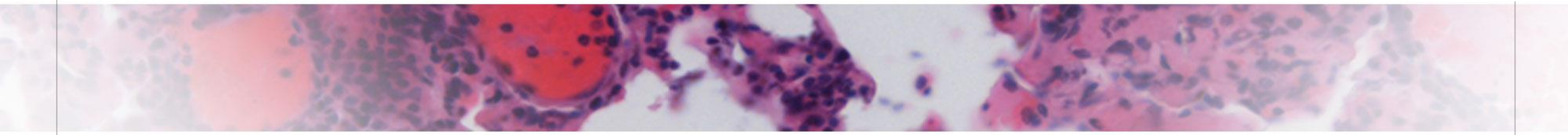
THE FUTURE OF INTERFERON IN MPN

Jean-Jacques KILADJIAN

Clinical Investigation Center, Hôpital Saint-Louis

Université de Paris, Paris, France

American Society of Hematology
Helping hematologists conquer blood diseases worldwide



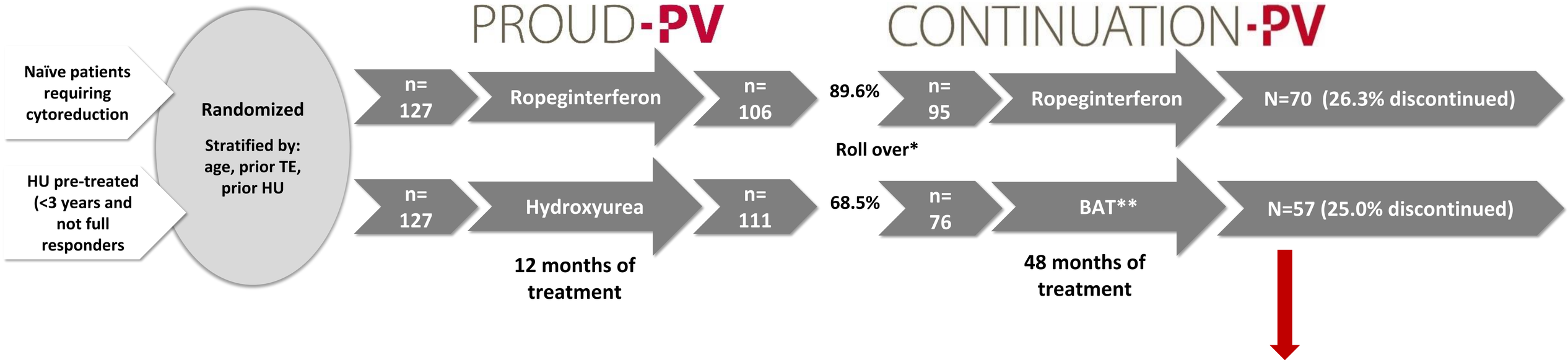
Long-Term Use of Ropeginterferon Alpha-2b in Polycythemia Vera: 5-Year Results from a Randomized Controlled Study and its Extension

Heinz Gisslinger, MD, Christoph Klade, PhD, Pencho Georgiev, MD, Dorota Krochmalczyk, MD, Liana Gercheva-Kyuchukova, MD, Miklos Egyed, MD, Petr Dulicek, MD, Arpad Illes, MD, Halyna Pylypenko, MD, Lylia Sivcheva, MD, Jiří Mayer, MD, Vera Yablokova, MD, Kurt Krejcy, MD, Victoria Empson, MSc, Hans C. Hasselbalch, MD, Robert Kralovics, PhD and Jean-Jacques Kiladjian, MD PhD for the PROUD-PV Study Group

Ropeginterferon alfa-2b (AOP2014/P1101)

- **New generation monopegylated Interferon alfa-2b** single isoform due to innovative pegylation technology
- **Administration under the skin once every 14 days** (once monthly in long-term maintenance)
- **European Medicines Agency approval in 2019** for the treatment of PV in adults without symptomatic splenomegaly

