Inmunoterapia &Hemopatías

Novedades en el tratamiento de la trombocitemia esencial y la policitemia vera

Alicia Senín Magán
Servicio Hematología, Hospital Duran i Reynals-ICO L'Hospitalet

Alberto Alvarez Larrán
Servicio Hematología, Hospital Clínic Barcelona

9 noviembre de 2023

Novedades en el tratamiento de la trombocitemia esencial y la policitemia vera

1. Policitemia vera
   - Tratamiento de los pacientes de bajo riesgo
   - Tratamiento de segunda línea

2. Trombocitemia esencial
   - Nuevos fármacos en segunda línea

Old Clinical trials in PV

- PVSG-01(1967-1974): Phlebotomies vs Chlorambucil vs P32 (n=435)
- PVSG-08 (1986): Hydroxyurea (n=52)
- EORTC (1967-1978): Busulphan vs P32 (n=293)
- FPSG (1980): Pipobroman versus Hu (n=285)

The Management of Polycythaemia Vera

Hematology, 1997, Vol. 2, pp. 55–64
Reprints available directly from the publisher
Photocopying permitted by license only

T. C. PEARSON[a,*] and T. BARBUI[b]

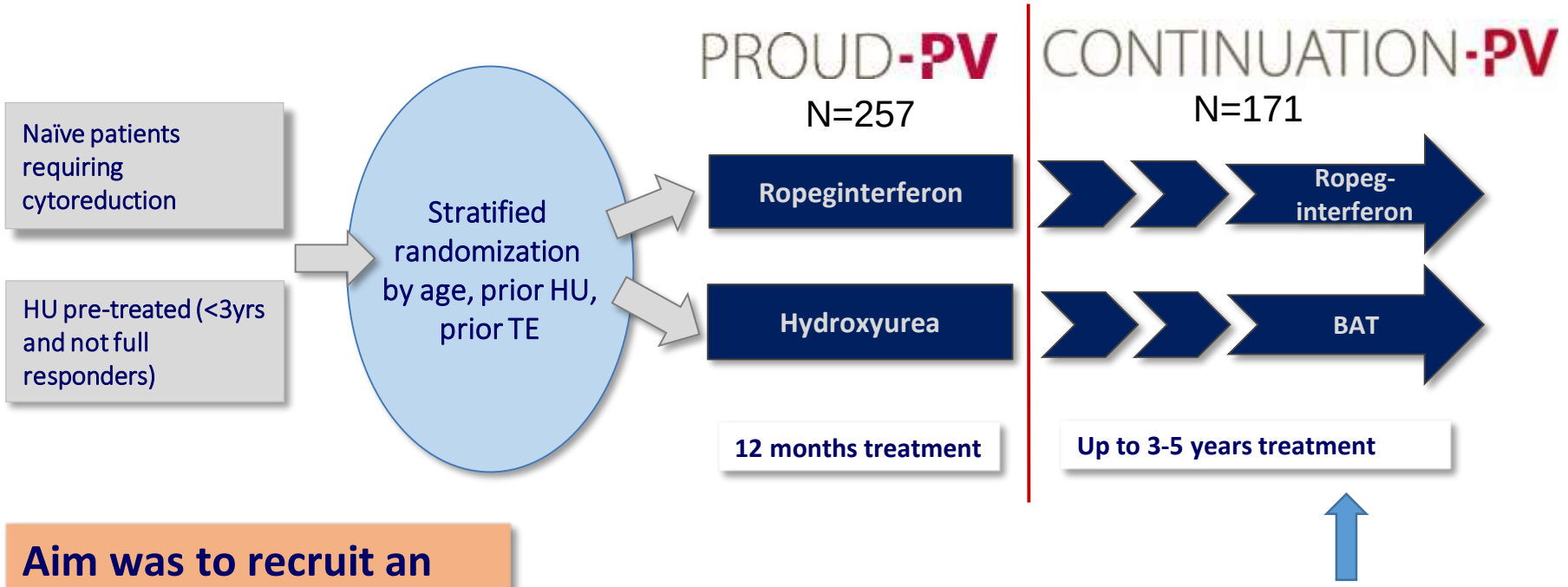
[a]*Division of Haematology, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London, UK.;* [b]*Divisione di Ematologia, Ospedali Riuniti, Bergamo, Italy*

(Received 30 July 1996; In final form 30 August 1996)

- Alkylating agents are effective in managing PV, reducing vascular occlusive events and delaying myelofibrosis. Their mutagenic potential suggest that they should not generally be used in patients under the age of 60 years.

- From the reports so far on the management of PV with hydroxyurea, this agent has a significant role at all ages. However, some anxiety remains about its leukaemogenic potential and thus in younger patients other agents, such as interferon or anagrelide should be considered

Ropeginterferon alfa-2b phase III development in PV: PROUD-PV and CONTINUATION-PV Studies



Aim was to recruit an "early PV" population.

Longitudinal interim analysis after 36 months of treatment (**PROUD-PV and CONTINUATION-PV**) in patients enrolled in CONTINUATION-PV Study:

- **Efficacy data up to 36 months**
- **All available safety data (mean 3.8 years)**

Gisslinger et al., Blood 2018 132:579

Baseline patient characteristics (at screening in PROUD-PV Study)

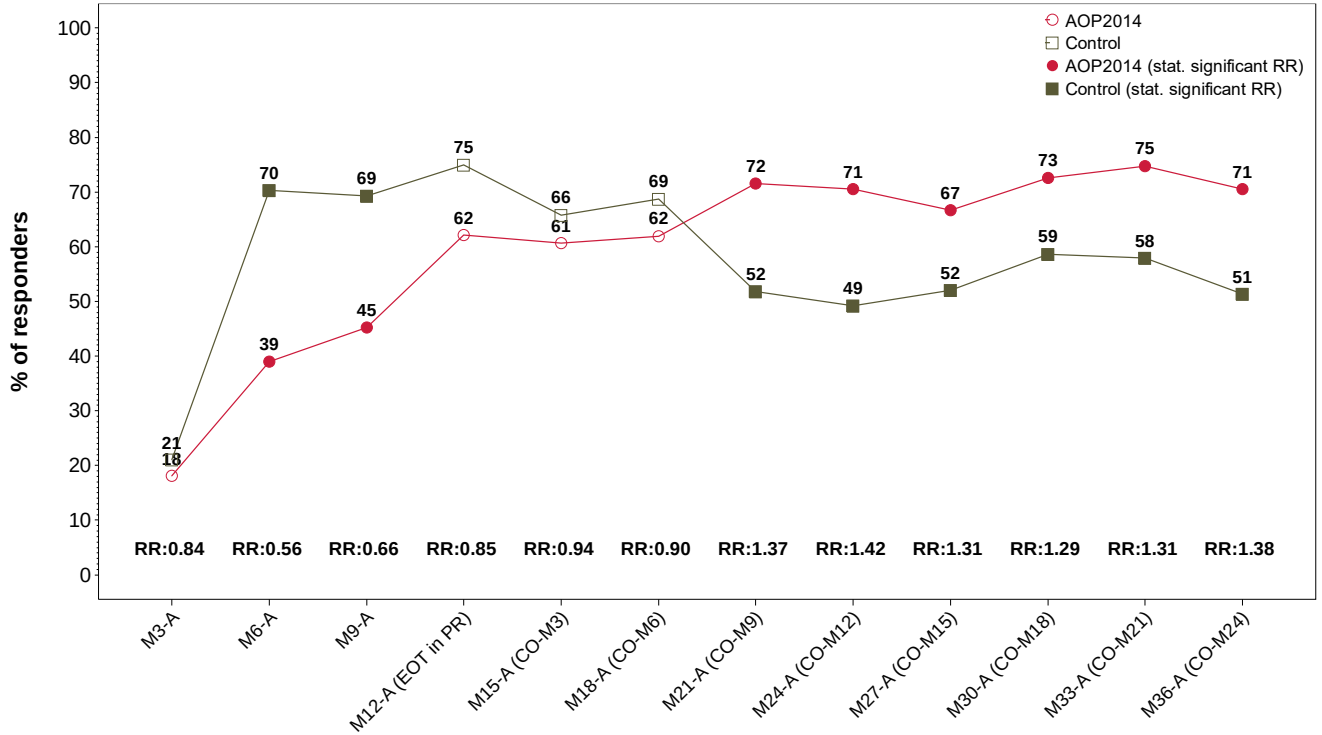
Inmunoterapia &Hemopatías

All patients enrolled in CONTINUATION-PV		
Characteristics at baseline (in PROUD-PV)	**Ropeginterferon (n=95)**	**Control (n=76)**
Caucasian	100%	100%
WHO2008 PV *	100%	100%
Female	48 (50.5%)	40 (52.6%)
Age (median, range)	**58 (30-85)**	**59 (32-79)**
History of thrombosis	**21 (22)**	**14 (18)**
Disease duration (median, range) All patients, both HU naïve and pre-treated	1.8 months (0-146)	1.6 months (0-92)
HU pretreated	31 (32.3%)	25 (32.9%)
Duration of prior HU treatment (n, median, range) In HU pre-treated patients only	**n=30** **9.5 months (0.9-30.9)**	**n=20** **8.2 months (1.0-36.4)**
Hematocrit (mean, SD)	48.3 (±5.30)	42.9 (±23.01)
Spleen length (median, range)	13.5 cm (8.5-25.0)	12.8 cm (7.5-22.0)
Clinically significant splenomegaly at baseline **	7 (7.4%)	8 (10.5%)
Disease-related symptoms at baseline	15 (15.8%)	17 (22.4%)
Median JAK2V617F burden (range)	37.3% (2.6-94.9)	38.1% (2.5- 86.6)

