

The Burden of Anemia in myeloproliferative disorders: Why It Matters More Than We Think



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Conflicts of Interest

Dr. Santiago Osorio has received:

Remuneration for participation in educational activities

Travel grants

Research project grants

Honoraria for participation in advisory boards

from the following companies: **Novartis, BMS, Pfizer, GSK, MSD, Incyte, and AbbVie.**

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Myeloproliferative disorders

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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Table 1. Myeloproliferative neoplasms.

Chronic myeloid leukaemia
Polycythaemia vera
Essential thrombocythaemia
Primary myelofibrosis
Chronic neutrophilic leukaemia
Chronic eosinophilic leukaemia
Juvenile myelomonocytic leukaemia
Myeloproliferative neoplasm, not otherwise specified

Leukemia (2022) 36:1703 – 1719

Anemia Polycythemia Vera

Anemia is not usually a significant problem¹

Iron-deficiency anemia is not uncommon, caused either by the disease overproduction of red blood cells (could lead to masked polycythaemia) or, more frequently, by phlebotomy.^{2,3}

Iron deficiency should not be treated if there is no anemia⁴

Another cause of anemia is the toxicity of cytostatic drugs⁵

The presence of non-iron-deficiency anemia, which cannot be clearly attributed to cytostatic therapy, should alert us to the possibility of progression to myelofibrosis or, less frequently, acceleration or exacerbation^{6,1}

Essential thrombocythemia

- 1. Anemia is also rare.**
- 2. When it does occur, it may indicate:**
 - Drug toxicity**
 - The onset of progression to myelofibrosis or acceleration/exacerbation**
- 3. Cytopenias are included in the criteria for resistance to hydroxyurea**
- 4. Indicate a poorer prognosis**

Table IV. Criteria for hydroxycarbamide resistance/intolerance modified* from (Barosi *et al*, 2010).

- 1 Need for unacceptably frequent* venesection to keep haematocrit <45% after 3 months of at least 2 g/d of HC or MTD,* OR
- 2 Uncontrolled myeloproliferation, i.e. platelet count >400 × 10⁹/l AND/OR WCC >10 × 10⁹/l after 3 months of at least 2 g/d of HC, or MTD,* OR
- 3 Failure to reduce massive† splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/d of HC, or MTD,* OR
- 4 Absolute neutrophil count <1 × 10⁹/l, OR platelet count <100 × 10⁹/l OR Hb <100 g/l at the lowest dose of HC required to achieve a complete or partial clinico-haematological response, OR
- 5 *Failure to control disease-related symptoms (including but not limited to those relating to splenomegaly), OR
- 6 *Thrombosis or haemorrhage related to disease despite therapy
- 7 Presence of leg ulcers or other unacceptable HC-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or *fever at any dose of HC

HC, hydroxycarbamide; WCC, white cell count; Hb, haemoglobin; MTD, maximum tolerated dose.

*Modification from the original paper.

†Organ extending by more than 10 cm from the costal margin.

Resistance/intolerance to
hydroxycarbamide. Mc
Mullin

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British Journal of Haematology, 2016, **172**, 337–349

Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera

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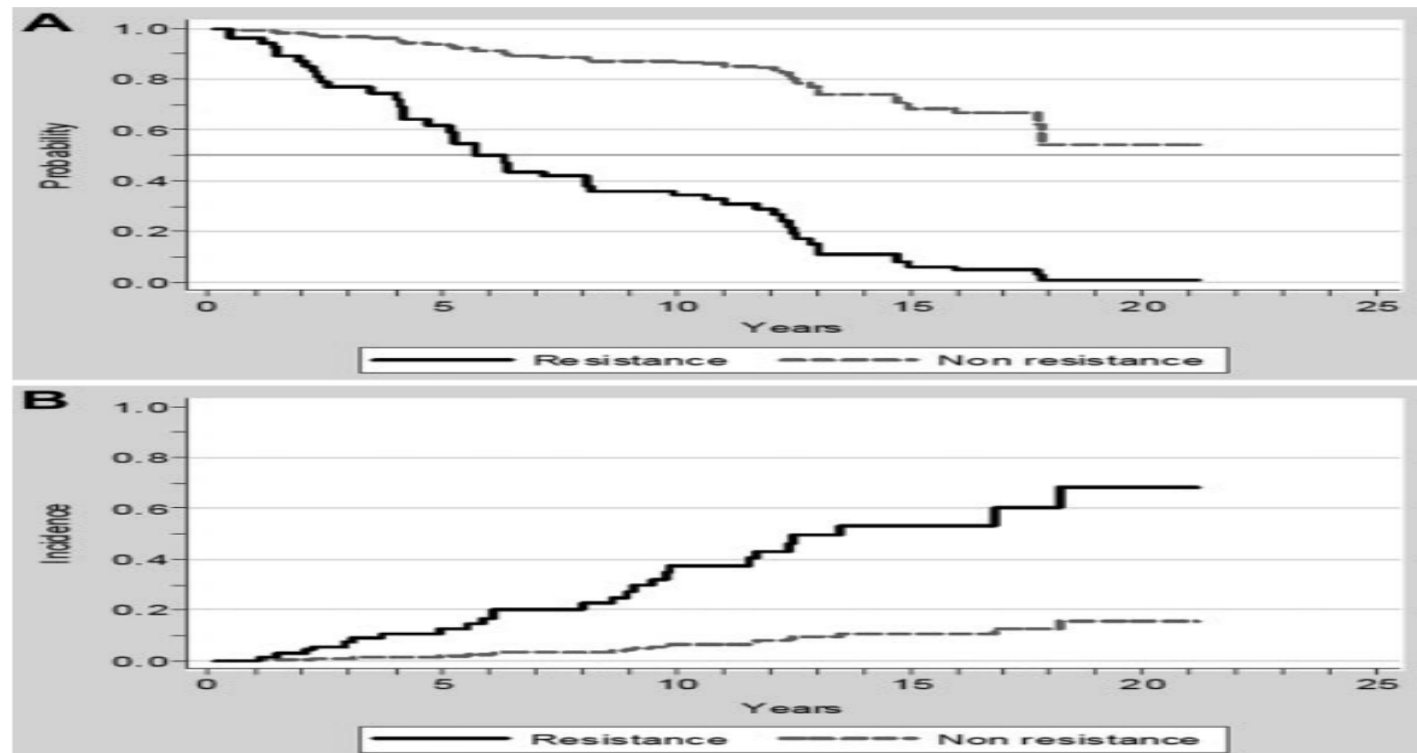


Figure 3. Effect of resistance to HU on survival and on risk of transformation to acute leukemia or myelofibrosis. (A) Effect of resistance to HU on survival. The



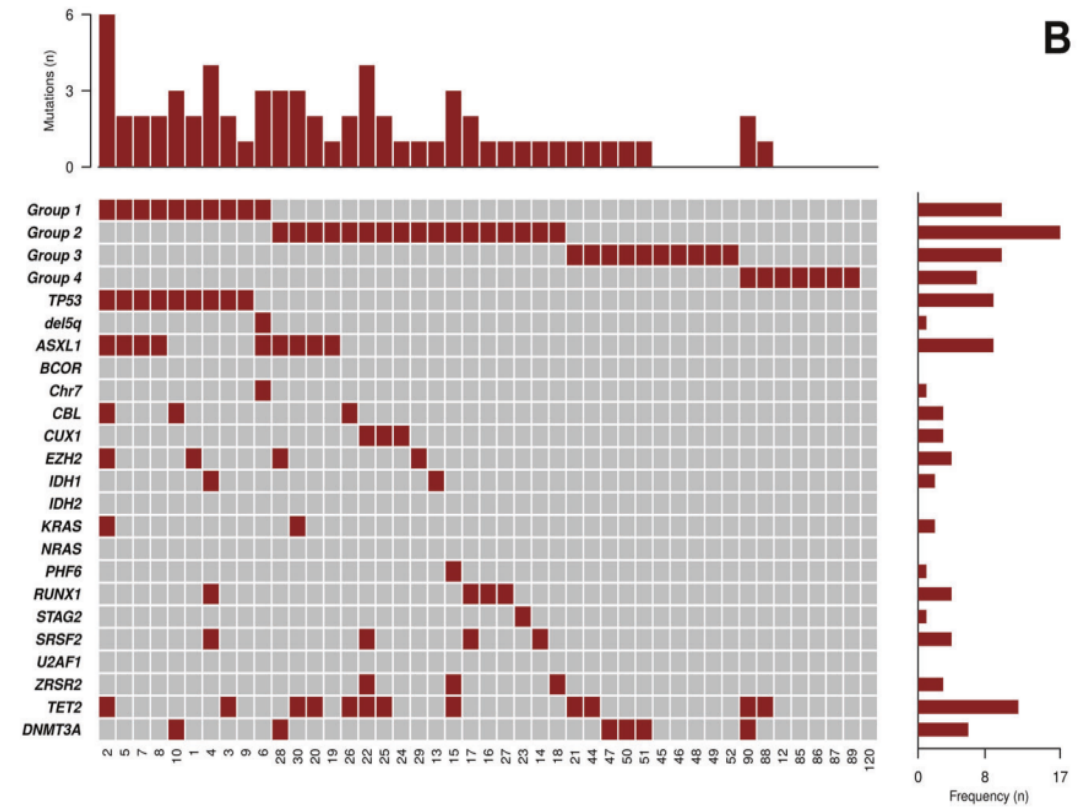
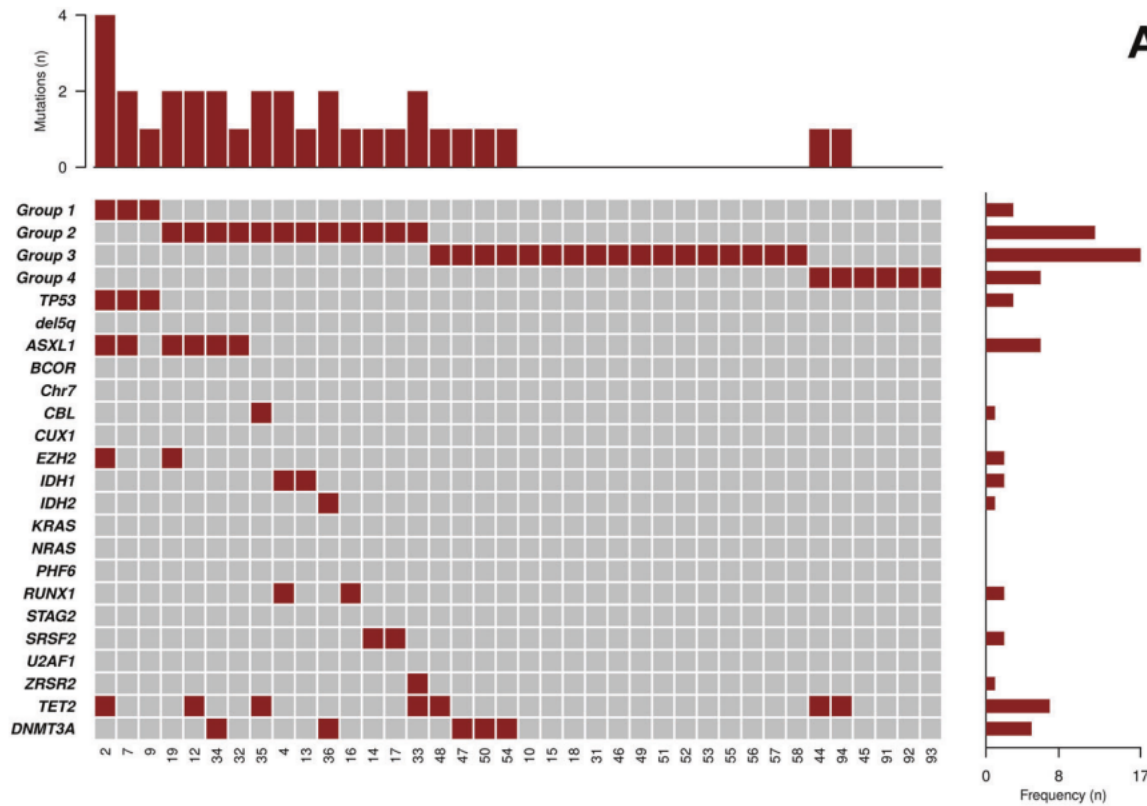
Chronic myeloproliferative neoplasms

Genomic characterization of patients with polycythemia vera developing resistance to hydroxyurea

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Polycythemia Vera and Essential thrombocythemia

- The onset of anemia and other cytopenias is not common and can have varying implications, but it is rarely good news



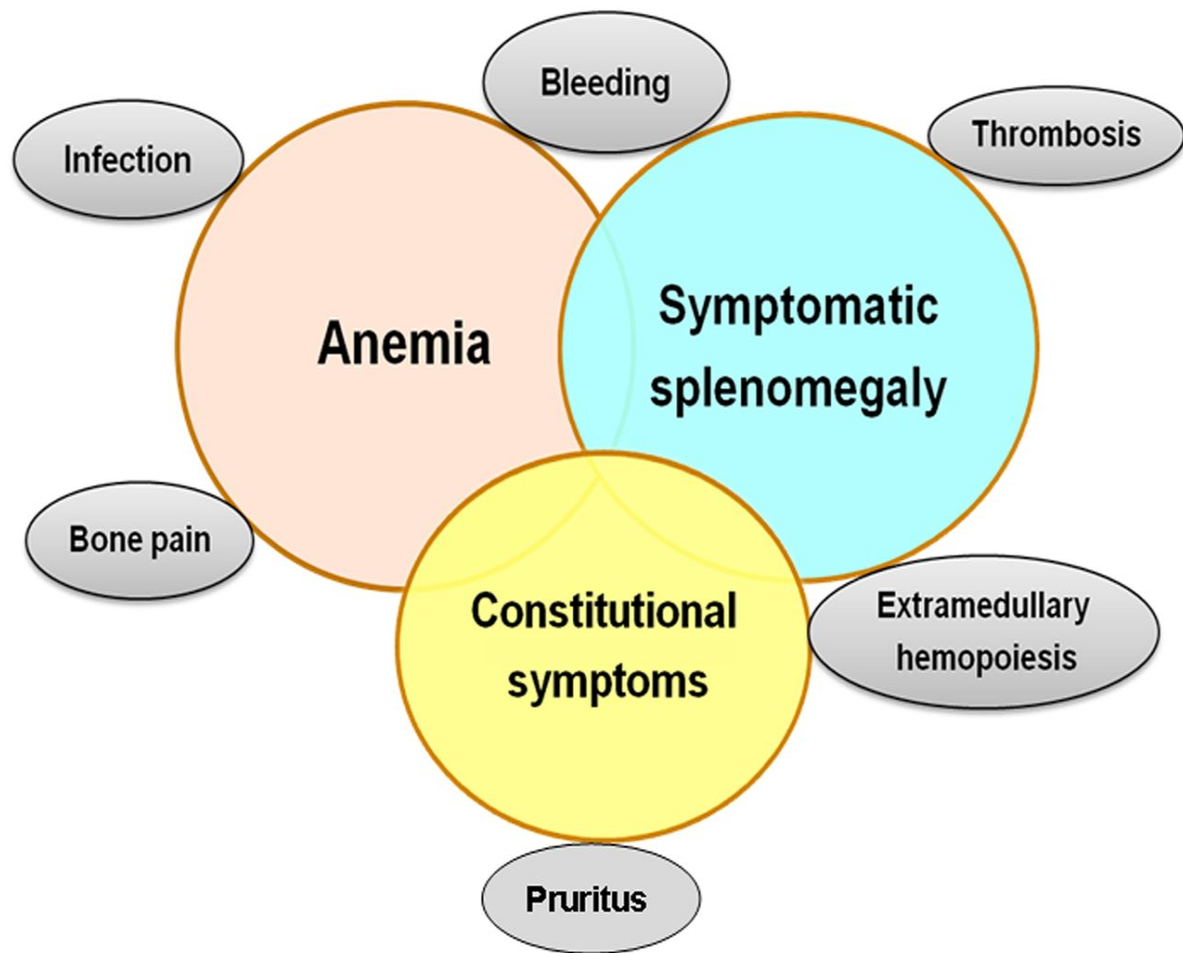
Anemia and myeloproliferative disorders

- Then we have to talk about myelofibrosis

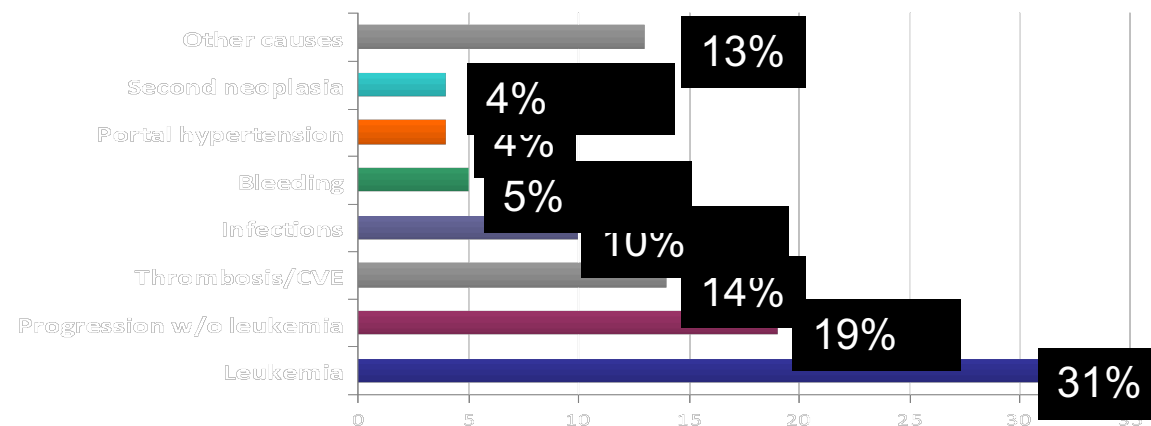


	MF	PV	ET
Incidence	0,3/100.000 year	0,7-1/100.000 year	0,7-1/100.000 year
Risk of leukaemic transformation		4-10%	3-7%
Overall Survival	5-6 years	14 years	20 years
Risk of secondary MF at 15 years	NA	5-30%	4-15%

