Updates and Future Directions in Polycythemia Vera

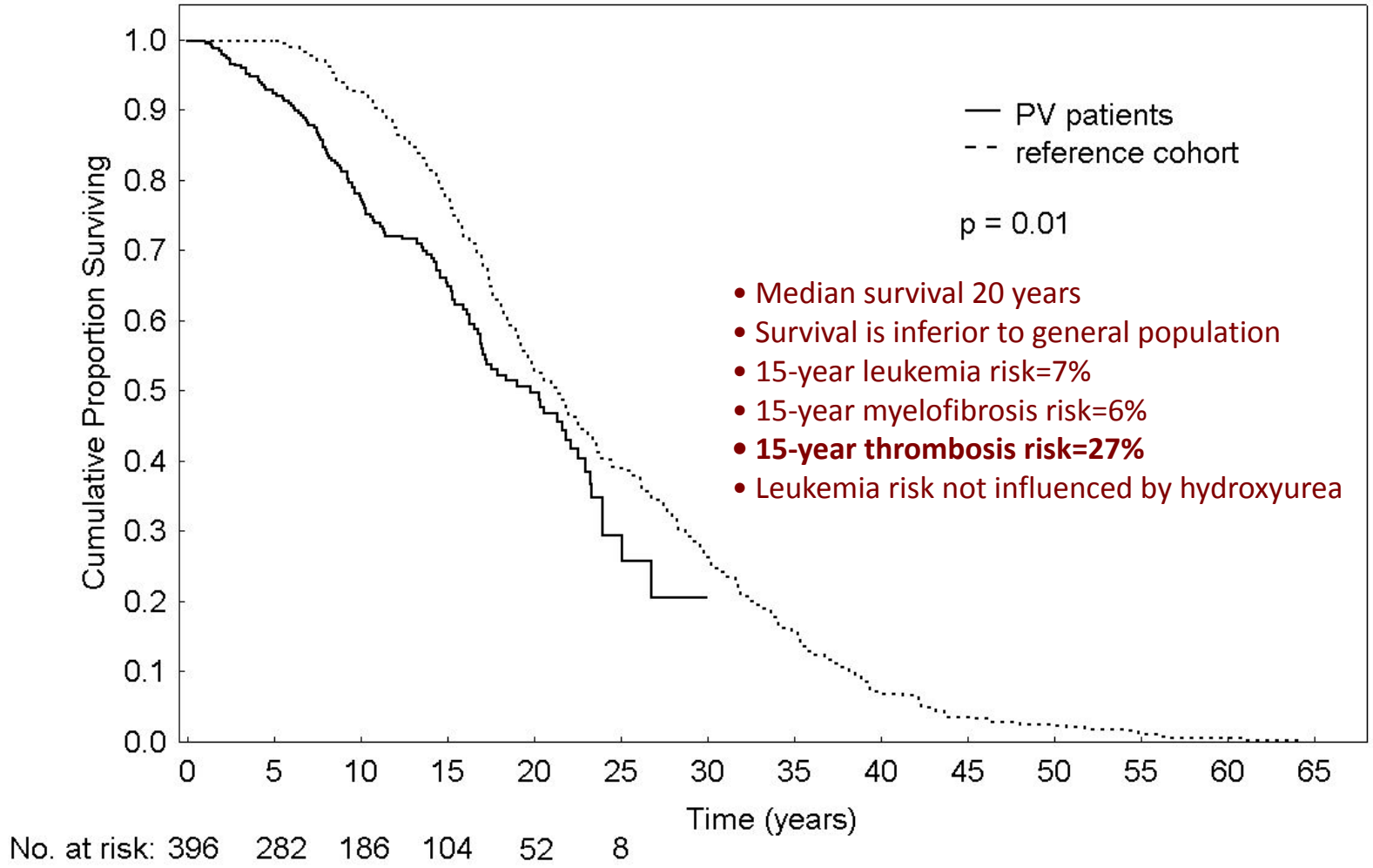
Raajit K. Rampal M.D. Ph.D
Associate Member
Director, Program in Myeloproliferative Neoplasms and Rare Hematologic Malignancies
Director, Center for Hematologic Malignancies
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering
Cancer Center

How do Approach the treatment of Polycythemia Vera in 2025?

How *might* we approach the treatment of Polycythemia Vera beyond 2025

MODERN NATURAL HISTORY OF PV



Passamonti *et al. Am J Med*. 2004

Therapy and goals in PV

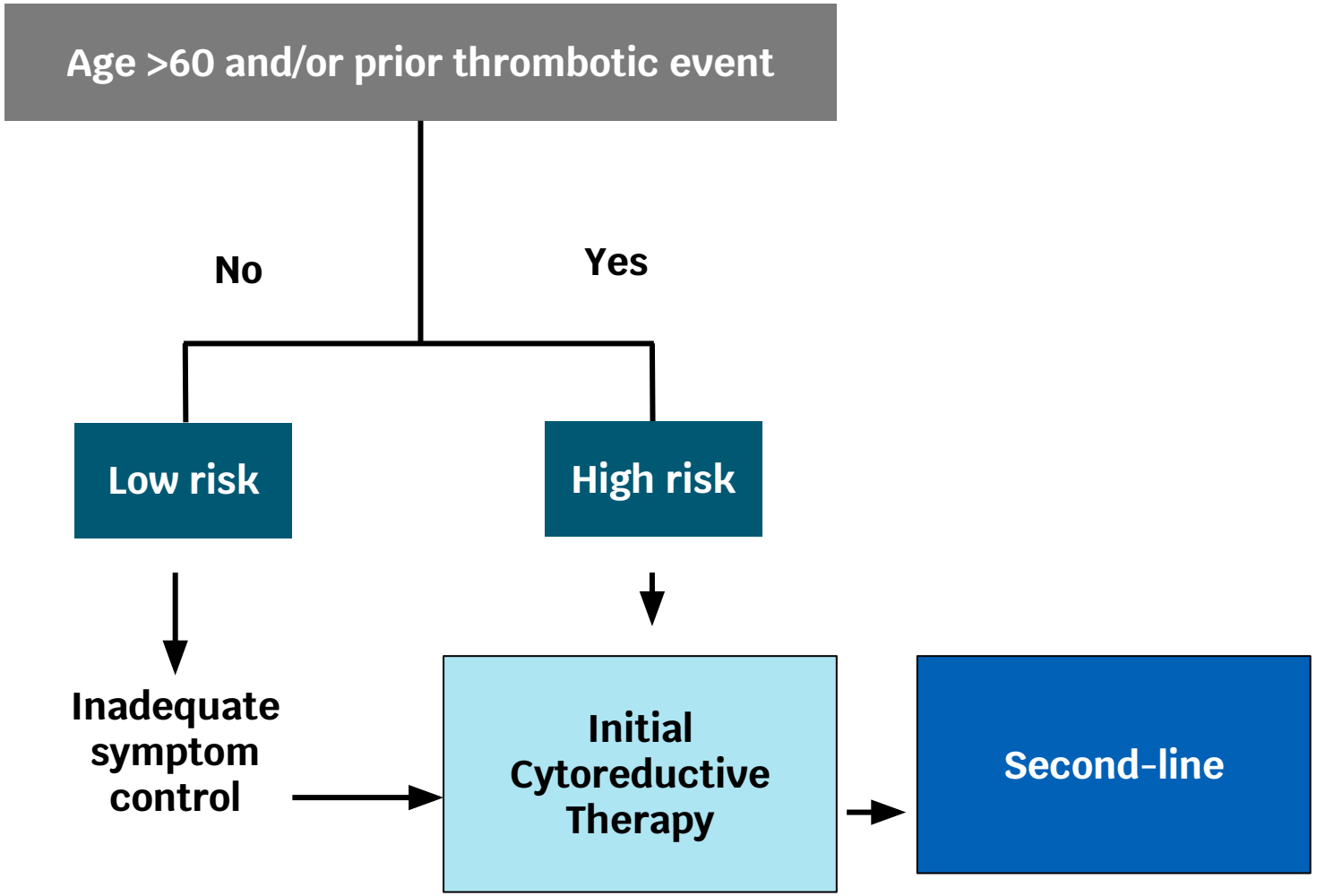
Goals of therapy

- Reduce symptoms burden
- Decrease risk of thrombotic events

Therapeutic modalities

- Therapeutic phlebotomy
- Cytoreductive therapies: hydroxyurea (HU), Interferon
- JAK inhibitors: ruxolitinib
- Antithrombotic modalities: Aspirin, lifestyle modification

Polycythemia Vera: Risk stratification and NCCN Guidelines



Low Risk- NCCN Preferred
-Ropeginterferon-Alfa 2b
-Clinical Trial

Other recommended
-Hydroxyurea
-Peginterferon alfa-2a

High Risk- NCCN Preferred
-Clinical Trial
-Ruxolitinib (For HU resistance/intolerance)

Other recommended (if not used previously)
-Ropeginterferon-Alfa 2b
-Hydroxyurea
-Peginterferon-alfa-2a

NCCN. Clinical practice guidelines in oncology: myeloproliferative neoplasms. v.2.2024. nccn.org.

Aspirin

Double-blind placebo controlled trial of ASA (100mg) in PV patients

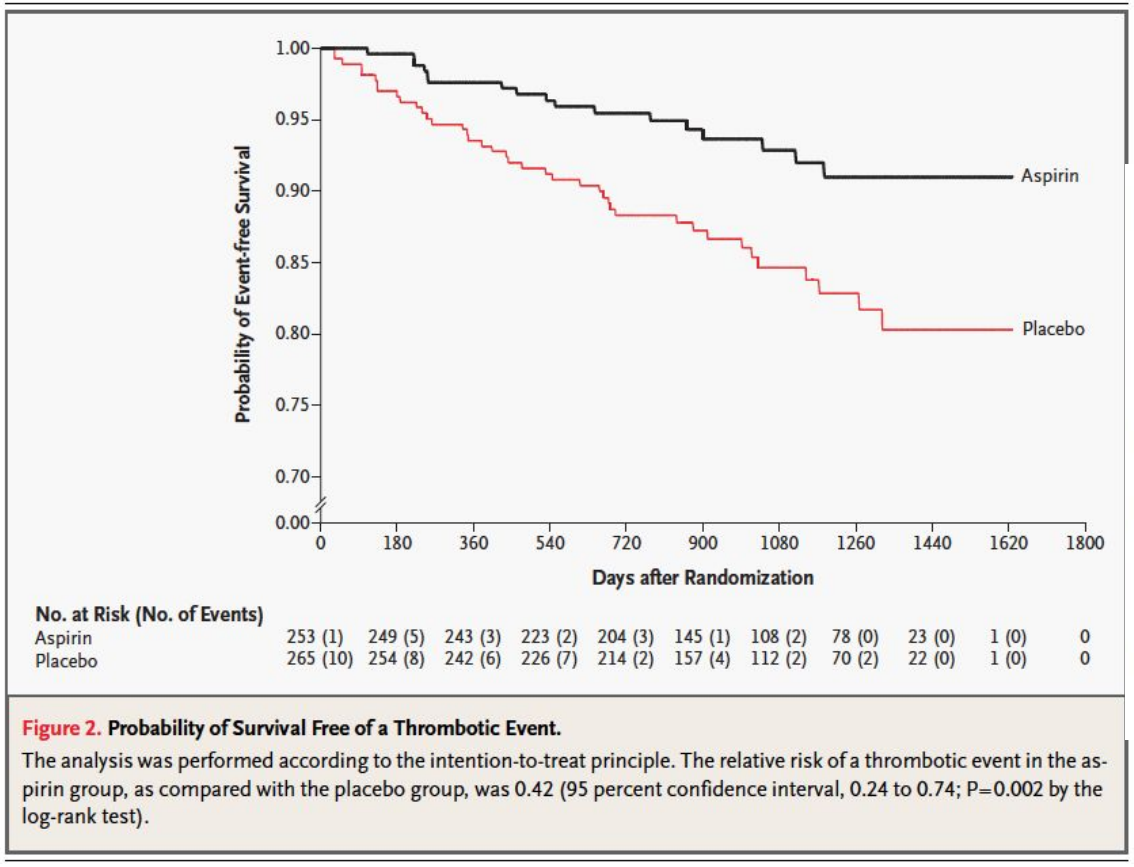


Figure 2. Probability of Survival Free of a Thrombotic Event.

The analysis was performed according to the intention-to-treat principle. The relative risk of a thrombotic event in the aspirin group, as compared with the placebo group, was 0.42 (95 percent confidence interval, 0.24 to 0.74; P=0.002 by the log-rank test).

