The emerging role of interferons in myeloproliferative neoplasms

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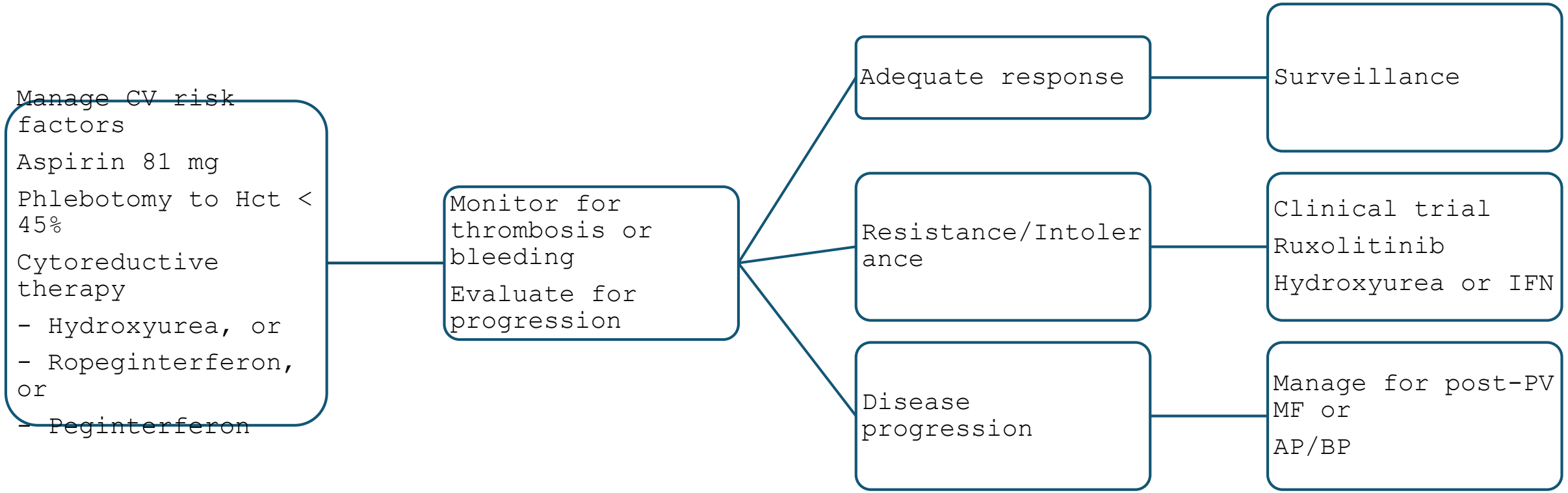
Potential conflict(s) of interest

- Research support – BMS, PharmaEssentia, Takeda
- Honoraria – Novartis, GSK, BMS
- Advisory Board – Novartis, PharmaEssentia, GSK

Objectives

1. Review the clinical relevance of *JAK2* V617F variant allele fraction (VAF)
2. Present data on interferons in PV and other myeloproliferative neoplasms (MPNs)
3. Discuss practical aspects of treatment with interferons

Treatment for high risk PV[1]



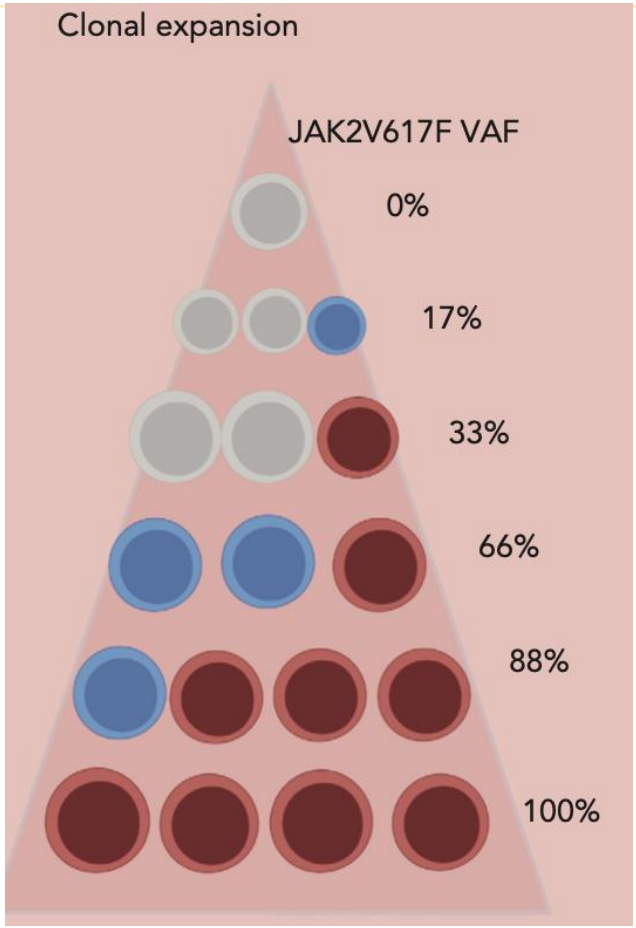
*IFN, Interferon – Ropeginterferon or peginterferon

Myeloproliferative neoplasms. NCCN Version 1.2026 – Jan 22, 2026

No monitoring or targeting *JAK2* V617F

Clinical relevance of *JAK2* V617F VAF

- *JAK2* V617F is the most frequent mutation in MPN, occurring in > 95% of PV, and 50-60% of ET and PMF, cases
- Results in ligand-independent activation of JAK2-STAT signaling, translating to panmyelosis and cytoses
- In PV, *JAK2* V617F VAF correlates with WBC[1], HCT,[1] thrombotic risk,[2-4] splenomegaly[5], and fibrotic progression[5]
- *JAK2* V617F VAF increases by 1.3-1.5% per year in patients with MPN[6,7]



Moliterno AR et al. Blood 2023

1. Vannucchi AM et al. *Leukemia* 2007, 2. Guglielmelli P et al. *Blood Cancer J.* 2021, 3. Soudet S et al. *Thromb Res.* 2022, 4. Zhang Y et al. *Cancer Med.* 2020, 5. Passamonti F et al. *Leukemia* 2010, 6.