Myelofibrosis. Clinical manifestations. Complications. Causes of death

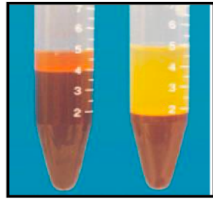


Causes of death

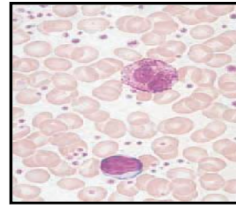
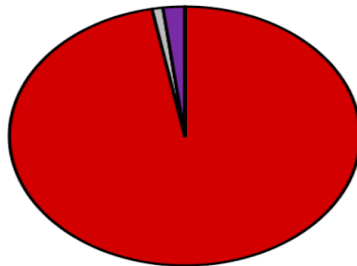


What lies behind Myelofibrosis

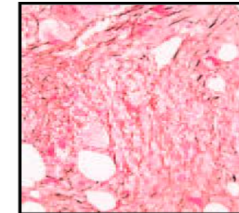
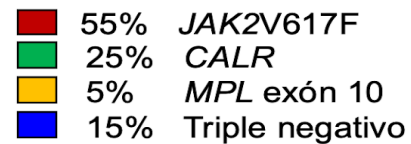
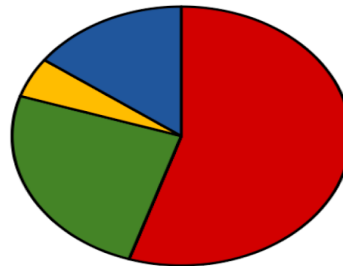
Frecuencia de mutaciones *driver* en NMP



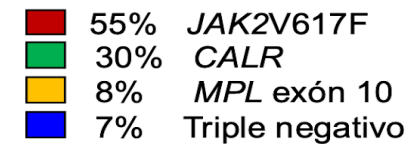
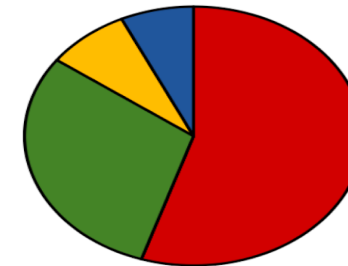
**Policitemia
Vera**



**Trombocitemia
Esencial**



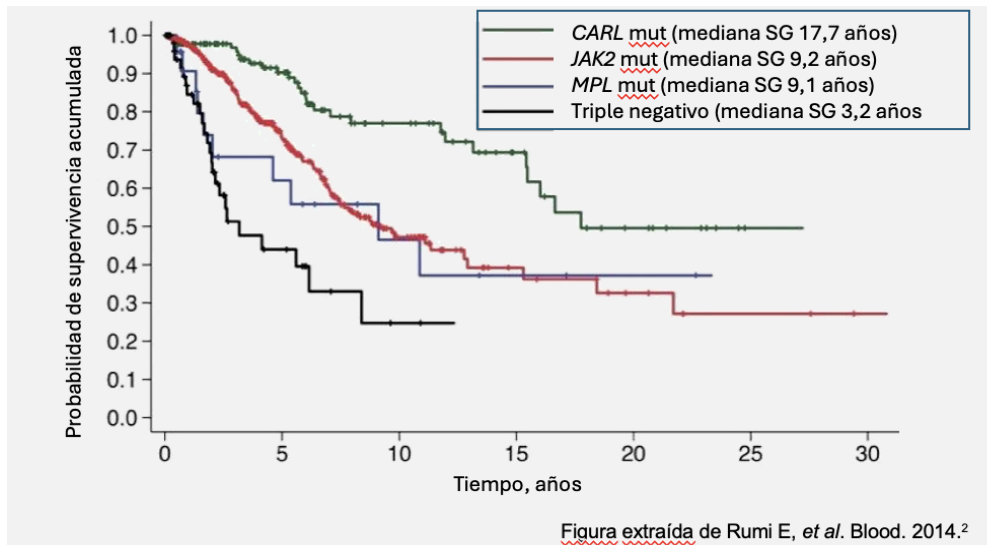
**Mielofibrosis
Primaria**



Molecular basis of myelofibrosis

Mutation	OS. Median years	Mortality rate %	Leukemic transformation at 10 years
CALR	17,7	19	9,4
JAK2	9,2	29	19,4
MPL	9,1	40	16,9
Triple negativo	3,2	45	34,4

Rumi E, et al. *Blood*. 2017⁵ y Rumi E, et al. *Blood*. 2014⁶



	PV	TE	MFP
TET2	10-22%	5-16%	10-20%
IDH 1/IDH2	1-2%	1%	3-6%
DNMT3A	2-7%	1-6%	2-15%
EZH2	1-3%	1-3%	5-10%
ASXL1	2-12%	2-11%	13-32%
SRSF2	3%	2%	8-15%
SF3B1	1-2%	3-5%	4-7%
U2AF1	<1%	1-2%	15%
ZRSR2	<1%	3%	5-10%
TP53	1%	2%	2-4%
RUNX1	2%	1%	1-2%
NFE2	2%	<1%	2-3%
LNK/SH2B3	<1%	1-6%	3-5%
CBL	<1%	1-2%	3-6%
KRAS/NRAS	<1%	<1%	4-9%
PTPN11	<1%	<1%	5-10%
GNAS	<1%	<1%	5-10%

Myelofibrosis phenotypes

Proliferative MF

Leukocytosis, normal platelets, mild or no anemia

More likely post-ET/PV MF

Lower risk scores

Fewer blasts

Less marrow fibrosis

More splenomegaly

Higher *JAK2* VAF

Better outcomes

More treatment options

Cytopenic MF

Low platelets, anemia, normal to low WBC

More likely primary MF

Higher risk scores

More blast

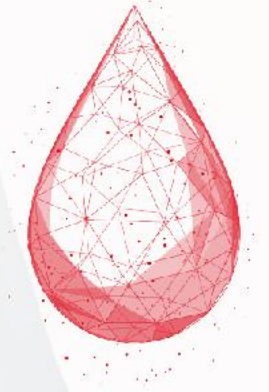
More marrow fibrosis

High molecular risk

Lower *JAK2* VAF

Worse OS; higher leukaemic transformation risk

Fewer treatment options



Presentation or phase of MF characterized by moderate-to-severe anemia and/or thrombocytopenia

These are not mutually exclusive, and patients may evolve over time from the former to the latter. Individual cases may have overlapping features of both phenotypes.

Molecular alterations in cytopenic phenotypes

- •Higher frequency of triple-negative patients ($p < 0.0001$)
- •Higher frequency of triple-negative patients ($p < 0.0001$)
- •ASXL1 mutations ($p = 0.0074$)
- •IDH1/2 ($p = 0.064$)
- •N/KRAS ($p = 0.0014$)
- •U2AF1 ($p < 0.0001$)
- •CUX1 ($p = 0.0002$)
- The presence of multiple high-risk mutations is frequently associated with myelodysplastic features, a cytopenic phenotype and a risk of progression to the blast phase.

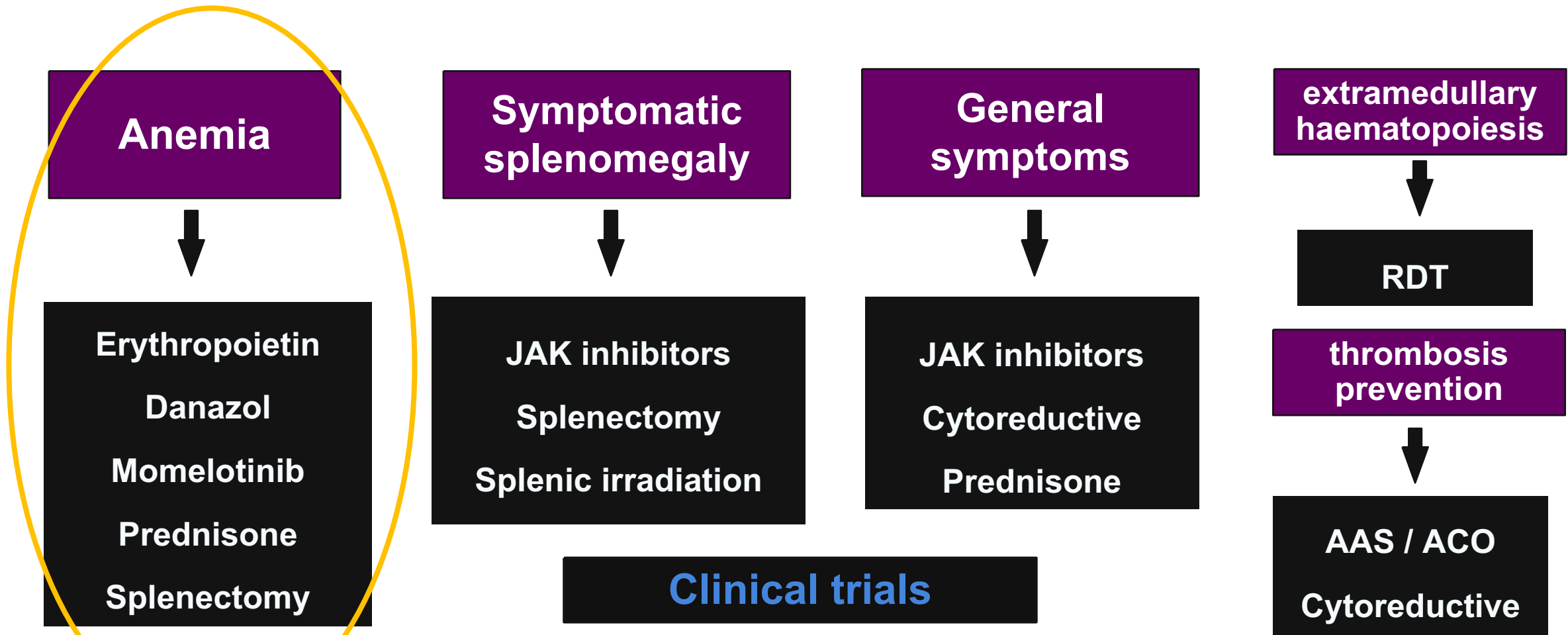
The importance of JAK2 allelic load

- Jak-2 allelic burden ranges from 1% to 100%, with medians around 50%, and it has been reported that high burdens are associated with an increased risk of progression from PV and TE to secondary MF

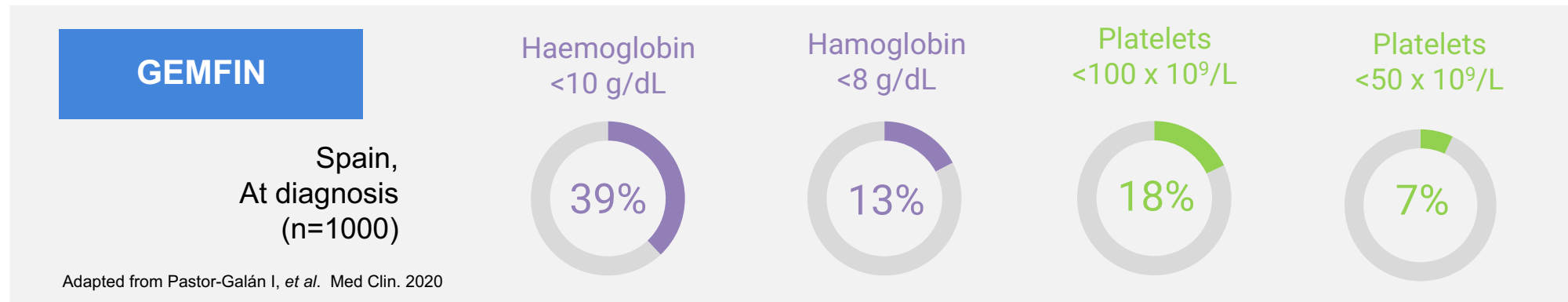
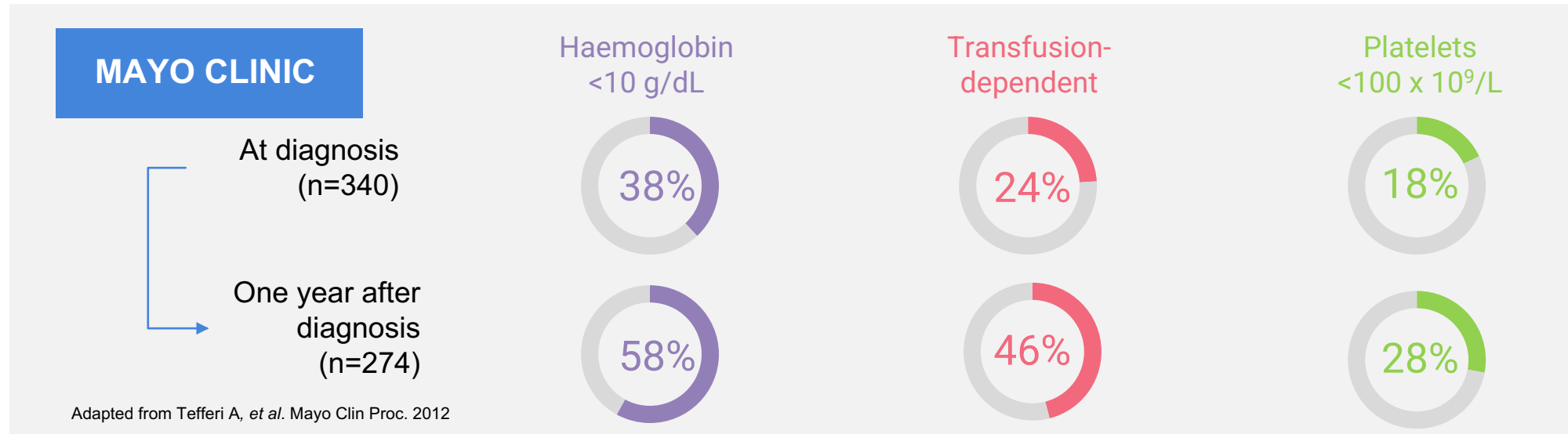
But in Myelofibrosis:

- Retrospective studies;
- Three categories with different Jak-2 allelic burdens: 1%–20%, 21%–55% and 56%–74%
- The influence of allelic burden on overall survival is dramatic: 20 months vs 77 months vs 132 months. (P = 0.008)
- Those with the lowest allelic burden had higher rates of leucopenia and anemia and higher mortality (p = 0.007): more medical complications such as infections than to progression to LAM
- These patients, the prognosis is poorer than in those with a high allelic load and similar to that of triple-negative Furthermore, ruxolitinib is less effective: the likelihood of a splenic response is 5.5 times higher if the allelic load is >50%

