Organizado por:

Clínica Universidad de Navarra

PUESTA AL DÍA

HEMATOLOGÍA EN 48H [LO QUE DEBES CONOCER PARA TU PRÁCTICA CLÍNICA]

X EDICIÓN

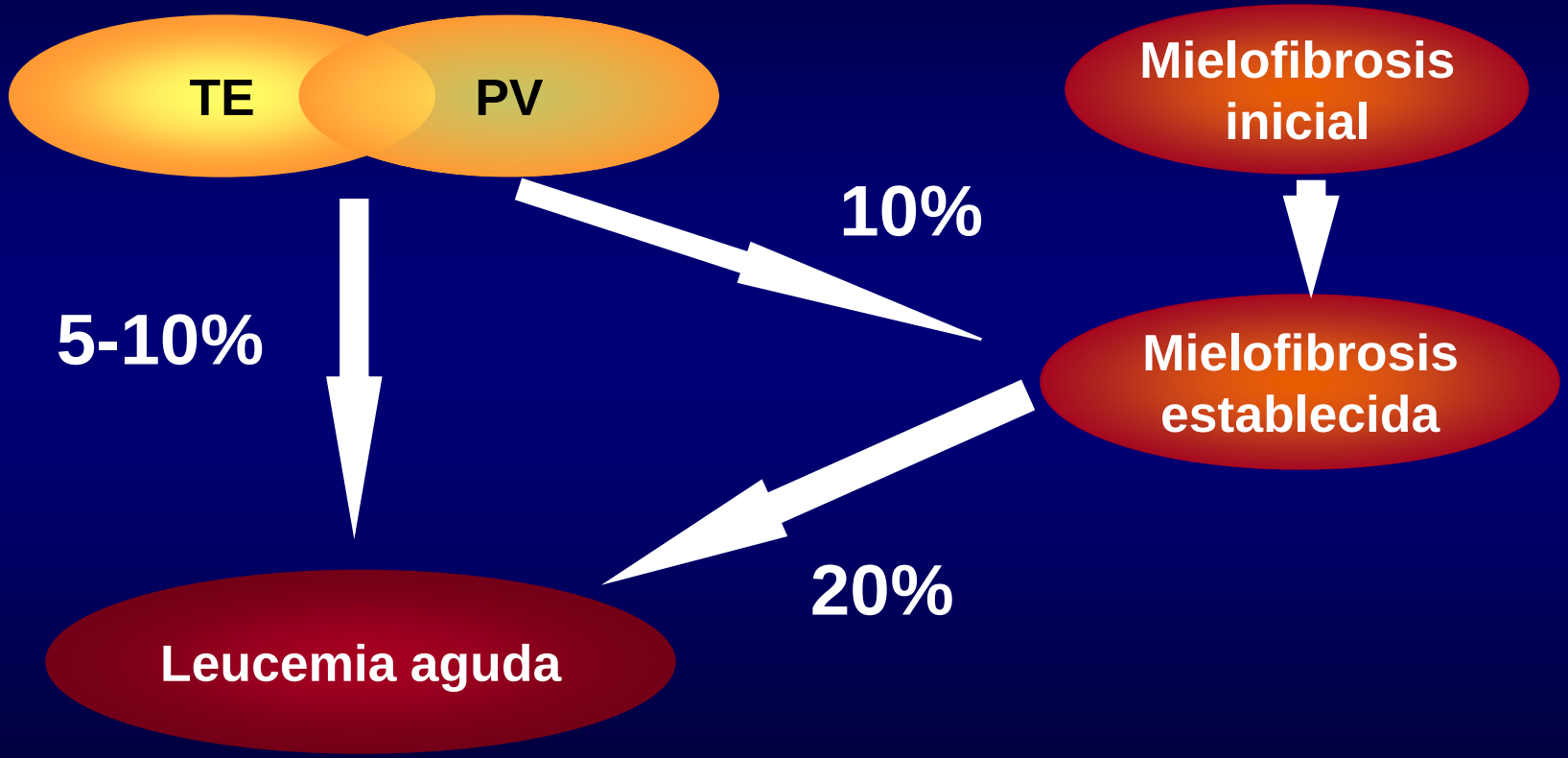
ACTUALÍZATE 48 HORAS

Controversias en Neoplasias Mieloproliferativas Crónicas

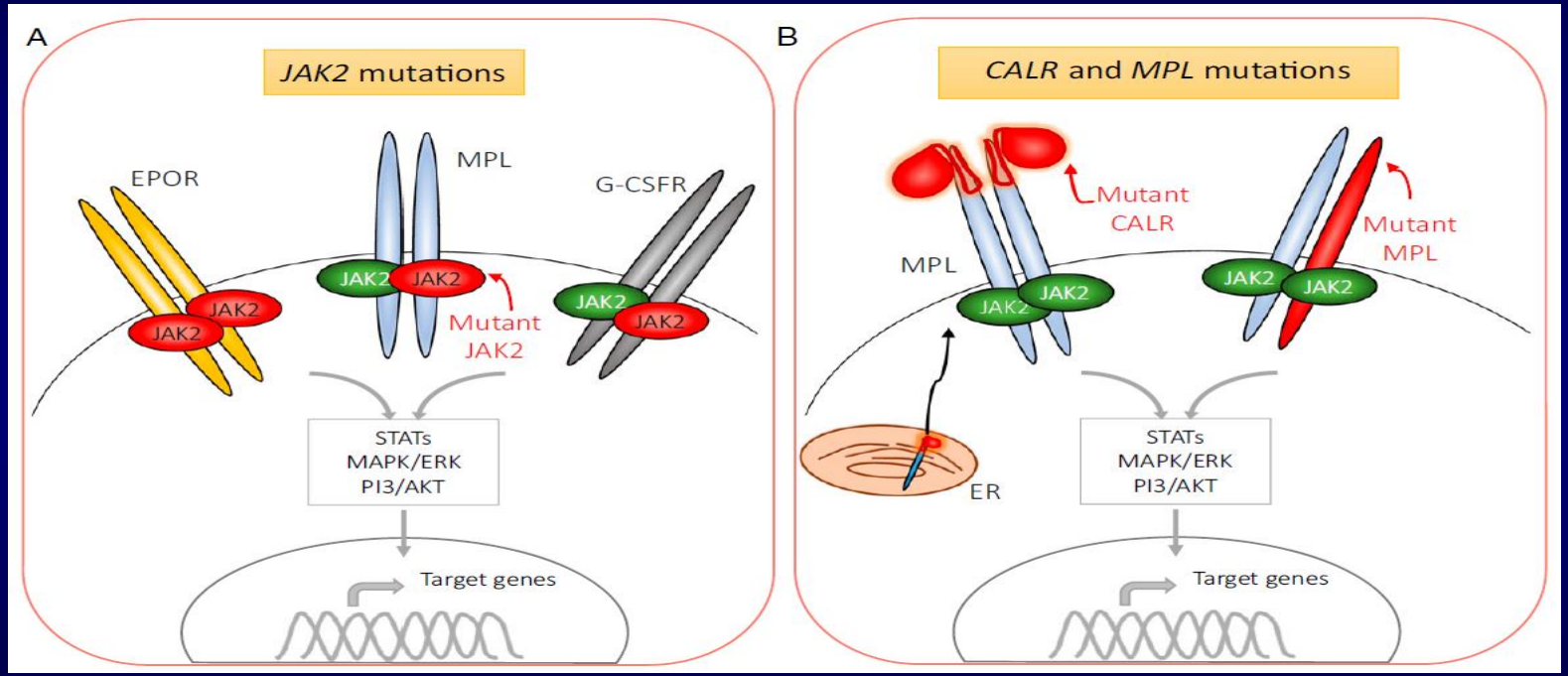
Juan Carlos Hernández Boluda

Hospital Clínico Universitario, Valencia

Historia natural de las NMP “clásicas”

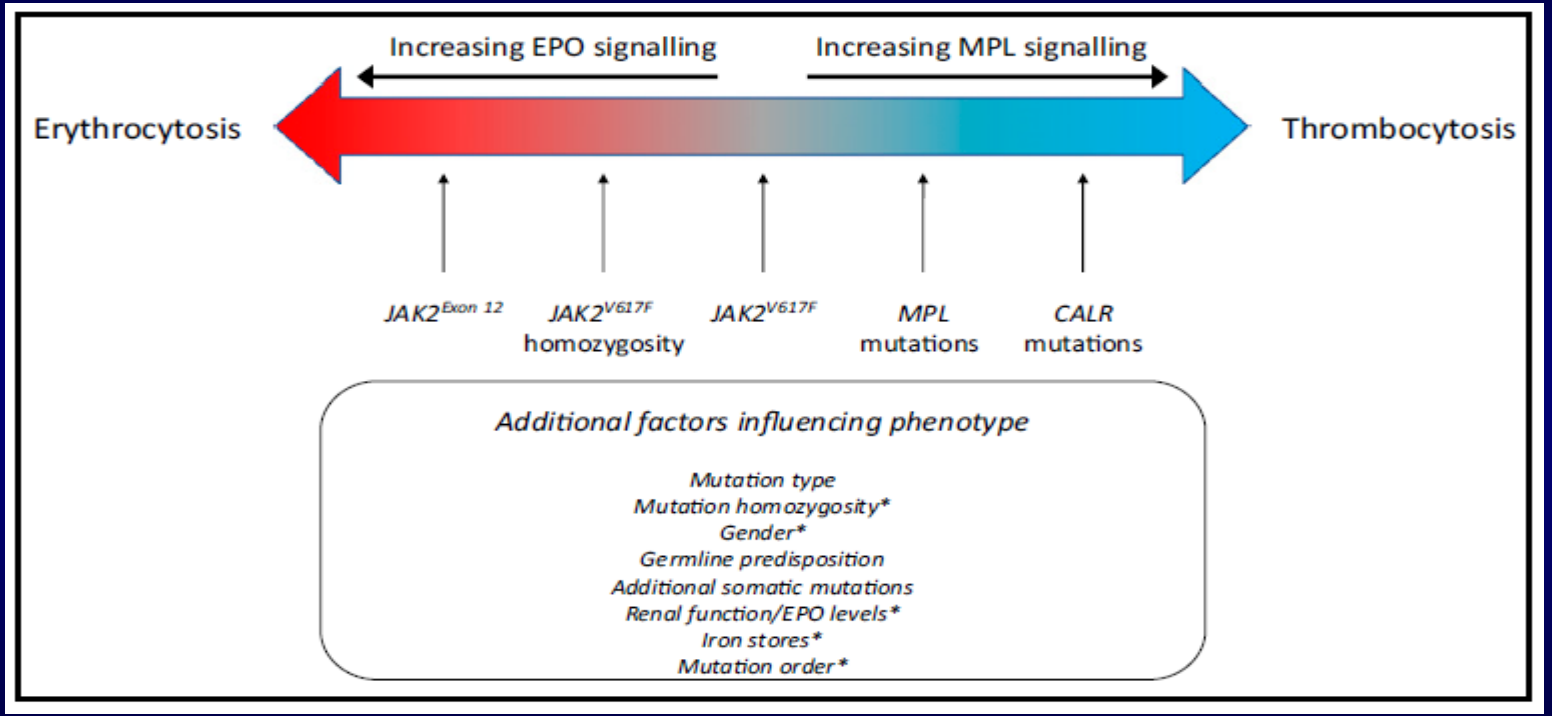


Patogénesis de las NMP



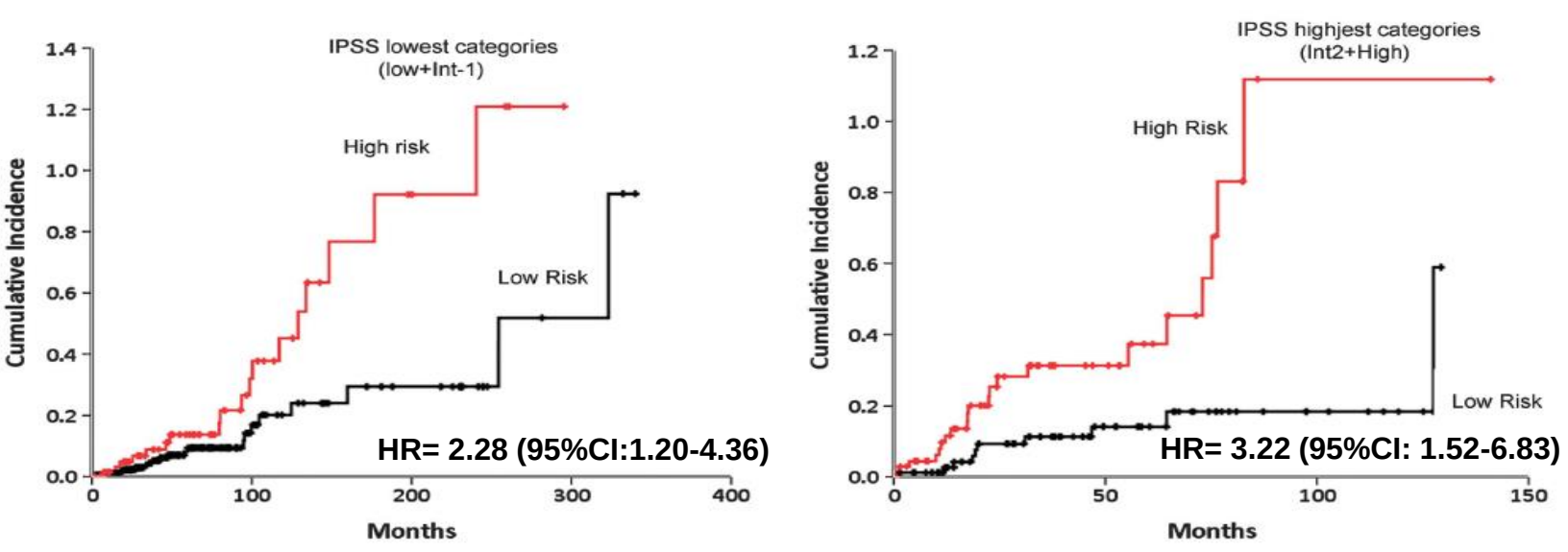
Nangalia J & Green AR, Blood 2017;130(23):2475-83

Determinantes del fenotipo de la NMP



Nangalia J & Green AR. Blood 2017;130(23):2475-83

Incidencia de leucemia en MFP según IPSS y perfil molecular

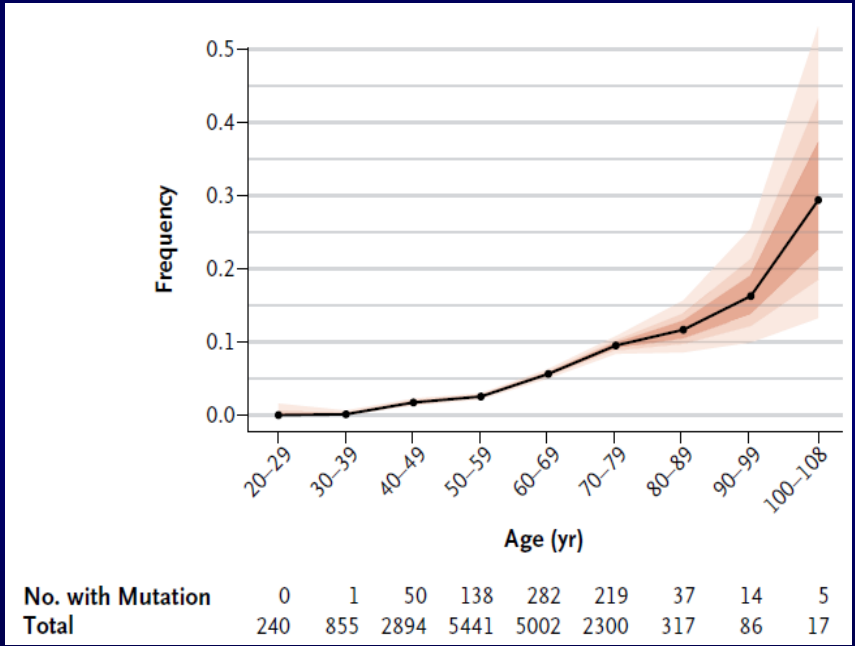


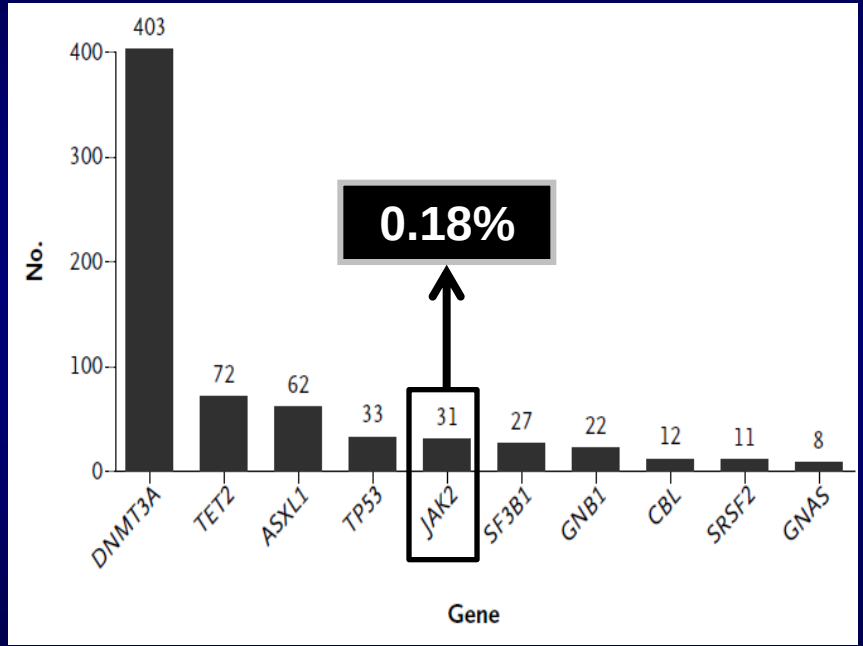
HMR (High Molecular Risk): ≥1 mutation in *ASXL1, EZH2, SRSF2, IDH1/2*

