What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Myelofibrosis

A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)

Faculty

Prithviraj Bose, MD

Angela G Fleischman, MD, PhD

Abdulraheem Yacoub, MD

Moderator

Andrew T Kuykendall, MD

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Faculty

Prithviraj Bose, MD
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Co-Leader, Section of Myeloproliferative Neoplasms
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Division of Hematology/Oncology
UC Irvine Health
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Moderator

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

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Dr Bose — Disclosures
Faculty

Advisory Committees	Blueprint Medicines, Geron Corporation, Karyopharm Therapeutics, PharmaEssentia
Consulting Agreements	AbbVie Inc, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Disc Medicine, GSK, Incyte Corporation, Ionis Pharmaceuticals Inc, Jubilant Pharma Limited, Keros Therapeutics, Morphic Therapeutic, MorphoSys, Novartis, Sumitomo Dainippon Pharma Oncology Inc
Contracted Research	Blueprint Medicines, Bristol Myers Squibb, Cogent Biosciences, CTI BioPharma, a Sobi Company, Disc Medicine, Geron Corporation, Incyte Corporation, Ionis Pharmaceuticals Inc, Janssen Biotech Inc, Kartos Therapeutics, Karyopharm Therapeutics, MorphoSys, Sumitomo Dainippon Pharma Oncology Inc, Telios Pharma Inc

Dr Fleischman — Disclosures
Faculty

Advisory Committees	CTI BioPharma, a Sobi Company, Incyte Corporation
Consulting Agreement	Ionis Pharmaceuticals Inc
Speakers Bureaus	CTI BioPharma, a Sobi Company, GSK, PharmaEssentia

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Dr Yacoub — Disclosures
Faculty

Consulting Agreements	AbbVie Inc, Acceleron Pharma, Apellis, CTI BioPharma, a Sobi Company, Gilead Sciences Inc, Incyte Corporation, Karyopharm Therapeutics, Notable Labs, Novartis, Pfizer Inc, PharmaEssentia, Protagonist Therapeutics, Servier Pharmaceuticals LLC

Dr Kuykendall — Disclosures
Moderator

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

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Commercial Support

This activity is supported by educational grants from CTI BioPharma, a Sobi Company, Geron Corporation, GSK, Incyte Corporation, and Karyopharm Therapeutics.

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This educational activity contains discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Alexander Perl, MD
Richard M Stone, MD
Eunice S Wang, MD
Andrew H Wei, MBBS, PhD

Moderator

Eytan M Stein, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Multiple Myeloma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Professor Philippe Moreau, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Sagar Lonial, MD

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Rounds with the Investigators: Compelling Teaching Cases Focused on the Management of Breast Cancer

A 3-Part CME Hybrid Satellite Symposium Series in Partnership with the 2024 San Antonio Breast Cancer Symposium®

HER2-Low and HER2-Ultralow Breast Cancer

Tuesday, December 10, 2024

7:15 PM – 8:45 PM CT

New Developments in Endocrine Treatment for Breast Cancer

Wednesday, December 11, 2024

7:15 PM – 9:15 PM CT

Management of Metastatic Breast Cancer

Thursday, December 12, 2024

7:00 PM – 9:00 PM CT

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Save The Date

Fourth Annual
National General Medical Oncology Summit

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

Friday to Sunday, February 28 to March 2, 2025

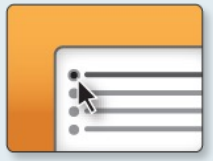
Fontainebleau Hotel, Miami Beach, Florida

Moderated by Neil Love, MD

Clinicians in the Meeting Room

Networked iPads are available.

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



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

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

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

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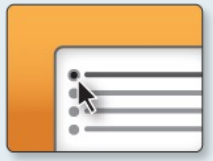
Clinicians Attending via Zoom

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



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

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

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

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
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Survey of General Medical Oncologists: November 22nd – December 5th

Results available on iPads and Zoom chat room

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Agenda

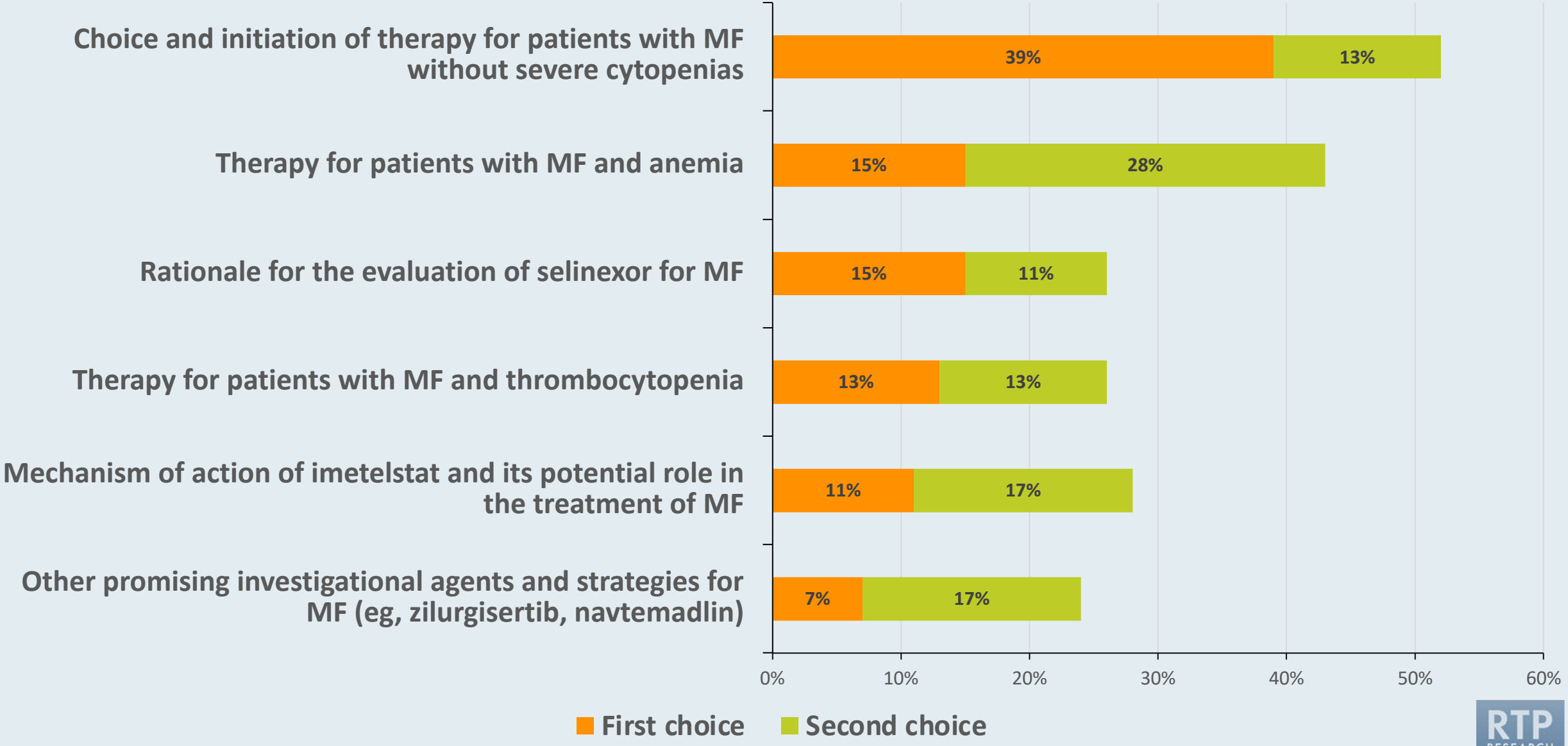
Module 1: Current Clinical Decision-Making for Myelofibrosis (MF) in the Absence of Severe Cytopenias — Dr Kuykendall

Module 2: Managing MF for Patients with Thrombocytopenia — Dr Bose

Module 3: Managing MF for Patients with Anemia — Dr Yacoub

Module 4: Future Directions in the Management of MF — Dr Fleischman

Topics of Interest for Future CME Programs



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Agenda

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

Module 2: Managing MF for Patients with Thrombocytopenia — Dr Bose

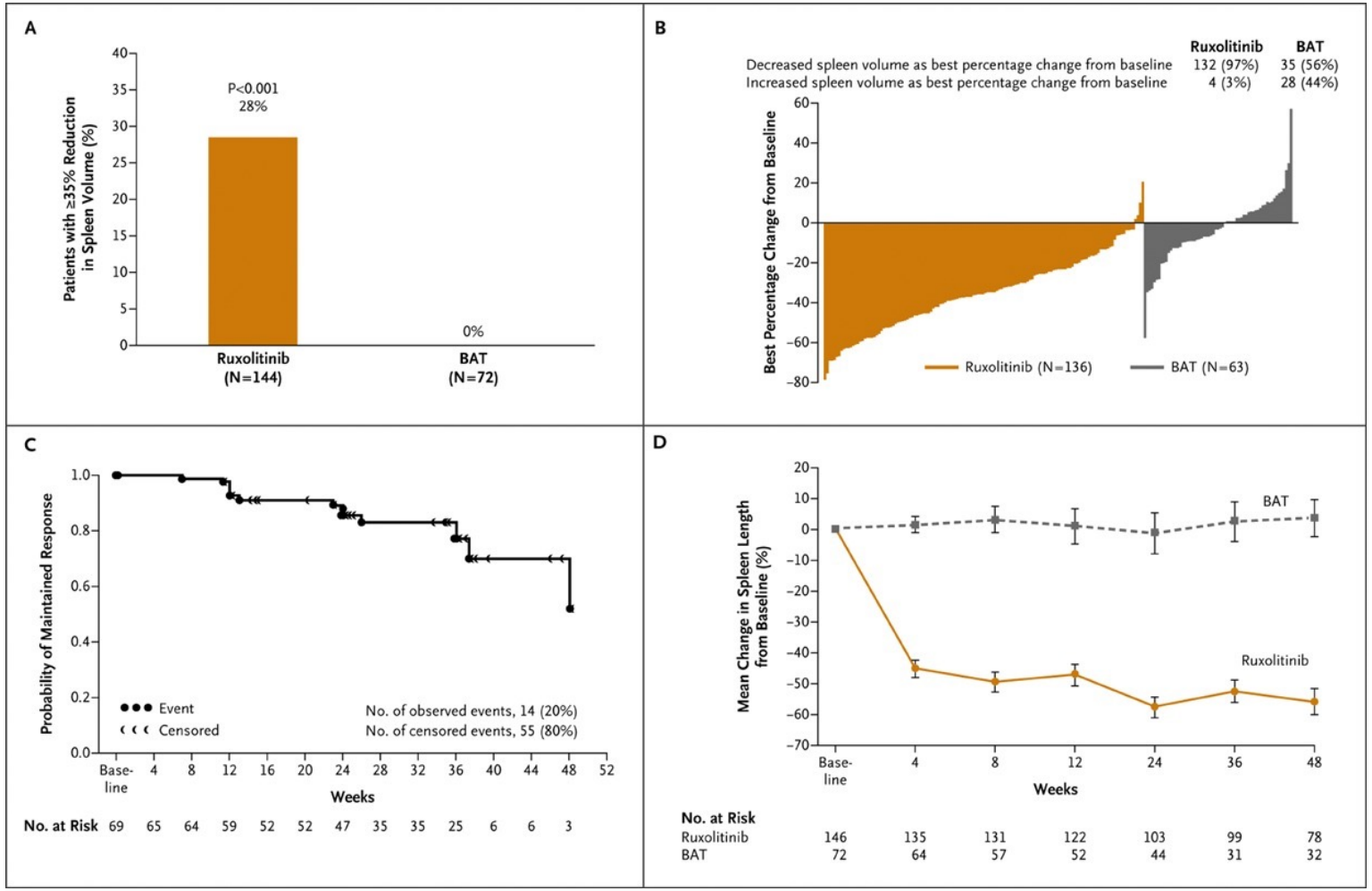
Module 3: Managing MF for Patients with Anemia — Dr Yacoub

Module 4: Future Directions in the Management of MF — Dr Fleischman

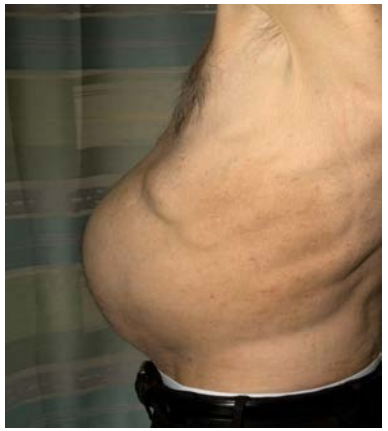
Current Clinical Decision-Making for Myelofibrosis in the Absence of Severe Cytopenias

Andrew Kuykendall, MD
Associate Member
Department of Malignant Hematology
Moffitt Cancer Center

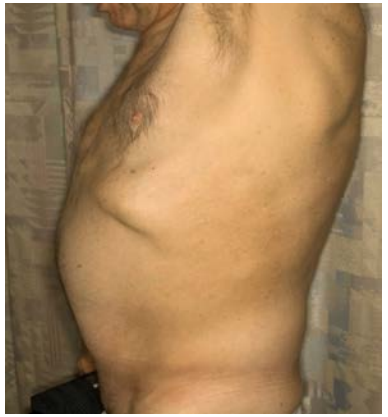
Ruxolitinib reduces spleen volume, improves symptoms and is associated with a survival benefit



Pre Ruxolitinib

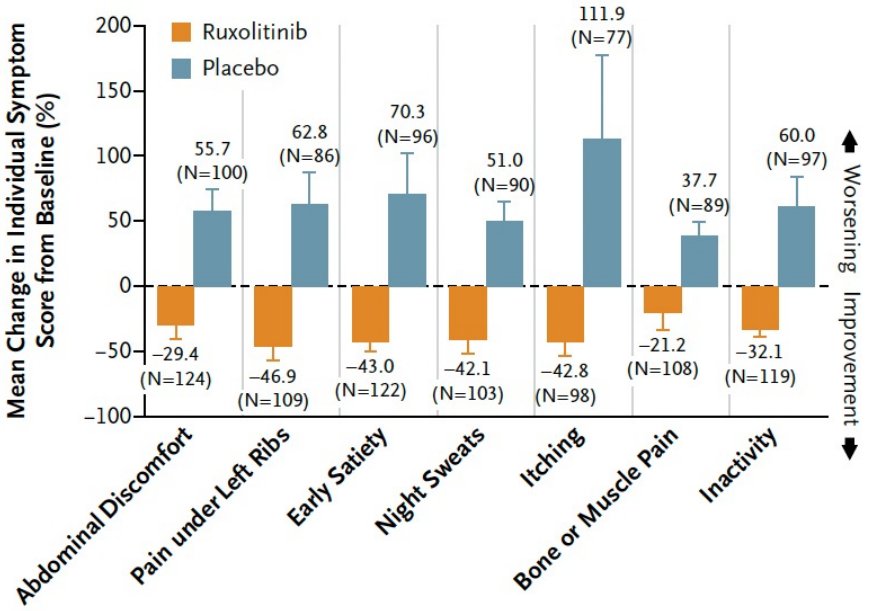


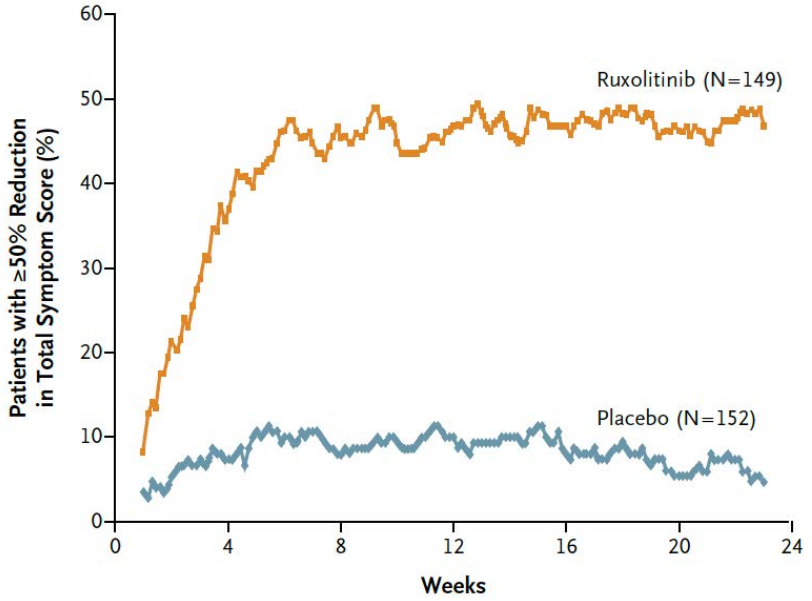
After 2 Mo Therapy

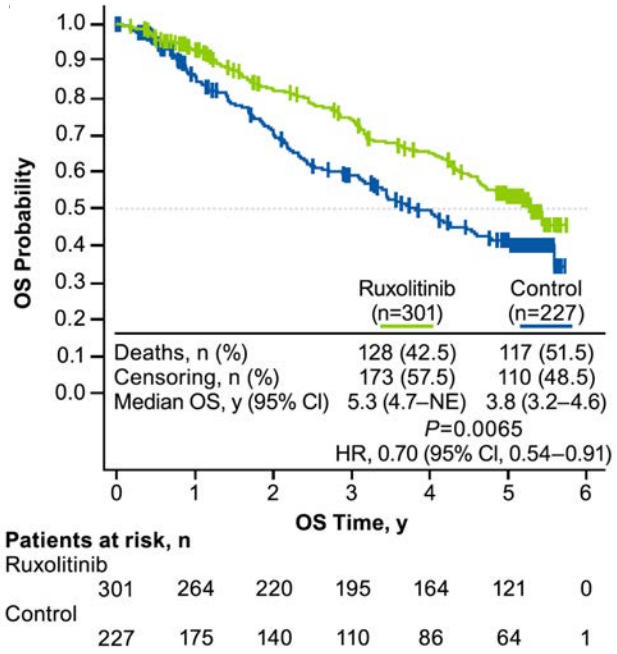


Harrison et al., NEJM, 2012; Images courtesy of Srdan Verstovsek, MD, PhD.

Ruxolitinib effectively reduces spleen volume, improves disease related symptoms, and is associated with a survival benefit







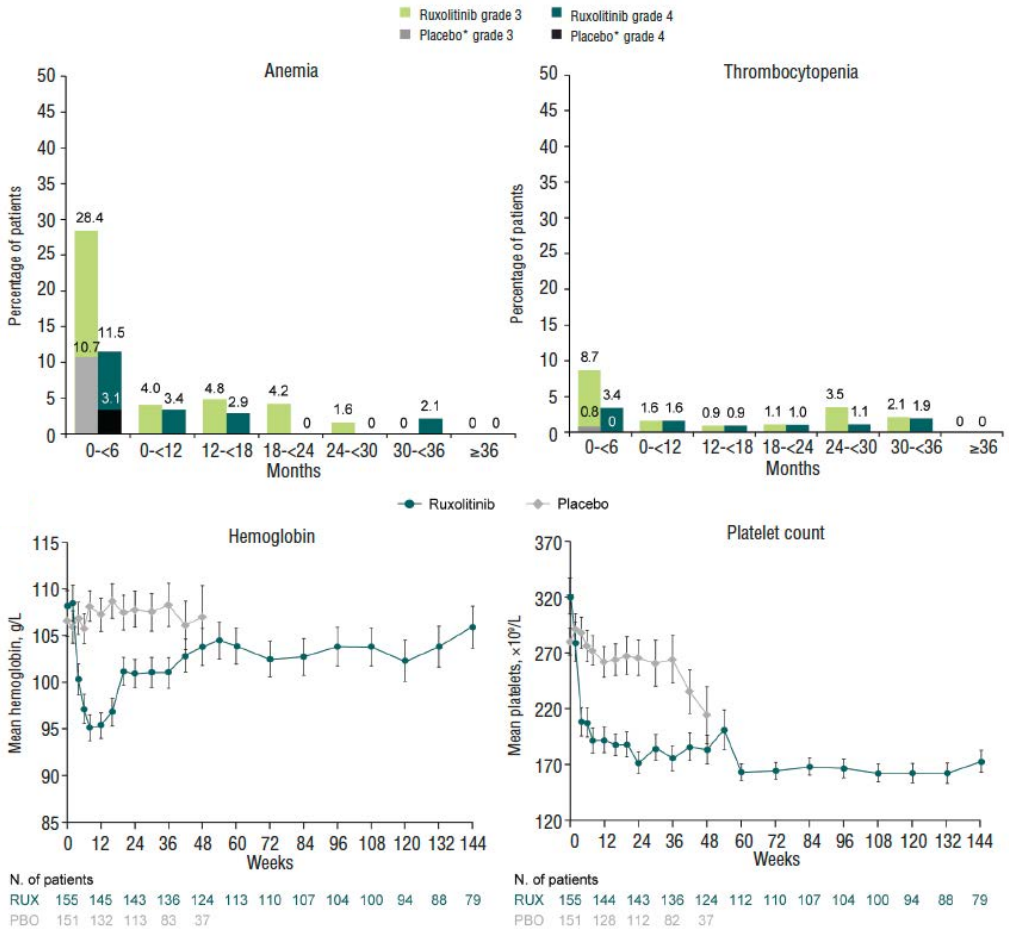
Verstovsek et al., NEJM, 2012; Verstovsek et al., J Hematol Oncol, 2017

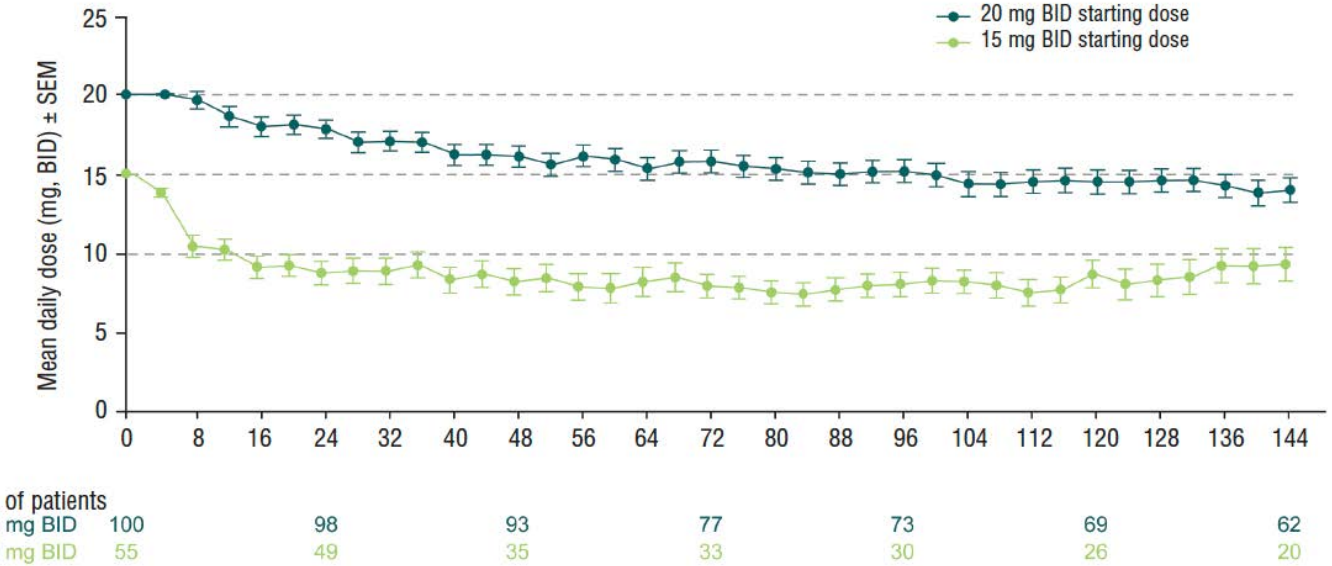
Early intervention with ruxolitinib may allow for enhanced response rates and less hematologic toxicity

		Week 24 Spleen Response	Grade ≥ 3 Anemia	Grade ≥ 3 Thrombocytopenia
Int-2 and high risk	COMFORT-I (n = 155)	41.9%	45.2%	12.9%
	COMFORT-II (n = 146)	32%	42%	8%
Int-1 risk patients	JUMP (n = 163)	63.8%	24.5%	11%
	ROBUST (n = 14)	57.1%	N/A	N/A
	Palandri (n = 17)	54.7%	21.7%	2.9%

1. Verstovsek. NEJM. 2012;366:799.
2. Harrison. NEJM. 2012;366:787.
3. Al-Ali. Haematologica. 2016;101:1065.
4. Mead. Br J Haematol. 2015;170:29.
5. Palandri. Hematol Oncol. 2018;36:285.

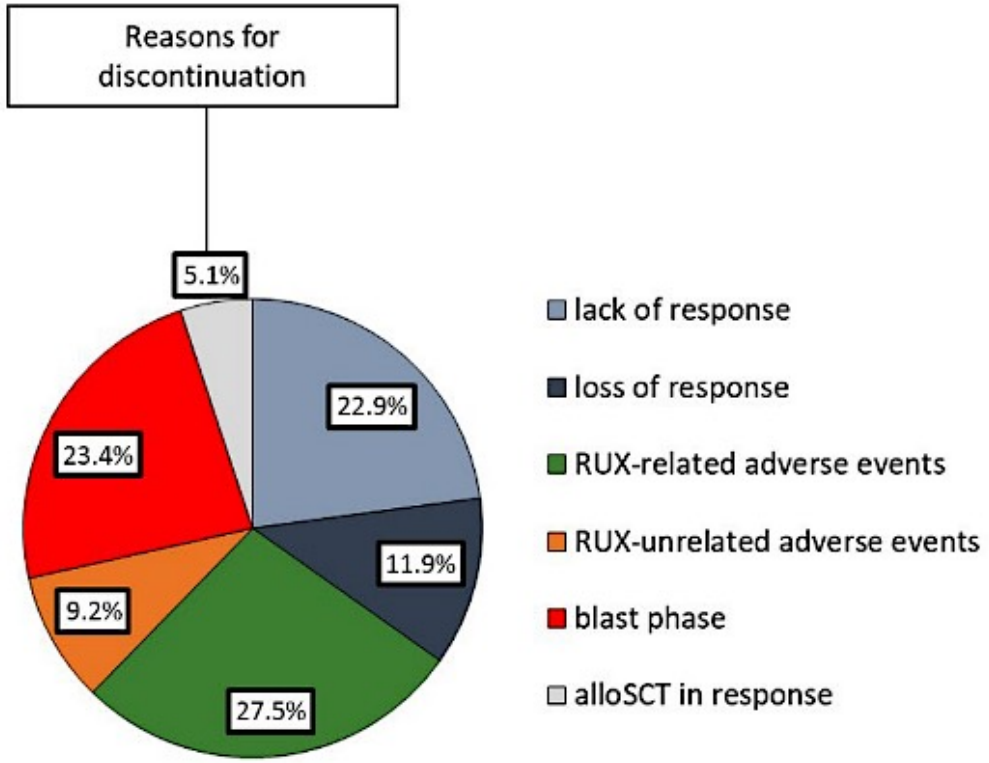
Ruxolitinib associated with anemia and thrombocytopenia that frequently leads to dose reductions

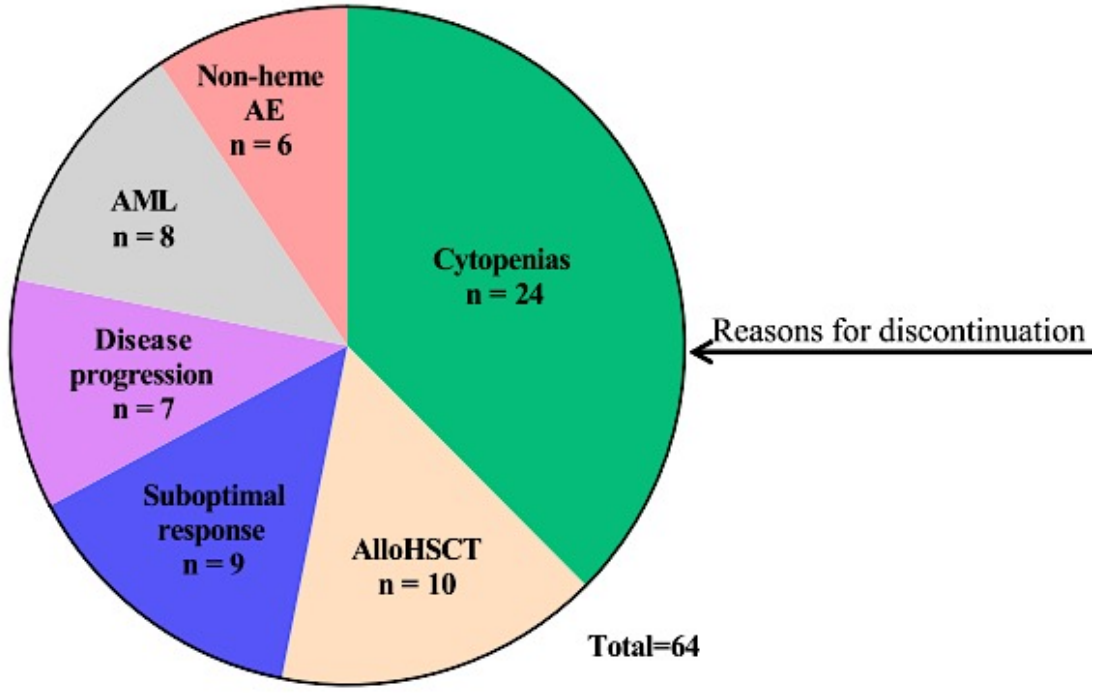




Verstovsek et al. Haematologica. 2015.

Anemia often results in ruxolitinib discontinuation

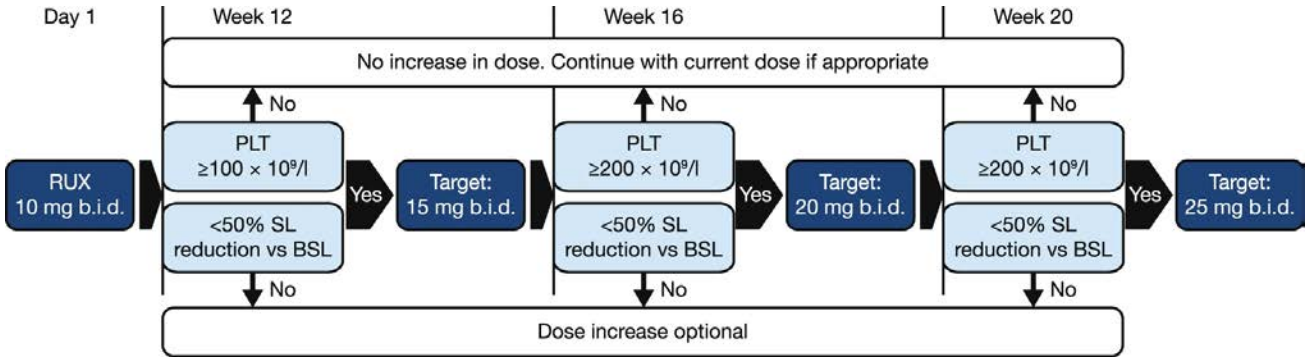




Palandri et al. Cancer. 2020; Kuykendall et al., Ann Hematol 2017

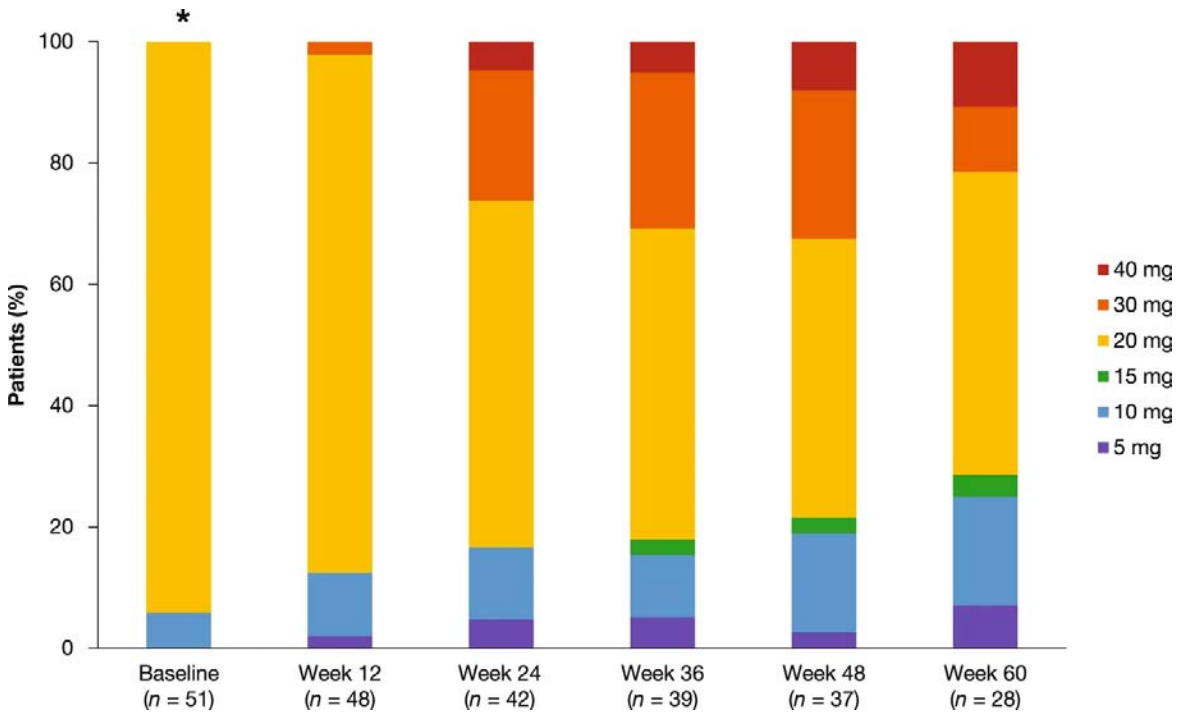
A modified dosing strategy may mitigate impact of anemia in MF patients

REALISE Study



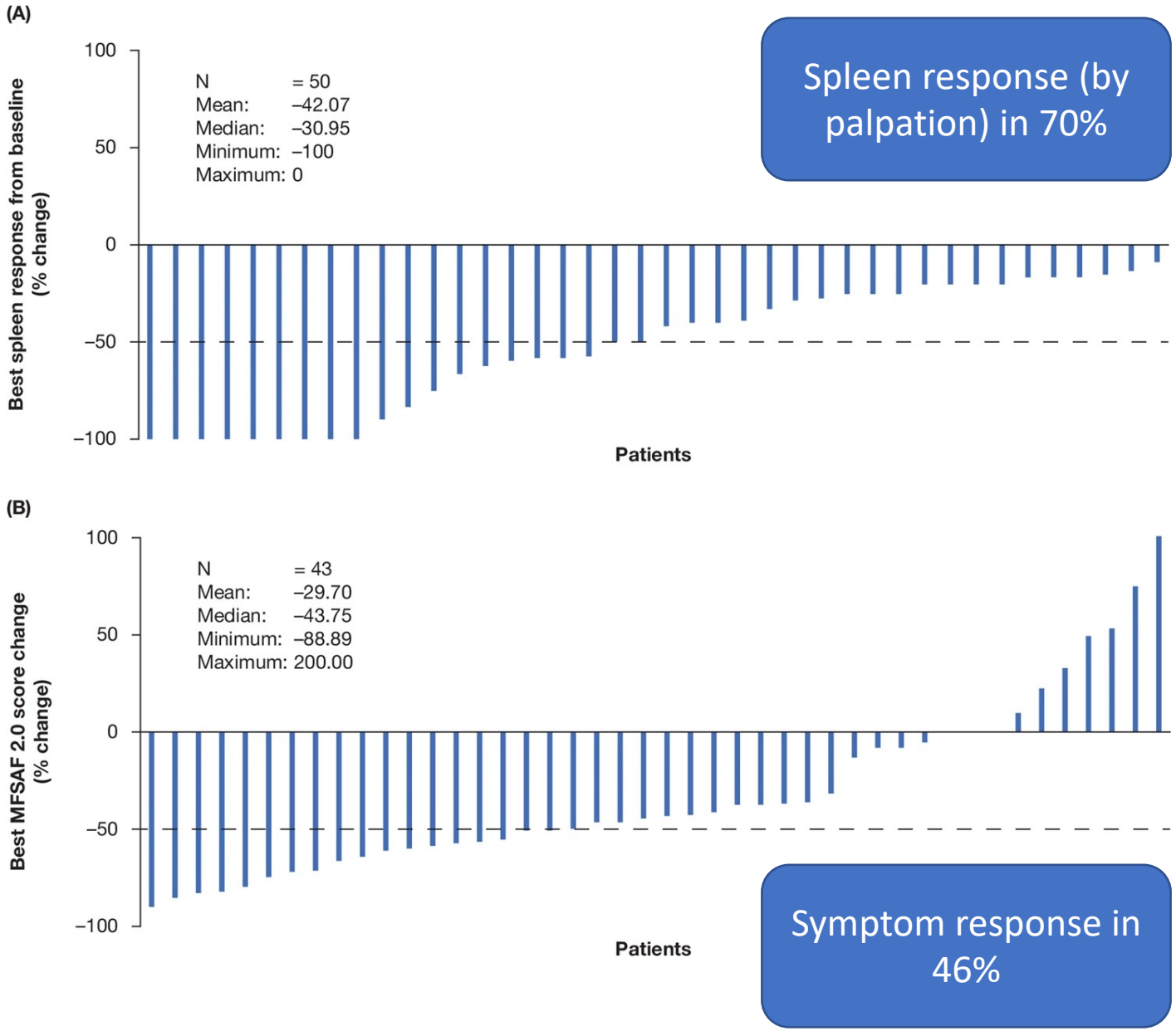
REALISE study was a phase 2 study that looked at a reduced starting dose with uptitration in anemic (hgb < 10 g/dL) MF patients

Total daily dose of ruxolitinib at various timepoints



Cervantes et al., Leukemia, 2021

Spleen and symptom responses occurred in the setting of stable hematologic parameters