Targeted treatment of myelofibrosis based on clinical presentation

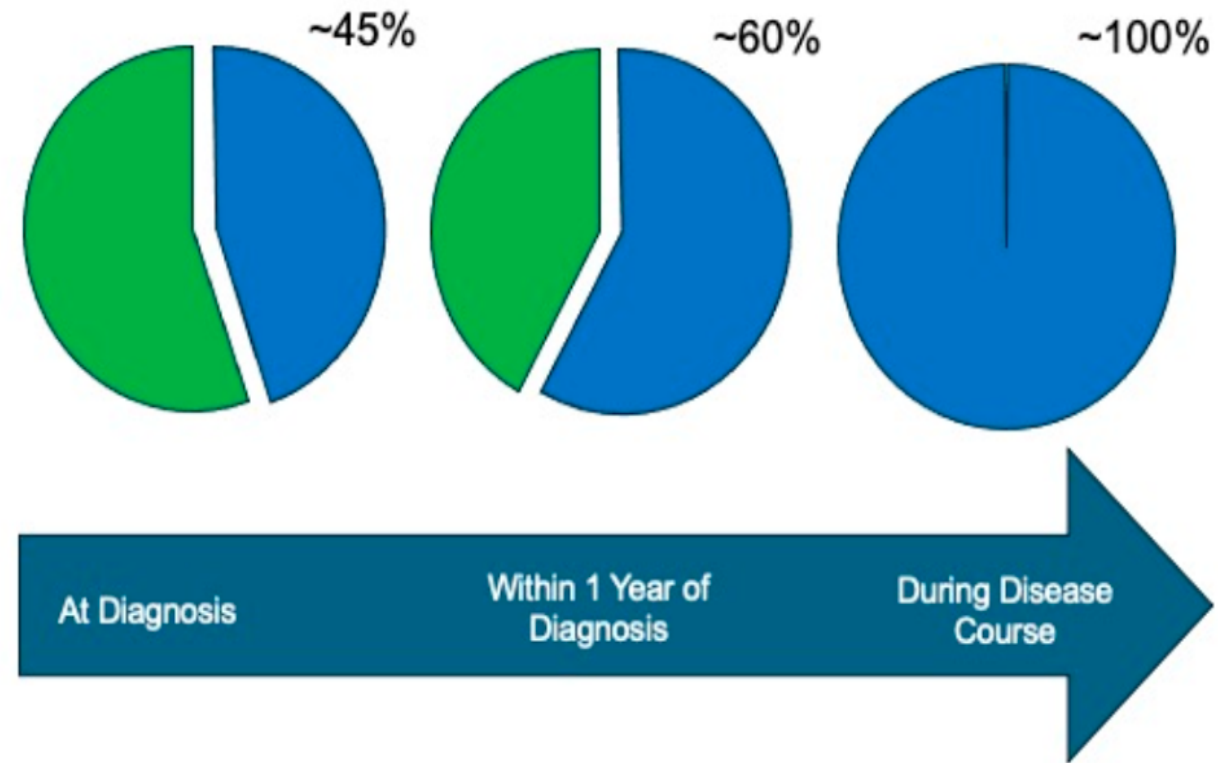


Anemia is highly prevalent in Myelofibrosis



Anemia is highly prevalent in Myelofibrosis

Figure 1. Prevalence of Myelofibrosis-Associated Anemia

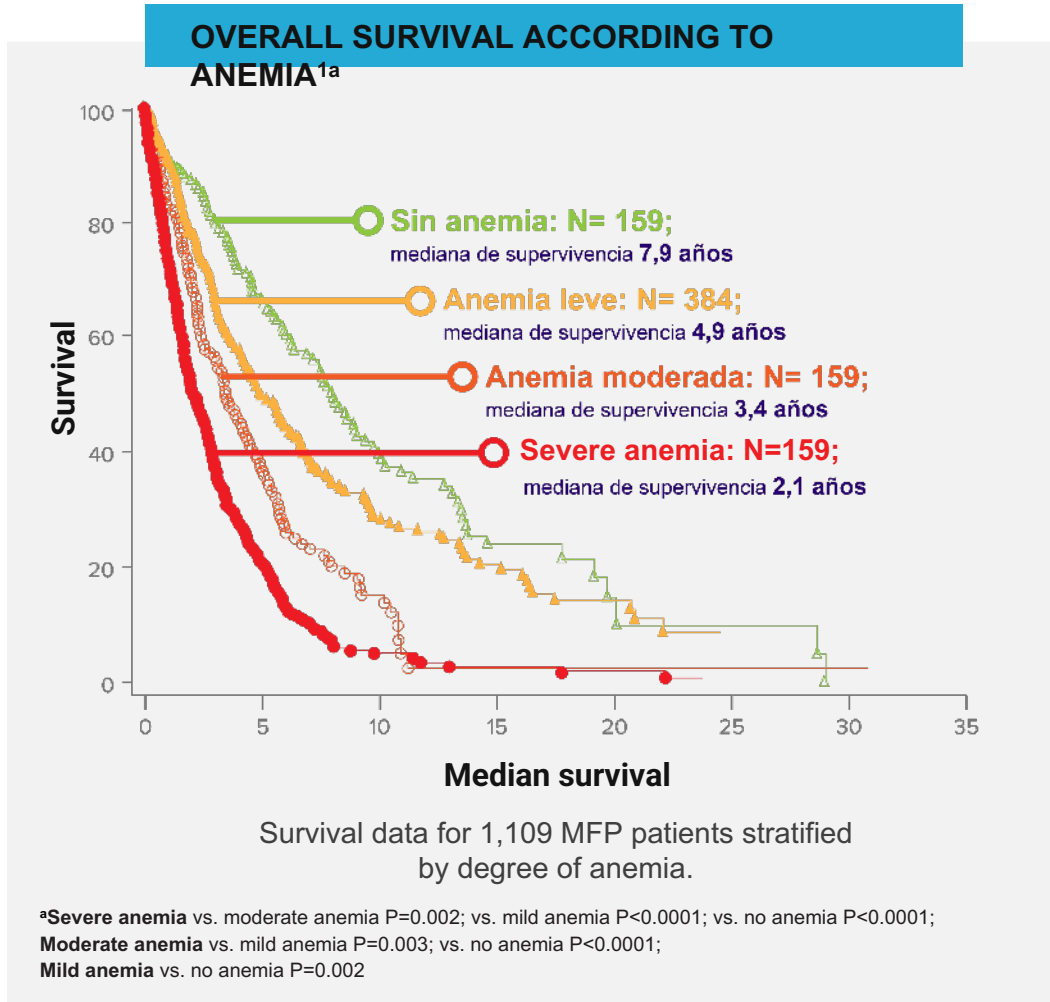


Cytopenias and Molecular phenotype

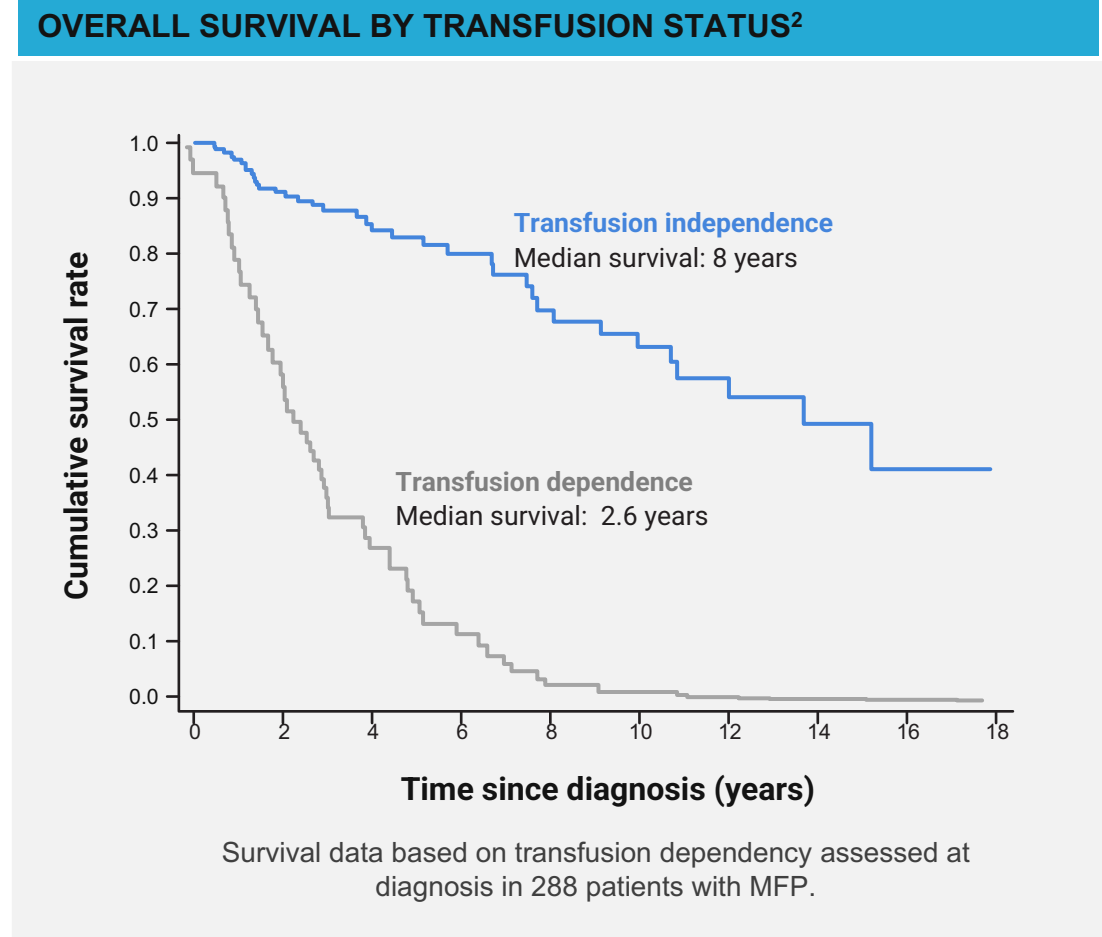
Table 1. Demographic and clinical features at diagnosis of 617 patients with PMF subdivided according to their genotype (*JAK2*, *CALR*, and *MPL* mutation status)

	<i>JAK2</i> (V617F)-mutant patients	<i>CALR</i> -mutant patients	<i>MPL</i> -mutant patients	Patients with nonmutated <i>JAK2</i> , <i>CALR</i> , and <i>MPL</i> (triple-negative subjects)	<i>P</i>
No. (%)	399 (64.7%)	140 (22.7%)	25 (4.0%)	53 (8.6%)	
Sex (male/female)	266/133	77/63	17/8	34/19	.101
Age at onset, median (range), y	63 (18-91)	50 (26-83)	64 (31-84)	67 (31-88)	<.001
Hemoglobin, median (range), g/dL	12 (3-19.6)	11.7 (7.1-15.9)	11 (6.5-15)	9.9 (5-19)	<.001
WBC count, median (range), $\times 10^9/L$	10 (1.6-106.2)	8.2 (2.2-45)	8.4 (2.1-20.3)	8.4 (2.4-90.8)	.002
PLT count, median (range), $\times 10^9/L$	310 (25-1963)	509 (46-1563)	307 (53-958)	175 (19-3279)	<.001
Circulating blasts, median (range), %	0 (0-20)	0 (0-10)	0 (0-4)	0 (0-16)	<.001
Lactate dehydrogenase, median (range), mU/mL	553 (149-3440)	692 (203-3610)	580 (183-2291)	531 (160-3173)	.208
Circulating CD34 ⁺ cells, median (range), $\times 10^6/L$	16.2 (0.8-1190)	34.2 (1.7-1902)	100 (6.3-506.3)	45.3 (1.6-485.5)	.022
IPSS risk group, %					
Low	31	51	28	10	<.001
Intermediate 1	31	23	36	26	
Intermediate 2	22	18	24	17	
High	16	8	12	47	

Anemia and transfusion dependency are associated with reduced overall survival^{1,2}



Graph adapted from Nicolosi, M, *et al.* Leukemia. 2018¹



Graph adapted from Elena C, *et al.* Haematologica. 2011²

MFP: primary myelofibrosis; OS: overall survival

1. Nicolosi M, Mudireddy M, Lasho TL, *et al.* Sex and severity influence the prognostic impact of anemia in primary myelofibrosis: an analysis of 1,109 consecutive patients. *Leukemia*. 2018;32(5):1254-1258 2. Elena C, Passamonti F, Rumi E, *et al.* Red blood cell transfusion dependency implies poor survival in primary myelofibrosis irrespective of IPSS and DIPSS. *Haematologica*. 2011;96:167-170.

Thrombocytopenia is also associated with poor prognosis in patients with myelofibrosis



Median OS By PLT Count in Patients With MF^a



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

MF, myelofibrosis; OS, overall survival; PLT, platelet.

^a Includes patients with primary or secondary MF.

Anemia worsens prognosis in myelofibrosis

	DIPSS	DIPSS ⁺	MIPSS-70	MIPSS-70 ⁺ version 2.0	MYSEC-PM 2.0
<i>Patients' characteristics (score)</i>	Age > 65 y (1) Constitutional symptoms (1)	Age > 65 y (1) Constitutional symptoms (1)	Constitutional symptoms (1)	Constitutional symptoms (2)	Age (0.15 × y) Constitutional symptoms (1)
<i>Laboratory values (score)</i>	Hb < 10 g/dl (2) WBC > 25 × 10 ⁹ /l (1) Blasts ≥ 1% (1)	RBC transfusions need (1) Hb < 10 g/dl (1) WBC > 25 × 10 ⁹ /l (1) Blasts ≥ 1% (1) PLT < 100 × 10 ⁹ /l (1)	Hb < 10 g/dl (1) WBC > 25 × 10 ⁹ /l (2) Blasts ≥ 2% (1) PLT < 100 × 10 ⁹ /l (2)	Severe anemia ² (2) Moderate anemia ³ (1) Blasts ≥ 2% (1)	Hb < 11 g/dl (2) Blasts ≥ 3% (2) PLT < 150 × 10 ⁹ /l (1)
<i>Driver mutation (score)</i>			Absence of type 1/like CALR (1)	Absence of type 1/like CALR (2)	Absence of CALR (2)
<i>Myeloid-gene variants (score)</i>			1 HMR (1) ≥ 2 HMR (2)	1 HMR included U2AF1Q157 (2) ≥ 2 HMR included U2AF1Q157 (3)	
<i>Karyotype (score)</i>		Unfavourable ¹ (1)		Unfavourable ⁴ (3) Very high-risk ⁵ (4)	
<i>Bone marrow (score)</i>			BMF grade ≥ 2 (1)		
Risk (score), median survival	Low (0), NR Int-1 (1–2), 14.2 y Int-2 (3–4), 4 y High (5–6), 1.5 y	Low (0), 15.4 y Int-1 (1), 6.5 y Int-2 (2–3), 2.9 y High (≥ 4), 1.3 y	Low (0–1), NR Int (2–4), 6.3 y High (≥ 5), 3.1 y	Very low (0), NR Low (1–2), 16.4 y Int (3–4), 7.7 y High (5–8), 4.1 y Very high (≥ 9), 1.8 y	Low (< 11), NR Int-1 (11–13), 9.3 y Int-2 (14–15), 4.4 y High (≥ 16), 2 y

Anemia impairs quality of life in myelofibrois

Pomalidomide + Prednisone for anemia in myelobifrois

Table II. Frequency and percent of patients meeting clinically important difference by responder cohort and cycle.

FACT-An PWB score	Responders (n = 29)		Nonresponders (n = 40)	
	n	%	n	%
Post-baseline visit				
Cycle 2, day 29	11	37.7	15	37.5
Cycle 3, day 57	13	44.8	9	22.5
Cycle 6, day 141	9	31.0	3	7.5
Cycle 9, day 225	13	44.8	1	2.5
Cycle 12, day 309	8	27.6	1	2.5
FACT-An FWB score	Responders (n = 30)		Nonresponders (n = 41)	
	n	%	n	%
Post-baseline visit				
Cycle 2, day 29	7	23.3	10	24.4
Cycle 3, day 57	12	40.0	4	9.8
Cycle 6, day 141	9	30.0	2	4.9
Cycle 9, day 225	11	36.7	3	7.3
Cycle 12, day 309	7	23.3	2	4.9

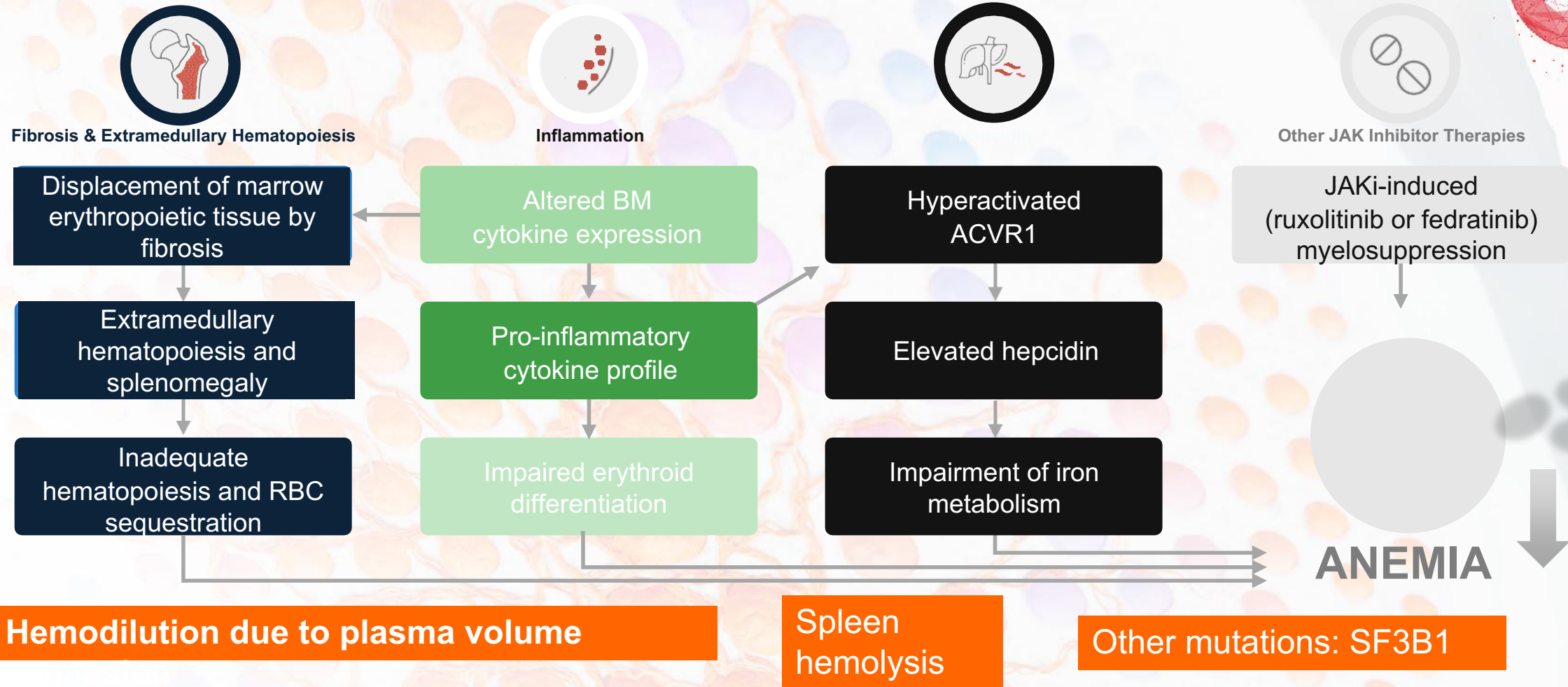
PWM: phisical well being, FWB: funcional well being

Anemia reversible causes in MF patients: The first thing to rule out

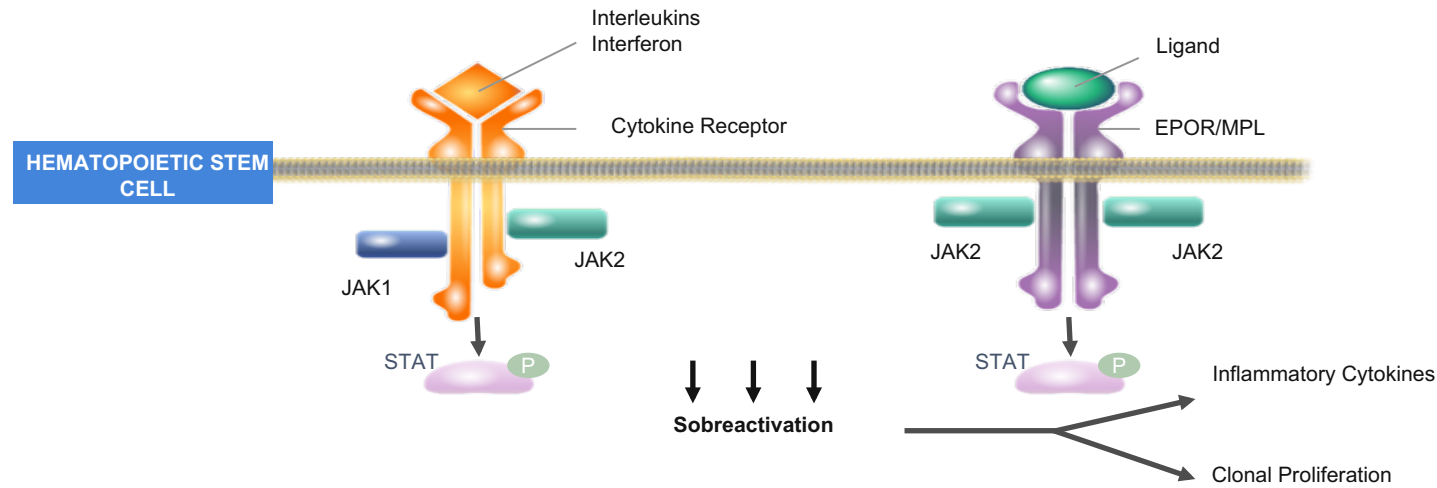
- Iron, folate and/or vitamin B₁₂ deficiency:
 - Deficiencies replacement
- Autoimmune hemolysis:
 - High reticulocyte counts, increased serum bilirubin, low haptoglobin, and markedly increased serum lactic dehydrogenase (LDH)
 - Treat with steroids

But not all hemolysis is immune: ineffective erythropoiesis and non-immune splenic haemolysis

Pathophysiology of Anemia in Myelofibrosis Is Multifactorial and Partially Understood^{1,2}



