

Myelofibrosis in 2026

Where do we stand and what lies ahead

Sao Paulo. May 2026

Santiago Osorio

Hospital Gregorio marañón. Madrid. Spain



Conflicts of Interest

Dr. Santiago Osorio has received:

Remuneration for participation in educational activities

Travel grants

Research project grants

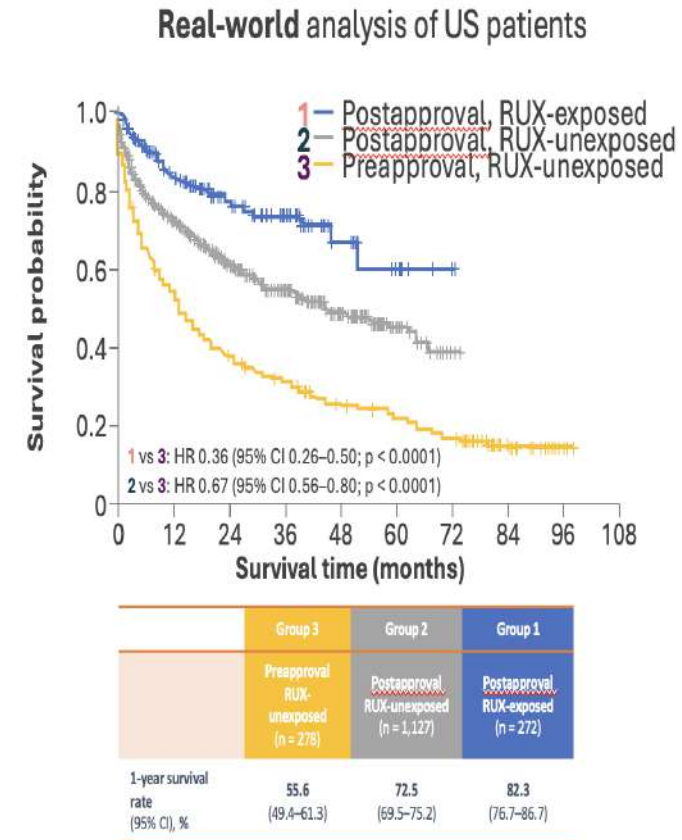
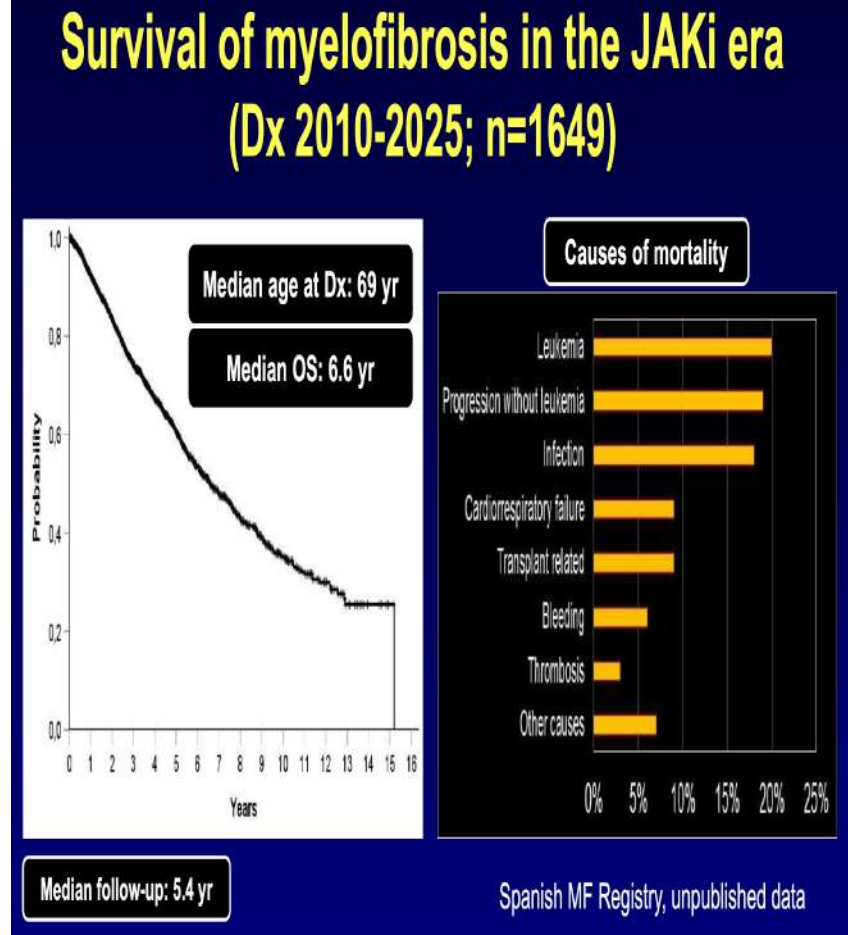
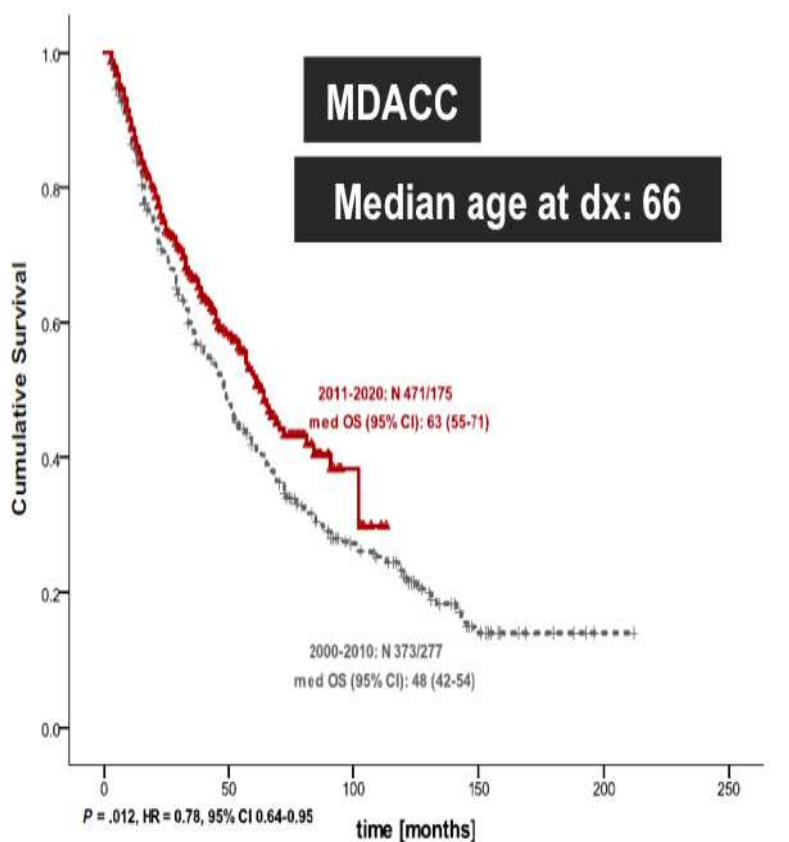
Honoraria for participation in advisory boards

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



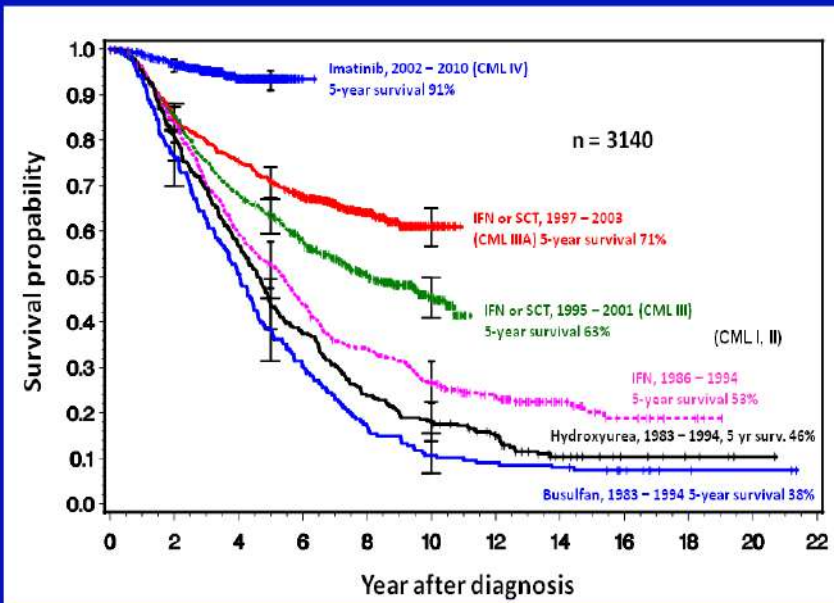


Myelofibrosis: Where do we stand?



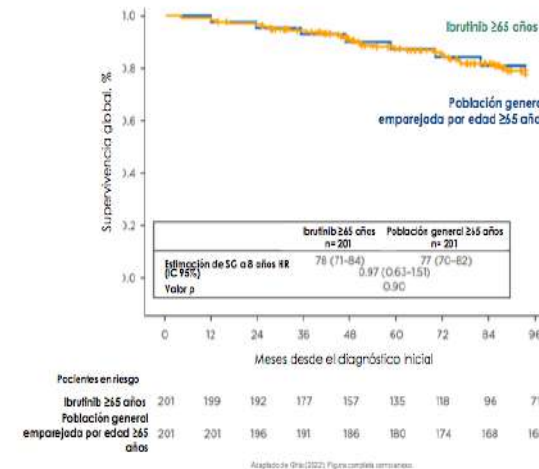
What Lies ahead?

Improvement of survival of CML 1983 – 2010



German CML Study Group

Supervivencia tto iBTK 1ºL vs población general

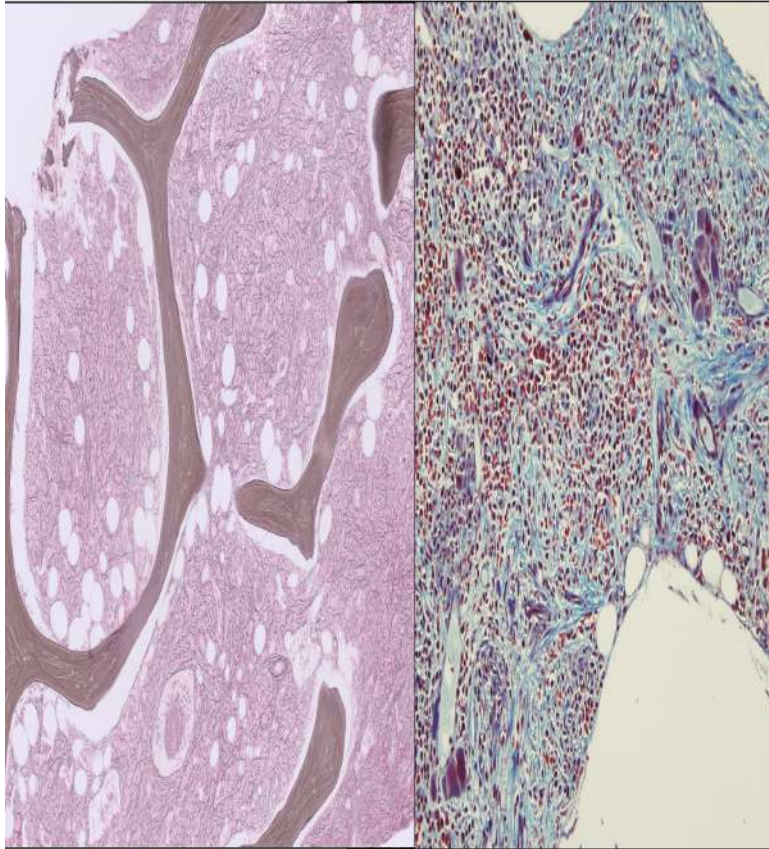


- La **supervivencia global** de los **pacientes ≥65 años** con LLC tratados con ibrutinib fue **similar** a la **supervivencia global** de la **población general ≥65 años**

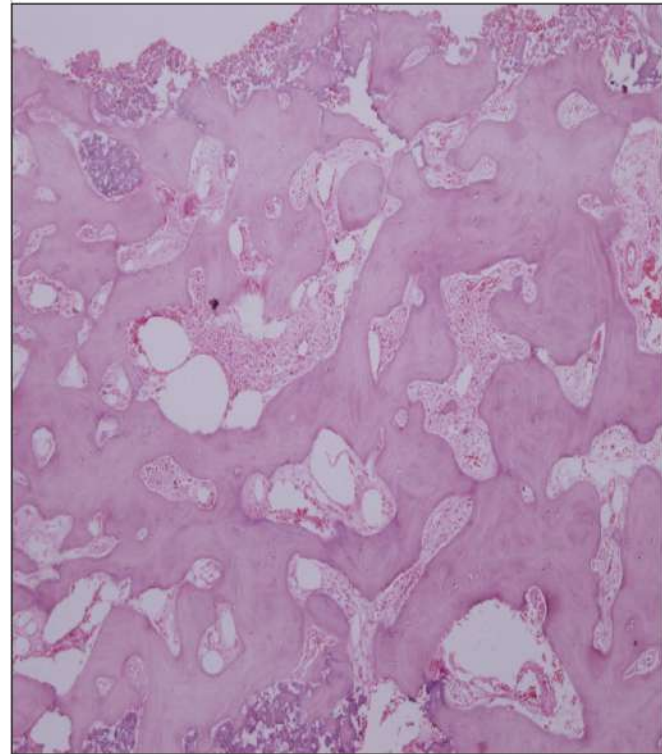
5 years, 10 years? But we are going to be there

What lies ahead

PMF, fibrotic stage



PMF, osteomyelosclerosis



Bone Marrow Transplantation (2000) 26, 437-441
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www.blackwell-science.com

Case report

Complete remission of idiopathic myelofibrosis following donor lymphocyte infusion after failure of allogeneic transplantation: demonstration of a graft-versus-myelofibrosis effect

F Cervantes, M Rovira, A Urbano-Ispizua, M Rozman, E Carreras and E Montserrat



We need to make this "miracle" without trasplant

It all began just 20 years ago

- James C, et al. Nature. 2005;434:1144-8.
- Levine RL, et al. Cancer Cell. 2005;7:387-97.
- Kralovics R, et al. N Engl J Med. 2005;352:1779-90.

JAK2 V617F

- Scott LM, et al. N Engl J Med. 2007;356:459-68.

JAK2 ex12

2006

2013

2005

2007

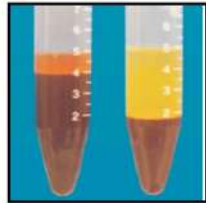
MPL W515

- Pikman Y, et al. PLoS Med. 2006;3:e270.

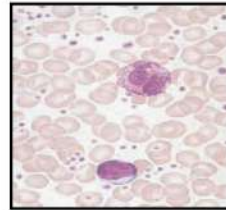
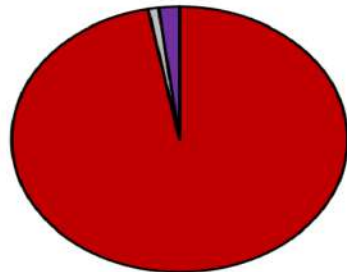
CALR ex9

- Nangalia J, et al. N Engl J Med. 2013;369:2391-405.
- Klampfl T, et al. N Engl J Med. 2013;369:2379-90.

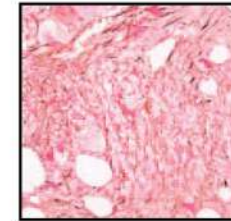
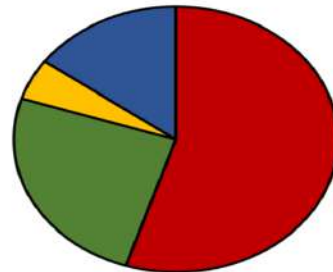
Drivers mutations in MPN



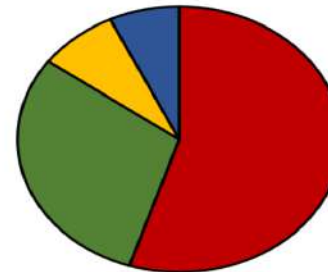
**Policitemia
Vera**



**Trombocitemia
Esencial**



**Mielofibrosis
Primaria**



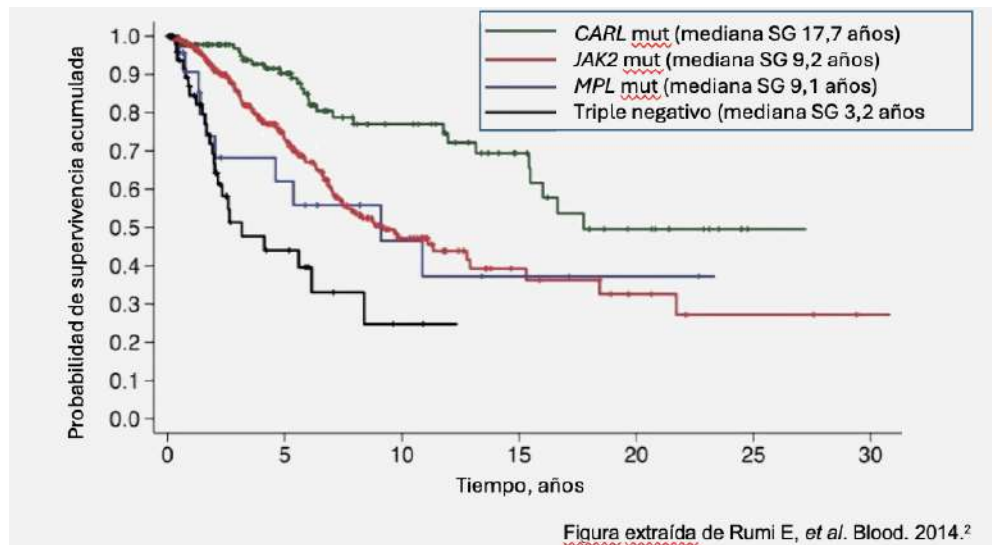
Drivers impact prognosis but there is more than the drivers

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

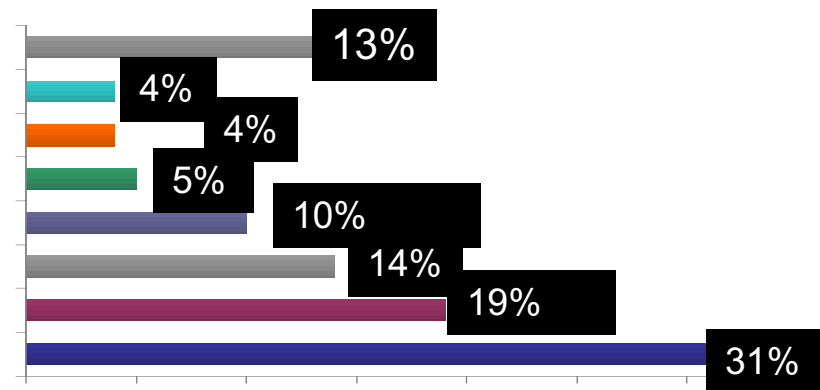
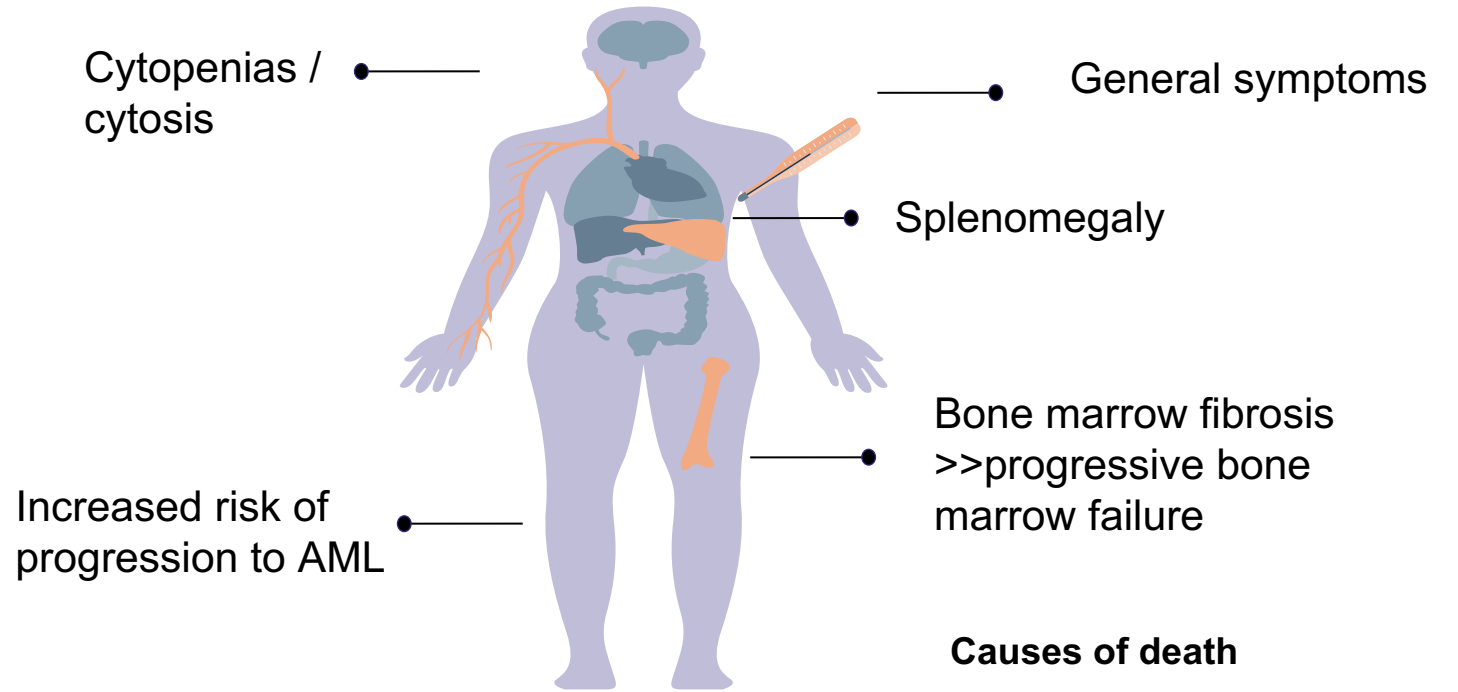
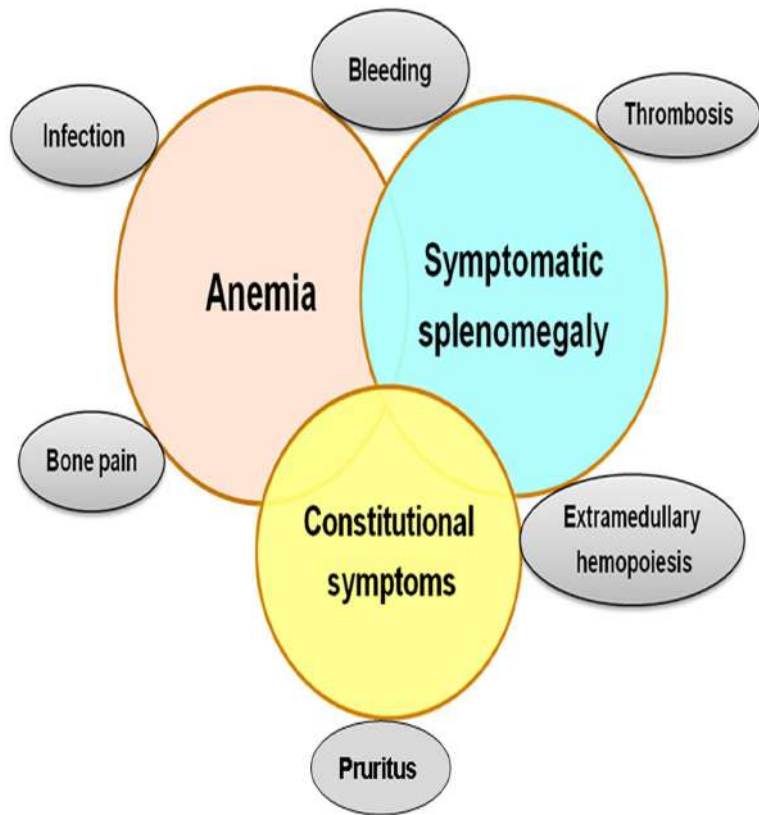