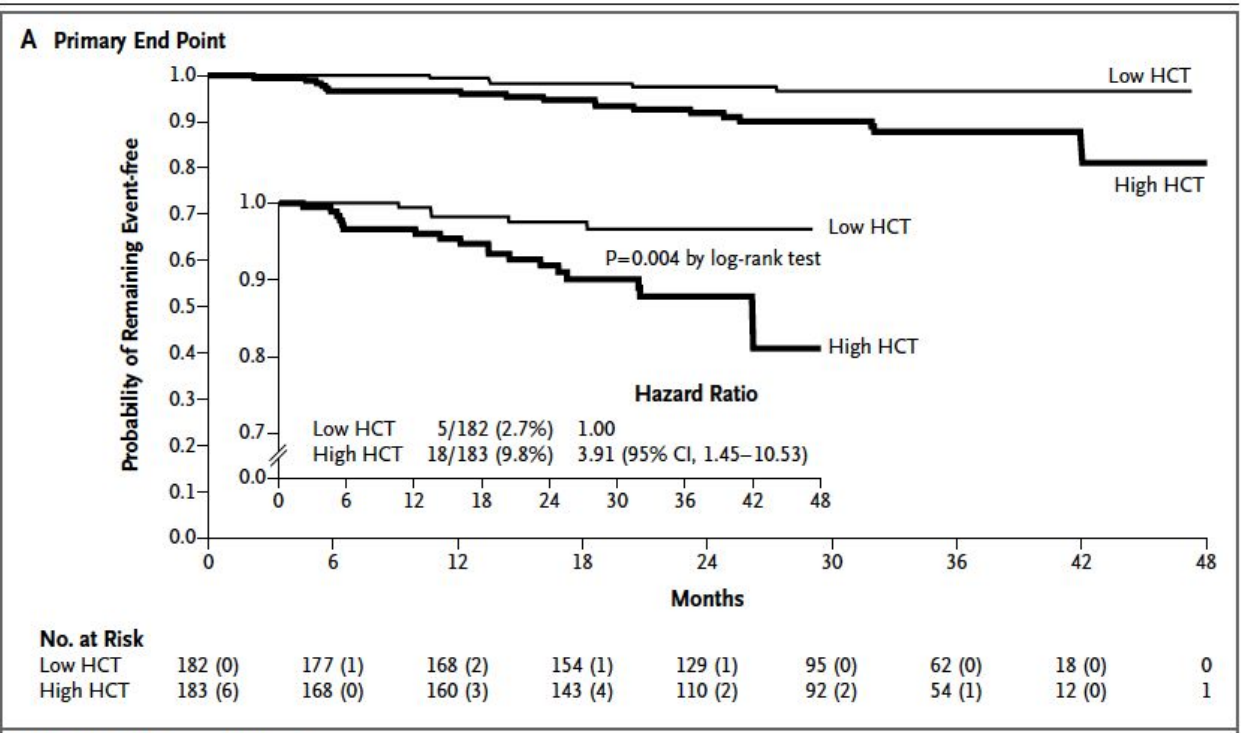
Table 3. Rates and Relative Risks of Bleeding Episodes in the Two Groups.*

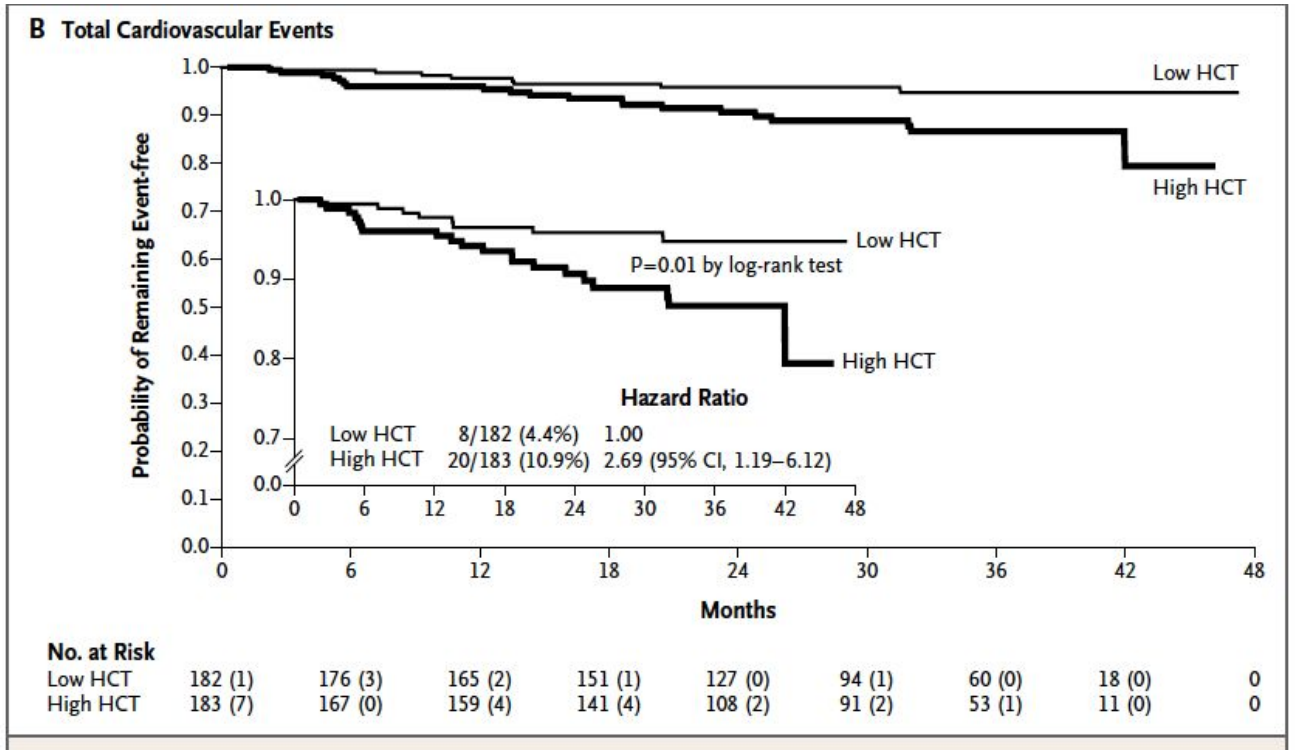
Type of Bleeding Episode	Aspirin Group (N=253)	Placebo Group (N=265)	Relative Risk (95% CI)	P Value
	no. (%)			
Any bleeding	23 (9.1)	14 (5.3)	1.82 (0.94–3.53)	0.08
Major bleeding	3 (1.2)	2 (0.8)	1.62 (0.27–9.71)	0.60
Gastrointestinal	2 (0.8)	0		
Intracranial	1 (0.4)	2 (0.8)		
Minor bleeding	20 (7.9)	12 (4.5)	1.83 (0.90–3.75)	0.10
Hematoma	2 (0.8)	2 (0.8)		
Gastrointestinal	7 (2.8)	3 (1.1)		
Hematuria	1 (0.4)	3 (1.1)		
Epistaxis	9 (3.6)	1 (0.4)		
Other	2 (0.8)	4 (1.5)		

Landolfi et al. *NEJM* 2004

Therapeutic Phlebotomy: what is the optimal goal?

Low hematocrit group (<45%) Versus high hematocrit group (45-50%)





Elevated Hct between 45% and 50%: 4-fold higher rate of cardiovascular death and major thrombosis[1]

- A significant increase in the risk of cardiovascular death and major thrombosis was demonstrated with Hct levels between 45% and 50% compared with Hct levels of <45% (HR, 3.91; 95% CI, 1.45–10.53; *P*=0.007)[1*]

Is this this optimal HCT goal for women?
Is <42% more appropriate?

Marchioli. *NEJM*. 2013

Hydroxyurea for Cytoreduction in Pts With PV

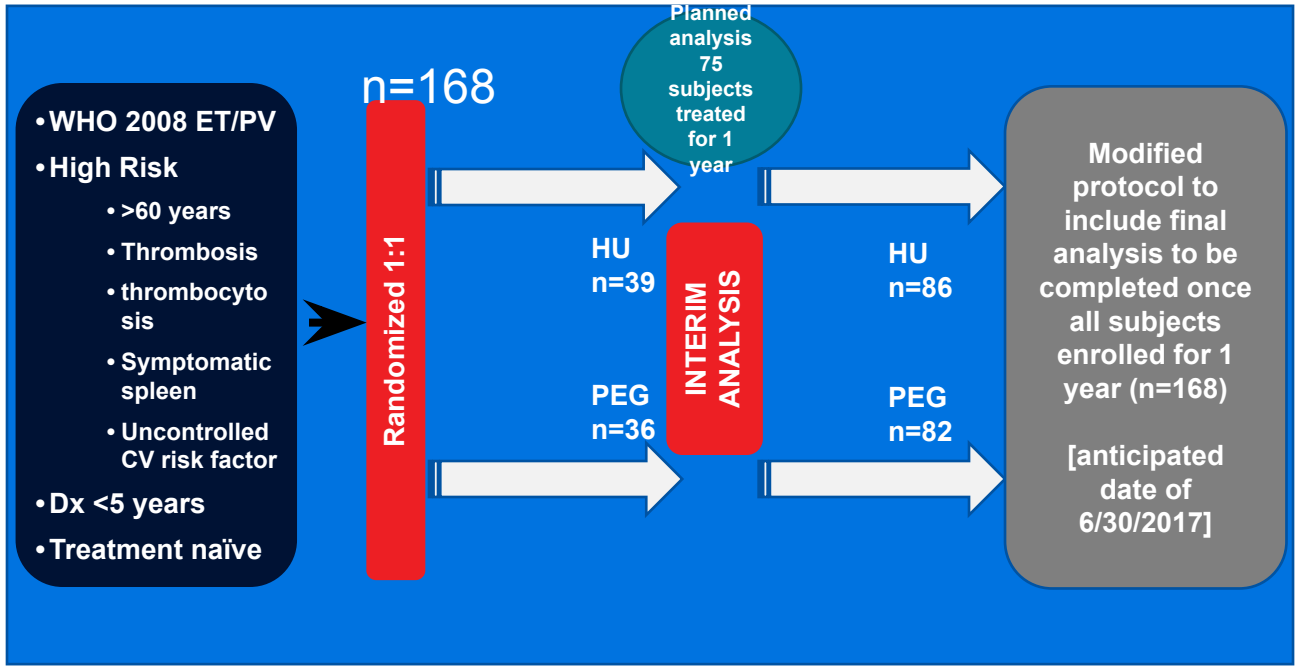
Study/Organization	Pts, N	Intervention	Comparator	Thrombosis
French PV Study Group[1]	292 < 65 yrs (median FU: 7 yrs)	HU (randomized)	Pipobroman	No significant difference
French PV Study Group[2]	285 (median FU: 16 yrs)	HU (randomized)	Pipobroman	No significant difference
PV cohort of ECLAP study[3]	1042 (median FU: ~ 30-35 mos)	HU (propensity matching)	Phlebotomy	CV events/100 PY: HU: 3.0 Phlebotomy: 5.8
Retrospective study[4]	235 with thrombosis history	Cytoreduction; 77% received HU	None	Cytoreduction reduced recurrence rates

1. Najean Y, et al. Blood. 1997;90:3370-3377. 2. Kiladjian JJ, et al. J Clin Oncol. 2011;29:3907-3913.
3. Barbui T, et al. Am J Hematol. 2017;92:1131-1136. 4. De Stefano V, et al. Haematologica. 2008;93:372-380.

PegIFN for Pts With PV

Study	Population	Findings
PVN[1,2] ▪ PegIFN α-2a	▪ N = 37 ▪ Newly diagnosed pts	▪ CHR: 95%; CR: 82% in extended FU – 0 thromboembolic events in 6 yrs ▪ CMR: 8 (28%); sustained improvements after d/c of treatment ▪ Grade 1/2 AEs: 89%; d/c for toxicity (1 yr): 24%
MDACC[3,4] ▪ PegIFN α-2a	▪ N = 43 ▪ ~ 50% previous cytoreductives ▪ Median FU: 83 mos	▪ Median response duration: hematologic: 65 mos; molecular: 58 mos – Failure to achieve CMR: more likely to have/acquire nondriver mutations ▪ Thrombosis and progression can occur ▪ Toxicity continued over time (new grade 3/4 events in 10% to 17% of PY); d/c for AEs: 22%
PEGINVERA[5,6] ▪ RopegIFN α-2b	▪ N = 51 ▪ HU pretreated: 33% ▪ Median FU: 80 wks	▪ CR: 43% to 57%; PR: 43%; CMR: 21% ▪ 1 TIA, 1 DVT during study period ▪ AEs (any): 88%; d/c for AEs: 20%

MPD-RC 112 Study



MPD-RC 112: First-line PegIFN α-2a vs HU for High-Risk PV and Essential Thrombocythemia

Interim Analysis: Overall Response Rates at 12 Months

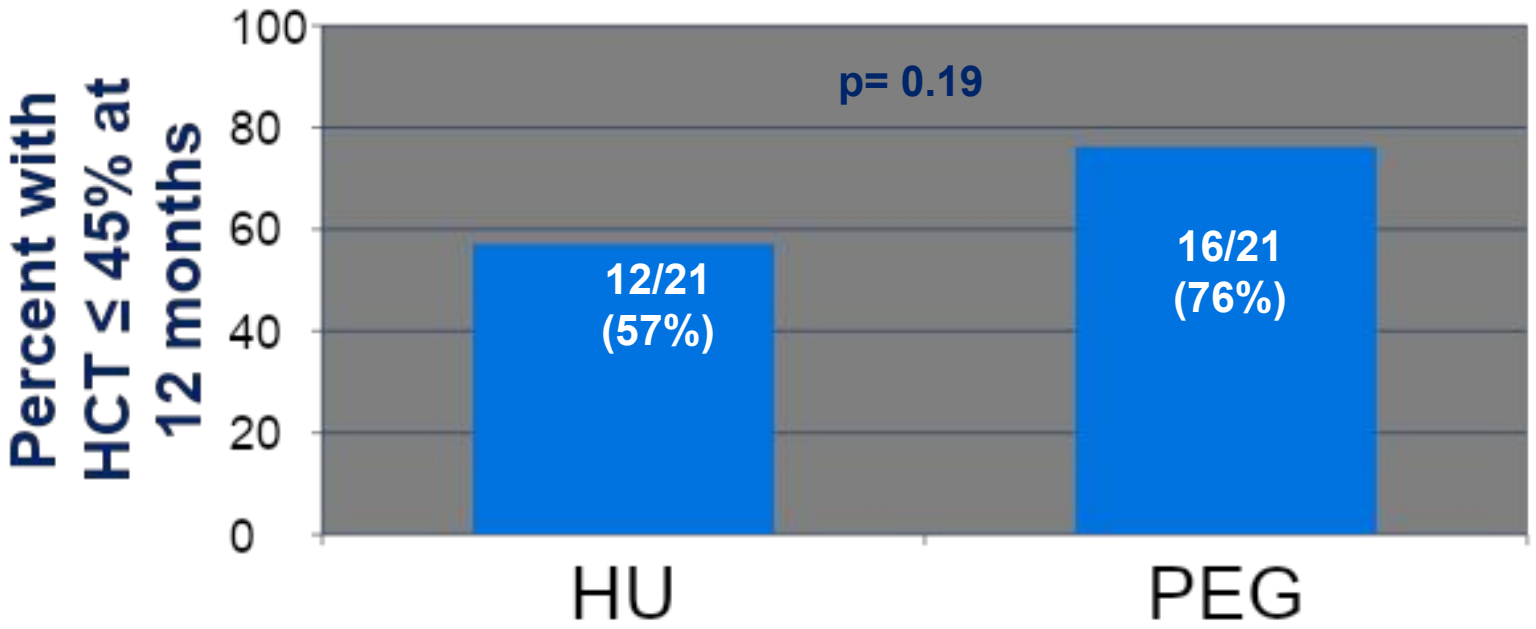
	Hydroxyurea (n = 39)			PegIFN α-2a (n = 36)			*P* value
	PR n (%)	**CR n (%)**	ORR n (%)	PR n (%)	**CR n (%)**	ORR n (%)	
Entire cohort (n = 75)	14 (36)	**13 (33)**	27 (69)	19 (53)	**10 (28)**	29 (81)	0.6*
PV (n = 44)	10/23 (44)	**6/23 (26)**	16/23 (70)	13/21 (62)	**4/21 (19)**	17/21 (81)	0.6
ET (n = 31)	4/16 (25)	**7/16 (44)**	11/16 (69)	6/15 (40)	**6/15 (40)**	12/15 (80)	0.8