Inflammation and ACVR pathway

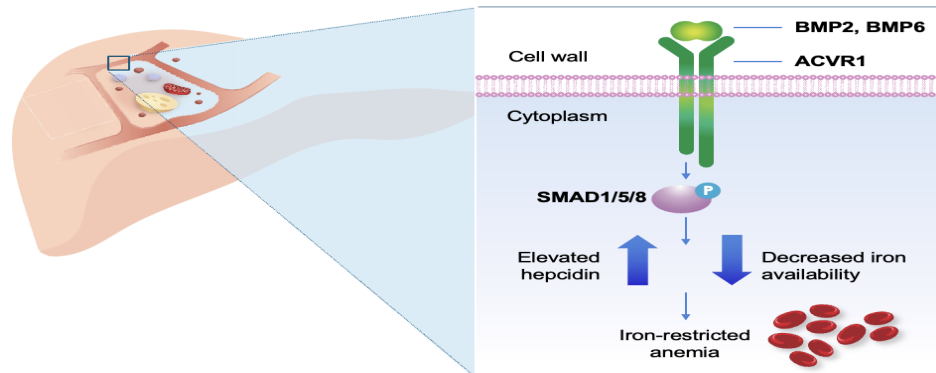


- Overproduction of inflammatory cytokines, that acts:
 - Locally → progressive bone marrow fibrosis
 - Systemically → debilitating constitutional symptoms.
- Clonal proliferation: myeloproliferation and genomic instability
- Extramedullary haematopoiesis and splenomegaly

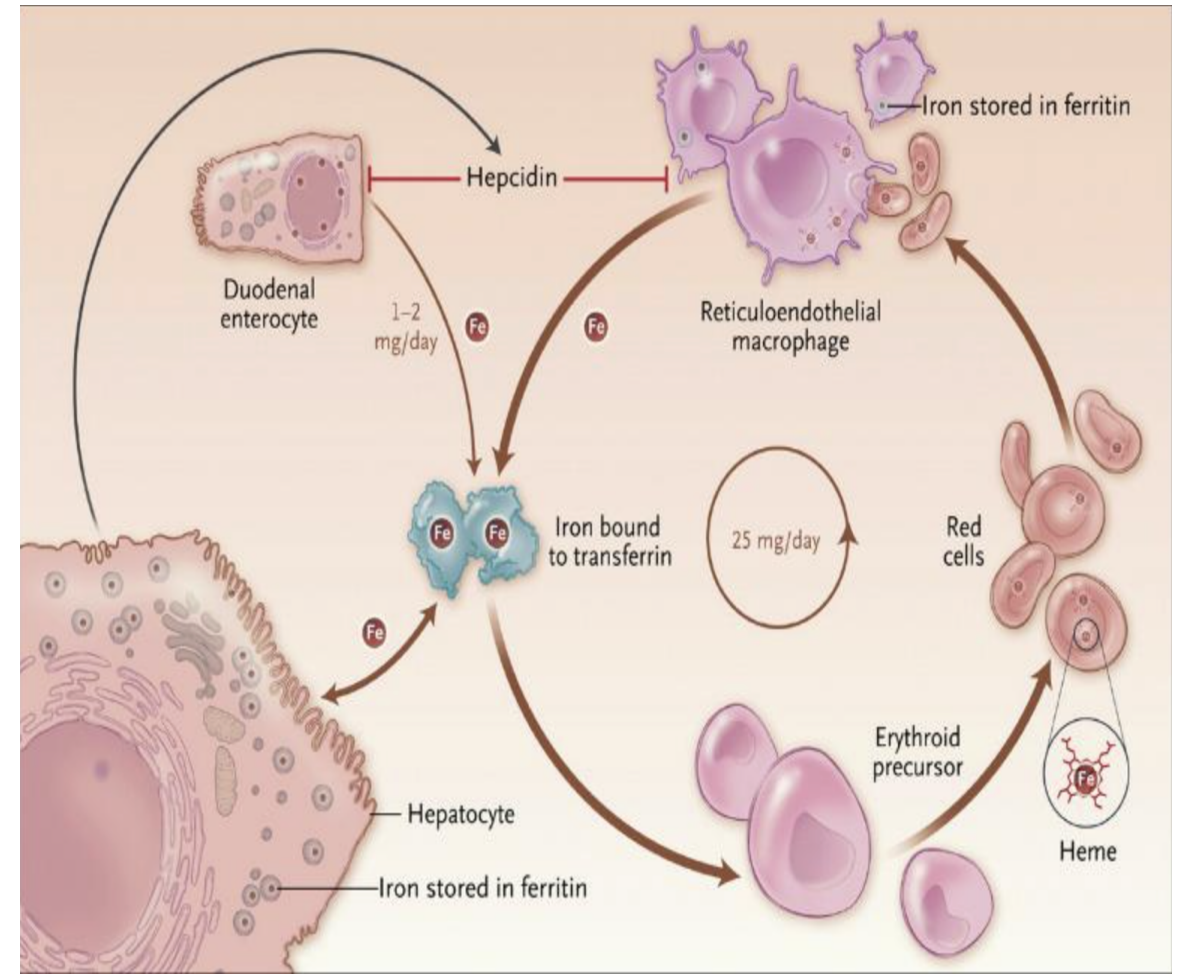
Anemia of Myelofibrosis: Role of ACVR1 and Hepcidin¹⁻⁵

- ACVR1 : key regulator of hepcidin production
- Chronic inflammation : hyperactivates ACVR1 elevating hepcidin levels in MF driving an iron-restricted anemia
- Inhibiting ACVR1 results in decreased hepcidin, and an increase in iron availability, thereby improving

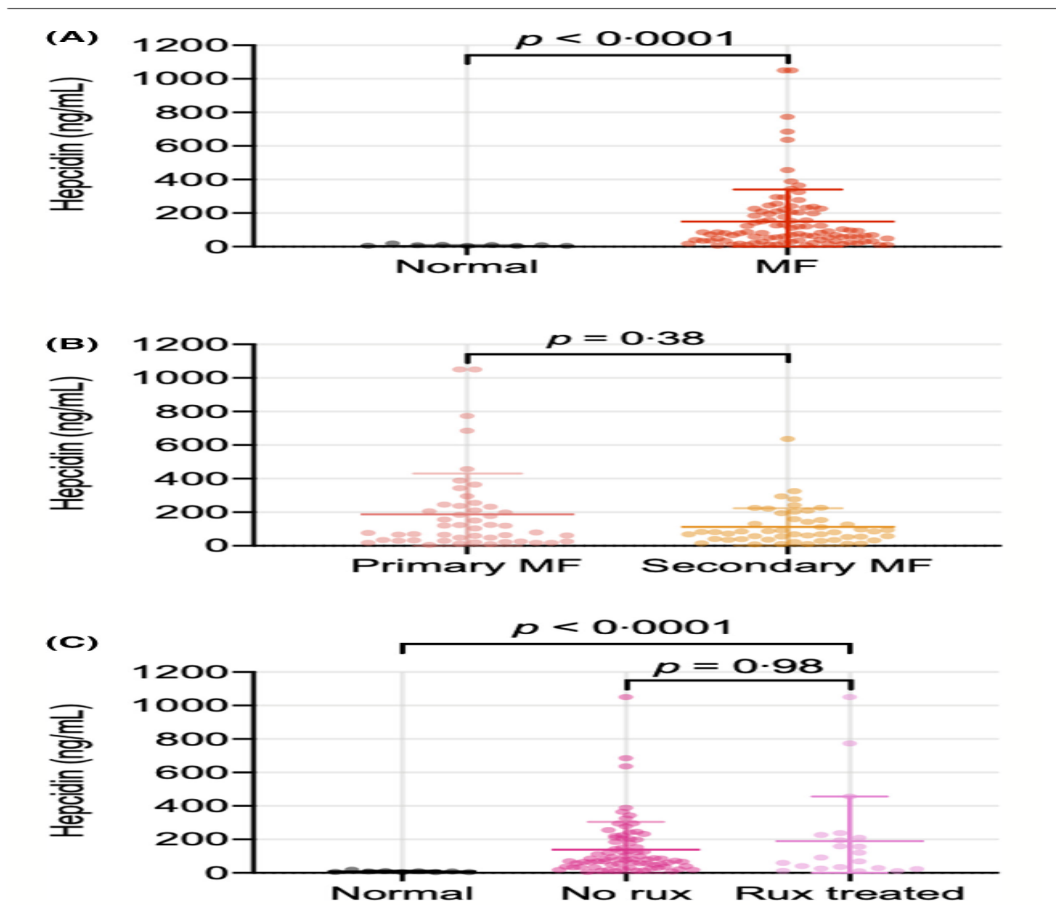
Dysregulated ACVR1 Signaling⁵



Reprinted from Chifotides HT, et al. *J Hematol Oncol*. 2021;15(1):7. Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>).

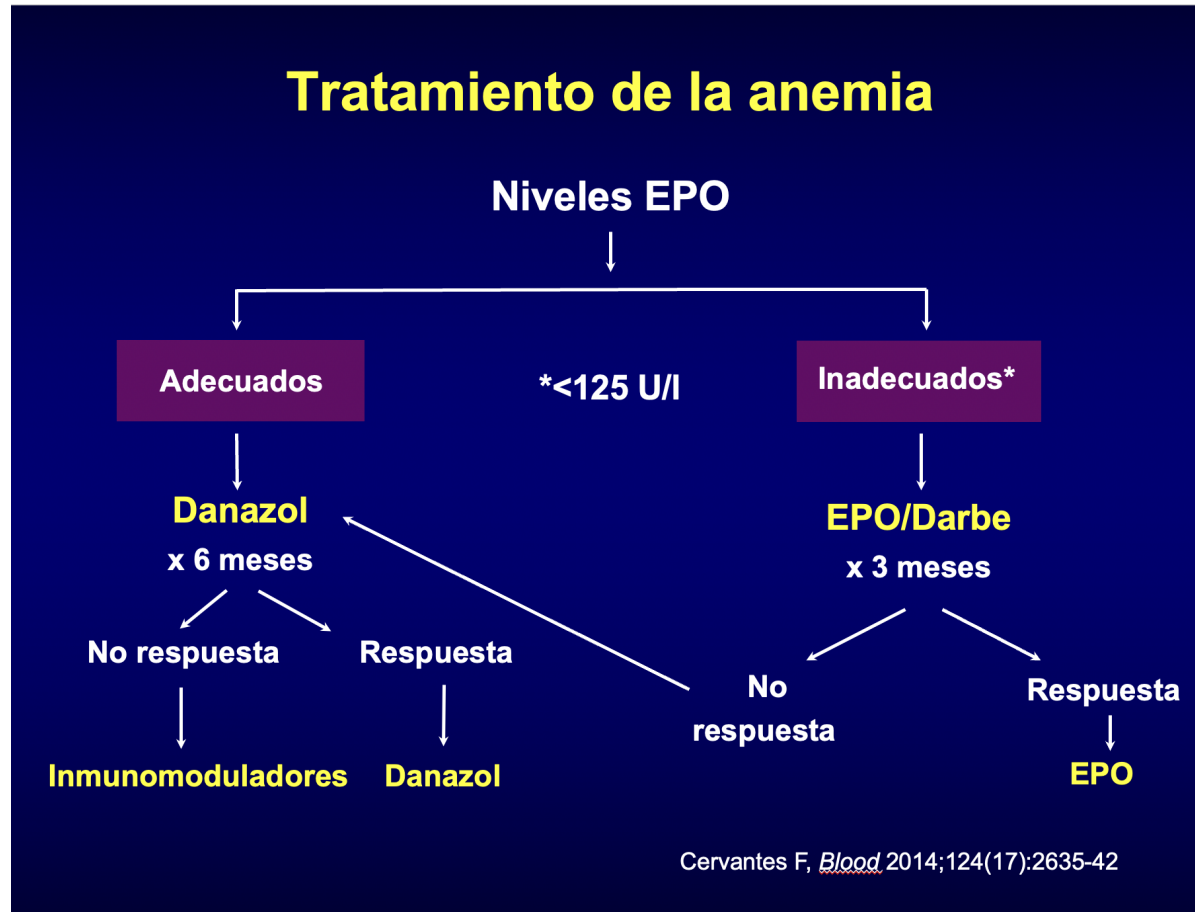


Hepcidin is elevated in primary and secondary myelofibrosis and remains elevated in patients treated with ruxolitinib



- 99 patients with PMF ($n = 49$) and secondary MF ($n = 50$)
- Hepcidin was significantly elevated in MF patients compared to normal controls (median 81.1 vs. 8.5 ng/mL)
- In a separate study including 203 patients with PMF, plasma hepcidin levels were found to be 12-fold higher in PMF patients (median, 156 279 pg/mL) as compared to normal controls (median, 13 449 pg/mL)

Classical anemia treatment



Erythropoiesis-stimulating agents (ESAs)

Table 1
Current therapies and disease management practices for MF-associated an

Agent (s)	Trial	Response rate ^a
ESAs	(Huang and Tefferi, 2009) (n = 43)	23% (0% among TD and 37% [only in patients with BL Hb < 10 g/dl]; P = 0.007) ^b
	(Tsiara et al., 2007) (n = 20)	60% ^c
	(Cervantes et al., 2006) (n = 20)	40% ^d
	(Cervantes et al., 2004) (n = 20)	45% (4 CR [20%] and 5 PR) ^e
	(Hernández-Boluda et al., 2017) (n = 163)	53% ^f (29% among TD patients, 57% among TI patients)

mDOR 19.3m

Table III. Pretreatment variables associated with a favourable response to recombinant human erythropoietin treatment at the univariate study in 51 patients with myelofibrosis with myeloid metaplasia.

Variable	No. responders/total	P-value
Serum EPO level (U/l)		
<125	26/39	0.002
≥125	2/12	
Hb concentration (g/dl)		
>8.5	22/33	0.02
≤8.5	6/18	
Transfusion requirement		
No	11/12	0.003
Yes	17/39	

Hb, haemoglobin; EPO, erythropoietin.

- Response within the first 3 months.
- Toxicity: slight enlargement of the spleen?, thrombosis?

Danazol

Results (n 50)

Anemia response	30%
- Transfusion dependency	(15/50)
-	18% (5/27)
Transfusion independency	43%
	(10/23)
Median time to response	3 months
Median dose on responders	200mg
Median duration of response	14 months
Thrombocytopenia	
- Increase $>50 \times 10^9$	23% (3/13)



Adverse events

Discontinued due to adverse events while on response	18% (5/50)
Increase liver enzymes	16% (8/50)
Severe cholestatic hepatitis	2
Prostate adenocarcinoma	1
Liver peliosis	

Immunomodulatory drugs

Talidomide: Around 15% responses (more with addition of corticoids), 30% Independence achievement. High drop-out rates due to toxicity.

Lenalidomide: similar responses but also toxicity.

Pomalidomide: not better

Studies	Barosi et al [6]	Merup et al [11]	Mesa et al [13]	Present Study
No. of patients	62*	15	21	63
Median age, years	65	68	63	68
Previous myeloproliferative disease	26%	40%	28%	22%
Thalidomide dose				
Minimum, mg/d	100	200	50	50
Maximum, mg/d	800	800	50	400
Associated treatments	Various	Various	Prednisone	Various
Transfusion-dependent patients	37%	46%	48%	41%
Median hemoglobin, g/dL	9.46†	10.1	9.0	9.2
Median WBC, 10 ⁹ /L	7.9	12.6	7.7§	7.5
Median platelet count, 10 ⁹ /L	150	235	154	140
Spleen size, median below costal arc, cm	13	NA	14	13
Dupriez score of 2	25%	6%	28%	19%
Severity score ≥ 4	63%	NA	NA	79%
Drop-out rate at 3 months	45%	36%	5%	24%
Response at efficacy analysis‡				
Increase by 2 g/dL of hemoglobin value in all patients	14%	0%	45%§	13%
Increase by 2 g/dL of hemoglobin value in transfusion-independent patients	NA	0%	54%§	13%
Transfusion interruption in transfusion-dependent patients	30%	0%	40%§	39%
Increase by > 50 × 10 ⁹ /L of platelet count in all patients	45%	0%	76%§	41%
Increase by > 50 × 10 ⁹ /L of platelet count in patients with a platelet count < 100 × 10 ⁹ /L	NA	0%	50%§	22%
Decrease of spleen size by > 2 cm from costal arc	37%	0%	43%§	42%
Decrease of spleen size by > 50%	NA	NA	19%§	19%

Tefferi A et al. Leukemia 2017, Mesa R et al. Blood 2010, Marchetti M et al. JCO 2004

Results (n 40)

Overall response rate	30% (12/40)
Major Hb response	30% (7/23)
- Partial Response	3
- Clinical improvement	4

Splenomegaly improvement	42% (10/24)
- Partial response	2
- Clinical improvement	8

Lenalidomide Plus Prednisone Results in Durable Clinical, Histopathologic, and Molecular Responses in Patients With Myelofibrosis

Alfonso Quintás-Cardama, Hagop M. Kantarjian, Taghi Manshouri, Deborah Thomas, Jorge Cortes, Farhad Ravandi, Guillermo Garcia-Manero, Alessandra Ferrajoli, Carlos Bueso-Ramos, and Srdan Verstovsek

Steroids for anemia in MF patients

30 patients out of 511 MF patients recorded in GEMFIN data base

(6%)	
Age, years*	68 (55-75)
History/presence of autoimmune features, <i>n</i> (%)	9 (30)
Constitutional symptoms	14 (47)
Spleen size below costal margin, cm*	3.5 (2-8)
Transfusion dependency, <i>n</i> (%)	19 (63)
Hemoglobin, g/dL*	7.8 (7.0-8.7)
< 10, <i>n</i> (%)	30 (100)
Reticulocytes, $\times 10^9/L^*$	47 (21-96)
WBC count, $\times 10^9/L^*$	4.9 (2.1-7.9)
Blood blasts*	1 (0-2)
Platelet count, $\times 10^9/L^*$	131 (52-207)
< 100, <i>n</i> (%)	11 (37)
< 50, <i>n</i> (%)	7 (23)
IPSS or DIPSS score [†]	
Low-risk	0
Intermediate-1	3
Intermediate-2	13
High-risk	14
Previous treatments	
None	8
Hydroxycarbamide	9
Danazol	12
Erythropoiesis-stimulating agents	12
Immunomodulators	3
IAK inhibitors	2

Anemia response	
Hb increase ≥ 2 g/dL in transfusion-independent patients [†]	6 of 11 (55%)
Transfusion interruption in transfusion-dependent patients	6 of 19 (32%)
Hb increase ≥ 2 g/dL or transfusion interruption	12 of 30 (40%)
Increase by at least $50 \times 10^9/L$ if baseline counts $< 100 \times 10^9/L$	3 of 11 (27%)
Increase by at least $50 \times 10^9/L$ if baseline counts $< 50 \times 10^9/L$	2 of 7 (29%)