Rumi E, et al. *Blood*. 2017⁵ y Rumi E, et al. *Blood*. 2014⁶

	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: manifestations and complications



Prognostic models for OS in MF

	IPSS	DIPSS	DIPSS+	AIPSS*	MIPSS70	MIPSS70+ v2.0	MYSEC PM	AIPSS-M*	MPN risk calculator																																								
MF type	PMF									All	All																																						
Time-point	Dx									Dx	Dx																																						
Prognostic factors	Clinical	<table border="1"> <thead> <tr> <th>Grupo de riesgo</th> <th>Mediana de supervivencia, años</th> </tr> </thead> <tbody> <tr> <td>Bajo (0 puntos)</td> <td>11,3</td> </tr> <tr> <td>Intermedio 1 (1 punto)</td> <td>7,9</td> </tr> <tr> <td>Intermedio 2 (2 puntos)</td> <td>4,0</td> </tr> <tr> <td>Alto (≥ 3 puntos)</td> <td>2,3</td> </tr> </tbody> </table>		Grupo de riesgo	Mediana de supervivencia, años	Bajo (0 puntos)	11,3	Intermedio 1 (1 punto)	7,9	Intermedio 2 (2 puntos)	4,0	Alto (≥ 3 puntos)	2,3	<table border="1"> <thead> <tr> <th>Grupo de riesgo</th> <th>Mediana de supervivencia, años</th> </tr> </thead> <tbody> <tr> <td>Bajo (0 puntos)</td> <td>> 20</td> </tr> <tr> <td>Intermedio 1 (1-2 puntos)</td> <td>14,2</td> </tr> <tr> <td>Intermedio 2 (3-4 puntos)</td> <td>4,0</td> </tr> <tr> <td>Alto (5-6 puntos)</td> <td>1,5</td> </tr> </tbody> </table>		Grupo de riesgo	Mediana de supervivencia, años	Bajo (0 puntos)	> 20	Intermedio 1 (1-2 puntos)	14,2	Intermedio 2 (3-4 puntos)	4,0	Alto (5-6 puntos)	1,5	<table border="1"> <thead> <tr> <th>Grupo de riesgo</th> <th>Mediana de supervivencia, años</th> </tr> </thead> <tbody> <tr> <td>Bajo (0 puntos)</td> <td>15</td> </tr> <tr> <td>Intermedio 1 (1 punto)</td> <td>6,6</td> </tr> <tr> <td>Intermedio 2 (2-3 puntos)</td> <td>2,9</td> </tr> <tr> <td>Alto (4-6 puntos)</td> <td>1,3</td> </tr> </tbody> </table>		Grupo de riesgo	Mediana de supervivencia, años	Bajo (0 puntos)	15	Intermedio 1 (1 punto)	6,6	Intermedio 2 (2-3 puntos)	2,9	Alto (4-6 puntos)	1,3	<table border="1"> <thead> <tr> <th>Grupo de riesgo</th> <th>Mediana de supervivencia, años</th> </tr> </thead> <tbody> <tr> <td>Bajo (0-1 puntos)</td> <td>27,7</td> </tr> <tr> <td>Intermedio (2-4 puntos)</td> <td>7,1</td> </tr> <tr> <td>Alto (≥5 puntos)</td> <td>2,3</td> </tr> </tbody> </table>		Grupo de riesgo	Mediana de supervivencia, años	Bajo (0-1 puntos)	27,7	Intermedio (2-4 puntos)	7,1	Alto (≥5 puntos)	2,3	Clinical	Clinical
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Reference	Cervantes 2009	Passamonti 2010	Gangat 2011	Mosquera 2022	Guglielmelli 2017	Tefferi 2018	Passamonti 2017	Mosquera 2024	Grinfeld 2018																																								

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

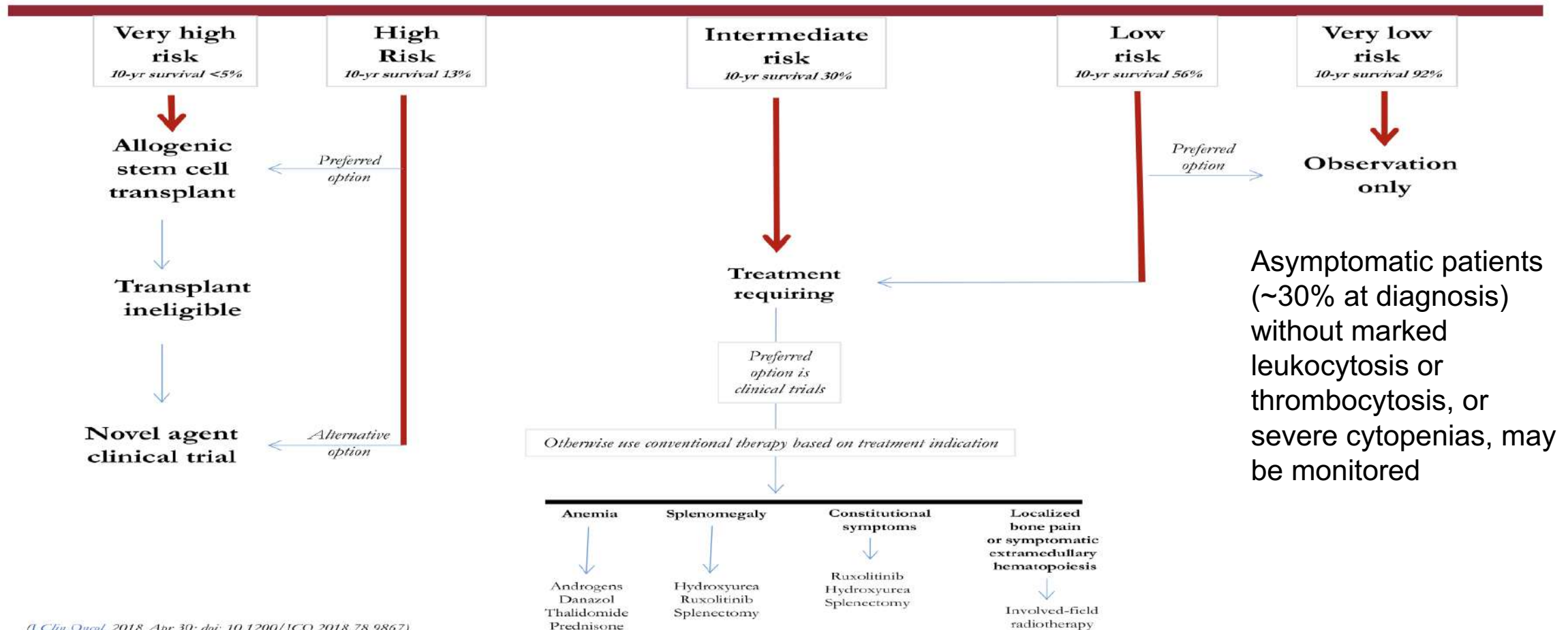
Cortesía Dr Hernández Boluda

General treatment approach

Given the clinical heterogeneity and the lack of an effective treatment for all of them, there is no standard treatment: The choice of treatment should be guided by the clinical manifestations

Treatment algorithm in myelofibrosis

based on risk stratification according to the mutation- and karyotype-enhanced international prognostic scoring system (MIPSS70+ version 2.0); see table 5 for risk variables and risk point allocations





Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: updated recommendations by the EBMT/ELN International Working Group

Nicolaus Kröger, Andrea Bacigalupo, Tiziano Barbui, Markus Ditschkowski, Nico Gagelmann, Martin Griesshammer, Vikas Gupta, Nada Hamad, Claire Harrison, Juan Carlos Hernandez-Boluda, Steffen Koschmieder, Tania Jain, John Mascarenhas, Ruben Mesa, Uday R Popat, Francesco Passamonti, Nicola Polverelli, Alessandro Rambaldi, Marie Robin, Rachel B Salit, Thomas Schroeder, Bart L Scott, Roni Tamari, Ayalew Tefferi, Alessandro M Vannucchi, Donal P McLornan, Giovanni Barosi

Transplant candidates according to the 2024 EBMT/ELN guidelines

Age < 70 years with no severe comorbidities (occasionally >70 years on a case-by-case basis)

Int-2 or high risk according to DIPSS or DIPSS Plus

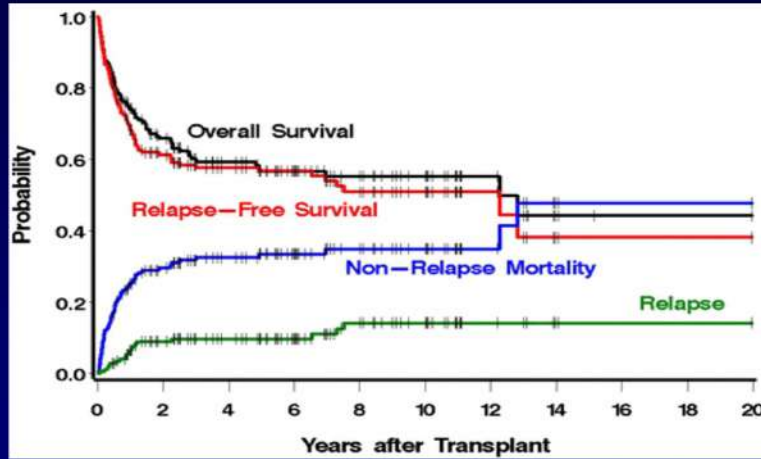
High-risk MIPSS70 or MIPSS 70 v2.0

MYSEC risk category 2 or high in secondary MF

MTSS low or intermediate risk

Intermediate-1 risk: not generally applicable, but should be considered in patients < 65 years of age with: transfusion-dependent anemia, severe thrombocytopenia, or peripheral blastosis > 2%

Allo-HCT is curative for myelofibrosis



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

How many MF patients undergo transplant ?

Spanish Myelofibrosis Registry

Calendar year: 2000-2023

N=1790, 60 centers

Median follow-up: 6.7 yr

Allo-HCT: 168 (9.4%)

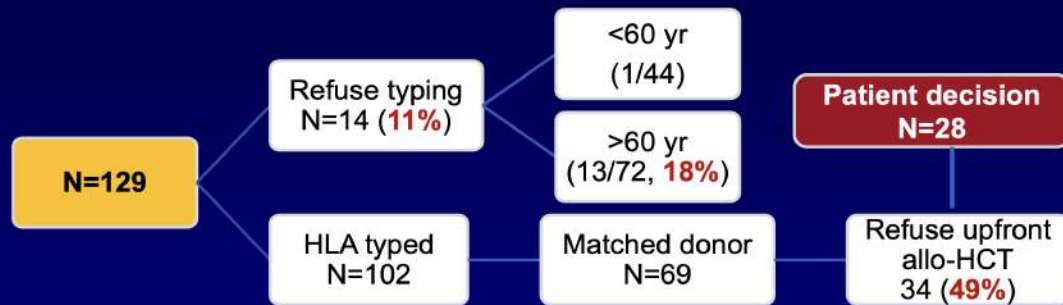
Time from Dx	N*
Year 1	51 (32%)
Year 2	39 (24%)
Year 3	10 (6%)
Later on	61 (38%)

Median time from MF Dx to HCT:
645 days (range: 51-7099)

*Available in 161 cases

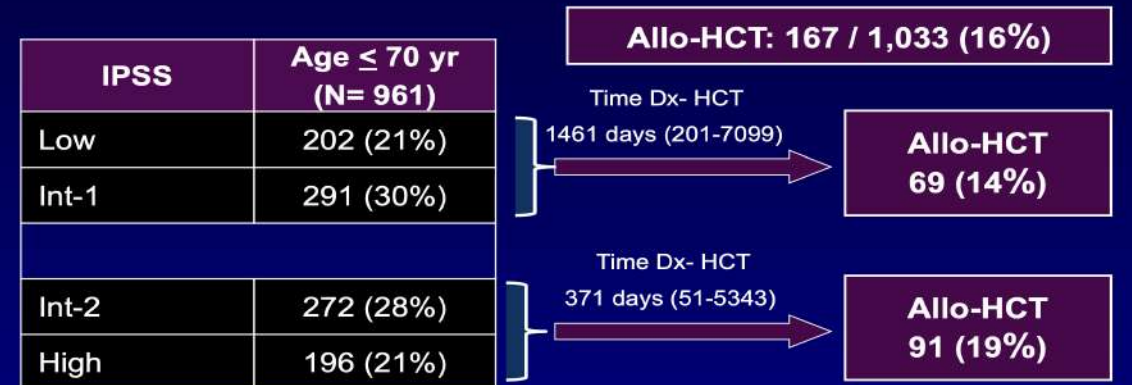
Unpublished data

Patient perceptions regarding allo-HCT in MF Princess Margaret



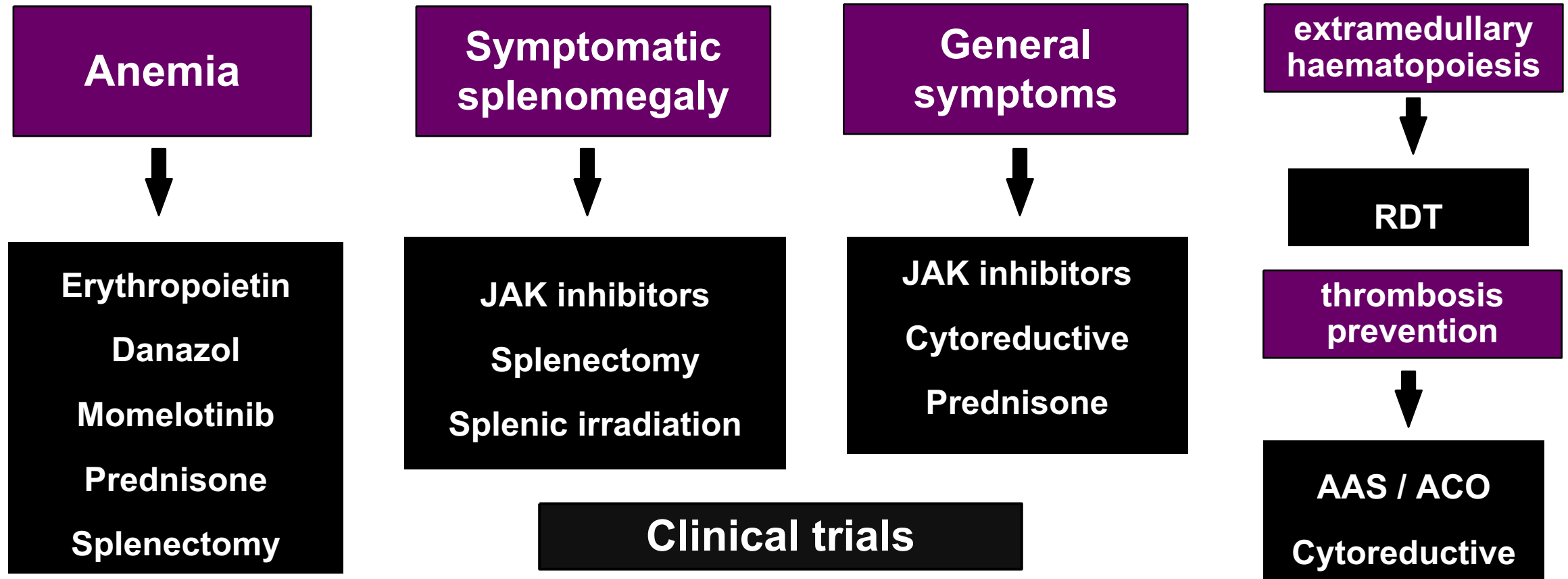
Smith E et al. Transplant Cell Ther 2021;27(7):600.e1-e8

How many MF patients diagnosed at age 70 or younger undergo transplant ?



GEMFIN Registry, unpublished data

Myelofibrosis treatment directed by clinical manifestations



“Traditional” treatments for anemia and thrombocytopenia

- **1. Erythropoietin** Particularly indicated for low levels (<125–150 U/L); their value is diminished when used in combination with Ruxo. Response rate: 40–55% (increase in Hb > 2 g/dL and/or transfusion independence), median duration 19 months **Cervantes. BJH 2006, Cervantes. BJH 2004, E. Crisa BJH 2008, JC Hdez-Boluda E J Hematol 2017**
- **2. Danatrol:** 600 mg/day (maintenance 200 mg/day). Response at 3–6 months
Response rate around 30%. Also improves platelets. Duration of response 14 months. **Cervantes. Ann Hematol 2015**
- **3. Immunomodulators:**
 - **Thalidomide:** A “pooled analysis” of 5 different studies of thalidomide monotherapy: **29% response in anemia, 38% improvement in thrombocytopenia, 41% improvement in splenomegaly.** Responses may be better with combinations of steroids +/- Danatrol +/- EPO.
JF Abragall et al. Hematologica 2006., X. Luo et al. Blood Cancer J 2018. 2. M. Marcheti. JCO 2004. Petra Bělohávková , Acta Medica 2016
 - **Lenalidomide: Responses: 22% for anemia, 33% for splenomegaly, and 50% for thrombocytopenia.**
Cytogenetic remission in del(5)(q13q33), reduction in JAK-
-EA gr ³/₄: neutropenia (31%) and thrombocytopenia (19%)
With steroids: **Responses: 30% anemia and 42% splenomegaly.** Reduction in allelic load and improvement in fibrosis described
A. Tefferi. Blood 2006. A. Quintas Cardama. JCO 2009

Others: steroids. Chelation.

Treatment of myeloproliferative manifestations

- In patients with myeloproliferation who have no other significant symptoms, management is similar to that of myeloproliferation in other non-myeloproliferative conditions (TE, PV), using classic cytoreductive agents and following similar management guidelines.
- Management with cytoreductive agents is more challenging when anemia is also present; in such cases, combination therapies may be useful.
- The most commonly used treatment is **hydroxyurea**; it may increase anemia, which may require reducing or discontinuing the treatment, or adding EPO. Responses in splenomegaly occur in about 40% of cases, but they are short-lived (median response duration of one year).
- Alkylating agents are also used: **melphalan**, **busulfan** in older patients
- Antiagregation

Tratamiento de las manifestaciones hiperproliferativas de la MF

Table 2 Response by specific features in 40 patients with myelofibrosis treated with hydroxyurea

	No. of patients	Response rate (%)
Constitutional symptoms	18	82
Symptomatic splenomegaly	8	45
Pruritus	2	50
Bone pain	2	100
Leukocytosis	9	81
Thrombocytosis	11	71

Responses include complete plus partial response according to the EUMNET criteria

Interferon and Myelofibrosis

- Cytosis Control
- Some studies show benefit in terms of VAF reduction and reduction of bone marrow fibrosis.

Meta-analysis of 141 patients from 10 studies

ORR (CHR + PHR) 49.9%

Spleen reduction rates 20–67%

P1101MF (NCT04988815): Ropeginterferon Alfa-2b for Pre-fibrotic

71 patients with MF **requiring cytoreduction**.