* confirmed by bone marrow biopsy ** Investigator assessment

Gisslinger et al. Blood 2020;136:33

PROUD PV: Continuation study
Complete Hematological Response at 36 Months



Definition of CHR:

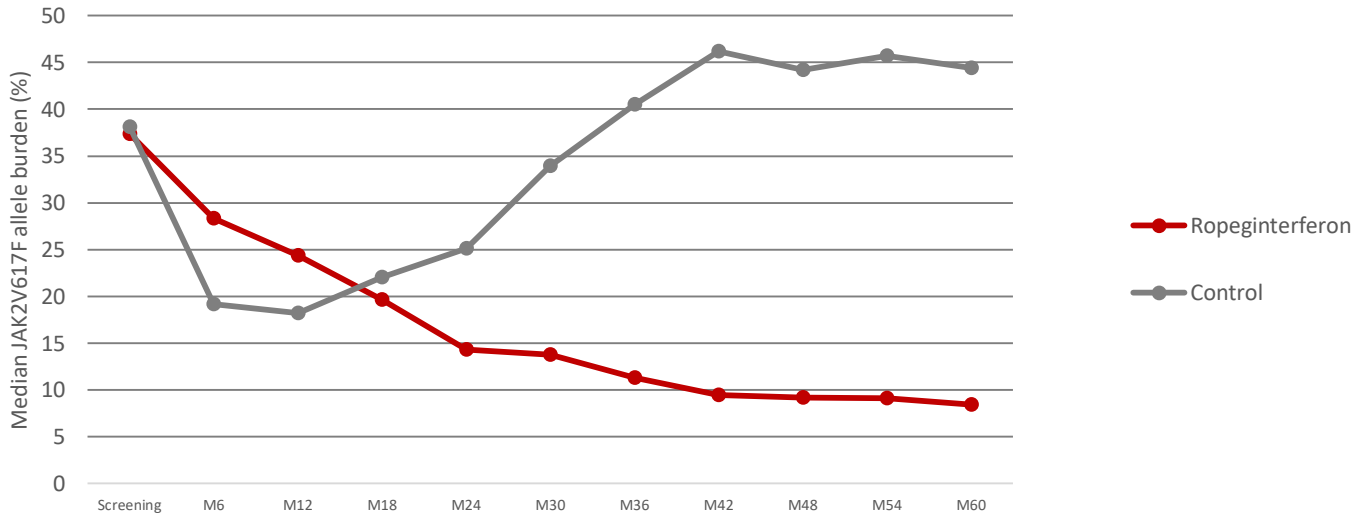
- Hct<45% and no phlebotomy for at least 3 months
- PLTs<400 x 10^9/L
- WBCs<10 x 10^9/L

Discontinued patients were counted as non-responders

	RopegIFN N=95	HU N=76	P value
Complete hematological response	70%	51%	0.01

Gisslinger et al.Blood 2020;136:33

PROUD PV: Continuation study
Molecular response at 60 Months



	RopegIFN N=95	HU N=76	P value
Partial molecular response	69%	22%	<0.001

Kiladjian et al Leukemia 2022

Adverse drug reactions of special interest to IFN therapy

In ropeginterferon-treated patients (N=127)

Disorders by system organ class	N (%) in ropegIFN arm
Endocrine	**6 (4.7%)**
Autoimmune thyroiditis Hypothyroidism Hyperthyroidism	2 (1.6%) 4 (3.1%) 1 (0.8%)
Psychiatric	**1 (0.8%)**
Depression, anxiety, altered mood, nervousness	1 (0.8%)
Musculoskeletal /connective tissue	**2 (1.6%)**
Rheumatoid arthritis Sjögren syndrome	1 (0.8%) 1 (0.8%)
Skin/subcutaneous tissue	**2 (1.6%)**
Psoriasis Increased antinuclear antibody	1 (0.8%) 1 (0.8%)
Immune system / blood and lymphatic system	**1 (0.8%)**
Sarcoidosis	1 (0.8%)

**Treatment related AEs of special interest to IFN therapy as assessed by the Investigator. Thromboembolic events are reported separately.*

Gisslinger et al. Blood 2020;136:33

Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study)

- Low-risk patients age < 60 years, no history of thrombosis
- Cytoreduction naïve
- No history of autoimmune disease or antithyroid antibodies
- No history of depression requiring treatment with antidepressant drugs
- **Htc < 45% prior to ramdomization (Phlebotomies 250-400 ml)**

Ropeginterferon N=50

- Ropeginterferon alfa-2b 100 mcg/2weeks (Fixed dose)

Phlebotomies N=50

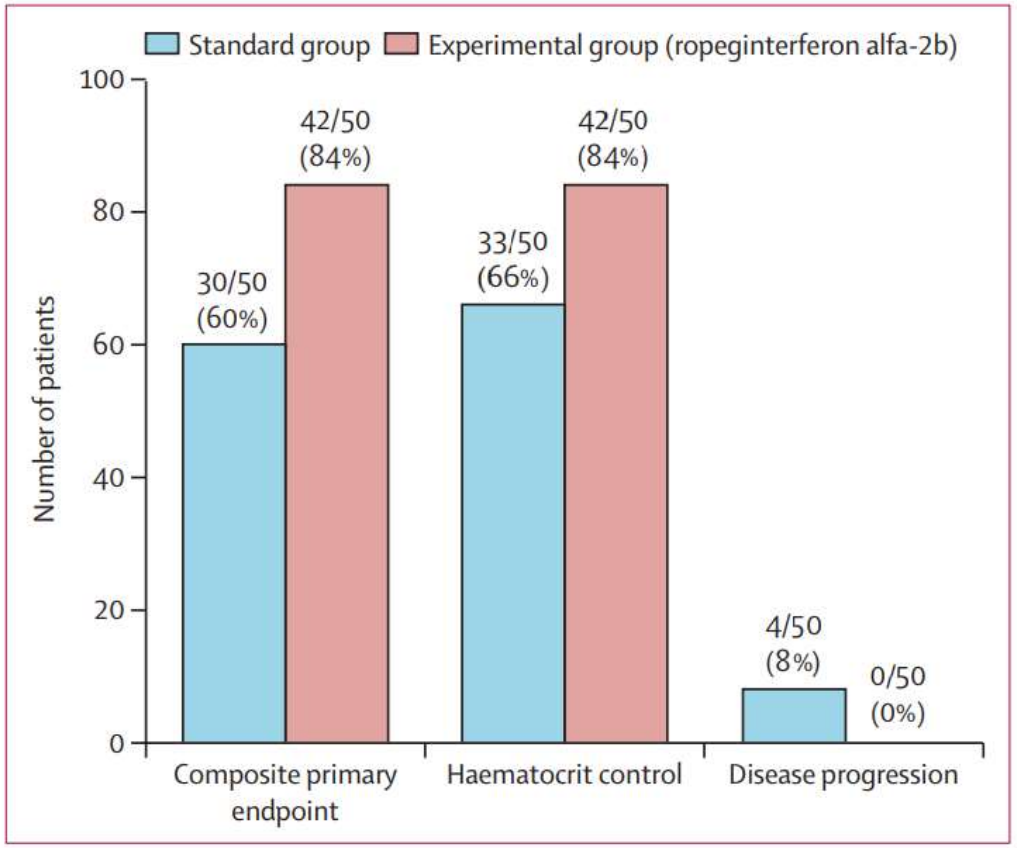
- Phlebotomies (300 ml)

