LONG TERM OUTCOMES OF INTERFERON IN MPNS

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Long-term outcomes of polycythemia vera patients treated with ropeginterferon Alfa-2b

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Leukemia (2022) 36:1408–1411; https://doi.org/10.1038/s41375-022-01528-x

Updated results presented at EHA 2024

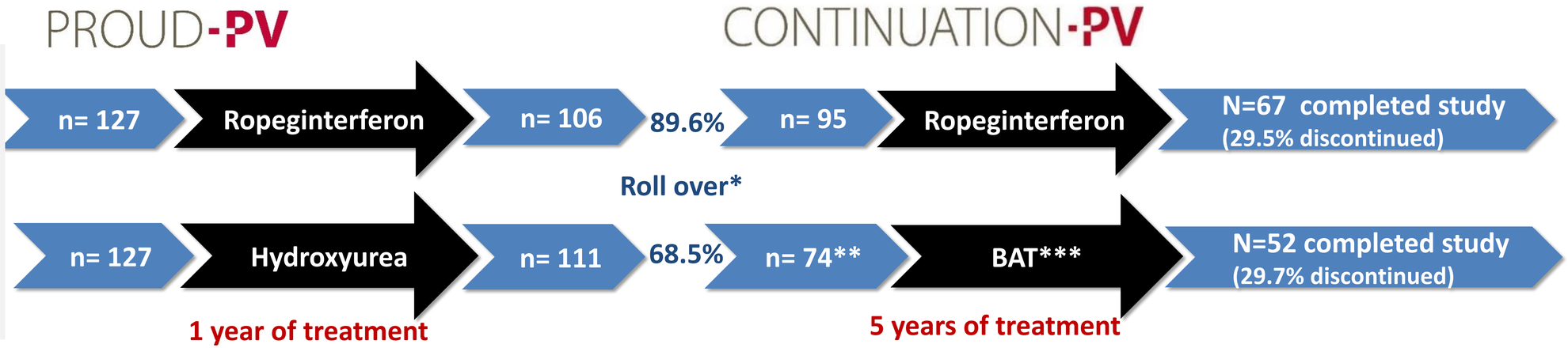
Kiladjian JJ et al. Leukemia. 2022;36(5):1408-1411

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.
- 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.

Naïve patients and HU pre-treated patients (<3 years, not full responders) **randomized**

Stratified by: age, prior thromboembolic event, prior HU



*There were no significant differences between patients who entered CONTINUATION-PV study 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

Final study results confirm higher response rates for ropeginterferon alfa-2b versus control treatment at 6 years

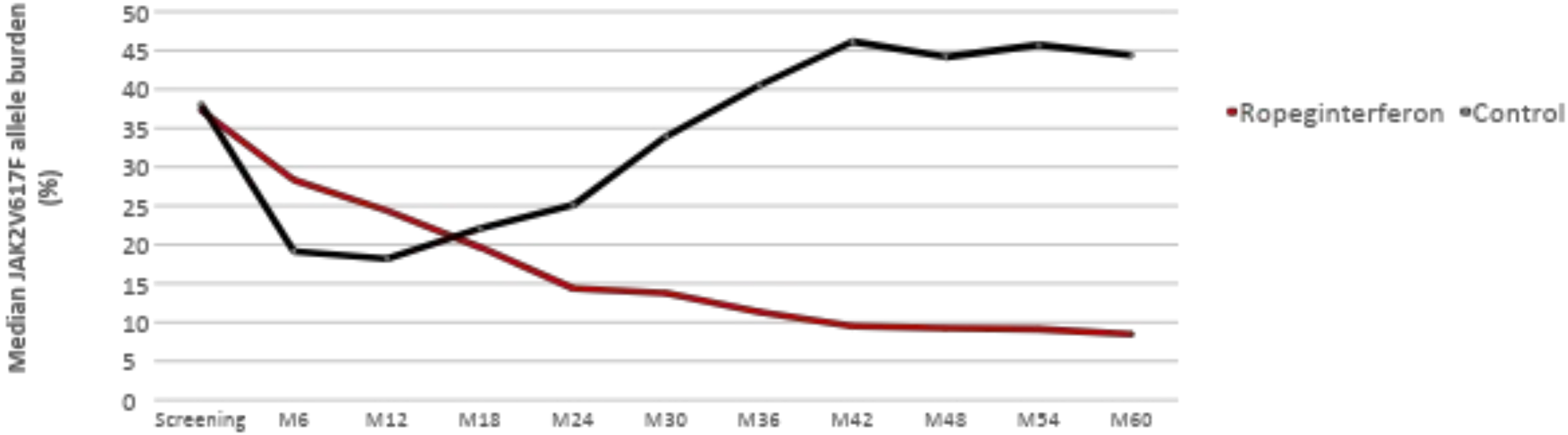
Results from CONTINUATION-PV at 6 years agreed with previously published interim analyses,[1,2] demonstrating higher rates of complete hematologic response (CHR) and molecular response (MR [partial/complete] using ELN criteria) among ropeginterferon alfa-2b treated patients compared to the control group

	Ropeginterferon N=95		Control N=74		RR (95% CI)	P-value
CHR*	48/88	54.6%	22/63	34.9%	1.55 (1.07 to 2.26)	**p=0.02**
MR*	62/94	66.0%	14/72	19.4%	3.23 (2.01 to 5.19)	**p<0.0001**

Full analysis set

[1] Gisslinger et al. Lancet Haematol. 2020 Mar;7(3):e196-e208
[2] Kiladjian et al. Leukemia. 2022 May;36(5):1408-1411.
*CHR based on blood counts; MR according to ELN criteria (Barosi et al Blood. 2009 May 14;113[20:4829-33] with last observation carried forward

Median *JAK2*V617F allele burden (LOCF)



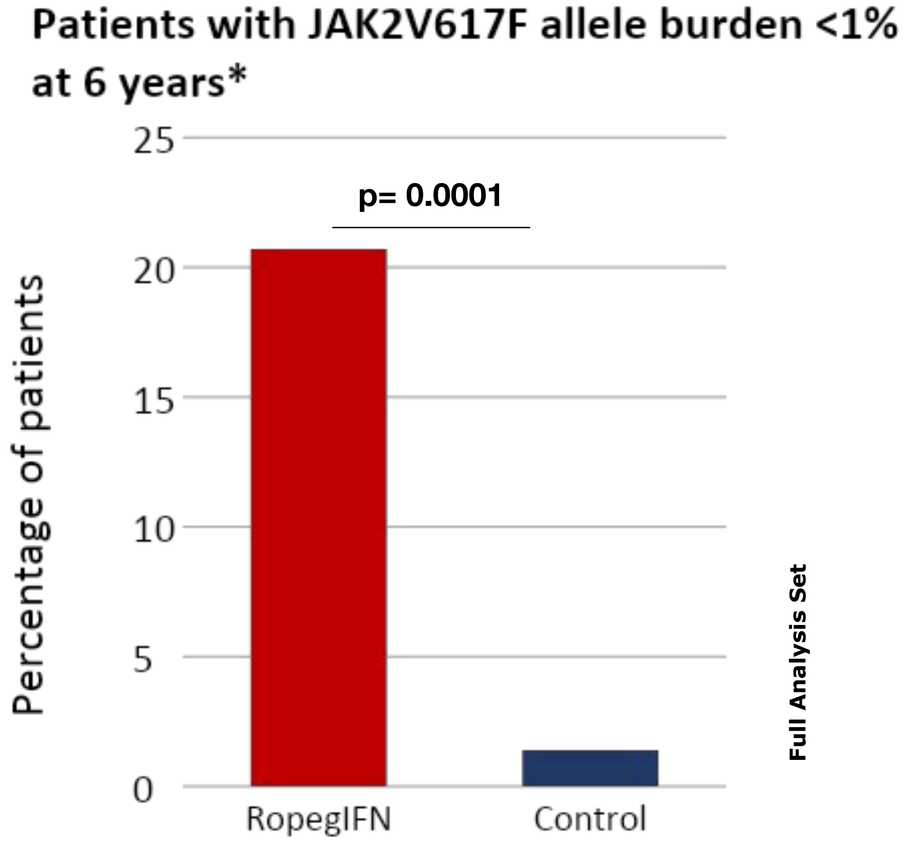
Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN/Control)
	Mean	Median	Mean	Median		
Baseline	42.8	37.3	42.9	38.1	-	-
MONTH 12	30.2	24.4	24.4	18.2	0.0244	6.646 (0.86 to 12.43)
MONTH 24	20.9	14.3	32.4	25.1	0.0003	-10.745 (-16.50 to -4.98)
MONTH 36	19.7	11.3	39.3	40.5	<0.0001	-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

Kiladjian JJ et al. *Leukemia*. 2022;36(5):1408-1411

Potential disease modification

- Depletion of the *JAK2*V617F allele burden may lower the risk of progression of PV to secondary myelofibrosis.[1,2]
- After 6 years of treatment, the *JAK2*V617F allele burden decreased to <1% in **20.7%** of patients in the ropeginterferon alfa-2b arm.
- In contrast, only **1.4%** of patients in the control arm achieved an allele burden <1% at 6 years of treatment (p=0.0001).