Hematologic responses at w24: Hb >10 (73.9%), WBC <10,000 (82%)

MPN SAF TTS >50% 42.9%

JAK2V617F reduction 34% at w24, 44% at w52; CALR reduction 53%

Bewersdorf et al. Clin Lymphoma Myeloma Leuk. 2020)

- Rule out contraindications (autoimmune diseases / severe psychiatric disorders).
- Start at a dose of 45–90 µg/week (baseline counts / other treatments).
- Monitor for potential toxicities: complete blood count, liver function tests, mood changes, thyroid dysfunction, type 1 diabetes.

RUXOPEG (NCT02742324): Ruxolitinib + Pegylated Interferon Alpha 2a in Treatment-Naïve Myelofibrosis Patients

Kiladjian et al. Blood. 2022

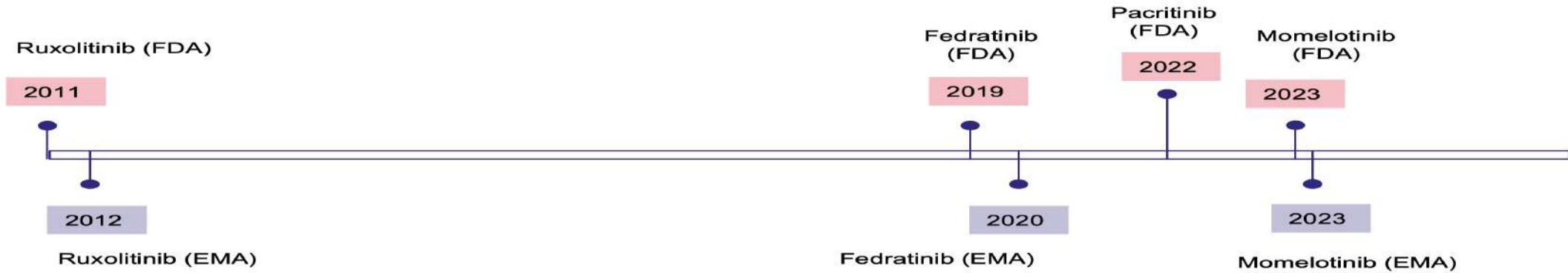
Phase 1/2. 37 patients.

>50% reduction in spleen size in 70% of patients at week 24.

Reduction in JAK2V617F from a median of 84% to 53% at 12 months.

BM biopsies under review; preliminary results showing fibrosis reduction.

The key players in the medical management of MF: JAKs

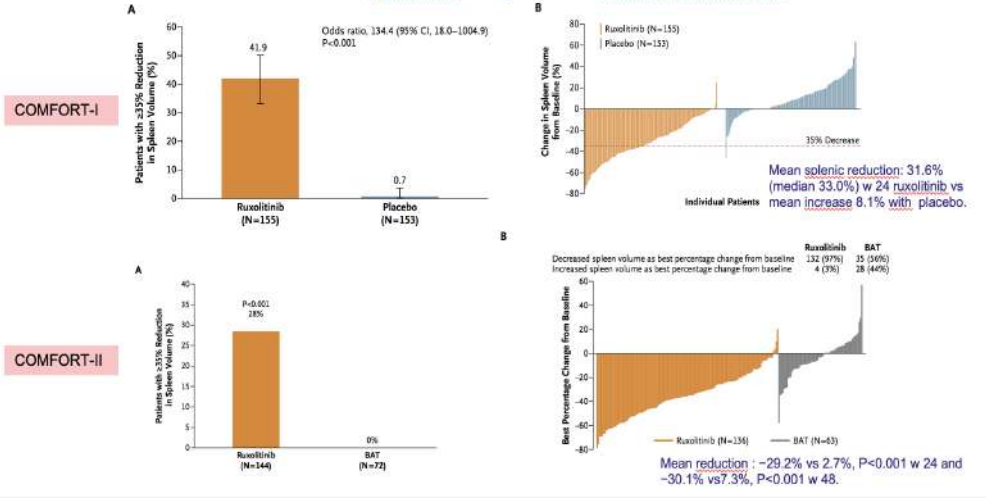


<u>Ruxolitinib</u>	Novartis	JAK2, JAK1	Aprobado EMA (2012)
<u>Fedratinib</u>	Celgene/BMS	JAK2, FLT3	Aprobado EMA (2021)
<u>Momelotinib</u>	GSK	JAK2, JAK1, ACVR1	Aprobado EMA (2024)*
<u>Pacritinib</u>	Sobi	JAK2, FLT3, IRAK1, ACVR1	Aprobado FDA (2022)**

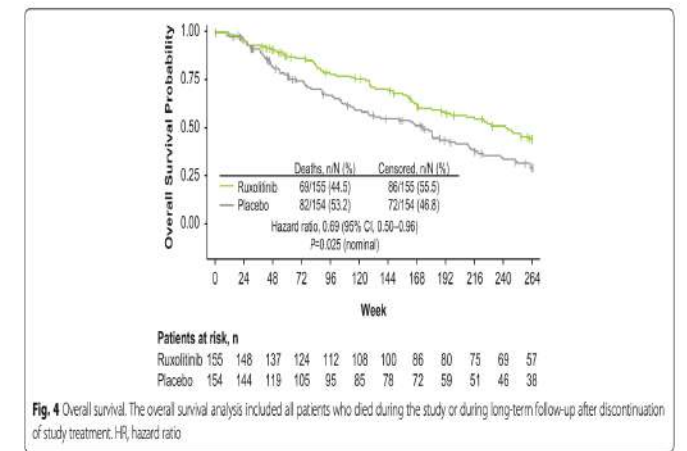
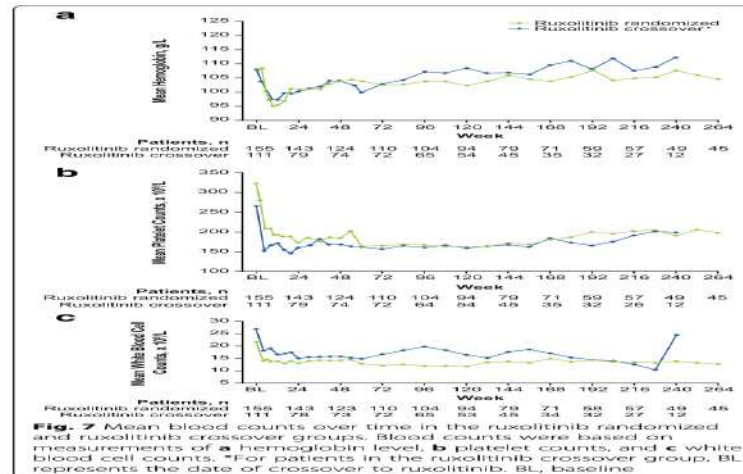
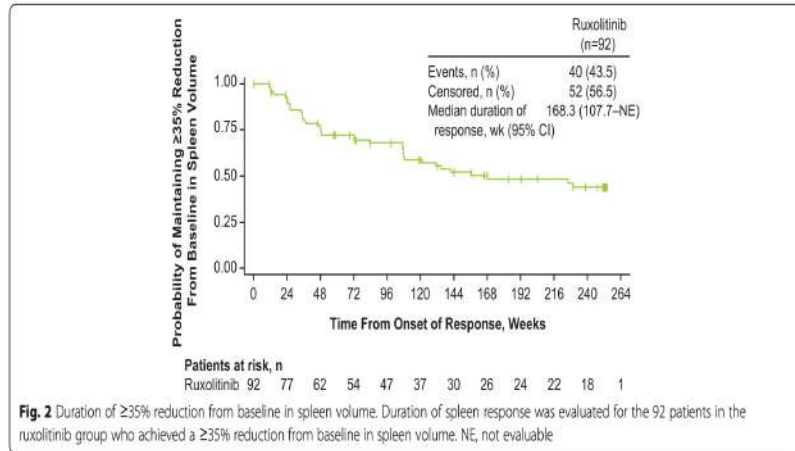
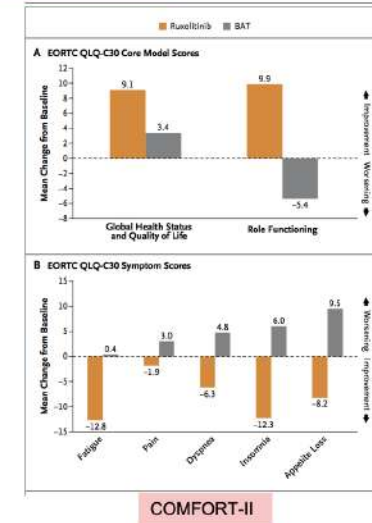
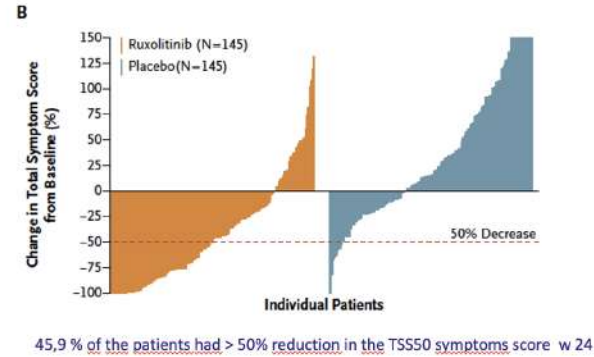
*Pacientes con anemia moderada/grave. **Pacientes con plaquetas < 50 x 10⁹/L.

Ruxolitinib. Phase 3 studies: COMFORT-I and II

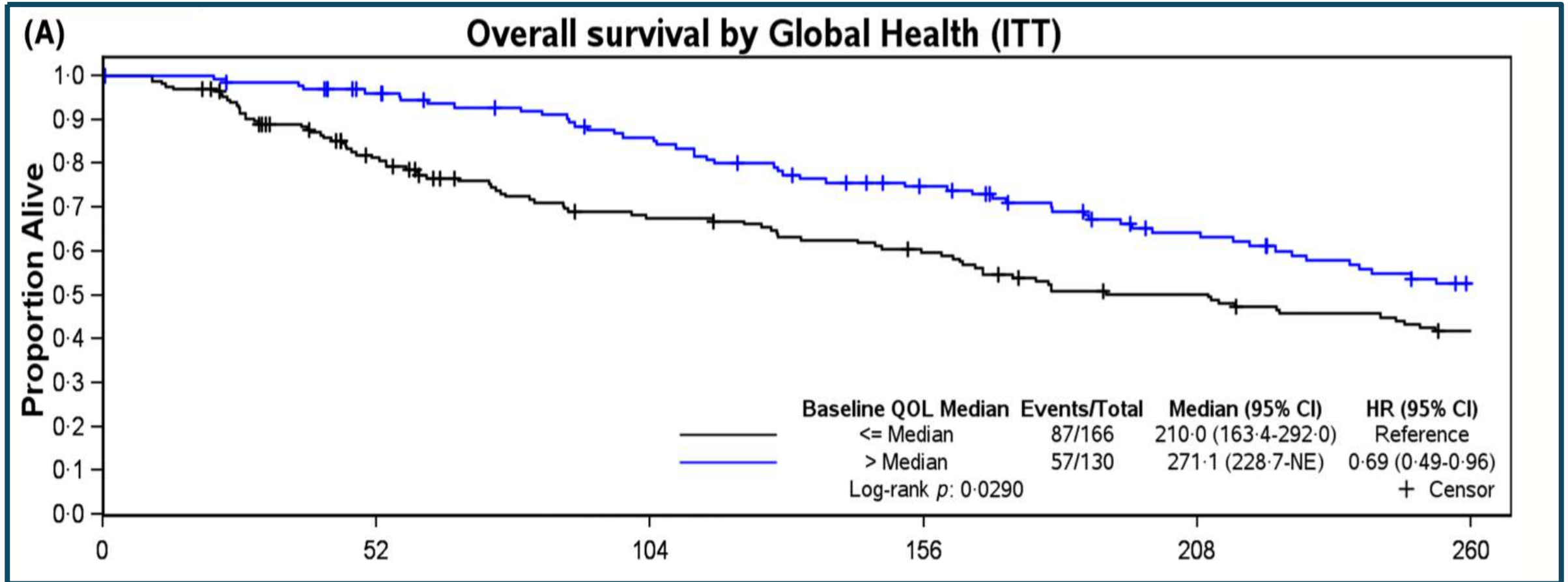
COMFORT-I Y COMFORT-II: Splenic responses with ruxolitinib



COMFORT-I Y II: Symptomatic responses with ruxolitinib



Quality of life independently predicts overall survival in myelofibrosis: Key insights from the COntrolled MyeloFibrosis Study with ORal Janus kinase inhibitor Treatment (COMFORT)-I study



For which patients should ruxolitinib be used?

- Patients with **significant systemic symptoms and/or symptomatic splenomegaly, regardless of risk group**

Other patients who may benefit from ruxolufib:

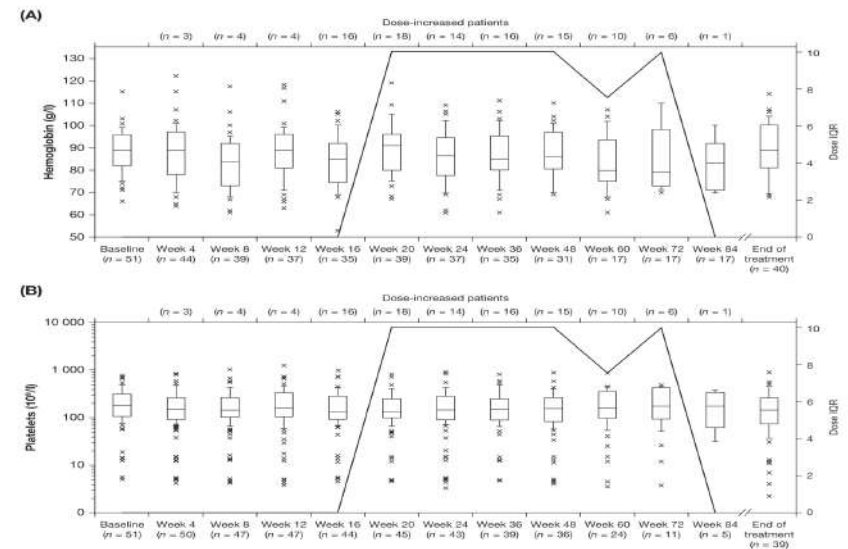
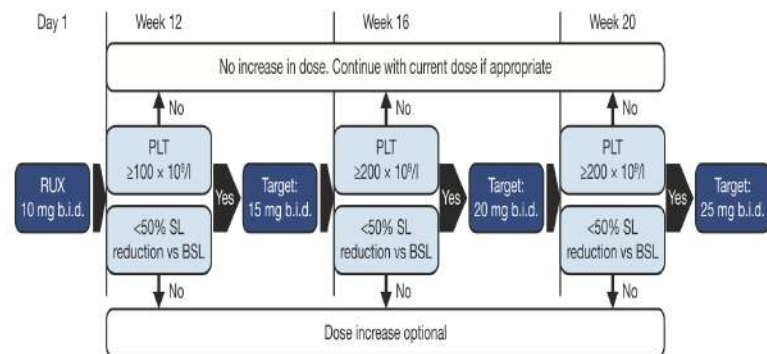
- Portal hypertension: improvements have been reported even in cases of bleeding varices
- Pulmonary hypertension
- Extramedullary hematopoiesis

Platelet count	Initial dose of ruxolitinib
>200×10⁹/L	20 mg twice daily
100 to 200×10⁹/L	15 mg twice daily
75 to <100×10⁹/L	10 mg twice daily
50 to <75×10⁹/L	5 mg twice daily
<50×10⁹/L	<50×10⁹/L

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

- Fase II. Un solo brazo. N: 51. esplenomegalia palpable y Hb <10
- Ruxo 10 mg/12 x 12 s, después escalada progresiva hasta máximo de 25 mg/12 hrs
- 70% alcanzan reducción del bazo >50% en algún momento.
- Reducción de síntomas en toda la población: -54% a 24 sem
- Globalmente responden más a más dosis, pero la dosis de 10 mg/12 es bastante efectiva
- Niveles de hb y requerimientos transfusionales no empeoran en la mayoría de los pacientes



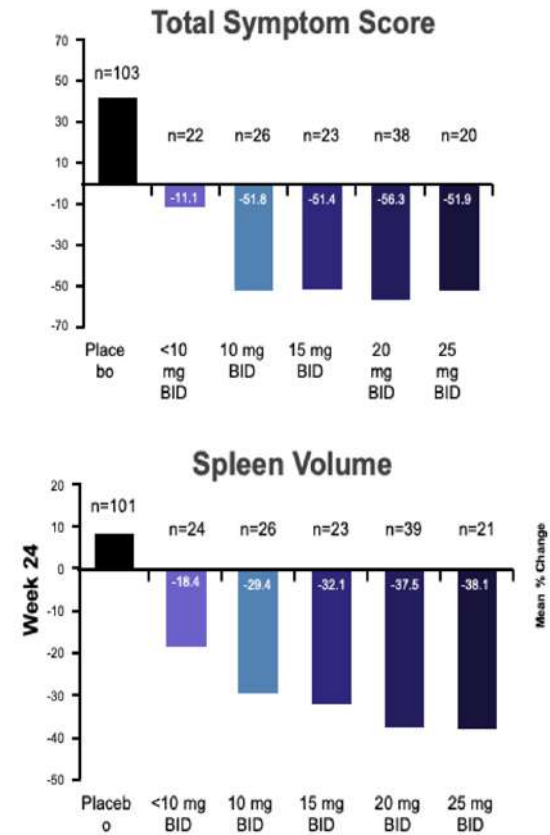
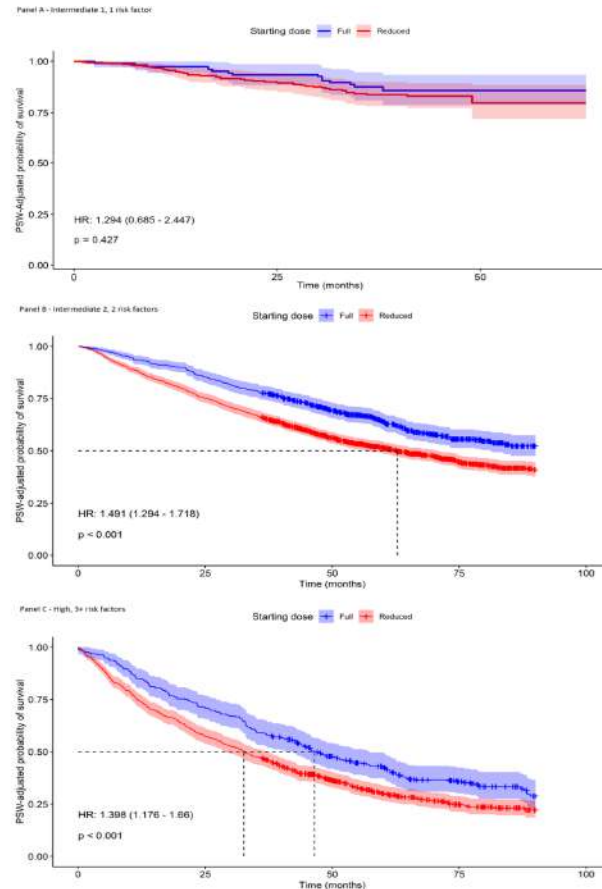
ORIGINAL PAPER

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  |

- N: 3494. Retrospective.
- 2,337 (66.9%) started on a reduced dose: these were older patients with higher risk scores and worse ECOG scores
- Attempting a matched adjustment by baseline characteristics: OS 78.2 months (95% CI 65.9–89) for those starting at full dose vs. 52.6 months (95% CI 49–56.6) for those starting at a reduced dose ($p < 0.001$).
- Most patients started on a reduced dose, and this has an impact on survival





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**

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.

- 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.

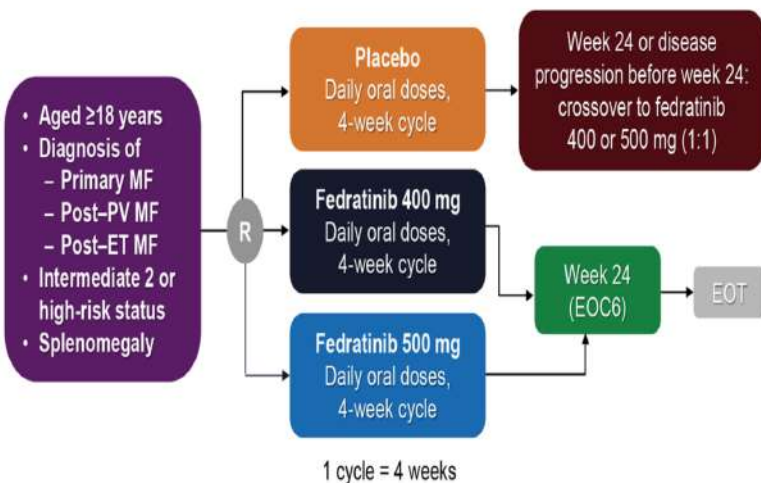
Gowin K, Kosiorek H, Dueck A, Mascarenhas J, Hoffman R, Reeder C, et al. Multicenter phase 2 study of combination therapy with ruxolitinib and danazol in patients with myelofibrosis. *Leuk Res*. 2017;60:31–5.

