Interferons and epigenetic modulators:

Redefining the therapeutic Landscape in PV

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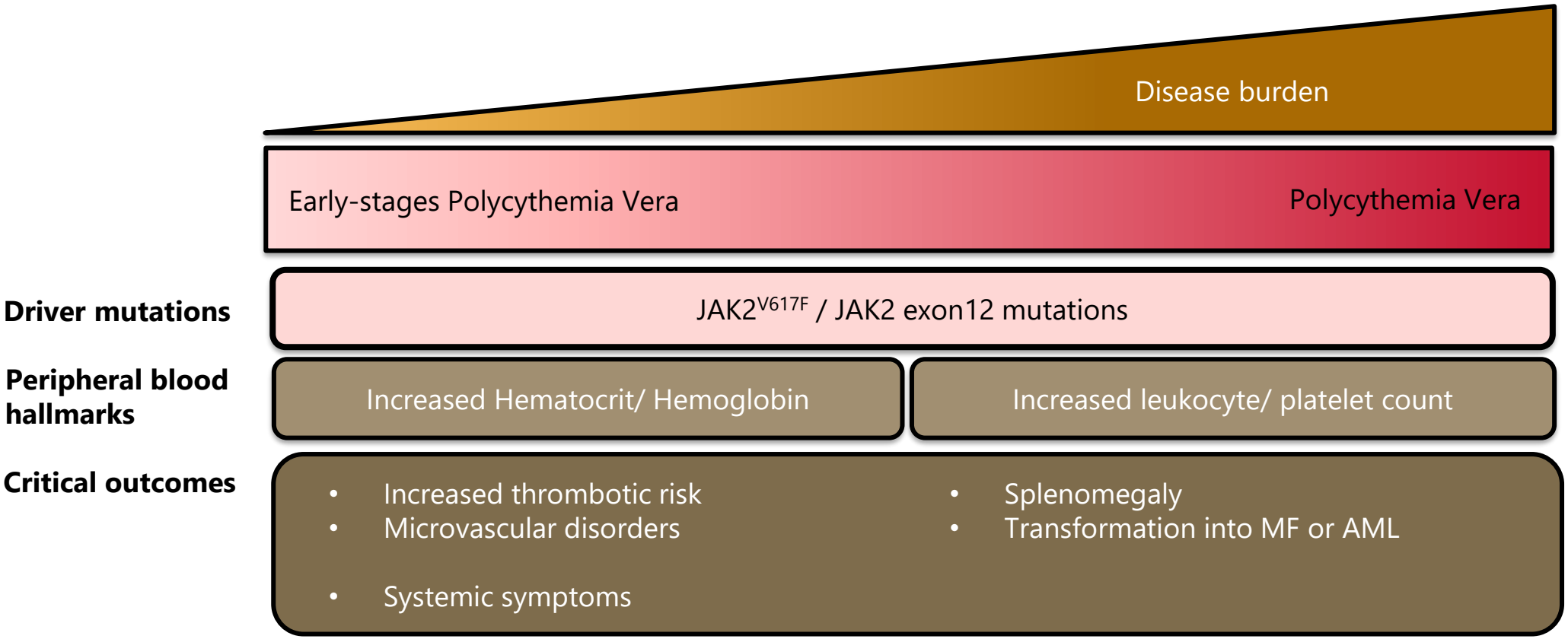
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board
Incyte			x			x
Novartis					x	x
AOP					x	x
Celgene/BMS					x	x
Grifols						x
Sobi						x
GSK					x	x
Kartos/Telios						x
Amgen					x	x
Sanofi						x
Takeda			x			x

Polycythemia Vera



Masarova L, Chifotides HT. Clin Lymphoma Myeloma Leuk. 2024 Mar;24(3):141-148. Tefferi A, Barbui T. Am J Hematol. 2023 Sep;98(9):1465-1487. Kuykendall AT, Fine JT, Kremyanskaya M. Clin Lymphoma Myeloma Leuk. 2024 Apr 16:S2152-2650(24)00151-4. Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311. Guglielmelli P, Vannucchi AM. Blood Rev. 2020 Jul;42:100714. Thiele J et Al. Am J Hematol. 2023 Jan;98(1):166-179; Tefferi A, et al. Leukemia 2013; Ferrari et al, Haematologica 2019

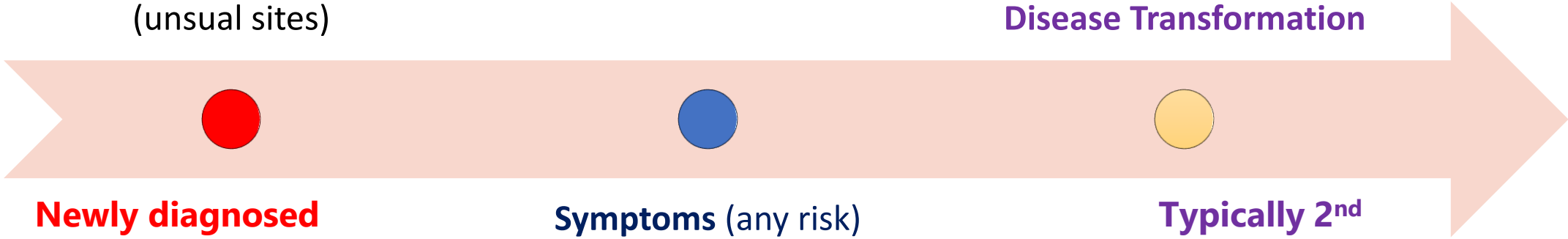
Critical Outcomes in PV

Median IR:
3.3 %p-yr

MF rate
5% @ 5yrs
34% @10 yrs

Thrombosis
(arterial>venous)
(unsual sites)

Disease Transformation



Newly diagnosed decade

Symptoms (any risk)
Cytokines: fatigue, itching;
Vascular: headache, dizziness, low mood

Typically 2nd

Disease transformation:
splenomegaly &
constitutional symptoms

AML rate 0.4%

Harrison CN, Polycythaemia vera. Nat Rev Dis Primers. 2025 Apr 17;11(1):26; Tremblay D,. Diagnosis and Treatment of Polycythemia Vera: A Review. JAMA. 2025 Jan 14;333(2):153-160. Tefferi A, Barbui T. Polycythemia vera: 2024 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 Sep;98(9):1465-1487. Mesa RA et al. Cancer. 2007;109:68-76; Scherber R et al. Blood. 2011;118:401-408; Geyer HL et al. Blood. 2014;123:3803-3810.

Overview of Polycythemia Vera Therapy

Low-risk patients with hypertension had a higher incidence of thrombosis Arterial hypertension was associated with highest levels of hematocrit

address CV risk factors

use low-dose aspirin

Probability of survival free of myocardial infarction, stroke, and death from cardiovascular causes, pulmonary embolism and DVT (ECLAP)

EFS including major thrombosis and death for CV cause was significantly lower for pts with Hct<45% compared with pts with Hct 45-48% (Cyto-PV)

keep hematocrit <45%

keep leukocytes <11 x 10^9/l

The risk of thrombosis is clearly increased in patients with WBC count >7 × 10^9/L, becoming statistically significant when WBC count was >11 × 10^9/L

Cytoreduction in patients at HIGH THROMBOTIC RISK

1. Barbui T et al, Am J Hematol. 2017 Jan;92(1):E5-E6. 2. Landolfi R et al, N Engl J Med 2004;350:114-24. 3. Marchioli R et al, N Engl J Med 2013;368(1):22-33; 4. Barbui et al, Blood. 2015 Jul 23;126(4):560-1.

ELN 2022 indications to cytoreduction in PV

High risk

CYTOREDUCTION MANDATORY

- Age ≥ 60 yo AND/OR
- Previous thrombosis

Low risk

CYTOREDUCTION RECOMMENDED

- Poor tolerance to phlebotomy (recurrent syncopes or blood phobia or severe difficulties in venous access)
- Symptomatic progressive splenomegaly (increase by >5 cm in the past year)
- Persistent leukocytosis (WBC >20×10^9 /L) for 3 months

CYTOREDUCTION SHOULD BE CONSIDERED

- Progressive leukocytosis.
- Extreme thrombocytosis (>1500 × 10^9 /L)
- Inadequate hematocrit control with phlebotomies (need for at least 6 phlebotomies per year for at least 2 years).

TRIAL OR CYTOREDUCTION CAN BE CONSIDERED

- High symptom burden (TSS ≥20) or severe itching (itching score ≥5) that are not ameliorated by phlebotomy, antiplatelet therapy, or antihistamine.
- Relevant cardiovascular risk.

ELN criteria for therapy start (strength of the recommendation: weak)

NCCN Guidelines 2026; 2. Marchioli R, Finazzi G, Specchia G, Masciulli A, Mennitto MR, Barbui T. *Thrombosis*. 2011;2011:794240; 3. Hernández-Boluda JC, Gómez M. *Eur J Haematol*. 2015;94(1):4-11; 4. Carobbio A, et al., Blood Adv. 2019 Jun 11;3(11):1729-1737; 5. Carobbio A, et al., Blood. 2011 Jun 2;117(22):5857-9.6. Palandri F, Breccia M, Elli EM, et al.. *Leukemia*. 2025;39(8):1928-1936; 7. Barbui T, Finazzi G, Carobbio A, et al. *Blood*. 2012;120(26):5128-5252