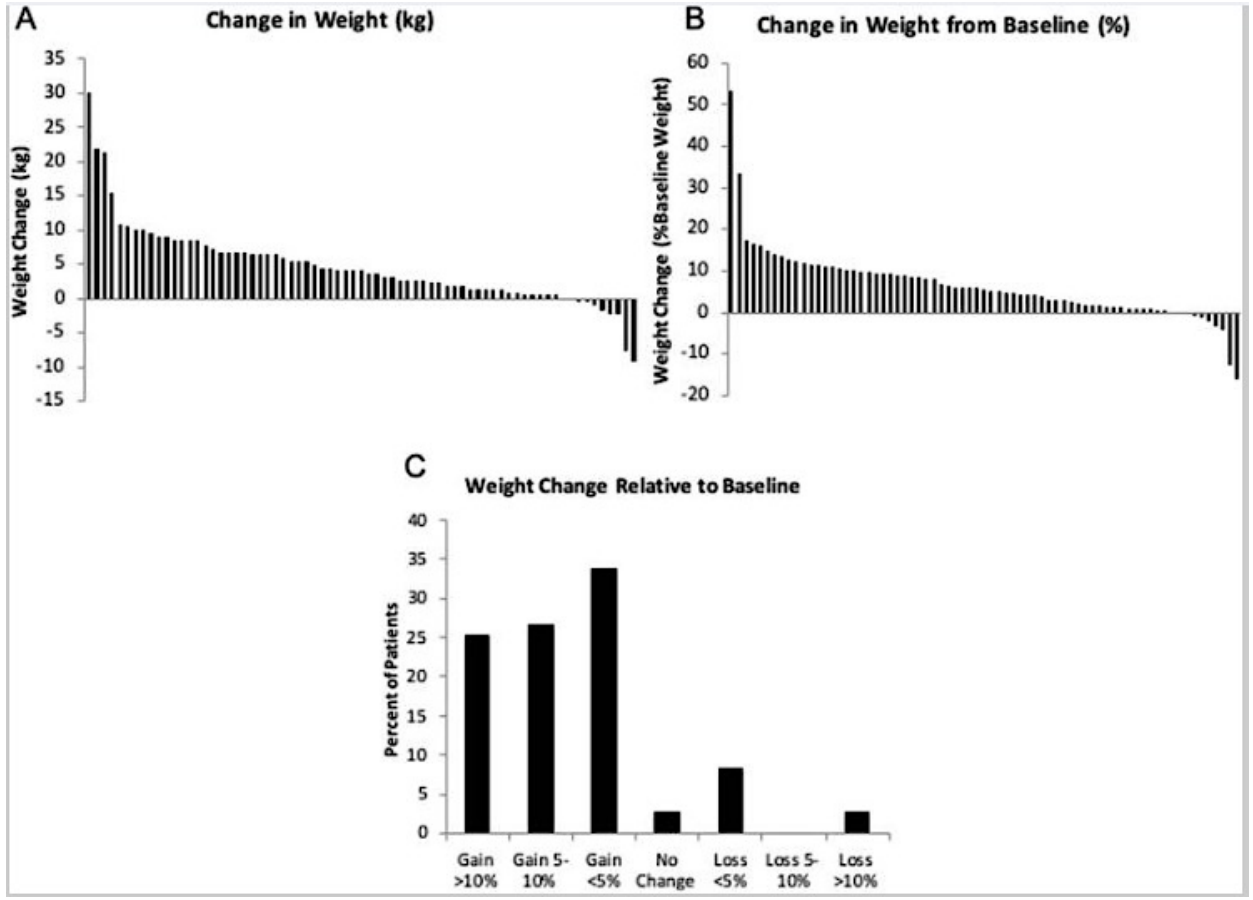


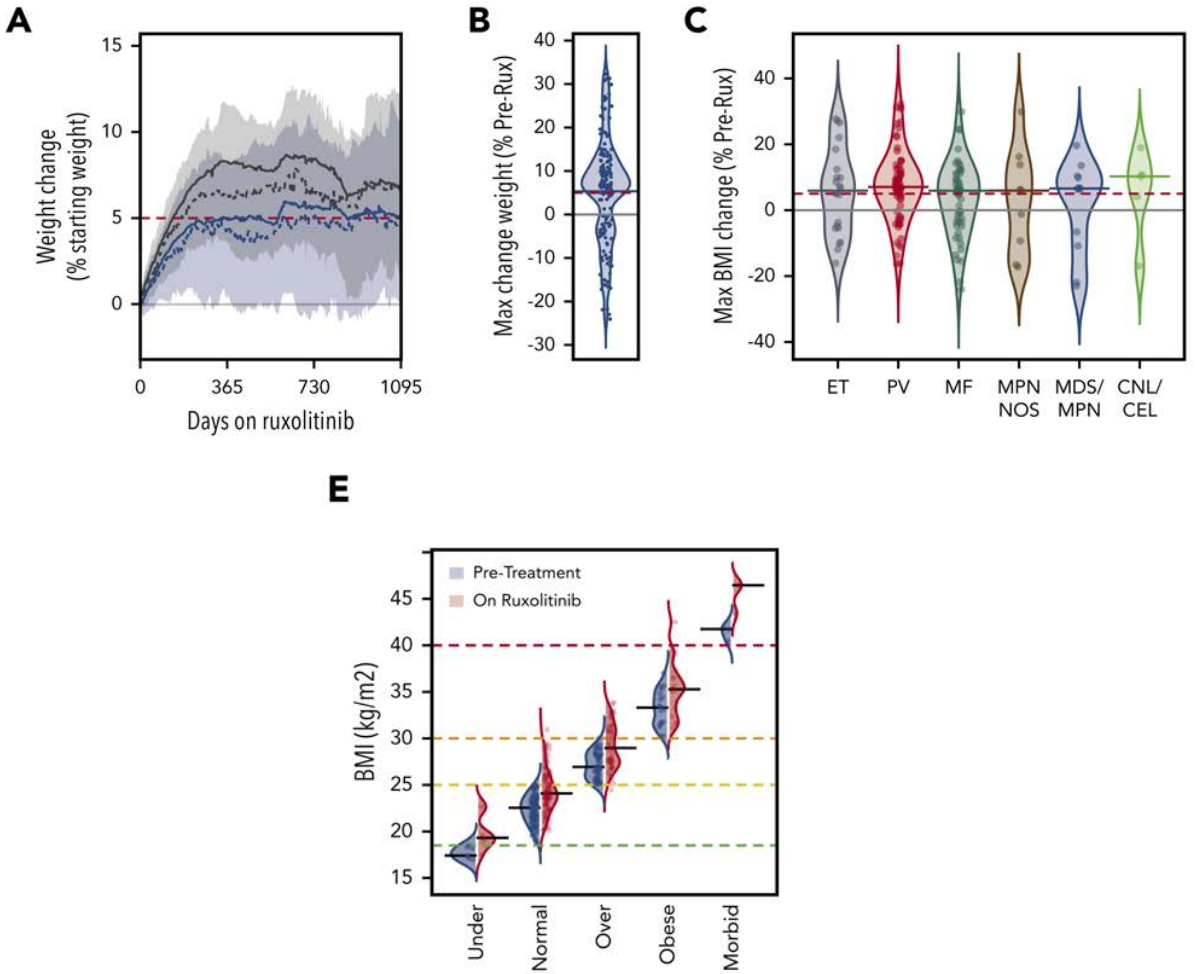
Spleen response (by palpation) in 70%

Symptom response in 46%

Cervantes et al., Leukemia, 2021

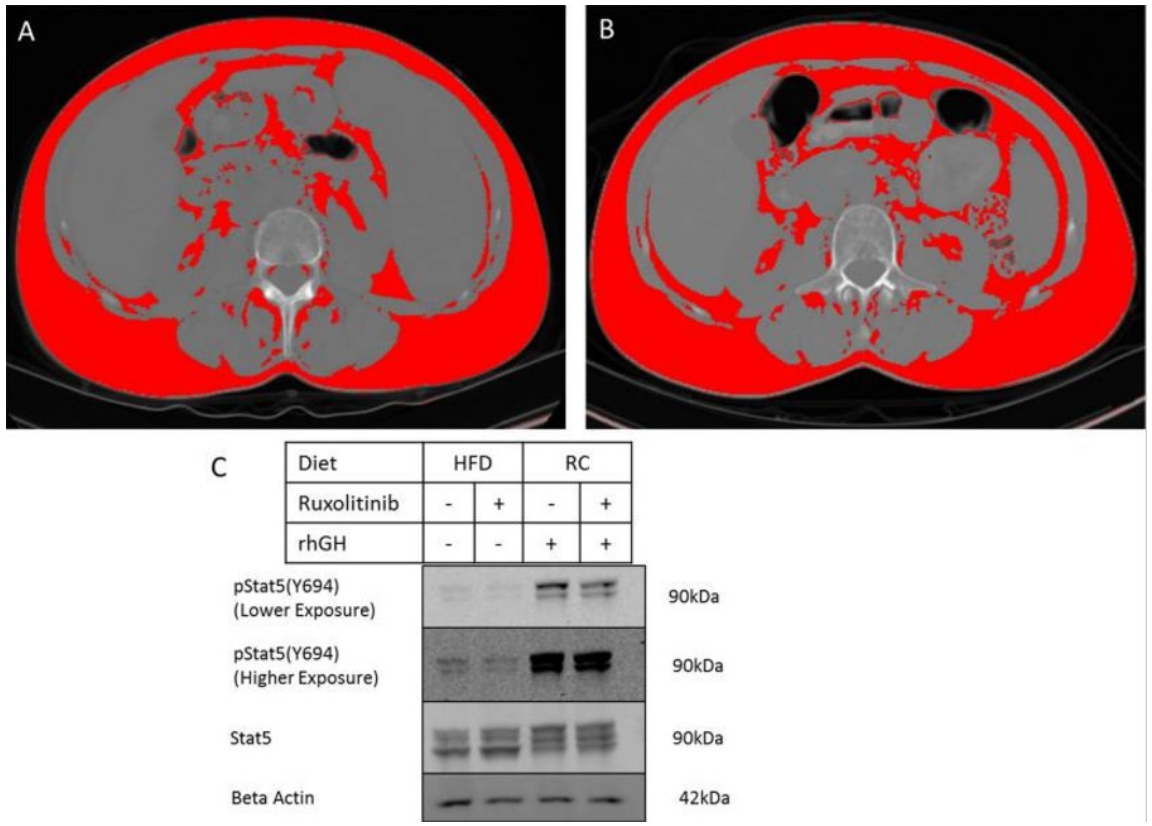
Ruxolitinib has consistently been associated with weight gain

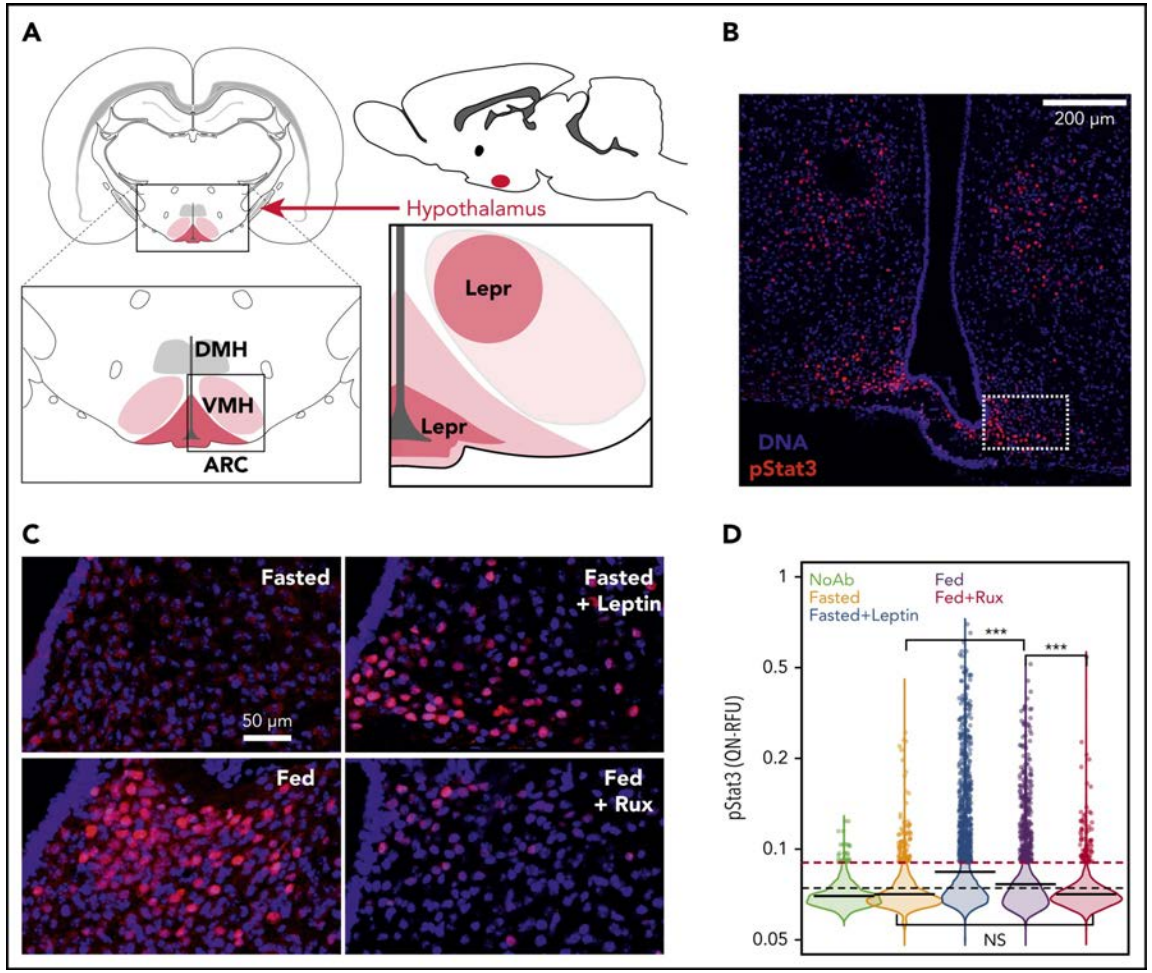




Sapre et al., Sci Rep, 2019; Molle et al., Blood, 2020.

Ruxolitinib-associated weight gain is associated with inhibition of leptin and decreased JAK-STAT signaling in adipose tissue





Sapre et al., Sci Rep, 2019; Molle et al., Blood, 2020.

Skin cancer type from JAK2 mutant patients	Number of events	HR (95% CI)	*P* value
NMSC	14	1.57 (0.61-4.02)	.35
BCC	6	0.82 (0.09-7.83)	.86
SCC	11	2.01 (0.70-5.73)	.19
Skin cancer type from non-JAK2 mutant patients	**Number of events**	**HR (95% CI)**	***P* value**
NMSC	31	**5.65 (1.70-18.75)**	**.0047**
BCC	18	3.14 (0.65-17.90)	.15
SCC	16	**7.40 (2.54-21.63)**	**.0003**

BCC, Basal cell carcinoma; *HR*, hazard ratio; *IV*, intravenous; *JAK*, Janus kinase; *NMSC*, nonmelanoma skin cancer; *PO*, *per os*; *SCC*, squamous cell carcinoma.

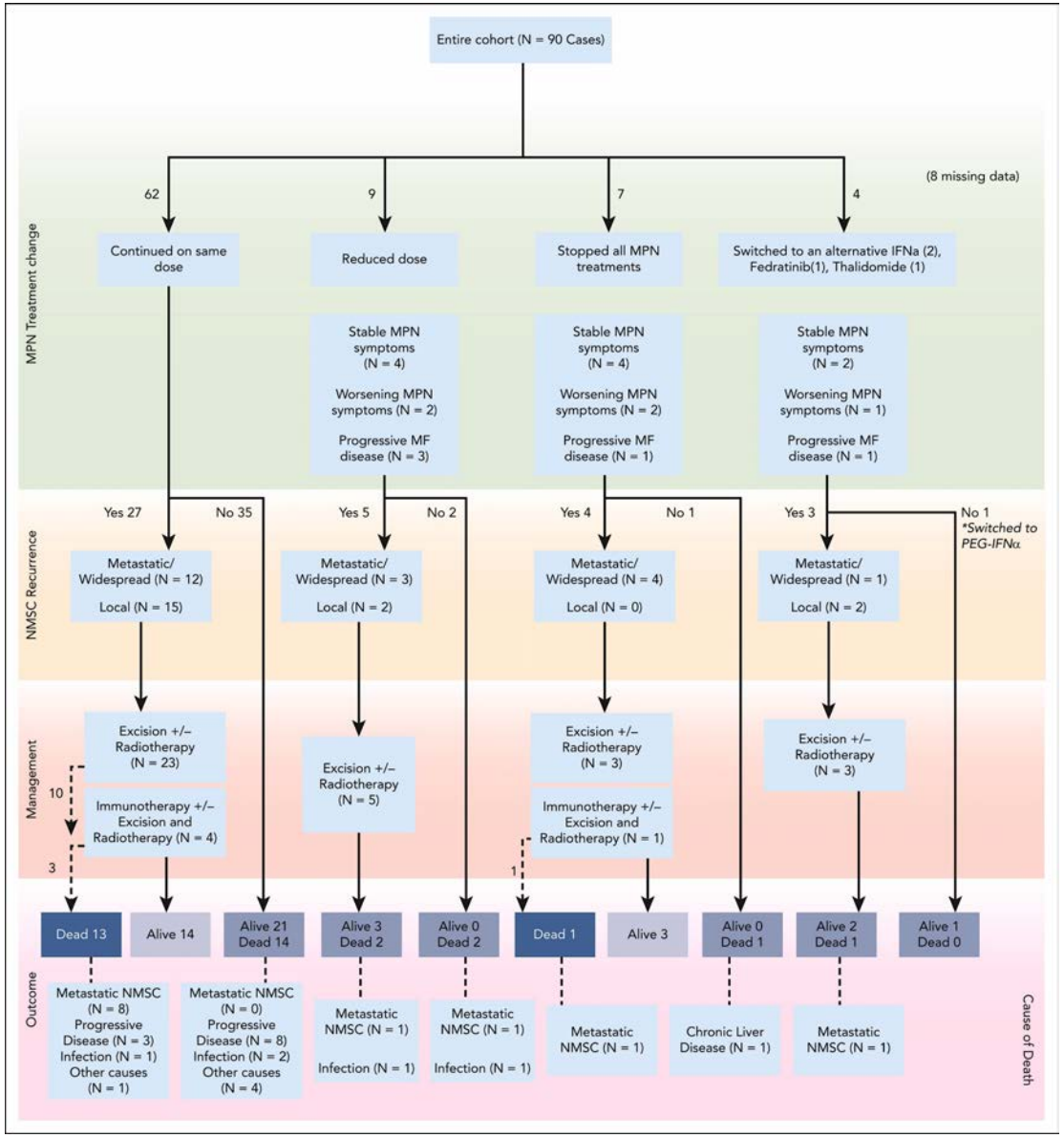
Table III. Hazard ratios for nonmelanoma skin cancer by Cox regression analysis

Variable	NMSC hazard ratio (95% CI)
Ruxolitinib exposure (yes vs no)	**2.70 (1.06-6.92)**
Age (per y)	1.03 (1.00-1.07)
Gender (male vs female)	1.76 (0.47-6.60)
Chemotherapy (IV) exposure (yes vs no)	0.64 (0.18-2.31)
Hydroxyurea (PO) exposure (yes vs no)	1.06 (0.35-3.21)
Radiation history (yes vs no)	2.07 (0.61-7.00)
Immunosuppression history*	**5.39 (1.34-21.61)**

IV, Intravenous; *NMSC*, nonmelanoma skin cancer; *PO*, *per os*.

Ruxolitinib is associated with an increased risk of non-melanoma skin cancers

Lin et al., Journal of the American Academy of Dermatology, 2022



Analysis of 90 patients who developed NMSC while receiving ruxolitinib

Rampotas A et al. Blood 2024.

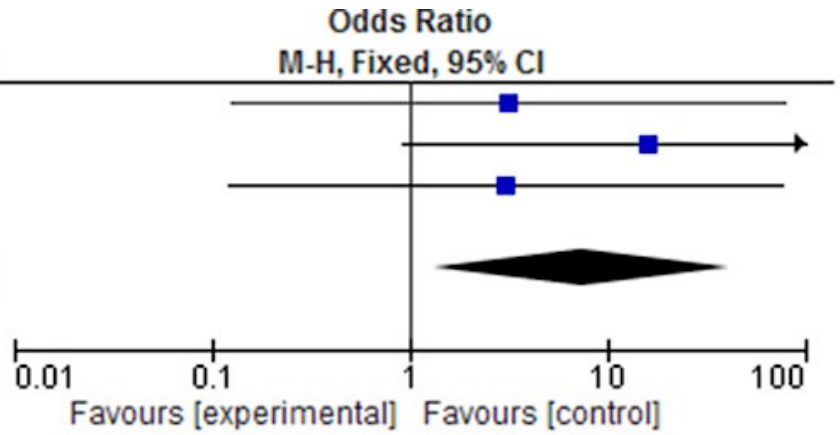
Ruxolitinib is associated with an increased risk of zoster reactivation

(A)

Study or Subgroup	Ruxo Events	Ruxo Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
RELIEF	1	54	0	56	33.5%	3.17 [0.13, 79.48]
RESPONSE 2015	7	110	0	112	32.4%	16.30 [0.92, 289.04]
RESPONSE-2	1	74	0	75	34.1%	3.08 [0.12, 76.87]
Total (95% CI)		**238**		**243**	**100.0%**	**7.39 [1.33, 41.07]**
Total events	9		0			

Heterogeneity: $Chi^2 = 0.84$, $df = 2$ ($P = 0.66$); $I^2 = 0\%$

Test for overall effect: $Z = 2.29$ ($P = 0.02$)

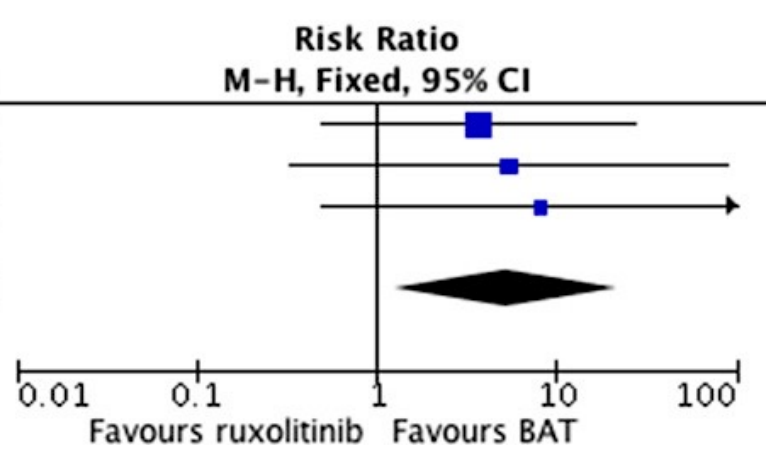


(B)

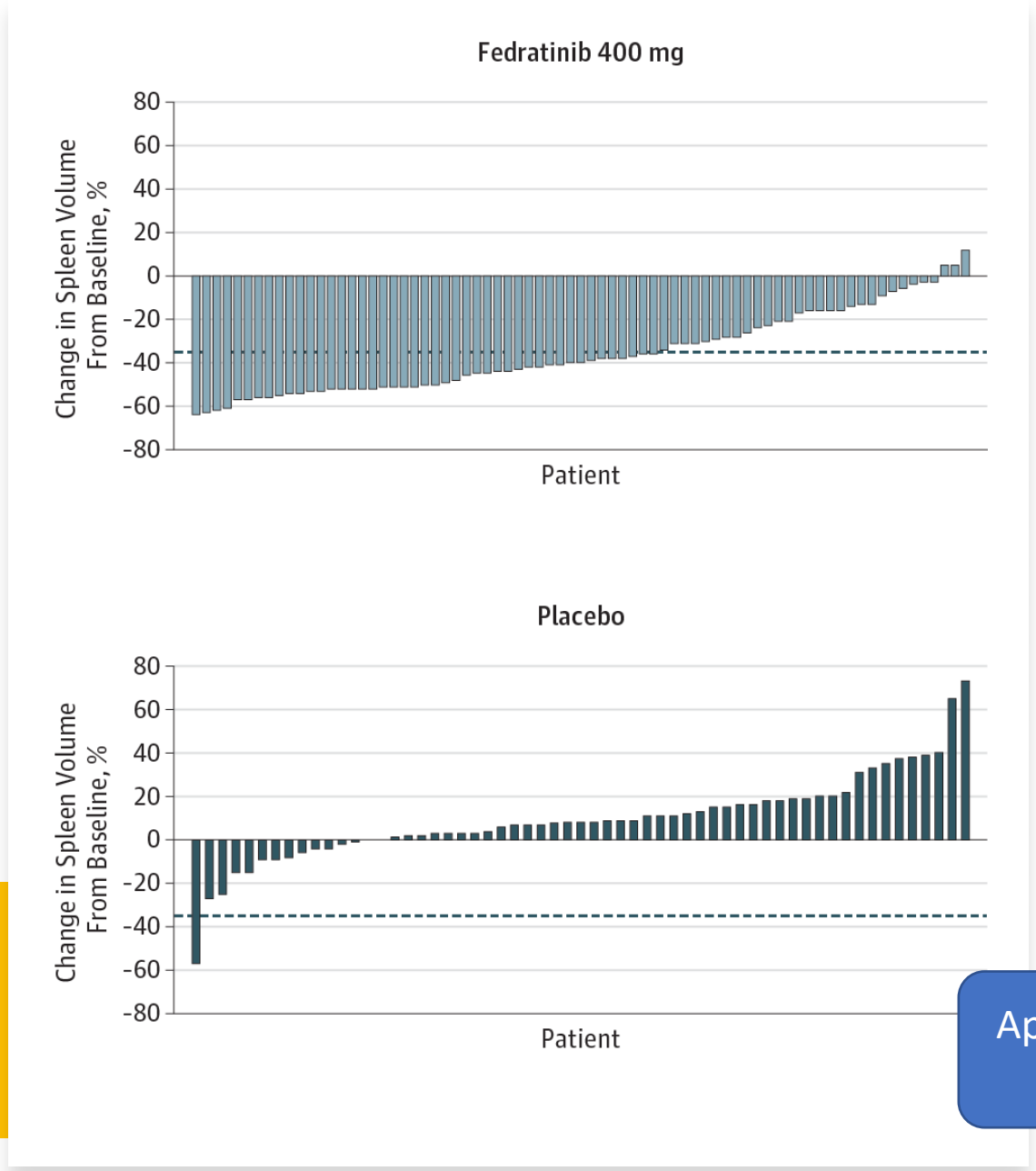
Study or Subgroup	Ruxolitinib Events	Ruxolitinib Total	BAT Events	BAT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
COMFORT-I 2012	16	453	1	104	50.2%	3.67 [0.49, 27.39]
COMFORT-II 2012	16	410	0	67	26.5%	5.46 [0.33, 89.94]
RESPONSE 2015	12	228	0	74	23.3%	8.19 [0.49, 136.63]
Total (95% CI)		**1091**		**245**	**100.0%**	**5.20 [1.27, 21.18]**
Total events	44		1			

Heterogeneity: $Chi^2 = 0.22$, $df = 2$ ($P = 0.90$); $I^2 = 0\%$

Test for overall effect: $Z = 2.30$ ($P = 0.02$)



Lussana et al., American Journal of Hematology. 2017.

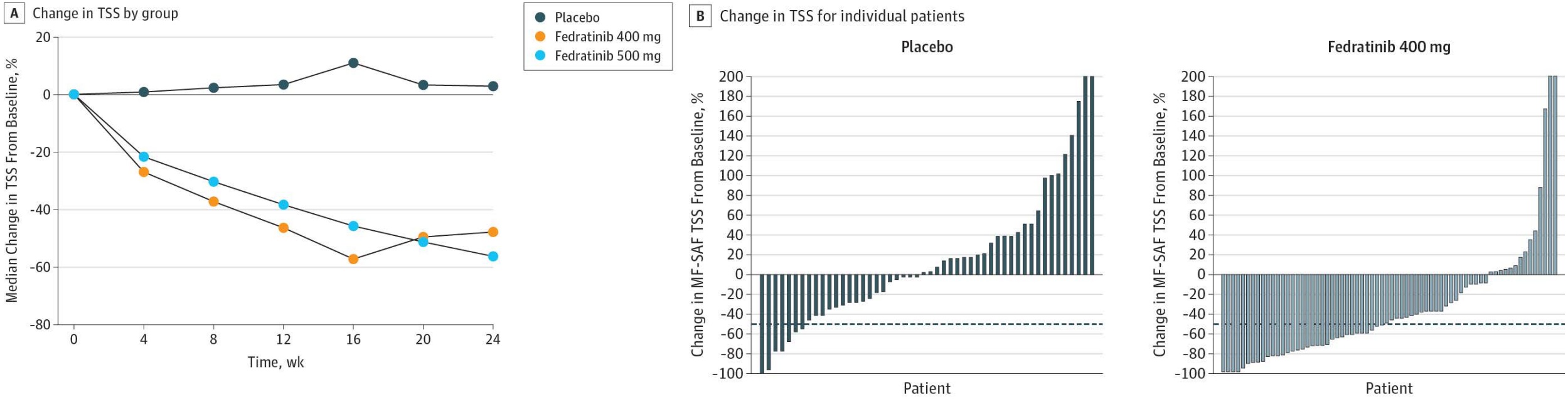


Fedratinib improves splenomegaly and symptoms comparably to ruxolitinib

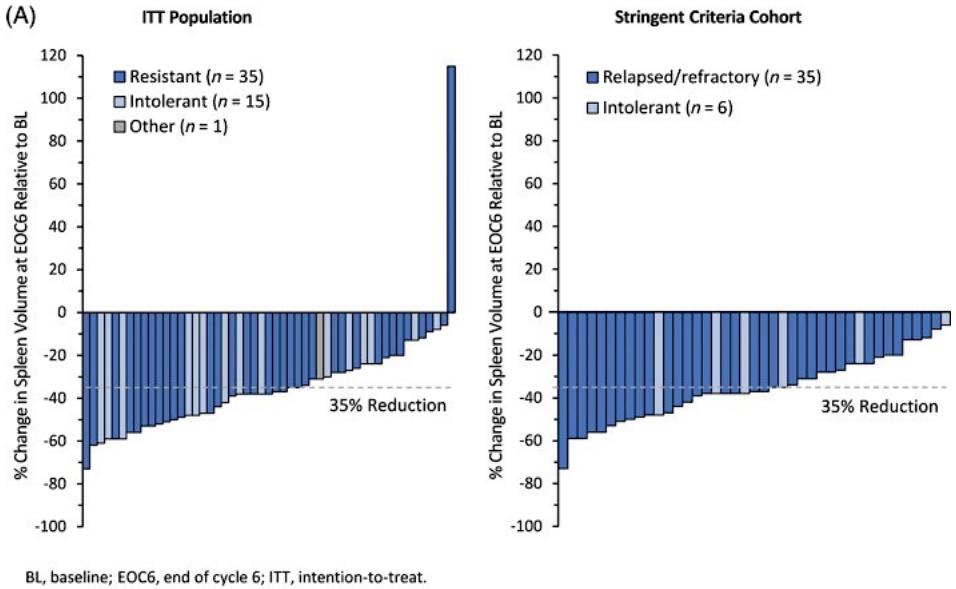
Approved for int-2 and high-risk MF in August, 2019

Pardanani et al., JAMA Oncology, 2015

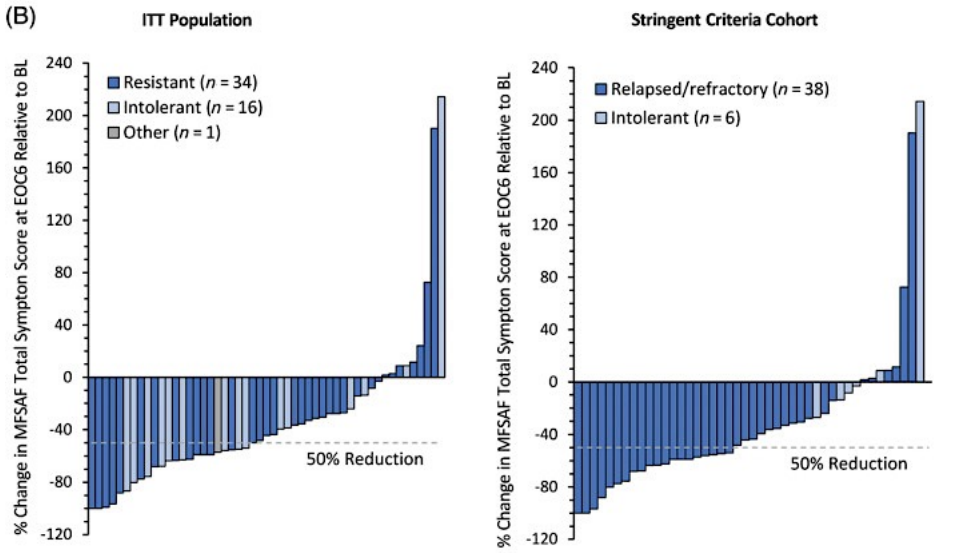
Fedratinib improves splenomegaly and symptoms comparably to ruxolitinib



Pardanani et al., JAMA Oncology, 2015



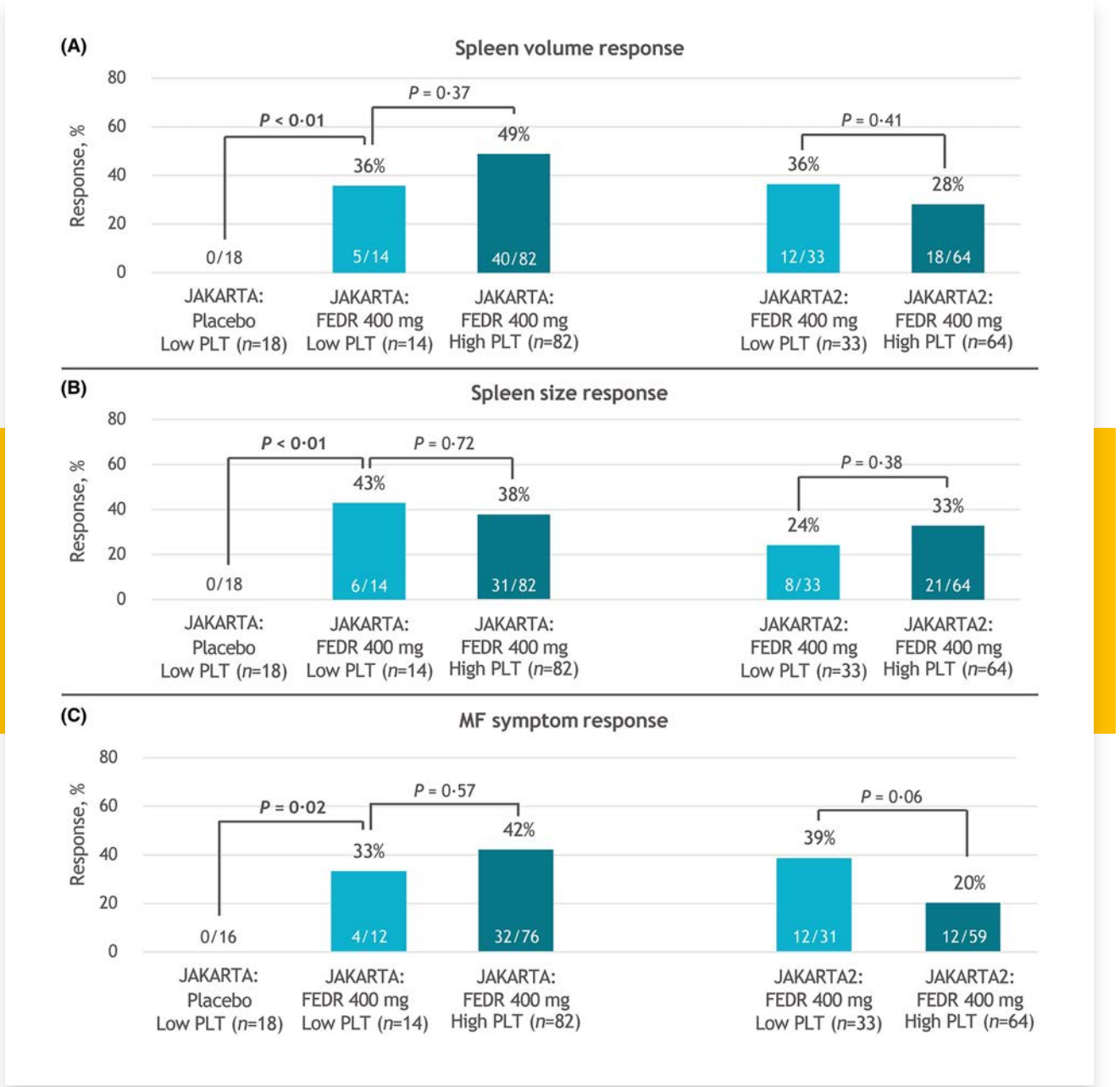
BL, baseline; EOC6, end of cycle 6; ITT, intention-to-treat.



BL, baseline; EOC6, end of cycle 6; ITT, intention-to-treat; MFSAF, Myelofibrosis Symptom Assessment Form; TSS, total symptom score.

