Bergamaschi Micaela
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Medicina Interna1 P.O. Pon

Mielofibrosi idiopatica: inibitori di Jak vecchi, nuovi e oltre

Non ho conflitti di interesse

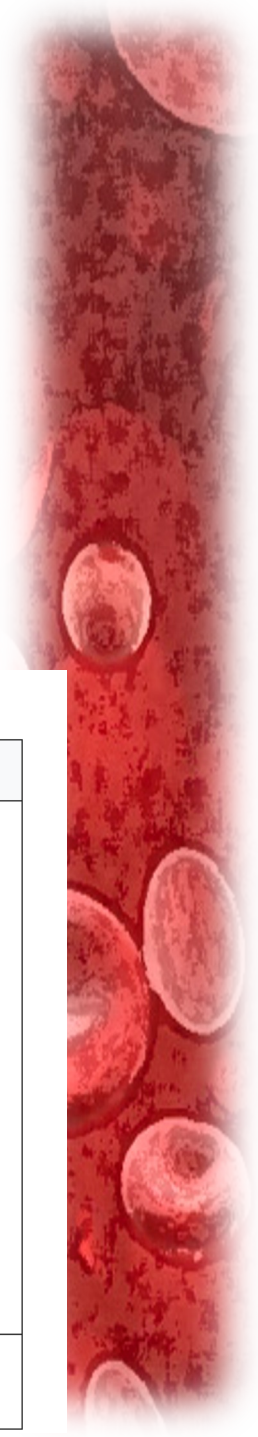
International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Diagnostic criteria for primary myelofibrosis (PMF)

PMF, early/prefibrotic stage (pre-PMF)	**PMF, overt fibrotic stage**
Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* bone marrow fibrosis grade < 2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. *JAK2*, *CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§ 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met	Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. *JAK2*, *CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§ 3. Diagnostic criteria for ET, PV, *BCR::ABL1*-positive CML, myelodysplastic syndrome, or other myeloid neoplasms‖ are not met
Minor criteria ▪ Anemia not attributed to a comorbid condition ▪ Leukocytosis ≥ 11 × 10^9/L ▪ Palpable splenomegaly ▪ Lactate dehydrogenase level above the above the reference range	Minor criteria ▪ Anemia not attributed to a comorbid condition ▪ Leukocytosis ≥ 11 × 10^9/L ▪ Palpable splenomegaly ▪ Lactate dehydrogenase level above the above the reference range ▪ Leukoerythroblastosis
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations	

Diagnostic criteria for polycythemia vera (PV) and post-PV myelofibrosis (post-PV MF)

PV	Post-PV MF
Major criteria 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass* 2. Presence of *JAK2* V617F or *JAK2* exon 12 mutation† 3. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia Minor criterion ▪ Subnormal serum erythropoietin level	Required criteria 1. Previous established diagnosis of PV 2. Bone marrow fibrosis of grade 2 or 3 Additional criteria 1. Anemia (ie, below the reference range given age, sex, and altitude considerations) or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion‡	The diagnosis of post-PV MF is established by all required criteria and at least 2 additional criteria



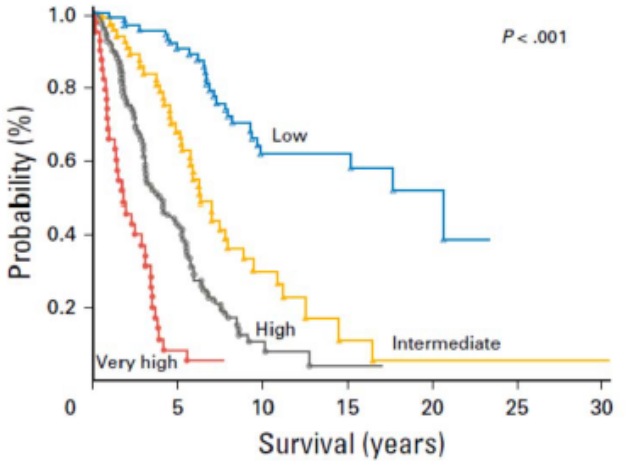
Diagnostic criteria for essential thromocythemia (ET) and post-ET myelofibrosis (post-ET MF)

ET	Post-ET MF
Major criteria 1. Platelet count ≥ 450 × 10^9/L 2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters*; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis† 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met 4. *JAK2*, *CALR*, or *MPL* mutation‡ Minor criteria ▪ Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis‖	Required criteria 1. Previous established diagnosis of ET 2. Bone marrow fibrosis of grade 2 or 3 Additional criteria 1. Anemia (ie, below the reference range given age, sex, and altitude considerations) and a >2 g/dL decrease from baseline hemoglobin concentration 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Elevated LDH level above the reference range 5. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria	The diagnosis of post-ET MF is established by all required criteria and at least 2 additional criteria

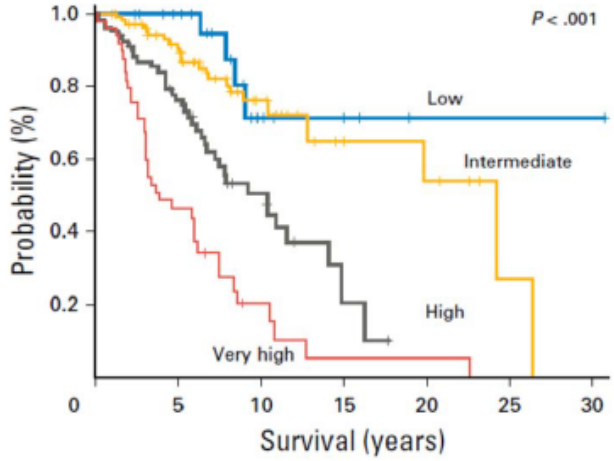
MIPSS70Plus:

- Punteggio di 1
  - Hb < 10
  - blasti circolanti ≥ 2
  - Sintomi costituzionali
  - 1 HMR
- Punteggio di 2
  - Assenza di mutazione di CARLty1
  - 2 o più HMR
- Punteggio di 3
  - Cariotipo sfavorevole**
- 4 categorie di rischio
  - Low (punteggio 0-2)
  - Intermediate(punteggio 3)
  - High(punteggio 4-6)
  - Very high (punteggio ≥7)

Guglielmelli et al, JCO 9 Dec 2017
**Tefferi et al, submitted



At risk time					
Low	86	67	28	17	4
Intermediate	63	38	10	12	1
High	127	43	4	1	0
Very high	39	3	0	0	0



At risk time					
Low	25	20	6	3	1
Intermediate	108	74	24	7	0
High	79	50	18	2	0
Very high	49	18	4	1	0

Leukemia (2017) 31, 2726–2731

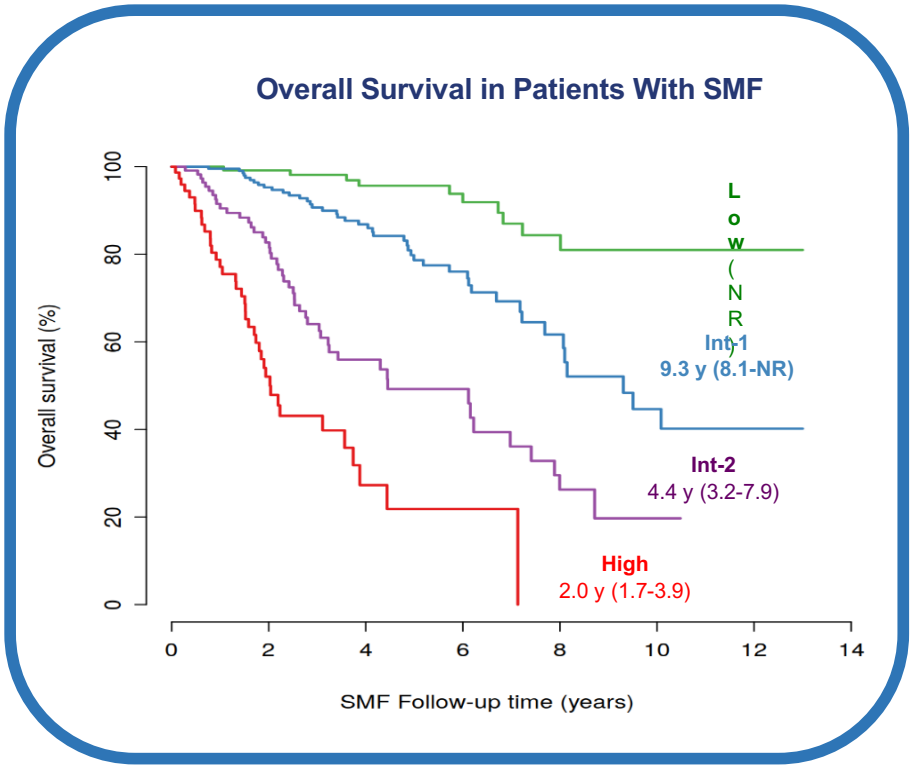
ORIGINAL ARTICLE

A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis

Covariate	HR (95% CI)	*P* value	Points
Age at MF diagnosis[a]	1.07 (1.05-1.09)	< .0001	0.15
Hb < 11 g/dL	2.3 (1.6-3.3	< .0001	2
PLT < 150 × 10^9/L	1.7 (1.2-2.5)	.006	1
PB blasts ≥ 3%	2.9 (1.8-4.8	< .0001	2
CALR wild-type	2.6 (1.2-5.3)	.001	2
Constitutional symptoms	1.5 (1.0-2.0)	.03	1

[a] Continuous, 0.15 point/year.

Hb, hemoglobin; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; NR, not reached; PLT, platelet count; PB, peripheral blood; SMF, secondary MF.

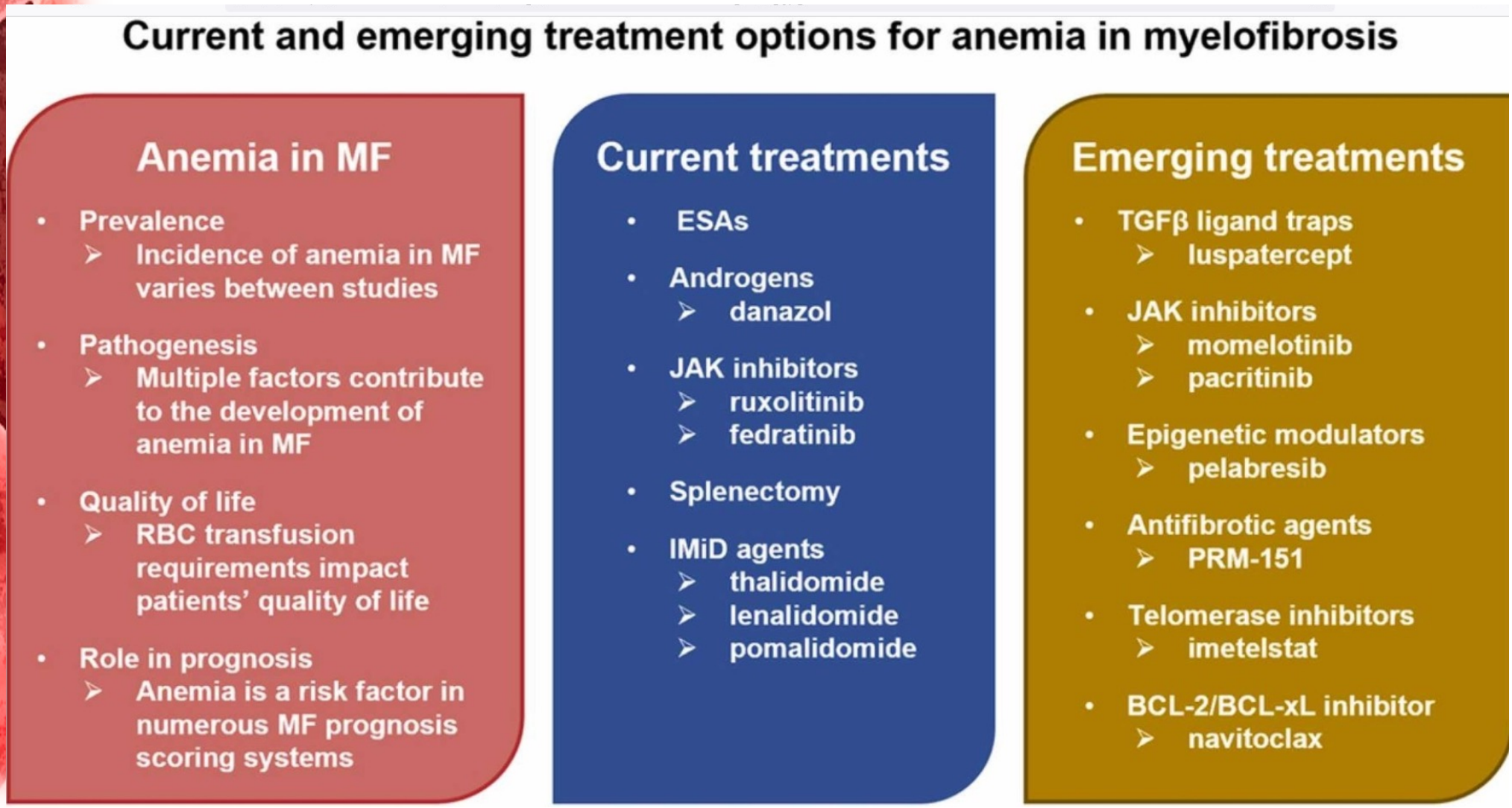


MYSEC-PM Calculator: http://www.mysec-pm.eu

Passamonti F, et al. *Leukemia*. 2017;31(12):2726-2731.