Limits of PV therapy

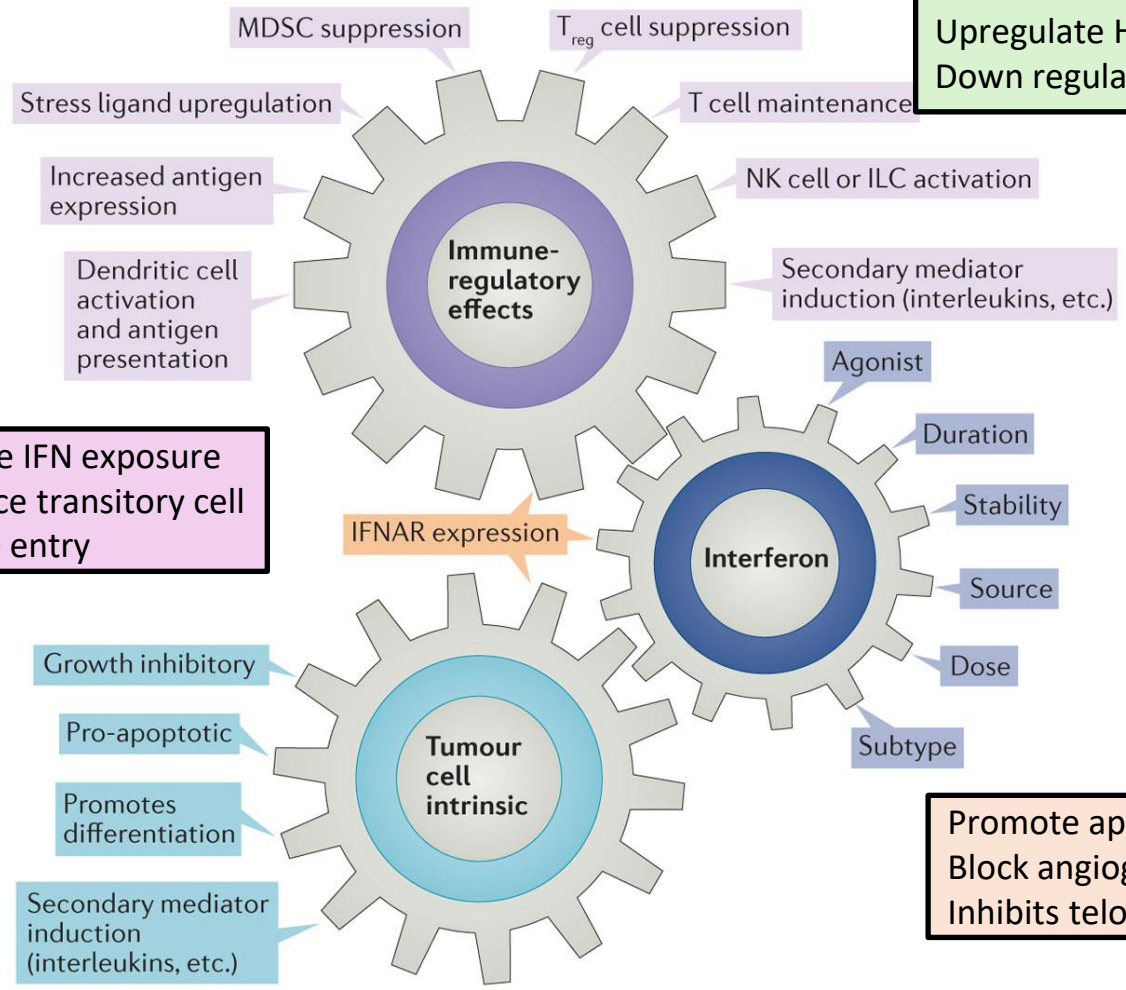
Thrombosis-Centric Treatment Paradigm	Phlebotomy are the backbone of therapy[2]	Frequent HU resistance/ intolerance[3]	Second-line options are limited	Symptom management is suboptimal	No Disease-Modifying or Curative Therapy
• Risk stratification relies solely on age (>60) and prior thrombosis history, which may be overly simplistic. • Despite treatment, thrombosis remains the leading cause of morbidity and mortality[1]	• PHL does not address the underlying clonal disease • PHL can cause symptomatic iron deficiency.	• Resistance or intolerance develops in a significant proportion of patients; • Long-term concerns about potential leukemogenicity persist, though causality is debated.	• RUX is the preferred second-line agent after HU (category 1)[4] • Clinical trial enrollment is also listed as preferred • This reflects the need for better therapies.	• Symptoms significantly impair quality of life. • Moderate-to-severe symptoms in low-risk patients on PHL alone increased from 43% to 67% over 24 months[5]	• PV **remains incurable** with current treatments.

These limitations are driving a conceptual shift toward early, disease-modifying, time-limited therapy — particularly with interferon and epigenetic modulators— initiated before clonal evolution and accumulation of adverse mutations.

1. Scheres LJJ, Lijfering WM, Cannegieter SC. Res Pract Thromb Haemost. 2018;2(2):199-208; 2. Tefferi A, Barbui T. Am J Hematol. 2023;98(9):1465-1487; 3. Heidel et al., Leukemia. 2025;39(7):1692-1701; 4. Harrison et al., J Clin Oncol. 2023;41(19):3534-3544; 5. Masarova et al., Clin Lymphoma Myeloma Leuk. 2024;24(3):141-148.

Interferons: mechanisms of action

- Direct cytotoxic effects on malignant cells
- Enhancement of the host immune response to malignant cells
- Stimulation of malignant stem cells to leave a quiescent state and enter the cell cycle



Increase NK and Treg
Upregulate HLA genes
Down regulate PD-L1

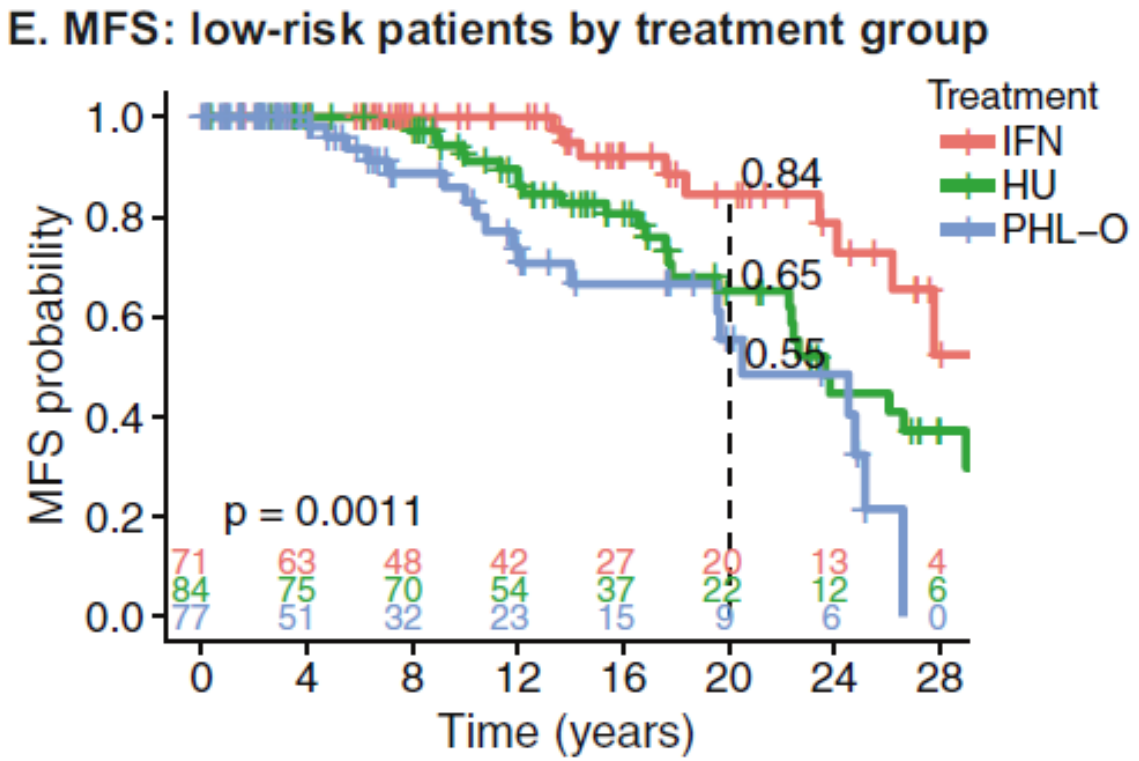
Acute IFN exposure induce transitory cell cycle entry

Promote apopotosis
Block angiogenesis
Inhibits telomerase

Parker et al. Nat Rev Cancer. 2016 Mar;16(3):131-44. Reviewed in Hasselbach HC, Seminars in Immunopathology 2019;41:5-19

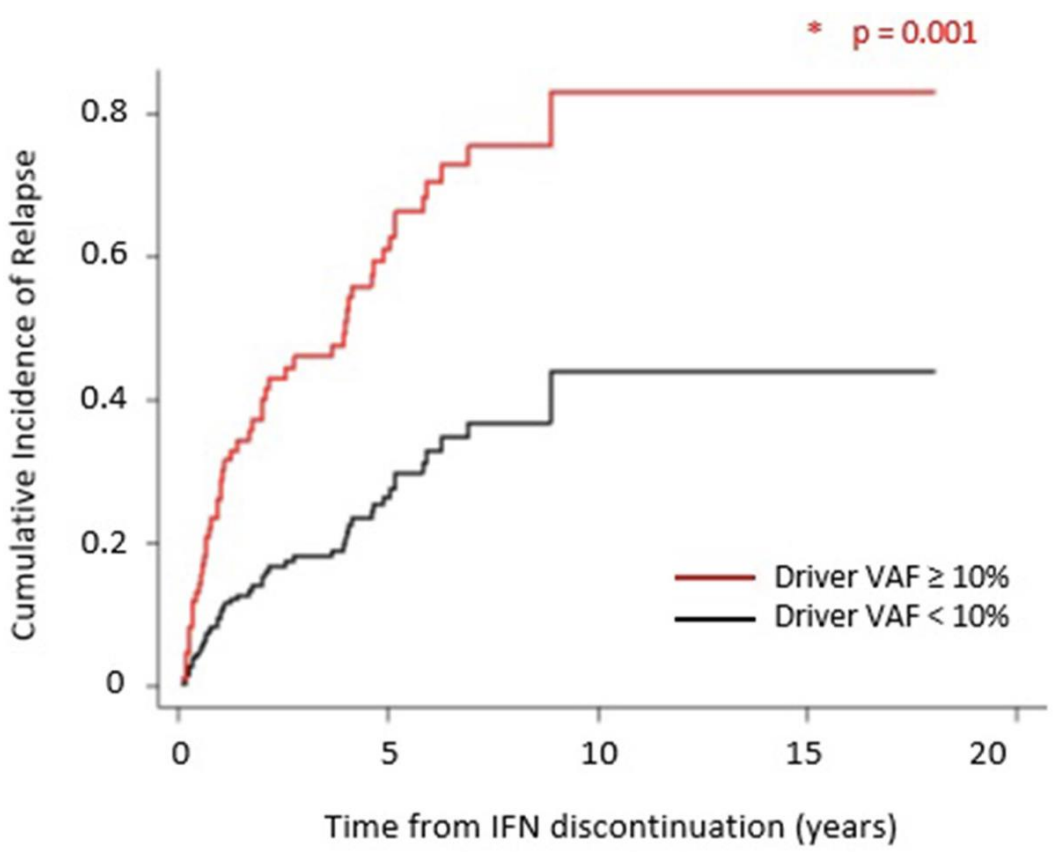
IFN-alpha yields improved myelofibrosis-free and overall survival in PV

- A retrospective study from Weill Cornell Medicine (NYC) included 470 PV patients with a median follow-up of 10 years (range 0-45)
- The primary treatment was rIFNα in 93 (20%), HU in 189 (40%), PHL-O in 133 (28%) and other cytoreductive drugs in 55 (12%).
- In low-risk patients, 20-year MFS for rIFNα, HU, and PHL-O was 84%, 65% and 55% respectively ($p < 0.001$).
- rIFNα was associated with a 9% PPV-MF risk reduction per year of treatment (HR 0.91, $p < 0.001$) and a 6% mortality risk reduction per year of treatment (HR 0.94, $p = 0.012$)



