MANAGEMENT OF MYELOFIBROSIS: 2023 UPDATES

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Disclosures for Jean-Jacques Kiladjian, MD, PhD

Royalty	N/A
Receipt of intellectual property/ Patent holder	N/A
Consulting fee, Advisory boards	Novartis, BMS, Abbvie, Incyte, AOP Health, GSK
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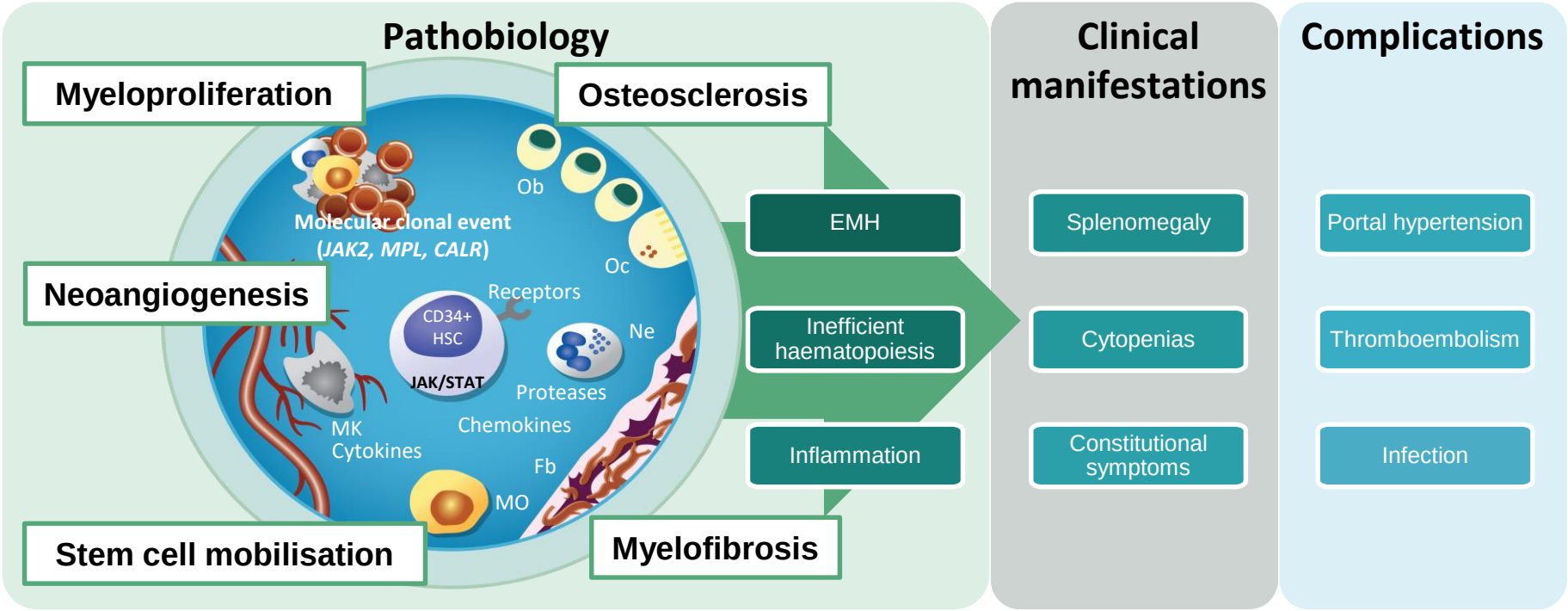
Fees for non-CME services	N/A
Contracted research (institutional)	N/A
Ownership interest (stocks, stock options)	N/A
Other	N/A

Clinical Manifestations of Myelofibrosis



CD34: cluster of differentiation 34; EMH: extramedullary haematopoiesis; Fb: fibroblast; HSC: haematopoietic stem cell; JAK: Janus kinase; MK: megakaryocyte; MO: monocyte; MPL: myeloproliferative leukaemia virus oncogene; Ne: neutrophil; Ob: osteoblast; Oc: osteoclast; STAT: signal transducer and activator of transcription.

Mughal TI et al. *Int J Gen Med*. 2014;7:89-101.

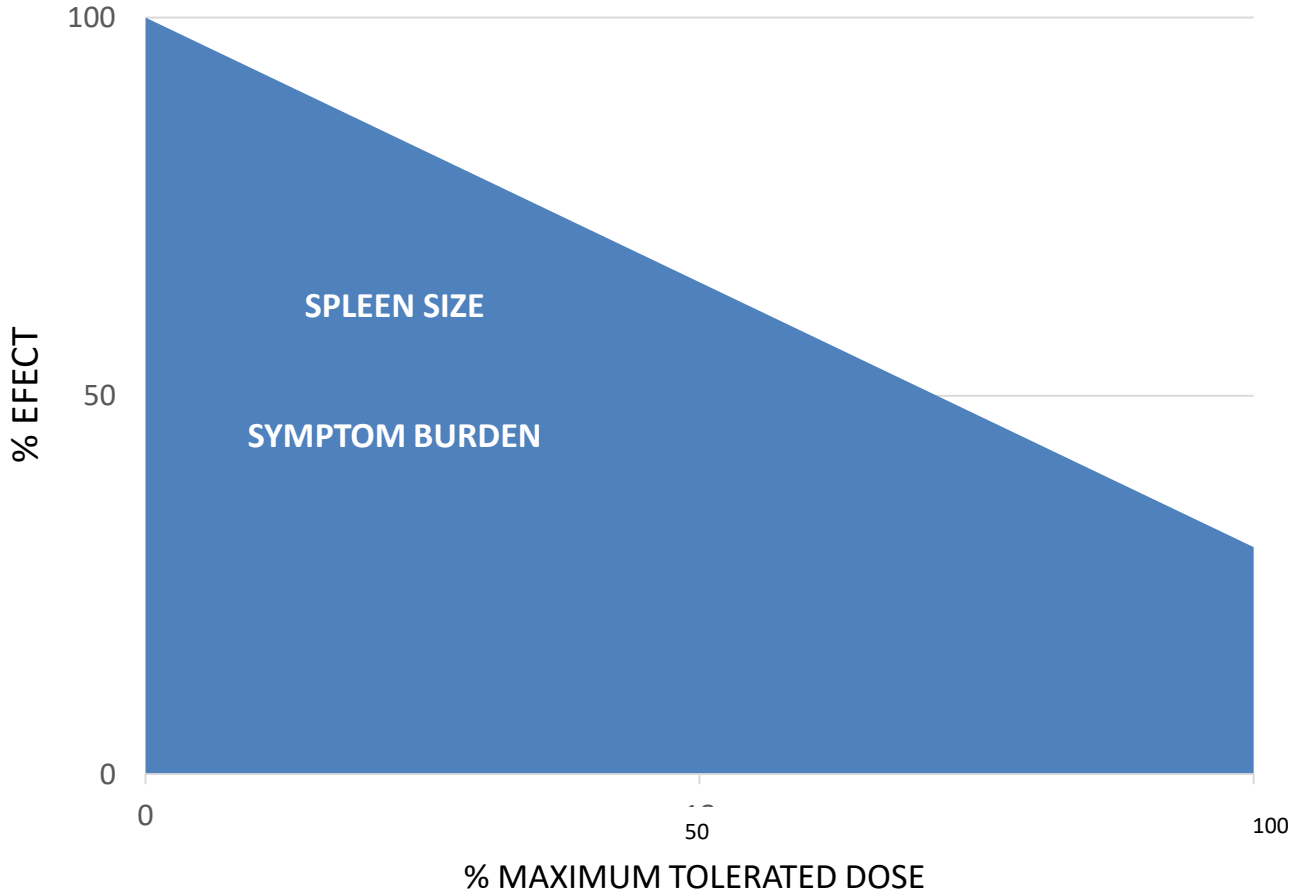
Key International MF Treatment Guidelines

	ELN[1]	NCCN[2]	ESMO[3]	BCSH[4,5]
Diagnosis	WHO 2016[6]	WHO 2016[6]	WHO 2008	Campbell and Green 2006[7] + CALR diagnostic
Treatment	Ruxolitinib for splenomegaly • Int-2 and high-risk • Int-1 if highly symptomatic (local symptoms or impairment of food intake) • Patients resistant to or intolerant of HU	Ruxolitinib for • Low/Int-1 risk if symptomatic • Int-2 and high risk if not a transplant candidate and platelet count > 50k	Ruxolitinib for patients with symptomatic splenomegaly or constitutional symptoms (if allowed by label for Low and Int-1 risk MF)	Ruxolitinib for • Symptomatic splenomegaly • MF symptoms that impinge upon QoL • Hepatomegaly and portal hypertension due to MF
Response	Tefferi Blood 2006[8]; updated in 2013	ELN (Tefferi Blood 2013)[9]	ELN (Tefferi Blood 2013)	• Tools like the MPN-SAF • ELN (Tefferi Blood 2013)