*CR comparison based on z-test; did not cross stopping boundary. CR, complete response; PR, partial response; ORR, overall response rate

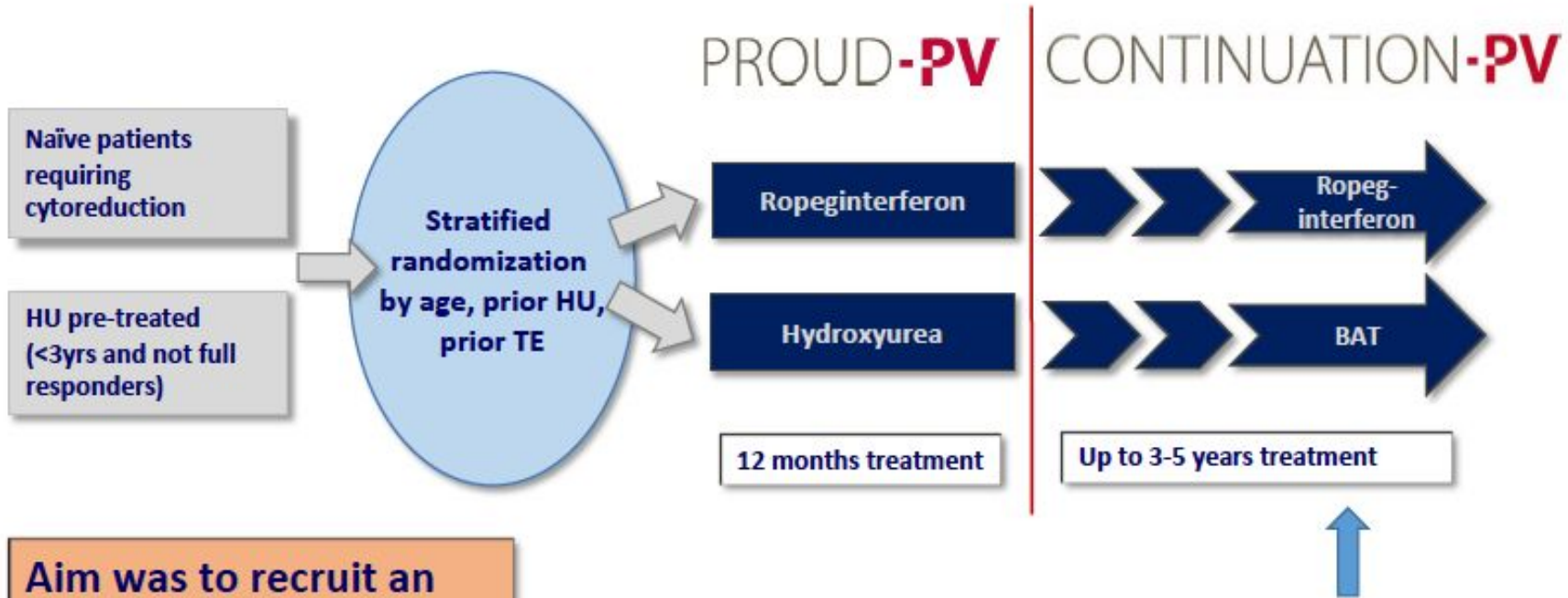
AE,† n (%)	Hydroxyurea (n = 36)	PegIFN α-2a (n = 36)	*P* Value
AE grade ≥ 3	5 (14)	17 (47)	.002
Depression	0	10 (28)	< .001
Dyspnea	1 (3)	7 (19)	.02
Fatigue	10 (28)	18 (50)	.05
Flulike symptoms	1 (3)	12 (33)	< .001
Injection-site reaction	0	9 (25)	.001
Pruritus	3 (8)	10 (28)	.03

Mascarenhas JO, et al. *Blood.* 2016;128: Abstract 479.

HCT Control in PV Patients by Treatment Arm (at 12 months or last visit)



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

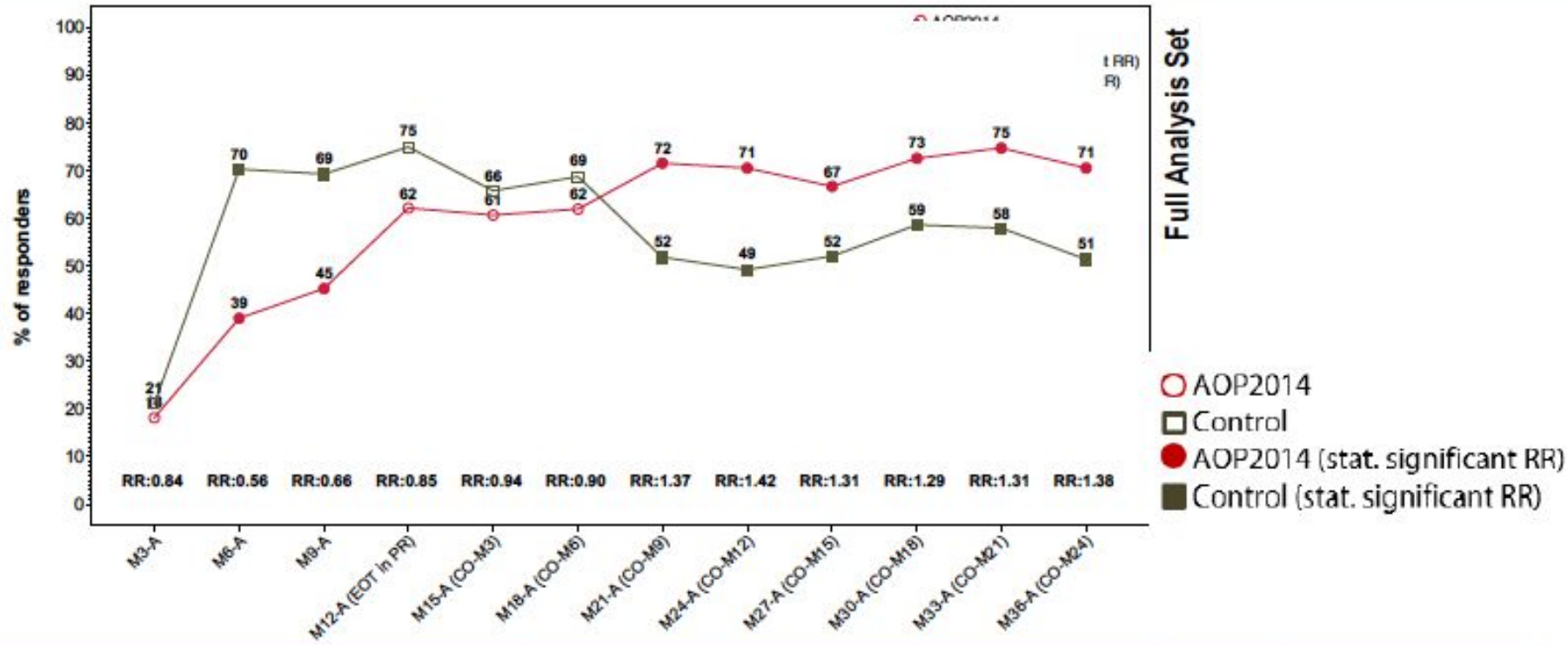


Aim was to recruit an "early PV" population.

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)**

Complete hematologic response (CHR)



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1201	0.85 [0.70-1.04]
MONTH 24	67/95	70.5	33/67	49.3	0.0111	1.42 [1.08-1.87]
MONTH 36	67/95	70.5	38/74	51.4	0.0122	1.38 [1.07-1.79]

PROUD-PV and CONTINUATION-PV: Safety

Most Common Grade 3/4 TRAEs w/ Ropeg:

- ↑ γ-glutamyltransferase (6%, n=7)
- ↑ alanine aminotransferase (3%, n=4)

Treatment-related serious AEs:

- Ropeg (2%, n=3) vs control 4% (n=5)

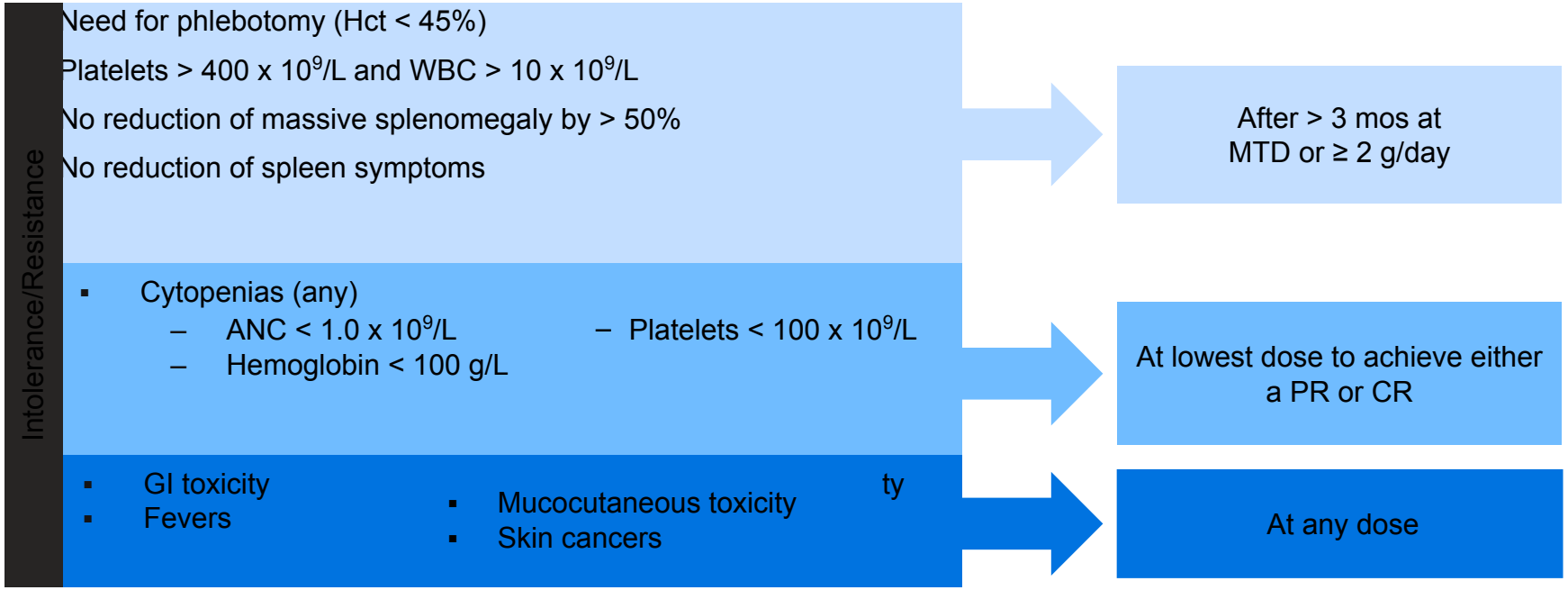
- 1 treatment-related death reported in standard therapy group (acute leukaemia)

AEs of Special Interest

	Ropeginterferon alfa-2b (N=127)	Control (N=127)
Endocrine disorders		
Any adverse event	8 (6%)	2 (2%)
Related to treatment	6 (5%)	0
Psychiatric disorders		
Any adverse event	5 (4%)	6 (5%)
Related to treatment	2 (2%)	1 (1%)
Musculoskeletal and connective tissue disorders		
Any adverse event	2 (2%)	0
Related to treatment	2 (2%)	0
Major cardiovascular and major thromboembolic adverse events		
Any major cardiovascular adverse event	13 (10%); 16 events	8 (6%); 25 events
Major thromboembolic adverse event	4 (3%); 6 events	4 (3%); 4 events
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Any neoplasm	9 (7%); 11 events	10 (8%); 12 events
Leukaemic transformation (acute leukaemia)	0; 0 events	2 (2%); 2 events
Skin cancers related to treatment (basal cell carcinoma and melanoma)	0; 0 events	3 (2%); 3 events

Gisslinger H, et al. *Lancet Haematol*. 2020;7:E196-E208.

HU Resistance and Intolerance: ELN Criteria



- Resistance and/or intolerance to HU associated with the following in a retrospective analysis of 261 pts
  - Increased risk of disease transformation to AML or MF (HR: 6.8; *P* < .001)
  - Reduced survival (HR: 5.6; *P* < .001)

Barosi G, et al. Br J Haematol. 2010;148:961-963. Sever M, et al. Leuk Lymphoma. 2014;55:2685-90.
Alvarez-Larrán A, et al. Blood. 2012;119:1363-1369.