Abu-Zeinah et al. Leukemia. 2021 Mar 2. doi: 10.1038/s41375-021-01183-8

IFN-alpha Therapy Discontinuation Is Feasible in MPN Patients with Complete Hematological Remission

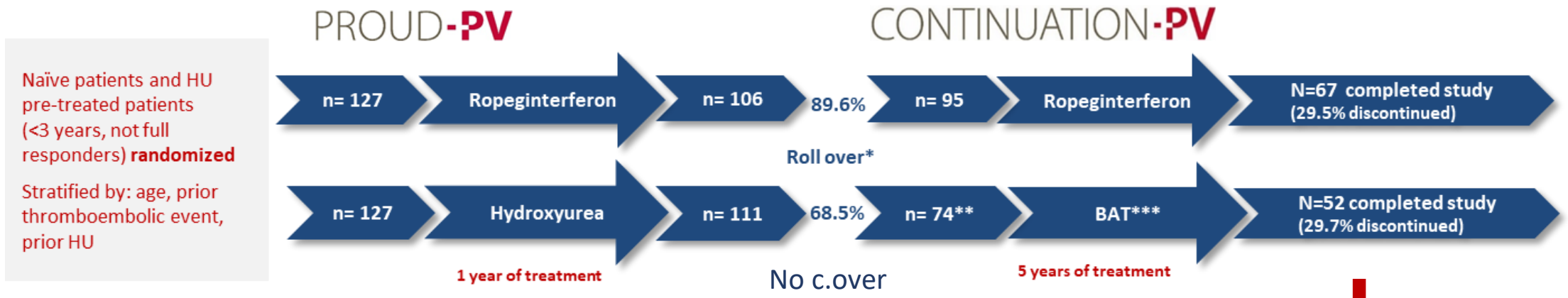


- 381 IFN treated patients were included in the study (171 PV, 169 ET and 34 PMF).
- **After a median follow-up of 72.4 months, 250 patients had discontinued therapy.**
- At time of IFN discontinuation, 170 (66.9%) patients were in CHR and the median driver mutation VAF was 12%.
- IFN was re-introduced in 61 patients who lost CHR with a second CHR rate of 83.6%.
- **In multivariate logistic regression analysis, a prolonged CHR and a JAK2 VAF<10% at the time of IFN stop were associated to a higher CHR without need for cytoreduction**

De Oliveira et al Volume 136 Supplement (1)5 November 2020, Pages 35-36

RopegIFN in Polycythemia Vera
PROUD/CONTI-PV

N=254 PV, 10% splenomegaly, 70% tx naïve, ~90%BAT=HU



*There were no significant differences between patients who entered CONTINUATION-PV study and those who did not roll-over
**Full analysis set (76 were enrolled, two of whom were excluded)
***Control group received best available treatment (BAT)

72 MONTH FINAL ANALYSIS:
(up to 7.3 years of treatment overall)

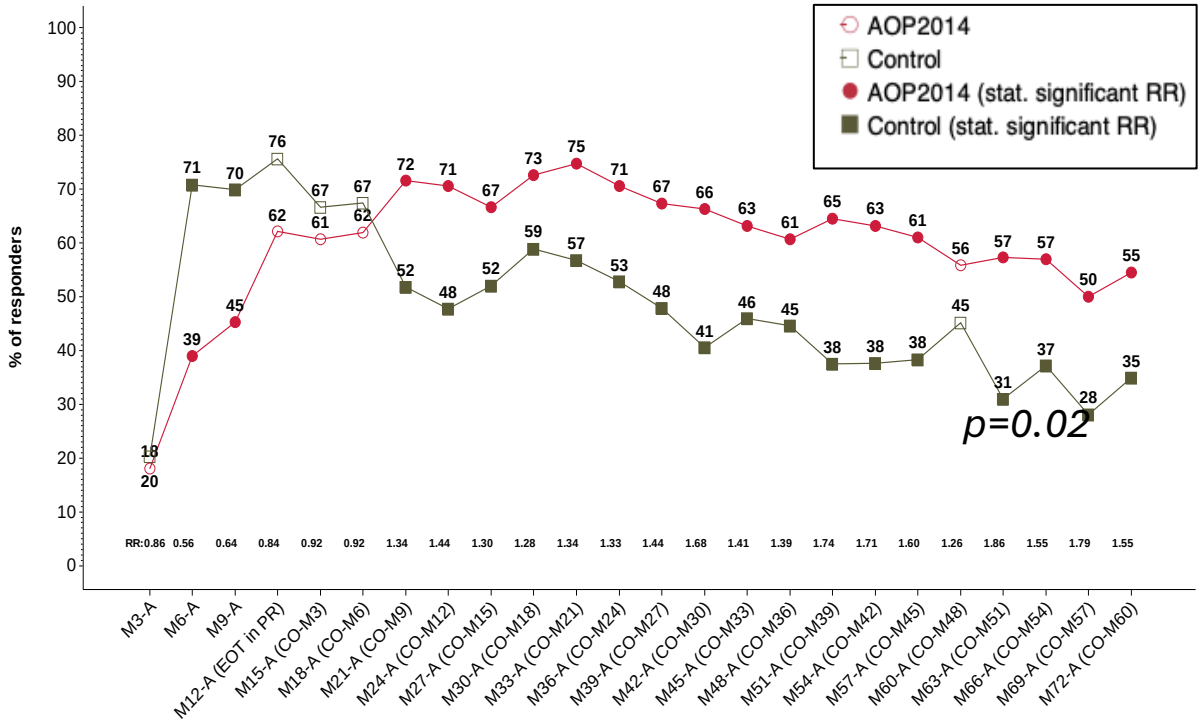
Ropeg initial dose: 100 µg (50 µg if previous HU) and up-titrations of 50 µg every 2 weeks to 500 µg maximumly

Gisslinger et al, Lancet Haematol 2020; Kiladjian et al, Leukemia 2022; Gisslinger et al, Leukemia 2023; Kiladijan et al, Hemasphere 2025.

Gisslinger et al, Lancet Haematol 2020; Kiladjian et al, Leukemia 2022; Gisslinger et al, Leukemia 2023

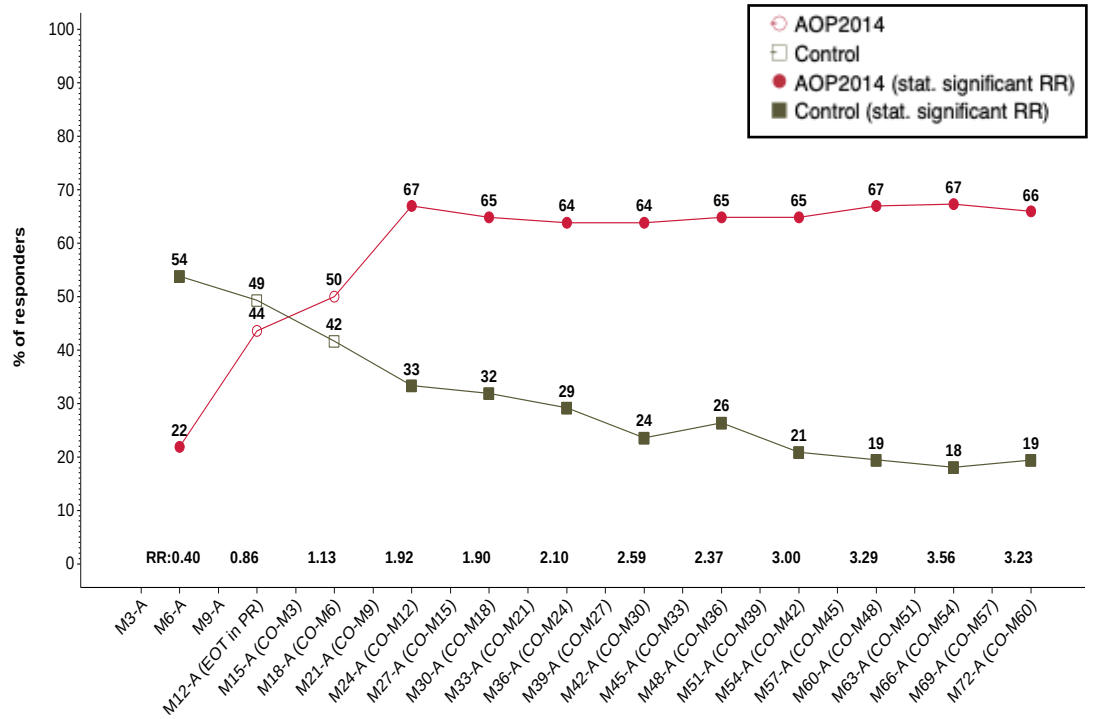
Hematologic and molecular responses PROUD/CONTI-PV

Complete Hematological Response*



- **CHR* & normal spleen at 1 year: 21% vs 28% (not "non inferior")**
- **More profound and durable ↓WBC**

Molecular Response§



- ***JAK2* VAF <1%:** 20.7% Ropeg *vs.* 1.4% HU/BAT (*p=0.0001*)
- ***JAK2* VAF reduction correlated with CHR at 5 years**

*CHR: Hct<45% and no Phls for at least 3 month & PLT <400 x 10^9/L & WBC <10 x 10^9/L

§ MR: *Partial MR*= ↓*JAK2* VAF ≥50% from BL if BL was <50%, ↓*JAK2* VAF ≥25% from BL if BL was >50%. *Complete* MR= undetectable

Gisslinger et al, Lancet Haematol 2020; Kiladjian et al, Leukemia 2022; Gisslinger et al, Leukemia 2023; Kiladijan et al, Hemasphere 2025.