Phase III studies PROUD-PV and CONTINUATION-PV:
Design and patient disposition



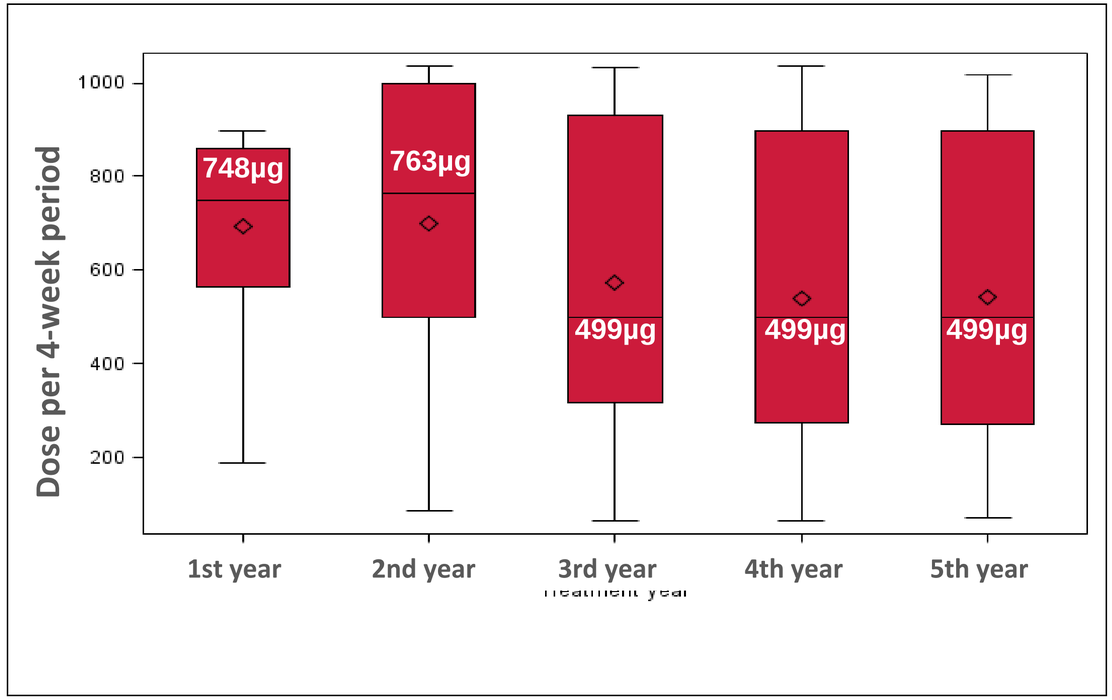
* There were no significant differences between patients who entered CONTINUATION-PV study and those who did not roll-over.
** Control group received best available treatment (BAT); 88% of patients received HU as of last available assessment)

60 MONTH INTERIM ANALYSIS:
Efficacy data up to month 60
All safety data up to database lock on 29.05.2020
(up to 6.3 years of treatment overall)