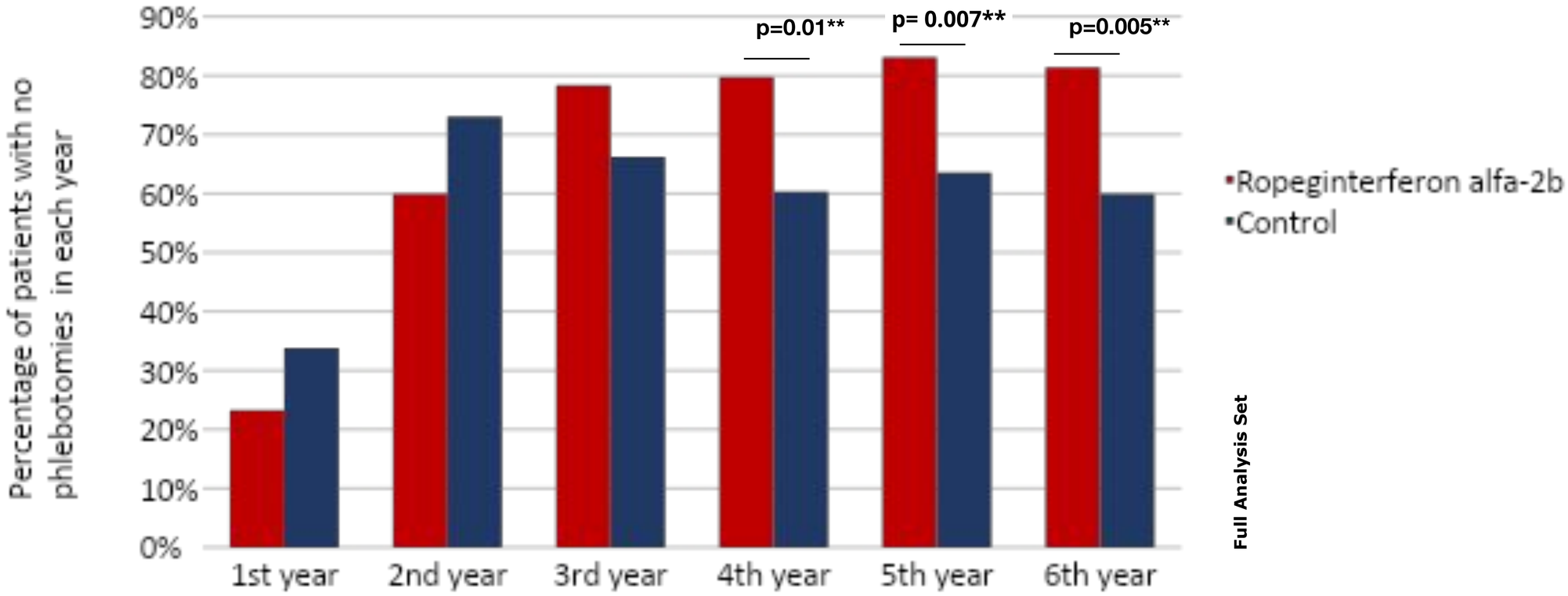
*Analyzed in patients with baseline allele burden >10%; last observation carried forward

[1] Alvarez-Larrán et al., 2014 Am J Hematol. 2014 May;89(5):517-23
[2] Passamonti et al., 2010. Leukemia. 2010 Sep;24(9):1574-9

ADDITIONAL BENEFITS OF ROPEG-IFN THERAPY IN PROUD-CONTI

- DECREASE OF PHLEBOTOMY NEEDS
- IMPROVEMENT IN SYMPTOMS
- IMPROVEMENT IN EVENT-FREE SURVIVAL

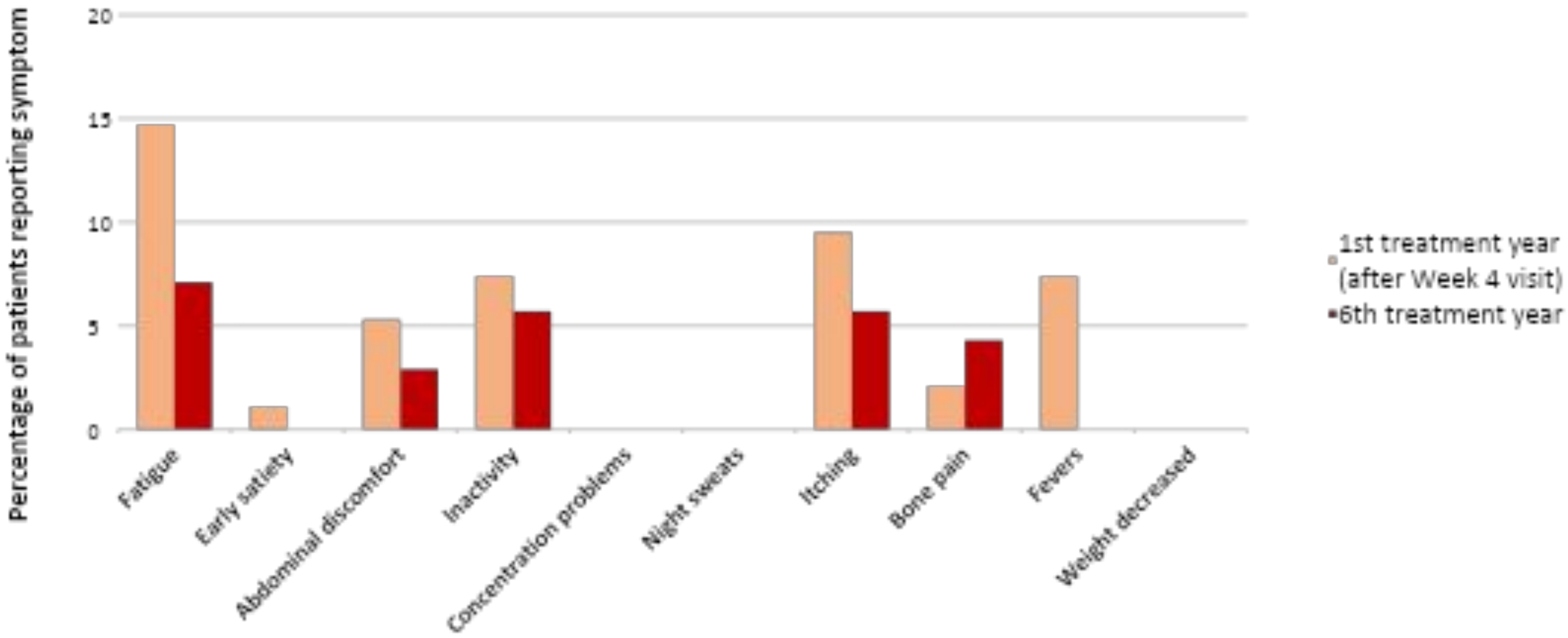
Freedom from phlebotomy



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)

Change in occurrence of symptoms during ropeginterferon alfa-2b treatment: Year 1 versus Year 6



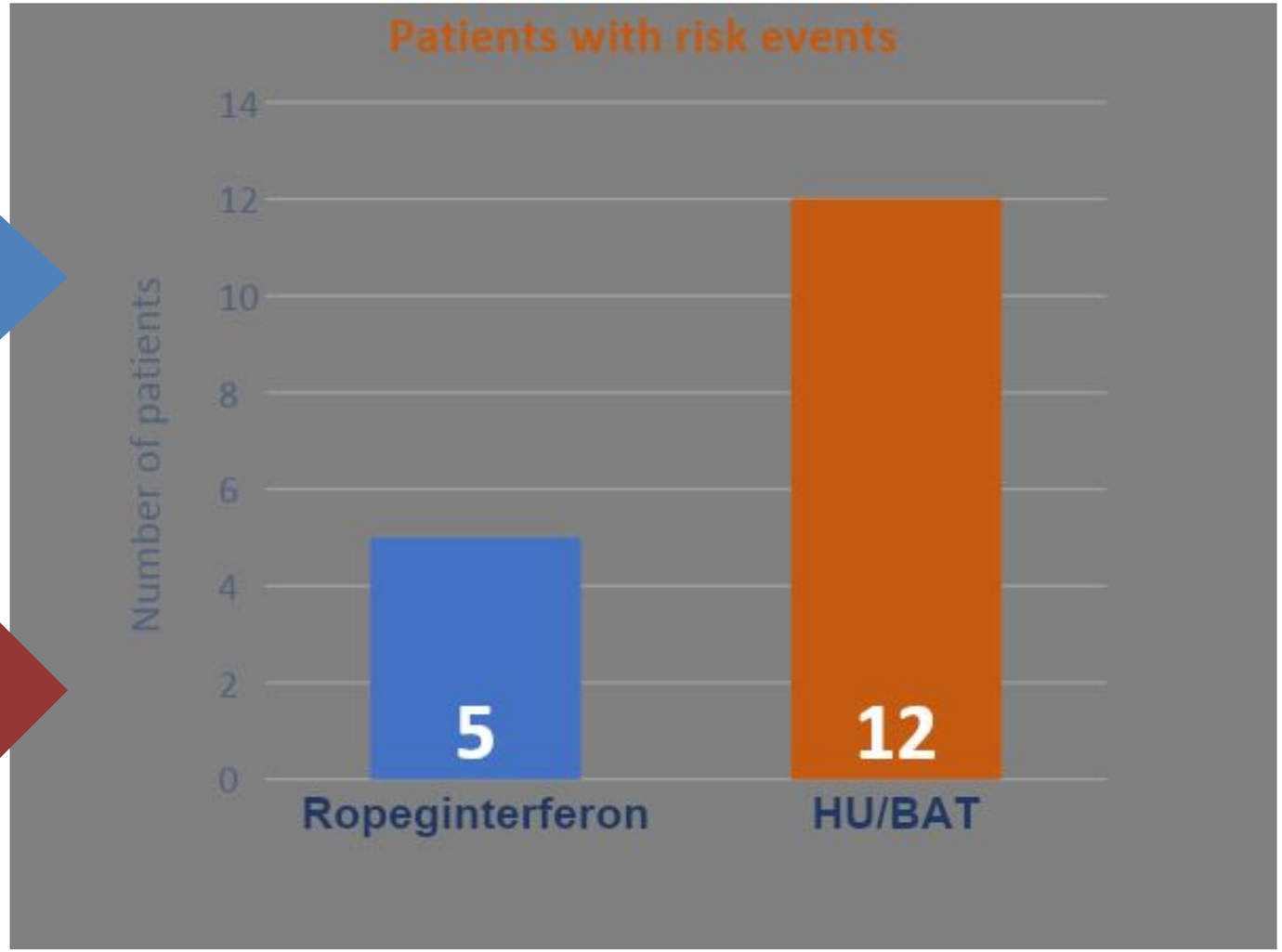
Occurrence of symptoms defined in the MPN-SAF-TSS ("MPN-10") was lower in the 6th year of treatment with ropeginterferon alfa-2b than during the 1st year (from Week 4) for 6 of the 10 symptoms