Fedratinib improved splenomegaly and symptoms in the second-line setting in JAKARTA-2

Harrison et al., Am J Hematology, 2020

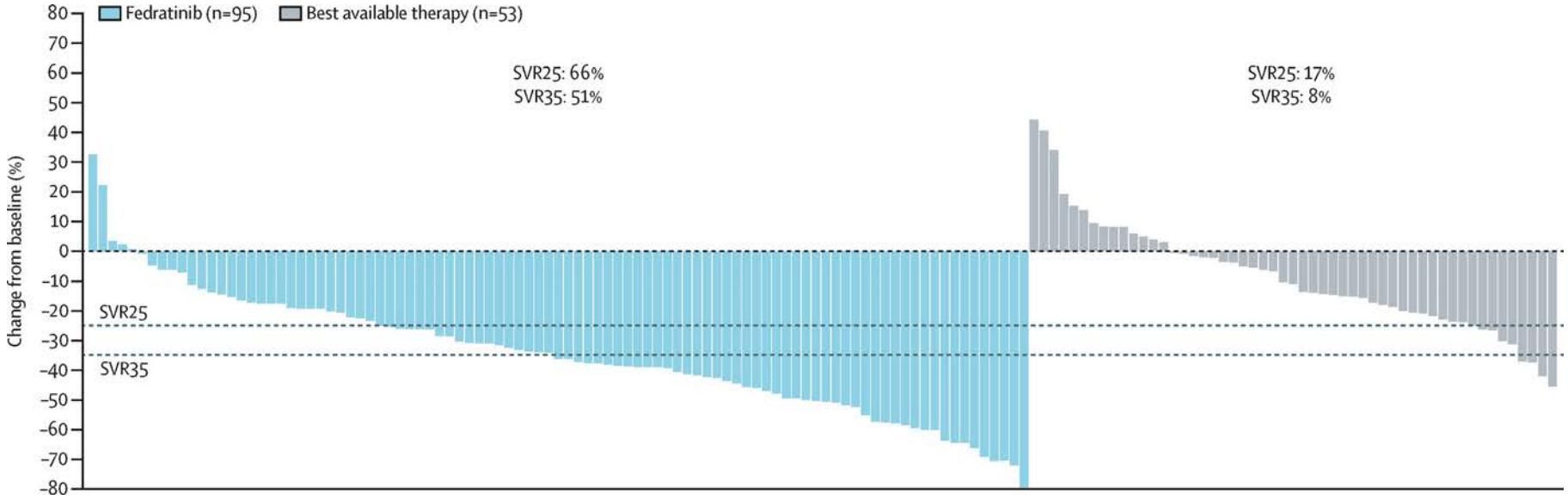


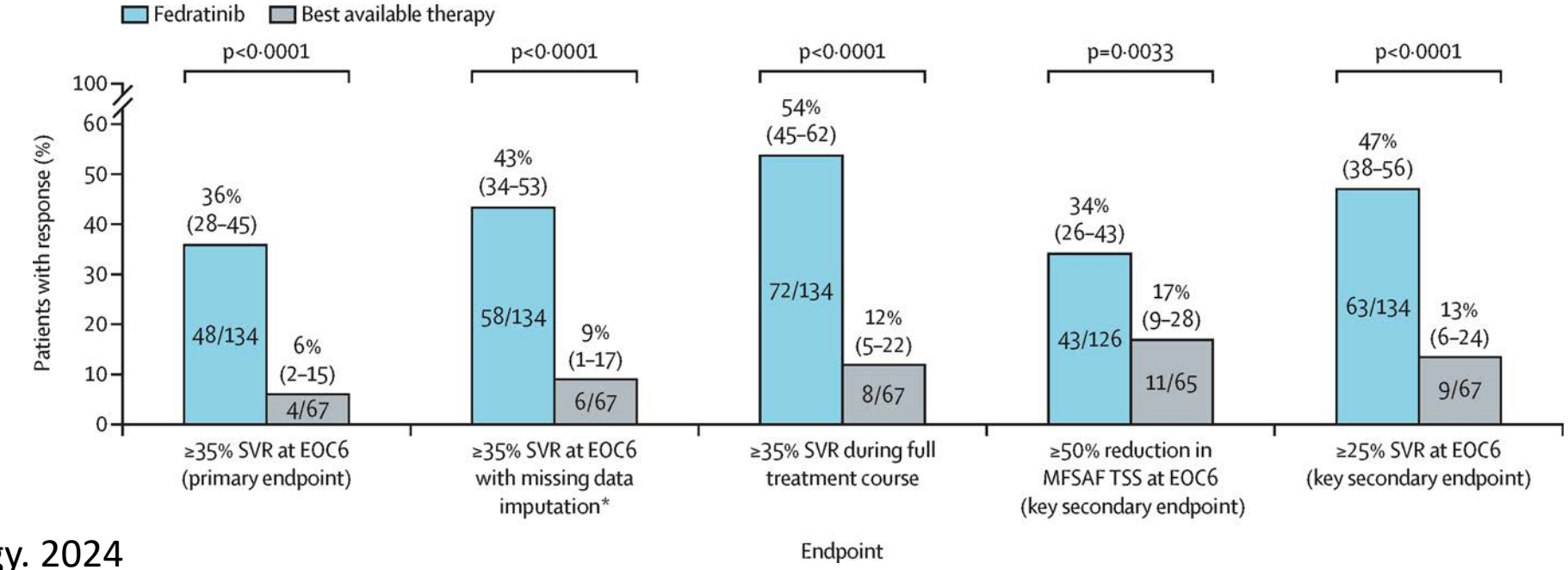
Fedratinib is effective in patients with moderate thrombocytopenia

Harrison et al., British Journal of Haematology, 2022

FREEDOM-2 study largely recapitulated data seen in JAKARTA-2

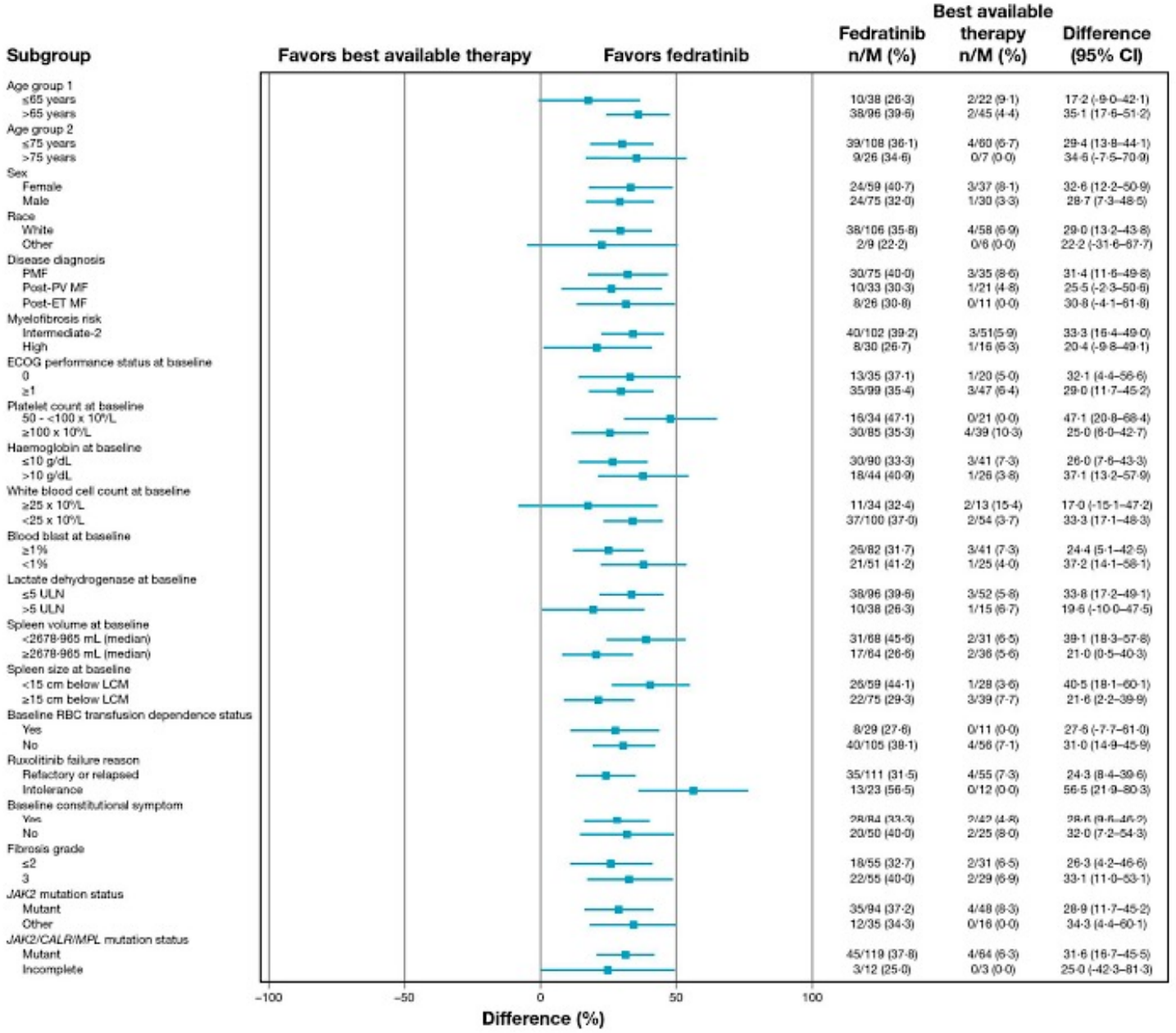
Dose reduction due to TEAE in 31% of fedratinib-treated patients





Harrison et al., Lancet Haematology. 2024

Figure S3: Subgroup analysis of spleen response



Subgroup analysis highlights moderate thrombocytopenia and ruxolitinib intolerance as groups more likely to benefit.

Harrison et al., Lancet Haematology. 2024

Fedratinib has more tolerability concerns than ruxolitinib, particularly related to GI concerns

Table 2. Adverse Events Observed in at Least 10% of Patients in Any Treatment Group

	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo (n = 95)	
Adverse Events, No. (%)	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Any TEAE	96 (100)	52 (54)	95 (98)	68 (70)	89 (94)	30 (32)
TEAE leading to treatment discontinuation to week 24	13 (14)	12 (13)	24 (25)	15 (16)	8 (8)	4 (4)
Serious TEAE	26 (27)	17 (18)	30 (31)	23 (24)	22 (23)	14 (15)
Nonhematologic[a]						
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
Dyspnea	8 (8)	0	10 (10)	1 (1)	6 (6)	2 (2)
Weight decrease	4 (4)	0	10 (10)	0	5 (5)	0
Hematologic[a]						
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)
Infections and infestations[b]	40 (42)	2 (2)	38 (39)	12 (12)	26 (27)	4 (4)
Laboratory parameter elevation						
Alanine transaminase	51 (53)	3 (3)	44 (46)	3 (3)	16 (17)	0
Aspartate transaminase	58 (60)	2 (2)	46 (48)	2 (2)	27 (29)	1 (1)
Hyperbilirubinemia	30 (31)	2 (2)	27 (28)	1 (1)	38 (40)	2 (2)
Creatinine	52 (54)	3 (3)	60 (63)	0	28 (30)	1 (1)
Amylase	25 (26)	2 (2)	22 (23)	3 (3)	7 (7)	0
Lipase	43 (45)	12 (13)	34 (36)	9 (9)	6 (6)	2 (2)

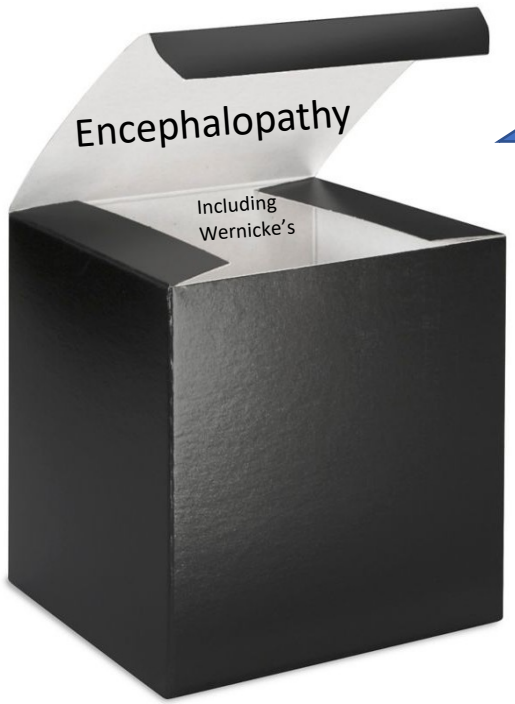
However,

In the **FREEDOM-2 study**, prophylactic anti-emetics, symptomatic antidiarrheals led to reduction in GI side effects

Nausea: **32%** (vs. 64%)
Vomiting: **14%** (vs. 42%)
Diarrhea: **38%** (vs. 66%)

Pardanani et al., JAMA Oncology, 2015

Fedratinib has a black box warning for encephalopathy, including Wernicke's



Check thiamine levels prior to starting fedratinib and consider oral supplementation

Fedratinib trials enrolling 670 patients

8 patients evaluated for encephalopathy

2 had inconclusive diagnosis

3 had possible Wernicke (1 definite)

3 had thiamine level/MRI results not supportive of Wernicke

1 with nausea/vomiting and developed neuro symptoms while NOT on drug

1 developed symptoms after being noted to have disseminated brain mets

2 with protracted nausea/vomiting → neuro deficits recovered while on fedratinib

1 severely malnourished, refused G-tube → malnutrition likely cause of thiamine deficiency

Harrison et al., Blood (2017) 130 (Supplement 1): 4197

Questions from General Medical Oncologists/Hematologists

- **A patient 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. He's not a transplant candidate. What treatment would you recommend?**
- **If a patient with symptomatic higher-risk MF did not experience reduction in spleen size or improvement in symptoms after 3 months of standard-dose ruxolitinib, what would you most likely recommend, assuming normal renal and hepatic function and a platelet count >200,000/μL?**

Questions from General Medical Oncologists/Hematologists

- **Which of the approved JAK inhibitors lead to an OS benefit? Do any of them offer a greater OS benefit than the others?**
- **How do you determine ruxolitinib failure and at what point to switch to a different JAK inhibitor? Please specify details WRT specific end points when one should switch from ruxolitinib to another JAK inhibitor (eg, counts, symptoms, spleen size, etc).**
- **In general, how do you sequence JAK inhibitors post-ruxolitinib?**

Questions from General Medical Oncologists/Hematologists

- **Is there any difference in the consideration for the use of JAK inhibitors in secondary versus primary MF?**
- **What is your usual starting dose of ruxolitinib? What about fedratinib?**
- **When switching from one JAK inhibitor to another is it necessary to taper the first one or can we just switch immediately since we are continuing therapy? If you taper, for how long?**

Agenda

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

Module 2: Managing MF for Patients with Thrombocytopenia — Dr Bose

Module 3: Managing MF for Patients with Anemia — Dr Yacoub

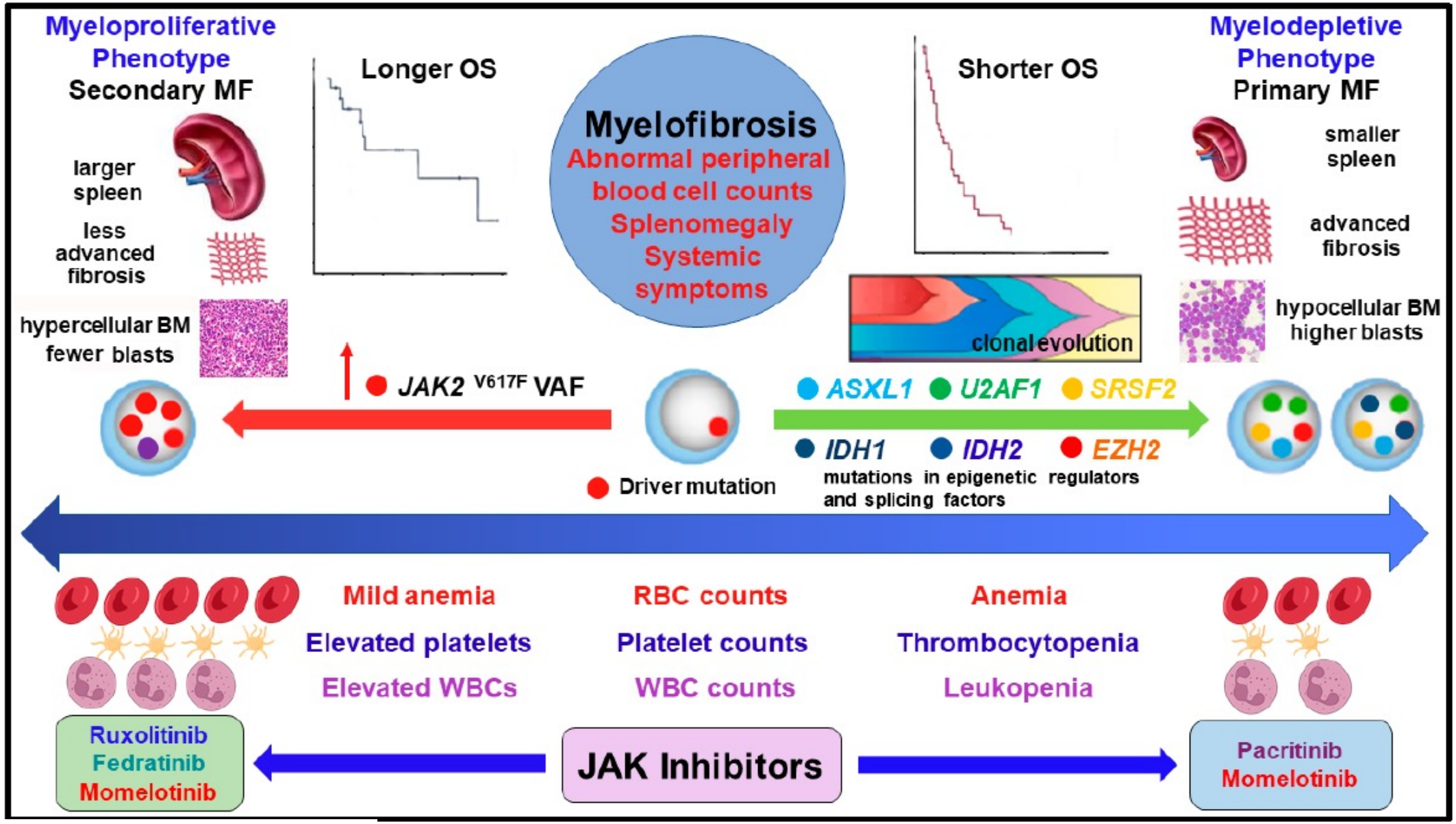
Module 4: Future Directions in the Management of MF — Dr Fleischman

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

Managing MF in Patients with Thrombocytopenia

Prithviraj Bose, M.D.
Professor, Department of Leukemia
Co-Leader, Section of Myeloproliferative Neoplasms

RTP ASH Friday Satellite Symposium, San Diego, CA, 12/06/24



Chifotides HT, Verstovsek S, Bose P. *Cancers.* 2023;15:3331.

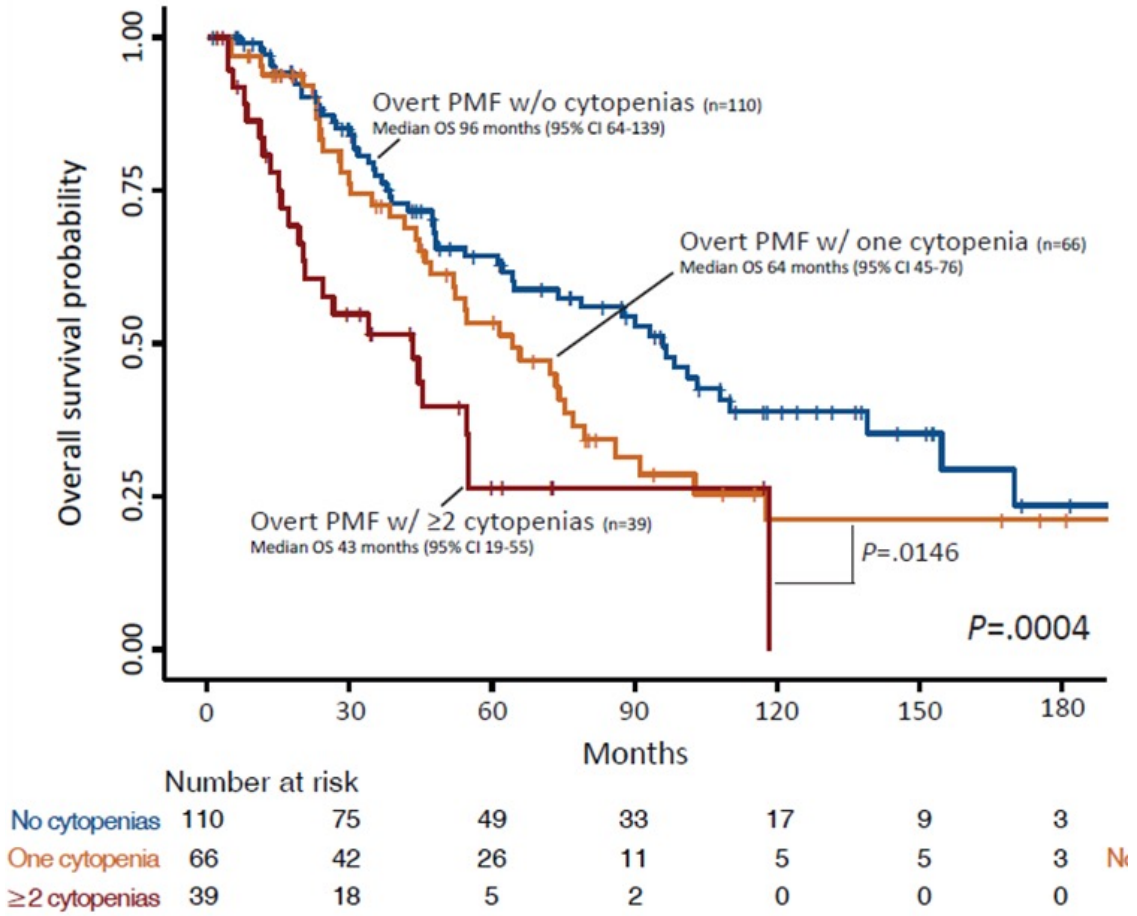
Cytopenic MF is More Aggressive

Cytopenic MF defined as **any one** of the following:

- Leukocytes <4 x 10^9/L
- Hemoglobin <11 g/dL (males) and <10 g/dL (females)
- Platelets <100 x 10^9/L

In overt PMF the impact on OS seemed to be affected mainly by the cytopenia severity, with anemia and thrombocytopenia having the greatest impact

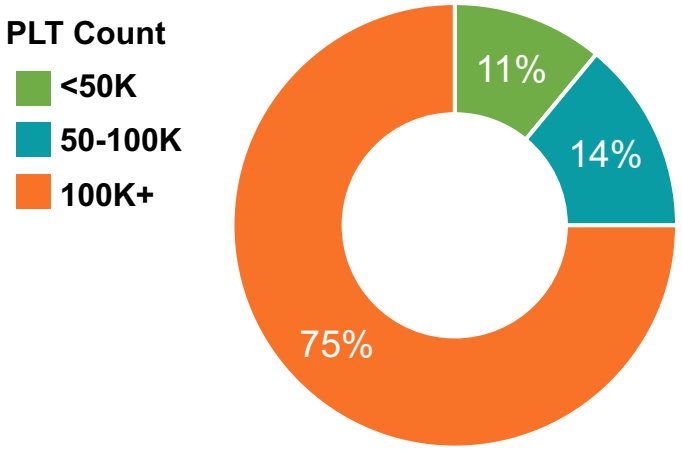
Median survival ~ 14 months post ruxolitinib discontinuation <100K platelets



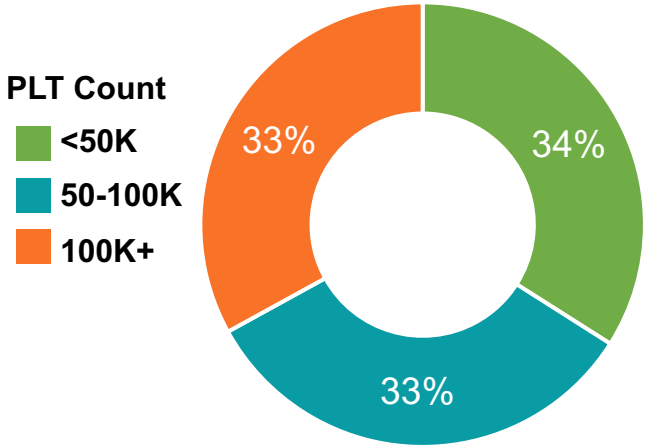
Coltro G, et al. *Blood Cancer J.* 2022;12:116.
Supplement to Coltro G, et al. *Blood Cancer J.* 2022;12:116.

Thrombocytopenia Is Common and a Poor Prognostic Indicator

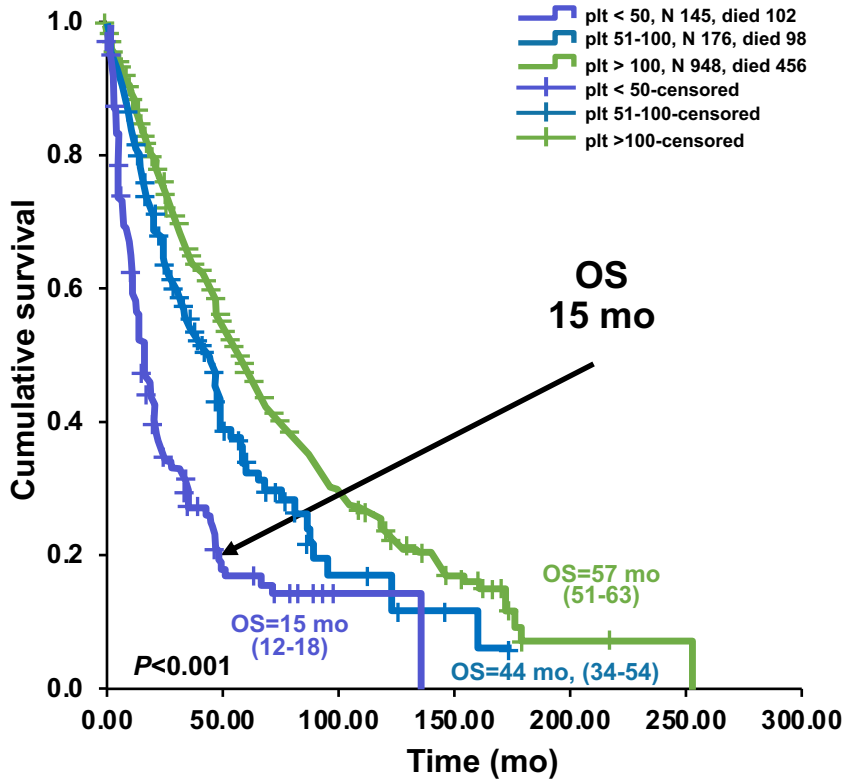
The incidence of thrombocytopenia (PLT count <100 × 10^9/L) is approximately 25% in patients newly diagnosed with MF



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



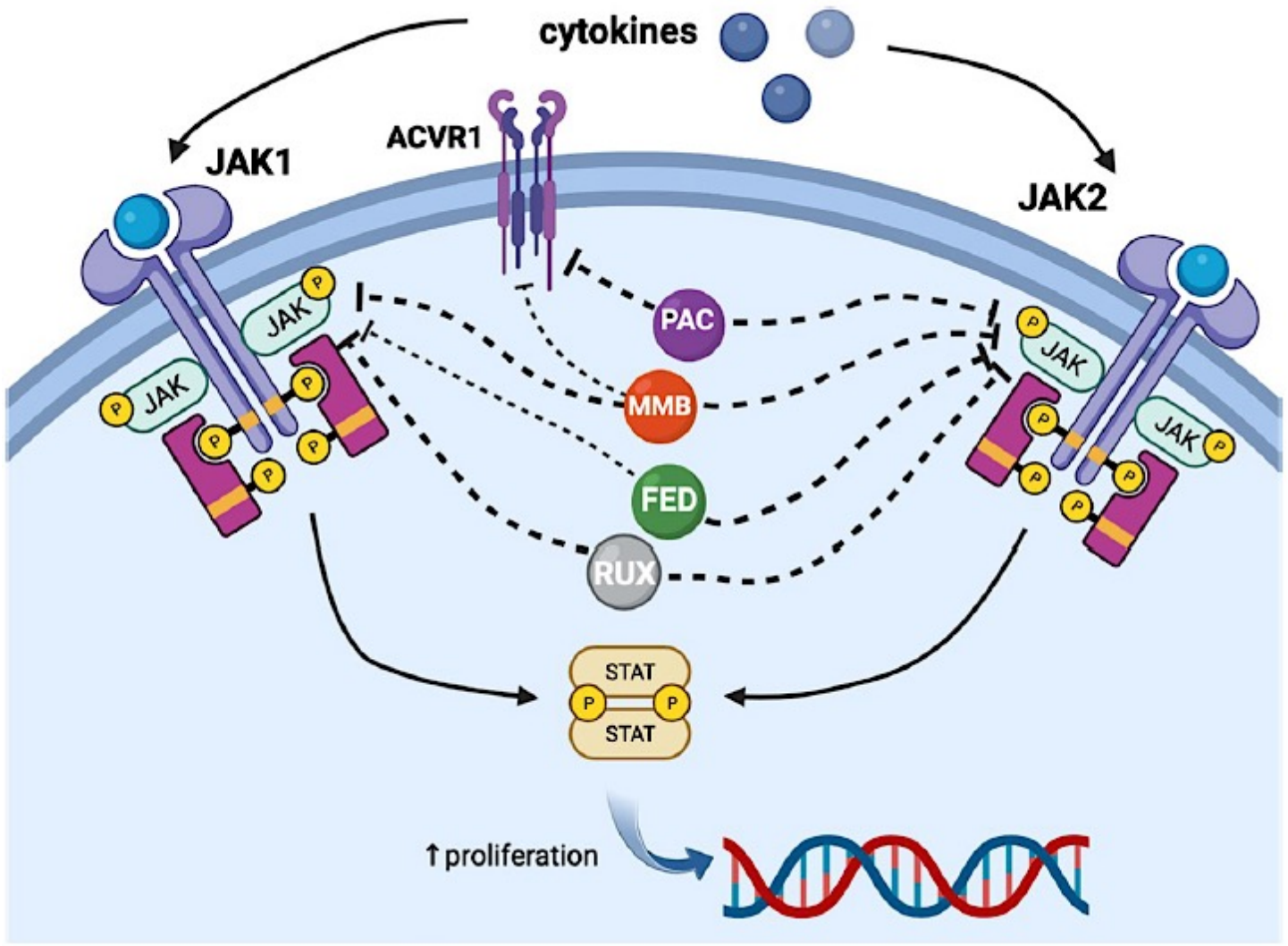
Overall Survival ~Platelets



OS, overall survival; PLT, platelet.

Masarova L, et al. *Eur J Haematol.* 2018;100(3):257-263. Masarova L, et al. *Leuk Res.* 2020;91:106338.

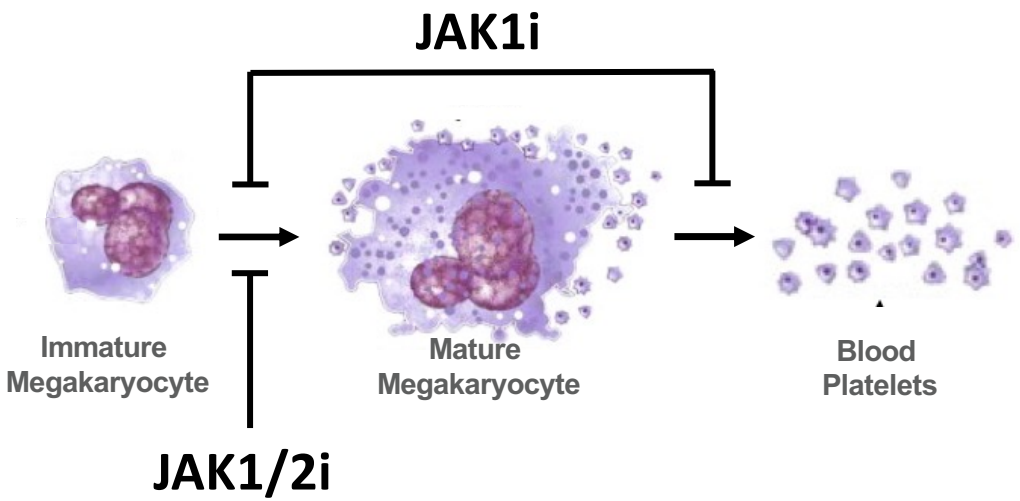
Therapeutic Targets of JAK Inhibitors



PAC: pacritinib; MMB: momelotinib;
FED: fedratinib; RUX: ruxolitinib

Duminuco A, et al. *Curr Hematol Malig Rep.* 2023;18:176-189.

Pacritinib (PAC) A selective inhibitor of JAK2 and IRAK1



- JAK1/2 inhibitors impair megakaryopoiesis while preserving thrombopoiesis, whereas JAK1 inhibition impairs both megakaryopoiesis and platelet release *in vitro* and can exacerbate thrombocytopenia in MF.*
- Minimal JAK1 inhibition uniquely positions Pacritinib for use in thrombocytopenic MF patients.

Kinase[1]	IC_{50} (nM)
JAK1	>1000
$JAK2^{wt}$	6.0
$JAK2^{V617F}$	9.4
JAK3	18.3
TYK2	27.0
FLT3-ITD	13.4
$FLT3^{D835Y}$	4.7
CSF1R	39.5
IRAK1	13.6

IC_{50}, half-maximal inhibitory concentration; **JAK**, Janus kinase; **TYK**, tyrosine kinase; **FLT**, FMS-like tyrosine kinase; **ITD**, internal tandem duplication; **CSF1R**, colony stimulating factor 1 receptor; **IRAK**, interleukin-1 receptor-associated kinase

*Jarocha DJ, et. al. Blood 2018;132(Supplement 1):2559.; Mascarenhas JO, et. al. Haematologica 2017; 102(2):327.

PERSIST-1 Study

- PMF, PPV-MF, or PET-MF
- ≥ 18 y old
- Int-1, -2, or high risk (DIPSS)
- PB < 10%
- Palpable spleen ≥ 5 cm
- ANC > 500
- TSS ≥ 13
- ECOG PS ≤ 3
- No prior HCT or JAKi

N = 327

Stratified by DIPSS, PLT, geographic region

R
2:1

PAC 400 mg orally once daily
n = 220

BAT;
HU (57%) and no Rx (25%)
Excluded JAKi
n = 107

- Primary endpoint: Number of patients in whom SVR was ≥ 35% from BL to week 24 as measured by MRI (or CT scan in applicable patients)
- Key secondary endpoint: Proportion of patients with ≥ 50% reduction in TSS at week 24
- Proportion of patients with BL or severe thrombocytopenia in whom SVR was achieved

HU, hydroxyurea; Rx, prescribed medication.