Anemia in myelofibrosis: current and emerging treatment options

Passamonti F, Harrison CN, Mesa RA, Kiladjian JJ, Vannucchi AM, Verstovsek S.. Crit Rev Oncol Hematol. 2022;180:103862. doi:10. 1016/j.critrevonc.2022.103862



Algoritmo terapeutico

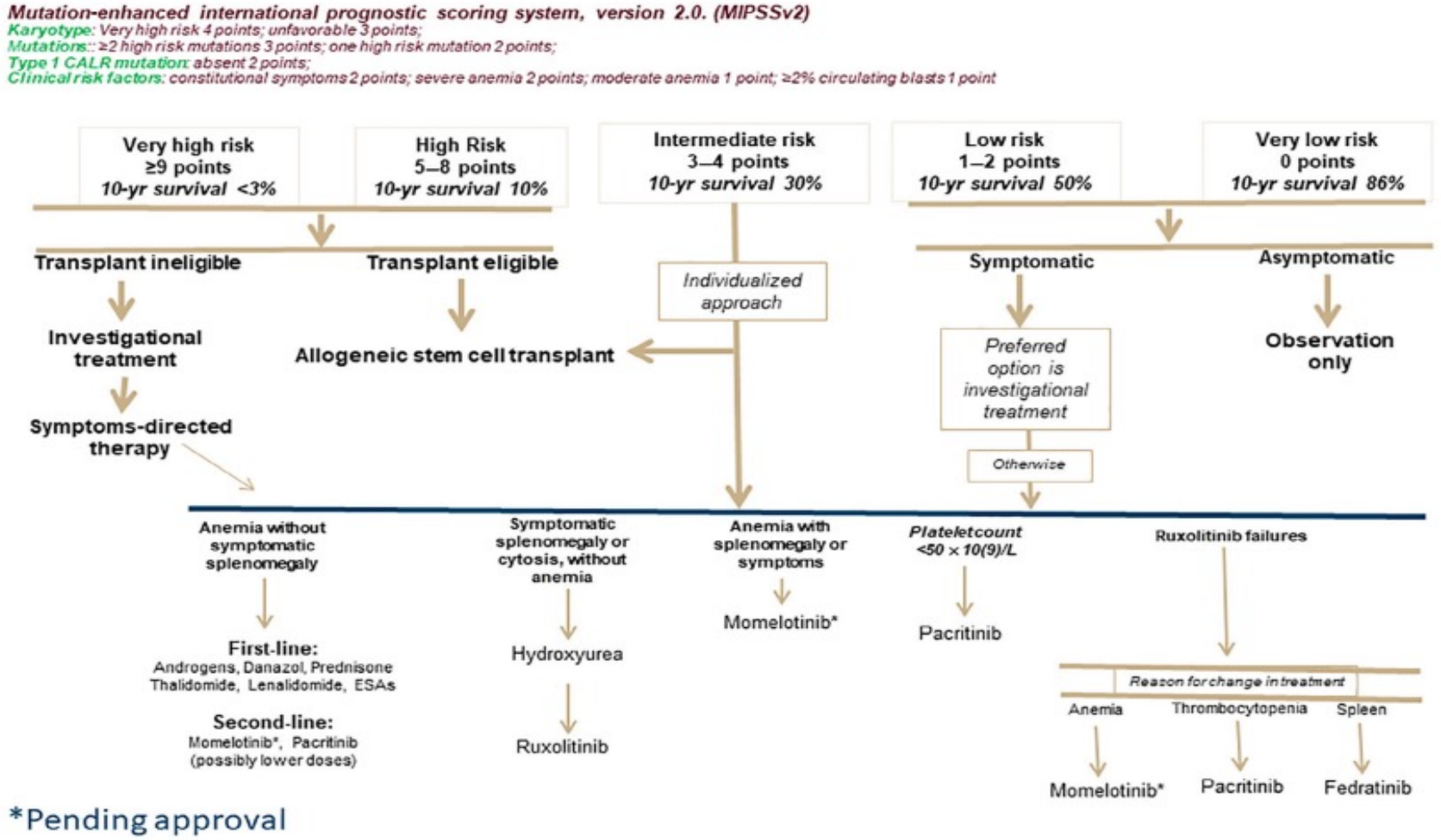


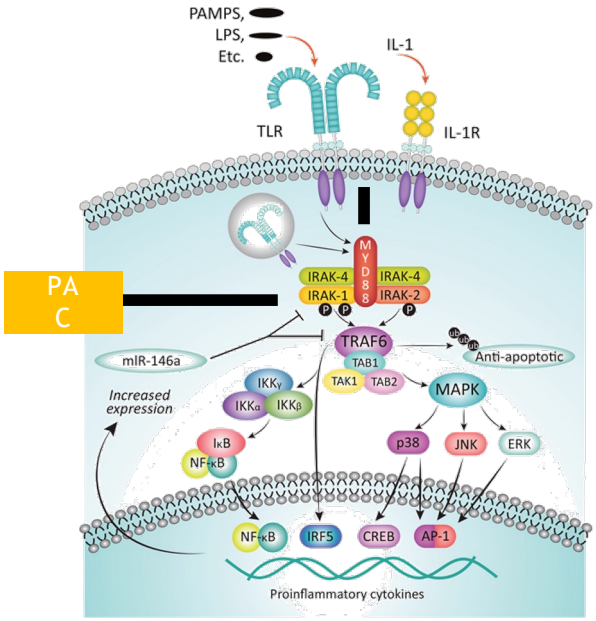
FIGURE 3 Risk-adapted treatment approach in primary myelofibrosis using the mutation-and karyotype-enhanced international prognostic system, version 2.0. (MIPSS v2; *see text for references*).

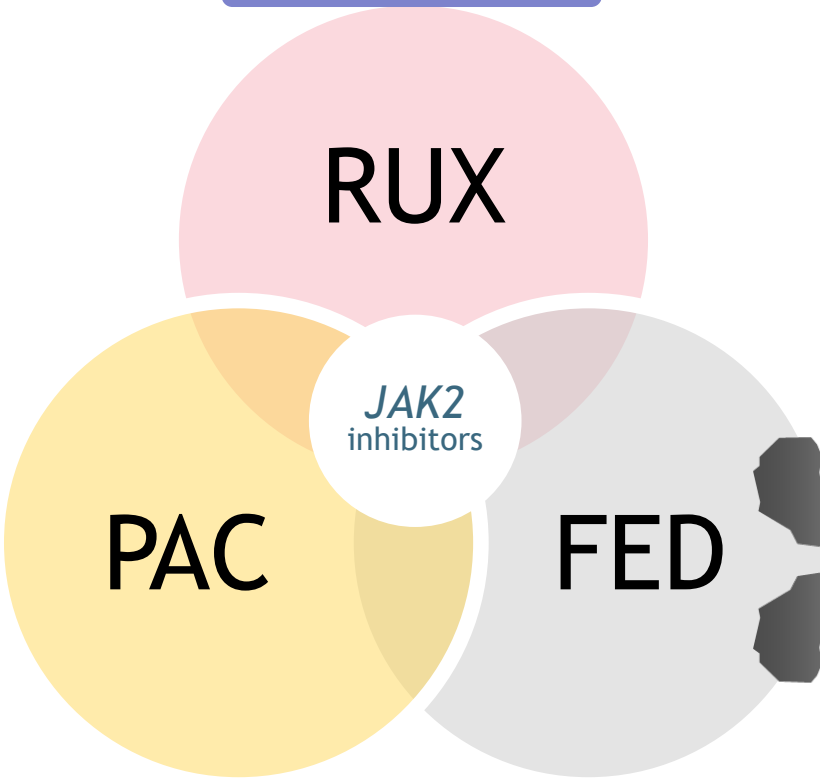
JAK2 inhibitors are not all the same

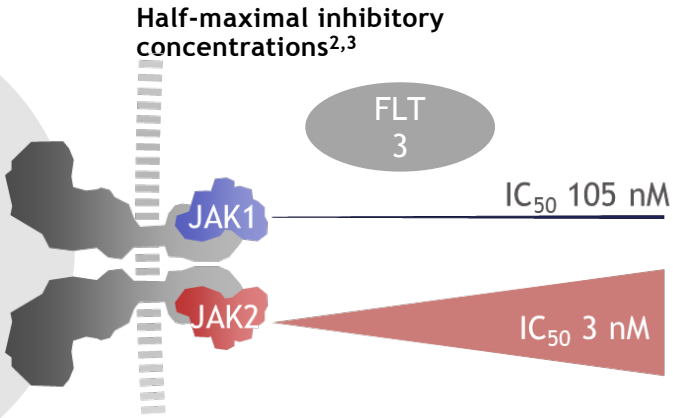
IRAK1, ACVR1

JAK1

FLT3, BRD4







1. Singer JW, et al. Oncotarget 2018;9(70):33416-39; 2. Santos FPS, Verstovsek S. Blood Rev 2011;25(2):53-63; 3. Wernig G, et al. Cancer Cell 2008;13(4):311-20.

cancers

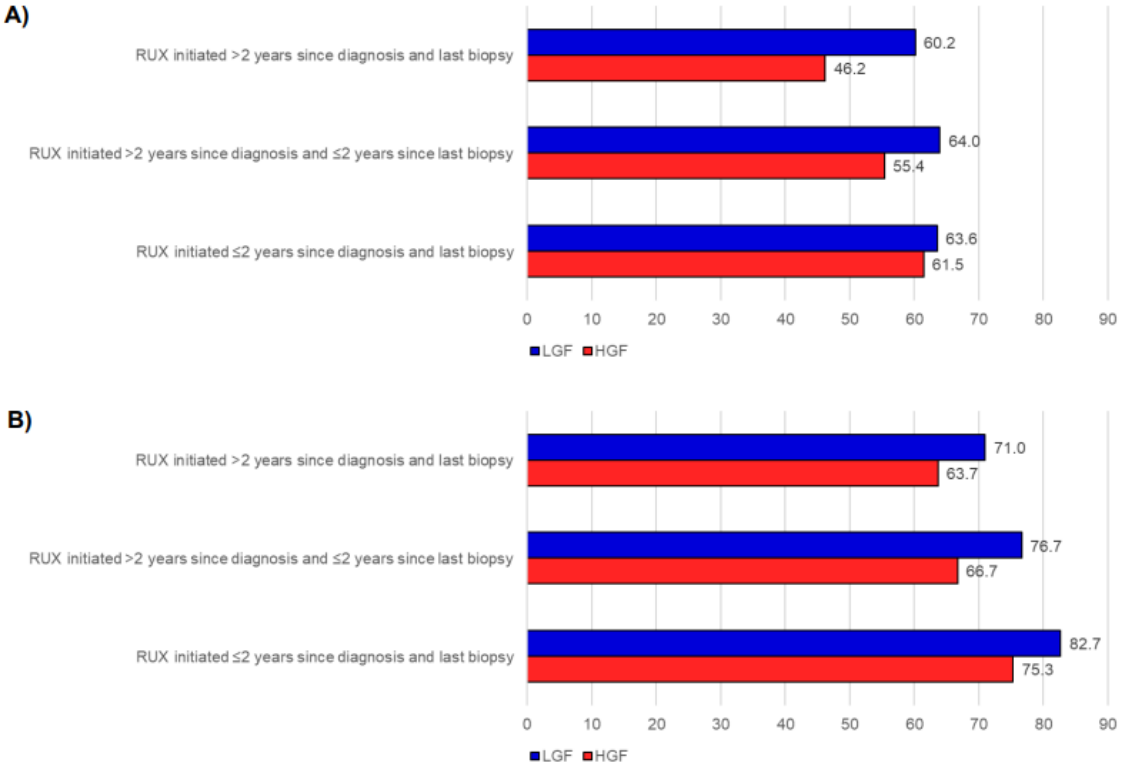
MDPI

Article

Benefit of Early Ruxolitinib Initiation Regardless of Fibrosis Grade in Patients with Primary Myelofibrosis: A Post Hoc Analysis of the Single-Arm Phase 3b JUMP Study