Risk events over the entire study period

Risk events: death, disease progression and thromboembolic events

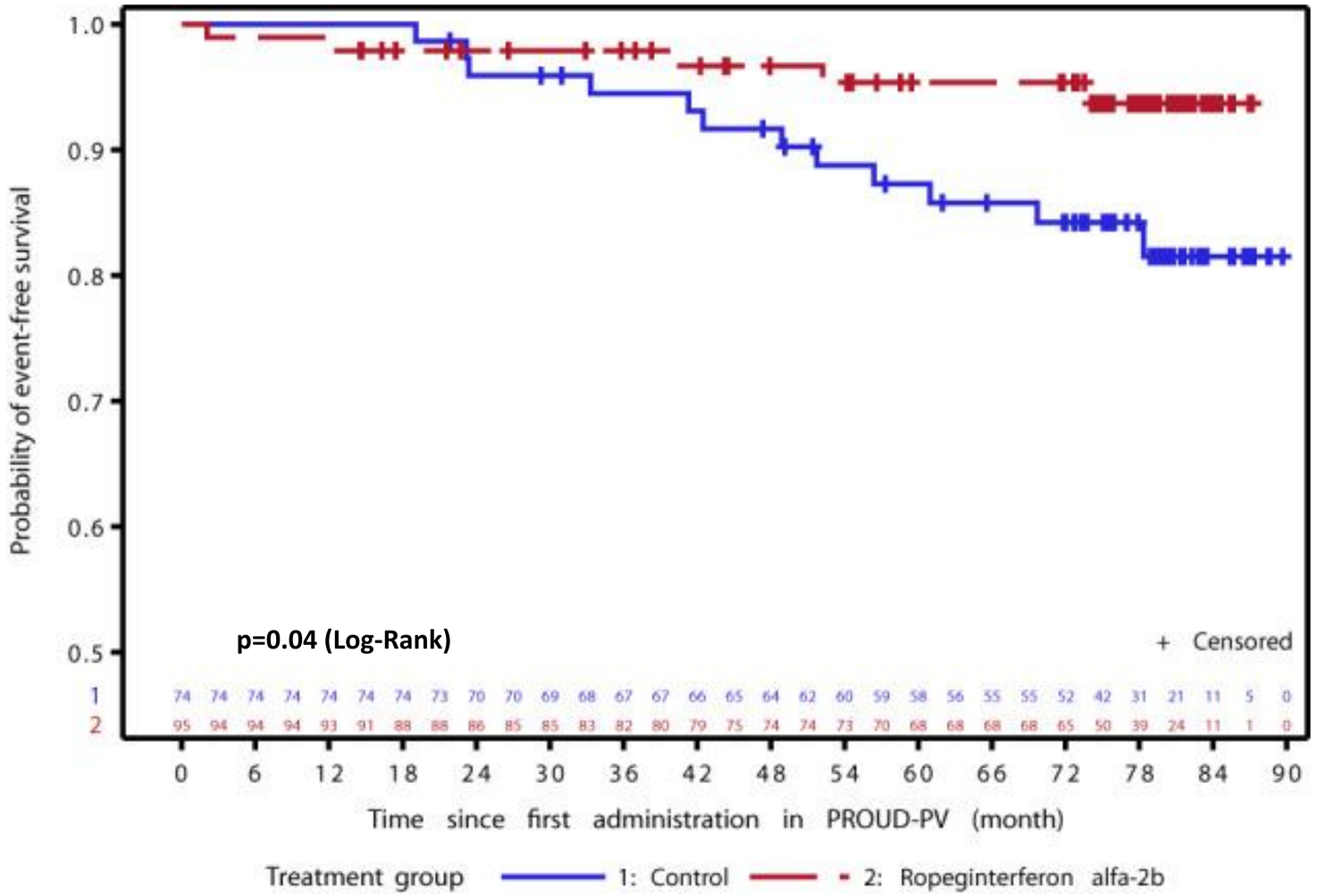
Ropeginterferon
6.3 years‘ median follow-up
568 patient-years

