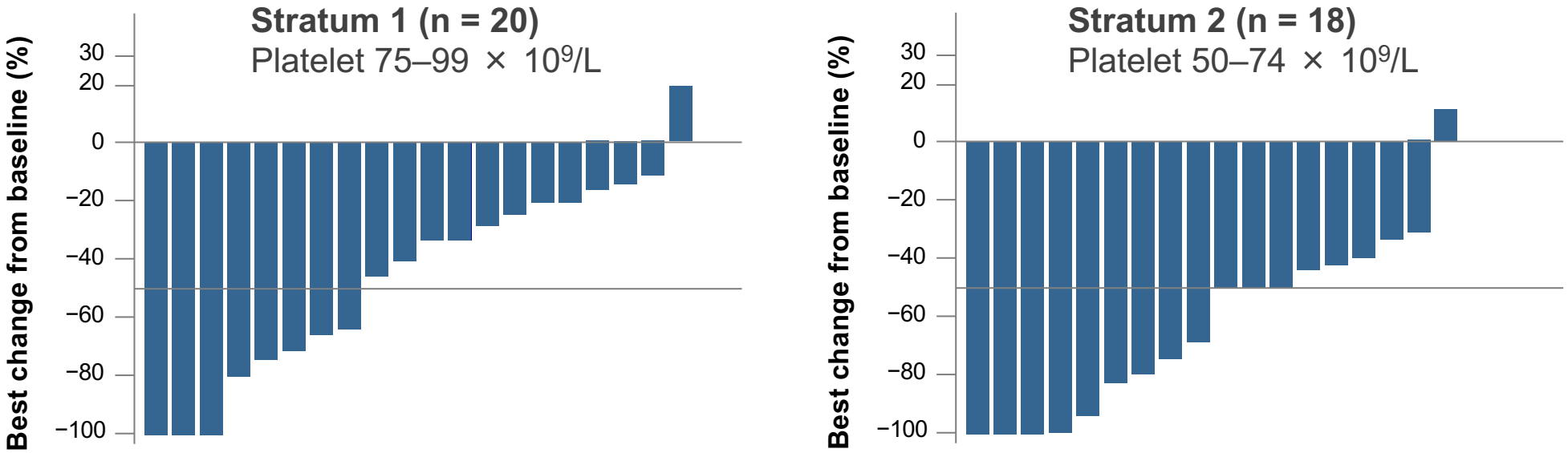
Cervantes F, et al. Leukemia. 2021;35:3455–3465.

Ruxolitinib in Patients with MF and Low Platelet Counts (50–100 × 10^9/L)

EXPAND Study

The **maximum safe starting dose** was established at **ruxolitinib 10 mg twice daily** for both groups of patients with low platelet counts in the Phase 1b trial

Spleen response



Adverse events

Grade 3/4 AE, %	Stratum 1	Stratum 2
Thrombocytopenia	35	78
Platelet count decrease	25	0
Anemia	20	17

AE, adverse event

Vannucchi AM, et al. *Haematologica.* 2019;104:947-54.

Early Intervention: Ruxolitinib in IPSS-1 Patients

Higher Response Rate and Lower Toxicities

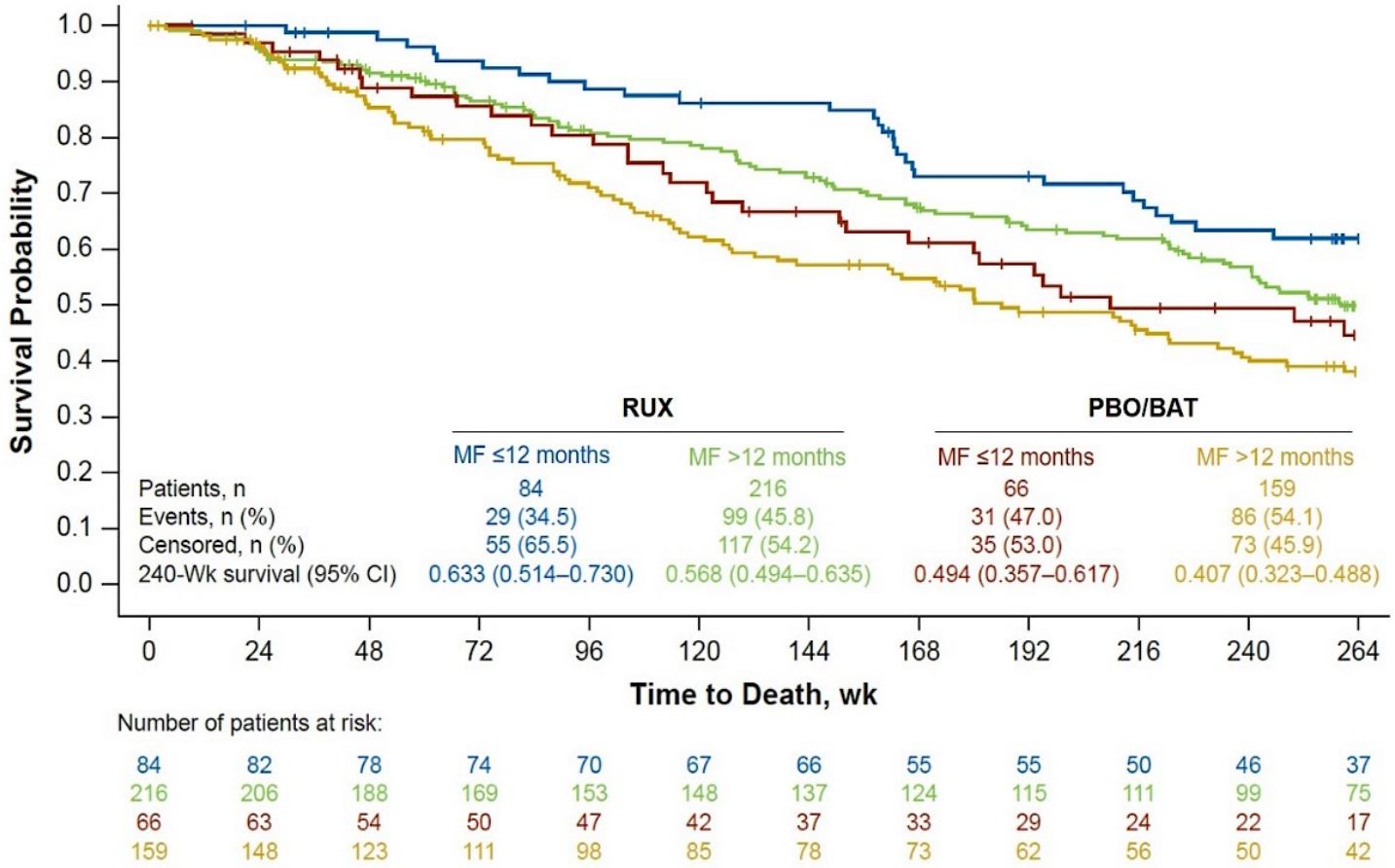
	Clinical Trial	Spleen Response at Week 24	Incidence of Anemia G3/G4	Incidence of Thrombocytopenia G3/G4	Incidence of Infections	Discontinuation Rate
Int-2 and high-risk patients	**COMFORT-I** (n=155)[1]	41.9%	45%	13%	~50%	21%
	COMFORT-II (n=146)[2]	32%	42%	8%	~50%	38%
Int-1-risk patients	**JUMP INTM-1** (n=163)[3]	56.9%	33%	12.5%	40%	19.6%
	ROBUST (n=48)[4]	50%	NA	NA	NA	NA
	Italian study (n=70)[5]	54.7%	40.6%	2.9%	17.1%	17.1%

IPSS intermediate-1 patients may possibly achieve higher reponse rates and experience lower toxicities than patients with higher-risk disease

1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807; 2. Harrison C, et al. N *Engl J Med.* 2012;366:787-98; 3. Al-Ali HK, et al. *Haematologica*. 2016;101:1065-73;
4. Mead AJ, et al. *Br J Haematol.* 2015;170:29-39; 5. Palandri F, et al. *Hematol Oncol.* 2018;36:285-290; 6. Verstovsek, et al. *Haematologica*. 2015;100:479-488.

Overall Survival in the COMFORT trials by disease duration

- OS at Week 240 was significantly improved among patients who initiated ruxolitinib at ≤12 vs >12 months (63% vs 57%; *P*=0.0430)
  - OS was longer with ruxolitinib vs placebo/BAT regardless of disease duration



Verstovsek S et al. ASH 2021

Fedratinib for Primary or Secondary MF

JAKARTA: International, Double-blind, Randomized Phase 3 Trial

Fedratinib: highly selective, potent inhibitor of wild-type and mutant JAK2; also inhibits FLT3

N=289
- Adults with primary, post-PV, or post-ET MF
- Int-2–risk or high-risk status
- Splenomegaly
- ECOG PS 0-2
- Life expectancy ≥6 mo

Fedratinib 400 mg PO QD
≥6 consecutive 4-wk cycles

Fedratinib 500 mg PO QD
≥6 consecutive 4-wk cycles

Placebo PO QD
≥6 consecutive 4-wk cycles

Patients assigned fedratinib continued treatment until PD, unacceptable toxicity, relapse

Patients assigned placebo permitted to crossover at Wk 24, or earlier for PD

Primary Endpoints
- Spleen response (≥35% reduction in spleen volume vs BL) at Wk 24 and confirmed 4 wk later

Secondary Endpoints
- Symptom response (≥50% reduction in TSS)
- Safety

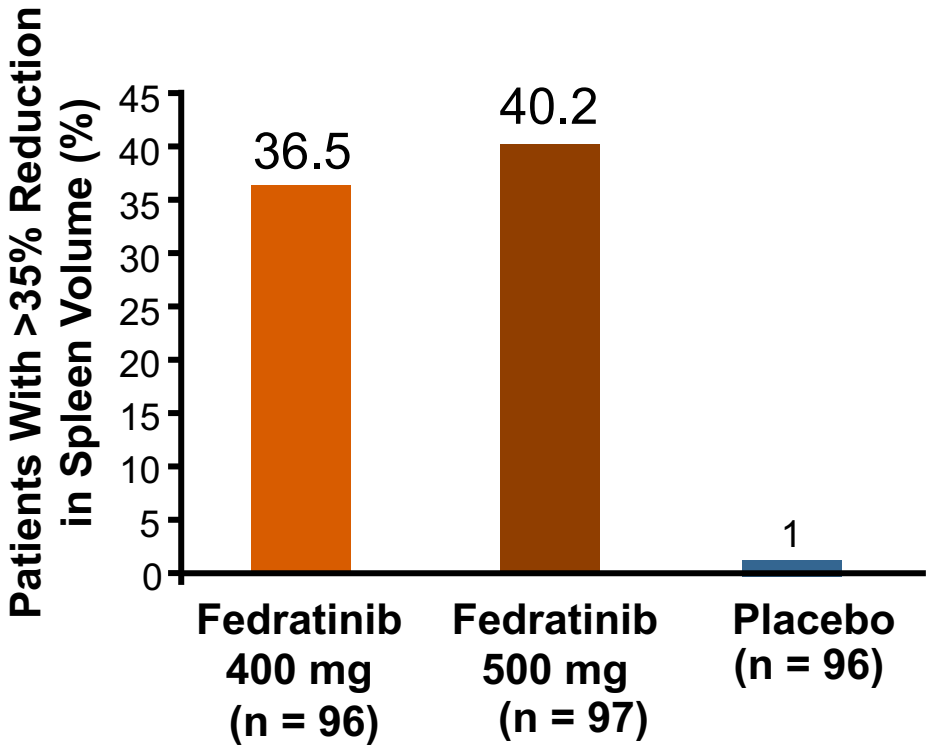
Pardanani, et al. *JAMA Oncol*. 2015;1:643.

Fedratinib for Primary or Secondary MF

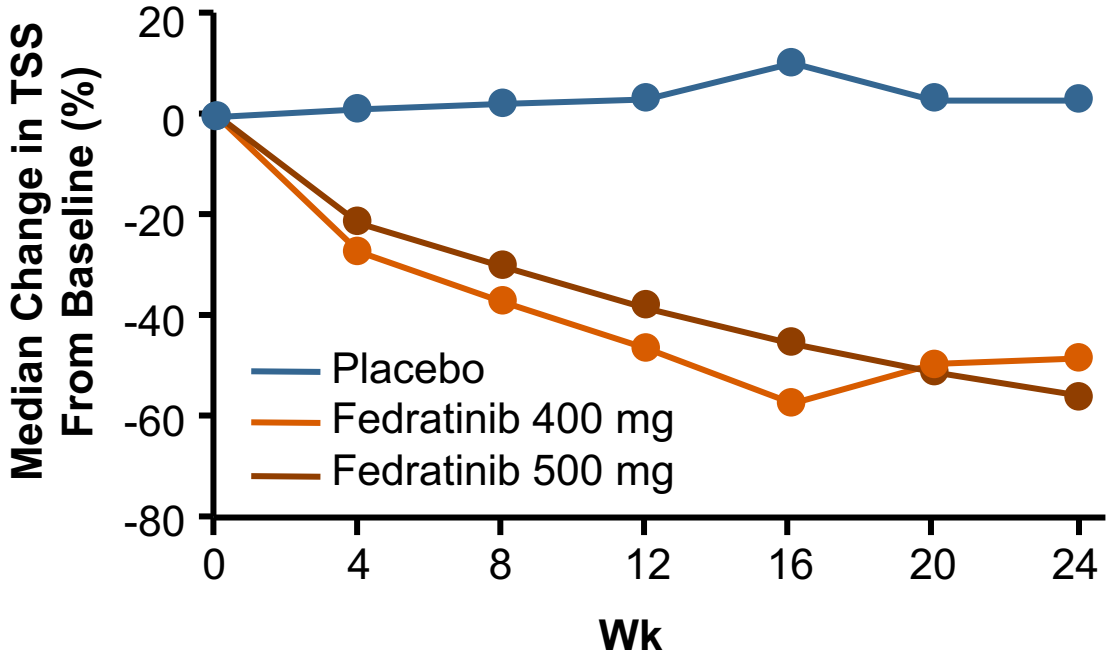
JAKARTA: Efficacy

FDA approved for patients with intermediate-2–risk or high-risk MF who have platelet counts ≥50 × 10^9/L

Spleen Response (Primary Endpoint)



Change in Total Symptom Score



Pardanani, et al. *JAMA Oncol*. 2015;1:643. Fedratinib PI.

Fedratinib for Primary or Secondary MF

JAKARTA: Safety

Adverse Events, n (%)	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nonhematologic						
Diarrhea	63 (66)	5 (5)	54 (56)	5 (5)	15 (16)	0
Vomiting	40 (42)	3 (3)	53 (55)	9 (9)	5 (5)	0
Nausea	61 (64)	0	49 (51)	6 (6)	14 (15)	0
Constipation	10 (10)	2 (2)	17 (18)	0	7 (7)	0
Asthenia	9 (9)	2 (2)	15 (16)	4 (4)	6 (6)	1 (1)
Abdominal pain	14 (15)	0	12 (12)	1 (1)	15 (16)	1 (1)
Fatigue	15 (16)	6 (6)	10 (10)	5 (5)	9 (10)	0
Hematologic						
Anemia	95 (99)	41 (43)	94 (98)	58 (60)	86 (91)	24 (25)
Thrombocytopenia	60 (63)	16 (17)	55 (57)	26 (27)	48 (51)	9 (9)
Lymphopenia	54 (57)	20 (21)	63 (66)	26 (27)	50 (54)	19 (21)
Leukopenia	45 (47)	6 (6)	51 (53)	15 (16)	18 (19)	3 (3)
Neutropenia	27 (28)	8 (8)	42 (44)	17 (18)	14 (15)	4 (4)
D/c for AEs, Wk 24	13 (14)		24 (25)		8 (8)	

Black Box Warning

- Wernicke encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

Considerations

- Measure and address thiamine levels prior to treatment initiation
- Do not start fedratinib in patients with thiamine deficiency

Pardanani, et al. *JAMA Oncol*. 2015;1:643. Fedratinib PI.

Review of Encephalopathy Cases

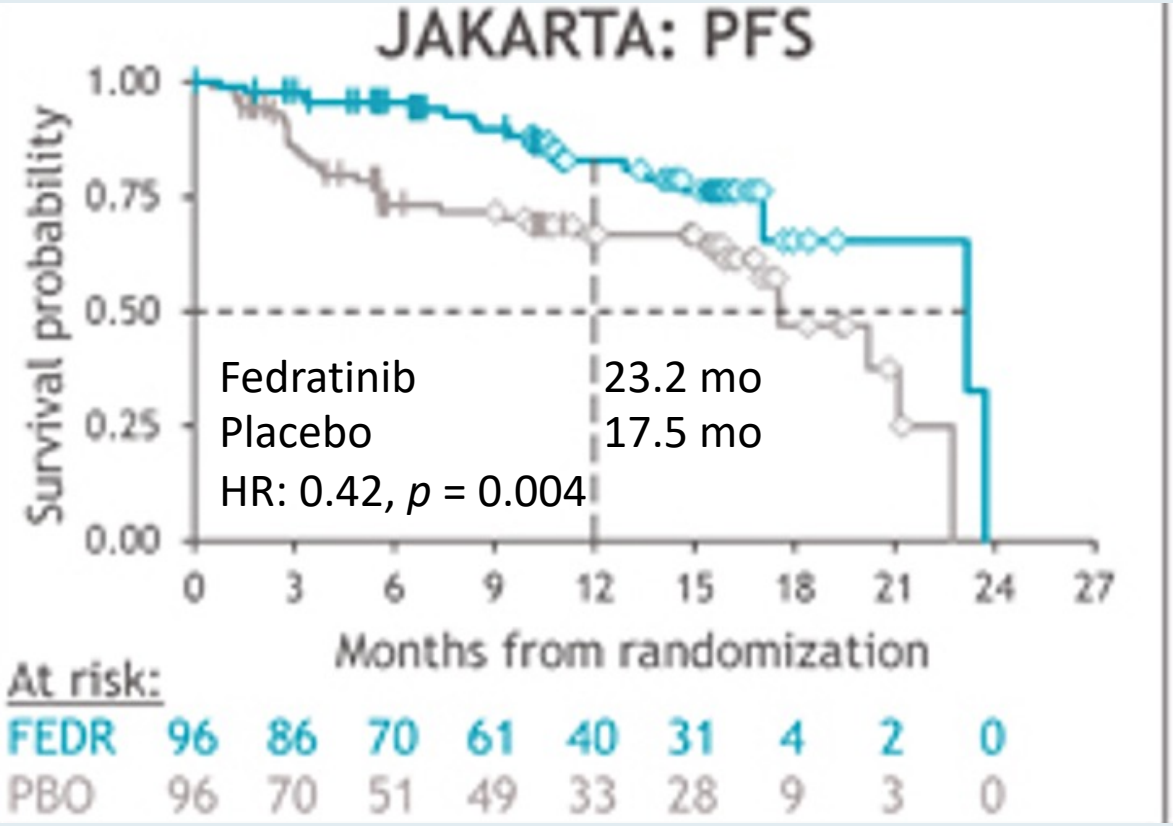
- Across nine fedratinib trials enrolling 670 MPN or solid tumor patients
- Five potential WE patients
- One subject had malnutrition related to protracted nausea and vomiting, as well as clinical signs and MRI findings consistent with WE
- Two subjects likely experienced WE, both of which recovered without a dose interruption, suggesting fedratinib does not inhibit thiamine absorption
- Two subjects inconclusive or not supportive of WE