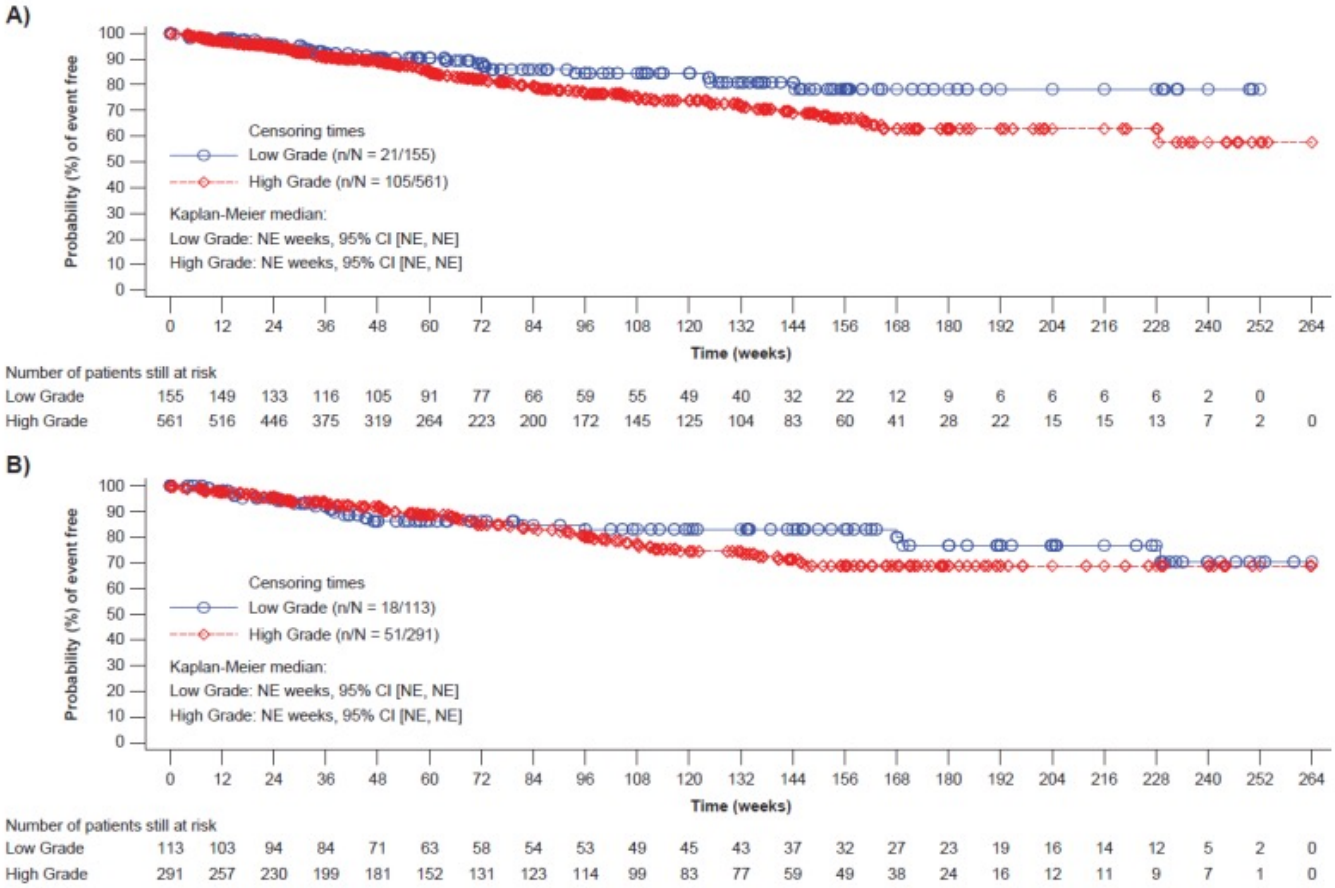
Francesca Palandri [1,*], Haifa Kathrin Al-Ali [2], Paola Guglielmelli [3], Mike W. Zuurman [4,†], Rajendra Sarkar [5] and Vikas Gupta [6]

Supplementary Figure S3. A. Proportion of patients with PMF achieving a spleen response at Week 24 stratified by time since diagnosis and time since last biopsy. **B.** Proportion of patients with PMF achieving a spleen response at any time during the study stratified by time since diagnosis and time since last biopsy.



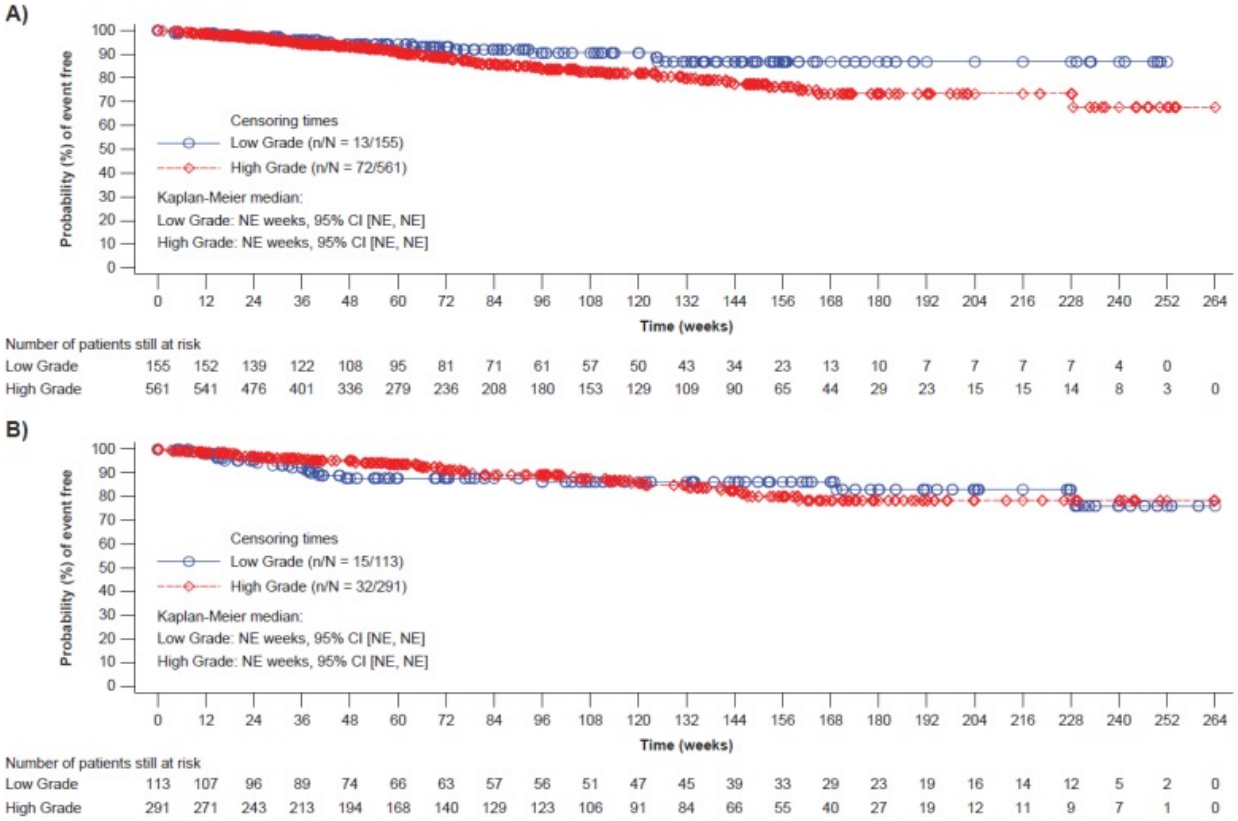
HGF, high-grade fibrosis; LGF, low-grade fibrosis; PMF, primary myelofibrosis; RUX, ruxolitinib.

Supplementary Figure S4. Progression-free survival in patients with PMF stratified by time since last biopsy. **A**, Patients who started ruxolitinib treatment ≤2 years since their last biopsy. **B**, Patients who started ruxolitinib treatment >2 years since their last biopsy.



CI, confidence interval; NE, not estimable; PMF, primary myelofibrosis.

Supplementary Figure S5. Overall survival in patients with PMF stratified by time since last biopsy. **A**, Patients who started ruxolitinib treatment ≤2 years since their last biopsy. **B**, Patients who started ruxolitinib treatment >2 years since their last biopsy.



CI, confidence interval; NE, not estimable; PMF, primary myelofibrosis.

CONCLUSIONI

-aumento del grado BMF è correlato a un livello più basso OS

-riduzione delle dimensioni spleniche a W24 è correlata a una OS migliore negli studi COMFORT I e II

- la tp di prima linea con ruxolitinib è un predittore indipendente della risposta splenica

- pz con LGF e HGF hanno ottenuto benefici clinici da ruxolitinib, dai dati sulla risposta della milza, sull'OS e sulla PFS

- pz con LGF hanno maggiori benefici rispetto ai pz con HGF

-Inizio ruxolitinib subito dopo la diagnosi migliora i risultati

- risp splenica a w 24 per i pz con HGF > per chi iniziato la tp entro 2aa dalla diagnosi e dall'ultima biopsia

REGULAR ARTICLE

blood advances

A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis

Margherita Maffioli,[1] Barbara Mora,[1,2] Somedeb Ball,[3] Alessandra Iurlo,[4] Elena Maria Elli,[5] Maria Chiara Finazzi,[6] Nicola Polverelli,[7] Elisa Rumi,[8,9] Marianna Caramella,[10] Maria Cristina Carraro,[11] Mariella D'Adda,[12] Alfredo Molteni,[13] Cinzia Sissa,[14] Francesca Lunghi,[15] Alessandro Vismara,[16] Marta Ubezio,[17] Anna Guidetti,[18] Sabrina Caberlon,[19] Michela Anghilieri,[20] Rami Komrokji,[3] Daniele Cattaneo,[4,6] Matteo Giovanni Della Porta,[17,21] Toni Giorgino,[22] Lorenza Bertù,[23] Marco Brociner,[1] Andrew Kuykendall,[3] and Francesco Passamonti[1,2]

RR6 MODEL

Ruxolitinib dose <20 mg bid	1 point
RBC transfusion at 3 and/or 6 months	1 point
Spleen reduction lenght <30% at 3 and 6 months	1.5 point
Need RBC transfusion at all timepoints	1.5 point

Low risk	0 points
Intermediate risk	1,1.5,2 points
High risk	2,5-4 points

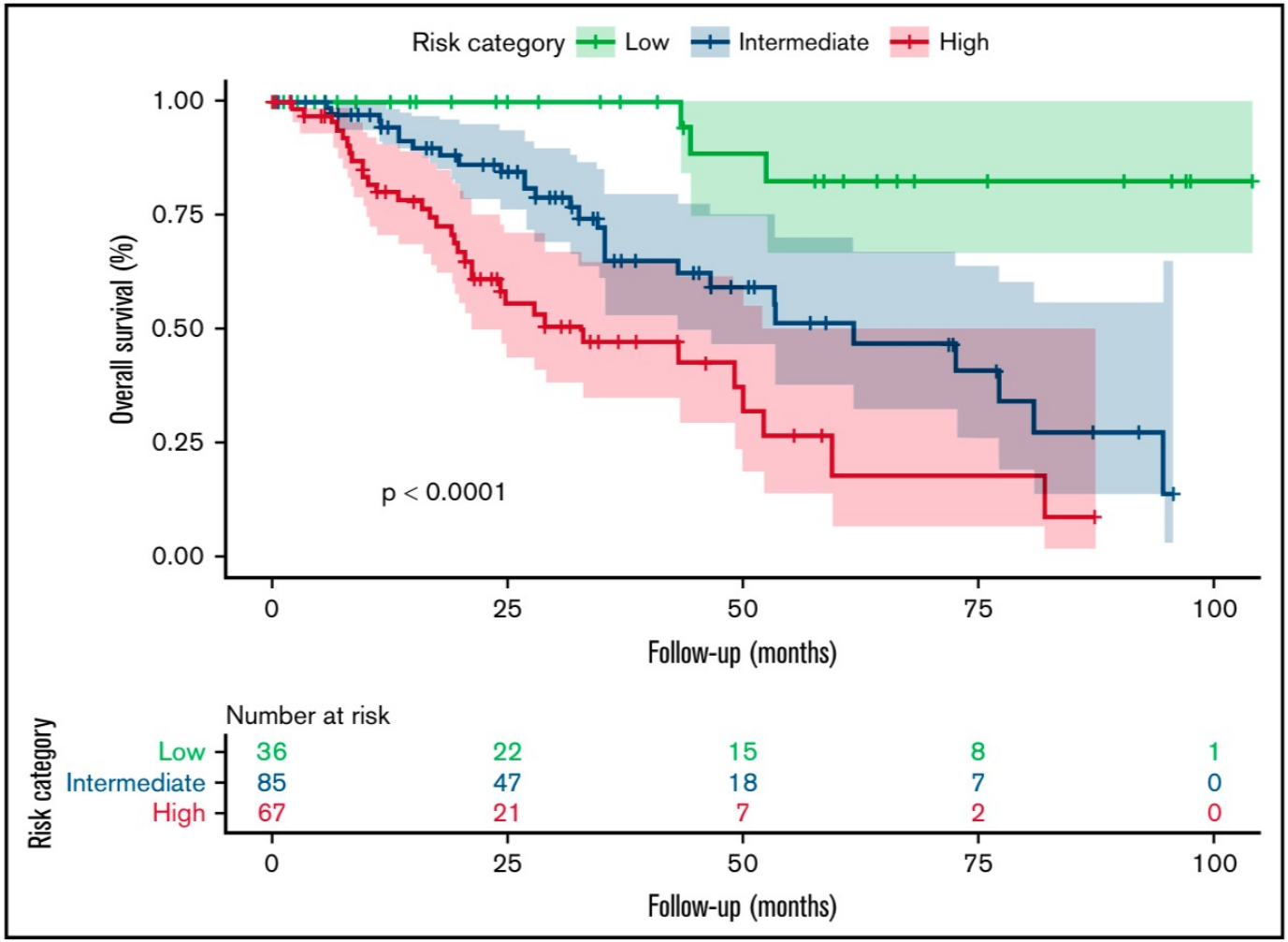
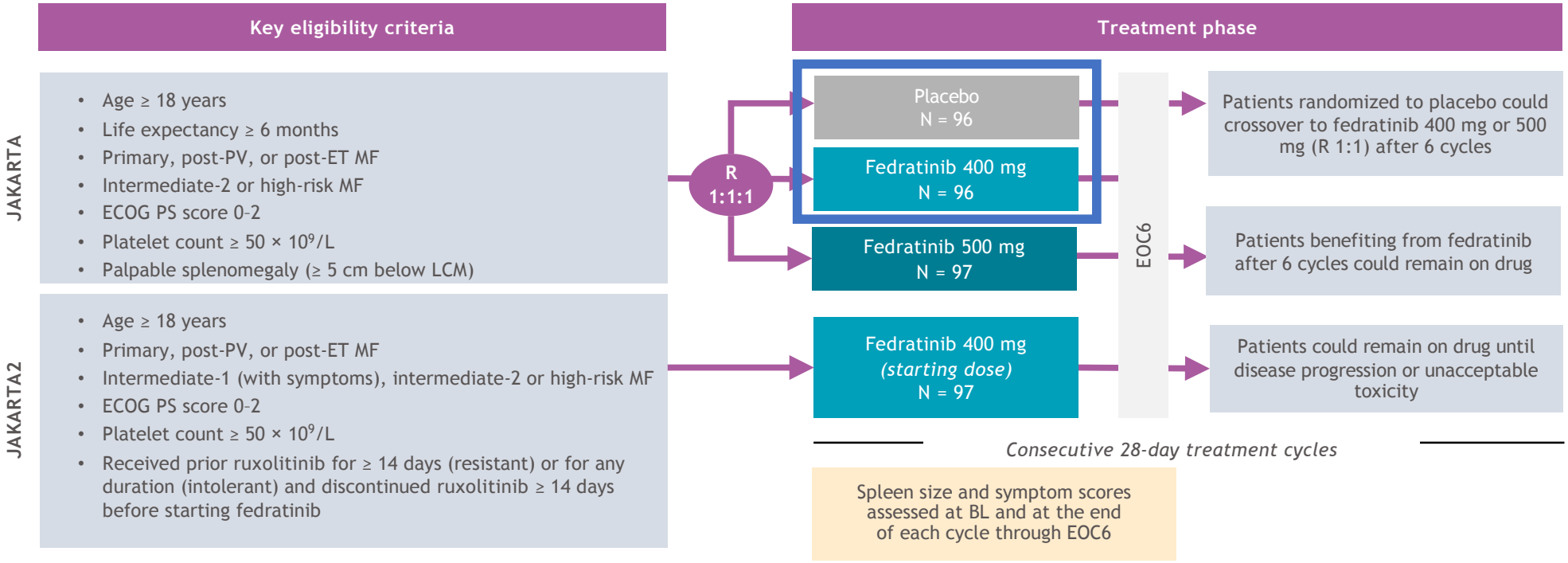