Molecular response definitions in MPN

- IWG-MRT/ELN 2013 molecular response criteria[1]:
  - **Complete molecular response (CMR):** Eradication of the pre-existing molecular abnormality
  - **Partial molecular response (PMR):** ≥ 50% decrease in allele burden in patients with at least 20% mutant allele burden at baseline
- Exploratory:
  - **Minor molecular response or PMR 20[2]:** 20-49% decrease in allele burden

1. Barosi et al. *Blood* 2013, 2. Ng et al. *Blood* 2024

Interferons in MPN treatment

- Interferons are cytokines with immunomodulatory properties
- Exert an apoptotic effect on *JAK2* V617F mutated progenitor cells[1,2]
- Induce cell cycle entry of mutated HSCs in mouse models[1,2]
- Pegylation increases stability, prolongs activity, and reduces immunogenicity.

Interferons used in MPN

- Interferon α-2b (Intron A)
- Recombinant interferon α-2a (Roferon-A)
- Pegylated interferon α-2b (PegIntron)
- Pegylated interferon α-2a (Pegasys)
- Ropeginterferon α-2b (Besremi)

1. Mullally A. et al. *Blood* 2013, 2. Mosca M. et al. *Blood* 2021

Pegylated interferons in MPN – Randomized trials

Clinical Trial	N	MPN Type	Clinical Response	Molecular Response	Safety
MPD-RC 112[1]	pIFNα n=82 HU n=86	1L ET/PV High risk	CR* at 12 months pINα2a 35% HU 37% P=0.80	Median greatest change in *JAK2* VAF -10.7% vs. -5.3%	pINα2a 2 events (bleed, CVA) HU 3 events (thrombotic, MF, lung CA)
DALIAH[2]	pIFNα n=164 HU n=38	All MPN Any risk	CHR# at 24 months (n=121) pFNα2a 21% pIFNα2b 30% HU 21% P=0.68	Median *JAK2* VAF reduction 0.11 vs 0.05, P=0.005 *CALR* response heterogeneous (NS)	Discontinuation pIFNα2a 30% pIFNα2ab 38% HU 8%
PROUD-PV[3]	Ropeg n=127 HU n=127	PV	CHR§ w N spleen at 12 months Ropeg 26/122 (21%) HU 34/123 (28%) P=0.23 (non-inferiority not shown)	Molecular response at 3 years^: Ropeg 62/94 (66%) HU 20/74 (27%) RR€ (95% CI) = 2.31 (1.56-3.42)	Discontinuation Ropeg 21/127 (17%) HU 16 /127 (13%)

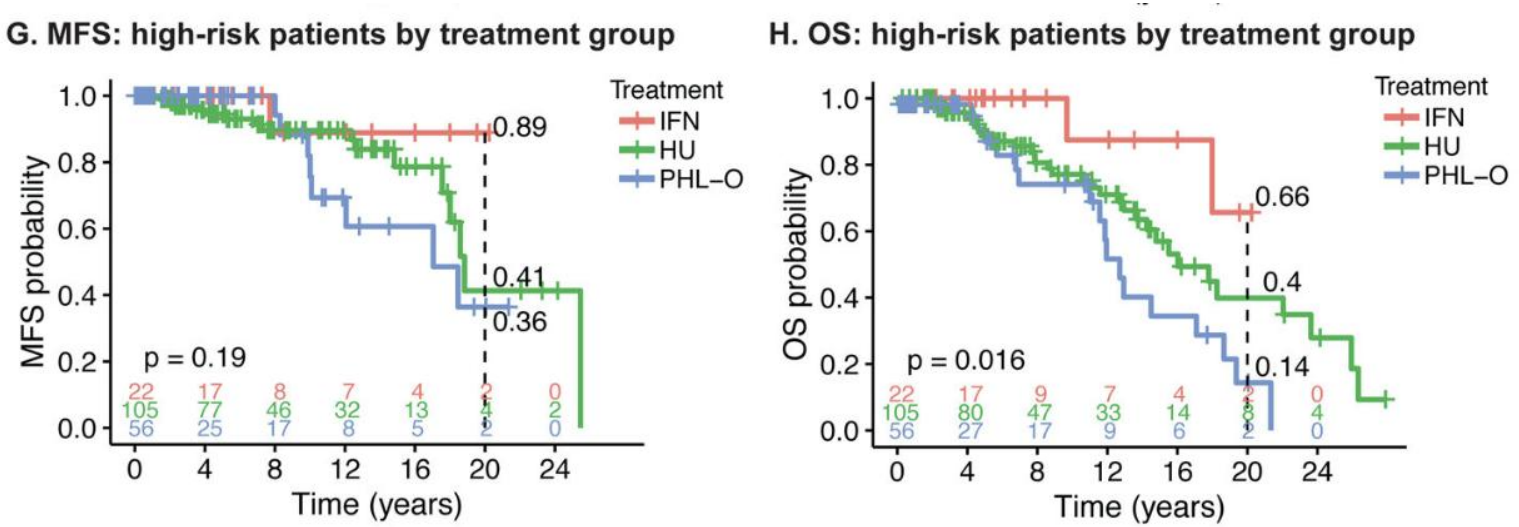
* CR : plt < 400 x 10^9/L, Hct < 45% without phlebotomy for PV only, WBC < 10 x 10^9/L, resolution of splenomegaly, resolution of disease-related symptoms; # CHR = Clinico-hematologic response by modified IWG/ELN; § CHR = complete hematological response; € Rate ratio

^ Complete = reduction to undetectable levels; Partial = ≥ 50% decrease if the baseline < 50%; ≥ 25% decrease if baseline ≥ 50%

1. Mascarenhas J. et al. Blood 2022; 2. Knudsen TA et al. Blood Advances 2022; 3. Gisslinger H et al. Lancet Haematol 2020

Interferon-alpha for PV – Retrospective data

- Single-center retrospective study of 470 patients with PV at Weill Cornell Medicine
- 208 (44%) were high risk
- Patients were treated with IFN 93 (20%), HU 189 (40%), or PHL 133 (28%)



- In high-risk patients, 20-year MFS was 89% for IFN, 41% for HU, and 36% for PHL (p=0.19), and 20-year OS was 66% for IFN, 40% for HU, 14% for PHL (p=0.016)

