

Aspectos clínicos y pronósticos de las Neoplasias Mieloproliferativas

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WHO Classification of the MPNs

Myeloproliferative neoplasms (MPN)

Chronic myelogenous leukemia, *BCR-ABL1*-positive

Chronic neutrophilic leukemia

Polycythemia vera

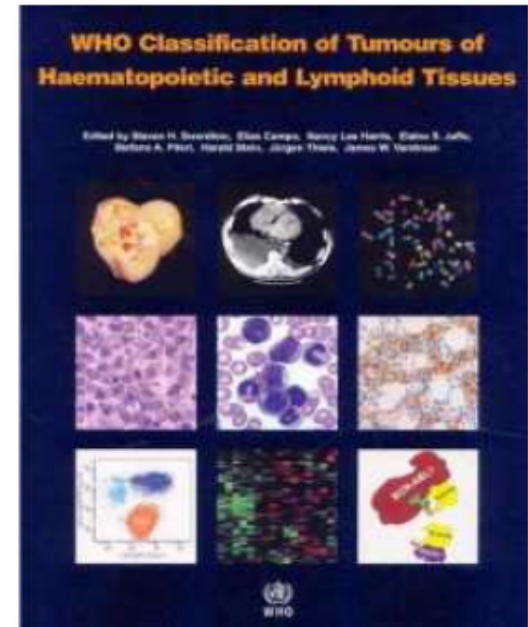
Primary myelofibrosis

Essential thrombocythemia

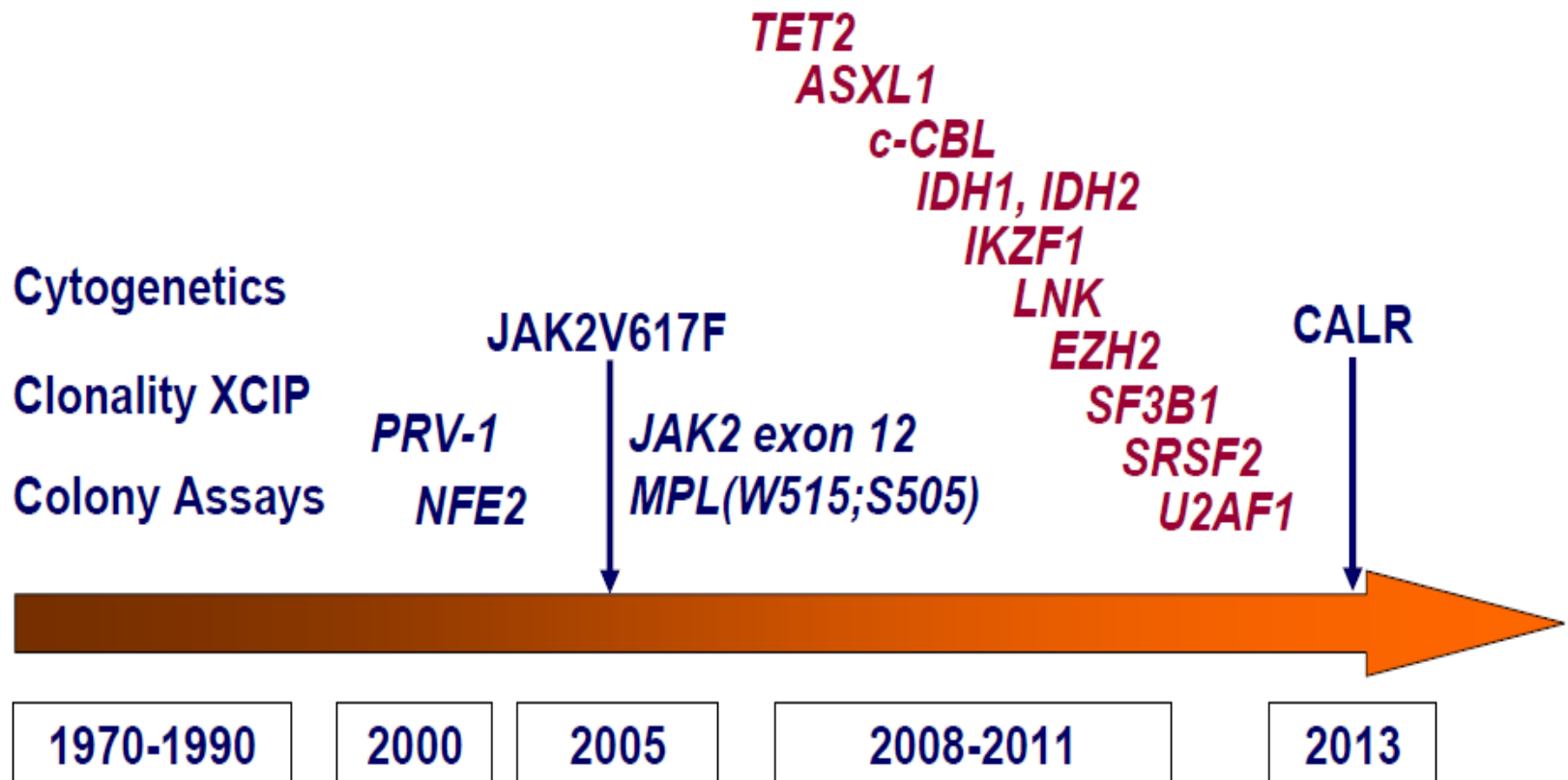
Chronic eosinophilic leukemia, not otherwise specified

Mastocytosis

Myeloproliferative neoplasms, unclassifiable



Biomarkers in Ph-negative MPNs



Proposal new WHO criteria

Leukemia (2014) 28, 1407–1413

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www.nature.com/leu

REVIEW

An overview on *CALR* and *CSF3R* mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms

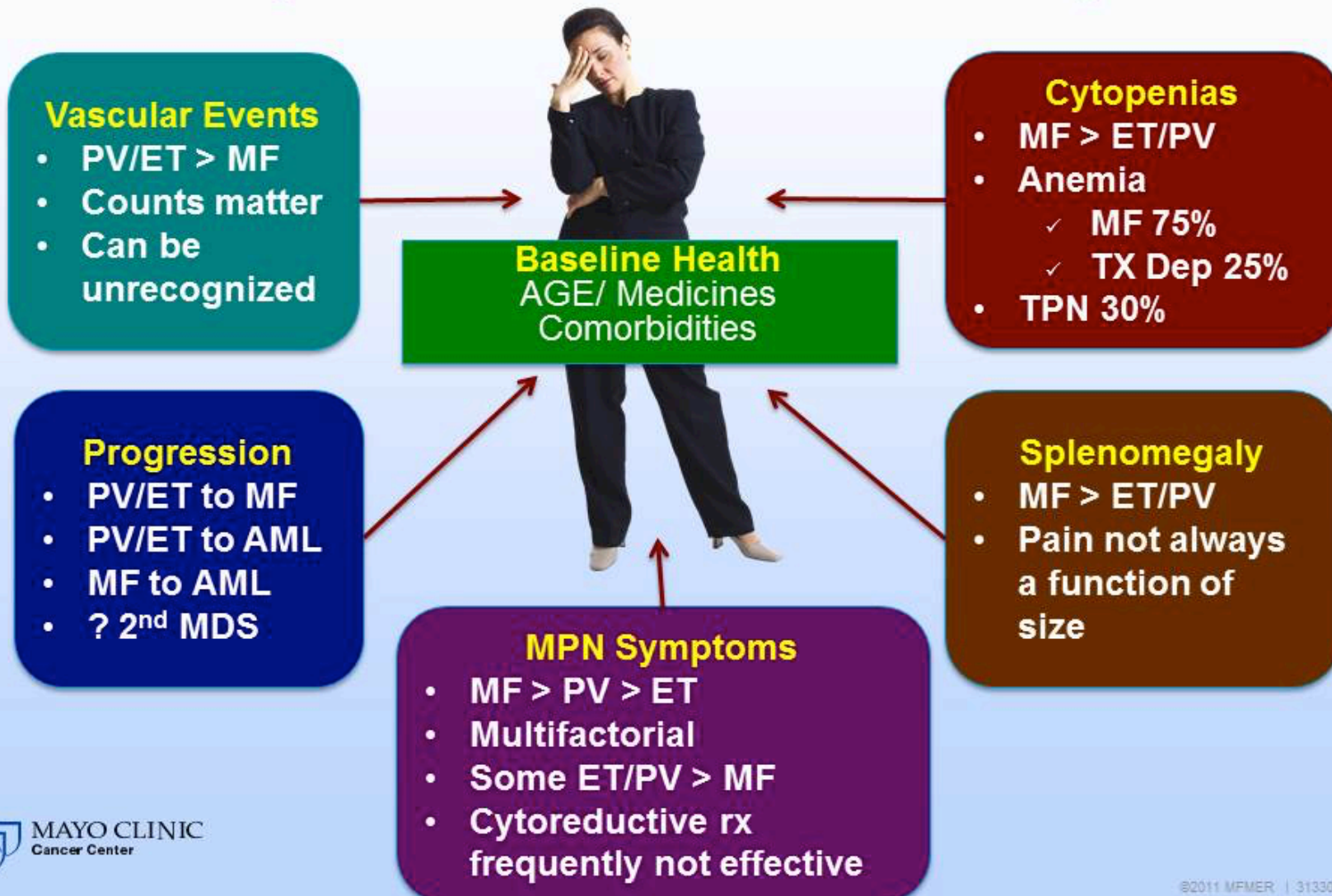
A Tefferi¹, J Thiele², AM Vannucchi³ and T Barbui⁴

Table 4. 2014 proposed revision for World Health Organization (WHO) diagnostic criteria for *BCR-ABL1*-negative myeloproliferative neoplasms

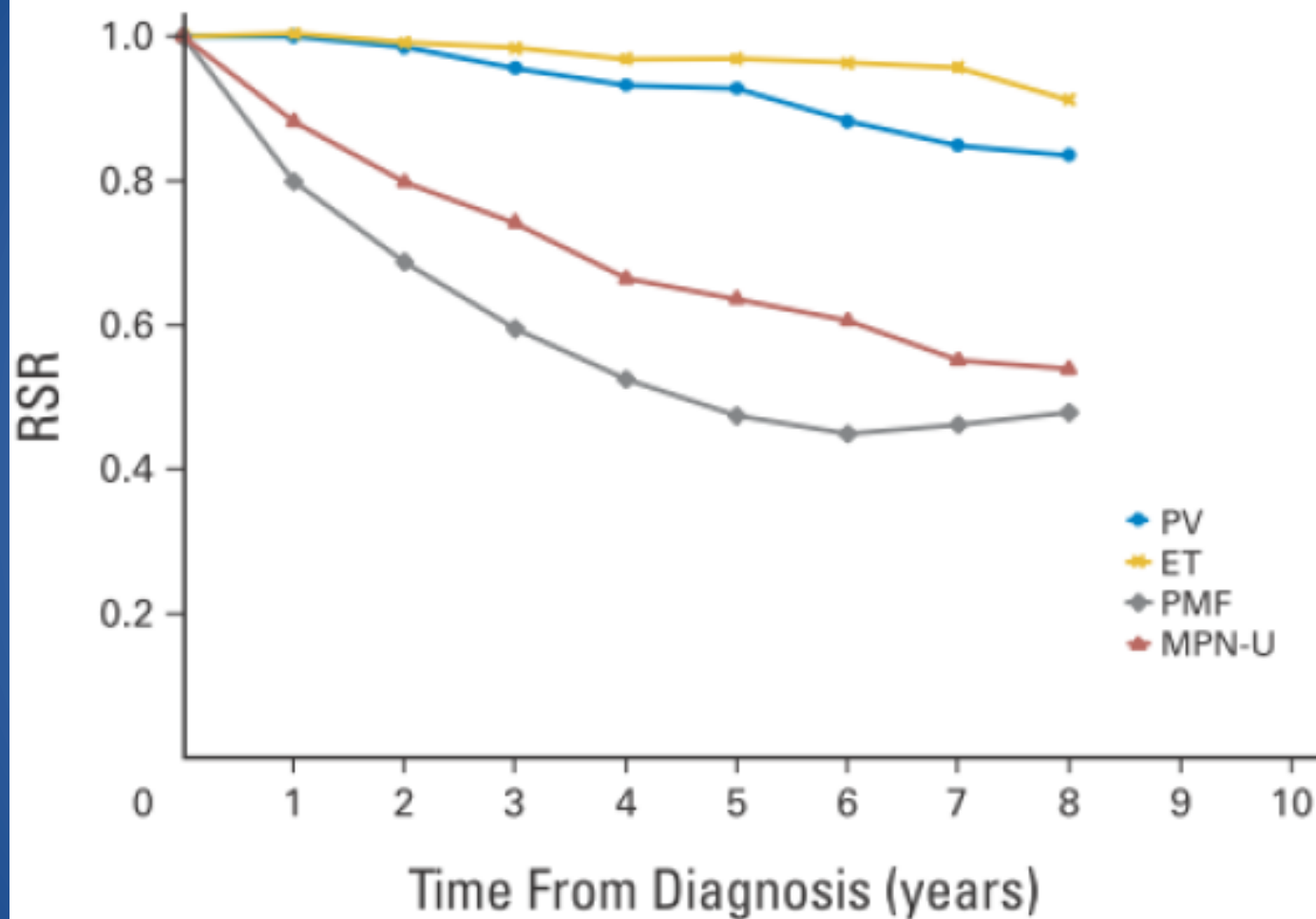
	<i>Polycythemia vera (PV)</i> ^a	<i>Essential thrombocythemia (ET)</i> ^b	<i>Primary myelofibrosis (PMF)</i> ^c
<i>Major criteria</i>			
1	Hemoglobin > 16.5 g/dl (men) > 16 g/dl (women) or hematocrit > 49% (men) > 48% (women)	Platelet count $\geq 450 \times 10^9/l$	Megakaryocyte proliferation and atypia ^d , accompanied by either reticulin and/or collagen fibrosis or ^e
2	BM trilineage myeloproliferation with pleomorphic megakaryocytes	Megakaryocyte proliferation with large and mature morphology	Not meeting WHO criteria for CML, PV, ET, MDS or other myeloid neoplasm
3	Presence of <i>JAK2</i> mutation	Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	Presence of <i>JAK2</i> , <i>CALR</i> or <i>MPL</i> mutation
4		Presence of <i>JAK2</i> , <i>CALR</i> or <i>MPL</i> mutation	
<i>Minor criteria</i>			
1	Subnormal serum erythropoietin level	Presence of a clonal marker (e.g. abnormal karyotype) or absence of evidence for reactive thrombocytosis	Presence of a clonal marker (e.g. abnormal karyotype) or absence of evidence for reactive bone marrow fibrosis
2			Presence of anemia or palpable splenomegaly
3			Presence of leukoerythroblastosis ^f or increased lactate dehydrogenase ^f

Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story



SURVIVAL of MPN

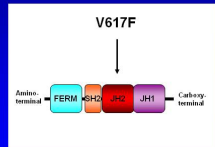


1) MIELOFIBROSIS

Mielofibrosis primaria.