Figure 2. Actuarial survival curves of the 3 risk groups of patients according to the Response to Ruxolitinib After 6 Months (RR6) model developed in RUX-treated MF patients (training cohort).

JAKARTA and JAKARTA2: study design and key eligibility criteria



Regulatory approvals of FEDR:

- **United States** approval in Aug 2019
- **European Union** approval in Feb 2021

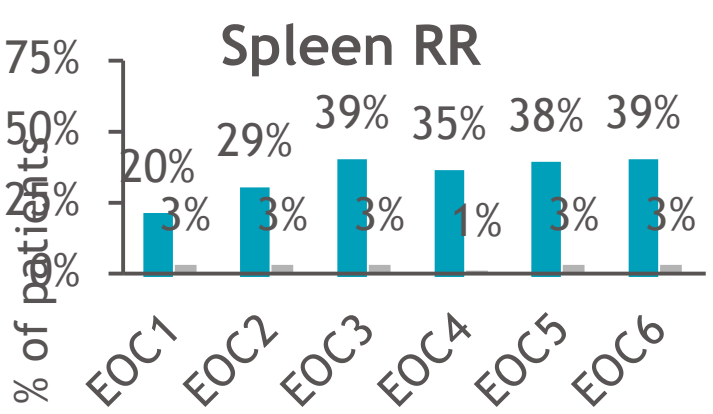
Major FEDR clinical trials in MF:

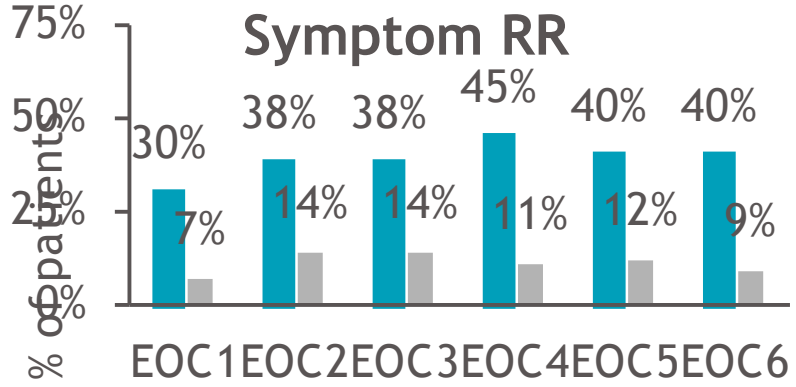
- **JAKARTA**: Ph. 3, JAKi-naïve; *completed*
- **JAKARTA2**: Ph. 2, post-RUX; *completed*
- **FREEDOM**: Ph. 3b, post-RUX; *ongoing*
- **FREEDOM2**: Ph. 3, post-RUX; *ongoing*

JAKARTA and JAKARTA2: Spleen and symptom response rate

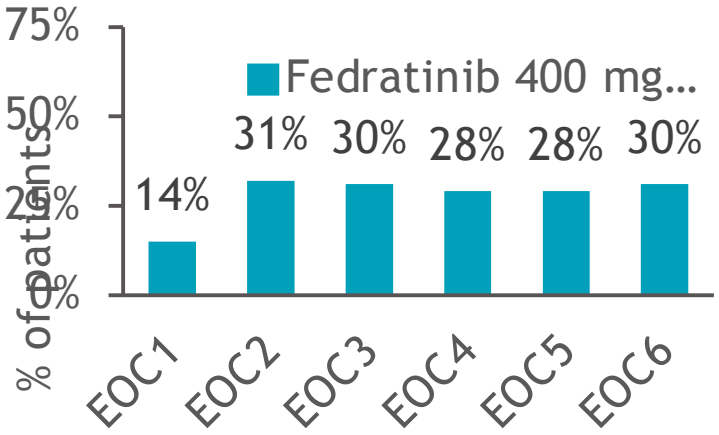
Passamonti F. et al., Presented at the 25th Congress of the European Hematology Association (EHA), June 11-14, 2020

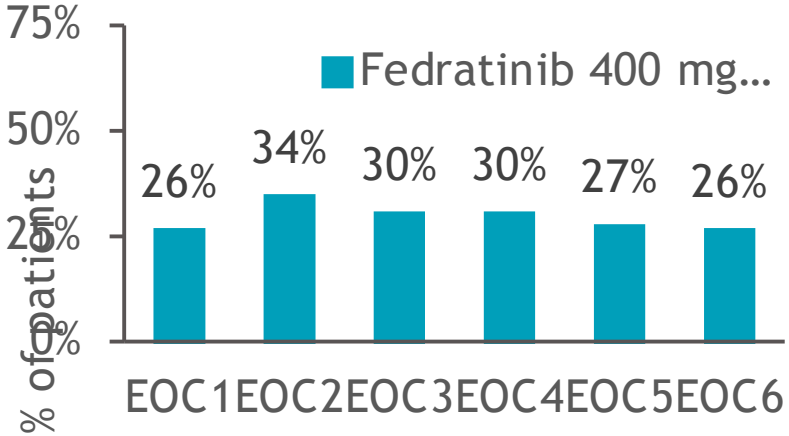
JAKARTA



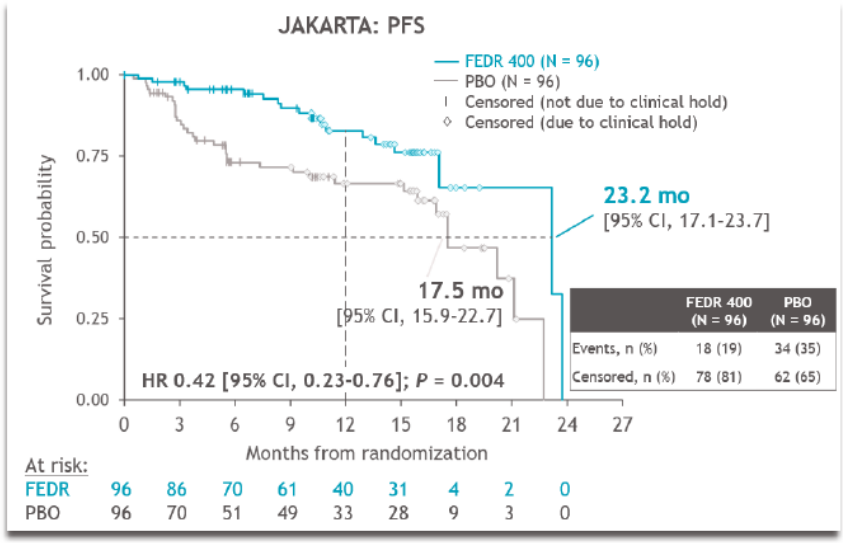


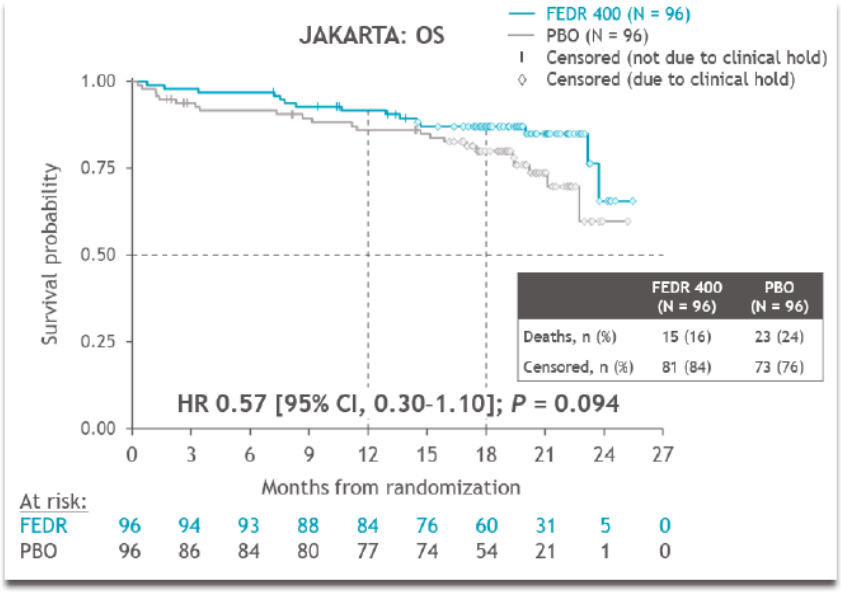
JAKARTA2





JAKARTA: PFS and OS





FEDR 400 significantly reduced the risk of disease progression vs. PBO (P = 0.004)
Median PFS was 5.7 months longer in the FEDR 400 arm vs. PBO: 23.2 vs. 17.5 mo, respectively.1-year PFS: FEDR 400 83%, PBO 67%

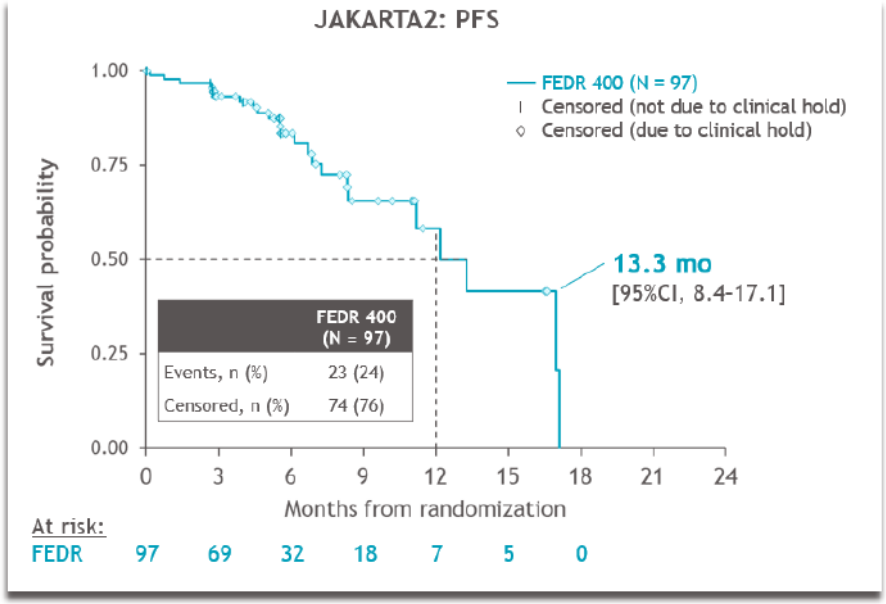
80 pts (42%) were still being followed for PFS at the time of clinical hold
Median follow-up: FEDR 400, 10.6 mo; PBO, 9.1 mo