All response occurred in first 4 months
 Median anemia response 12.3 months
 No variables were correlated with outcomes

Iron chelation

Deferasirox in the management of iron-overload in patients with myelofibrosis: a multicentre study from the Rete Ematologica Lombarda (IRON-M study)

- Response to chelation: Ferritin < 1000 or reduction >50% from baseline.
- Significant benefit observed in OS and LFS in patients responding to chelation.
- Erythroid response 46.4%
- 18.9% achieve transfusion independence

RESEARCH PAPER

DFIDELL

Deferasirox in the management of iron overload in patients with myelofibrosis treated with ruxolitinib: The multicentre retrospective RUX-IOL study

Elena Maria Elli¹ | Ambra Di Veroli² | Daniela Bartoletti^{3,4} | Alessandra Iurlo⁵

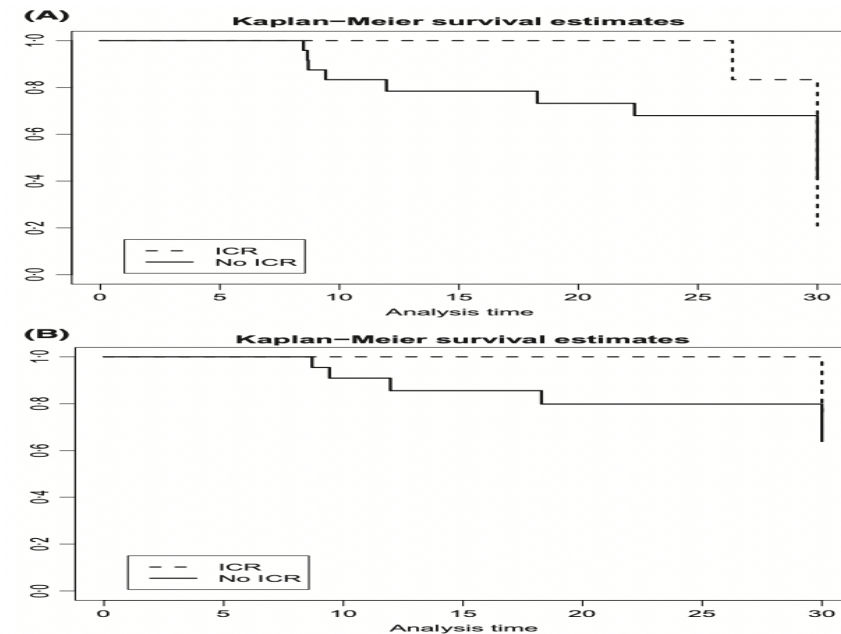
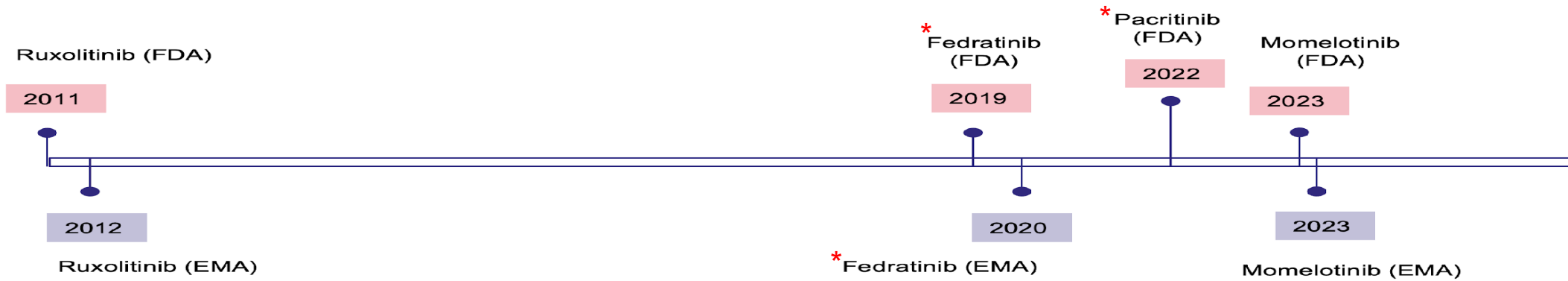


Fig 1. (A) Simon and Makuch 6-month-landmark overall survival estimates according to iron chelation response (ICR) to deferasirox (comparison at 2 years $P = 0.007$). (B) Simon and Makuch 6-month-landmark leukaemia-free survival estimates according to ICR to deferasirox (comparison at 2 years $P = 0.039$).

The key players in the medical management of MF: JAKs



Ruxolitinib

JAK2, JAK1

Aprobado EMA (2012)

Fedratinib

JAK2, FLT3

Aprobado EMA (2021)

Momelotinib

JAK2, JAK1, ACVR1

Aprobado EMA (2024)*

Pacritinib

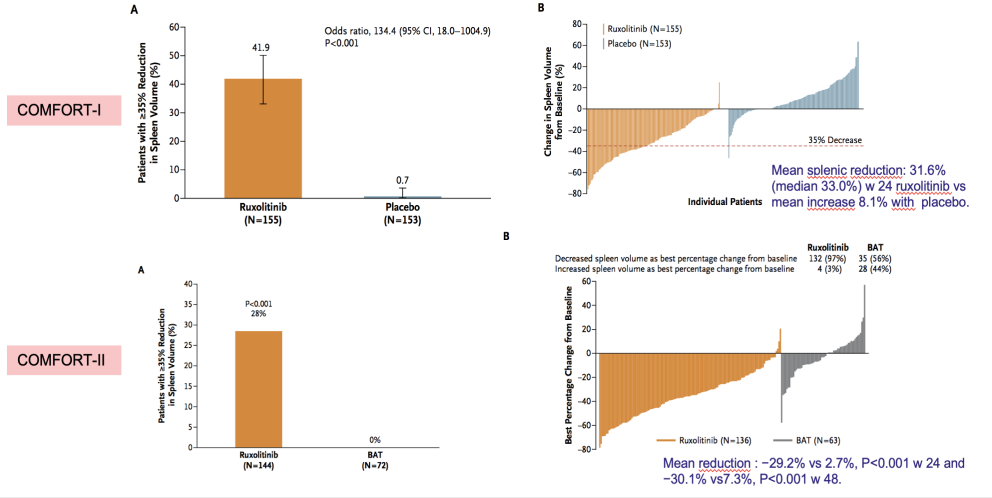
JAK2, FLT3, IRAK1, ACVR1

Aprobado FDA (2022)**

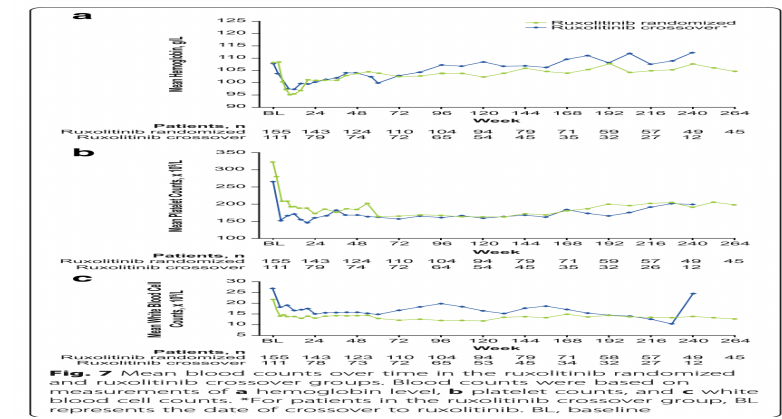
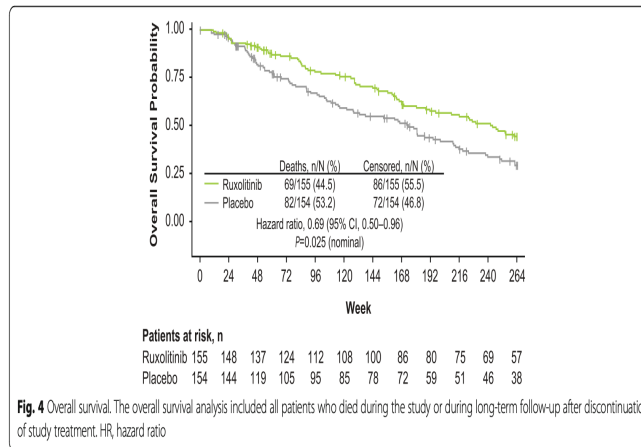
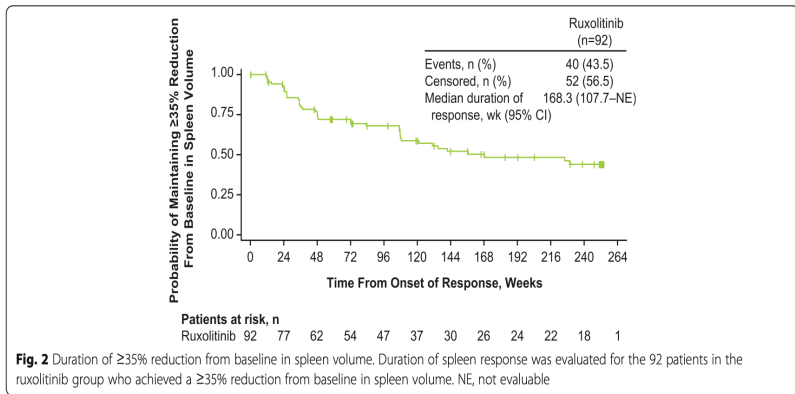
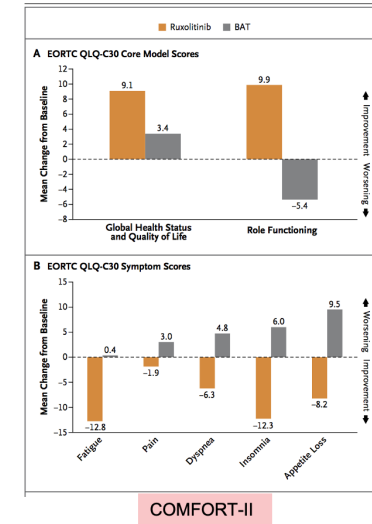
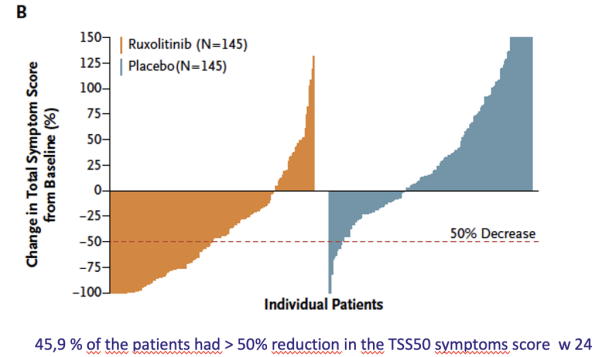
*Pacientes con anemia moderada/grave. **Pacientes con plaquetas < 50 x 10⁹/L.

Ruxolitinib. Estudio fase III

COMFORT-I Y COMFORT-II: Splenic responses with ruxolitinib



COMFORT-I Y II: Symptomatic responses with ruxolitinib



Haematological toxicity of ruxolitinib

Signalling via JAK-STAT is crucial for normal haematopoiesis.

Hematologic laboratory abnormalities.

Laboratory parameter	COMFORT-I				COMFORT-II			
	Ruxolitinib (n = 155)		Placebo (n = 151)		Ruxolitinib (n = 146)		Best available therapy (n = 73)	
	All grades (%)	≥grade 3 (%)	All grades (%)	≥grade 3 (%)	All grades (%)	≥grade 3 (%)	All grades (%)	≥grade 3 (%)
Anemia	83	45	44	16	82	40	49	21
Thrombocytopenia	71	14	21	2	69	9	29	7
Neutropenia	19	7	4	3	12	6	8	1

Data taken from [17].

Tabla 1 Dosis inicial en mielofibrosis

Recuento de plaquetas	Dosis inicial
Mayor de 200 000/mm ³	20 mg por vía oral dos veces al día
100 000 a 200 000/mm ³	15 mg por vía oral dos veces al día
75 000 a menos de 100 000/mm ³	10 mg por vía oral dos veces al día
50 000 a menos de 75 000/mm ³	5 mg por vía oral dos veces al día

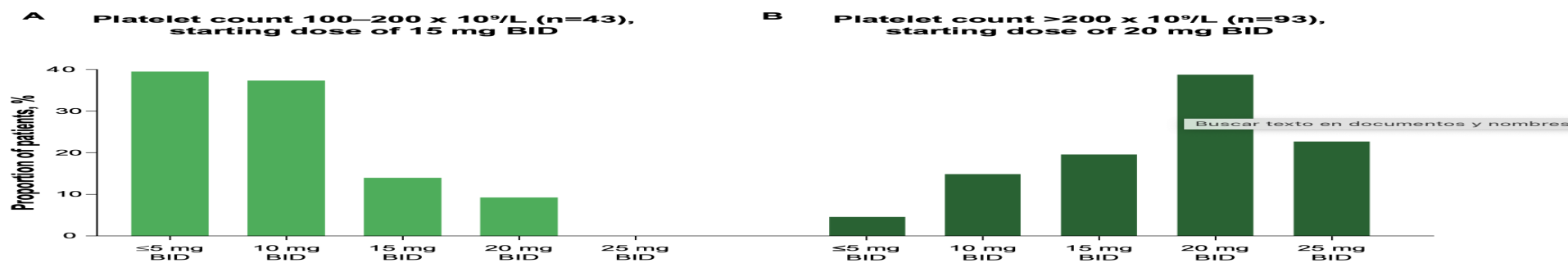


Figure 1 Distribution of patients per final titrated dose for patients starting ruxolitinib at 15 mg twice daily (bis in die [BID]) (A) versus 20 mg BID (B).

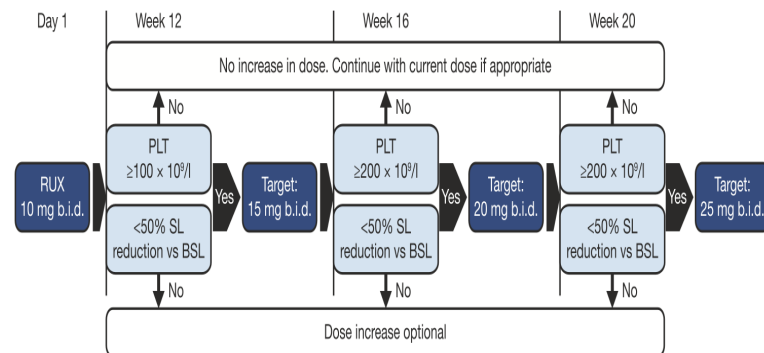
Efficacy and safety of a novel dosing strategy for ruxolitinib in the treatment of patients with myelofibrosis and anemia: the REALISE phase 2 study

Francisco Cervantes¹ · David M. Ross² · Atanas Radinoff³ · Francesca Palandri⁴ · Alexandr Myasnikov⁵

- Phase II. Single-arm trial. N: 51. Palpable splenomegaly and Hb <10
- Ruxo 10 mg every 12 hours for 12 weeks, followed by a gradual increase to a maximum of 25 mg every 12 hours
- 70% achieved a >50% reduction in spleen size at some point.
- Reduction in symptoms across the entire population: -54% at 24 weeks
- Overall, patients respond better to higher doses, but the 10 mg/12-hour dose is quite effective
- Haemoglobin levels and transfusion requirements do not worsen in the majority of patients

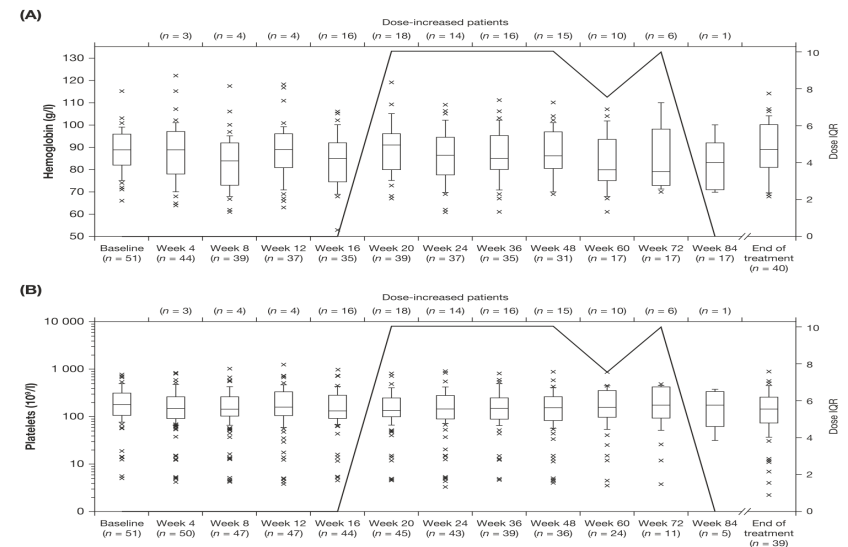
Efficacy and safety of a novel dosing strategy for ruxolitinib in the treatment of patients with...