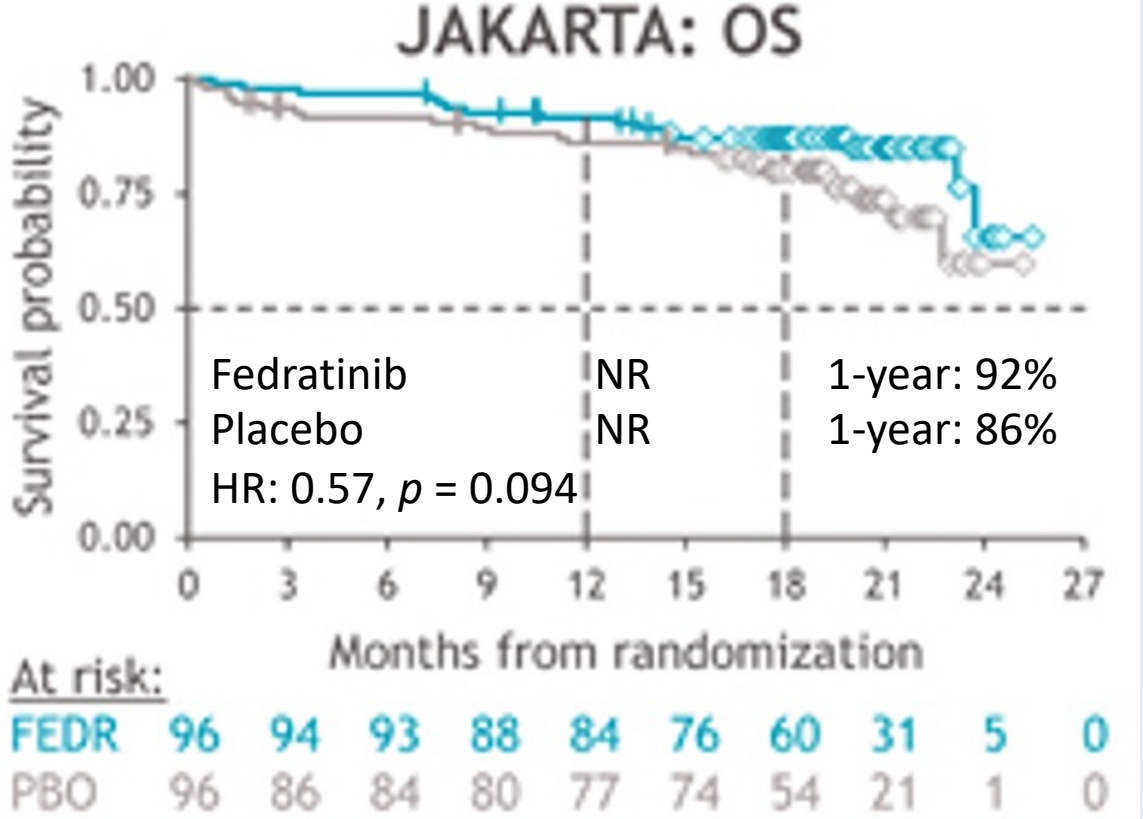
No clear link between WE and fedratinib

1. **Fedratinib does not appear to increase risk for thiamine deficiency beyond its potential to exacerbate malnutrition through poor management of preventable GI events**
2. **Proper management of GI is an important component of care for patients on fedratinib**

1. Harrison CN et al. *Blood*. 2017;130:4197.

JAKARTA: Survival Analysis





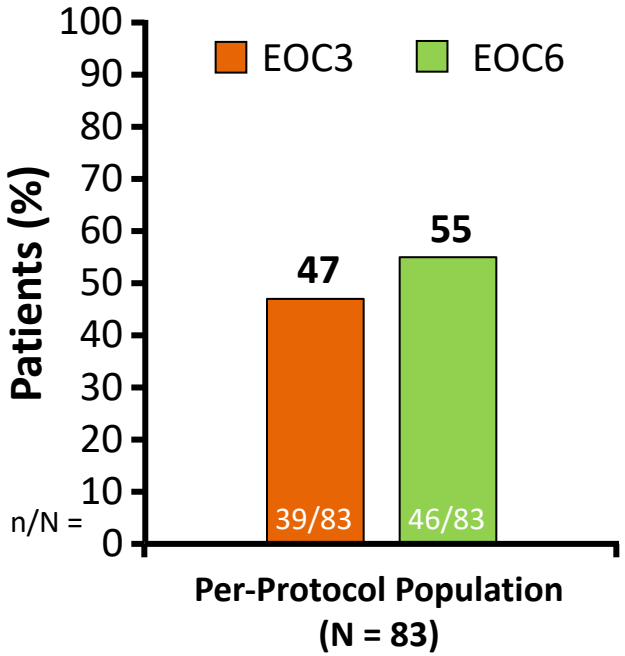
Harrison C et al. EHA 2021;Abstract S203.

RTP RESEARCH TO PRACTICE

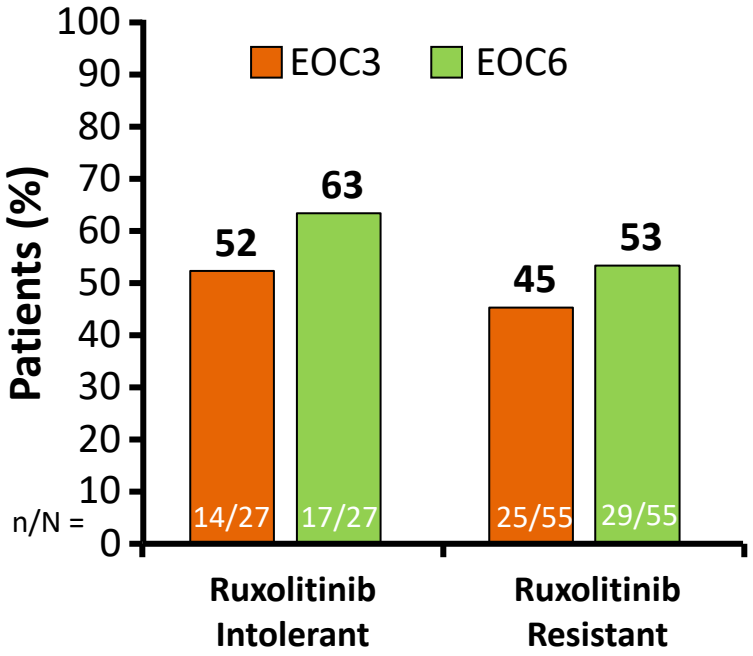
JAKARTA-2: Fedratinib in Patients With Intermediate-Risk or High-Risk MF Previously Treated With Ruxolitinib

- Open-label, single-arm phase II trial (N=97)

Primary Endpoint: ≥35% Spleen Volume Reduction From Baseline



≥35% Spleen Volume Reduction From Baseline by Reason for Ruxolitinib D/c*



Spleen Response by Subtype of Ruxolitinib Resistance

≥35% Spleen Volume Reduction From BL, n (%)	EOC3	EOC6
Insufficient response (n = 19)	8 (42)	10 (53)
Disease progression (n = 13)	5 (38)	5 (38)
Loss of response (n = 23)	12 (52)	14 (61)

- Due to early termination, 35/83 patients had EOC3, but no EOC6, spleen measurement; LOCF method was used to impute missing EOC6 data with EOC3 data (except for patients who discontinued before EOC6 due to PD)

*1 patient discontinued due to other reasons (not definable) and was therefore not classified as resistant or intolerant.

Harrison. Lancet Haematol. 2017;4:e317.

JAKARTA-2 Reanalysis: Fedratinib for Patients With MF Previously Treated With Ruxolitinib

- Aim: confirm efficacy of **fedratinib** in ITT analysis in all enrolled patients and in subgroups defined using **rigorous definitions of prior ruxolitinib response**

	Prior Analysis	Current Analysis
Resistance	RUX Tx ≥ 14 d with no response or stable disease per investigator, disease progression, or loss of response	*Relapsed:* RUX Tx ≥ 3 mo with regrowth, defined as < 10% SVR or < 30% decrease in spleen size from BL, following an initial response *Refractory:* RUX Tx ≥ 3 mo with < 10% SVR or < 30% decrease in spleen size from BL
Intolerance	RUX Tx ≥ 14 d before discontinuing Tx due to unacceptable toxicity	RUX Tx ≥ 28 d complicated by development of RBC transfusion requirement (≥ 2 units/mo for 2 mo); or grade ≥ 3 thrombocytopenia, anemia, hematoma/hemorrhage while on RUX

- 79/97 enrolled patients (81%) met more stringent criteria for RUX R/R (n = 65; 82%) or intolerance (n = 14; 18%); median prior RUX duration in RUX failure cohort, 11.5 mo (range: 1.0-62.4)

- In RUX failure cohort: median number of FEDR cycles, 7; **spleen volume RR 30%** (95% CI: 21%-42%); median spleen response duration, NE (95% CI: 7.2-NE); **symptom RR 27%** (95% CI: 17%-39%)

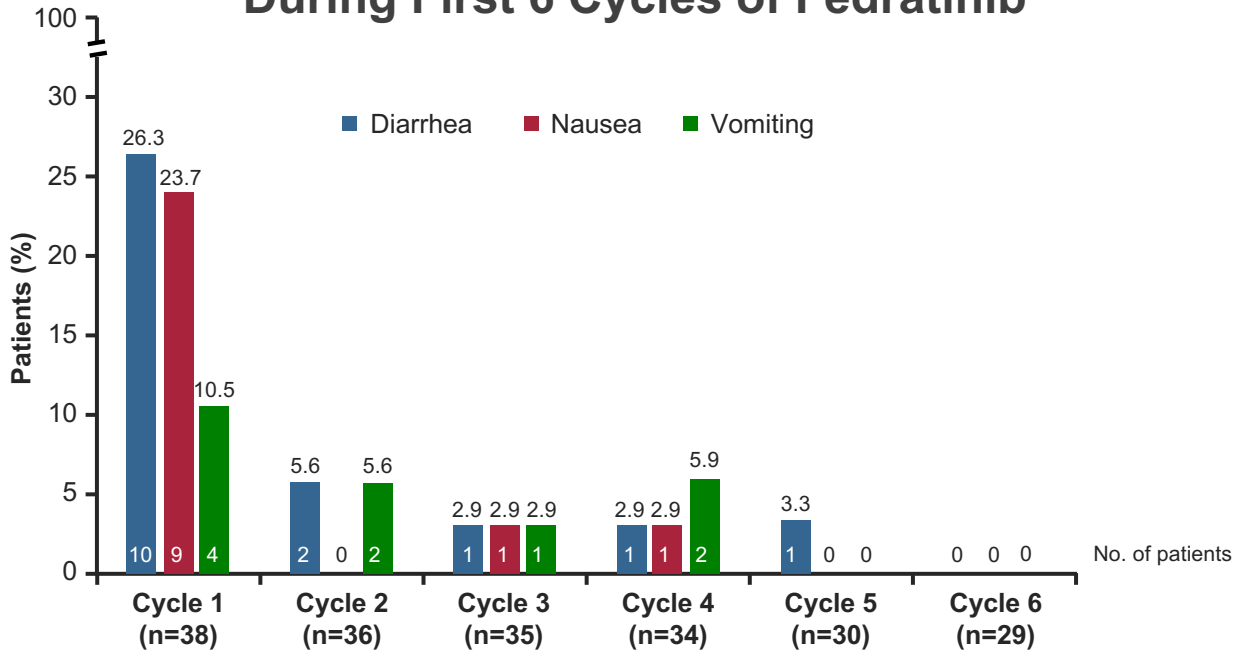
Harrison. ASCO 2019. Abstr 7057.

Exploring Fedratinib Safety and Efficacy in 2L

Phase 3b FREEDOM Trial: Focus on GI Adverse Events

Objective of Study: Assess efficacy of proactive strategies to mitigate AEs, including thiamine supplementation and antiemetic/antidiarrheal agents

Rates of Nausea, Vomiting, and Diarrhea During First 6 Cycles of Fedratinib



GI results:

- Vast majority of GI AEs were grade 1/2 and occurred during cycle 1, and decreased in the subsequent cycles
- Conclusion: Frequency and severity of GI AEs were substantially lower than in previous fedratinib trials, likely due to early implementation of prophylaxis

Includes events with new onset in each cycle. All events of diarrhea, nausea, and vomiting were grade 1 or 2 in severity.

Gupta V, et al. ASH 2022. Abstract 1711.

Additional Investigator Survey Results

A 68-year-old man with intermediate-risk MF receives ruxolitinib 15 mg BID, and after 10 months he develops increasing asymptomatic splenomegaly. Platelet count = 150,000/µL, Hgb = 13.8 g/dL. Regulatory and reimbursement issues aside, which treatment would you most likely recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Switch to fedratinib
 Dr Kuykendall	Increase dose of ruxolitinib
 Dr Mascarenhas	Switch to fedratinib
 Dr Gerds	Switch to fedratinib
 Prof Harrison	Increase dose of ruxolitinib
 Dr Mesa	Switch to fedratinib

Regulatory and reimbursement issues aside and assuming access, 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 changes would you most likely try (assuming normal renal and hepatic function and a platelet count >200,000/µL)?

 Dr Bose	Escalate dose of ruxolitinib
 Dr Kuykendall	Switch to fedratinib
 Dr Mascarenhas	Switch to fedratinib
 Dr Gerds	Switch to fedratinib
 Prof Harrison	Escalate dose of ruxolitinib
 Dr Mesa	Switch to fedratinib

A 65-year-old man with symptomatic, higher-risk MF and splenomegaly (baseline platelet count 110,000/µL) receives ruxolitinib 15 mg BID, to which he responds with significant symptom improvement and decrease in spleen size. Approximately 3 years later he presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 110,000/µL, Hgb = 11.2 g/dL. Regulatory and reimbursement issues aside and assuming access, which treatment would you most likely recommend next (assuming the patient is not a transplant candidate)?

 Dr Bose	Fedratinib
 Dr Kuykendall	Continue ruxolitinib at a higher dose
 Dr Mascarenhas	Fedratinib
 Dr Gerds	Fedratinib
 Prof Harrison	Continue ruxolitinib at a higher dose
 Dr Mesa	Fedratinib

Before starting fedratinib, which nutritional elements must be evaluated, repleted and monitored and at what frequency?

	Nutritional element(s)	Monitoring frequency
 Dr Bose	Thiamine	Every 3 months
 Dr Kuykendall	Thiamine	Every 3-6 months
 Dr Mascarenhas	Thiamine	Every 3 months
 Dr Gerds	Thiamine	Every 6 months
 Prof Harrison	Thiamine	Monthly at first, then every 3 months
 Dr Mesa	Thiamine	Monthly at first, then every 3 months

Agenda

Module 1 – Clinical Decision-Making for Patients with Myelofibrosis (MF) — Dr Bose

Module 2 – Management of MF in Special Patient Populations — Dr Mascarenhas

Module 3 – Future Directions in the Management of MF — Dr Kuykendall

A 65-year-old man with symptomatic, higher-risk MF and splenomegaly (baseline platelet count 110,000/µL) receives ruxolitinib 15 mg BID, to which he responds with significant symptom improvement and decrease in spleen size. Approximately 3 years later he presents with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 44,000/µL, Hgb = 11.2 g/dL. Regulatory and reimbursement issues aside and assuming access, which treatment would you most likely recommend next (assuming the patient is not a transplant candidate)?

 Dr Bose	Pacritinib
 Dr Kuykendall	Pacritinib
 Dr Mascarenhas	Pacritinib
 Dr Gerds	Pacritinib
 Prof Harrison	Pacritinib
 Dr Mesa	Pacritinib

A 55-year-old man presents with fatigue, drenching night sweats, weight loss, bone pain and a spleen measurement of 20 cm with significant abdominal symptoms and is diagnosed with MF. Platelet count = 44,000/µL, Hgb = 8.1 g/dL, WBC = 36,000/µL with 2% blasts. Genomic profiling is positive for JAK2 V617F, TET2 and ASXL1 mutations. Regulatory and reimbursement issues aside, which treatment would you most likely recommend?