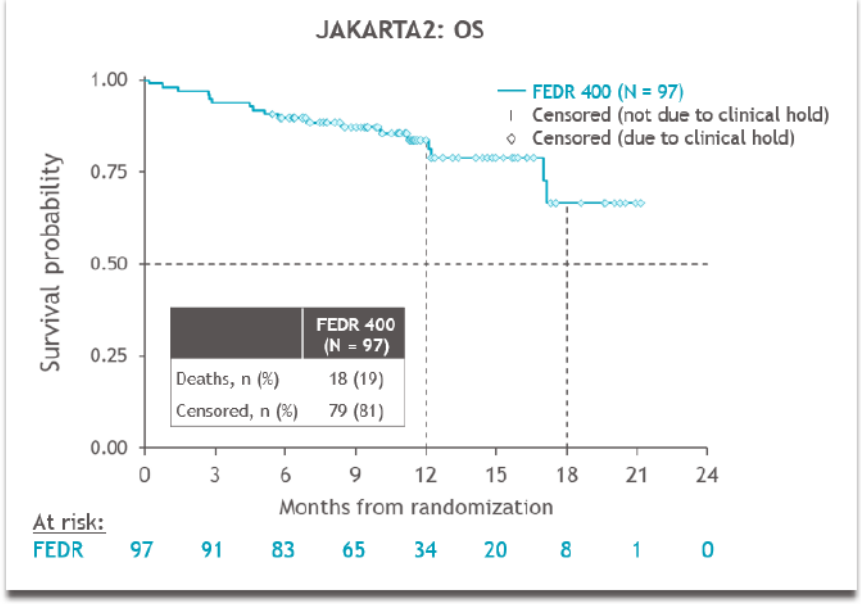
AML transformation was reported in 3 pts (3%) in the FEDR 400 arm and 2 pts (2%) in the PBO arm[a]

Harrison CN et al. Oral presentation at the EHA 2021 Annual Meeting; June 11-17, 2021; Abstract S203

- Median OS was not reached (NR) in the FEDR 400 [95%CI, 23.7 mo - NR] or PBO [22.7 - NR] arm
  - 1-year OS rates: FEDR 400 mg, 92%; PBO, 86%
  - 18-mo OS rates: FEDR 400 mg, 87%; PBO, 80%
- ITT analysis; 74% of PBO-randomized pts crossed-over to FEDR after EOC6
- 139 pts (72%) were censored for OS at the time of clinical hold
  - Median follow-up: FEDR 400 mg, 19.3 mo; PBO, 18.8 mo

JAKARTA2: PFS and OS





- Median PFS was 13.3 mo
  - 1-year PFS rate was 59%
- 62 pts (64%) were still being followed for PFS at the time of clinical hold
  - Median follow-up: 5.6 mo
- 2 pts (2%) experienced transformation to AML during the JAKARTA2 Tx period[a]

- Median OS was NR [95%CI, 17.1 - NR]
  - 1-year and 18-mo OS rates were 84% and 67%, respectively
- 79 pts (81%) were censored for OS at the time of clinical hold
  - Median follow-up: 10.8 mo

Harrison CN et al. Oral presentation at the EHA 2021 Annual Meeting; June 11-17, 2021; Abstract S203

FREEDOM

OBJECTIVE:

Assess the efficacy and safety of the JAK2 inhibitor, fedratinib, in patients with myelofibrosis previously treated with RUX

EA MITIGATION STRATEGIES:

FREEDOM includes proactive strategies to mitigate potential safety concerns, such as GI AEs, thiamine level decreases, and potential encephalopathy (including Wernicke's encephalopathy [WE])

AE, adverse event; FREEDOM, A Trial of Fedratinib in Subjects With DIPSS, Intermediate or High-Risk Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis and Previously Treated With Ruxolitinib; GI, gastrointestinal; MF, myelofibrosis; RUX, ruxolitinib; WE, Wernicke's encephalopathy.
Gupta V. et al., ASH 2022 poster 1711

Fedratinib GI Mitigation Strategy

Administration with a high fat meal may reduce the incidence of nausea and vomiting, therefore it is recommended to be taken with food; exposure to fedratinib is not affected by food

Nausea and Diarrhea Treatment

Nausea

- It is recommended that prophylactic anti emetics (e.g. 5 HT3 receptor antagonists) be used according to local practice for the first 8 weeks of treatment and continued thereafter as clinically indicated

Diarrhea

- Treat diarrhea with anti-diarrheal medications promptly at the first onset of symptoms

Dose Interruptions

- For Grade ≥ 3 nausea, vomiting, or diarrhea not responsive to supportive measures within 48 hours, interrupt fedratinib until resolved to Grade ≤ 1 or baseline
- Restart dose at 100 mg daily below the last given dose. Monitor thiamine levels and replenish as needed

INREBIC (fedratinib) [summary of product characteristics]. Utrecht, Netherlands: Celgene Europe; February 2021.

Original Study

Real-World Use of Fedratinib for Myelofibrosis Following Prior Ruxolitinib Failure: Patient Characteristics, Treatment Patterns, and Clinical Outcomes

John Mascarenhas,[1] Claire Harrison,[2] Tammy A. Schuler,[3] Djibril Liassou,[3] Marné Garretson,[3] Taavy A. Miller,[3] Sankar Mahadevan,[4] Ali McBride,[4] Derek Tang,[4] Irene S. DeGutis,[4] Pranav Abraham,[4,#] Jonathan Kish,[3,#] Bruce A. Feinberg,[3] Aaron T. Gerds[5]

Figure 1 Best reduction in spleen size during the initial 6 months of fedratinib treatment among patients with palpable spleen at fedratinib initiation (n = 112) Best percentage reduction in spleen size = greatest numeric reduction in spleen size at any point compared with an initiation of FEDR. Abbreviation: FEDR = fedratinib.

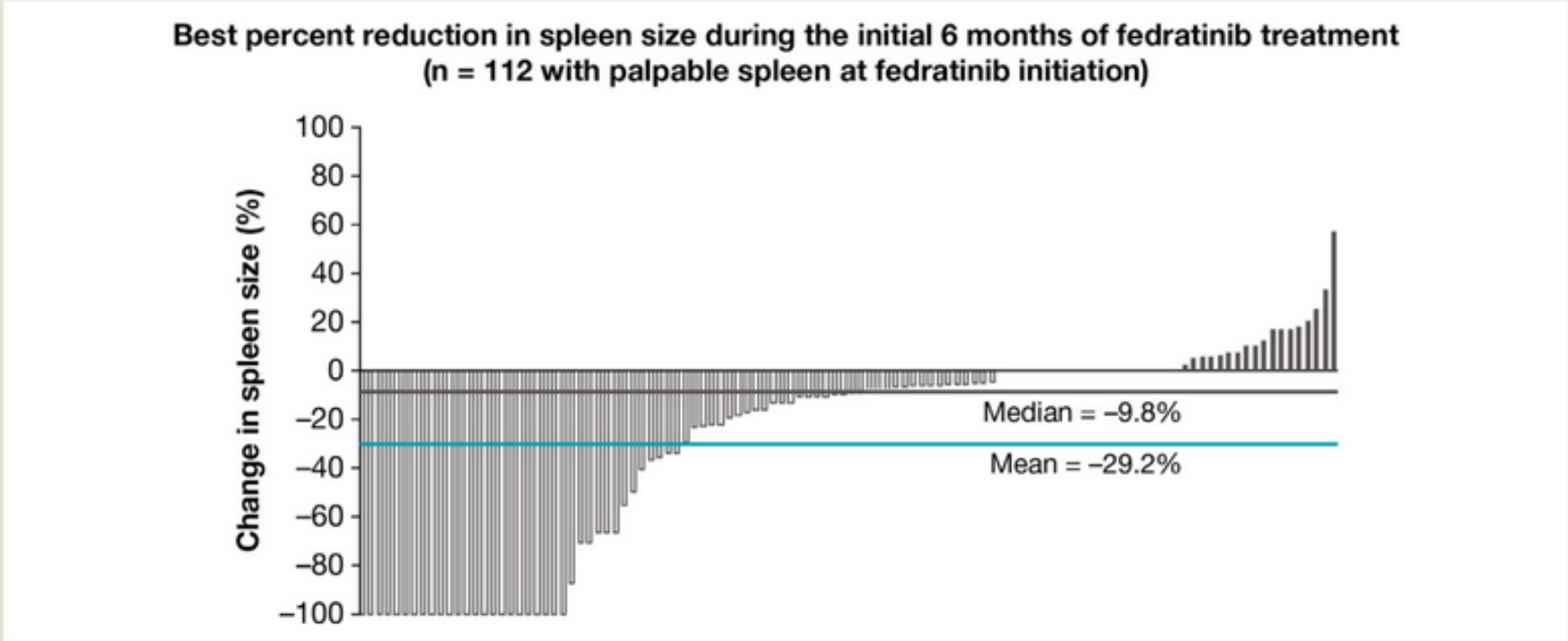
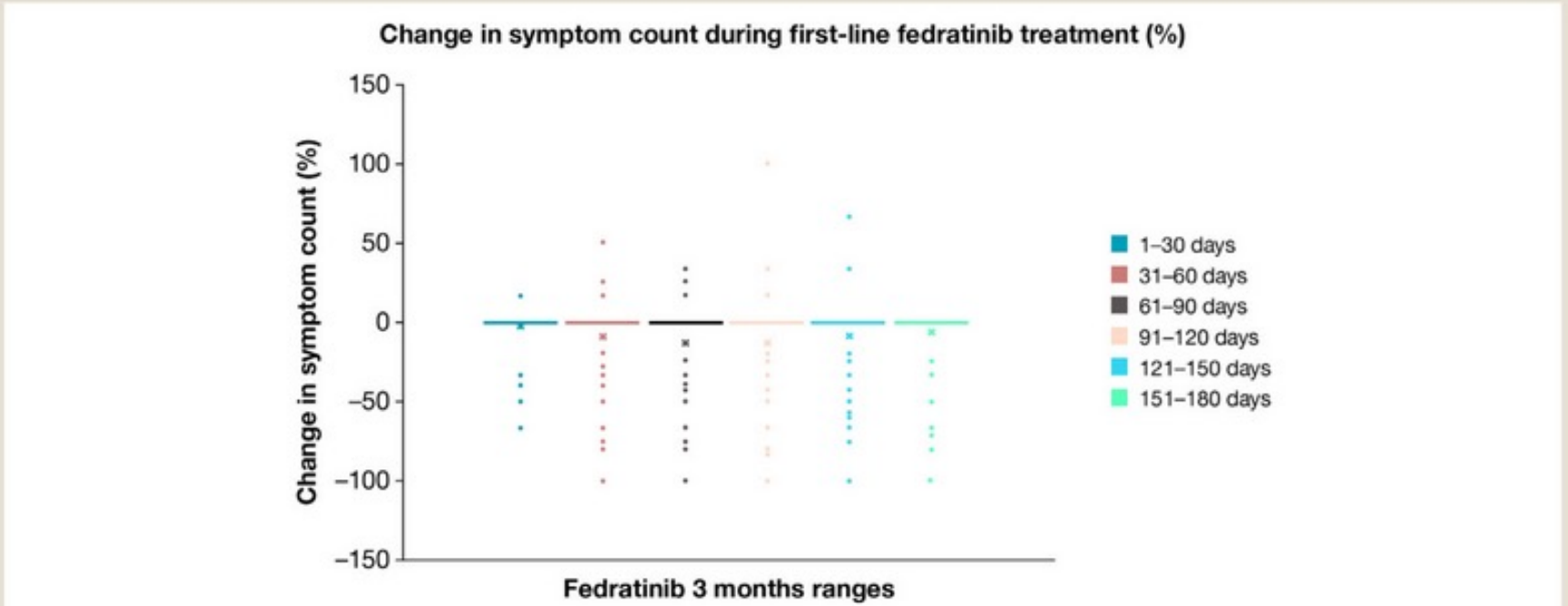


Figure 2 Percent change in symptom counts over the initial 6 months of fedratinib treatment among patients who had symptoms present at initiation (N = 141). Abbreviation: FEDR = fedratinib.



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OJJAARA safely and effectively. See full prescribing information for OJJAARA.