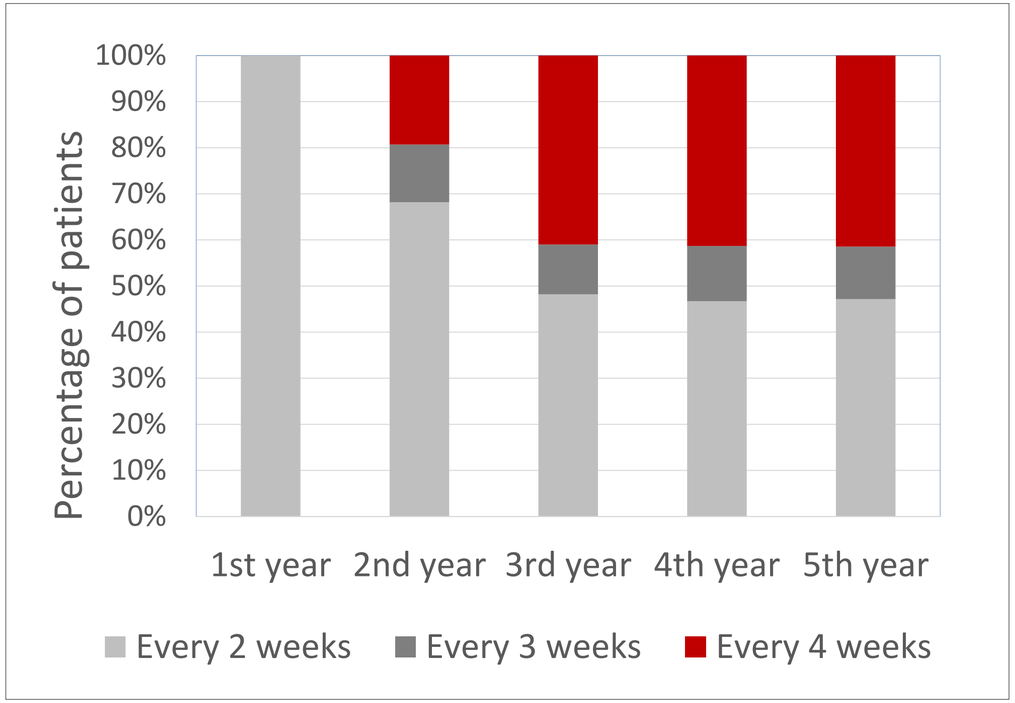
Dose of ropeginterferon alfa-2b (µg) per 4-week period

- Median dose per 4-week period in 5th year: 499 µg

- Eligible patients were permitted to switch from 2-weekly to 3 or 4-weekly administration (rate of switching >50%)