Mesa RA, et al. Lancet Haematol. 2017;4;e225-e236

PERSIST-1: Endpoints

≥ 35% SVR at Week 24

	ITT, n/N (%)			Evaluable, n/N (%)		
	PAC	BAT	*P* value	PAC	BAT	*P* value
Overall	42/220 (19)	5/107 (5)	.0003	42/168 (25)	5/85 (6)	.0001
PLT count						
< 100,000/μL	12/72 (17)	0/34	.0086	12/51 (24)	0/24	.0072
< 50,000/μL	8/35 (23)	0/16	.045	8/24 (33)	0/11	.037

≥ 50% Reduction in TSS

	Week 24			Week 48		
	PAC	BAT	*P* value	PAC	BAT	*P* value
Overall	19/100 (19)	5/48 (10)	.24	15/100	0/48	.0027
PLT count						
< 100,000/μL	7/28 (25)	1/13 (8)	.40	3/28 (11)	0/13	.54
< 50,000/μL	3/11 (27)	0/5	.51	2/11 (18)	0/5	> .99

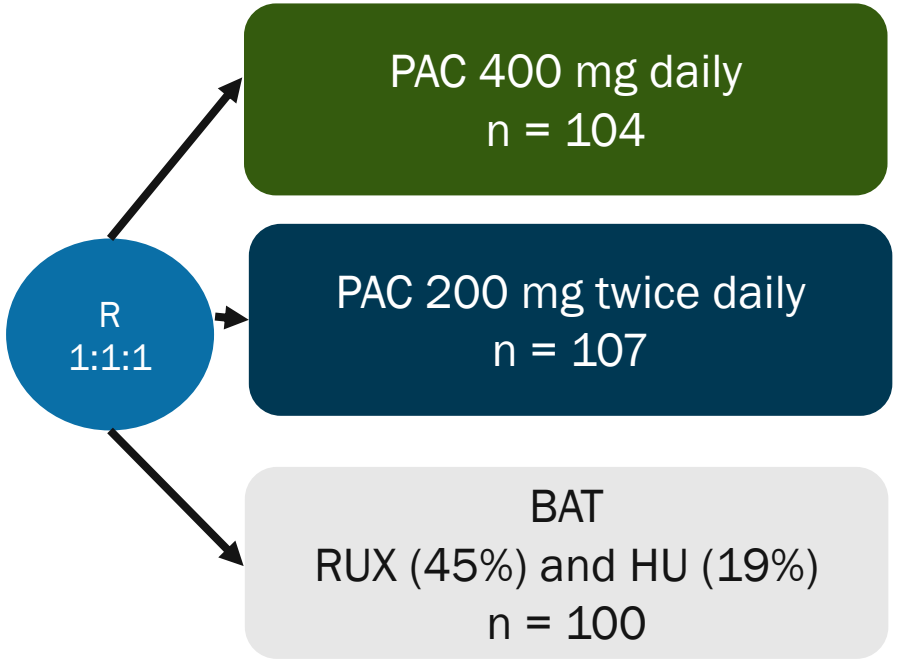
Mesa R, et al. Lancet Haematol. 2017;4;e225-e236

PERSIST-2 Study

Phase 3, randomized, international, multicenter study

- PMF, PPV-MF, or PET-MF
- Int-1, -2, or high risk (DIPSS)
- Palpable spleen > 5 cm
- PB < 10%
- ANC > 500
- PLT count ≤ 100,000
- ECOG PS ≤ 3
- TSS ≥ 13
- Prior Rx with JAKi allowed

N = 311

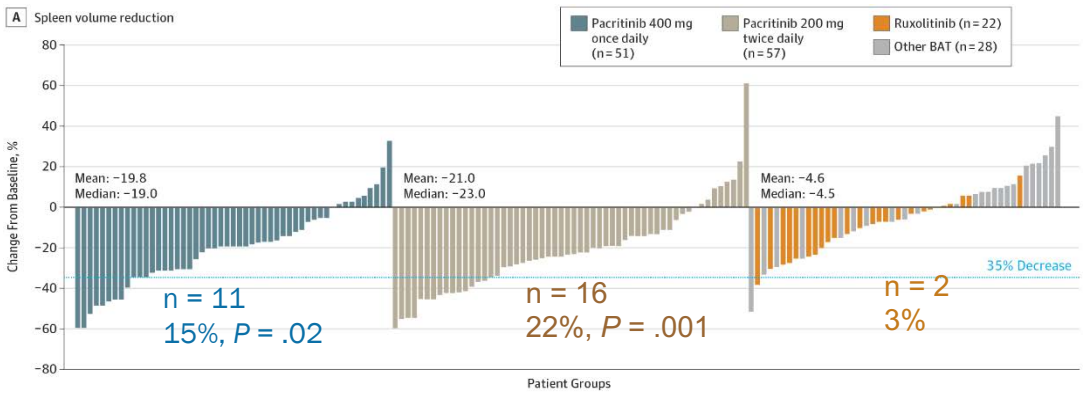


- Primary endpoint: ≥ 35% SVR from BL to week 24 as measured by MRI (or CT scan in applicable patients) and ≥ 50% reduction in TSS from BL to week 24 (MFSAF 2.0) powered to compare PAC as pooled group
- Key secondary endpoint: Compare efficacy of PAC 400 daily vs 200 twice daily vs BAT

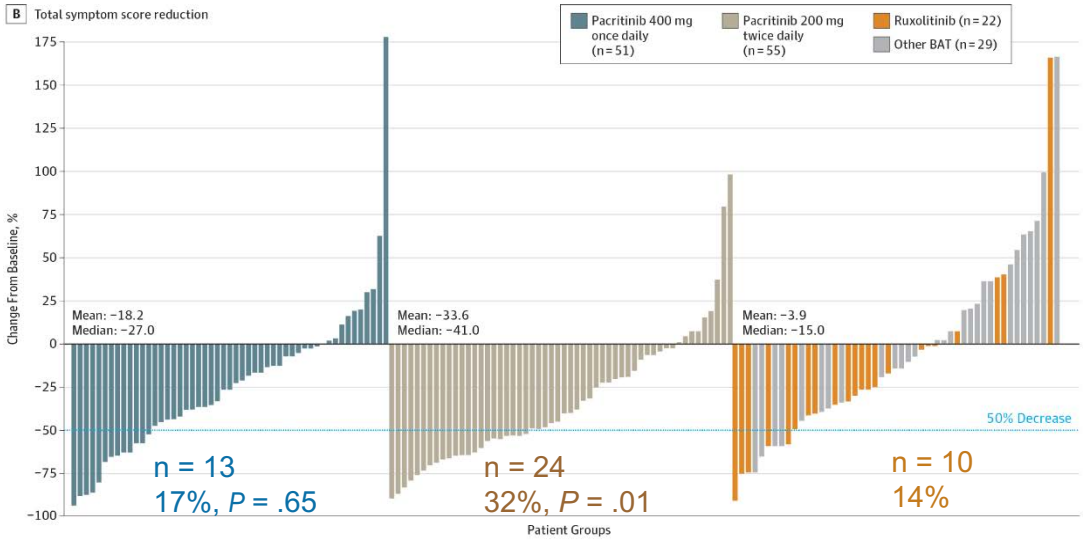
Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

PERSIST-2: Endpoints

N = 27
18%, *P* = .001

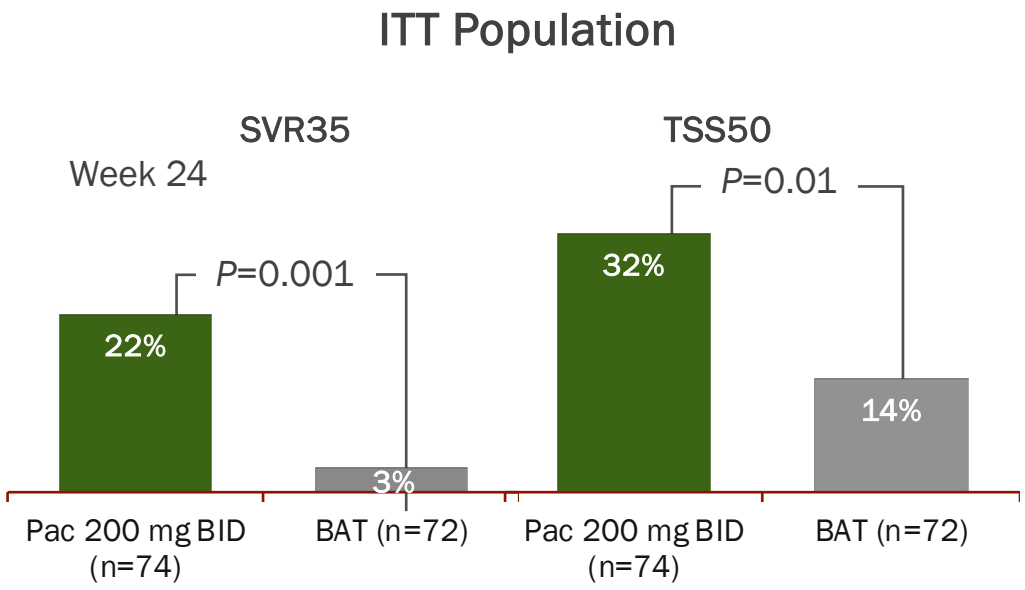


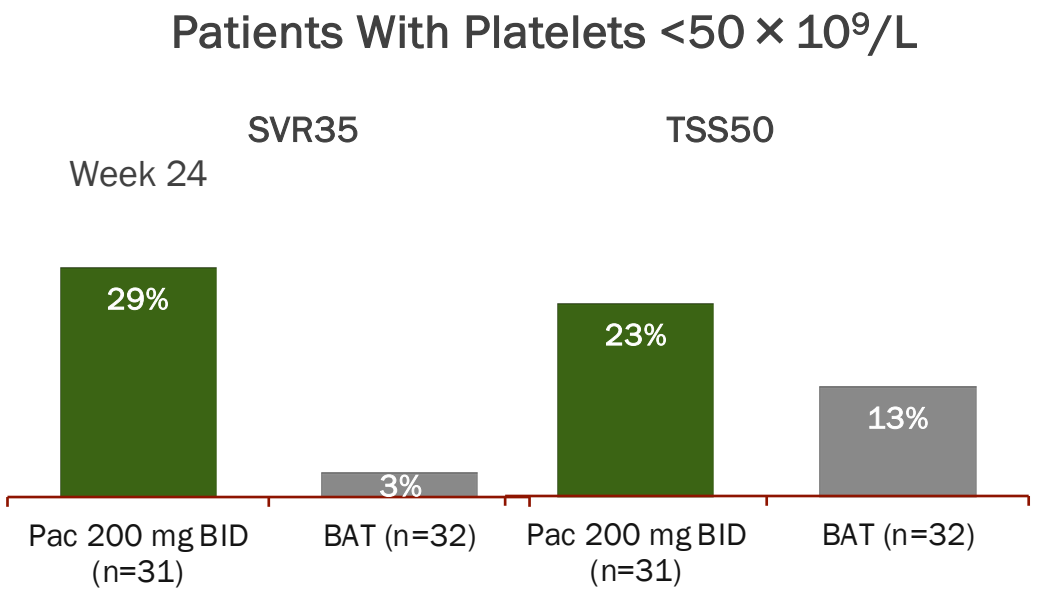
N = 37
25%, *P* = .08



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

PERSIST-2: Spleen/Symptom Response





Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

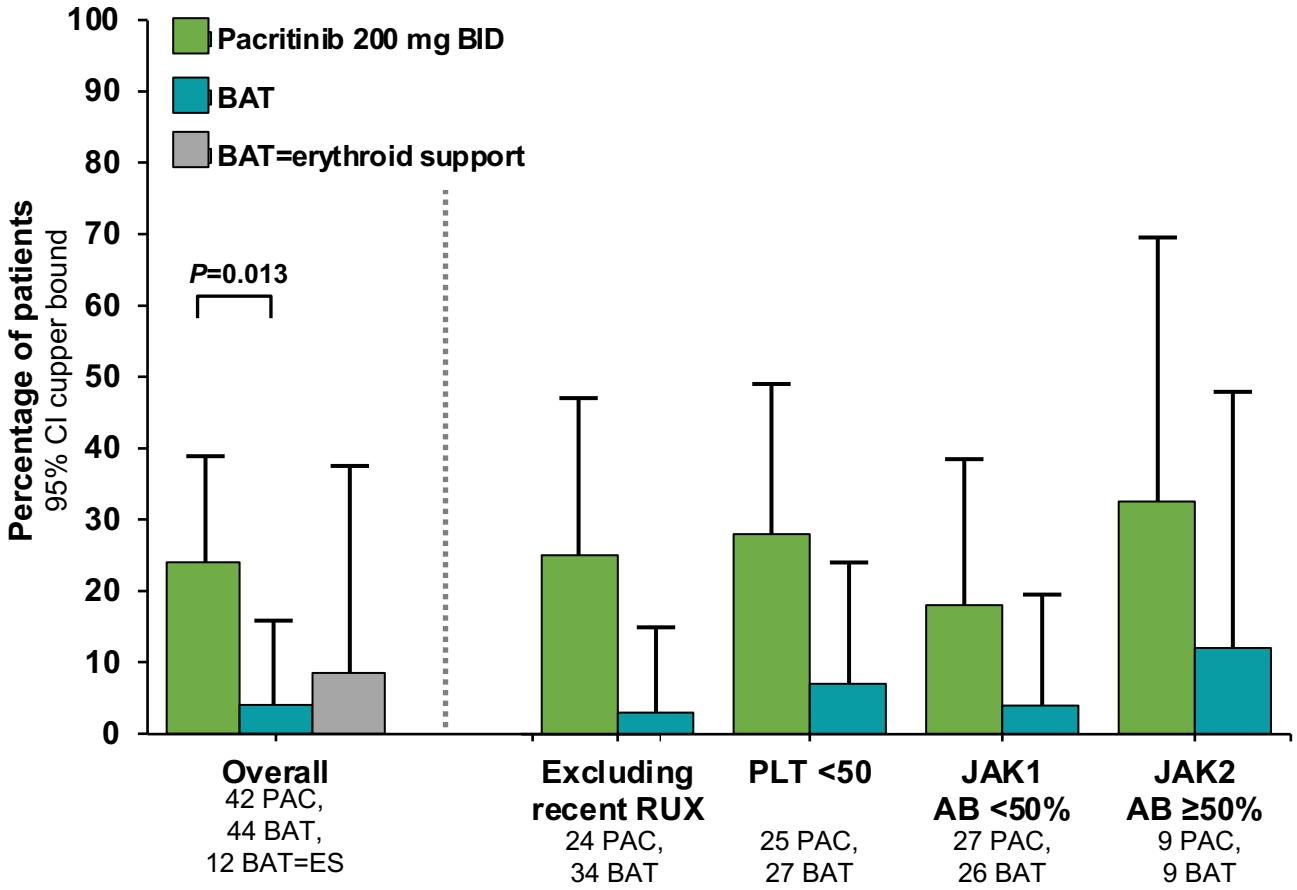
PERSIST-2 Trial: Achievement of TI Using Pacritinib in MF

TI Conversion Rate

PAC n=42	BAT n=44	*P*-value
24%	5%	0.013

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

Rate of TI (SIMPLIFY criteria) Through Week 24

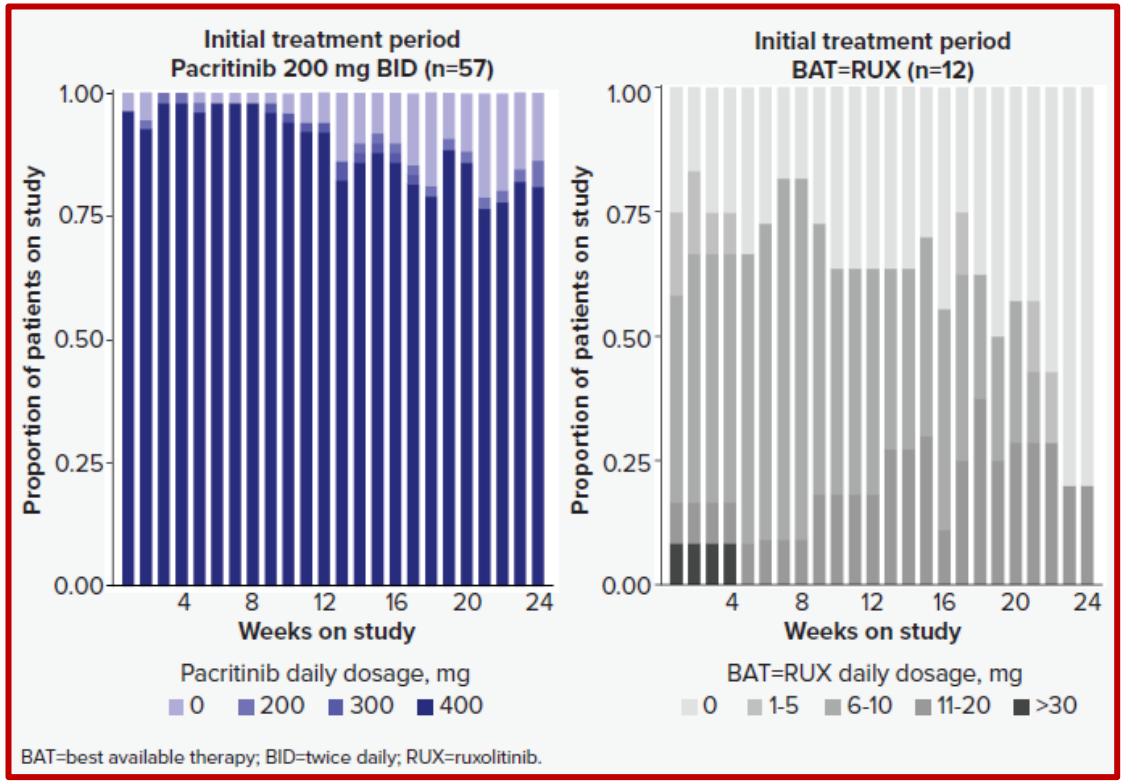


Recent RUX = no ruxolitinib in prior 30 days. AB, allele burden; BAT, best available therapy; ES, erythroid support; PAC, pacritinib; PLT, platelets; TI, transfusion independence.

Oh ST, et al. ASH 2022. Abstract 628; Oh ST, et al. Blood Adv. 2023;7:5835-5842.

PERSIST-2: PAC vs. RUX in RUX-naïve pts

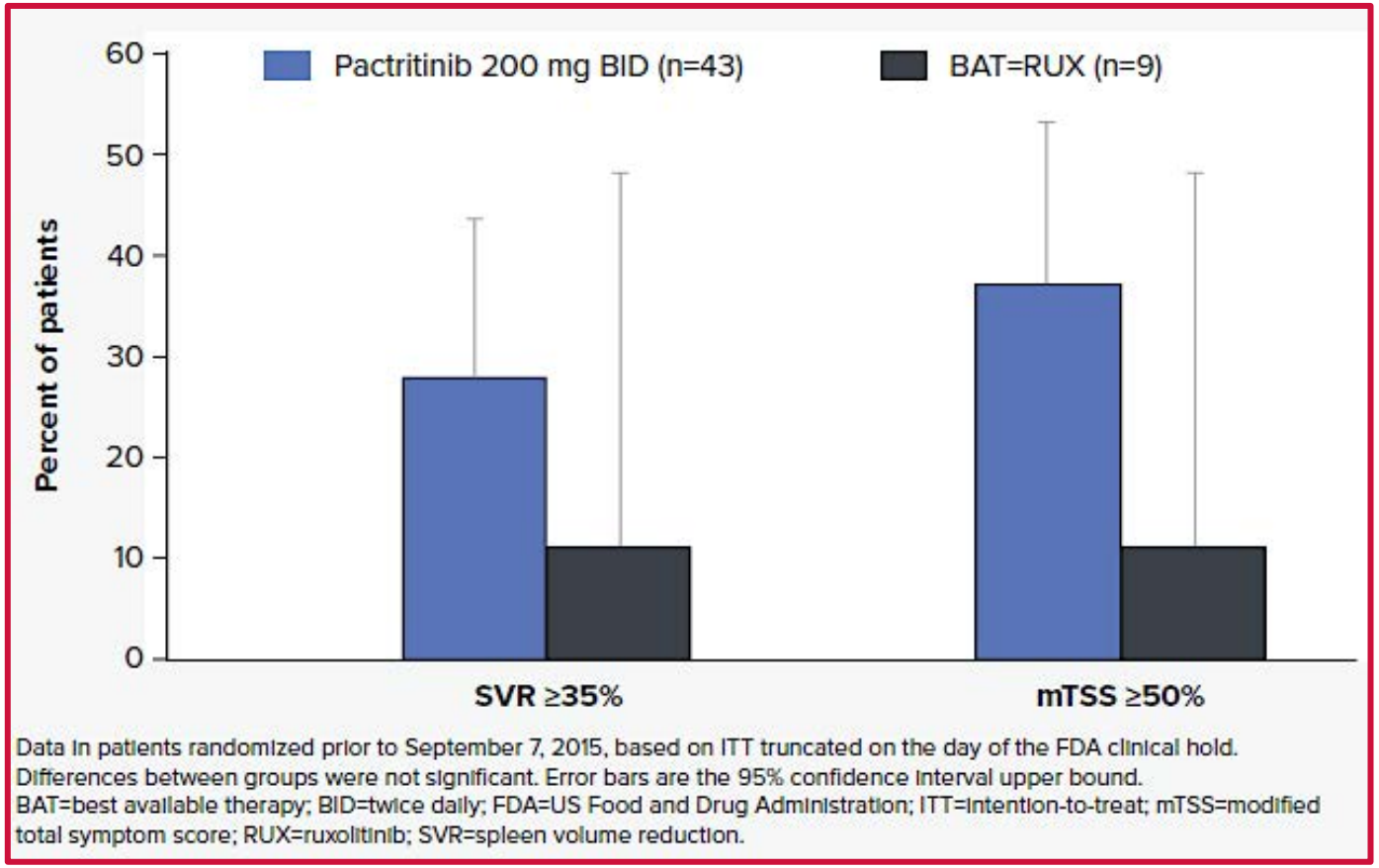
- The majority of patients treated with pacritinib were able to maintain full doses over time at weeks 12 and 24
  - (median dose = 400 mg/day)
- By contrast, patients on ruxolitinib received:
  - a median starting dose of 10 mg (interquartile range [IQR] 10-10 mg) daily at baseline
  - 10 mg (IQR, 0-10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



Mascarenhas J, et al. ASH 2021.
Mascarenhas J, et al. Blood (2021) 138 (Supplement 1): 3639.

PERSIST-2: PAC vs. RUX in RUX-naïve pts

- 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.



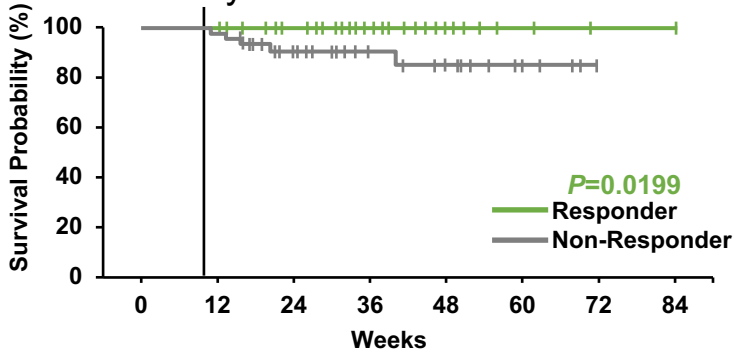
Data in patients randomized prior to September 7, 2015, based on ITT truncated on the day of the FDA clinical hold. Differences between groups were not significant. Error bars are the 95% confidence interval upper bound.
BAT=best available therapy; BID=twice daily; FDA=US Food and Drug Administration;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

Mascarenhas J, et al. ASH 2021.
Mascarenhas J, et al. Blood (2021) 138 (Supplement 1): 3639.

SVR Predicts Survival in MF Patients on Pacritinib but Not Best Available Therapy: Persist-2 Landmark Overall Survival Analysis

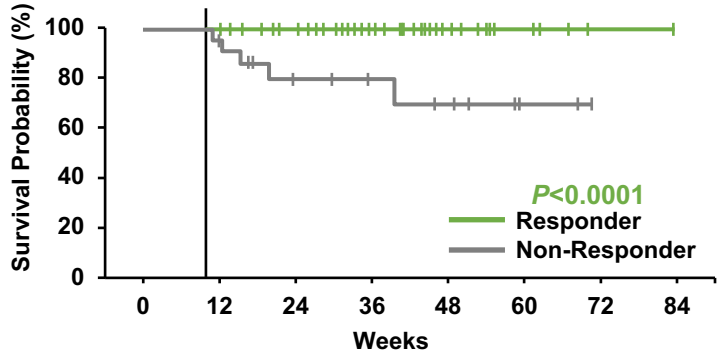
Pacritinib

(B) OS Stratified by **≥20% SVR**



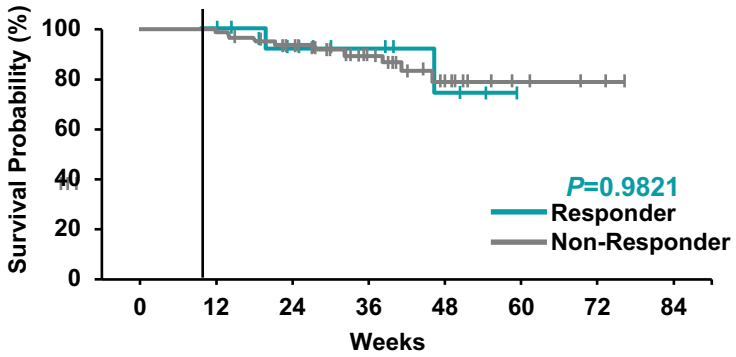
N							
Responder	43	34	25	12	4	1	0
Non-Responder	46	28	16	11	5	0	0

(C) OS Stratified by **≥10% SVR**

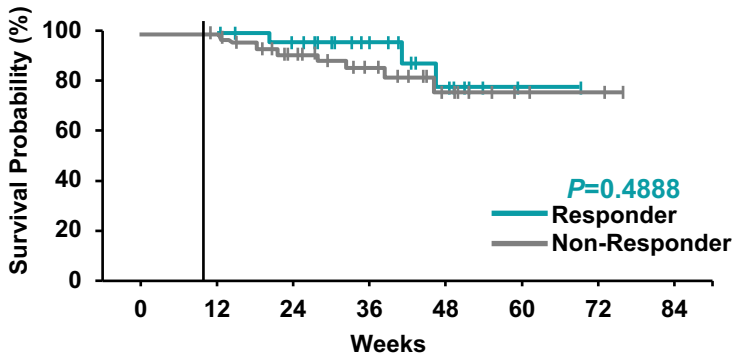


N							
Responder	65	51	33	17	6	1	0
Non-Responder	24	11	8	6	3	0	0

BAT (including RUX)



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

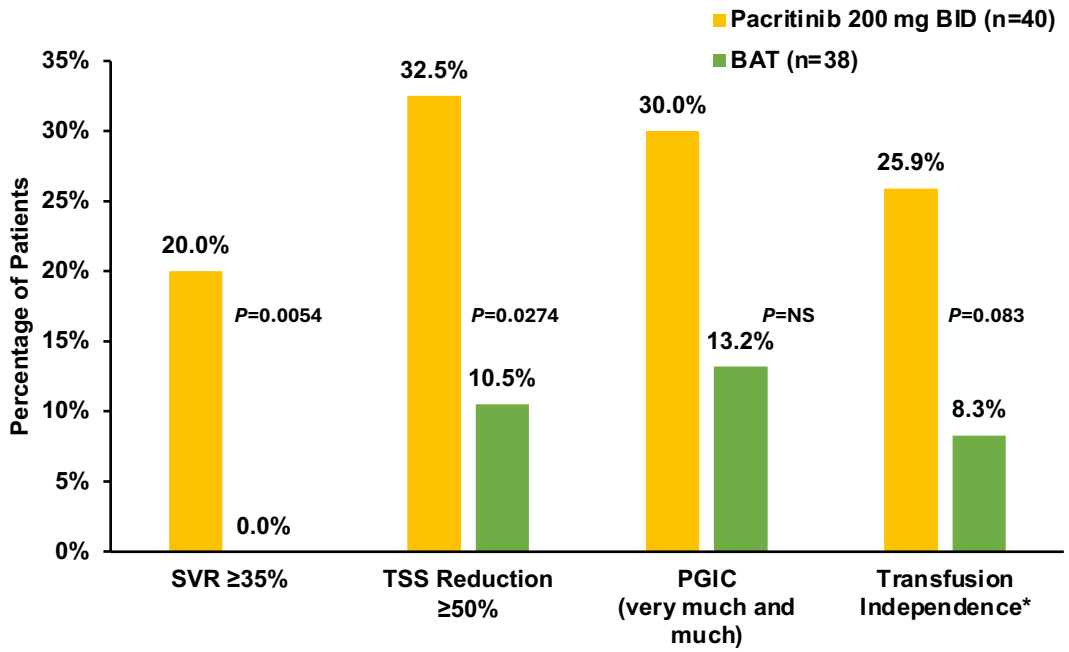


N							
Responder	28	23	16	7	1	0	0
Non-Responder	58	37	25	11	3	2	0

BAT, best available therapy; MF, myelofibrosis; OS, overall survival; RUX, ruxolitinib; SVR, spleen volume reduction.
Bewersdorf J. *EHA* 2023. Abstract P1030.

Efficacy of Pacritinib in Patients With MF Who Have Overlapping Thrombocytopenia and Anemia

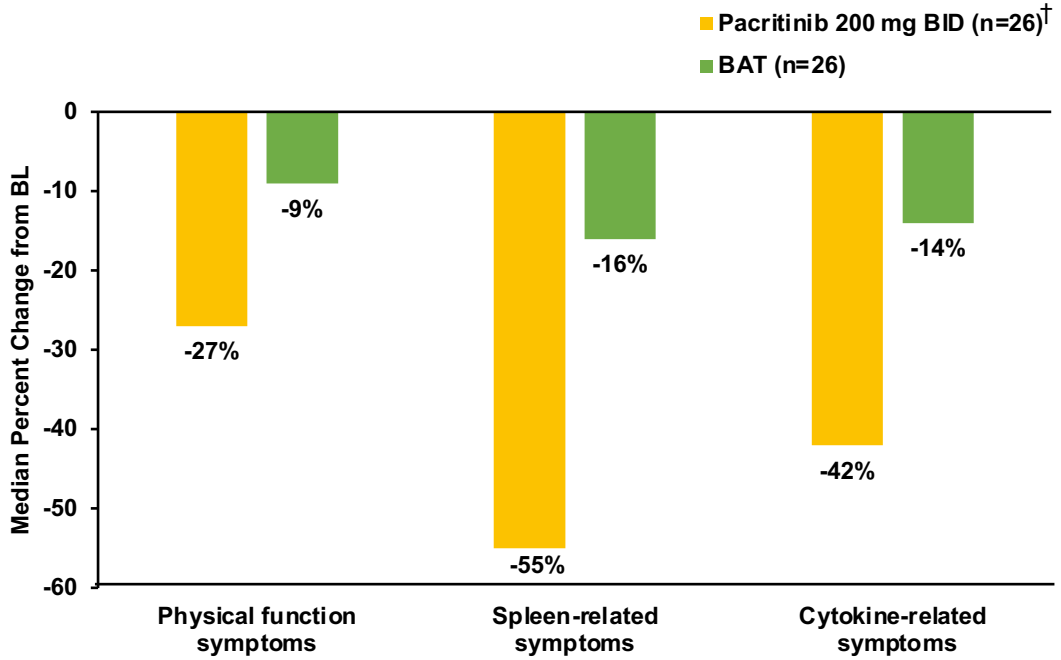
Efficacy Outcomes for Pacritinib vs BAT at Week 24



*TI-R was assessed among patients requiring RBC transfusion at baseline (within 90 days), with response defined as the absence of RBC transfusions over any 12-week period through 24 weeks (Gale criteria). Pacritinib, n=27; BAT, n=36. BAT, best available therapy; TI-R, transfusion independence response; SVR, spleen volume reduction; TSS, total symptom score (version 2.0, excluding tiredness); PGIC, Patient Global Impression of Change; NS, not significant.

Vachhani P, et al. *EHA* 2024. Abstract P1037.

Median Percent Change in Subscale Symptoms* From Baseline to Week 24 for Pacritinib vs BAT



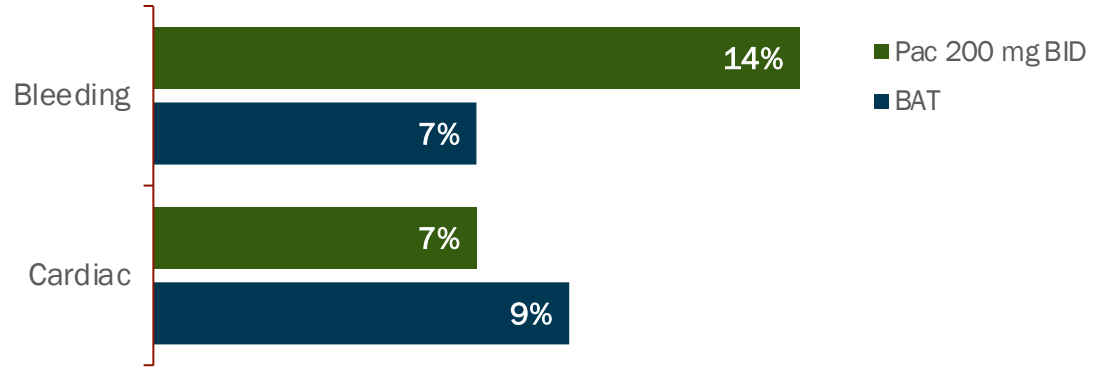
*Physical function scores (sum of 'tiredness' and 'inactivity'), spleen-related symptom scores (sum of 'abdominal discomfort', 'early satiety', and 'left rib pain'), and cytokine-related symptom scores (sum of 'itching', 'night sweats', and 'bone pain').
†Except for spleen-related symptoms subscale, n=25.
BAT, best available therapy; BI, baseline.

PERSIST-2: Adverse Event Profile[1]

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	23
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16
Grade ≥3 AEs in ≥5% of patients in either arm, %		
Thrombocytopenia	32	18
Anemia	22	14
Neutropenia	7	5
Pneumonia	7	3
Serious AEs in ≥3% of patients in either arm, %		
Anemia	8	3
Thrombocytopenia	6	2
Pneumonia	6	4
Congestive heart failure	4	2

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

Grade ≥3 Events (Pooled[a])



- Full clinical hold had been placed on pacritinib by the FDA due to concerns over bleeding and cardiovascular events and deaths on PERSIST-1 and -2; this hold was subsequently lifted and pacritinib is now approved for use in patients with platelets <50×10^9/L[2,3]

[a] Pooled, per standardized MedDRA queries.

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. 2. CTI BioPharma Announces Removal Of Full Clinical Hold On Pacritinib. Updated January 5, 2017. Accessed August 1, 2022. https://investors.ctibiopharma.com/news-releases/news-release-details/cti-biopharma-announces-removal-full-clinical-hold-pacritinib/ 3. CTI BioPharma Announces FDA Accelerated Approval of VONJO™ (pacritinib) for the Treatment of Adult Patients with Myelofibrosis and Thrombocytopenia. Updated February 28, 2022. Accessed August 1, 2022. https://investors.ctibiopharma.com/news-releases/news-release-details/cti-biopharma-announces-fda-accelerated-approval-vonjotm/

Study Design[1,2]

PACIFICA

Key eligibility criteria:

- Primary MF, post-essential thrombocythemia MF, post-polycythemia vera MF
- DIPSS intermediate- or high-risk disease
- Severe thrombocytopenia at baseline (platelet count <50 x 10^9/L)
- JAK1/2 inhibitor-naïve or limited duration of prior JAK1/2 inhibitor*,†

2:1 Randomization N=399

Stratification at randomization:

- Prior JAK1/2 inhibitor therapy
- Physician's choice therapy proposed

Pacritinib 200 mg BID

Physician's choice

- Low-dose ruxolitinib‡
- Hydroxyurea
- Danazol
- Corticosteroids

Co-primary endpoints at 24 weeks:

- SVR ≥35%
- Reduction in TSS ≥50%

Key secondary endpoints

- Overall survival
- PGIC
- Safety

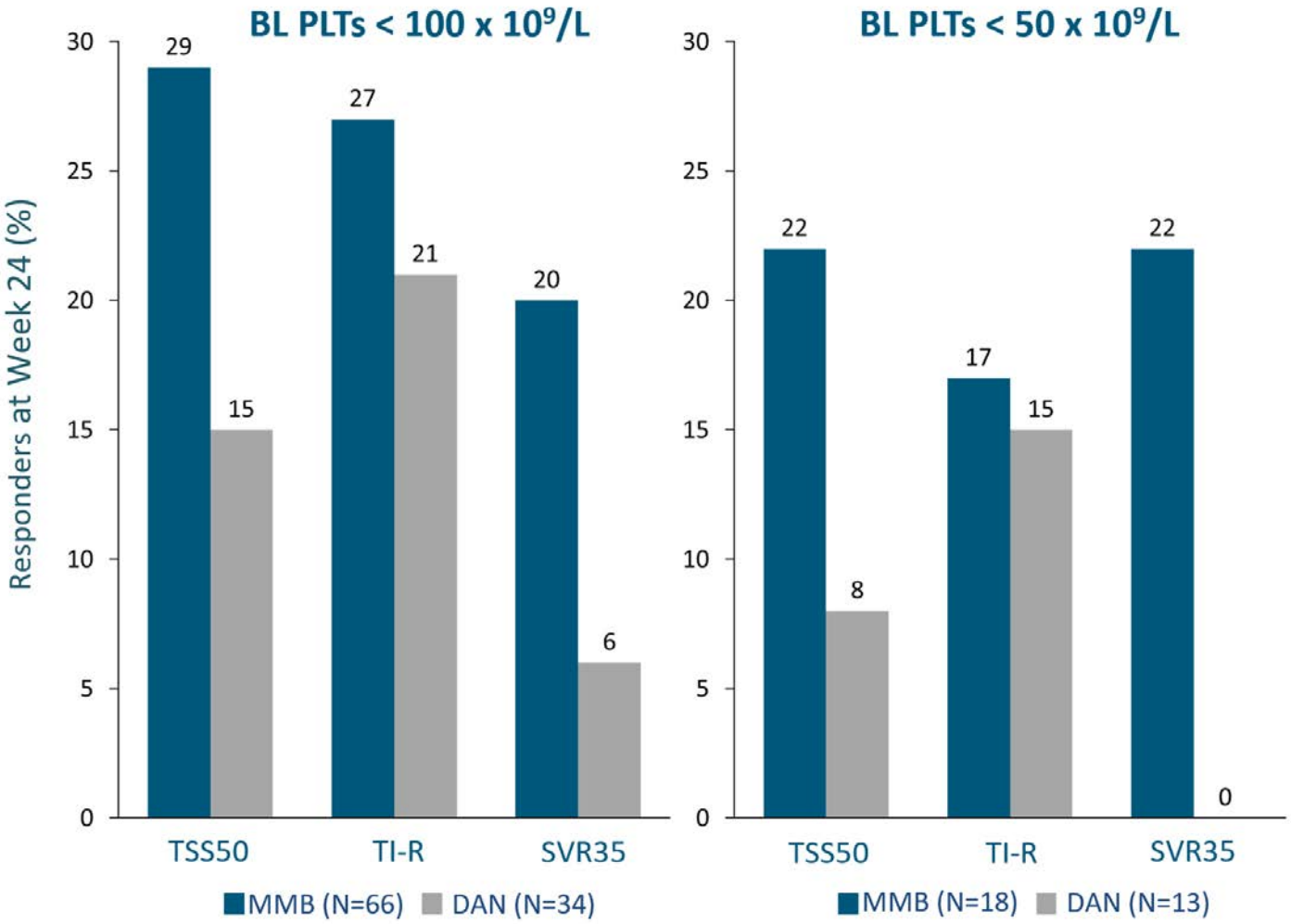
NP-37337

*Prior treatment with ruxolitinib for any duration provided that total daily dose remained ≤10 mg in the 120 days prior to treatment Day 1 OR prior treatment with ruxolitinib for any duration provided higher dose ruxolitinib (>10 mg daily) was given for no more than 90 days (from first to last dose regardless of whether dosing was continuous or intermittent). † A 2-week washout will be required for MF directed therapy and at least 28 days for experimental MF therapies. ‡ No more than 10 mg/day.

BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; MF, myelofibrosis; PGIC, patient's global impression of change; SVR, spleen volume reduction; TSS, total symptom score (version 2.0, excluding tiredness)

1. ClinicalTrials.gov NCT03165734. Accessed October 2023 **2.** PACIFICA trial page. Accessed October 2023.

MOMENTUM: Consistent Profile in Thrombocytopenic Subgroups



Verstovsek S et al. EHA 2022. Abstract S195

Questions from General Medical Oncologists/Hematologists

- **A patient presents with primary MF, constitutional symptoms and splenomegaly, with a baseline platelet count of <50,000/μL. The patient is not a transplant candidate, which treatment would you most likely recommend?**
- **Why is pacritinib better than ruxolitinib or fedratinib for patients with MF and severe thrombocytopenia?**

Questions from General Medical Oncologists/Hematologists

- **A 55-year-old patient 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 demonstrates JAK2 V617F, TET2 and ASXL1 mutations. What treatment would you recommend?**

Questions from General Medical Oncologists/Hematologists

- **A patient with symptomatic higher-risk MF and splenomegaly (baseline platelet count 110,000/μL) receives ruxolitinib 15 mg BID and responds with significant symptom improvement and decrease in spleen size. Approximately 3 years later they present with drenching night sweats, fatigue, abdominal discomfort and an increase in spleen size. Platelet count = 44,000/μL, Hgb = 11.2 g/dL. The patient is not a transplant candidate. Which treatment would you most likely recommend next?**

Questions from General Medical Oncologists/Hematologists

- **Based on available data, what expectations on the likelihood of splenic response and symptom improvement can we set for a patient with MF and severe thrombocytopenia who receives pacritinib?**
- **What dose and schedule of pacritinib do you generally start with? Is there a dose-adjustment schedule for pacritinib based on platelet levels?**

Agenda

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

Module 2: Managing MF for Patients with Thrombocytopenia — Dr Bose

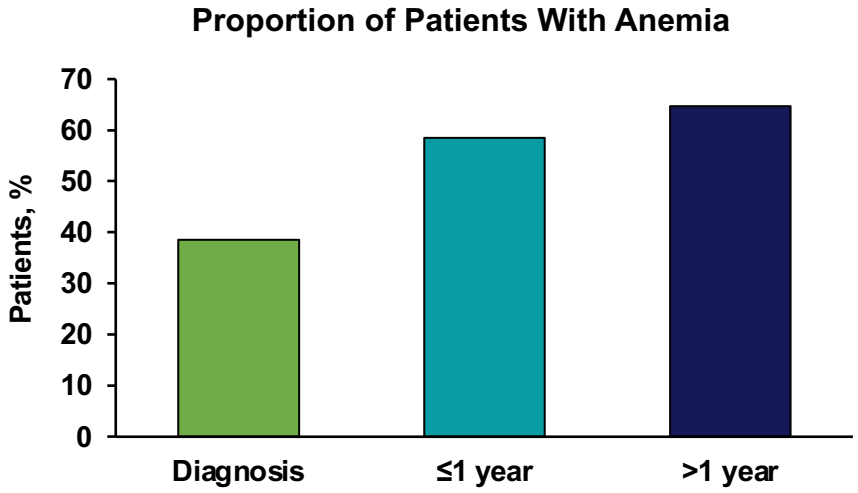
Module 3: Managing MF for Patients with Anemia — Dr Yacoub

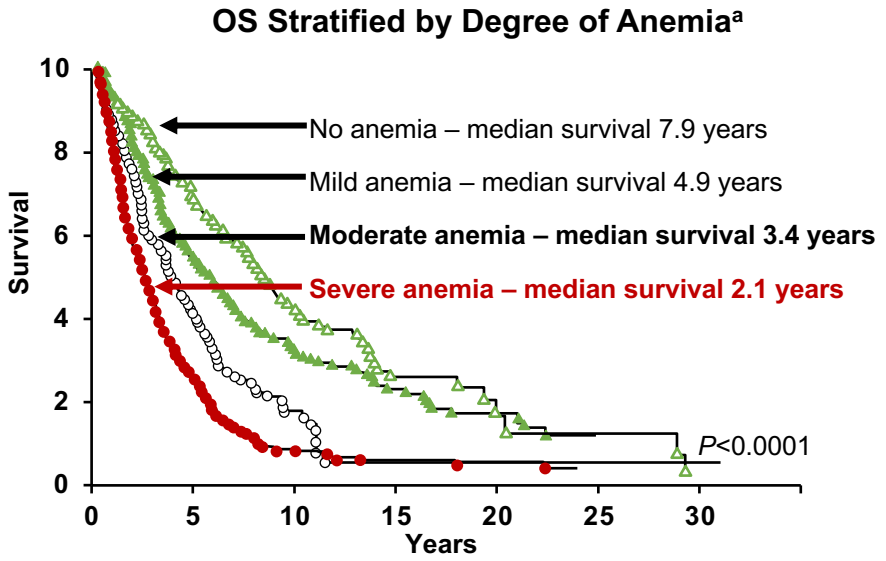
Module 4: Future Directions in the Management of MF — Dr Fleischman

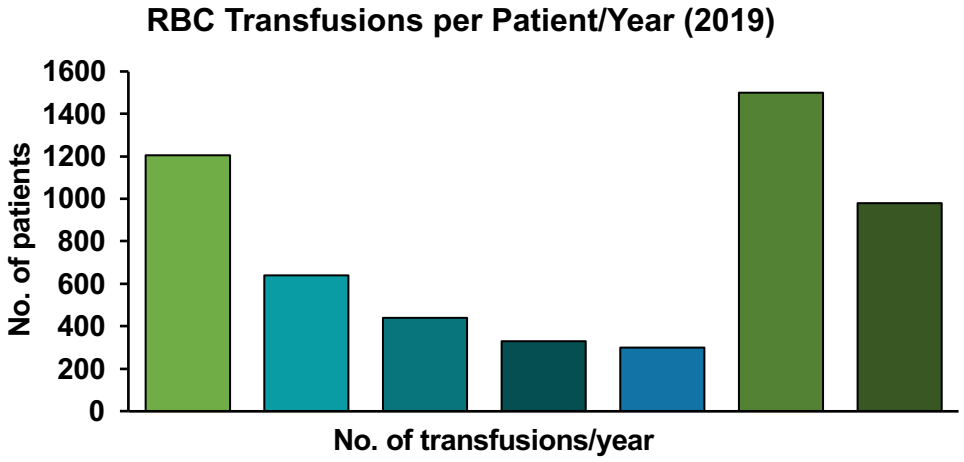
Managing MF in Patients with Anemia

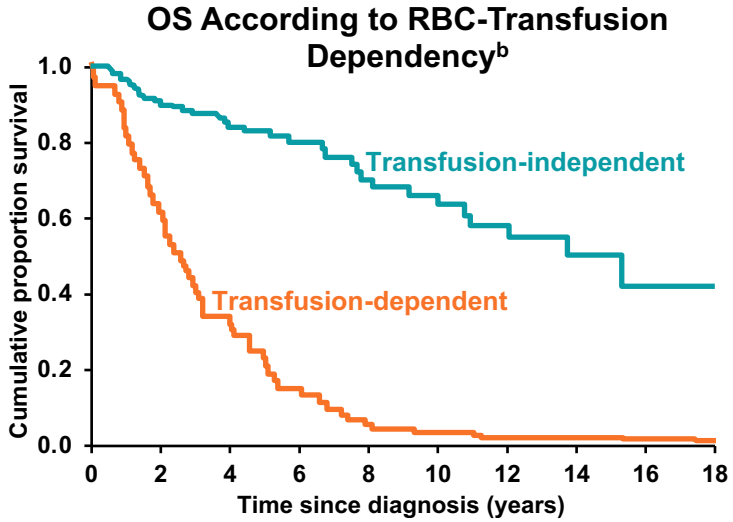
Abdulraheem Yacoub, MD
Professor of Medicine
Division of Hematologic Malignancies and Cellular Therapeutics (HMCT)
Department of Internal Medicine
The University of Kansas Cancer Center
Westwood, Kansas

Anemia Is Common and a Poor Prognostic Indicator



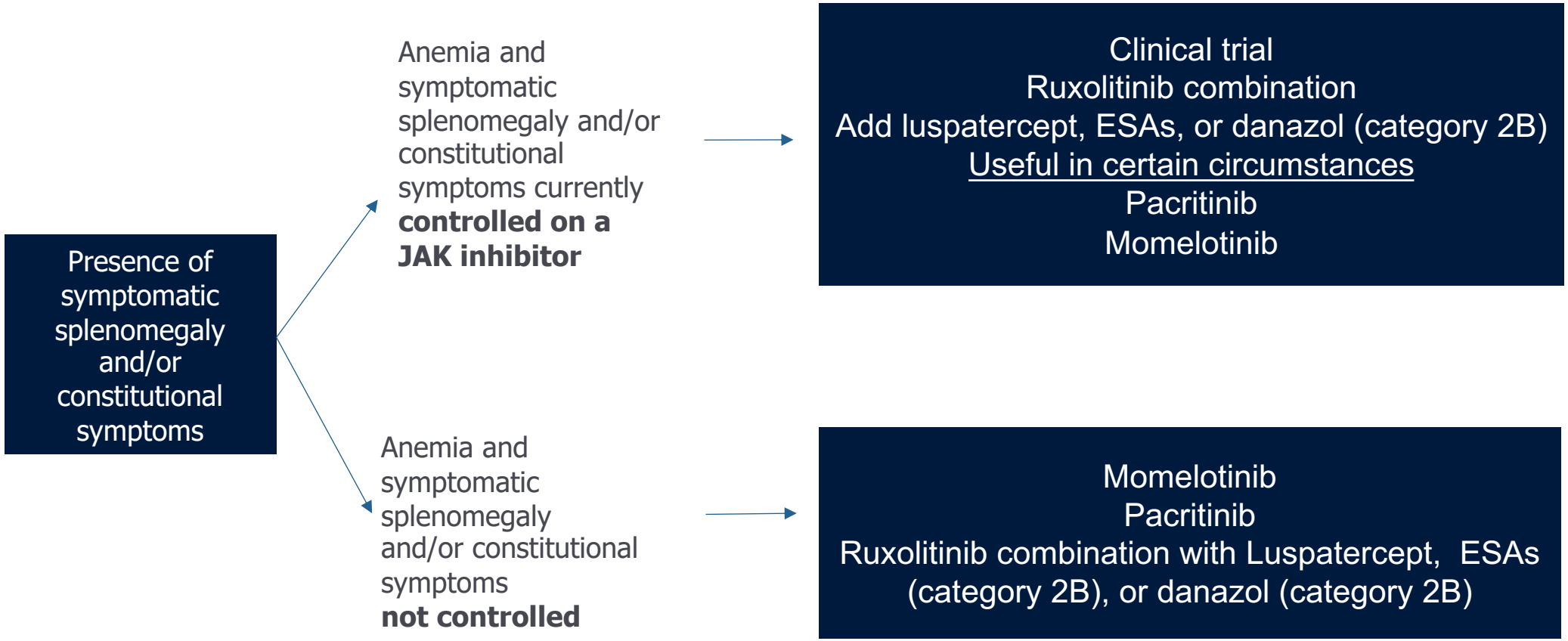






Tefferi A, et al. *Blood*. 2013;122(8):1395-1398. Rago A, et al. *Leuk Res*. 2015;39(3):314-317. Curto-Garcia N, et al. *Future Oncol*. 2018;14(2):137-150. Harrison CN, et al. *Leukemia*. 2016;30(8):1701-1707. Tefferi A, et al. *Mayo Clin Proc*. 2012;87(1):25-33. Nicolosi M, et al. *Leukemia*. 2018;32(5):1254-1258. Elena C, et al. *Haematologica*. 2011;96(1):167-170.

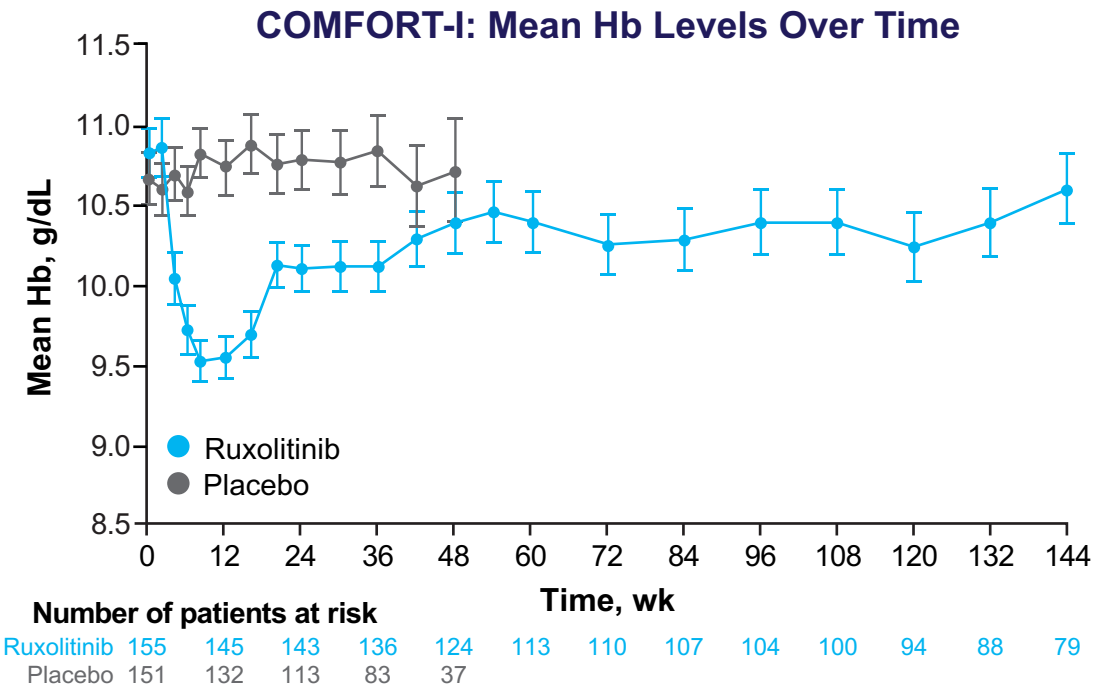
NCCN Guidelines: Management of MF-Associated Anemia

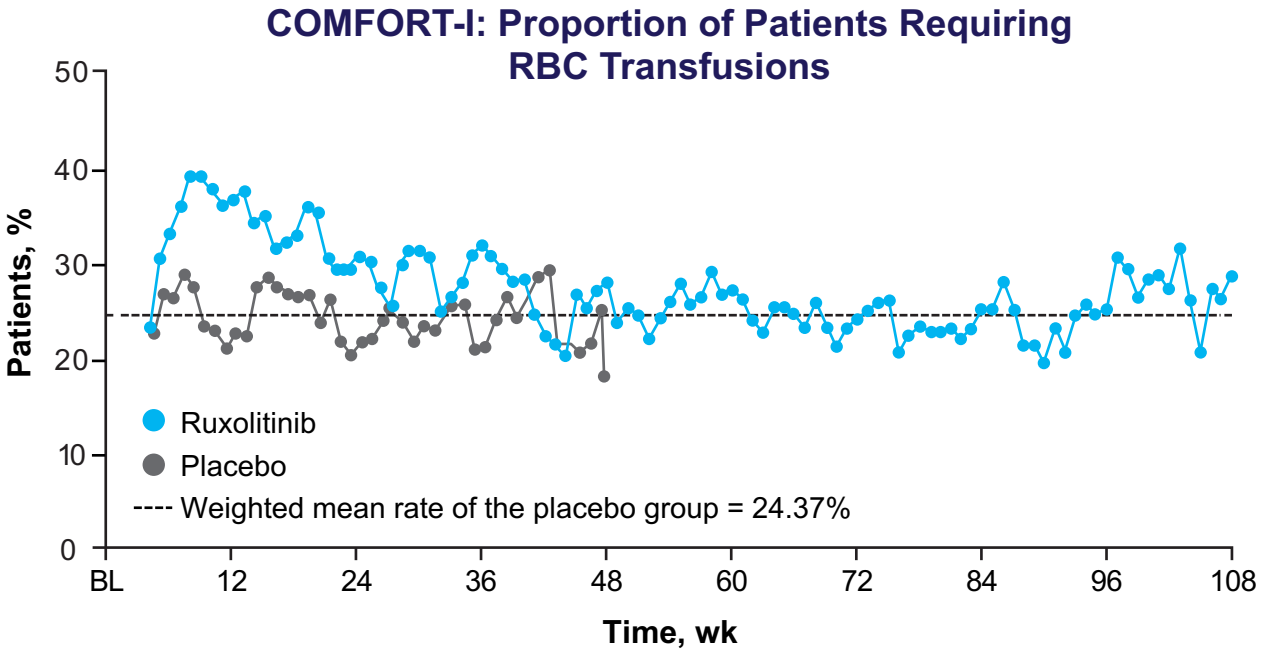


HCT, hematopoietic stem cell transplant; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.

NCCN. Myeloproliferative neoplasms. Version 2.2024. Accessed December 5, 2024.

Ruxolitinib and Anemia Challenges





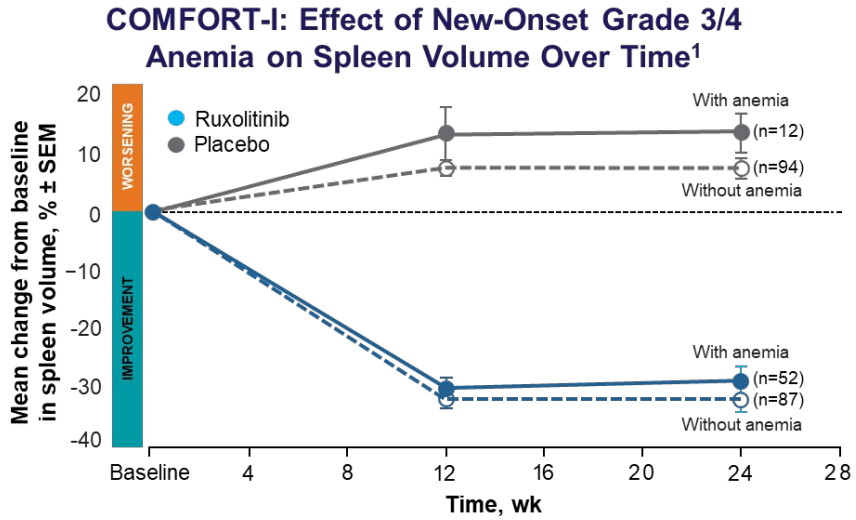
COMFORT-I Hematologic Adverse Reactions.

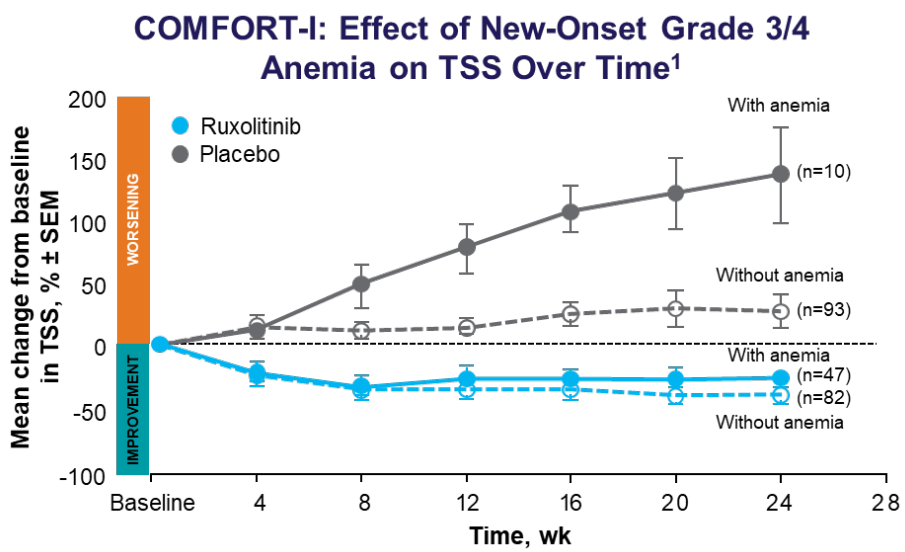
Hematologic Adverse Reactions	Ruxolitinib (n=155)		Placebo (n=151)	
	All Grades, %	Grades 3-4, %	All Grades, %	Grades 3-4, %
Anemia	96	45	87	19

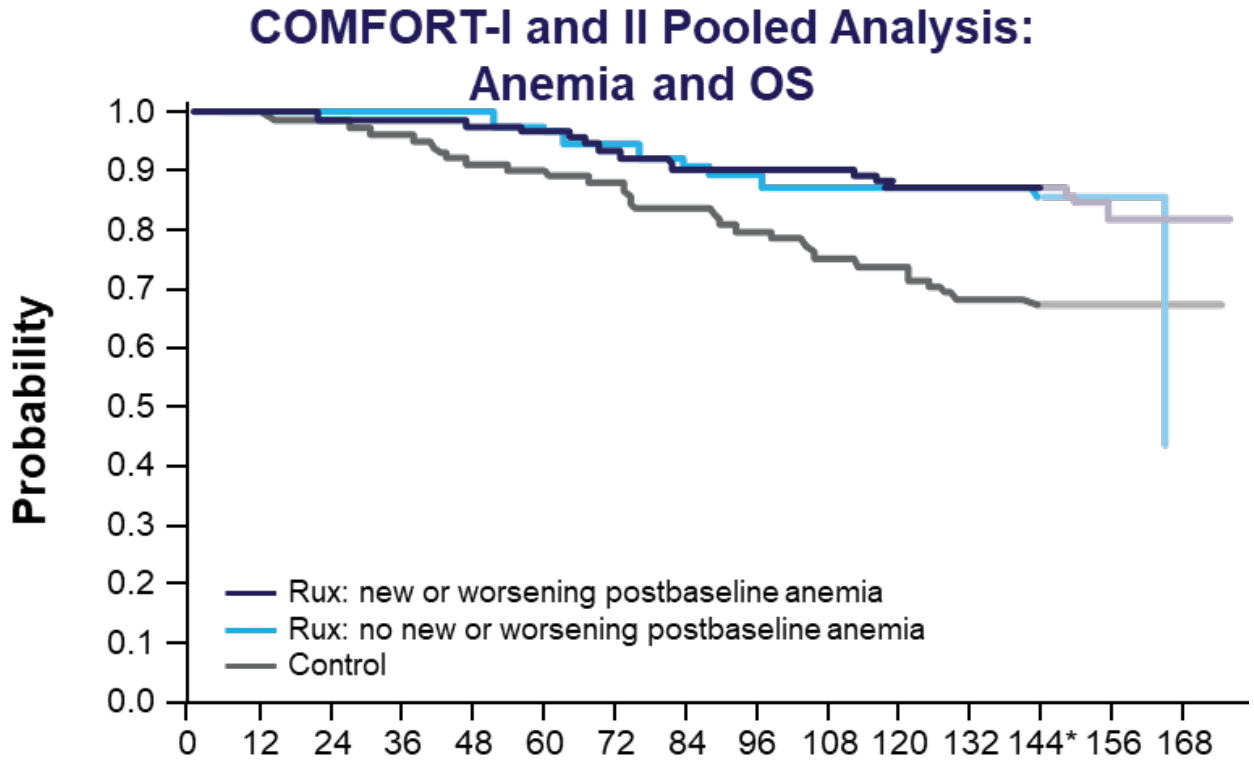
- <1% of patients receiving ruxolitinib in the COMFORT-I study discontinued due to anemia

References: Verstovsek S, et al. *Haematologica.* 2015;100(4):479-488; Verstovsek S, et al. *Haematologica*. 2013;98(12):1865-1871; Ruxolitinib Prescribing Information.

Treatment Related Anemia Did Not Impact Efficacy for Patients on Ruxolitinib

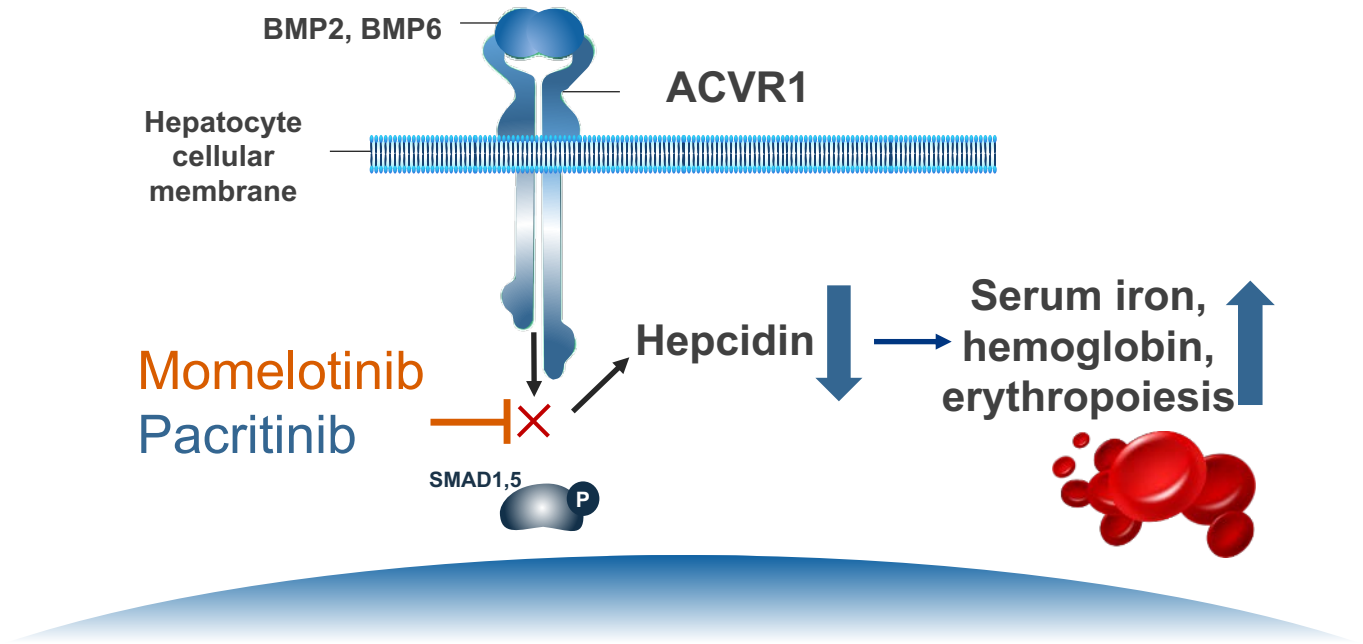






Verstovsek S, et al. *N Engl J Med*. 2012;366(9):799-807. Gupta V, et al. *Haematologica*. 2016;101(12):e482-e484.

Momelotinib and Pacritinib Inhibit ACVR1



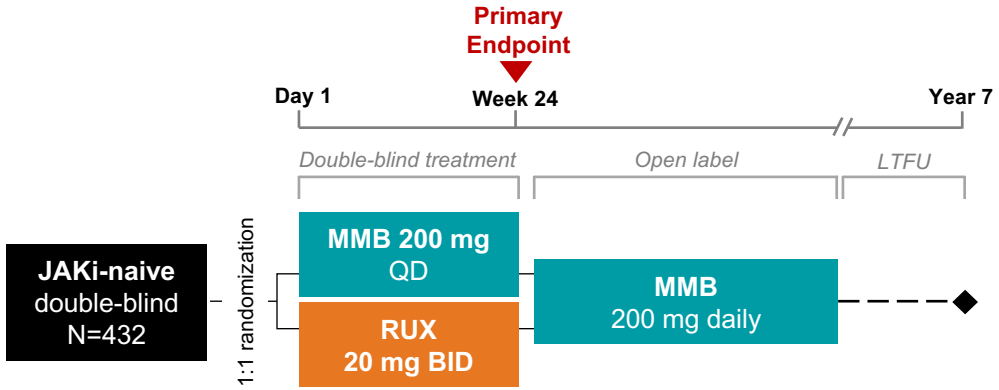
Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF[3,4]

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

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

SIMPLIFY-1 and -2: Momelotinib

SIMPLIFY-1: First-Line Population[1]
JAKi naive



Goal: Noninferiority

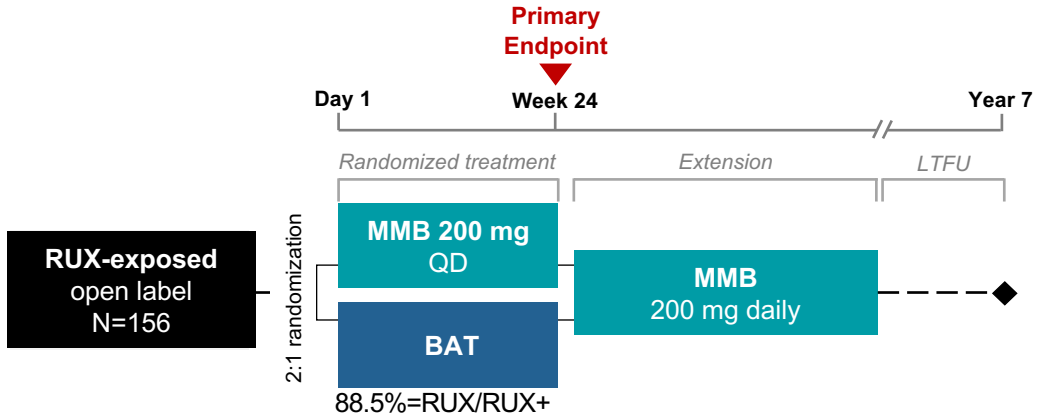
Momelotinib 200 mg QD: n=215

Ruxolitinib 20 mg BID: n=217

Primary Endpoint: SRR

Secondary Endpoints:
- TSS
- TI rate

SIMPLIFY-2: Second-Line Population[2]
Prior ruxolitinib with anemia, thrombocytopenia, or grade ≥3 bleeding



Goal: Superiority

Momelotinib 200 mg QD: n=104

Best Available Treatment: n=52

Primary Endpoint: SRR

Secondary Endpoints:
- TSS
- TI rate

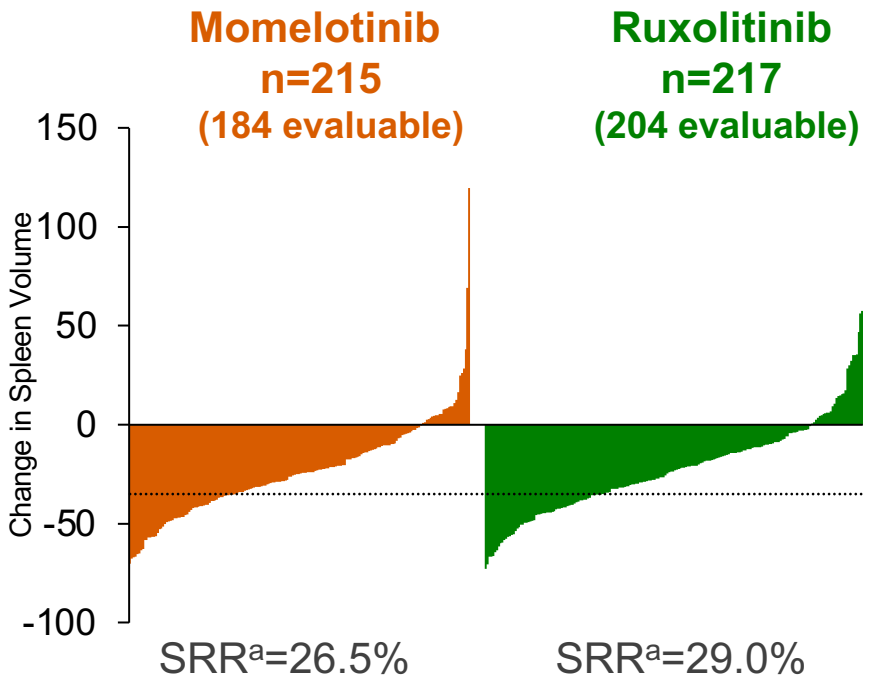
TI defined as absence of RBC transfusions and no Hb <8 g/dL in the prior 12 weeks.

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

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

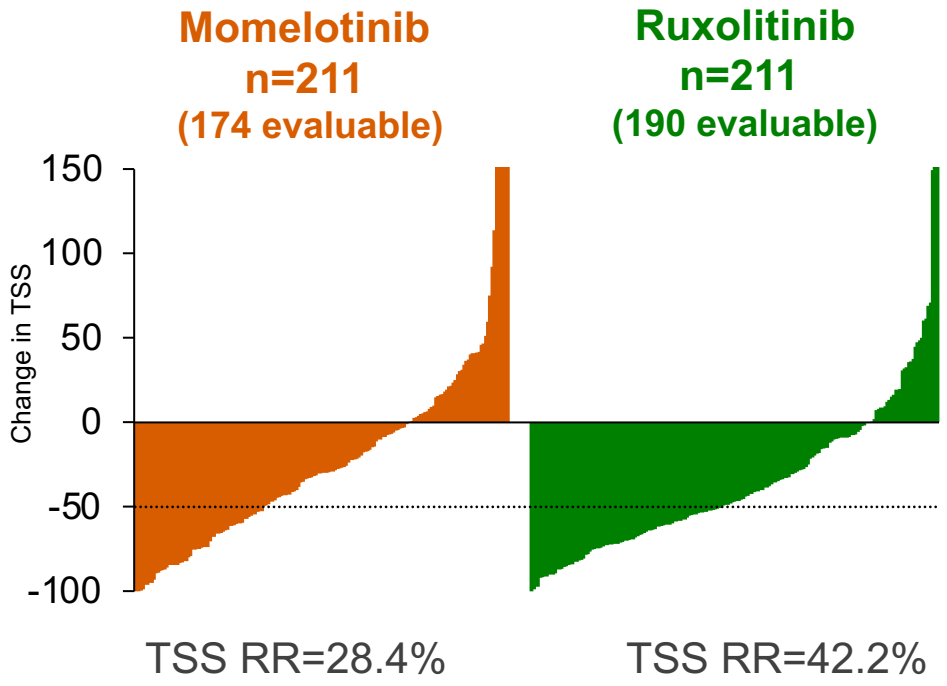
SIMPLIFY-1: Primary and Secondary Endpoints

Primary Endpoint: SRR



***P*=0.011**
Momelotinib is noninferior to ruxolitinib

Secondary Endpoint: TSS RR



***P*=0.98**
Momelotinib is inferior to ruxolitinib

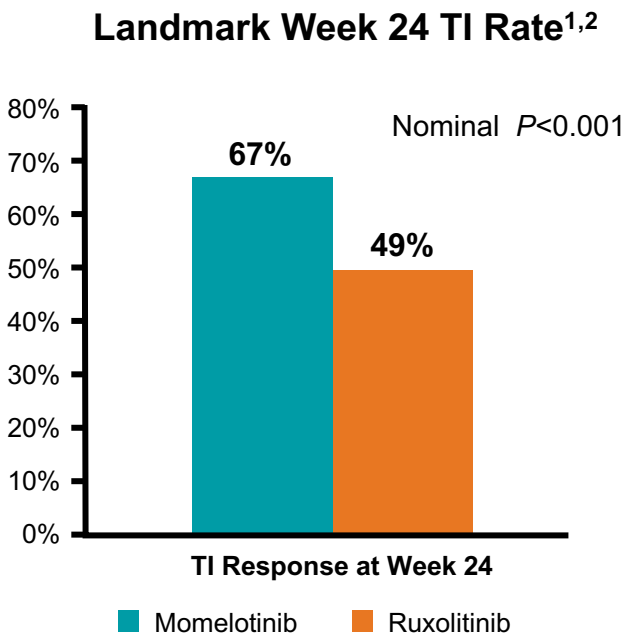
[a] Patients with missing baseline or week 24 spleen volume assessments were considered nonresponders.
SRR, splenic response rate; TSS RR, total symptom score response rate.

> Mesa RA, et al. *J Clin Oncol*. 2017;35:3844-3850.