OJJAARA (momelotinib) tablets, for oral use
Initial U.S. Approval: 2023

---------- INDICATIONS AND USAGE----------
OJJAARA is a kinase inhibitor indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage: 200 mg orally once daily with or without food. (2.1)
- Severe hepatic impairment (Child-Pugh Class C): Reduce the starting dose to 150 mg orally once daily. (2.3)

---------- DOSAGE FORMS AND STRENGTHS----------
Tablets: 100 mg, 150 mg, 200 mg. (3)

Momelotinib for the treatment of myelofibrosis with anemia

Douglas Tremblay[1] & Ruben Mesa*[,2]
[1]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[2]UT Health San Antonio Cancer Center, San Antonio, TX, USA
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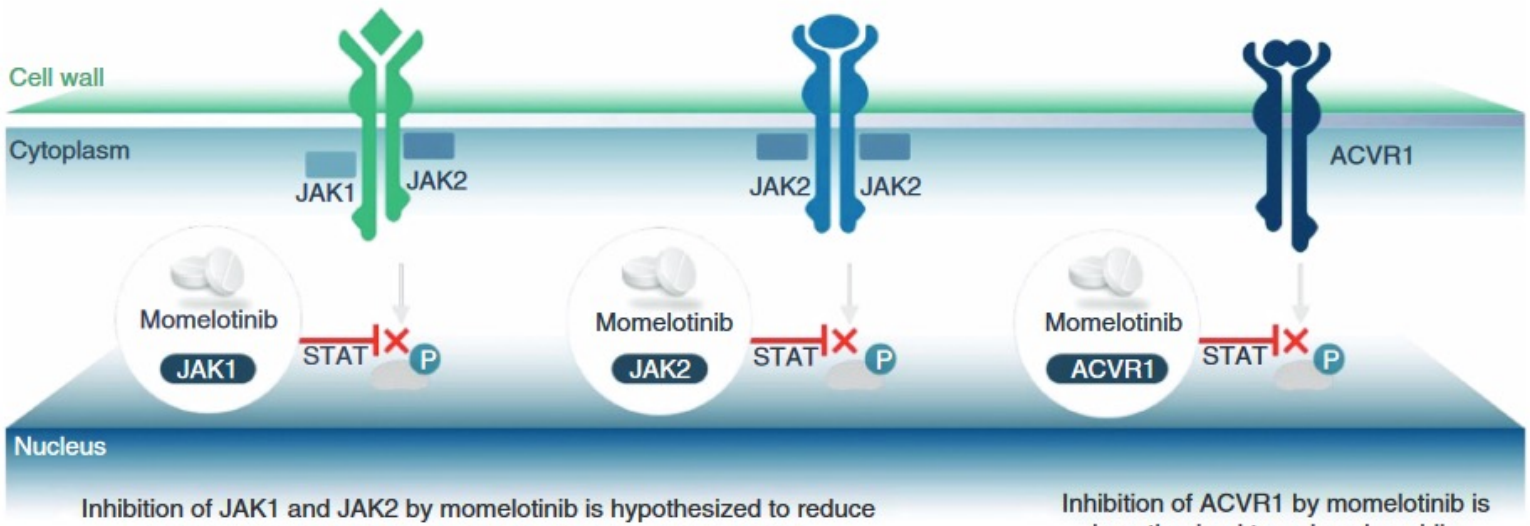

Inhibition of JAK1 and JAK2 by momelotinib is hypothesized to reduce inflammation, aberrant cytokine signaling, extramedullary hematopoiesis, constitutional symptoms and splenomegaly

Inhibition of ACVR1 by momelotinib is hypothesized to reduce hepcidin transcription, restore iron homeostasis and increase hemoglobin

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ORIGINAL REPORT

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

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

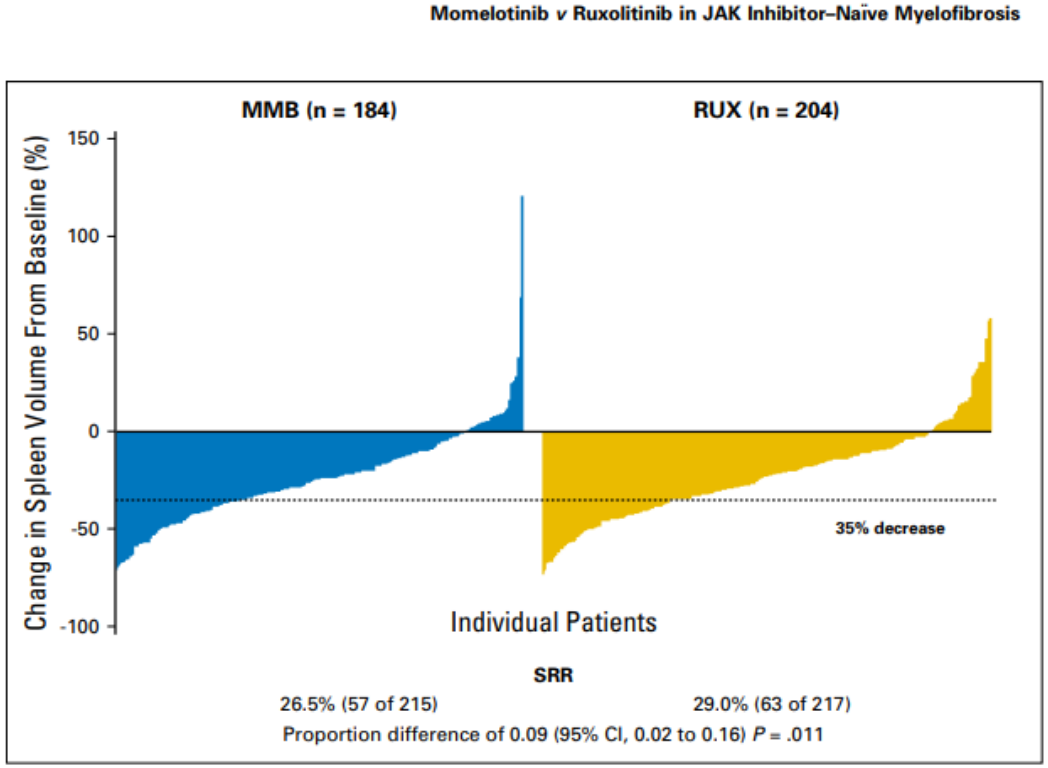


Fig 1. Change in spleen volume and spleen response rate (percentage of patients with a ≥ 35% reduction in spleen volume) at week 24. MMB, momelotinib; RUX, ruxolitinib; SRR, spleen response rate.

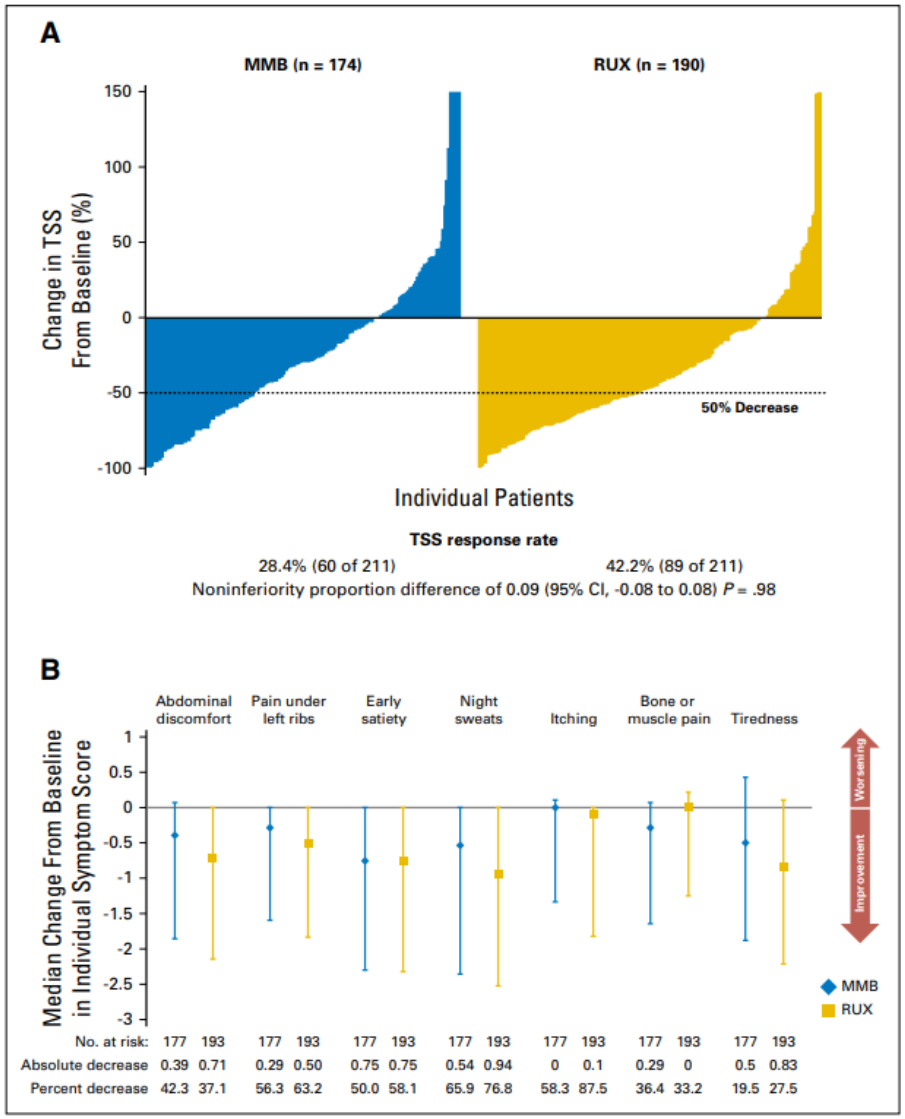


Fig 2. (A) Change in Total Symptom Score (TSS) from baseline and TSS response rate (percentage of patients with ≥ 50% reduction in TSS) at week 24. (B) Absolute and percent changes in individual symptoms of the Myeloproliferative Neoplasm Symptom Assessment Form from baseline to week 24. MMB, momelotinib; RUX, ruxolitinib.

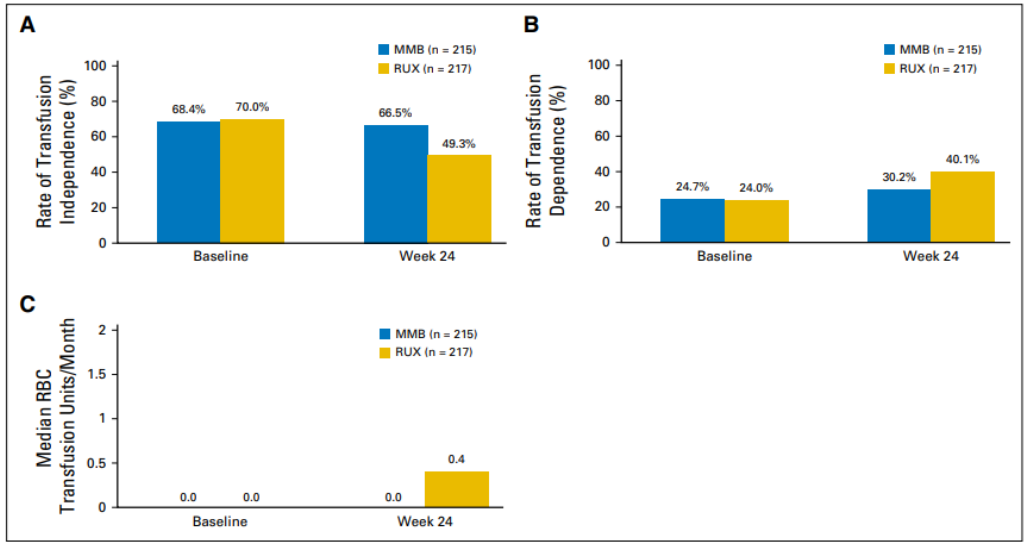


Fig 3. Comparison of momelotinib (MMB) and ruxolitinib (RUX) effects on transfusion requirements at week 24. (A) RBC transfusion independence rate (no RBC transfusion and no hemoglobin [Hb] < 8 g/dL in the prior 12 weeks; nominal $P < .001$). (B) RBC transfusion dependence rate (≥ 4 units of RBC transfusion or Hb < 8 g/dL in the prior 8 weeks; nominal $P = .019$). (C) Rate of RBC transfusions through week 24 (nominal $P < .001$).

Table 2. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Either Treatment Group

	Double-Blind Phase	
Treatment-Emergent Adverse Event	Momelotinib (n = 214)	Ruxolitinib (n = 216)
Thrombocytopenia	40 (18.7)	63 (29.2)
Diarrhea	38 (17.8)	43 (19.9)
Headache	37 (17.3)	43 (19.9)
Dizziness	34 (15.9)	25 (11.6)
Nausea	34 (15.9)	8 (3.7)
Fatigue	31 (14.5)	26 (12.0)
Anemia	29 (13.6)	82 (38.0)
Abdominal pain	22 (10.3)	24 (11.1)

NOTE. Data presented as No. (%).

