Hydroxyurea, interferons, ruxolitinib or clinical trials: what sequence in polycythemia vera?

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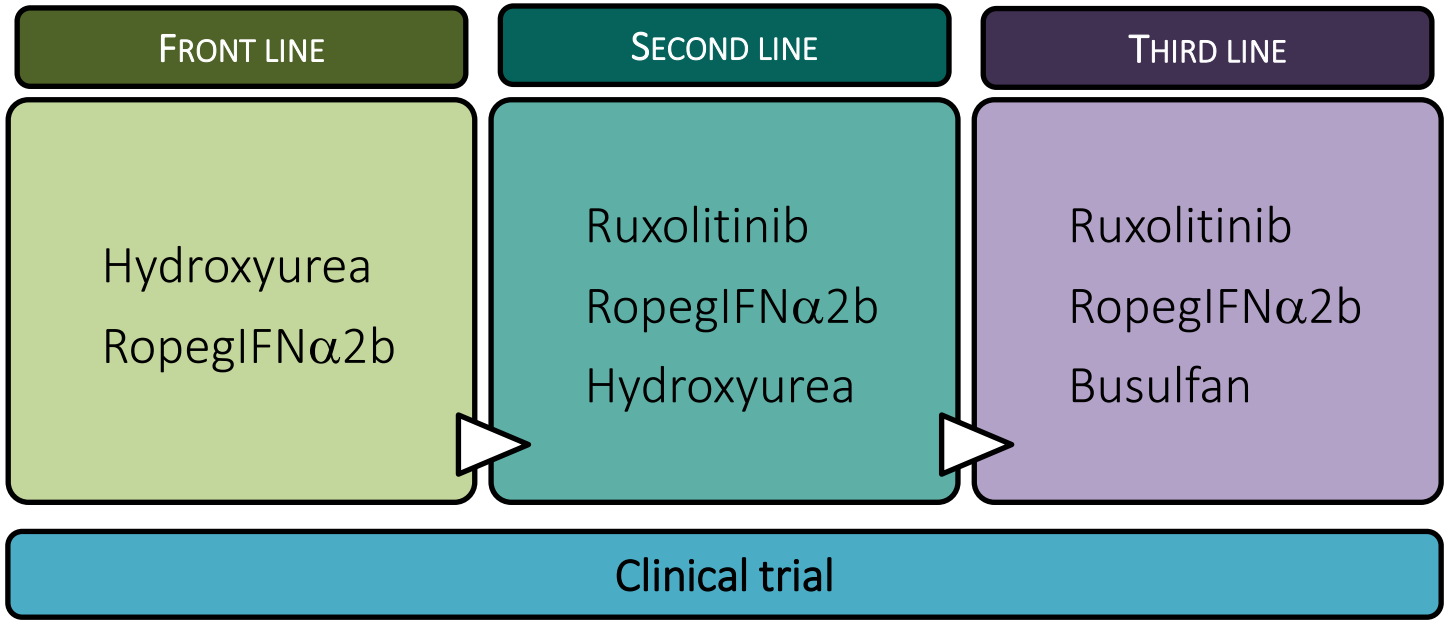
Disclosures of FRANCESCA PALANDRI

Acted as consultant and received honoraria from

- AbbVie
- Amgen
- AOP
- BMS Celgene
- Constellation/Morphosys
- CTI
- GlaxoSmithKline
- Grifols
- Karyopharm/Telios
- Novartis
- Sierra Oncology
- Sobi

Therapy of PV in 2023



Vannucchi AM, Haematologica. 2017 Jan;102(1):18-29 ;Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311. McMullin MF, Br J Haematol. 2019 Jan;184(2):176-191. Spivak JL, Blood. 2019 Jul 25;134(4):341-352; Tefferi A, Am J Hematol. 2023;98:1465–1487.

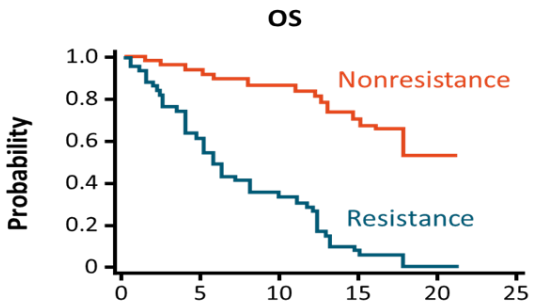
Very (very) sum of Hydroxyurea efficacy in PV

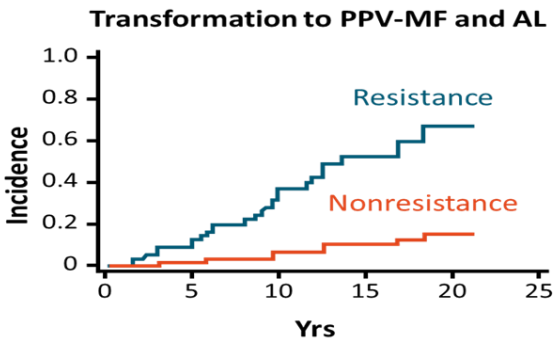
Retrospective results of HU in PV patients (Spanish registry and Italian study)

- Responses in 90% of patients (CR 24%, PR 66%)
- Resistance to HU (11%) implied a 5.6-fold increased risk of death
- CR rate is higher if median HU dose ≥1 g/d

HU prevents CV events but not recurrencies after SVT

- Sub-analysis of HR PV (ECLAP study): HU significantly reduces fatal/non-fatal CV events over PHL alone (p=0.017)
- Retrospective study on 1500 MPN patients with arterial/venous thrombosis (935/565): HU significantly reduces recurrence of arterial/venous thrombosis (but not venous recurrences after SVT)

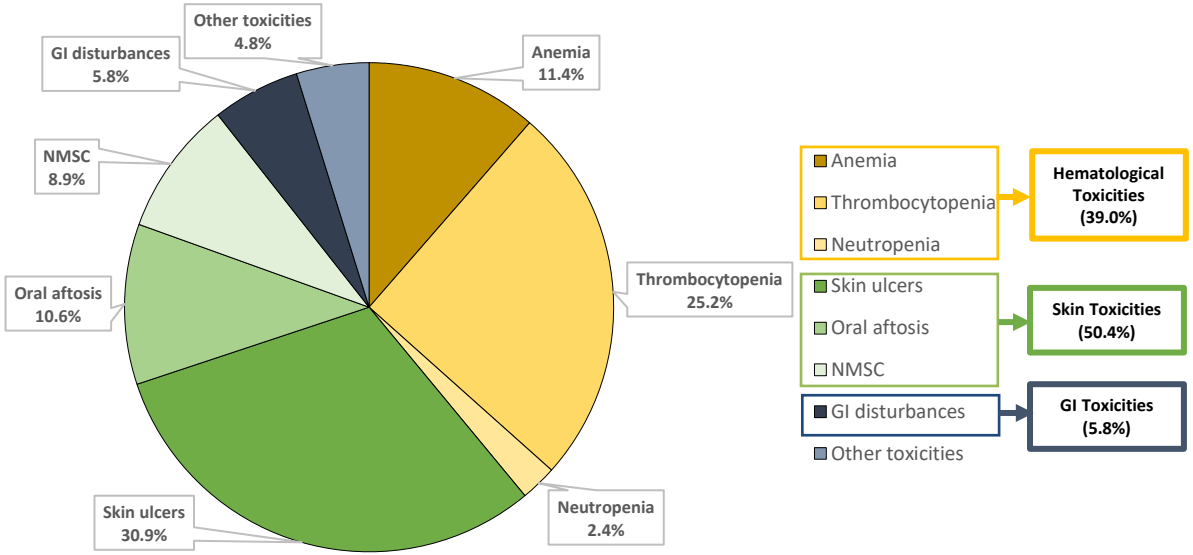


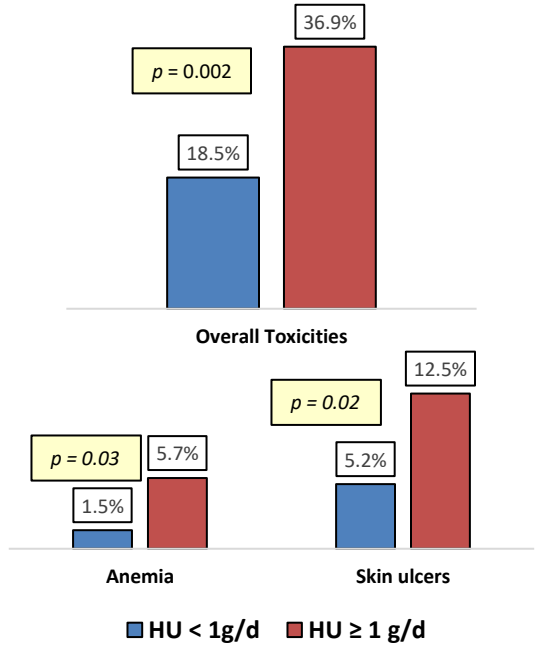


Barosi. Br J Haematol. 2010;148:961; Alvarez-Larrán. Blood. 2012;119:1363; Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-93; Alvarez-Larran et a. Leukemia 2020; Barbui T, Am J Hematol. 2017;92:1131–1136; De Stefano et al. Blood Cancer Journal (2018) 8:112. Palandri F, Cancers 2023, 15(14), 3706

Very (very) sum of Hydroxyurea safety in PV

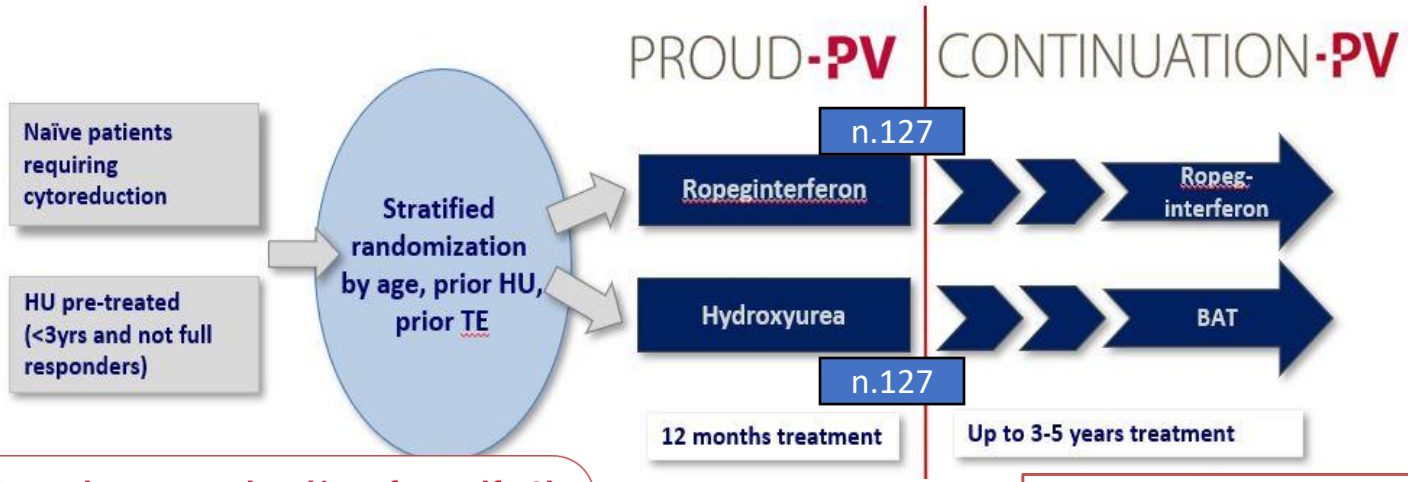
- In several retrospective studies, 10-15% of patients were intolerant to HU
- In an Italian cohort of 563 PV patients treated with HU for ≥12 months, ≥1 HU-related AE occurred in 23% of patients.
- HU intolerance was mainly due to hematological and skin toxicity
- Median HU dose ≥1 g/d was associated with increased incidence of HU-related AEs





Palandri F, Blood (2019) 134 (Supplement_1): 4174; Palandri F, Cancers 2023, 15(14), 3706; Barbui T, Am J Hematol. 2017;92:1131–1136; Alvarez-Larrán. Blood. 2012;119:1363; Alvarez-Larran et al; Br J Haematol. 2016 Mar;172(5):786-93; Alvarez-Larran et a. Leukemia 2020;

First-line RopegIFNα-2b vs HU in high-risk PV
PROUD-PV & CONTINUATION-PV phase 3 studies



- **A novel monopegylated interferon alfa-2b**, with only one single isoform
- **Administration every 14 days** (once monthly in long-term maintenance)
- **Pre-filled, dose-adjustable pen suitable for self-administration**

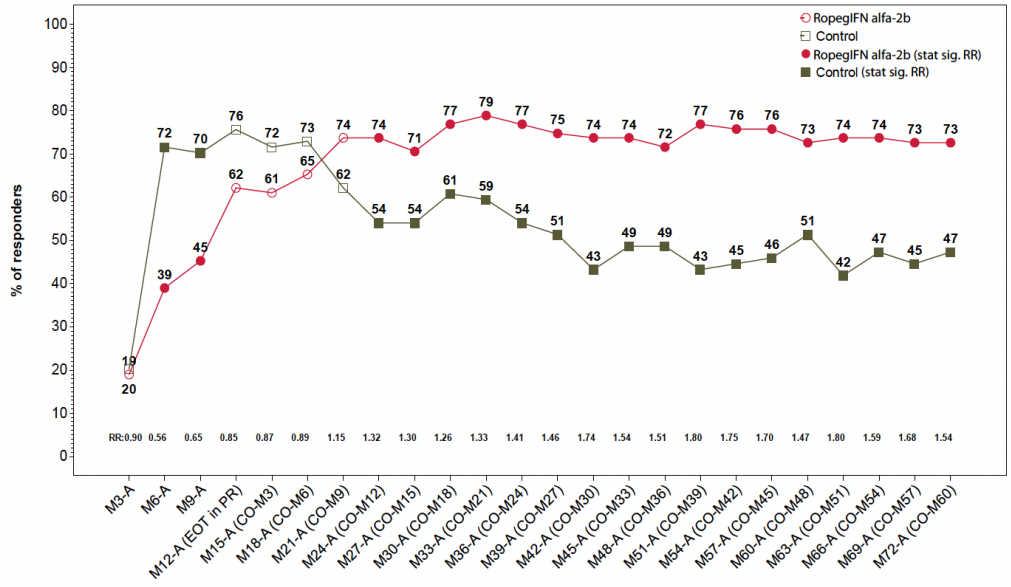
Press Release 20 Feb 2019
European Commission (EC) has granted Marketing Authorization for BESREMi® (Ropeginterferon alfa-2b) as first line monotherapy in adults for the treatment of Polycythaemia Vera (PV) without symptomatic splenomegaly.