Event-free survival
PROUD-PV & CONTINUATION-PV phase 3 studies

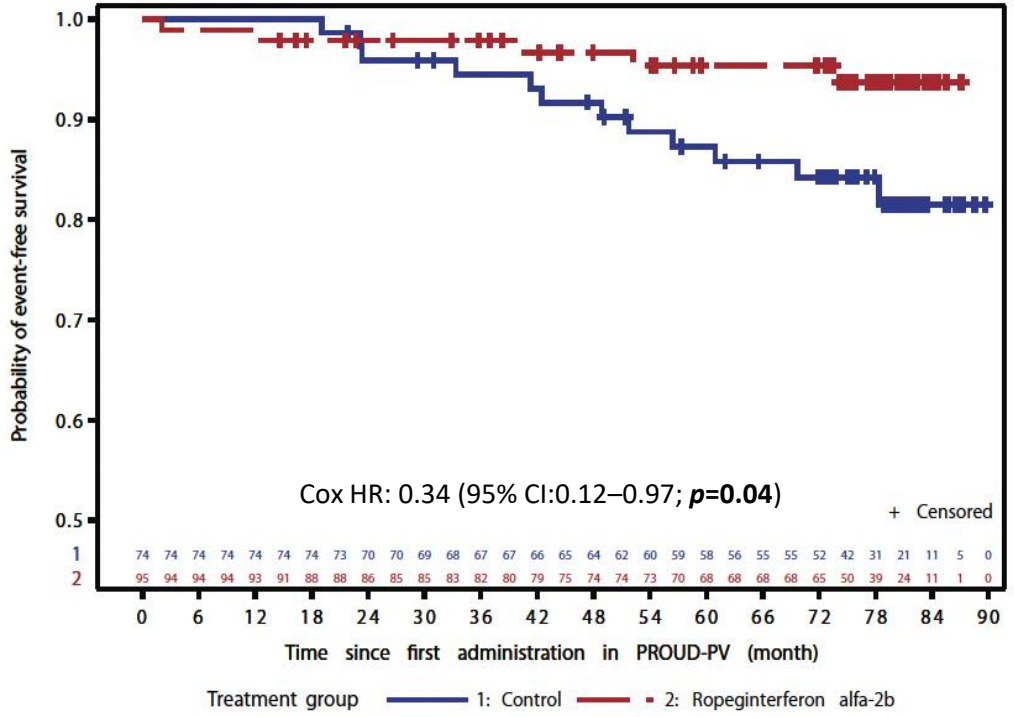
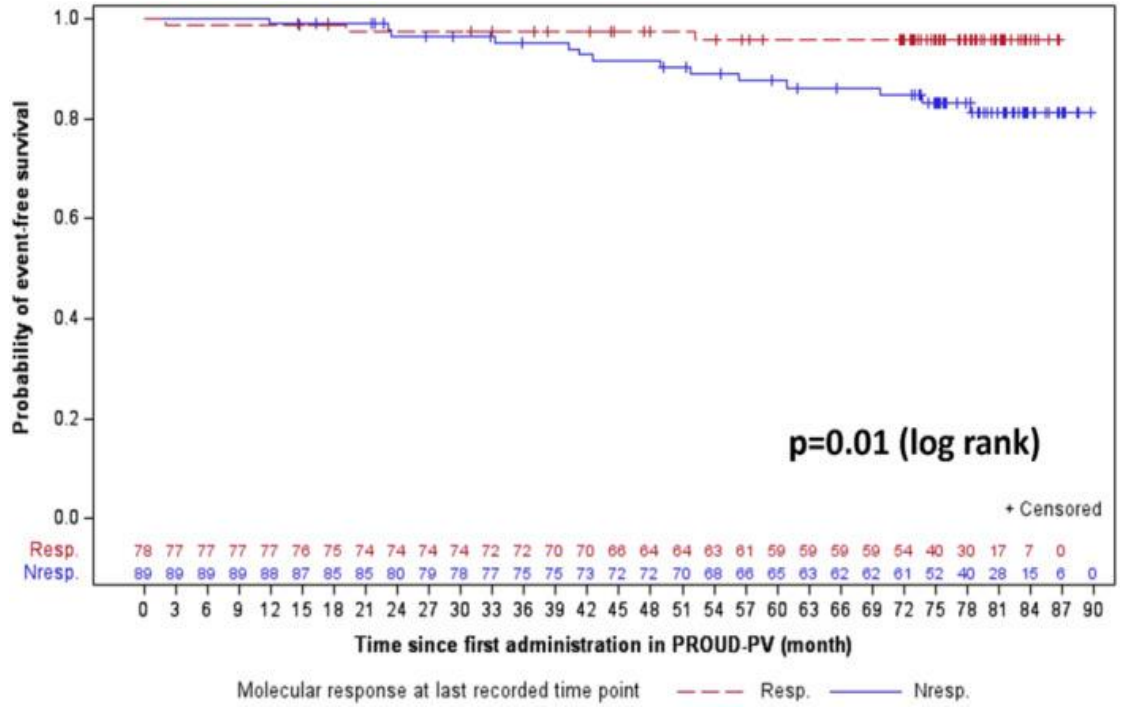


Fig. 1 Probability of event-free survival in patients with PV in the ropeginterferon alfa-2b arm and control arm (CONTINUATION-PV full analysis set). Risk events were defined as thromboembolic events, disease progression or death.



Analysis of the entire cohort regardless of treatment showed EFS was significantly improved among patients **who had an MR at the last available assessment** (events in 3/78 vs. 14/89 patients)

Gisslinger H et al, Leukemia. 2023 Oct;37(10):2129-2132; Kiladjian JJ, et al. *Hemasphere*. 2025;9(5):e70137.

RopegIFN safety
PROUD/CONTI-PV

	Entire treatment period		Fifth year of treatment	
	Ropeg IFN (N=127)	Control (N=127)	Ropeg IFN (N=78)	Control (N=66)
Adverse events (AEs)	116	117	45	45
	91.3%	92.1%	57.7%	68.2%
Serious adverse events (SAEs)	30	32	8	5
	23.6%	25.2%	10.3%	7.6%
Treatment-related SAEs	4	5	1	0
	3.1%	3.9%	1.3%	0
Adverse drug reactions (ADRs)	100	100	20	16
	78.7%	78.7%	25.6%	24.2%
Grade 3, 4 or 5 ADRs	21	21	3	0
	16.5%	16.5%	3.8%	0

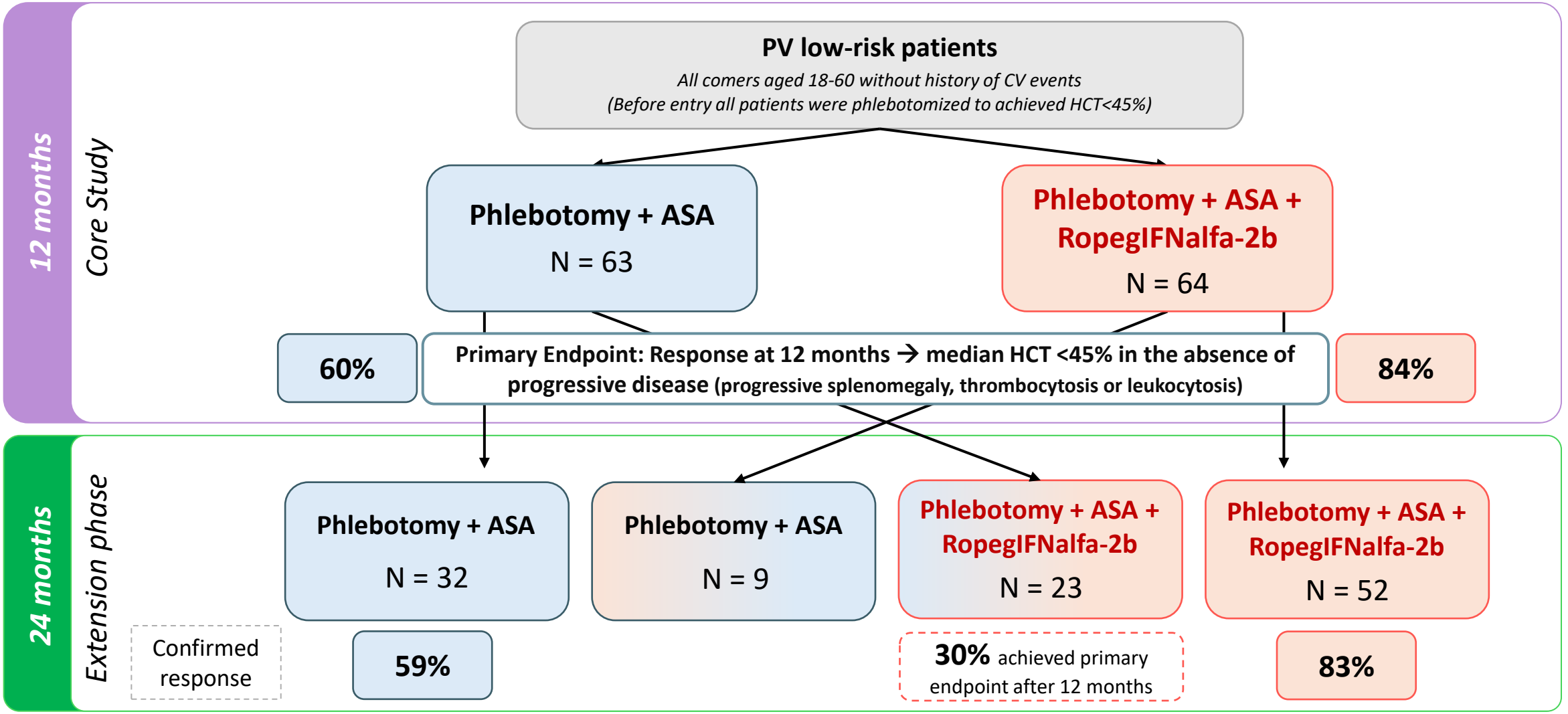
- RopegIFN had a good safety profile and no excess toxicity compared to HU and comparable rates of thrombosis
- RopegIFN shares common IFN-related toxicities (autoimmune diseases, mood depression)

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%)
Sarcoidosis	1 (0.8%)

	Ropeg IFN (N=127; 499 PYs)	Control (N=127; 401 PYs)
Events	6 (in 4 patients)	5 (in 5 patients)
Incidence (%-pt yr)	1.2	1.2

Gisslinger et al, Blood 2018 132:579. Kiladjian et al, Blood 2019 134:553. Gisslinger H et al, Lancet Haematol 2020; 7: e196–208; MR, Molecular Response; Gisslinger et al, Leukemia 2023; Kiladjian et al, Hemasphere 2025

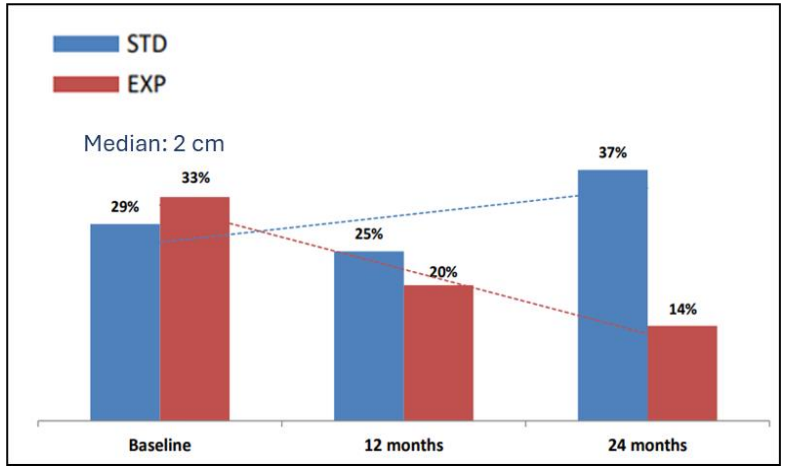
Ropeg-IFN vs. SOC for Low-Risk PV Patients: The phase II Low PV study