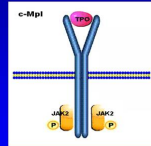
Main Molecular Abnormalities in PMF

JAK2 V617F
(60%)



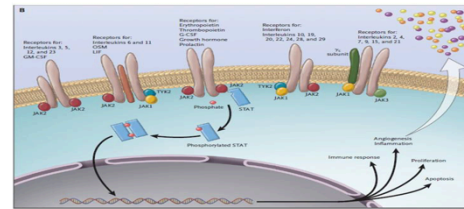
Lowins et al., *Cancer Cell*, 2005 Apr;7(4):387-97.
Jahnke et al., *Nature*, 2005 Apr 28;434(7071):1164-8.
Vignani et al., *N Engl J Med*, 2005 Apr 28;353(17):1779-90.
Baxter et al., *Lancet*, 2005 Mar 18;365(9464):1054-61.

MPL W515L/K
(5-10%)



Pisman et al., *PLoS Med*, 2006 Jul 3;3(7):e270.
Pardanani et al., *Blood*, 2006 Nov 16;108(10):3472-8.

Effects of JAK1 and JAK2 Inhibition



Vannucchi AM et al. *N Engl J Med*. 2010 Sep 16;363(12):1180-2.

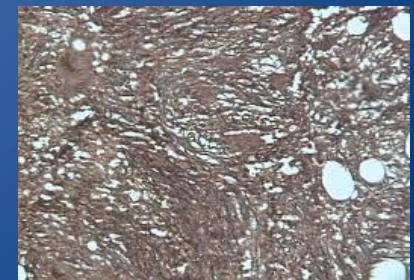
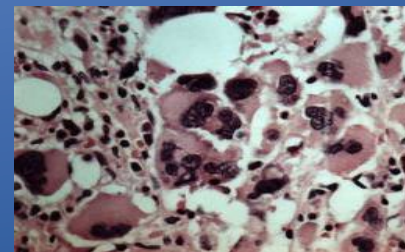
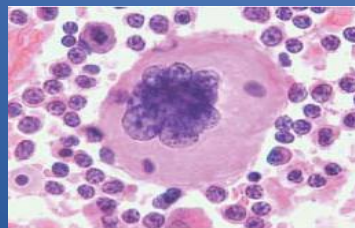
Efficacy of JAK2 Inhibitors in Myelofibrosis

	Spleen	MF Symptoms	Anemia	JAK2*	Targets
Ruxolitinib <i>NEJM</i> 2010, <i>EHA</i> 2011	X	X			JAK1/2
TG101348 (SAR302503) <i>JCO</i> 2011	X	X		?	JAK2-FLT3
SB1518 <i>EHA</i> 2011	X	X			JAK2-FLT3
CYT387 <i>ASCO</i> 2011	X	X	X	?	JAK1/2
CEP701	X	X			JAK2-FLT3

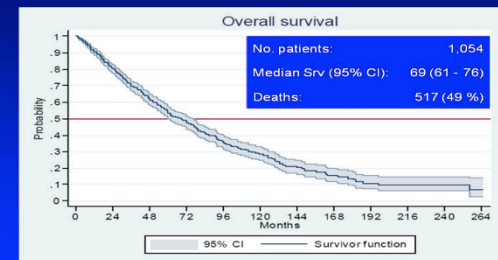
AZD1480
LY2784544
NS-018
BMS-9121543

Phase I Testing

* Reduction of the allele burden



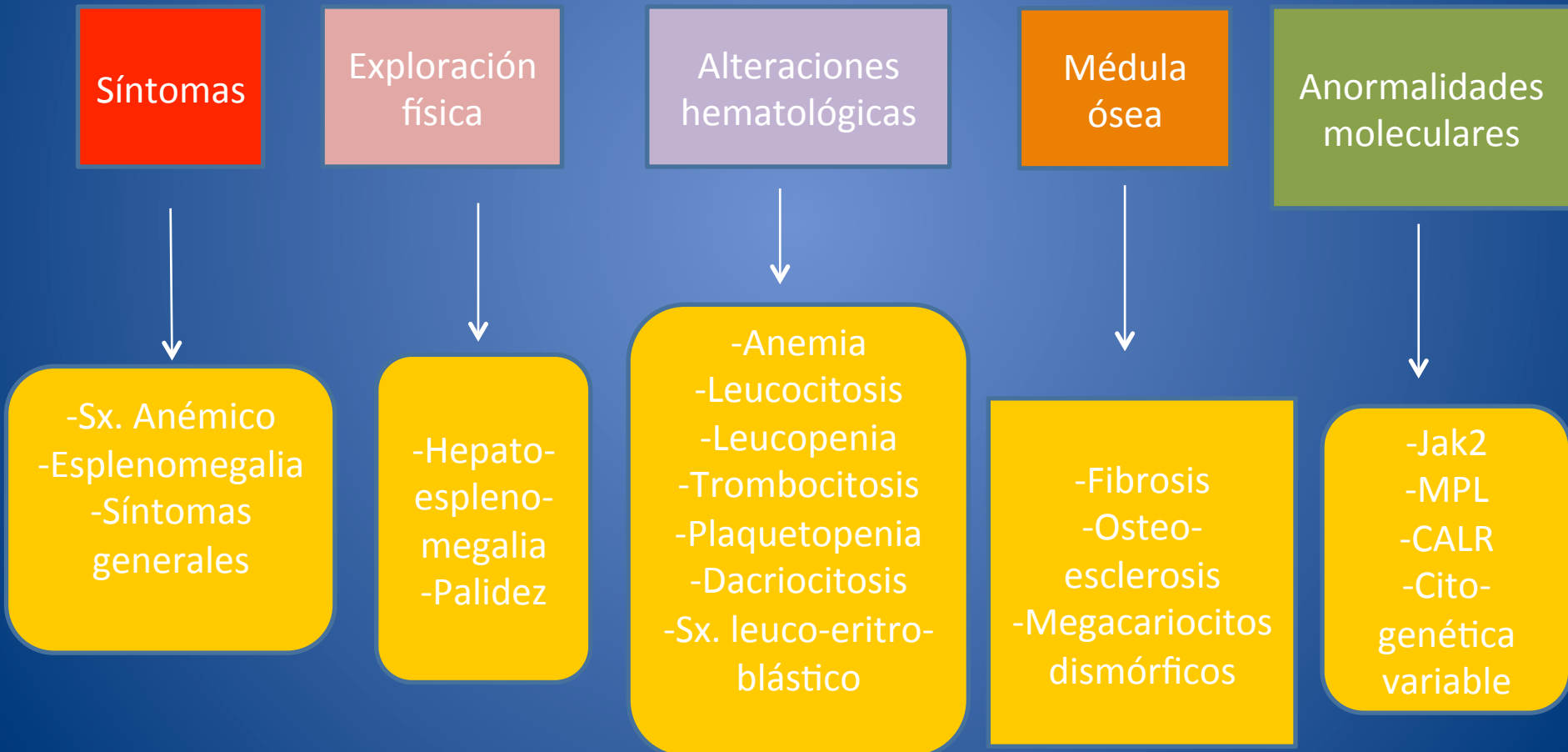
Survival in PMF



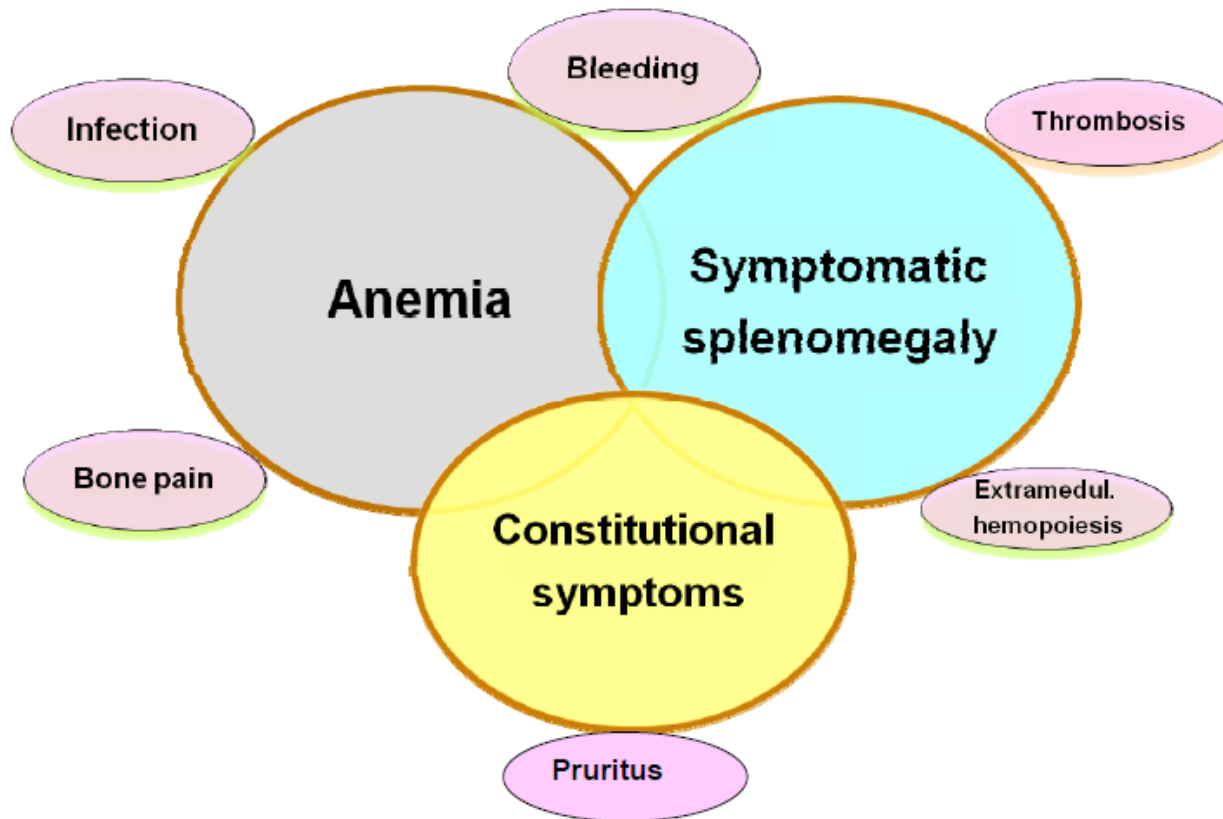
Cervantes et al *Blood*, 2009 Mar 26; 113(13):2895-901

Mielofibrosis Primaria

Expresión de la enfermedad

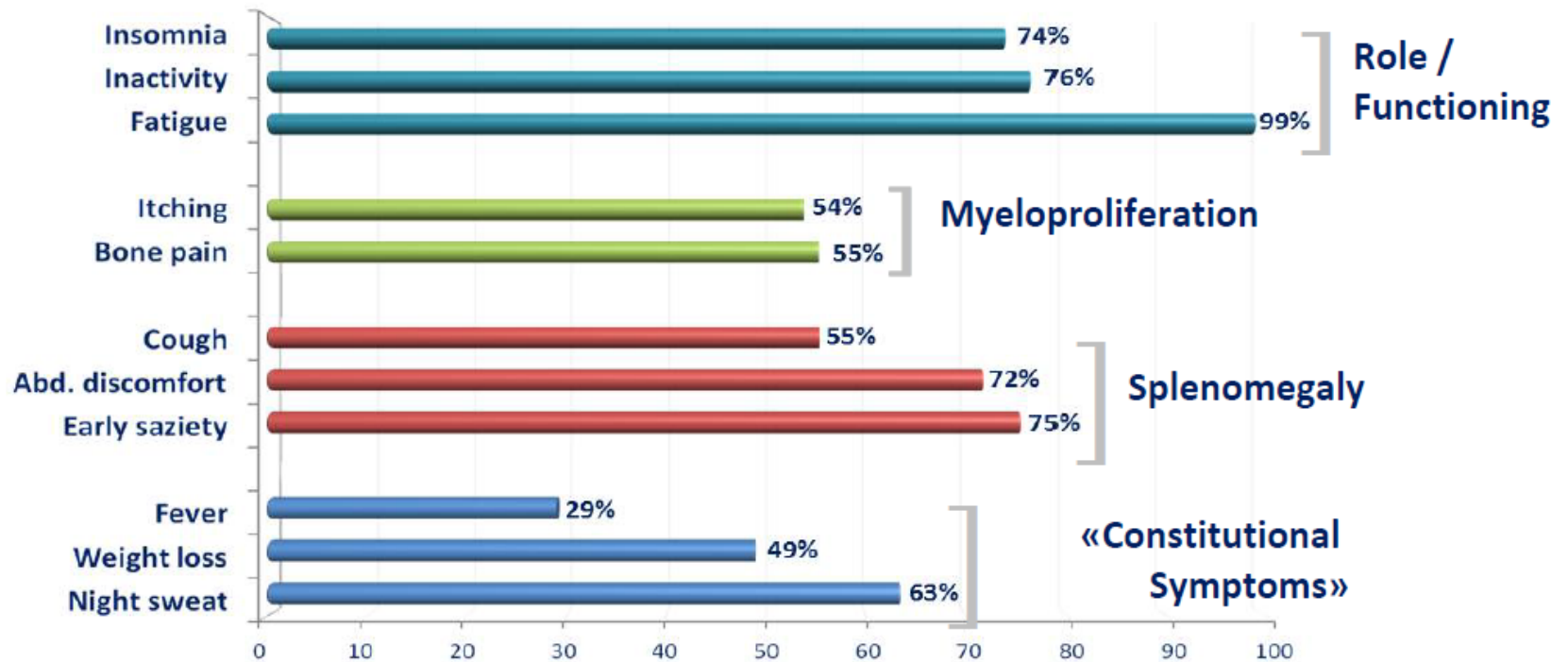


Clinical Manifestations of Myelofibrosis



Symptomatic Burden in PMF

Symptoms related to:



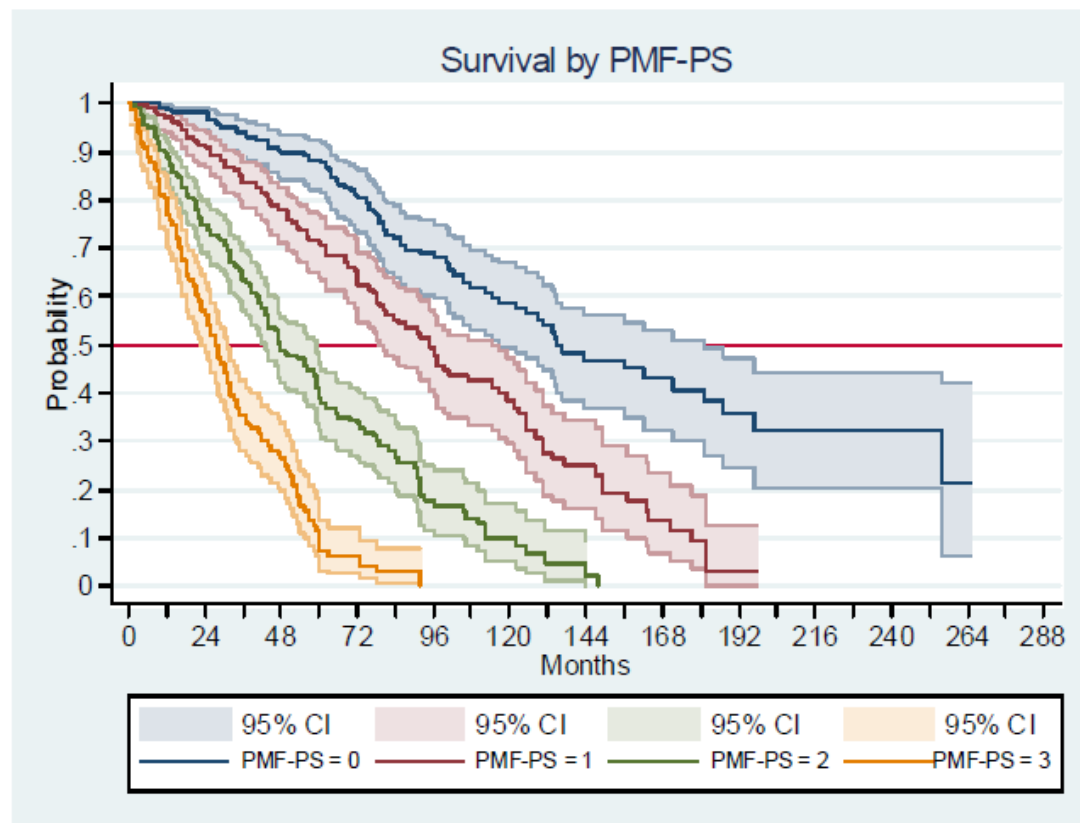
IPSS: Risk Classification of PMF at Presentation