Gisslinger et al, Blood 2018 132:579. Kiladjian et al, Blood 2019 134:553. Gisslinger H et al, Lancet Haematol 2020; 7: e196–208; Gisslinger H et al., Leukemia. 2023 Oct;37(10):2129-2132.

Complete Hematological response to RopegIFNα2b (Proud/Continuation-PV studies)

Hematologic response

Figure S3: Complete hematologic response rate over 72 months (last observation carried forward)



- Hematological response is achieved faster by HU
- After the 18-month timepoint, the percentage of patients in CHR is higher in ropegIFN-treated arm
- This superiority is maintained over time and was associated with higher percentage of patients who became phlebotomy independent

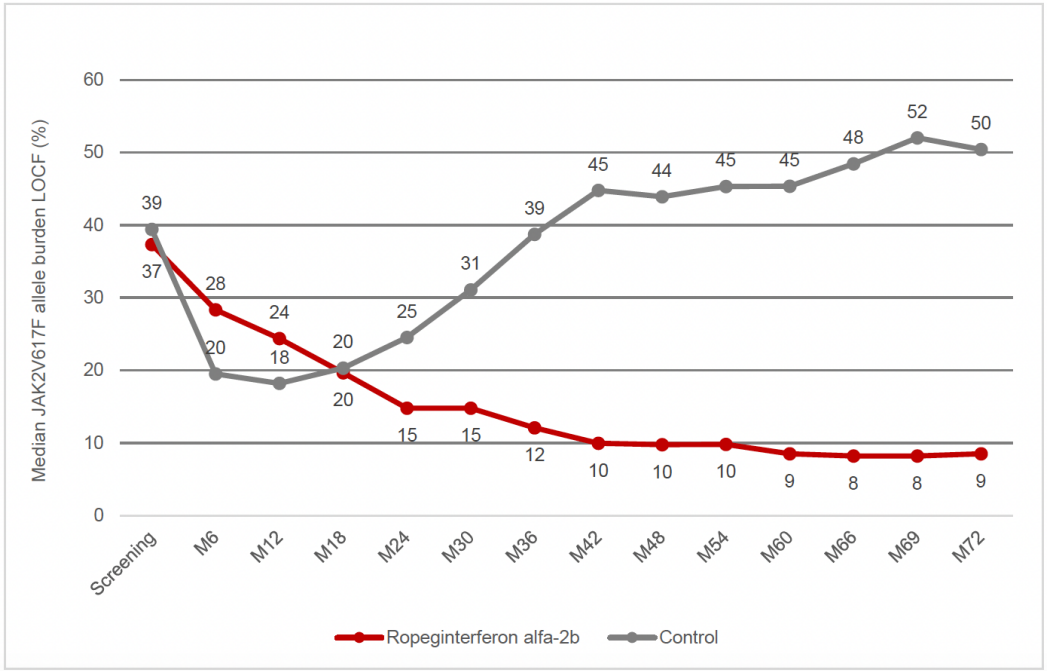
CHR:
- HCT <45% with no phlebotomy in the past 3 month AND
- PLT<400 × 10^9/L AND
- WBC <10 × 10^9/L AND
- normal spleen size by imaging (BUT: only 27 patients with large spleen)

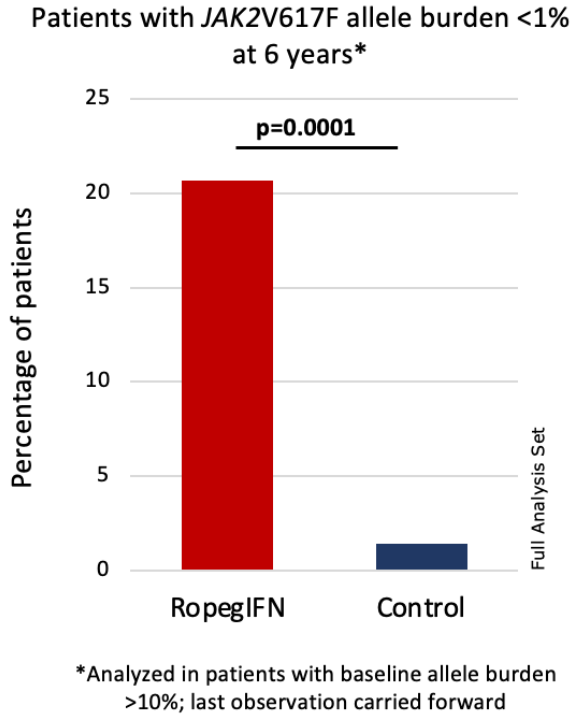
Gisslinger H et al., Leukemia. 2023 Oct;37(10):2129-2132.

JAK2V617F allele burden (Proud/Continuation-PV studies)

JAK2V617F allele burden

Figure S2: Median *JAK*2V617F allele burden over 72 months (last observation carried forward)





Safety profile overview of RopegIFNα2b vs HU (Proud/Continuation-PV studies)

	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

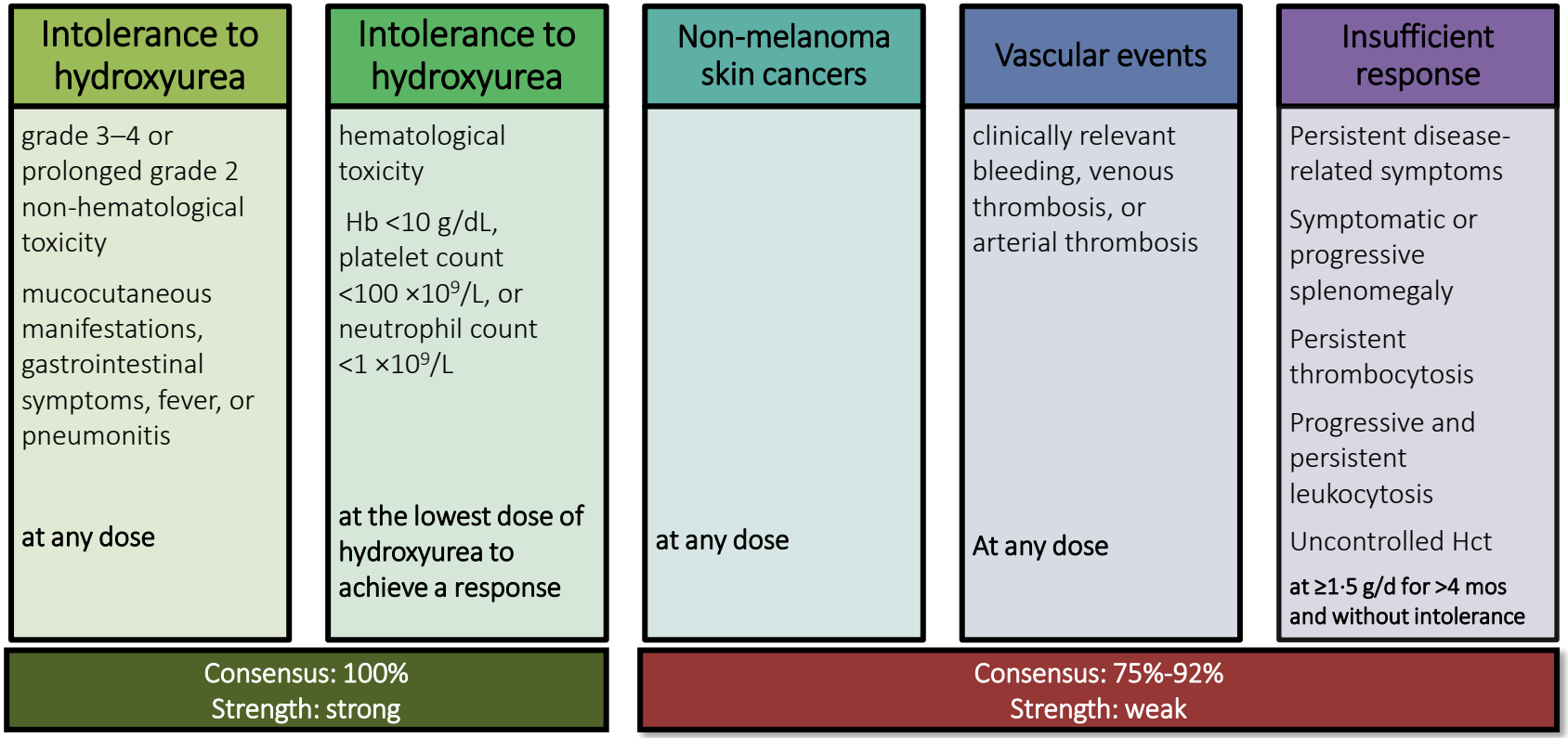
- ropegIFN shares common IFN-related toxicities (autoimmune diseases, mood depression)
- ropegIFN had a good safety profile and no excess toxicity compared to HU and comparable rates of thrombosis

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

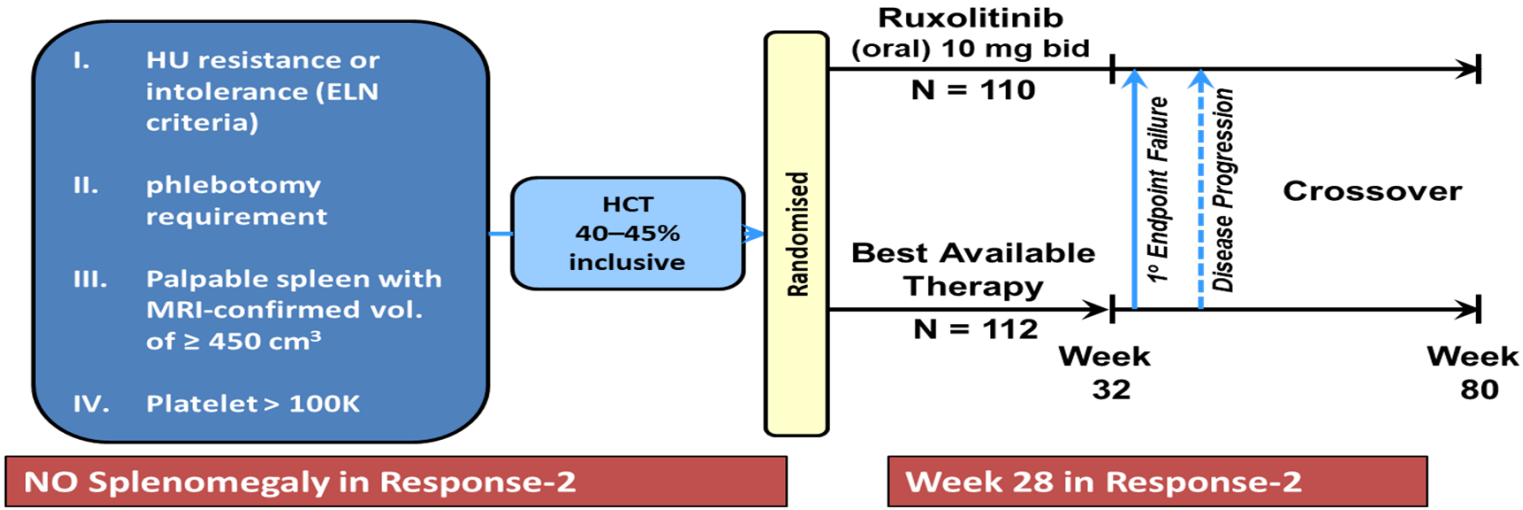
Gisslinger et al, Blood 2018 132:579. Kiladjian et al, Blood 2019 134:553.
Gisslinger H et al, Lancet Haematol 2020; 7: e196–208

ELN indications to switching from HU to 2L therapy



Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311.

Ruxolitinib in inadequately controlled PV
RESPONSE & RESPONSE-2 study design

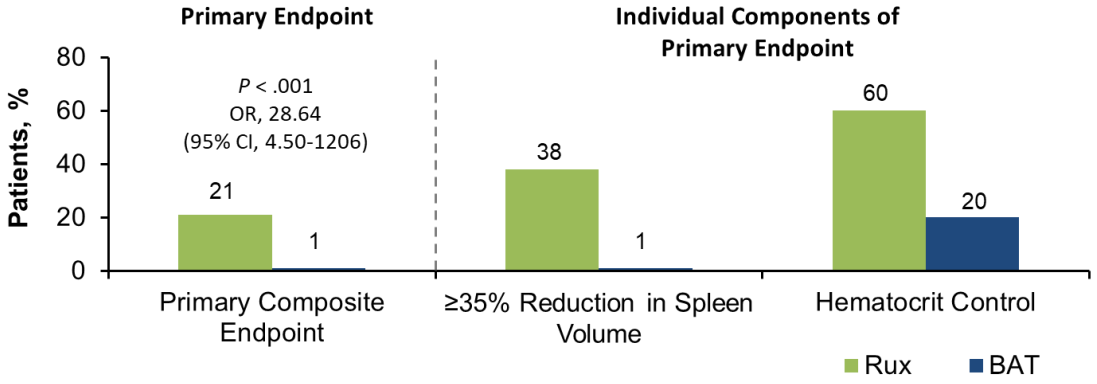


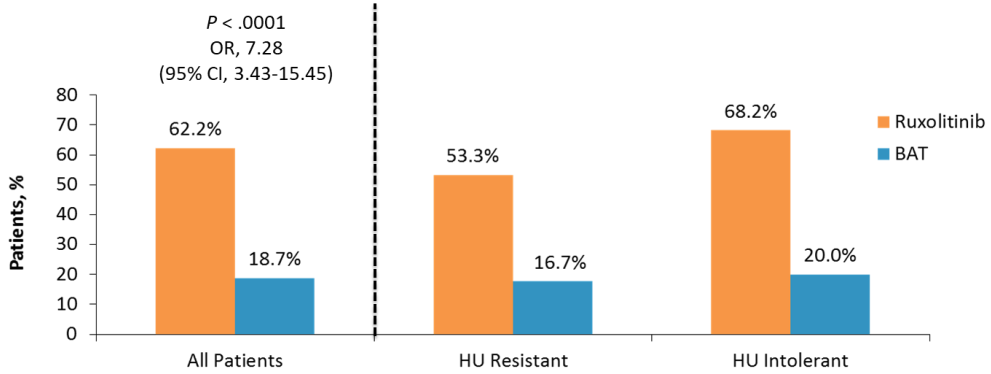
Primary composite endpoint: haematocrit control (phlebotomy independence from week 8 to 32, with ≤ 1 phlebotomy post randomization) in the absence of phlebotomy and 35% reduction in spleen volume at week 32 (this latter absent in Response 2)

Secondary endpoints: complete haematological remission at week 32 (absence of phlebotomy requirement, PLT count ≤ 400 x 10^9/L, and WBC count ≤ 10 × 10^9/L); % of patients who maintain primary endpoint response for ≥ 48 weeks; Symptom improvement (MPN-SAF diary) and quality of life (EORTC QLQ-C30; PGIC

Vannucchi AM et al, N. Engl. J. Med. 2015 Jan 29;372(5):426-35. Passamonti F et al, Lancet Oncol. 2017 Jan;18(1):88-99.