Barbui et al, Lancet Haematol. 2021; Barbui et al NEJM evidence 2023; Barbui at EHA 2025 (PS1847)

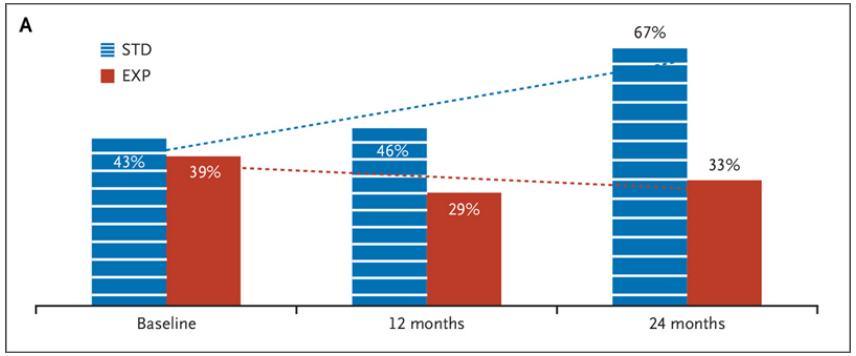
Ropeg-IFN α–2b in the Low PV study: Beyond hematological response

Palpable splenomegaly



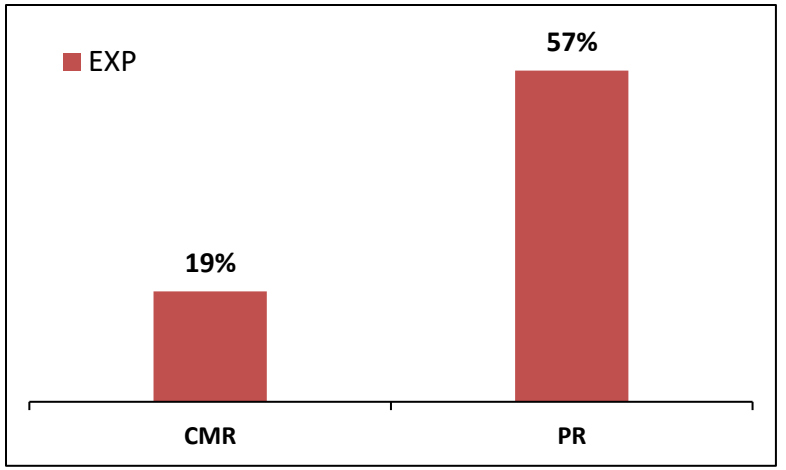
- *TAEs: 55% vs 6% (similar G ≥3, ~9%)*

Moderate or severe symptoms



- *Quality of life was measured with the MPN-SAF TSS.*
- *Percentage of patients with moderate or severe symptoms according to the classification proposed by Mesa et al.(i.e., scores 3 to 6 = moderate; scores ≥7 = severe)*

Molecular Response



- *JAK2 VAF (N=21) at BL: 48%.*
- *After a median follow-up of 5.9 years: CMR in 4/21 (19%); PR 12/21 (57%)*

Barbui et al, Lancet Haematol 2021; Barbui et al, NEJM evidence 2023; Barbui et al, Annals Haematol 2024. Barbui at EHA 2025 (PS1847)

Early Interferon Therapy in Low-Risk PV/ET – Pros & Cons

Disease-modifying potential

- Reduction of driver mutation VAF, associated with decreased thrombotic and progression risk
- Effects on thrombo-inflammation (NLR, CPR)
- Earlier intervention may prevent the emergence of additional clones

Thrombosis risk control without leukemogenic potential

- Earlier intervention before decades of cumulative clonal/inflammatory injury

Improvement of symptoms

- Improves quality of life

Reduction in phlebotomy requirements

- Decreased indirect social costs and better Hct control

High treatment and monitoring burden

- Frequent early titration, clinical visits, and laboratory monitoring
- Increase indirect social costs

Risk of overtreatment

- For low-risk patients without adverse biological features
- Potentially exposing LR patients to years of unnecessary therapy

Tolerability issues

- Potential cumulative effects of therapy
- Long.-term safety data are still accumulating

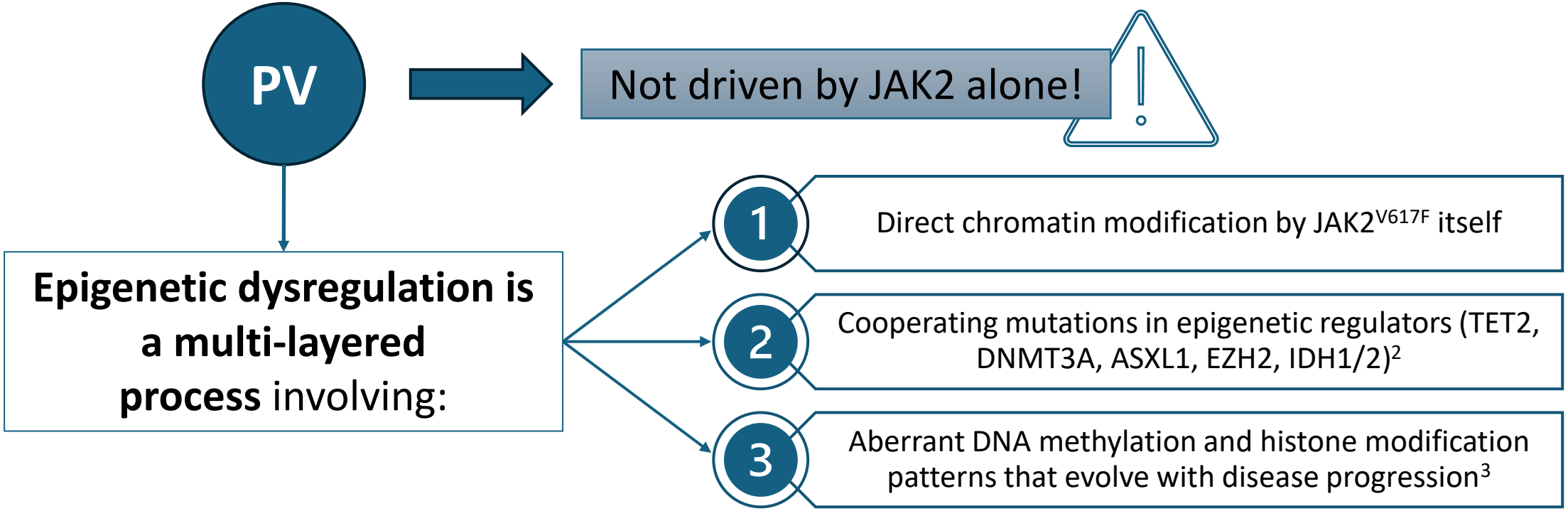
Costs Considerations

- Higher upfront drug costs: Early ropeginterferon adds ~50,960 EUR over long-term modeling vs phlebotomy alone

Leontyeva Y, Landtblom AR, Hultcrantz M, Lambe M, Bower H, Lambert PC, Andersson TM. Loss of life expectancy in patients with myeloproliferative neoplasms in Sweden. Haematologica. 2026 Mar 1;111(3):990-996. doi: 10.3324/haematol.2024.286697. Epub 2025 Sep 25. PMID: 40994348; PMCID: PMC12951144.

Epigenetic Genes in PV

Epigenetic regulators in PV cooperate with the JAK2 driver mutation to shape disease phenotype, influence clonal evolution, and determine risk of progression to myelofibrosis (MF) or acute myeloid leukemia (AML)[1]



This has opened a rich therapeutic landscape of **LSD1 inhibitors, BET inhibitors, HDAC inhibitors, and DNMT inhibitors** — many now in clinical trials, particularly for patients resistant/intolerant to standard cytoreductive therapy.

1. Maslah N, et al. Leukemia. 2023;37(5):957-963; 2. Dunbar A, Park Y, Levine R. Epigenetic Dysregulation of Myeloproliferative Neoplasms. Hematol Oncol Clin North Am. 2021 Apr;35(2):237-251. doi: 10.1016/j.hoc.2021.01.001. Epub 2021 Feb 5; 3. Greenfield G, McMullin MF. Front Oncol. 2023 Jul 13;13:1206965.

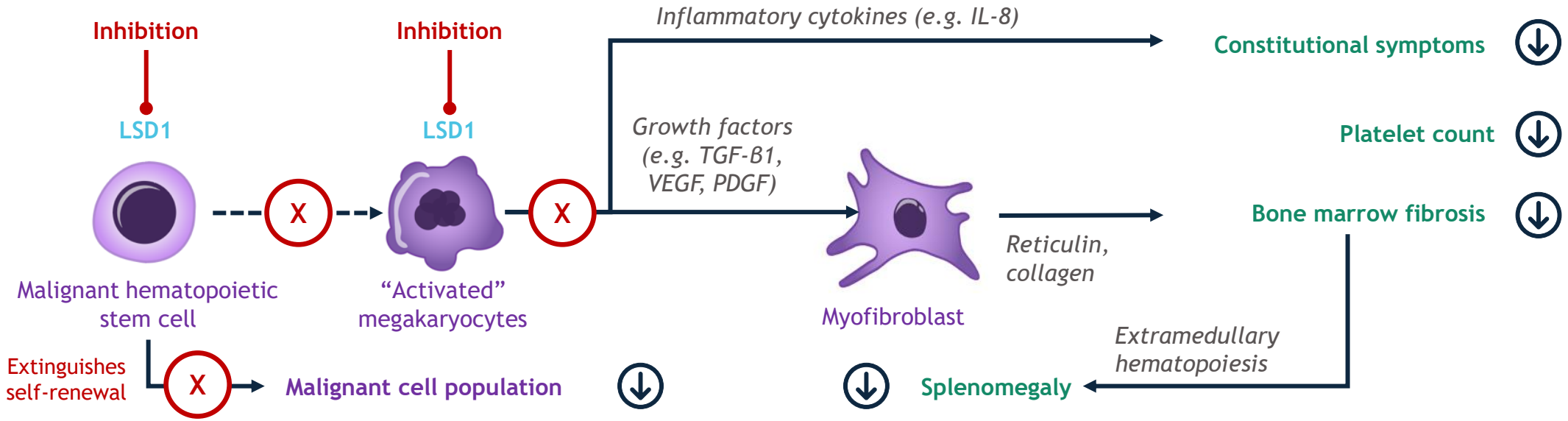
Main Non-driver Epigenetic Regulator Mutations In PV

Gene	Function	Epigenetic Mechanism	Frequency	Clinical Impact
TET2	DNA hydroxymethylation (5mC → 5hmC)	Loss-of-function → aberrant hypermethylation	~16%	Cooperates with JAK2 to drive progression[1]
DNMT3A	De novo DNA methylation	Loss-of-function → global hypomethylation; enhancer-driven inflammation	Variable	Cooperates with JAK2V617F to drive PV→MF progression; common in CHIP[2]
ASXL1	Chromatin remodeling (PRC2 interaction)	Loss-of-function → aberrant gene activation	~5–10%;	Associated with inferior OS[3]
EZH2	Histone H3K27 methyltransferase (PRC2 catalytic subunit)	Loss-of-function → derepression of target genes	Rare;	Associated with inferior OS[4]
IDH1/IDH2	Isocitrate dehydrogenase	Gain-of-function → inhibits TET2 → hypermethylation	Rare	Associated with AML transformation[5]

1. Padda J, Khalid K, Yadav J, et al. *Cureus*. 2021;13(9):e17854; 2. Kristiansen et al., *Br J Haematol*. 2025;207(3):1029-1037; 3. Andréasson B, et al. *Br J Haematol*. 2020;189(5):913-919; 4. Skov et al., *Blood* 2010; 116 (21): 4118; 5. Tefferi et al., *Leukemia*. 2010;24(7):1302-1309.