 Dr Bose	Pacritinib followed by ASCT
 Dr Kuykendall	Momelotinib followed by ASCT
 Dr Mascarenhas	Pacritinib followed by ASCT
 Dr Gerds	Momelotinib followed by ASCT
 Prof Harrison	Pacritinib followed by ASCT
 Dr Mesa	Pacritinib followed by ASCT

ASCT = autologous stem cell transplant

A 62-year-old woman presents with primary MF, constitutional symptoms and splenomegaly, with a baseline platelet count of <50,000/µL. Regulatory and reimbursement issues aside, which treatment would you most likely recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Pacritinib
 Dr Kuykendall	Momelotinib
 Dr Mascarenhas	Pacritinib
 Dr Gerds	Pacritinib
 Prof Harrison	Pacritinib
 Dr Mesa	Pacritinib

A 75-year-old woman with symptomatic MF receives ruxolitinib 15 mg orally BID, to which she responds for 2 years with symptom improvement. Over the past few weeks she has experienced a gradual increase in splenomegaly, hot flashes, fatigue and early satiety. Platelet count = 43,000/µL, Hgb = 8.4 g/dL, WBC = 14,000/µL. Regulatory and reimbursement issues aside, which treatment would you most likely recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Switch to pacritinib 200 mg BID
 Dr Kuykendall	Switch to momelotinib 200 mg qd
 Dr Mascarenhas	Switch to pacritinib 200 mg BID
 Dr Gerds	Switch to momelotinib 200 mg qd
 Prof Harrison	Increase ruxolitinib dose to 20 mg BID and switch JAKi if no improvement in symptoms or Hb
 Dr Mesa	Switch to pacritinib 200 mg BID

Management of MF in Special Patient Populations

John Mascarenhas

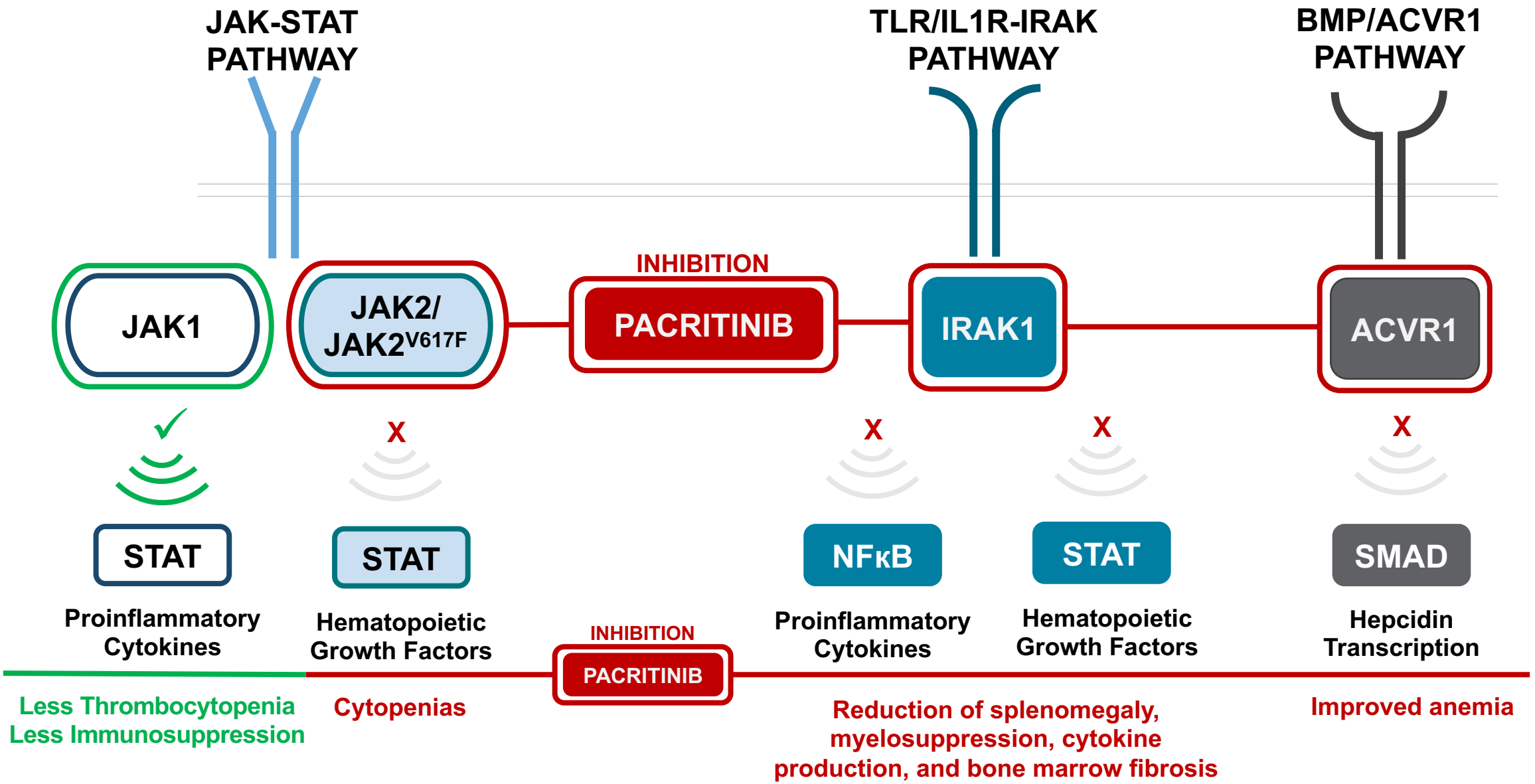
JAK Inhibitor Specificities

JAK and FLT3 Kinases IC_{50} (nM)				
Kinase	**Pacritinib**	**Ruxolitinib**	**Fedratinib**	**Momelotinib**
JAK1	1280	3.4	18	11
JAK2	6.0	4.5	1.1	18
$JAK2^{V617F}$	9.4	NR	NR	–
Non-tyrosine Kinases of Interest IC_{50} (nM)				
CSF1R	39.5	>3000	220	–
IRAK1	13.6	290	620	NR
ACVR1	16.7	>1000	273	52.5

CSF1R, colony stimulating factor 1 receptor; FLT, FMS-like tyrosine kinase; IRAK, interleukin-1 receptor-associated kinase; ITD, internal tandem duplication; TYK, tyrosine kinase.

Singer J, et al. *Blood*. 2014;124:1874; Mascarenhas JO, et al. *Haematologica*. 2017;102:327-335. Jadwiga J. et al. *Blood.* 2018 132 (Supplement 1): 2559. Duenas-Perez AB et al. *Ther Adv Hematol.* 2015: 186-201

Pacritinib Inhibits JAK2, IRAK1, and ACVR1 [Sparing JAK1[1–6]]



1. Jarochoa J. et al. Blood 2018; 132(supplement 1)"2559. 2. Mascarenhas J, et al. Haematologica 2017; 102(2); 327-335 3. Singer J et al. Abstract #1874 Oral presentation ASH2014 4. Fisher D. et al Leukemia 2019; 333(8) 1978-1995 5. Lay HY, et al. Blood Adv 2019; 3(2): 122-131 6. Balka KR, et al. J Leukoc Biol 2019; 105 (2): 339-351 6. Oh S. et al. Oral Presentation ASH2022 Abstract #628 Pacritinib exhibits inhibitory activity against additional cellular kinases (such as CSF1R and IRKA1), although the clinical relevance is unknown ACVR1= Activin A receptor type 1

Pacritinib: Phase III Trial PERSIST-2 – Pacritinib 400 mg QD or 200 mg BID vs BAT (including JAK1/2 inhibitors) in MF[1]

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

Key Eligibility Criteria

- PMF, PET-MF, PPV-MF
- Intermediate- or high-risk disease
- Moderate-to-severe thrombocytopenia at baseline (≤100 × 10^9/L)
- No exclusion for Hgb levels or RBC-TD
- Prior JAK1/2 inhibitors allowed

1:1:1 Randomization N = 311

Stratification at randomization

- Rebound platelet count[a]
- DIPSS risk category
- Geographic region

- **Pacritinib 400 mg QD**
- **Pacritinib 200 mg BID**
- **BAT[b]; including JAK1/2 inhibitors**

Coprimary Endpoints

Pooled pacritinib arms vs BAT

- SVR ≥35% by MRI/CT
- ≥50% reduction in TSS[c]

ITT-efficacy population,[d] baseline to week 24

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

PERSIST-2: Baseline Characteristics and BAT Received

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

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

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

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

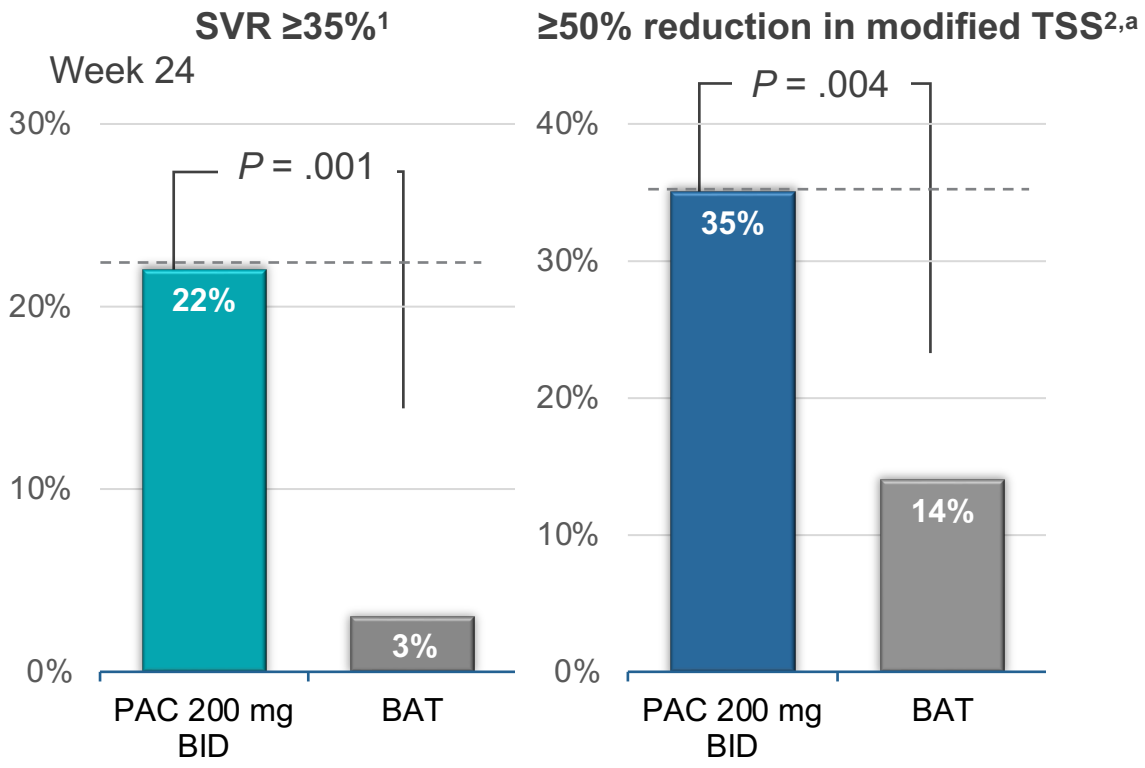
[a]By physician examination. [b]Defined according to Gale criteria; missing for 1 PAC patient. [c]Seventeen (39%) had baseline platelet counts <50 × 10^9/L and would not have been candidates for ruxolitinib by approved indication (or PERSIST-2 study protocol).

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

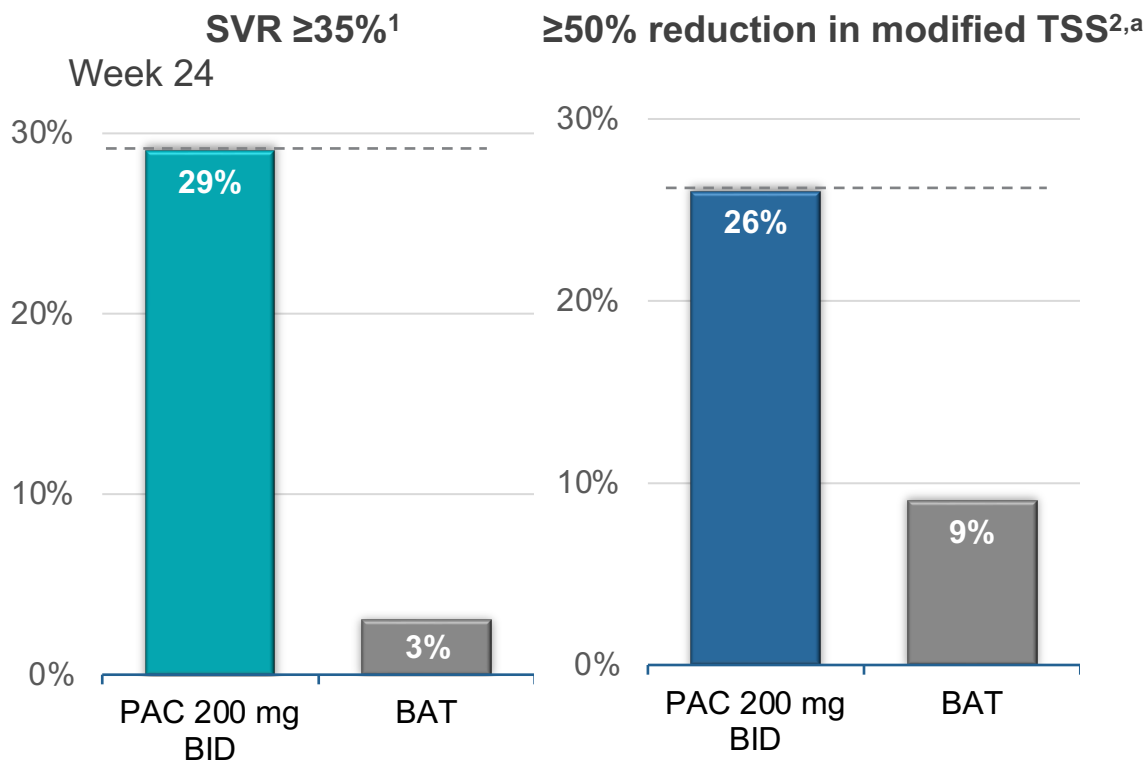
1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659; 2. Data accessed September 2023 - PERSIST-2 CSR; 3. Harrison C, et al. EHA 2017. Abstract P701.

PERSIST-2: Spleen/Symptom Response

ITT population



Patients with platelets <50 × 10^9/L



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

[a]Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
BAT, best available therapy; BID, twice daily; ITT, intention to treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.
1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659; 2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/208712Orig1s000IntegratedR.pdf

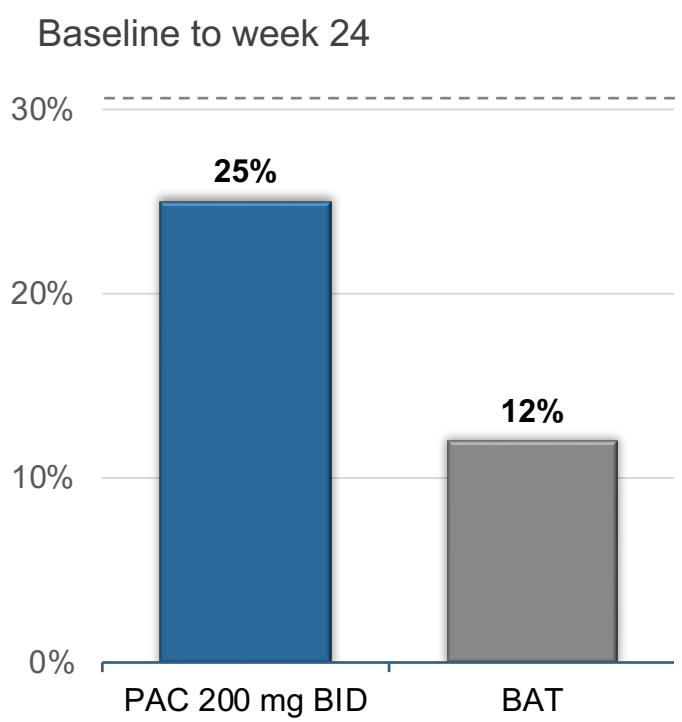
Improved Quality of Life Associated With 200 mg BID Pacritinib

- 56% reported "much improved" or "very much improved" in the 200-mg-BID-pacritinib arm
- 13% reported "much worse" in the BAT arm

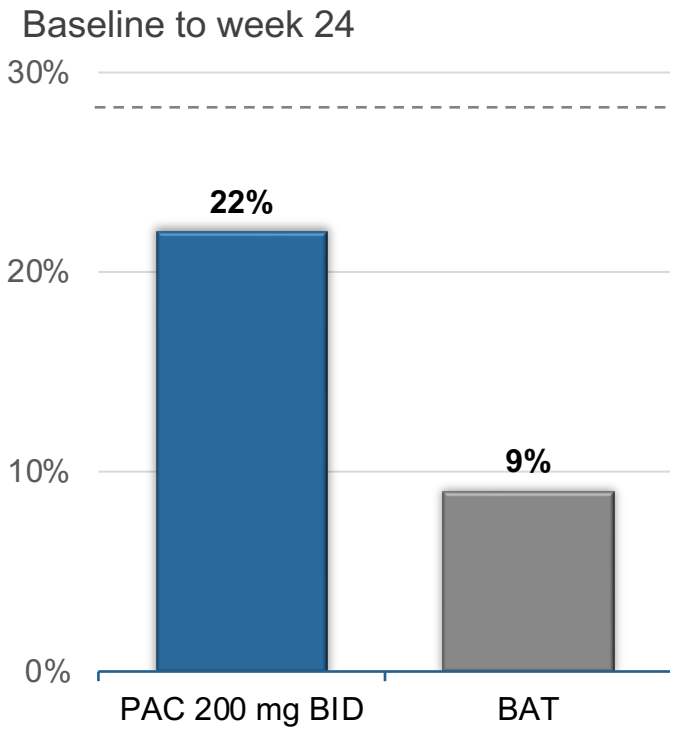
BID, twice daily; PAC, pacritinib; QD, once daily. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

PERSIST-2: Hematologic Stability

Clinical improvement in hemoglobin levels in patients with baseline anemia: Increase of Hgb by ≥ 2.0 g/L or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL



Pacritinib reduced transfusion burden in patients not TI at baseline



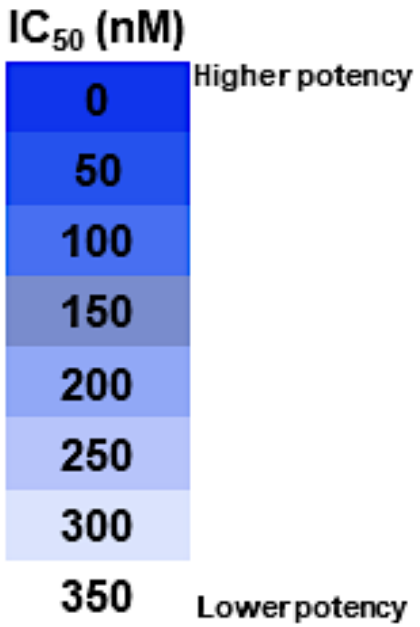
TI defined according to Gale criteria (0 units over the course of 12 weeks).

BAT, best available therapy; BID, twice daily; PAC, pacritinib; RBC, red blood cell.