Monthly visits

If HTC > 45%

Phlebotomies in both arms

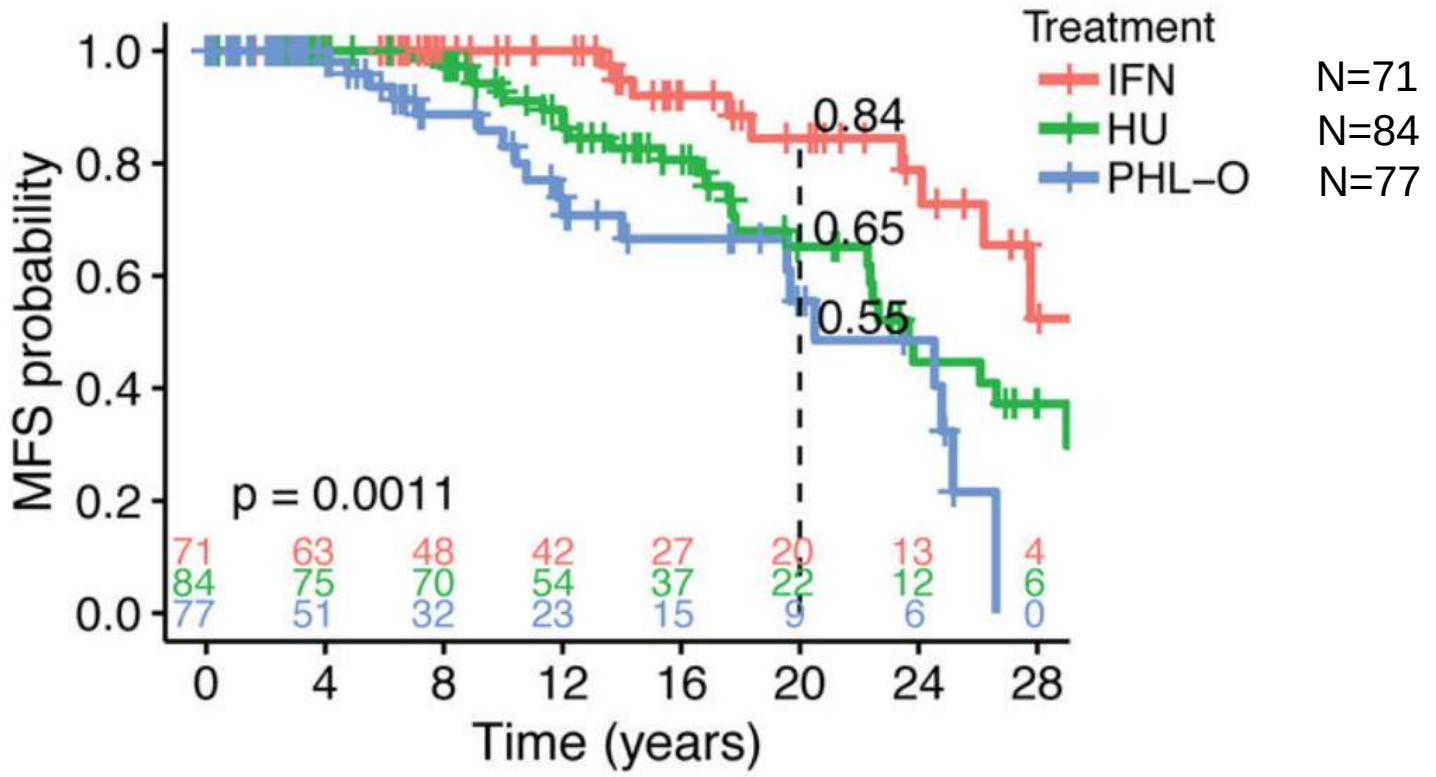
Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study): efficacy at 12 months



Composite endpoint: maintenance of median HTC <45% during the 12-month period, in the absence of progressive disease.
Disease progression: progressive symptomatic thrombocytosis and progressive leukocytosis, thrombosis or major bleeding

- **Composite endpoint:** (OR 3·5, 95% CI 1·3–10·4; absolute difference 24%, 95% CI 7–41%, p=0·0075; figure 2)
- **Disease progression:** thrombocytosis plus microvascular symptoms n=3, splenic vein thrombosis n=1
- **Adverse events attributed to treatment:** 6% versus 48% in the standard and experimental group, respectively (p<0·0001)

Interferon-alpha improved myelofibrosis-free survival in low risk patients n=262



Median follow-up 10 years

Abu-Zeinah G, leukemia 2021

ELN indications of cytoreductive therapy in low-risk PV

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

Recommended

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

Should be considered

- Persistently high cardiovascular risk
- Persistently high symptom burden

Can be considered

Marchetti, et al. Lancet Haematology 2022

PERSONAL RECOMMENDATIONS REGARDING CYTOREDUCTIVE THERAPY IN LOW-RISK PV

- Peg-IFN is the preferred option for young patients (< 50 years)
- In patients 50-60 years old, Peg-IFN or HU according to patient characteristics and preferences
- Ropeginterferon or other available formulations (pegasys) might be used
- Besides ELN indications, Peg-IFN treatment in those cases with *JAK2*V617F > 50%

Novedades en el tratamiento de la trombocitemia esencial y la policitemia vera

1. Policitemia vera
   - Tratamiento de los pacientes de bajo riesgo
   - Tratamiento de segunda línea

2. Trombocitemia esencial
   - Nuevos fármacos en segunda línea

Resistance/Intolerance to HU: modified criteria

Need of phlebotomies Myeloproliferation Massive splenomegaly	→	After 3 months at MTD of HU
Symptoms Thrombosis or bleeding	→	At any HU dose
Cytopenia	→	At the lowest dose of HU to achieve response
Extrahematological toxicity	→	At any HU dose

McMullin et al, BJH 2015

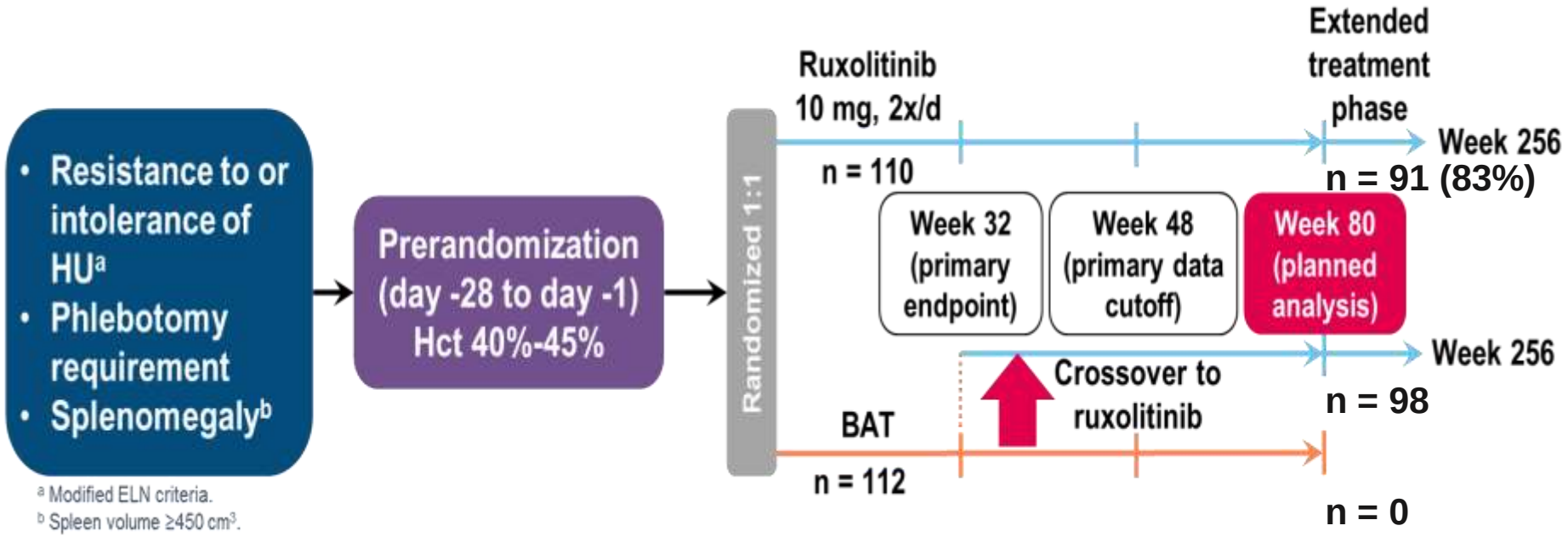
Genomic classification of PV patients treated with HU

Genomic subgroup	HU Resistant N=61	Controls N=59	Grinfeld N=356
TP53 disruption/aneuploidy	16%	1.7%	< 2%
Chromatine/spliceosome mutation*	38%	12%	11%
PV with homozygous *JAK2* mutation	28%	44%	45%
PV with heterozygous *JAK2* mutation	16%	41%	40%

*≥1 aberrations in chromatin or spliceosome genes (EZH2, IDH1, IDH2, ASXL1, PHF6, CUX1, ZRSR2, SRSF2, U2AF1, KRAS, NRAS, GNAS, CBL, Chr7/7qLOH, Chr4q/LOH, RUNX1, STAG2, and BCOR) according to Grinfeld et al NEJM 2018