LMR (Low Molecular Risk): no mutation in the 4-gene set

Vannucchi A, et al. Leukemia 2013;27:1861-9

Hematopoyesis clonal de potencial indeterminado (CHIP)

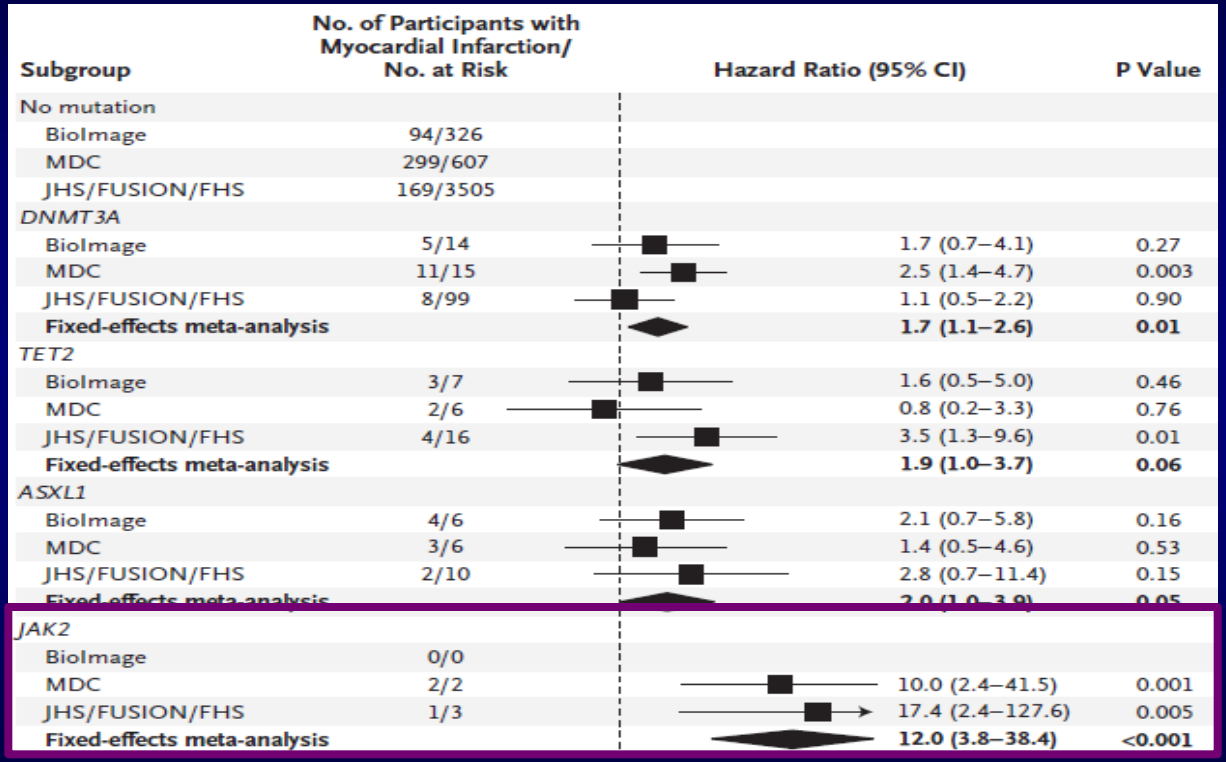




WES, sensibilidad 3.5%

Jaiswal S, et al. NEJM 2014;371(26):2488-98

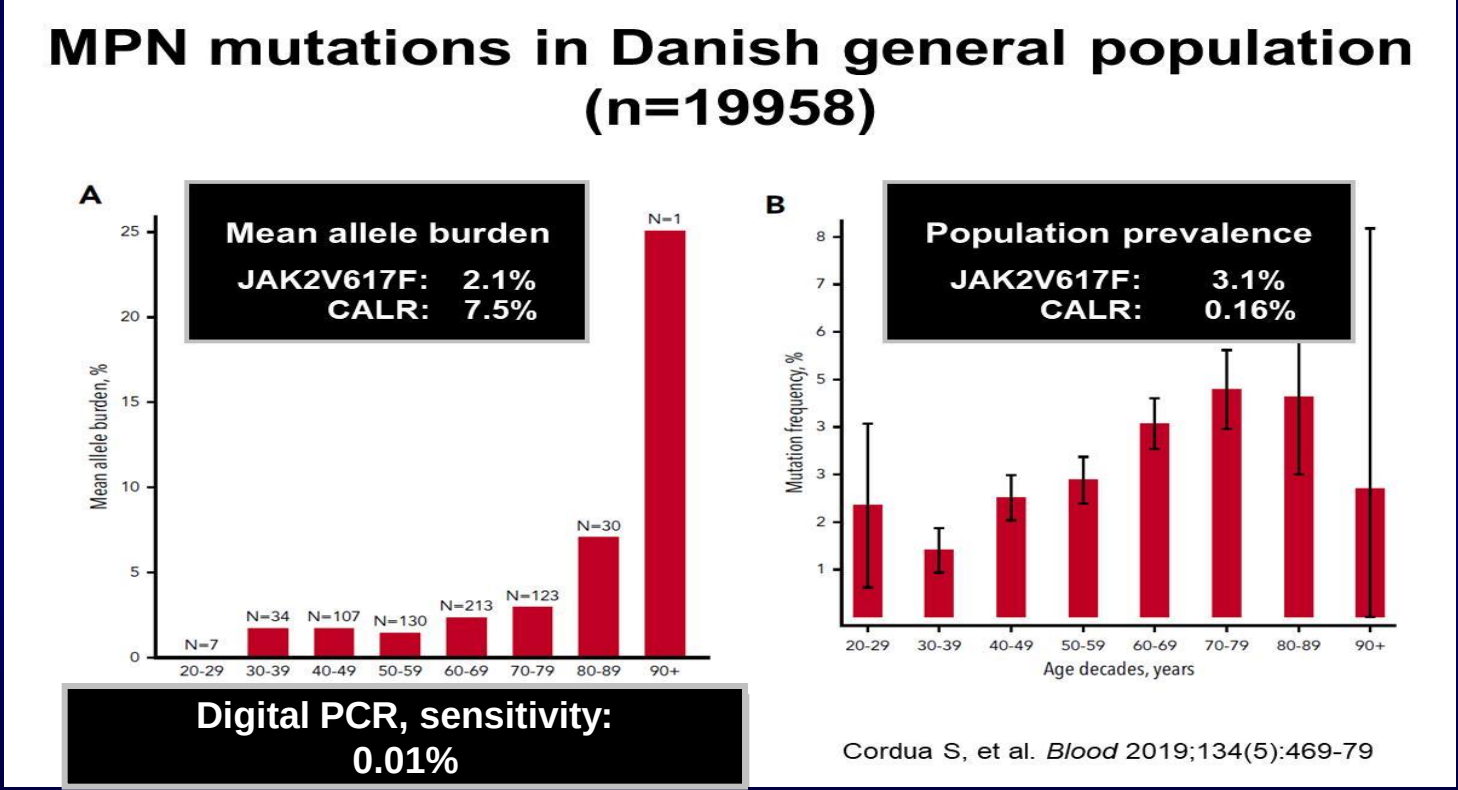
CHIP y riesgo de isquemia coronaria



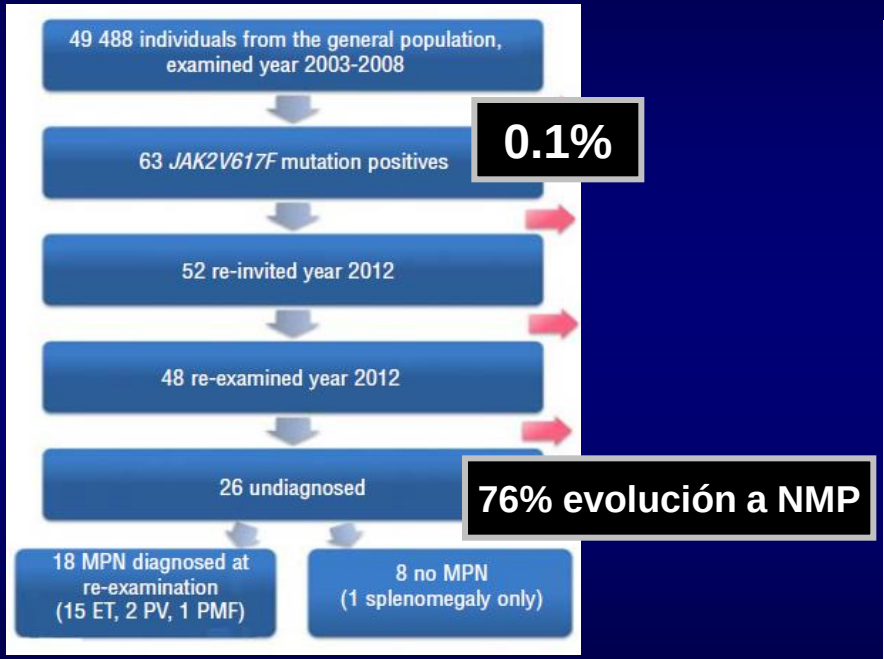
Subgroup	No. of Participants with Myocardial Infarction/ No. at Risk	Hazard Ratio (95% CI)	P Value
No mutation			
BioImage	94/326		
MDC	299/607		
JHS/FUSION/FHS	169/3505		
DNMT3A			
BioImage	5/14	1.7 (0.7–4.1)	0.27
MDC	11/15	2.5 (1.4–4.7)	0.003
JHS/FUSION/FHS	8/99	1.1 (0.5–2.2)	0.90
Fixed-effects meta-analysis		**1.7 (1.1–2.6)**	**0.01**
TET2			
BioImage	3/7	1.6 (0.5–5.0)	0.46
MDC	2/6	0.8 (0.2–3.3)	0.76
JHS/FUSION/FHS	4/16	3.5 (1.3–9.6)	0.01
Fixed-effects meta-analysis		**1.9 (1.0–3.7)**	**0.06**
ASXL1			
BioImage	4/6	2.1 (0.7–5.8)	0.16
MDC	3/6	1.4 (0.5–4.6)	0.53
JHS/FUSION/FHS	2/10	2.8 (0.7–11.4)	0.15
Fixed-effects meta-analysis		**2.0 (1.0–3.9)**	**0.05**
JAK2			
BioImage	0/0		
MDC	2/2	10.0 (2.4–41.5)	0.001
JHS/FUSION/FHS	1/3	17.4 (2.4–127.6)	0.005
Fixed-effects meta-analysis		**12.0 (3.8–38.4)**	**<0.001**