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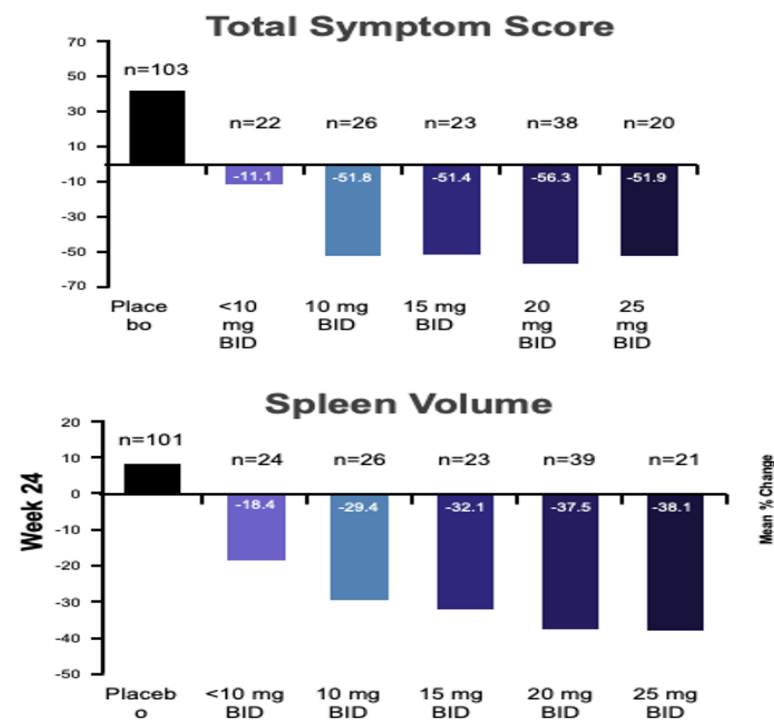
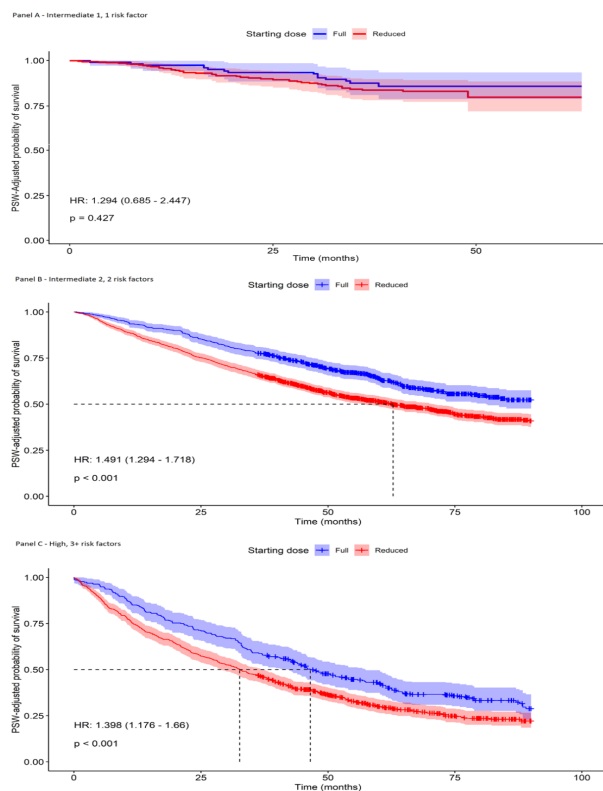
F. Cervantes et al.



ORIGINAL PAPER

Haematological Malignancy – Clinical

The impact of starting dose on overall survival in myelofibrosis patients treated with ruxolitinib: A prospective real-world study on AIFA monitoring registries

 Massimo Breccia¹  | Simone Celant² | Francesca Palandri³  | Francesco Passamonti⁴  |

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



The use of erythropoiesis-stimulating agents with ruxolitinib in patients with myelofibrosis in COMFORT-II: an open-label, phase 3 study assessing efficacy and safety of ruxolitinib versus best available therapy in the treatment of myelofibrosis

Mary Frances McMullin^{1*}, Claire N. Harrison², Dietger Niederwieser³, Hilde Demuyne⁴, Nadja Jäkel³, ...

- Fewer than 10% of patients in COMFORT-2 and 14% in JUMP received ESAs. Post hoc analyses found no significant increase in toxicity or reduced efficacy of ruxolitinib when combined with an ESA
- Analysis of EPO in COMFORT-II (darbepoetin alfa, n = 3; erythropoietin alfa, n = 9; unspecified, n = 1)
13 of 146 patients treated with Ruxo also received ESA
- Post hoc analyses found no significant increase in toxicity or reduced efficacy of ruxolitinib when combined with an ESA
- A separate retrospective study reported significant anemia improvement in 54% of patients using ESAs with ruxolitinib, with durable responses lasting up to five years in 76% of cases.
- **Conclusions: ESA are well tolerated and do not compromise response**
- There is also a Phase II study combining Ruxo and Danatrol. N: 27. Stabilisation or improvement of Hb by 55% when adding danatrol. It may also improve thrombocytopenia.

Al-Ali HK, *Haematologica*. 2016;101(9):1065-1073. Gupta V, *Blood*. 2023;142(Supplement 1):5174-5174.

Maffioli M A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis. *Blood Adv*. 2022;6(6):1855-1864. McMullin MF et al. *Exp Hematol Oncol*. 2015;4:26.. Crisà E, Cilloni D, Elli EM, et al. *Br J Haematol*. 2018;182(5):701-704.

Gowin K, Kosiorek H, Dueck A, Mascarenhas J, Hoffman R, Reeder C, et al. Multicenter phase 2 study of combination therapy with ruxolitinib and danazol in patients with myelofibrosis. *Leuk Res*.

USO DE AGENTES ESTIMULANTES DE LA ERITROPOYESIS PARA EL TRATAMIENTO DE LA ANEMIA EN PACIENTES CON MIELOFIBROSIS TRATADOS CON RUXOLITINIB: EXPERIENCIA GRUPO GEMFIN

Sara Garrido^{1,2}, Jorge Verdejo³, Alba Puyuelo^{1,2}, Lucía Pérez-Lamas³, Sonia Garcés⁴, Blanca Xicoy⁵, Ulises Ferrandiz⁵, Jason Villarreal⁶, Miriam Ratia⁶, Natalia de las Heras⁷, Federico Herrera⁸, Alicia Cruz Gómez⁸, Marta López Olivetti⁹, Beatriz Cuevas¹⁰, Manuel Pérez Encinas¹¹, Marta Gómez-Núñez¹², Brais Lamas¹³, Elvira Mora¹³, Elena Magro¹⁴, Teresa Cobo¹⁵, Sofia Martín-Consuegra¹⁶, Reyes Jiménez¹⁷, Santiago Redondo¹⁸, Gonzalo Carreño¹⁹, Alicia Senín²⁰, Laura Fox^{1,2}.

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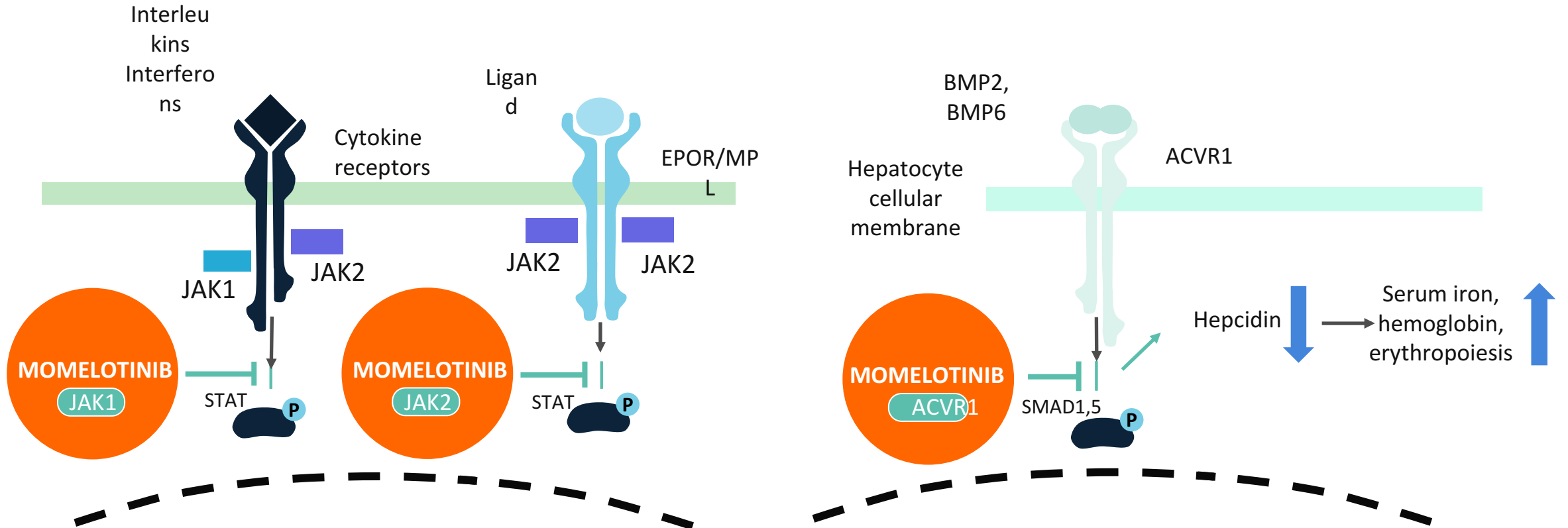
N: 97

OVIEDO

IWG-MRT response rate 2013	43 (48.9%)
Time to response (months)	5 months (2–14)
Duration of response	69 months (53–X)
IWG-ELN ‘minor’ response rate 2024	70 (79.6%)

Alternatives to Ruxolitinib: Momelotinib

Momelotinib: Mechanism of Action



Dysregulation of the **JAK-STAT** signaling pathway in FM leads to the overproduction of inflammatory cytokines, bone marrow fibrosis, **systemic symptoms**, and clonal proliferation, resulting in extramedullary hematopoiesis and **splenomegaly**^{1,2}

Chronic inflammation also causes **ACVR1** hyperactivation, elevated **hepcidin**, and dysregulation of iron metabolism, contributing to MF-associated **anemia**.^{3,4}

Momelotinib

SIMPLIFY-1 IJAK naive

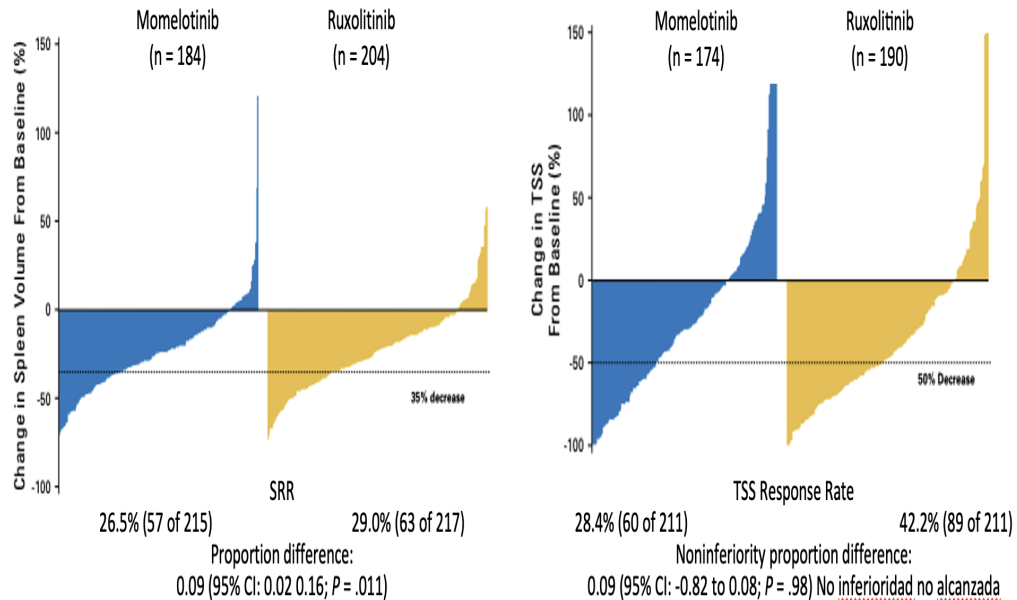
Adults with primary, post-PV or post-ET MF; symptomatic int-1, int-2, or high risk; platelets $\geq 50 \times 10^9/L$ (n = 432)

Momelotinib 200 mg PO daily

Ruxolitinib 20 mg PO daily

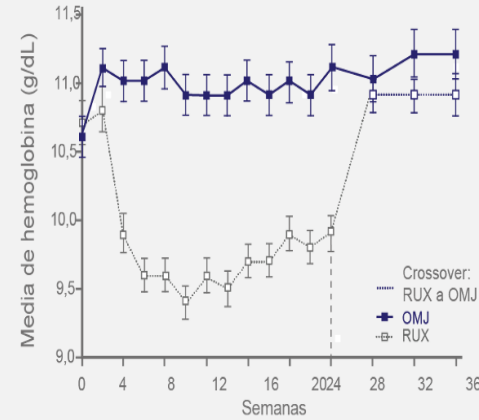
Cross over allowed after 24 wk

Mesa. JCO. 2017;35:3844.

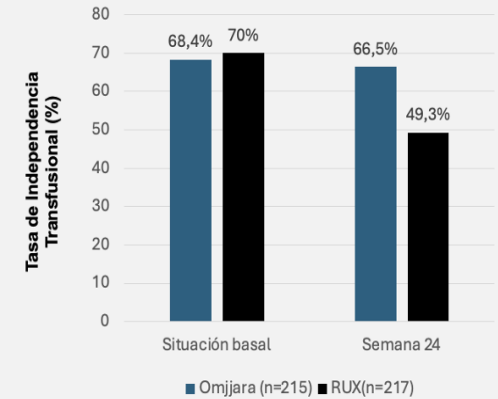


J Clin Oncol 35:3844-3850. 2017

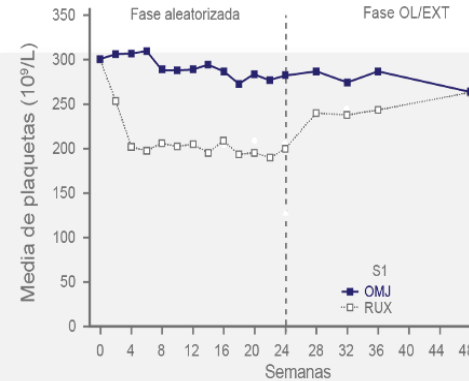
Hb



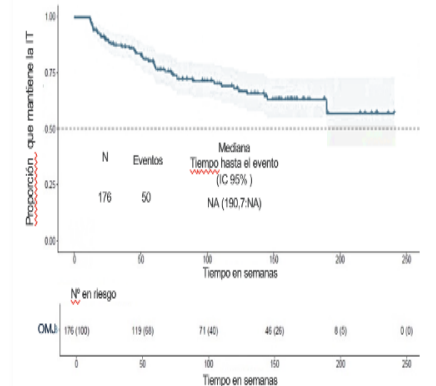
Transfusion independence



Platelets



TI duration



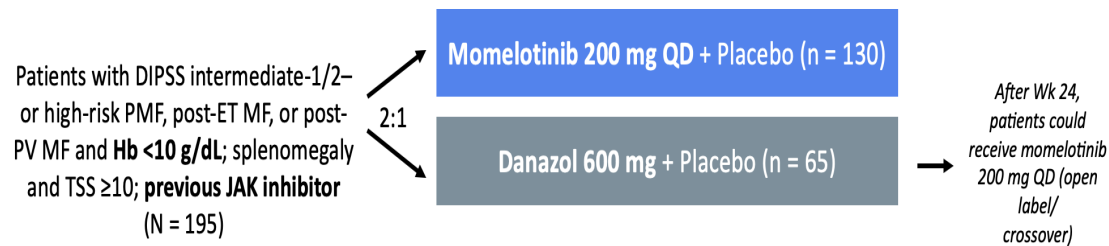
Gráfica adaptada de Mesa R, et al. Leuk Lymphoma, 2022.1

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



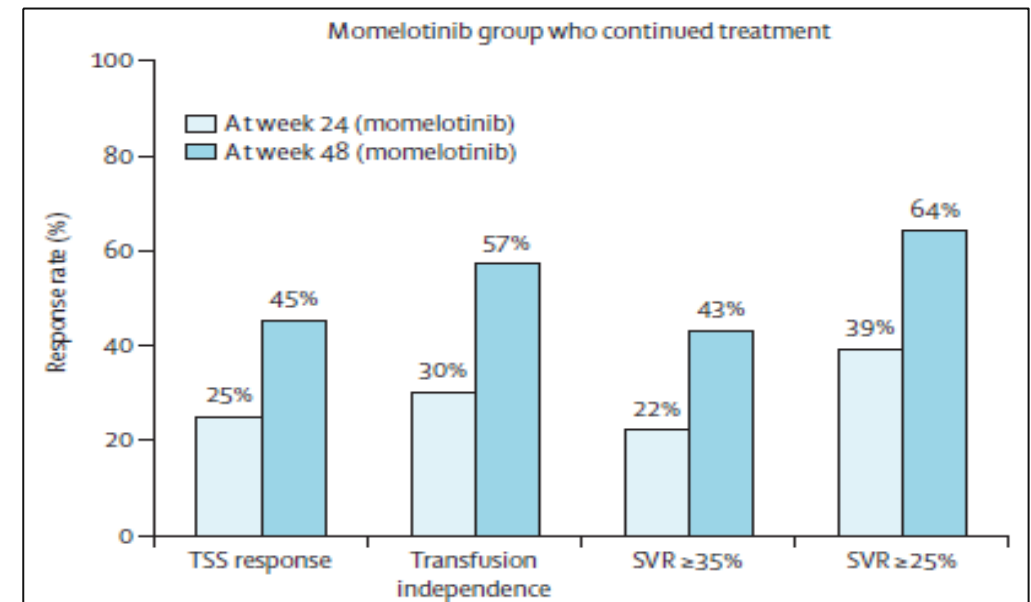
Srdan Verstovsek, Aaron T Gerds, Alessandro M Vannucchi, Haifa Kathrin Al-Ali, David Lavie, Andrew T Kuykendall, Sebastian Grosicki