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

Pacritinib Is a Potent ACVR1 Inhibitor

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



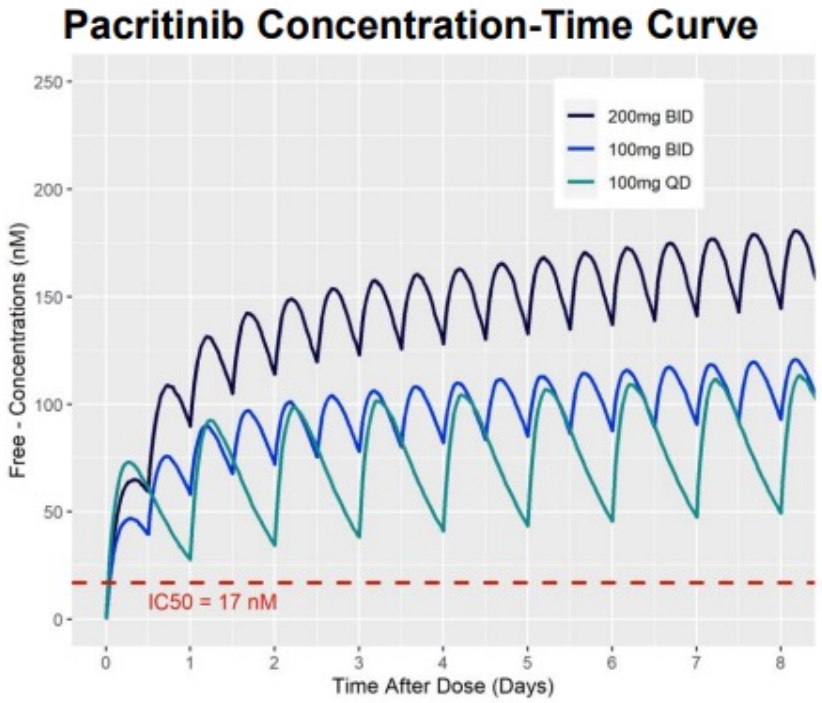
[a]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

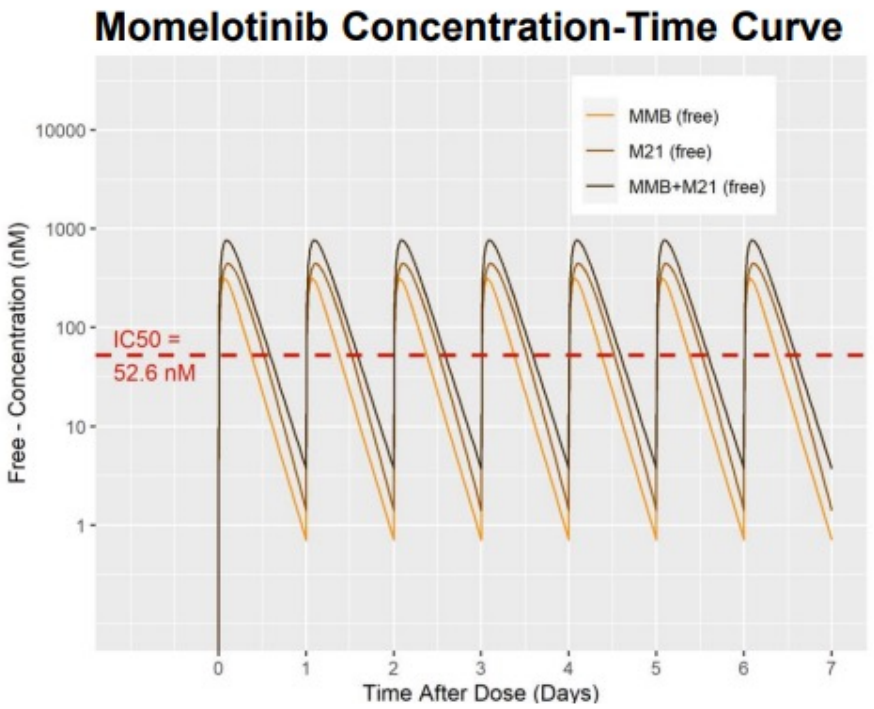
ACVR1, activin A receptor type I; C_{max}, maximum concentration; FED, fedratinib; IC_{50}, half maximal inhibitory concentration; MMB, momelotinib; PAC, pacritinib; RUX, ruxolitinib.

Pacritinib is ~4× more potent than momelotinib against ACVR1

Pacritinib Is a Potent ACVR1 Inhibitor

- Pacritinib concentration exceeds ACVR1 IC_{50} **100% of the time at all dose levels**
- Momelotinib concentration exceeds ACVR1 IC_{50} **50% of the time (accounting for both momelotinib and its metabolite [M21])**





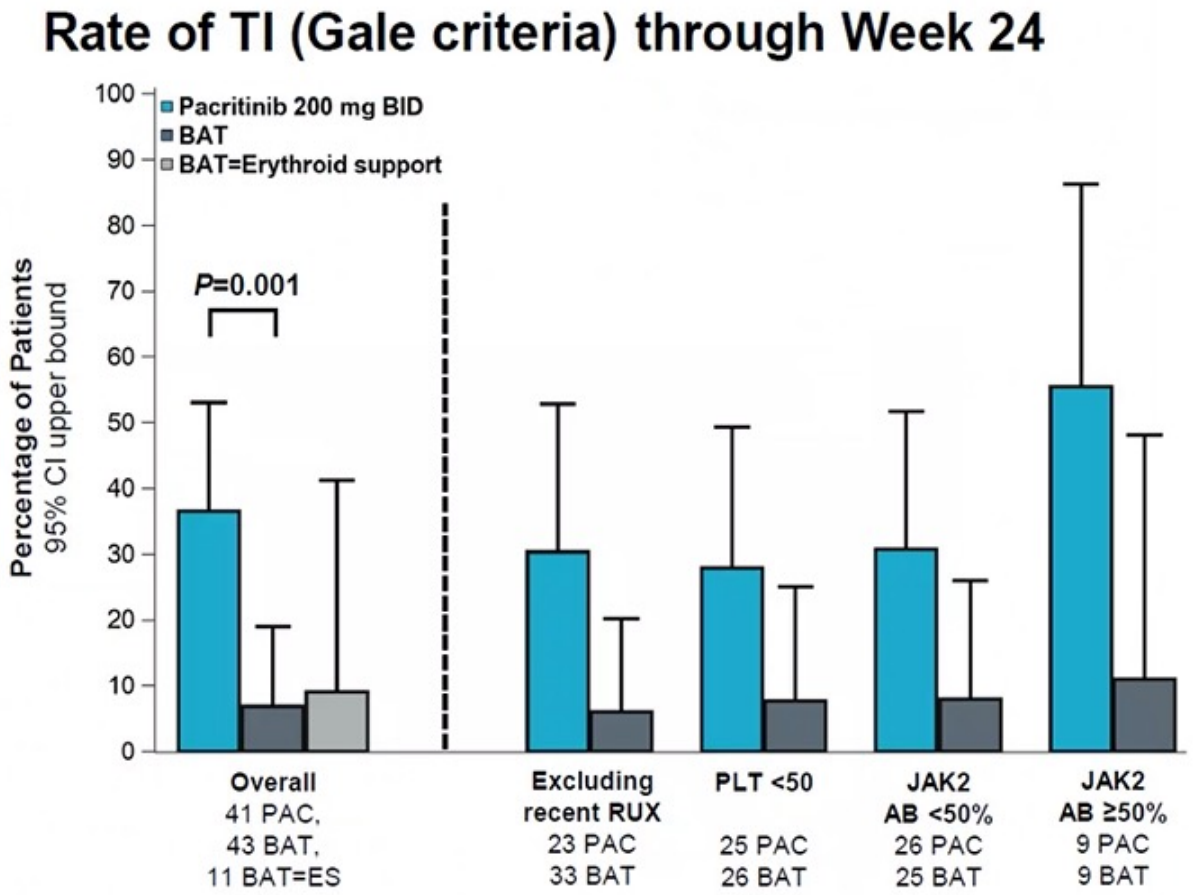
ACVR1, activin A receptor type I; C_{max}, maximum concentration; FED, fedratinib; IC_{50}, half maximal inhibitory concentration; MMB, momelotinib; PAC, pacritinib; RUX, ruxolitinib.

More Pacritinib Patients Achieved TI (Gale Criteria)

TI Conversion Rate

Pacritinib N = 41	BAT N = 43	*P* Value
37%	7%	.001

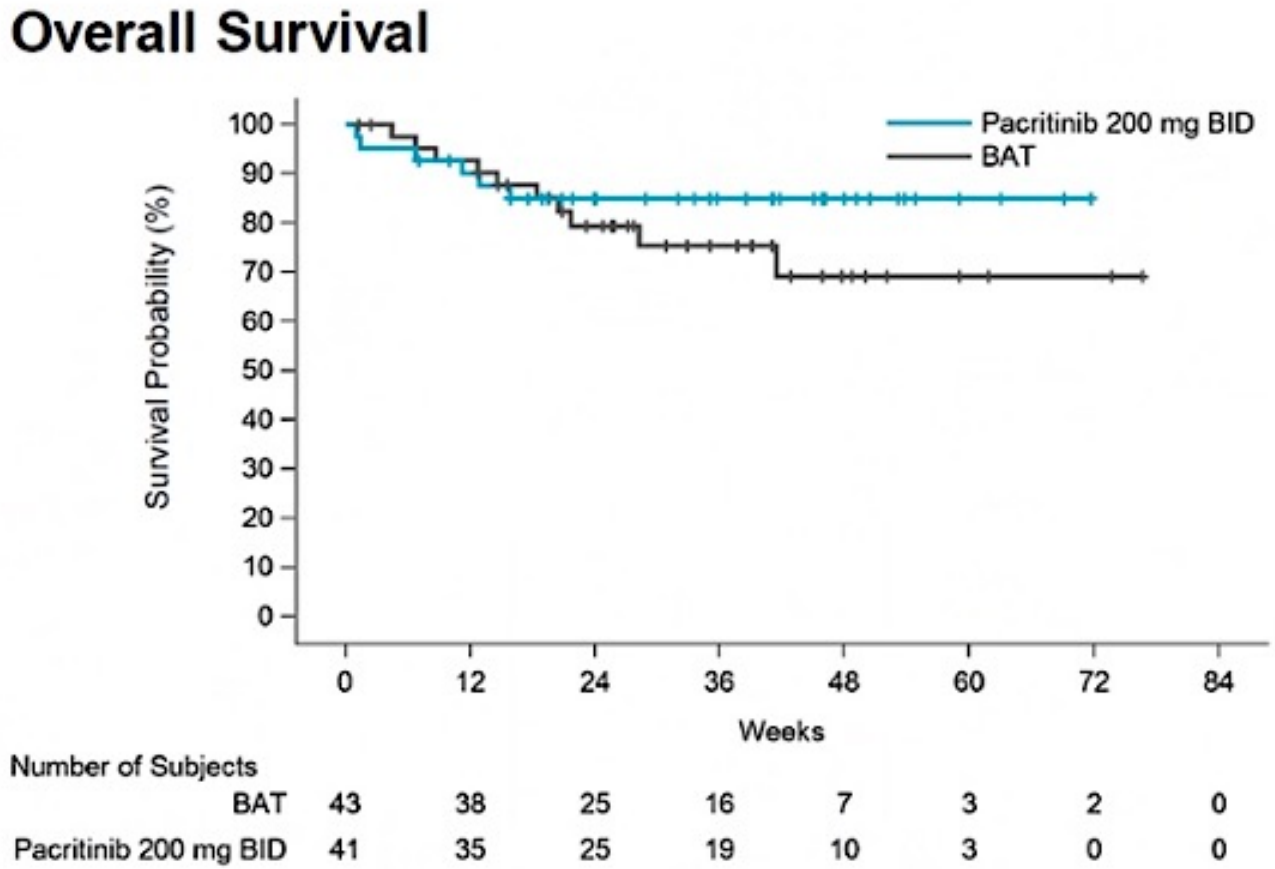
- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
- Erythroid support agents were prohibited on the pacritinib arm



BAT, best available therapy; BID, twice daily; HR, hazard ratio; Hr_{adj}, adjusted HR.

Survival Trend on Pacritinib

- Among patients who were not transfusion independent at baseline
  - **HR = 0.61 (95% CI: 0.22–1.68)**
- After adjusting for baseline transfusion rate
  - **HR_{adj} = 0.64 (95% CI: 0.23–1.76)**



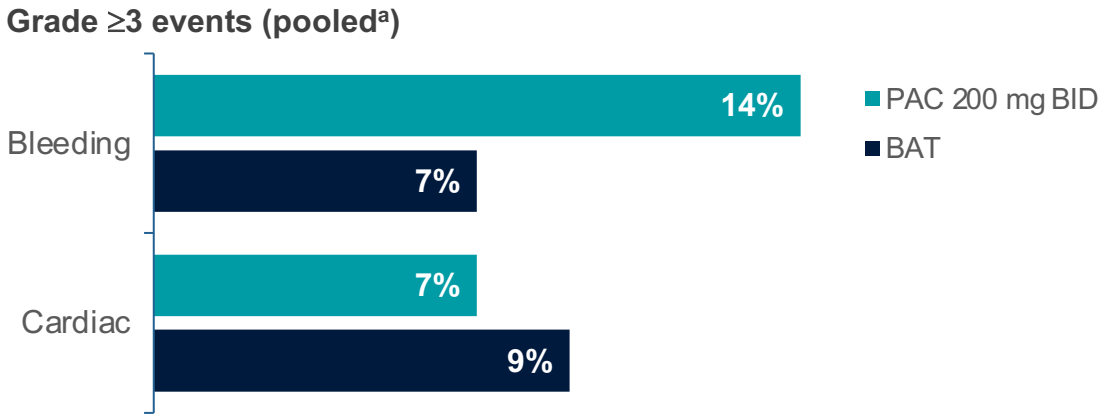
BAT, best available therapy; BID, twice daily; HR, hazard ratio; Hr_{adj}, adjusted HR.

PERSIST-2: Adverse Event Profile

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

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

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



- **Fatal AEs were 9% in the BAT arm and 8% in the PAC 200 mg BID arm**
- **Safety outcomes with pacritinib were similar for those with <50 × 10^9/L vs 50–100 × 10^9/L platelets at baseline**

Risk Adjusted AEs of Interest

Patients with Events Per 100 Patient-Years at Risk (Number of Patients / Total Patient-Years)	PAC203 PAC	PERSIST-2			Pooled PAC
		PAC	BAT	BAT=RUX	
Cancers					
Malignancy – excluding leukemic transformation[a]	**0** (0/29.6)	**8** (5/63.7)	**7** (3/40.8)	**11** (2/17.8)	**5** (5/93.3)
Non-melanoma skin cancer[b]	**0** (0/29.6)	**5** (3/64.2)	**7** (3/40.8)	**11** (2/17.8)	**3** (3/93.8)
Vial Infections					
Viral infection[c]	**7** (2/29.2)	**5** (3/65.1)	**12** (5/41.1)	**11** (2/18.3)	**5** (5/94.3)
Zoster[d]	**0** (0/29.6)	**0** (0/65.7)	**2** (1/41.5)	**6** (1/18.3)	**0** (0/95.3)
Fungal infection	**10** (3/29.1)	**5** (3/64.1)	**12** (5/40.8)	**6** (1/18.3)	**6** (6/93.1)

a Includes all events within the Systems Order Class (SOC) 'Neoplasms benign, malignant, and unspecified', excluding acute leukemia, myelofibrosis, and benign tumors.
b Includes basal cell and squamous cell carcinoma of the skin, as determined by medical review.
c Includes any infection event attributed to a specific virus (e.g., cytomegalovirus reactivation, herpes keratitis), or described as being "viral" (e.g., viral gastroenteritis, viral upper respiratory tract infection), as determined by medical review
d Includes any infection event relating to 'zoster' or 'shingles', as determined by medical review

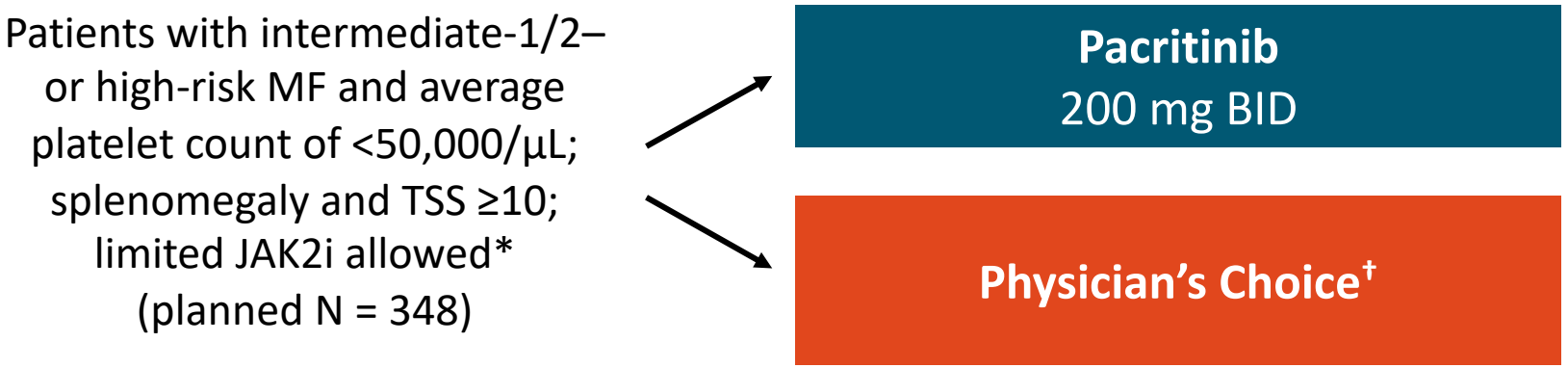
Risk-adjusted incidence rate calculated based on exposure-adjusted incidence per 100 patient-years:
100 X (number of patients with an event / Total patient-years at risk of the event)
Total patient-years at risk of the event calculated as:

- For patients with no event: [(date last dose – date first dose)] + 1/365.25
- For patients with an event: [(date event – date first dose)] + 1/365.25

Pemmaraju N, et al. Poster (#7058) presented at ASCO 2022, Chicago, IL

PACIFICA: Phase III Trial of Pacritinib for Patients With MF and Platelet Count <50,000/µL

- International, randomized phase III trial



- Primary endpoints: SVR ≥35% at 24 wk, TSS ≥50% reduction at 24 wk
- Secondary endpoints: OS, patient global impression of change, safety

*Could have JAK2i for ≤90 days or ruxolitinib ≤10 mg daily dose for ≤270 days. †Choice of the following single agents: corticosteroids, hydroxyurea, danazol, or low-dose ruxolitinib.

NCT03165734.

Emerging Therapies: Momelotinib for Patients With MF

- **Momelotinib**: JAK1/2 inhibitor with potential to improve anemia

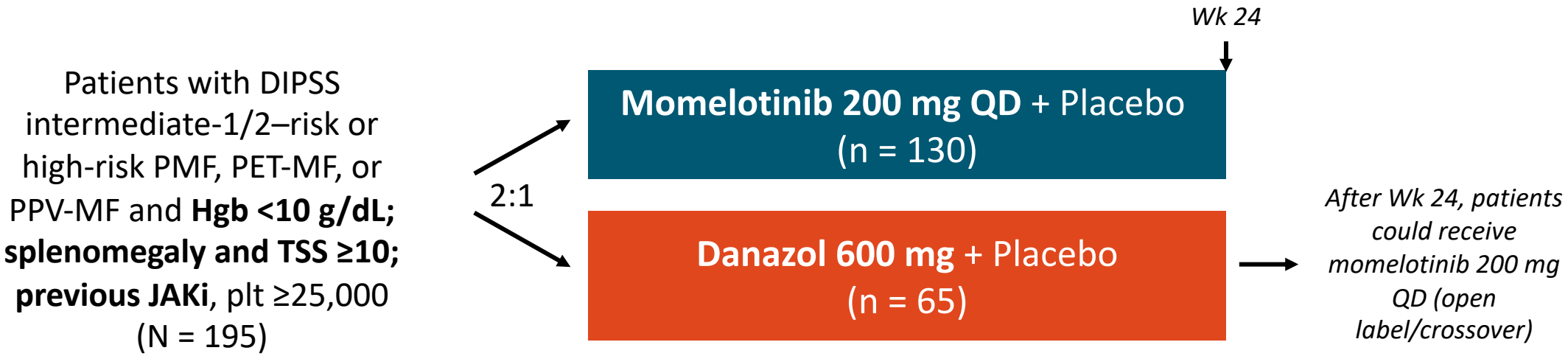
Phase III RCT (N)	Design (N)	Primary Endpoint	OS, %[4-5]
SIMPLIFY 1[2]	JAK inhibitor–naive patients with MF (N = 432)	**SVR ≥35% at Wk 24** Momelotinib: 26.5% Ruxolitinib: 29% (noninferior)	2 yr Momelotinib: 81.6 Ruxolitinib: 80.6
SIMPLIFY 2[3]	MF previously treated with ruxolitinib (N = 156)	**SVR ≥35% at Wk 24** Momelotinib: 7% BAT: 6% (*P* = .90)	2 yr Momelotinib: 65.8 BAT: 61.2
MOMENTUM[5]	MF previously treated with JAK inhibitor with TSS ≥10 (N = 195)	**TSS Response*** Momelotinib: 24.6 Danazol: 9.2 (superior)	24 wk Momelotinib: 88 Danazol: 80

*TSS response (≥50% reduction from baseline per MFASF v4.0 at Wk 24.