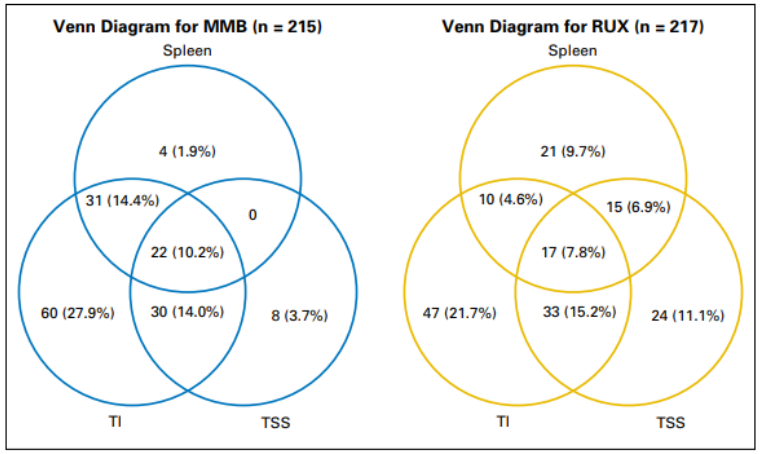


Fig 4. Patients (n, %) who achieved spleen response (≥ 35% reduction in spleen volume), Total Symptom Score (TSS) response (≥ 50% reduction in score), and transfusion independence (TI; no RBC transfusion and no Hb < 8 g/dL in the prior 12 weeks) at week 24. MMB, momelotinib; RUX, ruxolitinib.

Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study

*Srdan Verstovsek, Aaron T Gerds, Alessandro M Vannucchi, Haifa Kathrin Al-Ali, David Lavie, Andrew T Kuykendall, Sebastian Grosicki, Alessandra Iurlo, Yeow Tee Goh, Mihaela C Lazaroiu, Miklos Egyed, Maria Laura Fox, Donal McLornan, Andrew Perkins, Sung-Soo Yoon, Vikas Gupta, Jean-Jacques Kiladjian, Nikki Granacher, Sung-Eun Lee, Luminita Ocroteala, Francesco Passamonti, Claire N Harrison, Barbara J Klencke, Sunhee Ro, Rafe Donahue, Jun Kawashima, Ruben Mesa, on behalf of MOMENTUM Study Investigators**

The primary endpoint was MFSAF TSS response rate at week 24, defined as the proportion of patients with a 50% or more reduction in mean MFSAF TSS over the 28 days immediately before the end of week 24 compared with baseline

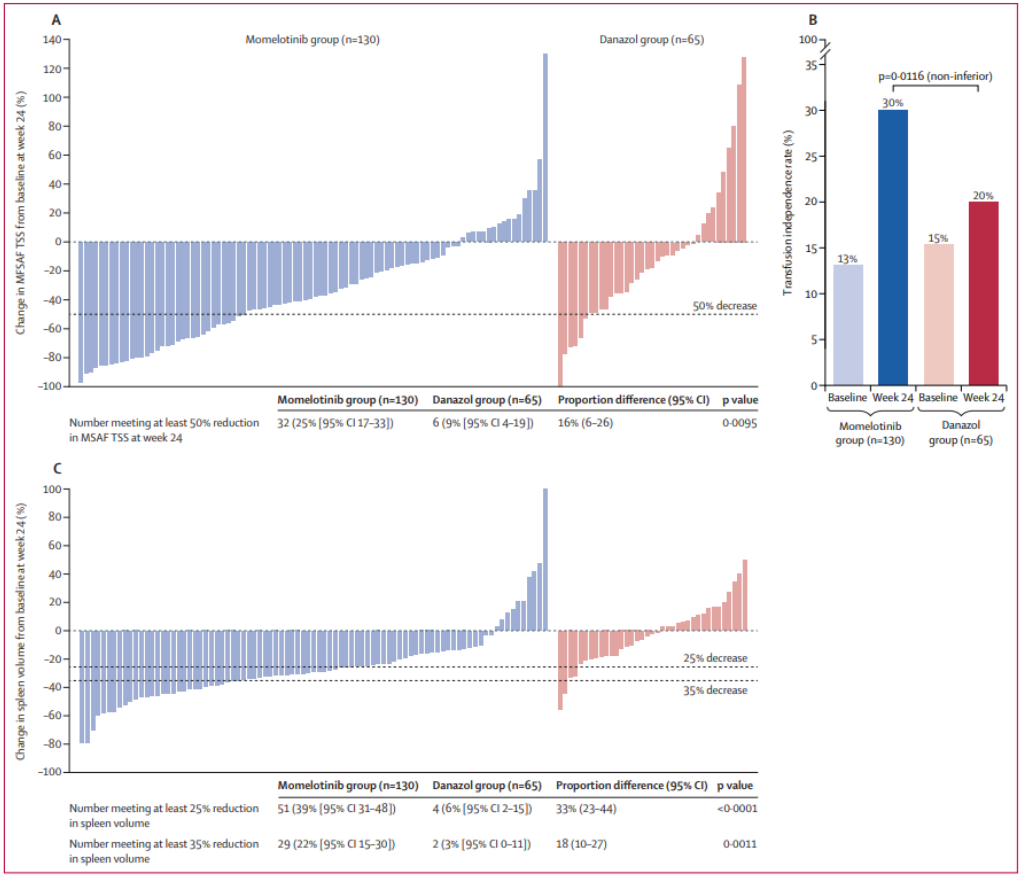


Figure 2: **Change in symptom scores, transfusion independence, and spleen volume**
(A) Percentage change of TSS from baseline to week 24 for each patient. (B) Change in transfusion independence rate from baseline to week 24. (C) Percentage change of spleen volume from baseline

	Momelotinib group (n=130)		Danazol group (n=65)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Non-haematological abnormalities (preferred term)				
Diarrhoea	29 (22%)	0	6 (9%)	1 (2%)
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Asthenia	17 (13%)	1 (1%)	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Weight decreased	14 (11%)	0	4 (6%)	0
Blood creatinine increased	10 (8%)	1 (1%)	10 (15%)	2 (3%)
Dyspnoea	10 (8%)	3 (2%)	9 (14%)	1 (2%)
Peripheral oedema	10 (8%)	2 (2%)	9 (14%)	0
Fatigue	8 (6%)	1 (1%)	7 (11%)	2 (3%)
Acute kidney injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)
Haematological abnormalities*				
Anaemia	129 (99%)	79 (61%)	65 (100%)	49 (75%)
Thrombocytopenia	99 (76%)	36 (28%)	40 (62%)	17 (26%)
Neutropenia	38 (29%)	16 (12%)	17 (26%)	6 (9%)

Data are n (%). *Haematological abnormalities are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase of the study, regardless of whether this grade was a change from baseline.

Table 3: **Treatment-emergent adverse events observed in at least 10% of patients in either treatment group during the 24-week randomised treatment period**

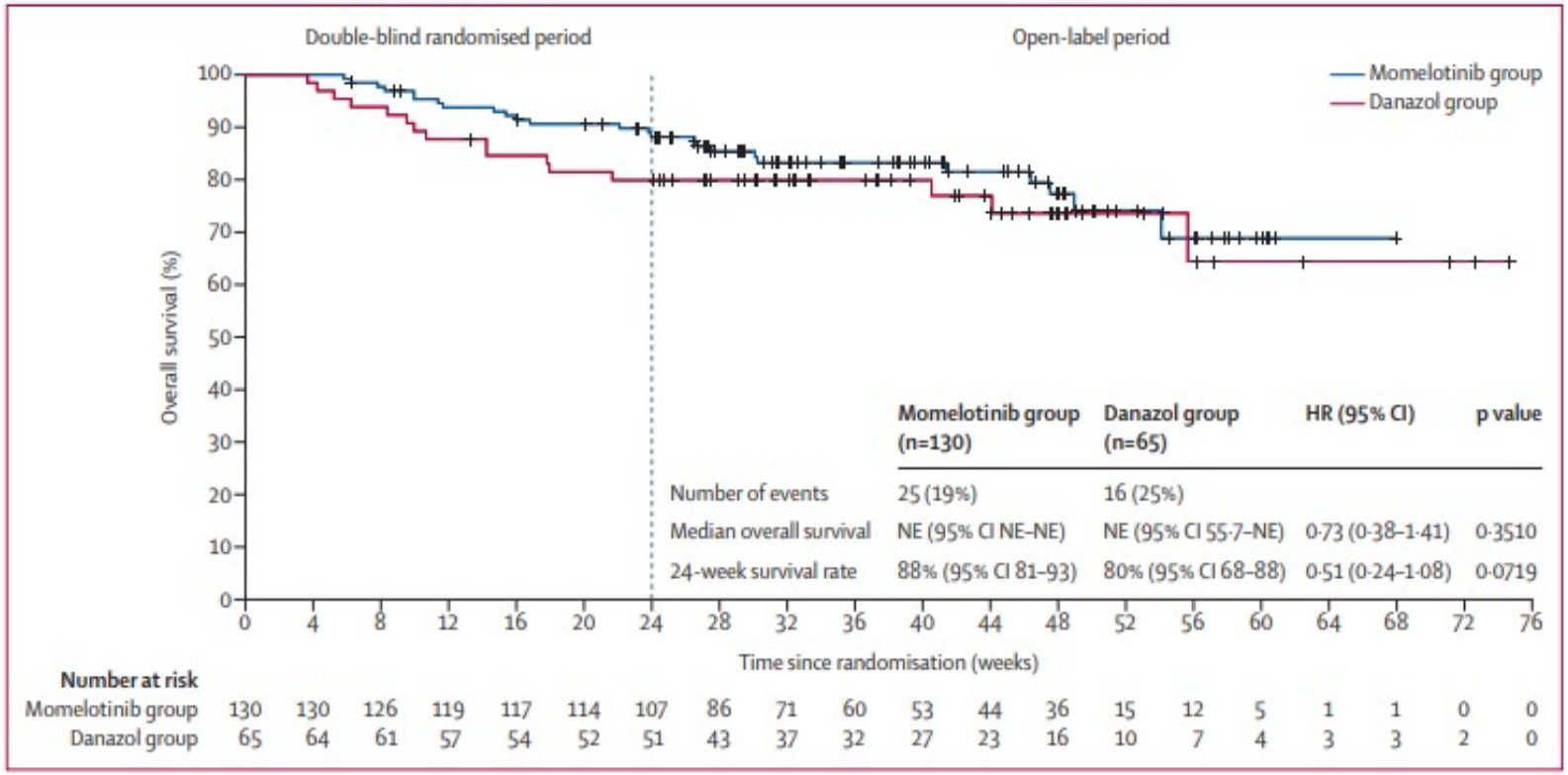


***Figure 3*: Overall survival in the intention-to-treat population**

Kaplan-Meier estimates of overall survival in the intention-to-treat population from the time of randomisation to the data cutoff date (Dec 3, 2021). The vertical line at week 24 indicates the transition between the double-blind randomised period and the open-label period when patients ongoing in the study started receiving open-label momelotinib treatment. p value from a stratified log-rank test; HR (momelotinib group *vs* danazol group) from a stratified Cox proportional hazards model with a single factor of treatment group and stratified by baseline stratification factors. HR=hazard ratio. NE=not estimable.

In conclusion, treatment with momelotinib was associated with clinically significant improvements in myelofibrosis-associated symptoms, anaemia measures, and spleen size, with favourable safety compared with danazol in symptomatic patients with anaemia and previous JAK inhibitor exposure.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VONJO safely and effectively. See full prescribing information for VONJO.

VONJO™ (pacritinib) capsules, for oral use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

VONJO is a kinase inhibitor indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 10^9/L (1).

This indication is approved under accelerated approval based on spleen volume reduction. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

- Recommended dosage is 200 mg orally twice daily (2.1).
- May be taken with or without food (2.1).