LSD1 inhibition in MPNs

- LSD1 inhibition impairs function of both “activated” megakaryocytes and malignant stem cells
- Megakaryocytes produce cytokines and growth factors that drive bone marrow remodeling (MF)



LSD1 is a central epigenetic regulator of chromatin
Its inhibition reduces production of megakaryocytes, growth factors and cytokines = <u>symptom improvement</u>
Potential to extinguish self-renewal of malignant stem cells = <u>potential to improve OS</u>

IL, interleukin; LSD1, lysine-specific demethylase 1; MF, myelofibrosis; MPN, myeloproliferative neoplasm; OS, overall survival; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

AAMDS. Non Transplant Therapy of MPNs 2022. Available at: https://www.aamds.org/sites/default/files/06_Mesa_MPN%20non-transplant%20therapies.pdf.

Bomedestat, the ph. 2 Shorespan 004 study in PV

Population Characteristics

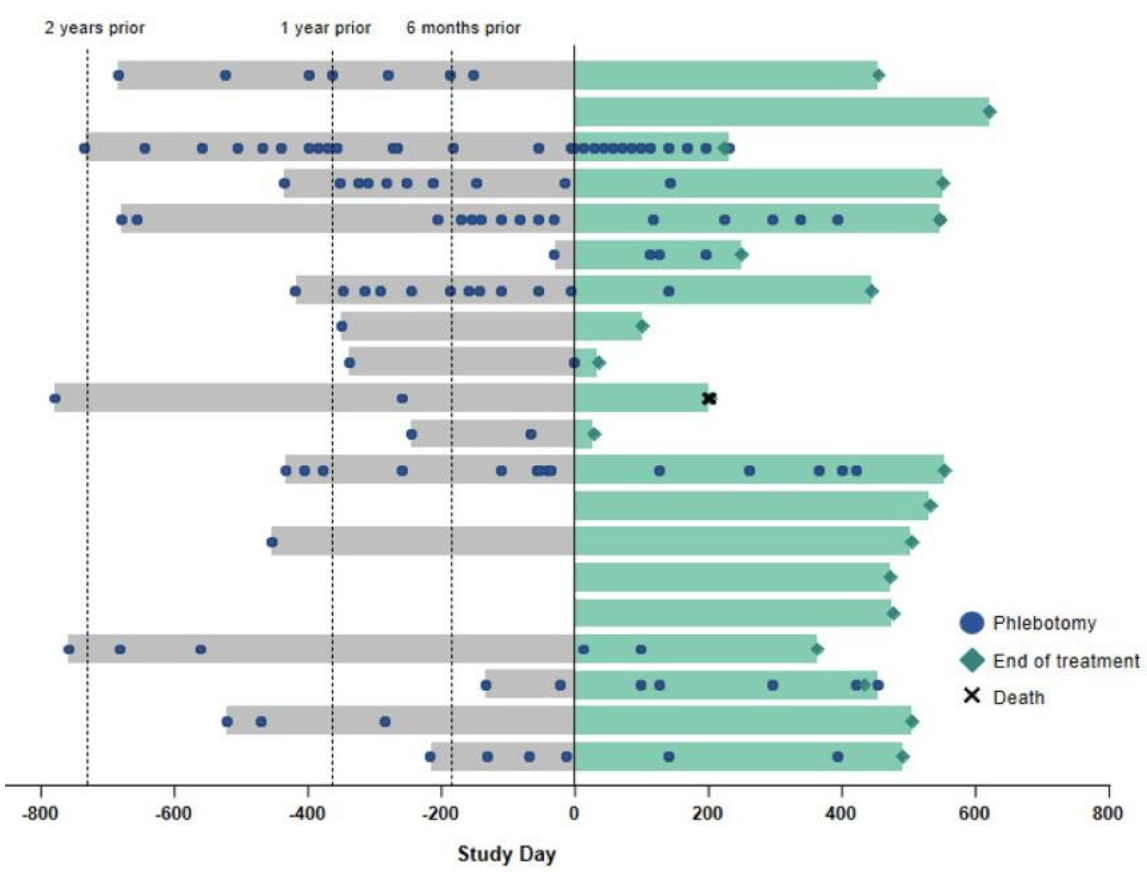
- N=20 patients R/I to cytoreduction
- Starting dose: 40 mg/day PO titrated to Hct target <42%

Efficacy

- 45% had a sustained reduction in Hct to <45% by W36
- 50% had a sustained reduction in Hct to <45% by W52
- 90% had PLT reduction <450x10^9/L, by W36
- 75% had a WBC reduction <10 x10^9/L, by W36

Safety

- 10% G ≥3 AEs; 40% G1-2 gastrointestinal effects



Rein et al, ASH 2025

Bomedemstat Ongoing clinical trials

Phase 3 randomized Shorespan-006 MK-3543-006 clinical trial

- Bomedemstat compared to best available therapy (BAT) as treatment in patients with **ET** who have an **inadequate response to or are intolerant of hydroxyurea**.
- Primary endpoint: durable clinic-hematologic response (DCHR) rate
- Key secondary endpoints: duration of clinic-hematologic response (DOCHR), duration of hematologic remission (DOHR), PFS and EFS

NCT06079879

Phase 3 randomized double-blind Shorespan-007 clinical trial

- Bomedemstat compared to HU, in **ET** patients **who have previously not received cytoreductive therapy**.
- Primary endpoint: durable clinic-hematologic response rate (DCHR).
- Key secondary endpoints: MFSAF v4.0 individual fatigue symptom item score, Patient-reported Outcomes Measurement Information System (PROMIS), Fatigue SF-7a score, MFSAF v4.0 TSS; duration of hematologic remission, PFS and EFS

NCT06456346

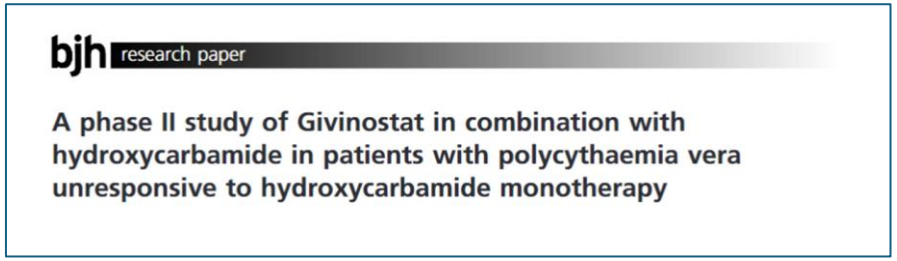
Phase 2/3 randomized open label MK-3543-025 clinical trial

- Bomedemstat compared to BAT, in **PV** patients who have an **inadequate response to or are intolerant of hydroxyurea**.
- Primary endpoint: compare clinicohematological response (CHR) in patients treted with bomedemstat vs BAT.
- Key secondary endpoints: Duration of CHR (DOCHR); duration of hematological remission (HR); phlebotomy incidence; Thrombotic events; disease progression (MF/MDS/AML), major hemorrhagic events; changes in total symptoms score (MFSAF v4.0); changes in total fatigue score (PROMIS Fatigue SF-7a)

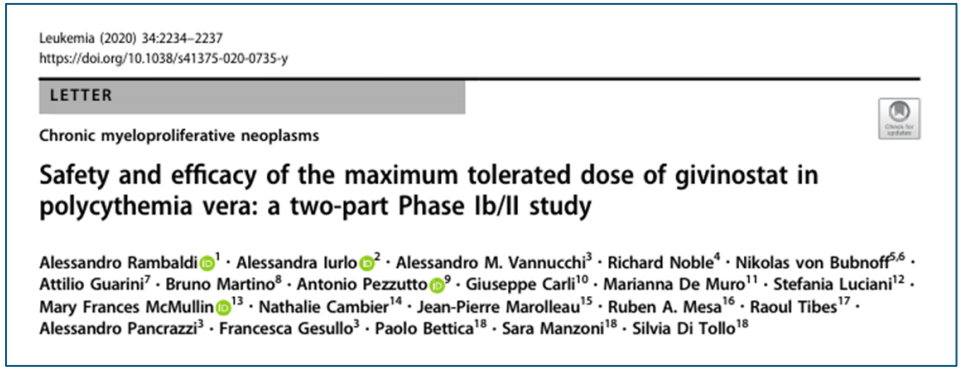
NCT060709879

Givinostat: an Italian clinical investigation in PV

- **Rambaldi A**, Long-term safety and efficacy of givinostat in polycythemia vera: 4-year mean follow up of three phase 1/2 studies and a compassionate use program. **Blood Cancer J. 2021 Mar 6;11(3):53.**
- **Rambaldi A**, Safety and efficacy of the maximum tolerated dose of givinostat in polycythemia vera: a two-part Phase Ib/II study. **Leukemia. 2020 Aug;34(8):2234-2237**.
- **Finazzi G**, A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythaemia vera unresponsive to hydroxycarbamide monotherapy. **Br J Haematol. 2013 Jun;161(5):688-694.**
- **Rambaldi A**, A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. **Br J Haematol. 2010 Aug;150(4):446-55.**
- **Guerini V**, The histone deacetylase inhibitor ITF2357 selectively targets cells bearing mutated JAK2(V617F). **Leukemia. 2008 Apr;22(4):740-7.**


bjh research paper

A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythaemia vera unresponsive to hydroxycarbamide monotherapy