Alvarez Larrán et al, Leukemia 2020

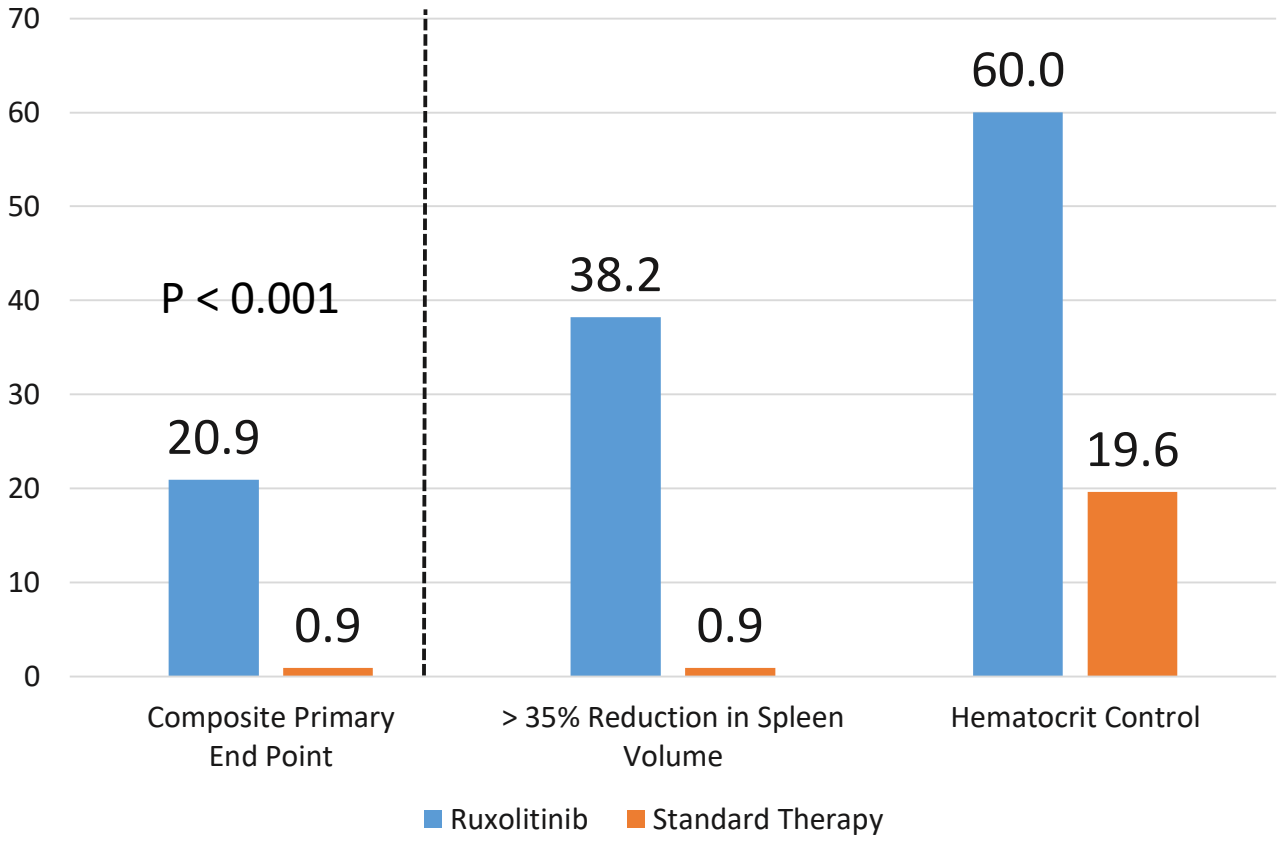
Ruxolitinib in PV: Response study



- **Primary composite endpoint:** hematocrit control in the absence of phlebotomy and ≥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
- **BAT:** hydroxyurea, IFN/peg-IFN, anagrelide, pipobroman, IMIDS or observation

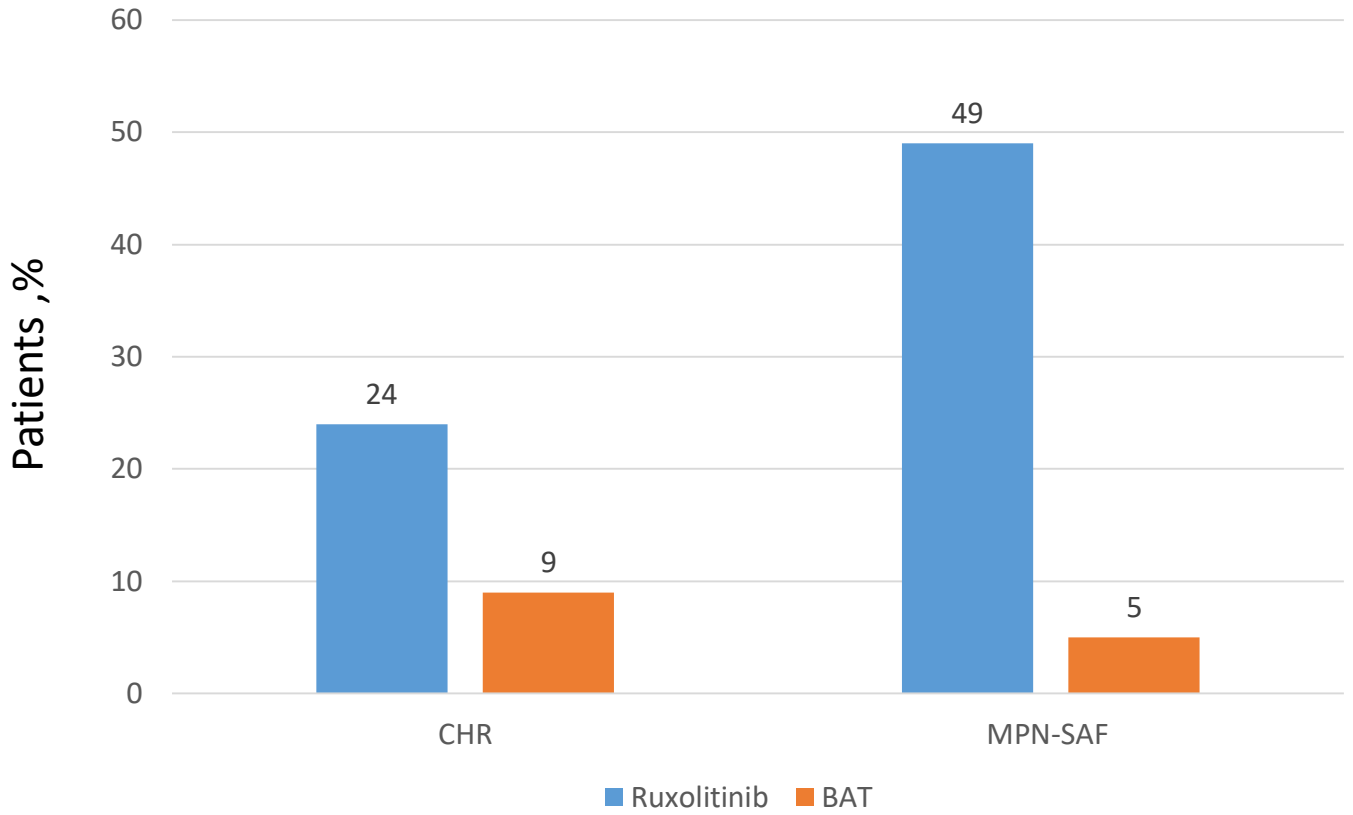
Kiladjian et al, EHA 2015

Response: primary endpoint at week 32



Vannucchi et al NEJM 2015

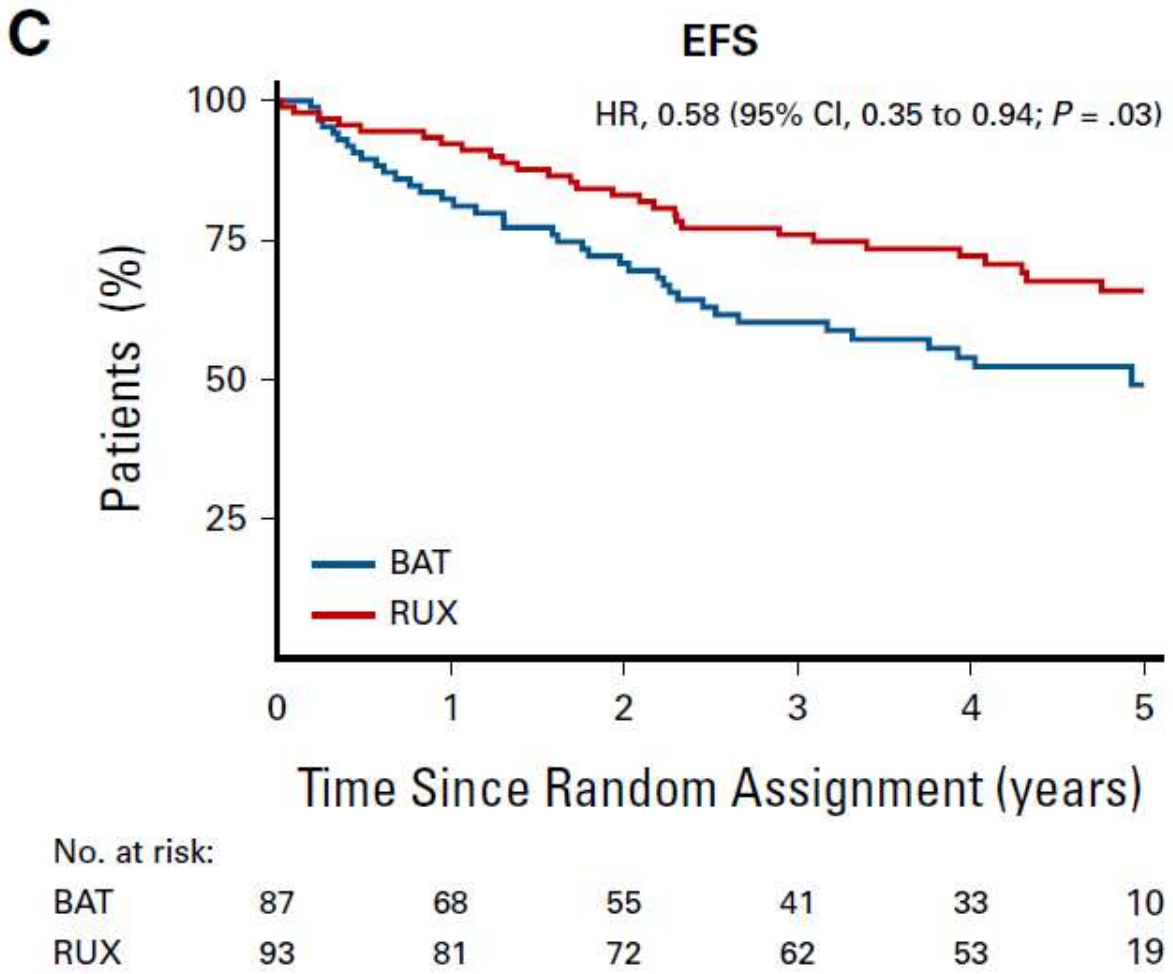
Efficacy of ruxolitinib in polycythemia vera: RESPONSE TRIAL