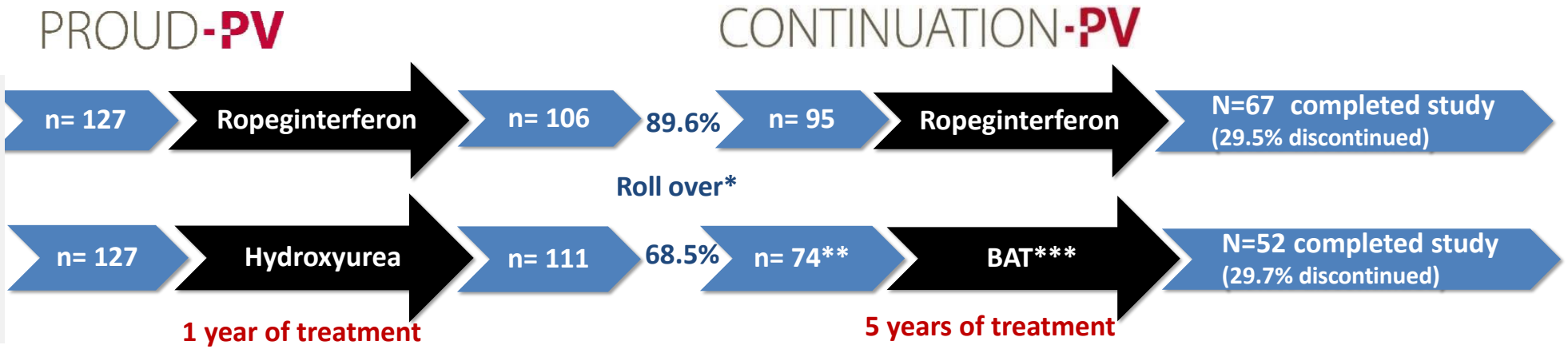
*IFN included recombinant interferon alpha-2a (Roferon-A), recombinant interferon alpha-2b (Intron A), and pegylated interferon alpha-2a (Pegasys).

Abu-Zeinah G. et al. *Leukemia* 2

PROUD-PV / CONTINUATION-PV trials

- The randomized phase 3 trial PROUD-PV and its extension CONTINUATION-PV were conducted to compare the safety and efficacy of ropeginterferon alfa-2b with standard of care (hydroxyurea [HU]/best available treatment) in patients with PV and were completed in July 2021[1].
- The final efficacy analysis for CONTINUATION-PV (N=169) was conducted once all patients completed 6 years of treatment; maximum treatment duration was 7.3 years[2].

- PV with JAK2 mutation
- Untreated with indication for cytoreductive therapy
- HU < 3y without resistance/intolerance



*No significant differences between pts who entered CONTINUATION-PV and those who did not roll-over
**Full analysis set
***Control group received best available treatment (BAT); 88% of patients received HU as of month 72

1. Gisslinger H et al. *Lancet Haematol*. 2020
2. Kiladjian JJ et al. *Leukemia*. 2022

PROUD-PV / CONTINUATION-PV baseline characteristics

	PROUD-PV		CONTINUATION-PV*	
	Ropeginterferon alfa-2b (n=127)	Hydroxyurea (n=127)	Ropeginterferon alfa-2b (n=95)	Best available treatment (n=76)
Female	68 (54%)	67 (53%)	48 (51%)	40 (53%)
Male	59 (46%)	60 (47%)	47 (49%)	36 (47%)
Age, years				
Median	60·0 (52·0–66·0)	60·0 (48·0–67·0)	58·0 (50·0–64·0)	59·0 (49·0–65·5)
Range	30–85	21–81	30–85	32–79
Hydroxyurea pretreated	45 (35%)	37 (29%)	30 (32%)	20 (26%)
Median duration of previous hydroxyurea therapy, months†	10·2 (2·1–21·3)	7·9 (2·7–19·2)	9·5 (2·8–25·1)	8·2 (2·6–23·0)
Median duration of polycythaemia vera, months‡	1·9 (0·7–11·2)	3·6 (0·7–20·0)	1·8 (0·6–6·8)	1·6 (0·7–15·1)
Previous thromboembolic event	25 (20%)	23 (18%)	21 (22%)	14 (18%)
Positive status for *JAK2* Val617Phe mutation§				
Number	126 (99%)	125 (98%)	94 (99%)	74 (97%)
Mean allele burden, %	41·9% (24)	42·8% (24)	42·8% (23)	42·9% (23)
Median haematocrit, %	47·1% (44·2–51·3)	48·0% (45·0–52·2)	47·7% (44·4–52·0)	49·9% (46·2–53·1)
Median platelet count, 10^9/L	485·0 (350·0–671·0)	452·0 (329·0–666·0)	488·0 (350·0–701·0)	451·0 (329·0–678·5)
Median leucocyte count, 10^9/L	10·6 (8·0–13·4)	10·5 (7·9–14·5)	10·9 (8·0–14·6)	11·3 (8·7–15·1)
Median spleen size, cm	13·1 (11·0–15·0)	13·0 (11·5–15·2)	13·5 (11·5–15·0)	12·8 (11·3–15·5)
Presence of splenomegaly¶	12 (9%)	15 (12%)	7 (7%)	8 (11%)

Data are n (%), mean (SD), median (IQR). *Characteristics for the CONTINUATION-PV population at baseline in PROUD-PV. †Duration of previous hydroxyurea therapy was assessed from start of therapy until the time of screening in PROUD-PV. ‡Duration of polycythaemia vera was assessed from diagnosis until the time of screening in PROUD-PV. §Data were not available for one patient in the ropeginterferon alfa-2b group, and for two patients in the control group in PROUD-PV at baseline. Positive status for *JAK2* Val617Phe mutation was confirmed at subsequent visit. ¶Splenomegaly as assessed by investigator.