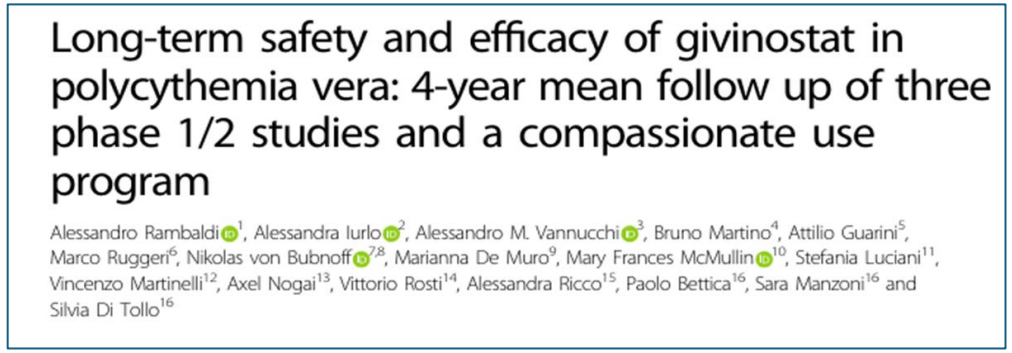

Leukemia (2020) 34:2234–2237
https://doi.org/10.1038/s41375-020-0735-y

LETTER

Chronic myeloproliferative neoplasms

Safety and efficacy of the maximum tolerated dose of givinostat in polycythemia vera: a two-part Phase Ib/II study

Alessandro Rambaldi[1] · Alessandra Iurlo[2] · Alessandro M. Vannucchi[3] · Richard Noble[4] · Nikolas von Bubnoff[5,6] · Attilio Guarini[7] · Bruno Martino[8] · Antonio Pezzutto[9] · Giuseppe Carli[10] · Marianna De Muro[11] · Stefania Luciani[12] · Mary Frances McMullin[13] · Nathalie Cambier[14] · Jean-Pierre Marolleau[15] · Ruben A. Mesa[16] · Raoul Tibes[17] · Alessandro Pancrazzi[3] · Francesca Gesullo[3] · Paolo Bettica[18] · Sara Manzoni[18] · Silvia Di Tollo[18]


Long-term safety and efficacy of givinostat in polycythemia vera: 4-year mean follow up of three phase 1/2 studies and a compassionate use program

Alessandro Rambaldi[1], Alessandra Iurlo[2], Alessandro M. Vannucchi[3], Bruno Martino[4], Attilio Guarini[5], Marco Ruggeri[6], Nikolas von Bubnoff[7,8], Marianna De Muro[9], Mary Frances McMullin[10], Stefania Luciani[11], Vincenzo Martinelli[12], Axel Nogai[13], Vittorio Rosti[14], Alessandra Ricco[15], Paolo Bettica[16], Sara Manzoni[16] and Silvia Di Tollo[16]

Givinostat: mechanism of action

- Potent, orally available, histone deacetylases (HDAC) inhibitor

Reducing cell proliferation and inducing cell death in cancer cells

(proteasomal degradation of *JAK2*^{V617F} and apoptosis of *JAK2*^{V617F}+ cell lines)

Reducing pro-inflammatory cytokine levels

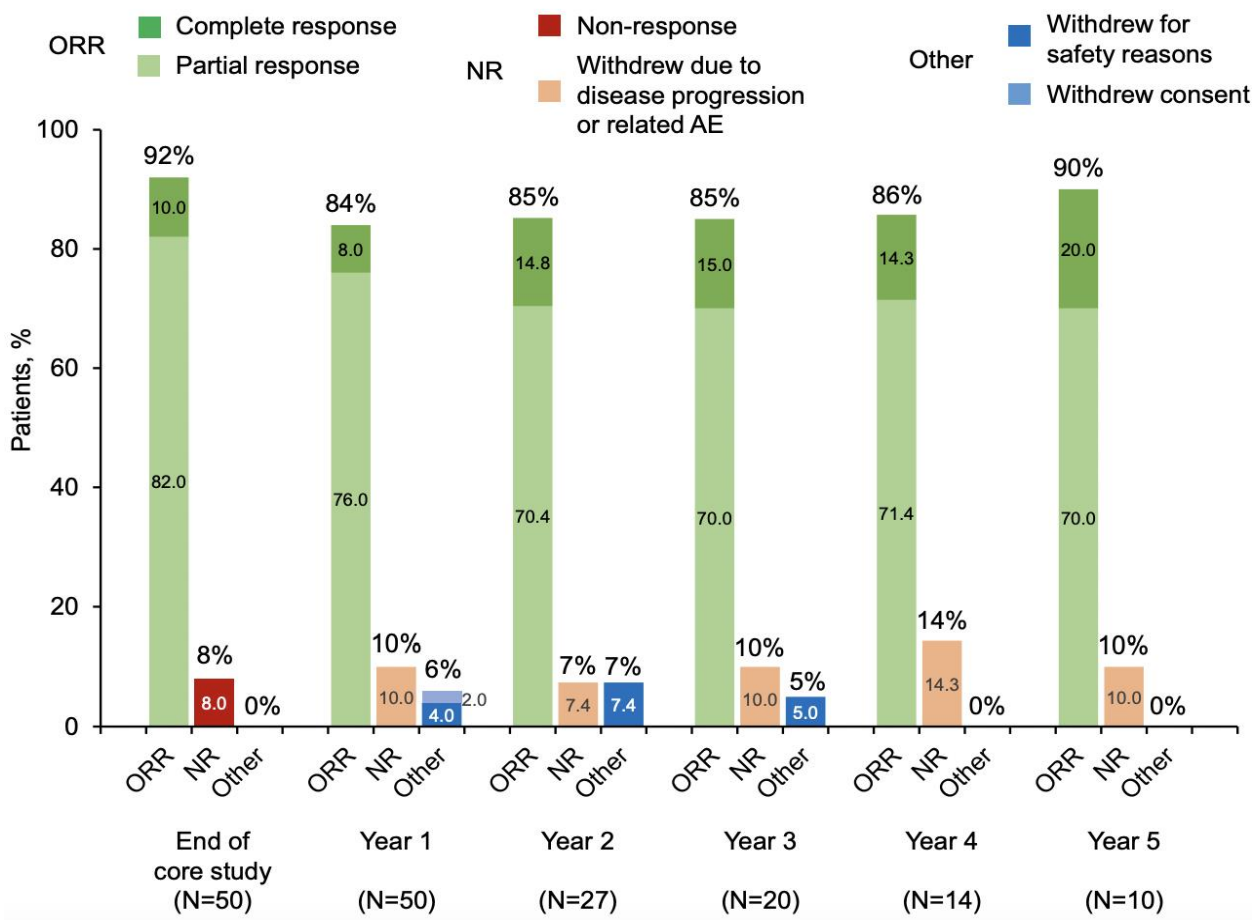
involved in sustaining neoplastic cell proliferation

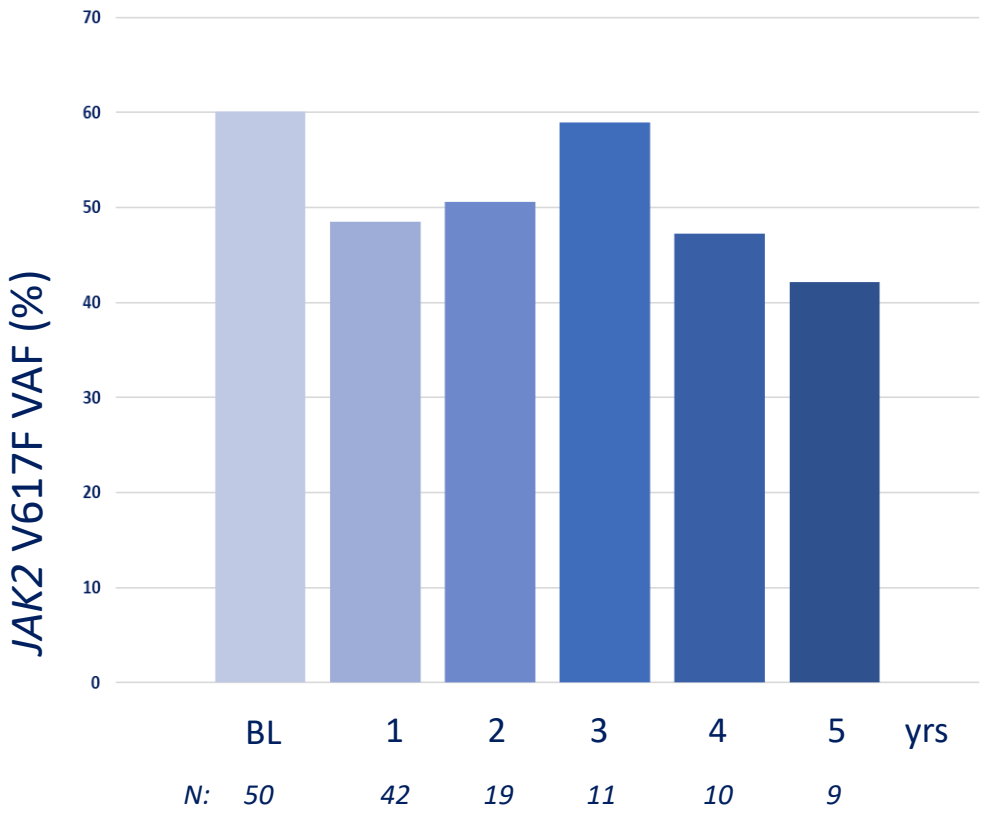
Affecting the JAK2-STAT signalling via STA5 interference

especially in cells carrying the *JAK2*^{V617F} mutation

1. West AC, et al. J Clin Invest. 2014;124(1):30–39. 2. Dawson MA, et al. Nature. 2009;461(7265):819–822.; 3. Skov V, et al. Leuk Lymphoma. 2012;53(1):123–129. 4. Wang JC, et al. Leuk Lymphoma. 2008;49(12):2321–2327.; 5. Yue L, et al. Blood. 2020;135(3):191–207. 6. Amaru Calzada A, Exp Hematol. 2013 Mar;41(3):253-60.e2. 7. Amaru Calzada A. Exp Hematol. 2012 Aug;40(8):634-45.e10.

The HDAC-inhibitor Givinostat: summary of ph I/II studies





- More than 80% of patients had a PR/CR, maintained during follow-up. More pronounced effect in the GIV monotherapy group
- A reduction in mean JAK2V617F allele burden was observed at most of the annual visits.