FEDRATINIB

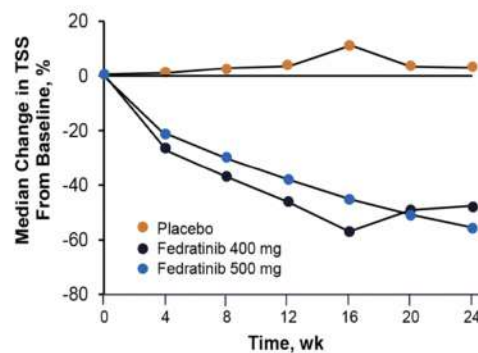
- Inhibidor de Jak-2 (más específico) y FLT3, y prot BET
- Aprobado MF de riesgo intermedio o alto, 1^a o 2^a,
- pretratados o no con IJAK en base a estudio JAKARTA
- y JAKARTA-2.
- Dosis recomendada 400 mg (Acl 15-30 ml/min: bajar a 200 mg)

JAKARTA: Phase 3 Study Design¹

i-Jak naive

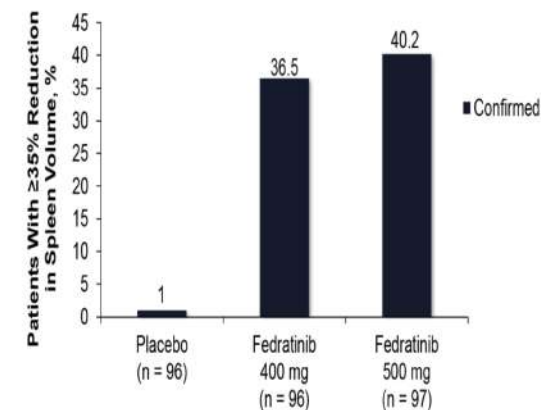


Symptom Responses: Change in TSS by Group¹



Síntomas:
(reducción ≥50% MPN-TSS semana 24) : 36% y 34% con 400 mg y 500 mg respectivamente. 7% placebo.

Primary Endpoint: Spleen Response (ITT Population)¹



35/96 and 39/97 patients in the fedratinib 400-mg and 500-mg groups vs 1/96 in the placebo group ($P < .001$)

JAKARTA-2: Open-Label Study With Fedratinib¹

- Aged ≥18 years
- Intermediate-2 or high-risk status
 - Primary MF
 - Post-PV MF
 - Post-ET MF
- Platelet count ≥50 x 10⁹/L
- Received RUX for ≥14 days
- Discontinued RUX ≥14 days prior to starting fedratinib

Fedratinib

Once daily, starting dose 400 mg
Consecutive 4-week cycles

- Permitted dose adjustments = 200-600 mg/day
- Dose up-titration permitted if <50% reduction in spleen volume by palpation to EOC6
- Dose-titration permitted in event of toxicity
- Patients who continued to benefit clinically could remain on study until the occurrence of disease progression or unacceptable toxicity

66%

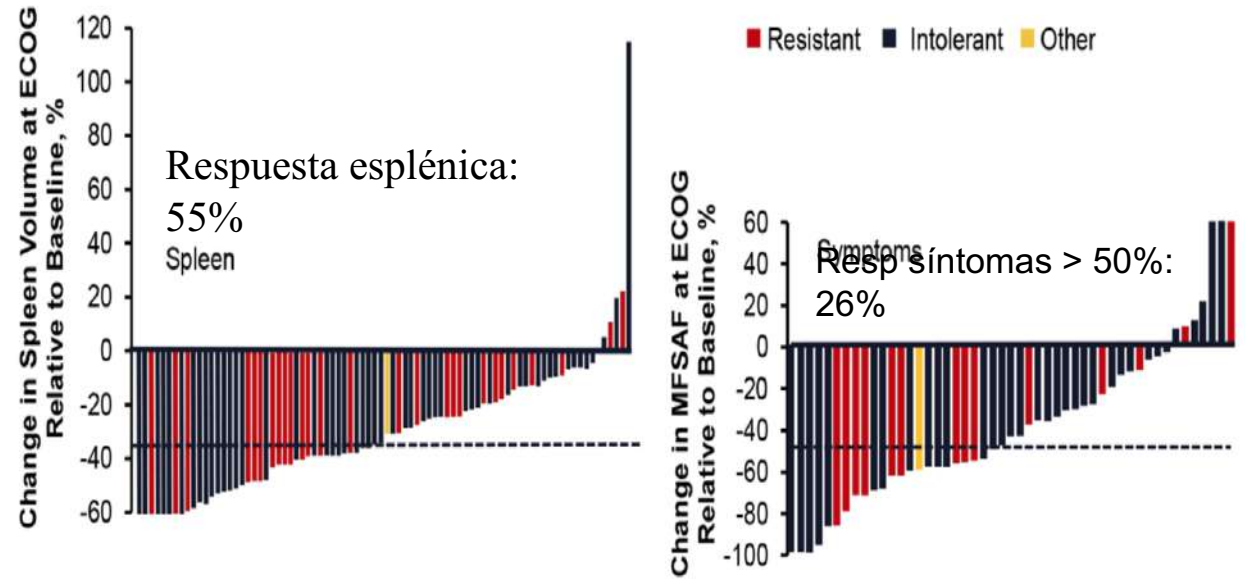
RUX
resistant

33%

RUX
intolerant

Classification made by treating physician

Fedratinib Is Effective in Patients With MF Previously Treated With Ruxolitinib: Results From JAKARTA-2¹



Fedratinib: orphan drug designation for the treatment of secondary and primary myelofibrosis; currently under FDA priority review for treatment of MF

1. Harrison CN et al. *Lancet Haematol.* 2017;4:e317-e324.

1. Harrison CN et al. *Lancet Haematol.* 2017;4:e317-e324.

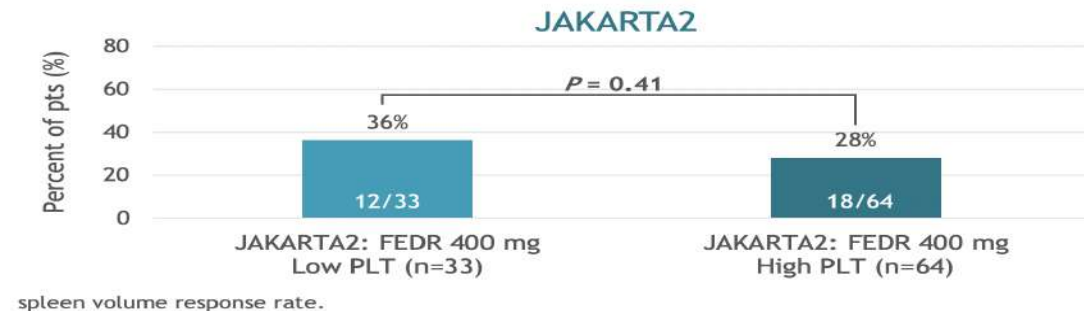
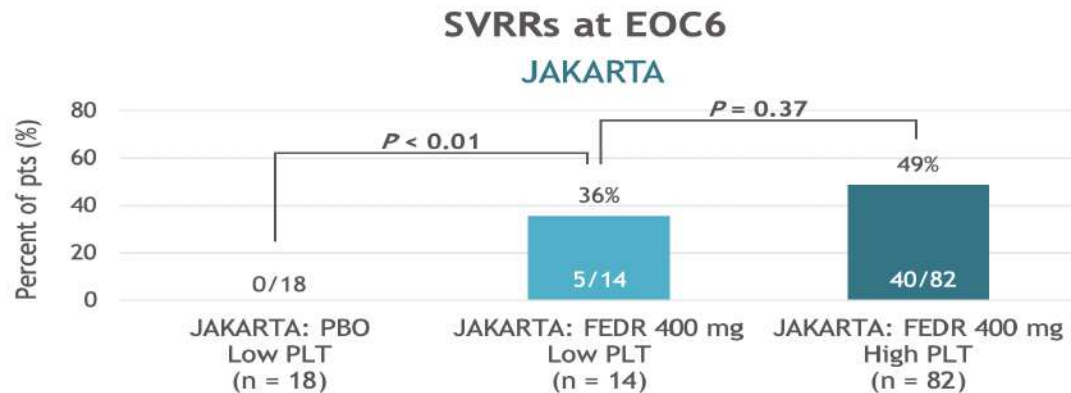
Problemas de seguridad:

- Toxicidad gastrointestinal
- Posibles casos de encefalopatía de Wernicke: suplementar tiamina o monitorizar

Safety and efficacy of fedratinib, a selective oral inhibitor of Janus kinase-2 (JAK2), in patients with myelofibrosis and low pretreatment platelet counts

Claire N. Harrison¹ | Nicolaas Schaap² | Alessandro M. Vannucchi³ |
Jean-Jacques Kiladjian⁴ | Francesco Passamonti⁵ | Sonja Zweegman⁶ | Moshe Talpaz⁷ |
Srdan Verstovsek⁸ | Shelonitda Rose⁹ | Jun Zhang^{9,†} | Oumar Sy⁹ | Ruben A. Mesa¹⁰

- Fedratinib 400 mg in patients with platelet counts of 50 to $<100 \times 10^9/L$ (“Low-Platelets” cohorts), including 14 of 96 patients (15%) in JAKARTA and 33 of 97 (34%) in JAKARTA2
- At 24 weeks: similar splenic response with low and high platelet counts: JAKARTA (36% vs. 49% ; $p = 0.37$) or JAKARTA2 (36% vs. 28%; $p = 0.41$). No differences in symptom response either
- Worsening or onset of thrombocytopenia: more frequent with low platelet counts: 44% vs. 9%, but without associated serious adverse events. Thrombocytopenia was managed with dose modifications; only 3/48 discontinued treatment for this reason
- These results compare favorably with those of the JUMP study: Rates of worsening thrombocytopenia and anemia in JUMP were 73% and 53%, respectively. Fifty-five percent of patients required dose reductions and 30% required treatment interruptions

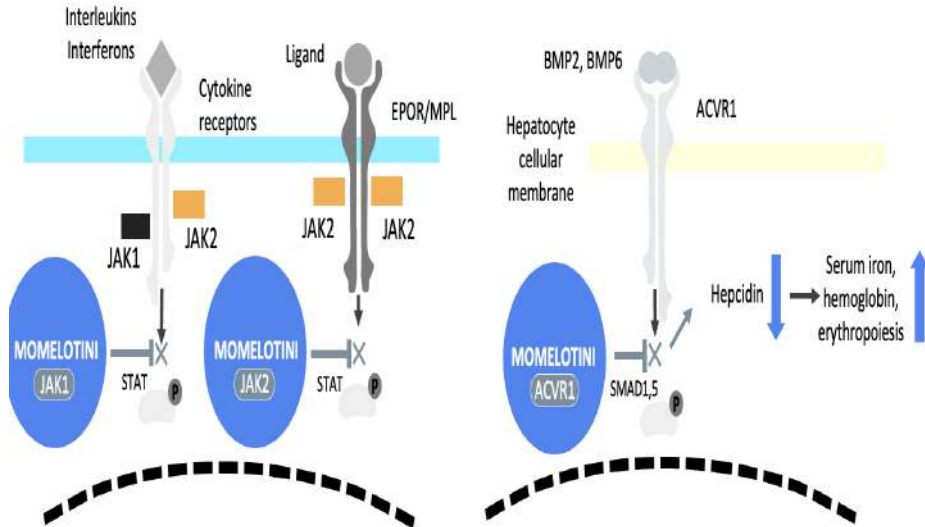


Momelotinib

bone morphogenetic proteins

Small mothers against decapentaplegic (SMAD)1/5/8 pathway,

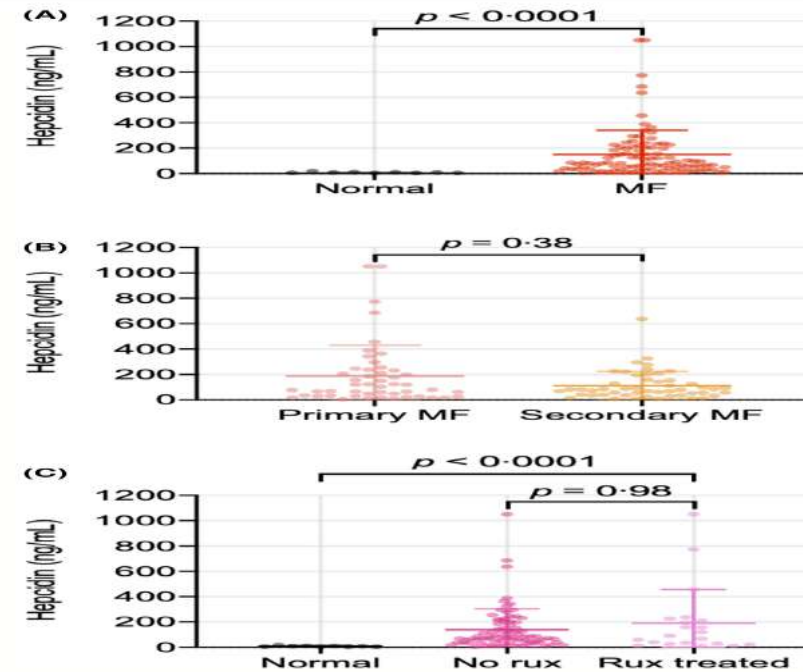
Momelotinib: mechanism of action



Deregulation of the **JAK-STAT** signalling pathway in MF leads to overproduction of inflammatory cytokines, bone marrow fibrosis, **systemic symptoms** and clonal proliferation, resulting in extramedullary haematopoiesis and **splenomegaly**.

Chronic inflammation also causes hyperactivation of **ACVR1**, elevation of **hepcidin**, and dysregulation of iron metabolism, contributing to **anaemia** in MF.

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



A. Pardanani, C. Finke, R. A. Abdelrahman, T. L. Lasho, and A. Tefferi, "Associations and Prognostic Interactions Between Circulating Levels of Hepcidin, Ferritin and Inflammatory Cytokines in Primary Myelofibrosis," *American Journal of Hematology* 88, no. 4 (2013): 312–316.

A. Zhou, T. Kong, J. S. Fowles, et al., "Hepcidin Is Elevated in Primary and Secondary Myelofibrosis and Remains Elevated in Patients Treated With Ruxolitinib," *British Journal of Haematology* 197, no. 4 (2022): e49–e52.

SIMPLIFY-1

IJAK naive

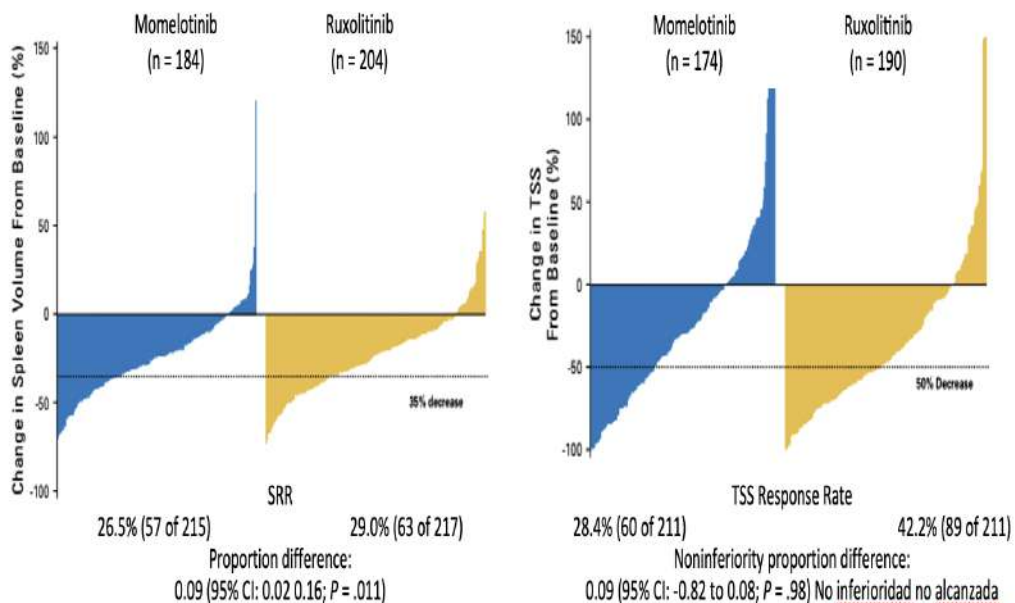
Adults with primary, post-PV or post-ET MF; symptomatic int-1, int-2, or high risk; platelets $\geq 50 \times 10^9/L$ (n = 432)

Momelotinib 200 mg PO daily

Ruxitinib 20 mg PO daily

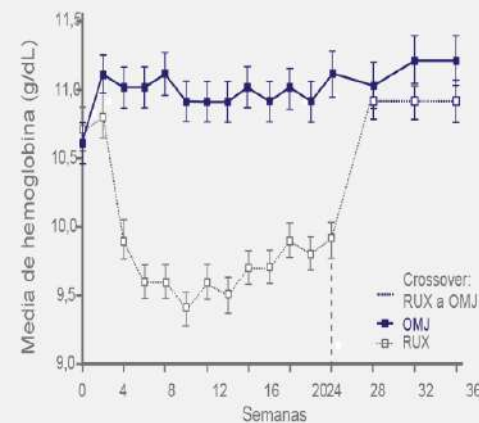
Cross over allowed after 24 wk

Mesa. JCO. 2017;35:3844.

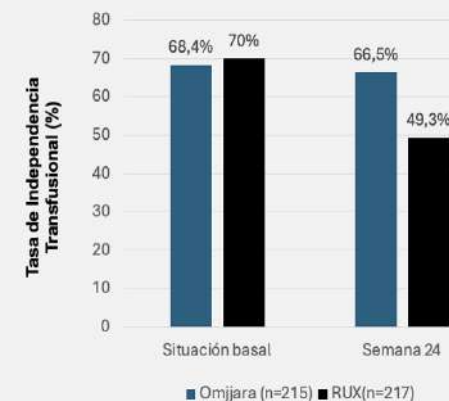


J Clin Oncol 35:3844-3850. 2017

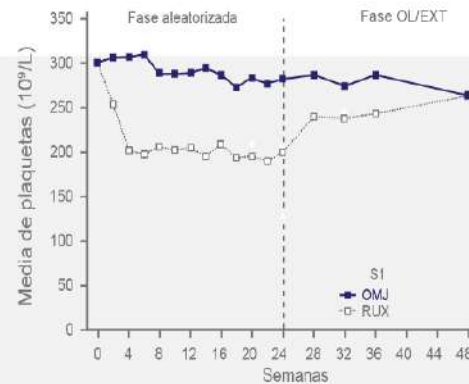
Hb



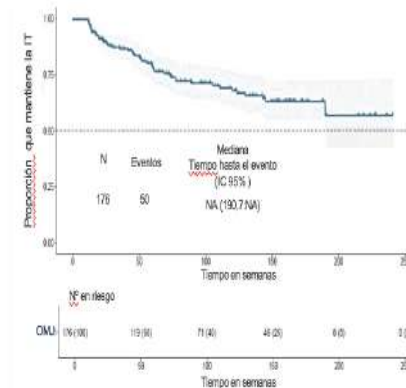
Transfusion independence



Platelets



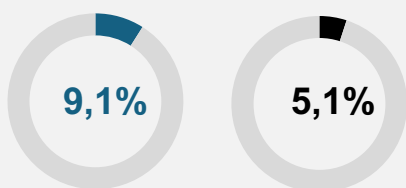
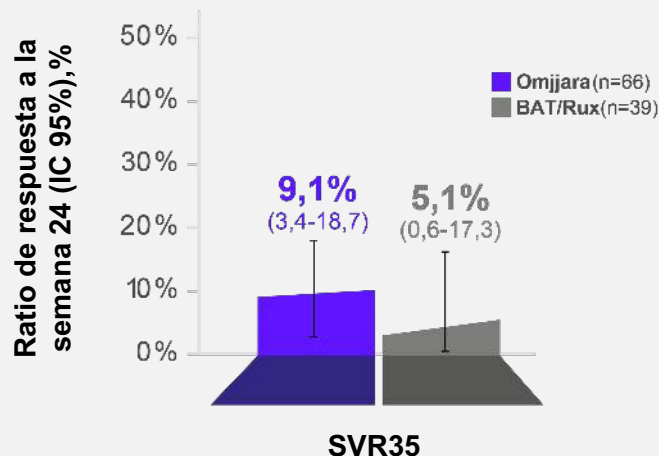
TI duration



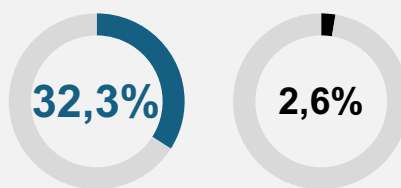
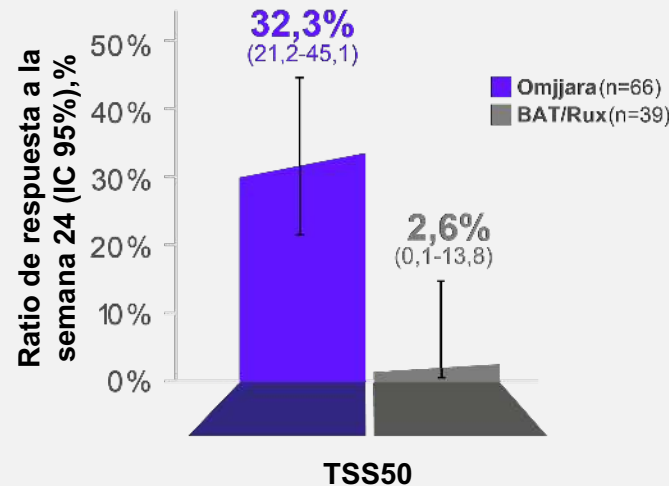
Gráfica adaptada de Mesa R, et al. Leuk Lymphoma, 2022.