Prognostic factors

- Age > 65 years
- Constitutional symptoms
- Hb < 10 g/dL
- Leukocytes > 25 x 10⁹/L
- Blood blasts ≥ 1%

Risk groups

- | | |
|------------------|-----|
| • Low | 0 |
| • Intermediate-1 | 1 |
| • Intermediate-2 | 2 |
| • High | ≥ 3 |



DIPSS-plus Risk Stratification of PMF

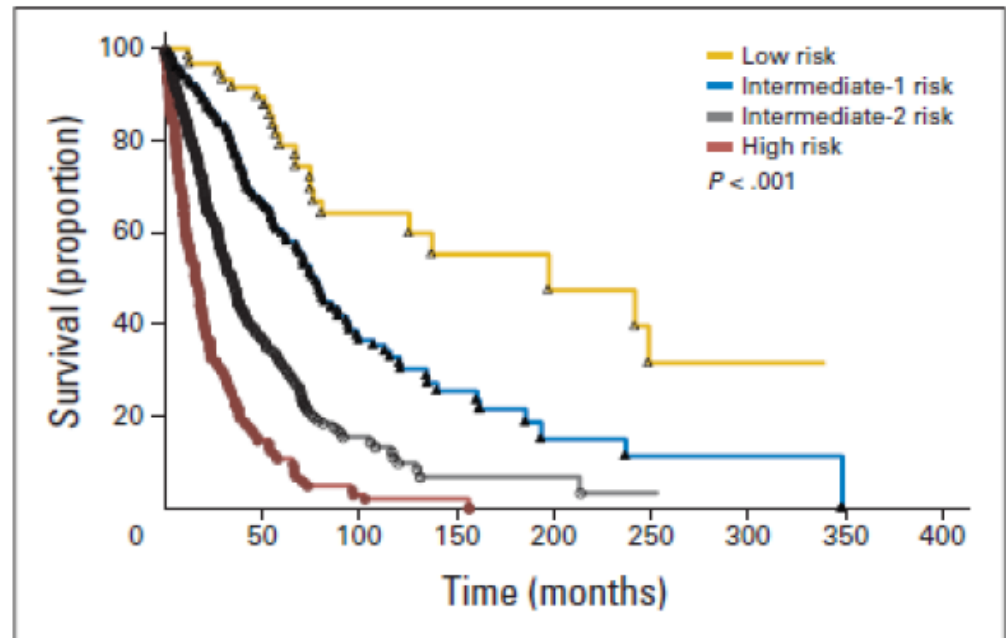
Factors Score

DIPSS int-1:	1
int-2:	2
high:	3
Platelets < 100 x 10 ⁹ /L	1
RBC transfusion need	1
Unfavorable karyotype *	1

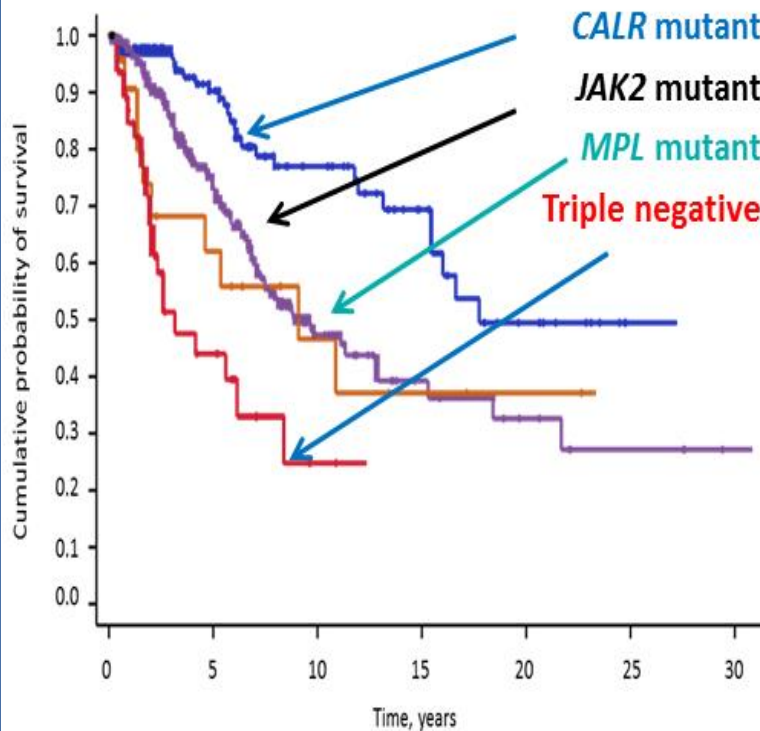
* +8, -7/7q-, -5/5q, i17q, 12p-, 11q23 rearr.

Risk groups

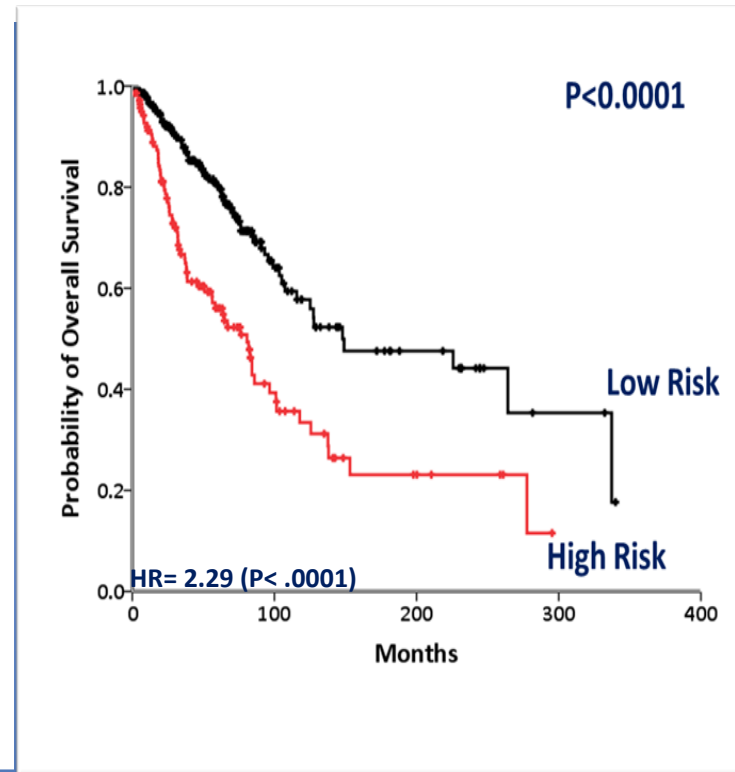
• Low	0
• Intermediate-1	1
• Intermediate-2	2-3
• High	4-6



Mutations impact in PMF prognosis



HR: 2.3 for *JAK2V617F* ($P < .001$)
 2.6 for *MPL* ($P = .009$)
 6.2 for TN ($P < .001$)

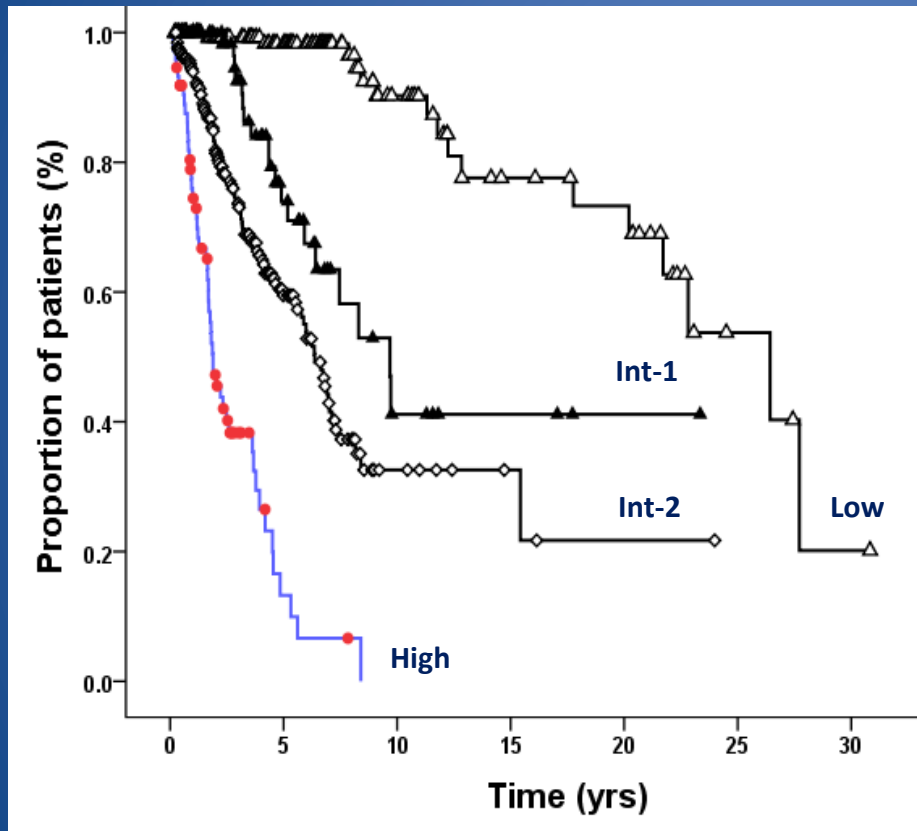


High risk:
 any mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*

MIPSS: Molecular International Prognostic Scoring System for PMF

MULTIVARIATE ANALYSIS			Weighted value
Variables	HR (95% CI)	P	
Age > 60 yrs	3.8 (2.60-5.51)	<0.0001	1.5
Hb < 100 g/L	1.4 (1.01-1.99)	0.04	0.5
Constitutional symptoms	1.5 (1.13-2.16)	0.007	0.5
PLT < 200x10 ⁹ /L	2.5 (1.77-3.42)	<0.0001	1.0
Triple negativity	3.9 (2.20-6.80)	<0.0001	1.5
JAK2/MPL mutation	1.8 (1.11-2.90)	0.016	0.5
ASXL1 mutation	1.4 (1.06-1.99)	0.02	0.5
SRSF2 mutation	1.7 (1.08-2.58)	0.02	0.5

MIPSS score

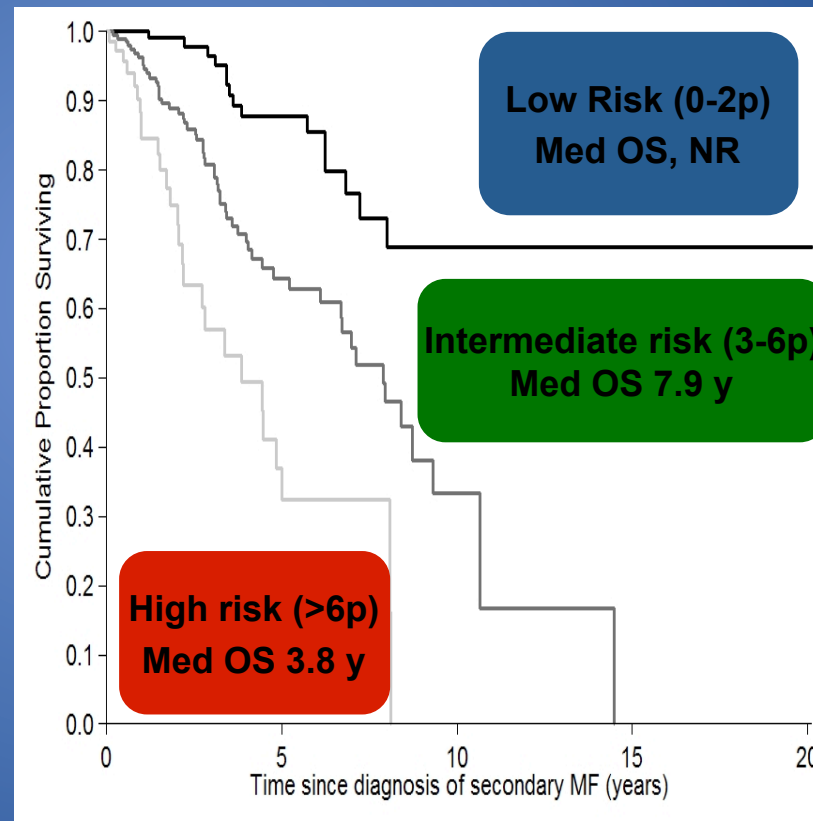


Risk category	Score	% of pts	OS (y)	HR
Low	0-0.5	27	26.4	1
Int-1	1-1.5	14	9.7	4.7
Int-2	2-3.5	46	6.4	9.9
High	≥4	13	1.9	36.5

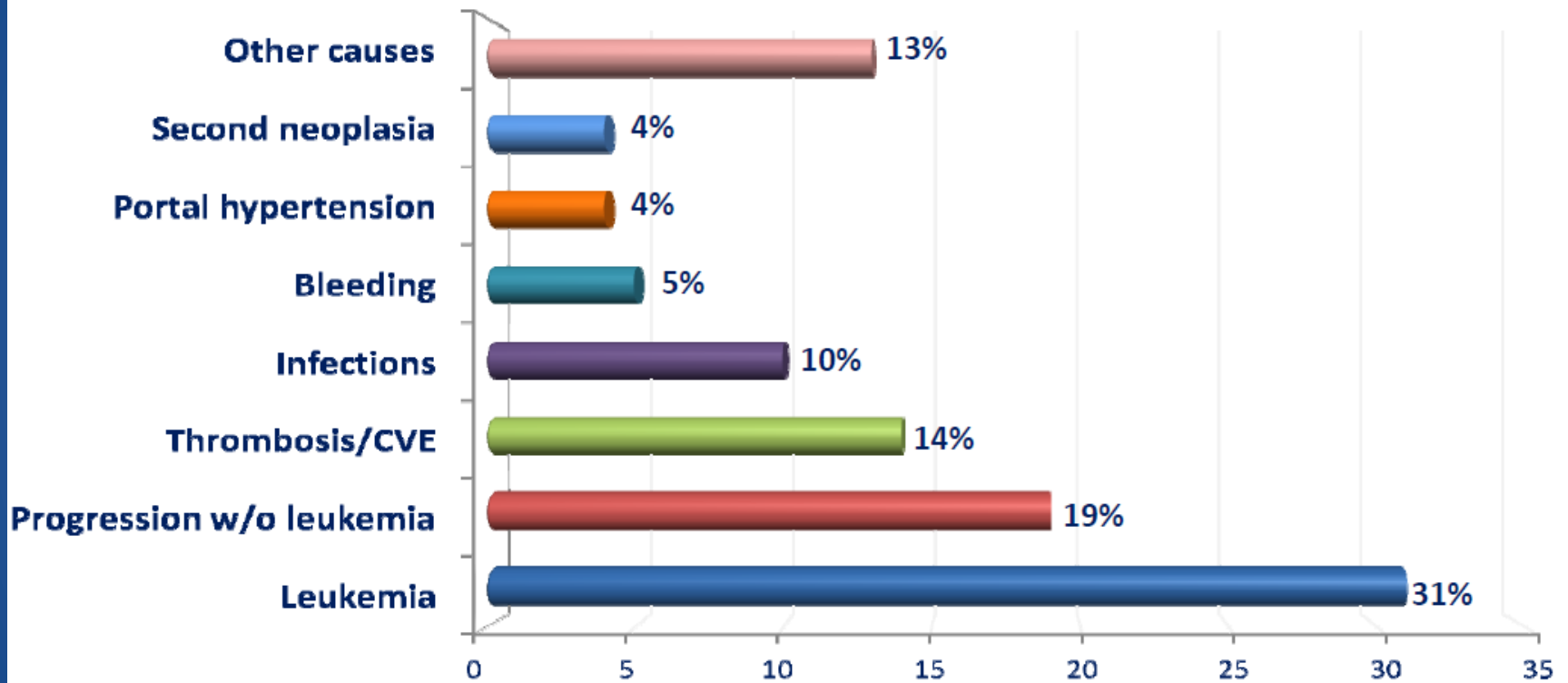
Akaike information criterion indicated that MIPSS performed better than IPSS in predicting survival (1611.6 vs 1649.0).