- CHR: Hematocrit control, platelets < $400x10^9$/L and WBC < $10x10^9$
- MPN-SAF: percentage of patients with ≥ 50% improvement in MPN-SAF symptom score

Vannucchi et al NEJM 2015

MAJIC-PV: Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide



- CR was achieved in 40 (43%) patients on ruxolitinib versus 23 (26%) on BAT (odds ratio, 2.12; 90% CI, 1.25 to 3.60; P 5 .02).
- Duration of CR was superior for ruxolitinib (hazard ratio [HR], 0.38; 95% CI, 0.24 to 0.61; P < .001).
- Symptom responses were better with ruxolitinib and durable.
- Molecular response was more frequent with ruxolitinib with >50% reduction observed in 56% and 25% of ruxolitinib and BAT, respectively (P < .001)

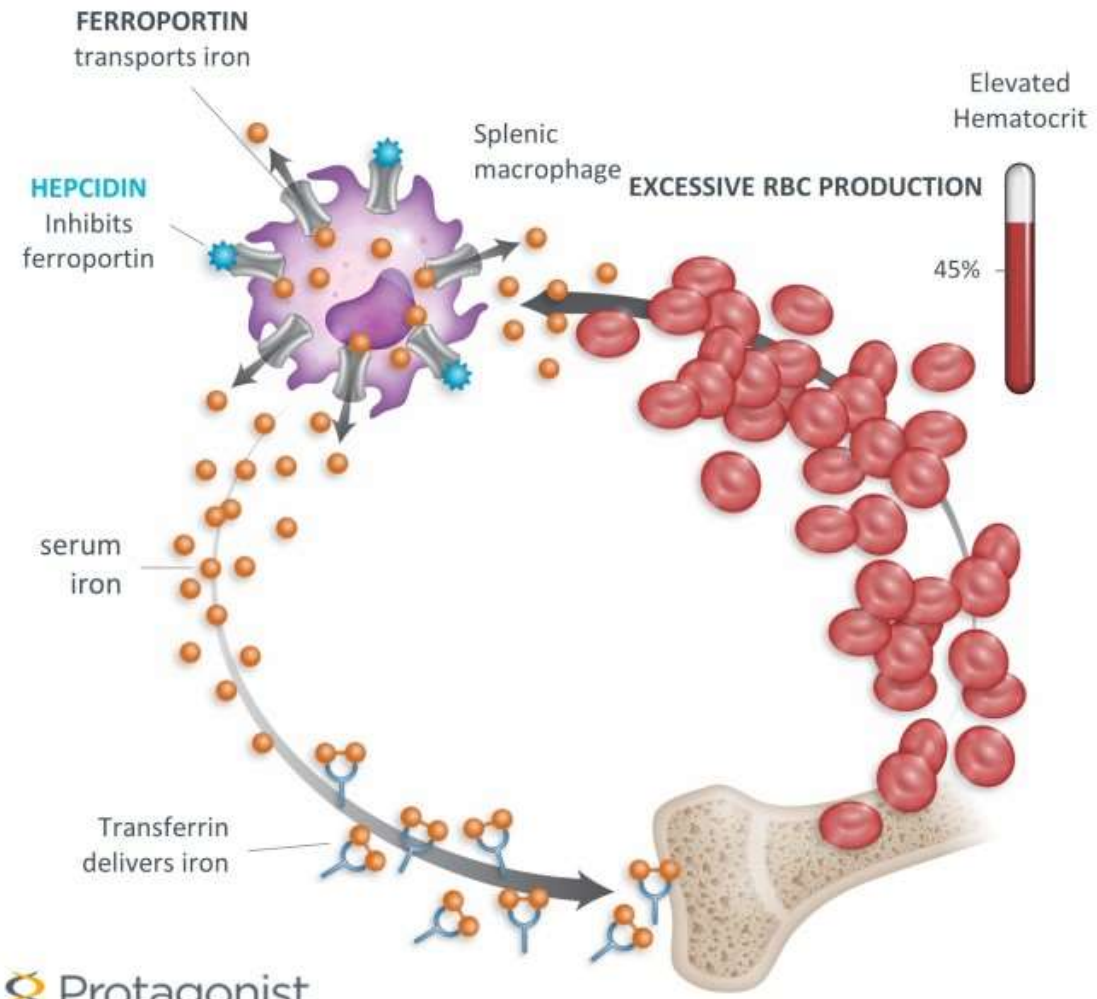
Harrison, JCO 2023

PERSONAL RECOMMENDATIONS REGARDING SECOND LINE CYTOREDUCTIVE THERAPY IN PV

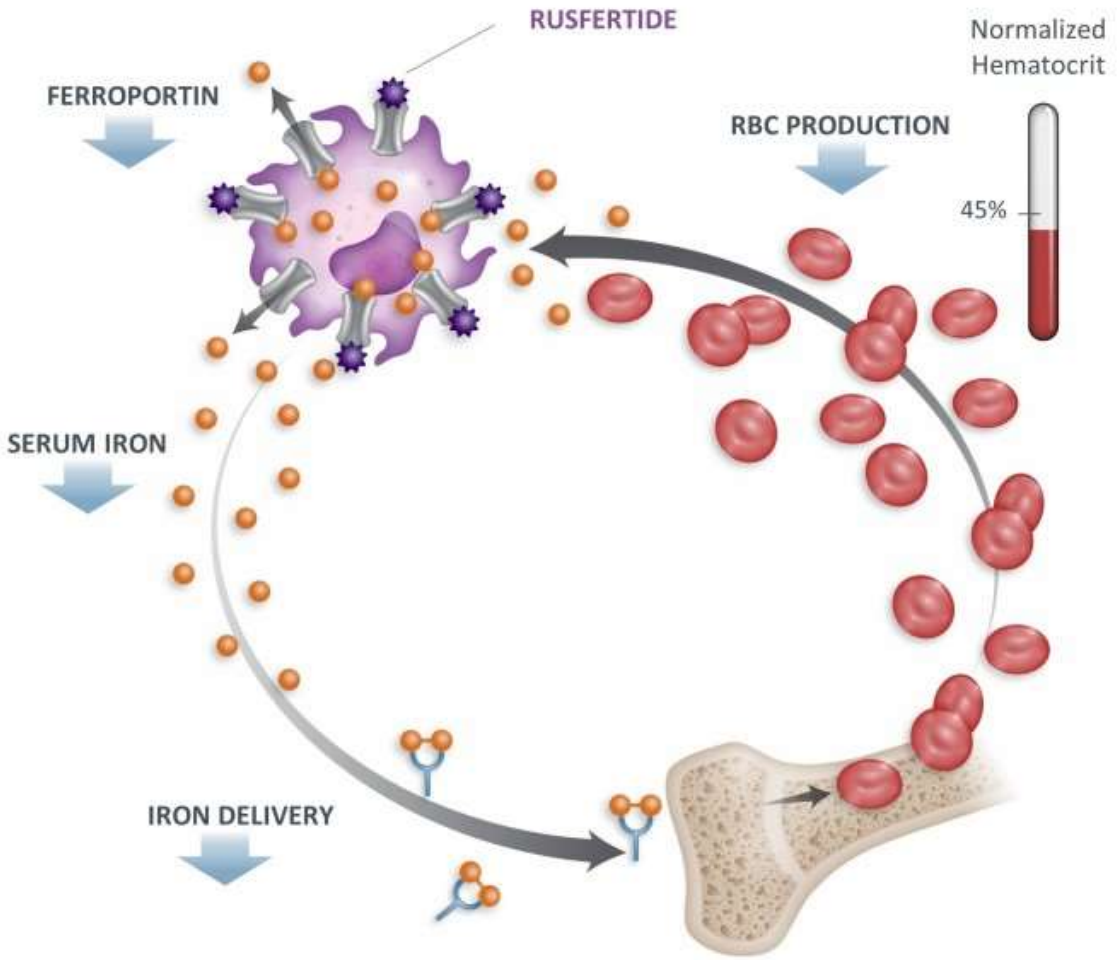
- Ruxolitinib is the preferred option in the majority of patients
- Anagrelide might be added in those cases with persistent thrombocytosis instead of increasing ruxolitinib dose
- Peg-IFN for young patients (< 50 years)
- Busulphan in selected old patients with intolerance to HU