HU/BAT
6.0 year‘s median follow-up
451 patient-years



Event-free survival

Risk events: death, disease progression and thromboembolic events

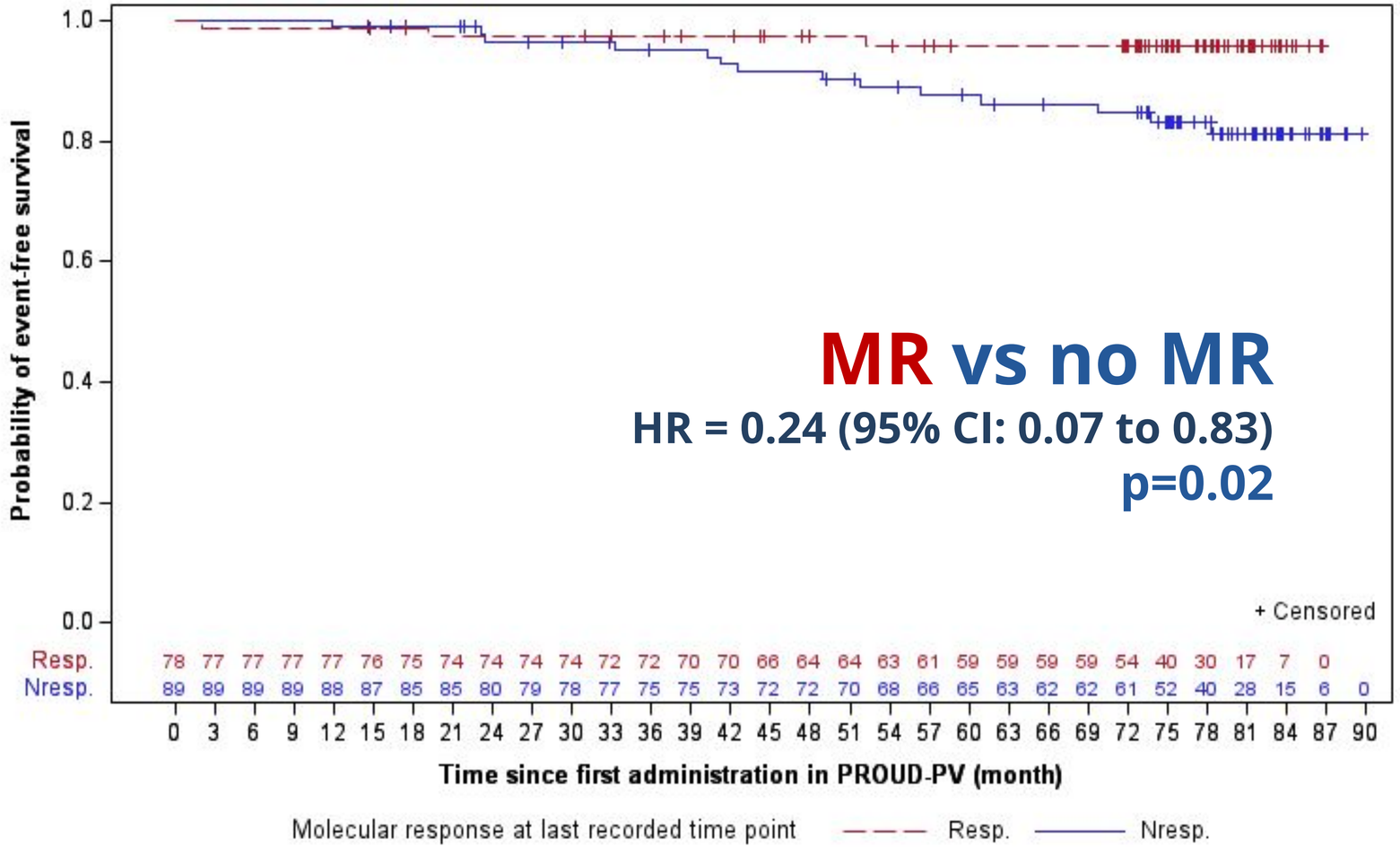


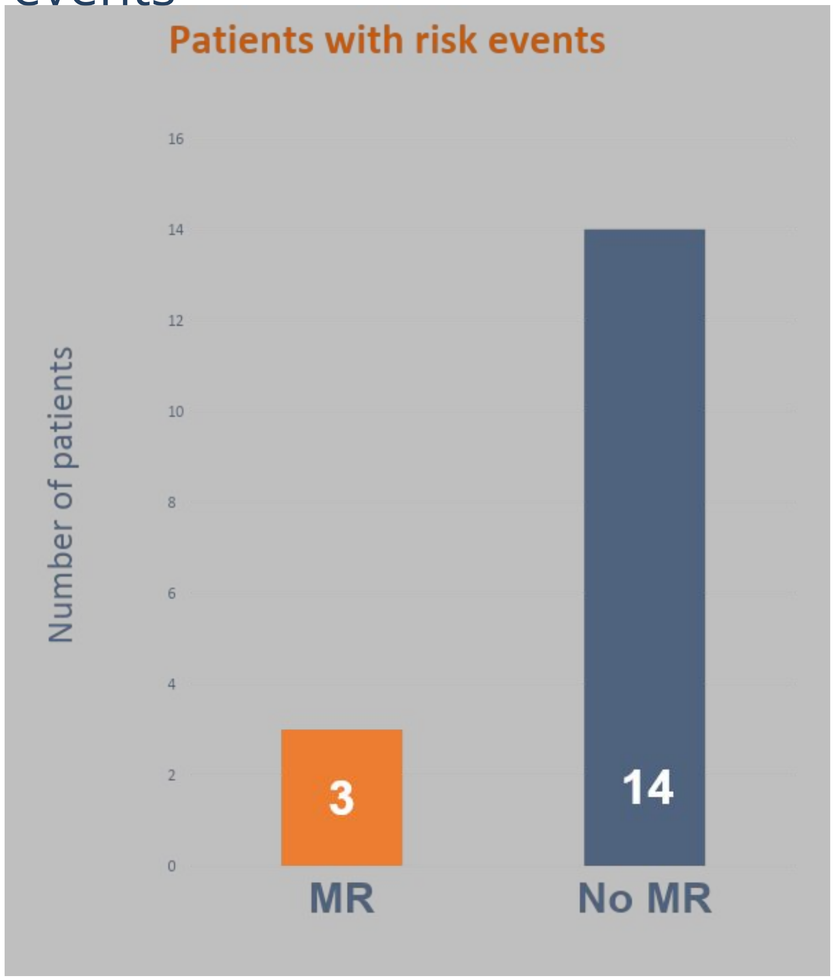
The probability of event-free survival was significantly higher among patients treated with ropeginterferon alfa-2b compared to the control arm (maximum treatment period 7.3 years)

Gisslinger et al., Leukemia, 2023; 37, 2129–2132

Event-free survival by molecular response

- Risk events occurred in only 3 (3.8%) of the patients who had a MR at their last available assessment
- In those with no MR at their last assessment, 14 (15.7%) had risk events



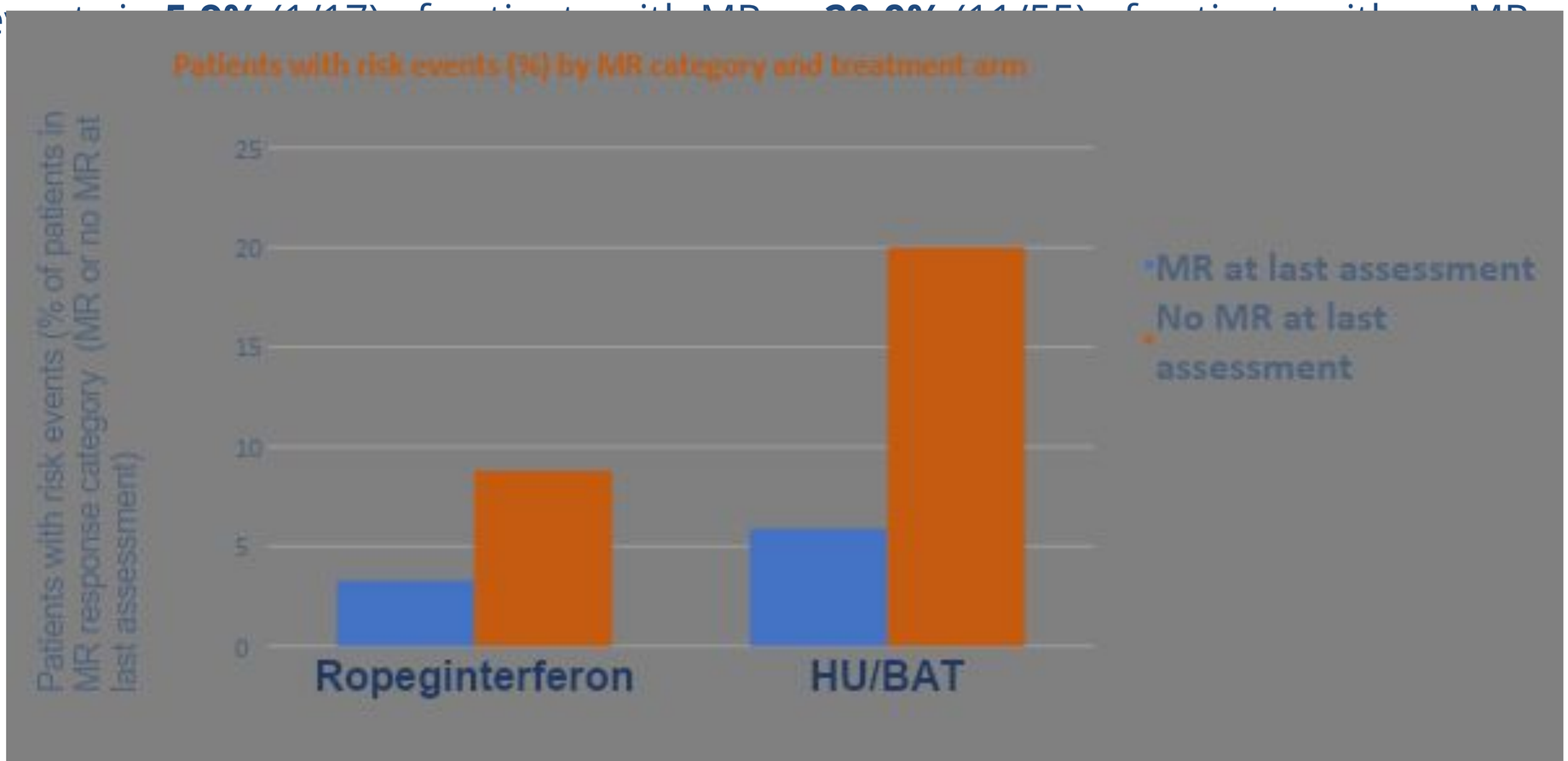


Risk events by MR and treatment arm

The overall trend indicating improved event-free survival in patients with MR at the last available assessment was also observed within each treatment arm.

Ropeginterferon alfa-2b arm: events in **3.3%** (2/61) of patients with MR vs **8.8%** (3/34) of patients with no MR

Control arm: e



Comparable findings in other PV studies

- Better EFS in patients achieving molecular response : MAJIC-PV

- Decreased risk of progression and better survival with IFN: Cornell retrospective study

Original Reports | Hematologic Malignancy

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

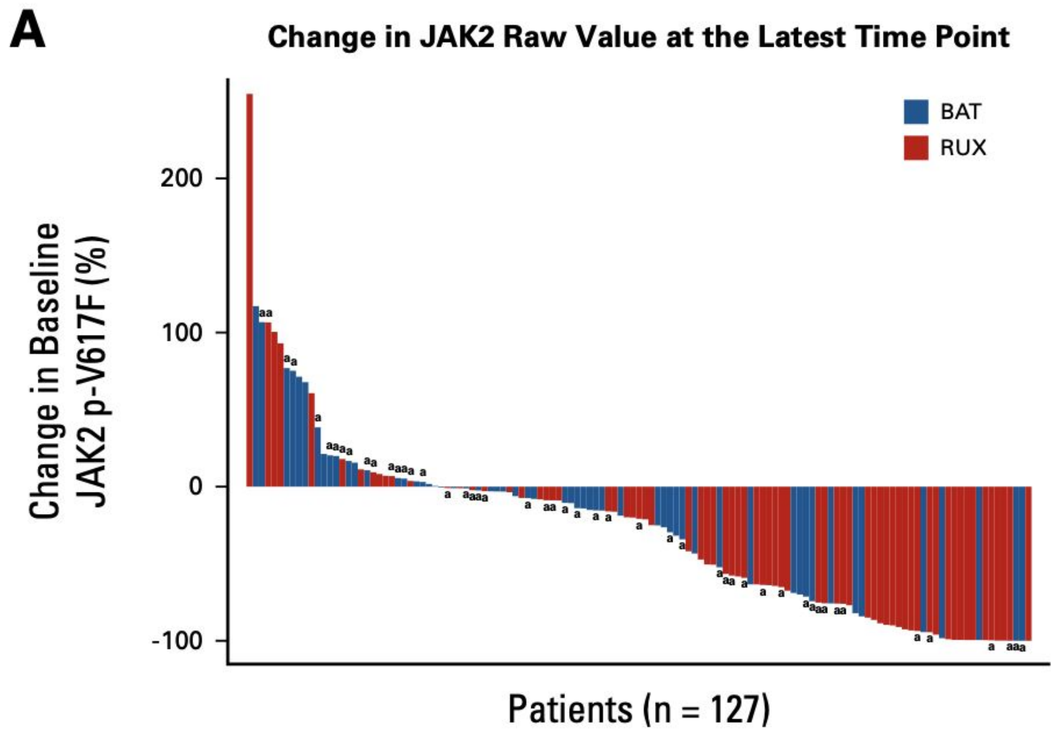
Claire N. Harrison, DM, FRCP[1]; Jyoti Nangalia, MB BChir, PhD[2,3,4]; Rebecca Boucher, PhD[5]; Aimee Jackson, MSc[5]; Christina Yap, PhD[5,6]; Jennifer O'Sullivan, MB BCh BAO[1,7]; Sonia Fox, BSc[5]; Isaak Ailts, MD[8]; Amylou C. Dueck, PhD[9]; Holly L. Geyer, MD[8]; Ruben A. Mesa, MD, FACP[10]; William 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]