A new International multicenter-based model to predict survival in Myelofibrosis SEcondary to polycythemia and thrombocythemia: MYSEC Prognostic Model (MYSEC-PM)

Age >65 years	3
Time to SMF >15 years	2
History of thrombosis	2
Constitutional symptoms	2
Hemoglobin <10 g/dL	1
Circulating blast $\geq 1\%$	2



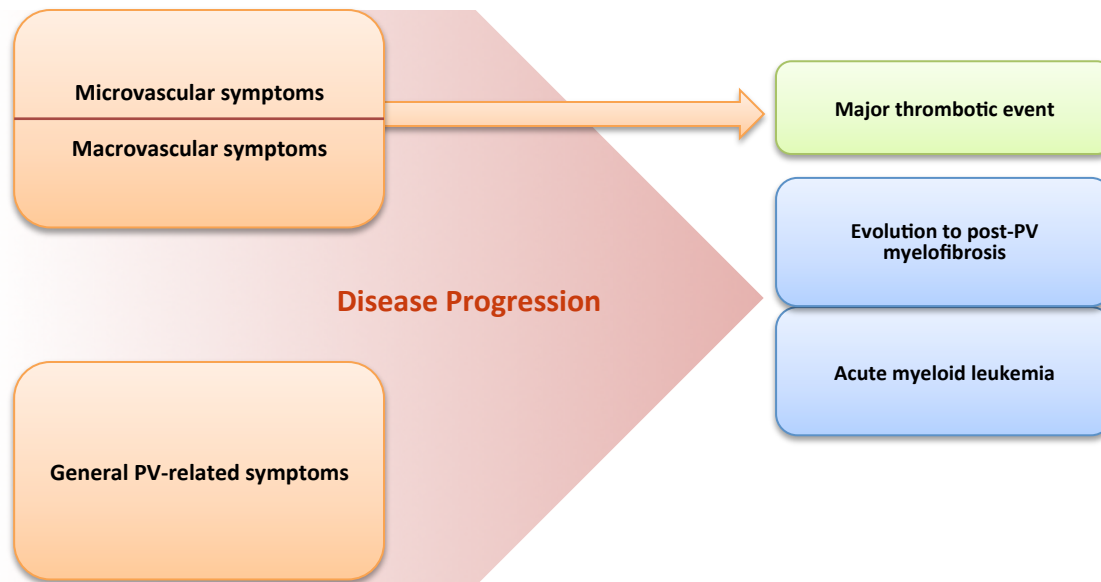
Causes of Death in PMF



2) POLICITEMIA VERA

Natural History of PV

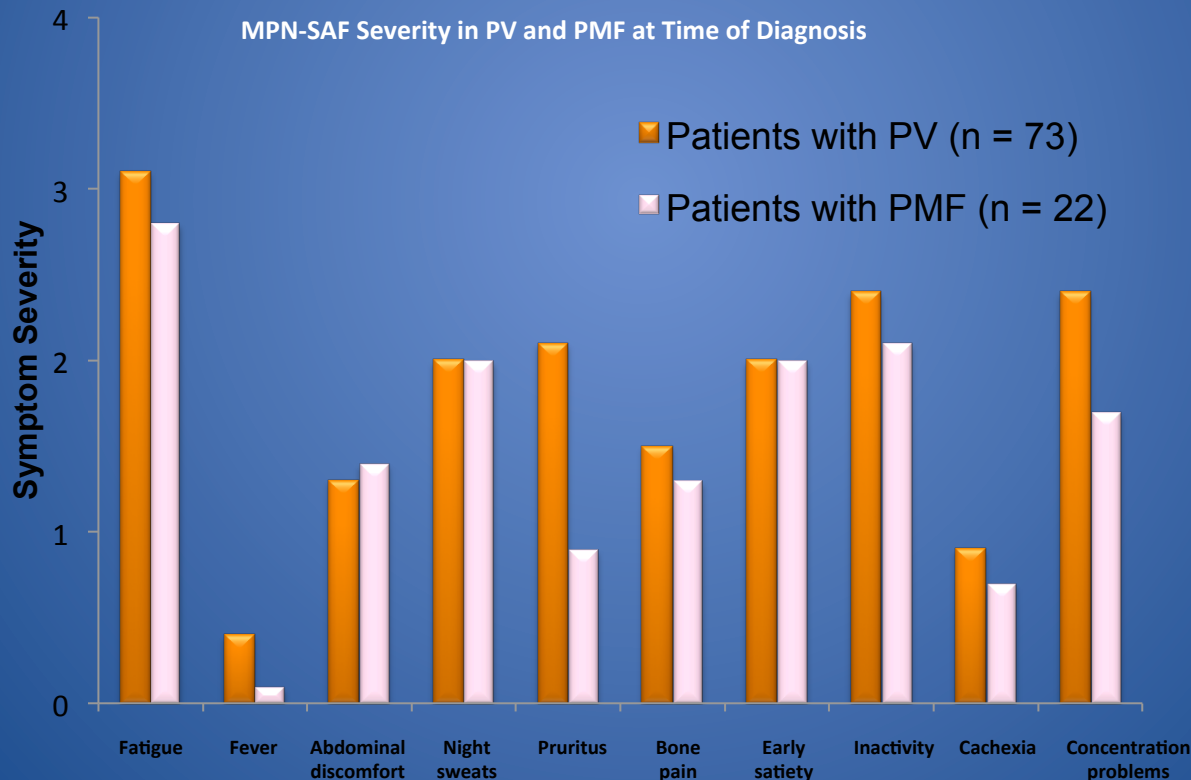
- PV can persist for many years without distinct stages or clear progression¹
- Disease evolution occurs in patients with PV
 - Progression to post-PV MF occurs in up to 10% of patients per 10 years²
 - Transformation to acute myeloid leukemia (AML) occurs in up to 15% of patients per 10 years³



1. Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC; 2008.
2. Tefferi A. *Am J Hematol*. 2008;83:491-497.
3. Finazzi G, et al. *Blood*. 2005;105:2664-2670.

PV Symptom Burden

- The severity of symptoms at diagnosis in PV is as high as that in primary MF¹
- PV symptoms are severe throughout the course of the disease²
- Symptoms may worsen in patients treated with conventional therapies, such as phlebotomy or hydroxyurea³



1. Abellsson J, et al. *Leuk Lymphoma*. 2013;54:2226-2230.

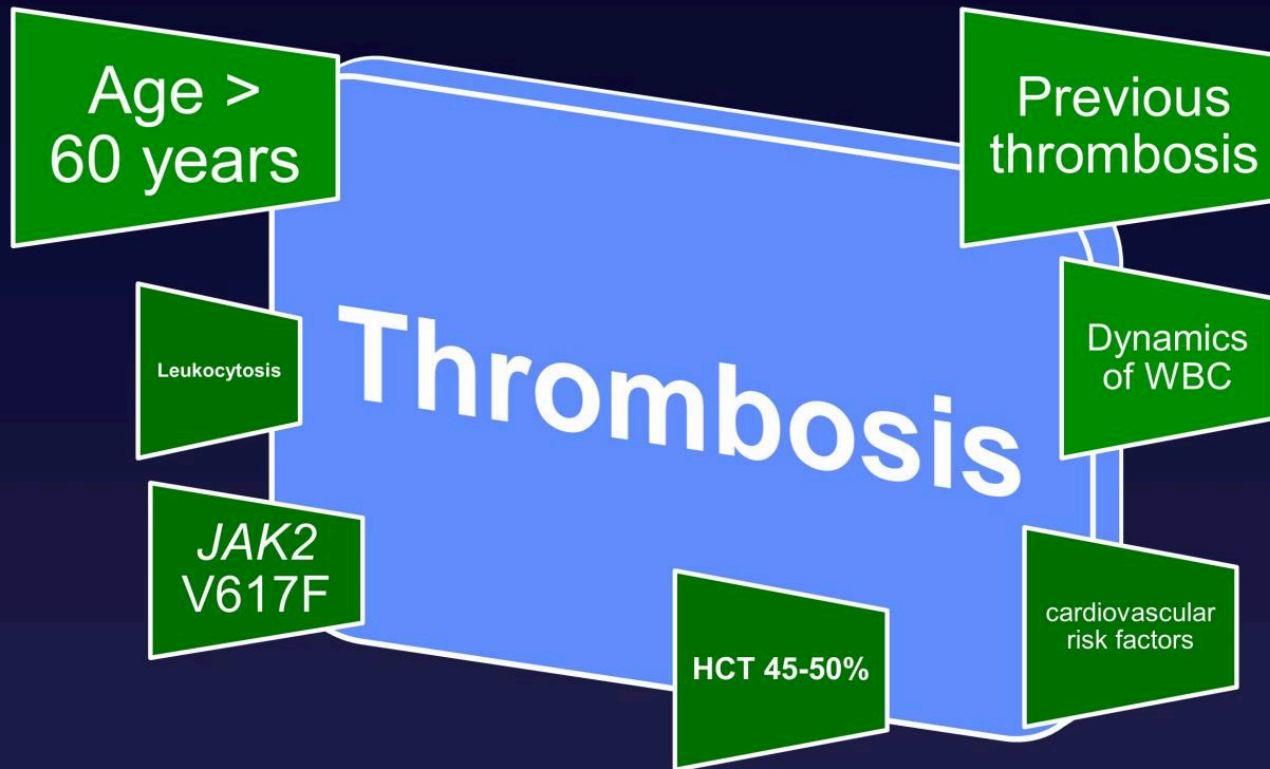
2. Scherber R, et al. *Blood*. 2011;118:401-408.

3. Emanuel R, et al. *Haematologica*. 2013;98:118-119.

Events Determining the Prognosis of PV and ET

- **Vascular events:**
 - **Thrombosis**
 - Bleeding
 - **Evolution to myelofibrosis**
 - **Evolution to AML & MDS**
-

Risk factors for thrombosis in PV



Barbui et al. J Clin Oncol. 2011; Marchioli et al. J Clin Oncol. 2005;23(10):2224-32;
Carobbio et al. Blood. 2008 15;112(8):3135-7; Landolfi et al. N Engl J Med. 2004;350(2):114-124;
Carobbio et al. J Clin Oncol. 2008;1;26(16):2732-6; Passamonti et al, J Thromb Haemost. 2009;7(9):1587-9;
Barbui et al. Blood 2012;120(26):5128-33; Marchioli et. al. N Engl J Med 2013; 368:22-33.

RISK CLASSIFICATION OF PV

High risk

- Age > 60 years
- Previous thrombosis

Low risk

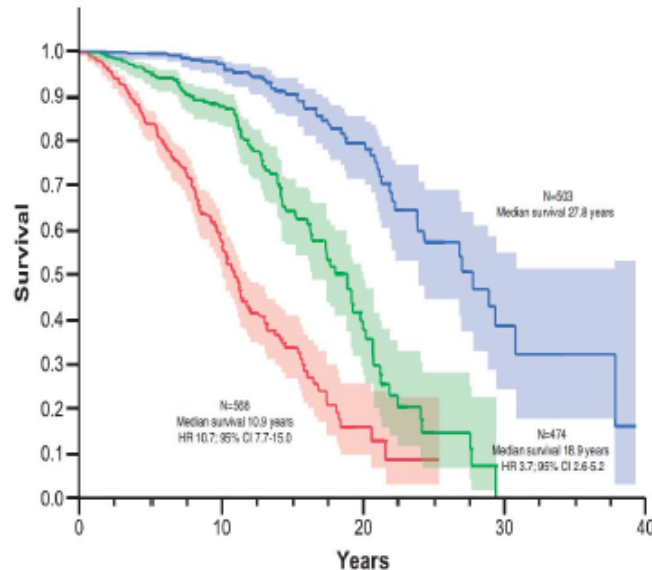
- Age \leq 60 years
- No previous thrombosis

* Platelets > 1,500 x 10⁹/L: high risk for bleeding

Intermediate risk ?