Ruxolitinib in inadequately controlled PV
RESPONSE & RESPONSE-2 studies

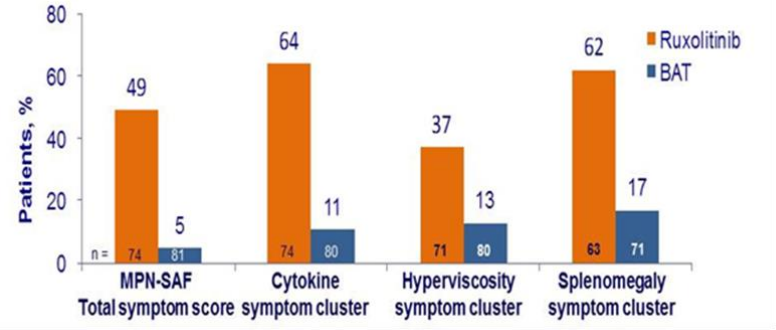


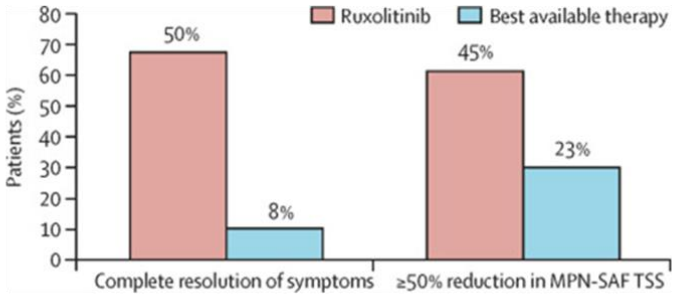


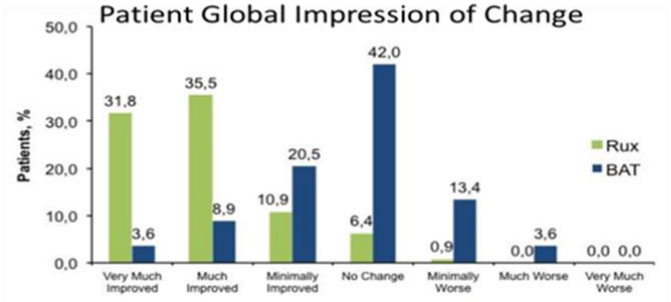
- RUX is superior to BAT in achieving Hct control and spleen reduction
- RUX is superior to BAT in achieving Hct control both in HU resistant and intolerant patients with no palpable splenomegaly

Vannucchi AM et al, N. Engl. J. Med. 2015 Jan 29;372(5):426-35. Passamonti F et al, Lancet Oncol. 2017 Jan;18(1):88-99.

RUX significantly improves PV symptoms & QoL



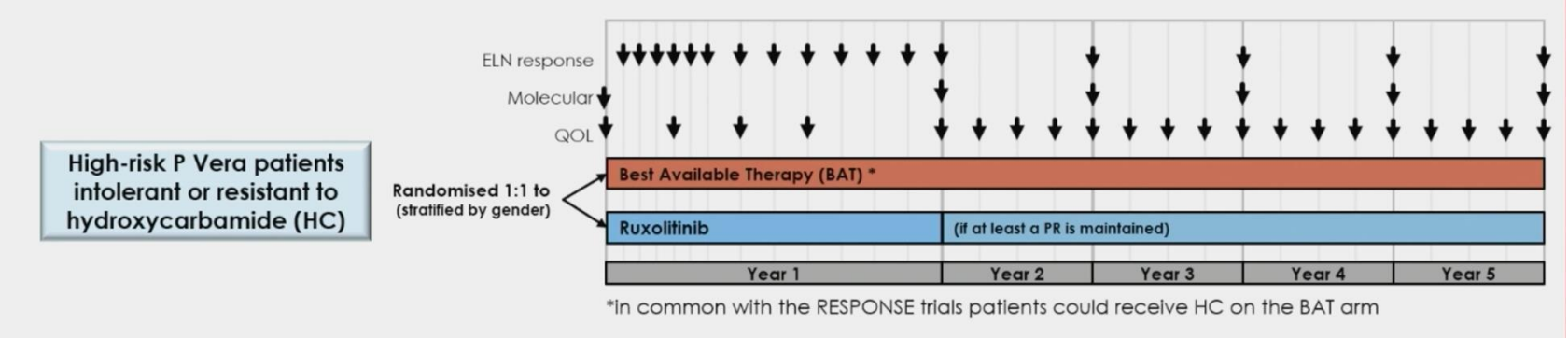




Mean change from baseline to Week 32 in EORTC QLQ-C30* HRQoL and functional domain scores (Response study)

Vannucchi AM et al, N. Engl. J. Med. 2015 Jan 29;372(5):426-35. Passamonti F et al, Lancet Oncol. 2017 Jan;18(1):88-99.
Passamonti F et al, Lancet Haematol 2022 Jul;9(7):e480-e492. doi: 10.1016/S2352-3026(22)00102-8.

MAJIC-PV phase 2 trial: RUX vs BAT in HU intolerant/resistant PV patients



- **MAJIC-PV is an open label, randomized phase 2 trial of RUX vs BAT in patients with intolerance/resistance to HU**
- **180 patients were randomized**
- **BAT: HU ±IFN:44%; IFN:15%**

PRIMARY OUTCOME

- ELN Complete response (WBC <10; HCT <45%; PLT <400)

SECONDARY OUTCOME

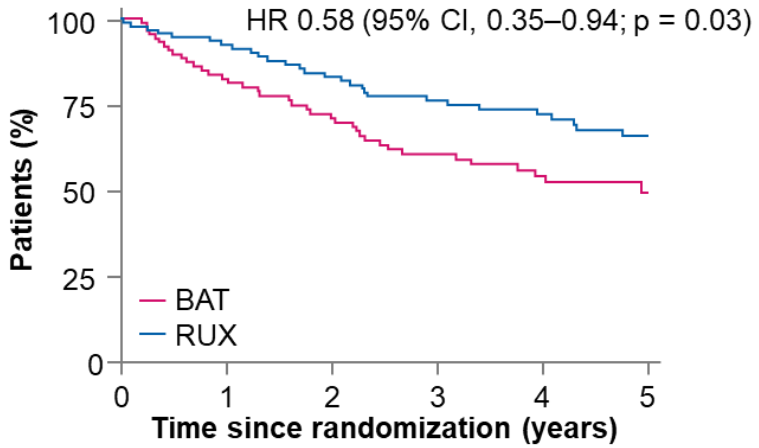
- Duration of CR
- Thrombotic/hemorrhagic events
- PFS/OS
- QoL and symptoms

CR, complete response; EFS, event-free survival; HR, hazard ratio; MPN, myeloproliferative neoplasm; OS, overall survival; PFS, progression-free survival, VAF, variant allele frequency.

Harrison C, et al. J Clin Oncol. 2023 Jul 1;41(19):3534-3544

MAJIC-PV: Event-free survival

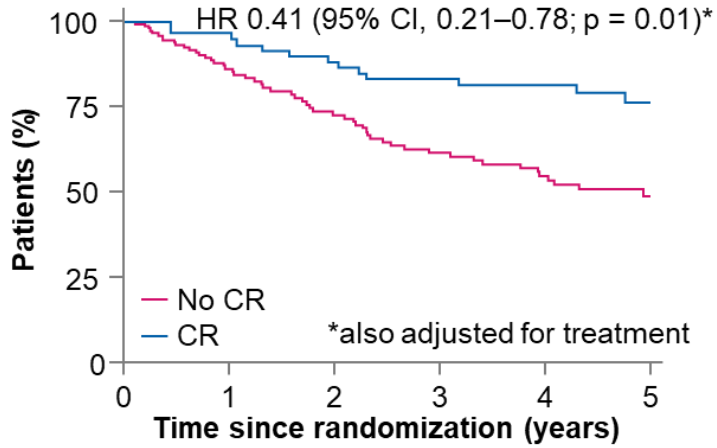
RUX vs BAT



Number at risk

BAT	87	68	55	41	33	10
RUX	93	81	72	62	53	19

CR vs no CR



Number at risk

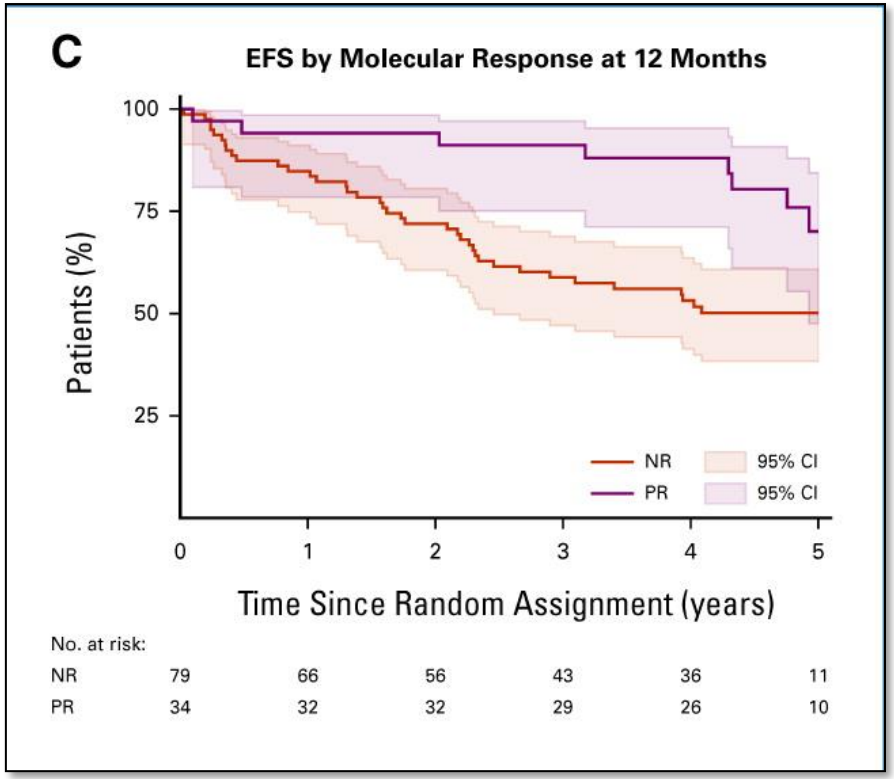
No CR	180	101	74	57	46	14
CR	0	50	53	46	40	15

- **CR was achieved in 43% patients on RUX vs 26% on BAT (p = 0.02)**
- **EFS (major hemorrhage, thrombosis, transformation, death) was superior in RUX and in pts in CR within 1 year**

CR, complete response; EFS, event-free survival; HR, hazard ratio; MPN, myeloproliferative neoplasm; OS, overall survival; PFS, progression-free survival, VAF, variant allele frequency.

Harrison C, et al. J Clin Oncol. 2023 Jul 1;41(19):3534-3544

MAJIC-PV: EFS by molecular response



Molecular response: 50% reduction in *JAK2*V617F VAF

Molecular response (RUX vs BAT)
@ 12 months: 14% vs 18%
@ last time-point: 56% vs 25% (p<0.001)

Median time to molecular response was 36 months for RUX

Molecular response @12 months was associated with improved EFS

Harrison CN, et al. J Clin Oncol. 2023 Jul 1;41(19):3534-3544

Lessons learned (and open questions) from the MAJIC-PV study

The achievement of a CR correlates with better outcome, regardless of type of cytoreduction (HU or RUX)

- CR is a key target of therapy!
- Impact of timing and duration of CR is still to be defined

The achievement of a molecular response correlates with better outcome, regardless of type of cytoreduction (HU or RUX)

- Is it time for molecular monitoring in PV? When? with what practical effect?

The switch to RUX in patients with HU-resistant/intolerant PV is associated with better outcome

- Is it time to change therapy more readily in case of HU resistance or intolerance?