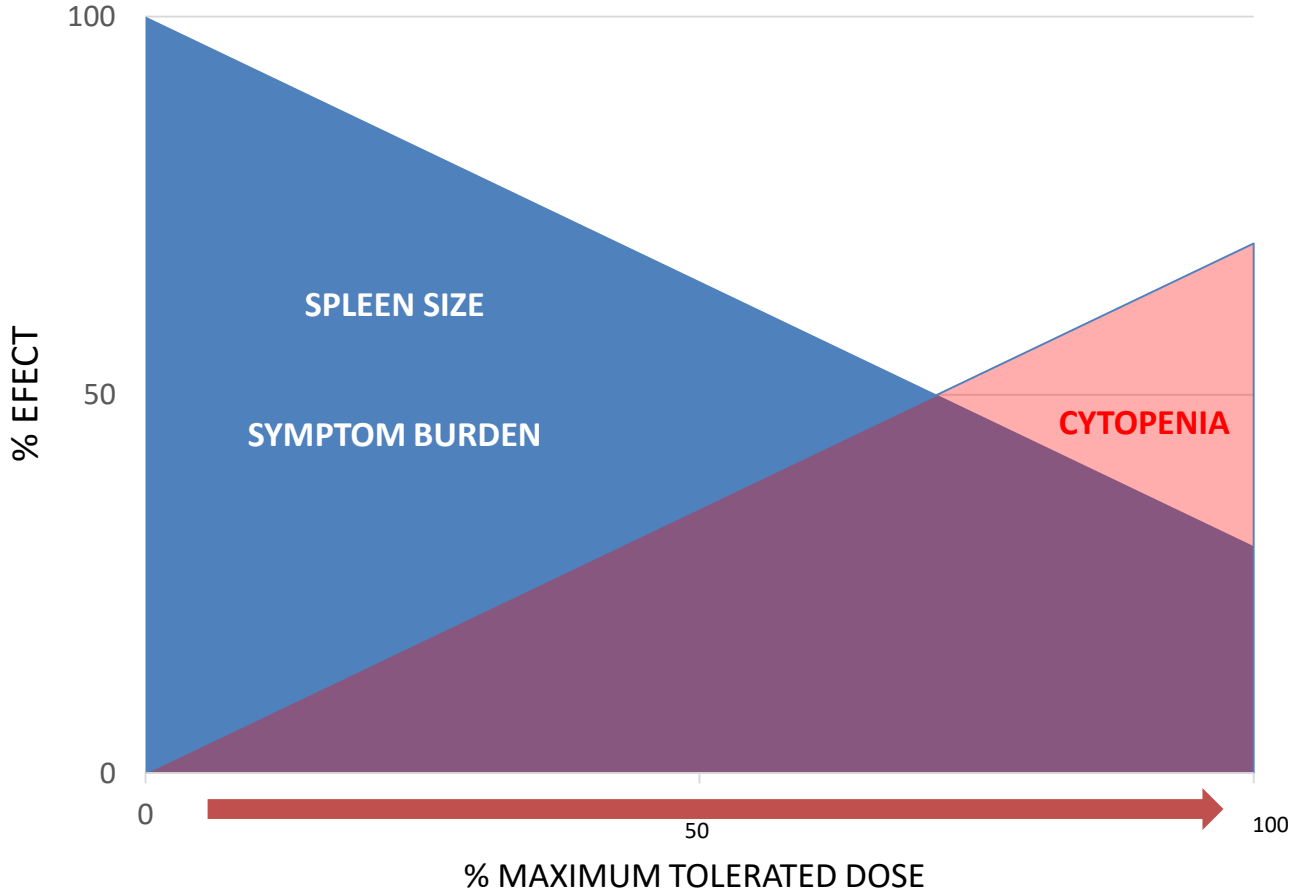
1.Barbui T, et al. Leukemia. 2018.
2.NCCN Clinical Practice Guidelines in Oncology Version 1.2017 – September 26, 2016.
3.Vannucchi AM et al, Annals of Oncology. 2015(Supplement 5);v85-v99.
4.Reilly JT, et al. Br J Haematol. 2012;158:453-471.
5.Reilly JT, et al. Br J Haematol. 2014;167:418-438.
6.Arber D, et al. Blood. 2016;127:2391-2405.
7.Campbell PJ and Green AR. N Engl J Med. 2006;355:2452-2466.
8.Tefferi A, et al. Blood. 2006;108(5):1497-1503.
9.Tefferi A, et al. Blood. 2013;122(8):1395-1398.

BCSH, British Committee for Standards in Hematology, ELN, European LeukemiaNet, ESMO, European Society of Molecular Oncology; Int-1, intermediate-1; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasm-Symptom Assessment Form; NCCN, National Comprehensive Cancer Network; QoL, quality of life; WHO, World Health Organization.

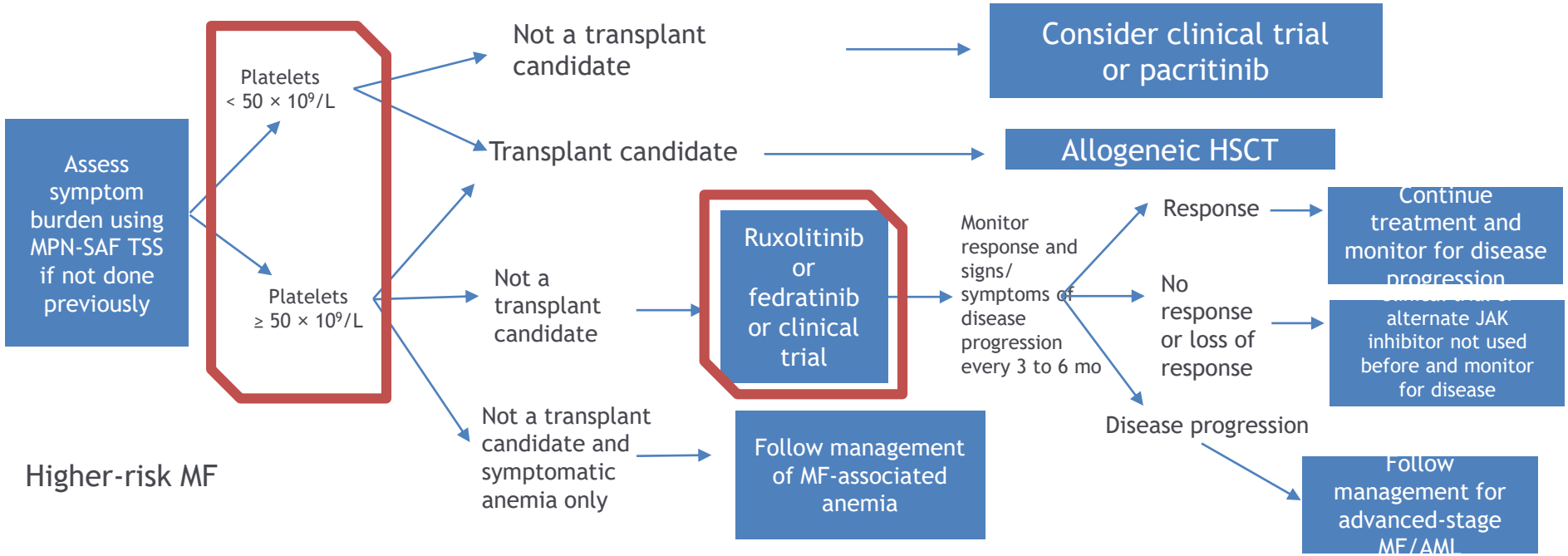
IMPACT OF RUXOLITINIB DOSING



IMPACT OF RUXOLITINIB DOSING



Updated NCCN Guidelines - Treatment for Higher-Risk MF

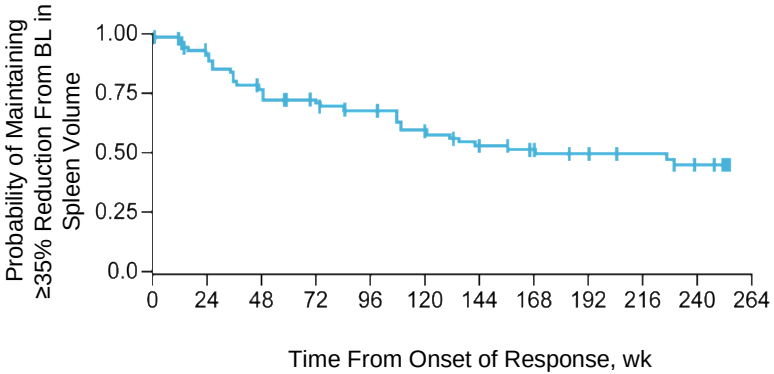


- Adapted from NCCN Guidelines by J.J. Kiladjian. Myeloproliferative neoplasms (V3.2022). 2022. https://www.nccn.org/guidelines.

COMFORT-I and COMFORT-II: Outcomes

COMFORT-I

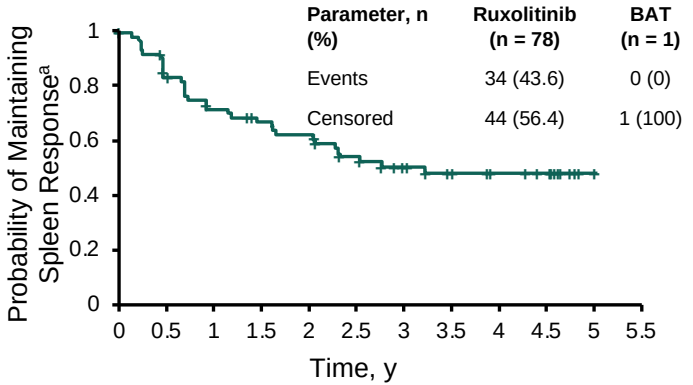
Randomised, phase 3 study in which patients with Int-2 risk/ high-risk MF received **ruxolitinib** (15/20 mg BID) vs **PBO**



59.4% (92/155) had achieved a ≥35% SVR at any time during the study, with a median duration of response of **168.3 wks**

COMFORT-II

Randomised, phase 3 study in which patients with Int-2 risk/ high-risk MF received **ruxolitinib** (15/20 mg BID) vs **BAT**



≥35% SVR among ruxolitinib-randomised patients were sustained with long-term therapy (median, 3.2 y); probability of maintaining SVR at 3 years: 0.51 (95% CI, 0.38-0.62) and at 5 years: 0.48 (95% CI, 0.35-0.60)

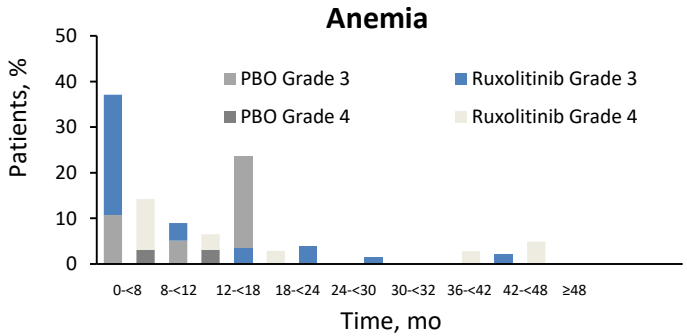
[a] Interval from first spleen volume measurement of ≥35% reduction from baseline at any time on study and the first scan that is no longer a 35% reduction and that is a >25% increase over on-study nadir.