SIMPLIFY-2: Momelotinib versus best available therapy in patients exposed to ruxolitinib

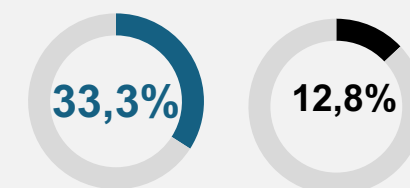
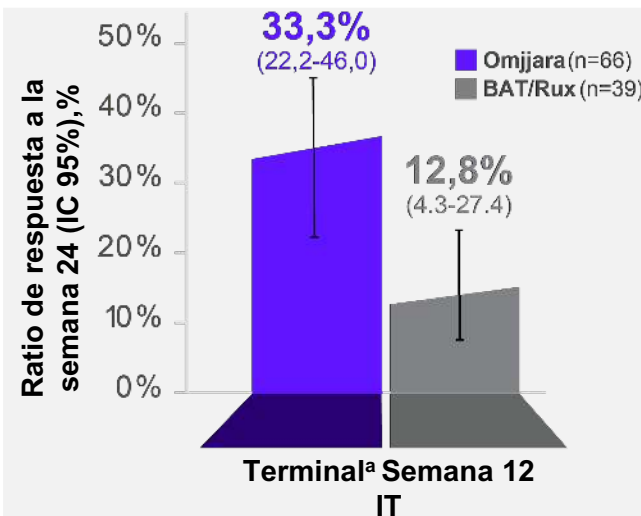
SPLENIC REDUCTION AT WEEK 24



SYMPTOMS (TSS RESPONSE) AT WEEK 24



TRANSFUSIONAL INDEPENDENCE AT 24 WEEKS



Gráficas adaptadas de Harrison CN, *et al.* Adv Ther. 2024.¹

Hb: hemoglobina; IC: intervalo de confianza; IT: independencia transfusional; RUX: ruxolitinib; SVR35: respuesta del volumen del bazo con reducción $\geq 35\%$; TSS: puntuación total de síntomas; TSS50: puntuación total de síntomas con reducción $\geq 50\%$.

1. Harrison CN, Vannucchi AM, Recher C, *et al.* Momelotinib versus Continued Ruxolitinib or Best Available Therapy in JAK Inhibitor-Experienced Patients with Myelofibrosis and Anemia: Subgroup Analysis of SIMPLIFY-2. Adv Ther. 2024;41(9):3722-3735..

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

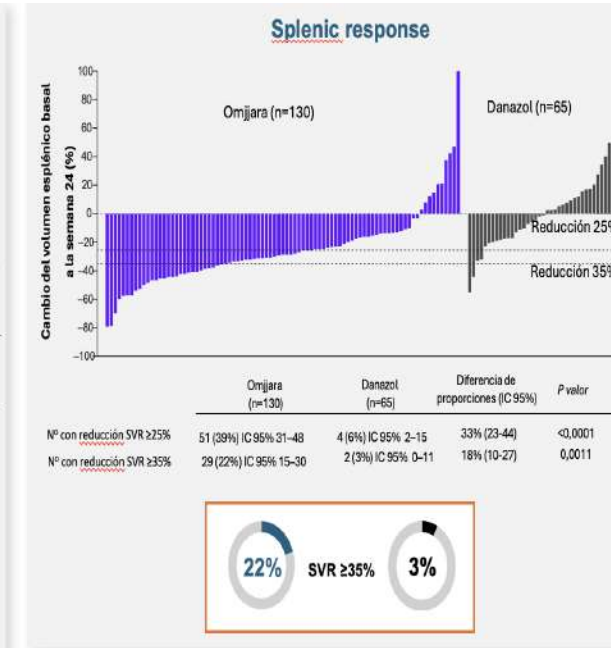
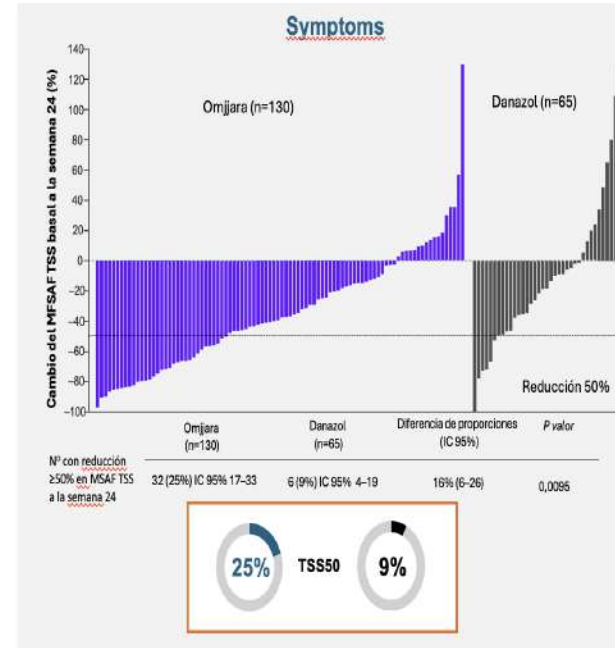


Srdan Verstovsek, Aaron T Gerds, Alessandro M Vannucchi, Haifa Kathrin Al-Ali, David Lavie, Andrew T Kuykendall, Sebastian Grosicki

The Lancet January 2023



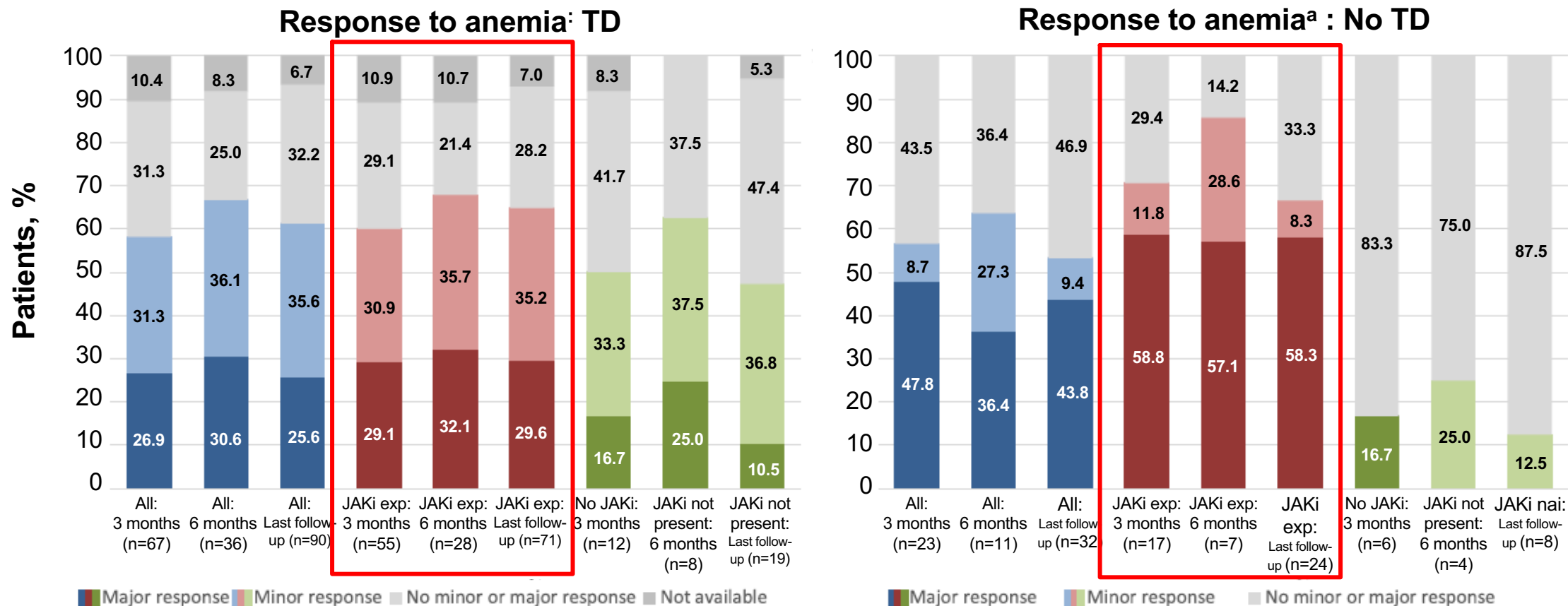
- $P_{it} > 25.000$
- 48% en el grupo de momelotinib vs 52% en el de danazol eran transfusión dependientes
- Adicionalmente 38% de los de momelotinib y 32% de los de danazol habían requerido transfusiones en las últimas 8 sem, pero sin cumplir criterio de DT



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 ($\geq 35\%$ 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

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 naive 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

Rapid and durable recovery of immune effector cells in myelofibrosis patients treated with momelotinib

by Jasmine Makker, Kyaw Htin Thaw, Amna Sheikh, Llywelyn Cadman-Davies, Andrea Duminuco, Elena Torre, Margherita Panetta, Conor Stanley, Hugues de Lavallade, Natalia Curto-Garcia, Priya Srisankaran, Jennifer O'Sullivan, Deepthi H. Radha, Claire Woodley, Benissa Narciso, Susan Asirvatham, Bethan Psaila, Shahram Kordasti, Claire Harrison and Patrick Harrington

'Real-world' cohort . N: 46. (16 patients were high-risk, 24 intermediate-risk 2) . Momelotinib patients with sequential PB samples over 48-week : assess changes in immune cell

Comparator: 10 healthy controls (HC)

85% had prior ruxolitinib exposure (median time: 1.5 years)

At baseline, patients had significantly lower frequencies of total lymphocytes, CD3+ and CD4+ T cells, and NK cells compared to HC (B cells were comparable)

Immune subset (Reference ranges)	Baseline	6 weeks	12 weeks	24 weeks	48 weeks	HC
Total lymphocytes	1041 (738-1544) n=33	1556.5 (1263.8-2657.8) n=34 p=0.005	1623 (1191-2877) n=25 p=0.008	1450 (1031-2156) n=27 p=0.07	1857 (1322.3-2249.3) n=20 p=0.009	1557 (1300-1785.3) n=10 p=0.03
CD3+ cells (700-2100)	724 (454-923) n=33	968 (737-1598.5) n=34 p=0.01	1112 (736-1696) n=25 p=0.005	876 (625.5-1366.5) n=27 p=0.08	1082 (744-1327.5) n=19 p=0.03	1085.5 (867.3-1348.8) n=10 p=0.01
CD4+ T cells (300-1400)	476 (299-537) n=33	552.5 (416-896.3) n=34 p=0.03	714 (413-1093) n=25 p=0.02	486 (351.5-1025.5) n=27 p=0.19	721 (456.3-952.5) n=20 p=0.03	716 (579-903.8) n=10 p=0.005
CD8+ T cells (200-900)	229 (138-393) n=33	324 (186-787) n=34 p=0.04	368 (265-621) n=25 p=0.05	316 (192-446.5) n=27 p=0.28	316 (203.3-466.5) n=20 p=0.13	379.5 (317.5-416.8) n=10 p=0.07
NK cells (90-600)	92 (61-176) n=33	204.5 (100.8-306) n=34 p=0.005	202 (121-332) n=25 p=0.001	162 (97.5-313) n=27 p=0.01	270.5 (140-392) n=20 p=0.002	216.5 (185-252.5) n=10 p=0.004
B cells (100-500)	176 (83.5-301.3) n=32	289.5 (165-494.5) n=34 p=0.02	225 (147-425) n=25 p=0.12	180 (125.5-289) n=27 p=0.46	277 (157.5-419.5) n=19 p=0.04	201.5 (141.5-222.8) n=10 p=0.54

Clear recovery of T and NK cells after momelotinib initiation reaching levels equal to controls

In Ruxolitinib treated and naive patients

- Ruxolitinib has markedly lower IC50 for both JAK1 and JAK2 vs Momelotinib:
- IC50 for JAK 2 of 3.2 nM vs 11 nM
- This heightened inhibition of JAK1 and JAK2 signaling, which is central to the cellular function of both T and NK cells, may explain some of the effects

Some indirect comparisons suggest fewer skin cancers with Momelotinib
Contradictory data with infections

PACRITINIB

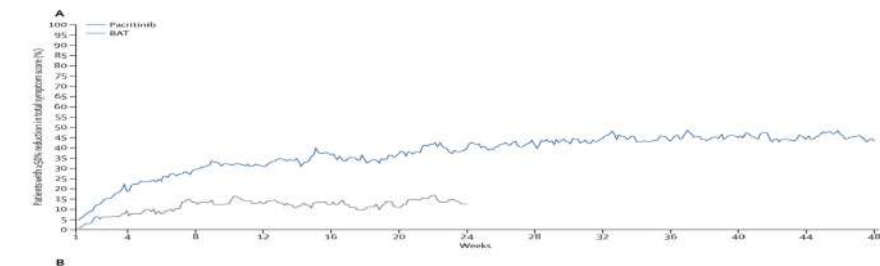
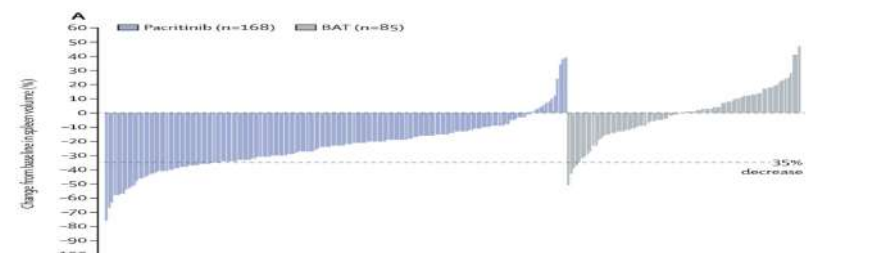
JAK2/ACVR1/FLT3/IRAK1/CSF1R inhibitor. No JAK-1. More potent inhibitor of ACVR1 as compared to momelotinib. IRAK1 play a role also in anemia

Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial

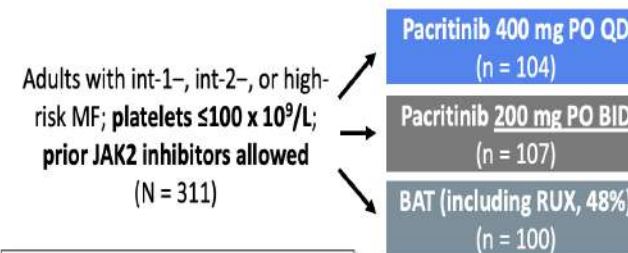
Pacritinib vs. best available therapy (excluding ruxolitinib) in JAKi-naive patients

No lower platelet count limit

Primary endpoint: SVR \geq 35% (19% with pacritinib vs. 5% with best available therapy; p=0.0003)

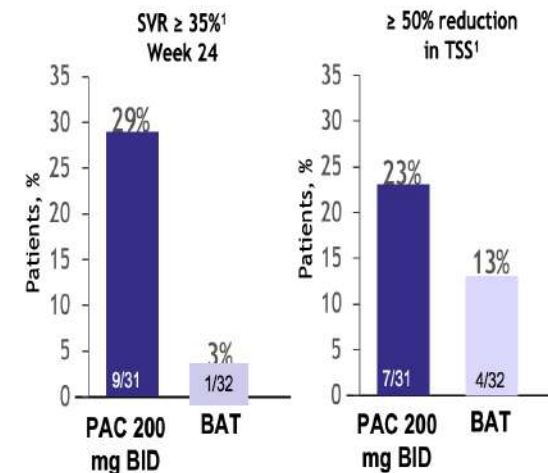
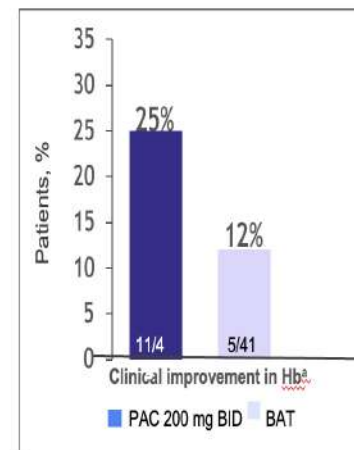


Persist-2



All treatment to PD, unacceptable toxicity, or loss of benefit
Patients receiving BAT could cross over to pacritinib if splenomegaly progression or after treatment *Wk* 24 with or without progression

Patients with platelets $< 50 \times 10^9/L$
(PAC 200 mg BID [n = 31], BAT [n = 32])



Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659;incl suppl; 2.

Trial halted due to alleged excess mortality from hemorrhagic and cardiovascular complications, which was later not confirmed

Determining the recommended dose of pacritinib: results from the PAC203 dose-finding trial in advanced myelofibrosis

Aaron T. Gerds,¹ Michael R. Savona,² Bart L. Scott,³ Moshe Talpaz,⁴ Miklos Egyed,⁵ Claire N. Harrison,⁶ Abdulraheem Yacoub,⁷

Pacritinib is a potent ACVR1 inhibitor with significant anemia benefit in patients with myelofibrosis

Stephen T. Oh,¹ Ruben A. Mesa,² Claire N. Harrison,³ Prithviraj Bose,⁴ Aaron T. Gerds,⁵ Vikas Gupta,⁶ Bart L. Scott,⁷ Jean-Jacques Kiladjian,⁸ Alessandro Lucchesi,⁹ Tim Kong,¹ Sarah A. Buckley,¹⁰ Shanthakumar Tyavanagimatt,¹⁰ Bryan G. Harder,¹⁰ Karisse Roman-Torres,¹⁰ Jennifer Smith,¹⁰ Adam R. Craig,¹⁰ John Mascarenhas,¹¹ and Srdan Verstovsek⁴

A

	+ Control LDN 193189 ^a	PAC C _{max} 213 nM	MMB C _{max} 168 nM	FED C _{max} 275 nM	RUX C _{max} 47 nM	Legend
Replicate 1 ACVR1 IC ₅₀ (nM)	20.4	22.6	70.2	312.0	>1000	Higher potency Lower potency
Replicate 2 ACVR1 IC ₅₀ (nM)	32.4	10.8	34.9	235.0	>1000	
Mean ACVR1 IC ₅₀ (nM)	26.4	16.7	52.6	273.5	>1000	
Potency ^b (C _{max} :IC ₅₀)	N/A	12.7	3.2	1.0	<0.01	

C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans. Darker blue indicates higher potency (lower IC₅₀).

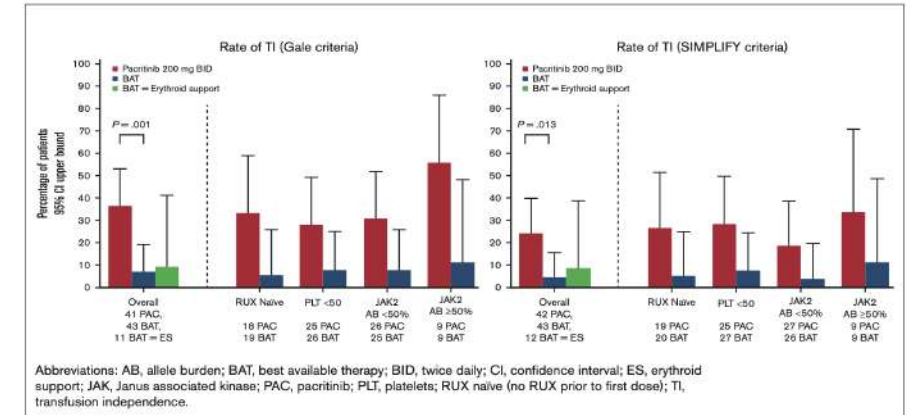


Figure 3. Rate of transfusion independence. Percentage of patients achieving transfusion independence over any 12 weeks through week 24 among patients who were not TI at baseline based on Gale criteria (left) and SIMPLIFY criteria (right) over any 12-week interval. Data shown in overall population (including statistical testing), as well as in subgroups.