Jaiswal S, et al. NEJM 2017;377:111-21

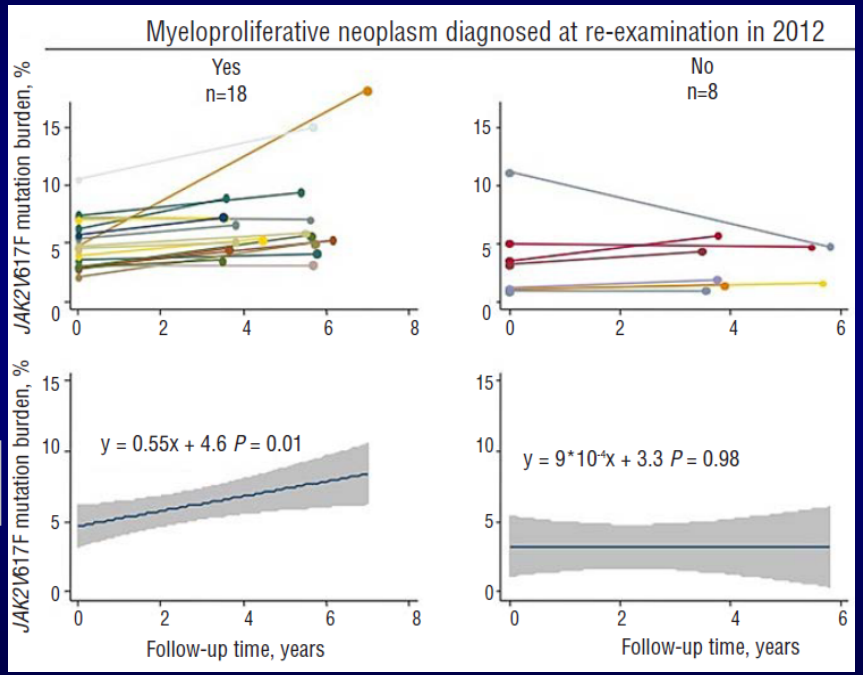
Fase preclínica o latencia de las NMP



Mutación *JAK2* en población general: riesgo de progresión

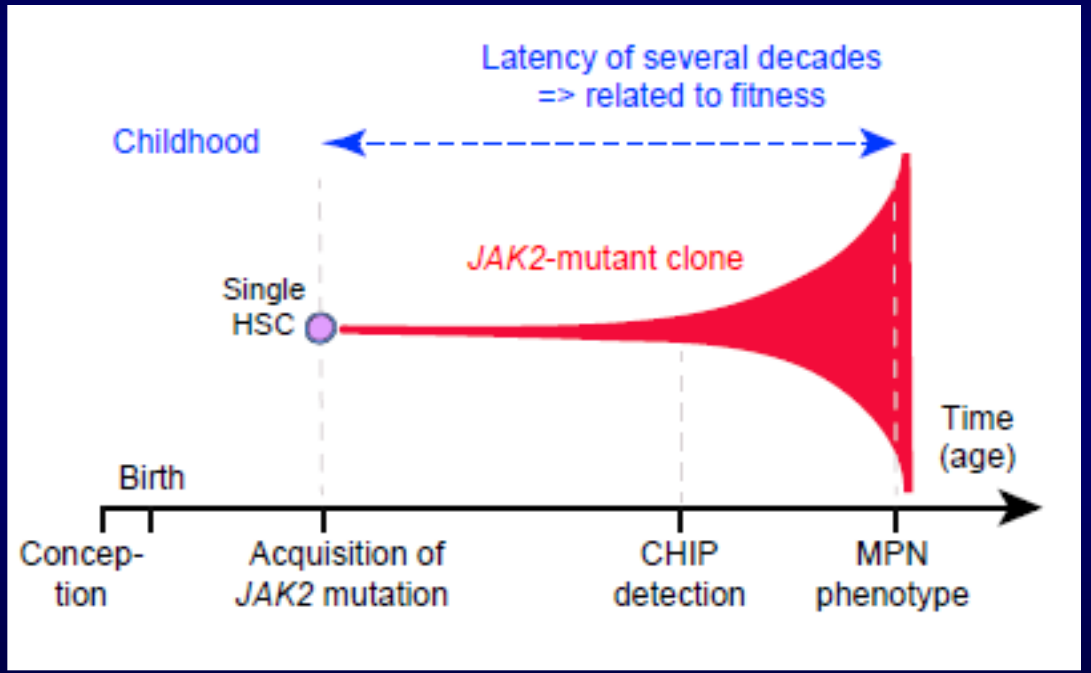


Q-PCR, sensitivity: 0.8%



Nielsen C, et al. Haematologica 2014;99(9):1448-55

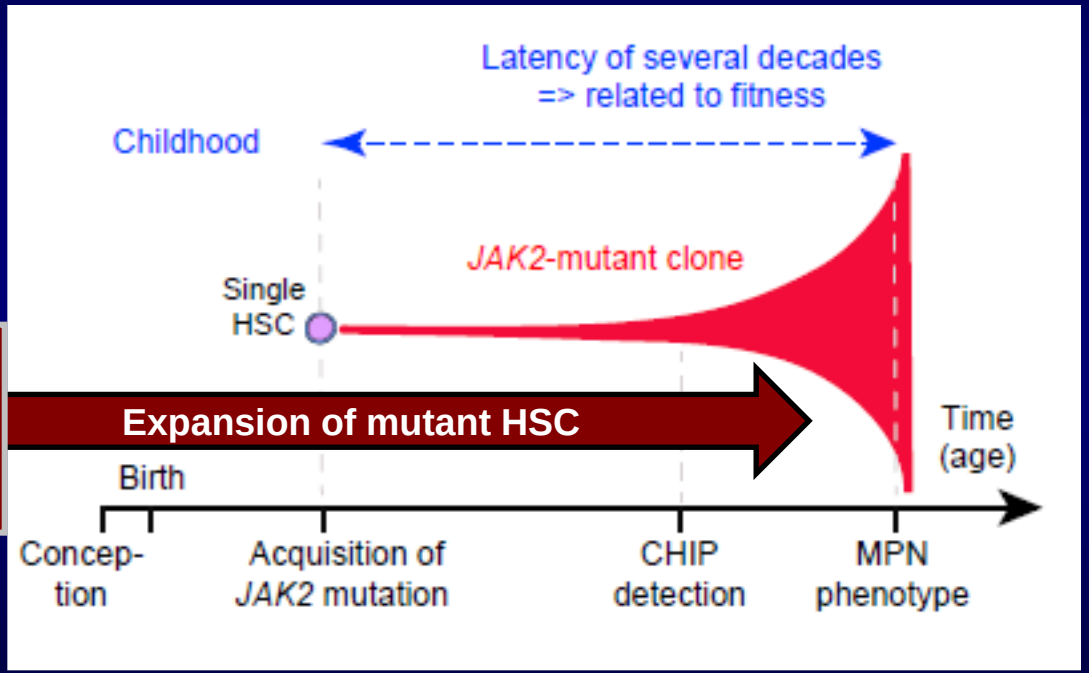
Cronograma de la evolución clonal de las NMPs



Luque Paz D, et al. Cell Stem Cell 2021;28(3):359-61

Cronograma de la evolución clonal de las NMPs

- **Genetic predisposition**
- **Somatic mutations**
- **Inflammation / immunity**



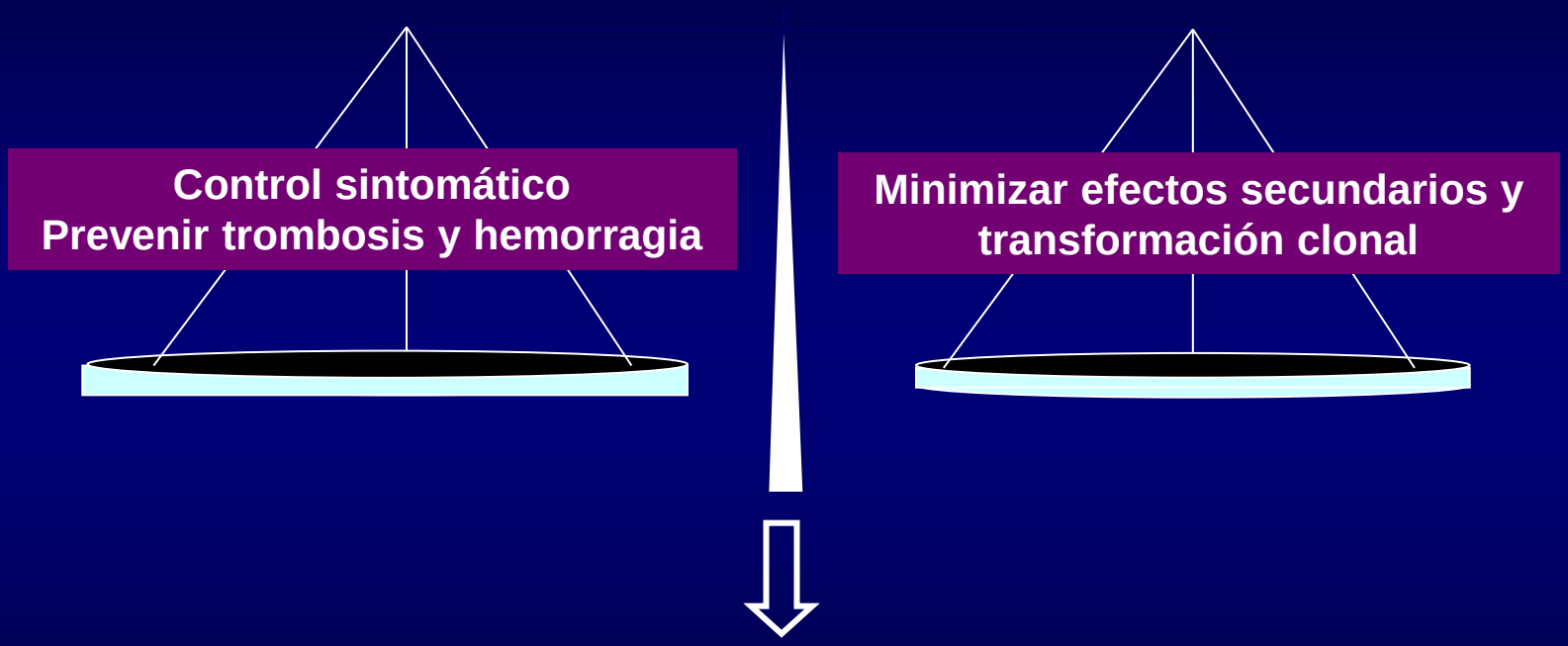
Luque Paz D, et al. Cell Stem Cell 2021;28(3):359-61

NMP Ph-negativas: complicaciones

	MFP	TE	PV
Carga sintomática	+++	+	++
Hemorragia mayor	5-20%	10%	5%
Trombosis mayor	10%	25%	35%
Arterial	+	+++	+++
Venosa	+	+	++
Transf. mieloide (a 10 años)			
Mielofibrosis	-	5-10%	15%
Leucemia aguda	20%	5%	5-10%
Causas muerte			
Cardiovascular	15%	25%	25%
Leucemia	30%	10%	20%
No relacionada con NMP	15%	40%	30%

Emanuel, JCO 2012; Lee, BJH 2000; Visani, BJH 1990; Dupriez, Blood 1996; Elliott & Tefferi, BJH 2004; Passamonti, AJM 2004; Landolfi, Leukemia 2008; Kiladjian, JCO 2011; Cervantes, JCO 2012

Tratamiento de la TE/PV



ESTADIFICACIÓN DE RIESGO

Tratamiento de la TE

BAJO RIESGO

Resto situaciones

ALTO RIESGO

Edad >60 y/o trombosis previa

Plaq > 1.500 x 10^9/L

Control FRCV[1] y AAS a dosis bajas[2,3]

HU / IFN[4]

2ª línea: ANA

[1] HTA / tabaquismo / DM / dislipemia

[2] Valorar citorreducción si trombocitosis extrema

[3] Anticoagulación en lugar de AAS si trombosis venosa inicial

[4] IFN en pacientes jóvenes

Barbui T, et al. Leukemia 2018;32:1057-69

Incidence rate of thrombosis in essential thrombocythemia according to the revised-IPSET in the original cohort and in a large real-world study

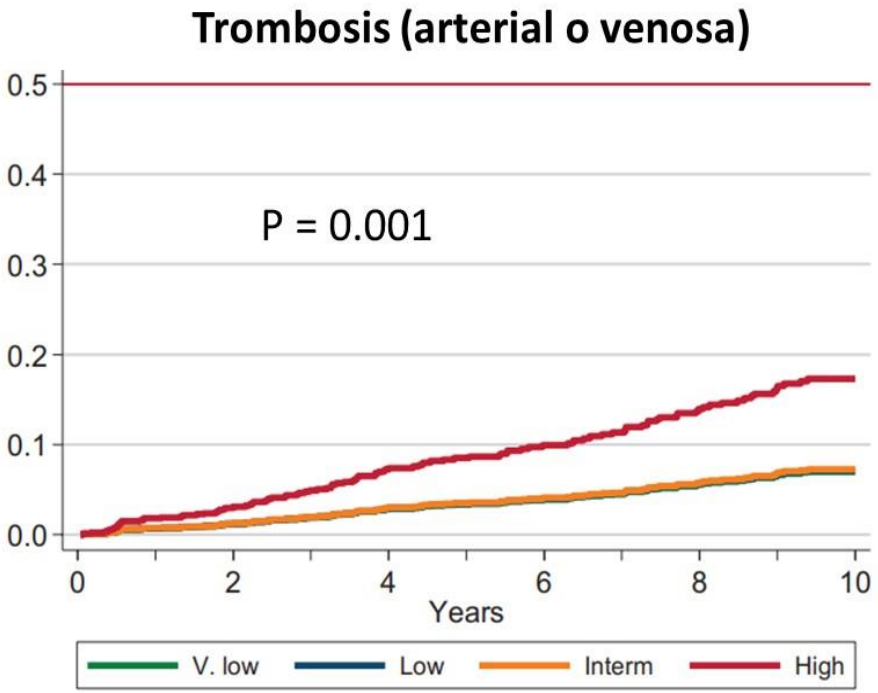
Essential thrombocythaemia: A contemporary approach with new drugs on the horizon. Ferrer-Marín et al BJH 2024

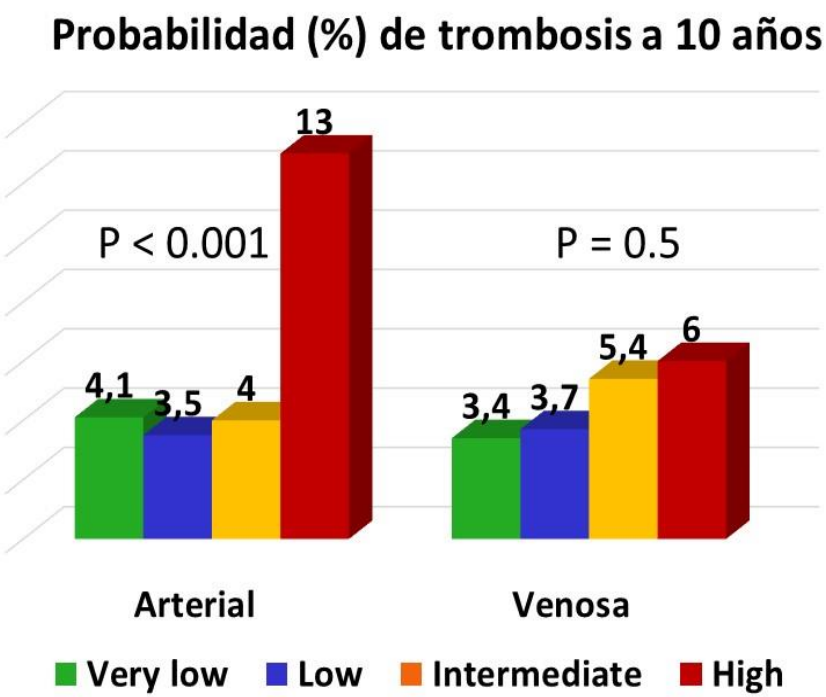
	Original cohort[1] N=1014			Spanish registry[2] N=1366		
Risk Group	N	Events/pers on years	*Rate %patients/year	N	Events/pers on years	Rate %patients/year
Very low Age < 60 years, *JAK2-*, no thrombosis	236	10/NP	0.4-1.05	211	11/1525	0.7
Low Age < 60 years, *JAK2+*, no thrombosis	265	29/NP	1.6-2.6	319	16/2188	0.7
Intermediate Age > 60 years, *JAK2-*, no thrombosis	155	14/NP	1.4-1.6	207	10/1286	0.8
High Age > 60 years and *JAK2+* or history of thrombosis	358	55/NP	2.4-4.2	629	69/3520	1.96

[1]Barbui et a BCJ 2015 [2]Alvarez-Larrán et al HemaSphere 2023

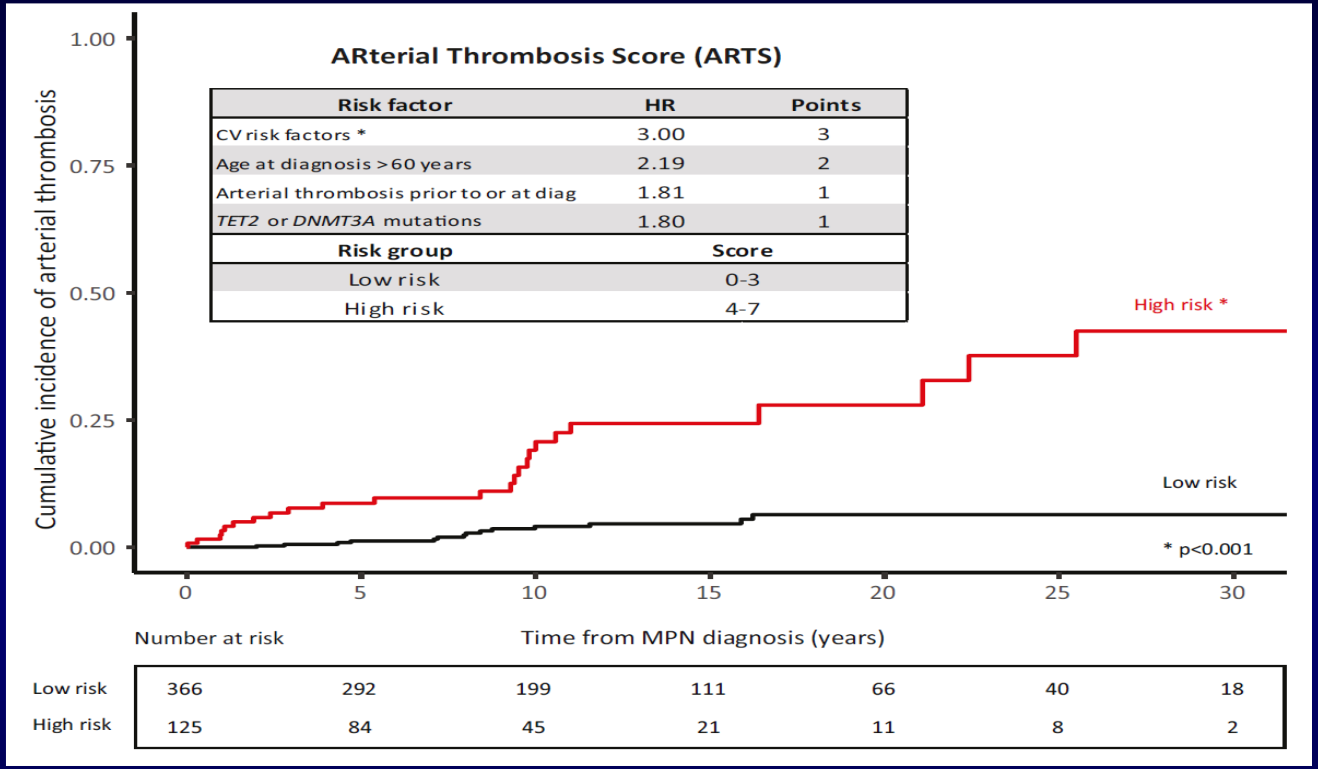
*Rates correspond to the absence and presence of cardiovascular risk factors, respectively. NP: time at risk not provided