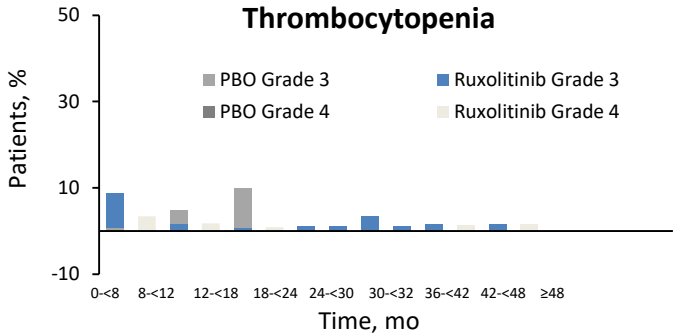
BAT: best available therapy; BL: baseline; Int: Intermediate; PBO: placebo; SVR: spleen volume reduction.

Verstovsek S et al. *J Hematol Oncol*. 2017;10:55. Harrison CN et al. *Leukemia*. 2016;30:1701-1707.

COMFORT-I and COMFORT-II: 5-Year Safety Findings

Preferred Term, n (Exposure-Adjusted Rate)	Ruxolitinib Randomised (n = 146)	Ruxolitinib Randomised + Extension (n = 146)	BAT Randomised (n = 73)	Ruxolitinib Crossover (n = 45)	Total Ruxolitinib (n = 191)
Any AE	71 (41.7)	104 (25.4)	24 (35.8)	26 (32.6)	130 (26.6)
Anemia	21 (12.3)	31 (7.6)	5 (7.5)	12 (15.1)	43 (8.8)
Thrombocytopenia	14 (8.2)	20 (4.9)	4 (6.0)	9 (11.3)	29 (5.9)
Pneumonia	2 (1.2)	10 (2.4)	4 (6.0)	1 (1.3)	11 (2.2)
General physical health deterioration	2 (1.2)	5 (1.2)	3 (4.5)	3 (3.8)	8 (1.6)
Acute renal failure	3 (1.8)	4 (1.0)	0	3 (3.8)	7 (1.4)[d]





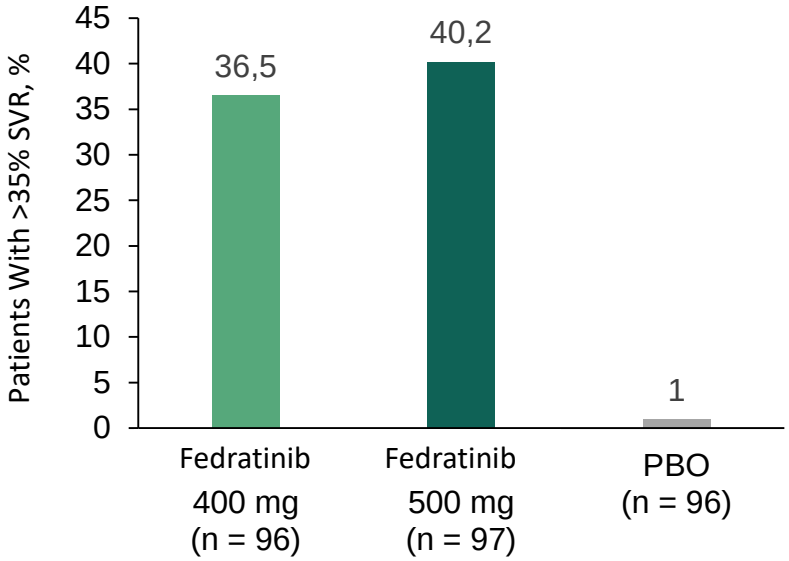
AE: adverse event.

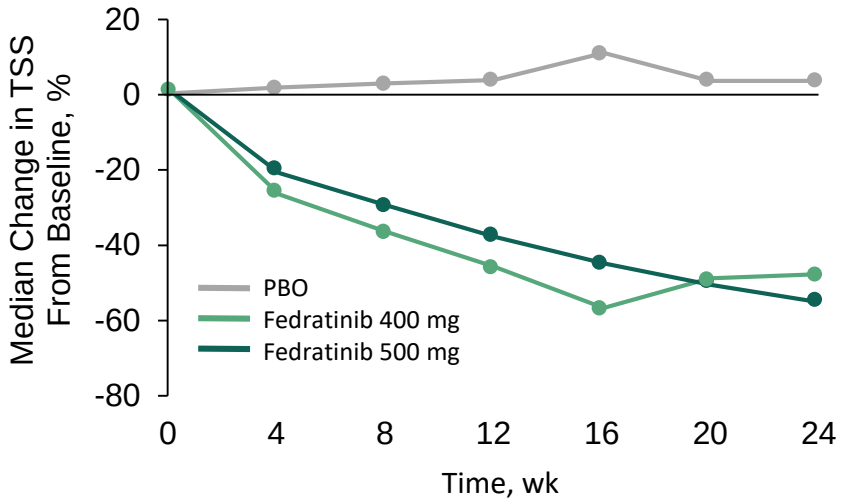
Verstovsek S et al. *J Hematol Oncol*. 2017;10:55.
Harrison CN et al. *Leukemia*. 2016;30:1701-1707.

JAKARTA: Outcomes

JAKARTA

Randomised, phase 3 study in which JAKi-naïve patients with Int-2 risk/ high-risk MF received **fedratinib** (400/500 mg OD) vs **PBO**





TSS: Total Symptom Score.

Pardanani A et al. *JAMA Oncol.* 2015;1:643-651.

JAKARTA: Safety Profile

AEs, n (%)	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		PBO	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nonhaematologic						
Diarrhoea	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)
Haematologic						
Anaemia	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)

Thiamine levels to be checked before starting treatment and periodically during treatment

Black box warning of Wernicke encephalopathy

Pardanani A et al. *JAMA Oncol.* 2015;1:643-651.

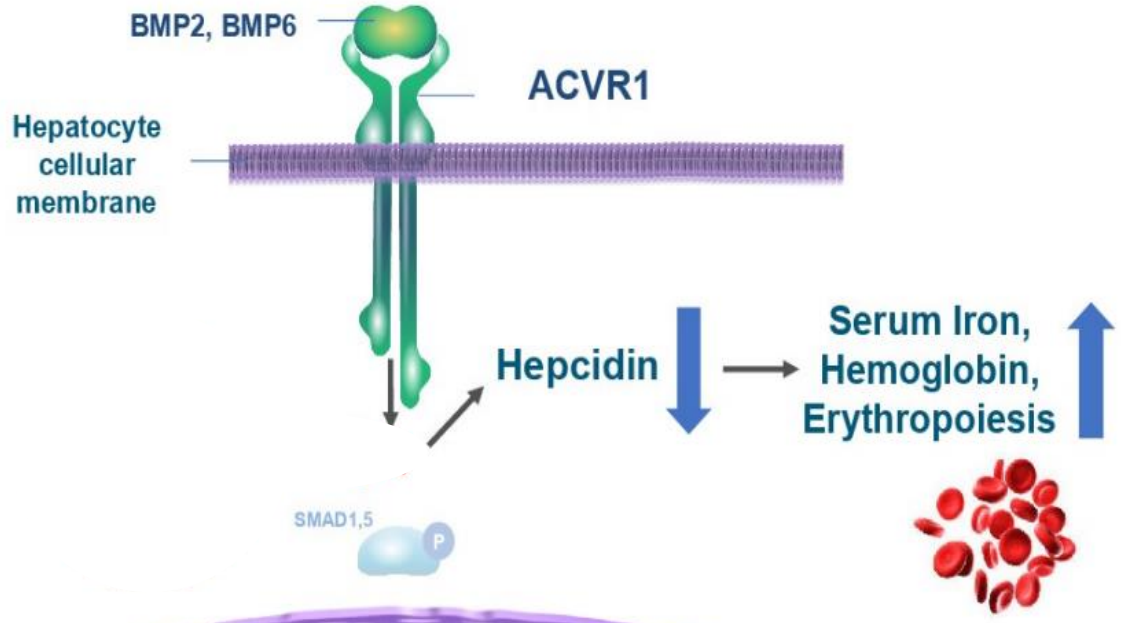
JAK Inhibitors - *Kinome Mapping*

	IC_{50} (nanomolar)						
	JAK1	*JAK2*	*JAK3*	*TYK2*	*ACVR1*	*IRAK1*	*FLT3*
Ruxolitinib[a,b]	2.8	4.5	322	30	> 1000	---	---
Fedratinib[a,b,c]	105	3	> 1000	405	273	---	15
Pacritinib[a,b,d]	1280	6.0	18.3	27	16.7	13.6	14.8
Momelotinib[a,b,e]	11	18	155	17	52.5	---	401

- IC50, half-maximal inhibitory concentration.
- a. Duenas-Perez AB, Mead AJ. Ther Adv Hematol. 2015;6:186-201; b. Oh S, et al. Clin Lymphoma Myeloma Leuk. 2022; 22(Suppl2): S327/ Poster MPN-145; c. Talpaz M, et al. Leukemia. 2021;35:1-17; d. Singer JW, et al. J Exp Pharmacol. 2016;8:11-19; e. Azhar M, et al. Blood Adv. 2022;6:1186-1192.

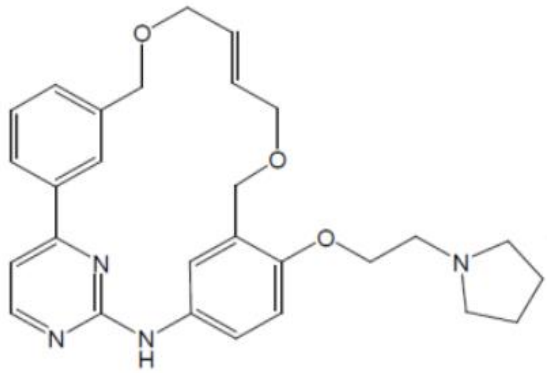
ACVR1 Signaling Pathway in MF

Chronic inflammation drives hyperactivation of ACVR1 in MF, leading to elevated hepcidin, dysregulated iron homeostasis, and anemia



- ACVR1, activin receptor 1.
- Mesa RA, et al. J Clin Oncol. 2022;40(16_suppl): Abstract 7002.