In PERSIST-2: pacritinib vs best available therapy including ruxolitinib, in patients with thrombocytopenia, a significantly greater proportion of patients who were TD at baseline became transfusion independent (per Gale criteria) on pacritinib vs those treated with best available therapy (37% vs 7%, $P = .001$)

According to the modified “SIMPLIFY” criteria used in this analysis (no transfusions and Hb < 8 g/dL over any “rolling” 12 weeks), significantly more pacritinib-treated patients achieved TD compared to BAT (24% versus 5%, $p = 0.013$)

$\geq 50\%$ reduction in transfusion burden through week 24 (49% versus 9%, respectively, $p < 0.0001$)

Indirect treatment comparisons of momelotinib vs pacritinib safety and anemia outcomes in patients with myelofibrosis

Lucia Masarova^a, Srdan Verstovsek^{a,*}, Francesca Palandri^b, Ruben Mesa^c, Claire Harrison^d, Balázs Dobi^e, Boris Gorsh^{f,#}, Zhaohui Wang^f, Catherine Ellis^f, Dwaipayan Patnaik^g, Tom Liu^f and Venediktos Kapetanakis^h

^aDepartment of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ^bIRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ^cWake Health, Winston-Salem, NC, USA; ^dGuy's and St Thomas' NHS Foundation Trust, London, UK; ^eEvidera, Budapest, Hungary; ^fGSK plc, Philadelphia, PA, USA; ^gGSK plc, Baar, Switzerland; ^hEvidera, London, UK

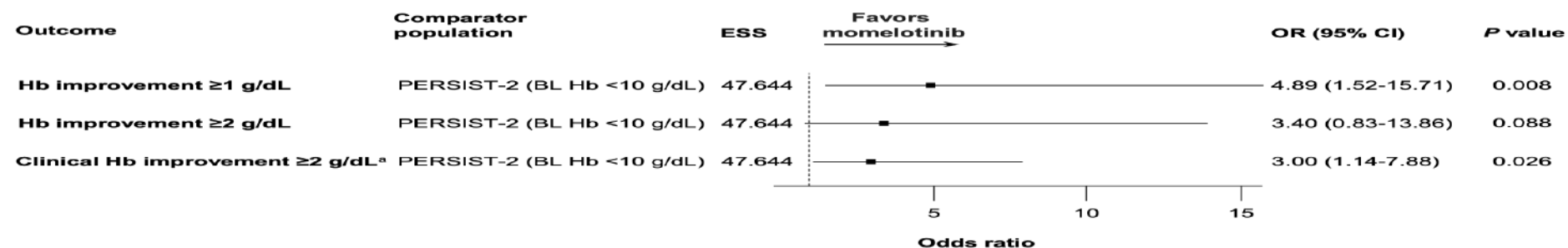
ARTICLE HISTORY

Received 20 December 2024

Accepted 23 May 2025

KEYWORDS

Myelofibrosis; JAK inhibitor; momelotinib; indirect treatment comparison; safety; pacritinib



Momelotinib was also superior in tolerance with better Odds for most side effects

LETTER TO THE EDITOR

Predictors of response to pacritinib therapy and survival among 60 Mayo Clinic patients with myelofibrosis treated outside of clinical trials

Despite recent reports on the drug's mechanistically unique erythropoietic activity, the anemia response rate seen with PAC in the current real-world study was underwhelming; only one (2.4%) of 41 JAKi-treated and none of 19 JAKi-naïve patients met the revised IWG-MRT criteria for anemia response

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 anaemia < 10 g/dl or severe thrombocytopenia < 50,000

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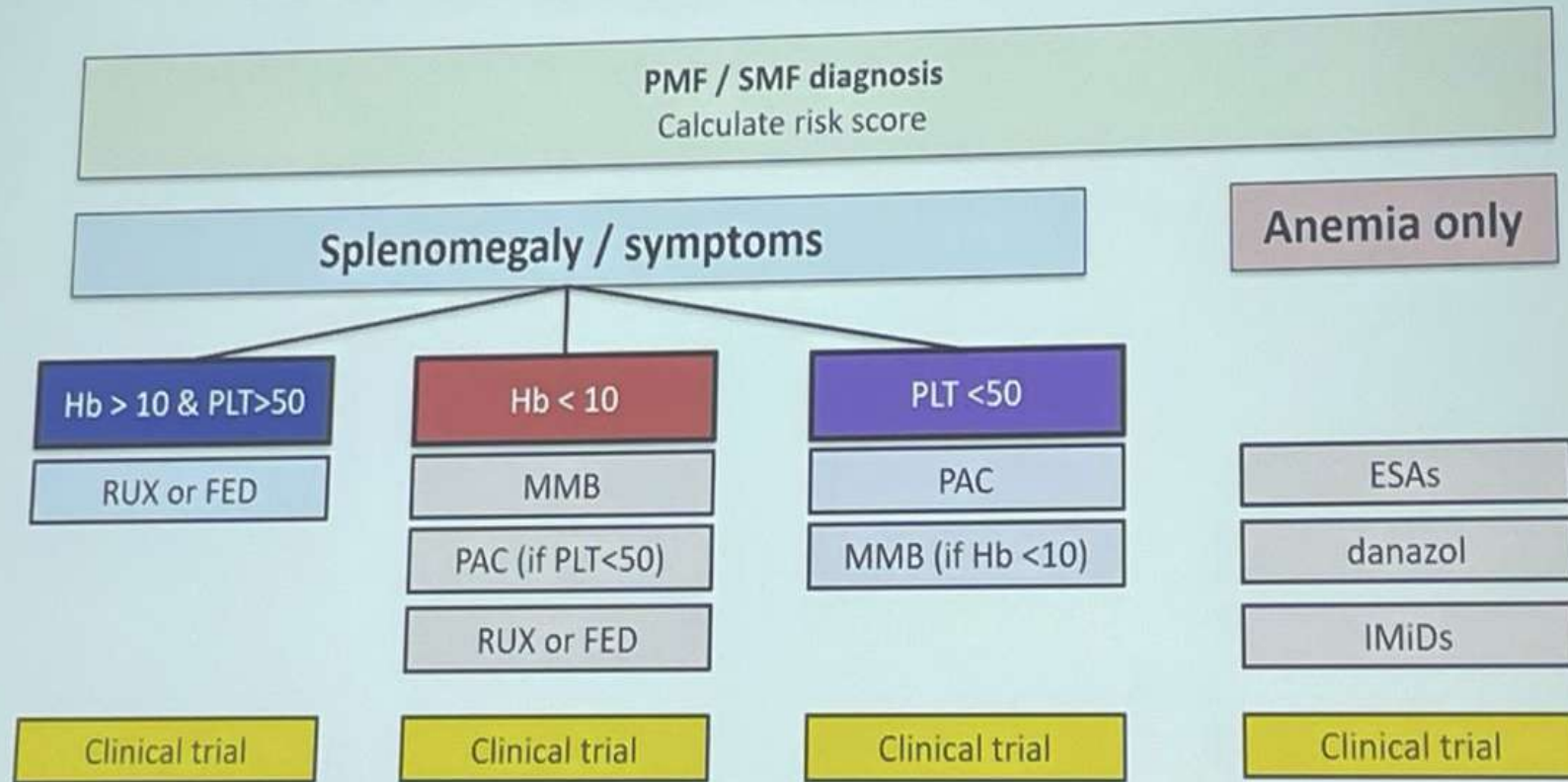
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Second Line

- Fedratinib: if the primary aim is symptom management and/or splenomegaly
- Momelotinib: if anaemia 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

Personalized approach of MF in 2025



Adapted from: Koschmieder, S. (2024), Novel approaches in myelofibrosis. HemaSphere, 8: e70056.

But what do we need to do to really improve the results

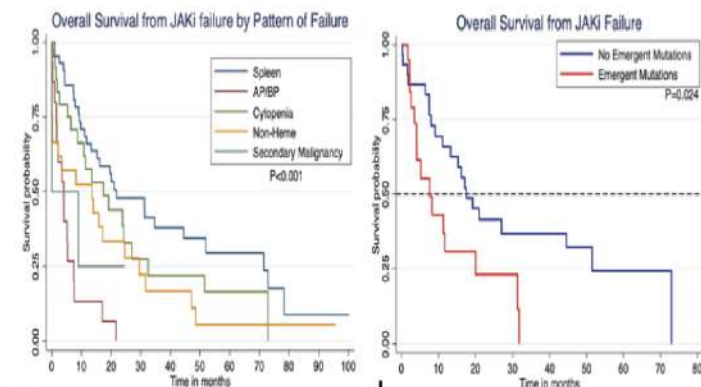
-Modify the natural history of the disease: ¿but what is this?: Not clearly defined

Probably should include

- Revert fibrosis
- Reduce the allelic burden
- Reduce citoquine production
- Reduce the risk of progresion to advanced phases
- And the end of the day improve overall survival

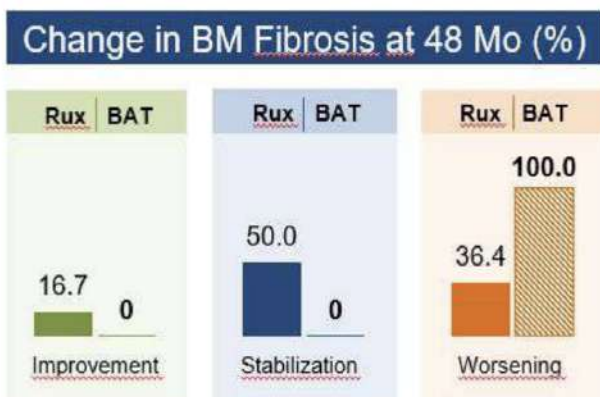
Is Ruxolutinib doing that?

Overall survival from JAKi failure



Median OS: 14 months

England JT *et al.* Leukemia 2022;36(6):1689-92



CONFORT II study %Reducción V617F 48sem

	MTD	Ruxolitinib
<10%	21 (95%)	40 (59%)
10%-20%	1 (5%)	14 (21%)
>20%	0	14 (21%)

- No reduction of advanced phases
- Modest improvement in survival

And what is coming

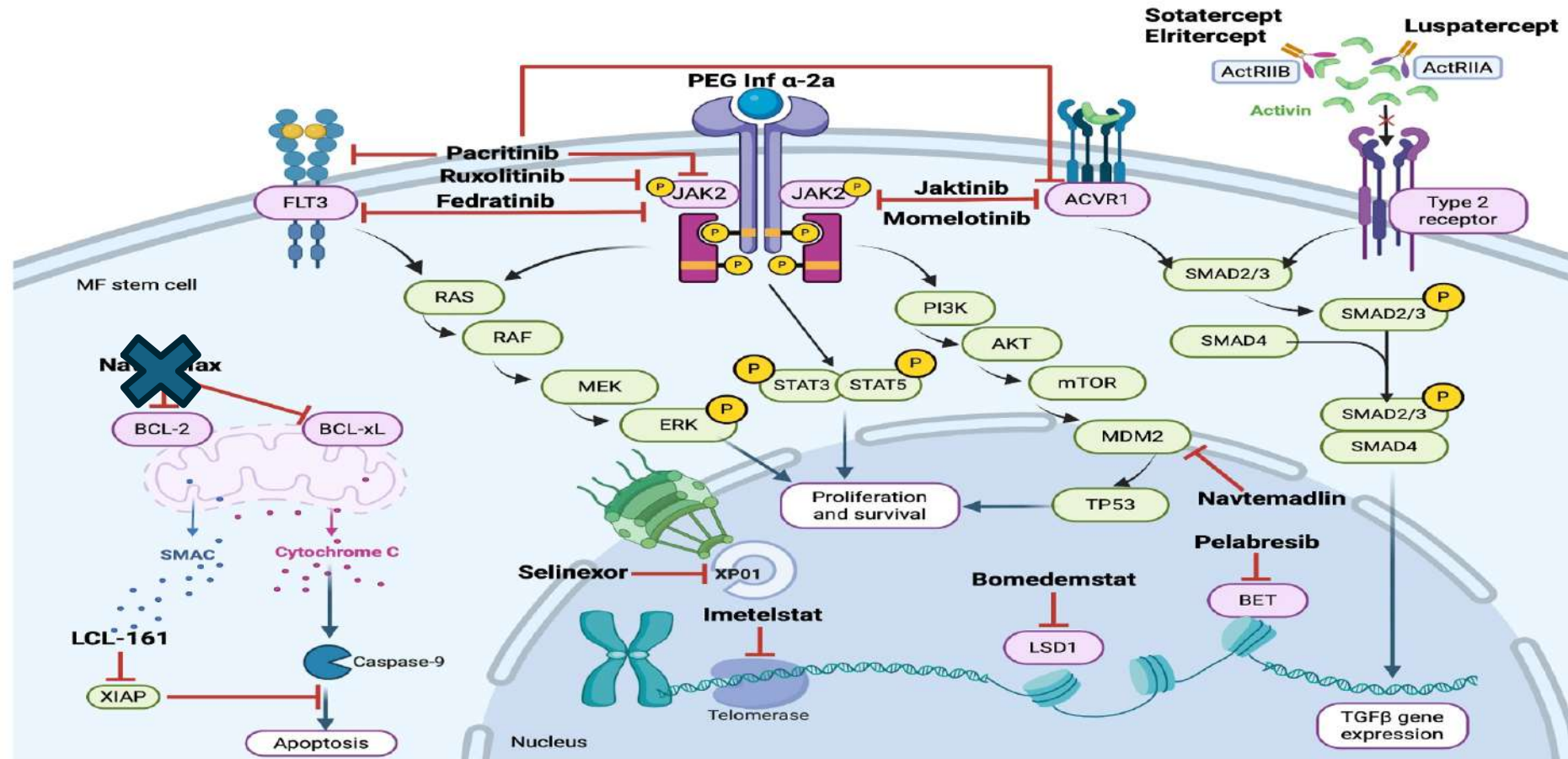


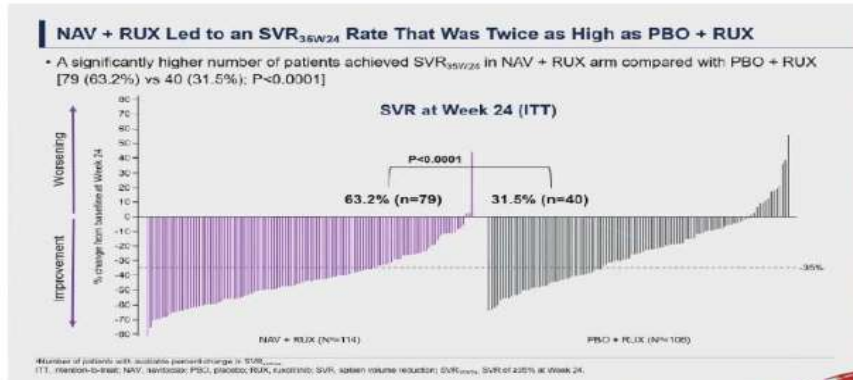
FIGURE 1 | Approved (ruxolitinib, fedratinib, momelotinib and pacritinib) and novel therapies target multiple pathways in MF pathophysiology. ActRIIA, activin receptor type IIA; ActRIIB, activin receptor type IIB; ACVR1, Activin A receptor type I BCL-2/xL, B-cell lymphoma 2/xL; BET, bromodomain and extraterminal; FLT3, Fms-like tyrosine kinase 3; JAK, Janus Kinase; LSD1, lysine-specific demethylase 1; MDM2, mouse double minute 2; TGF- β , transforming growth factor- β ; XPO1, exportin 1.

But the way is not easy: not everything will reach the shore

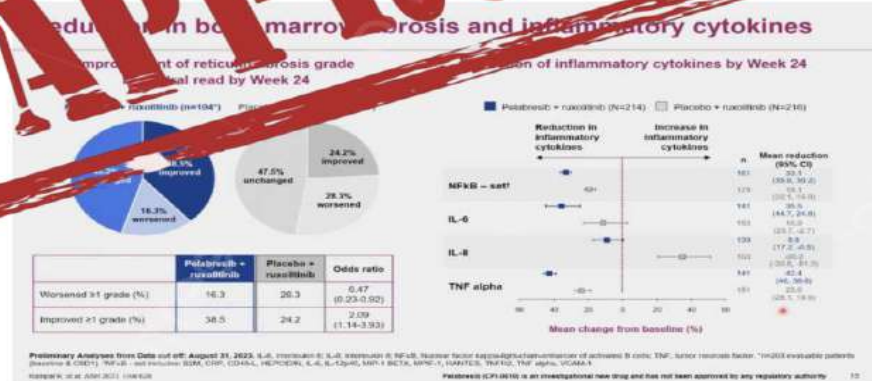
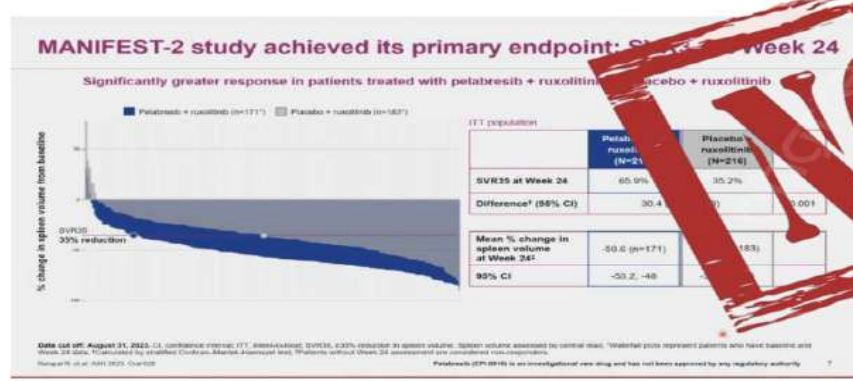
Combinations of Ruxo with navitoclax or Pelabresib

• Beneficio esplenomegalia

• Beneficio "control enfermedad"



Navitoclax Evidence Generation Program: REFINE (Cohort 1a) – Overall Survival by BMF Improvement and VAF Reduction



NOT APPROVED

Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis

Aaron T. Gerds,¹ Claire Harrison,² Jean-Jacques Kiladjian,³ Ruben Mesa,⁴ Alessandro M. Vannucchi,⁵ Rami Komrokji,⁶ Prithviraj Bose,⁷

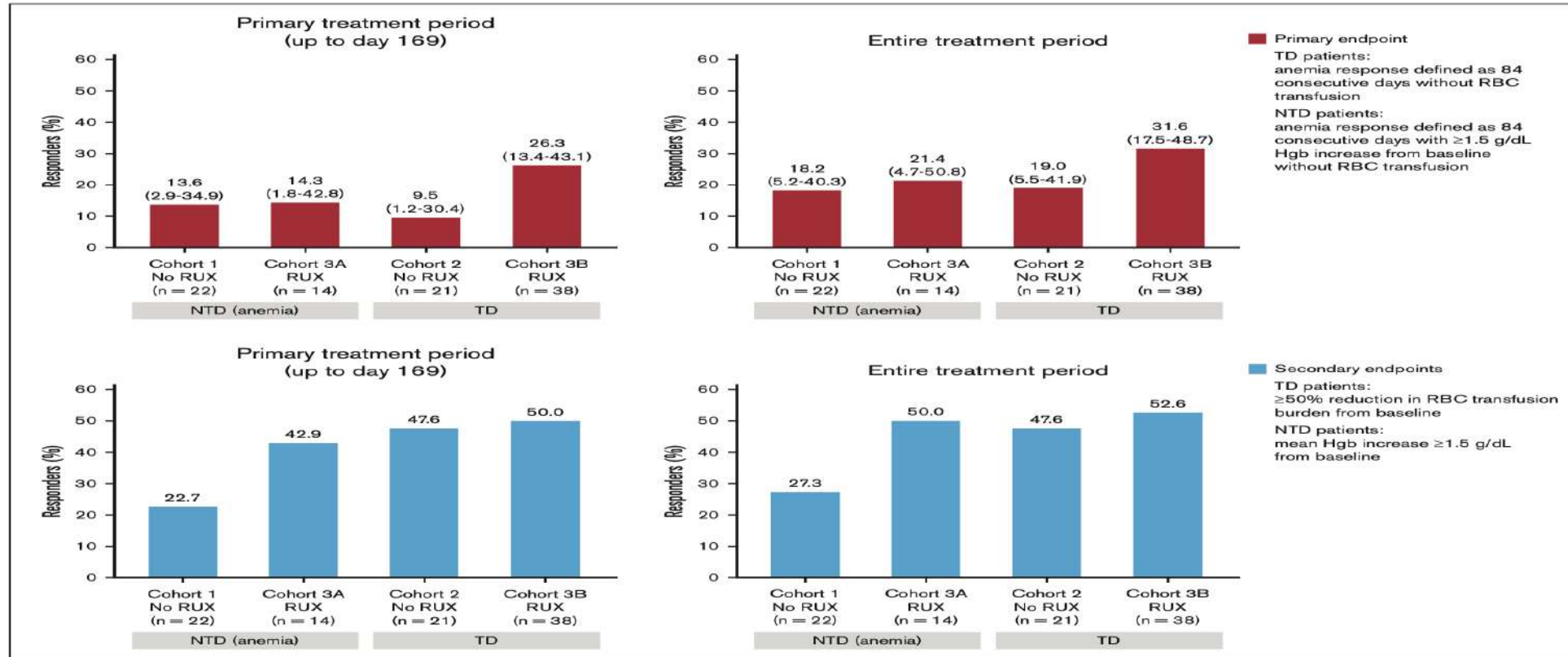


Figure 1. Primary and key secondary end points across all cohorts in the primary and entire treatment periods. TD patients: anemia response defined as 12 consecutive weeks without RBC transfusion; NTD patients: anemia response defined as 12 consecutive weeks with ≥ 1.5 g/dL Hb increase from baseline without transfusion. Values above bars show % patients; top panel shows % patients (95% CI). RUX, ruxolitinib.

The Phase 3 INDEPENDENCE trial will assess **luspatercept** in combination with JAKi for patients with transfusion dependent MF



Key inclusion criteria (N = 309)

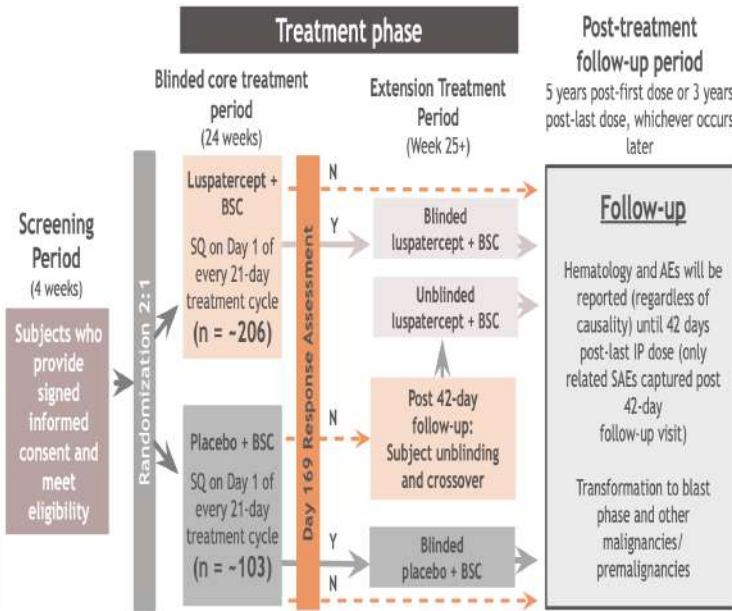
- Baseline transfusion burden (4-12 RBC units/12 weeks)
- JAK2 inhibitor therapy for at least 32 weeks

Primary endpoint:

- RBC-TI ≥ 12 weeks (RBC-TI 12)

Key secondary endpoints:

- RBC-TI ≥ 16 weeks (RBC-TI 16)
- Duration of RBC-TI 12
- Reduction, duration, and change of transfusion burden^a



^a Reduction of transfusion burden defined as proportion of subjects who reduce their transfusion burden by $\geq 50\%$ and by ≥ 4 units/12 weeks from baseline over any consecutive 12-week period.
 AE, adverse event; BSC, best supportive care; DMC, Data Monitoring Committee; EDT, end of treatment; JAK2, janus kinase 2; IP, investigational product; MF, myelofibrosis; MPN, myeloproliferative neoplasm; n, number of subjects; N, Patient did not meet Day 169 Response Assessment criteria; PA1, Protocol Amendment 1; RBC, red blood cell; RBC-TI, red blood cell transfusion independence; SAE, serious adverse event; SQ, subcutaneously; TGF- β , transforming growth factor-beta; Y, Patient met Day 169 Response Assessment criteria.
 1. NCT04717414. Available at: <https://clinicaltrials.gov/ct2/show/NCT04717414>. Accessed November 2024; 2. Kiladjan JJ, et al. Clinical Lymphoma Myeloma and Leukemia; 23: S390.