Probabilidad de trombosis según la categoría IPSET-Trombosis revisado en 1366 pacientes con TE incluidos en el RETE





Alvarez-Larrán et al HemaSphere 2023



*FRCV: tabaquismo, hipercolesterolemia, diabetes mellitus, HTA

Pasquer H, et al. Leukemia 2024;38(2):326-39

Manejo de la TE según la estratificación de riesgo IPSET-trombosis revisado:

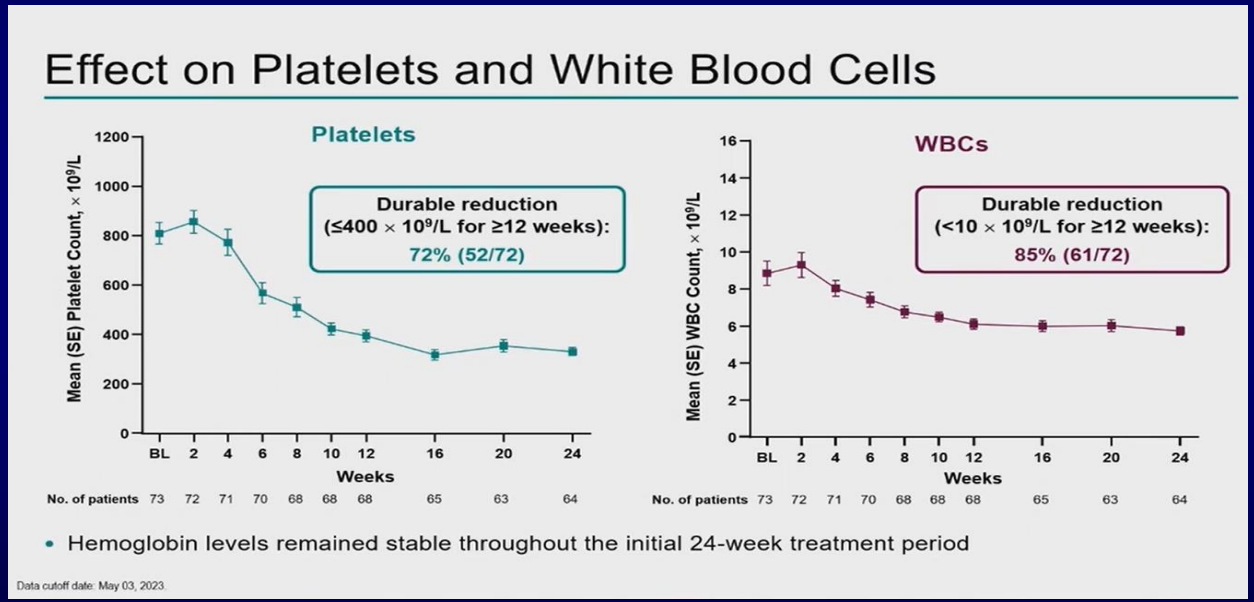
Essential thrombocythaemia: A contemporary approach with new drugs on the horizon, Ferrer-Marín et al BJH 2024

	Muy bajo Age < 60 years, *JAK2*-, no thrombosis	**Bajo** Age < 60 years, *JAK2*+, no thrombosis	**Intermedio** Age > 60 years, *JAK2*-, no thrombosis	**Alto** Age > 60 years and *JAK2+* or history of thrombosis
Tratamiento inicial	Observación*	AAS	Citorreducción	Citorreducción + AAS
Otros factores clínicos	*Considerar AAS si síntomas microvasculares, FRCV o mutaciones *TET2/DNMT3A* Considerar citorreducción si: Plaquetas >1500x10^9/l, EVWA***, síntomas microvasculares y plaquetas > 1000x10^9/l		Considerar AAS si FRCV o mutaciones *TET2/DNMT3A*	ACO si ACxFA o trombosis venosa* *Considerar ACO indefinida si *JAK2*V617F VAF > 50%
Tipo citorreductor	IFN**, HU, ANA		HU o ANA	HU, IFN**

** de elección en menores de 50 años ***Actividad de FVW < 30%

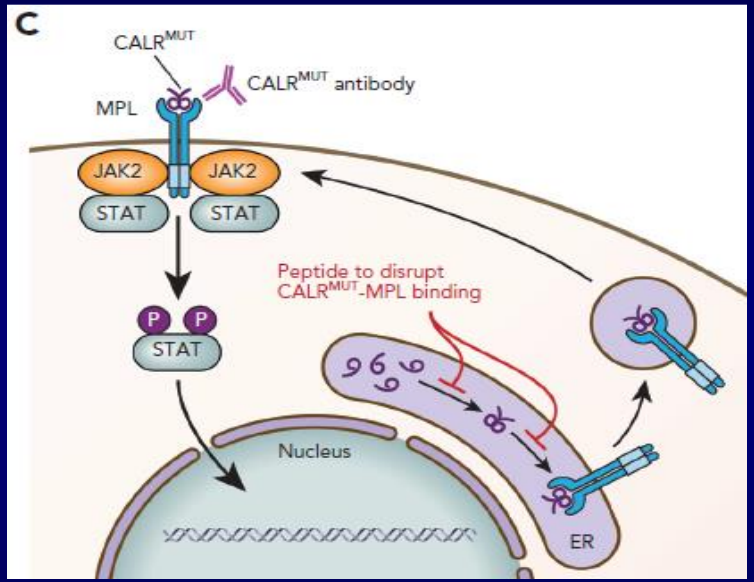
Nuevos tratamientos para la TE

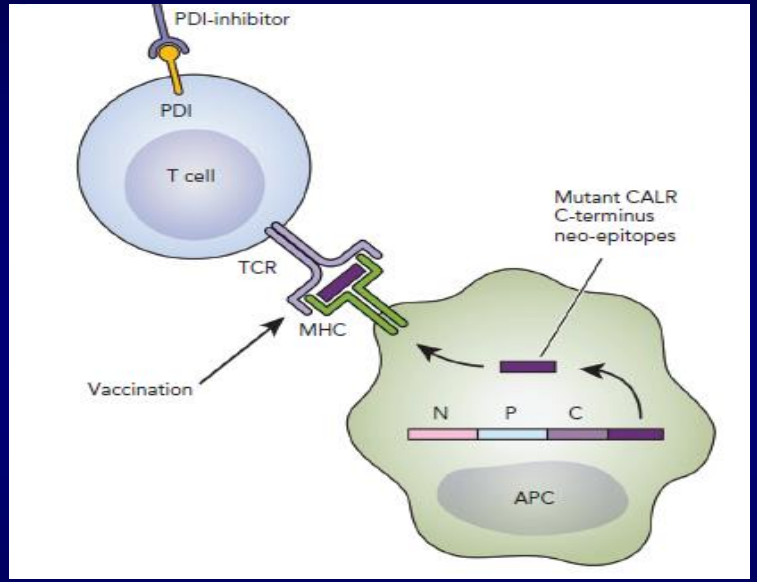
Bomedemstat



Göthert JR, et al. ASH 2023; abstr #747

Nuevos tratamientos para la TE



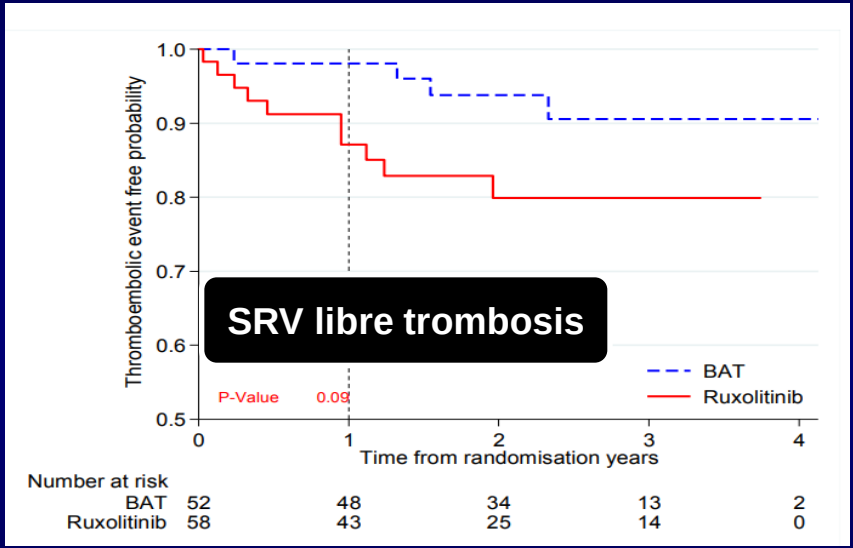


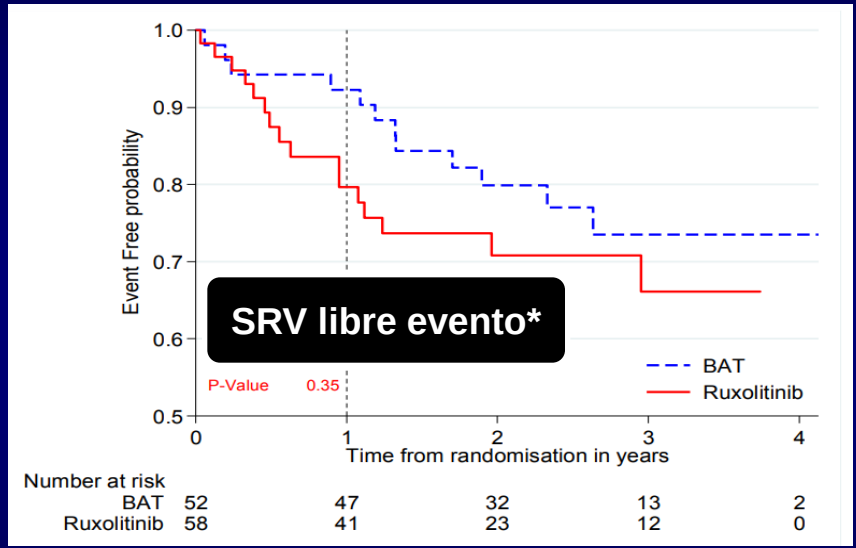
Anticuerpos

Vacunas

How J, et al. Blood 2023;141(16):1922-33

Ruxolitinib en TE tras fallo a HU
Estudio MAJIC-TE





Objetivo primario: RC 46.5% (ruxo) vs 44.2% (BAT)

BAT: HU (71%), ANA (48%), IFN (40%)

*Evento: trombosis, hemorragia, transformación

Harrison CN, et al. Blood 2017;130(17):1889-97

Tratamiento de la PV

BAJO RIESGO

Resto situaciones

ALTO RIESGO

Edad >60 y/o trombosis previa

Control FRCV[1] y AAS a dosis bajas[2,3]

Sangrías para mantener Hto < 45%

HU / IFN

2ª línea: Ruxo

[1] HTA / tabaquismo / DM / dislipemia

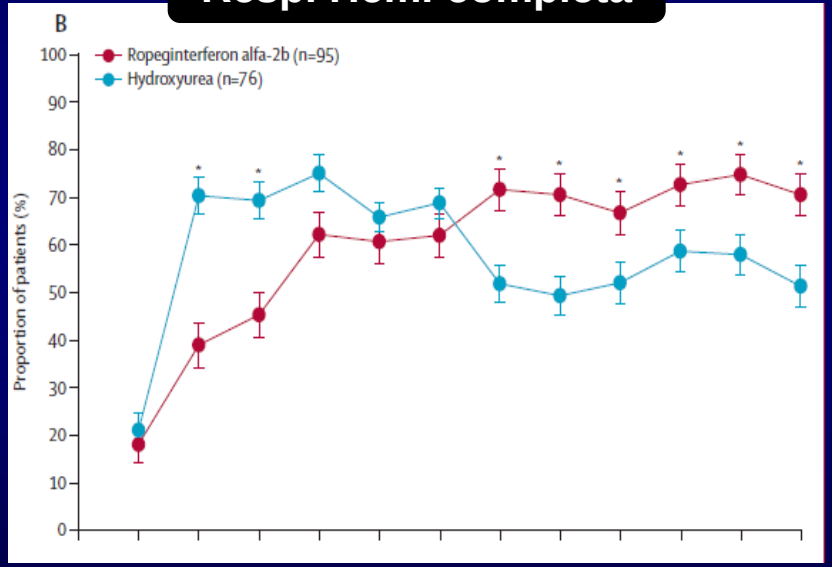
[2] Valorar citorreducción si trombocitosis extrema

[3] Anticoagulación en lugar de AAS si trombosis venosa inicial

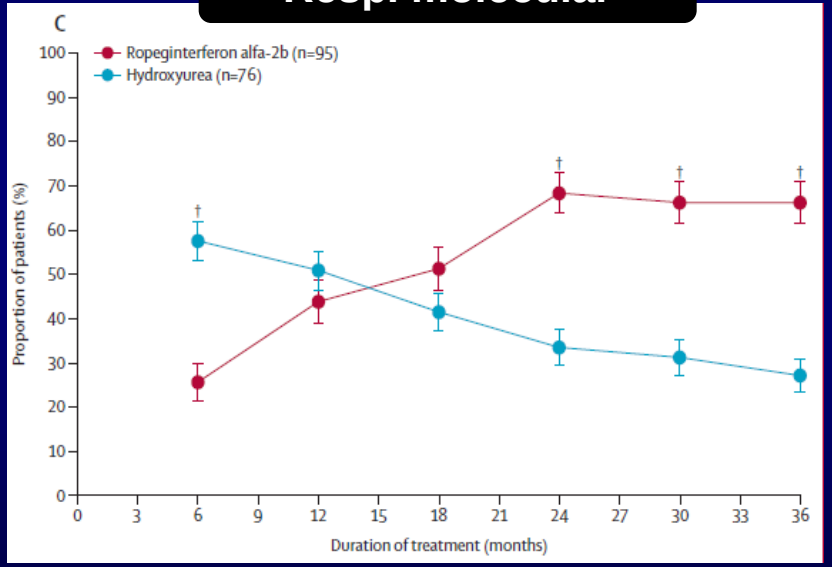
Barbui T, et al. Leukemia 2018;32:1057-69

Ropeg-IFN vs. HU en PV: estudios Proud-PV y Continuation-PV

Resp. Hem. completa

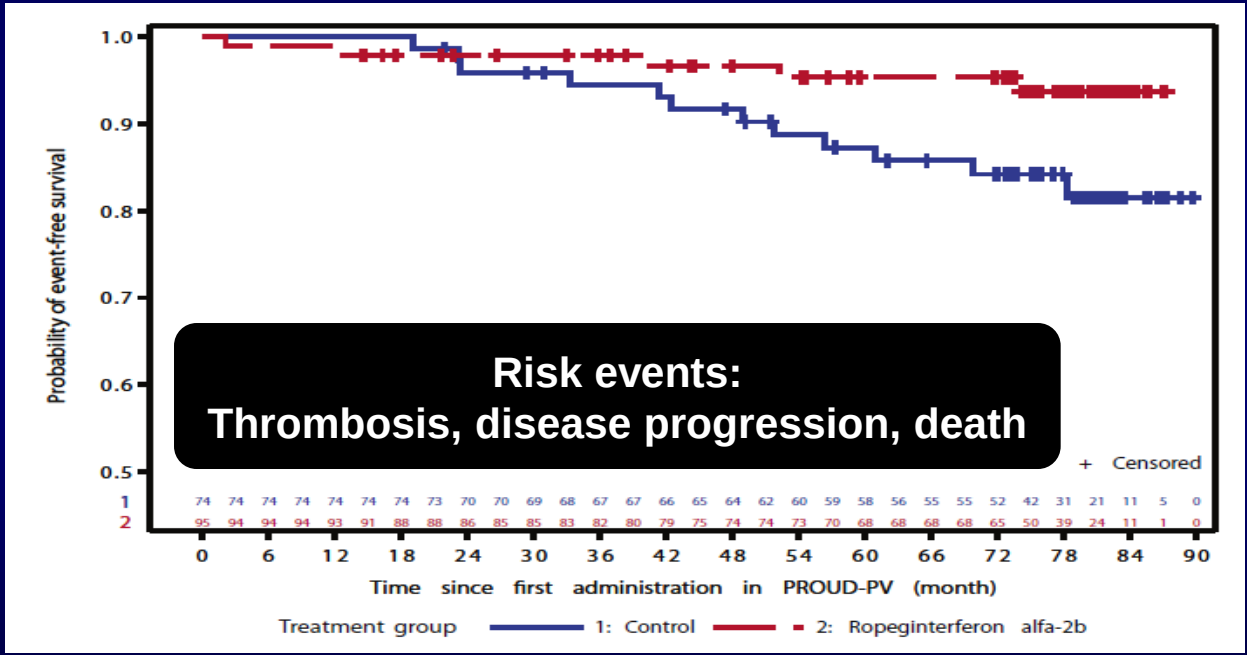


Resp. molecular



Gisslinger H, et al. Lancet Haematol 2020;7(3):e196-208

Ropeg-IFN vs. HU en PV: estudios Proud-PV y Continuation-PV



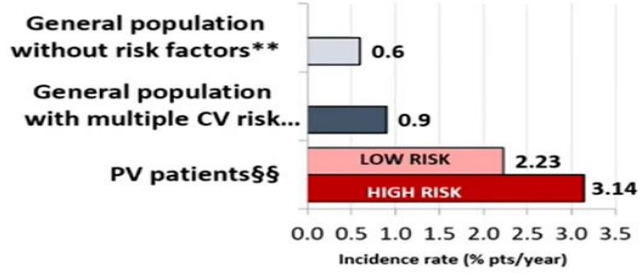
Gisslinger H, et al. Leukemia 2023;37:2129-32

La incidencia de trombosis en PV de bajo riesgo es mayor que la de la población general

Low-risk PV: is it time to change?