Pacritinib: Selective JAK2, ACVR1, and IRAK1 Inhibitor



Pacritinib

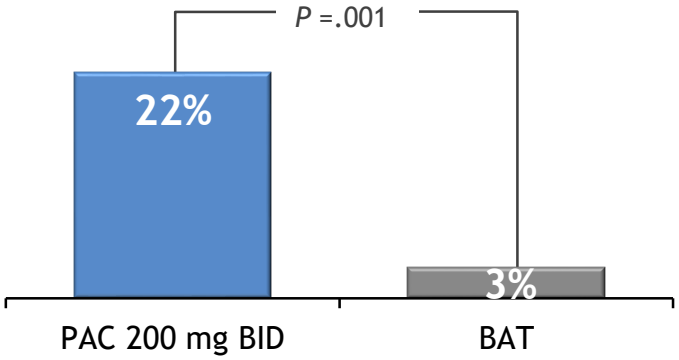
- Pacritinib is an oral JAK2, ACVR1, and IRAK1 inhibitor approved in 2022 by FDA (not EMA) for intermediate- or high-risk primary or secondary MF with platelet counts < 50 × 10^9/L[a]
- Pacritinib has high selectivity for JAK2 over JAK3 and TYK2 and does not inhibit JAK1; this inhibitory profile results in minimal exacerbation of thrombocytopenias[b]
- Pacritinib also strongly inhibits ACVR1, thus enhancing erythropoiesis and reducing transfusion dependence[c]
- PERSIST-1 and PERSIST-2: phase 3 studies of pacritinib in 430 patients with MF[a,d,e]
- Most frequent nonhematologic AEs: diarrhea, nausea, and peripheral edema[a]

- a. Pacritinib [PI]. Approved 2022; b. Singer JW, et al. J Exp Pharmacol. 2016;8:11-19; c. Oh ST, et al. To be presented at: 64th ASH Annual Congress, New Orleans, LA; December 11, 2022. Abstract 628. Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236; d. Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

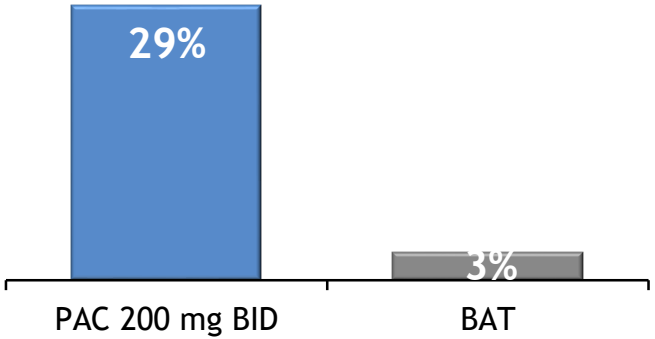
PERSIST-2

Spleen Volume Responses ≥ 35% at Week 24

ITT Population



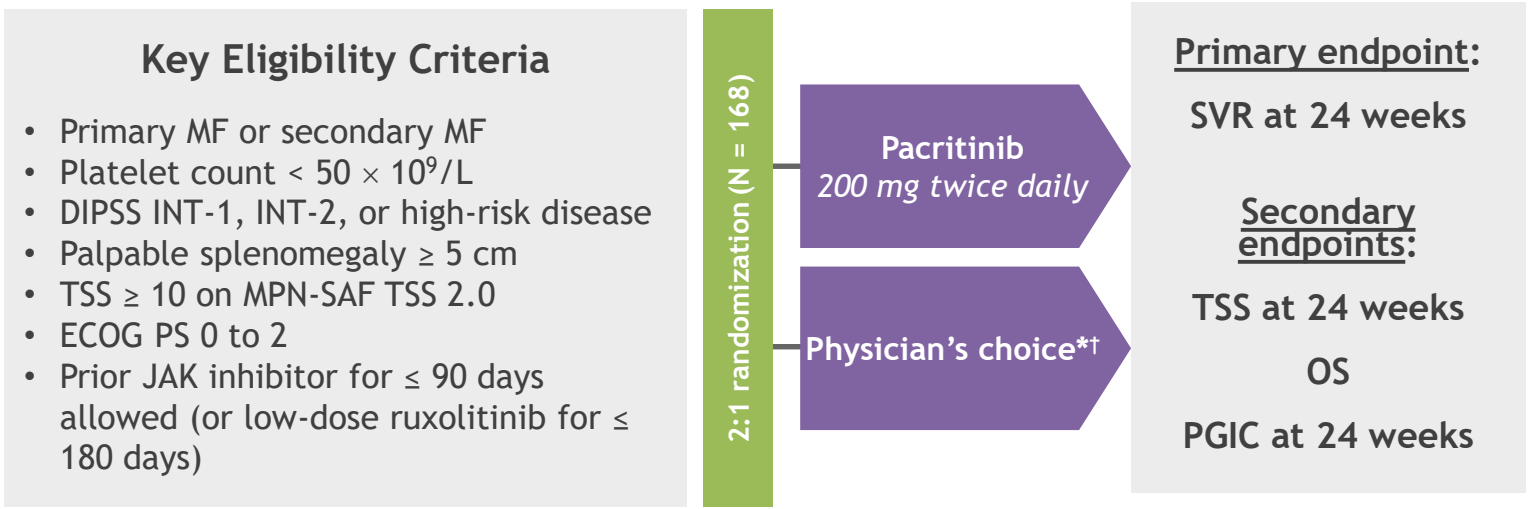
Patients With Platelets < 50 × 10^9/L



Additional subgroup analyses demonstrated patients receiving pacritinib achieved SVR ≥ 35% regardless of subgroup (eg, sex, age, *JAK2* V617F mutation status, prior treatment with JAK2 inhibitors, and baseline cytopenias)

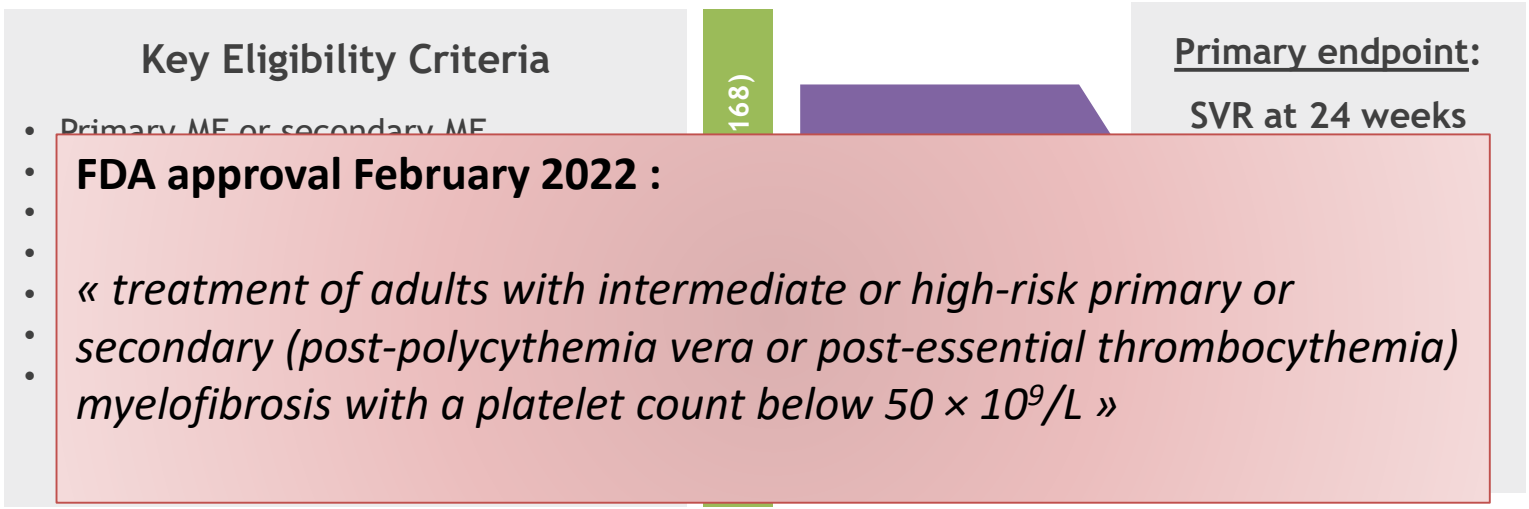
- PAC, pacritinib.
- Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

PACIFICA: Phase 3 Pacritinib Trial



- *Physician's choice includes any one of the following: low-dose ruxolitinib, corticosteroids, hydroxyurea, danazol. Investigators may select individual physician's choice agents but cannot combine agents or give them sequentially.
†Crossover not permitted.
ClinicalTrials.gov. https:/clinicaltrials.gov/ct2/show/NCT03165734

PACIFICA: Phase 3 Pacritinib Trial

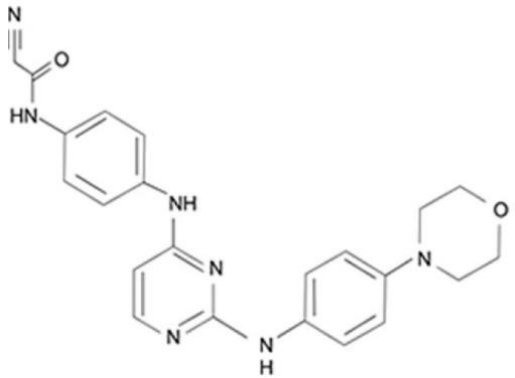


FDA approval February 2022 :

« 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 »

- *Physician's choice includes any one of the following: low-dose ruxolitinib, corticosteroids, hydroxyurea, danazol. Investigators may select individual physician's choice agents but cannot combine agents or give them sequentially.
†Crossover not permitted.
ClinicalTrials.gov. https:/clinicaltrials.gov/ct2/show/NCT03165734

Momelotinib: Emerging JAK1, JAK2, and ACVR1 Inhibitor



Momelotinib

- Momelotinib is an emerging inhibitor of JAK1, JAK2, and ACVR1 [a,b]
- This September FDA has approved momelotinib for the treatment of intermediate or high-risk myelofibrosis, including primary MF or secondary MF (post-PV and post-ET), in adults with anemia. [c]
- SIMPLIFY-1 and SIMPLIFY-2: completed phase 3 trials of momelotinib in first-line and second-line settings[a,b]
- MOMENTUM: completed phase 3 trial comparing momelotinib to danazol for MF with anemia[d]
- Most frequent nonhematologic AEs: diarrhea, nausea, and asthenia/fatigue[d]

- a. Mesa RA, et al. J Clin Oncol. 2017;35:3844-3850; b. Harrison CN, et al. Lancet Haematol. 2018;5:e73-e81;c. GSK announces extension of FDA review period for momelotinib | GSK d. Mesa RA, et al. J Clin Oncol. 2022;40(S16): Abstract 7002.