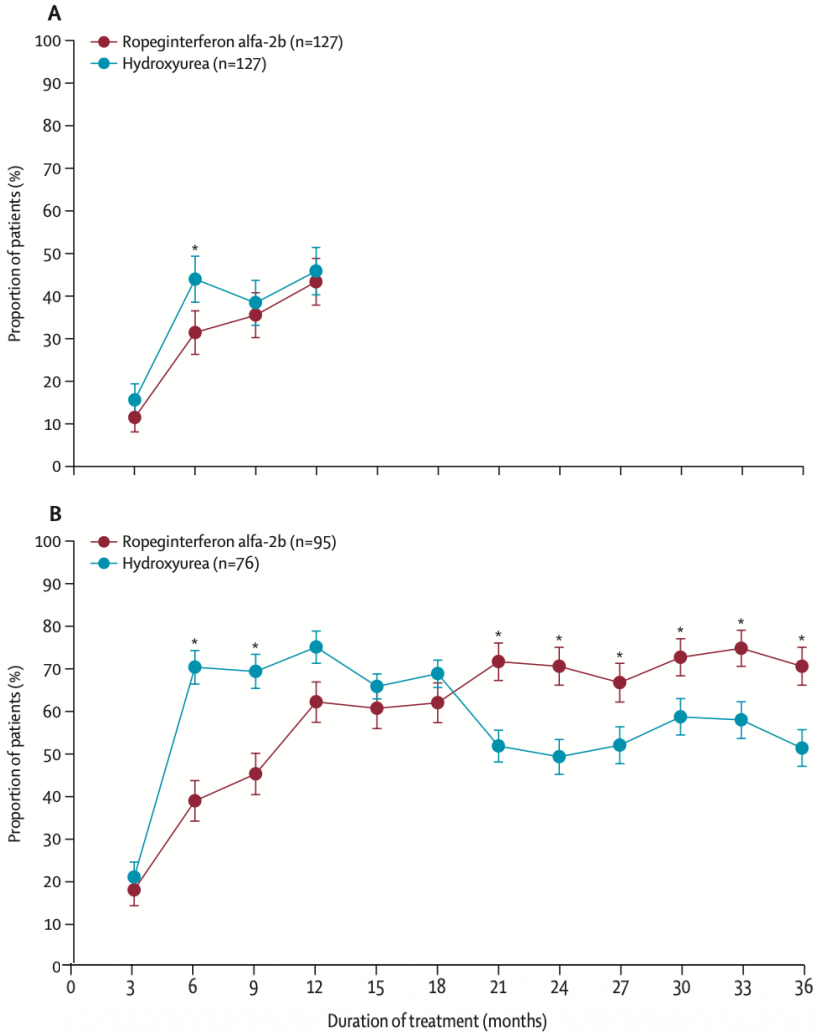
Table 1: **Baseline characteristics of the trial patients**

Gisslinger H et al. *Lancet Haematol*. 2020

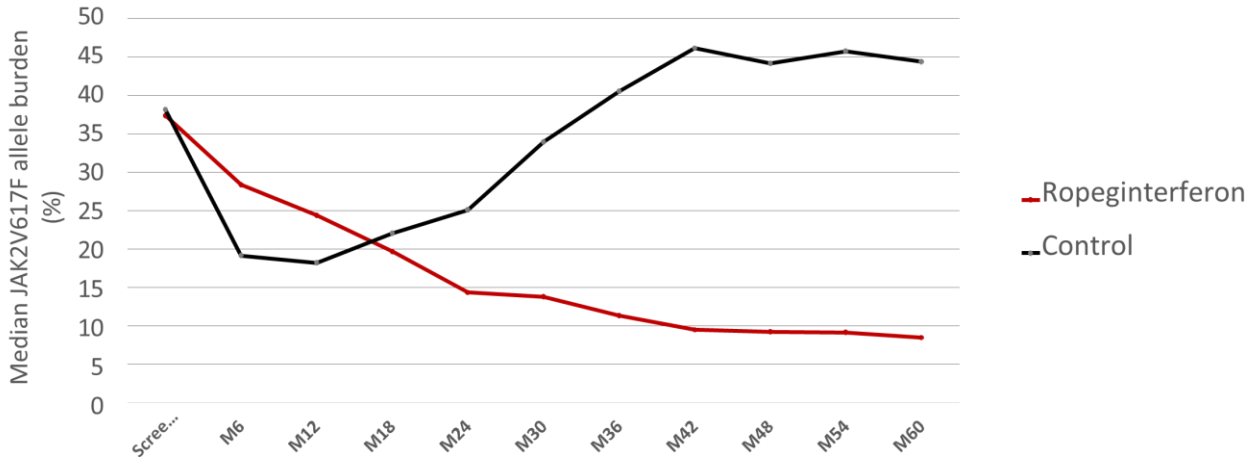
PROUD-PV / CONTINUATION-PV hematologic response

The primary endpoint and prespecified noninferiority margin (10.5%) were not met at 12 months

CHR with normal spleen size	Ropeg	HU	Difference (95% CI)	*P* Value
% patients	21%	28%	-6.57 (-17.23 to 4.09)	0.23 (NS)
# patients	26 / 122	34 / 123		



Median *JAK2* V617F allele burden



At 60 months:

- Complete hematologic response was achieved in 53/95 (55.8%) in the ropeg arm vs. 33/75 (44%) in the BAT arm, p=0.097
- Molecular response rate was 65/94 (69.1%) in the ropeg arm vs. 16/74 (21.6%) in the BAT arm, RR: 3.04 (95% CI: 1.96–4.71), p < 0.0001

Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN/Control)
	Mean	Median	Mean	Median		
Baseline	42.8	37.3	42.9	38.1	-	-
MONTH 12	30.2	24.4	24.4	18.2	0.0244	6.646 (0.86 to 12.43)
MONTH 24	20.9	14.3	32.4	25.1	0.0003	-10.745 (-16.50 to -4.98)
MONTH 36	19.7	11.3	39.3	40.5	<0.0001	-18.722 (-24.49 to -12.96)
MONTH 48	19.3	9.2	44.8	44.2	<0.0001	-24.582 (-30.35 to -18.82)
MONTH 60	18.9	**8.5**	44.0	**44.4**	**<0.0001**	**-23.959 (-29.72 to -18.20)**