Ruxolitinib Phase III Trial (RESPONSE)

The NEW ENGLAND JOURNAL of MEDICINE

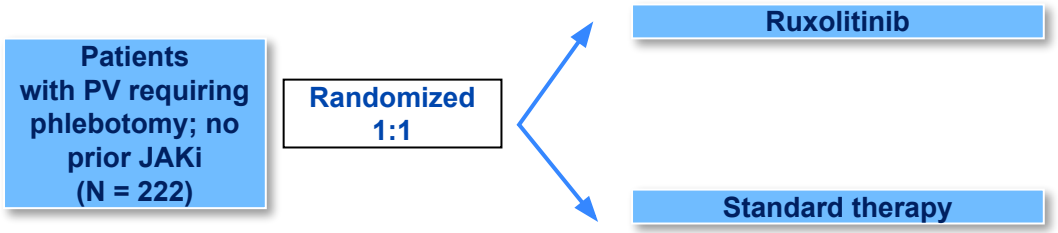
ORIGINAL ARTICLE

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

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

Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study

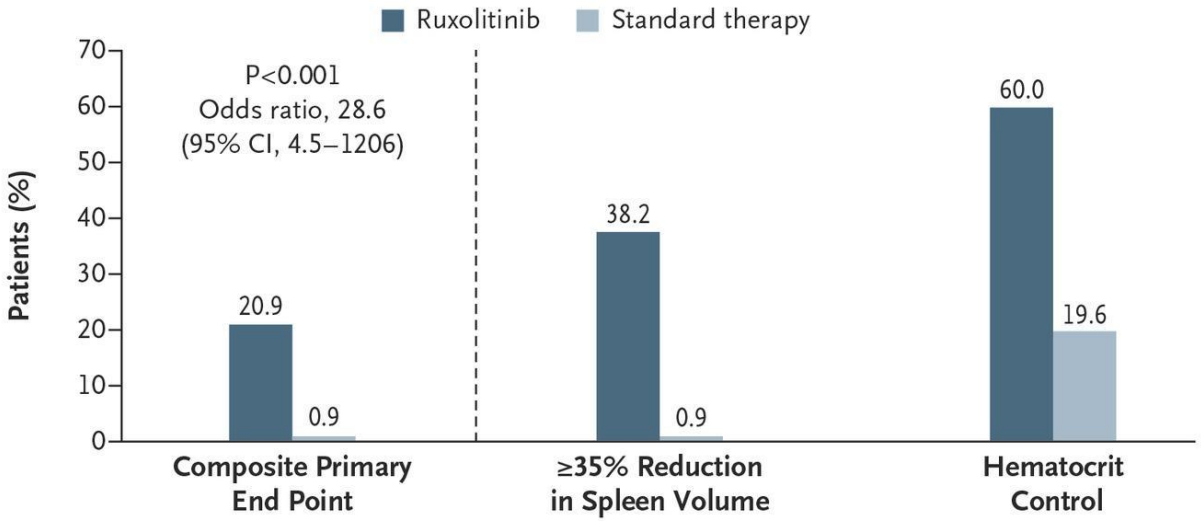
Jean-Jacques Kiladjian, Pierre Zachee, Masayuki Hino, Fabrizio Pane, Tamas Masszi, Claire N Harrison, Ruben Mesa, Carole B Miller, Francesco Passamonti, Simon Durrant, Martin Griesshammer, Keita Kirito, Carlos Besses, Beatriz Moiraghi, Elisa Rumi, Vittorio Rosti, Igor Wolfgang Blau, Nathalie Francillard, Tuochuan Dong, Monika Wroclawska, Alessandro M Vannucchi, Srdan Verstovsek



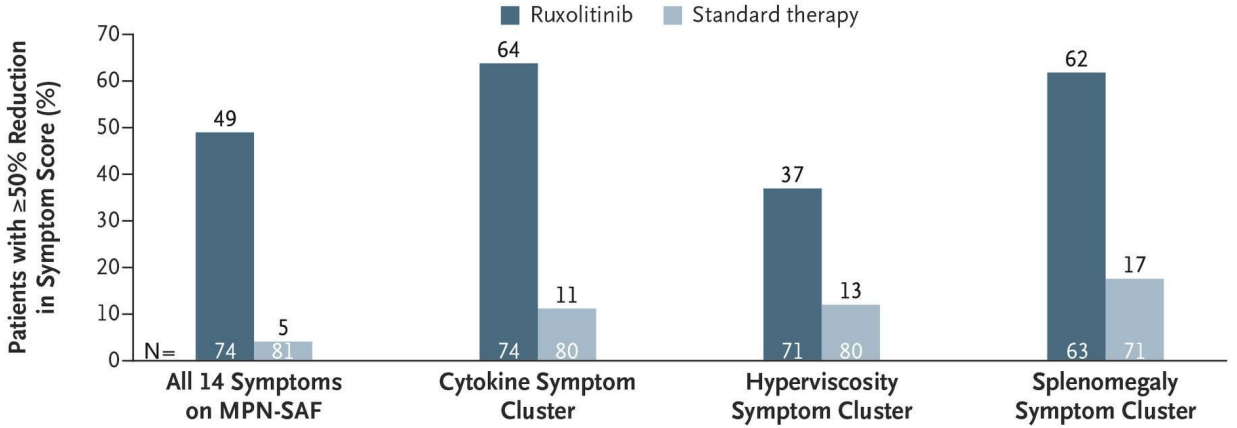
Vannucchi AM, et al. *N Engl J Med*. 2015;372:426.
Kiladjian JJ, et al. *Lancet Haematol*. 2020;7(3):e226.

Ruxolitinib Phase III Trial (RESPONSE)

Hematocrit control/ Spleen response



Symptom reduction



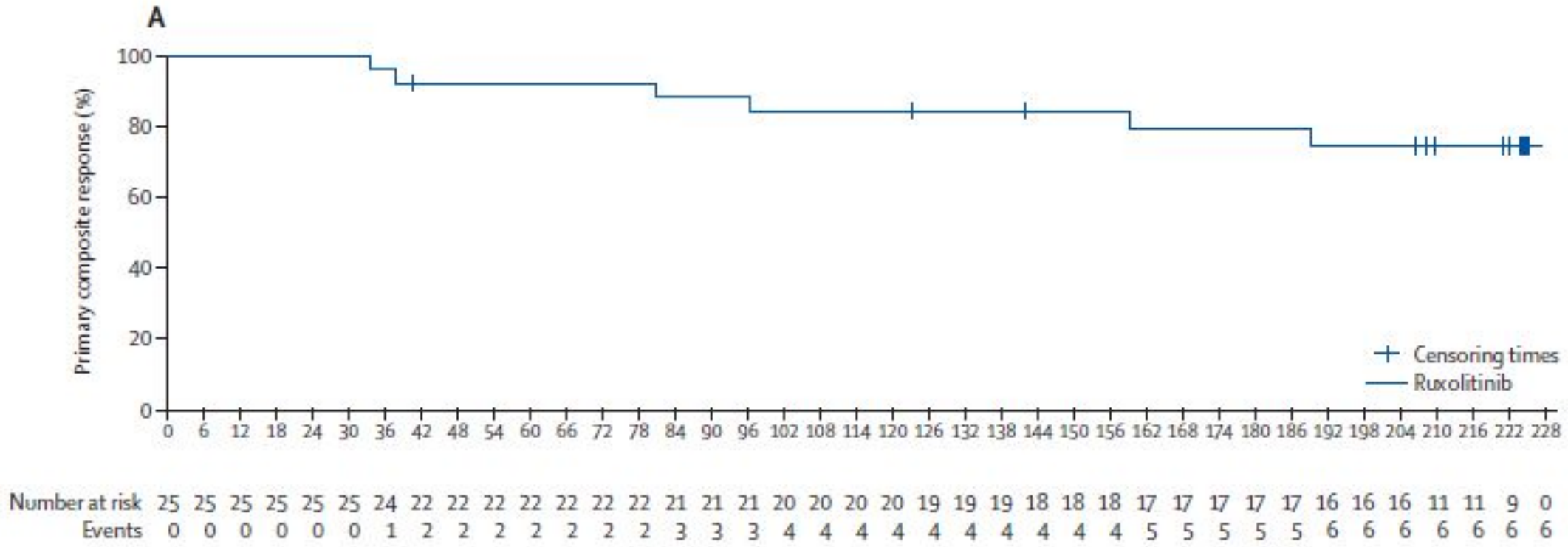
72:426.

Phase III RESPONSE: Long-Term Efficacy and Safety (5 Years)

- Duration of **HCT control** at 224 weeks (starting from week 32)
  - **0.73** (95% CI: 0.60-0.83).

- Duration **maintaining ≥ 35% of reduction in the spleen volume** at week 224 (starting from week 32)

Durability of Primary Response (HCT and spleen)



Kiladjian JJ, et al. *Lancet Haematol.* 2020;7(3):e226.

Second-line Treatment Options for Pts With PV Who Require Cytoreductive Therapy

First line “low risk”: ASA +Phlebotomy

First line “high risk”: ROPEG-interferon, Hydrea

Second line:

Ruxolitinib

- Indicated for pts with intolerance/inadequate response to HU

PegIFN

- If intolerance/inadequate response to first-line HU

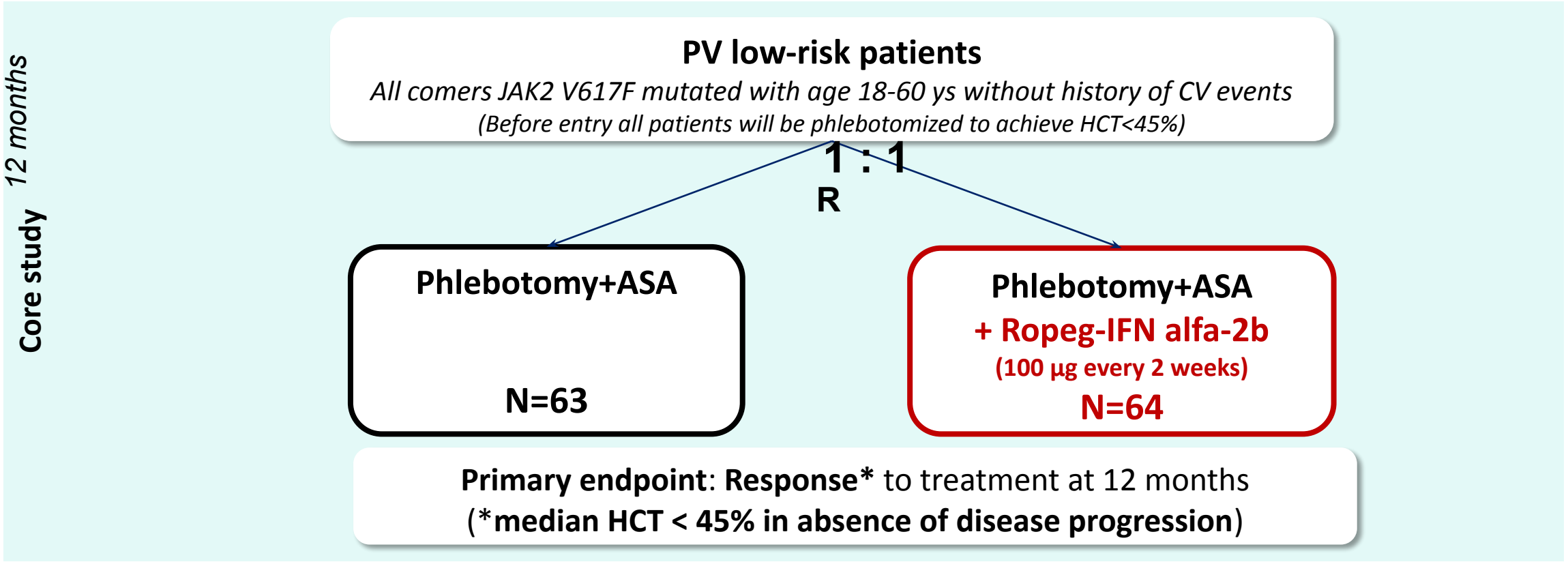
HU

If intolerance/inadequate response to first-line

Emerging:
Rusfertide (hepcidin-mimetic in phase III)

Ruxolitinib [package insert]. 2017. Barbui T, et al. J Clin Oncol. 2011;29:761-770.
Tefferi A, et al. Am J Hematol. 2015;90:162-173.

Ropeginterferon Alfa-2b Versus Standard Therapy for Low-Risk Patients with Polycythemia Vera. Final Results of Low-PV Randomized Phase II Trial

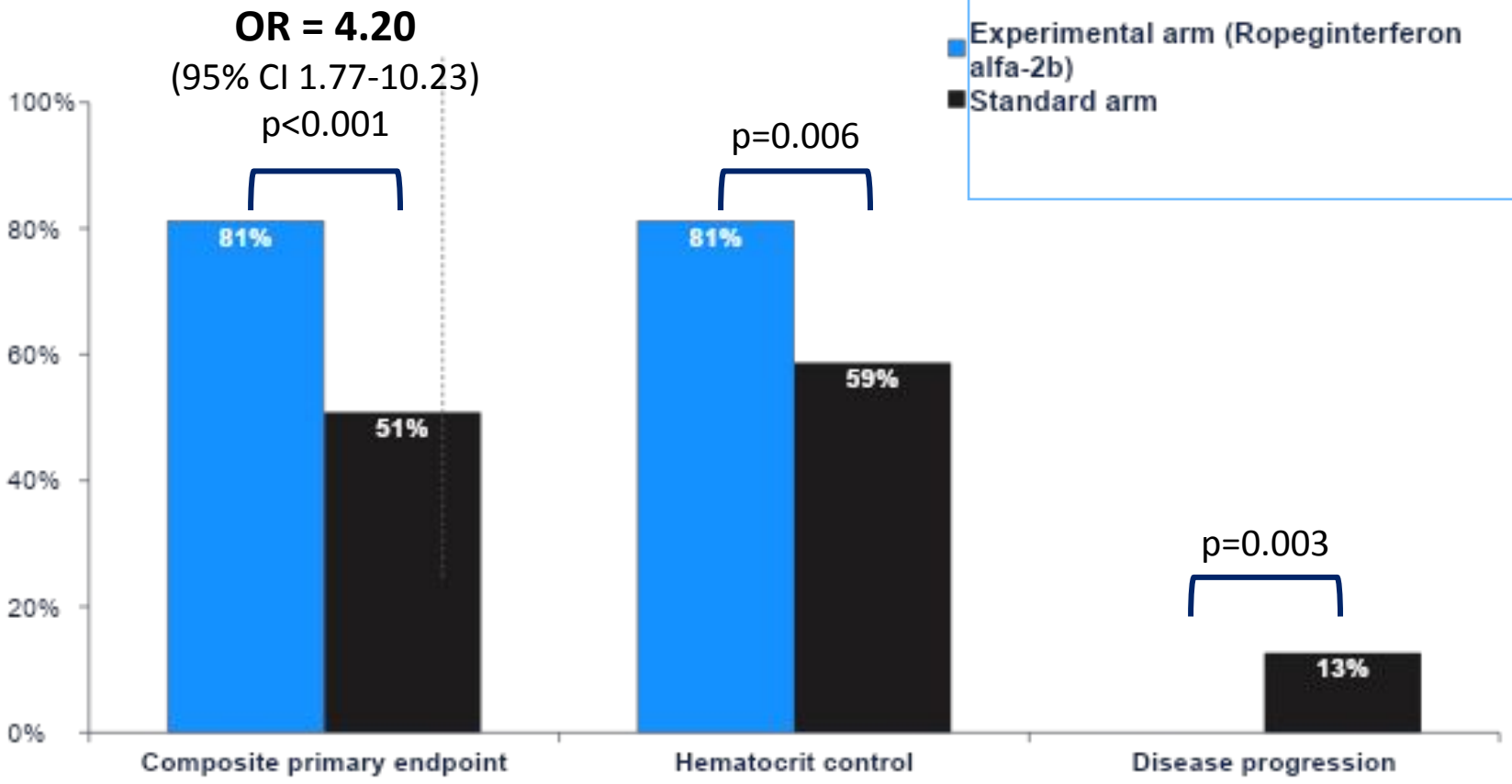


Barbui, et al. *NEJM Evidence*

Core study: primary endpoint

Mean number of phlebotomy per pat/year:

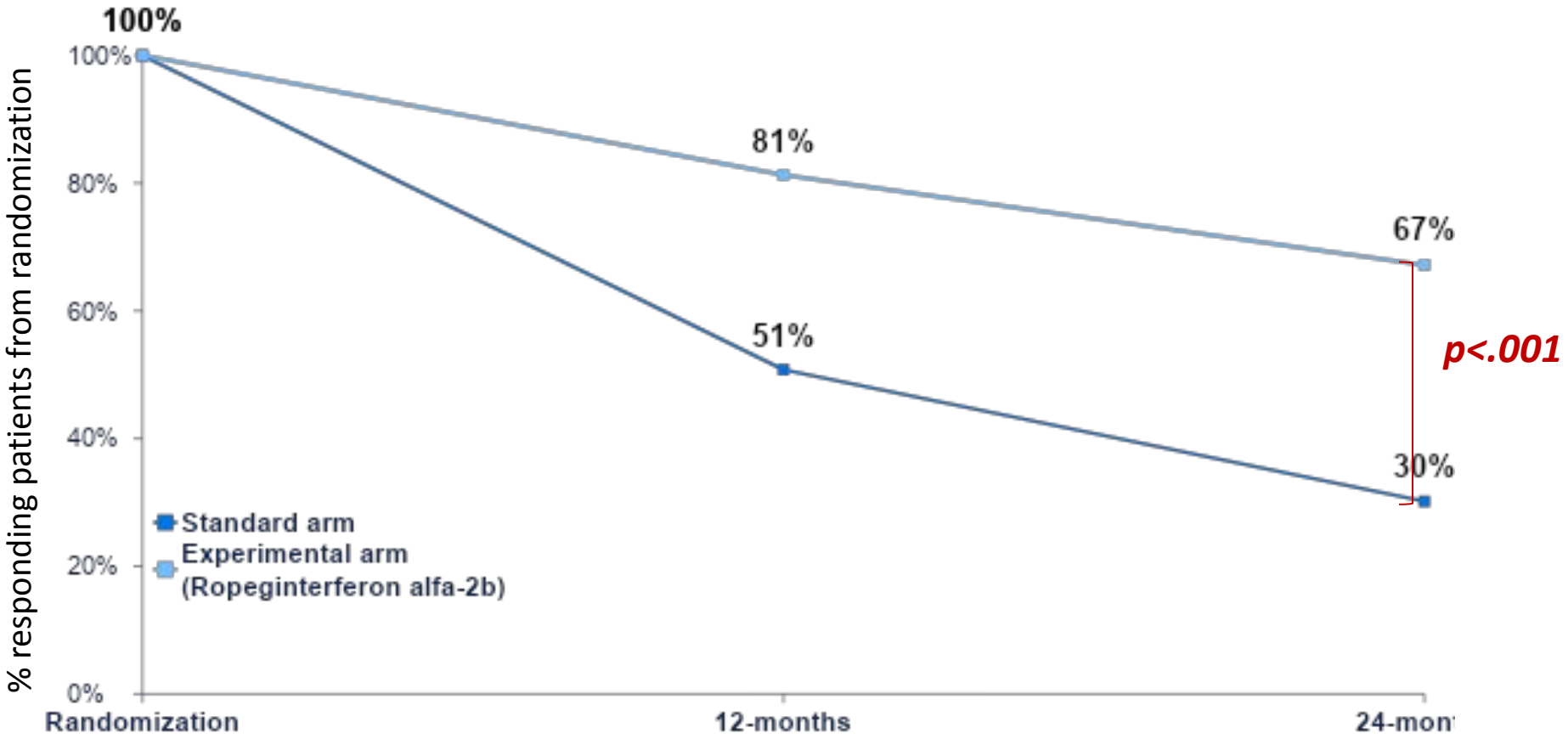
Experimental arm (Ropeginterferon alfa-2b)	**2.91**	**p=0.019**
Standard arm	**4.17**	



Disease progression was observed in **8 patients** (all in standard arm):

- **In 6**, platelet count progression to >1000x10^9/L in pts with baseline values lower than 600x10^9/L.
- **In 2,** splenic infarction and transient ischemic attack, respectively

Treatment response maintenance, by ITT*



** All randomized patients included. Patients crossed-over were censored at 12 months as non-responders of the orginal arm*

Towards Disease Modification in PV: Allele burden reduction and its significance

Allele burden / Variant Allele Fraction (**VAF**) – The amount of the *JAK2* V617F mutation in the blood or bone marrow

Phlebotomy: Tried and True or Historical Relic?

Bloodletting surgeon preparing to let blood by cupping

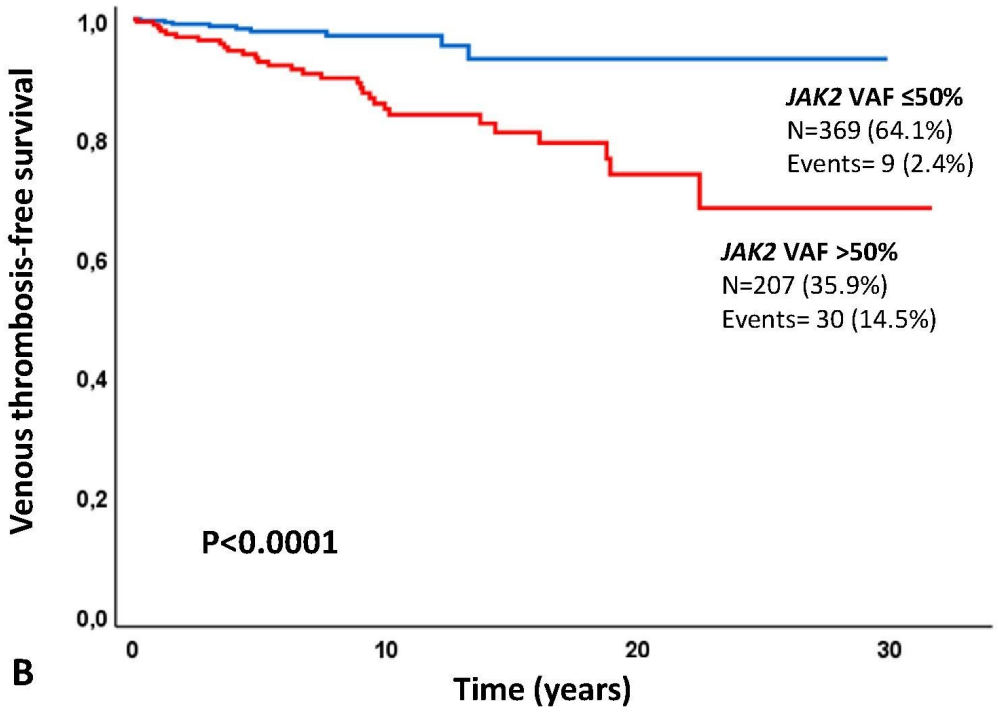
A surgeon preparing to let blood by cupping, his apprentice warming the cupping glass. 18th century oil painting attributed to Jan Baptist Lambrechts.(less)

Wellcome Collection, London

JAK2 allele burden Associations in PV

Increased *JAK2* V617F allele fraction is correlated with:

- **Increased WBC**
- **Venous thrombosis risk** (potential life-threatening event)
- **Presence of splenomegaly** (impaired quality of life)
- **Risk of progression to myelofibrosis** (disease progression)



Risk Factors for Arterial Thrombosis

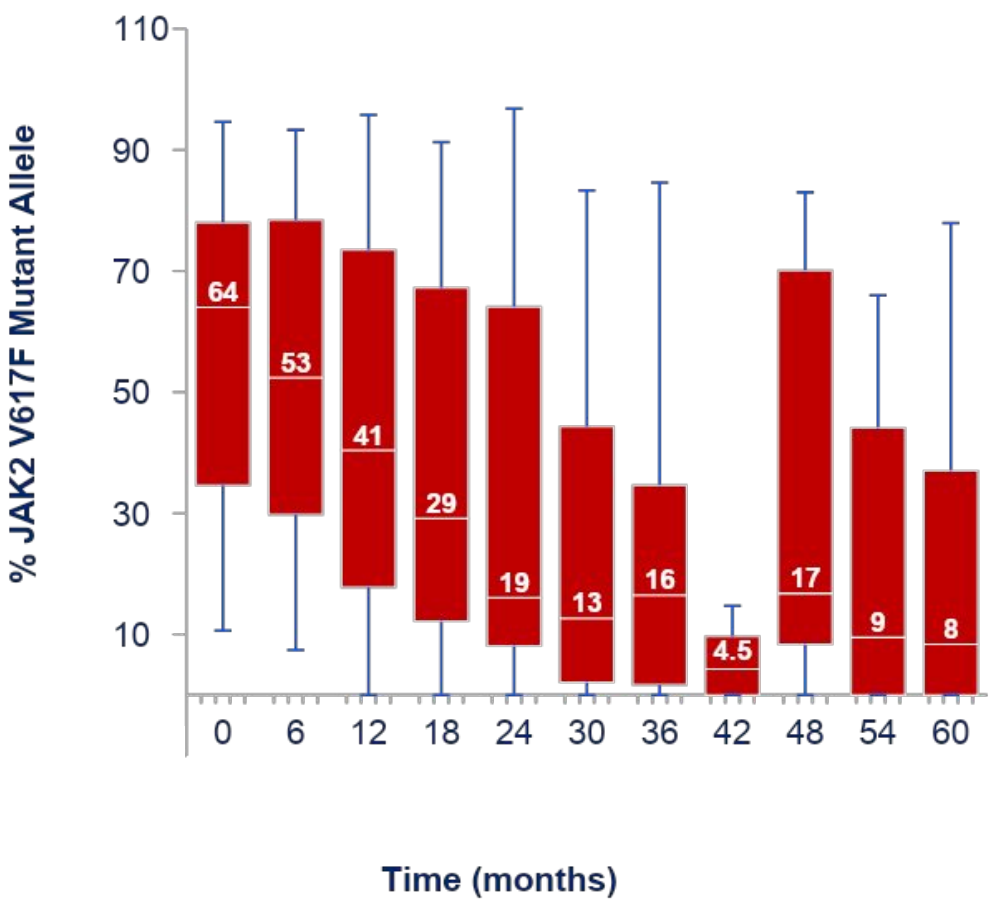
- Diabetes
- Hyperlipidemia
- Previous arterial thrombosis

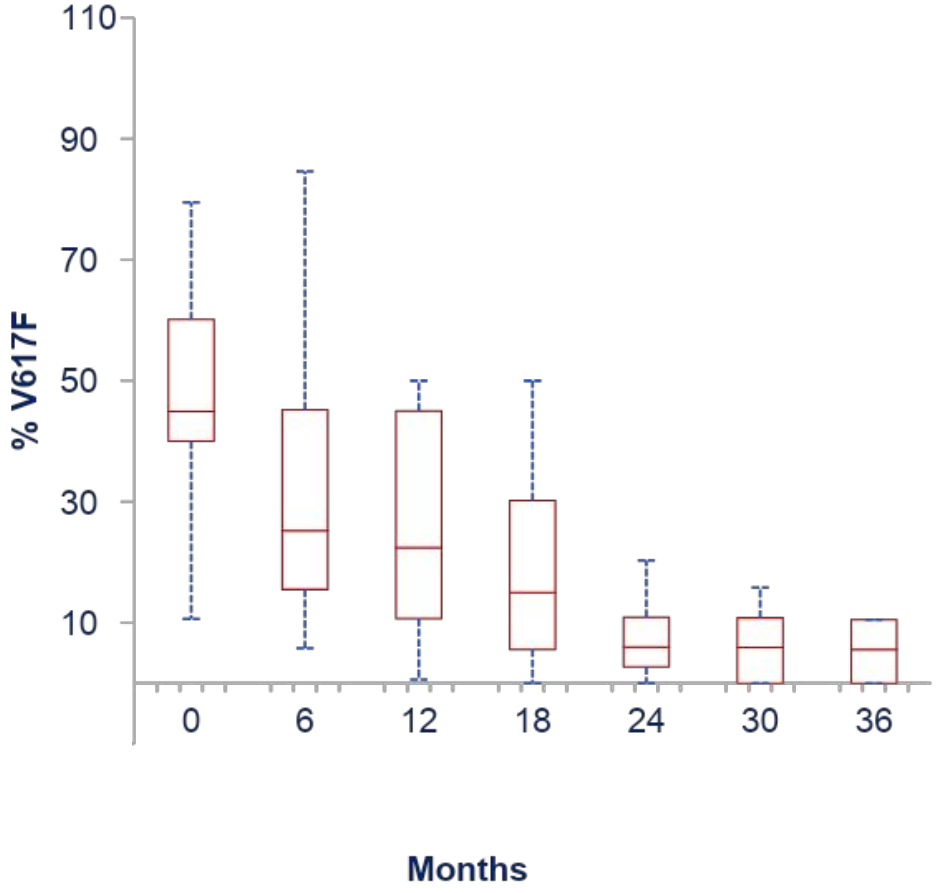
Risk Factors for Venous Thrombosis

- JAK2 VAF > 50%
- Previous VTE

Moliterno. Blood. 2023;141:1934.