Rusfertide: Mechanistic Rationale for Potential Treatment of PV

Polycythemia Vera



MOA of rusfertide

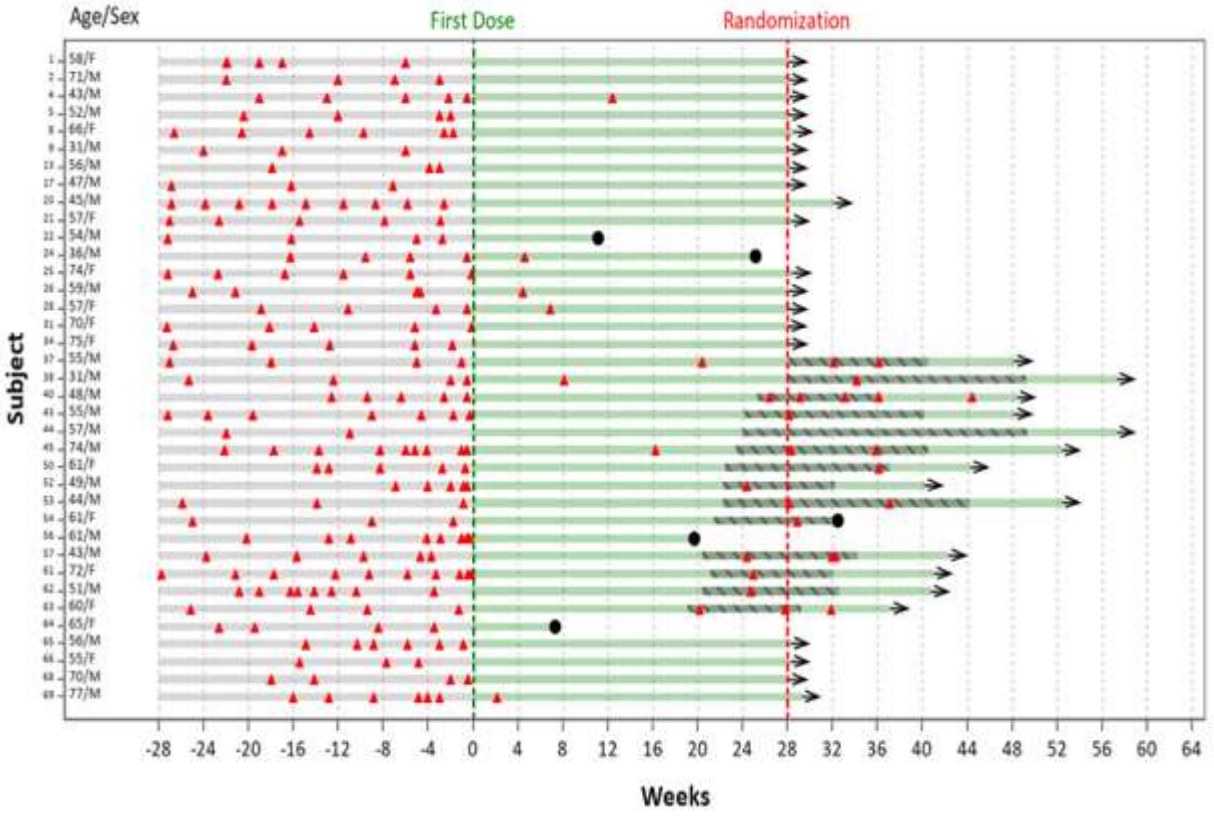


Protagonist Therapeutics

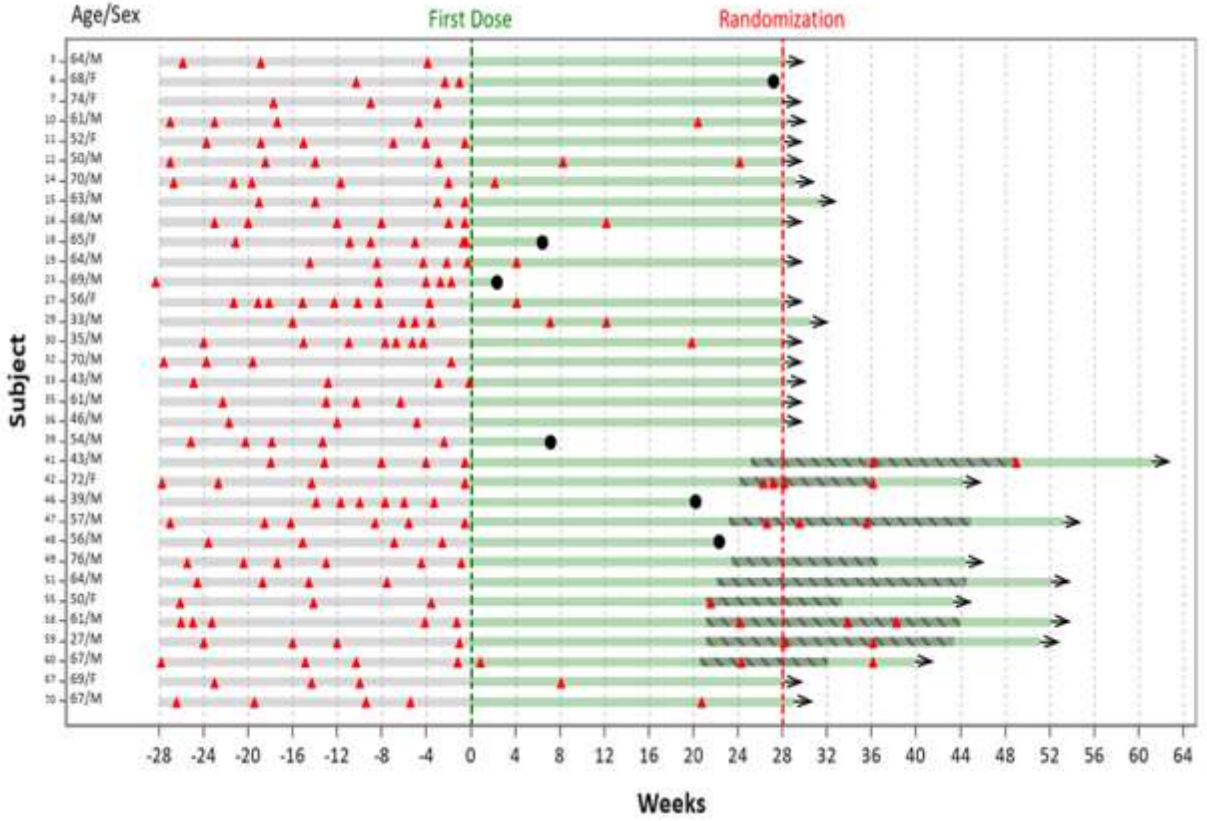
REVIVE TRIAL Part 1: Dose Finding and Efficacy Evaluation, Weeks 1-28

Inmunoterapia &Hemopatías

Phlebotomy Only (n=37)



Phlebotomy + Cytoreductive (n=33)



Screening | Part 1 - Dose Finding | Drug Suspension | Phlebotomy | Last Dose on Study

FUTURE INDICATIONS OF RUSFERTIDE IN PV

- Rusfertide will be an alternative option for low-risk patients with intolerance or requiring frequent phlebotomies

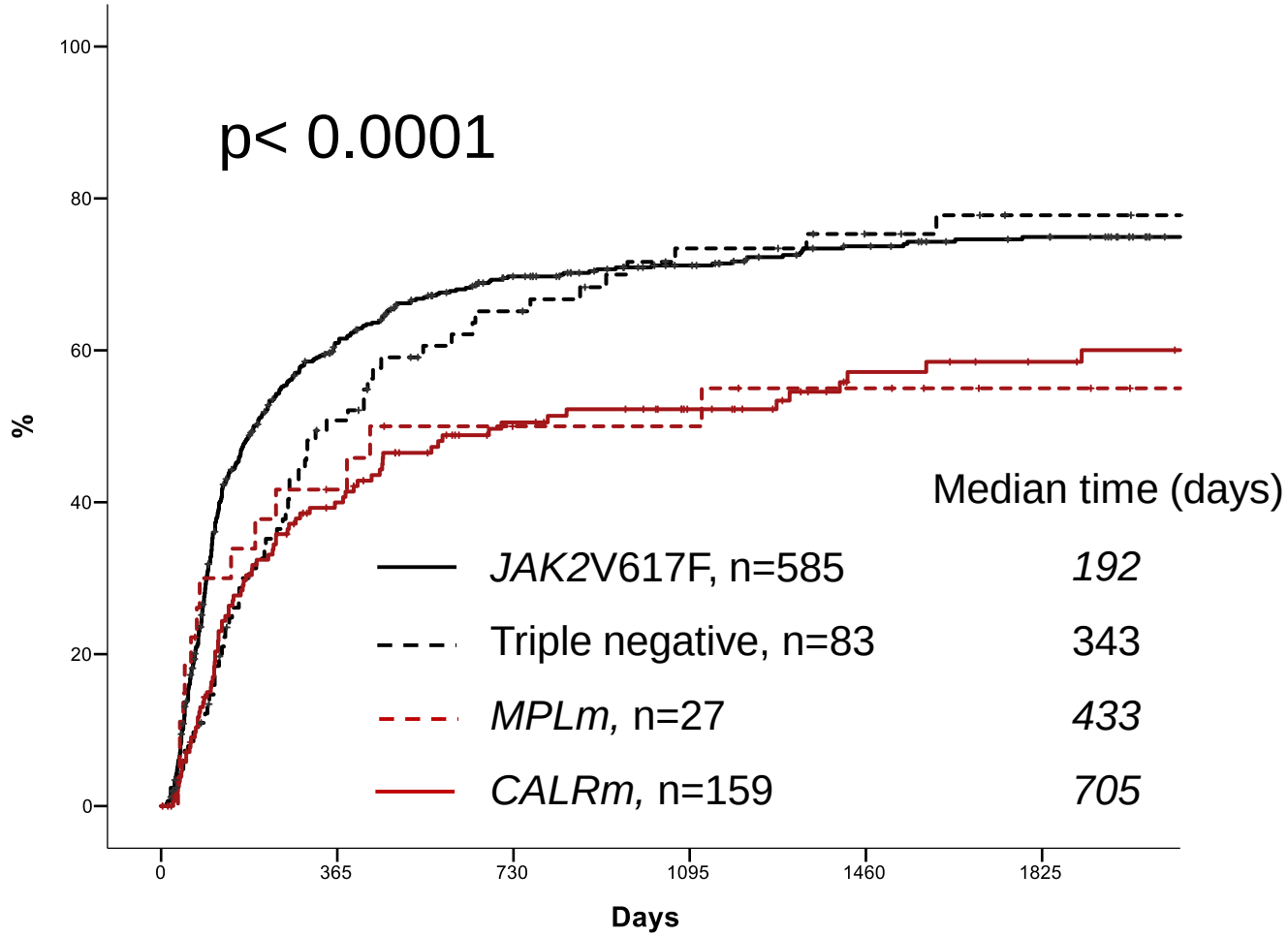
- Rusfertide will be the best option for the majority of high-risk patients requiring frequent phlebotomies under HU therapy