Full Analysis Set

JAK2 V617F VAF <1% in 18/92 (19.6%) on

Kiladjian JJ et al. *Leukemia*. 2022

Adverse Events

Common AEs in PROUD/CONTINUATION-PV

	Ropeginterferon alfa-2b (n=127)			Control (n=127)		
	Grade 1–2*	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	113 (89%)	40 (32%)	3 (2%)	114 (90%)	33 (26%)	1 (1%)
Thrombocytopenia	27 (21%)	3 (2%)	0	36 (28%)	5 (4%)	0
Leucopenia	23 (18%)	3 (2%)	0	28 (22%)	6 (5%)	0
Anaemia	16 (13%)	1 (1%)	0	31 (24%)	2 (2%)	0
Fatigue	17 (13%)	0	0	17 (13%)	1 (1%)	0
γ-glutamyltransferase increased	20 (16%)	9 (7%)	1 (1%)	2 (2%)	2 (2%)	0
Headache	15 (12%)	0	0	16 (13%)	0	0
Diarrhoea	12 (9%)	0	0	14 (11%)	1 (1%)	0
Dizziness	14 (11%)	0	0	10 (8%)	0	0
Alanine aminotransferase increased	16 (13%)	5 (4%)	0	2 (2%)	0	0
Arthralgia	15 (12%)	1 (1%)	0	5 (4%)	0	0
Hypertension	5 (4%)	4 (3%)	0	6 (5%)	5 (4%)	0
Nasopharyngitis	7 (6%)	0	0	13 (10%)	0	0
Nausea	4 (3%)	0	0	15 (12%)	0	0
Aspartate aminotransferase increased	13 (10%)	3 (2%)	0	2 (2%)	0	0
Asthenia	10 (8%)	0	0	6 (5%)	1 (1%)	0
Platelet count decreased	3 (2%)	0	0	12 (9%)	2 (2%)	0

n=127 in both arms

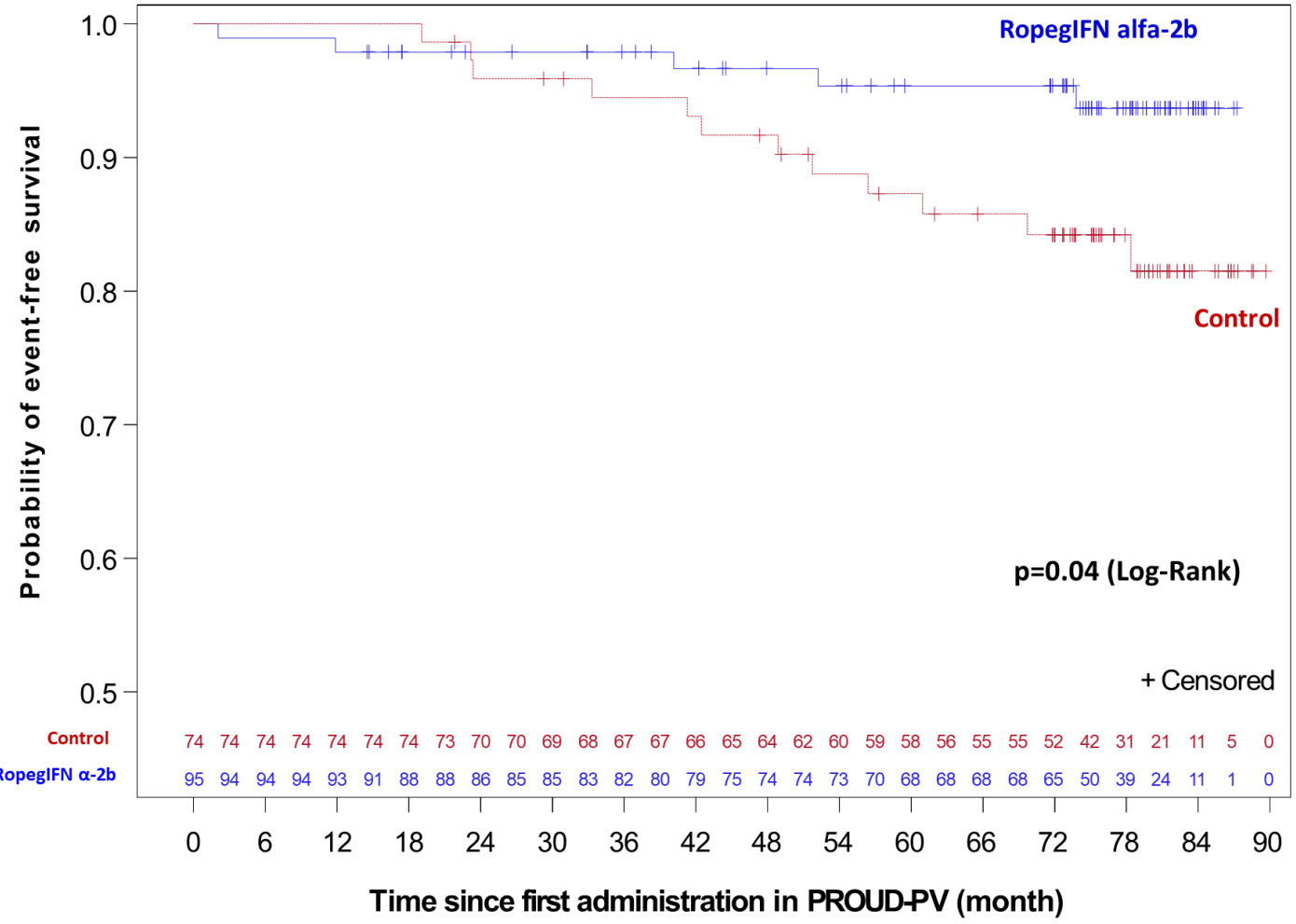
AEs of special interest at 5-year follow up

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

Gisslinger H et al. *Lancet Haematol*. 2020
Kiladjian JJ et al. *Leukemia*. 2022

Event Free Survival

Risk events: death, disease progression and thromboembolic events



At 6 years, EFS was higher in patients treated with ropeg vs. BAT, p=0.04

Risk events occurred in 5/95 (5.3%) in ropeg arm vs. 12/74 (16.2%) in the control arm

Risk events ropeg arm:

- Thrombosis, n=2
- MF, n=1
- Death, n=2

Risk events BAT arm:

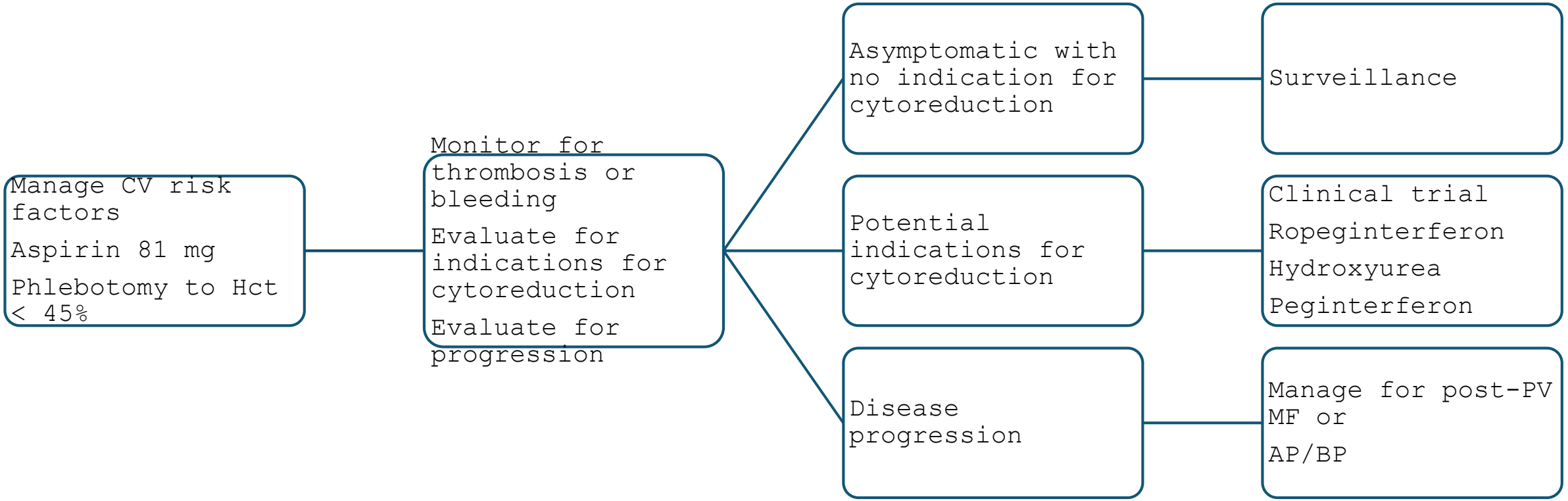
- Thrombosis, n=5
- MF, n=2
- Acute leukemia, n=2
- Death, n=3

Gisslinger H. et al. *Leukemia* 2023

Limitations of *JAK2* V617F VAF as a surrogate for disease modification

- *JAK2* V617F VAF in PV / ET is a reflection of the mature myeloid component
- Durability of clonal suppression unclear
- Less value in advanced MPN
- Co-mutations may contribute to disease progression
- *CALR, MPL* clonal dynamics less established

Treatment for low risk PV[1]



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ELN Guidelines for Cytoreduction in PV

High Risk	Low Risk		
CYTOREDUCTION INDICATED	CYTOREDUCTION RECOMMENDED	CYTOREDUCTION SHOULD BE CONSIDERED	CYTOREDUCTION CAN BE CONSIDERED
Age ≥60y, and/or Prior thrombosis	Poor phlebotomy tolerance Symptomatic progressive splenomegaly Persistent leukocytosis > 20 x 10^9/L for at least 3 months	Progressive[1] and persistent leukocytosis > 15 x 10^9/L for at least 3 months Extreme thrombocytosis > 1500 x 10^9/L or bleeding Inadequate Hct control with phlebotomies[2]	High symptom burden not relieved by phlebotomy, antiplatelet therapy or antihistamines In select patients with relevant cardiovascular risk after primary prevention strategies

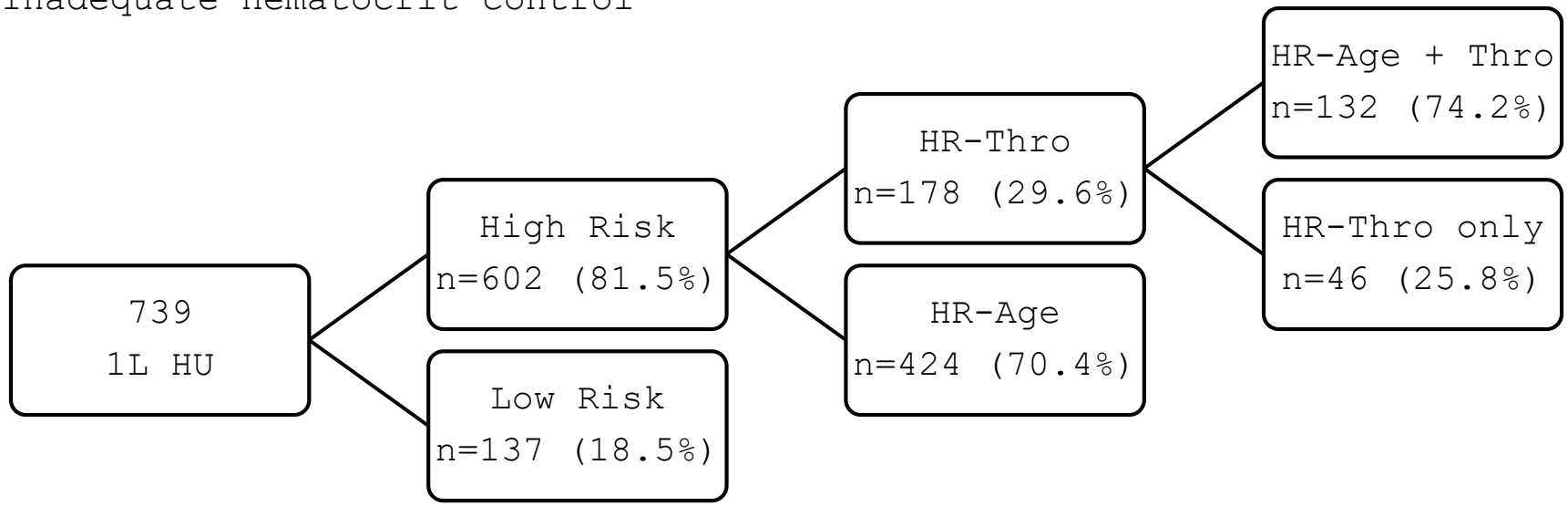
[1]At least 100% increase if baseline count is <10 × 10^9/L or at least 50% increase if baseline count is >10 × 10^9/L
[2]At least 6 phlebotomies/year for at least 2 years