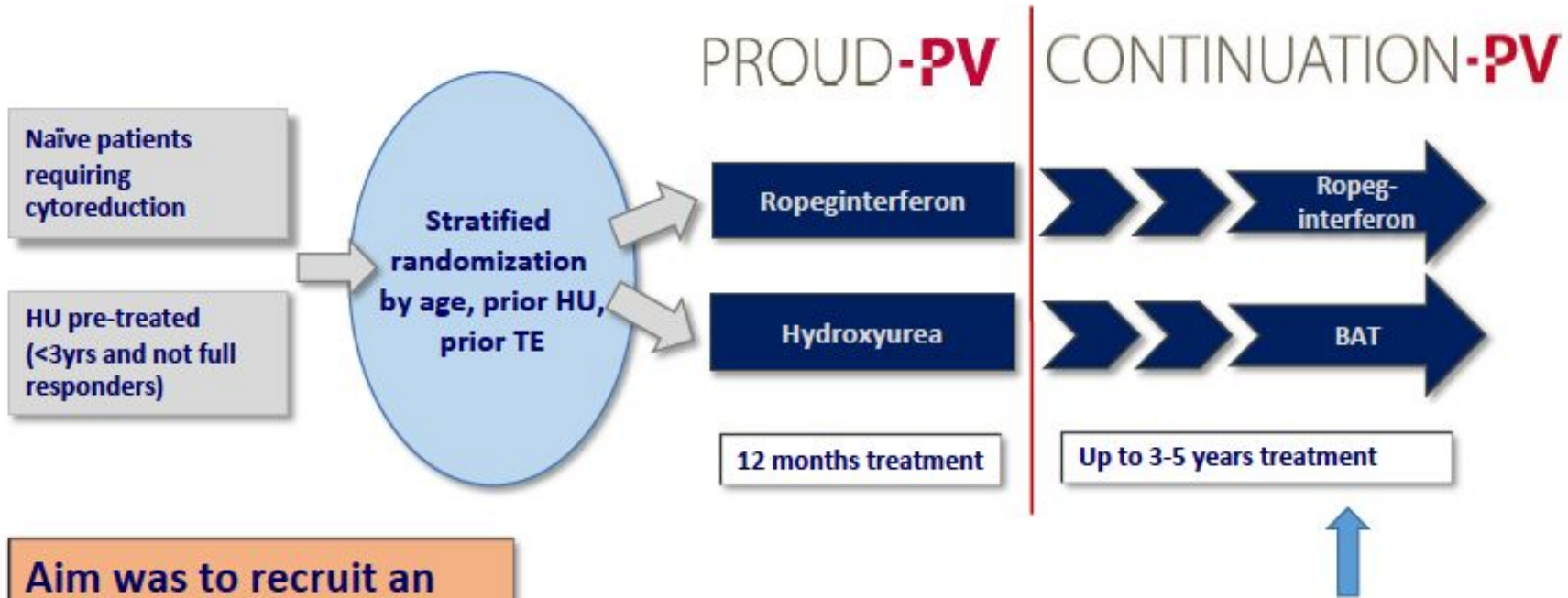
Interferon has consistently shown the ability to reduce *JAK2* VAF





Quintas-Cardama et al., Blood. 2013; Kiladjian et al., Blood. 2008

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



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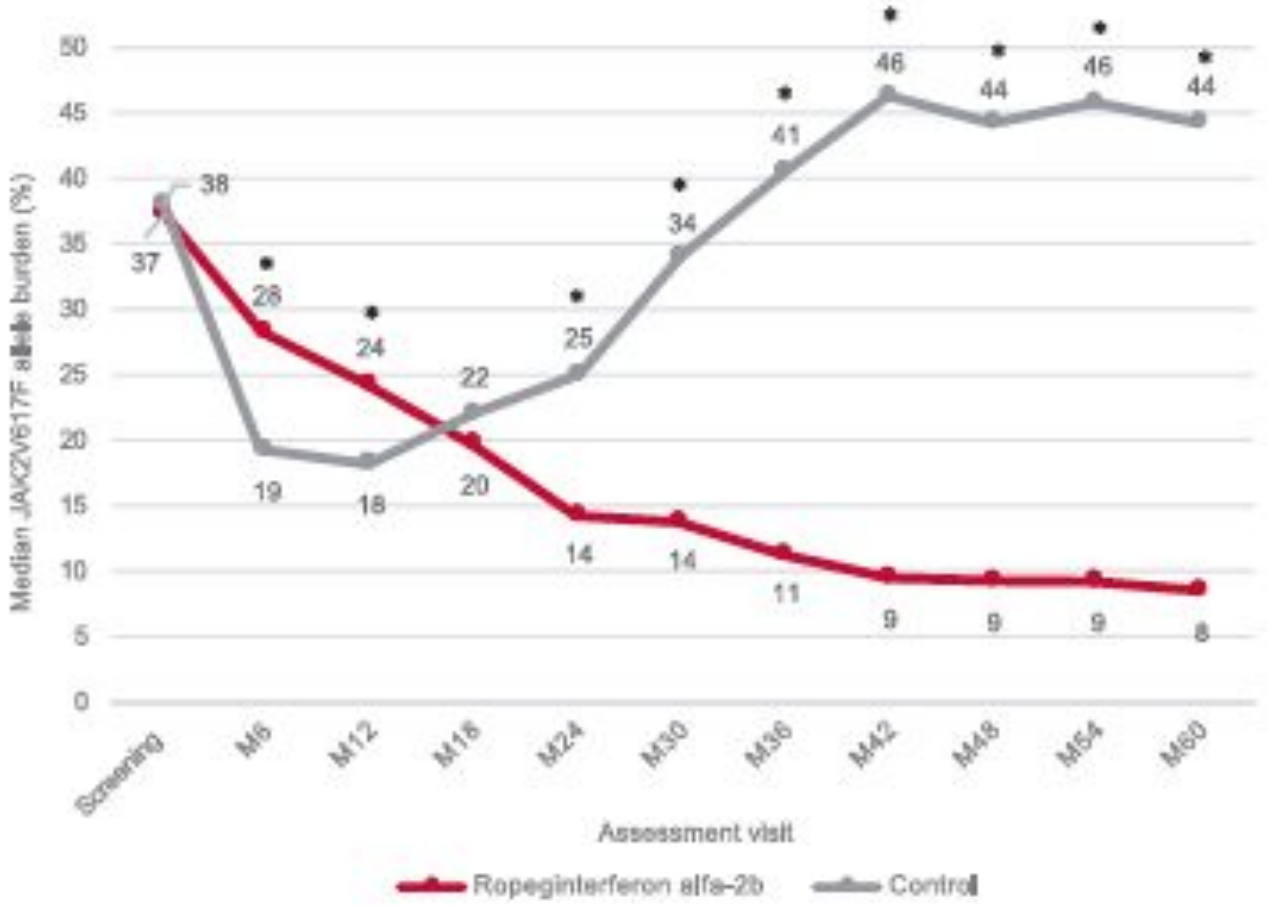
- **All available safety data (mean 3.8 years)**

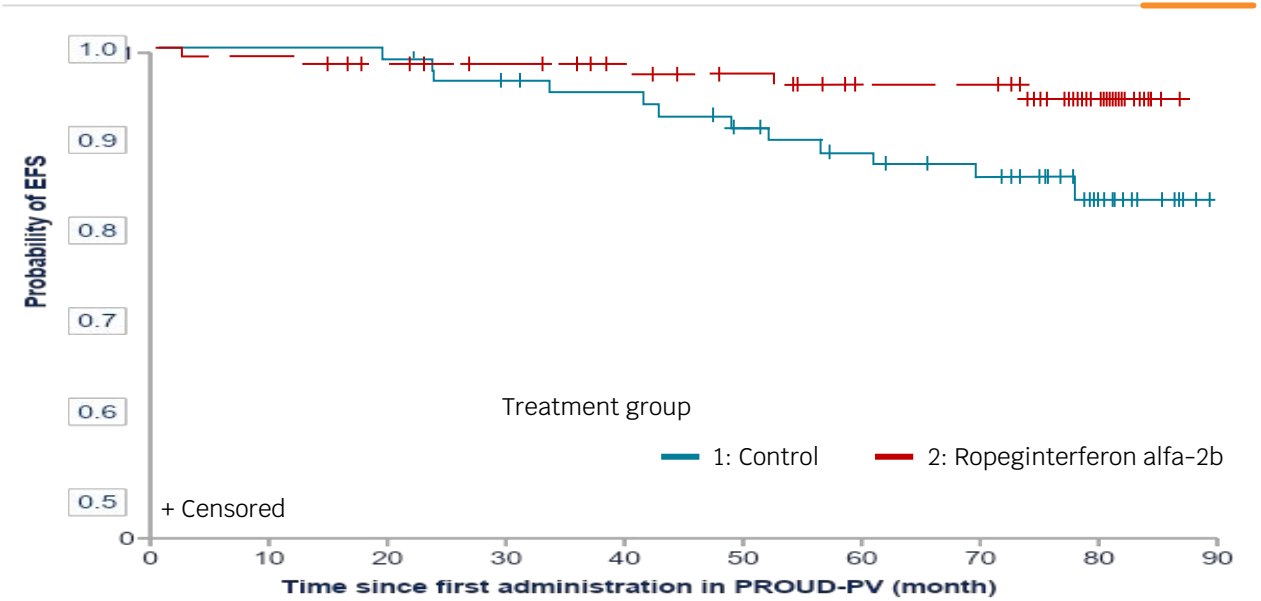
ROPEG-INF versus Hydrea: Impact on *JAK2*V617F VAF



Kiladjian et al. *Leukemia* 2022

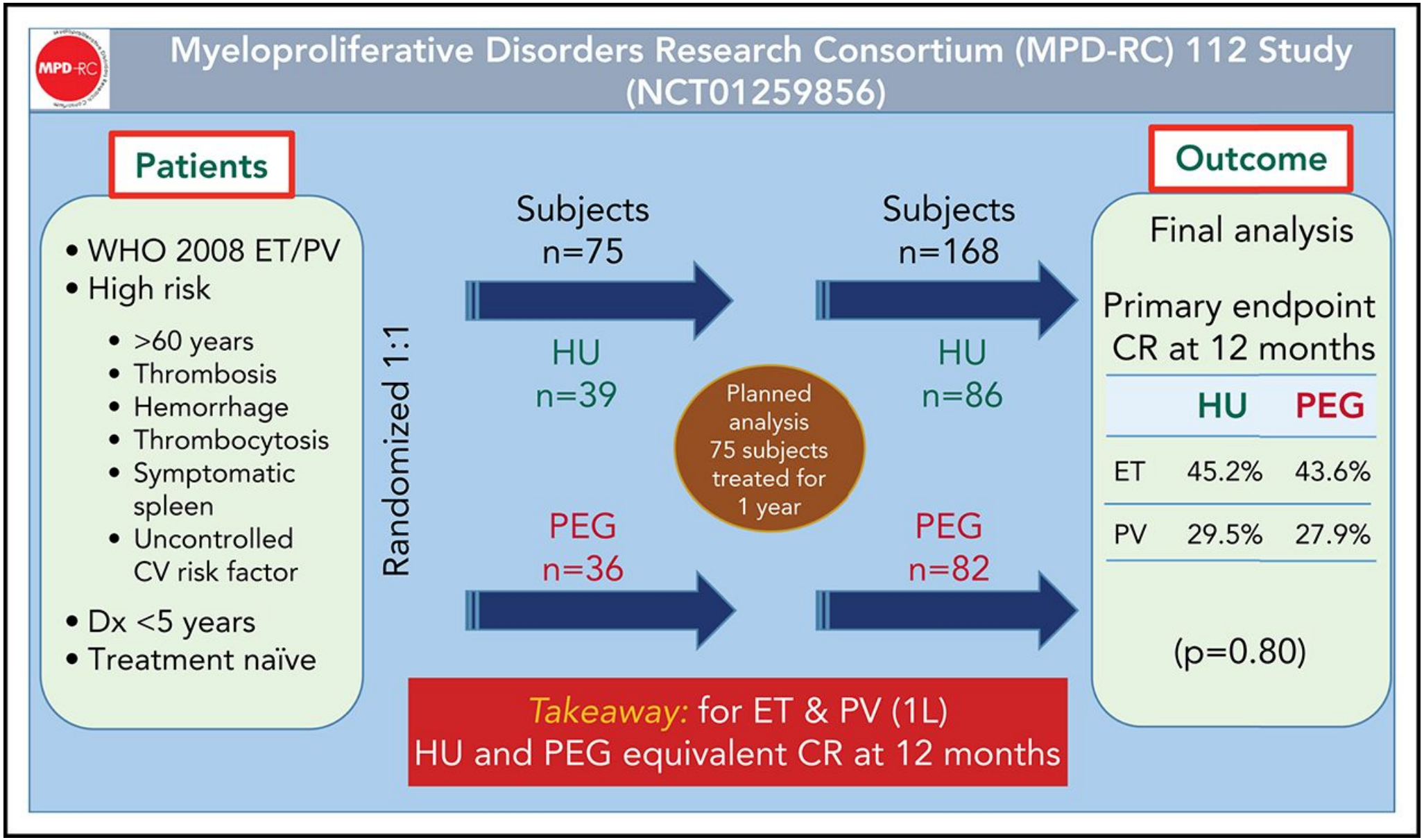
PROUD-PV/CONTINUATION-PV Trials- Other Clinically Significant Findings

EFS @ 6 years

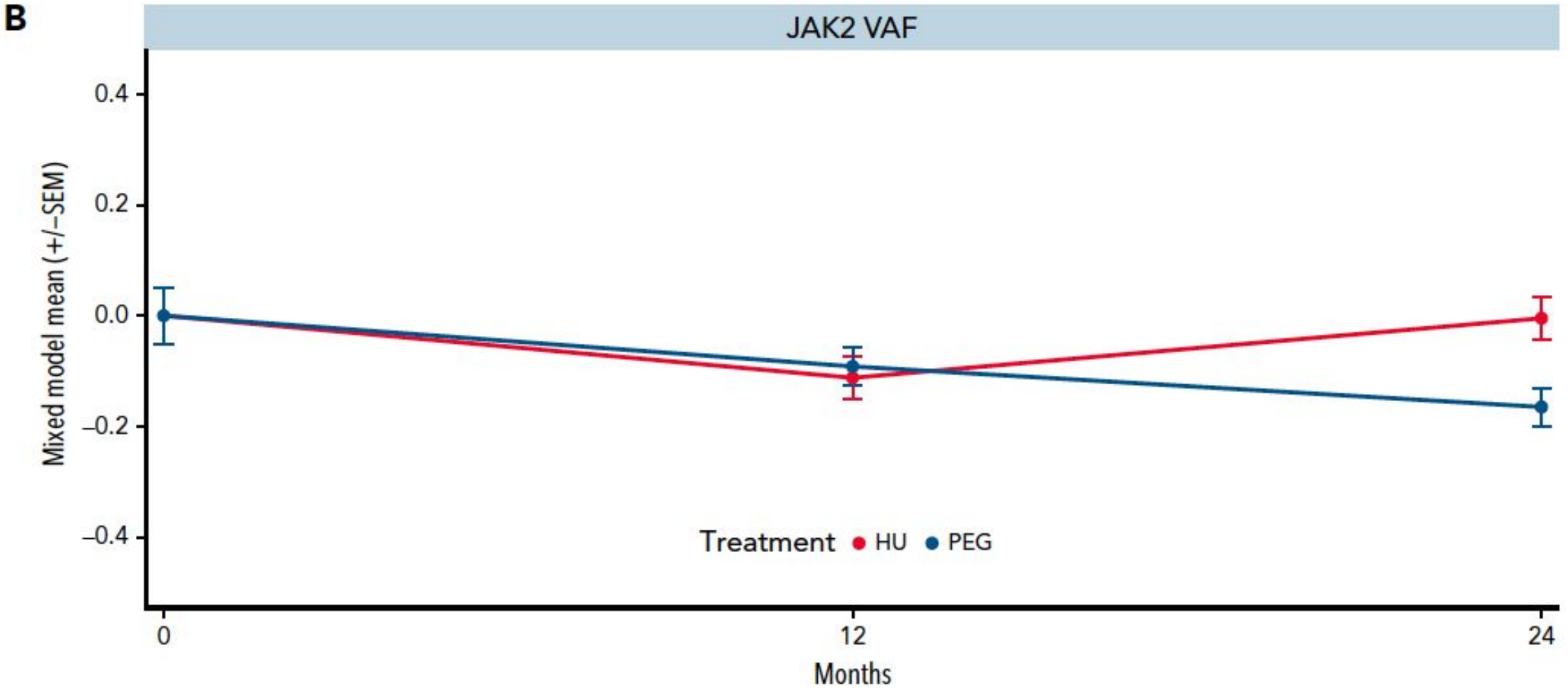


@ 6 years	roPEG-INF-α-2b	Hydroxyurea/BAT	P-value
Risk events, n(%)	5/95 **(5.3%)**	12/74 **(16.2%)**	**HR:0.34** (p=0.04)
Thromboembolism	2	5	
Myelofibrosis	1	2	
Death	2	3	
Acute leukemia	0	2	