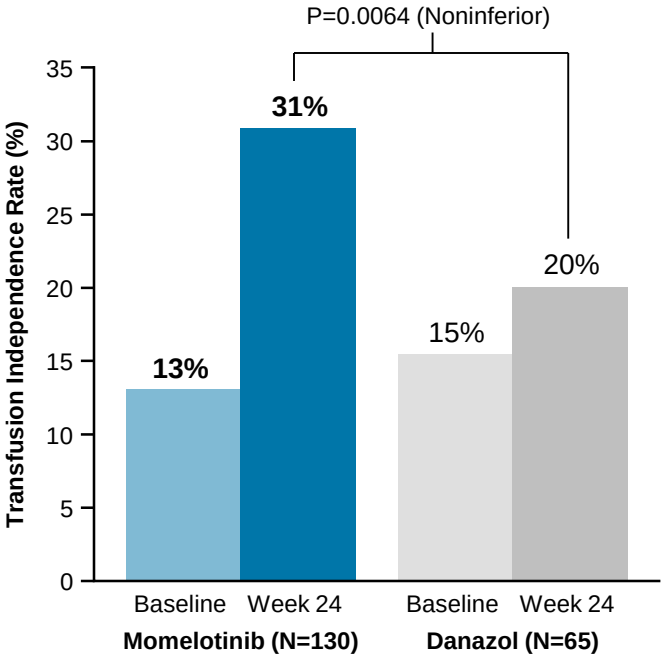
SIMPLIFY-1, SIMPLIFY-2, and MOMENTUM Trials

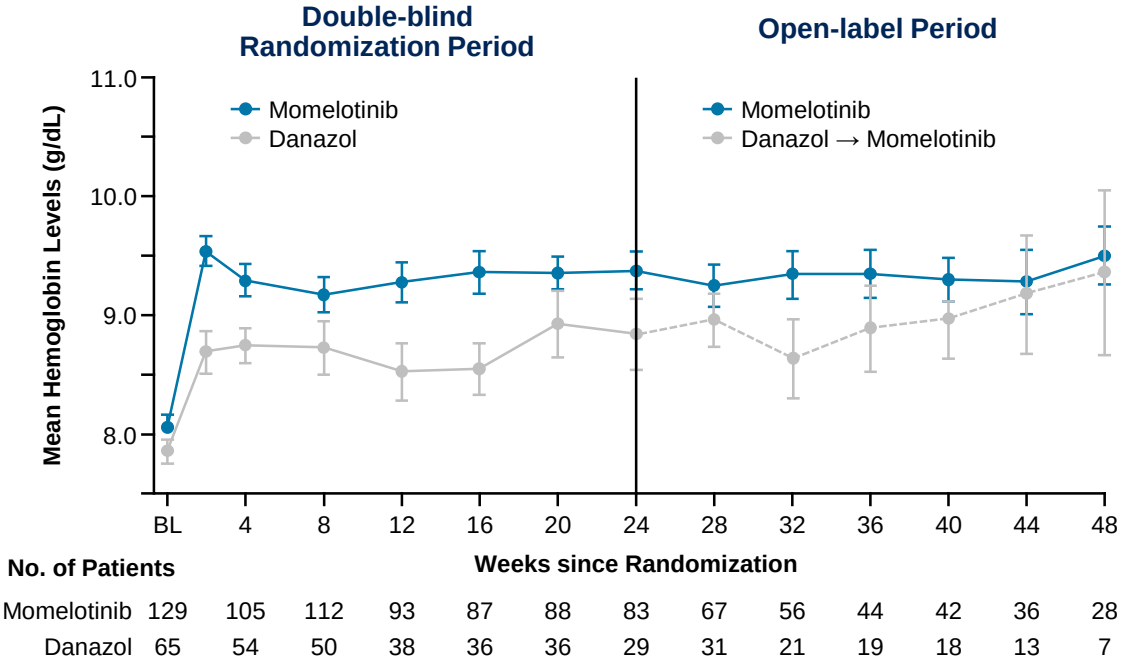
Agent	Trial	SVR 35	TSS 50 (at Wk 24)	Additional Outcomes	TRAEs
Momelotinib	**SIMPLIFY-1** MOM vs RUX (n = 432) (Mesa et al. 2017)	27% vs 29% (*P* = .011; noninferior)	28% vs 42% (*P* = .98; noninferiority was not met)	Transfusion rate, TI, and TD improved with MOM (nominal *P* ≤ .19 for all)	Anaemia, thrombocytopenia, infections, peripheral neuropathy
	SIMPLIFY-2 MOM vs BAT (n = 156) (Harrison et al. 2018)	7% vs 6% (*P* = .90)	26% vs 6% (nominal *P* = .0006)	TI: 43% vs 21% (*P* = .0012)	Anaemia, thrombocytopenia, peripheral neuropathy
	MOMENTUM MOM (n = 130) vs Danazol (n = 65) (Verstovsek et al. 2023)	23% vs 3% (*P* = .0006)	25% vs 9% (*P* = .0095)	TI: 31% vs 20% (*P* = .0064, one-sided; noninferior)	Thrombocytopenia, anaemia, infections

TRAE: treatment-related AE.

Mesa RA et al. *J Clin Oncol.* 2017;35:3844-3850. Harrison CN et al. *Lancet Haematol.* 2018;5:e73-e81. Verstovsek S et al. *Lancet*. 2023;401:269-280. Passamonti F et al. *Crit Rev Oncol Hematol*. 2022;180:103862.

Transfusion Independence* Rate at W24 and Mean Hemoglobin Over Time





*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.

Verstovsek S et al. *HemaSphere* 2022;6:S3;96-97; abstract S195.

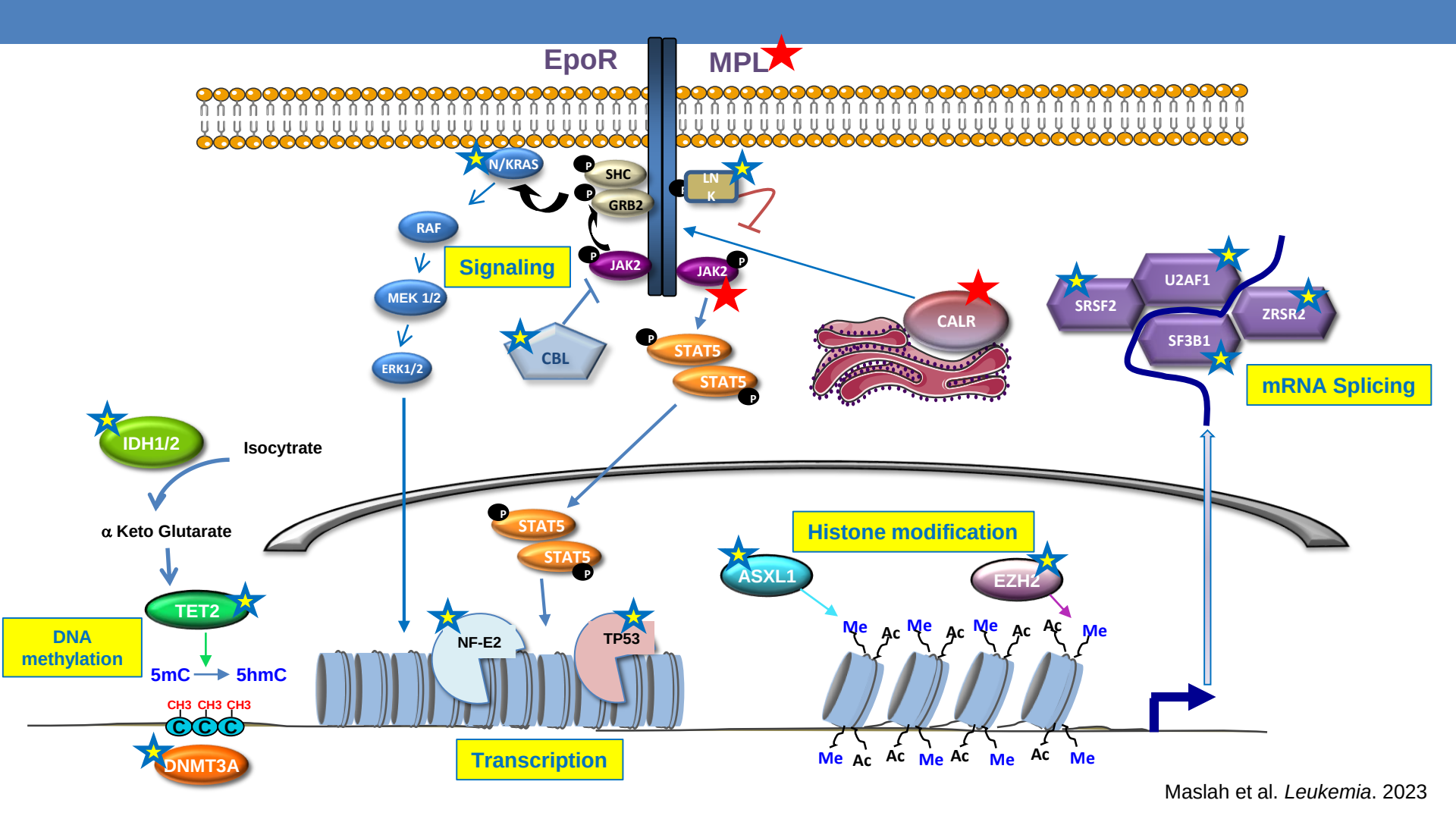
Potential future sequence of JAKi therapy..?