SIMPLIFY-1: TI and Duration of TI

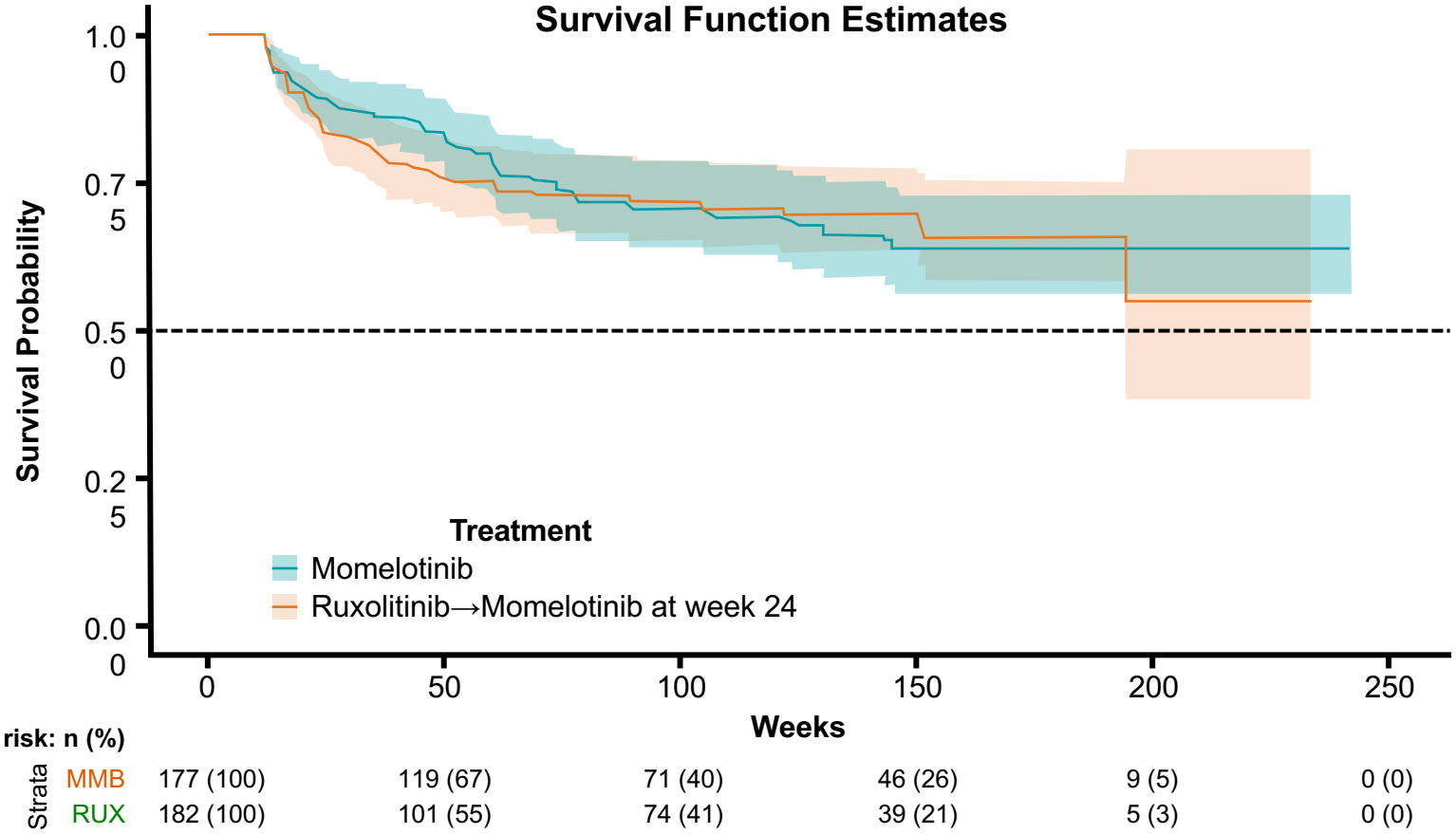
Baseline TI rate was maintained with momelotinib[1]

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



Baseline TI rate[1]:

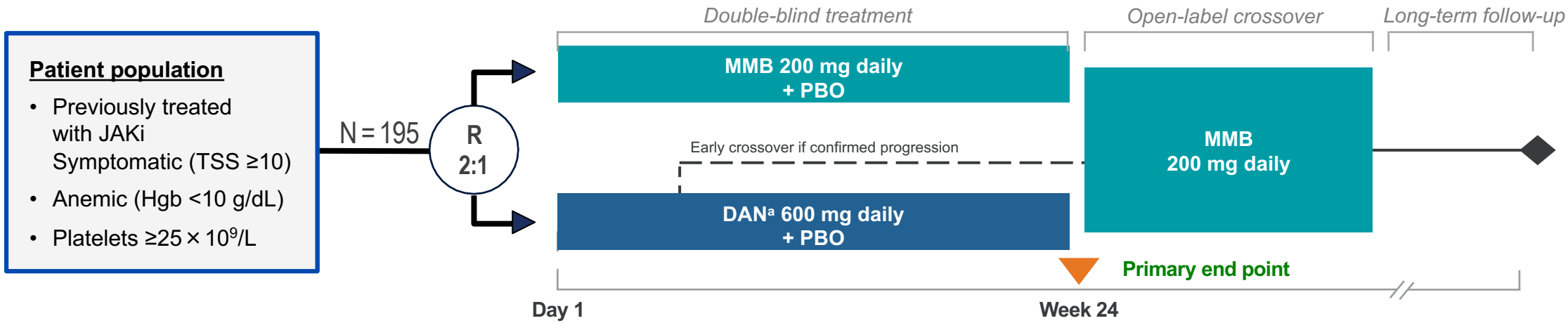
- Momelotinib 68%
- Ruxolitinib 70%



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

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

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



MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met

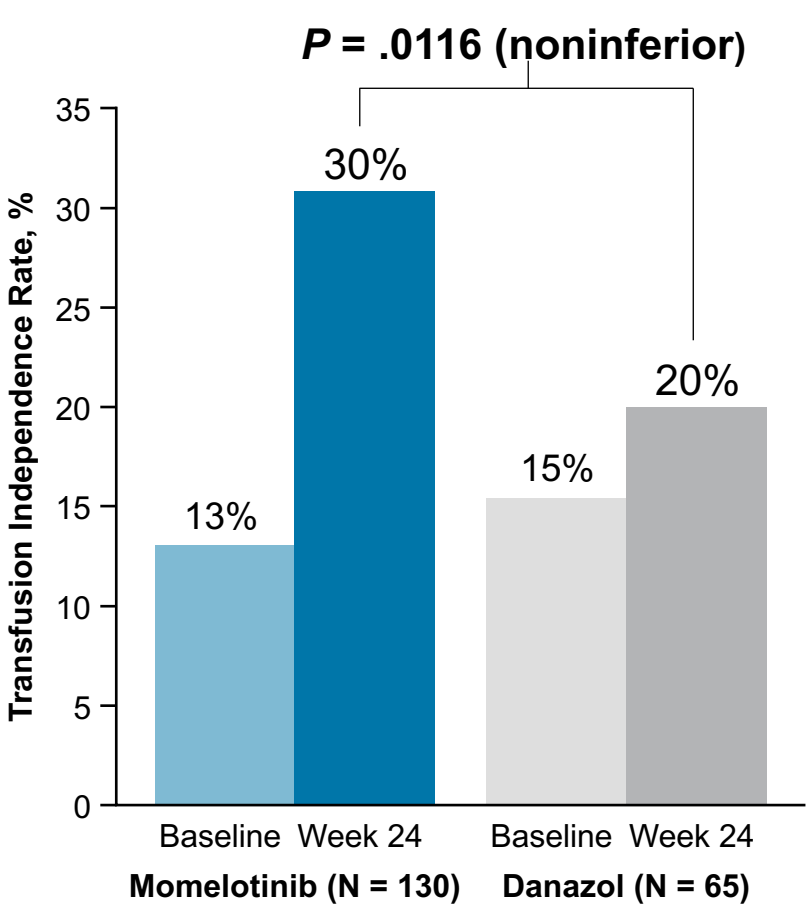
	MFSAF TSS response rate (primary end point)	TI response rate	SRR (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

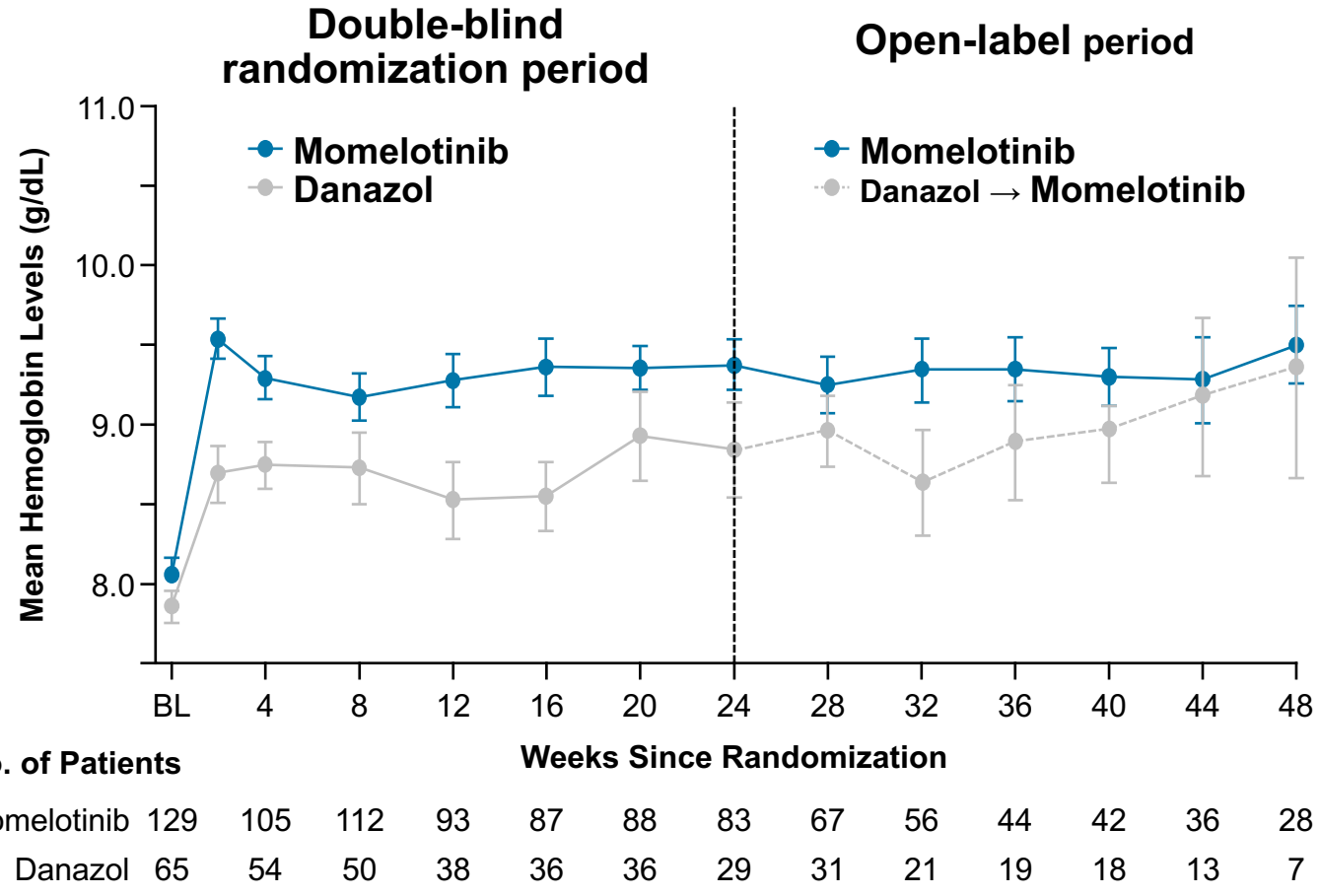
- Most common Gr ≥3 TEAEs in the RT phase of the study were thrombocytopenia (MMB, 22%; DAN, 12%) and anemia (MMB, 8%; DAN, 11%)
- Gr ≥3 infections occurred in 15% of MMB and 17% of DAN pts
- Peripheral neuropathy occurred in 5 (4%) of MMB (all Gr ≤2) and 1 (2%) of DAN (Gr ≤2) pts in the RT phase, and none discontinued study drug.

MMB, momelotinib; DAN, danazol; TSS, total symptom score; SRR, splenic response rate; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; MFSAF, Myelofibrosis Symptom Assessment Form; TI, transfusion independence; SRR, splenic response rate; PBO, placebo.

Mesa RA, et al. *J Clin Oncol.* 2022;40:16_Suppl

Momelotinib vs Danazol: MOMENTUM – Transfusion Independence at Week 24, Mean Hemoglobin Over Time





Verstovsek S, et al. EHA 2022. Abstract S195; Mesa R, et al. ASCO 2022. Abstract 7002; Verstovsek S, et al. Lancet 2023;401(10373):269-80.

Momelotinib Long-term Safety: Integrated Analysis

AEs with momelotinib were mostly grade 1/2, noncumulative, and associated with low rates of discontinuation; 12% of patients received momelotinib for ≥ 5 years

Largest patient population treated with a JAKi in randomized studies of myelofibrosis

SIMPLIFY-1:
momelotinib vs ruxolitinib
(JAKi naive)

SIMPLIFY-2:
momelotinib vs BAT
(JAKi experienced)

MOMENTUM
momelotinib vs danazol
(JAKi experienced)

725 patients treated with momelotinib (2013-2021)

Momelotinib experience:
1261 person-years

BAT, best available therapy

AEs of clinical importance over time

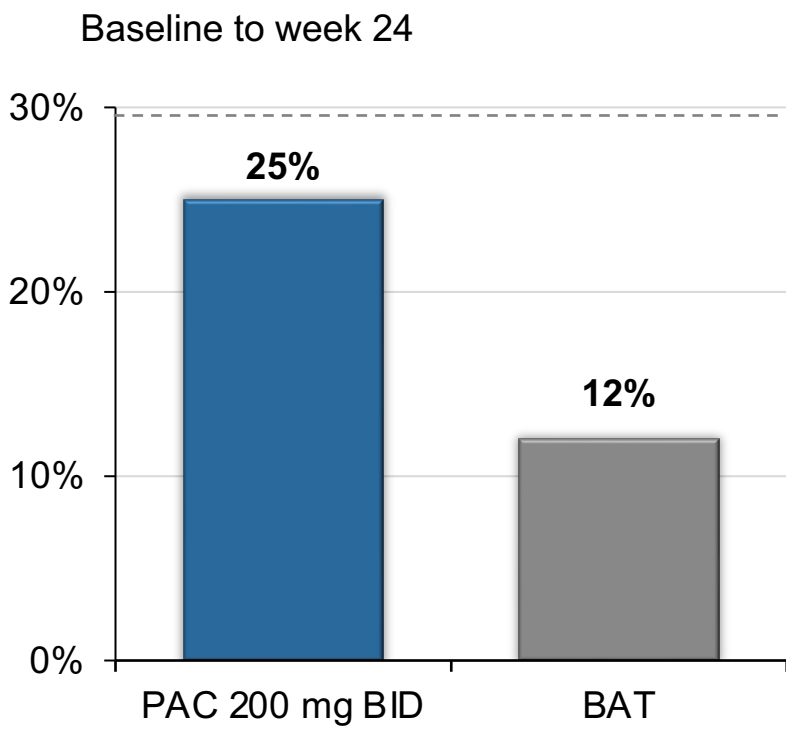
Time window, weeks	0-24	25-48	49-96	97-144	145-192	193-240	241-288	≥289
	n = 725	n = 510	n = 367	n = 213	n = 150	n = 109	n = 93	n = 64
Any AE, %	91.4	72.7	76.3	74.6	66.0	55.0	54.8	31.3
All infections, %	36.3	26.1	33.0	30.0	25.3	20.2	21.5	12.5
Opportunistic infections, %	1.8	1.4	2.5	3.8	2.0	0	4.3	1.6
Malignancies, %	5.2	4.1	6.3	6.1	8.0	2.8	7.5	4.7
AML/malignant transformation, %	1.7	0.2	1.6	0.5	1.3	0	0	0
Nonmelanoma skin cancer, %	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

MACE, major adverse cardiovascular event

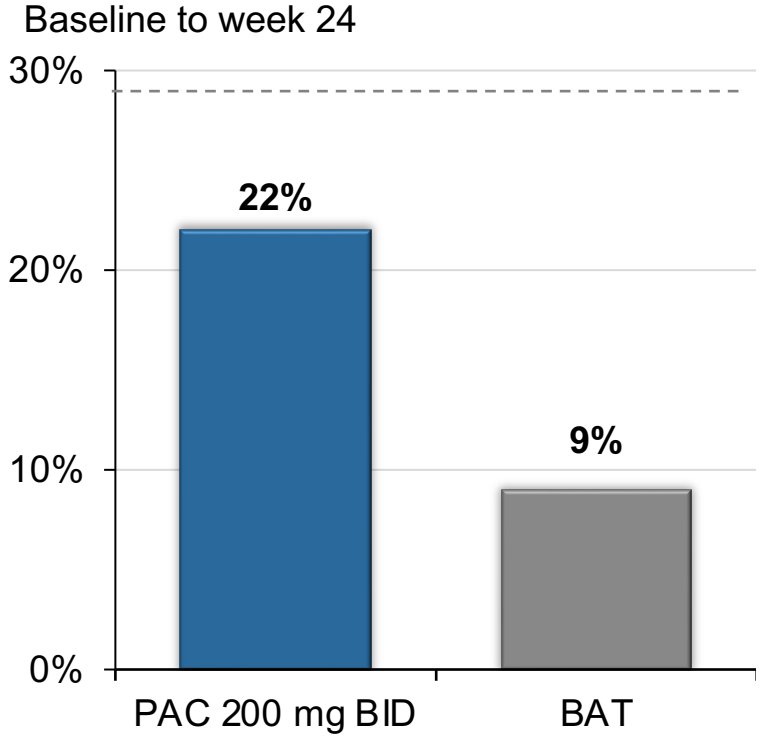
Verstovsek S, et al. Blood Adv. 2023;7:3582-3591.

Pacritinib in PERSIST-2: Hematologic Stability

Clinical improvement in Hgb 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 Hgb <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(5):652-659.

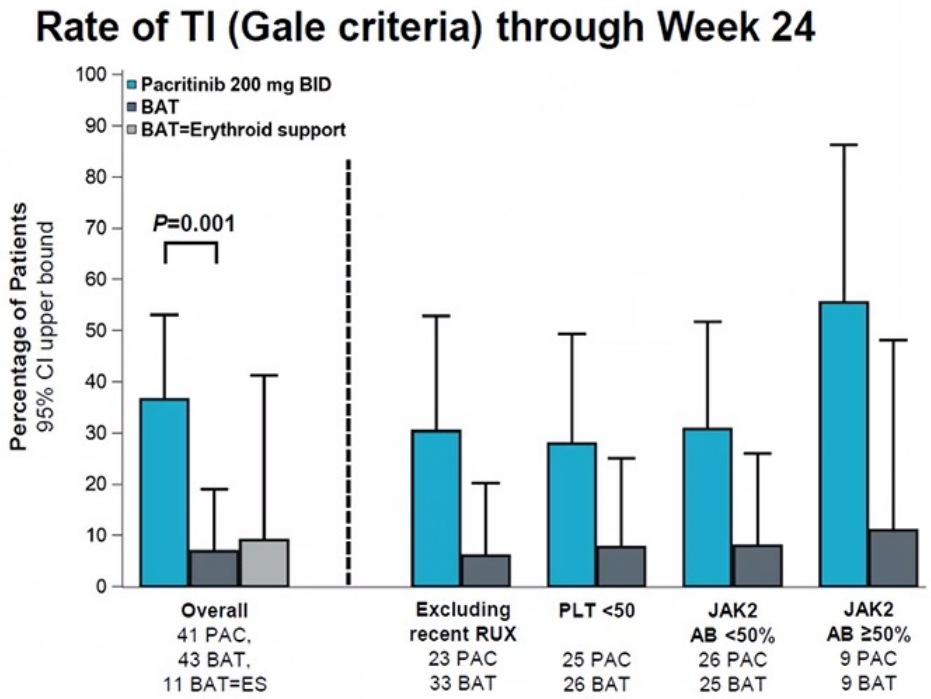
More Pacritinib Patients Achieved Anemia Benefit

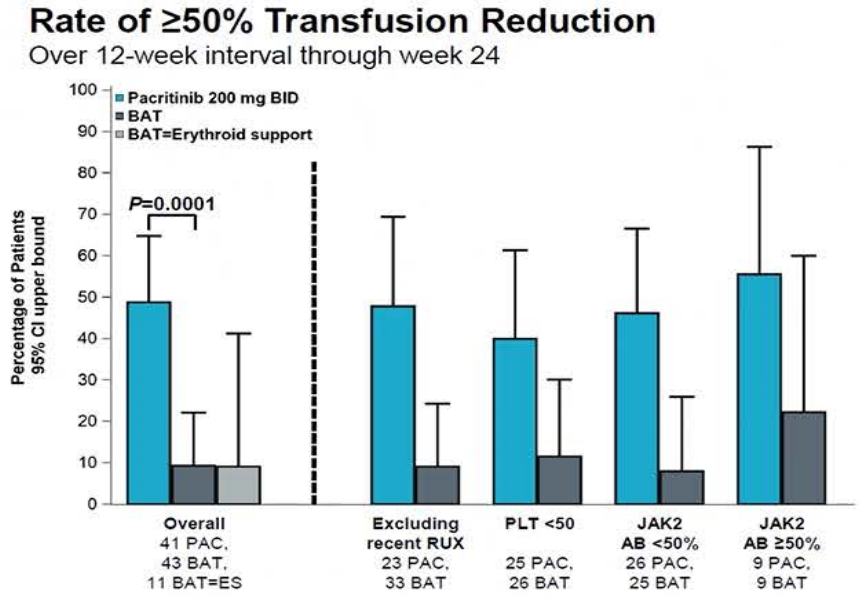
TI Conversion Rate

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

Transfusion Reduction

Pacritinib N = 41	BAT N = 43	*P* Value
49%	9%	.0001





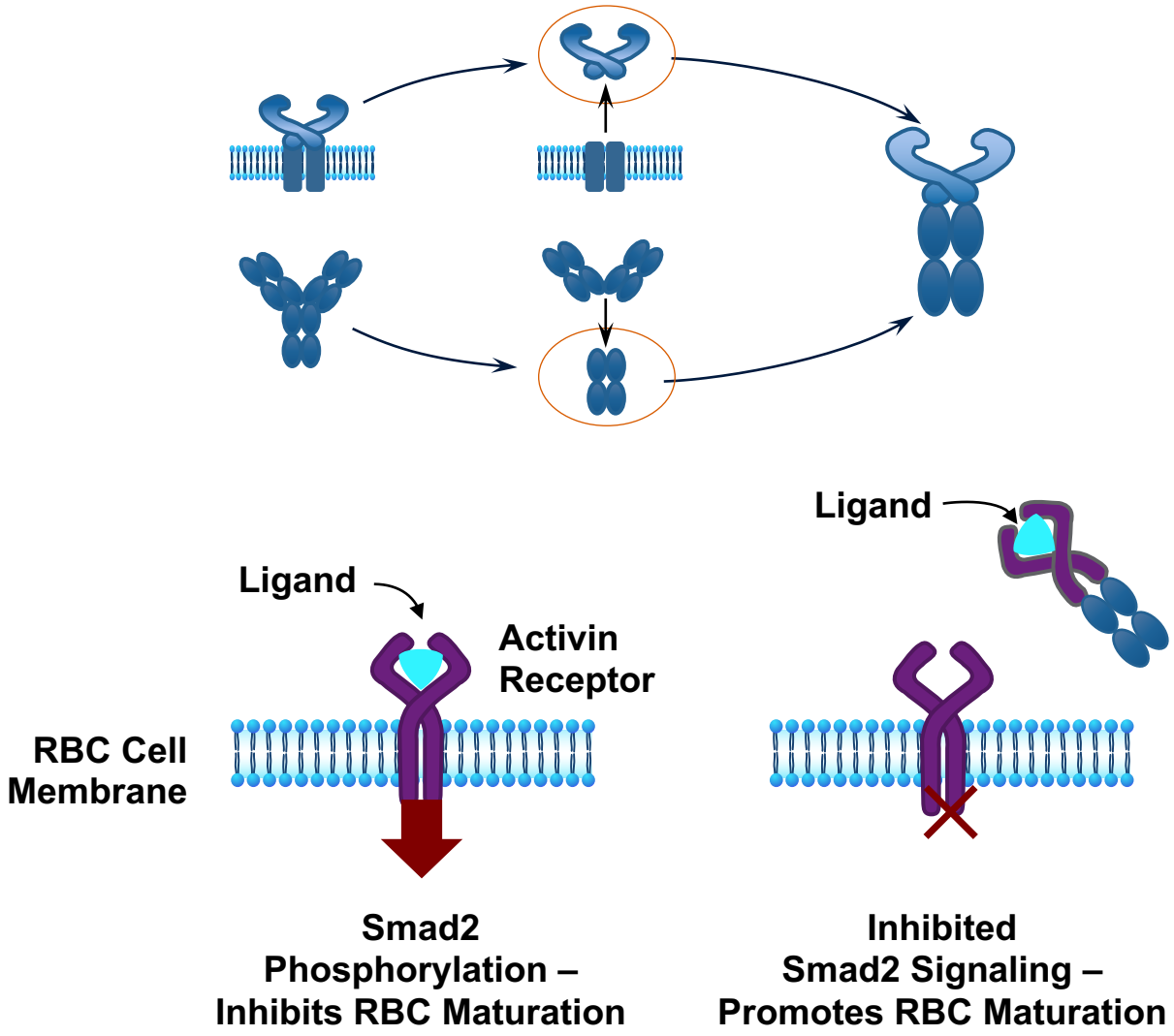
BAT, best available therapy; BID, twice daily; HR, hazard ratio; Hr_{adj}, adjusted HR.

Oh S, et al. *Blood*. 2022;140(suppl 1):1518–1521.

Anemia Therapy in Combination with a JAK Inhibitor

Luspatercept

- Fusion protein that acts as activin receptor ligand trap[2]
- Sequester ligands of TGFß superfamily, (eg, GDF11) secreted by BM stroma, that inhibit terminal erythropoiesis[1]



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

Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis (MF)

ACE-536-MF-001 (NCT03194542) is a phase 2, multicenter, open-label study

	Not receiving RUX	Receiving stable dose of RUX*
No RBC transfusions within last 12 weeks	Cohort 1 (n = 22)	Cohort 3A (n = 14)
Received RBC transfusions within last 12 weeks†	Cohort 2 (n = 21)	Cohort 3B‡ (n = 38)

21

Patients were treated with 1.0-1.75 mg/kg luspatercept in 21-day cycles

D169

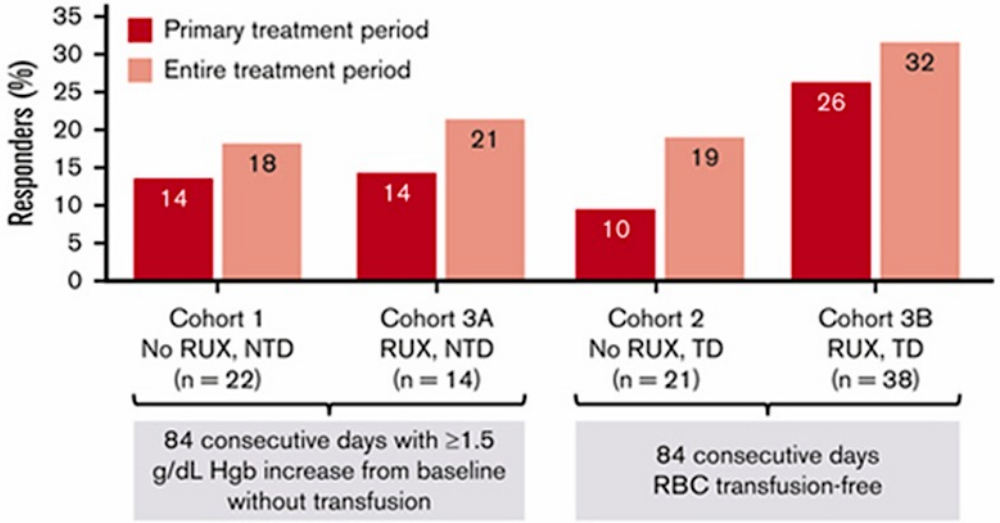
Response was assessed after the **primary treatment period** at D169 (week 24)

Patients with clinical benefit continued treatment into the **extension phase**

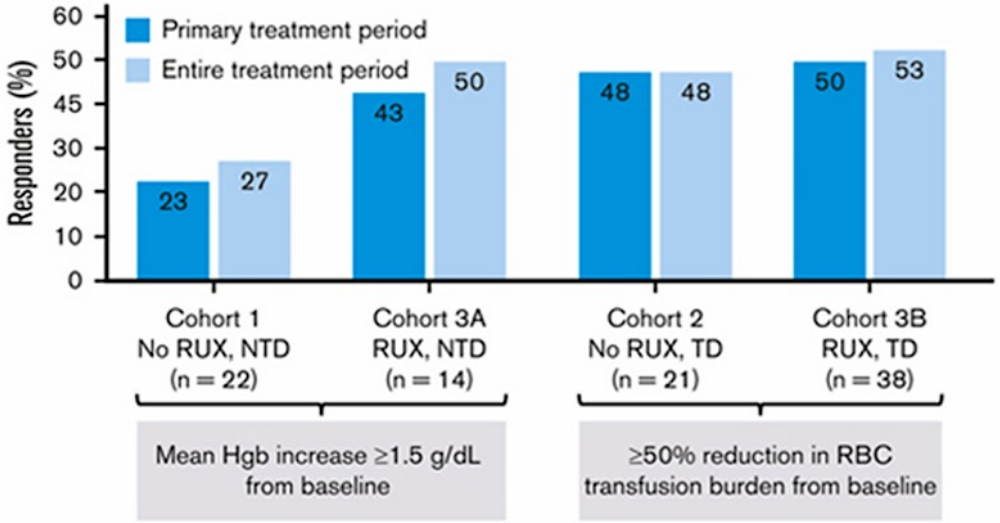
Follow-up is ongoing

*A stable daily dose of ruxolitinib for ≥16 weeks at enrollment; for patients enrolled in expansion cohort 3B, patients had received ruxolitinib treatment per local standard of care for 40 weeks (without interruptions ≥2 consecutive weeks) and a stable ruxolitinib dose for 16 weeks at enrollment. †4-12 units/84 days. ‡Including patients enrolled in the expansion cohort. D169, day 169; RBC, red blood cell; RUX, ruxolitinib.

Primary endpoint



Key secondary endpoints



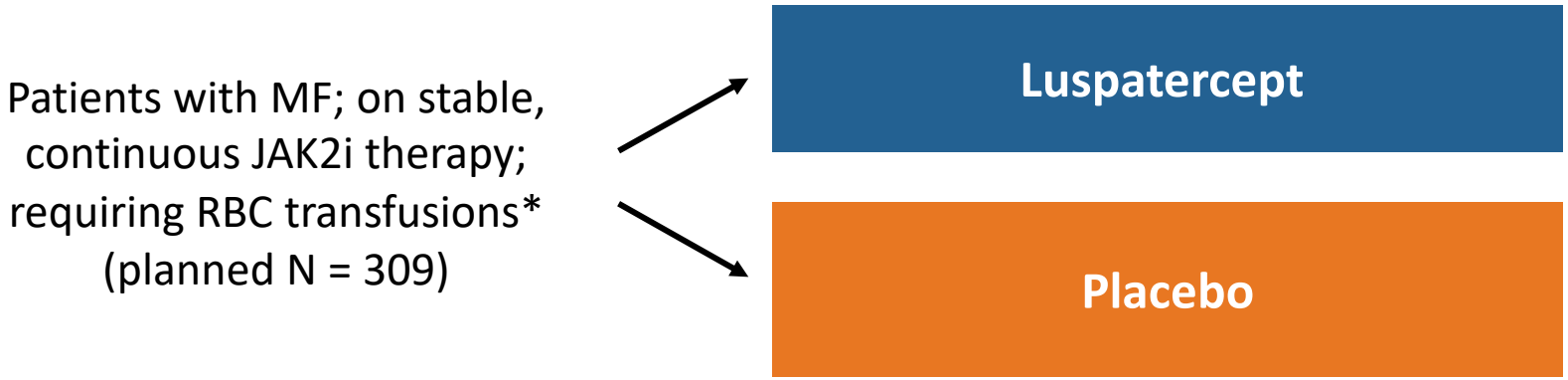
Hgb, hemoglobin; NTD, non-transfusion dependent; RBC, red blood cell; RUX, ruxolitinib; TD, transfusion-dependent.

- Luspatercept improved anemia in transfusion-dependent and non-transfusion-dependent patients with MF, particularly in patients who received concomitant ruxolitinib
- Luspatercept safety profile was consistent with previous studies; no new safety signals were identified

Gerds, et al. Blood Adv, 2024,

INDEPENDENCE: Luspatercept in Patients with MF and Anemia Receiving JAK Inhibitor Therapy

- International, double-blind, randomized phase III trial



- Primary endpoint: RBC-TI ≥12 wk at Wk 24
- Secondary endpoints: additional RBC-TI parameters, reduction of transfusion burden, Hgb increase, change in serum ferritin, AEs

*Transfusion frequency 4-12 RBC units/12 wk prior to randomization with no interval of >6 wk without a transfusion; transfusions scored in determining eligibility when given for treatment of symptomatic anemia with pretransfusion Hgb ≤9.5 g/dL or asymptomatic anemia with pretransfusion Hgb ≤7 g/dL.

NCT04717414.

Questions from General Medical Oncologists/Hematologists

- **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?**
- **An 80-year-old patient has been on treatment with ruxolitinib for MF for 2 years and his Hgb has dropped from a baseline of 10 g/dL to 7.0 g/dL. He reports worsening fatigue and dyspnea on exertion from anemia but no other symptoms. What would you recommend?**

Questions from General Medical Oncologists/Hematologists

- **A 75-year-old patient 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. The patient is not a candidate for transplant. What would you recommend?**

Questions from General Medical Oncologists/Hematologists

- **What features differentiate momelotinib from other JAK inhibitors? What mechanism explains the anemia benefit seen with momelotinib?**
- **Given the recent availability, has the panel switched over to momelotinib as their JAK inhibitor of choice for all patients with higher-risk MF who present with anemia (Hgb <10 g/dL)?**

Questions from General Medical Oncologists/Hematologists

- If a patient is unable to tolerate ruxolitinib due to worsening anemia, at what point do you decide to switch to momelotinib? If symptoms worsen with ruxolitinib, but counts are not low, would you consider switching? What would be your approach in such a case?
- What would you recommend for a patient with severe anemia and thrombocytopenia; symptomatic splenomegaly. Ruxolitinib SVR >50%. How do you choose among the JAK inhibitors in those that have both anemia and symptomatic splenomegaly?

Agenda

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

Module 2: Managing MF for Patients with Thrombocytopenia — Dr Bose

Module 3: Managing MF for Patients with Anemia — Dr Yacoub

Module 4: Future Directions in the Management of MF — Dr Fleischman

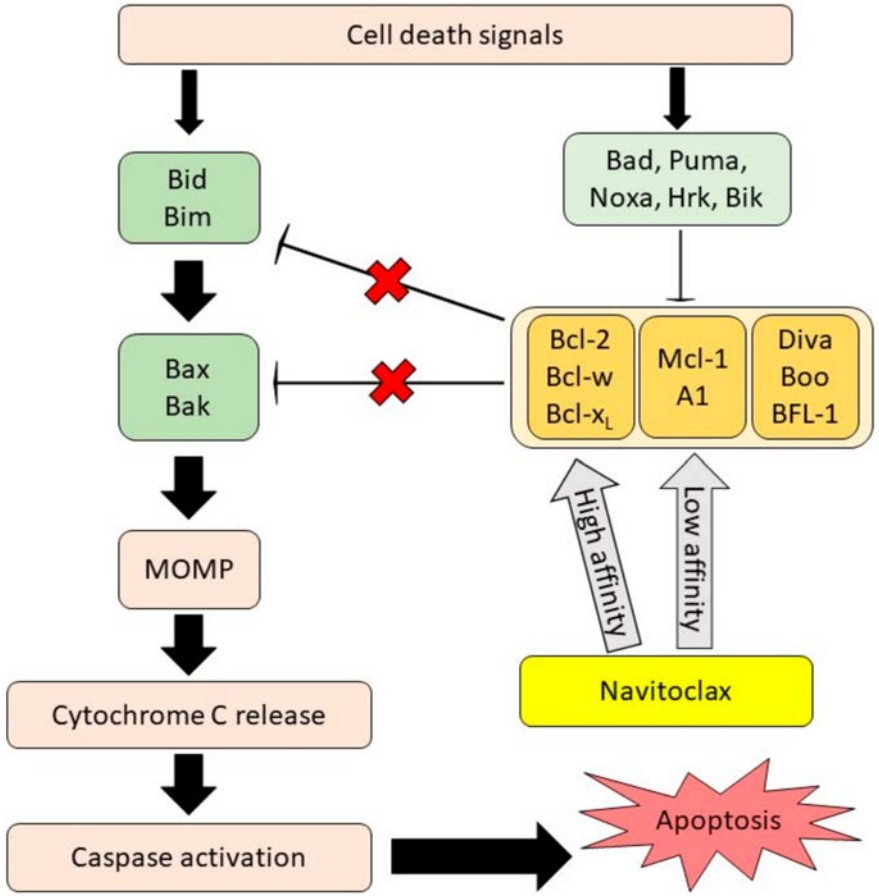
Future Directions in the Management of MF

Angela Fleischman MD PhD
Associate Professor, Division of Hematology/Oncology
University of California, Irvine

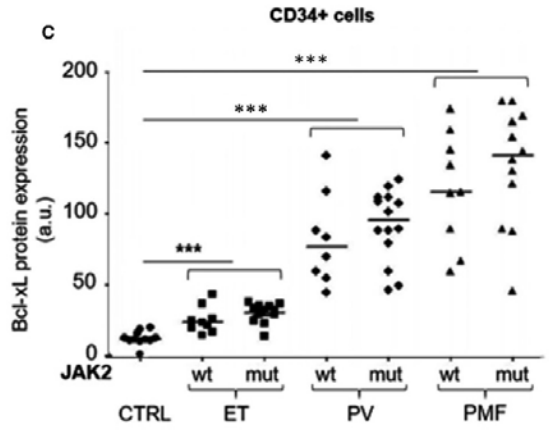
Novel agents in MF we'll be talking about today:

- Navitoclax (Bcl-xL inhibitor)
- Pelabresib (BET inhibitor)
- Selinexor (XPORT inhibitor)
- Imetelstat (telomerase inhibitor)

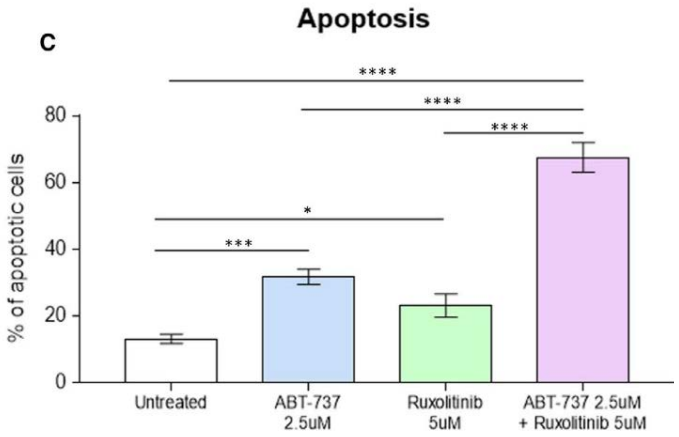
Navitoclax is a Bcl-xL inhibitor



Hisam et al. *Pharmaceutics* **2021**, *13*, 1353. https://doi.org/10.3390/pharmaceutics13091353



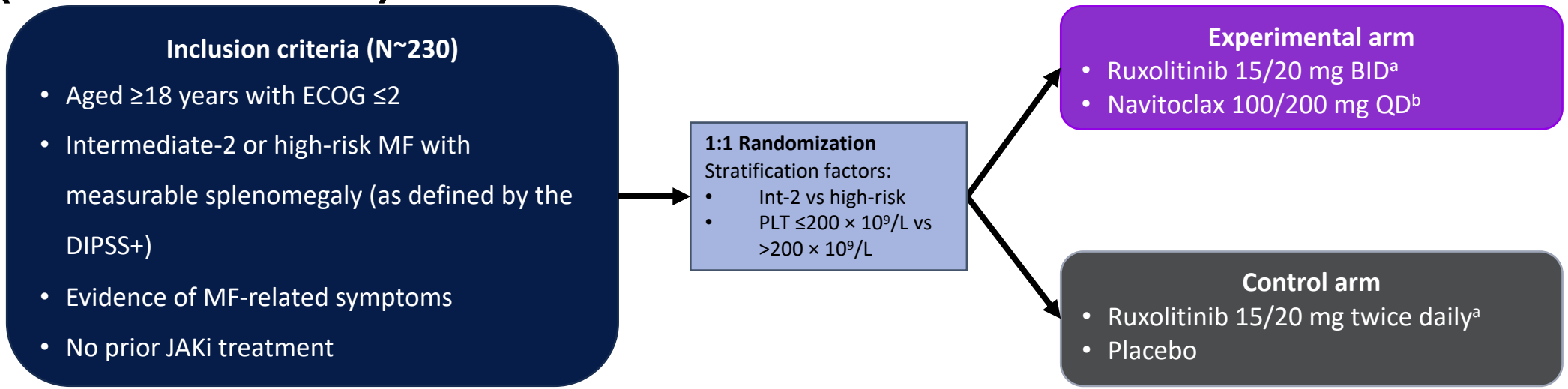
Bcl-xL is upregulated in MPN



Navitoclax + Ruxolitinib combo induces apoptosis in MPN patient samples

Petiti J et al. J Cell Mol Med. 2020 Sep;24(18):10978-10986. doi: 10.1111/jcmm.15730.