Gisslinger et al, Leukemia, 2023

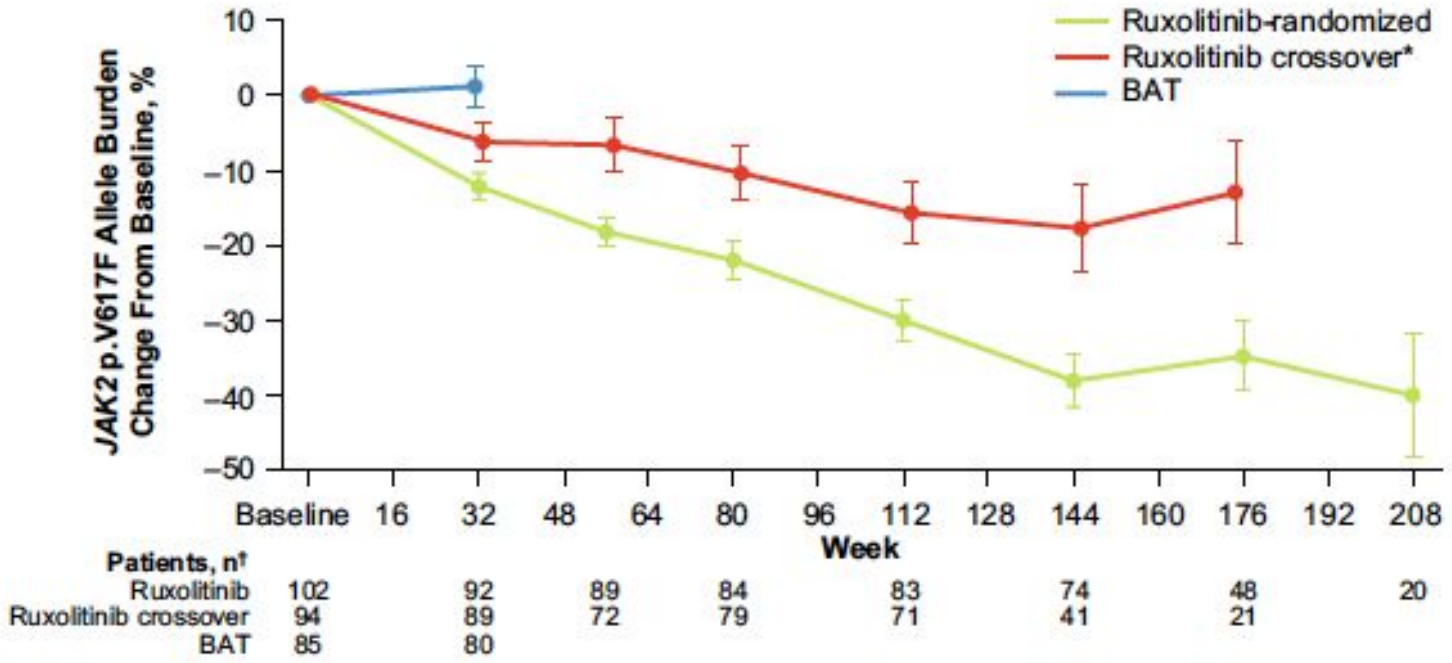

Myeloproliferative Disorders Research Consortium (MPD-RC) 112 Study
(NCT01259856)
Patients
• WHO 2008 ET/PV
• High risk
• >60 years
• Thrombosis
• Hemorrhage
• Thrombocytosis
• Symptomatic spleen
• Uncontrolled CV risk factor
• Dx <5 years
• Treatment naïve
Randomized 1:1
Subjects n=75
HU n=39
PEG n=36
Planned analysis 75 subjects treated for 1 year
Subjects n=168
HU n=86
PEG n=82
Outcome
Final analysis
Primary endpoint CR at 12 months
HU PEG
ET 45.2% 43.6%
PV 29.5% 27.9%
(p=0.80)
Takeaway: for ET & PV (1L)
HU and PEG equivalent CR at 12 months

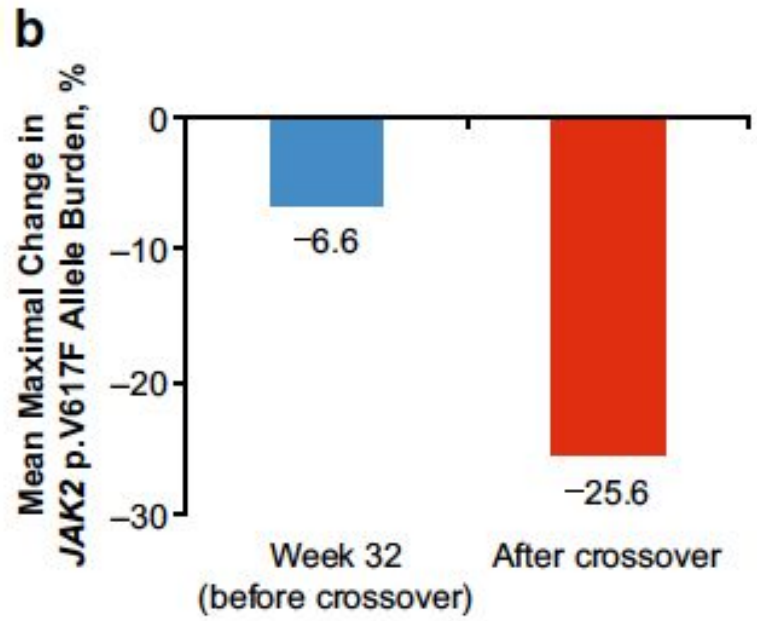
Pegasys versus Hydrea: Impact on *JAK2*V617F VAF



Mascarenhas et al. *Blood*

Impact of Ruxolitinib on *JAK2*V617F Allele Burden in Polycythemia Vera (RESPONSE Trial)





Vannuchi et al. *Ann Hem* 2017

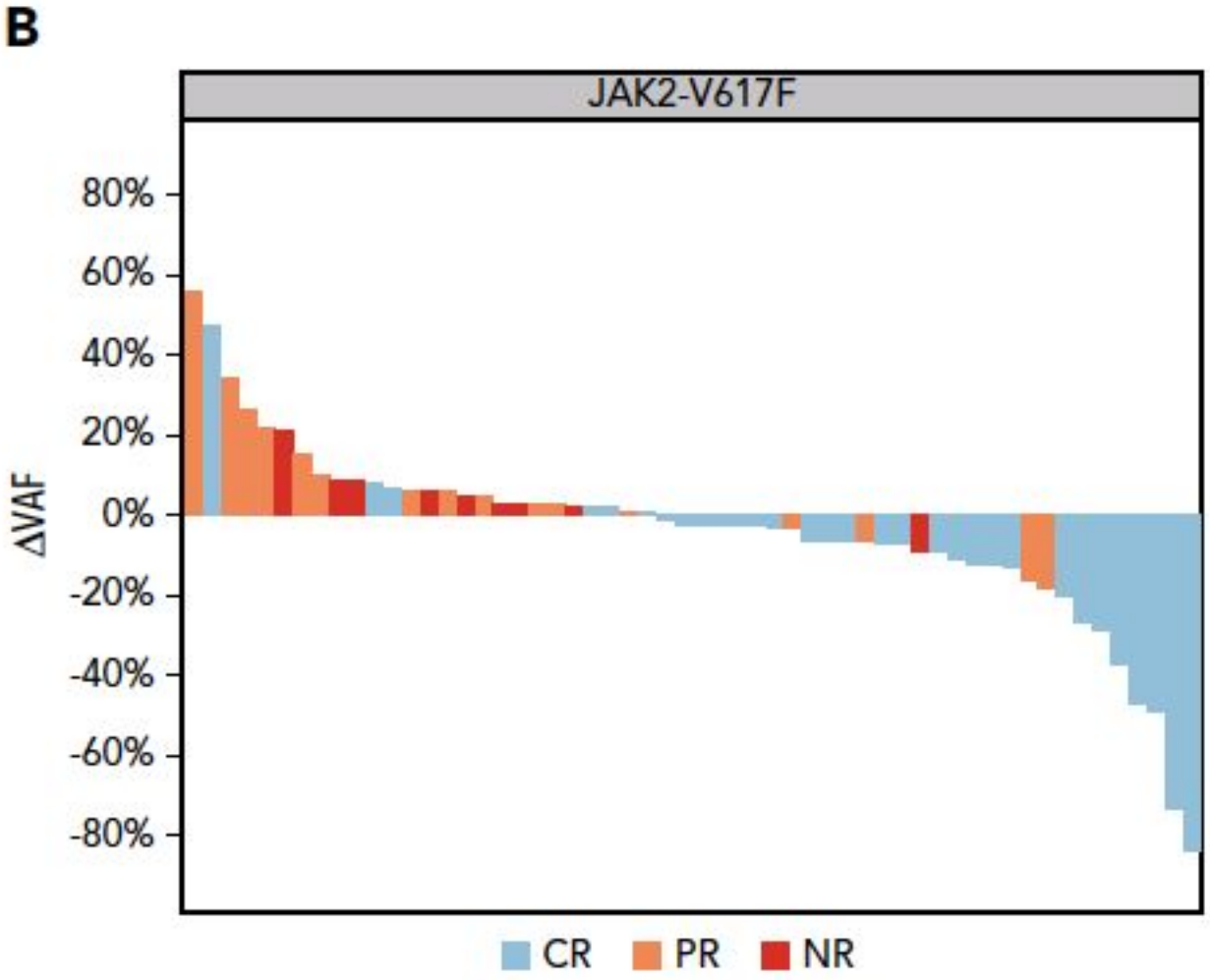
How Well Do Changes in *JAK2*VAF Correspond to Spleen Responses? (RESPONSE Trial)

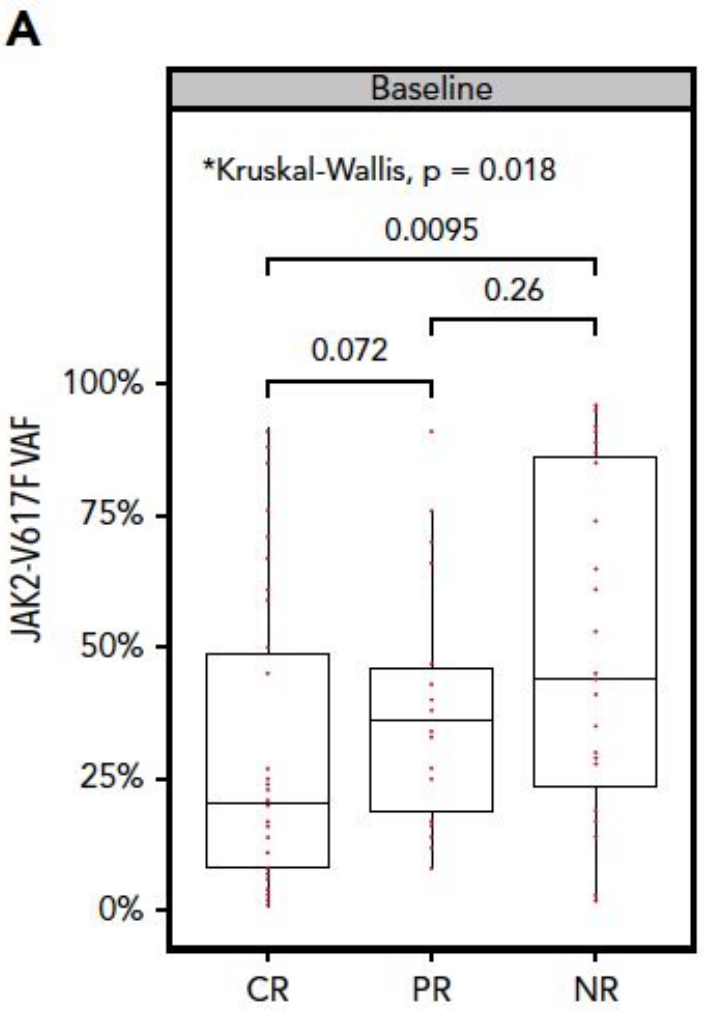
Table 4 Final percentage reduction from baseline in *JAK2* p.V617F allele burden and spleen volume

	Ruxolitinib-randomized		Ruxolitinib crossover	
JAK2 p.V617F allele burden reduction	≥20% (n = 52)	<20% (n = 47)	≥20% (n = 32)	<20% (n = 60)
Spleen volume reduction, n (%)				
≥35%	45 (86.5)	18 (38.3)	25 (78.1)	20 (33.3)
<35%	7 (13.5)	29 (61.7)	7 (21.9)	40 (66.7)

Vannuchi et al. *Ann Hem* 2017

How Well Do Changes in *JAK2*VAF Correspond to Hematologic Responses? MPD-RC 111 Trial