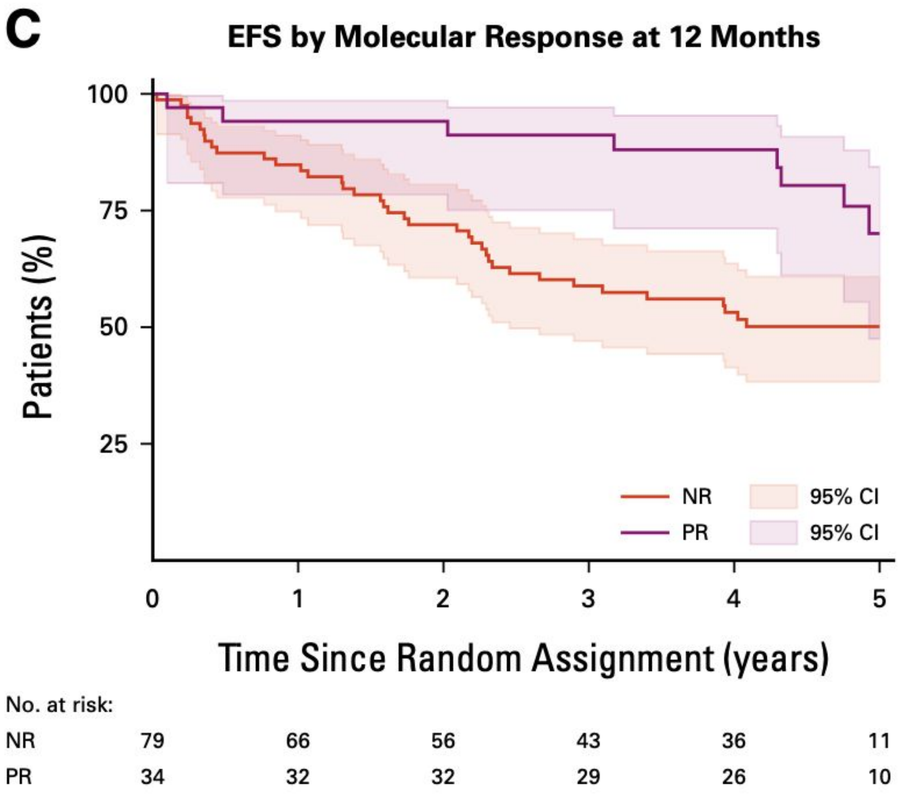
DOI https://doi.org/10.1200/JCO.22.01935

Harrison et al. *J Clin Oncol*. 2023;41(19):3534-3544

JAK2V617F VAF, molecular response and clinical endpoints:

Those achieving molecular response at 1 year had superior EFS





No. at risk:

NR	79	66	56	43	36	11
PR	34	32	32	29	26	10

Harrison et al. *J Clin Oncol*. 2023;41(19):3534-3544

JAK2V617F VAF, molecular response and clinical endpoints:

Those achieving molecular response at 1 year had superior EFS

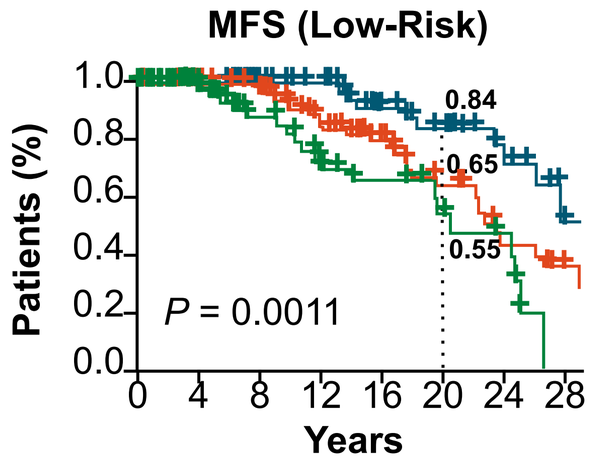
Those with durable molecular response at last time point had significant improvements in EFS, PFS and OS regardless of treatment arm

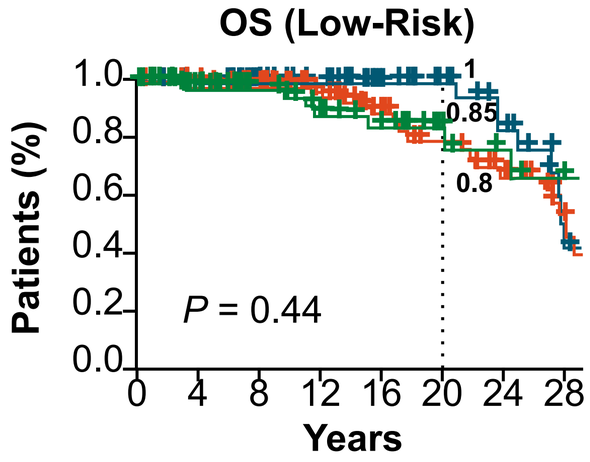
	Any Treatment			
Outcome	Whole Trial (n = 127), Events, No. (%)	NR[a] (n = 74), Events, No. (%)	PR[b] (n = 53), Events, No. (%)	*P*
Thromboembolic event[c]	38 (30)	28 (38)	10 (19)	.02
Hemorrhagic event[c]	28 (22)	23 (31)	5 (9)	.004
Progression-free survival[c]	35 (28)	29 (39)	6 (11)	.001
EFS[c]	53 (42)	40 (54)	13 (25)	.001
OS[c]	22 (17)	18 (24)	4 (8)	.01
CR achieved at 1 year	49 (39)	22 (30)	27 (51)	.02

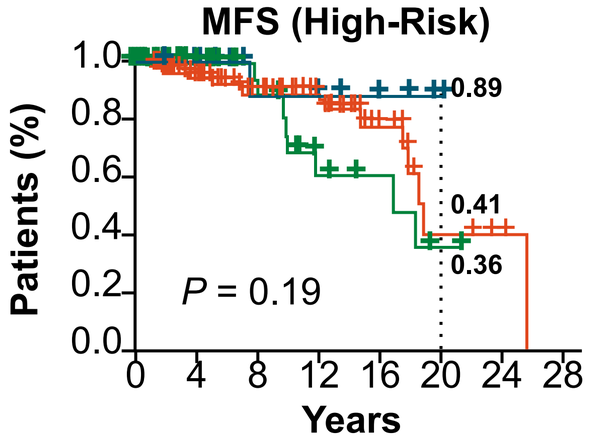
Harrison et al. *J Clin Oncol*. 2023;41(19):3534-3544

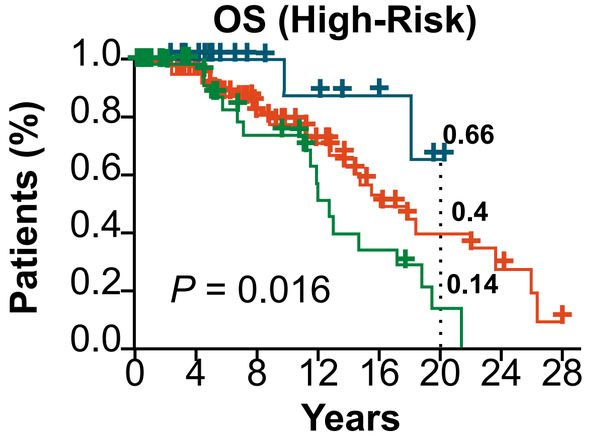
Decreased Risk of Disease Progression and Favorable Survival

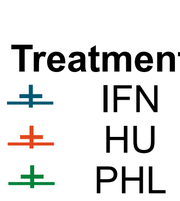
Single-center retrospective chart review of patients with PV (N=470)

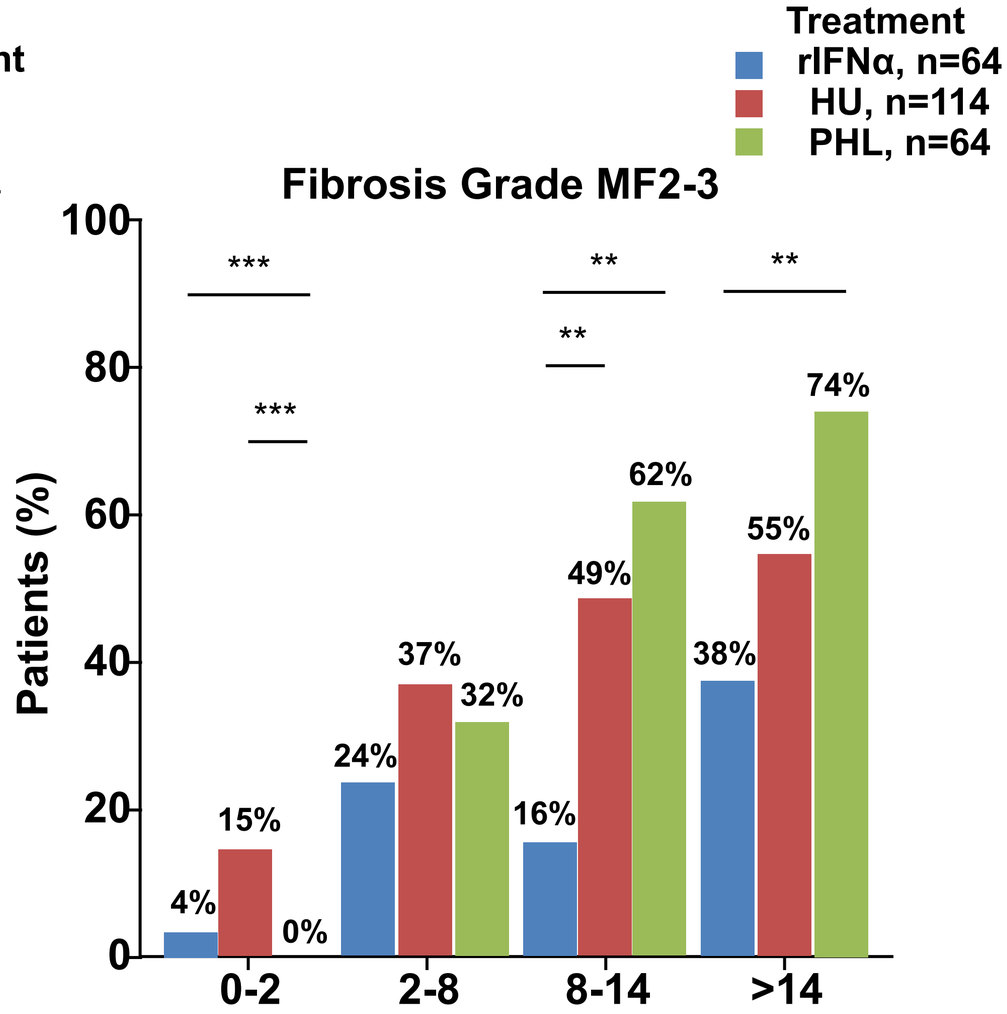












MFS = myelofibrosis-free survival.