Rambaldi A et al. Br J Haematol. 2010; Rambaldi A. et al Blood Cancer J. 2021; NCT06093672

Main Clinical Trial Safety Results

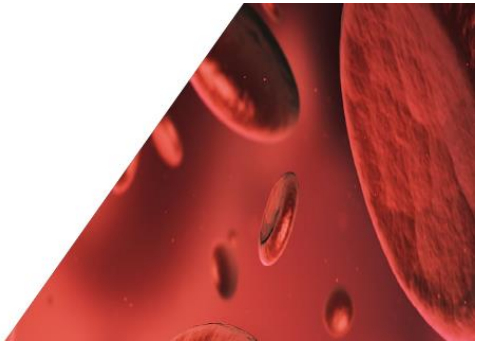
In the long-term phase II study in PV patients, nearly all patients experienced at least one AE during the long-term study, the majority were Grade < 3	No drug-related grade 4-5 AE occurred	5 patients (10.0%) experiencing Grade 3 events (asthenia, thrombocytopenia, gastrointestinal disorder, hypertension and QTc prolongation)	3 patients (6.0%) experienced drug-related QTc prolongation during treatment with givinostat → only one patient (2.0%) had a Grade 3 event, which resulted in treatment discontinuation.

Rambaldi A, Blood Cancer J. 2021 Mar 6;11(3):53. Rambaldi A. Leukemia. 2020 Aug;34(8):2234-2237. Finazzi G, Br J Haematol. 2013 Jun;161(5):688-694.

Study Design

GIV·IN PV

GIVinostat IN Polycythemia Vera

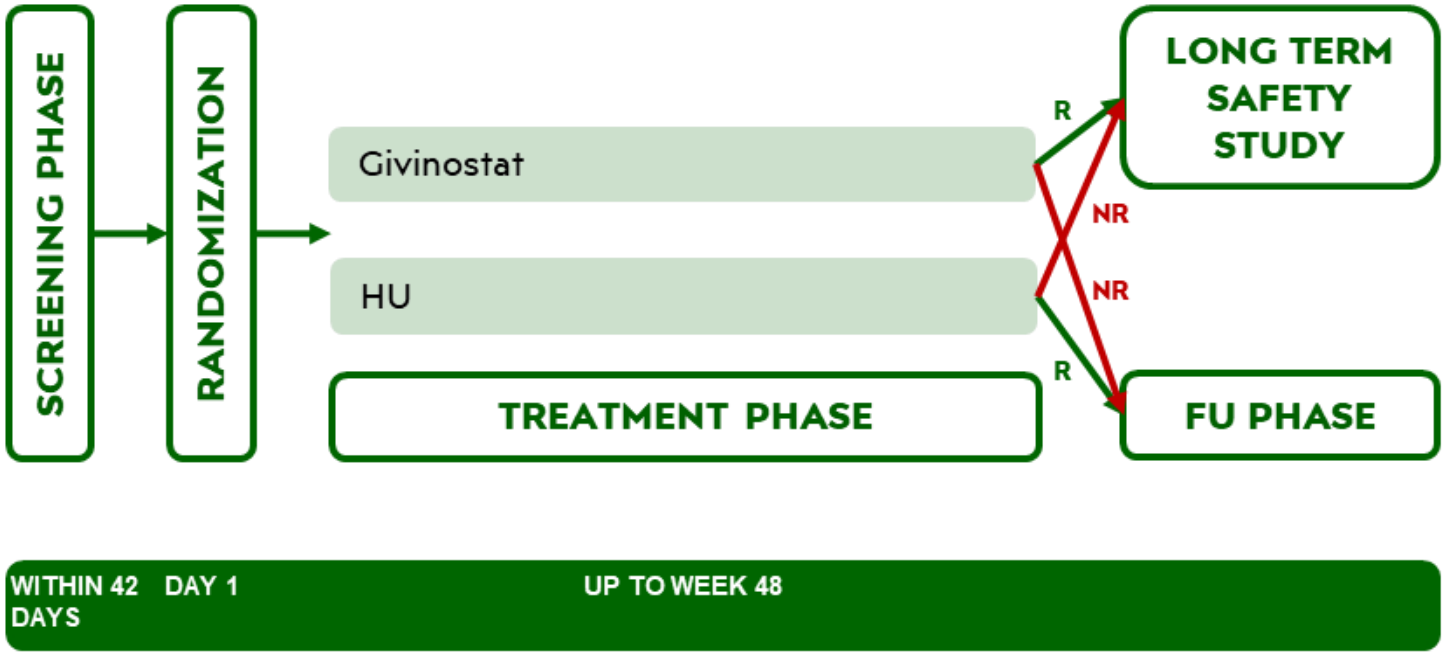


PATIENT POPULATION:

- **JAK2^{V617F}-positive High risk Polycythemia Vera** adult patients of both genders in need of treatment*
- Diagnosis of **PV confirmed according to the 2016 WHO criteria** within 3 years before randomization
- **HU naïve or HU pretreated** without resistance or intolerance

STRATIFICATION FACTORS:

- Previous **HU exposure**
- Presence of **major TEs** in the past
- Presence/absence of **splenomegaly**
- **JAK2^{V617F} allele burden** (i.e. ≤50% or >50%).



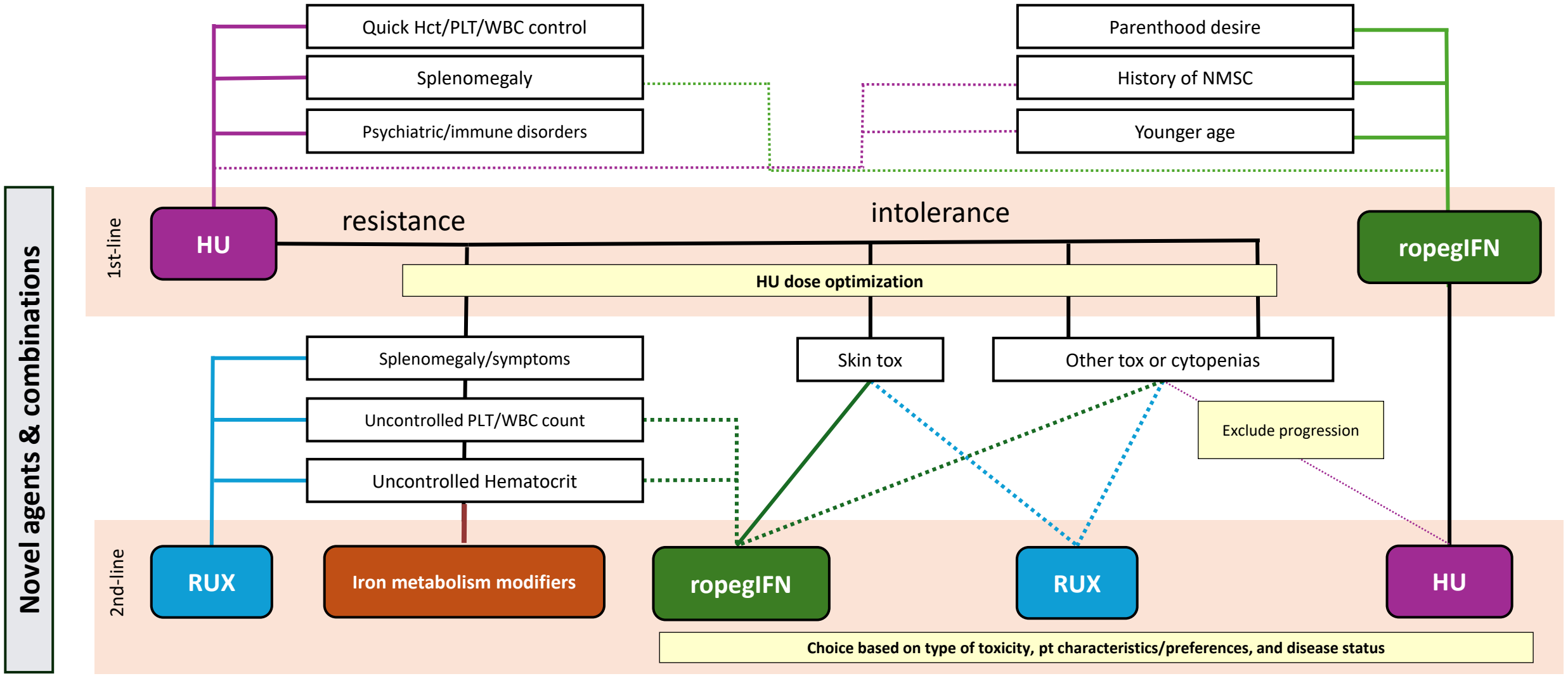
Currently open for enrolment!

R = responders

NR = non responders

*HCT ≥ 45% or HCT < 45% with at least 1 phlebotomy performed in the 3 months before screening, or WBC count > 10 × 10^9/L, or PLT count > 400 × 10^9/L

PV: Targeting the clone and delaying progression



Palandri et al. Annals of Hematology 2026 in press

Thanks!

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Epigenetic therapies under investigation in PV

Drug Class	Agent(s)	Target	Phase	Key Findings / Status
LSD1 inhibitor[1,2]	**Bomedemstat**	Lysine-specific demethylase 1	Phase 2 (PV); Phase 3 (ET)	Regulates megakaryocyte/erythrocyte maturation; durable platelet/WBC reduction and symptom improvement in ET; PV trial ongoing
LSD1/HDAC6 dual inhibitor[3,4]	JBI-802	LSD1 + HDAC6	Phase 1/2 (ET, MDS/MPN)	First oral dual inhibitor; dose-dependent platelet reduction; trial ongoing
BET inhibitor[5]	Pelabresib (CPI-0610)	BRD2/3/4 (epigenetic readers)	Phase 3 (MF)	Modulates inflammatory/fibrotic pathways; SVR35 in 3/7 pts at ≥10 mg mono; combo with ruxolitinib ongoing
BET inhibitor	INCB057643[6]	BRD2/3/4	Phase 1 (MF) CLOSED	SVR35 in 3/7 at ≥10 mg; TSS50 in 5/8 at ≥10 mg; well tolerated at 4–10 mG
BET inhibitor (BD2-selective)	ABBV-744[7]	BDII domain of BET proteins	Phase 1b (MF)	SVR35 24% at Wk 12, 33% at Wk 24; TSS50 29% at Wk 12
HDAC inhibitor[8,9]	Givinostat	HDAC1/2 (class I)	Phase 2	HDAC1/2 inhibition → SIAH2 stabilization → JAK2V617F proteasomal degradation; spares normal HSCs

1. https://clinicaltrials.gov/study/NCT05558696; 2. Rein L, et al. *Blood* 2025; 146 (Supplement 1): 83; 3. Zhang J, et al. Expert Opin Ther Pat. 2025;35(5):493-501; 4. Melda S. et al., *J Clin Oncol* **43**, TPS6589-TPS6589(2025); 5. Rampal et al., *Nat Med* **31**, 1531–1538 (2025); 6. Watts et al., *Blood* 2024; 144 (Supplement 1); 7. Mascarenhas et al., *Hemasphere*. 2023;7(Suppl):e8258903; 8. Rambaldi et al., Leukemia. 2020 Aug;34(8):2234-2237; 9. https://clinicaltrials.gov/study/NCT06093672