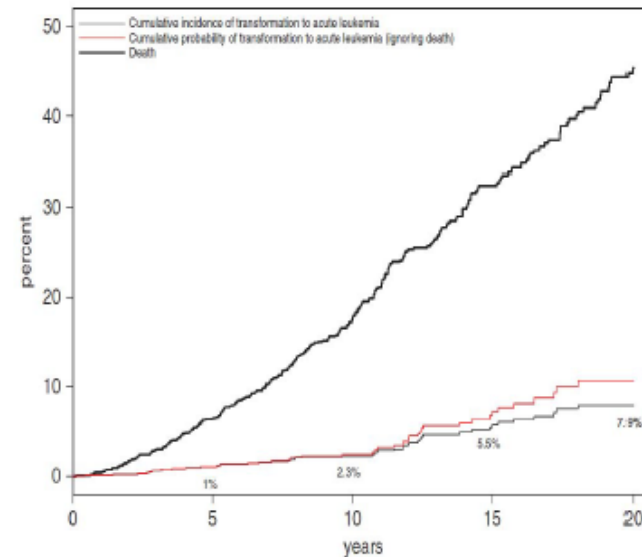
- Not high risk but
- CV risk factors or
- Age 40-60 years

Survival and leukemic transformation in 1545 patients with contemporary PV



Risk factors for survival

- Age
- **Leukocyte count**
- Venous thrombosis

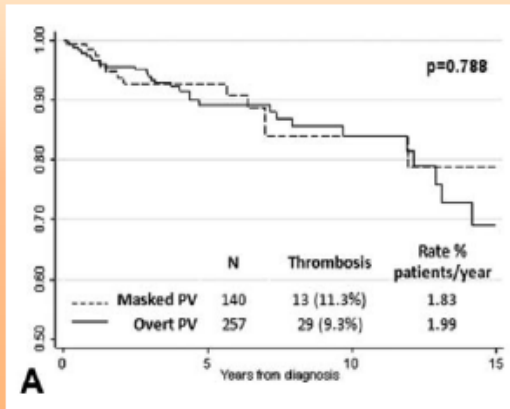


Risk factors for leukemia

- Age
- **Leukocyte count**
- Cytoreductive therapy

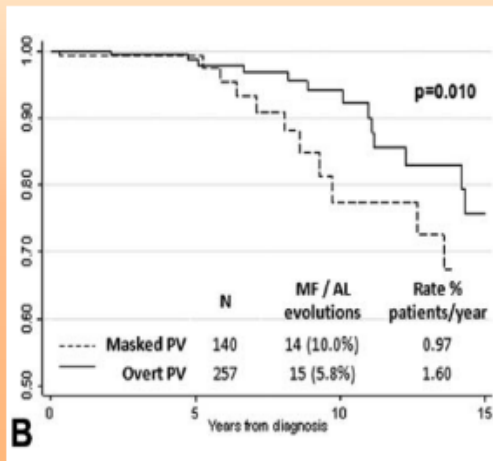
Masked PV: proposal of a new entity with different outcome

TROMBOSIS

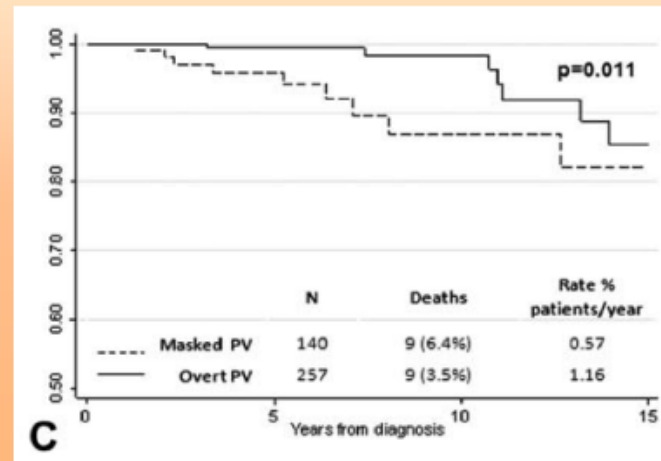


- Predominio masculino
- Hb y Hto por debajo de los criterios OMS2008
- Plaquetas más altas
- Historia de trombosis más frecuente
- Más Fibrosis medular
- Diagnóstico basado en la BMO

TRANSFORMACIÓN



SUPERVIVENCIA



3) TROMBOCITEMIA ESENCIAL

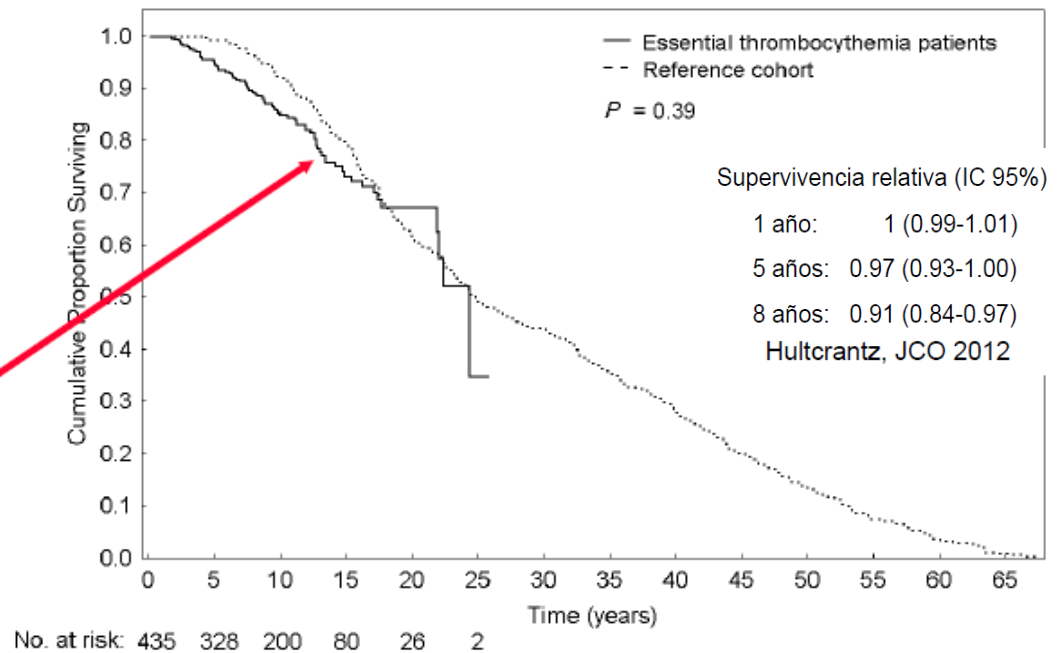
Life Expectancy of ET

N= 435 patients

Median f-u: 9.3 years

**Median survival:
22.6 years**

**No difference
compared to
the general
population**



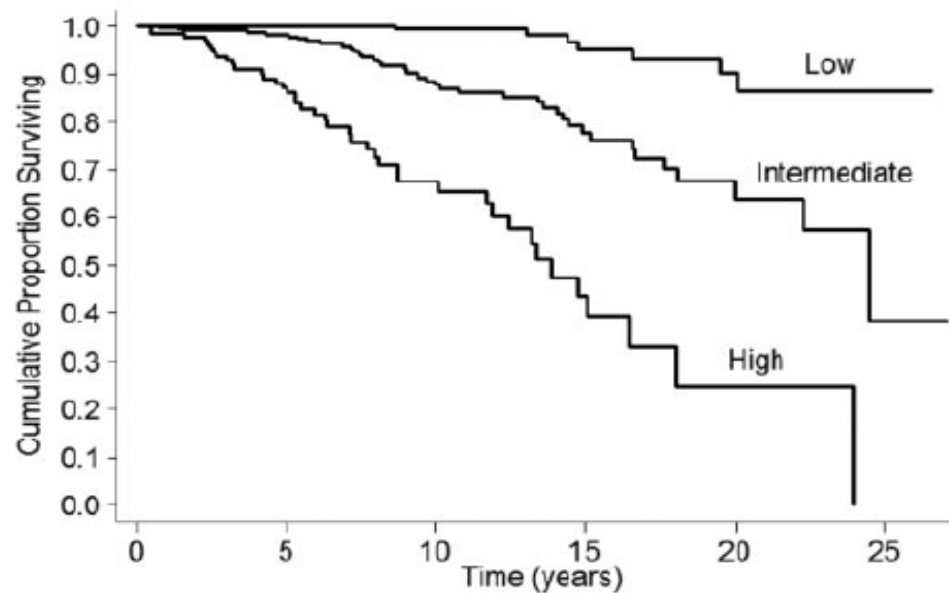
INTERNATIONAL PROGNOSTIC SCORE FOR ET (IPSET)

	Puntuación		
	0	1	2
Edad	< 60		≥ 60
Leucocitos, x10 ⁹ /L	< 11	≥ 11	
Historia de trombosis	No	Sí	

Bajo riesgo: 0 puntos

Riesgo intermedio: 1 – 2 puntos

Alto riesgo: 3 – 4 puntos



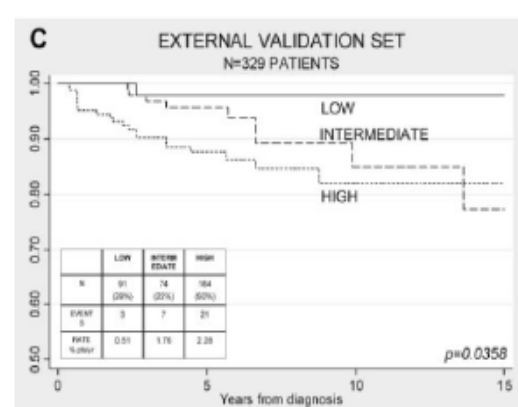
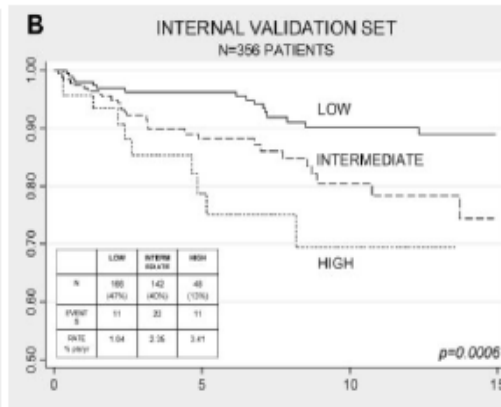
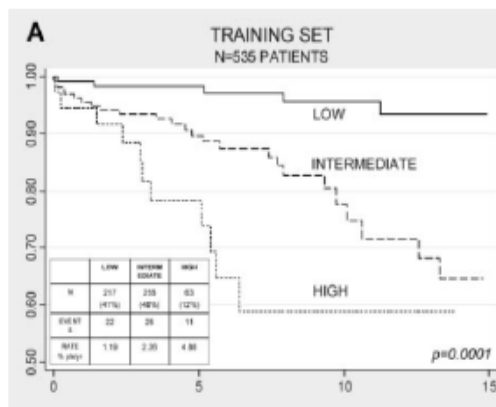
INTERNATIONAL PROGNOSTIC SCORE OF THROMBOSIS FOR ET (IPSET-THROMBOSIS)

	Puntuación		
	0	1	2
Edad	≤ 60	>60	
FRCV	No	Sí	
Historia de trombosis	No		Sí
JAK2V617F			Sí

Bajo riesgo: < 2 puntos

Riesgo intermedio: 2 puntos

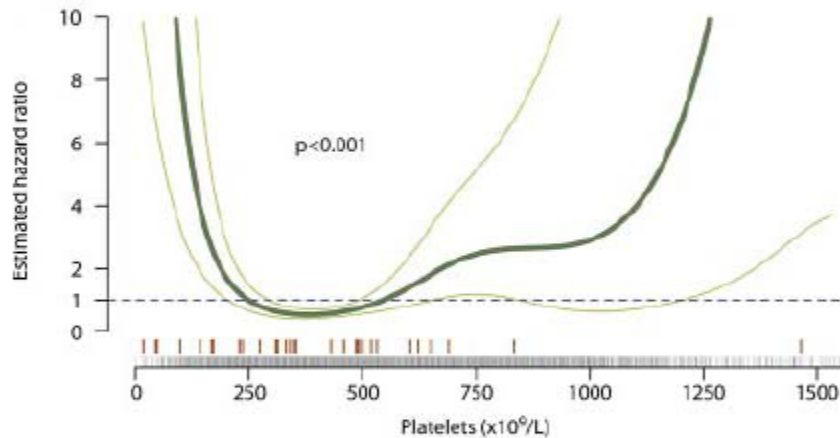
Alto riesgo: > 2 puntos



Barbui *et al*; Blood 2012;120:5128

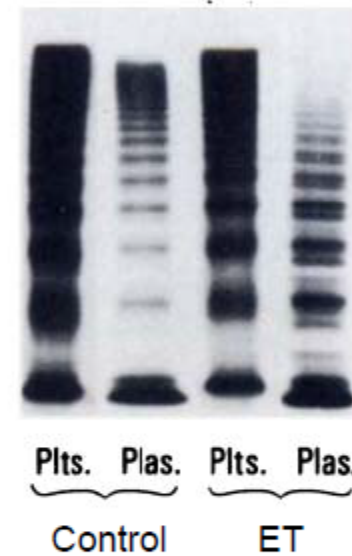
RISK OF BLEEDING IN ET

Risk of major bleeding in the PT-1 cohort according to platelet counts during follow-up



Campbell et al Blood 2012

Electrophoresis of plasma and platelet vWF



Budde et al Blood 1984

Extreme thrombocytosis has been associated with an increased risk of bleeding

Tratamiento de la Mielofibrosis:
Transición desde lo convencional a
los inhibidores de Jak 1/2.
Impacto de Ruxolitinib, eficacia y
seguridad