Marchetti M. et al. *Lancet Haematol* 2022

Clinical signs and symptoms associated with increased risk of thrombosis

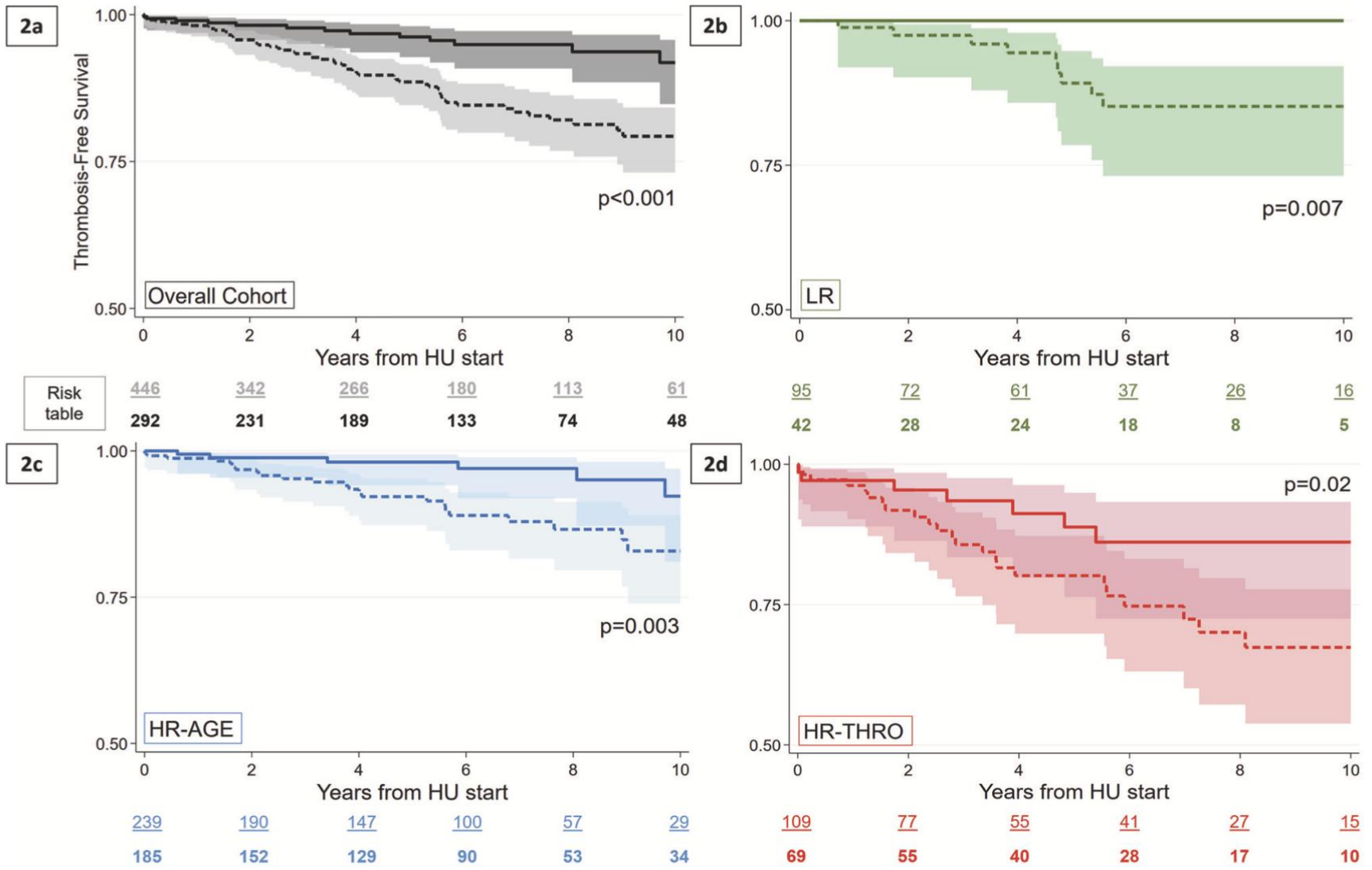
- The PV-ARC study evaluated 739 patients with PV who were treated with 1L HU and had data on CSS available
- Evaluated incidence of thrombosis among PV patients receiving HU in different risk categories and the impact of '**clinical signs and symptoms for therapy start (CSS)**' per ELN criteria:

1. Persistent/progressive leukocytosis
2. Extreme persistent thrombocytosis: platelets >1000 $x10^9$/L
3. Progressive splenomegaly: >5 cm below costal margin
4. Inadequate hematocrit control
5. Frequent phlebotomies: >6 phlebotomies/yr
6. Uncontrolled cardiovascular risk factors
7. Severe itching: score ≥5/10



Palandri F et al. *Leukemia* 2025

Thrombosis-free survival



Palandri F et al. *Leukemia* 2025

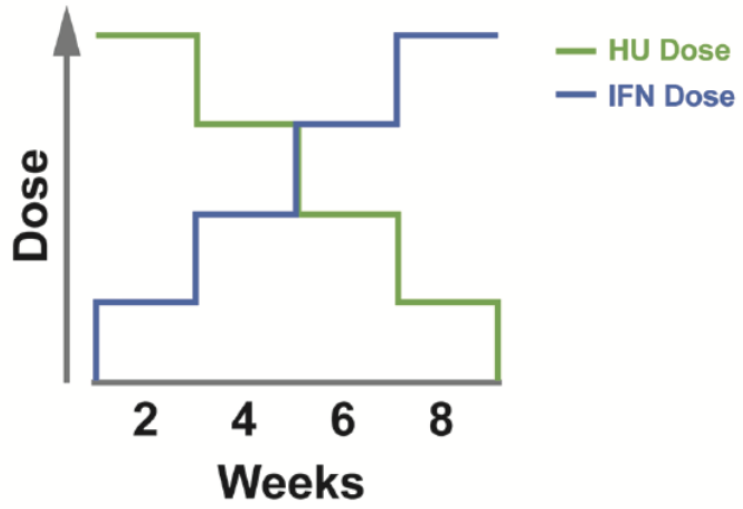
Hydroxyurea vs. interferon comparison

	Hydroxyurea	Interferon
Route	Oral	Subcutaneous
Hematologic response[1-3]	21-37%	21-35%
Disease modification	No	Molecular response
Leukemogenicity	?	No
Gonadotoxicity	Yes	No
Adverse effects		
Common	Cytopenias, GI toxicity, mucocutaneous effects	Fatigue, flu-like symptoms, MSK pain, liver enzyme abnormalities, cytopenias
Less common	Fever, infection, hepatitis, cholestasis, leg ulcers, pneumonitis	Depression, ocular toxicity, CVS events, pulmonary toxicity, colitis, pancreatitis, hypersensitivity
Discontinuation[4,5]	13-37%	6.5-38%