1. First-line → ruxolitinib
   - Fedratinib 1st line: very large spleen and thrombocytopenia? Specific co-morbities (cancer, opportunistic infection…)
2. Second-line spleen and thrombocytopenia → fedratinib
   - (FREEDOM study)
3. Second-line anemia and ? Thrombocytopenia → momelotinib
   - (MOMENTUM study)
4. Second- or first-line thrombocytopenia → pacritinib
   - (PACIFICA study)

Speaker's own opinion

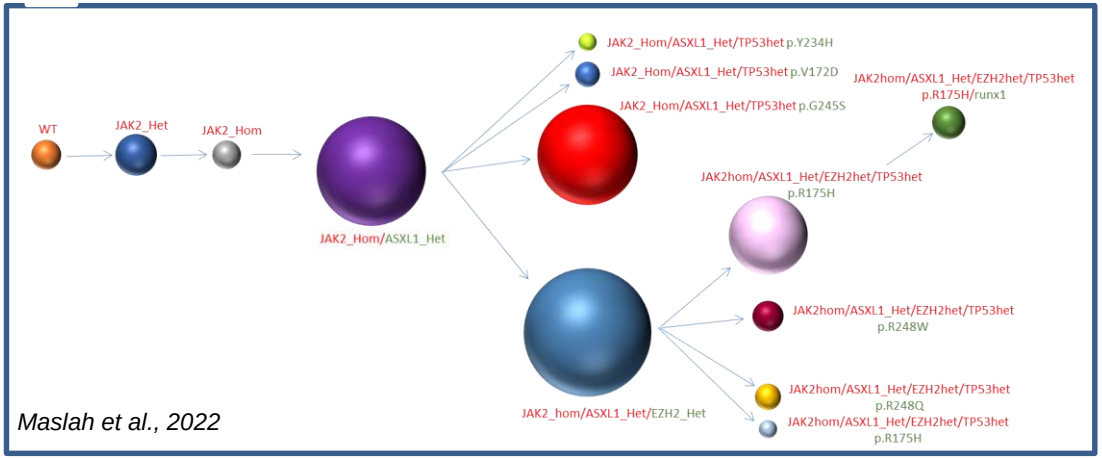
OBSTACLES TO CURE

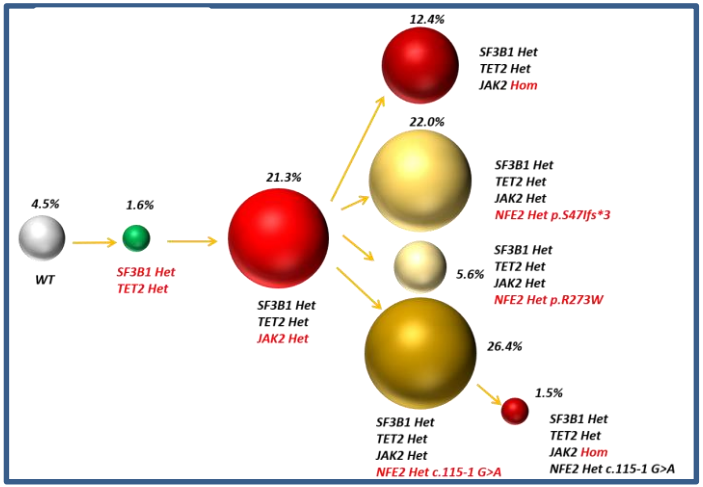
- Disease complexity
- Dynamic changes of clonal architecture
- Limitations of currently available drugs

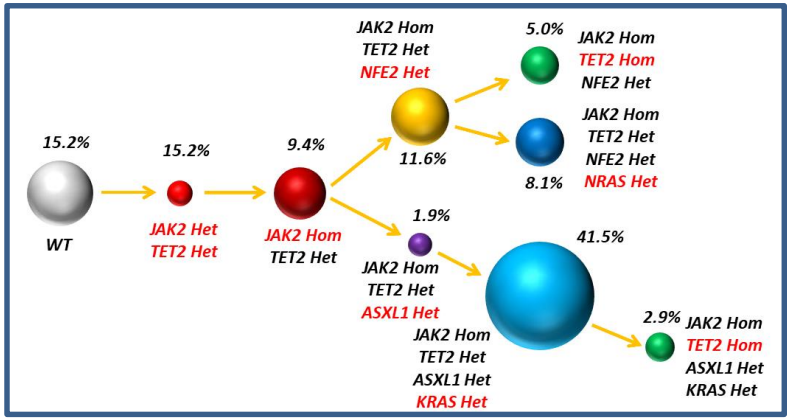


Maslah et al. *Leukemia*. 2023

Clonal architecture in MPN: from very simple to very complex







PATH TO CURE

- Disease modifying therapies

What is a disease modifying therapy?

Disease modifying activity:

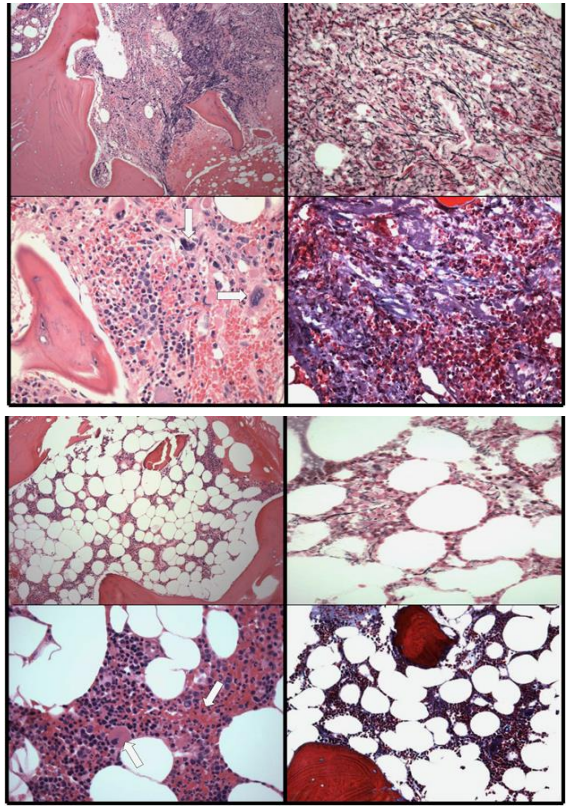
- Block the underlying pathophysiology of the disease

Potential biomarkers of interest in classical MPNs:

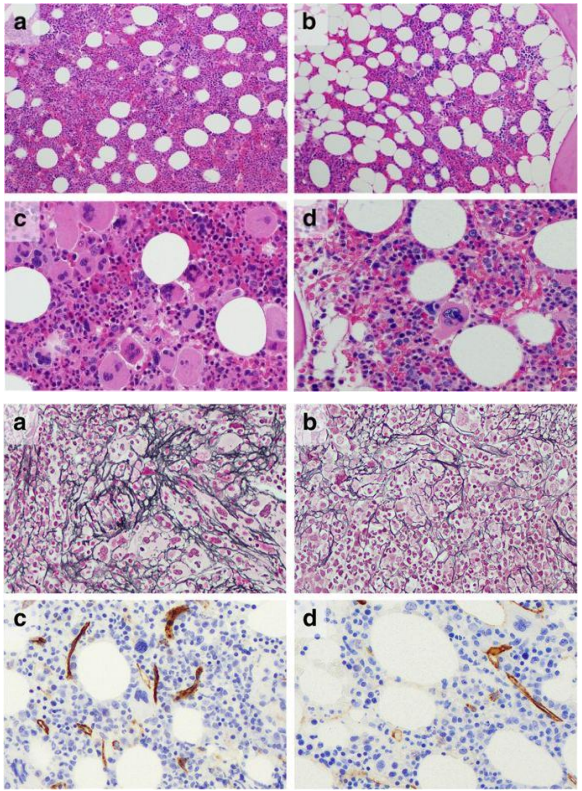
- Bone marrow histopathology
- Molecular lesions
- Inflammation

What is a disease modifying therapy?

- Histological responses
  - In early MF
    - *rIFN alpha-2b*



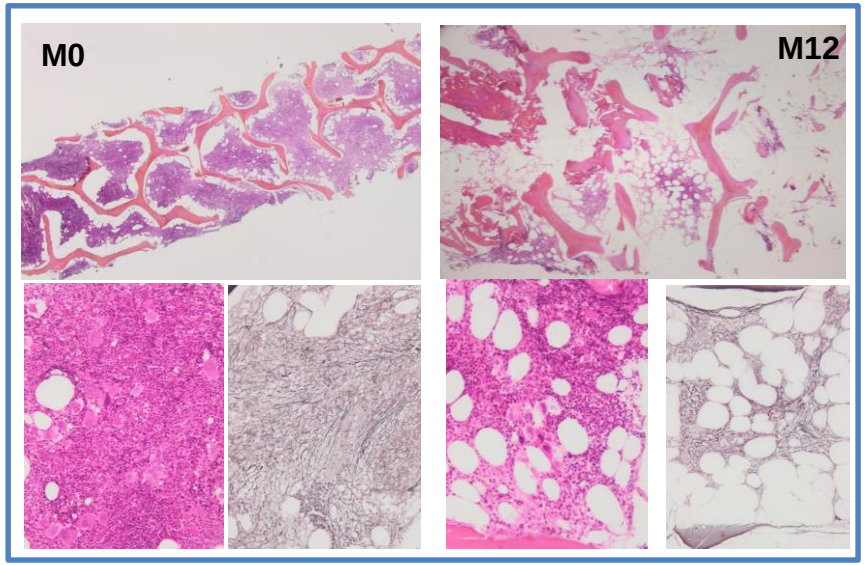
Silver RT, et al. *Leukemia*. 2009;23(7):1366-9.