Abu-Zeinah G, et al. *Leukemia*. 2021;35(9):2592-2601.

Courtesy R. Rampal

LONG-TERM SAFETY OF ROPEG-IFN THERAPY IN PROUD-CONTI

Safety profile overview:

Number of patients (%) with adverse events

	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

Adverse drug reaction= treatment-related AE
Safety Population; all patients dose at least once in PROUD-PV

Kiladjian JJ et al. *Leukemia*. 2022;36(5):1408-1411

Adverse drug reactions of special interest to IFN therapy*

In ropeginterferon-treated patients (N=127)

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

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

Kiladjian JJ et al. *Leukemia*. 2022;36(5):1408-1411

Skin toxicity

Skin AEs reported more than once in either arm; all skin neoplasms

Adverse event	Ropeginterferon (N=127)		Control (N=127)	
	AE	n (%)	AE	n (%)
Skin ulcer	**-**	**-**	**11**	**7 (5.5%)**
Rash	3	3 (2.4%)	7	5 (3.9%)
Dry skin	2	2 (1.6%)	5	5 (3.9%)
Actinic keratosis	-	-	2	2 (1.6%)
Dermatitis	-	-	2	2 (1.6%)
Rosacea	-	-	2	2 (1.6%)
Basal cell carcinoma	**-**	**-**	**2**	**2 (1.6%)**
Fibrous histiocytoma	**-**	**-**	**2**	**1 (0.8%)**
Malignant melanoma	**-**	**-**	**1**	**1 (0.8%)**
Hyperhidrosis	4	4 (3.1%)	1	1 (0.8%)
Psoriasis	2	2 (1.6%)	1	1 (0.8%)
Eczema	6	1 (0.8%)	1	1 (0.8%)
Xeroderma	4	2 (1.6%)	-	-
Alopecia	9	6 (4.7%)	-	-

Kiladjian JJ et al. *Leukemia*. 2022;36(5):1408-1411

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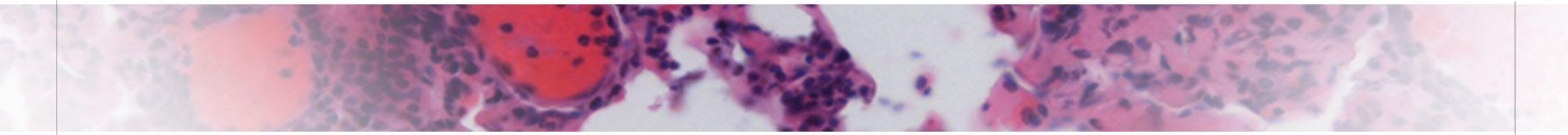

Interferon-alpha therapy discontinuation is feasible in MPN patients with complete hematological remission

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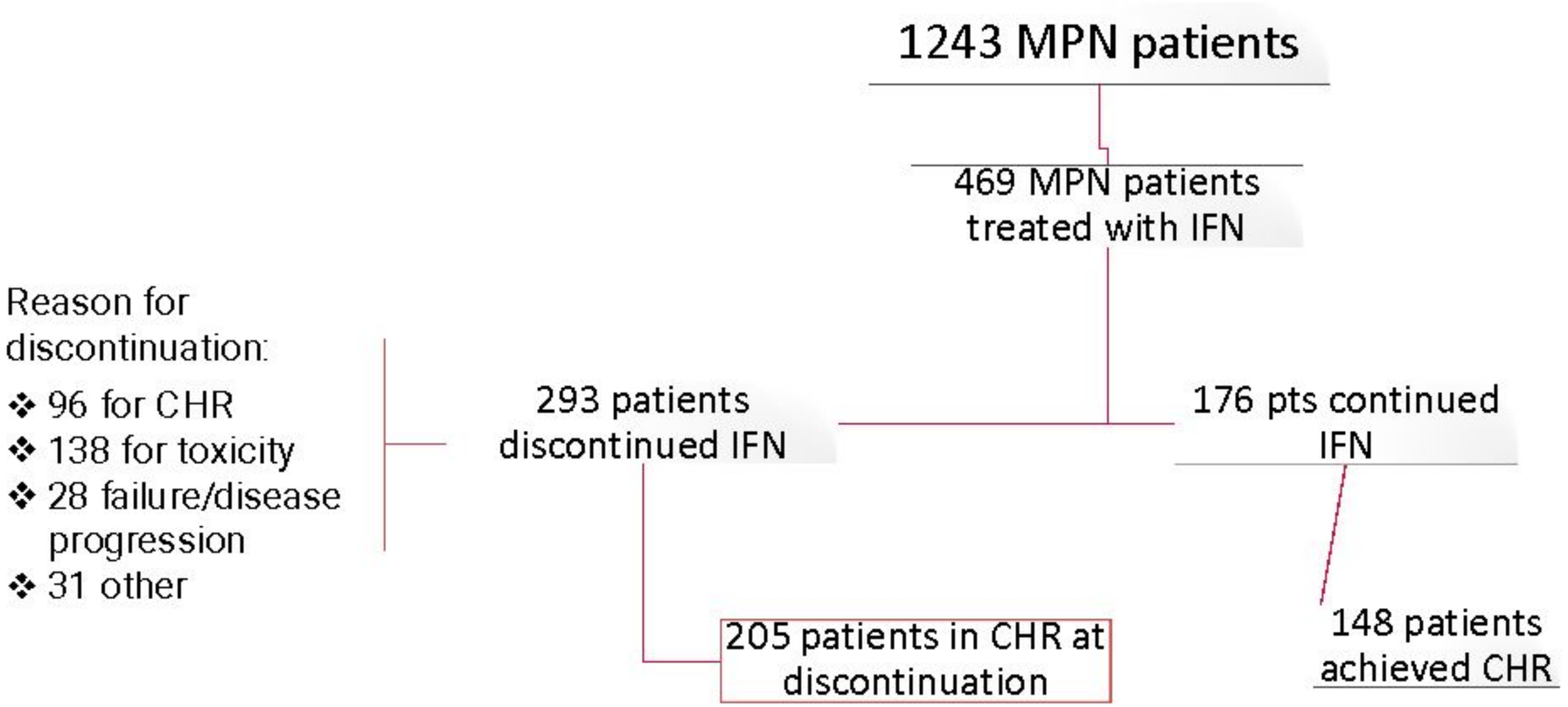
Hématologie I Immunologie I Oncologie

Methods

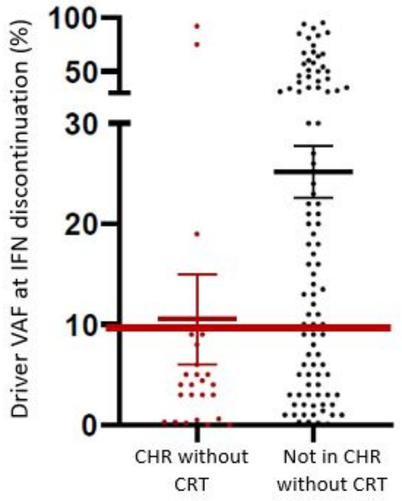


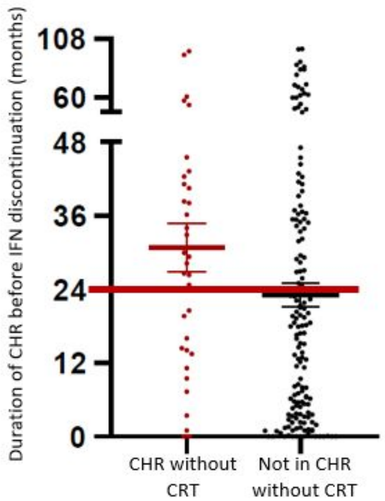
- **MPN patients diagnosed (WHO criteria) between January 2000 to August 2020**
- **All patients received at least 3 months of IFNα treatment.**
- **Discontinuation was defined as a minimum of 3 months of IFNα interruption.**

Results

Factors associated with persistent CHR: logistic regression model

Variables	Univariate analysis		
	OR	95% CI	pval
Age at IFN discontinuation	0,985	[0.965; 1.005]	0,145
Female	1,62	[0.851; 3.087]	0,142
MPN subtype			
ET	1	.	.
PV	0,512	[0.266; 0.985]	**0,045**
PMF	0,598	[0.165; 2.171]	0,434
Driver mutation			
JAK2 V617F	1	.	.
CALR	1,006	[0.434; 2.327]	0,990
MPL	1,006	[0.211; 4.784]	0,994
Triple negative	2,285	[0.749; 6.976]	0,147
Cytoreductive treatment before IFN	1,421	[0.689; 2.931]	0,341
Number of lines before IFN	0,916	[0.619; 1.354]	0,659
Reasons for IFN start			
Young age (< 50y)	1	.	.
Resistance	0,829	[0.333; 2.062]	0,687
Intolerance	1,500	[0.577; 3.899]	0,405
Pregnancy	1,500	[0.286; 7.856]	0,631
Other	0,675	[0.297; 1.532]	0,347
Reasons for IFN discontinuation			
CR, CHR	1	.	.
Other (toxicity, failure…)	0,213	[0.113; 0.403]	**<0.001**
Time from MPN diagnosis to IFN start ≥ 36 months	1,373	[0.749; 2.515]	0,305
Time to obtain CR/CHR ≥ 6 months	1,202	[0.567; 2.548]	0,631
Duration of CR/CHR before IFN discontinuation ≥ 24 months	2,969	[1.390; 6.341]	**0,005**
Cumulative dose of IFN at time of discontinuation (ug), median (IQR)	1,000	[0.999; 1.000]	0,427
Driver VAF at time of IFN discontinuation ≥ 10%	0,087	[0.024; 0.311]	**<0.001**
Number of additionnal mutations	0,906	[0.667; 1.233]	0,531
HMR mutations	0,831	[0.296; 2.337]	0,726