Novedades en el tratamiento de la trombocitemia esencial y la policitemia vera

1. Policitemia vera
   - Tratamiento de los pacientes de bajo riesgo
   - Tratamiento de segunda línea

2. Trombocitemia esencial
   - Nuevos fármacos en segunda línea

Time to complete hematologic response according to genotype in ET



Complete hematologic response was defined as normalization of the platelet count (< 400 x 10^9/L) in the absence of disease-related symptoms, with a normal spleen size and a leukocyte count ≤ 10 x 10^9/L. Response was assessed in 916 out of 1104 patients. Cytoreductive treatment included HU n = 977, anagrelide n = 113, interferón n = 10, radioactive phosphorus n = 2, or HU plus anagrelide n = 2.

Alvarez-Larrán et al BJH 2021

Studies reporting efficacy in clinical practice of available cytoreductive agents in *CALR*-mutated essential thrombocythemia

Author (year)	Type of study	Treatment line	Medication (patients)	Efficacy
Alvarez-Larrán et al (2021)	Retrospective	First	Hydroxyurea (n=166) Anagrelide (n=38)	CR 40% at 12 months
Ito et al (2019)	Retrospective	First	Anagrelide (n=11)	CR 36%, PR 55%
Mela Osorio et al (2016)	Retrospective	First and second	Anagrelide (n=19)	CR 47%, PR 47%
Verger et al (2015)	Retrospective	First and second	Peg-rIFNα (n=31)	CR 77%, PR 23%
Yacoub et al (2019)	Retrospective	Second	Peg-rIFNα (n=23)	CR 57%
Desterro et al (2019)	Retrospective	First	rIFNα (n=22)	CR 59%

RECRUITING

Ropeginterferon Alfa-2b (P1101) vs. Anagrelide in Essential Thrombocythemia Patients With Hydroxyurea Resistance or Intolerance (SURPASS ET)

ClinicalTrials.gov ID NCT04285086

Key recommendations for high risk *CALR*-mutated ET

- **Cytoreduction** is recommended for patients older than 60 years, or have a history of thrombosis, or have extreme thrombocytosis (platelet count >1500 × 10^9):

  - Pegylated interferon for younger patients.
  - Both hydroxyurea or anagrelide might be given to the remainder.
  - Normalization of platelet count is recommended. However, if this approach results in toxicity, a lower intensity threshold might be appropriate

A consensus-based proposal from the European LeukemiaNet

Lancet Haematology 2021

blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS AUTHOR CENTER ABOUT

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL | NOVEMBER 15, 2022

A Phase 2 Study of the LSD1 Inhibitor Bomedemstat (IMG-7289) for the Treatment of Essential Thrombocythemia (ET)

Harinder Gill, Francesca Palandri, David M Ross, Tara Cochrane, Courtney Tate, Steven W Lane, Stephen R Larsen, Aaron T. Gerds, Anna B. Halpern, Jake Shortt, James M. Rossetti, Kristen M. Pettit, James Liang, Adam J Mead, Monia Marchetti, Alessandro M. Vannucchi, Andrew J Wilson, Joachim R Göthert, Merit Hanna, Francesco Passamonti, William S Stevenson, Claire Harrison, Moshe Talpaz, Nicola Vianelli, Hugh Young Rienhoff, Jr.

Volume 140, Issue Supplement 1
November 15 2022

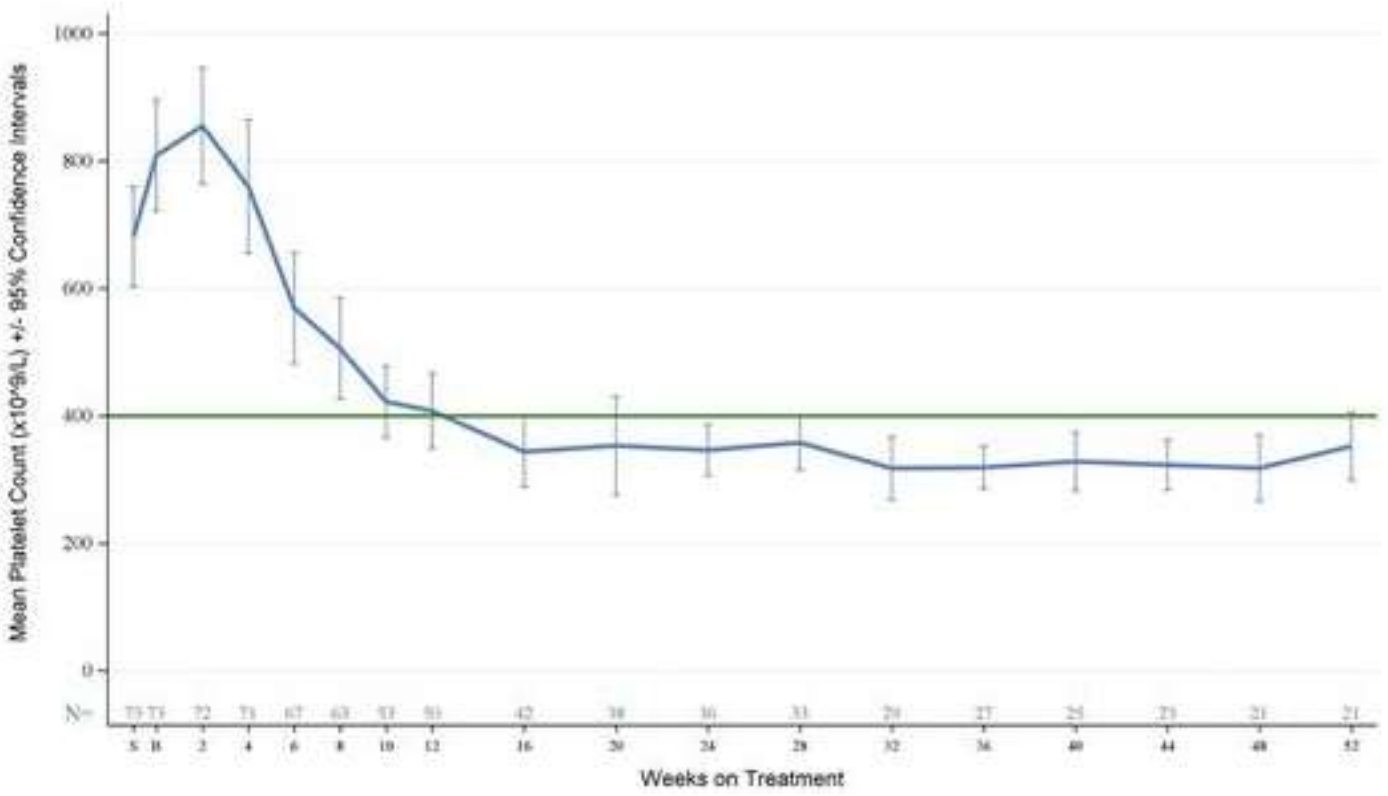
Previous Article Next Article

- Lysine-specific demethylase-1 (LSD1) is an enzyme critical for the self-renewal of malignant cells and hematopoietic differentiation
- LSD1 licenses progenitors to mature into megakaryocytes
- Bomedemstat is an orally active LSD1 inhibitor

COMPLETED

NCT04254978

Study of Bomedemstat in Participants With Essential Thrombocythemia (IMG-7289-CTP-201/MK-3543-003)



- 73 patients enrolled
- **90%** met ELN criteria for resistance/intolerance
- *JAK2* (51%), *CALR* (36%), and *MPL* (4%)
- Patients treated ≥24 weeks, **94%** (34/36) achieved a platelet count response ≤400x10^9/L
- Disgeusia in 43% o patients