The Lancet January 2023

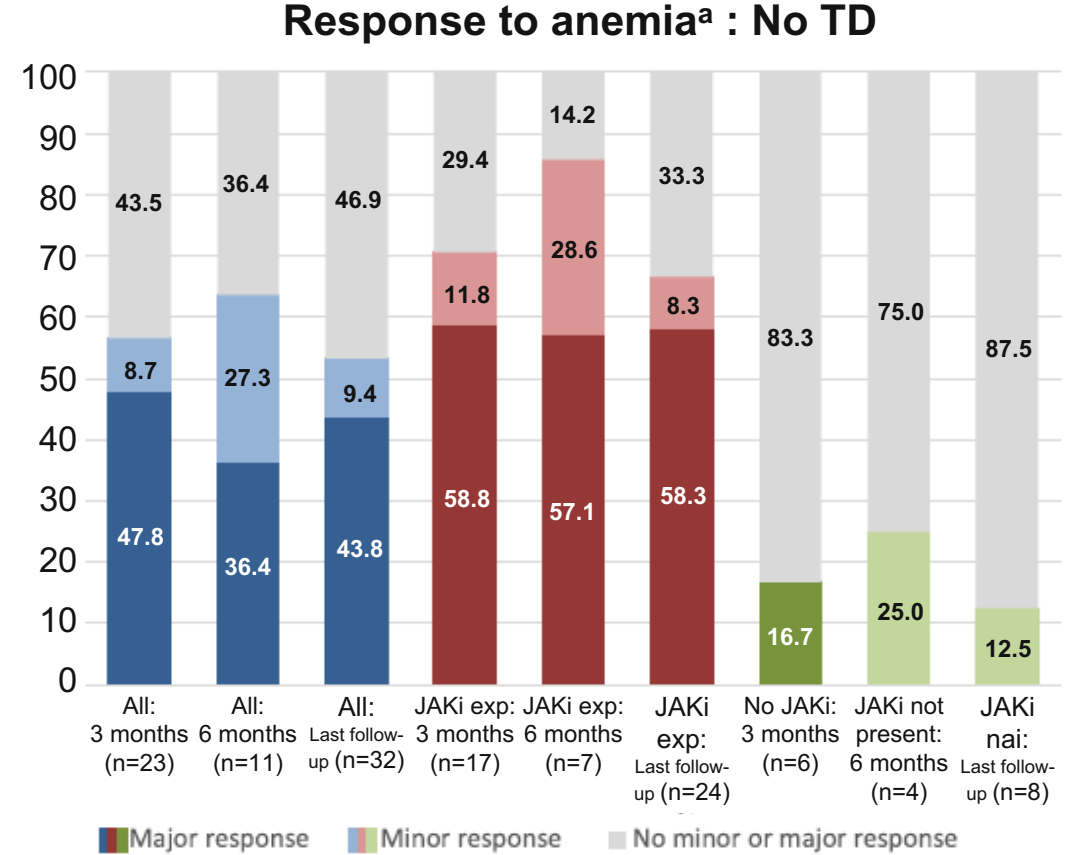
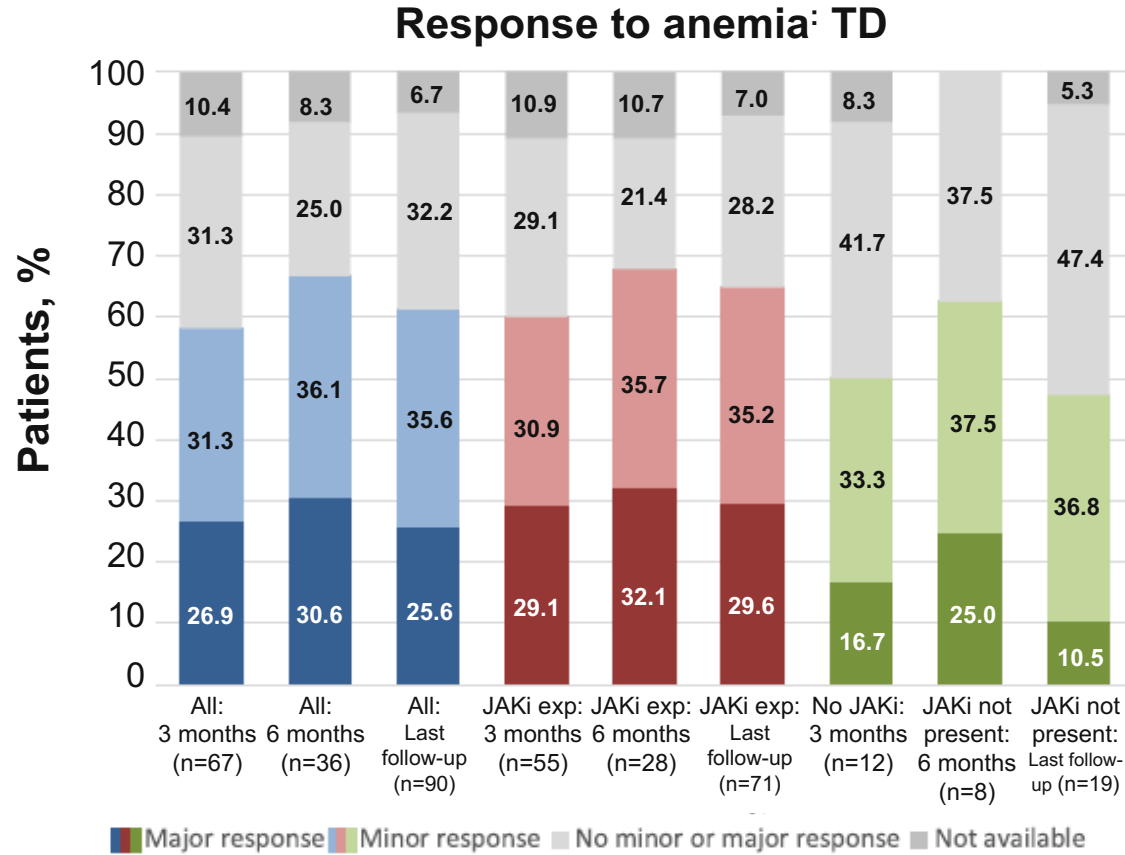


Outcome, Wk 24	Criterion for Significance	Momelotinib (n = 130)	Danazol (n = 65)	P Value
TSS response rate (primary endpoint), * %	Superiority ($P \leq .05$)	25	9	.0095 (superior)
Transfusion independence rate, † %	Noninferiority	30	20	.0116 (noninferior)
TSS change from baseline	Superiority ($P \leq .05$)	11.5	-3.9	.0014 (superior)
Splenic response rate (≥35% reduction), %	Superiority ($P \leq .05$)	22	3	.0011 (superior)
No transfusion to Wk 24, %	Superiority ($P \leq .05$)	35	17	.0012 (superior)

Verstovsek. Lancet. 2023;401:269.



Momelotinib in real-world practice in Spain: hematological response



48.4% achieved transfusion independence at 3 months and 45.7% at 6 months

The median Hb increased from 8.9 to 10.2 g/dL at 3 months and remained at 10.1 g/dL at 6 months

There were differences in the response rates between patients treated with MMB + EPO and those treated with MMB monotherapy at 3 months but not at 6 months

Momelotinib in real-world practice in Spain

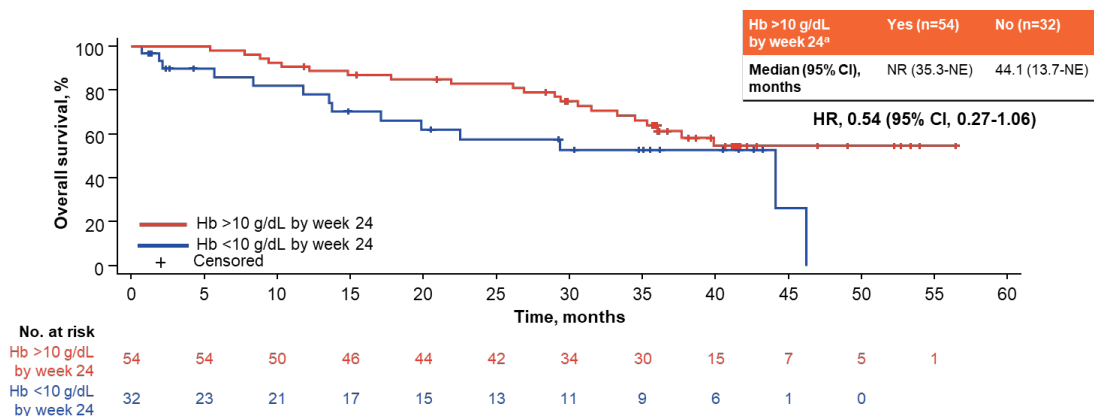
	At last assessment			During follow up		
	All patients n=45	JAKi naïve n=11	JAKi exposed n=34	3 months n=29	6 months n=14	9 months n=8
Cm below costal margin, median, (IQR) [range]						
Previous MMB start, median (IQR) [range]	10 (8) [5-25]	10 (5) [5-20]	8 (7.7) [5-25]			
During follow up, median (IQR) [range]				7.5(4.75) [0-25]	8 (4) [0-12]	6 (2.5) [0-10]
Overall reduction, n (%)	28 (62.2)	7 (63.6)	21 (61.8)	19 (65.5)	7 (50)	4 (50)
Cm of reduction						
median, (IQR) [range]	5 (5) [2-15]	5 (8) [2-15]	4 (4) [2-12]	4 (3) [2-15]	8 (4) [3-12]	9 (3) [6-12]
mean, (SD)	5.89 (3.91)	6.57 (5.29)	5.47 (3.44)	5.37 (3.62)	7.29 (3.20)	9 (2.58)
Patients with reduction according to the 2013 ELN (IWG- MRT) criteria, n (%)	11 (24.4)	3 (27.3)	8 (23.5)	7 (24.1)	5 (35.7)	4 (50)
Cm of reduction						
median, (IQR) [range]	10 (6) [6-15]	12 (3.5) [8-15]	8 (6) [6-12]	8 (5) [6-15]	8 (2) [6-12]	9 (3) [6-12]
mean, (SD)	9.5 (3.27)	11.7 (3.51)	8.75 (3.0)	9 (3.51)	8.8 (2.28)	9 (2.58)
No, but controlled stable splenomegaly, n (%)	12 (26.7)	2 (18.1)	10 (29.4)	6 (20.1)	5 (35.7)	3 (37.5)
Refractoriness, n (%)	3 (6.7)	1 (9.1)	2 (5.9)	4 (13.8)	2 (14.2)	1 (12.5)
Increase, n (%)	2 (4.4)	1 (9.1)	1 (2.9)	0	0	0

28 of 45 (62.2%) patients experienced a reduction in spleen size (median reduction of 5 cm). JAKi-naïve patients achieved a greater reduction in spleen size (12 cm vs. 8 cm).

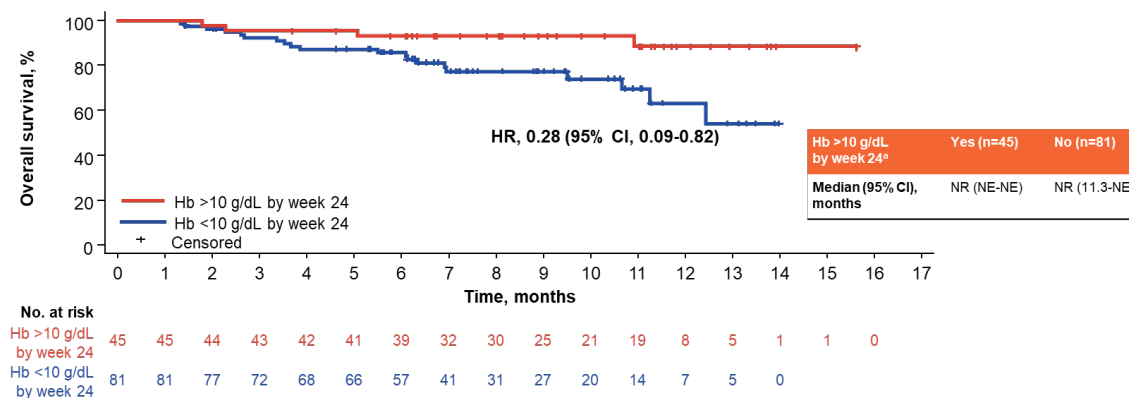
116 of the 126 patients (92%) experienced an improvement in at least one of the initial symptoms. The symptomatic responses were similar in both JAKi-treated and JAKi-naïve patients.

OS according to Hb response

SIMPLIFY-1 JAK inhibitor naive



MOMENTUM JAK inhibitor experienced



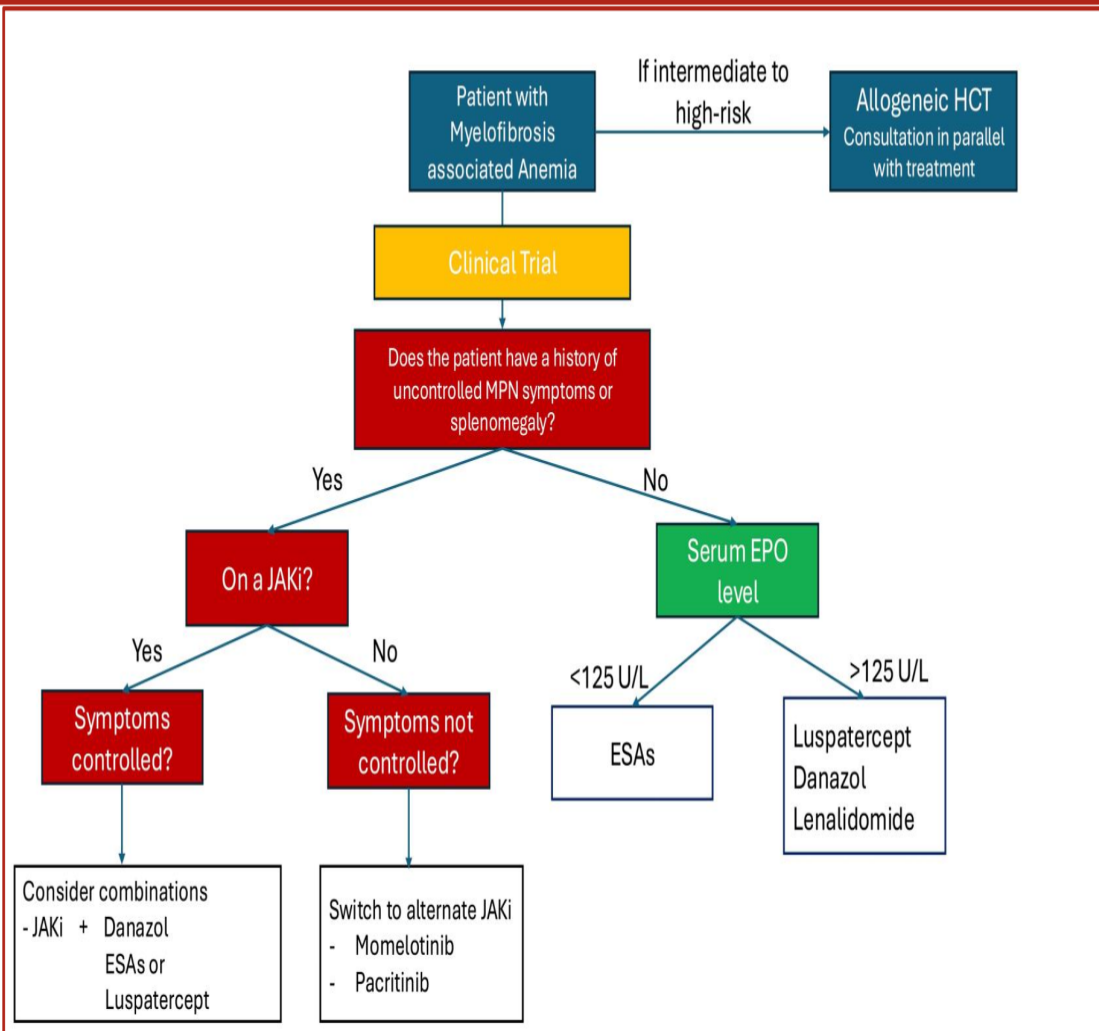
- In SIMPLIFY-1, median OS was NR (95% CI, 35.3 months-NE) vs 44.1 months (95% CI, 13.7 months-NE) in patients with baseline Hb <10 g/dL who did or did not achieve Hb >10 g/dL by week 24 (HR, 0.54; 95% CI, 0.27-1.06)
 - OS was longer in patients who achieved this Hb threshold than those who did not in both moderate (median, NR vs NR; HR, 0.55; 95% CI, 0.22-1.36) and severe (median, NR vs 44.1 months; HR, 0.76; 95% CI, 0.25-2.27) subgroups
- Achieving Hb >10 g/dL by week 24 was associated with longer OS regardless of baseline anemia severity or JAK inhibitor experience (HR, 0.28; 95% CI, 0.09-0.82)

CI, confidence interval; Hb, hemoglobin; HR, hazard ratio; JAK, Janus kinase; NE, not estimable; NR, not reached; OS, overall survival.

^a Defined based on patients who achieved Hb ≥10 g/dL by week 24, excluding all Hb values in the 4 weeks post transfusion. 1. Palandri F, et al. Presented at the European Hematology Association 2025 Congress (Poster PF828) June 12-15, 2025, Milan, Italy.