Treatment Options for Myelofibrosis



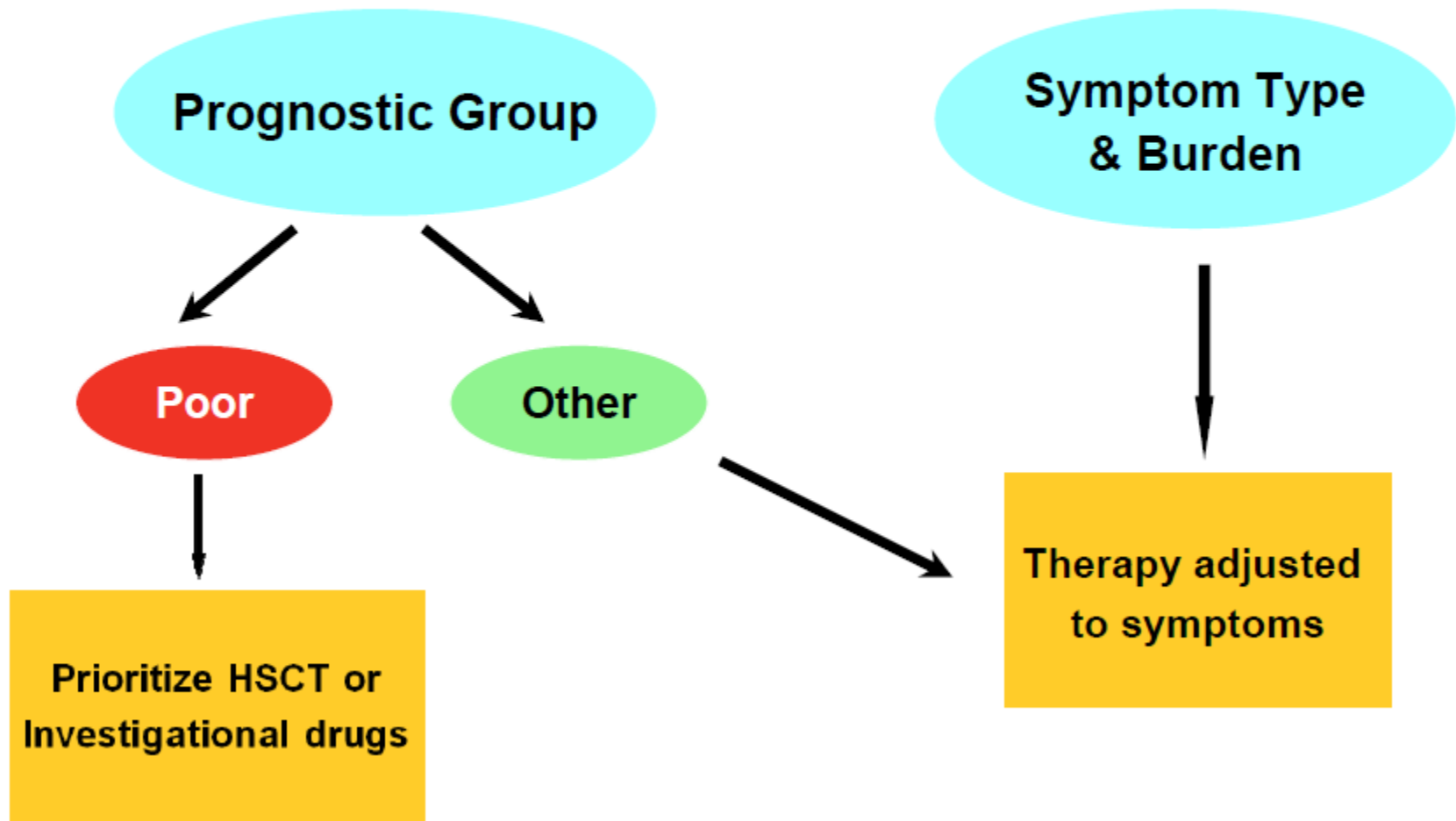
Wait & see

**Conventional
treatment**

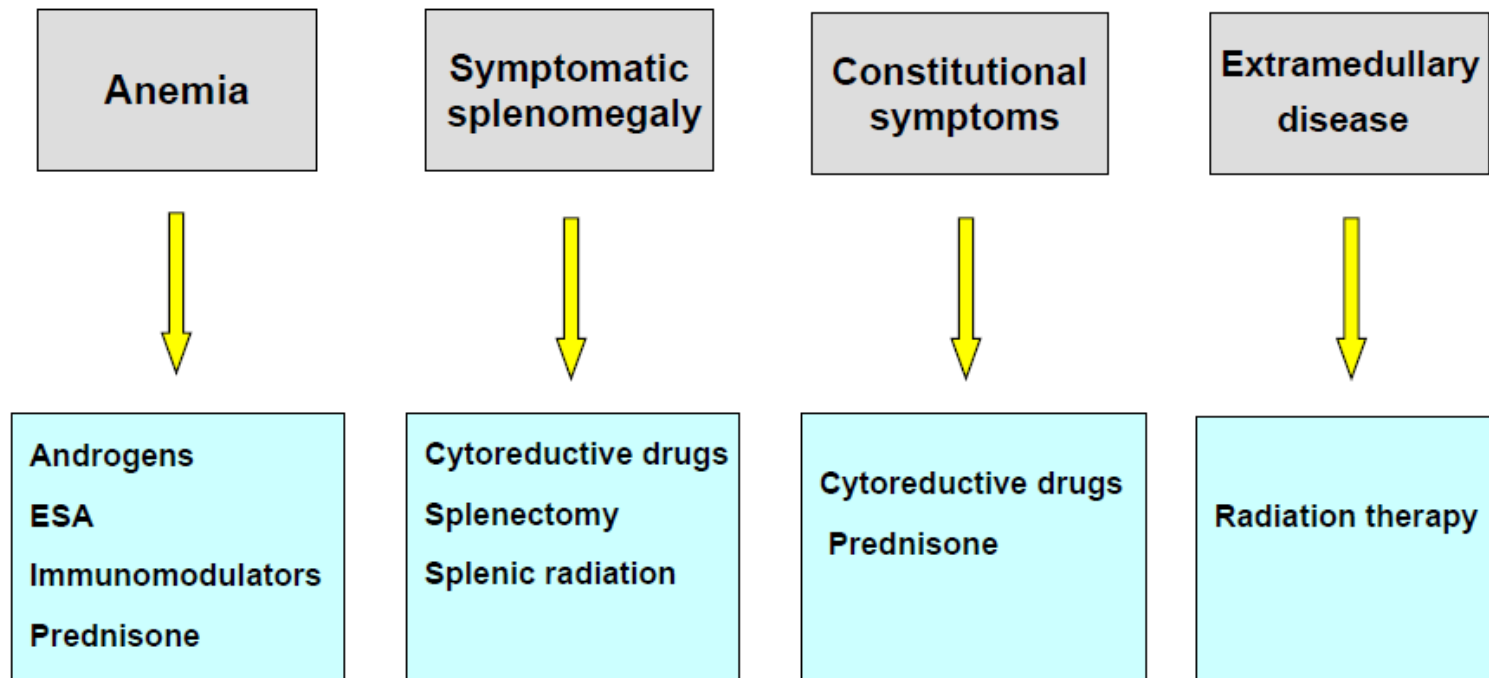
**Investigational
drugs**

Allo-HSCT

Factors Driving Therapy Choice in Myelofibrosis



Clinically-adjusted Conventional Treatment of Myelofibrosis



Splenectomy in Myelofibrosis

Associated risks

- 40% morbidity
- 10% mortality
- Liver failure development
- Higher acute transformation rate?

Contraindication

Thrombocytosis

Main indications

- Symptomatic splenomegaly unresponsive to treatment
- Severe refractory anemia
- Unresponsive constitutional symptoms
- Uncontrollable hemolysis
- Portal hypertension

Splenic Radiation in Myelofibrosis

Indications

- **Symptomatic splenomegaly in poor candidates to surgery**
- Severe pain from splenic infarction

Dose & Results

- Dose: variable, median 2.8 Gy, fractionated
- **Effect duration: median 6 mos.**

Contraindication

As preparation for splenectomy

Associated Risk

Long-lasting cytopenias (43%)

Allogeneic HSCT for Myelofibrosis

	Median ages	TRM (1 y)	OS (5 y)
Myeloablative (n= 504)	40-49	20-42%	31-61%
RIC (n= 263)	50-56	0-37%	50-67%

Adapted from Alchalby *et al.*, CHMR 2010; 5:53-61

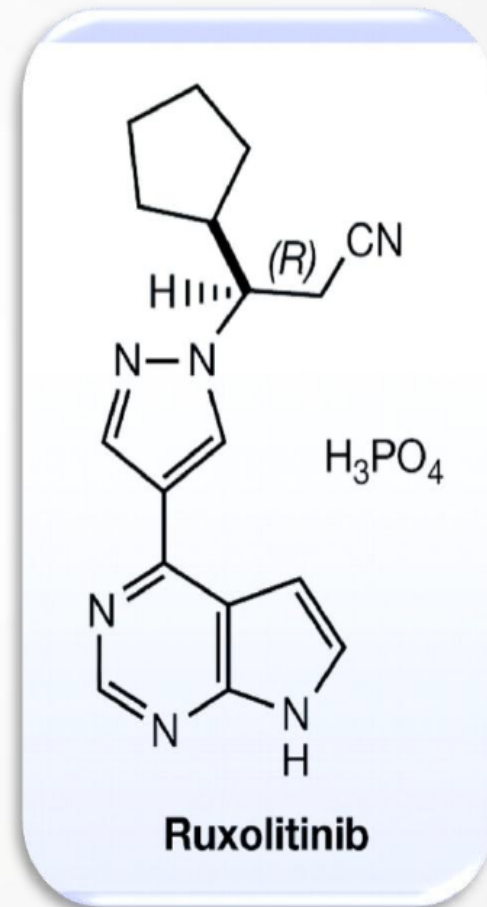
RUXOLITINIB

📖 Primer inhibidor de JAK aprobado por FDA para MF y PV.

📖 Inhibidor potente de JAK1 y JAK2.

📖 Excelente biodisponibilidad oral, vida media de 3-5 horas.

📖 Información disponible de estudios fase III.



RUXOLITINIB. PHASE III STUDIES



COMFORT I

- ❖ Sep 2009-Abril 2010
- ❖ N= 309
- ❖ Aleatorización: 1:1, Doble ciego
- ❖ Ruxolitinib vs Placebo
- ❖ IPSS Int-2/Alto
- ❖ 41.9% Reducción esplénica 24 sem
- ❖ Beneficio en la supervivencia

COMFORT II

- ❖ Cohorte hasta Abril 2011
- ❖ N= 219
- ❖ Aleatorización: 2:1
- ❖ Ruxolitinib vs Mejor tratamiento disponible
- ❖ IPSS Int-2/Alto
- ❖ 28.5% Reducción esplénica 48 sem
- ❖ Beneficio en la supervivencia

COMFORT-I

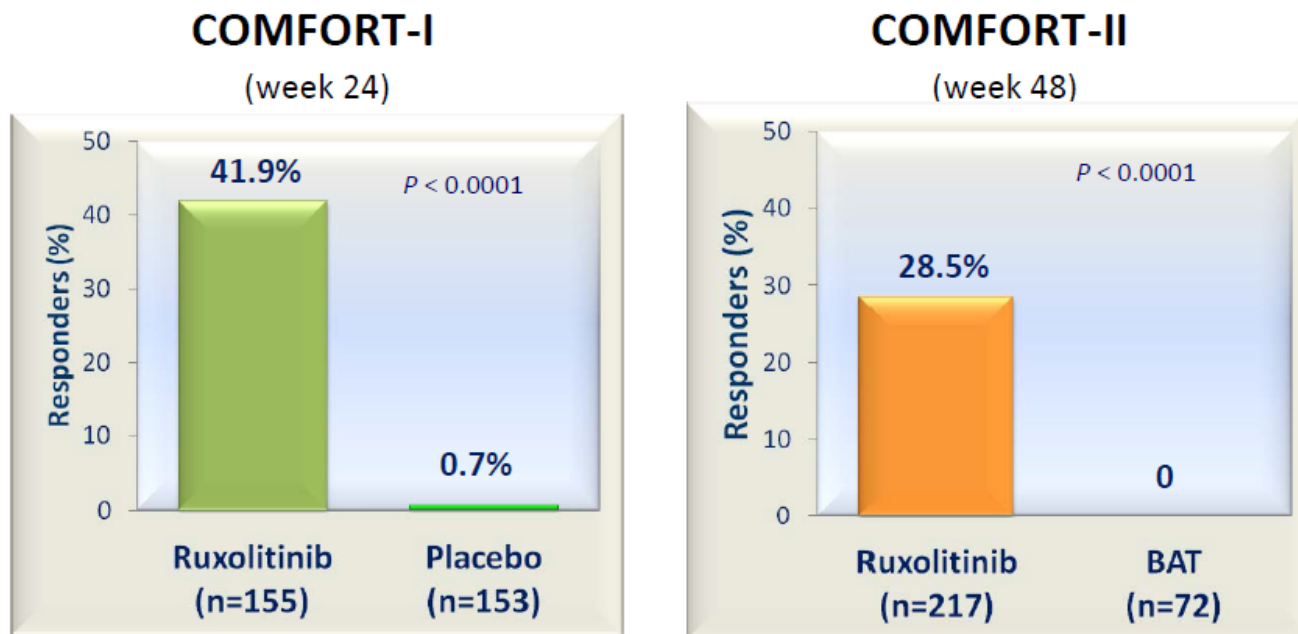
Parámetro	COMFORT-I	
Objetivo primario	Reducción en la esplenomegalia de $\geq 35\%$ por IRM o TAC a las 24 semanas (41.9% vs 0.7%, $p < 0.001$)	De estos, 67% mantuvieron la respuesta esplénica por al menos 48 semanas.

Parámetro	COMFORT-I
Control de síntomas (TSS)	Reducción de $\geq 50\%$ en la TSS a la semana 24 (45.9% vs 5.3%, $p < 0.001$)

COMFORT-II

Parámetro	COMFORT-II
Objetivo primario	Reducción en la esplenomegalia de $\geq 35\%$ por IRM o TAC a las 48 semanas (28.5% vs 0%, $p < 0.001$)

Ruxolitinib and Spleen Volume Reduction



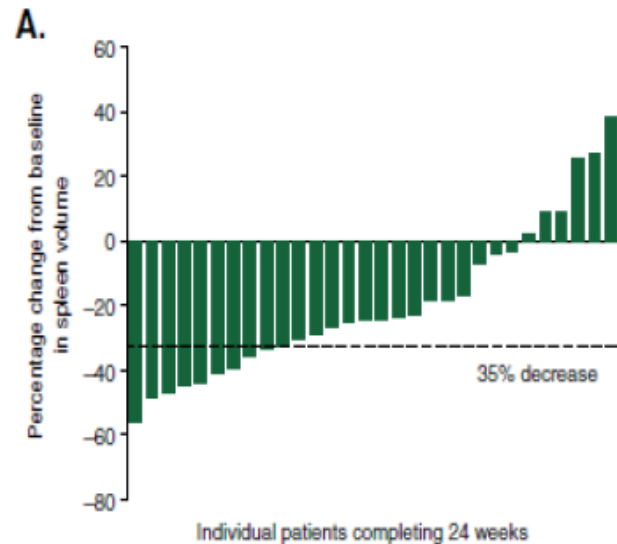
- **Response: $\geq 35\%$ reduction of spleen volume by MRI/CT**
- It occurred at a median of 12 weeks and was maintained at 48 wks in 80% of responders
- A spleen volume reduction by MRI of 35%: \cong **52% reduction in spleen length by palpation**

Verstovsek S *et al.*, NEJM 2012; 366:799-07

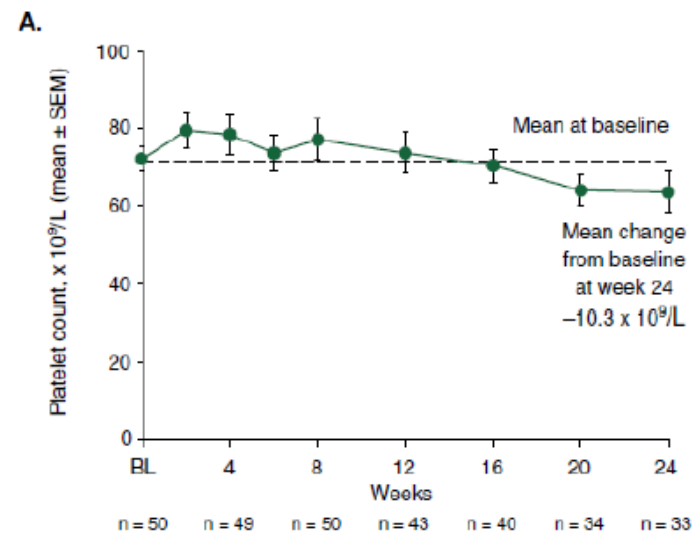
Harrison C *et al.*, NEJM 2012; 366:787-98