	LOW RISK	HIGH RISK
Dx before 2005 IR per 100 person/yrs	IR: 2.03 % pts/yr; 95% CI: 1.58-2.61	**IR: 4.01 %** pts/yr; 95% CI: 3.28-4.90
Dx after 2005 IR per 100 person/yrs	IR: 2.24 % pts/yr; 95% CI: 1.33-3.78	**IR: 2.93 %** pts/yr; 95% CI: 1.89-4.54

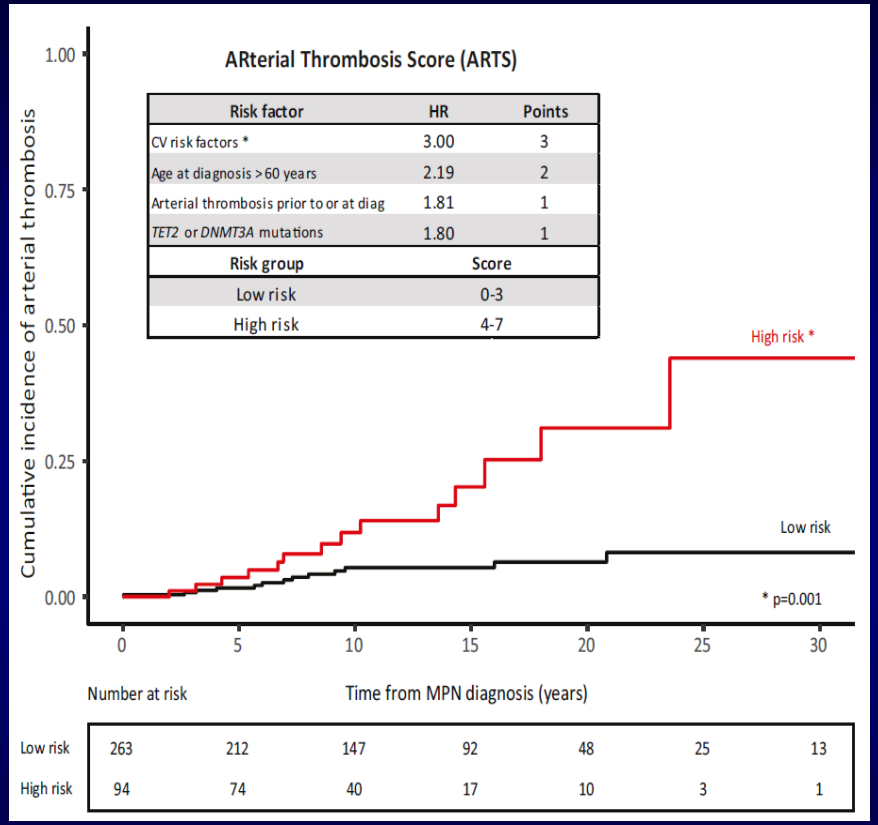
The incidence of thrombosis in low-risk PV patients has remained stable over time

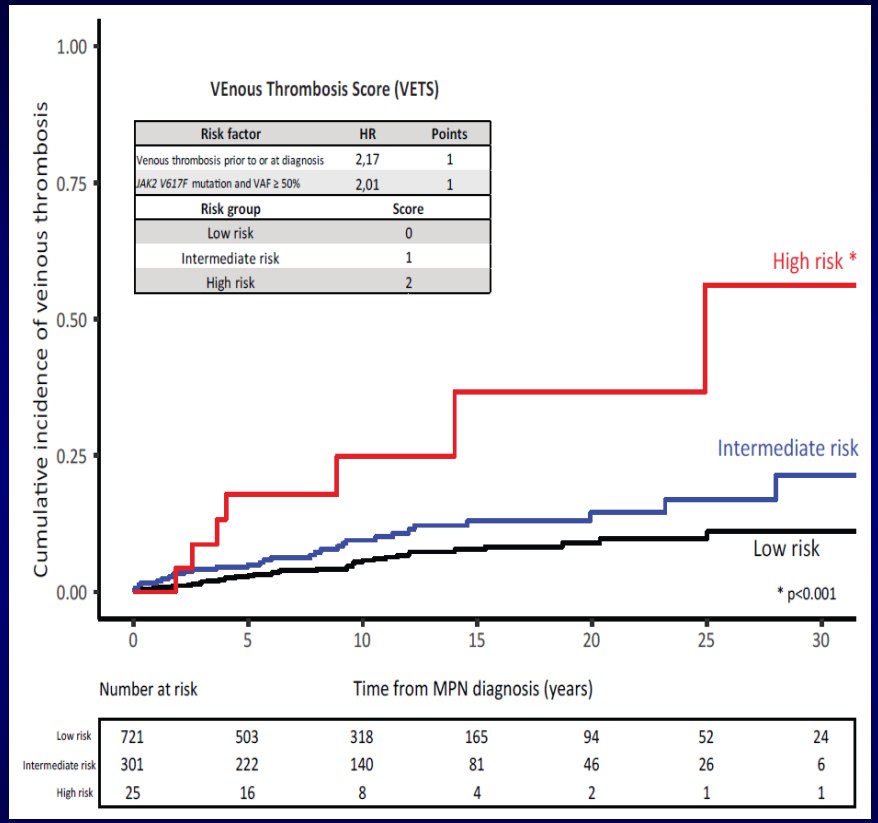


Low-risk PV patients have a two-fold increased risk of thrombosis compared to general population

** Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual partecipant data from randomized trials, Lancet 2009; 373:1849-1860.. Yusef S et al Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease NEJM 2016*
***The Risk and Prevention Study Collaborative Group. N–3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. N Engl J Med 2013;368:1800-8.*
§ Barbui T, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer Journal. In press
§§ Barbui T, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood 2014 124: 3021-3023

Slide courtesy of T Barbui





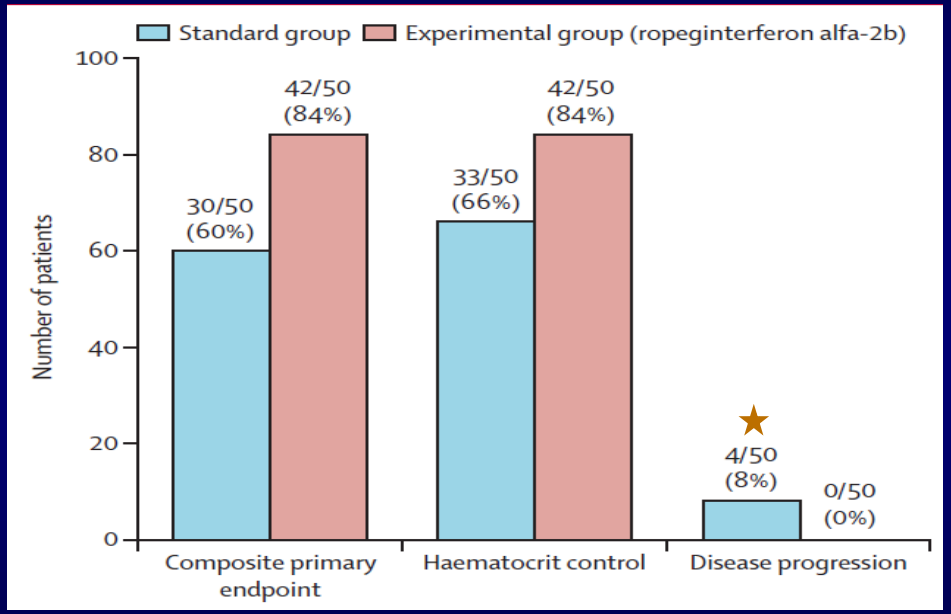
Pasquer H, et al. Leukemia 2024;38(2):326-39

Ropeg-IFN vs. Flebotomías en PV de bajo riesgo

Composite primary endpoint:

% pts maintaining the median HCT ≤ 45% during 12 mo, in the absence of progressive disease (i.e. thrombosis, bleeding, progressive leukocytosis, symptomatic or extreme thrombocytosis, symptomatic splenomegaly or other uncontrolled symptoms).

	Standard group (n=50)		Experimental group (n=50)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Neutropenia	0 (0%)	0 (0%)	5 (10%)	4 (8%)
Pruritus	1 (2%)	0 (0%)	2 (4%)	1 (2%)
Hypertransaminasemia	0 (0%)	0 (0%)	2 (4%)	1 (2%)
Flu-like symptoms	0 (0%)	0 (0%)	8 (16%)	0 (0%)
Asthenia	2 (4%)	0 (0%)	5 (10%)	0 (0%)
Skin symptom	0 (0%)	2 (4%)	1 (2%)	0 (0%)
Pain not otherwise specified	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Knee impingement syndrome	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Thrombosis	0 (0%)	1 (2%)	0 (0%)	0 (0%)

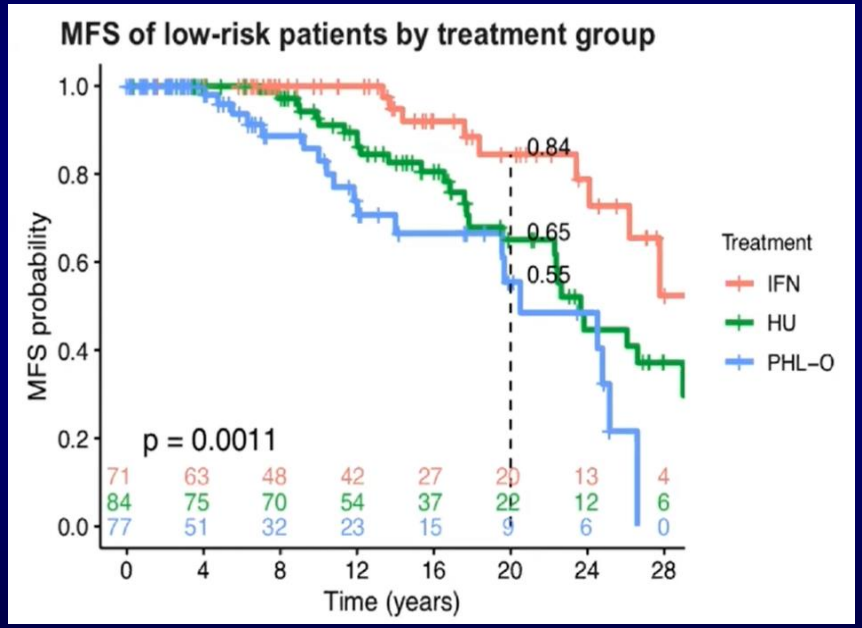


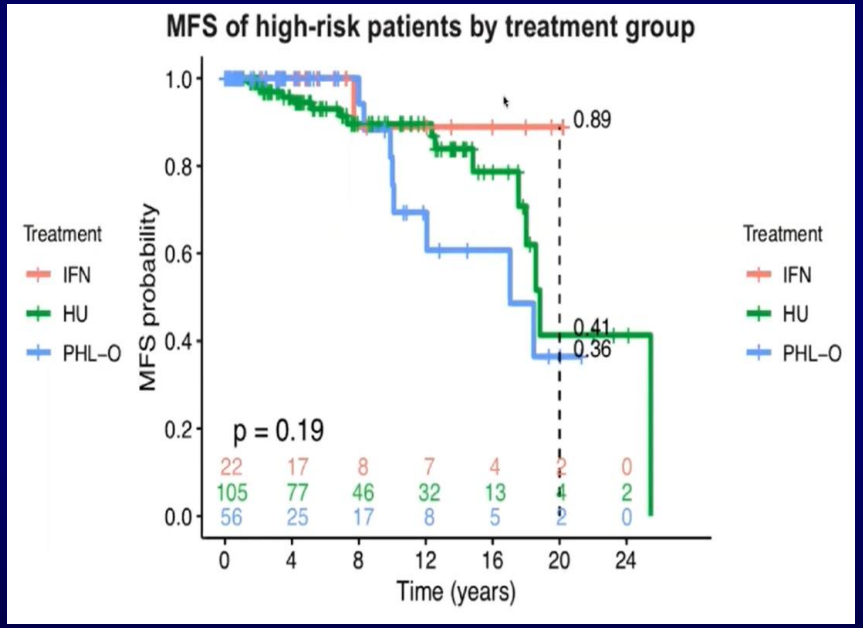
* Trombocitosis + sint microvasc (n=3), tromb venosa bazo (n=1)

Barbui T, et al. Lancet Haematol 2021;8:e175-84

IFN pegilado en PV: transformación a MF

Weill Cornell Medicine, NY





Ghaith Abu-Zeinah, et al. Leukemia 2021;35(9):2592-601

ELN indications of cytoreductive therapy in low-risk PV

- Intolerance to phlebotomy
- Symptomatic progressive splenomegaly
- Persistent leucocytosis (>20 × 10^9/l)

Recommended

- Extreme thrombocytosis (>1500×10^9/l)
- Inadequate hematocrit control (≥ 6 Phl/per year)

Should be considered

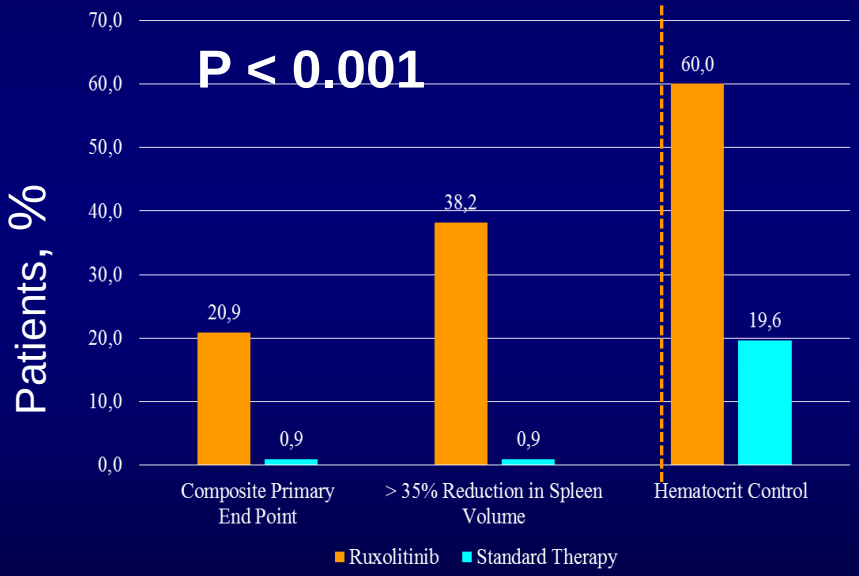
- Persistently high cardiovascular risk
- Persistently high symptom burden