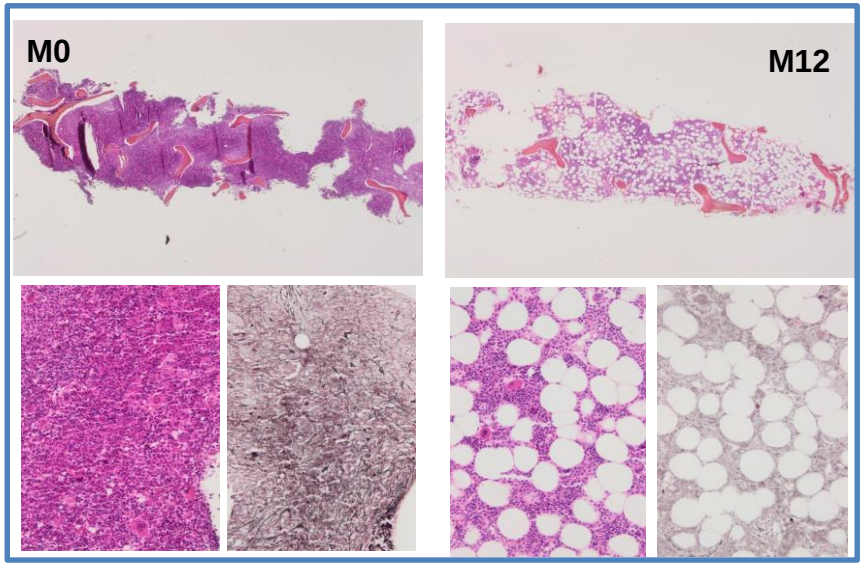


Pizzi M, et al. *Mod Pathol.* 2015;28(10):1315-23.

What is a disease modifying therapy?

- Histological responses
  - In early MF
  - In MF *- ruxolitinib + peg-IFNa 2a (RUXOPEG)*





Kiladjian JJ, et al. *Blood* (2022) 140 (S1): 577–578.

What is a disease modifying therapy?

- Histological responses
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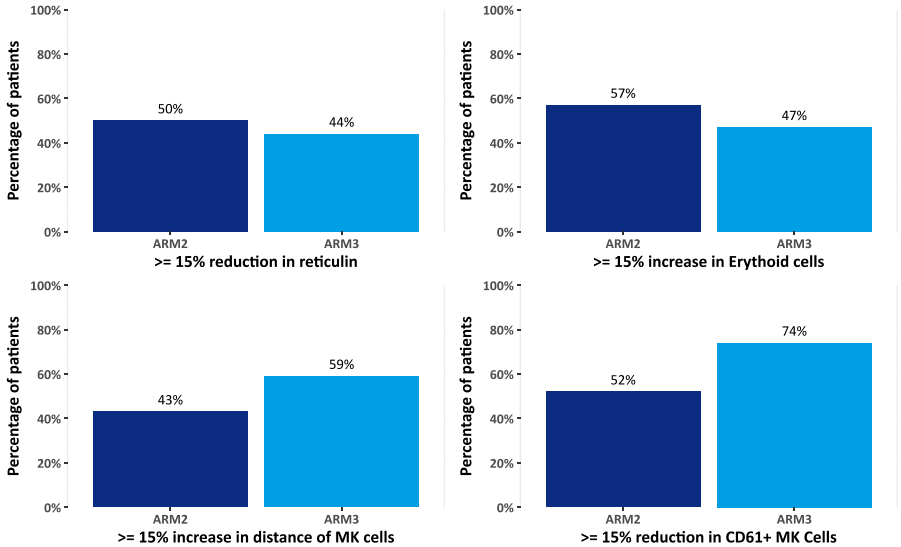

Bone marrow improvement is quantified by decrease in megakaryocyte clusters, reduced reticulin density and increase in erythrocytes

Mascarenhas et al. *EHA 2022, S198*

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Clinical relevance of histological response ?

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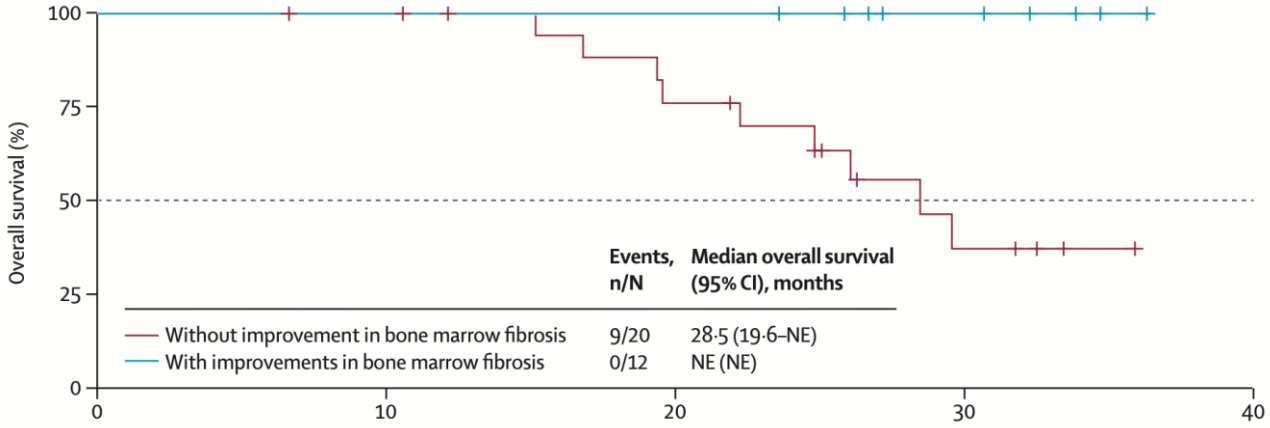

Pemmaraju et al. *Lancet Haematol. 2022;9(6):e434-e444.*

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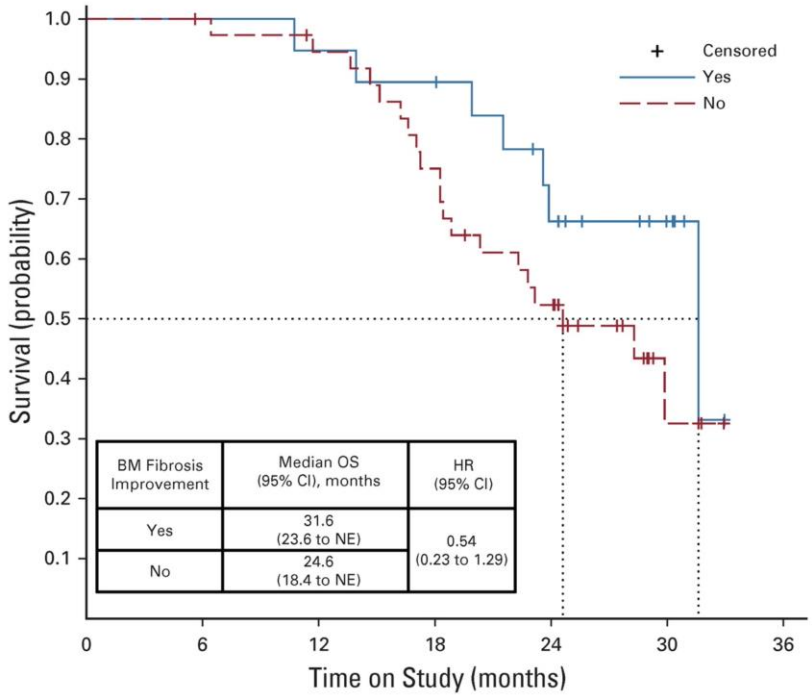

Mascarenhas et al. *J Clin Oncol*. 2021;39(26):2881-2892

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Disease modifying activity:

- Block the underlying pathophysiology of the disease

Potential biomarkers of interest in classical MPNs:

- Bone marrow histopathology
- Molecular lesions
- Inflammation

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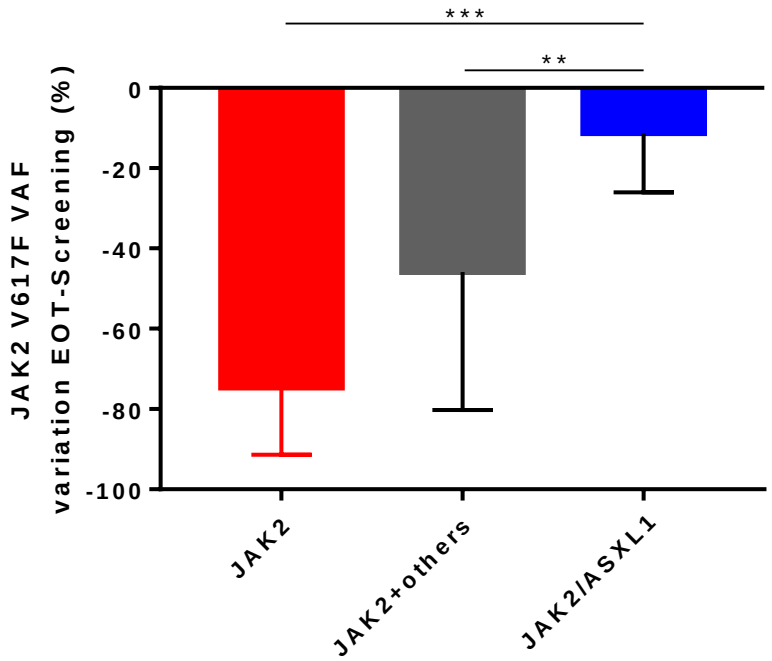

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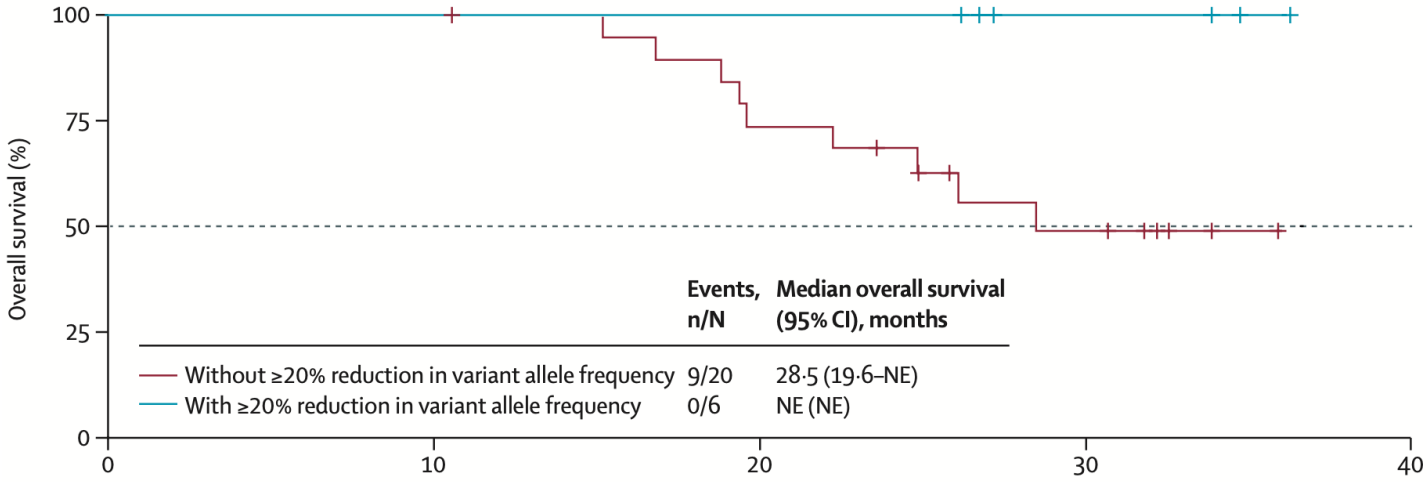