DOSAGE FORMS AND STRENGTHS

Capsules: 100 mg (3)

JAMA Oncology | Original Investigation

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

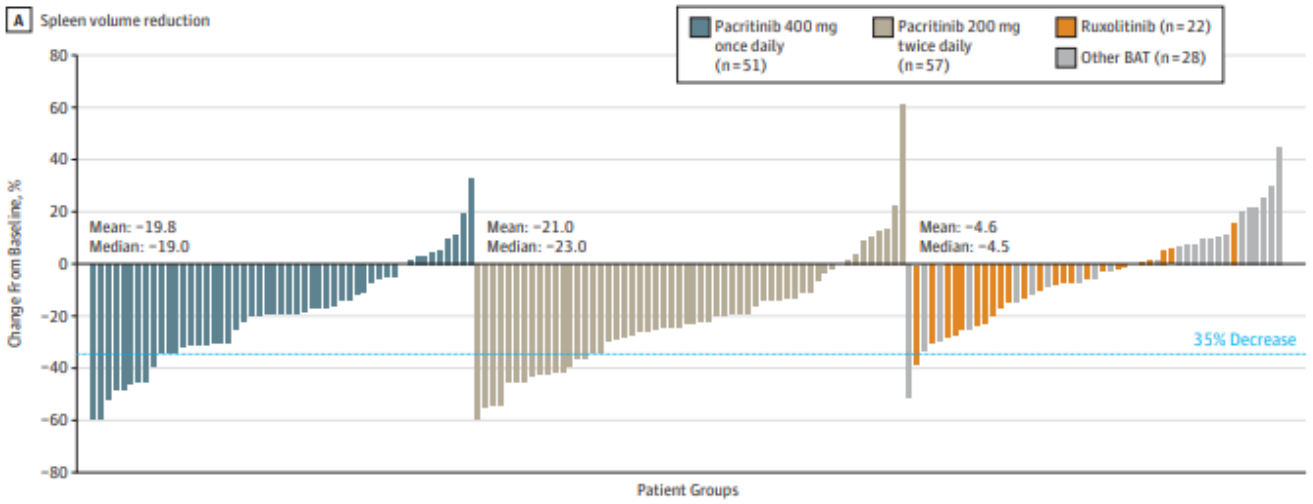
A Randomized Clinical Trial

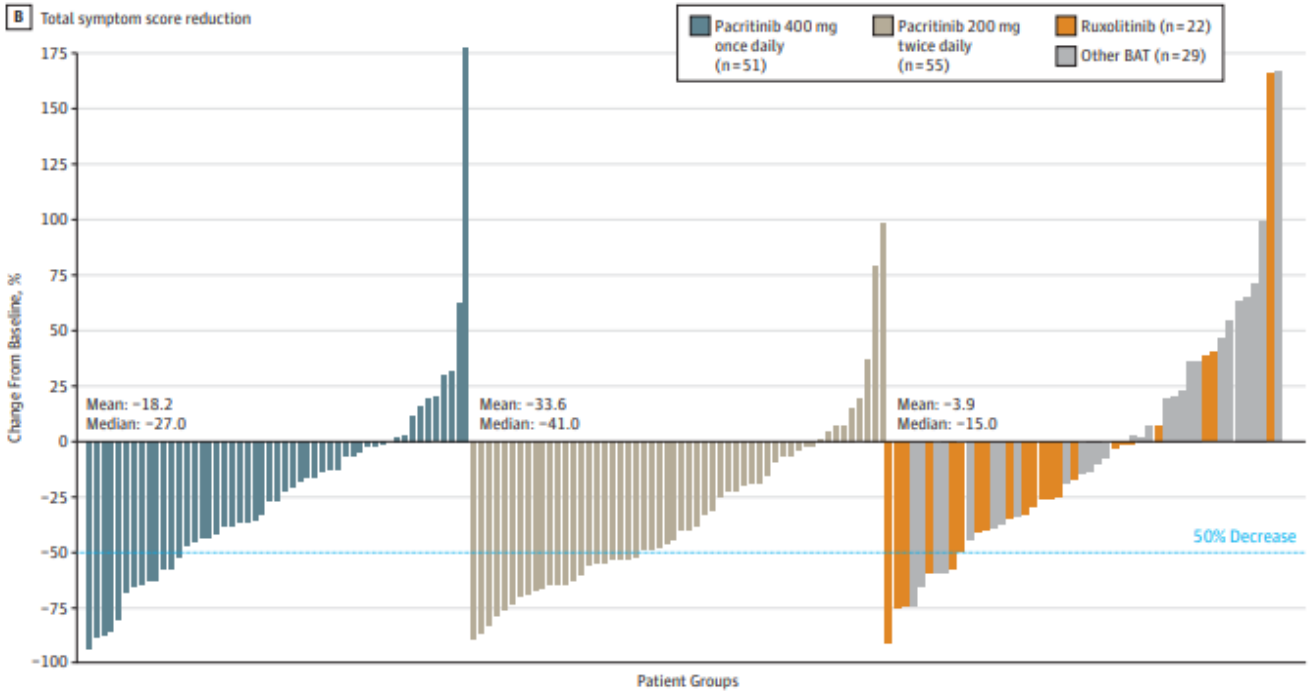
John Mascarenhas, MD; Ronald Hoffman, MD; Moshe Talpaz, MD; Aaron T. Gerds, MD; Brady Stein, MD; Vikas Gupta, MD, FRCP, FRCPath; Anita Szoke, MD; Mark Drummond, MBChB, PhD, FRCPath; Alexander Pristupa, MD; Tanya Granston, PhD; Robert Daly, PhD; Suliman Al-Fayoumi, PhD; Jennifer A. Callahan, MS; Jack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

Adult patients with primary or secondary myelofibrosis were eligible if they had intermediate-1, intermediate-2, or high risk disease by the Dynamic International Prognostic Scoring System (DIPSS), platelet count less than or equal to 100 × 109 /L, and palpable splenomegaly 5 cm or larger below the left costal margin.

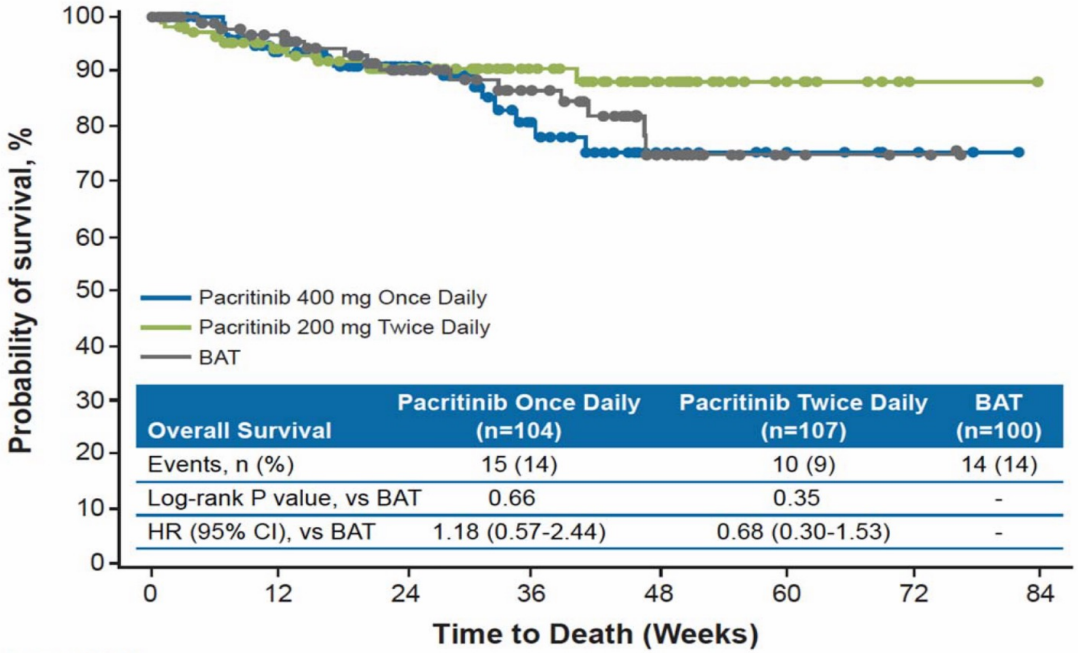
Patients were centrally randomized 1:1:1 via interactive web or voice response system to pacritinib 400 mg once daily, pacritinib 200 mg twice daily, or BAT; BAT included any physician selected treatment for myelofibrosis, symptom-directed treatment, or watch-and-wait

Figure 2. Spleen Volume Reduction and Reduction in Total Symptom Score in Evaluable Patients





PERSIST 2 OS



Overall Survival	Pacritinib Once Daily (n=104)	Pacritinib Twice Daily (n=107)	BAT (n=100)
Events, n (%)	15 (14)	10 (9)	14 (14)
Log-rank P value, vs BAT	0.66	0.35	-
HR (95% CI), vs BAT	1.18 (0.57-2.44)	0.68 (0.30-1.53)	-

Patients at Risk, n

Pacritinib 400 mg Once Daily	104	80	55	31	13	7	3	0
Pacritinib 200 mg Twice Daily	107	85	62	41	22	9	1	0
BAT	100	83	60	41	18	4	2	0

eFigure 4. Overall Survival (Intention-to-Treat, Censored at Date of Clinical Hold).
Kaplan-Meier estimates of overall survival are shown for the 3 treatment arms. Prior to week 24, overall survival was similar across the 3 arms, while after week 24, there was a trend towards improved survival with pacritinib twice daily, though it did not reach statistical significance. Abbrevations: BAT, best available therapy; BID, twice daily; HR, hazard ratio; RBC, red blood cell.

- **Pacritinib** vs Best Available Therapy, Including Ruxolitinib, in Patients With **Myelofibrosis**: A Randomized Clinical Trial. Mascarenhas J, Hoffman R, Talpaz M, Gerds AT, Stein B, Gupta V, Szoke A, Drummond M, Pristupa A, Granston T, Daly R, Al-Fayoumi S, Callahan JA, Singer JW, Gotlib J, Jamieson C, Harrison C, Mesa R, Verstovsek S. JAMA Oncol. 2018 May 1;4(5):652-659. doi: 10.1001/jamaoncol.2017.5818.

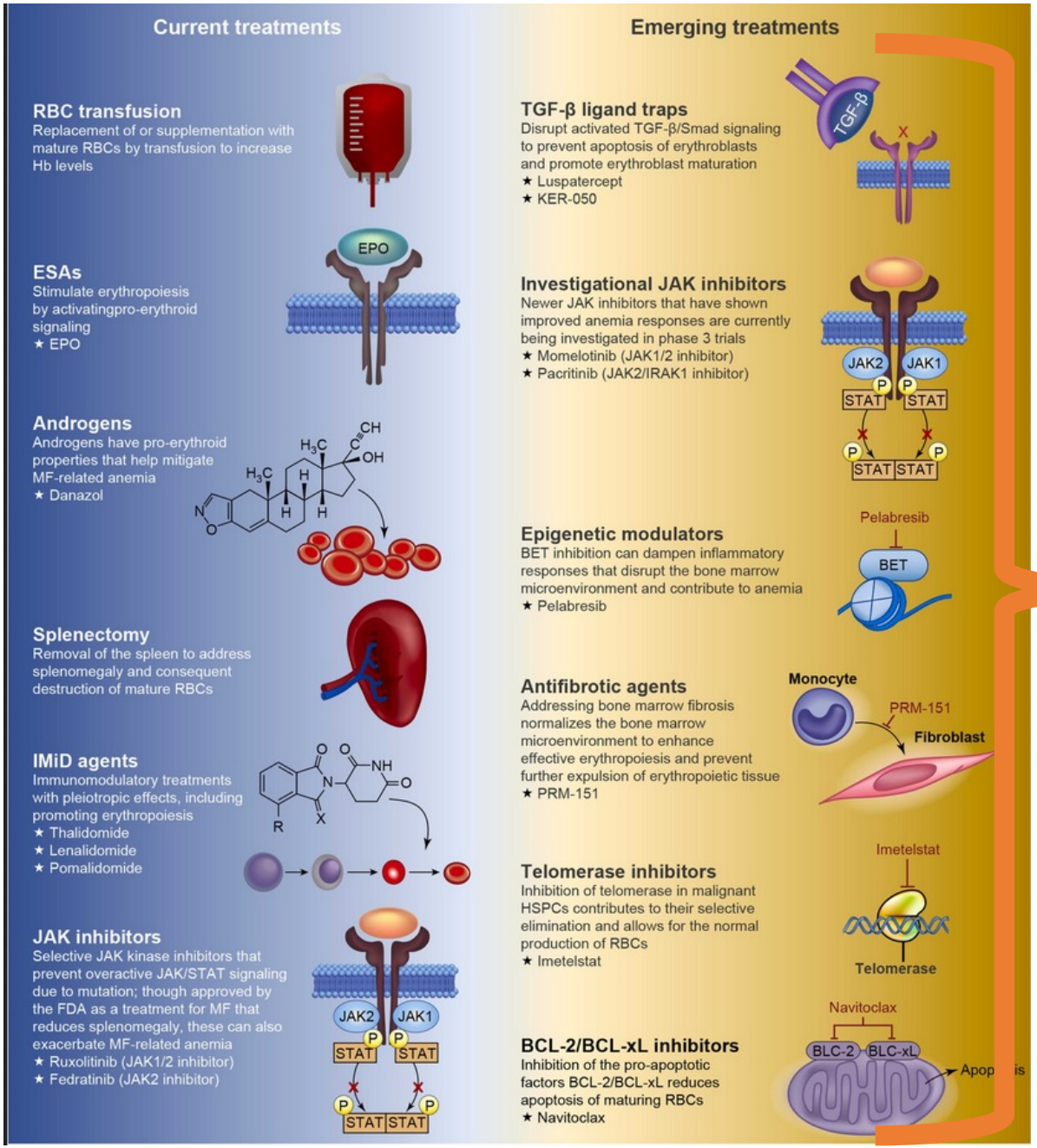
Conclusions

The results of PERSIST-2 demonstrate the clinical benefit of pacritinib in patients with myelofibrosis and thrombocytopenia including those with prior JAK2i therapy

The benefit of pacritinib in terms of SVR and TSS reduction was observed in patients with baseline platelet count less than 50 × 109 /L and those with prior ruxolitinib treatment

The pacritinib twice daily arm met both coprimary SVR and TSS reduction end points, and reduce grade and frequency of gastrointestinal toxic effects

Clinical improvement in hemoglobin and reduction in transfusion requirements were also more frequent in patients who received pacritinib, particularly with twice-daily dosing



- FUTURO

Passamonti F, Harrison CN, Mesa RA, Kiladjian JJ, Vannucchi AM, Verstovsek S. Anemia in myelofibrosis: Current and emerging treatment options. Crit Rev Oncol Hematol. 2022 Dec;180:103862. doi: 10.1016/j.critrevonc.2022.103862. Epub 2022 Nov 1. PMID: 36332787.

GRAZIE
DELL'ATTENZIONE