Can be considered

Marchetti M, et al. Lancet Haematol 2022;9:e301-1

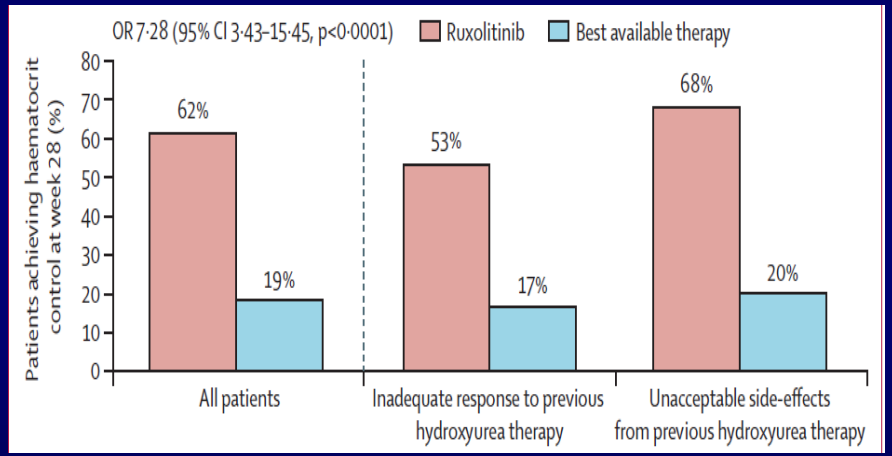
Efficacy of ruxolitinib in PV tras fallo a HU: RESPONSE TRIALS*

RESPONSE



Vannucchi A, et al. NEJM 2015;372(5):426-35

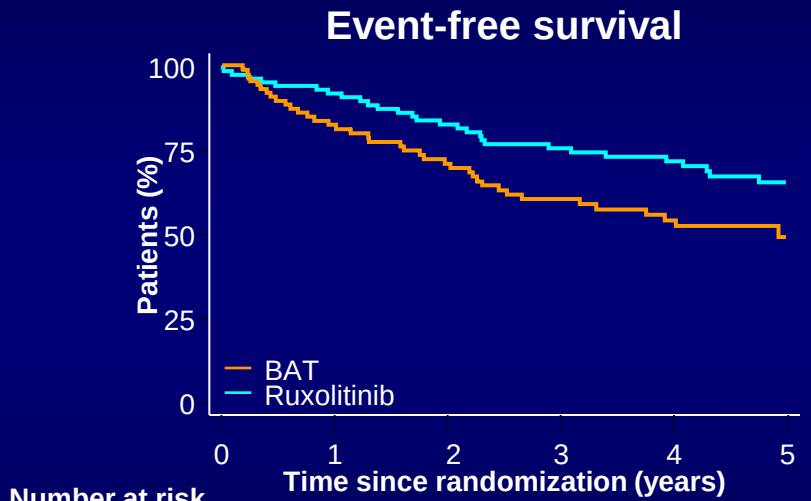
RESPONSE-2



*BAT: IFN (12% Response, 13% Response-2)

Passamonti F, et al. Lancet Oncol 2017;18:88-99

Ruxolitinib superior to BAT for event-free survival (thrombosis, haemorrhage, transformation, death)



*Adjusted for gender
**Adjusted for gender, age, hemoglobin, number of previous therapies, previous thrombosis, hydroxycarbamide resistance/intolerance, baseline splenomegaly.
EFS, event-free survival.

*BAT: HU (32%), IFN (15%), IFN-HU (12%)

MAJIC-PV

EFS was **superior** for **ruxolitinib** treatment
HR 0.58 (95% CI 0.35–0.94; p = 0.03)

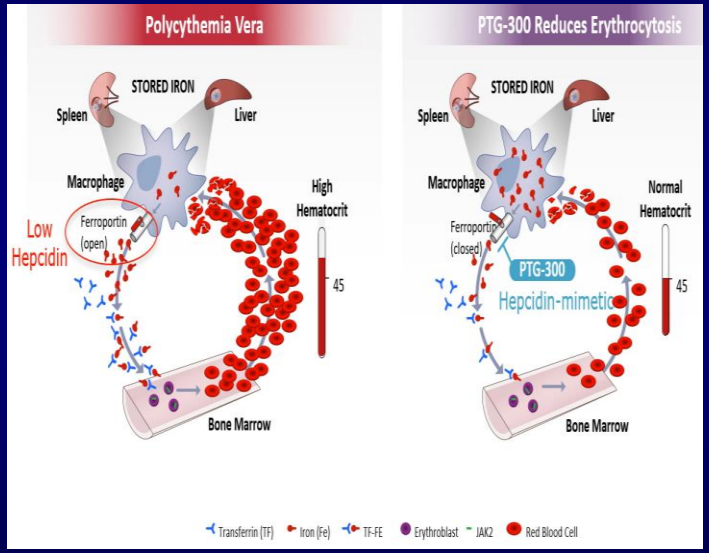
42% reduction in risk of major thrombosis, major hemorrhage, transformation, or death with ruxolitinib

>50% JAK2 VAF reduction in 56% of ruxo pts

Harrison CN, et al. J Clin Oncol 2023;41:3534-44

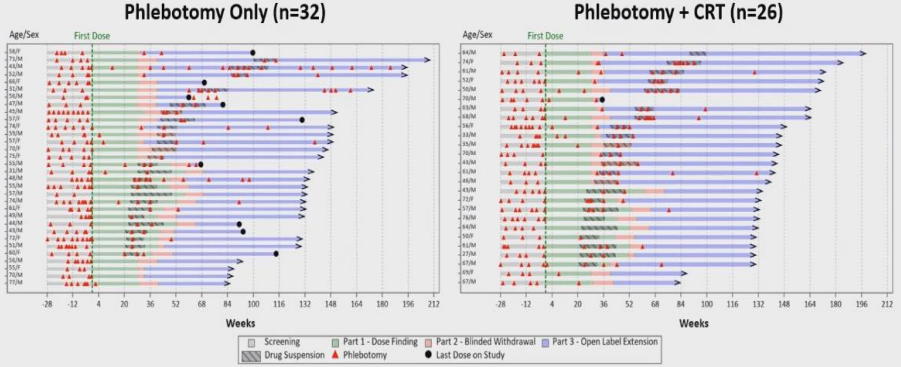
Nuevos tratamientos para la PV

Rusfertide



Rusfertide Decreased the Frequency of Therapeutic Phlebotomy With or Without Concurrent Cytoreductive Therapy

- In patients who continued onto Part 3, 32 (55.2%) and 26 (44.8%) patients were treated with phlebotomy alone or phlebotomy with CRT, respectively
  - Of those patients receiving phlebotomy with CRT, 13 (22.4%) received hydroxyurea, 7 (12.1%) received interferon, 5 (8.6%) received a JAK inhibitor, and 1 patient (1.7%) received hydroxyurea and interferon

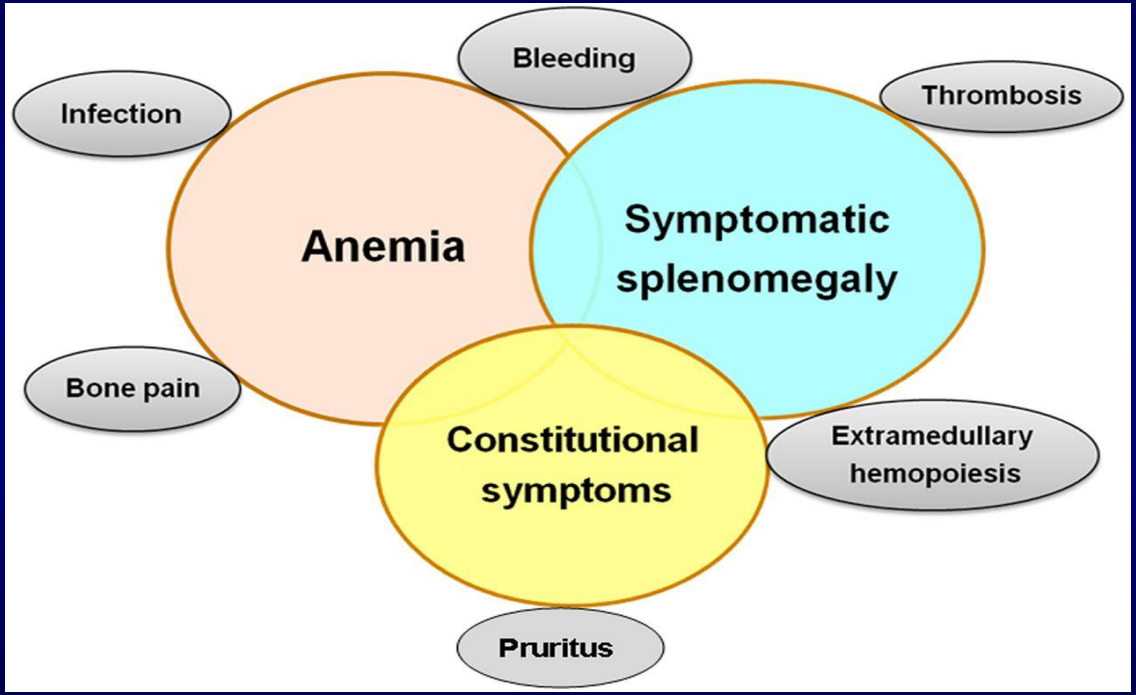


CRT, cytoreductive therapy.

Data cutoff: 17 October 2023

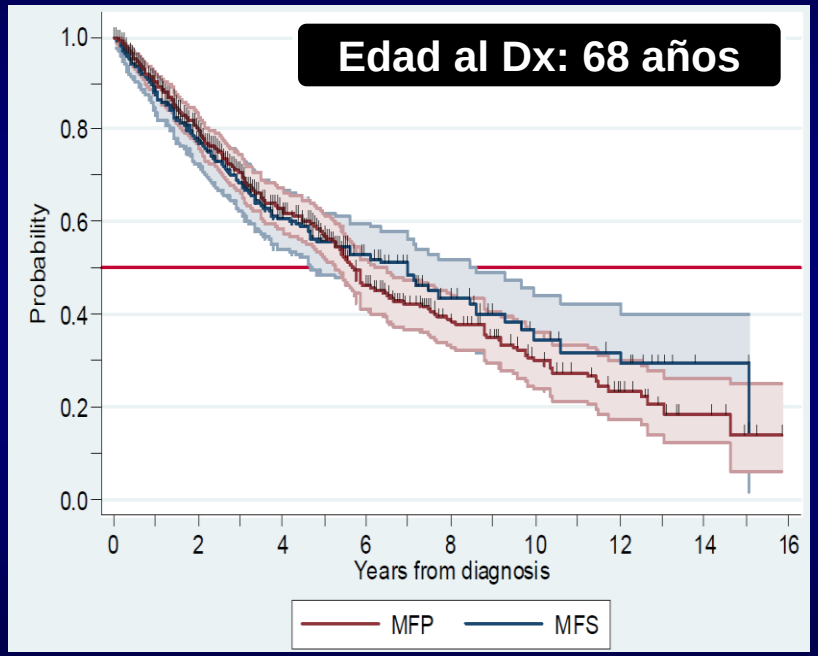
Ritchie EK, et al. ASH 2023; abstr #745

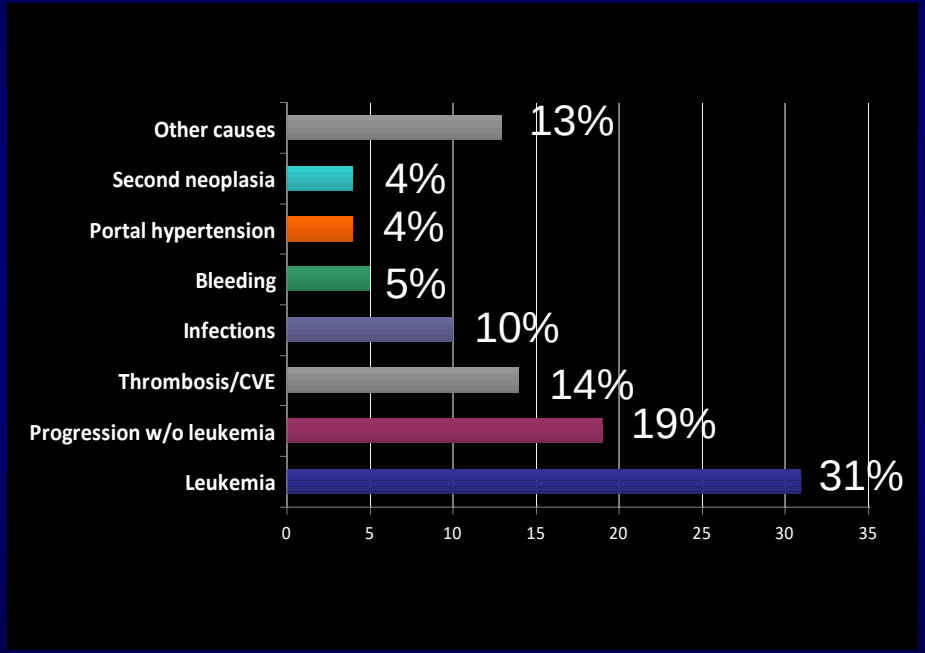
Manifestaciones clínicas de la MF



Cervantes F, Blood 2014;124:2635-42

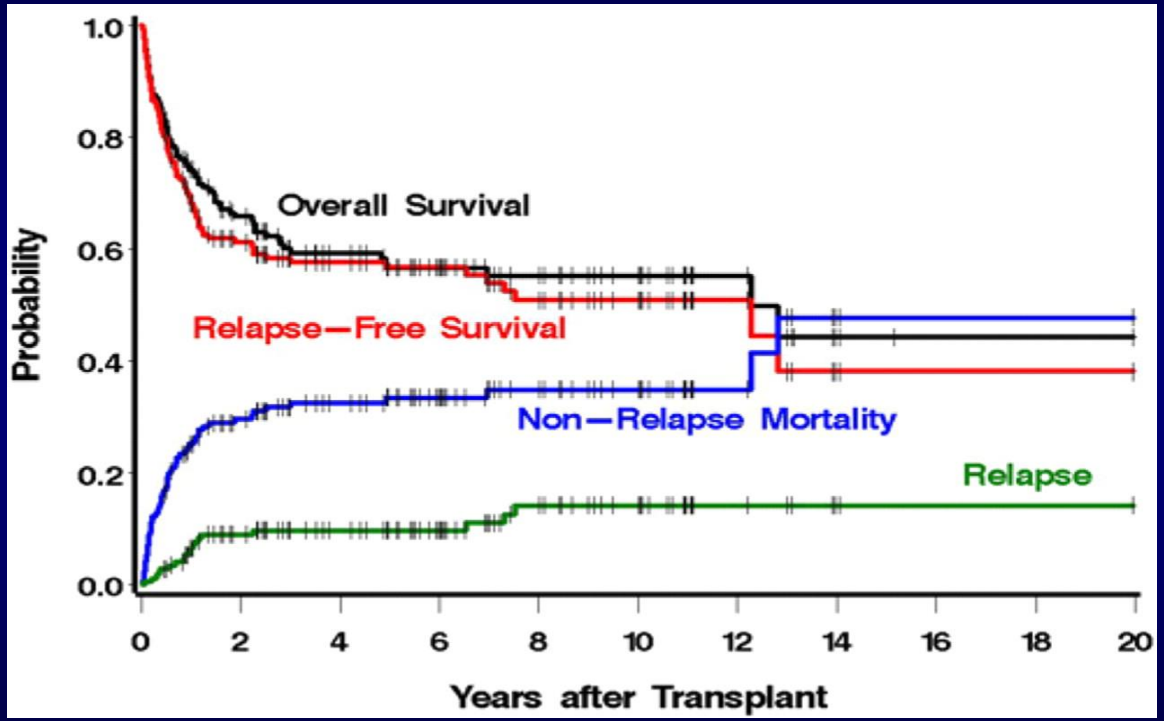
Supervivencia y causas de fallecimiento





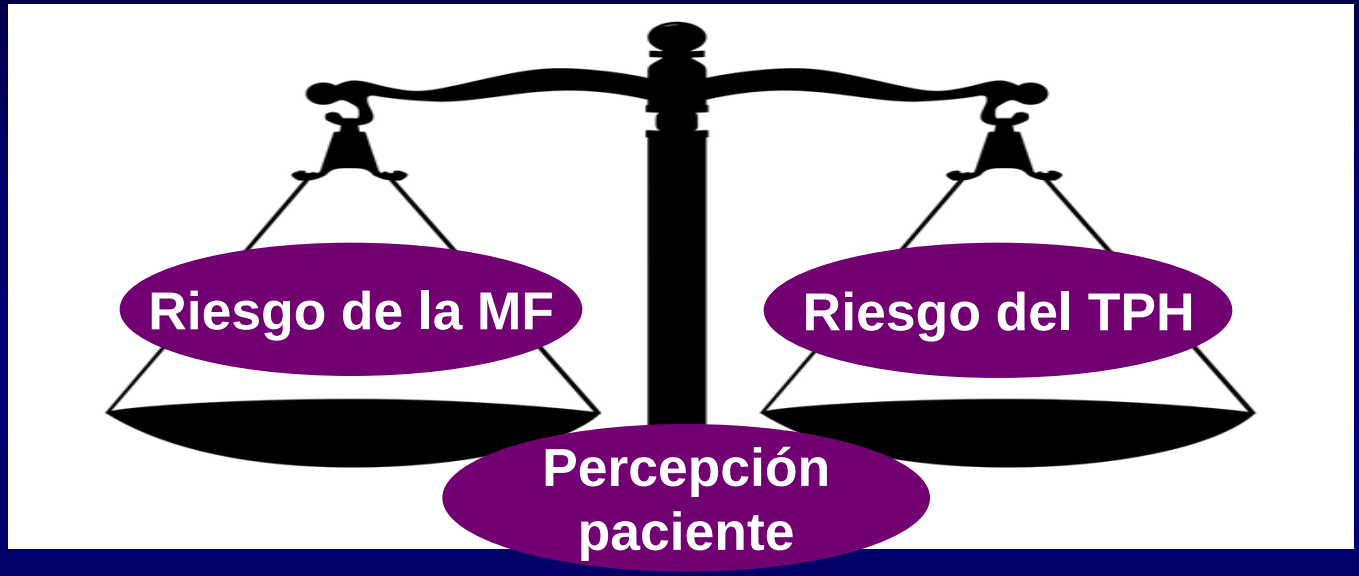
Pastor-Galán I, et al. Med Clin (Barc) 2020;155(4):152-8 Cervantes F, et al. Blood 2009;113:2895-901