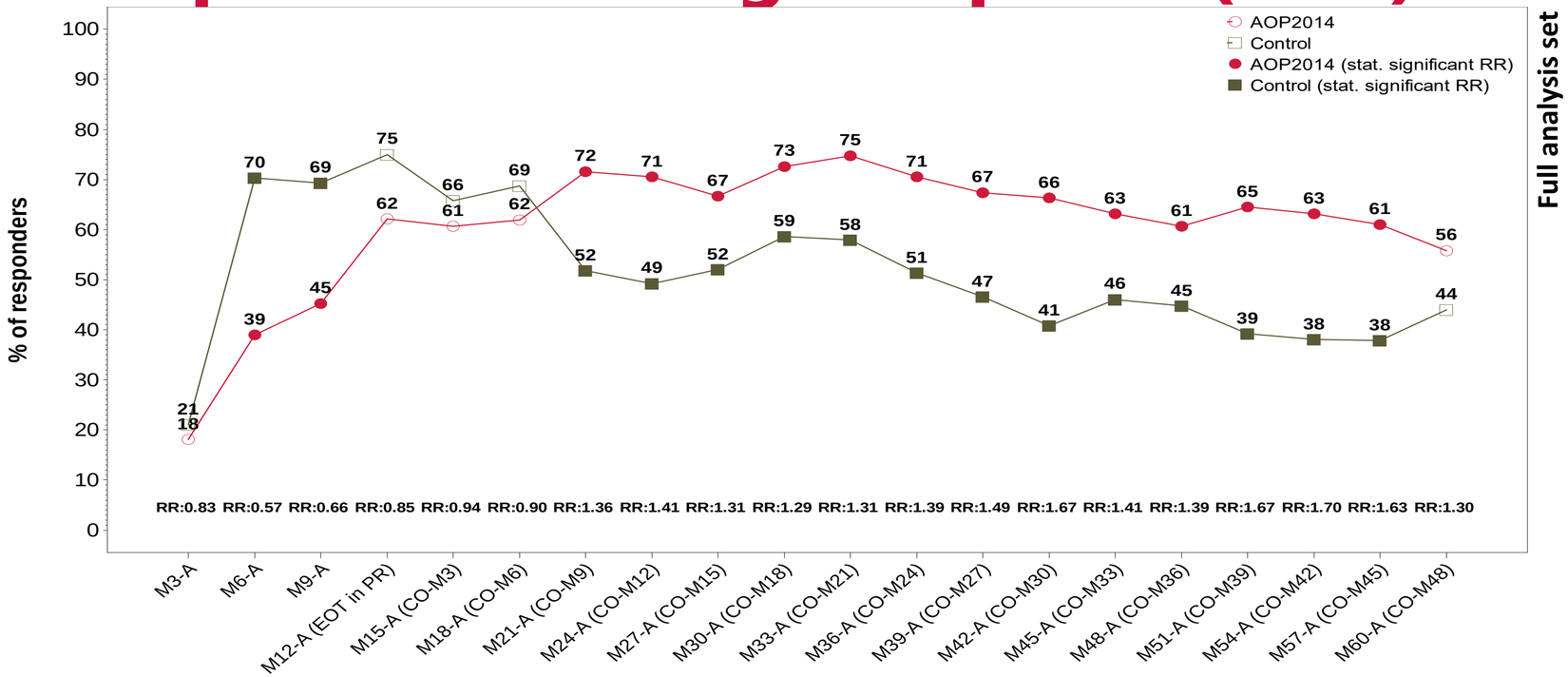
Cumulative dose per 4-week period



Administration schedule

Legend: diamonds: mean; boxes: median (Q1-Q3); whiskers: min-max: circles: outliers.
Full analysis set. Mean dose per 4 weeks was defined as cumulative dose between assessment visits/number of days in corresponding period x 28 days.

Complete hematologic response (CHR)



Definition of CHR:

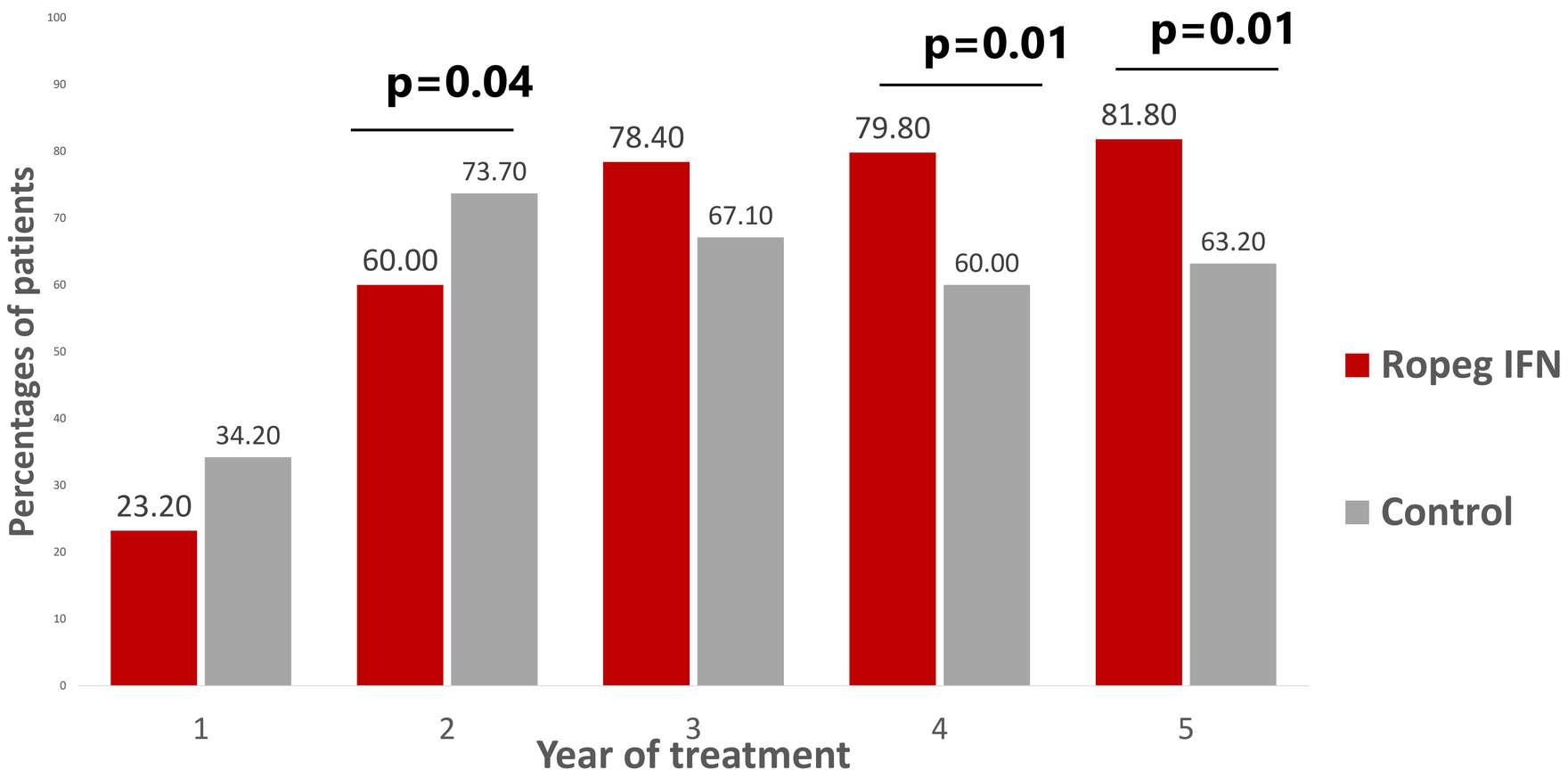
- **Hct<45% and no phlebotomy for at least 3 months**
  - **PLTs<400 x 10^9/L**
  - **WBCs<10 x 10^9/L**