1. Asshoff. Blood. 2017;129:1823. 2. Harrison. Lancet Haematol. 2018;5:e73.
3. Mesa. JCO. 2017;35:3844. 4. Mesa. Leukemia. 2022;36:2261. 5. Verstovsek. Lancet. 2023;401:269.

MOMENTUM: Momelotinib for Anemic Patients With MF and Previous JAKi Therapy

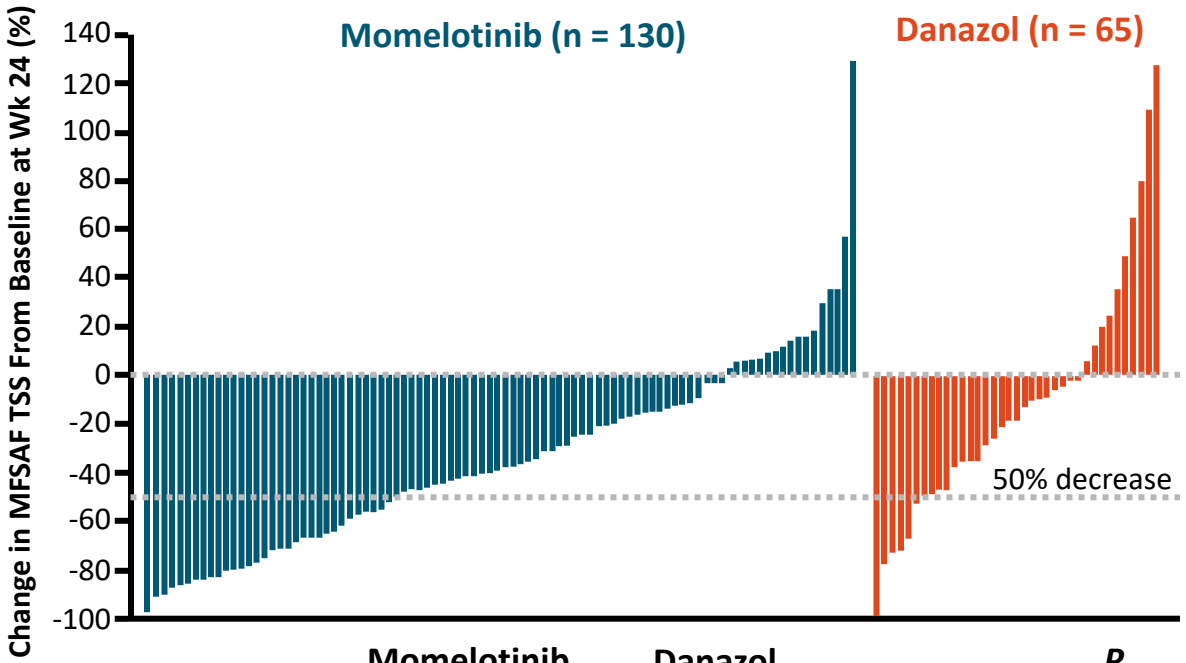
- International, double-blind, randomized phase III trial



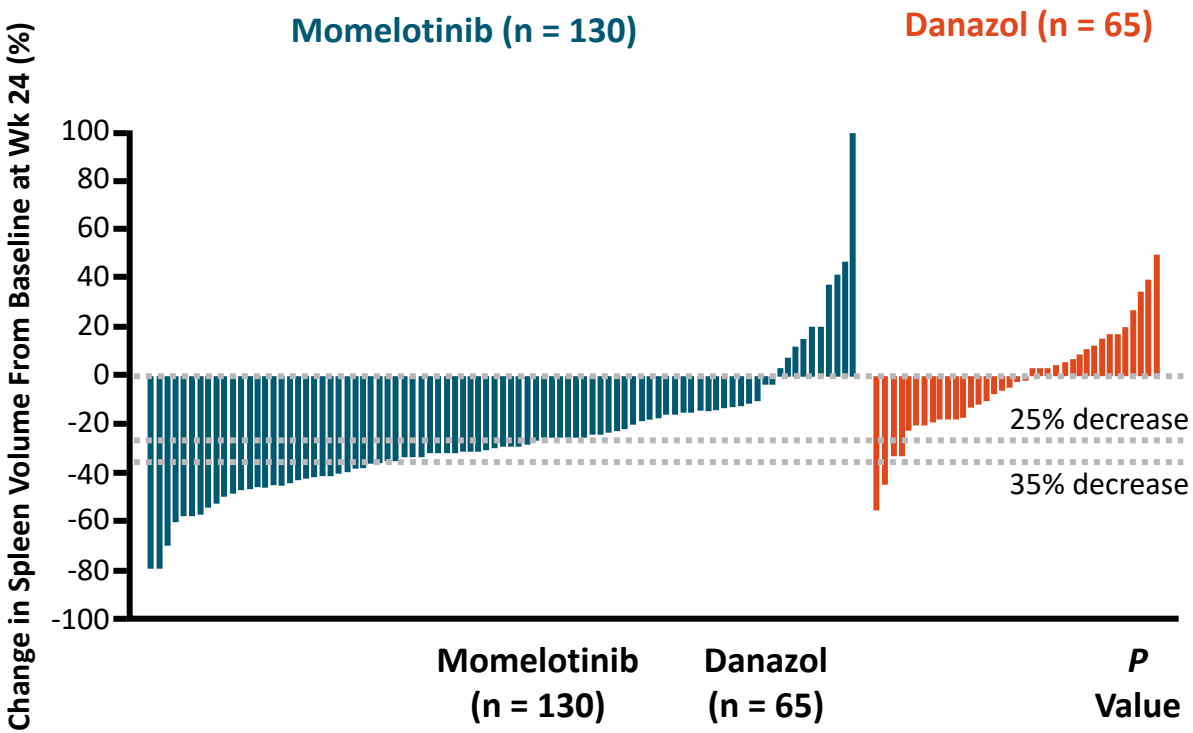
- Primary endpoint: TSS at Wk 24
- Secondary endpoints: transfusion independence, splenic response rate at Wk 24

Verstovsek. Lancet. 2023;401:269.

MOMENTUM: TSS and Spleen Response Rate at Wk 24



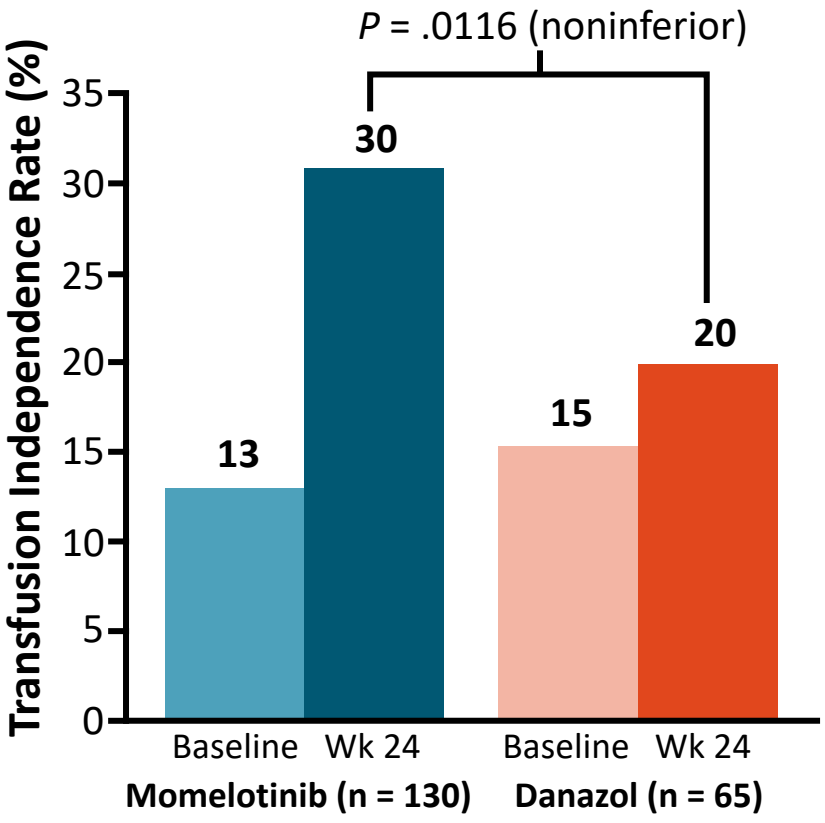
	Momelotinib (n = 130)	Danazol (n = 65)	*P* Value
≥50% MSAF TSS reduction at Wk 24, n (%) [95% CI]	32 (25) [17-33]	6 (9) [4-19]	.0095

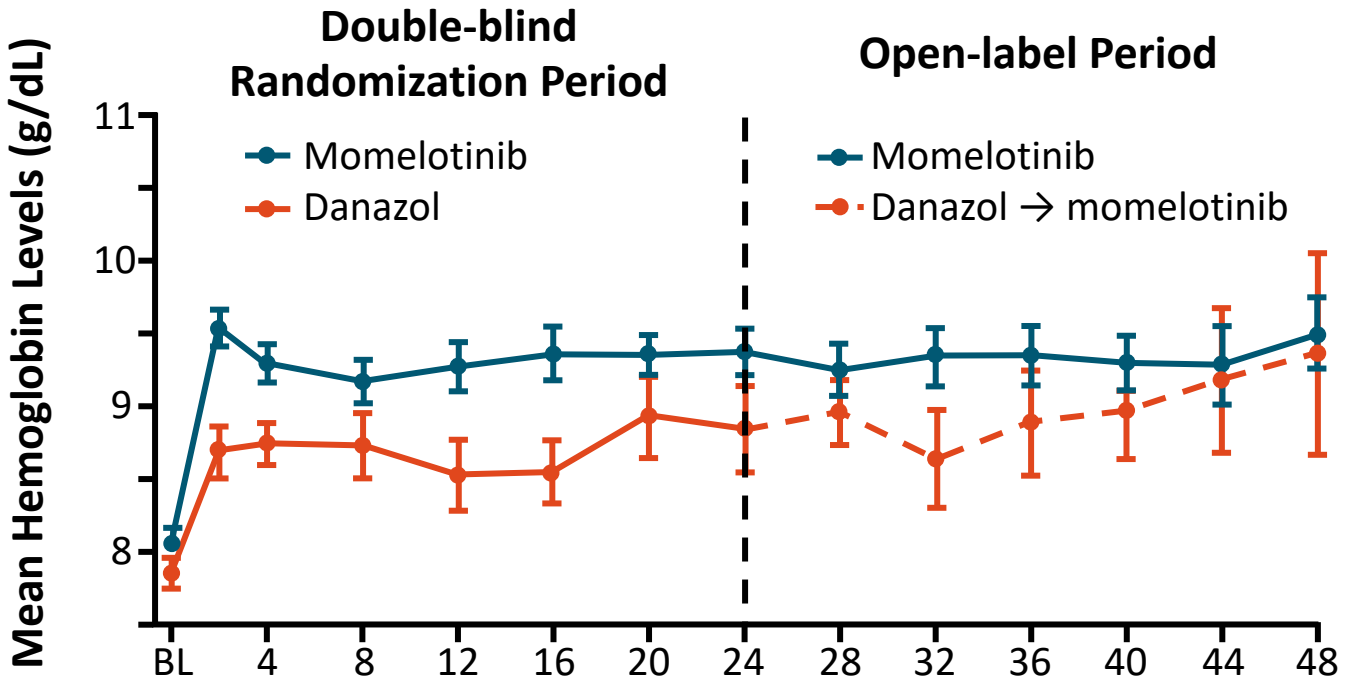


	Momelotinib (n = 130)	Danazol (n = 65)	*P* Value
≥25% SVR, n (%) [95% CI]	51 (39) [31-48]	4 (6) [2-15]	<.0001
≥35% SVR , n (%) [95% CI]	29 (22) [15-30]	2 (3) [0-11]	.0011

Verstovsek. Lancet. 2023;401:269.

MOMENTUM: Transfusion Independence Rate at Wk 24 and Mean Hemoglobin Over Time



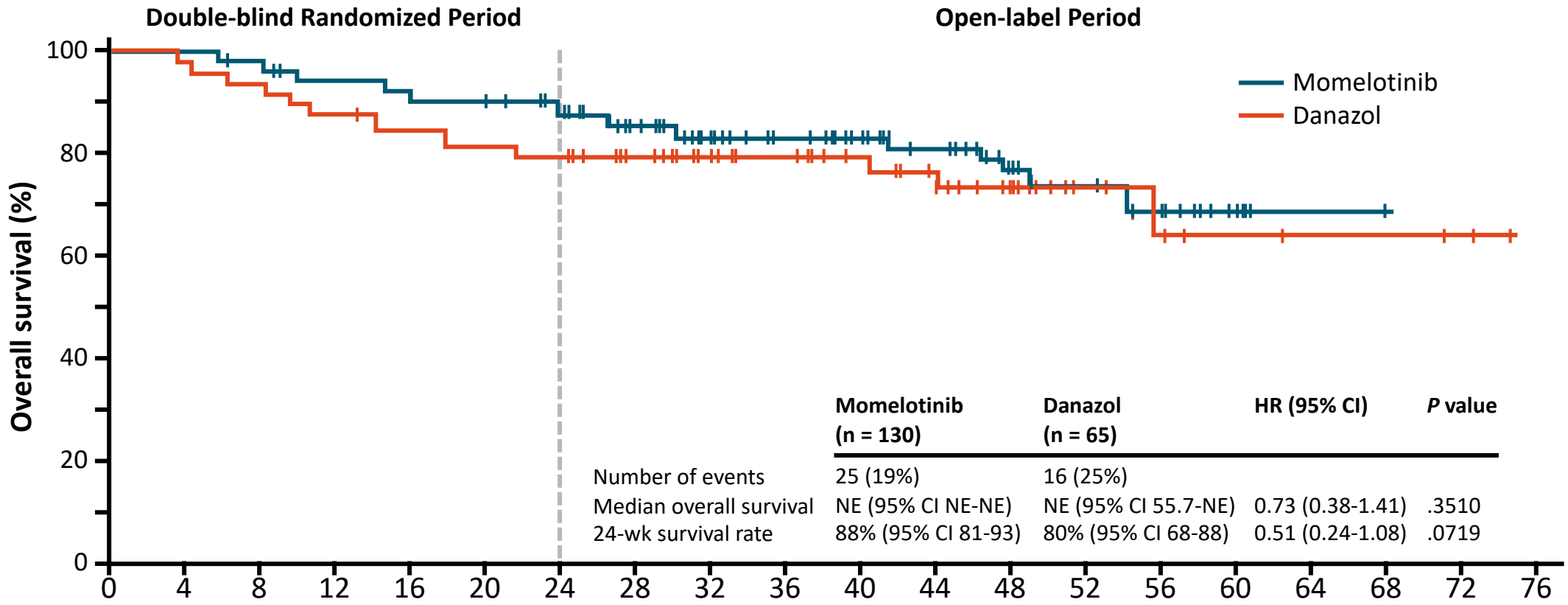


Patients at Risk, n

Momelotinib	129	105	112	93	87	88	83	67	56	44	42	36	28
Danazol	65	54	50	38	36	36	29	31	21	19	18	13	7

Verstovsek. Lancet. 2023;401:269.

MOMENTUM: OS



	Momelotinib (n = 130)	Danazol (n = 65)	HR (95% CI)	*P* value
Number of events	25 (19%)	16 (25%)		
Median overall survival	NE (95% CI NE-NE)	NE (95% CI 55.7-NE)	0.73 (0.38-1.41)	.3510
24-wk survival rate	88% (95% CI 81-93)	80% (95% CI 68-88)	0.51 (0.24-1.08)	.0719

Number at risk

Momelotinib group	130	130	126	119	117	114	107	86	71	60	53	44	36	15	12	5	1	1	0	0
Danazol group	65	64	61	57	54	52	51	43	37	32	27	23	16	10	7	4	3	3	2	0

Verstovsek. Lancet. 2023. 401:269.

MOMENTUM: Safety Through Wk 24 of Randomized Treatment

AE Overview, %	Momelotinib (n = 130)		Danazol (n = 65)	
Grade ≥3 AEs	54		65	
Serious AEs	35		40	
TEAEs in ≥10% of Patients, %	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Nonhematologic events				
▪ Diarrhea	22	0	9	2
▪ Nausea	16	2	9	3
▪ Asthenia	13	1	9	2
▪ Pruritus	11	2	11	0
▪ Weight decreased	11	0	6	0
▪ Blood creatinine increased	8	1	15	3
▪ Dyspnea	8	2	14	2
▪ Peripheral edema	8	2	14	0
▪ Fatigue	6	1	11	3
▪ Acute kidney injury	5	3	12	9
Hematologic events*				
▪ Thrombocytopenia	76	28	62	26
▪ Anemia	99	61	100	75
▪ Neutropenia	29	12	26	9

*Hematologic abnormalities are based on lab values and do not reflect any changes from baseline.

Verstovsek. Lancet. 2023;401:269.

Momelotinib Long-Term Safety: Pooled Data from Phase 3 RCTs Frequent AEs

	24 weeks N=725	25-48 weeks N=510	49-96 weeks N=367	97-144 weeks N=213	145-192 weeks N=150	193-240 weeks N=109	241-288 weeks N=93	≥ 289 weeks N=64
Any AEs, %	91.4	72.7	76.3	74.6	66.0	55.0	54.8	31.3
All Infections	36.3	26.3	33.0	30.0	25.3	20.2	21.5	12.5
Opportunistic Infections	1.8	1.4	2.5	3.8	2.0	0	4.3	1.6
Malignancies	5.2	4.1	6.3	6.1	8.0	2.8	7.5	4.7
AML/Leukemic Transformation	1.7	0.2	1.6	0.5	1.3	0	0	0
NMSC	1.2	2.7	2.7	2.3	2.0	0.9	3.2	4.7
MACE	2.8	1.8	4.9	3.8	2.7	0.9	2.2	1.6
Thromboembolism	3.4	2.4	5.2	3.8	4.0	1.8	3.2	3.1
Peripheral Neuropathy	7.6	5.5	5.4	6.1	3.3	2.8	0	0

AE, adverse events; AML, acute myeloid leukemia; NMSC, non-melanoma skin cancer; MACE, major adverse cardiovascular events

Verstovsek S, et . al. Blood Adv. 2023 Apr 12:bloodadvances.2022009311. doi: 10.1182/bloodadvances.2022009311. Epub ahead of print.