TRANSFORM-1: A Phase 3, Double-Blind, Multicenter Study (NCT04472598)



Endpoints

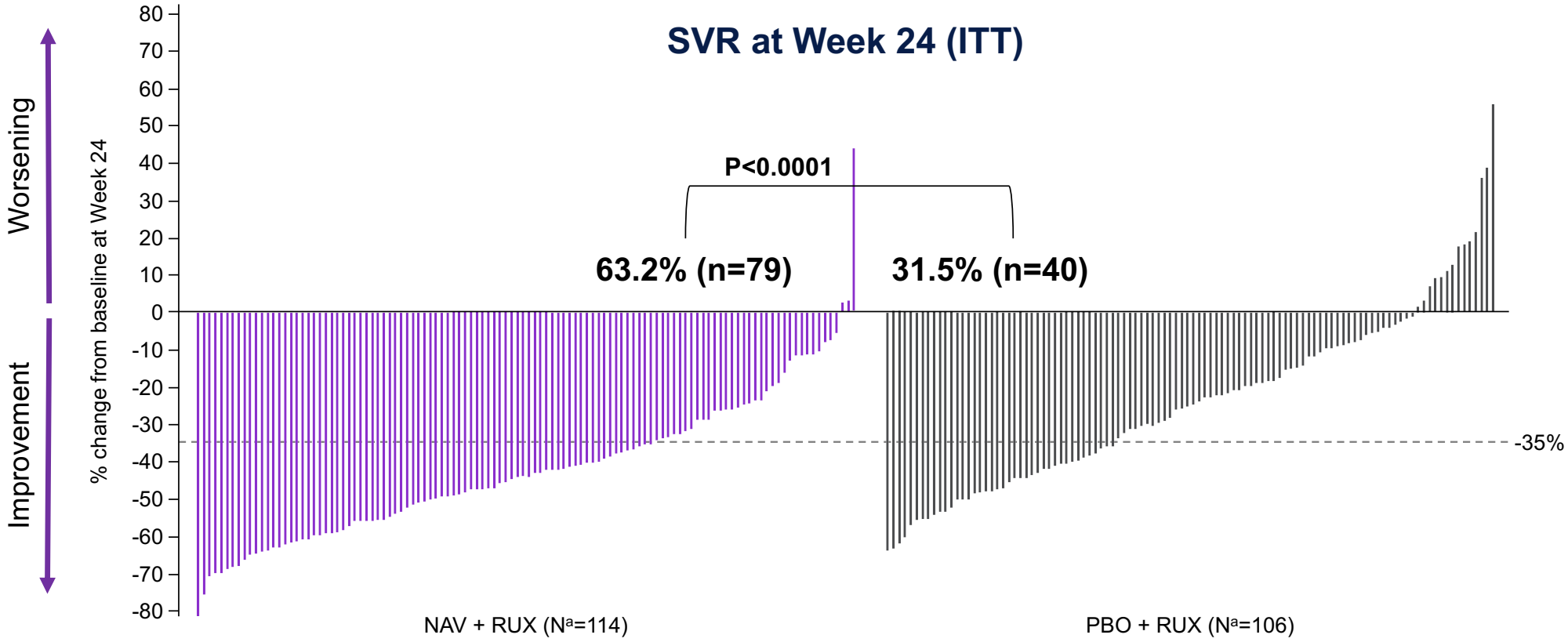
- Primary endpoint: SVR_{35W24} (assessed for superiority) as measured by MRI or CT scan, per IWG criteria
- Secondary endpoints:
  - Change in TSS[c] from baseline at Week 24 as measured by MFSAF v4.0
  - SVR_{35} at any time
  - Duration of SVR_{35}
  - Anemia response per IWG criteria
- Safety endpoints: AEs

[a]PLT >200×10⁹/L: 20 mg BID, PLT 100 × 10⁹/L to 200 × 10⁹/L: 15 mg BID; [b]PLT >150 × 10⁹/L: 200 mg QD, PLT ≤150 × 10⁹/L: 100 mg QD and escalate to 200 mg after ≥7 days, if tolerable (platelets ≥75 x 10⁹/L). [c]TSS includes patient assessed fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. AEs, adverse events; BID, twice daily; CT, computed tomography; DIPSS+, Dynamic International Prognostic Scoring System Plus; ECOG, Eastern Cooperative Oncology Group; Int-2, intermediate-2; IWG, International Working Group, JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PLT, platelet; QD, once daily; SVR_{35}, spleen volume reduction of ≥35%; SVR_{35W24}, SVR of ≥35% at Week 24; TSS, total symptom score.

Pemmaraju N et al. ASH 2023; Abstract 620

NAV + RUX Led to an SVR_{35W24} Rate That Was Twice as High as PBO + RUX

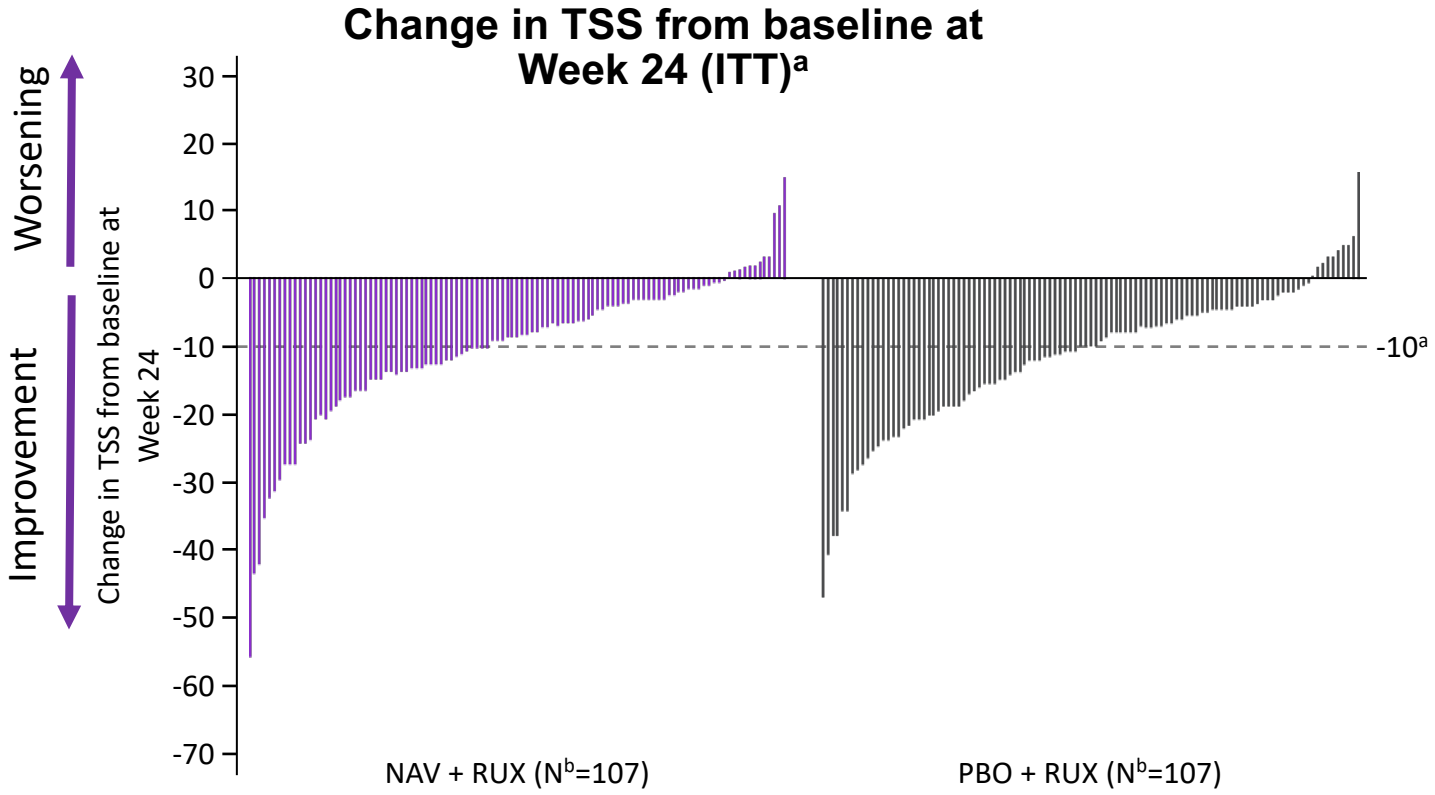
- A significantly higher number of patients achieved SVR_{35W24} in NAV + RUX arm compared with PBO + RUX [79 (63.2%) vs 40 (31.5%); P<0.0001]

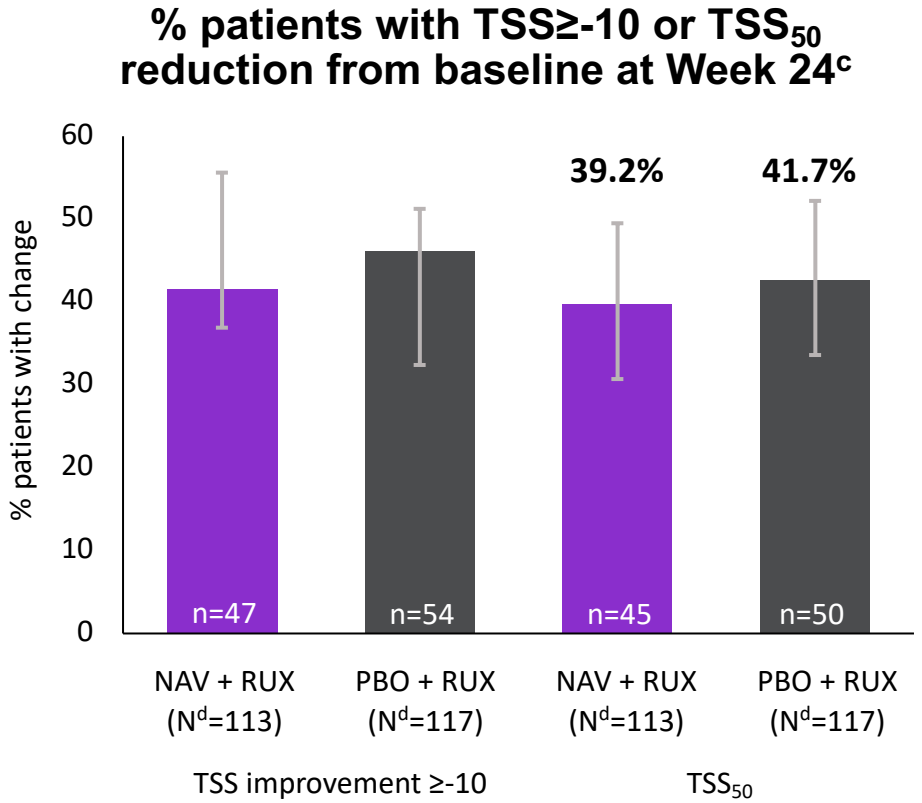


[a]Number of patients with available percent change in SVR_{35W24}.
ITT, intention-to-treat; NAV, navitoclax; PBO, placebo; RUX, ruxolitinib; SVR, spleen volume reduction; SVR_{35W24}, SVR of ≥35% at Week 24.

TSS Responses Were Not Significantly Different Between Groups

- At Week 24, the mean change in TSS from baseline was -9.7 (95% CI: -11.8, -7.6) with NAV + RUX compared with -11.1 (95% CI: -13.2, -9.1) with PBO + RUX arm in ITT population (P=0.2852)





TRANSFORM-1 closed early after failing to meet TSS endpoint (secondary endpoint)

[a]TSS was calculated based on reporting on the Myelofibrosis Symptom Assessment Form v4.0. A 10-point improvement (scale: 0–70) was estimated to be the level of change in TSS that patients would perceive to be meaningful improvement in MF-related symptoms; [b]Number of patients with available data for change in TSS at Week 24; [c]Error bars represent 95% CI. [d]Includes patients with baseline TSS ≥12 or at least 2 symptoms with a baseline symptom score ≥3 with TSS available at baseline and week 24. CI, confidence interval; ITT, intention-to-treat; NAV, navitoclax; RUX, ruxolitinib; TSS, total symptom score

Pemmaraju N et al. ASH 2023; Abstract 620
Ross DM et al. *Blood* (2024) 144 (16): 1679–1688.

AEs of Thrombocytopenia, Anemia, and Neutropenia Were Common But Manageable

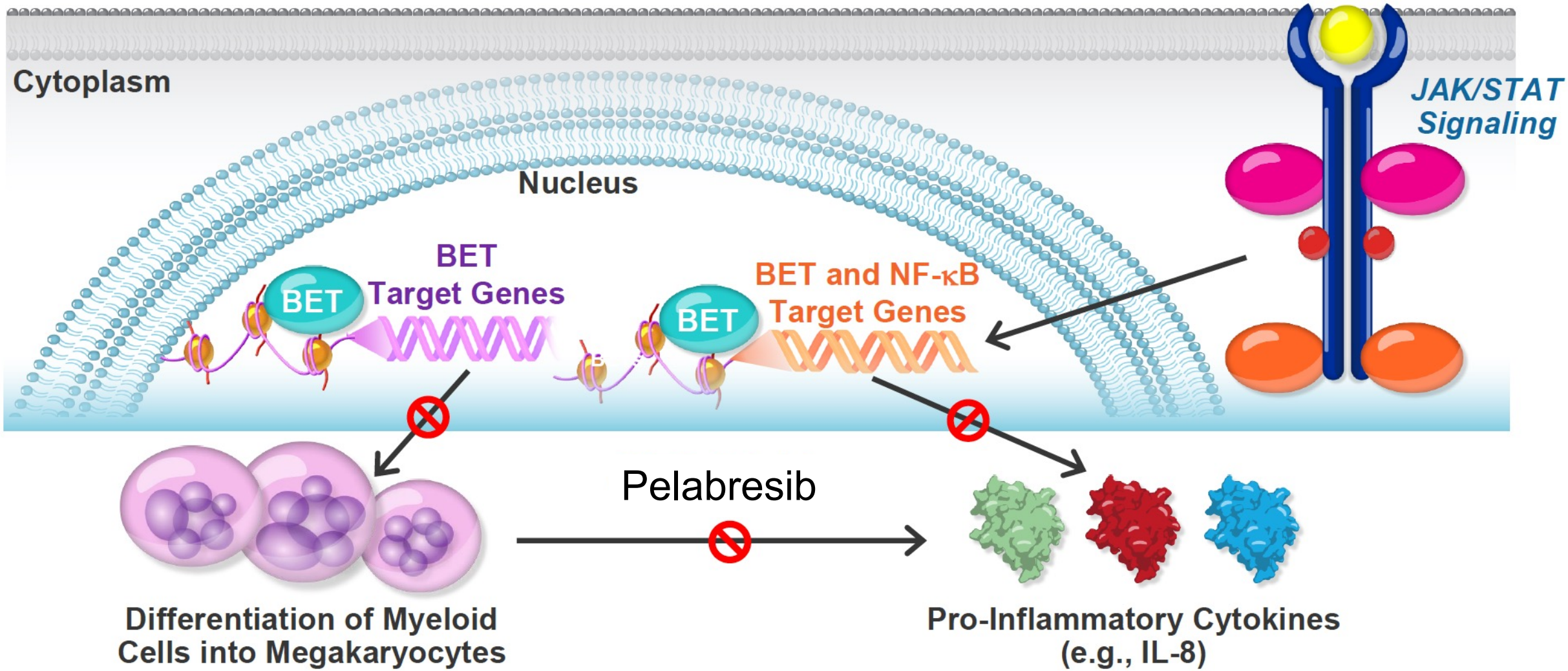
	NAV + RUX (N=124)[a] N (%)		PBO + RUX (N=125)[a] N (%)	
Any AE	124 (100)		121 (97)	
Any AE grade ≥3	105 (85)		87 (70)	
Most common AEs (>30% patients receiving NAV)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Thrombocytopenia	112 (90)	63 (51)	62 (50)	19 (15)
Anemia	74 (60)	57 (46)	61 (49)	49 (39)
Neutropenia	56 (45)	47 (38)	7 (6)	5 (4)
Diarrhea	42 (34)	6 (5)	17 (14)	0
Bleeding/hemorrhagic events	30 (24)	2 (2)	27 (22)	7 (6)
COVID-19	26 (21)	1 (1)	23 (18)	7 (6)
Contusion	13 (10)	0	7 (6)	0
Abdominal pain	11 (9)	1 (1)	8 (6)	1 (1)
Abdominal pain upper	9 (7)	1 (1)	10 (8)	1 (1)
Bone pain	9 (7)	0	6 (5)	0
Any serious AE	32 (26)		40 (32)	
AEs leading to dose reduction				
Navitoclax/placebo	101 (81)		39 (31)	
Ruxolitinib	112 (90)		76 (61)	
AE leading to dose interruption				
Navitoclax/placebo	87 (70)		44 (35)	
Ruxolitinib	78 (63)		41 (33)	
All deaths	13 (10)		13 (10)	
Deaths ≤30 days following last dose of study drug	6 (5)		5 (4)	

- Most commons AEs were thrombocytopenia, anemia, neutropenia, and diarrhea
- Most common serious AEs reported were
  - COVID-19 pneumonia and pneumonia in 3 patients each with NAV + RUX and 2 each with PBO + RUX
- Dose reductions and interruptions were mostly due to thrombocytopenia, none were due to bleeding

[a]All AEs are presented as n (%).
AEs, adverse events, NAV, navitoclax; PBO, placebo; RUX, ruxolitinib.

Pemmaraju N et al. ASH 2023; Abstract 620

BET inhibitor mechanism of action in MF



MANIFEST-2: randomized, double-blind, Phase 3 study

Study population

JAKi-naïve patients with MF (N=430)
(primary or post-ET/PV)

- DIPSS Int-1 or higher
- Splenomegaly (≥450 cm^3) by CT/MRI
- TSS ≥10 (≥3 for two symptoms, MFSAF v4.0)

Double-blind randomization (1:1)

1:1 randomization stratified by:

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

Treatment arm

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

21-day cycles

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

Primary endpoint

- SVR35 at Week 24

Key secondary endpoints

- TSS absolute change from baseline at Week 24
- TSS50 at Week 24

Safety

- AEs of all grades and serious AEs

AE, adverse event; BID, twice daily; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int, intermediate; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imagining; PO, orally; PV, polycythemia vera; QD, once daily; SVR35, ≥35% reduction in spleen volume; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score.

*The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD; †Ruxolitinib was started at 10 mg BID (baseline platelet count 100–200 × 10^9/L) or 15 mg BID (baseline platelet count >200 × 10^9/L) with a mandatory dose increase by 5 mg BID after one cycle and a maximum dose of 25 mg BID per label.

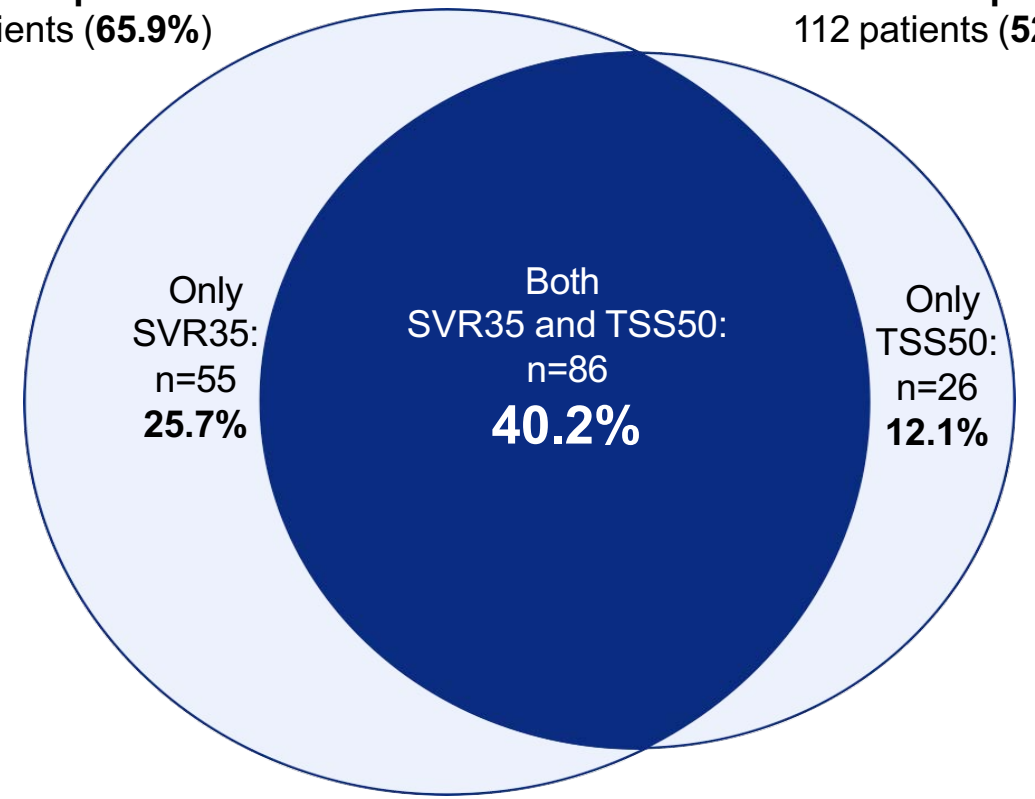
Harrison CN, et al. *Future Oncol*. 2022;18(27):2987-29977.

Two-fold increase in patients achieving both SVR35 and TSS50 with pelabresib + ruxolitinib vs placebo + ruxolitinib

Pelabresib + ruxolitinib (N=214)

SVR35 response:
141 patients (**65.9%**)

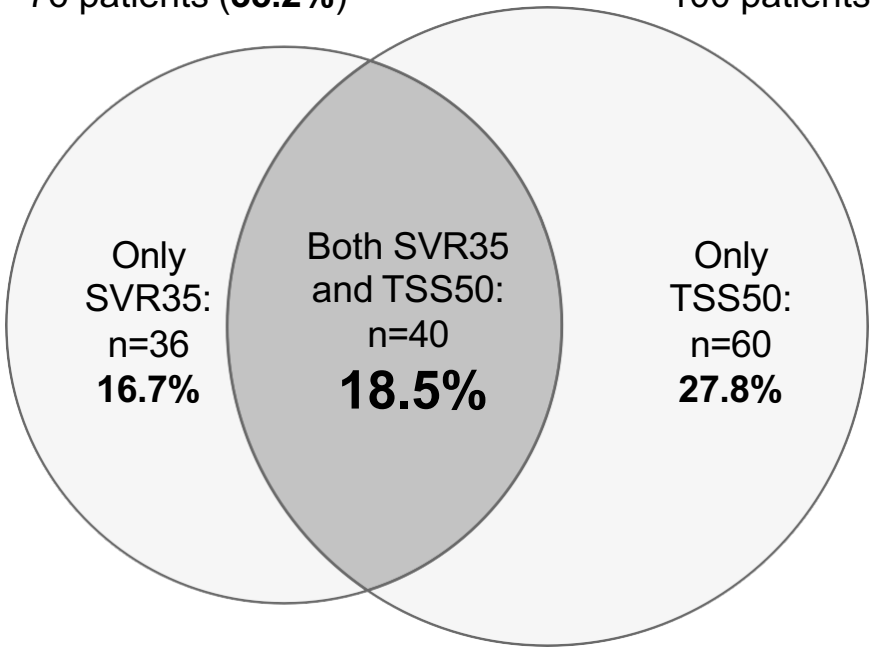
TSS50 response:
112 patients (**52.3%**)



Placebo + ruxolitinib (N=216)

SVR35 response:
76 patients (**35.2%**)

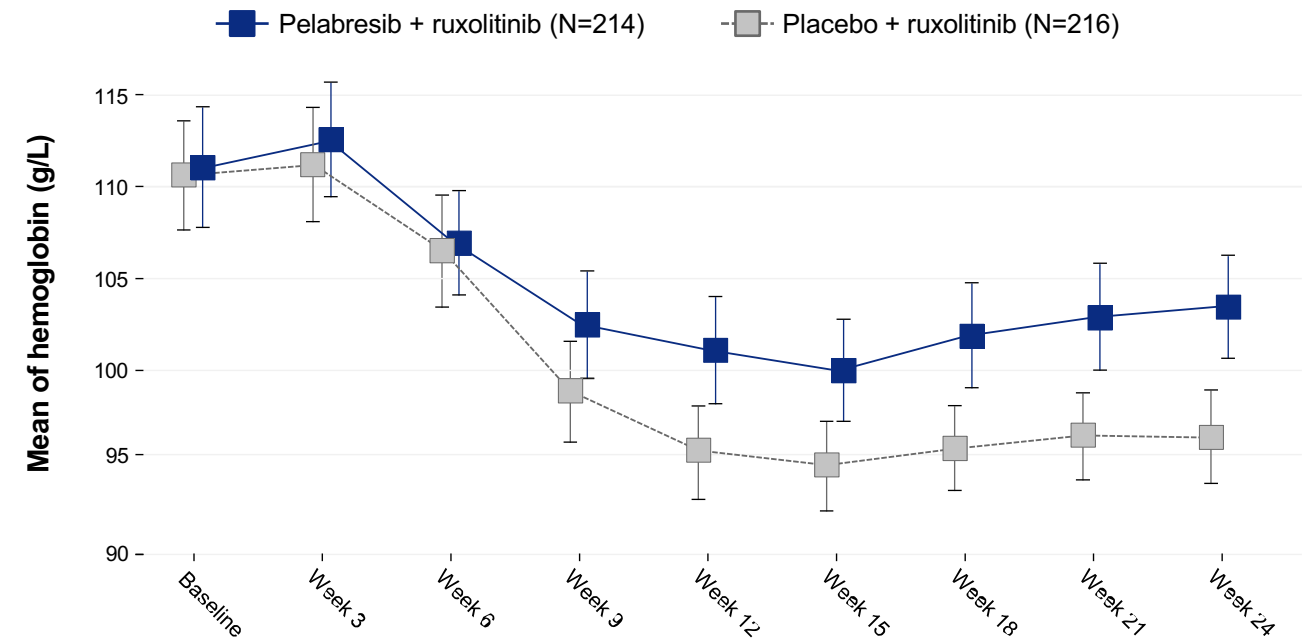
TSS50 response:
100 patients (**46.3%**)



Data cut off: August 31, 2023. N, number of patients; SVR35, ≥35% reduction in spleen volume; TSS50, ≥50% reduction in total symptom score. Diagrams are not drawn to scale.

Rampal R et al. ASCO 2024; Abstract 6502

A numerically greater proportion of patients achieved hemoglobin response with pelabresib + ruxolitinib vs placebo + ruxolitinib



Number of patients

Pelabresib + ruxolitinib	212	204	209	199	193	189	186	185	184
Placebo + ruxolitinib	214	206	211	209	207	205	204	199	196

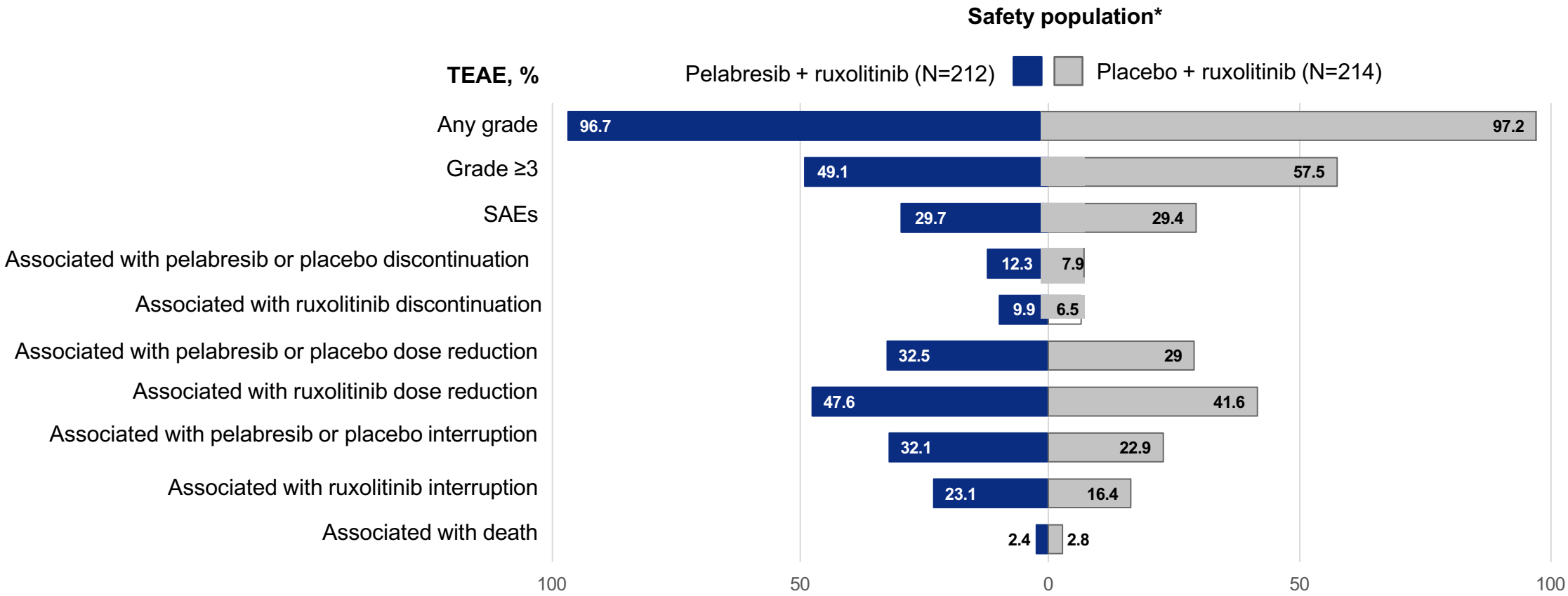
ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Hemoglobin response* ≥1.5 g/dL mean increase (95% CI)	9.3% (5.45, 13.25)	5.6% (2.50, 8.61)
Patients requiring RBC transfusion during screening, n (%)	35 (16.4)	25 (11.6)
Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)	66 (30.8)	89 (41.2)

Preliminary Analyses from Data cut off: August 31, 2023. CI, confidence interval; RBC, red blood cell. *Hemoglobin response is defined as a ≥1.5 g/dL mean increase in hemoglobin from baseline in the absence of transfusions during the previous 12 weeks. Baseline hemoglobin defined as the last assessment prior to or on Cycle 1 Day 1, regardless of blood transfusions. A similar effect was observed across DIPSS categories.

Rampal R et al. ASCO 2024; Abstract 6502

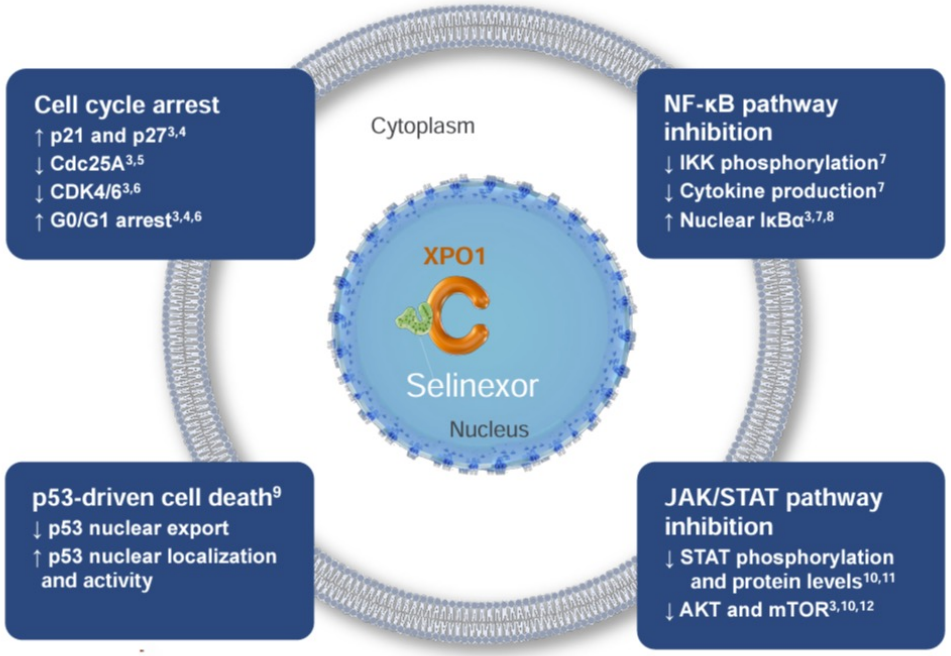
The safety profile of the pelabresib + ruxolitinib combination was consistent with prior trials



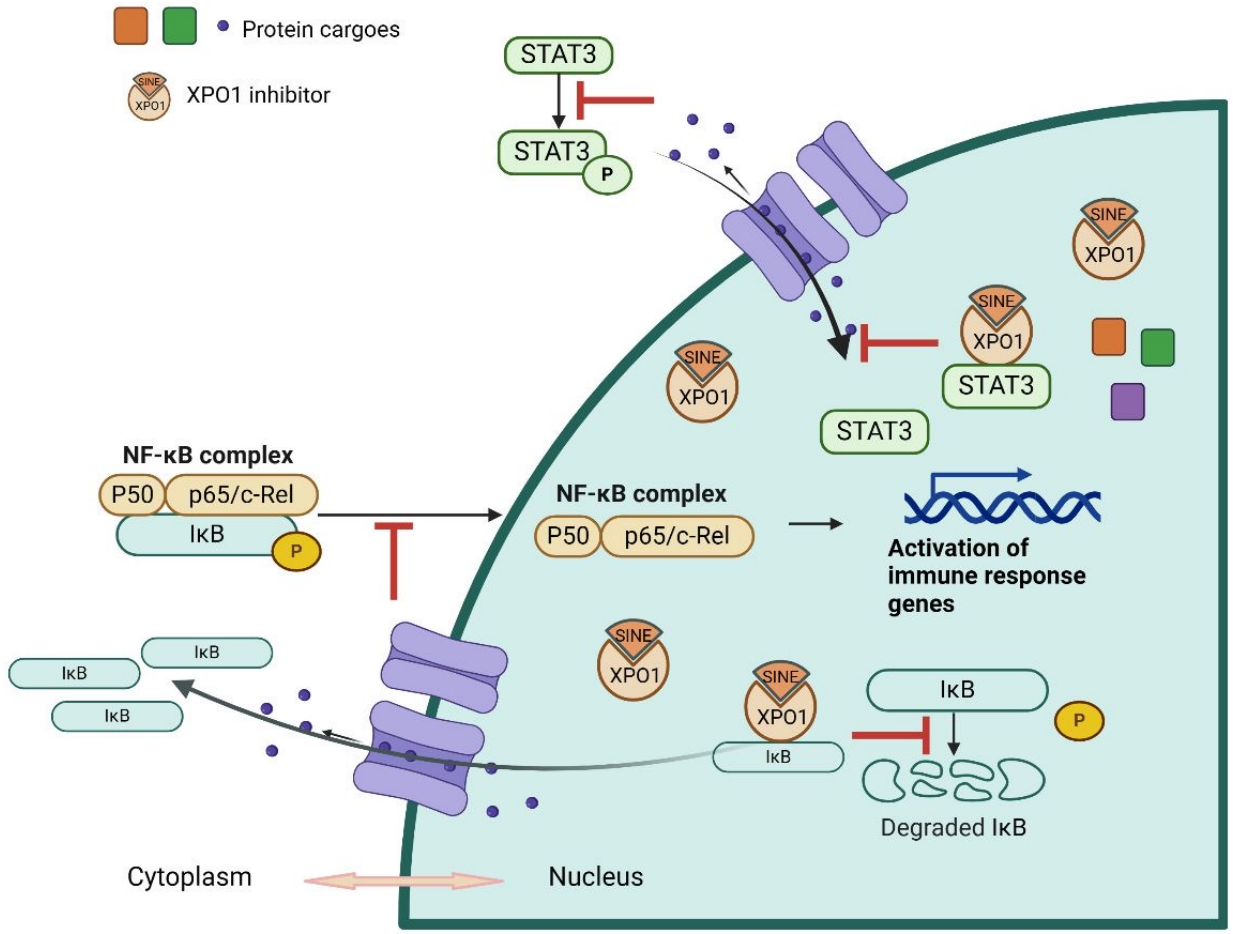
Preliminary Analyses from Data cut off: August 31, 2023. TEAE, treatment-emergent adverse event; SAE, serious adverse event. *Safety population: received at least one dose of study drug. TEAEs are regardless of relationship to study drug. A TEAE for the double-blinded treatment period is defined as an adverse event that has a start date on or after the first dose of the pelabresib/placebo and before 30 days after the last dose of pelabresib/placebo or before the start of alternative (off-study) treatment for MF, whichever occurs first. MF, myelofibrosis.