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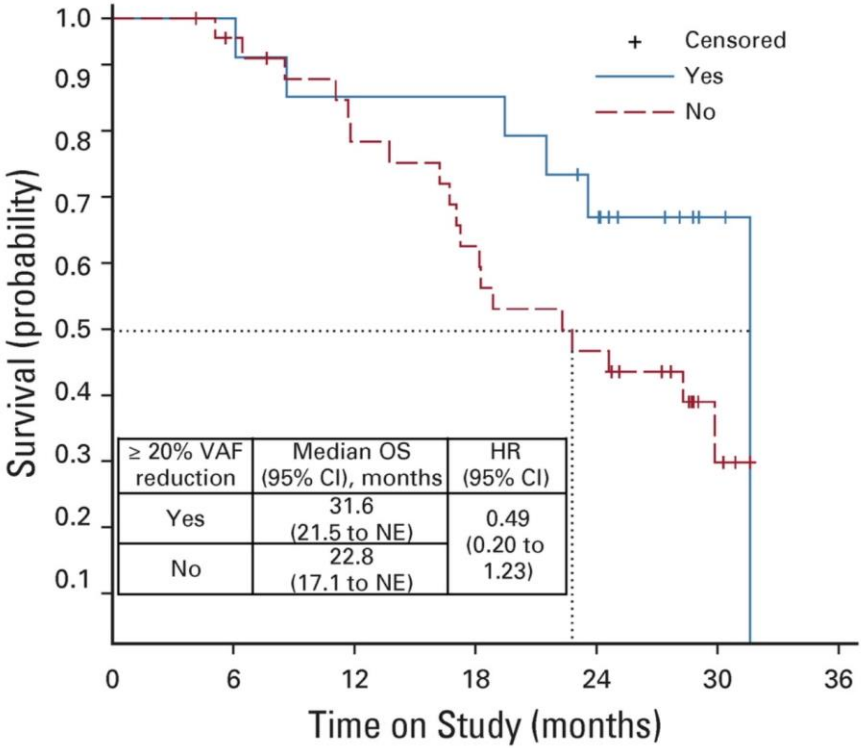

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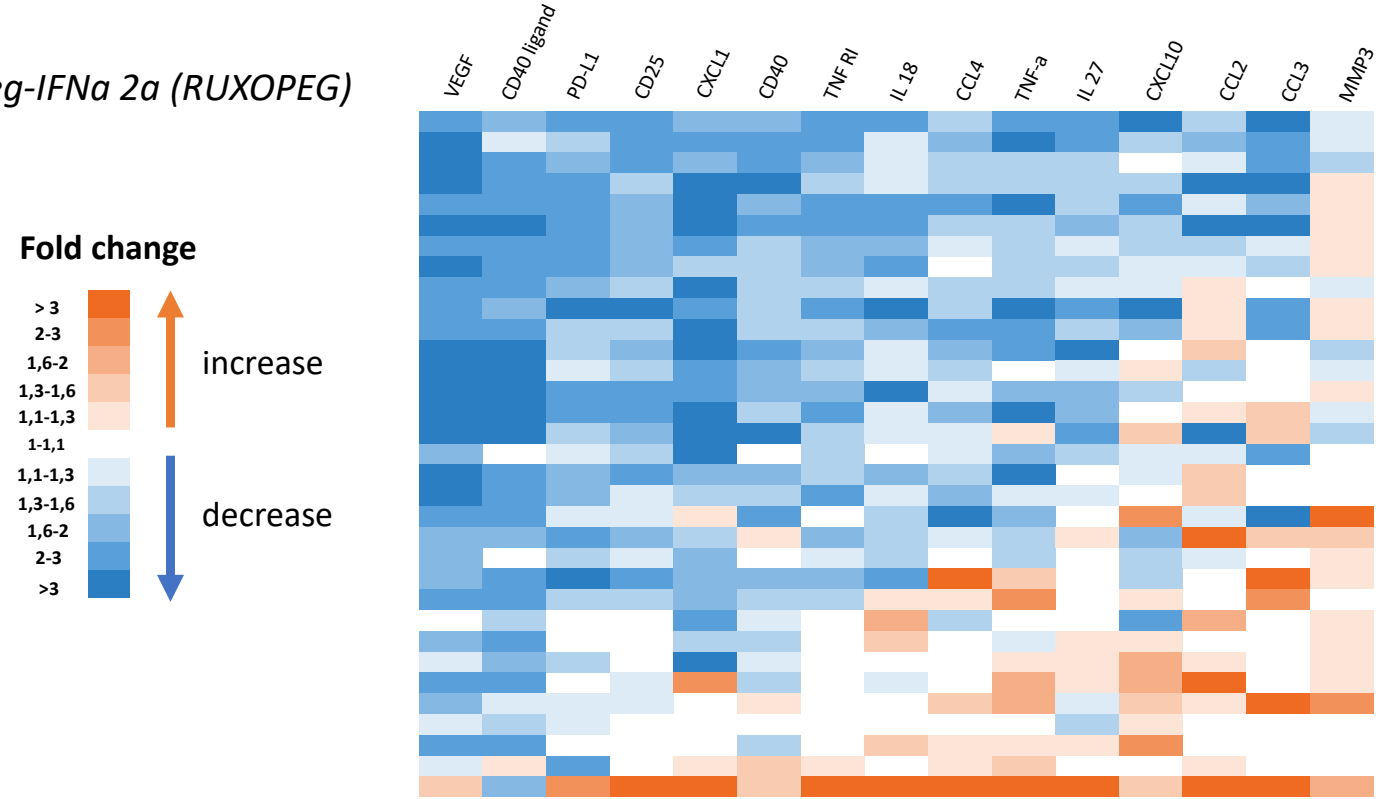

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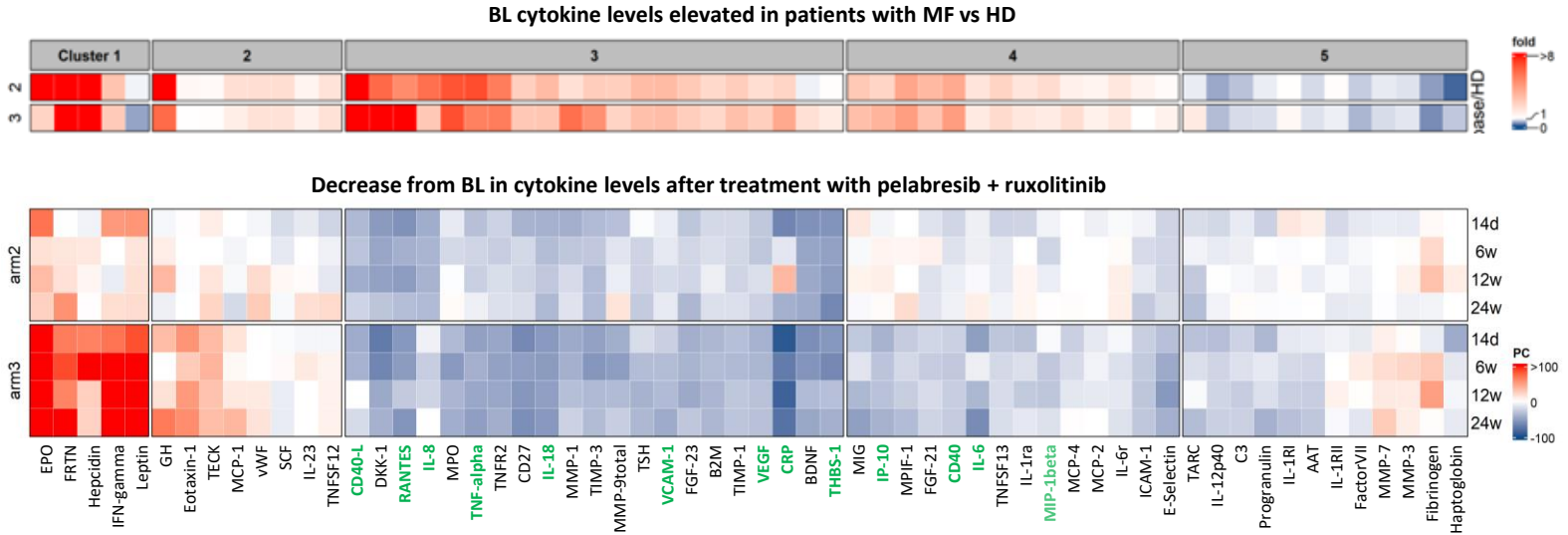
Cytokines previously shown to be NF-kB targets, inflammation related and elevated in MF patients (clusters 3 and 4) are strongly decreased during treatment. Downregulation was rapid (14 days) and durable (through 24 weeks)



BL, baseline; d, day; HD, healthy donors; MF, myelofibrosis; NF-kB, nuclear factor kappa B; w, week.

Mascarenhas et al. *EHA 2022, S198*

Conclusion

- Allo-HSCT is still the best curative option in MF, but remains a very high risk procedure in many patients
- Myelofibrosis is often an oligo/polyclonal disease unlikely to be cured by a single targeted therapy
- Treatments received during the chronic phase of MPN clearly impact survival and risk of transformation through emergence or selection of high risk mutations
- Treatments combining JAK inhibition + drugs targeting complementary pathways could lead to (operational) cure in the near future…

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Dr Nabih MASLAH

Clinical Hematology Departments

INSERM UMRS-1131

INSERM UMR-944

Comprehensive MPN Center

French Intergroup of MPN (FIM)