Trasplante alogénico en MF



Scott BL, et al. Blood 2012;119:2657-64

Decisión de trasplante en MF



Pacientes con supervivencia estimada inferior a 5 años deben considerarse potenciales candidatos a trasplante

Kröger NM, et al. Lancet Haematol 2024;11(1):e62-e74

Prognostic models for OS in MF

	IPSS	DIPSS	DIPSS+	AIPSS*
MF type	PMF	PMF	PMF	All
Time-point	Dx	Follow-up	Any time	Dx
Prognostic factors	Clinical	Clinical	Clinical Cytog	Clinical
Prediction	Risk groups			Personalized
Reference	Cervantes 2009	Passamonti 2010	Gangat 2011	Mosquera 2022

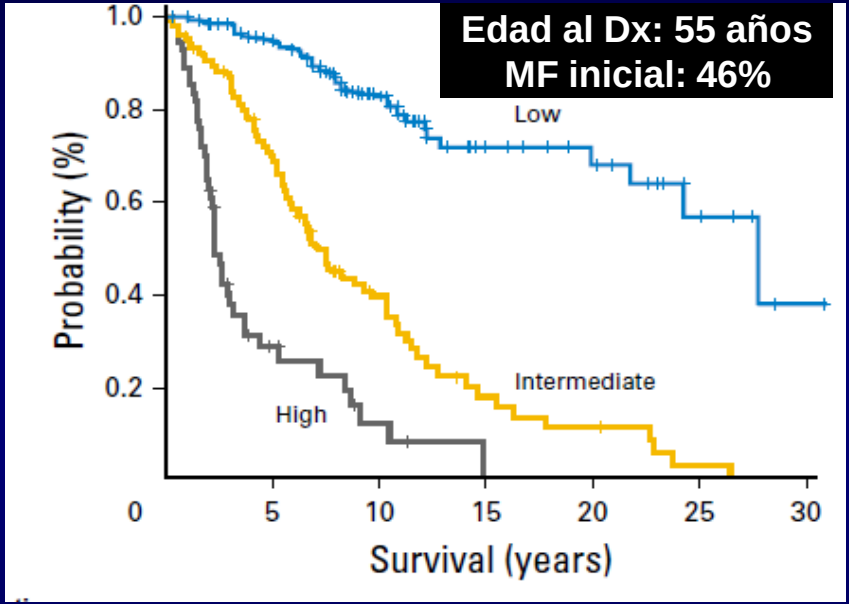
MIPSS70	MIPSS70+ v2.0	MYSEC PM	AIPSS-M*	MPN risk calculator
PMF	PMF	SMF	All	All
Any time	Any time	Dx	Dx	Dx
Clinical Histology Driver mut HRM**	Clinical Cytog Driver mut HRM**	Clinical Driver mut	Clinical Driver mut BMP***	Clinical Cytog Driver mut BMP***
Risk groups			Personalized	
Guglielmelli 2017	Tefferi 2018	Passamonti 2017	Mosquera 2024	Grinfeld 2018

*Machine learning model; **High risk mutations; ***Broad mutational profile.

MIPSS70

Factor de riesgo	Puntos
Sínt. constitucionales	1
Hb < 10 g/dL	1
Blastos SP ≥ 2%	1
Fibrosis MO ≥ 2	1
Mutac. *CALR* tipo 1 negativa	1
Mutac. alto riesgo*	1
WBC > 25 x 10^9/L	2
Plaquetas < 100 x 10^9/L	2
Mutac. alto riesgo* ≥ 2	2

***ASXL1, EZH2, SRSF2, IDH1, IDH2**

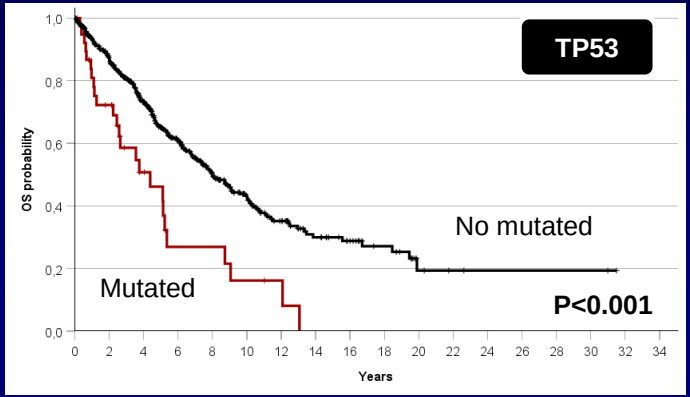


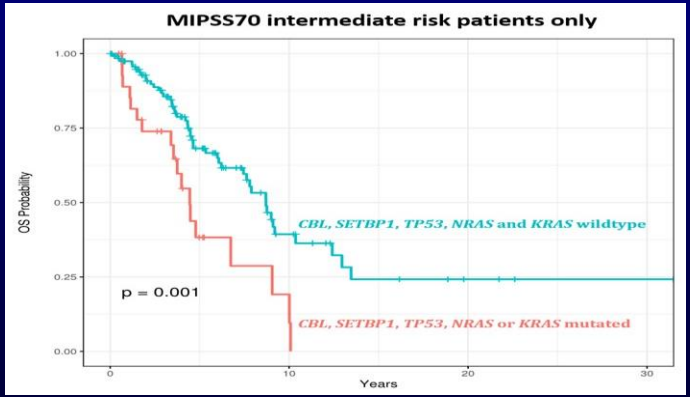
Risk	Score	No. cases (%)	Median SRV (yr)
Low	0-1	238 (49%)	27.7
Int	2-4	198 (40%)	7.1
High	≥ 5	54 (11%)	**2.3**

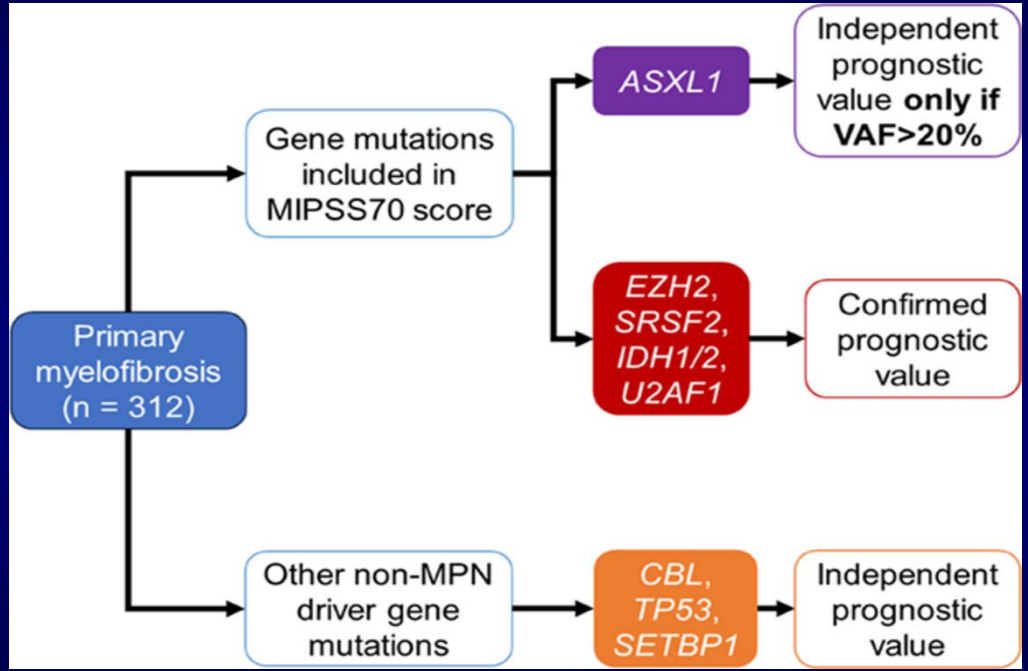
http://www.mipss70score.it/

Guglielmelli P, et al. JCO 2018;36(4):310-8

Prognostic impact of non-driver gene mutations and VAF in PMF (GEMFIN database)

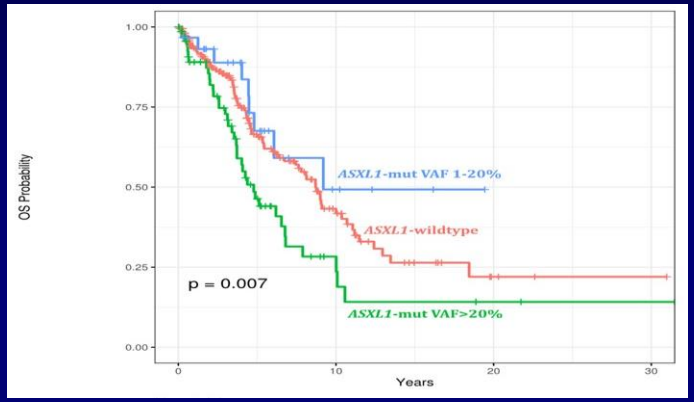


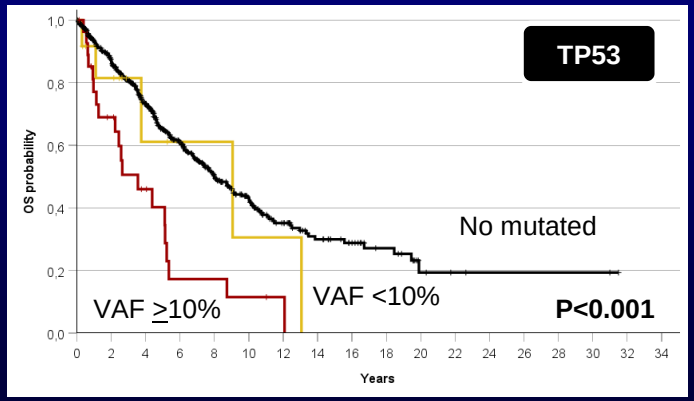


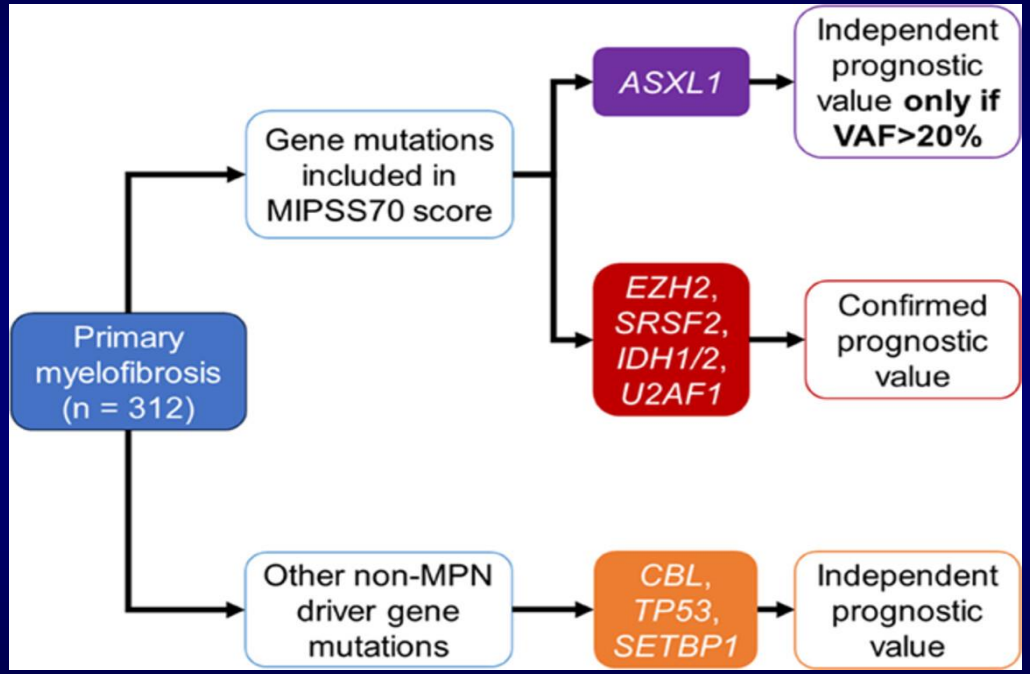


Hernandez-Sánchez A et al. AJH 2024;99(4):755-8

Prognostic impact of non-driver gene mutations and VAF in PMF (GEMFIN database)

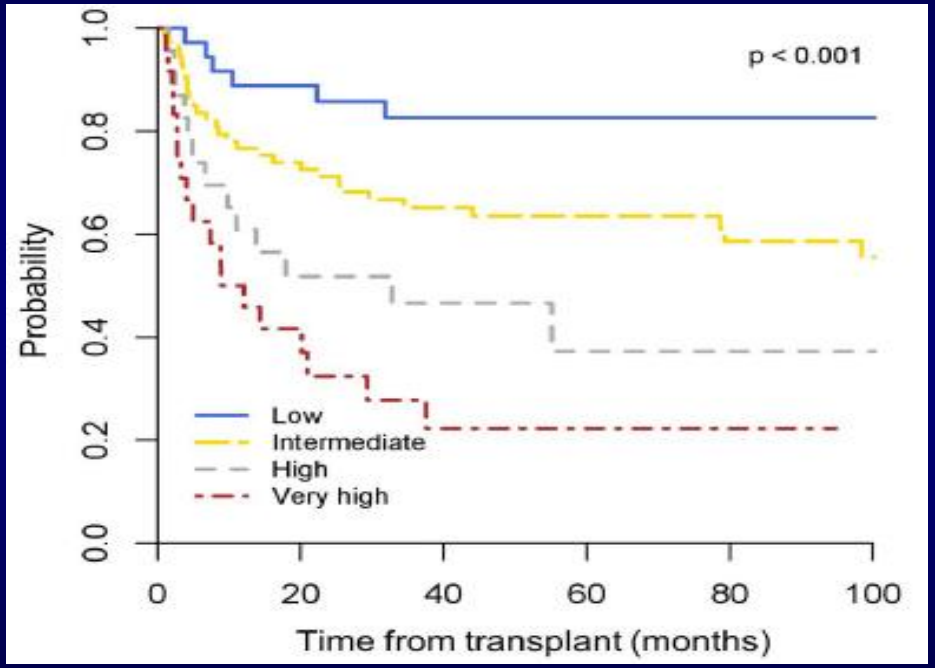






Hernandez-Sánchez A et al. AJH 2024;99(4):755-8

Myelofibrosis Transplant Scoring System (MTSS)