Rampal R et al. ASCO 2024; Abstract 6502

Selinexor's mechanism of action in MF

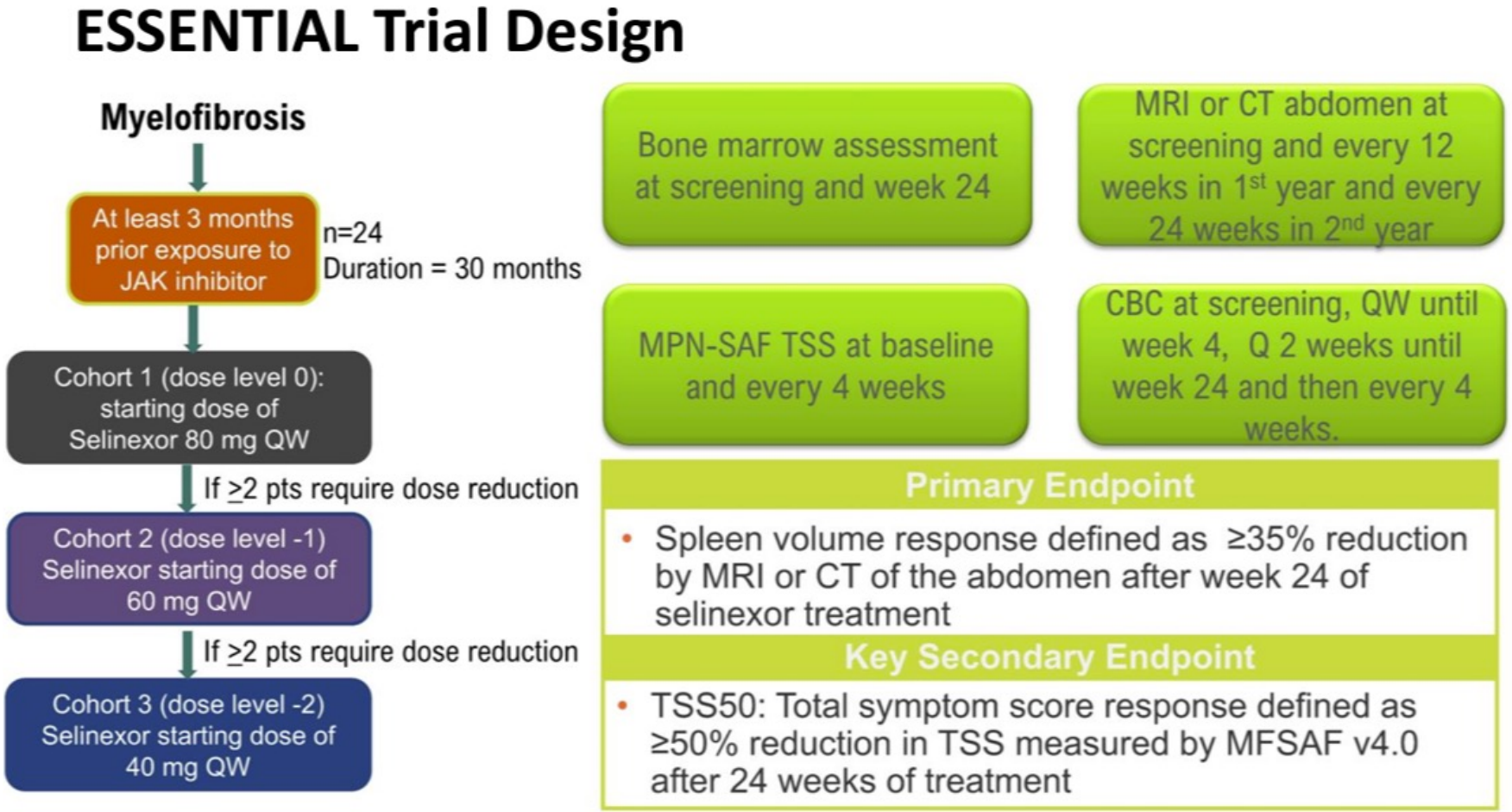


Tantravahi SK et al, EHA 2024; Abstract P1069



Li D et al, Front Immunol. 2024 May 10;15:1398927. doi: 10.3389/fimmu.2024.1398927

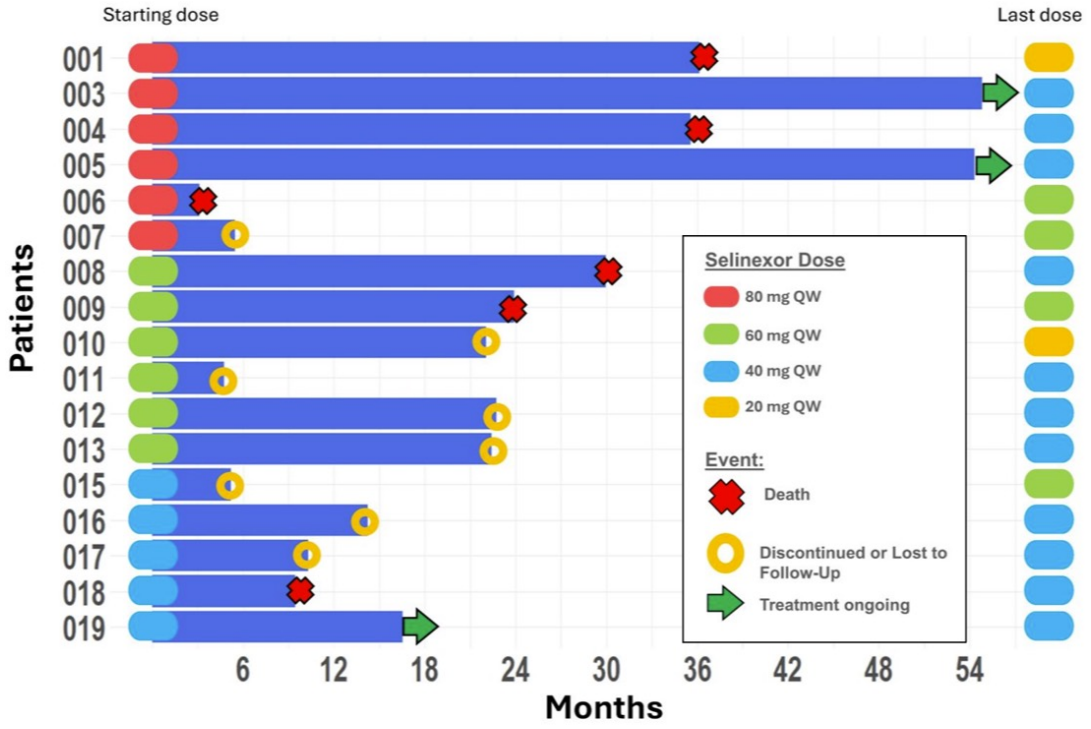
Selinexor in Patients with Myelofibrosis Refractory or Intolerant to JAK Inhibitors



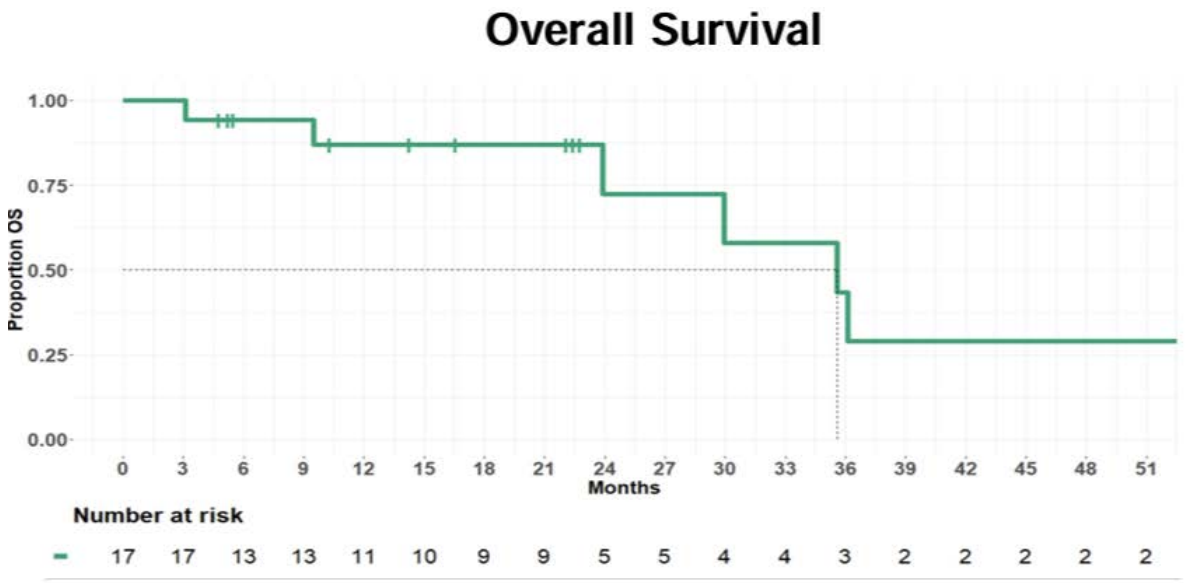
Tantravahi SK et al, SOHO 2024; Abstract MPN-652

Selinexor in Patients with Myelofibrosis Refractory or Intolerant to JAK Inhibitors

Treatment Duration and Disposition

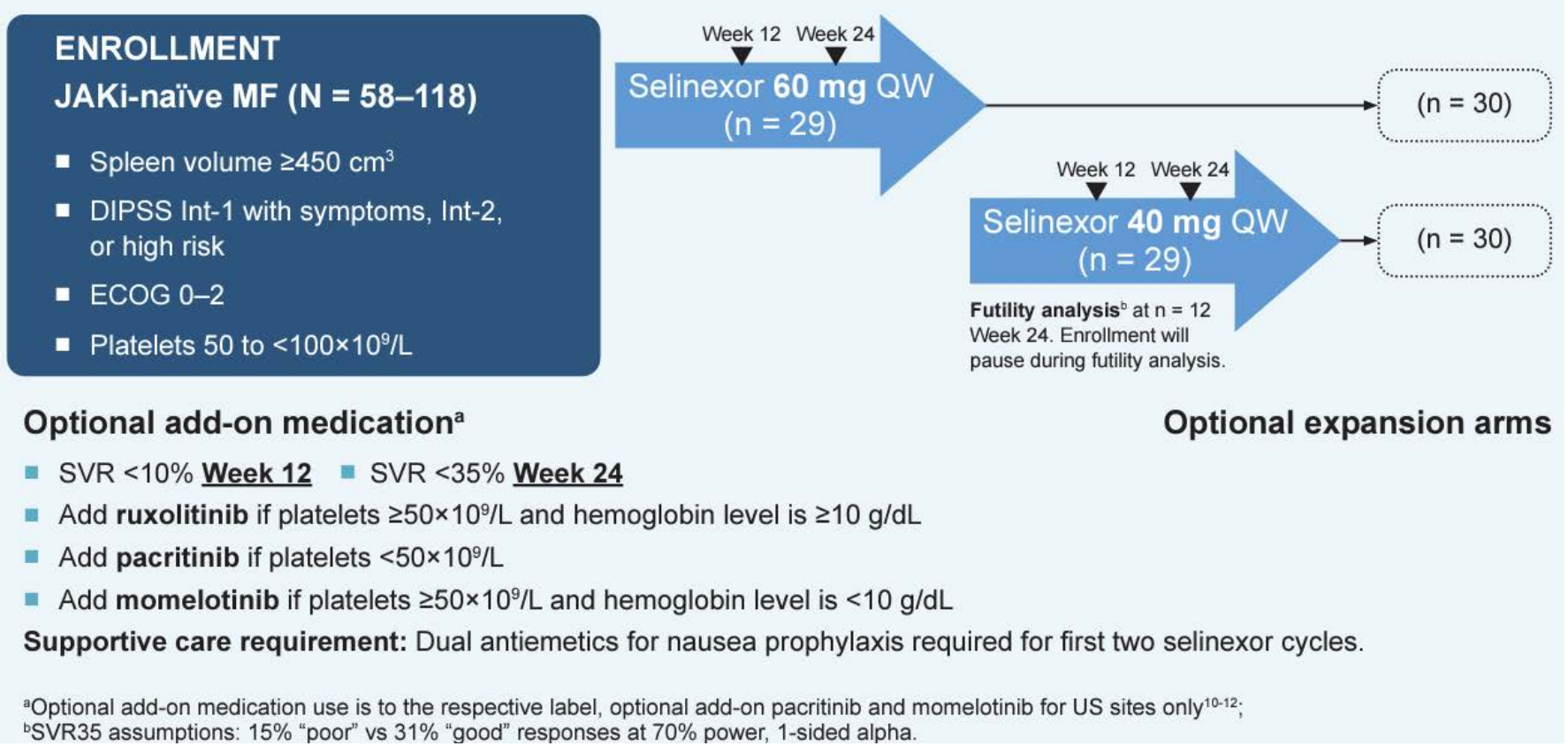


For patients with treatment ongoing, last dose received is shown as colored bar



Tantravahi SK et al, SOHO 2024; Abstract MPN-652

SENTRY-2 (XPORT-MF-044): A Phase 2 Study to Evaluate the Efficacy and Safety of Selinexor Monotherapy in Patients with JAKi-naïve Myelofibrosis and Moderate Thrombocytopenia (NCT05980806)

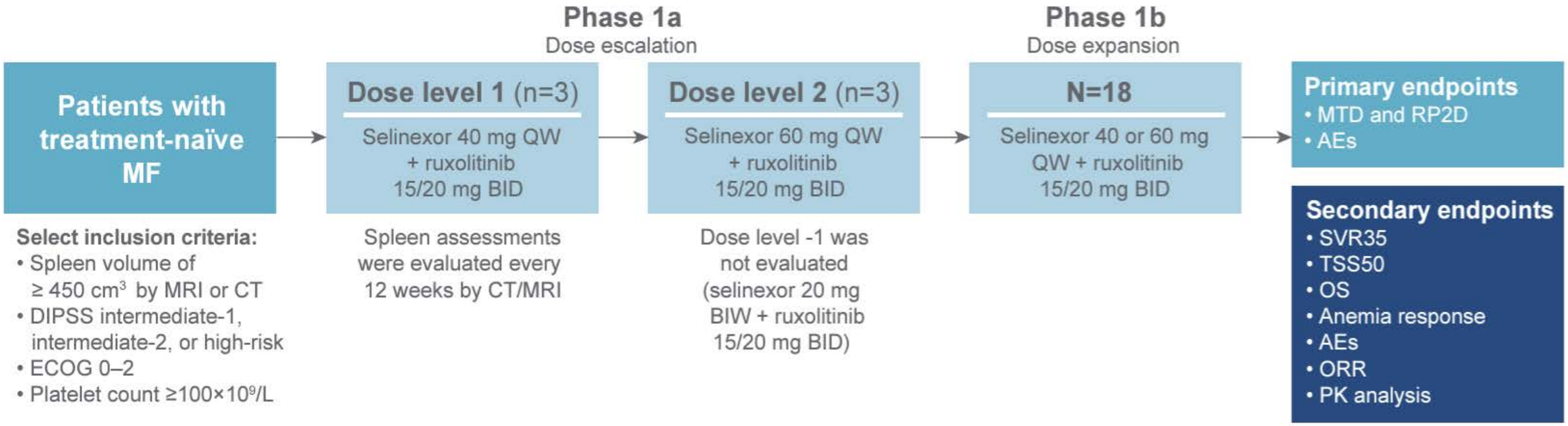


Primary Endpoint:

Spleen volume reduction ≥35% (SVR35) at Week 24

SENTRY (XPORT-MF-034) (NCT04562389)

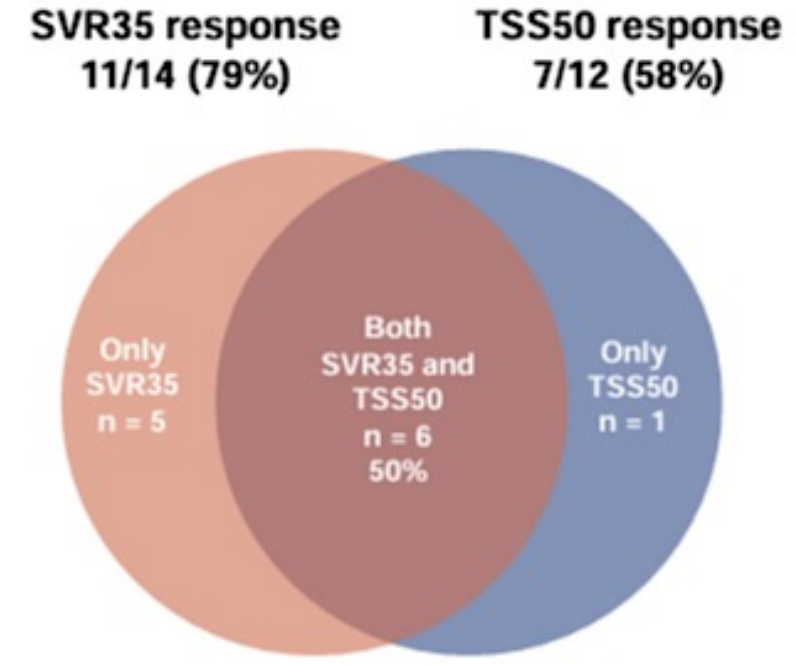
Phase III study of selinexor in combination with ruxolitinib in JAK inhibitor-naïve MF



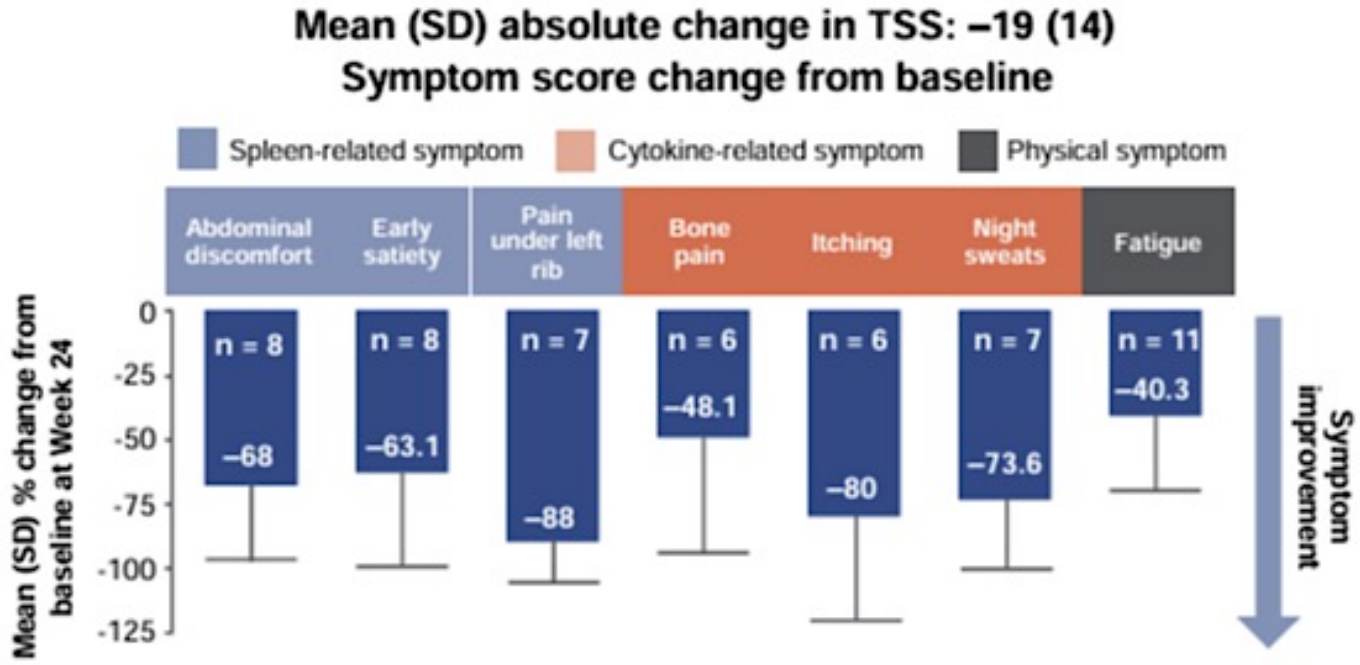
Cycle is defined as 28 days.

SENTRY – Impact on Spleen and Symptoms

Overlap of SVR35 and TSS50 response at Week 24

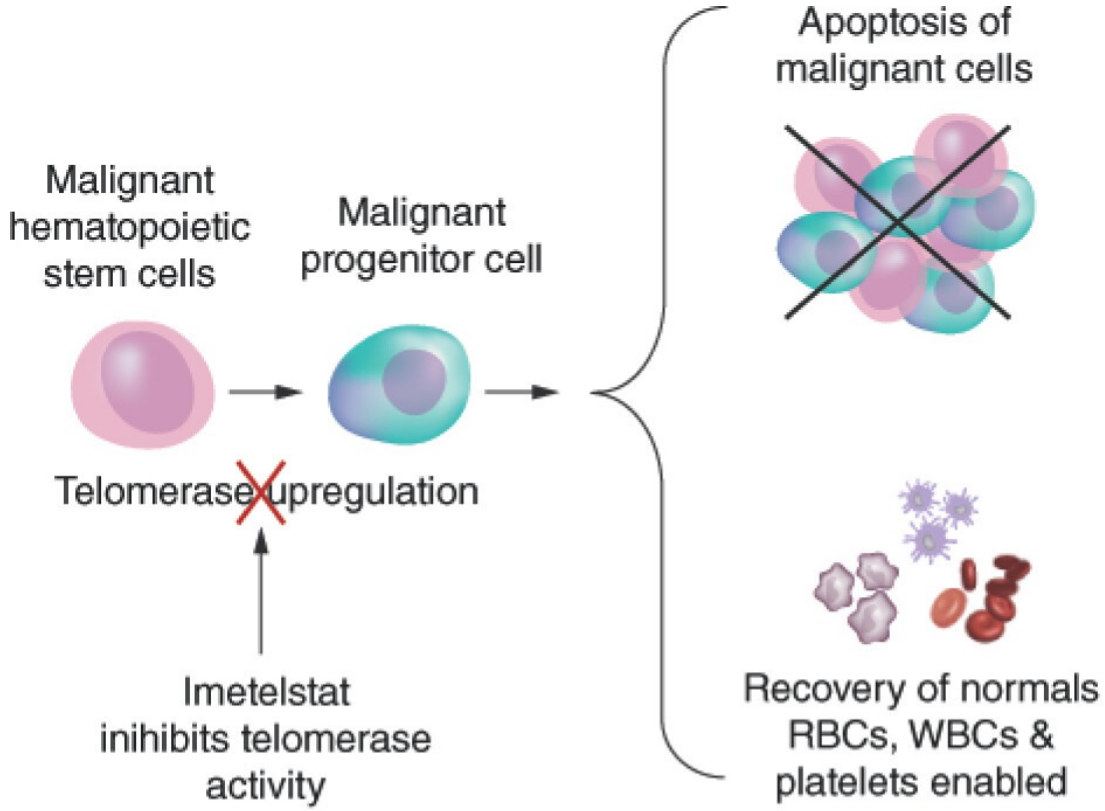


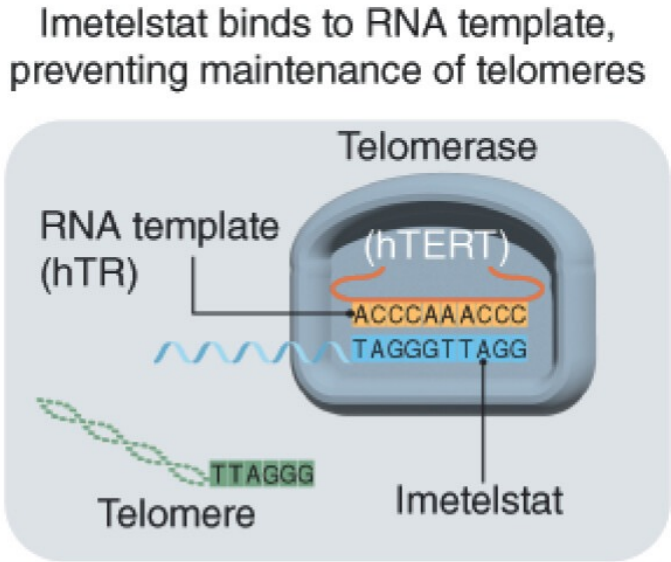
Symptom improvement at Week 24



Ali H, et al. AACR 2023; Abstract CT261
Ali H, et al. ASCO 2023; Abstract 7063

Mechanism of action of imetelstat





Mechanism of action:

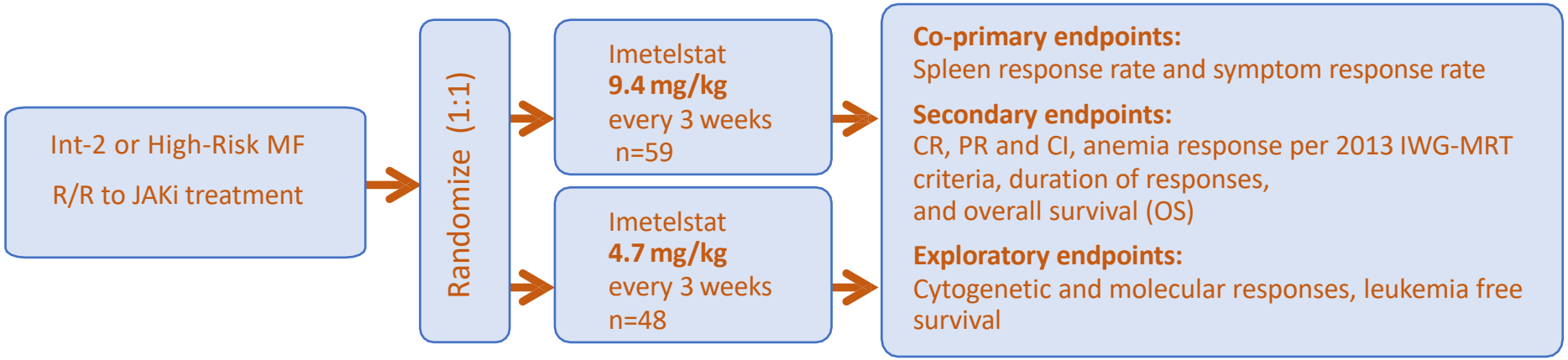
– **Potent competitive inhibitor of telomerase activity**

– **Structure:** proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently bound lipid tail to increase cell permeability

– **Disease-modifying potential:** selective killing of malignant stemand progenitor cells enabling normal blood cell production

Mascarenhas J et al. *Future Oncology*, *18*(22), 2393–2402. https://doi.org/10.2217/fon-2022-0235

MYF2001 Phase 2 Study of Imetelstat in R/R MF



Patient Population:

- Patients with Intermediate-2 or High-risk MF (Int-2/High-risk) who have relapsed after or are refractory to prior treatment with a janus kinase (JAK) inhibitor
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy, OR
    - Worsening splenomegaly at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT, or
      - Increase in spleen size by palpation

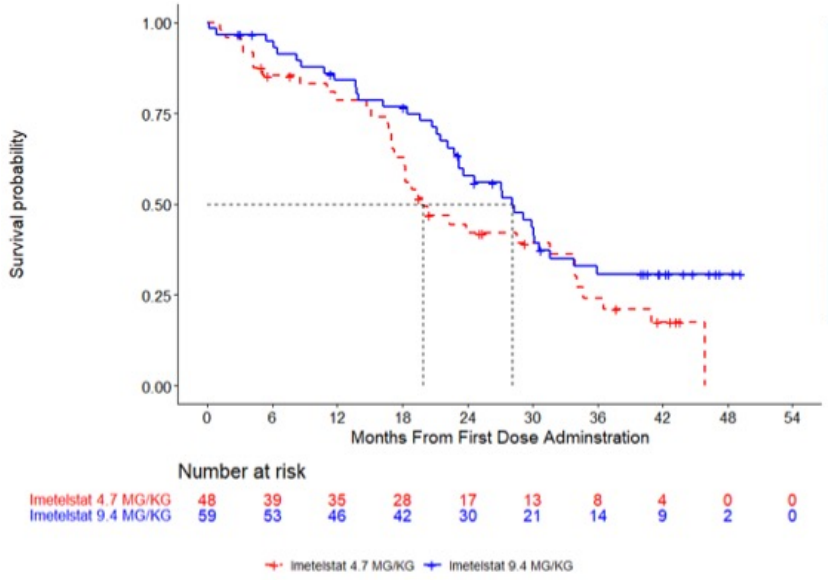
MYF2001 Key Safety Data

	4.7 mg/kg (n=48)		9.4 mg/kg (n=59)	
n (%)	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Hematologic (≥ 10% in either arm)				
Thrombocytopenia	11 (23)	11 (23)	29 (49)	24 (41)
Anemia	15 (31)	15 (31)	26 (44)	23 (39)
Neutropenia	5 (10)	5 (10)	21 (36)	19 (32)
Leukopenia	3 (6)	3 (6)	8 (14)	8 (14)
Non-hematologic (≥ 20% in either arm)				
Nausea	15 (31)	1 (2)	20 (34)	2 (3)
Vomiting	10 (21)	1 (2)	8 (14)	1 (2)
Diarrhea	18 (38)	2 (4)	18 (31)	0
Fatigue	10 (21)	3 (6)	16 (27)	4 (7)
Cough	11 (23)	0	9 (15)	0
Dyspnea	9 (19)	6 (13)	14 (24)	3 (5)
Abdominal Pain	10 (21)	2 (4)	14 (24)	3 (5)
Asthenia	9 (19)	3 (6)	14 (24)	6 (10)
Pyrexia	8 (17)	1 (2)	13 (22)	3 (5)
Edema peripheral	13 (27)	0	11 (19)	0

Mascarenhas J, et al, ASH 2018

MYF2001 Key Efficacy Data

Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
Symptoms Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)
Reduction in bone marrow fibrosis , n/N (%)	4/20 (20.0%)	16/37(43.2%)
≥ 25% Reduction in VAF of JAK2, CALR or MPL , n/N (%)	1/18 (5.6%)	8/19 (42.1%)

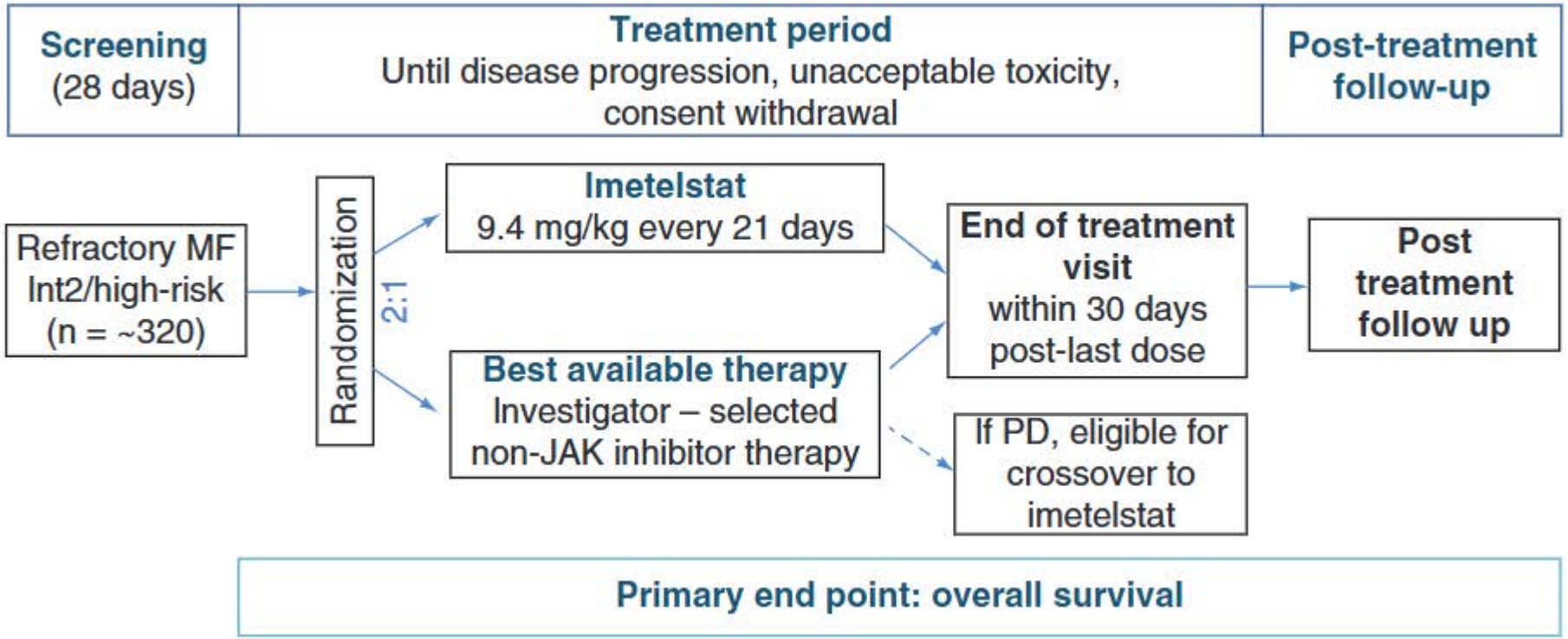


	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Number of events, n (%)	35 (72.9%)	36 (61.0%)
Number censored, n (%)	13 (27.1%)	23 (39.0%)
Median Overall Survival (months) (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
12-months survival rate % (95% CI)	78.6 (63.9, 87.9)	84.0 (71.6, 91.4)
24-months survival rate % (95% CI)	42.0 (27.4, 56.0)	57.9 (43.6, 69.7)

Similar results were observed when sensitivity analyses accounted for confounding factors of subsequent therapies, including stem cell transplantation and dose escalation from 4.7 mg/kg to 9.4 mg/kg.

Mascarenhas J, et al, ASH 2018
Mascarenhas J, et al, EHA 2020; Abstract EP1107

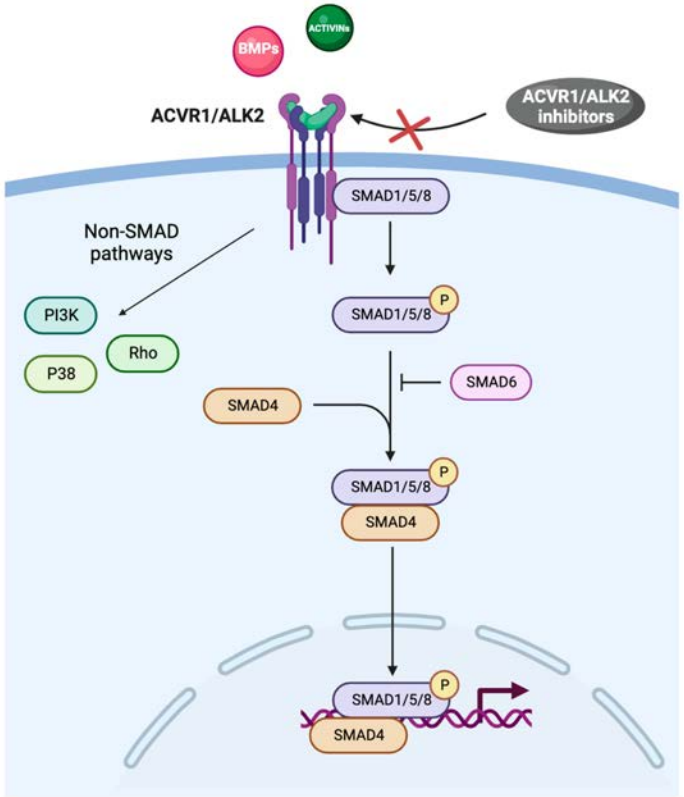
Imetelstat in intermediate-2 or high-risk myelofibrosis refractory to JAK inhibitor: IMpactMF phase III study design



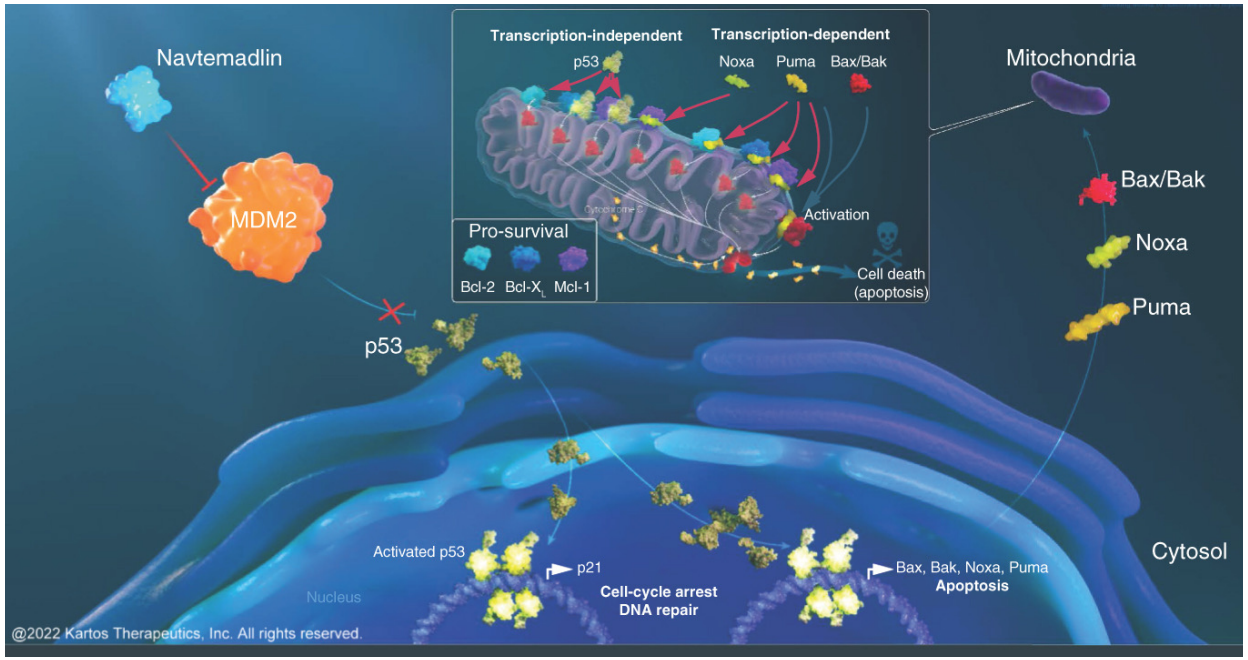
Mascarenhas J, et al. *Future Oncology*, *18*(22), 2393–2402.

Other promising investigational agents and strategies

zilurgisertib



navtemadlin



Questions from General Medical Oncologists/Hematologists

- Is there any promising role for selinexor or pelabresib?
- Does it make sense to combine selinexor with ruxolitinb? If so, why?
- What is your perspective on the efficacy and tolerability of the combination in JAK inhibitor-naïve MF from the early data reported?
- What is the optimal approach to antiemetic prophylaxis for patients receiving selinexor?

Questions from General Medical Oncologists/Hematologists

- What is imetelstat and when should it be used? Is it used alone or in combination with a JAK inhibitor?
- What is the current evidence on imetelstat monotherapy in JAK inhibitor-refractory MF?
- Are there any other promising investigational agents and strategies for MF?

What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Acute Myeloid Leukemia

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Alexander Perl, MD
Richard M Stone, MD
Eunice S Wang, MD
Andrew H Wei, MBBS, PhD

Moderator

Eytan M Stein, MD

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What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Multiple Myeloma

A CME Friday Satellite Symposium and Webcast Preceding the 66th ASH Annual Meeting

Friday, December 6, 2024

3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)

Faculty

Professor Philippe Moreau, MD
Robert Z Orlowski, MD, PhD
Noopur Raje, MD
Paul G Richardson, MD

Moderator

Sagar Lonial, MD

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