Conclusions

- Multiple available JAK inhibitors provides better options for MF patients with cytopenias
- Pacritinib is a JAK2/IRAK1/ACVR1 inhibitor
  - MF patients with thrombocytopenia regardless of line of therapy
  - Anemia responses in setting of thrombocytopenia
- Momelotinib is a JAK1/JAK2/ACVR1 inhibitor
  - MF patients with anemia
  - Safe clinical profile

Additional Investigator Survey Results

A 65-year-old man with symptomatic, higher-risk MF and splenomegaly (baseline platelet count 210,000/µL) receives ruxolitinib 20 mg BID, to which he responds with significant symptom improvement and decrease in spleen size. Approximately 3 years later he presents with transfusion-dependent anemia. Regulatory and reimbursement issues aside and assuming access, which treatment would you most likely recommend next (assuming the patient is not a transplant candidate)?

 Dr Bose	Momelotinib
 Dr Kuykendall	Continue ruxolitinib and add luspatercept
 Dr Mascarenhas	Start an erythropoietin-stimulating agent
 Dr Gerds	Start an erythropoietin-stimulating agent
 Prof Harrison	Momelotinib
 Dr Mesa	Momelotinib

A 78-year-old man with symptomatic MF receives ruxolitinib 10 mg BID but develops severe anemia and cardiac symptoms. Ruxolitinib dose is decreased to 5 mg BID with no change in symptoms. Platelet count = 77,000/µL, Hgb = 6.16 g/dL, WBC = 32,500/µL with 2% blasts, spleen is 12 cm below left costal margin. Regulatory and reimbursement issues aside, which treatment would you most likely recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Switch to momelotinib
 Dr Kuykendall	Switch to momelotinib
 Dr Mascarenhas	Switch to momelotinib
 Dr Gerds	Switch to momelotinib
 Prof Harrison	Switch to momelotinib
 Dr Mesa	Switch to momelotinib

A 75-year-old woman with MF receives ruxolitinib 15 mg BID for 2 years with good response. However, at a recent follow-up visit she is experiencing worsening cytopenias, new-onset splenomegaly and an increased symptom burden. Platelet count = 76,000/µL, Hgb = 6.7 g/dL. Regulatory and reimbursement issues aside, which treatment would you most likely recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Switch to momelotinib 200 mg qd
 Dr Kuykendall	Switch to momelotinib 200 mg qd
 Dr Mascarenhas	Switch to pacritinib 200 mg BID
 Dr Gerds	Switch to momelotinib 200 mg qd
 Prof Harrison	Switch to momelotinib 200 mg qd
 Dr Mesa	Switch to momelotinib 200 mg qd

Regulatory and reimbursement issues aside and assuming access, for a 65-year-old patient with higher-risk, symptomatic MF, splenomegaly and transfusion-dependent anemia (Hgb 8.0 g/dL), which treatment would you generally recommend (assuming the patient is not a transplant candidate)?

 Dr Bose	Momelotinib
 Dr Kuykendall	Momelotinib
 Dr Mascarenhas	Momelotinib
 Dr Gerds	Momelotinib
 Prof Harrison	Momelotinib
 Dr Mesa	Momelotinib

Agenda

Module 1 – Clinical Decision-Making for Patients with Myelofibrosis (MF) — Dr Bose

Module 2 – Management of MF in Special Patient Populations — Dr Mascarenhas

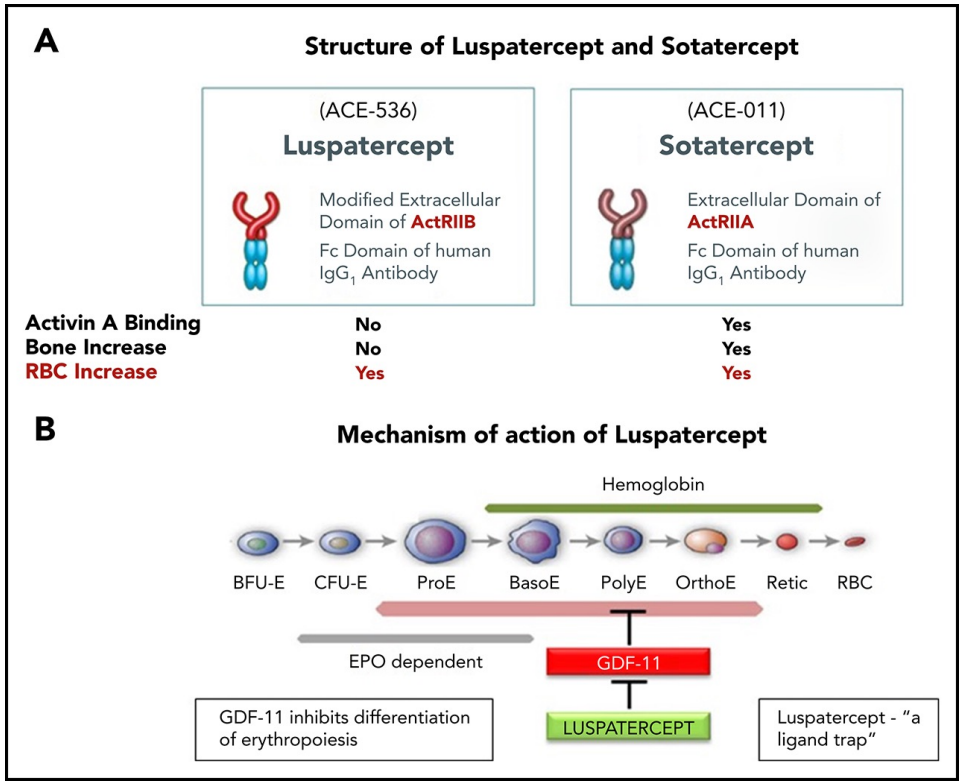
Module 3 – Future Directions in the Management of MF — Dr Kuykendall

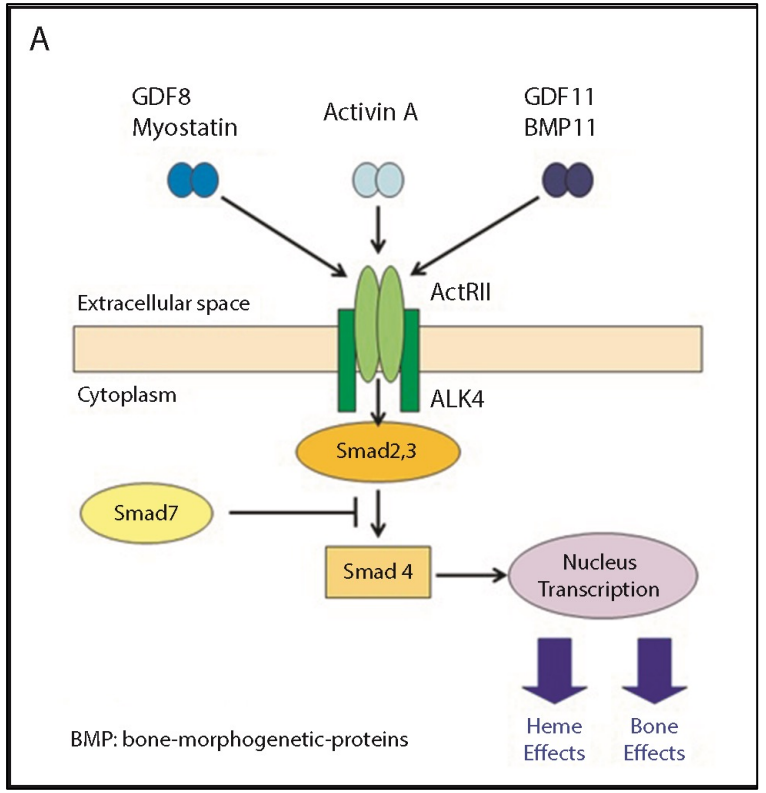
RTP
RESEARCH
TO PRACTICE

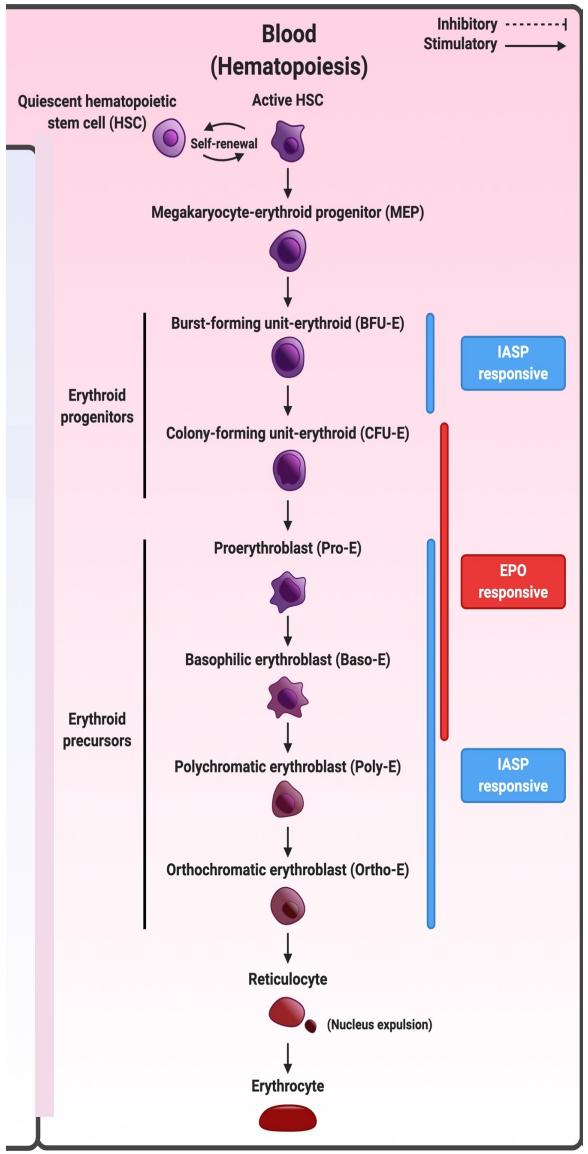
Future Directions in the Management of Myelofibrosis

Andrew Kuykendall
Assistant Member
Department of Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

Luspatercept is an activin ligand trap that promotes erythroid differentiation







Fenaux et al., Blood, 2019; Lodberg A, Cytokine & Growth Factor Reviews, 2021.

Luspatercept has demonstrated anemia responses with and without ruxolitinib in transfusion-dependent and transfusion-independent patients with MF

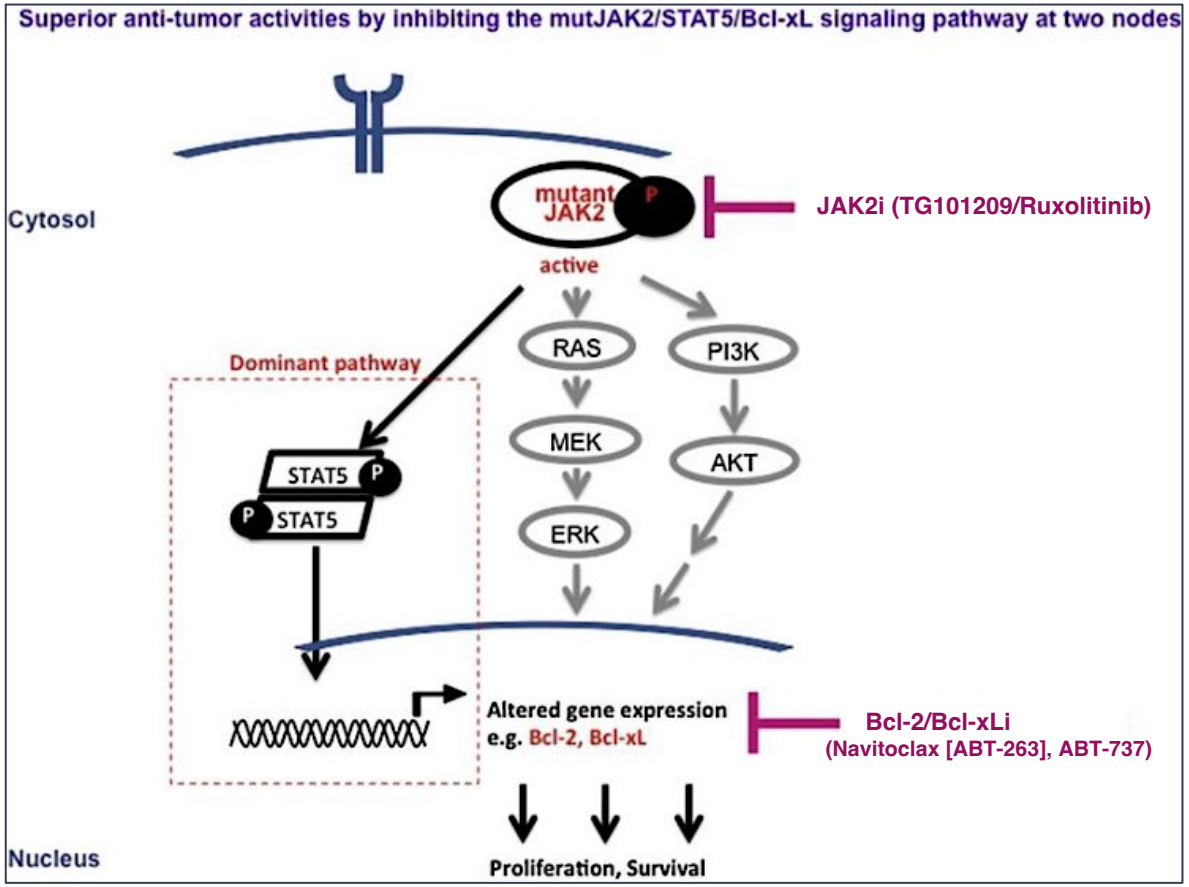
Anemia response in the ITT population

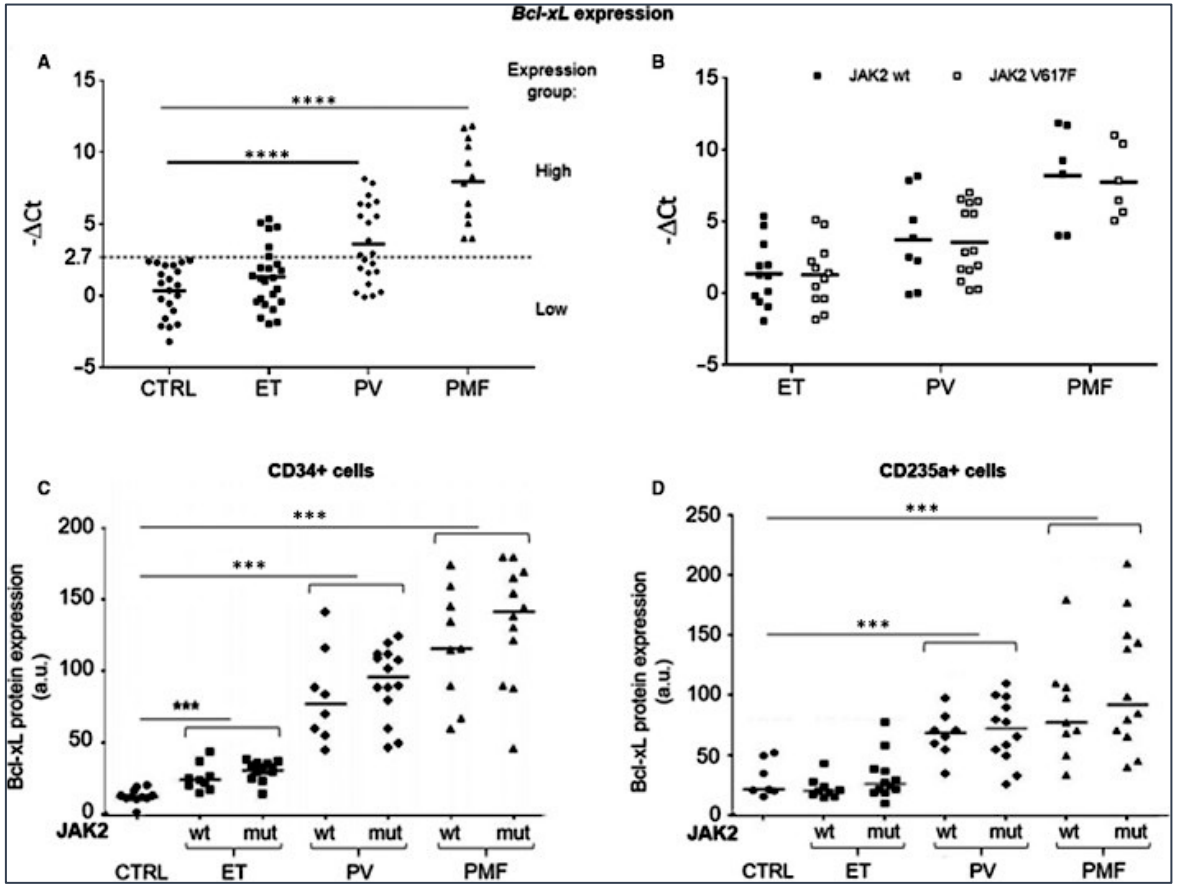
Anemia responders	Cohort 1 No RUX (n = 22)	Cohort 3A RUX (n = 14)	Cohort 2 No RUX TD (n = 21)	Cohort 3B RUX TD (n = 38)
Primary treatment period				
n (%)	3 (13.6)	2 (14.3)	2 (9.5)	10 (26.3)
[95% CI]	[2.91–34.91]	[1.78–42.81]	[1.17–30.38]	[13.40–43.10]
Entire treatment period				
n (%)	4 (18.2)	3 (21.4)	4 (19.0)	12 (31.6)
[95% CI]	[5.19–40.28]	[4.66–50.80]	[5.45–41.91]	[17.50–48.65]

CI, confidence interval; dL, deciliter; hemoglobin; ITT, intent-to-treat; RBC, red blood cell; RUX, ruxolitinib; TD, transfusion dependence.

Gerds et al., Presented at EHA 2023.