Palandri F, personal considerations

Harrison C, et al. Blood. 2022;140 (Suppl 1):1781–3.
Harrison C, et al. J Clin Oncology. 2023

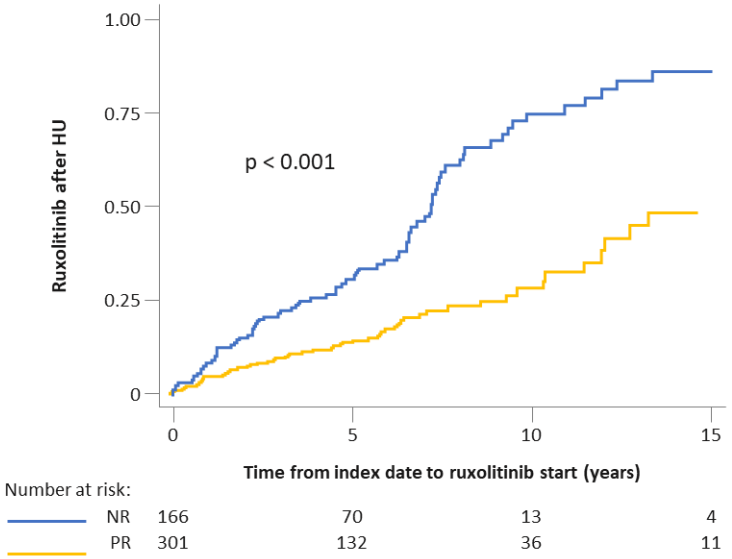
Only 30% of patients with HU-resistant PV switch to RUX in real life

In a retrospective real-world study on 563 patients with PV treated with HU ≥ 12 months, 283 (50.3%) patients never achieved a CR

Among these poor responders, only 30% switched to RUX

The probability of RUX switch was significantly higher in patients with NR compared with patients with PR

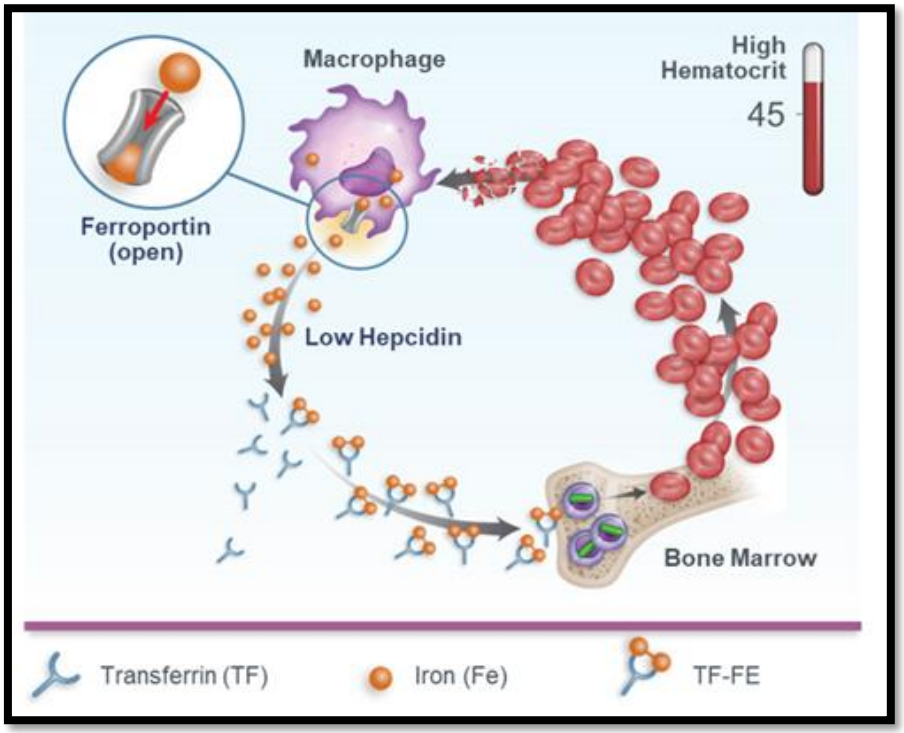
Only 30% of suboptimal responders switched to ruxolitinib within two years



Palandri F et al, Cancers 2023 Jul 21;15(14):3706

Iron metabolism modifiers

Hepcidin down-regulation increases iron availability for RBC production in PV



Hepcidin is the master regulator of iron homeostasis

Hepcidin expression is inhibited by iron deficiency, expansion of erythropoiesis, anemia/hypoxia, testosterone.

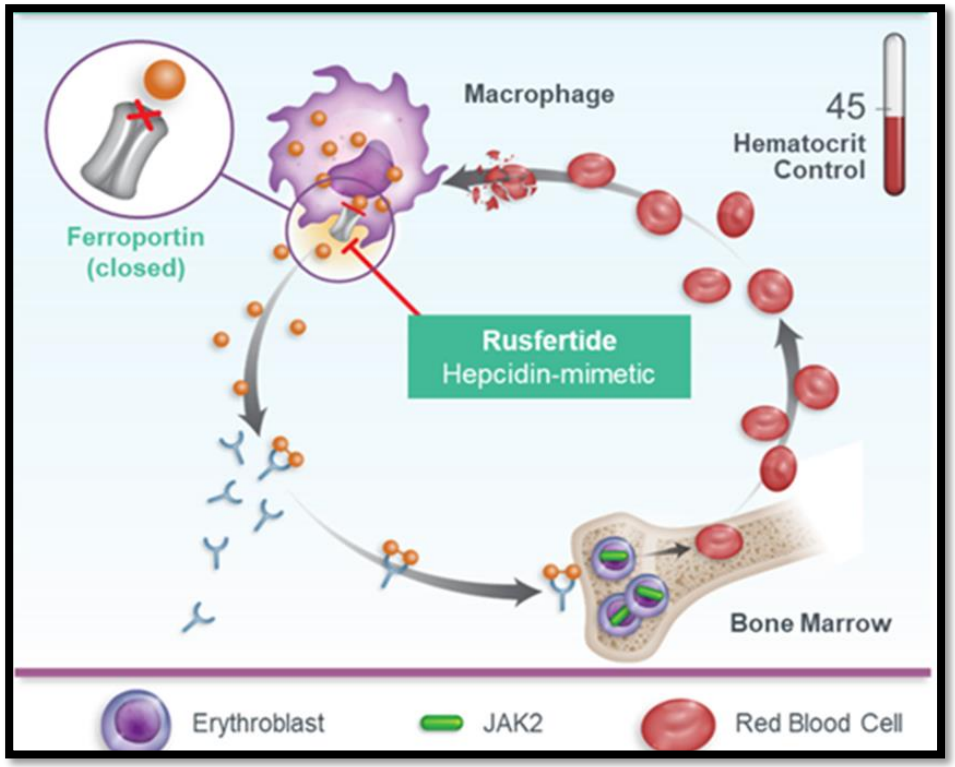
In PV, hepcidin suppression is due to EPO-independent JAK-STAT activation

LOW HEPCIDIN LEVELS induce

Increased GI iron absorption	Lower iron sequestration by the reticulo-endothelial system	Increased iron availability for erythropoiesis

Bennet C, Blood. 2023 Jun 29;141(26):3199-3214, Girelli D, Blood. 2023 Jun 29;141(26):3132-3134.
Camaschella C, Haematologica. 2020 Jan 31;105(2):260-272
Handa S, Curr Opin Hematol. 2023 Mar 1;30(2):45-52

Rusfertide (PTG-300) is a hepcidin-mimetic agent that suppresses RBC production in PV



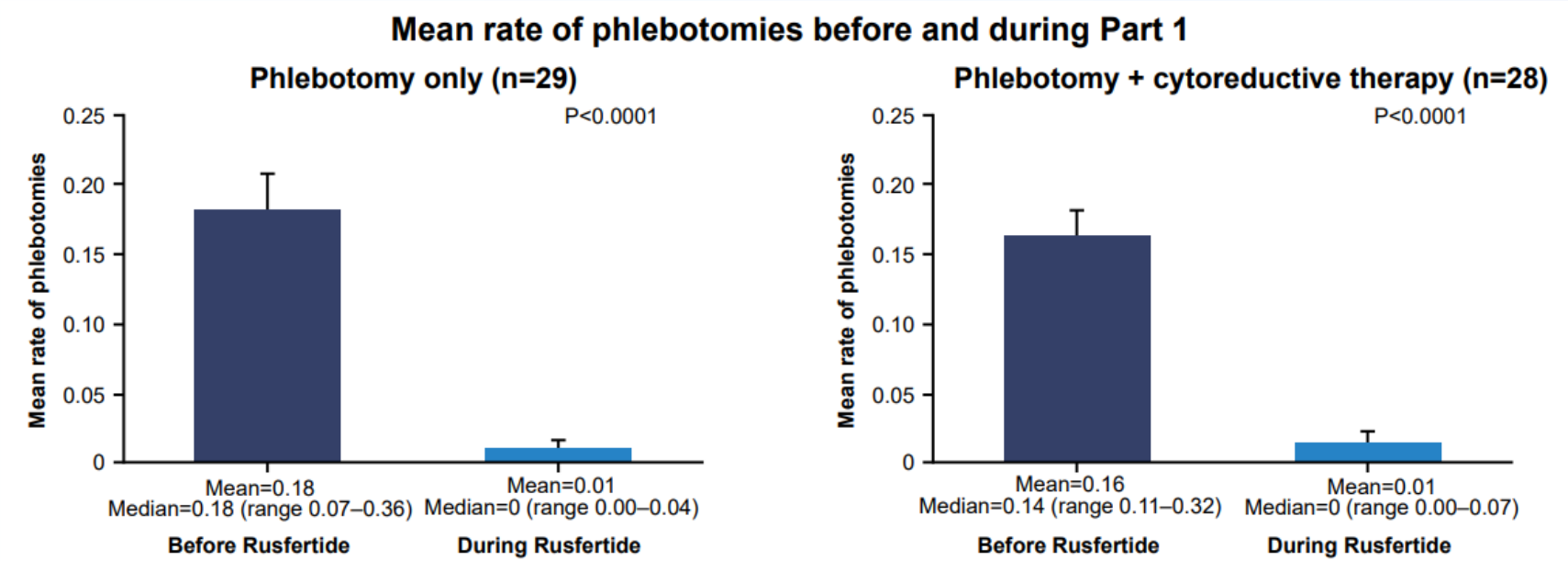
Rusfertide is an injectable peptide mimetic of the natural hormone hepcidin

Rusfertide restricts the availability of iron for red blood cell production, thus decreasing hematocrit and phlebotomies need

Rusfertide is being developed for PV patients with uncontrolled erythrocytosis despite standard therapy

Hoffman R, et al. J Clin Oncol. 2022:40;7003.

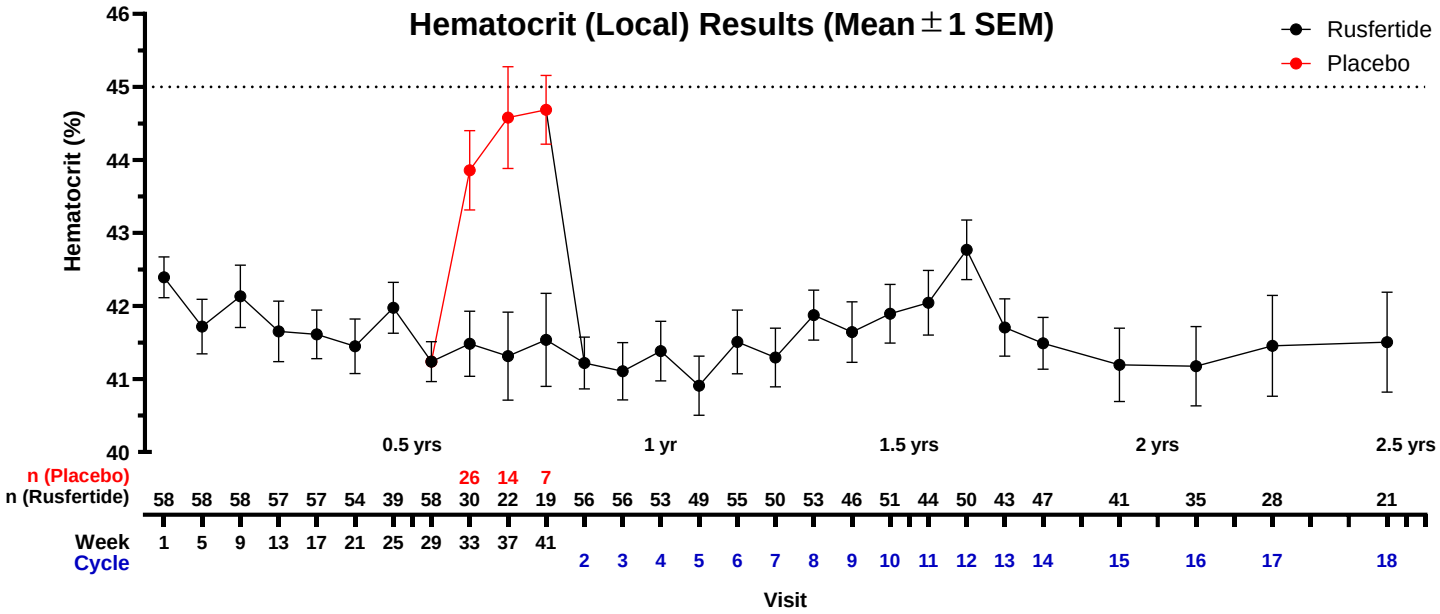
Revive Phase 2 study
Rusfertide Significantly Decreased Phlebotomy Requirements



- Phlebotomy dependent PV patients (≥3 phlebotomies in 6 months with/out cytoreductive therapy)
- Doses of 10-120 mg administered subcutaneously weekly added to prior standard therapy
- Most treatment-emergent adverse events (TEAEs) were grade 1-2, no grade 3 events related to rusfertide, no grade 4 or 5 TEAEs

Hoffman R, et al. J Clin Oncol. 2022:40;7003.