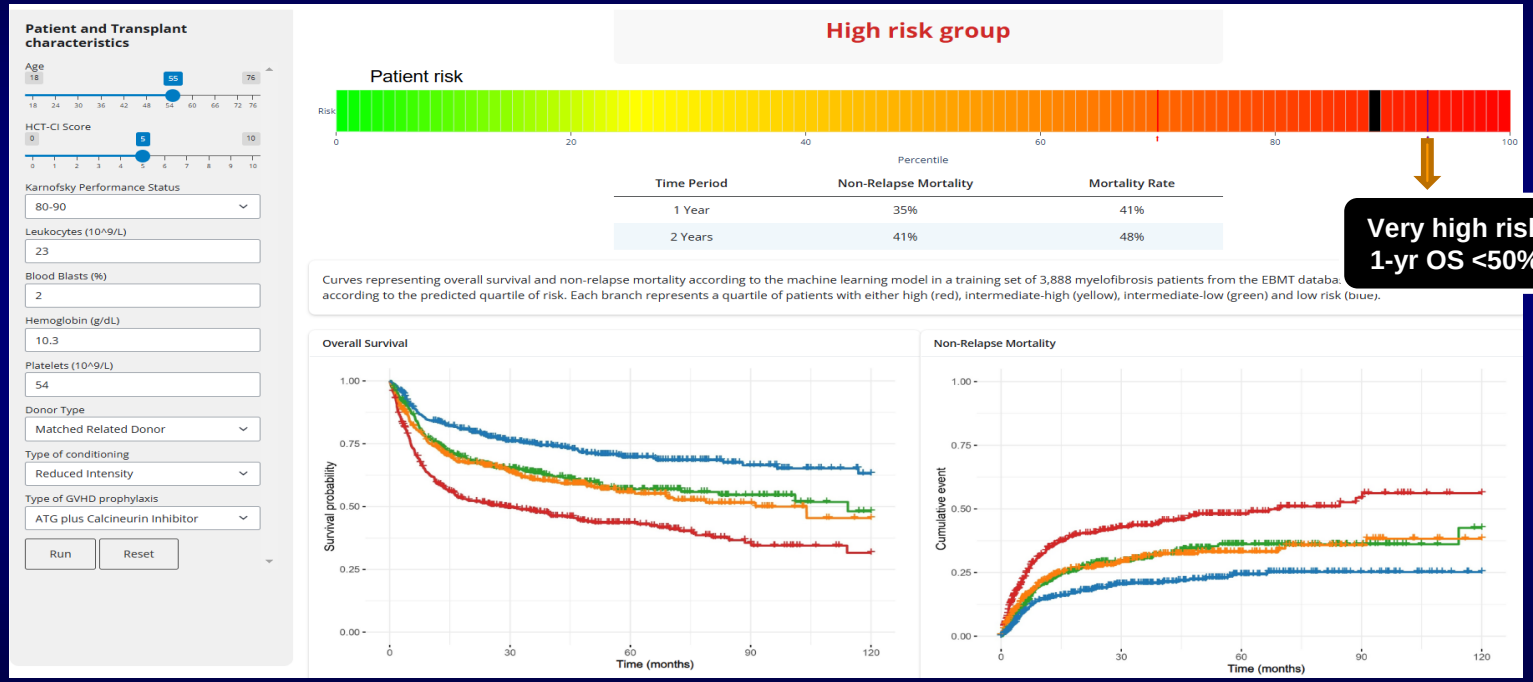


Gagelmann N, et al. Blood 2019;133(20):2233-42

Factor de riesgo	Puntos
Edad ≥ 57	1
Karnofsky < 90%	1
Leucocitos > 25 x 10^9/L	1
Plaquetas < 150 x 10^9/L	1
Mutación *ASXL1*	1
Genotipo *JAK2*+/triple negativo	2
Donante no familiar HLA dispar	2

Riesgo	Score	% pac.	SRV (5 años)
Bajo	0-2	23	83%
Intermedio	3-4	47	64%
Alto	5	15	37%
Muy alto	≥ 6	15	22%

EBMT prognostic scoring system for OS based on ML techniques



https://gemfin.click/ebmt

Hernandez-Boluda JC, Mosquera-Orgueira A et al. Blood 2025

Treatment decision

	MIPSS70	MIPSS70+ v2.0
Disease risk group	High	High
Median survival	< 5 yr	< 5 yr

	MTSS	EBMT-AI
Transplant risk group	Low	Low
Outcome	5-yr survival 83%	1-yr mortality 15%

Discuss with the patient the risk-benefit balance

Tratamiento de la mielofibrosis dirigido por problemas clínicos*

Anemia

- A. eritropoyéticos
- Danazol
- Momelotinib
- Prednisona
- Inmunomoduladores
- Esplenectomía

Esplenomegalia sintomática

- Inhibidores JAK
- Esplenectomía
- Irradiación esplénica

Síntomas constitucionales

- Inhibidores JAK
- Citorreductores
- Prednisona

Infilt. extramedular

- RDT local

Prevención trombosis

- AAS / ACO
- Citorreductores

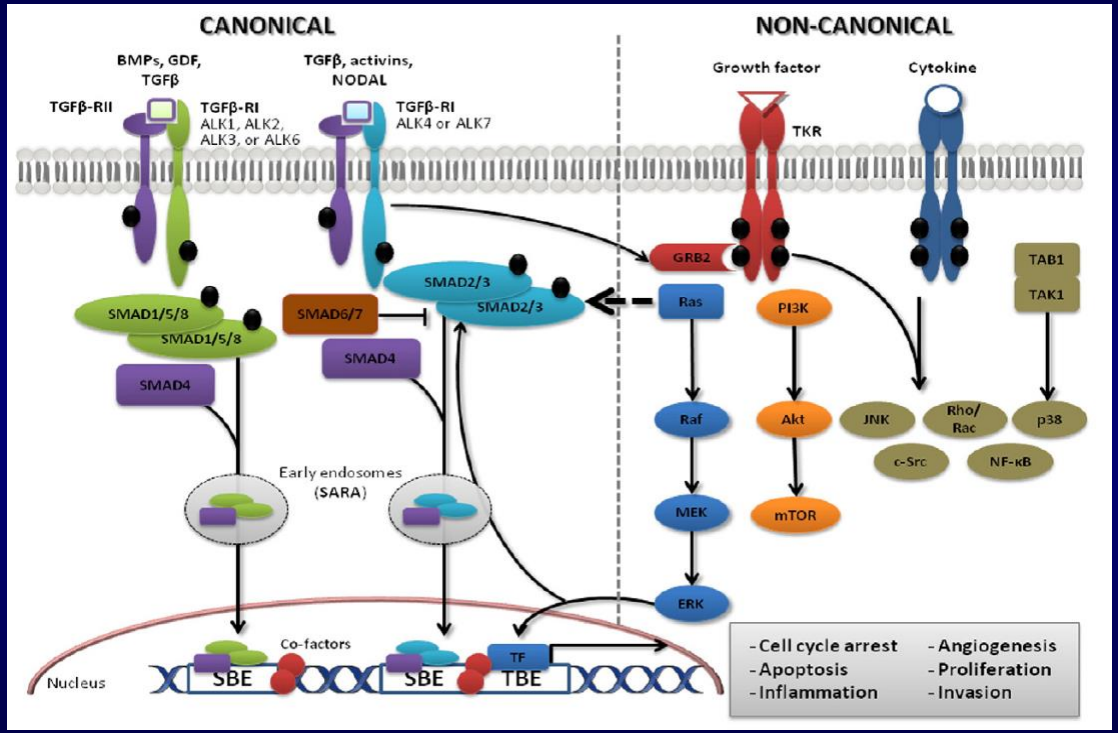
*Aproximación personal

Inhibidores de JAK2 en mielofibrosis

Fármaco	Compañía	Dianas	Fase
Ruxolitinib	Novartis	**JAK2**, JAK1	Aprobado EMA (2012)
Fedratinib	Celgene/BMS	**JAK2**, FLT3	Aprobado EMA (2021)
Momelotinib	GSK	**JAK2**, JAK1, **ACVR1**	Aprobado EMA (2024)*
Pacritinib	Sobi	**JAK2**, FLT3, IRAK1, **ACVR1**	Aprobado FDA (2022)**

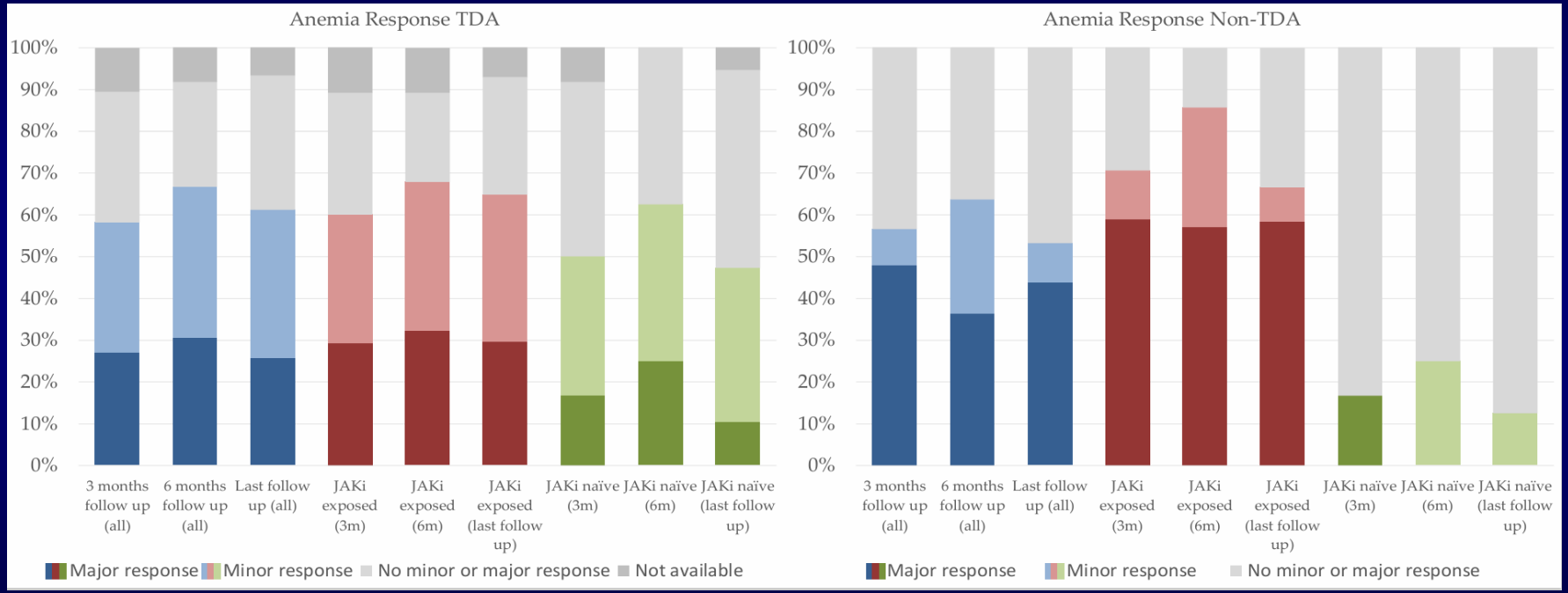
*Pacientes con anemia moderada/grave. **Pacientes con plaquetas < 50 x 10^9/L.

Señalización de la familia TGF-β



Neuzillet C et al, Pharmacol & Ther 2015;147:22-31

Momelotinib en “vida real”: resp de la anemia Serie española (n=154)



Pérez-Lamas L et al, BCJ 2015; aceptado

Nuevos fármacos para la anemia de la mielofibrosis

	Diana	Fase ensayo clínico
Luspatercept[1]	ACVR2B ligand trap	III
Zilurgisertib[2]	Inh ACVR1	I/II
Elritercept (KER-050)[3]	ACVR2A ligand trap	I/II

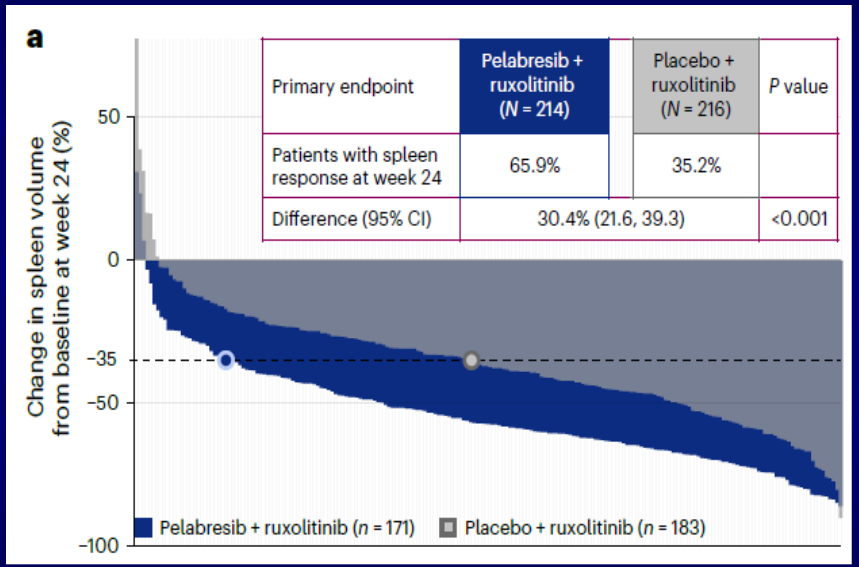
[1]Gerds AT, ASCO 2023; [2]Mohan S, ASH 2023; [3]Harrison C, ASH 2023

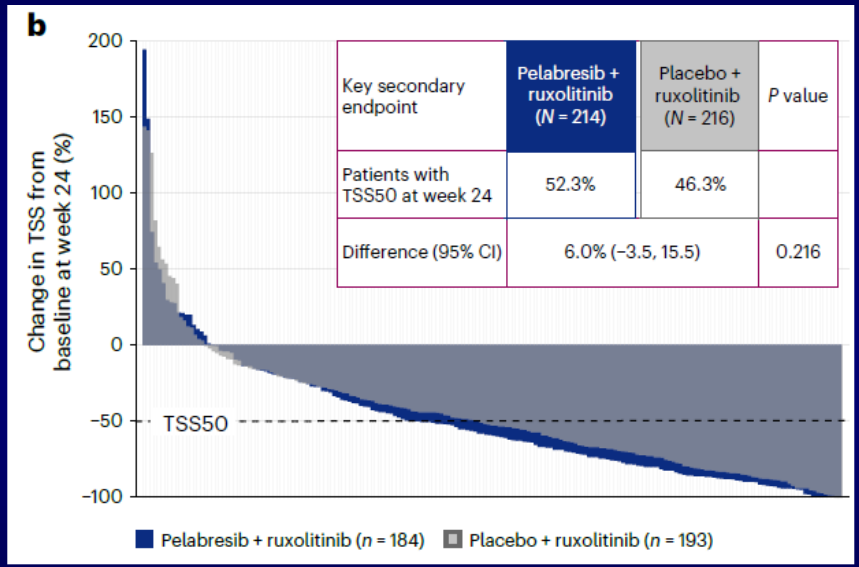
Nuevos fármacos frente a la mielofibrosis

	Diana	Eficacia clínica
Imetelstat[1]	Inh. telomerasa	Control síntomas / resp histol-molecular
Pelabresib[2]	Inh. BET	Control sínt-espleno-anemia / resp histol-molecular
Navtemadlin[3]	Inh. MDM2	Control sínt-esplenomegalia / resp histol-molecular
Selinexor[4]	Inh. XPO1	Control síntomas-esplenomegalia

[1]Mascarenhas J, JCO 2021; [2]Mascarenhas J, JCO 2023; [3]Vachani P, ASH 2021; [4]Ali H, ASCO 2023

Ruxo + pelabresib vs Ruxo + placebo
MANIFEST-2 trial





Rampal R, et al. Nat Med 2025

MUCHAS GRACIAS POR ESCUCHAR