Ruxolitinib in MF Patients with Platelet Counts 50-100 x 10⁹/L

Effect on Spleen

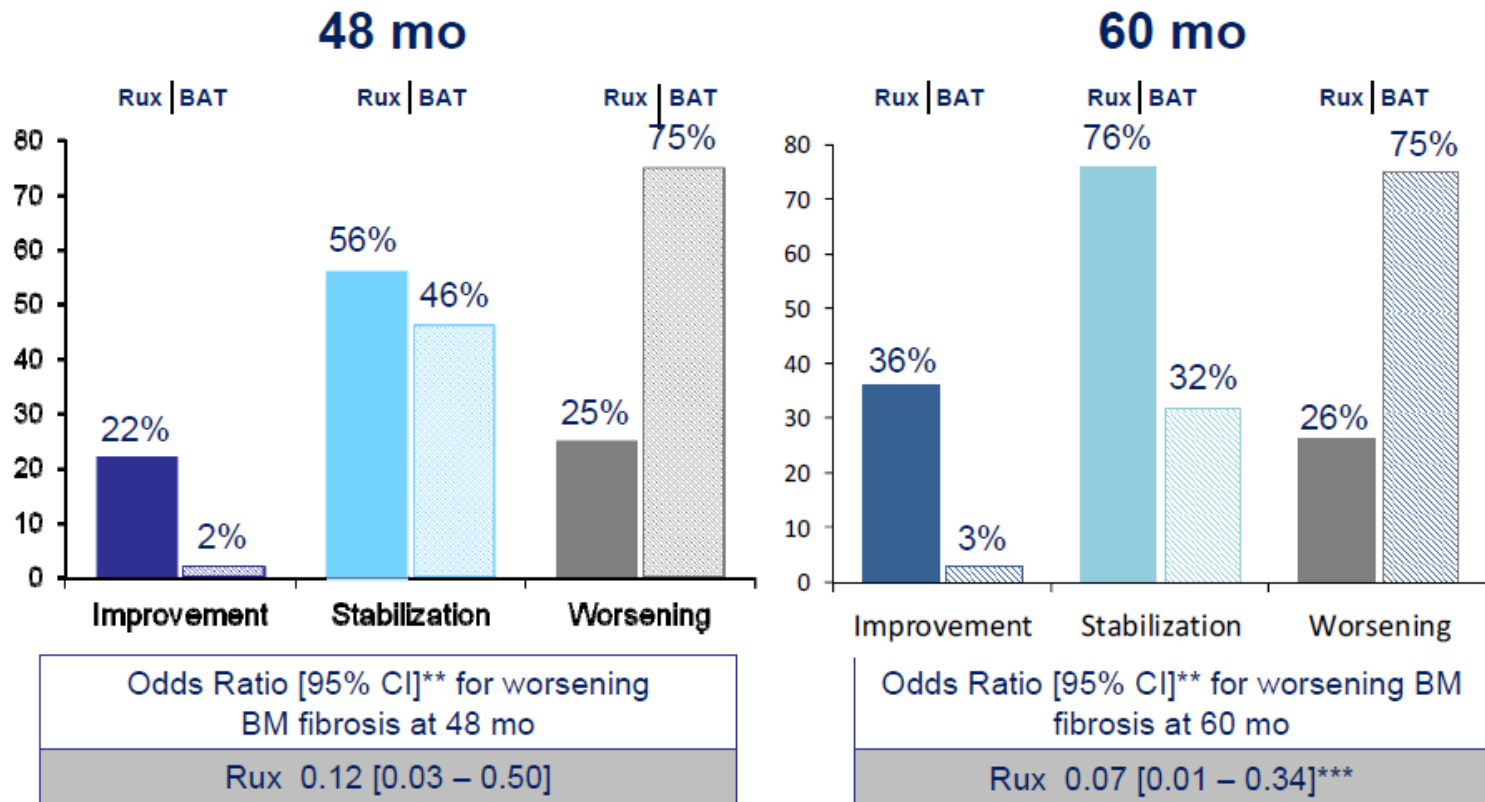


Effect on Platelet Counts



Change in BM Fibrosis Over Time with Ruxolitinib and BAT*

SC2

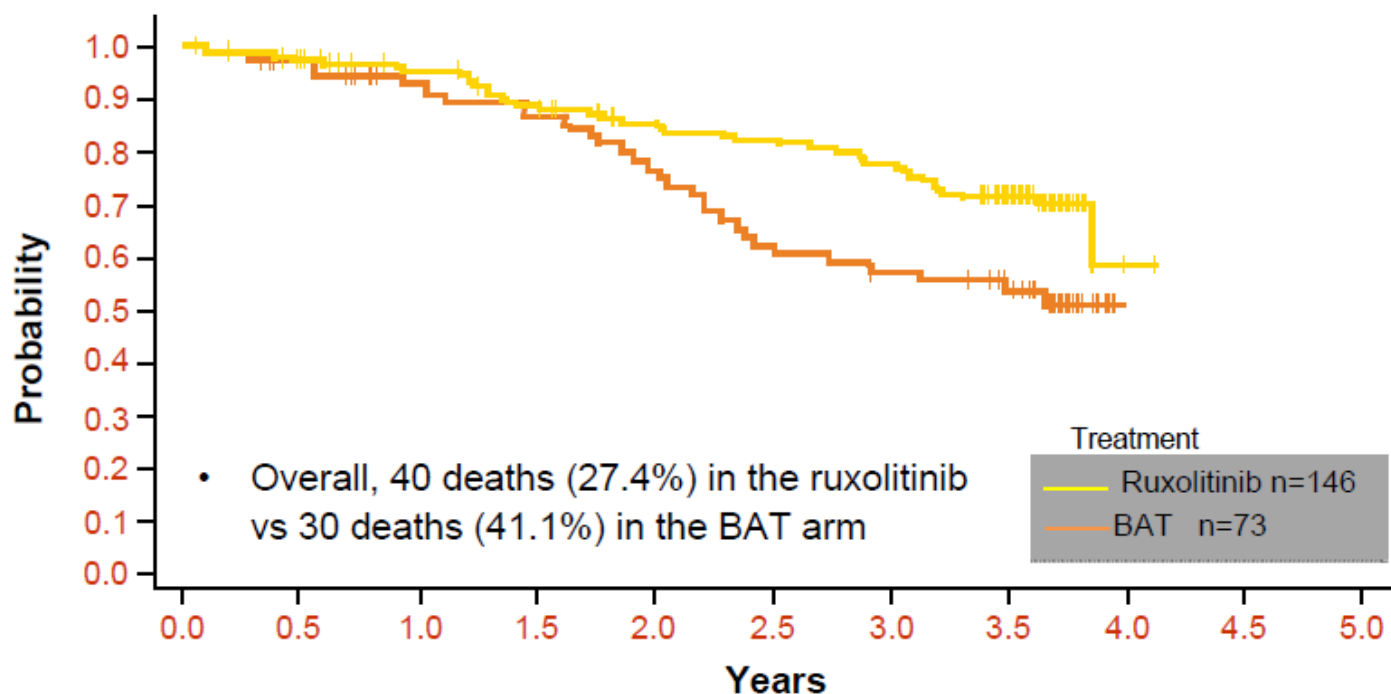


* Compilation of data - not a formal comparison

** Logistic regression method

*** Last available grade from 54, 60, or 66 mo

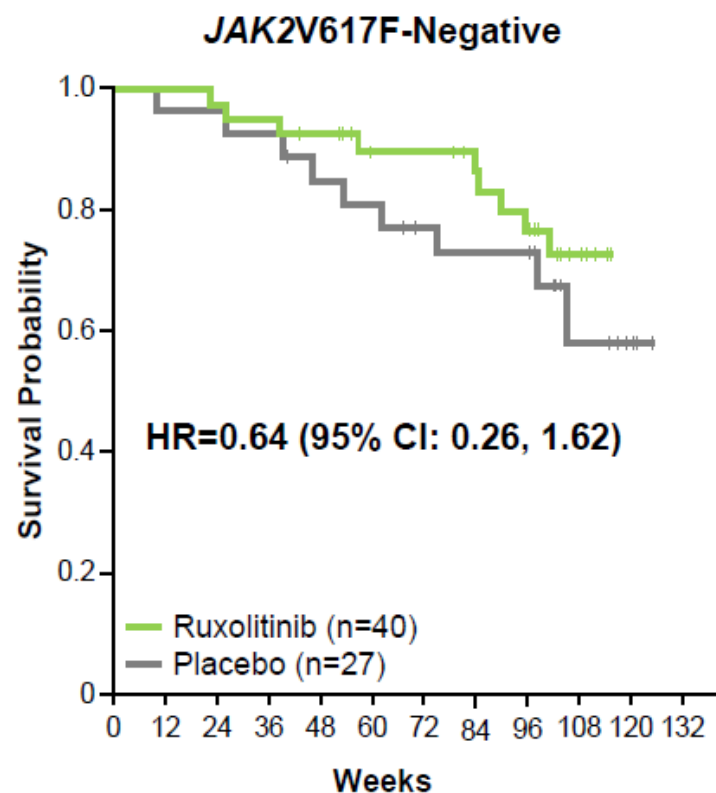
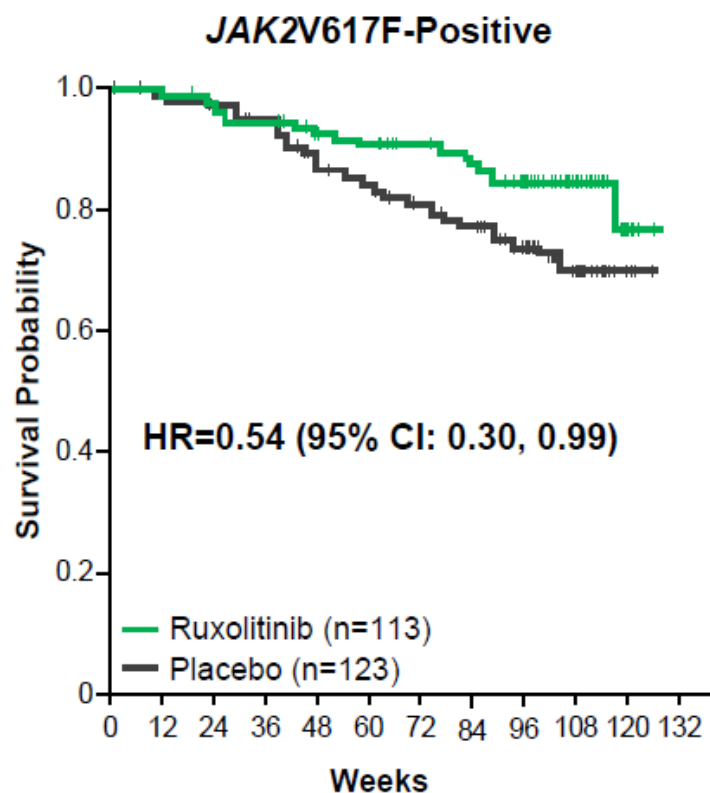
COMFORT-II (Ruxolitinib vs BAT): Overall Survival at 3.5 years



- The estimated survival probability at 3.5 years was 0.71 (95% CI, 0.63-0.78) in the ruxolitinib arm and 0.54 (95% CI, 0.41-0.65) in the BAT arm
- There was a significant overall reduction in risk of death of 42% with ruxolitinib treatment compared with BAT (HR = 0.58; 95% CI, 0.36-0.93; log-rank test $P = .022$)

COMFORT-I

Overall Survival by *JAK2V617F* Mutation Status



Conclusión

COMFORT-I / COMFORT-II

El tratamiento con ruxolitinib en pacientes con MF de riesgo intermedio o alto, produjo una mejoría significativa en la esplenomegalia y los síntomas asociados a MF con un perfil de toxicidad aceptable.

Beneficios independientes del subtipo de MF, el estado mutacional de JAK2, el tamaño inicial del bazo, nivel inicial de Hb.

Ruxolitinib Dose Optimization

Platelet Count	Starting Dose
Greater than 200,000/mm ³	20 mg orally twice daily (BID)
100,000/mm ³ to 200,000/mm ³	15 mg orally BID
50,000/mm ³ to 100,000/mm ³	Maximum: 5 mg orally BID*
With concomitant CYP3A4 inhibitors, severe renal impairment, or any hepatic impairment	Reduce BID starting dose by 50%

Dose reduction or interruption during therapy	
Platelet count below 100,000/mm ³	Consider dose reduction to avoid dose interruption due to thrombocytopenia
Platelet count below 50,000/mm ³ or absolute neutrophil count below 500/mm ³	Interrupt treatment. When blood cell counts rise above these levels, restart treatment at 5mg orally BID. Gradually increase dose as blood cell counts recover
Dose increase during therapy	
If efficacy is considered insufficient and platelet and neutrophil counts are adequate	Consider increasing dose by 5mg orally BID at 2-weeks intervals*

*Titrate cautiously.

JAKAVI, Summary of Product Characteristics.

Open questions on Ruxolitinib for MF Treatment

- Different dosing?
- Thrombocytopenic patients
- Role in SCT
- Treatment at earlier stages?
- Combinations

Manejo actual de la Policitemia Vera

Current Management of PV

- **Treatment objective**
 - Controlling symptoms
 - Preventing thrombotic and bleeding complications without increasing the risk of transformation
 - Reduce or eliminate *JAK2* mutant clone
 - Cure the disease
- **General basis of treatment**
 - Reduction of red cell mass with phlebotomies
 - Low-dose aspirin
 - Strict correction of cardiovascular risk factors
 - Cytoreductive therapy with hydroxyurea for:
 - Age > 60 years
 - History of thrombosis
 - Poor tolerance of phlebotomy
 - Severe disease-related symptoms
 - Symptomatic or progressive splenomegaly
 - Progressive leukocytosis
 - Platelet count > 1500 x10⁹/L

Treatment options and targets

- Phlebotomy
- Hydroxyurea
- Busulfan
- Interferon
- JAK2 inhibitors
- Histone deacetylases Inhibitors

ELN definition of clinicohematologic response in PV

Response criteria (2009)

1. Hct < 45% without phlebotomy
2. Platelet count < $400 \times 10^9/L$
3. WBC count < $10 \times 10^9/L$
4. Normal spleen size on imaging
5. No disease-related symptoms

COMPLETE RESPONSE

All criteria are achieved

PARTIAL RESPONSE

Hct < 0.45 L/L without phlebotomy or
Response in ≥ 3 criteria

Response criteria (2013)

- A. No disease-related symptoms and normal spleen
- B. Hct < 45% without phlebotomy, platelet count < $400 \times 10^9/L$ and WBC count < $10 \times 10^9/L$
- C. No disease progression, no vascular complications
- D. Normal bone marrow