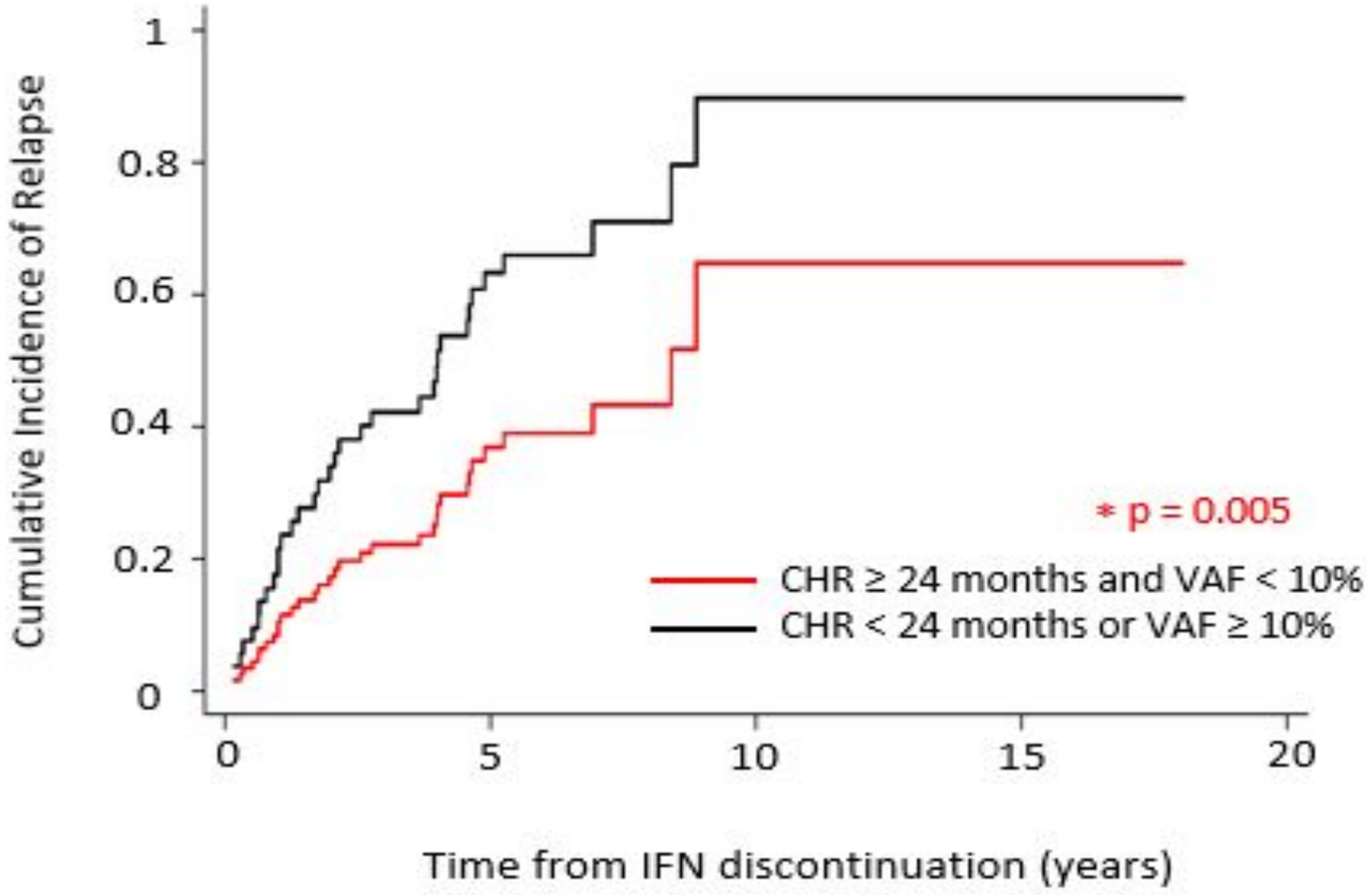




Variables	Multivariate analysis		
	OR	95% CI	pval
Driver VAF at time of IFN discontinuation ≥ 10%	0,128	[0.025; 0.638]	**0,012**
Duration of CR/CHR before IFN discontinuation ≥ 24 months	14,612	[1.765; 120.944]	**0,013**

Results

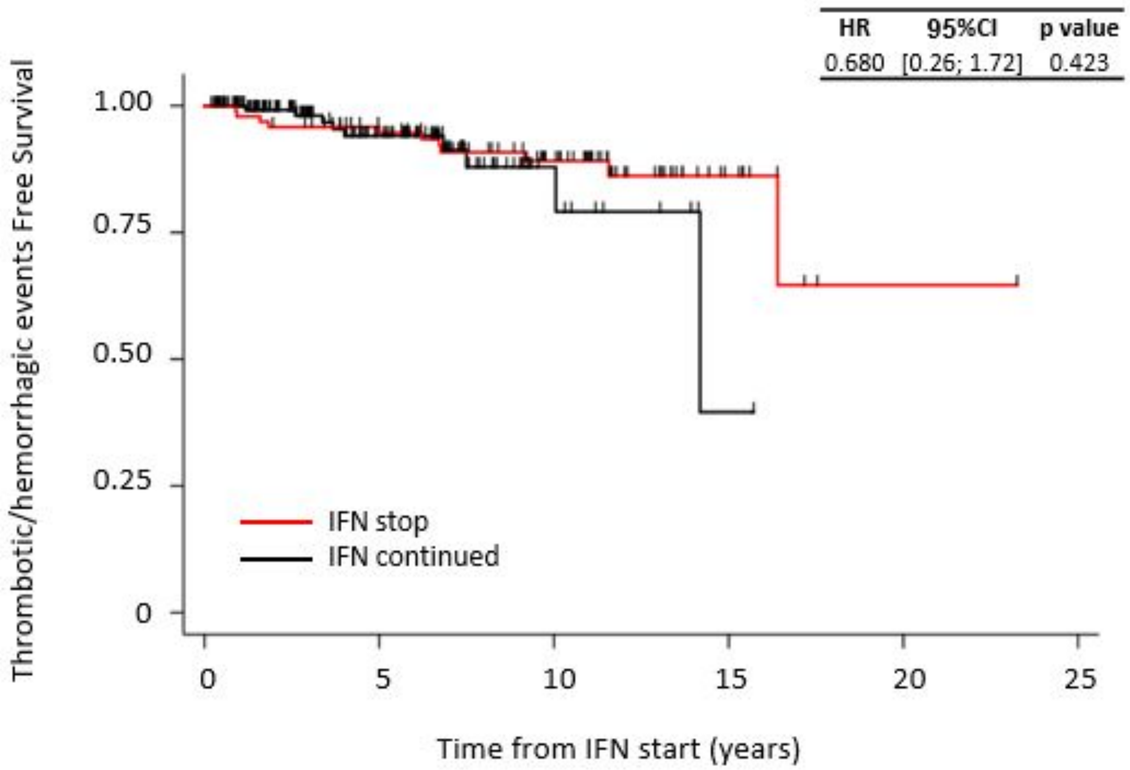
Factors associated with post-discontinuation relapse: COX regression model



Results

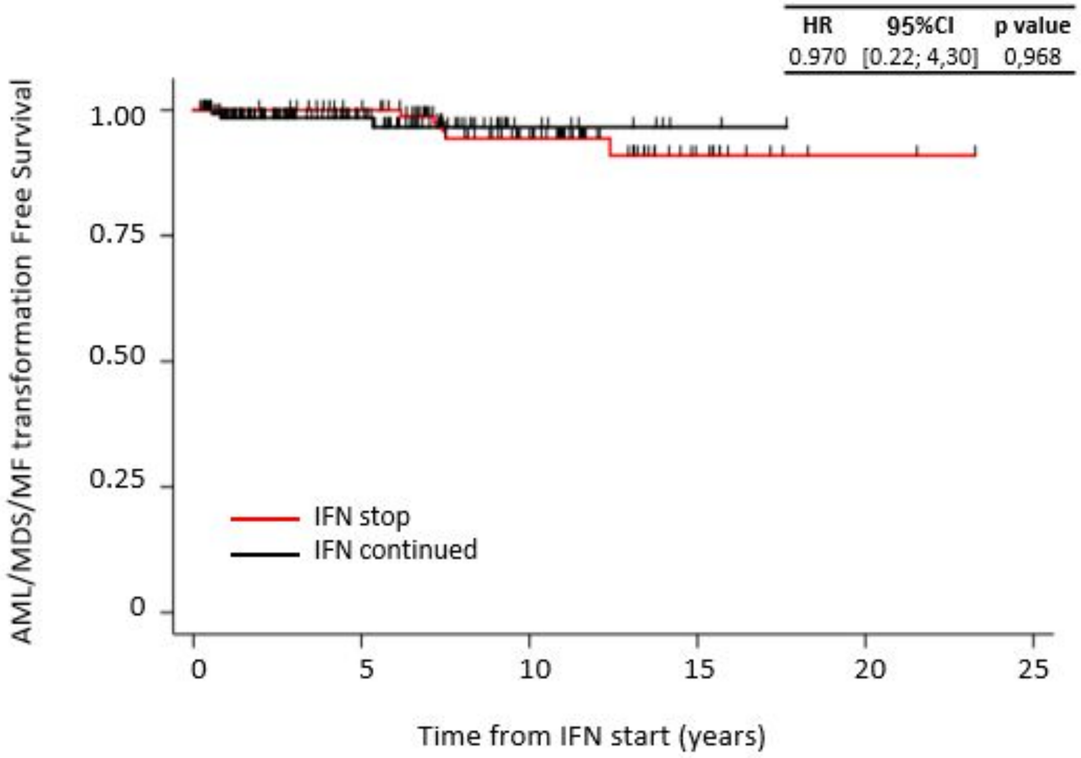
Post-discontinuation outcomes: event free survival