The Phase 2 ODYSSEY trial will assess **momelotinib** in combination with **luspatercept** in patients with transfusion dependent MF



Key inclusion criteria (N = 56)

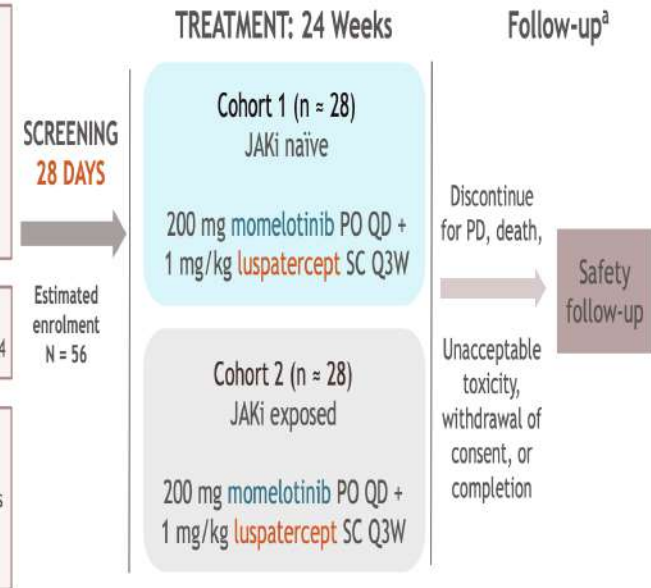
- JAKi naïve or previously treated with either ruxolitinib or fedratinib for MF
- High risk, intermediate-2, or intermediate-1 risk
- TD defined as requiring RBC transfusion ≥ 4 units or Hb < 8 g/dL in the 8 weeks prior to the first dose of study treatment

Primary endpoint:

- Percentage of participants with TI response by Week 24

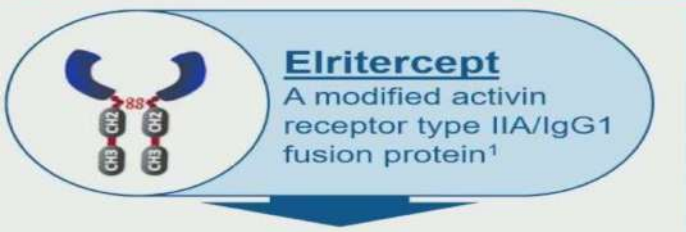
Key secondary endpoints:

- Safety (AEs, SAEs)
- Clinically important changes in laboratory parameters (vital signs, ECOG PS)
- Plasma concentration of momelotinib



^a 42 days after last study treatment.
 AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, hemoglobin; JAKi, janus kinase inhibitor; MF, myelofibrosis; PD, progressive disease; PMF, primary myelofibrosis; PO, by mouth; QD, once daily; Q3W, every 3 weeks; SAE, serious adverse event; SC, subcutaneously; TD, transfusion dependent; TI, transfusion independent.
 Bose P, et al. ASH 2024. Poster presentation 3191.

Elritercept

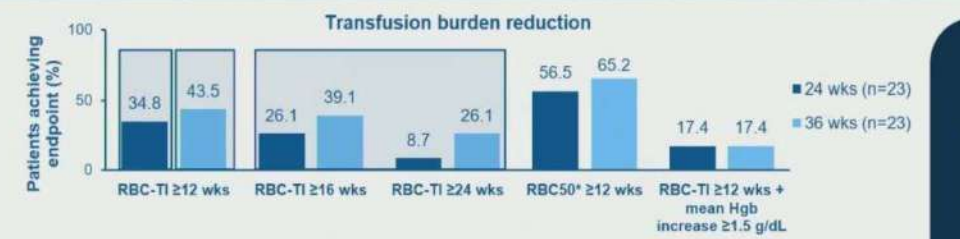


Selectively binds and potentially **blocks downstream signaling** of the TGF- β superfamily ligands **activin A and B** and **GDF8 and 11**¹

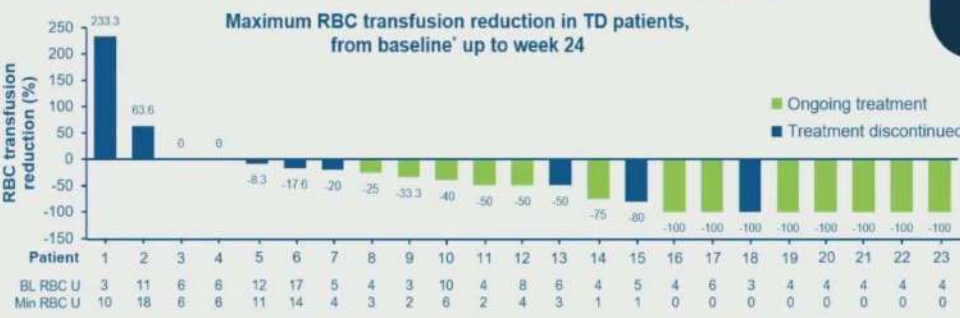
Preclinical data with RKER-050* have demonstrated reversed ruxolitinib-associated reductions in platelet counts⁴

14.3% (2/14) achieved spleen volume reduction $\geq 25\%$, 19% (4/21) achieved $\geq 50\%$ reduction in MF-SAF TSS. Additionally, 36.8% (14/38) of pts achieved mean platelet increase of $\geq 30 \times 10^9/L$

RBC transfusion response in TD patients treated with elritercept plus ruxolitinib

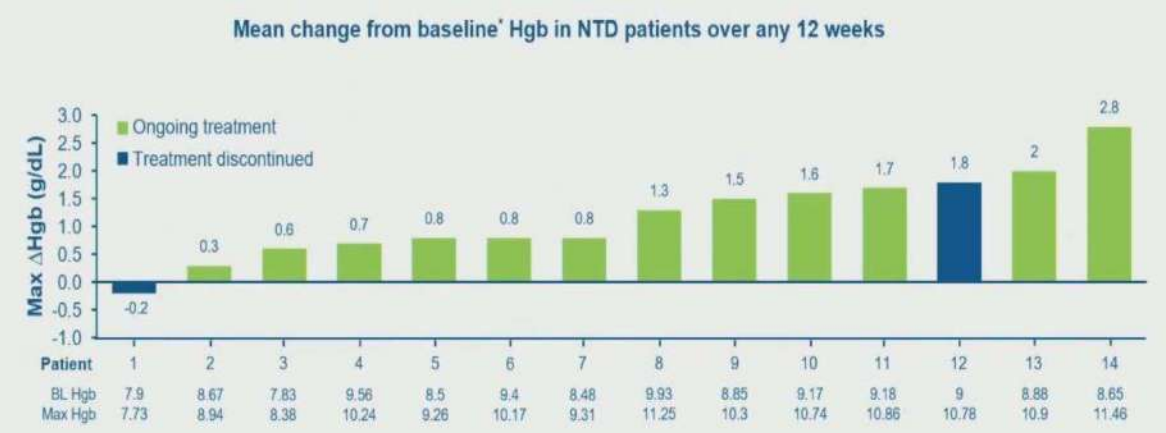


- At the Week 36 assessment:
- 43.5% of patients achieved RBC-TI ≥ 12 weeks
 - 39.1% of patients achieved long responses with RBC-TI ≥ 16 weeks
 - 65.2% of patients achieved at least a 50% reduction in RBC transfusion



*RBC50 was defined as a $\geq 50\%$ decrease in the number of RBC transfusions from baseline over a period of ≥ 12 consecutive weeks within the time period indicated.
 *Baseline was defined as the total number of RBC units/12 weeks.
 BL, baseline; RBC-TI, red blood cell transfusion independence; TD, transfusion dependent (≥ 3 RBC units/12 weeks).
 Data cutoff date: July 21, 2025.

Anemia response among NTD patients treated with elritercept plus ruxolitinib at Week 24

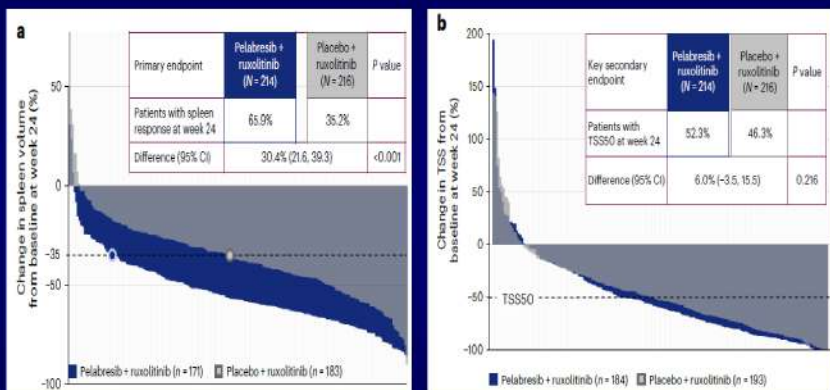


In NTD patients, 35.7% (5/14) and 50.0% (7/14) achieved mean Hgb increases of ≥ 1.5 g/dL and ≥ 1.0 g/dL, respectively, over any 12-week period

Durable efficacy and long-term safety with pelabresib plus ruxolitinib in JAK inhibitor-naïve myelofibrosis: 96-week results from the Phase III MANIFEST-2 study

Raajit Rampal,* John Mascarenhas, Sebastian Grosicki, Dominik Chraniuk, Elisabetta Abruzzese, Prithviraj Bose, Aaron T. Gerds, Francesca Palandri, Vikas Gupta, Sung-Eun Lee, Alessandro Lucchesi, Andrew Kuykendall, Stephen Oh, Andrea Patriarca, Alberto Álvarez-Larrán, David Lavie, Moshe Talpaz, Jean-Jacques Kiladjian, Ruben Mesa, Monika Wroclawska, Xuechan Li, Thomas Lehmann, Harald J. Maier, Claire Harrison, Alessandro M. Vannucchi

Ruxo + pelabresib vs Ruxo + placebo MANIFEST-2 trial

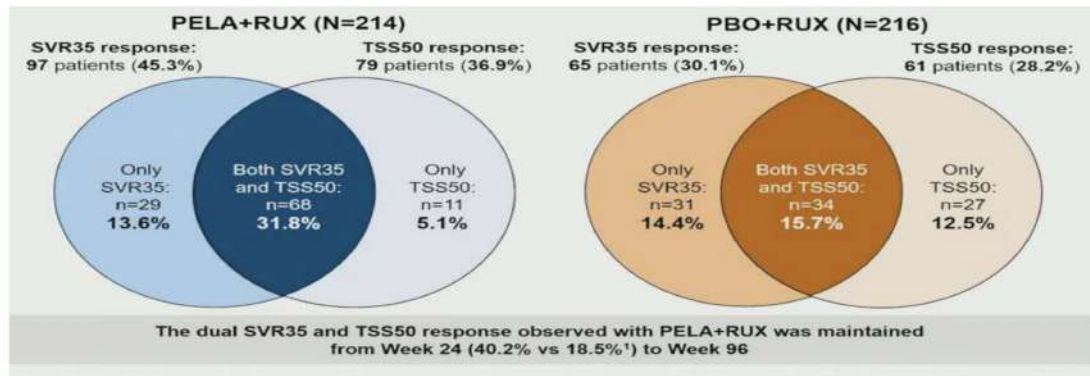


Rampal R, et al. Nat Med 2025;31(5):1531-8

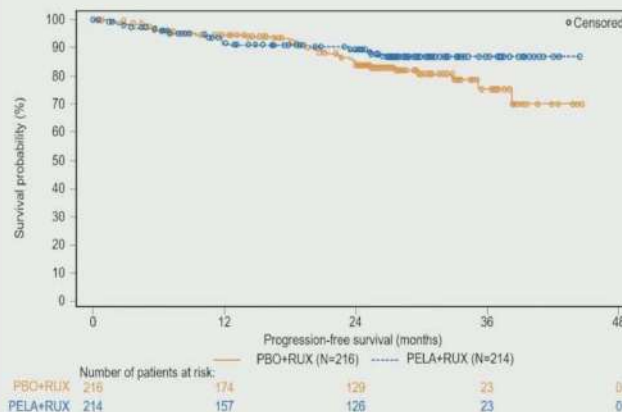
- Mejoría en Hb
- Mejoría en fibrosis
- Mejoría en VAF

En general moderadas

Eficacia



Fewer PFS events were reported in the PELA+RUX arm vs the PBO+RUX arm at the Week 96 data cutoff

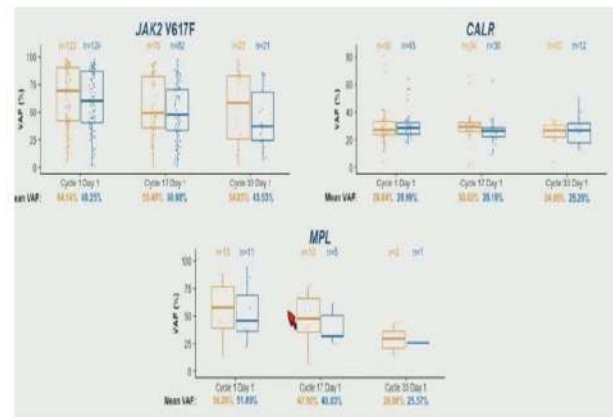
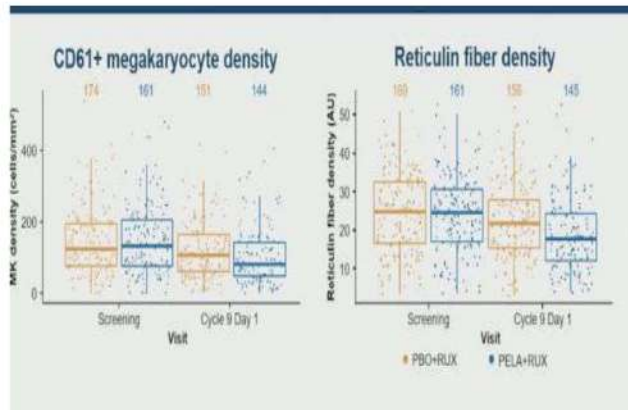
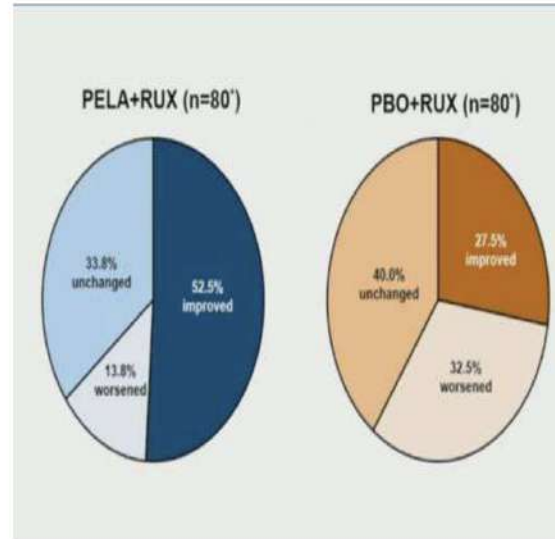
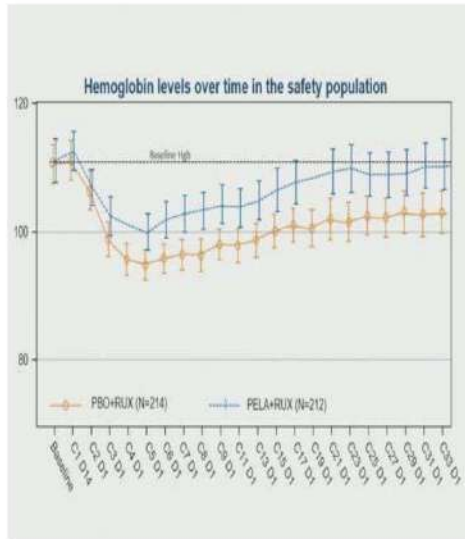


	PELA+RUX	PBO+RUX
Total PFS* events, n (%)	22 (10.3)	34 (15.7)
Progression	11 (5.1)	18 (8.3)
Death without progression	11 (5.1)	16 (7.4)
Hazard ratio (95% CI)	0.746 (0.432-1.291)	

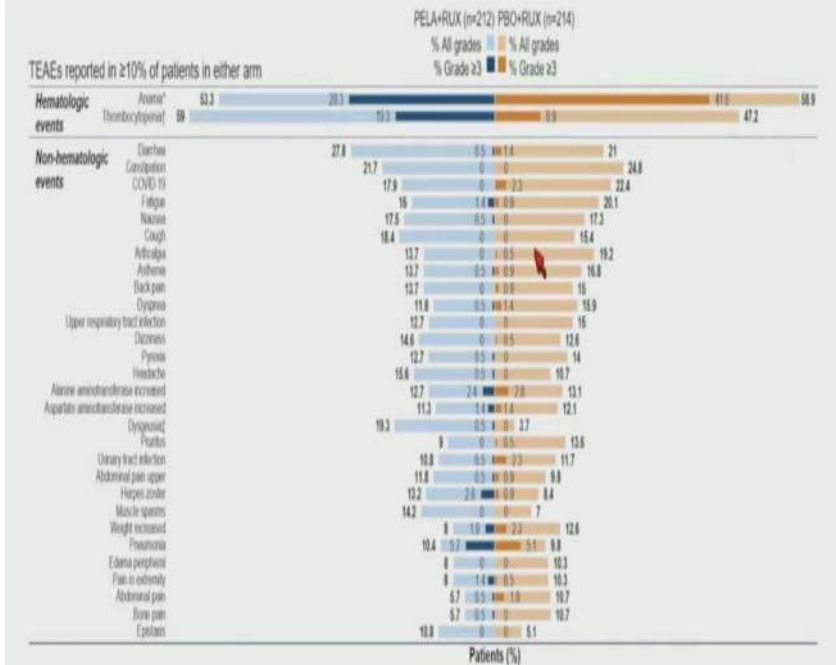
Progression was defined as progressive splenomegaly (enlargement of spleen volume by MRI or CT of ≥25% compared to baseline) or leukemic transformation (confirmed by blast of ≥20%),¹ whichever comes first

Fewer PFS events continue to be observed in the PELA+RUX arm compared with the PBO+RUX arm

Potencial efecto modificador de la enfermedad?



Treatment-emergent adverse events were similar between treatment arms at the Week 96 data cutoff



The majority of TEAEs in both treatment arms were low grade (Grade ≤2)

Data cutoff date: March 9, 2025

AEs are coded using the MedDRA dictionary Version 26.1. A TEAE for the double-blind treatment period is defined as an AE that has a start date on or after the first dose of PELA+RUX and before 30 days after the last dose of PBO+RUX or before the start of alternative (off-study) treatment for WF, whichever occurs first. * Anemia includes preferred terms of anemia and hemoglobin decrease. † Thrombocytopenia includes preferred terms of thrombocytopenia and platelet count decrease. ‡ Dyspnea was successfully managed in most patients by dose modifications of PELA.

AE, adverse event; COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; WF, myelofibrosis; PBO, placebo; PELA, pelabresib; RUX, ruxolitinib; TEAE, treatment-emergent adverse event.