COMPLETE RESPONSE

All criteria are achieved

PARTIAL RESPONSE

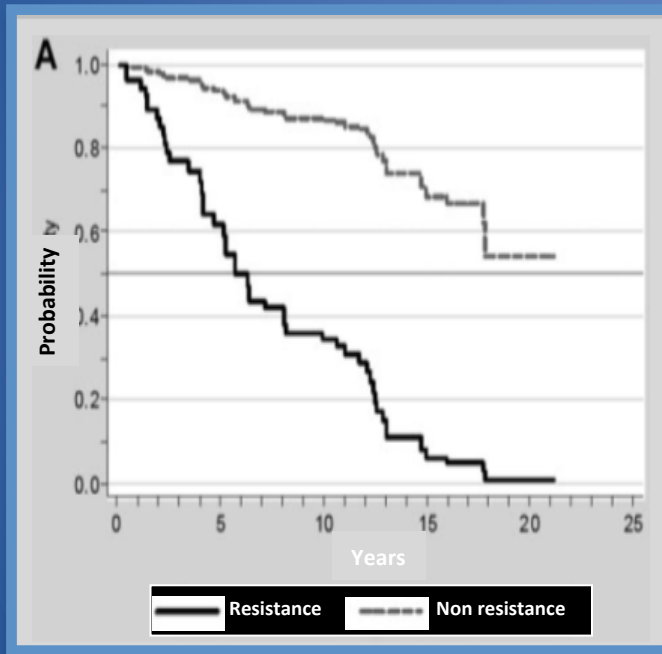
A + B + C criteria

HYDROXIUREA IN PV

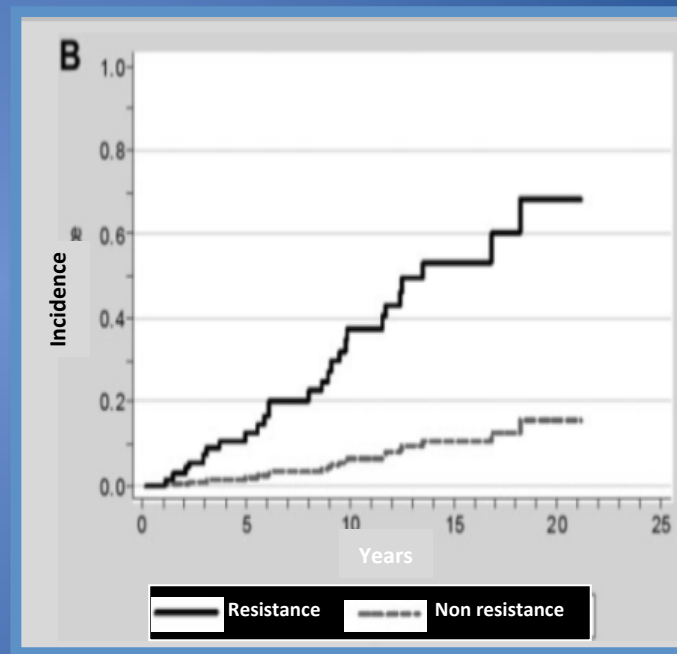
- Starting dose: 15 mg/kg/day (1000 mg/day)
- Objective:
 - Hct < 0,45 L/L
 - Platelet count < 400x10⁹/L
 - No PV-related symptoms
- PVSG08: hydroxyurea (n=52) versus phlebotomies (historical series)
 - No differences in survival
 - Lower incidence of thrombosis with Hu (6.6% versus 14% at 2 y.)
 - Higher rate of acute leukemia with Hu (5,4% versus 1,5%)
- Leukemogenic effect not clearly demonstrated

The Implication of resistance to Hydroxyurea in PV

Survival



Risk of disease evolution (MF & AML)



Resistance to HU was associated with a 5.6 fold increase in the risk of death

ELN CRITERIA FOR RESISTANCE/INTOLERANCE TO HYDROXIUREA IN PV

1. Need for phlebotomy to keep hematocrit < 0.45 L/L after 3 months of at least 2 g/day of HU, OR
2. Uncontrolled myeloproliferation (platelet count $> 400 \times 10^9/L$ and WBC count $> 10 \times 10^9/L$ after 3 months of at least 2 g/day of HU), OR
3. Failure to reduce massive* splenomegaly by more than 50% or as measured by palpation after 3 months of at least 2 g/day of HU, OR
4. **Absolute neutrophil count $< 1 \times 10^9/L$ or Hb level < 100 g/L or platelet count $< 100 \times 10^9/L$ at the lowest dose of HU required to achieve a CR or a PR, OR**
5. Leg ulcers or other unacceptable HU-related non-hematological toxicities at any HU dose.

* Extending > 10 cm from costal margin

Advantages of IFN- α in PV

- **Marked reduction of the PV clone**
- **Clinical remissions without cytoreductive therapy**
- **Reduction of vascular events**
- **Change in the disease natural history (evolution to MF, AML, MDS)?**
 - Clinicohematological CR
 - Molecular CR
 - Histopathological CR

Ruxolitinib en PV

A Phase 2 Study of Ruxolitinib, an Oral JAK1 and JAK2 Inhibitor, in Patients With Advanced Polycythemia Vera Who Are Refractory or Intolerant to Hydroxyurea

Srdan Verstovsek, MD, PhD¹; Francesco Passamonti, MD²; Alessandro Rambaldi, MD³; Giovanni Barosi, MD⁴; Peter J. Rosen, MD⁵; Elisa Rumi, MD⁴; Elisabetta Gattoni, MD⁶; Lisa Pieri, MD⁷; Paola Guglielmelli, PhD⁷; Chiara Elena, MD⁴; Shui He, PhD⁸; Nancy Contel, DVM⁸; Bijoyesh Mookerjee, MD⁹; Victor Sandor, MD⁸; Mario Cazzola, MD^{4,9}; Hagop M. Kantarjian, MD¹; Tiziano Barbui, MD³; and Alessandro M. Vannucchi, MD⁷

- **OBJETIVO:** Conocer la eficacia y seguridad a largo plazo de Ruxolitinib en pacientes con PV resistentes o intolerantes a HU.
- **DISEÑO:** Estudio fase 2, N= 34 pacientes con PV resistentes o intolerantes a HU.
- **RESULTADOS:** Con una mediana de seguimiento de 35 meses, 97% de los pacientes obtuvo una reducción del Hto a <45% sin flebotomía a la semana 24. De los pacientes con esplenomegalia, 63% redujeron el tamaño (no palpable) a la semana 144. Al mes de tratamiento hubo mejoría de la sintomatología (prurito, diaforesis, dolor óseo). Trombocitopenia y anemia grado 3 ocurrió en 9% de los pacientes.
- **CONCLUSIÓN:** Ruxolitinib fue bien tolerado y produjo respuestas rápidas y duraderas en pacientes con PV avanzada intolerantes o resistentes a HU.

ORIGINAL ARTICLE

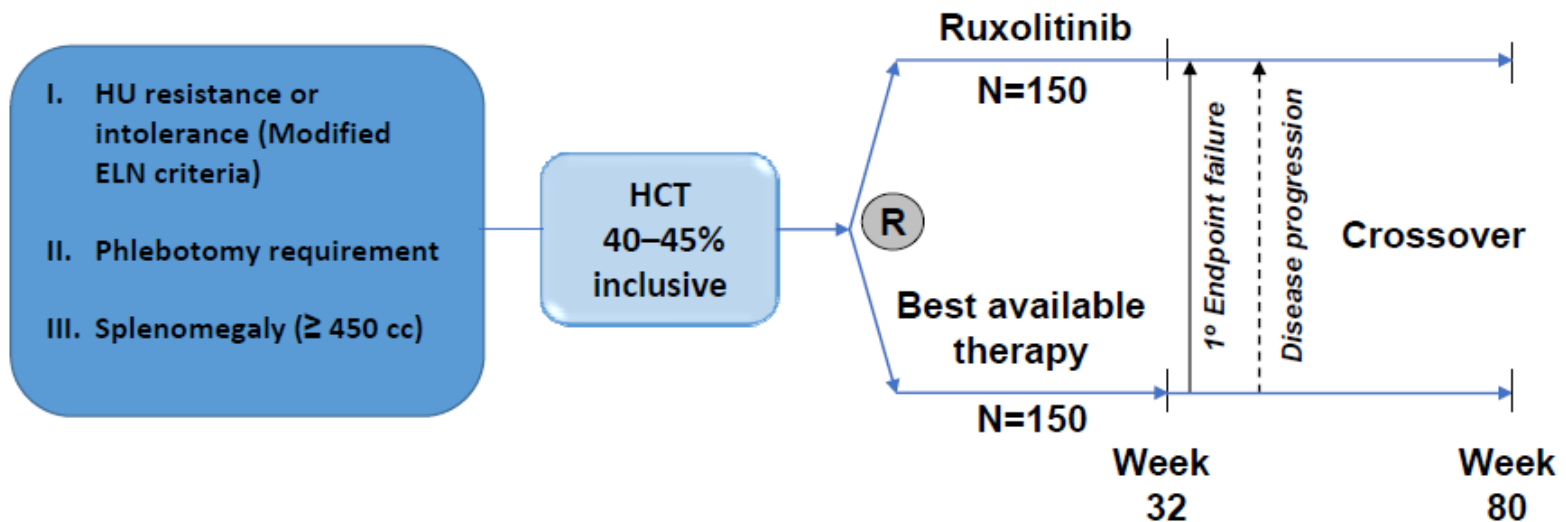
Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjian, M.D., Ph.D.,
Martin Griesshammer, M.D., Tamas Masszi, M.D., Ph.D., Simon Durrant, M.D.,
Francesco Passamonti, M.D., Claire N. Harrison, D.M., Fabrizio Pane, M.D.,
Pierre Zachee, M.D., Ph.D., Ruben Mesa, M.D., Shui He, Ph.D.,
Mark M. Jones, M.D., William Garrett, M.B.A., Jingjin Li, Ph.D.,
Ulrich Pirron, Ph.D., Dany Habr, M.D., and Srdan Verstovsek, M.D., Ph.D.

▣ **OBJETIVO:** Evaluar la eficacia y seguridad de Ruxolitinib vs tratamiento estándar en pacientes intolerantes o resistentes a HU.

▣ **MÉTODOS:** Estudio Fase 3, aleatorizado 1:1, de etiqueta abierta, N= 22. Desenlace: control de Hto y reducción de al menos 35% del tamaño del bazo a la semana 32.

Phase III trial of Ruxolitinib in PV: The RESPONSE study



- Special protocol assessment agreement reached with FDA
- Primary composite endpoint: hematocrit control in the absence of phlebotomy and $\geq 35\%$ reduction in spleen volume at Week 32
- Secondary endpoints: Complete hematologic remission at Week 32; % of subjects who maintain primary endpoint response for ≥ 48 weeks
- NCT01243944; www.responsetrial.com

Treatment modalities in Response Trial

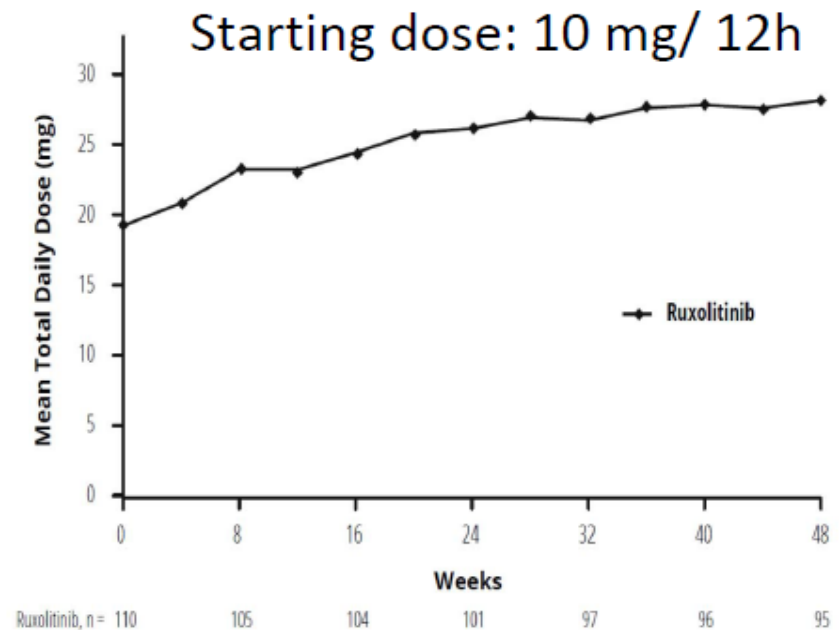
Standard therapy n=112

- Hydroxyurea: 59%
- Interferon: 12%
- Anagrelide: 7%
- Immunomodulators: 4.5%
- Pipobroman: 2%
- No medication: 15%

Discontinuation

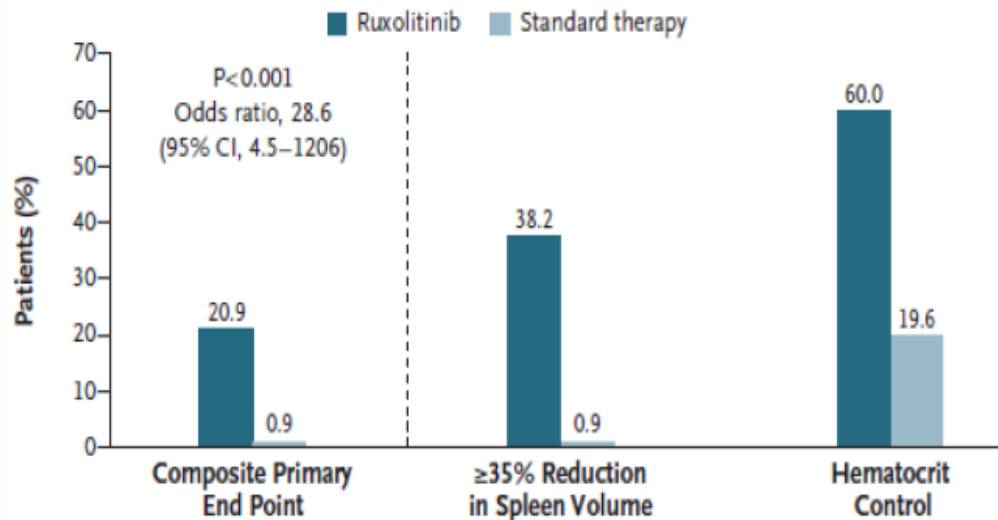
- Standard therapy: 96%
- Ruxolitinib: 15%

Ruxolitinib n=110

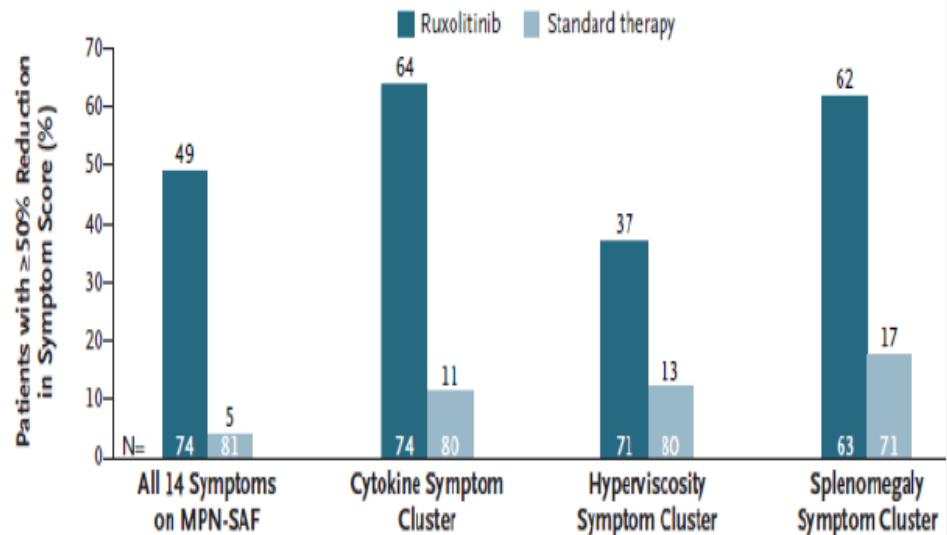


Vannucchi et al, NEJM 2015

Ruxolitinib en PV



CONCLUSIÓN: En pacientes intolerantes o resistentes a HU, ruxolitinib fue superior a la terapia convencional en controlar el Hto, reducir el bazo, y mejorar los síntomas asociados a PV.



- GRACIAS