Median EFS : 170 months IFN continued *vs* Not Reached in IFN discontinued



Number at risk						
IFN continued	148	57	10	1	0	0
IFN stop	96	82	45	9	1	0

Median EFS : NR for both groups

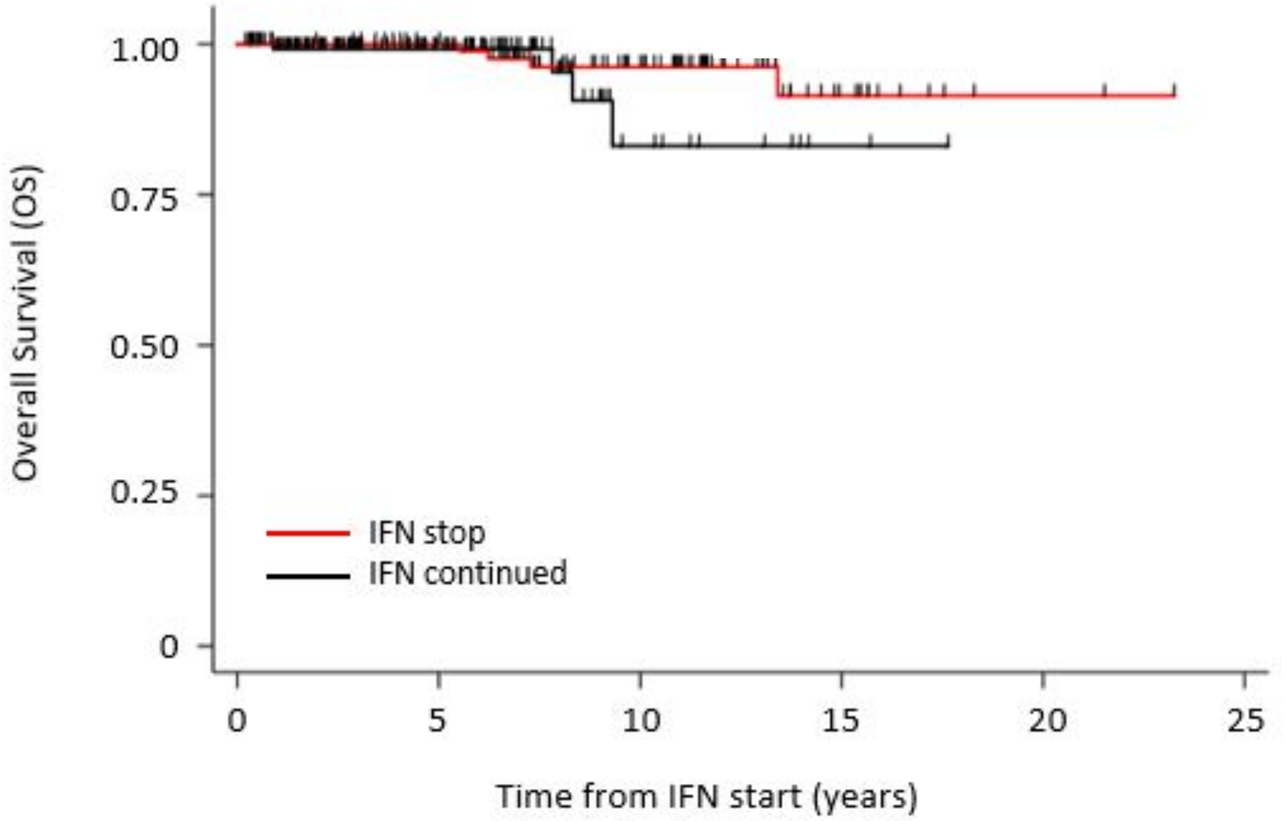


Number at risk						
IFN continued	148	57	10	2	0	0
IFN stop	96	86	49	12	2	0

Results

Post-discontinuation outcomes: overall survival

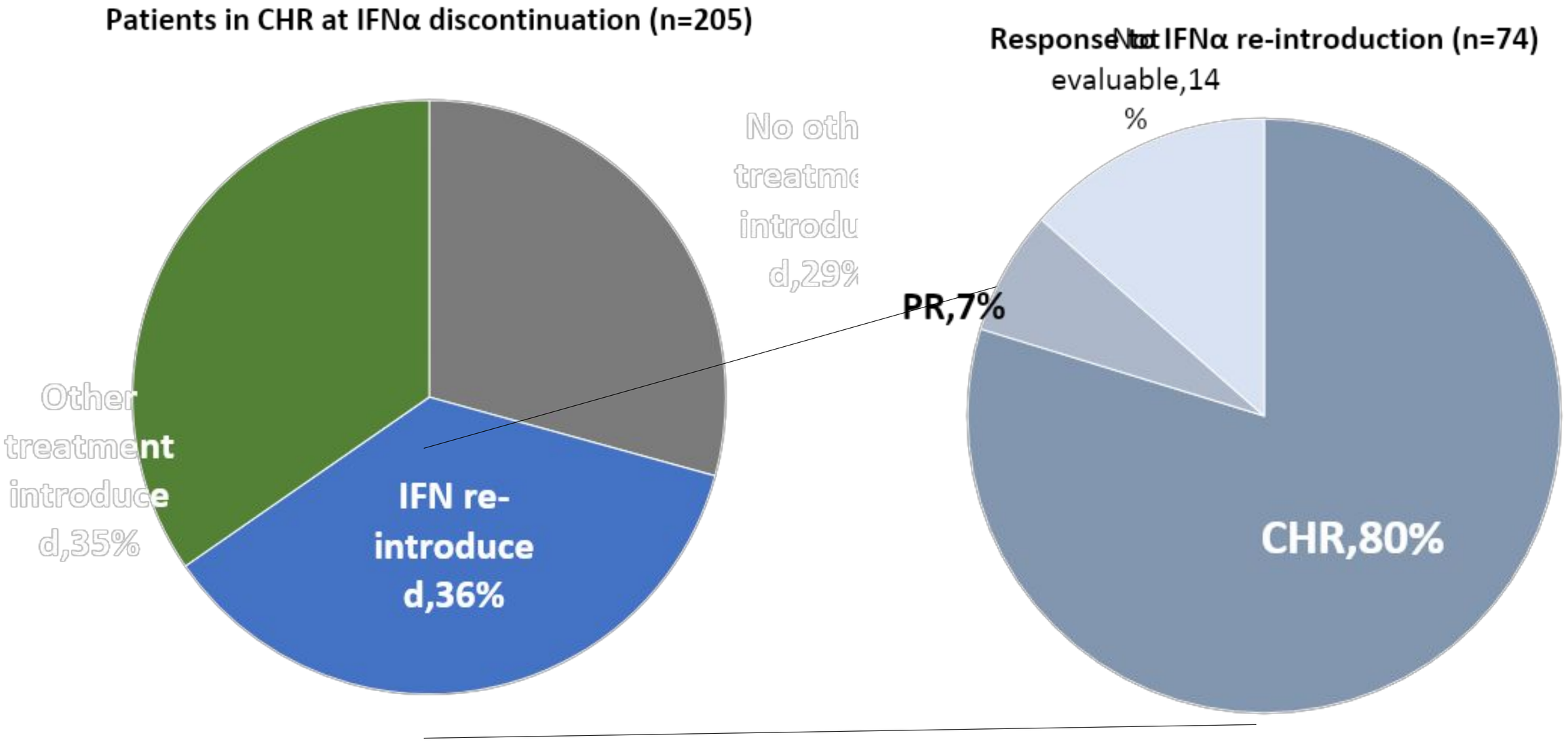
Median OS : NR for both groups



Number at risk						
IFN continued	148	58	10	2	0	0
IFN stop	96	86	51	12	2	0

Results

Post-discontinuation outcomes: response to IFN re-introduction



*It is not enough to know the science; one must know **HOW** to apply it.*

Marcus Tullius Cicero

Safety profile

Main adverse reactions include:

- Flu-like symptoms
- Endocrine and metabolic (thyroid, diabetes)
- Auto-immunity
- Neuro-psychiatric effects
- …

Treatment initiation

Start at low dose, titration until CHR

Peg-IFNa 2a : 45 mcg/w, increase by 45 mcg/ 2w

Max: 180 mcg/w

Ropeg-IFNa 2b: 100 mcg/ 2w, increase by 50 mcg/2w

Max: 500 mcg/2w

Dose adjustments

Possible decrease after one year of CHR

- Peg-IFNa 2a : by 45 mcg/injection every 6 months
  by expanding the interval

- Ropeg-IFNa 2b: by 50 mcg/injection every 6 months
  by expanding the interval

Maintain the lowest sufficient dose or consider discontinuation

Nothing in life is to be feared, it is only to be understood.

Now is the time to understand more, so that we may fear less.

Marie Curie