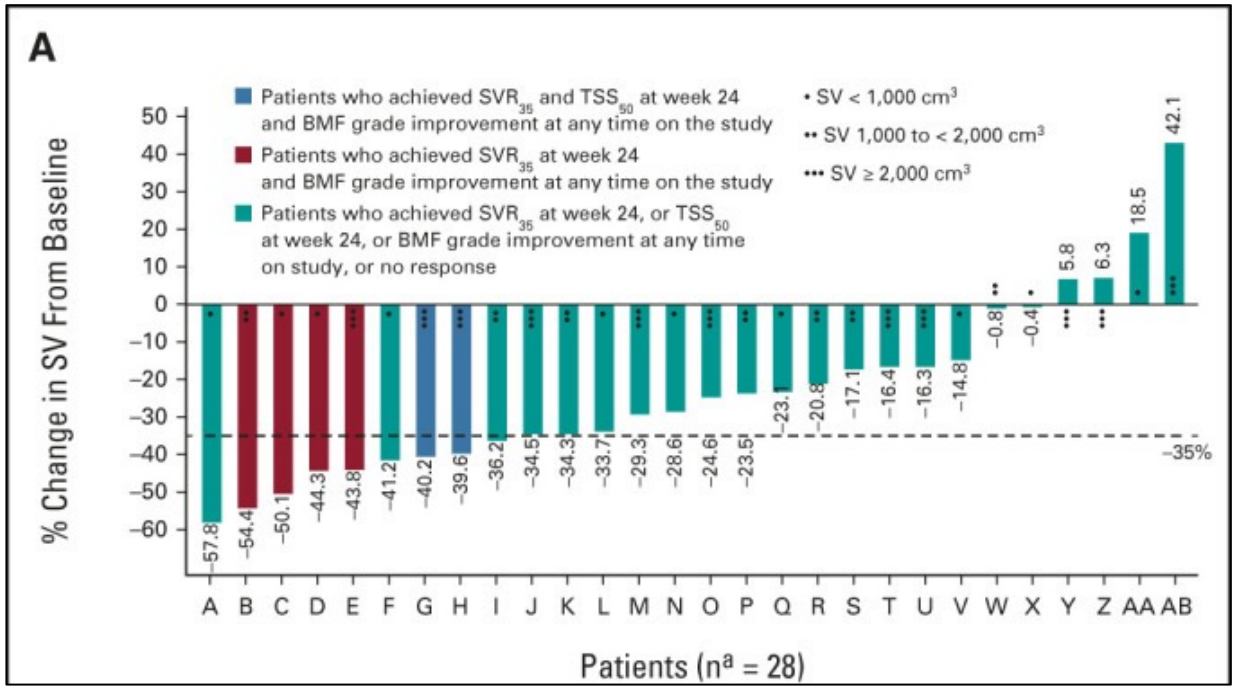
Bcl-2/Bcl-xL inhibition synergizes with JAK inhibition

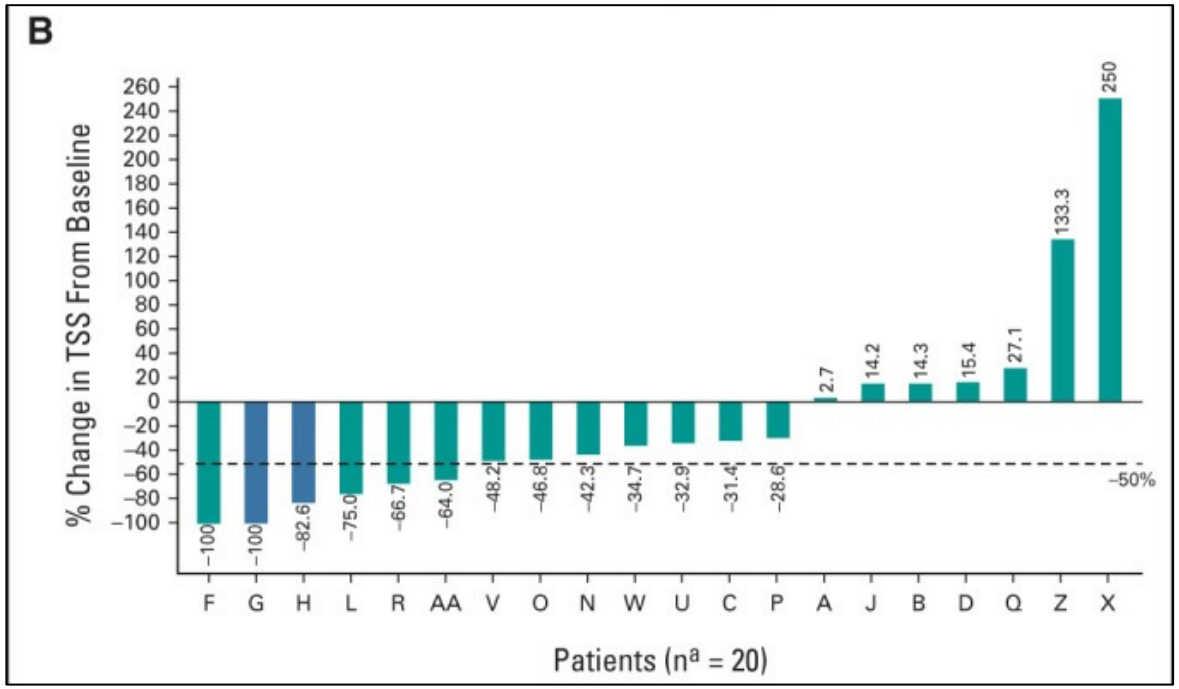




Waibel et al., Cell Rep, 2013; Petiti et al., J Cell Mol Med, 2020

The addition of navitoclax to ruxolitinib led to spleen responses in suboptimal responders



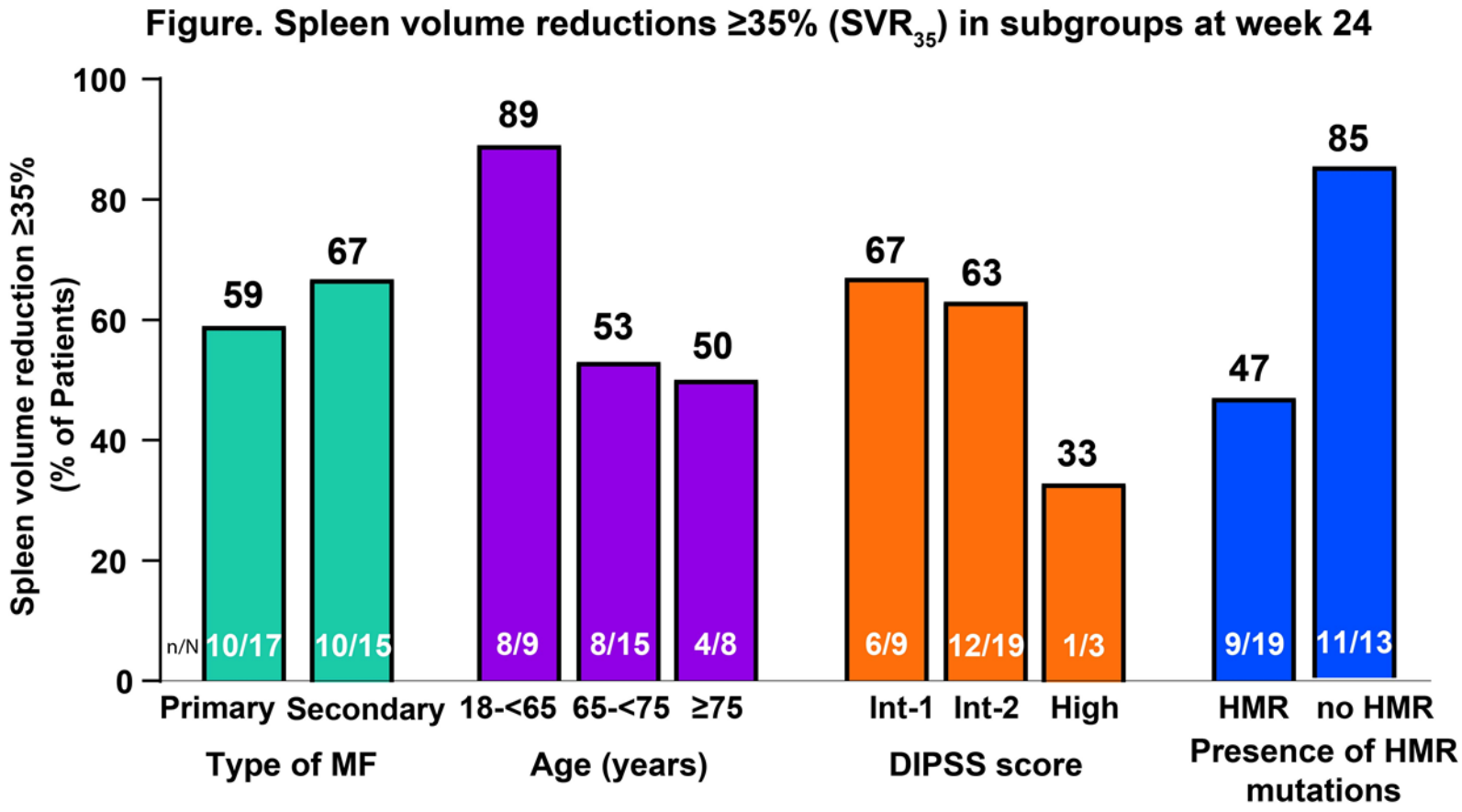


NCT04468984: TRANSFORM-2 is a study of navitoclax + ruxolitinib vs BAT in R/R MF.

Harrison et al., JCO, 2022

Combination of ruxolitinib + navitoclax induced impressive spleen responses in REFINE

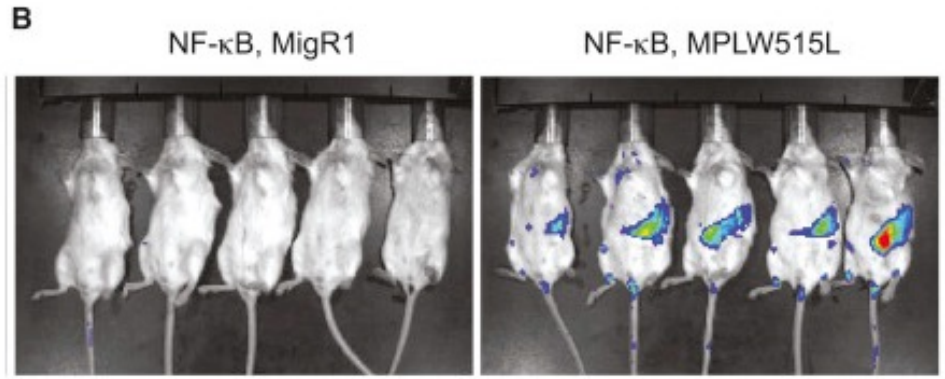
Cohort-3 of the phase 2 REFINE study enrolled JAKi-naïve patients with MF

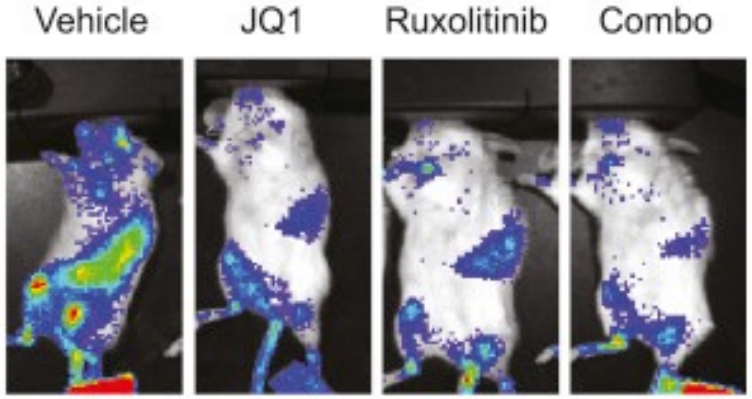


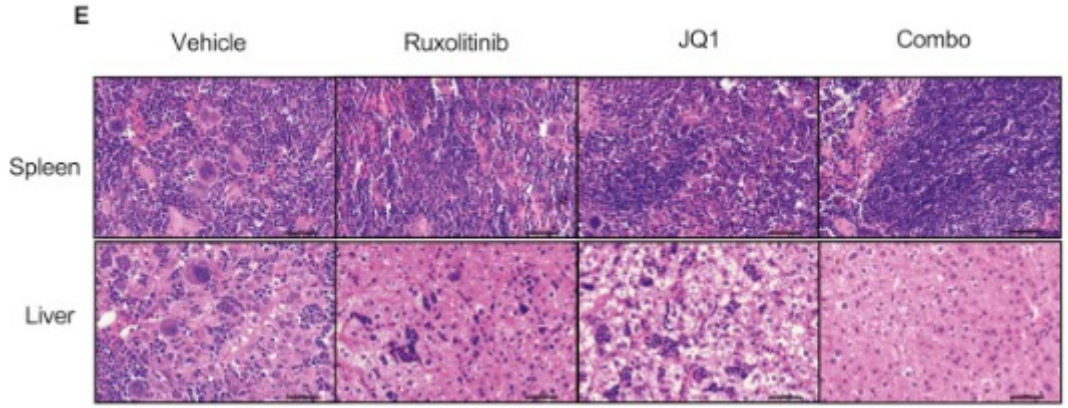
NCT04472598: TRANSFORM-1 is a study of navitoclax + ruxolitinib vs. ruxolitinib in MF.

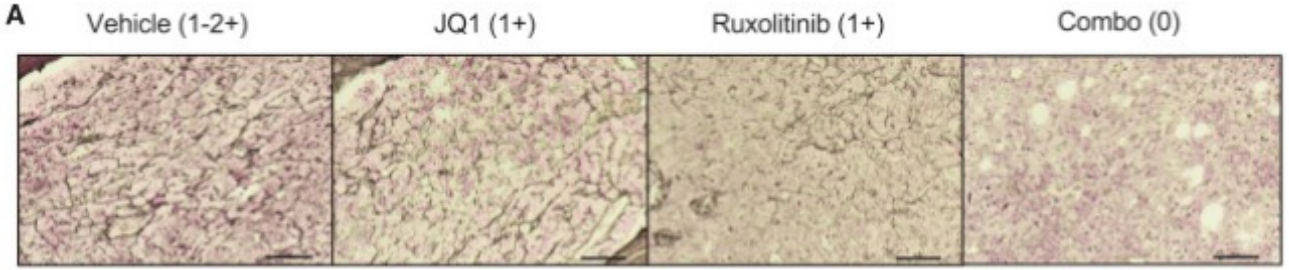
Passamonti et al., Presented at ASH 2022.

NF-κB signaling is a critical pathway in MPN that can be attenuated by BET inhibition



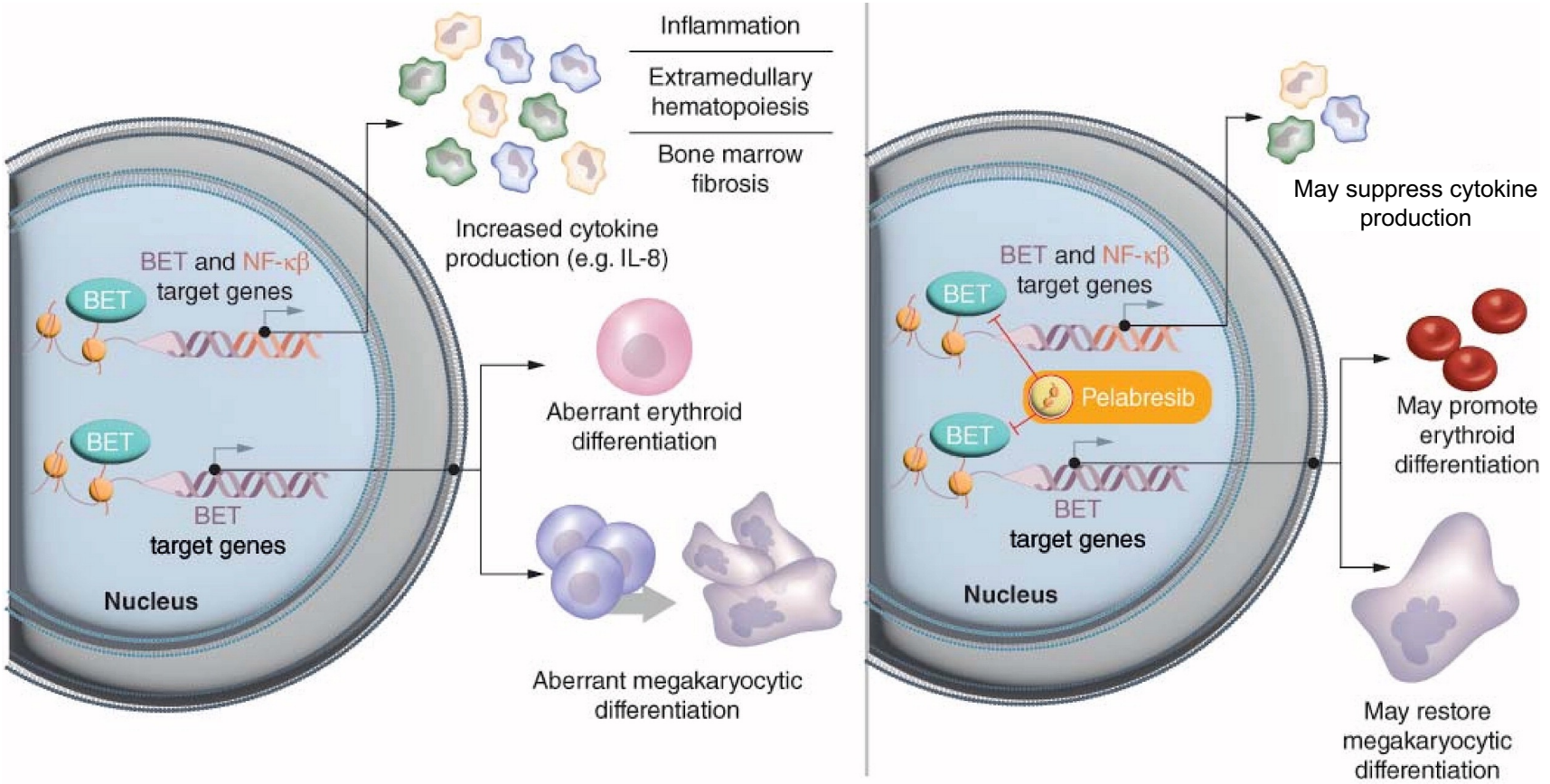






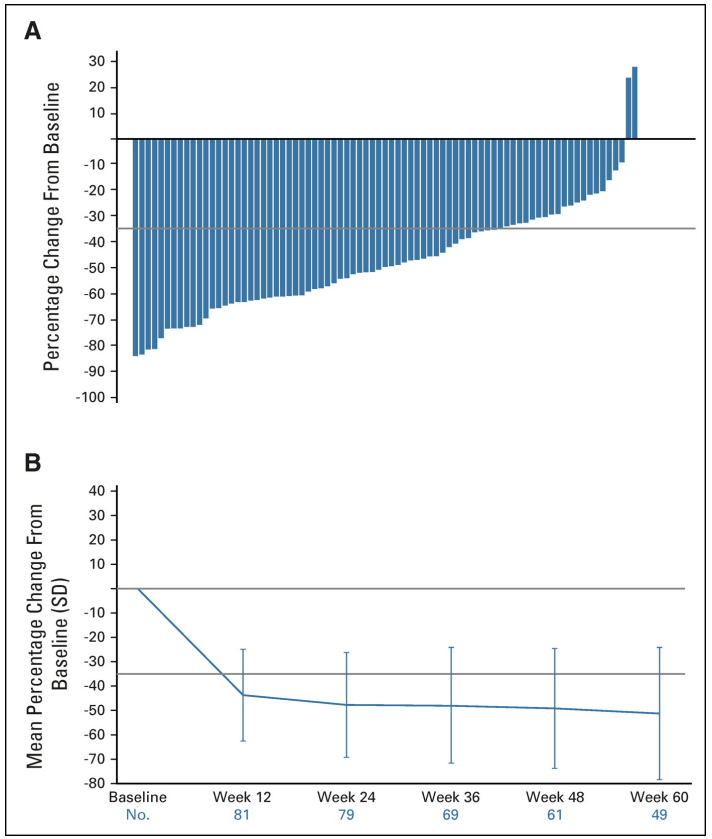
Kleppe et al., Cancer Cell, 2018

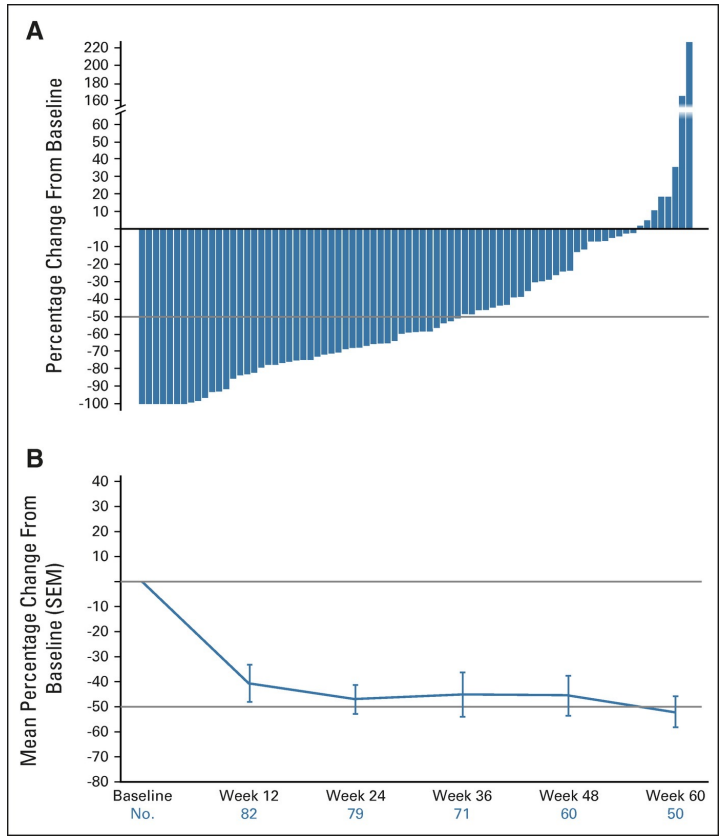
BET inhibition has the potential to reduce pro-inflammatory cytokine expression and promote erythroid/megakaryocytic differentiation