Rusfertide Provided Durable Control of Hematocrit Through 2.5 Years



- Rusfertide treatment resulted in consistent maintenance of hematocrit <45%

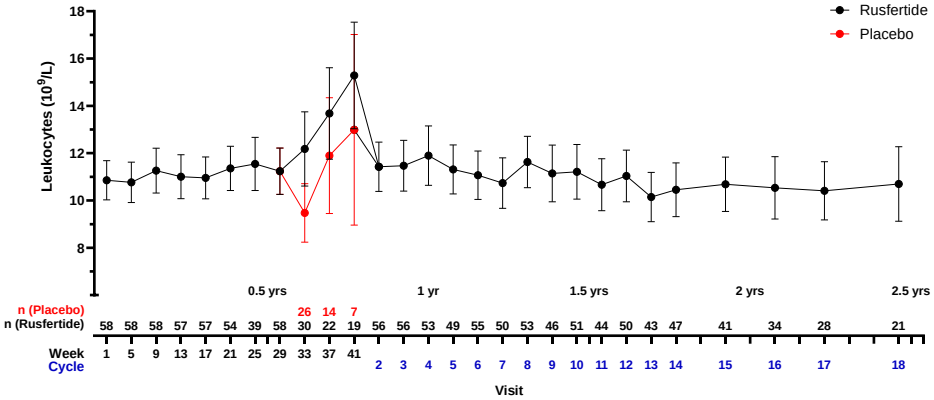
Dotted horizontal line, hematocrit <45%.
SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

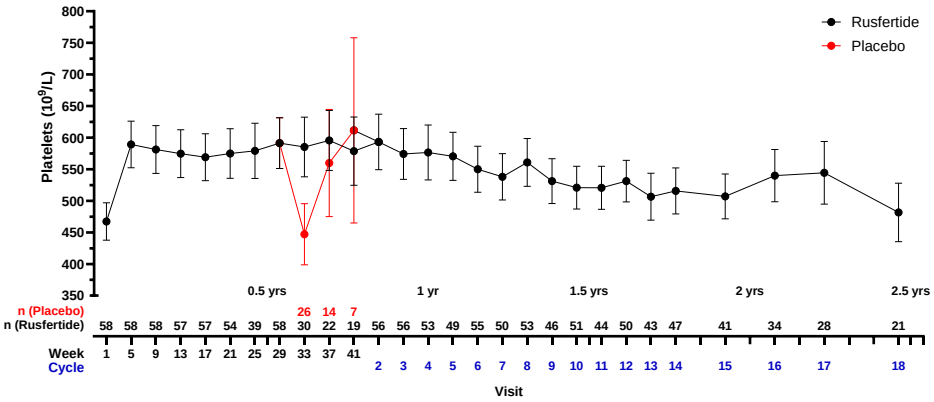
Leukocytes Were Stable; Platelet Counts Increased During Initial Treatment and Remain Stable Over Time

Leukocytes (Local) Results (Mean ± 1 SEM)



- Mean leukocyte counts remained stable and did not change meaningfully over the duration of the trial

Platelets (Local) Results (Mean ± 1 SEM)



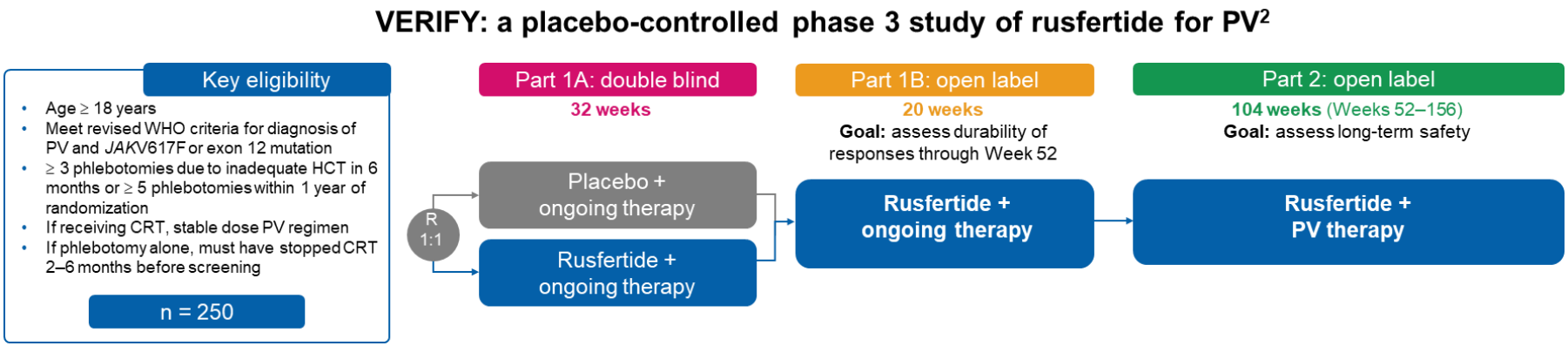
- After increasing by approximately 30% post-baseline, mean platelet counts stabilized over time

SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

Ritchie E et al, abstract #745, ASH2023 oral presentation
***Blood* (2023) 142 (Supplement 1): 745.**

VERIFY (rusfertide phase III study) ongoing in 2024



Rusfertide + ongoing therapy in PV requiring ≥3 PHL in 6 months or ≥ 5 in 12 months

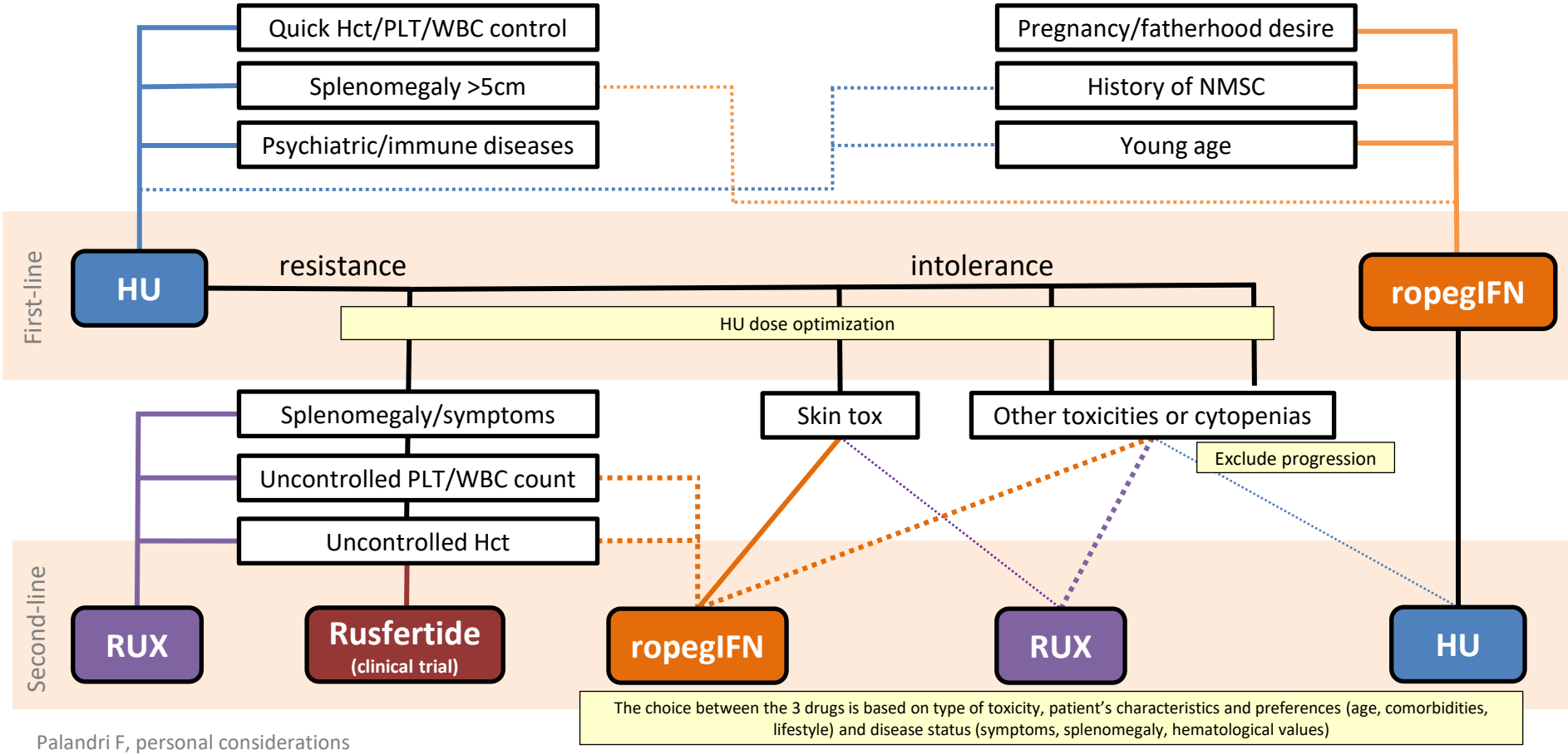
Primary Efficacy Endpoint

- Proportion of patients achieving a response in Part 1a from Week 20 through Week 32
- A response is defined as absence of phlebotomy eligibility (HCT>45% and >3% higher than BL)

Key Secondary Efficacy Endpoints

- Mean number of phlebotomies between Week 0 to 32
  Proportion of patients with HCT<45% between Week 0 to 32
- Mean change in total fatigue score @wk32
- Mean change in TSS @ wk32

PV cytoreductive treatment algorithm



Palandri F, personal considerations

Thanks!

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MPN/ITP Unit - Bologna

Medical Doctors

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Event-free survival (Proud/Continuation-PV studies)

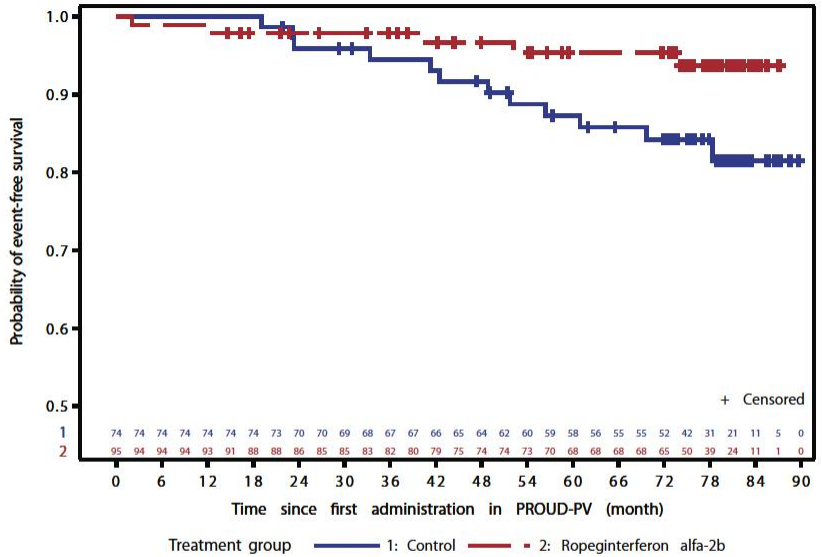


Fig. 1 Probability of event-free survival in patients with PV in the ropeginterferon alfa-2b arm and control arm (CONTINUATION-PV full analysis set). Risk events were defined as thromboembolic events, disease progression or death.

- The probability of event-free survival was significantly higher in the ropeginterferon alfa-2b arm compared with the control HU treatment group (0.94 versus 0.82; log-rank test; p=0.04)

The Cox proportional **hazard ratio** was 0.34 (95% CI:0.12–0.97; ***p*=0.04**).

Risk events occurred in 5/95 patients (5.3%) in the ropeginterferon alfa-2b arm:

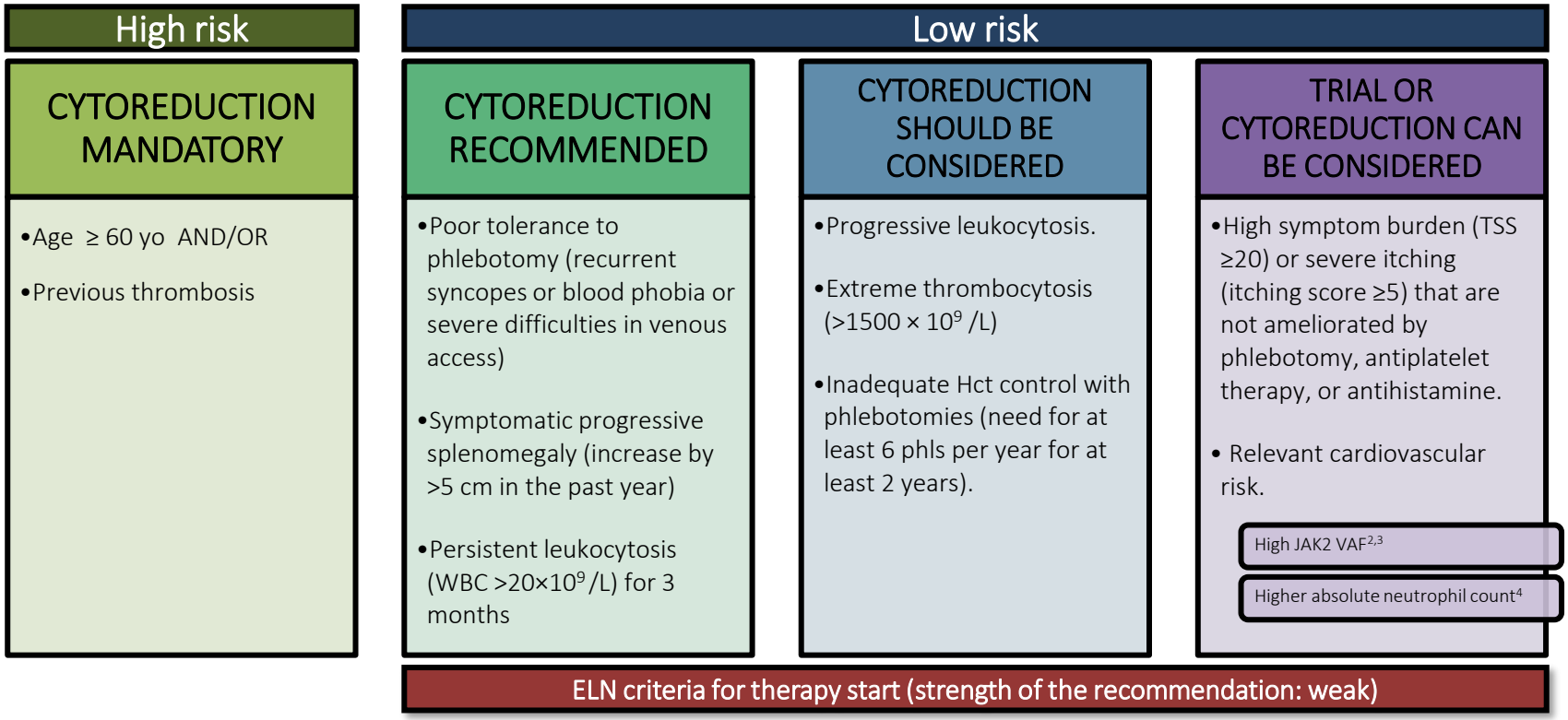
- **thromboembolic events** [n=2];
- **myelofibrosis** [**n=1**];
- **death** [**n=2**]

compared with 12/74 patients (16.2%) allocated to hydroxyurea/BAT:

- **thrombotic events** [n=5]
- **myelofibrosis** [**n=2**]
- **acute leukemia** [**n=2**]
- **death** [**n=3**]

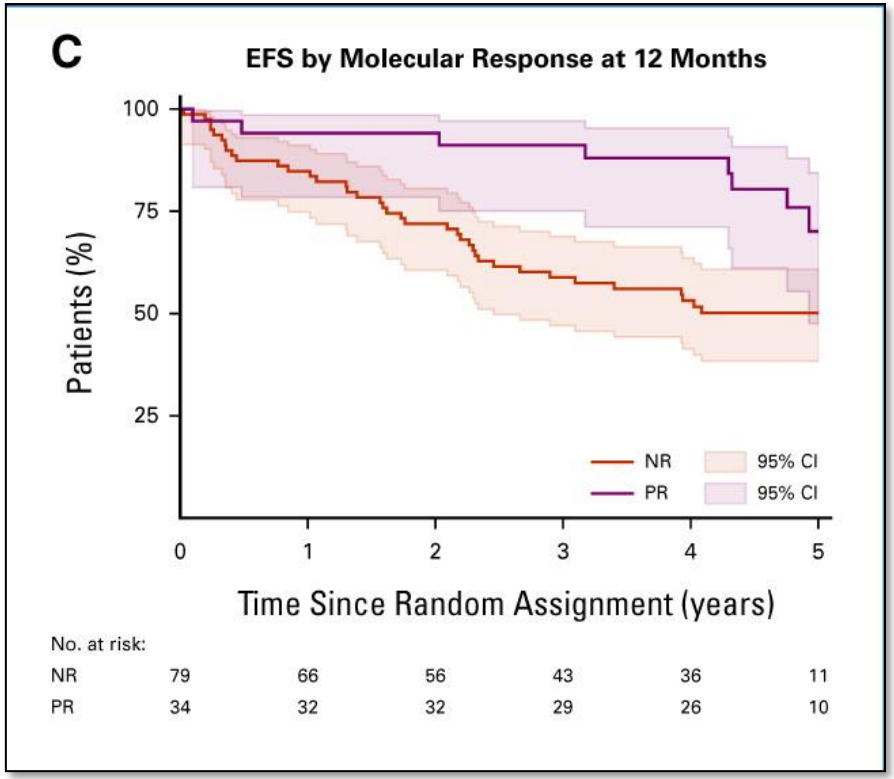
Gisslinger H et al, Leukemia. 2023 Oct;37(10):2129-2132.

ELN indications to cytoreduction in PV[1]



1. Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311. 2. Vannucchi AM, Leukemia. 2007; 21: 1952-1959. 3. Guglielmelli P, Blood Cancer J. 2021 Dec; 11(12): 199. 4. Carobbio A, Blood Cancer J. 2022; 12: 28.

MAJIC-PV: EFS by molecular response



Molecular response: 50% reduction in *JAK2*V617F VAF

Molecular response (RUX vs BAT)

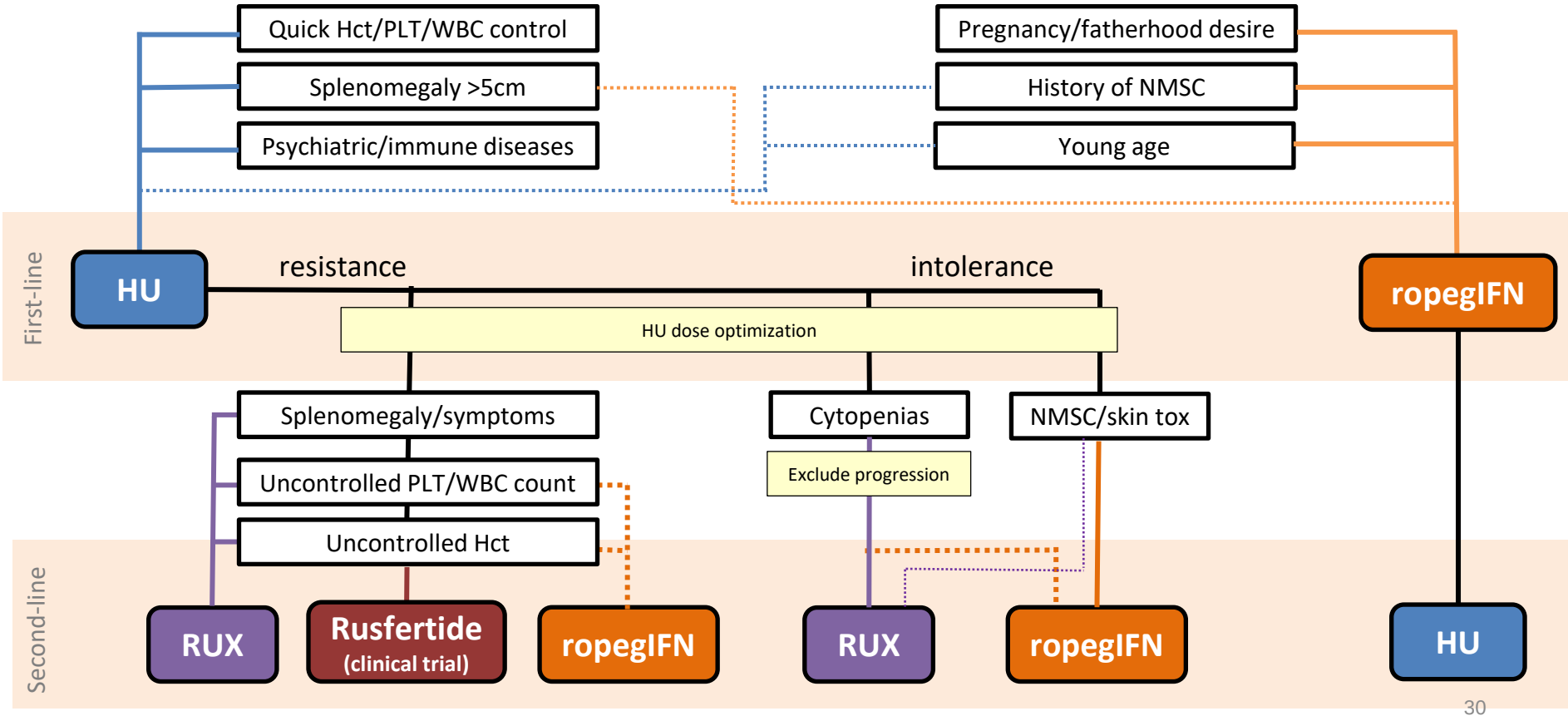
@ 12 months: 14% vs 18% @ final evaluable time-point: 56% vs 25%

Median time to molecular response was 36 months for RUX

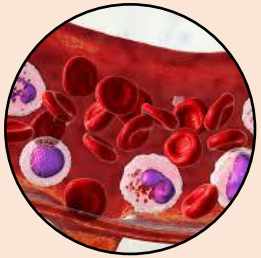
Molecular response was associated with CR, improved PFS, EFS, OS

Harrison C, et al. J Clin Oncol. 2023 Jul 1;41(19):3534-3544

PV cytoreductive treatment algorithm

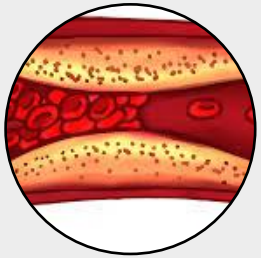


Iron metabolism modifiers may substitute for use of phlebotomies in PV?



No effect on other aspects of myeloproliferation

Cytoreduction is required in HR patients!



Main effect is the drug-dependent, consistent reduction of Hct

Translation into a long-term reduction on thrombotic risk must be proven

Induction of a functional iron deficiency

Translation into a better clinical benefit compared to true iron deficiency (from PHL) must be proven

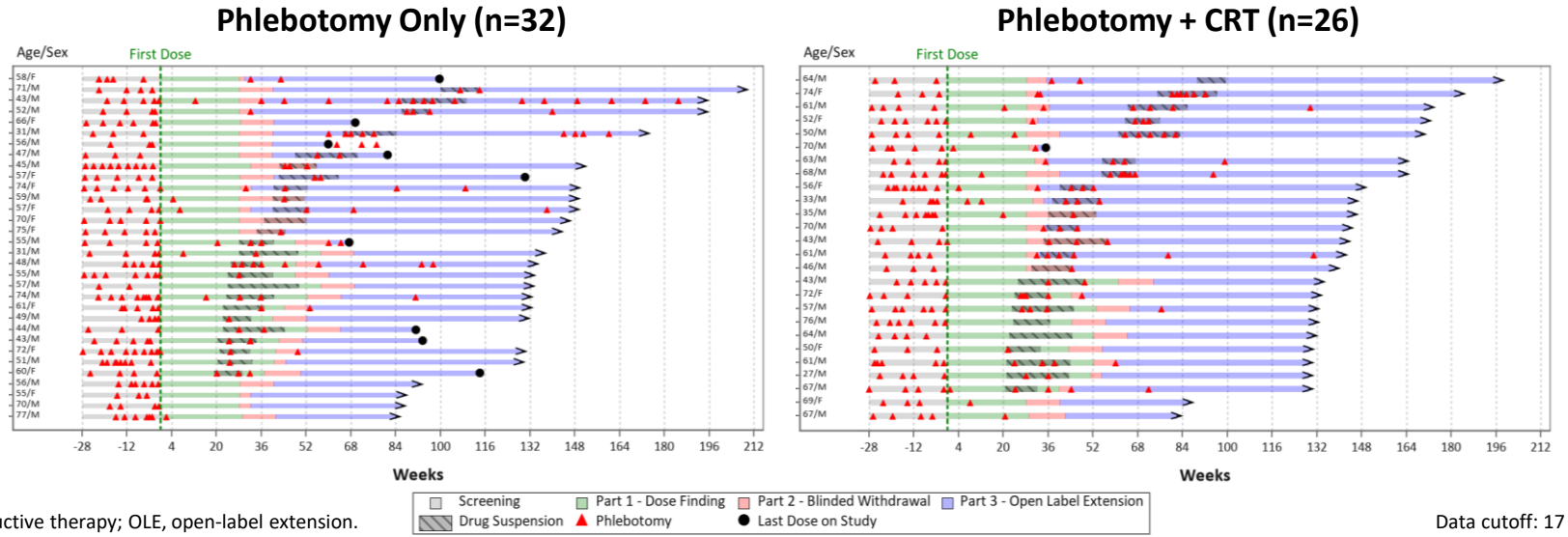
Pharmacological hepcidin increase may have off-target consequences

Elevated hepcidin may increase HIF-mediated gene expression, possibly leading to increased risk of thrombosis

1. Hoffman R, et al. J Clin Oncol. 2022:40;7003.
2. Verstovsek S, et al. Presented at ASH2022; abstract 1709.

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

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



CRT, cytoreductive therapy; OLE, open-label extension.

Data cutoff: 17 October 2023

ELN indications to switching from HU to 2L therapy

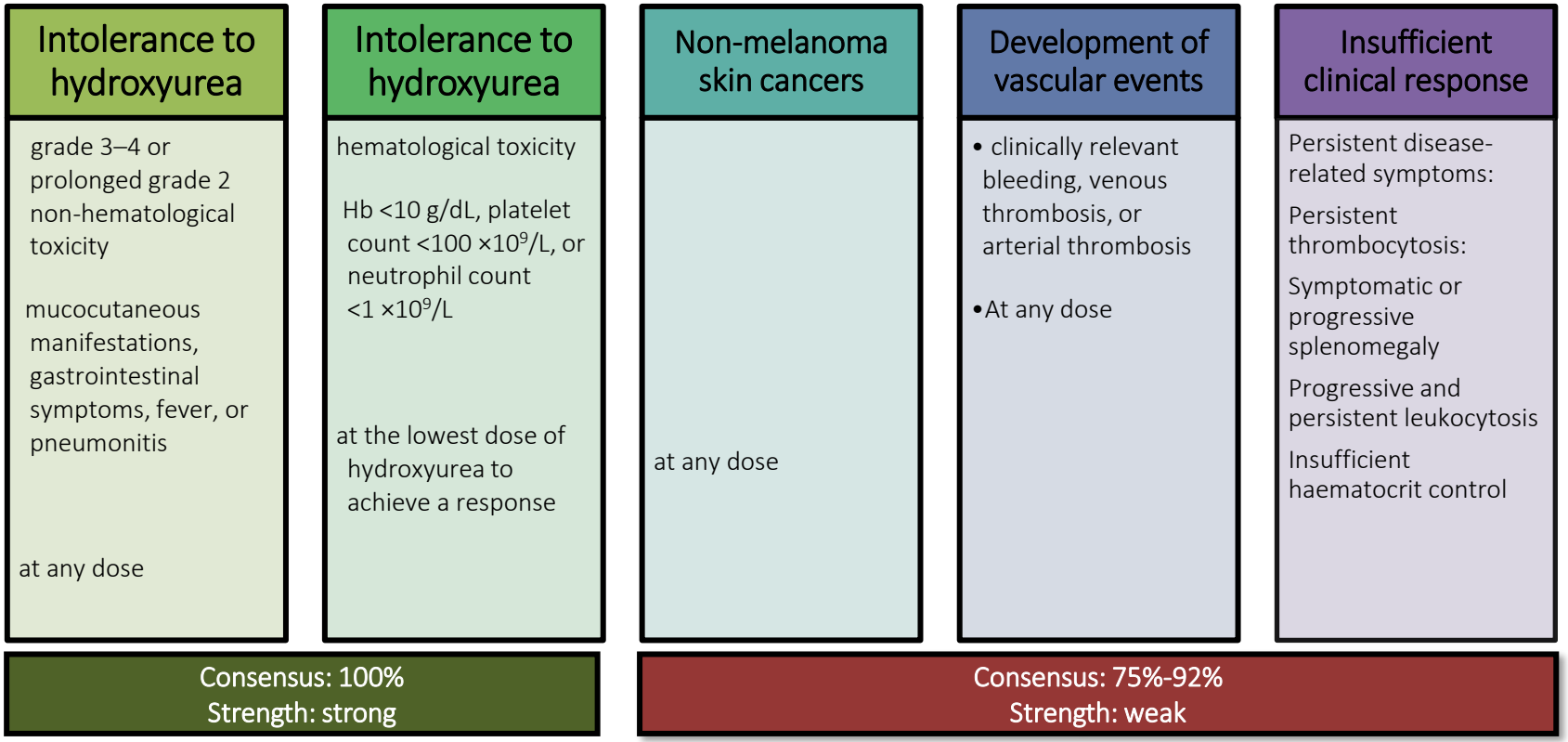
Intolerance to hydroxyurea	Intolerance to hydroxyurea	Non-melanoma skin cancers	Development of vascular events	Insufficient clinical response
grade 3–4 or prolonged grade 2 non-hematological toxicity mucocutaneous manifestations, gastrointestinal symptoms, fever, or pneumonitis at any dose	hematological toxicity Hb <10 g/dL, platelet count <100 ×10^9/L, or neutrophil count <1 ×10^9/L at the lowest dose of hydroxyurea to achieve a response	at any dose	•either clinically relevant bleeding, venous thrombosis, or arterial thrombosis •At any dose	Persistent disease-related symptoms: a TSS>20 or an itching >6/10 for > 6 months Persistent thrombocytosis: a PLT >1000 × 10/L, microvascular symptoms, or both, persisting for >3 months Symptomatic or progressive splenomegaly: increased in spleen size by more than 5 cm from the left costal margin in 1 year Progressive (at least 100% increase if baseline count is <10 × 10 9 cells per L or at least 50% increase if baseline count is >10 × 10 9 cells per L) and persistent leukocytosis (leukocyte