Inmunoterapia &Hemopatías

NOT YET RECRUITING

NCT06079879 NEW

A Study of Bomedemstat (IMG-7289/MK-3543) Compared to Best Available Therapy (BAT) in Participants With Essential Thrombocythemia and an Inadequate Response or Intolerance of Hydroxyurea (MK-3543-006)

blood

ISSUES FIRST EDITION ABSTRACTS COLLECTIONS AUTHOR CENTER ABOUT

PLENARY ABSTRACTS | NOVEMBER 15, 2022

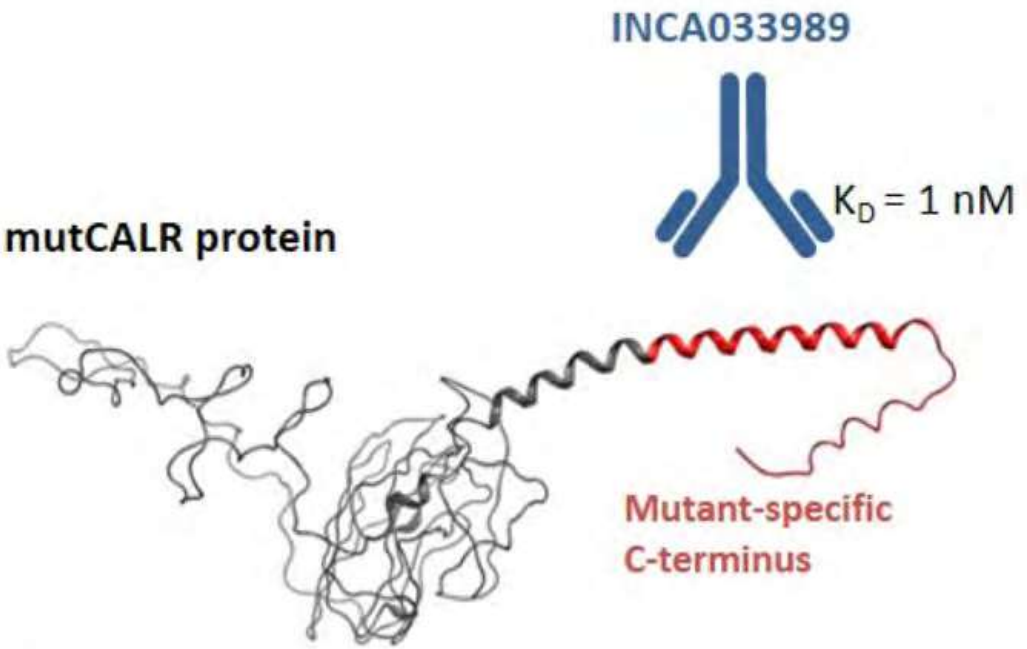
Volume 140, Issue Supplement 1
November 15 2022

Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms (MPNs)

Edimara Reis, Rebecca Buonpane, Hamza Celik, Caroline Marty, Angela Lei, Fatoumata Jobe, Mark Rupar, Yue Zhang, Darlise DiMatteo, Rahel Awdew, William Vainchenker, Jing Zhou, Ian Hitchcock, Isabelle Plo, Horacio Nastri, Patrick Mayes

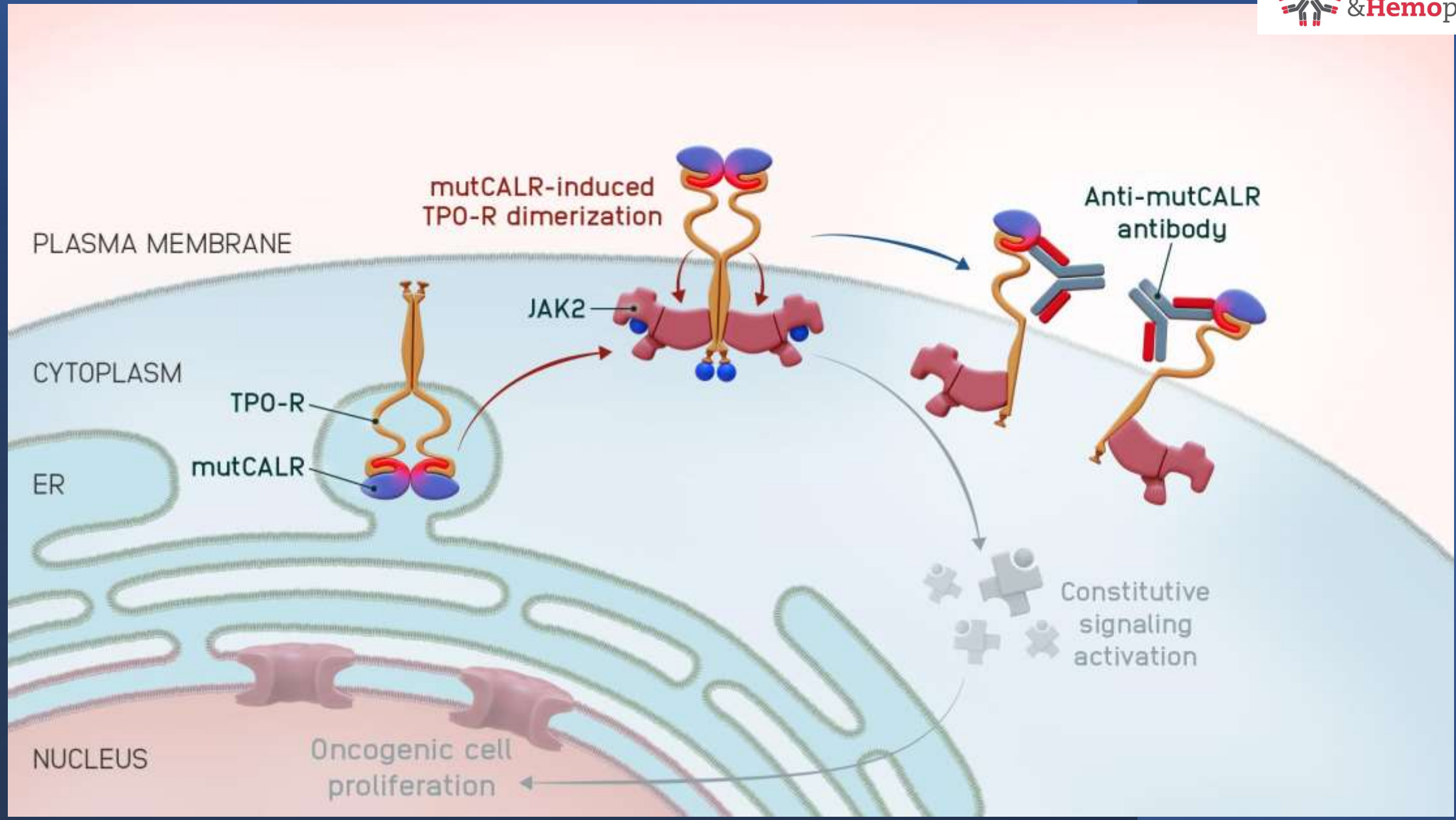
Previous Article Next Article

- Fully human IgG1
- Fc-silent
- Selective binding to mutCALR
- Antagonizes mutCALR-induced signaling and oncogenic function



Structure generated with RaptorX (Toyota Technological Institute at Chicago, IL, USA).
IgG, immunoglobulin G; Fc, fragment crystallizable; K_D, equilibrium dissociation constant.

Reis et al, ASH 2022


mutCALR-induced
TPO-R dimerization
PLASMA MEMBRANE
JAK2
Anti-mutCALR
antibody
CYTOPLASM
TPO-R
mutCALR
ER
Constitutive
signaling
activation
NUCLEUS
Oncogenic cell
proliferation

Discovery of INCA033989, a Monoclonal Antibody That Selectively Antagonizes Mutant Calreticulin Oncogenic Function in Myeloproliferative Neoplasms

1. INCA033989 is a potent antagonist of mutant calreticulin function
   - Selective inhibition of JAK/STAT signaling and proliferation of *CALR*-mutated stem/progenitor cells
   - Potential to alter the course of disease in ET and MF patients by targeting disease-initiating (stem) cells

2. Provide a strong rationale for the clinical investigation of INCA033989 in MF and ET patients with *CALR* mutations and a Phase 1 study of INCA033989 is planned in 2023

Reis et al, ASH 2022

Conclusiones

- El interferón pegilado se ha posicionado como el estándar de tratamiento en los pacientes con policitemia vera de bajo riesgo que requieren tratamiento citorreductor
- Estamos asistiendo a un cambio en los objetivos del tratamiento de la policitemia vera en el que además de la prevención de las complicaciones vasculares se persigue la modificación de la evolución natural de la enfermedad
- Ruxolitinib no solo consigue un mejor control hematológico y sintomático, sino que también ofrece una mejor supervivencia libre de evento en pacientes con policitemia vera resistente/intolerante a la hidroxiurea
- Rusfertide es un fármaco especialmente útil para pacientes con policitemia vera que requieren flebotomías frecuentes o no las toleran
- Existe una clara necesidad de nuevos tratamientos para la trombocitemia esencial, especialmente para pacientes con mutación de *CALR*
- Bomedemstat se postula como una nueva opción para pacientes con resistencia/intolerancia a la hidroxiurea

Muchas gracias por su atención

Inmunoterapia &Hemopatías