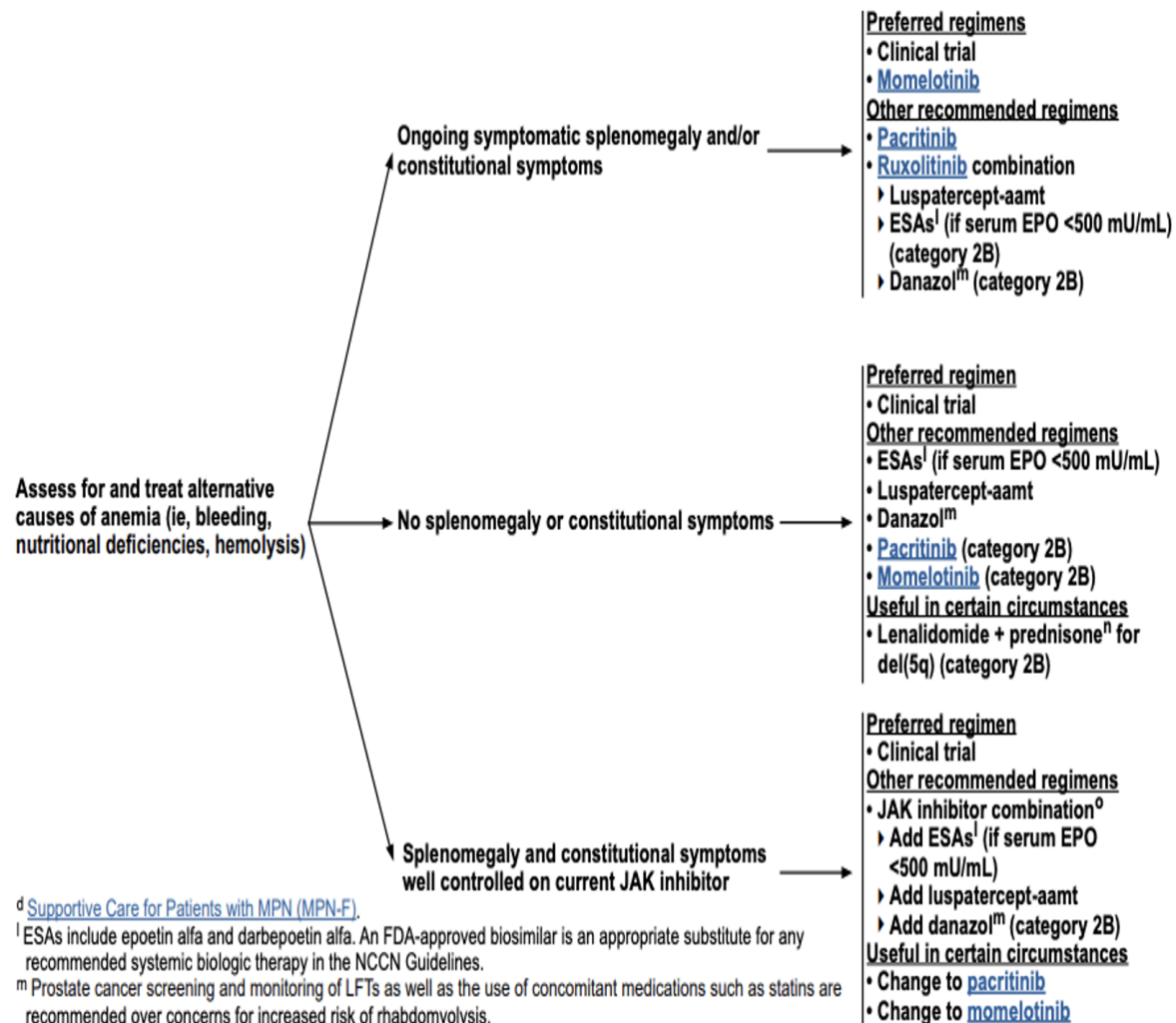
Treatment of anemia

How We Treat Myelofibrosis-Associated Anemia



Blood 2025. A. Jaints, A. Gerds

MANAGEMENT OF MF-ASSOCIATED ANEMIA^d



Spanish GEMFIN guidelines 2025

Tabla 4.8. Recomendaciones generales de los autores sobre el uso de los inhibidores de JAK2 en pacientes

First line

- Ruxolitinib: the treatment of choice for most patients, based on high efficacy, a favourable toxicity profile and extensive clinical experience
- *Fedratinib: may be considered as an option in cases of moderate thrombocytopenia (50–75,000)
- Momelotinib: Consider as a first-line option in cases of anemia < 10 g/dl or severe thrombocytopenia < 50,000

segunda línea

Second Line

- *Fedratinib: if the primary aim is symptom management and/or splenomegaly
- Momelotinib: if anemia develops whilst taking ruxolitinib and/or fedratinib. Ideally after dose optimisation and consideration of treatment with erythropoietin

Tabla extraída de: Manual de recomendaciones en neoplasias mieloproliferativas crónicas filadelfia negativas de GEMFIN. Edición 2025

Spanish GEMFIN guidelines 2025

Tabla 4.9. Criterios de fallo a ruxolitinib y recomendaciones de tratamiento*

Criterio de fallo	Descripción	Recomendación terapéutica
Respuesta subóptima del bazo	Reducción de menos del 25% en la longitud palpable del bazo después de al menos 3 meses de tratamiento con dosis óptima.	- Incremento de dosis si lo permite la cifra de plaquetas y hemoglobina. - Cambio a fedratinib.
Pérdida de respuesta del bazo	Aumento de >50% en la longitud del bazo desde la mejor respuesta alcanzada.	- Incremento de dosis en función de dosis utilizada, cifra de plaquetas y hemoglobina. - Cambio a fedratinib (plantear momelotinib en caso de anemia moderada/severa y/o trombocitopenia severa).
Anemia dependiente de transfusiones	4 o más unidades de transfusión de glóbulos rojos en 8 semanas, después de 6 meses de tratamiento, si era previamente independiente de transfusiones.	- Cambio a momelotinib ¹ +/- uso de agentes eritropoyéticos.
Trombocitopenia severa	Incapacidad para mantener un recuento de plaquetas por encima de $35-50 \times 10^9/L$ en pacientes con anticoagulación, o por encima de $25 \times 10^9/L$ en el resto.	- Reducción de dosis en función de dosis previa, cifra de plaquetas y respuesta a tratamiento. - Cambio a momelotinib ² .
Transformación a fase acelerada o blástica	Progresión de la mielofibrosis a fase acelerada o blástica.	- Candidato a trasplante: valorar tratamiento tipo leucemia aguda secundaria (quimioterapia intensiva vs agentes hipometilantes + venetoclax) previo a trasplante ³ . - No candidato a trasplante: tratamiento citorrductor (hidroxiurea, agentes hipometilantes +/- venetoclax) o tratamiento paliativo en función del estado del paciente. - El estudio NGS puede detectar
Desarrollo de cáncer secundario	Aparición de una segunda neoplasia maligna durante el tratamiento, especialmente si es una forma agresiva.	Suspensión de ruxolitinib. Puede plantearse inhibidor alternativo en caso de beneficio claro del tratamiento ⁴ .
Infecciones recurrentes	Infecciones frecuentes y graves, posiblemente relacionadas con la inmunosupresión inducida por ruxolitinib.	Suspensión de ruxolitinib. Puede plantearse inhibidor alternativo en caso de beneficio claro del tratamiento ⁴ .

1. El cambio a momelotinib es razonable en caso de anemia moderada sin necesidad de dependencia transfusional.
2. Si disponibilidad, pacritinib, sería una alternativa en casos con trombocitopenia mantenida $< 50 \times 10^9/L$.
3. La indicación de tratamiento para reducir la carga tumoral previo al trasplante en pacientes con fase de aceleración no está bien establecida.
4. El efecto inmunosupresor de ruxolitinib es bien conocido. Por el contrario, se dispone de menor información al respecto con los otros inhibidores de JAK.

*En todas las situaciones considerar la inclusión del paciente en ensayo clínico.

Anemia dependiente de transfusiones	4 o más unidades de transfusión de glóbulos rojos en 8 semanas, después	- Cambio a momelotinib ¹ +/- uso de agentes eritropoyéticos.
Trombocitopenia severa		

Transfusion-dependent anemia
-Switch to momelotinib
-Combination of erythropoietic agents

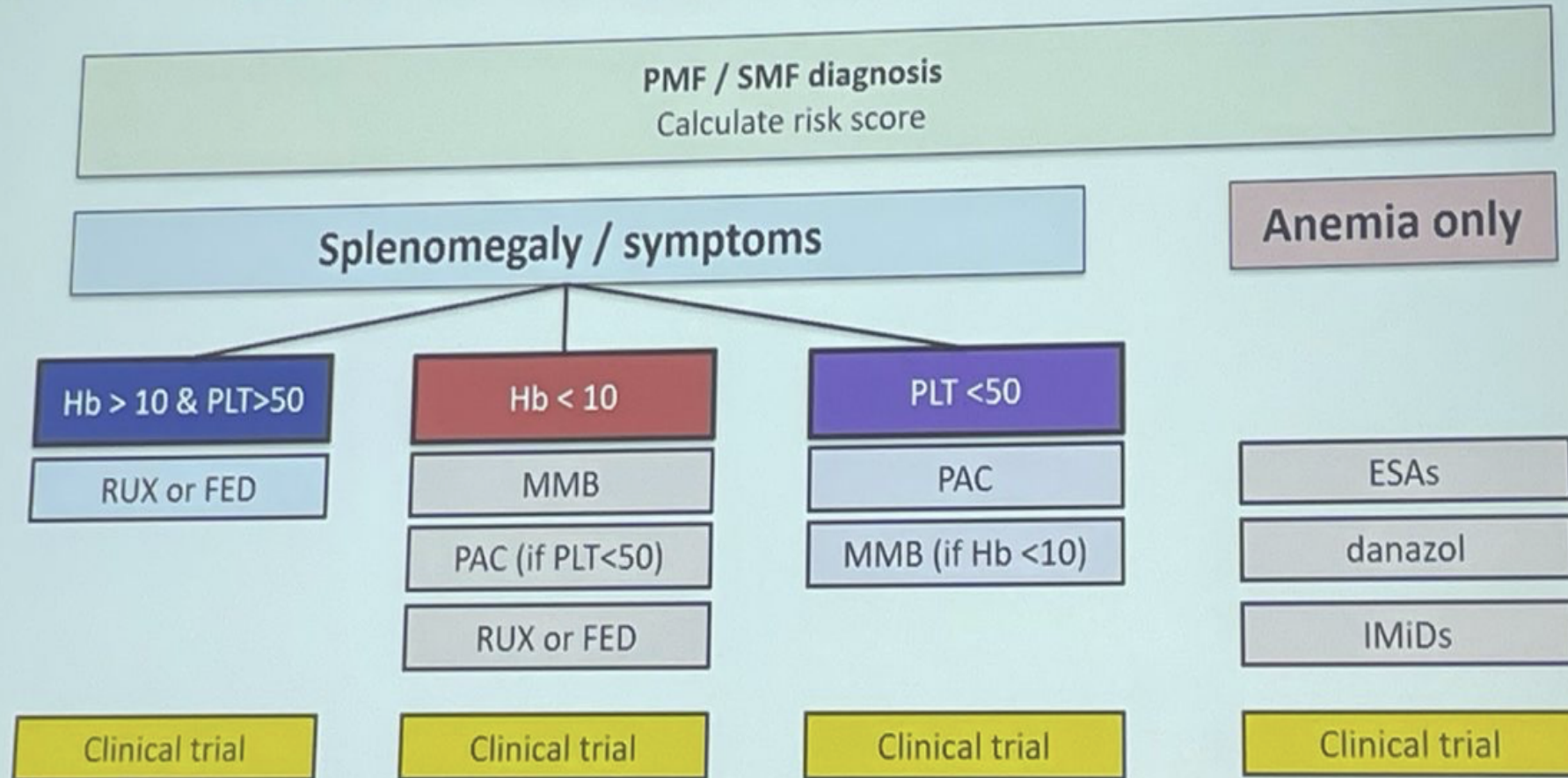
Switching to momelotinib may also be appropriate in cases of non-transfusion-dependent anemia

Thrombocytopenia < 50,000
-Adjust dose
-Switch to momelotinib
-If *pacritinib is available, consider this option

*En todas las situaciones considerar la inclusión del paciente en ensayo clínico.

Tabla adaptada de: Manual de recomendaciones en neoplasias mieloproliferativas crónicas filadelfia negativas de GEMFIN. Edición 2025

Personalized approach of MF in 2025





Emerging Therapeutic Approaches for Anemia in Myelofibrosis

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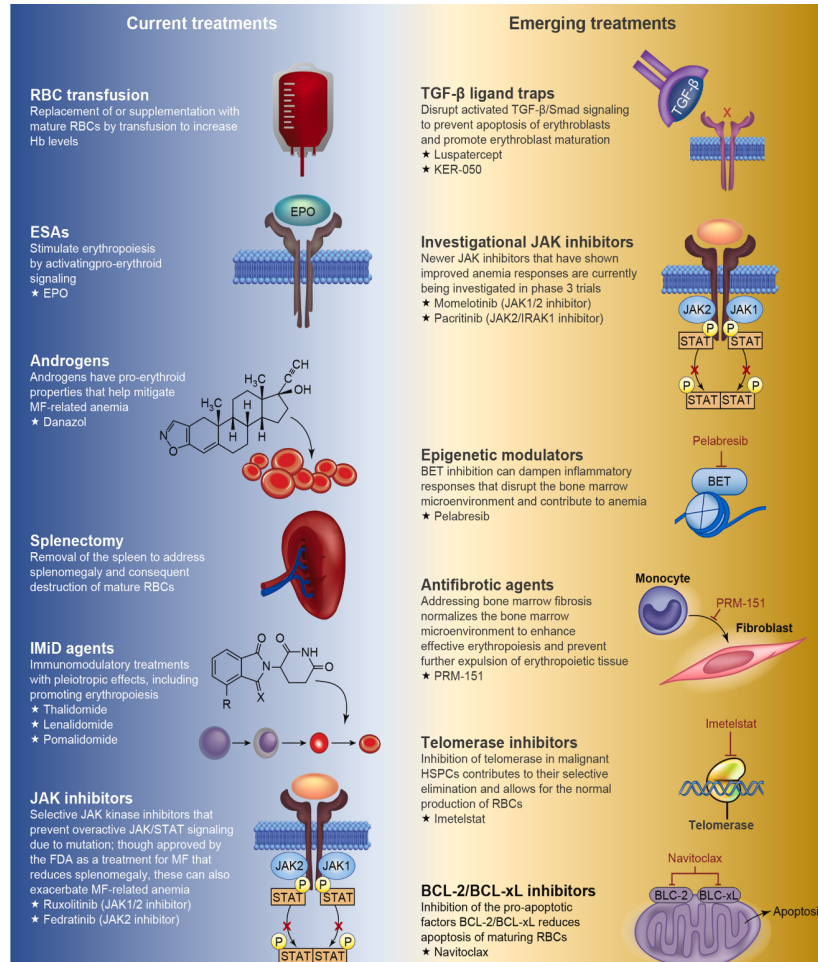


Table 1 Agents targeting the TGF-β/BMP/SMAD signaling pathway, conferring anemia-related benefits in MF patients

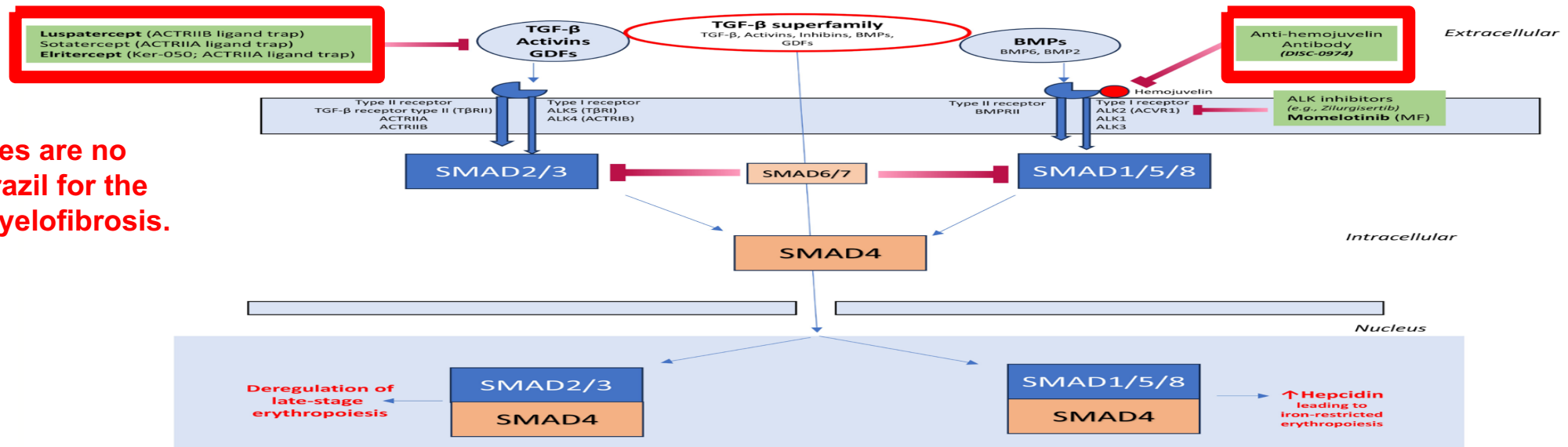
Agent	Mechanism of action regarding anemia	Regulatory approval/ Clinical status in MF	References
Momelotinib	ACVR1 inhibitor	Approved in the US in 2023 for intermediate or high-risk MF and anemia	Chifotides HT, et al. <i>J. Hematol. Oncol.</i> 2022 [46]
Pacritinib	ACVR1 inhibitor	Approved in the US in 2022 for intermediate or high-risk MF and platelet counts $50 \times 10^9/L$	Oh S, et al. <i>Blood Adv.</i> 2023 [66]
Jaktinib	ACVR1 inhibitor	In clinical development in China/Phase 3 trial (NCT04617028)	Zhang Y, et al. <i>Hemasphere</i> 2023 [71]
Zilugisertib	ACVR1 inhibitor	Clinical development discontinued	Bose P, et al. <i>Hemasphere</i> 2024 [90]
DJISC-0974	Anti-HJV monoclonal antibody	In clinical development/Phase 1b/2 trial (NCT05320198)	Gangat N, et al. <i>Blood</i> 2024 [72]
Luspatercept	ActRIIB ligand trap	In advanced clinical development/Phase 3 trial (INDEPENDENCE™; NCT04717414)	Kiladjian JJ, et al. <i>Clin Lymphoma Myeloma Leuk.</i> 2023 [79]
Luspatercept + momelotinib	ActRIIB ligand trap + ACVR1 inhibitor	In clinical development/Phase 2 trial (ODYSSEY; NCT06517875)	Bose P, et al. <i>Blood</i> 2024 [80]
Sotatercept	ActRIIA ligand trap	Clinical development discontinued	Bose P, et al., <i>Haematologica</i> 2024 [81]
Elrtercept	ActRIIA ligand trap	In clinical development/Phase 2 trial (RESTORE; NCT05037760)	Harrison C, et al. <i>Blood</i> 2024 [88]

ACVR1 activin A receptor type 1, ActRII activin receptor type II, BMP bone morphogenetic protein, HJV hemojuvelin, TGF-β transforming growth factor-β, MF myelofibrosis, SMAD small mothers against decapentaplegic

These molecules are not approved in Brazil for the treatment of myelofibrosis.

Erythropoiesis regulation

- Tightly regulated process through Epo: main regulator of early- stage erythropoiesis TGF- β superfamily: regulators of late-stage erythropoiesis . Negatively regulate erythrocyte differentiation and maturation, resulting in increased apoptosis of late stage erythroblasts



These molecules are not approved in Brazil for the treatment of myelofibrosis.

- TGF- β superfamily ligands comprise activins, cytokines, TGF- β , BMPs, and growth and differentiation factors (GDFs), which regulate cell proliferation and differentiation, including hematopoietic progenitor cells.
- By binding to activin receptors, they activate downstream SMAD signaling, leading to suppression of late stage erythropoiesis, ineffective red blood cell production and anemia
- Transforming Growth Factor- β (TGF- β) Ligand Traps bind ligands, such as activins and GDFs, inhibit SMAD2/3 signaling, and promote erythroid maturation and late-stage erythropoiesis.

Conclusions

- Anemia is one of the main signs of Myelofibrosis and is associated with worse prognosis and quality of life.
- Its pathogenesis is complex, and many factors must be taken into consideration when treating MF-associated anemia.
- Classic treatments are limited with EPO being the best choice in asymptomatic/no splenomegaly patients or in those with ruxo-associated anemia (beware of ruxolitinib failure!)
- Momelotinib both JAK and ACVR1 inhibition controls symptoms and splenomegaly as well as improves anemia.
- This make momelotinib the best choice for first-line anemic patients and after ruxolitinib failure due to cytopenias.
- New treatments might arrive in the close future.