1. Knudsen TA et al. Blood Advances 2022; 2. Mascarenhas J. et al. Blood 2022; 3. Gisslinger H et al. Lancet Haematol 2020, 4. Bewersdorf J.P. et al. *Clin Lymphoma Myeloma Leuk* 2020, 5. Samuelsson J. et al. *Cancer* 2006

Interferon – Practical aspects

- Starting dose
  - Peginterferon α-2a 45-90 µg sc weekly
  - Ropeginterferon α-2b 100 µg sc every 2 weeks (50 µg if receiving HU)
- Taper HU by reducing the total weekly dose by 20–40% every 2 weeks
- Baseline
  - Psychiatric, cardiac, pulmonary assessment
  - CBC, chemistry, liver function tests, thyroid function, ANA, hepatitis B/C serology
  - Retinal exam
- Monitoring
  - CBC, chemistry, liver function tests, thyroid function every 2 – 4 weeks in the first 3 months of therapy
  - Yearly retinal exam



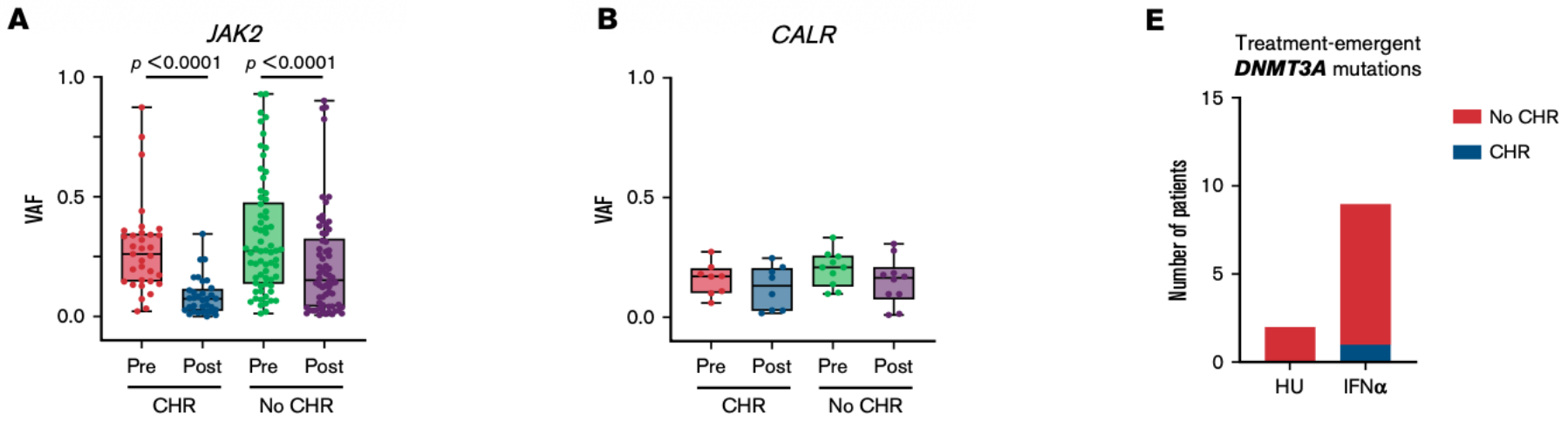
Vachhani P. et al. *Ther Adv Hematol* 2024

Interferon adverse effects

- Flu-like symptoms
- Cytopenias
- Liver enzyme elevation
- Endocrine toxicity – hypo/hyperthyroidism, hypo/hyperglycemia
- Autoimmune toxicity - thyroiditis, RA, SLE, psoriasis
- Depression
- Ocular toxicity – retinopathy, retinal hemorrhage, retinal artery or vein occlusion
- Cardiovascular toxicity – HTN, HF, arrythmia, CAD
- Pulmonary toxicity – pulmonary infiltrates, pneumonia, pneumonitis
- Dermatologic toxicity
- Colitis
- Pancreatitis
- Hypersensitivity

Biomarkers and response

- *JAK2*-UPD associated with greater molecular responses[1]
- Germline *IFNL4* diplotype status associated with molecular response[2]
- *CALR* VAF minimally reduced with IFNα or HU[1]
- Treatment-emergent *DNMT3A* mutations in patients not achieving CHR[1]
- Additional somatic mutations enriched in patients not achieving CHR[3]
- Concurrent *TET2* mutations associated with reduced molecular responses[3,4]



1. Mascarenhas J. et al. *Blood* 2022; 2. Jager R. et al. *Blood* 2021; 3. Quintás-Cardama A. et al *Blood* 2013; 4. Kiladjian JJ et al. *Leukemia* 2010.

Beyond PV

- Essential thrombocythemia
  - SURPASS ET showed that ropeg was superior to anagrelide in the 2L setting

- Myelofibrosis
  - HOPE PMF study is randomizing patients with prefibrotic PMF and early fibrotic PMF to ropeginterferon vs. placebo

- Combination therapy
  - RUXOPEG – phase I/II study of ruxolitinib + pegylated interferon in MF
    - No DLTs; > 50% spleen length reduction at 24 weeks in 70%
    - *JAK2* 617F VAF 84% at baseline → 53% at 1 year
  - COMBI – phase II study of ruxolitinib + pegylated interferon in PV/early MF
    - 31% and 44% of patients had ELN/IWG-defined remission; discontinuation 6% and 32%
    - *JAK2* V617F VAF 47% at baseline → 12% at 2 years ; 41% of patients had MR at 2 years

Conclusions

- Pegylated interferons are a treatment option for patients with high risk PV and select patients with low risk PV with additional clinical signs and symptoms
- Pegylated interferons are a 1L treatment option in ET in select clinical circumstances and a 2L option for patients with HU resistance/intolerance
- In patients with *JAK2 V6*17F-mutated MPN, molecular responses are more frequent in patients treated with interferons
- Pegylation improves tolerability; unique side effect profile requires careful monitoring