Discontinued patients were counted as non-responders

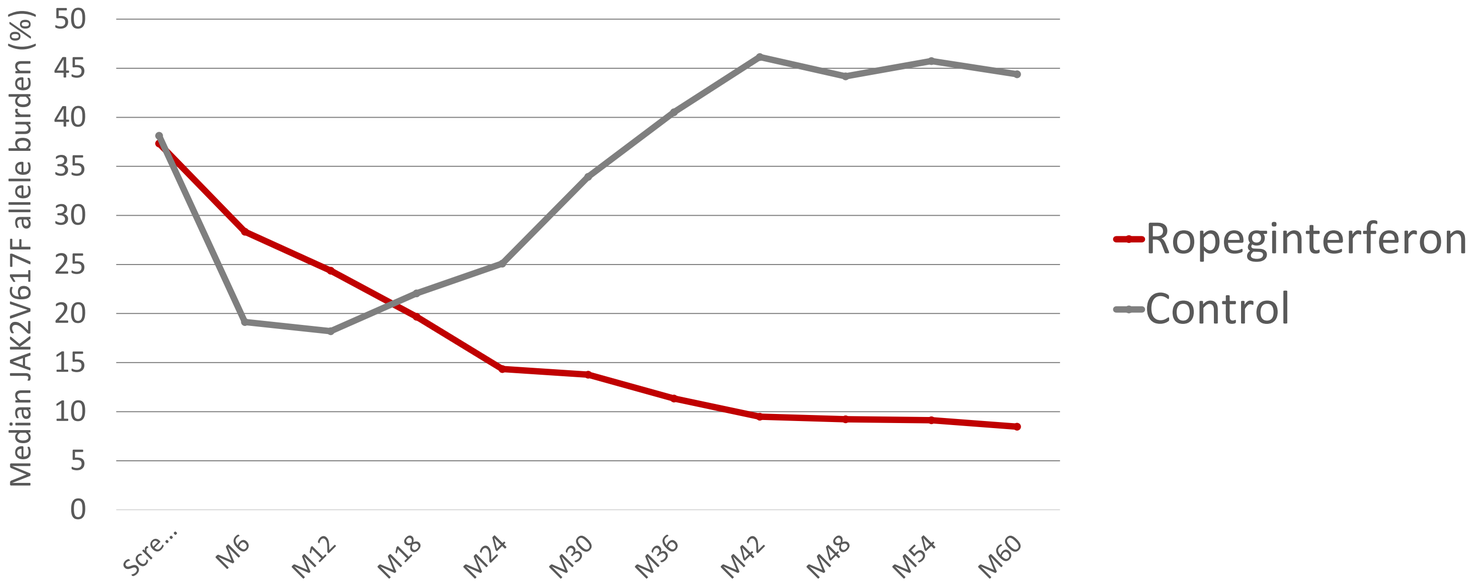
Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg IFN (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1303	0.85 [0.70-1.05]
MONTH 24	67/95	70.5	33/67	49.3	**0.0129**	1.41 [1.07-1.84]
MONTH 36	67/95	70.5	38/74	51.4	**0.0104**	1.39 [1.08-1.78]
MONTH 48	57/94	60.6	34/76	44.7	**0.0275**	1.39 [1.04–1.86]
MONTH 60	53/95	**55.8**	33/75	44.0	0.0974	1.30 [0.95-1.77]