Consensus: 100%
Strength: strong

ELN criteria for therapy start in Low risk PV

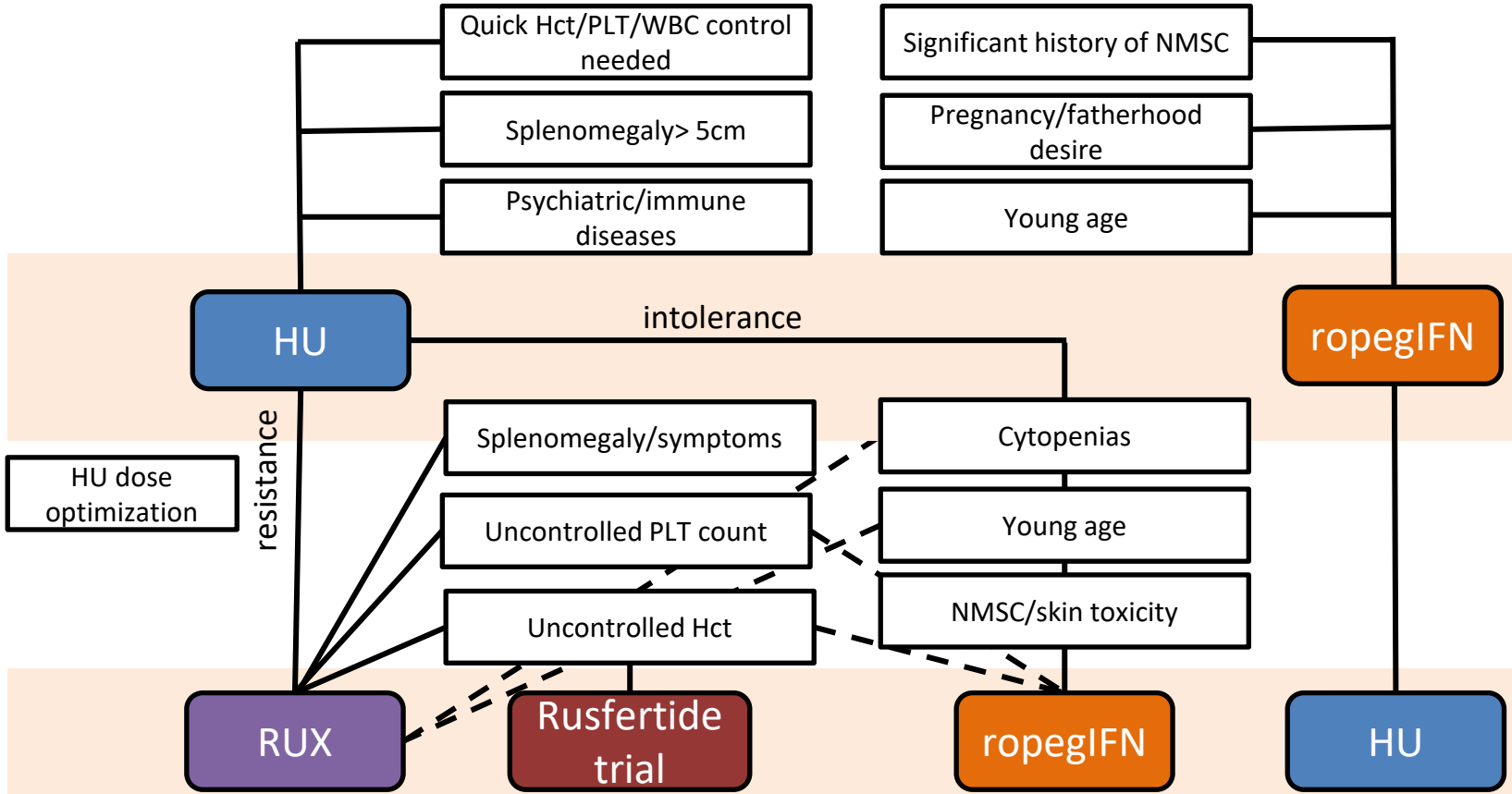
Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311.

ELN indications to switching from HU to 2L therapy



Marchetti M. et al. Lancet Haematol 2022 Apr;9(4):e301-e311.

High-risk PV


Quick Hct/PLT/WBC control needed
Splenomegaly> 5cm
Psychiatric/immune diseases
Significant history of NMSC
Pregnancy/fatherhood desire
Young age
HU
intolerance
ropegIFN
resistance
HU dose optimization
Splenomegaly/symptoms
Uncontrolled PLT count
Uncontrolled Hct
Cytopenias
Young age
NMSC/skin toxicity
RUX
Rusfertide trial
ropegIFN
HU

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Thanks!

francesca.palandri@unibo.it

New Drugs in Hematology

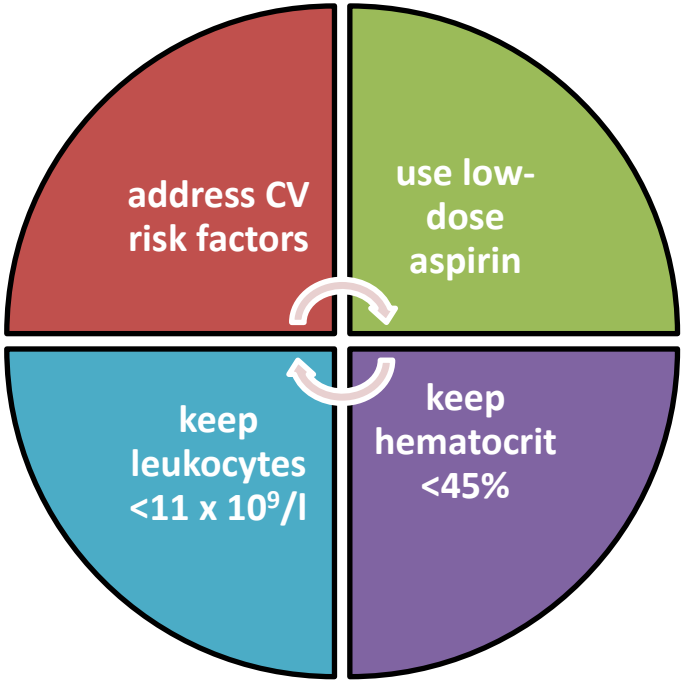
President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

The 4 “must-do” in all patients

Low-risk patients with hypertension have a higher incidence of thrombosis
Arterial hypertension was associated with highest levels of hematocrit (retrospective studies)[1]

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 (Cyto-PV)[4]



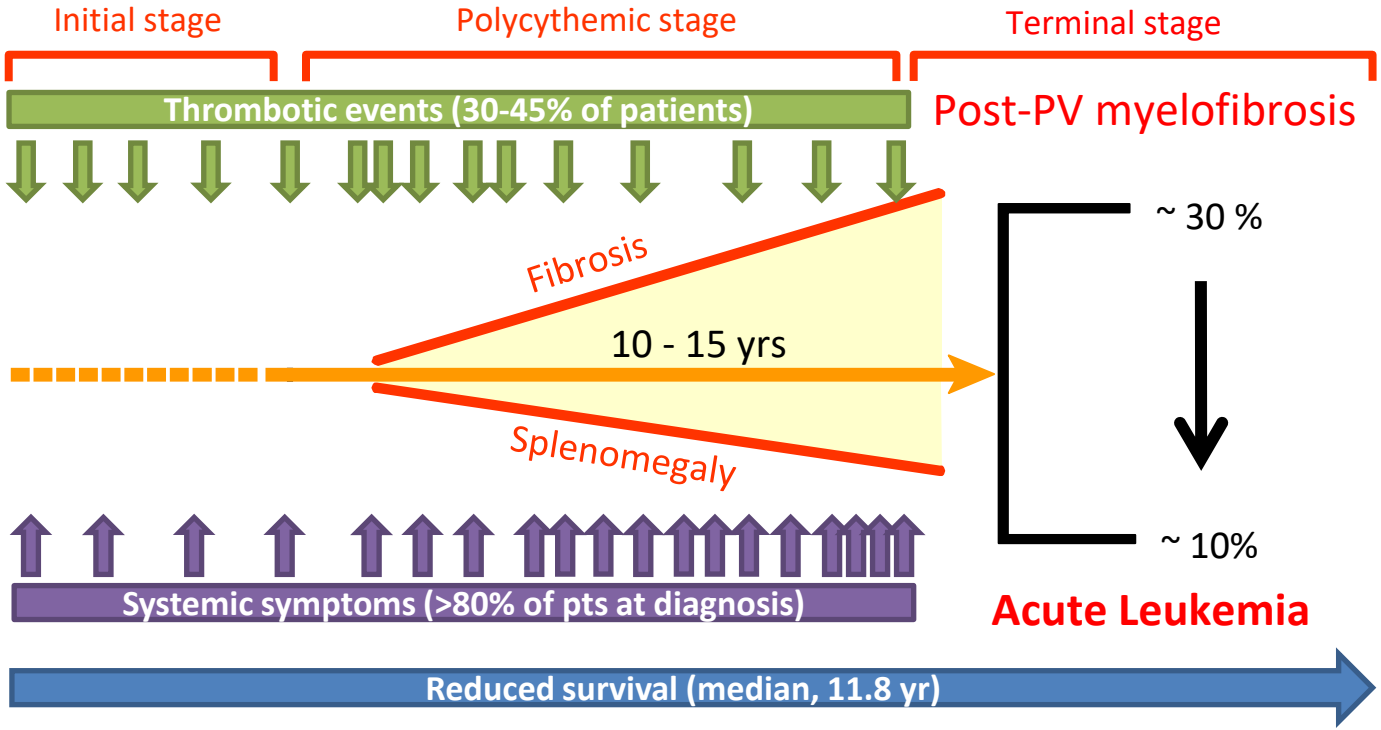
Probability of survival free of myocardial infarction, stroke, and death from cardiovascular causes, pulmonary embolism and DVT is better in pts receiving aspirin compared to placebo (ECLAP study)[2]

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)[3]

[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.

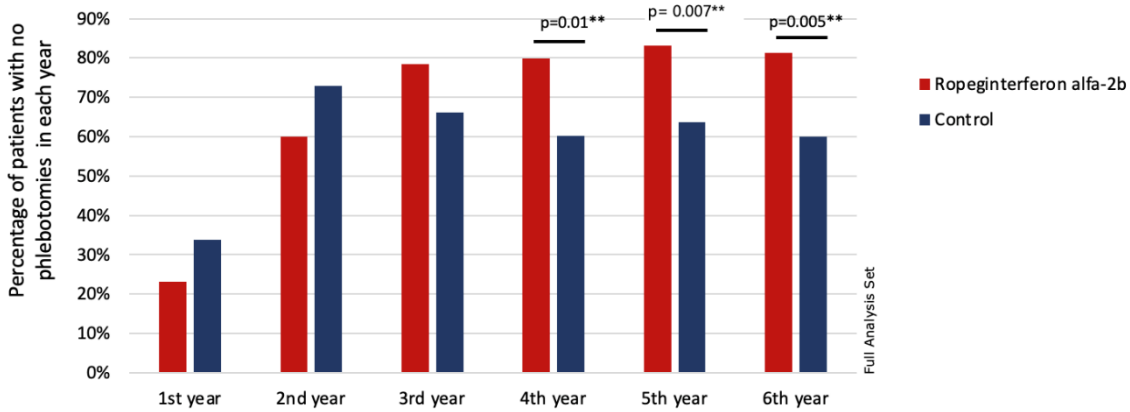
Polycythemia Vera

- Erythrocytosis is the clinical hallmark of PV
- The excess production of RBC is caused by hyper-activation of the JAK-STAT signaling



Srour et al. Br J Haematol. 2016;174(3):382-96; Tefferi et al. Blood 2014; 124: 2507-13; Marchioli et al, J Clin Oncol. 2005;23(10):2224-2232. Tefferi et al, Leukemia. 2013;27(9):1874-1881. Harrison C, et al. Ann Hematol. 2017 Aug 5 . Mesa et al. BMC Cancer. 2016 Feb 27;16:167. Figure modified from Barbui T et al, Leukemia 2013

Freedom from phlebotomy (Proud/Continuation-PV studies)