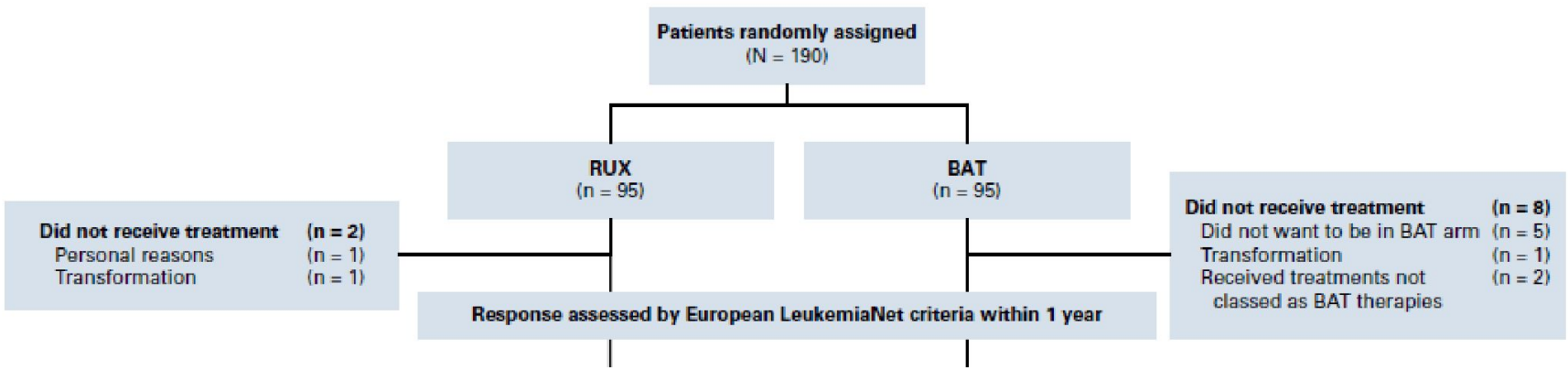


Yacoub et al. *Blood* 2019

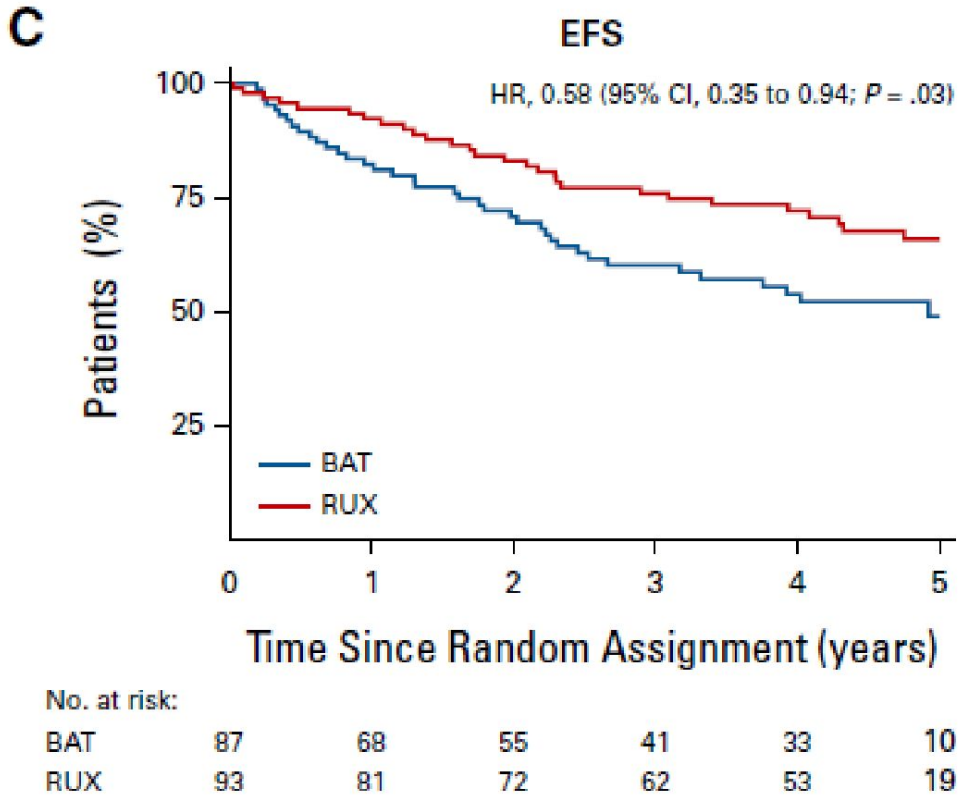
Ruxolitinib Versus Best Available Therapy for Polycythemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomized Trial

Claire N. Harrison, DM, FRCP[1]; Jyoti Nangalia, MB BChir, PhD[2,3,4]; Rebecca Boucher, PhD[5]; Aimee Jackson, MSc[5]; Christina Yap, PhD[5,6]; Jennifer O'Sullivan, MB BCh BAO[1,7]; Sonia Fox, BSc[5]; Isaak Ailts, MD[8]; Amylou C. Dueck, PhD[9]; Holly L. Geyer, MD[8]; Ruben A. Mesa, MD, FACP[10]; William G. Dunn, MB ChB[4]; Eugene Nadezhdin, PhD[3]; Natalia Curto-Garcia, MB BCh, MRCPath[1]; Anna Green, MB BS[1]; Bridget Wilkins, PhD, MRCPath[1]; Jason Coppell, MBBS[11]; John Laurie, MBChB, MRCPath[12]; Mamta Garg, MB, FRCP, FRCPath[13]; Joanne Ewing, MD, PhD[14]; Steven Knapper, BMBCh, FRCPath[15]; Josephine Crowe, MBBS, MRCPath[16]; Frederick Chen, PhD, FRCP, FRCPath[17]; Ioannis Koutsavlis, MB, FRCPath[18]; Anna Godfrey, BMBCh, PhD[4]; Siamak Arami, MD, FRCPath[19]; Mark Drummond, PhD, FRCPath[20]; Jennifer Byrne, PhD, FRCPath[21]; Fiona Clark, MB, FRCP, FRCPath[17]; Carolyn Mead-Harvey, MS[9]; Elizabeth Joanna Baxter, PhD[22]; Mary Frances McMullin, MD, FRCP, FRCPath[23]; and Adam J. Mead, MB BChir, PhD[7,24]

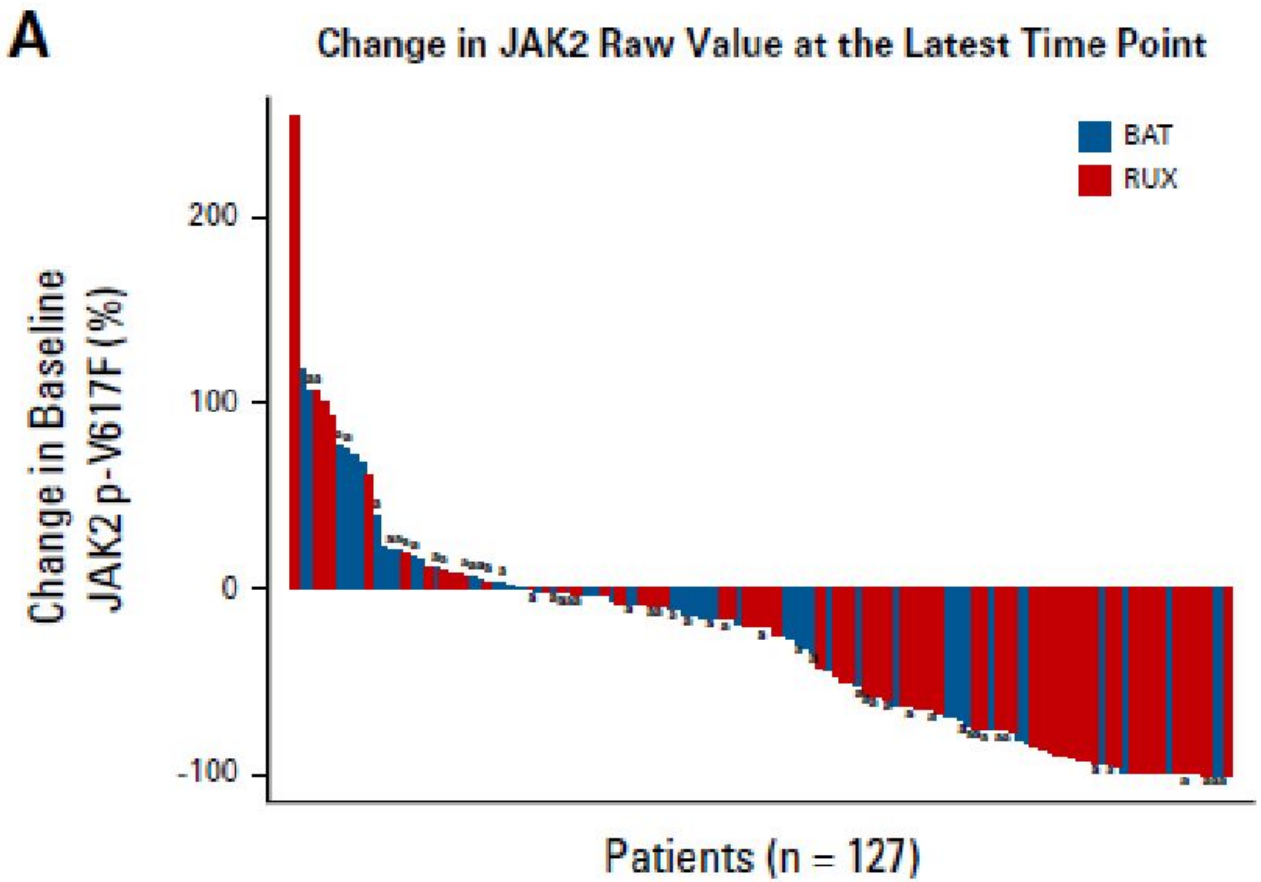
DOI https://doi.org/10.1200/JCO.22.01935

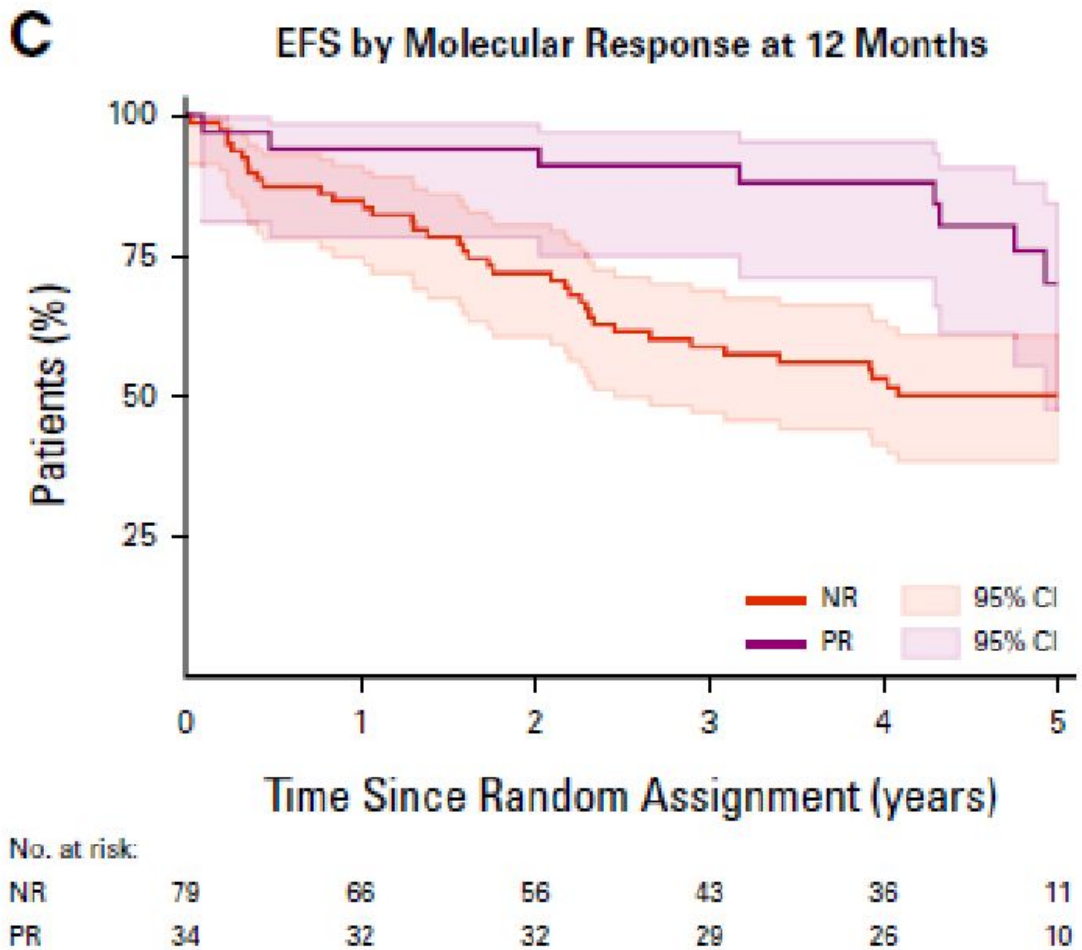


Ruxolitinib Improves Event-Free Survival



EFS:
Major thrombosis
Major hemorrhage
Disease transformation
Death


A
Change in JAK2 Raw Value at the Latest Time Point
BAT
RUX
Change in Baseline JAK2 p-V617F (%)
200
100
0
-100
Patients (n = 127)


C
EFS by Molecular Response at 12 Months
Patients (%)
100
75
50
25
NR
95% CI
PR
95% CI
0
1
2
3
4
5
Time Since Random Assignment (years)
No. at risk:
NR 79 66 56 43 36 11
PR 34 32 32 29 26 10

Conclusions

Phlebotomy and Aspirin remain standard of care for “low-risk” PV patients. Recent prospective and retrospective evidence suggests that earlier intervention with cytoreductive therapy (particularly interferon) may have benefit. More data is needed.

Ropeg-interferon and ruxolitinib have both demonstrated superiority to hydrea in randomized trials when assessing HCT control as an outcome. Does this translate into better long-term outcomes? Early data suggests this. More data is needed.

Current mediations such intereferon, hydrea, and ruxolitinib all have demonstrated the ability to reduce *JAK2*V617F allele burden to varying degrees. However this reduction is relatively modest and “elimination” of the mutant allele is the exception not the rule

Emerging evidence is beginning to suggest that reduction in allele burden may correlate with important clinical outcomes, and that starting treatment when allele burden is lower may make responses more likely. More data is needed.

https://pubmed.ncbi.nlm.nih.gov/37729609/

rampalr@mskcc.org