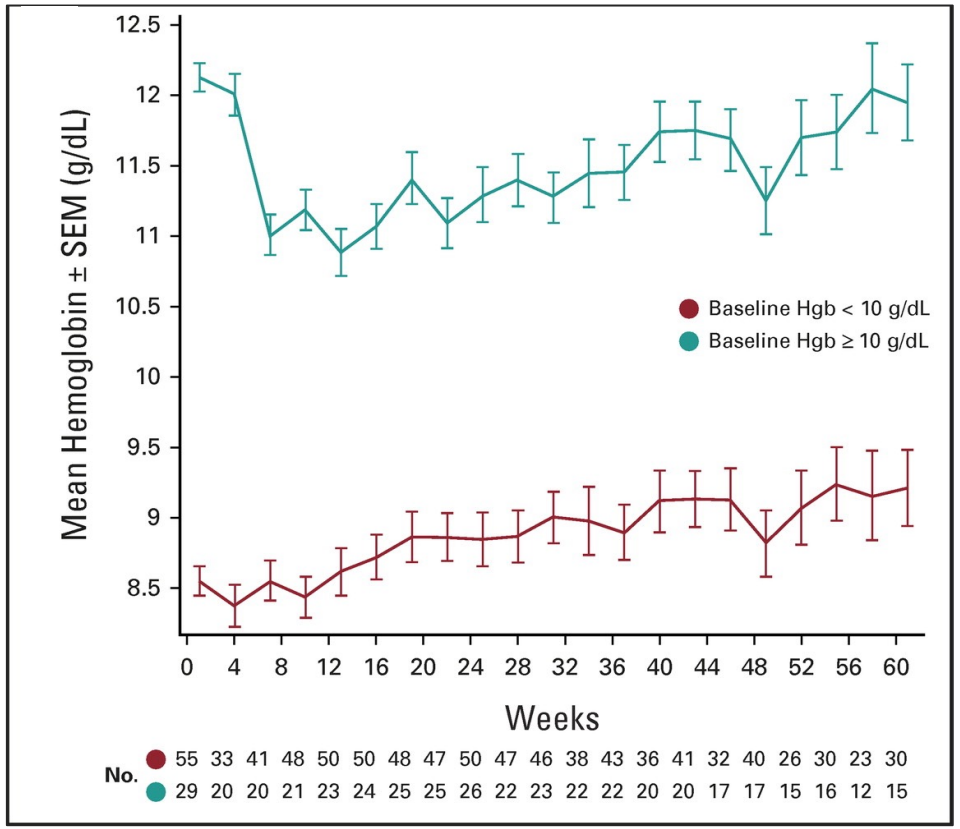


Harrison et al., Future Oncology, 2022

Pelabresib is a BET inhibitor that produced impressive spleen and symptom responses in the phase 2 MANIFEST study







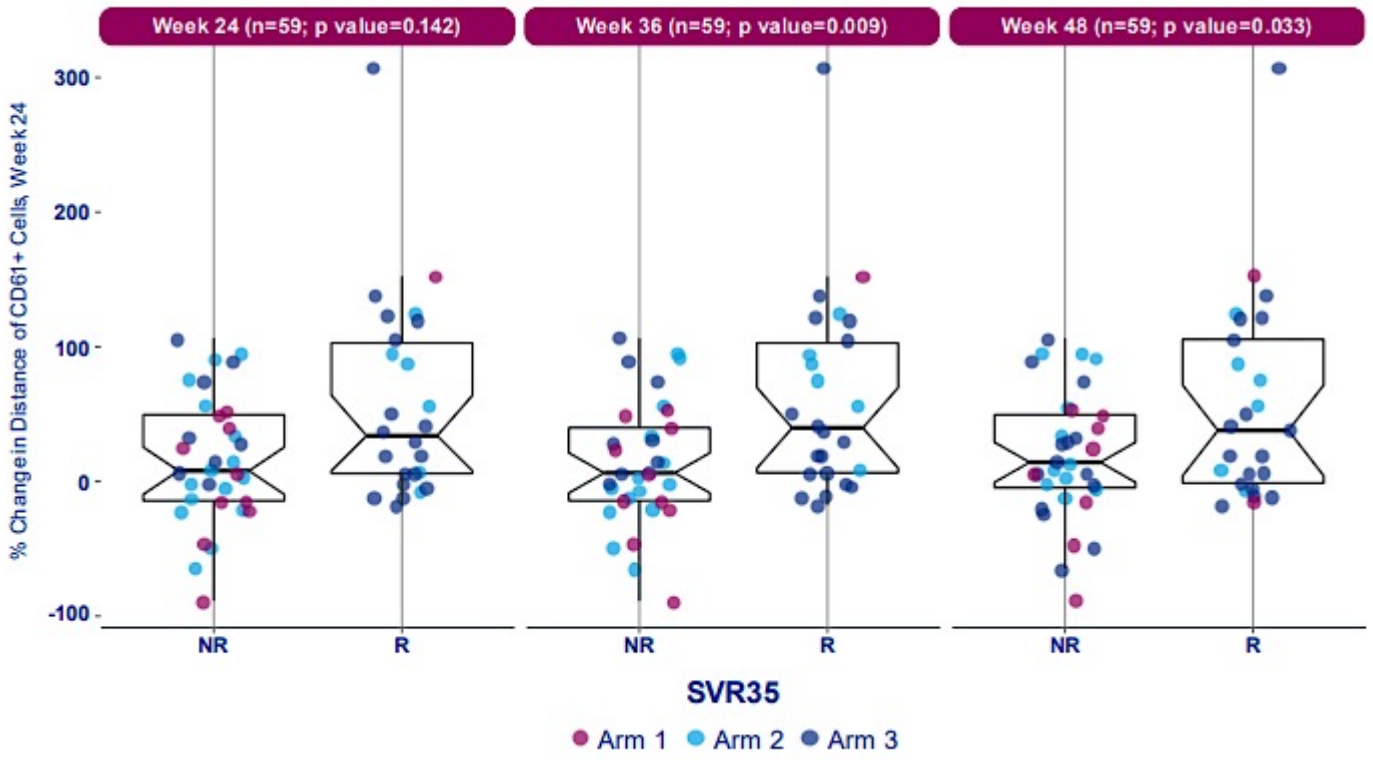
Spleen response rate: 68%

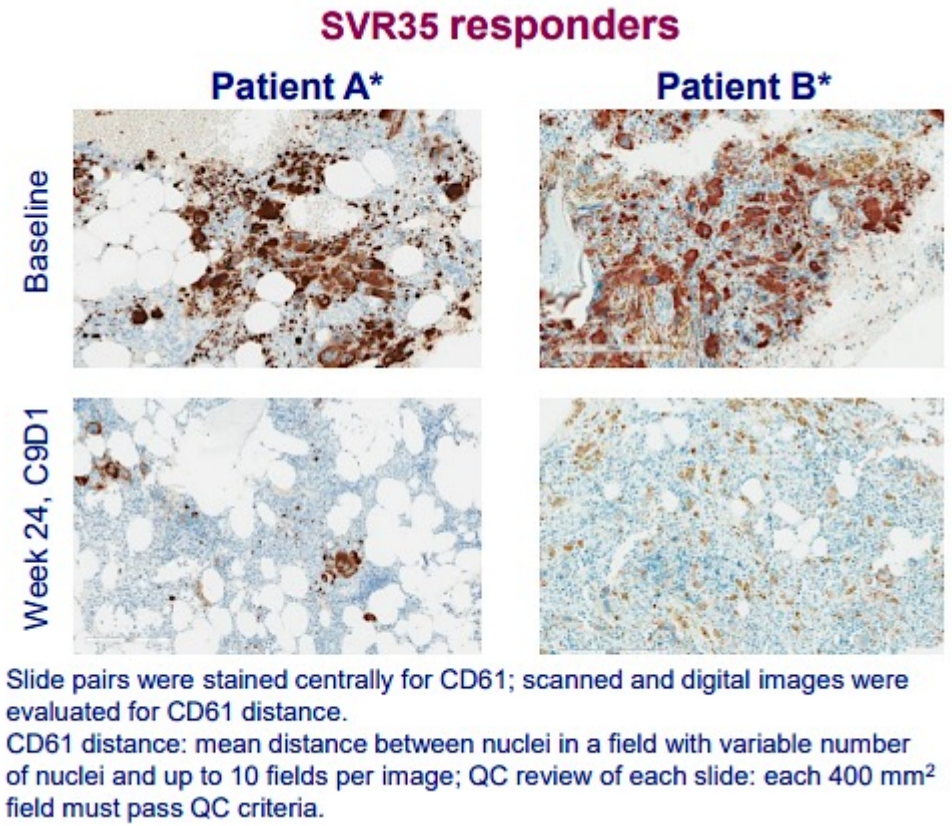
Symptom response rate: 56%

Stable/Improvements in hemoglobin

Mascarenhas et al., JCO, 2023

SVR responses have been associated with increase in megakaryocyte distance in response to pelabresib treatment





Slide pairs were stained centrally for CD61; scanned and digital images were evaluated for CD61 distance.
CD61 distance: mean distance between nuclei in a field with variable number of nuclei and up to 10 fields per image; QC review of each slide: each 400 mm^2 field must pass QC criteria.

Scandura et al., Presented at ASH 2022.

BMS-986158 is a potent BET inhibitor being evaluated alone and in combination with ruxolitinib or fedratinib in the CA011-023 study

Table. SVR rate and mean change from baseline[a]

Outcome	Part 1A BMS-986158 + RUX	Part 1B BMS-986158 + FED
SVR rate at 12 weeks, n	6	6[b]
SVR35, n (%)	5 (83)	0
(95% CI)	(35.9–99.6)	(0–45.9)
SVR rate at 24 weeks, n	6	3
SVR35, n (%)	6 (100)	1 (33)
(95% CI)	(54.1–100)	(0.8–90.6)
Mean % SV change from baseline at 12 weeks, n	6	6[b]
% (SD)	-50.3 (14.5)	-9.9 (11.4)
Mean % SV change from baseline at 24 weeks, n	6	3
% (SD)	-56.8 (9.7)	-32.7 (11.2)

[a]By MRI/CT investigator assessed. [b]One patient not eligible for end of C3 response assessment. SD, standard deviation; SVR, spleen volume reduction; SVR35, SVR ≥ 35%.

Ayala et al., Presented by Haifa Kathrin Al-Ali at EHA 2023

Emerging agents of interest

	Imetelstat	Navtemadlin	Selinexor	Bomedemstat	Zilurgisertib
Proposed Mechanism of Action	Telomerase inhibitors	MDM2 inhibitor	XPO1 inhibitor	LSD1 inhibitor	ALK2 inhibitor
Phase	3	3	3	2	1/2
Administration	Single agent and combo	Single agent and combo	Combo	Combo	Single agent and combo
Efficacy Endpoint	OS	SVR	SVR	SVR and TSS	Anemia
Notes	OS 29.9 mo in R/R MF	Spleen and symptom responses in R/R	SVR 78.6% in Tx-naïve ITT population	Dosed to goal platelet count	Induces hepcidin reduction

Consensus or Controversy? Documenting and Discussing Clinical Investigators' Practice Patterns in Myelofibrosis

A CME Satellite Symposium During the Society of Hematologic Oncology 2023 Annual Meeting

Thursday, September 7, 2023
6:34 PM – 7:34 PM CT

Faculty

Prithviraj Bose, MD
Andrew T Kuykendall, MD

Moderator

John Mascarenhas, MD

RTP RESEARCH TO PRACTICE

Cases from the Community: Investigators Discuss the Application of Available Research in the Care of Patients with Diffuse Large B-Cell Lymphoma

A CME Satellite Symposium During the Society of Hematologic Oncology 2023 Annual Meeting

Friday, September 8, 2023
11:37 AM – 12:37 PM CT

Faculty

Matthew Lunning, DO
Laurie H Sehn, MD, MPH

Moderator

Christopher R Flowers, MD, MS

RTP
RESEARCH
TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Clinicians in the Meeting Room:

Please complete the postevent survey by following the instructions included on the handout with your program syllabus.

Attendees on Zoom:

The survey will remain open for 5 minutes after the meeting ends.

How to Obtain CME Credit

In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.

Online/Zoom attendees: The CME credit link is posted in the chat room.

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Appendix

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

 Dr Bose	Ruxolitinib
 Dr Kuykendall	Ruxolitinib
 Dr Mascarenhas	Ruxolitinib
 Dr Gerds	Ruxolitinib
 Prof Harrison	Ruxolitinib or peginterferon alfa-2a
 Dr Mesa	Ruxolitinib

In approximately what proportion of your patients receiving fedratinib have you observed clinically meaningful gastrointestinal adverse events?

 Dr Bose	20%
 Dr Kuykendall	20%
 Dr Mascarenhas	40%
 Dr Gerds	25%
 Prof Harrison	10%, assuming adequate prophylaxis
 Dr Mesa	40%

If administering fedratinib to a patient with higher-risk, symptomatic MF, splenomegaly and a platelet count of 90,000/µL, which starting dose would you generally use?

 Dr Bose	400 mg daily
 Dr Kuykendall	400 mg daily
 Dr Mascarenhas	400 mg daily
 Dr Gerds	400 mg daily
 Prof Harrison	400 mg daily
 Dr Mesa	400 mg daily

When administering the JAK inhibitor fedratinib to a patient with MF, how do you generally approach the prevention and management of associated toxicities?

 Dr Bose	These are most common in cycle 1. Important to make the patient aware and treat promptly
 Dr Kuykendall	Counsel for GI toxicity; prophylactic antiemetics and PRN antidiarrheals; advise to take med with high-fat meal; assess for risk factors of malnutrition; check thiamine levels and recommend supplementation
 Dr Mascarenhas	Antiemetic initially and antidiarrheal if needed, and check thiamine levels q3m
 Dr Gerds	Start antiemetic, antidiarrheal and thiamine, and then taper off antiemetic and antidiarrheal as tolerated
 Prof Harrison	Patient education, supplementation and checking levels and symptoms
 Dr Mesa	Antinausea, antidiarrheals and thiamine. Usually can stop the GI drugs after awhile

Based on current clinical trial data and your personal experience, how would you indirectly compare the overall efficacy and tolerability of pacritinib to that of ruxolitinib and of fedratinib for patients with MF?

	Efficacy	Tolerability
 Dr Bose	Ruxolitinib is most efficacious	Available data are insufficient at this time
 Dr Kuykendall	Ruxolitinib is most efficacious	Ruxolitinib is most tolerable
 Dr Mascarenhas	Available data are insufficient at this time	Ruxolitinib is most tolerable
 Dr Gerds	All are about the same – they each perform in their niches very well	All are about the same
 Prof Harrison	Ruxolitinib is most efficacious	Ruxolitinib is most tolerable
 Dr Mesa	Available data are insufficient at this time	Available data are insufficient at this time

When administering the JAK inhibitor pacritinib to a patient with MF, how do you generally approach the prevention and management of associated toxicities (eg, diarrhea and thrombocytopenia)?

 Dr Bose	Diarrhea is mostly limited to the first 8 wk. Patients need loperamide on hand. Platelets typically stay stable and occasionally improve.
 Dr Kuykendall	Counsel on potential for GI side effects; prophylactic antiemetics for 6-8 wk then PRN antidiarrhreals with lab checks q2-4wk after starting
 Dr Mascarenhas	Treat through cytopenias, ondansetron for nausea +/- loperamide for diarrhea, which is usually limited to the first 1-2 months
 Dr Gerds	Prescribe an antidiarrheal and monitor platelet counts closely; order regular EKGs to monitor QTc
 Prof Harrison	Patient education, prophylaxis and monitoring
 Dr Mesa	Antinausea and antidiarrheal drugs, usually can be stopped

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

 Dr Bose	Yes
 Dr Kuykendall	Yes
 Dr Mascarenhas	Yes
 Dr Gerds	No – it is a concern for any patient with cytopenic MF regardless of treatment
 Prof Harrison	Yes
 Dr Mesa	No

In your experience, what are the most important tolerability issues associated with momelotinib?

 Dr Bose	I have not used momelotinib
 Dr Kuykendall	Mild GI side effects
 Dr Mascarenhas	Likely potential for peripheral neuropathy
 Dr Gerds	Most treatment discontinuations due to efficacy reasons
 Prof Harrison	GI upset
 Dr Mesa	GI side effects