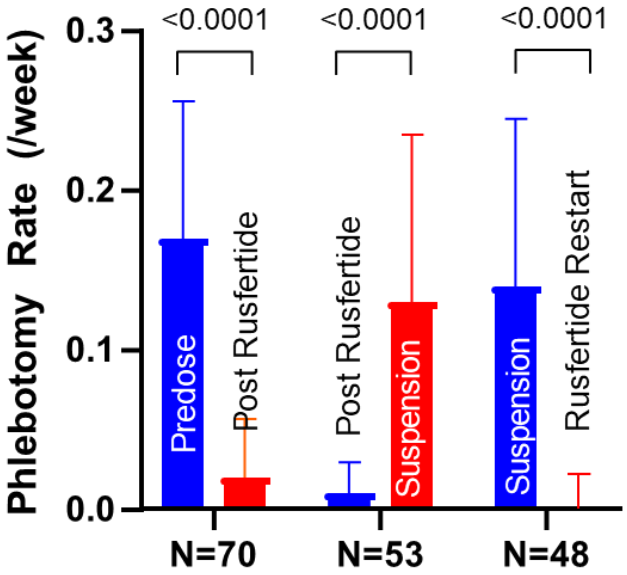


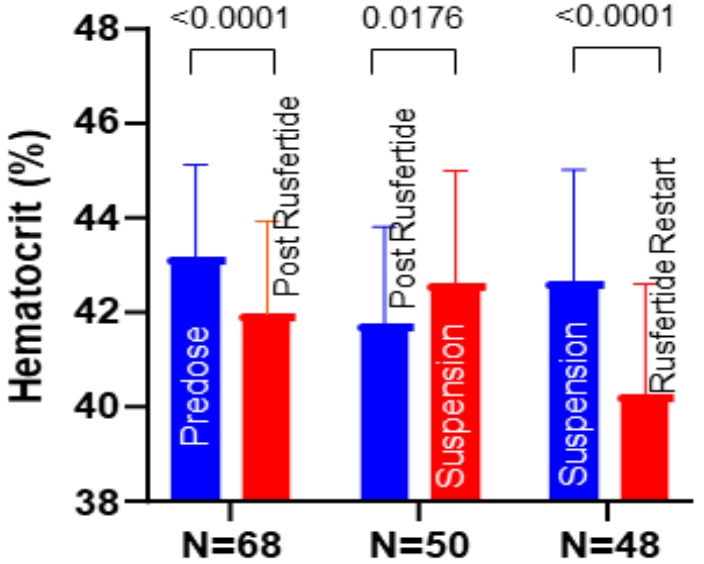
In the 6th year of treatment, no phlebotomies were required to maintain hematocrit <45% in 81.4% of patients receiving ropeginterferon alfa-2b compared with 60.0% of patients in the control arm (p=0.005).

*Among patients with available data for each treatment year **Likelihood of ratio test (incidence ratio for no phlebotomy vs at least 1 phlebotomy)

Gisslinger H et al., S196: ROPEGINTERFERON ALFA-2B ACHIEVES PATIENT-SPECIFIC TREATMENT GOALS IN POLYCYTHEMIA VERA: FINAL RESULTS FROM THE PROUD-PV/CONTINUATION-PV STUDIES; HemaSphere 6():p 97-98, June 2022. | DOI: 10.1097/01.HS9.0000843676.80508.b5

Revive Phase 2 study
Rusfertide suspension leads to loss of effect



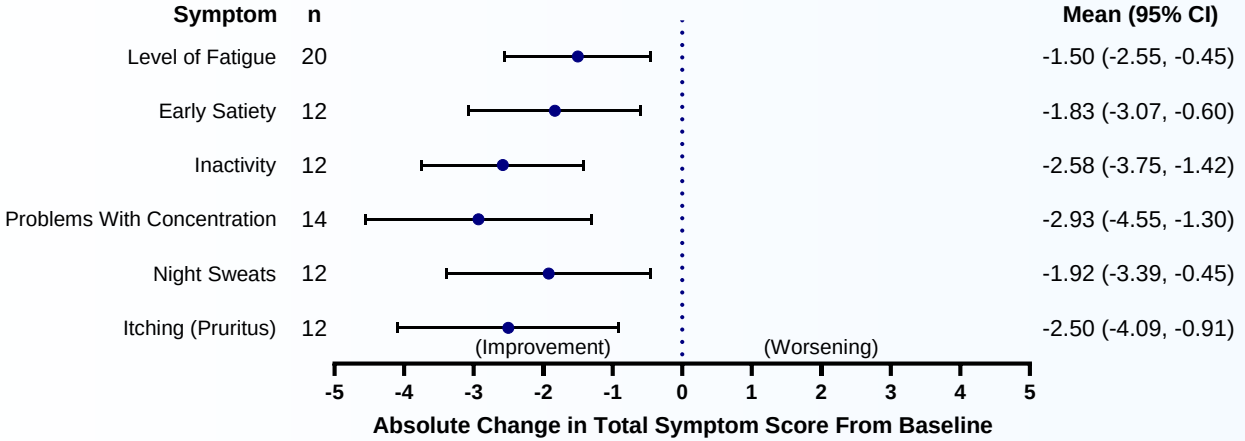


- Treatment suspension leads to loss of effect (increased phlebotomy rate, increase in HCT and RBC)
- Rusfertide restart restores therapeutic benefits

Hoffman R, et al. J Clin Oncol. 2022:40;7003.

REVIVE Part 1: Rusfertide Improved Patient-Reported Outcomes

- In Part 1, PROs were assessed using the MPN-SAF TSS
  - Mean change from Baseline (Week 1) to Week 29 of ISSs from the MPN-SAF for patients with moderate (score, 4-6 out of 10) to severe symptoms (score, 7-10 out of 10) at Baseline
  - In patients with moderate or severe ISSs at Baseline (≥4 out of 10), rusfertide significantly decreased symptoms in fatigue, early satiety, night sweats, problems with concentration, inactivity, and itching



Error bars represent 95% CIs around the mean change from baseline. No multiplicity adjustments were made for analyses for all the supportive efficacy endpoints. Symptoms presented are limited to those with at least 10 patients.

CI, confidence interval; ISS, individual symptom score; MPN-SAF, myeloproliferative neoplasm symptom assessment form; PROs, patient-reported outcomes.

Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

REVIVE: Long-Term Safety Profile of Rusfertide – No New Safety Signals

Summary of Reported TEAEs (Any Grade) in ≥10 Patients (Overall)

TEAEs (Any Grade) by Preferred Term, n (%)	Part 1 N=70	Part 2		Part 3 n=58	Overall (N=70)
		Placebo n=29	Rusfertide n=30		
Patients with at least 1 TEAE	69 (98.6)	16 (55.2)	24 (80.0)	51 (87.9)	70 (100.0)
Injection site erythema	46 (65.7)	2 (6.9)	7 (23.3)	23 (39.7)	**46 (65.7)**
Injection site pain	25 (35.7)	1 (3.4)	3 (10.0)	6 (10.3)	**28 (40.0)**
Injection site pruritus	26 (37.1)	0	4 (13.3)	11 (19.0)	**28 (40.0)**
Fatigue	16 (22.9)	1 (3.4)	1 (3.3)	8 (13.8)	23 (32.9)
Injection site mass	17 (24.3)	0	2 (6.7)	12 (20.7)	**21 (30.0)**
Arthralgia	13 (18.6)	0	0	7 (12.1)	19 (27.1)
Pruritus	14 (20.0)	3 (10.3)	2 (6.7)	7 (12.1)	19 (27.1)
Injection site swelling	15 (21.4)	0	4 (13.3)	8 (13.8)	**18 (25.7)**
COVID-19	5 (7.1)	1 (3.4)	0	13 (22.4)	17 (24.3)
Dizziness	10 (14.3)	0	0	8 (13.8)	17 (24.3)
Headache	11 (15.7)	2 (6.9)	0	7 (12.1)	16 (22.9)
Nausea	11 (15.7)	2 (6.9)	1 (3.3)	6 (10.3)	16 (22.9)
Anemia	12 (17.1)	0	0	6 (10.3)	15 (21.4)
Injection site irritation	11 (15.7)	0	4 (13.3)	9 (15.5)	**14 (20.0)**
Injection site bruising	9 (12.9)	1 (3.4)	2 (6.7)	6 (10.3)	**11 (15.7)**
Diarrhea	7 (10.0)	1 (3.4)	0	5 (8.6)	10 (14.3)
Dyspnea	6 (8.6)	2 (6.9)	1 (3.3)	5 (8.6)	10 (14.3)
Hyperhidrosis	5 (7.1)	0	0	6 (10.3)	10 (14.3)
Injection site warmth	9 (12.9)	0	0	3 (5.2)	**10 (14.3)**

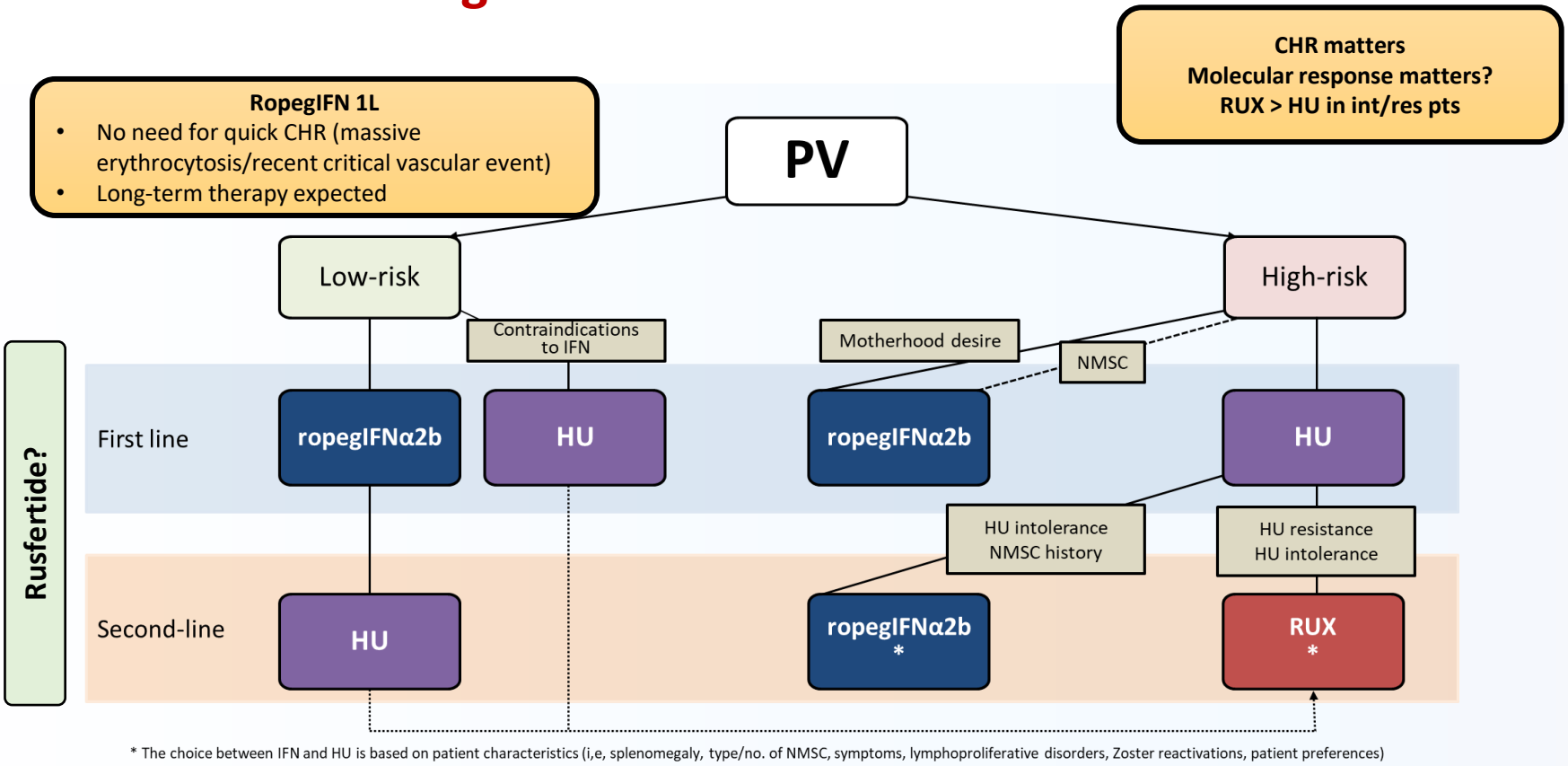
- The most common TEAEs were injection site reactions, which were localized and grade 1-2 in severity and decreased in incidence
- Overall, 77.1% of TEAEs had a maximum grade of 2
- Overall, 21.4% of TEAEs were grade 3; there were no grade 4 or 5 TEAEs
- Overall, the median duration of exposure to rusfertide was 105.4 weeks (range, 3-182 weeks)

COVID-19, Coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Data cutoff: 17 October 2023.

Ritchie E et al, abstract #745, ASH2023 oral presentation
Blood (2023) 142 (Supplement 1): 745.

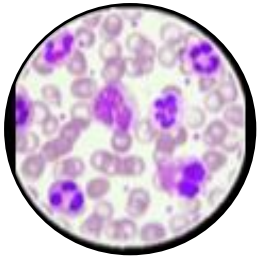
Possible treatment algorithm of PV in 2024



* The choice between IFN and HU is based on patient characteristics (i,e, splenomegaly, type/no. of NMSC, symptoms, lymphoproliferative disorders, Zoster reactivations, patient preferences)

Palandri F, personal considerations

Iron metabolism modifiers may substitute for use of phlebotomies in PV?



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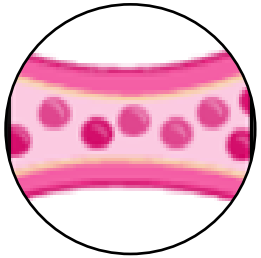
Cytoreduction is required in HR patients!



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Hydroxyurea, interferons, ruxolitinib or clinical trials: what sequence in polycythemia vera?

Francesca Palandri
IRCCS S. Orsola-Malpighi, Bologna

New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

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