INCA033989 Is a mutCALR-Targeted Therapy for Patients With MF and Essential Thrombocythemia (ET)

- INCA033989 has a unique mechanism of action compared with other available therapies
 - INCA033989 is a novel, fully human, high-affinity, Fc-silenced, immunoglobulin G1 monoclonal antibody that selectively targets mutCALR in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells¹

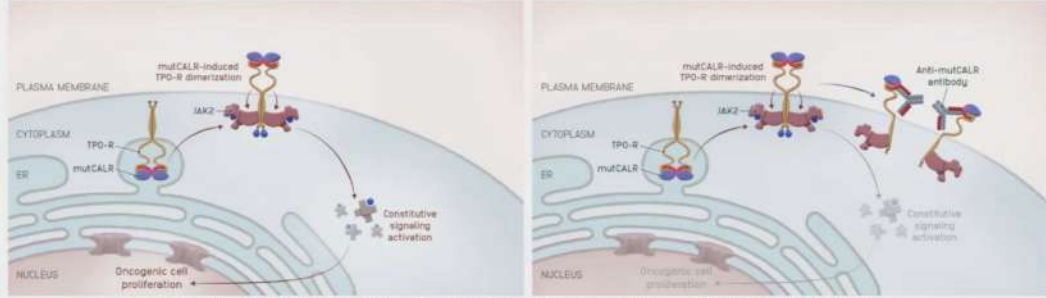
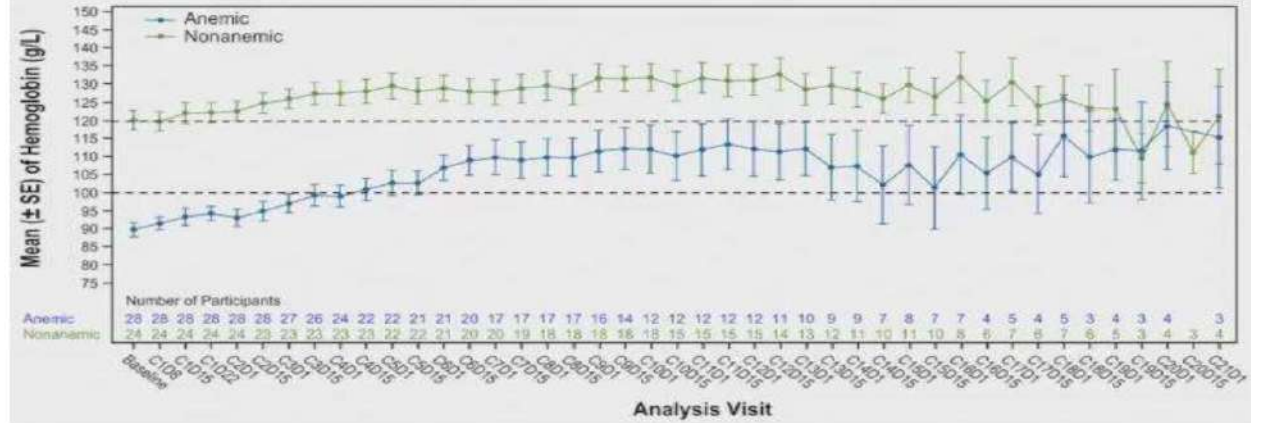
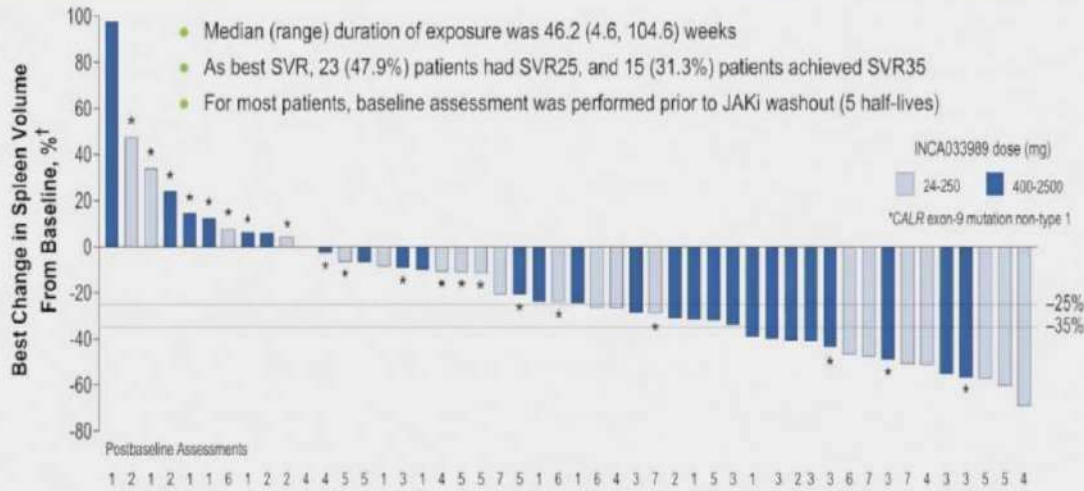


Figure reprinted from Reis E, et al. Blood. 2024;144:2336-2349 [visual abstract] with permission of Elsevier Inc. Copyright © 2024 American Society of Hematology.

Mean Hemoglobin During Study by Anemic Status*

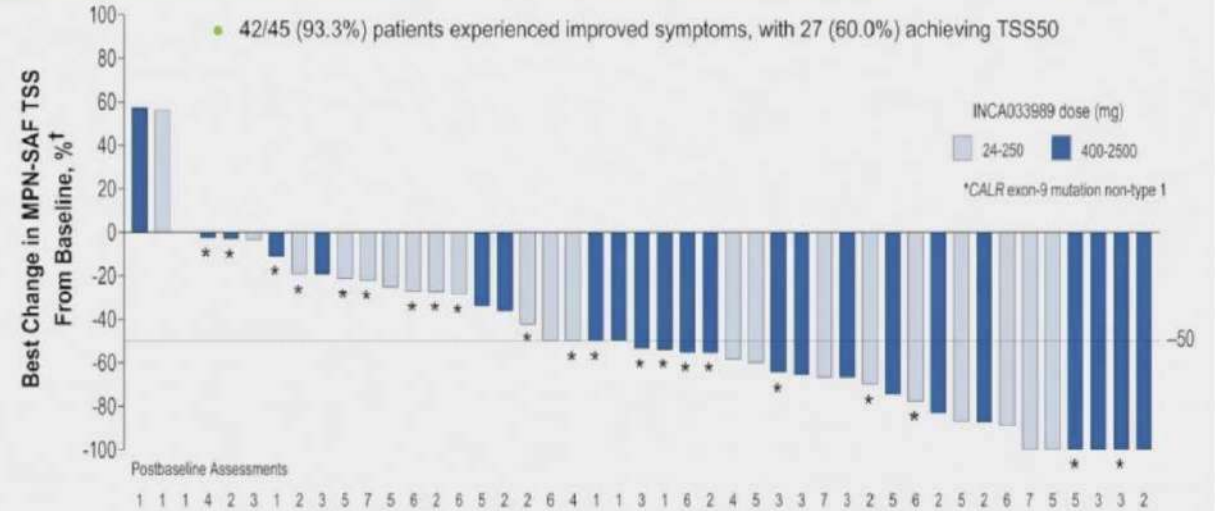


Spleen Volume Reductions Observed With INCA033989 Monotherapy



	SVR at Week 24 (N=36)		
	Total	No Prior JAKi	R/R or Intolerant to JAKi [†]
SVR25, n/N (%)	15/36 (41.7)	5/7 (71.4)	10/29 (34.5)
SVR35, n/N (%)	12/36 (33.3)	4/7 (57.1)	8/29 (27.6)

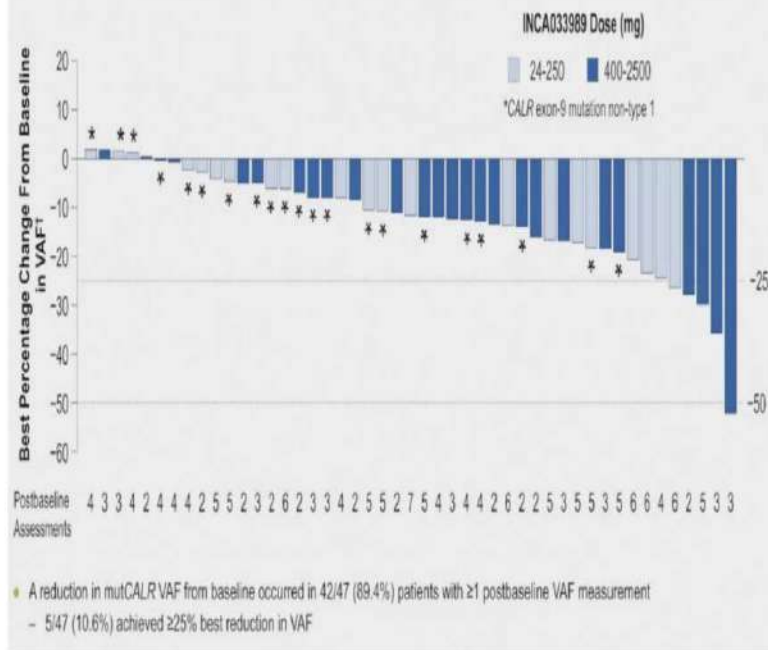
Most Patients Experienced Symptom Improvements With INCA033989 Monotherapy



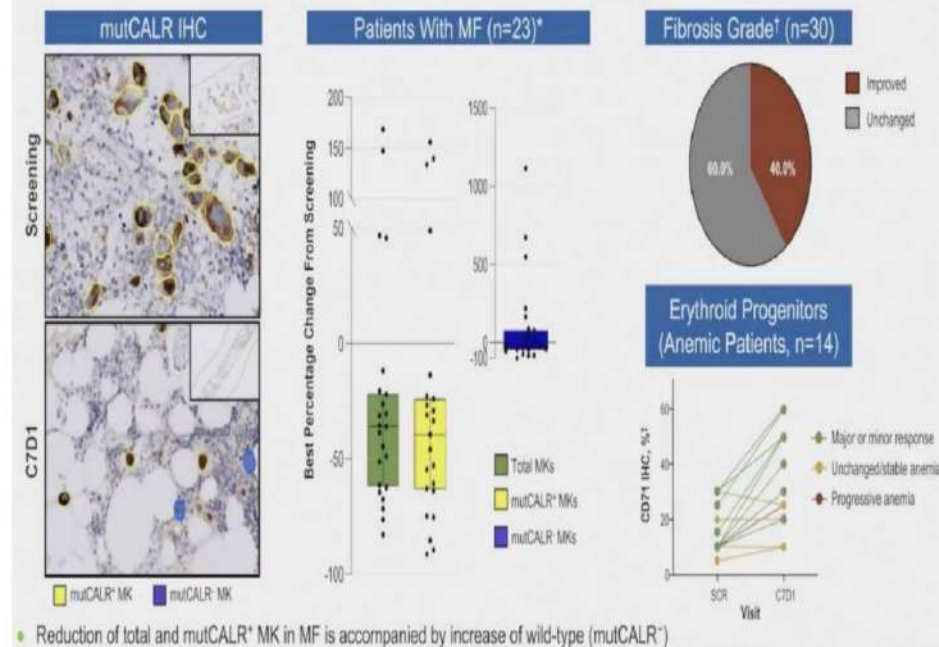
	TSS50 at Week 24 (N=33)		
	Total	No Prior JAKi	R/R or Intolerant to JAKi [†]
TSS50, n/N (%)	13/33 (39.4)	3/5 (60.0)	10/28 (35.7)

Potencial effect in disease modification

Most Patients Experienced VAF Reduction With INCA033989 Monotherapy



Improvement in Bone Marrow Pathology With INCA033989



Most Common TEAEs ($\geq 15\%$ of Patients)

TEAE, % n (%)	N=52			
	Any Grade	Grade 1	Grade 2	Grade ≥ 3 [§]
Anemia	16 (30.8)	7 (13.5)	5 (9.6)	4 (7.7)
Fatigue	14 (26.9)	9 (17.3)	5 (9.6)	0
Thrombocytopenia	13 (25.0)	7 (13.5)	2 (3.8)	4 (7.7) [¶]
Arthralgia	11 (21.2)	5 (9.6)	6 (11.5)	0
AST increased	11 (21.2)	8 (15.4)	2 (3.8)	1 (1.9)
Cough	11 (21.2)	9 (17.3)	2 (3.8)	0
Diarrhea	11 (21.2)	10 (19.2)	1 (1.9)	0
Headache	11 (21.2)	7 (13.5)	4 (7.7)	0
Leukopenia	11 (21.2)	1 (1.9)	6 (11.5)	4 (7.7) [¶]
Nausea	11 (21.2)	9 (17.3)	2 (3.8)	0
Pruritus	11 (21.2)	10 (19.2)	1 (1.9)	0
Hyperglycemia	10 (19.2)	6 (11.5)	3 (5.8)	1 (1.9)
Neutropenia	10 (19.2)	0	5 (9.6)	5 (9.6) [¶]
Nasal congestion	8 (15.4)	6 (11.5)	2 (3.8)	0
Pain in extremity	8 (15.4)	7 (13.5)	1 (1.9)	0

Development of a subcutaneous formulation is ongoing

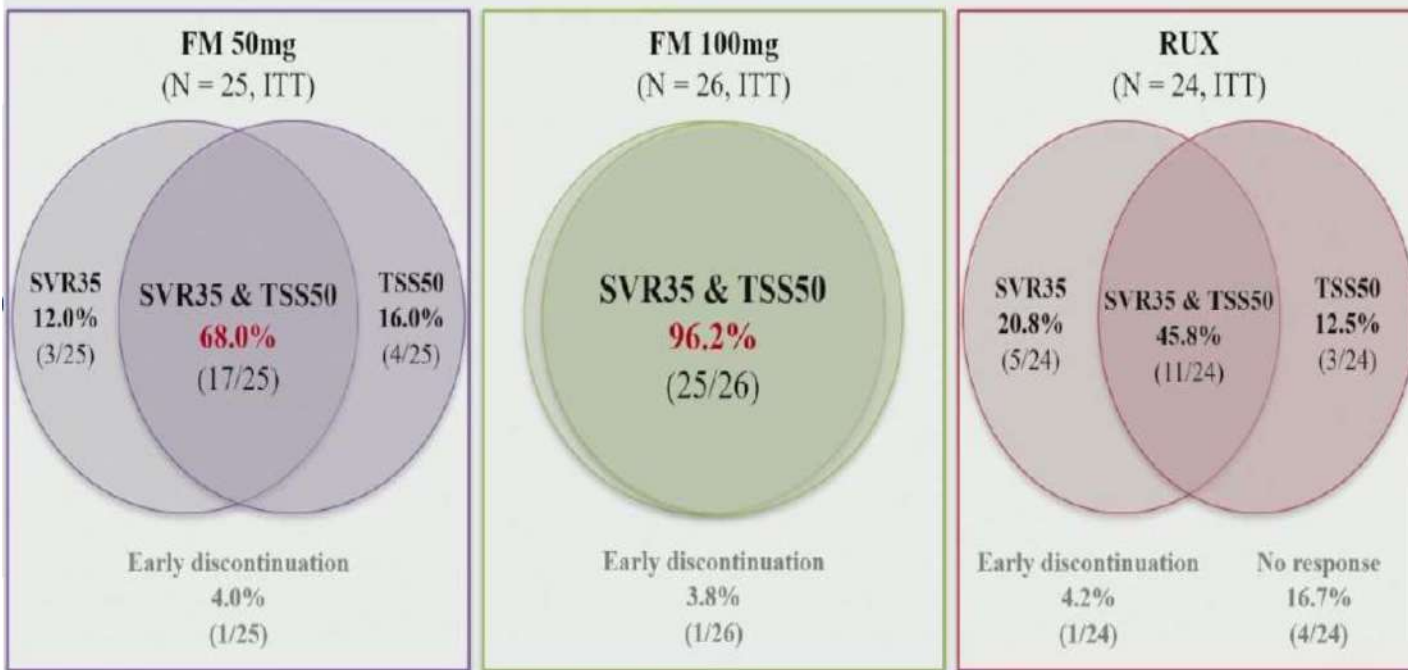
A reduction in mutCALR VAF from baseline occurred in 42/47 (89.4%) patients with ≥ 1 postbaseline VAF measurement
 – 5/47 (10.6%) achieved $\geq 25\%$ best reduction in VAF

Preliminary analysis of a phase 2b, randomized, active-control study of flonoltinib maleate (FM) vs. ruxolitinib in intermediate-2 or high-risk myelofibrosis patients

Lijuan Chen¹, Na Gao², Wei Yang³, Qike Zhang⁴, Hu Zhou⁵, Zhihua Zhang⁶, Lin Liu⁷, Yong Wu⁸, Jinxiao Yao⁹, Zhenfang Liu¹⁰, Zhenya Hong¹¹, Yanping

Song¹², Xiaoyu Zhu¹³, Jia Miao¹⁴, Jinrong Yang¹, Ke Tan¹⁵, Rui Liang¹⁵, Zefeng Xu¹⁶, Ting Niu¹, Zhijian Xiao¹⁶

Updated Efficacy: Over lap of SVR35 and TSS50 response at week 24



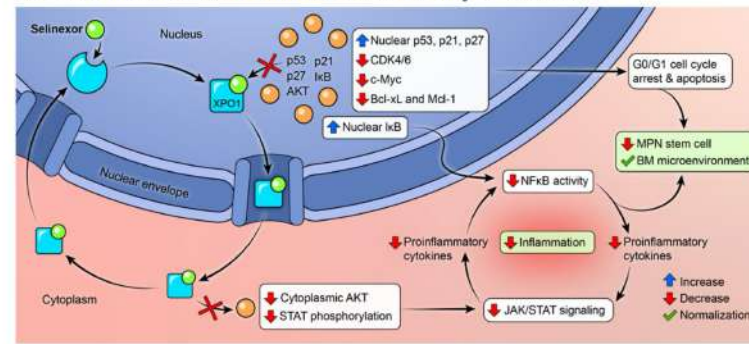
- FM achieved robust dual-endpoint responses at both doses .
- In the FM 100 mg arm, 96.2% of patients achieved both SVR35 and TSS50 at week 24, representing an over two-fold increase in the dual-endpoint response rate with FM vs. RUX

Conclusions

- FM outperformed ruxolitinib in myelofibrosis (MF), with much higher SVR35 and TSS50 response rates at 24 weeks.
- JAK2^{V617F}- and CALR-mutated MF patients could **both benefit** from FM treatment in terms of SVR35 and TSS50 responses.
- Baseline platelet level (≥ 100 or $50-100 \times 10^9/L$) **DOES NOT** affect benefits from FM treatment.
- FM shows superior efficacy in severe **cytopenic** patients.
- Patients on FM treatment are more likely to have **improved / stabilized bone marrow fibrosis**.
- A multicenter, randomized, RUX active-controlled **pivotal Phase 3 trial** are currently ongoing in China.

Selinexor

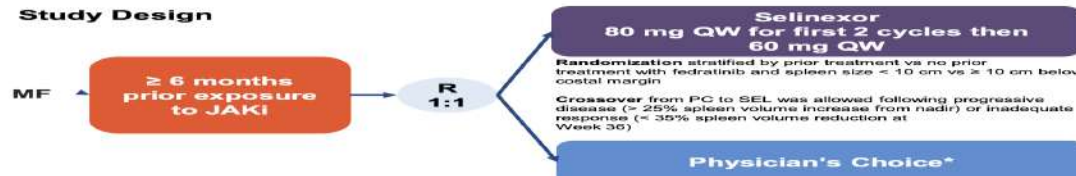
Mechanism of XPO1 inhibition in myelofibrosis



XPORT-MF-035

- This phase 2, global, multicenter, randomized, open-label study evaluated the safety and efficacy of single-agent SEL versus treatment of physician's choice (PC) in patients with previously treated MF (NCT04562870)
 - 16 sites located in China, France, Greece, Hungary, Italy, Poland, Spain, and the United States

Study Design



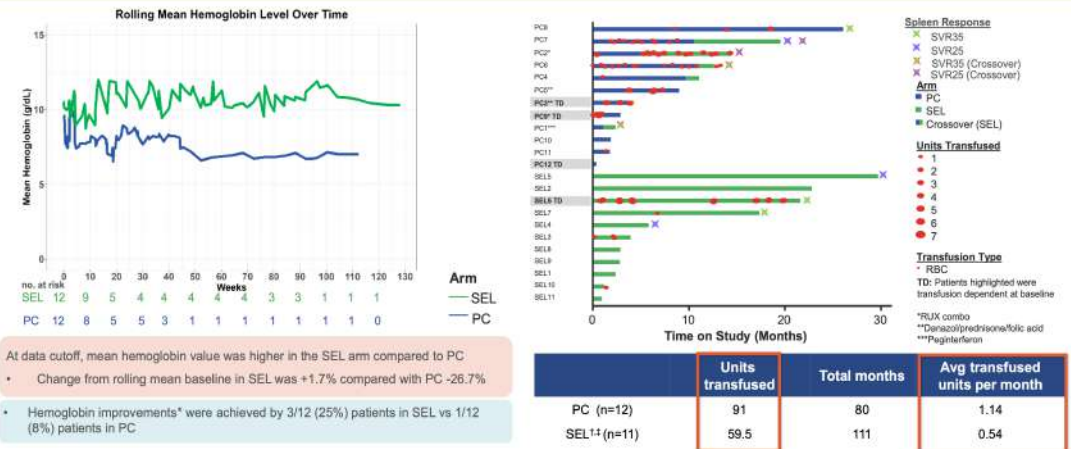
- Primary endpoint**
- SVR35¹
- Key secondary endpoints**
- SVR25
 - TSS50
 - AbsTSS, absolute mean change from baseline to week 24

- Select additional secondary and exploratory endpoints**
- AEs
 - Hemoglobin
 - RBC transfusions
 - Plasma cytokines (up to 71 cytokines/chemokines measured in samples available at screening and week 4)

Spleen Volume Reduction and Symptom Improvement With Selinexor Monotherapy Compared With PC (Efficacy Evaluable)



Hemoglobin Improvements and Reduced Transfusion Frequency With Selinexor Monotherapy



- In the efficacy evaluable population, greater SVR rates were observed with SEL monotherapy compared with PC
 - 11/12 patients in SEL had SVR vs 4/8 in PC

Abb. average; PC, physician's choice; RBC, red blood cell; RUX, ruxitinib; SEL, selinexor; SVR25, spleen volume reduction ≥ 25%; SVR35, spleen volume reduction ≥ 35%; TD, transfusion dependent at baseline.
¹Hemoglobin improvements defined as Hgb change from baseline ≥ 1.5 g/dL without transfusions in the preceding 12 weeks. [†]One patient in SEL only received 1 dose but was later transfused with 9 units. This patient is excluded.
[‡]Does not include SEL after crossover.
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