Patients who were phlebotomy-free

In the 5th year of treatment, 81.8% of patients in the ropeginterferon alfa-2b arm versus 63.2% in the control arm were phlebotomy-free.



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

*JAK2*V617F allele burden in patients on study at month 60 using different thresholds

Allele burden category at 60 months*	Ropeg IFN N=70	Control N=57
JAK2V617F <0.01% (undetectable):**	**N=5**	**N=0**
Range of baseline JAK2 values	14-56%	NA
JAK2V617F undetectable and CHR	4/5	NA
JAK2V617F ≥0.01% to <1%:	**N=10**	**N=1**
Range of baseline JAK2 values	10-75%	47%
JAK2V617F ≥0.01% to <1% and CHR	9/10	1/1
JAK2V617F ≥1% to <10%:	**N=22**	**N=6**
Range of baseline JAK2 values	19-84%	12-41%
JAK2V617F ≥1 to <10% and CHR	19/22	3/6
Total patients with JAK2V617F <10%	**N=37** ***53%***	**N=7** ***12%***

p<0.0001

*** Only patients with a baseline value ≥10% were included in the analysis**

****Below limit of detection using the Ipsogen® JAK2 MutaQuant® kit; QIAGEN GmbH**

Thromboembolic adverse events

Very few patients experienced a major thromboembolic adverse event over the entire treatment period.

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

Disease progression

Progression of polycythemia vera occurred in only 1 patient in ropeginterferon arm versus 4 patients in the control arm. Leukemic transformation occurred only in the control arm.

	Ropeg IFN (N=127; 499 PYs)	Control (N=127; 401 PYs)
Events	Myelofibrosis (n=1)	Myelofibrosis (n=2) Acute leukemia (n=2)
Incidence (%-patient year)	**0.2**	**1.0**

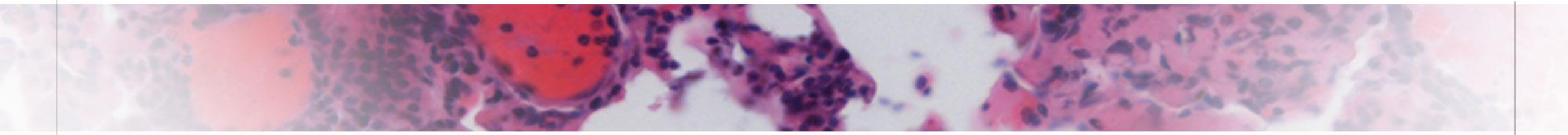
Safety profile overview:

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

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

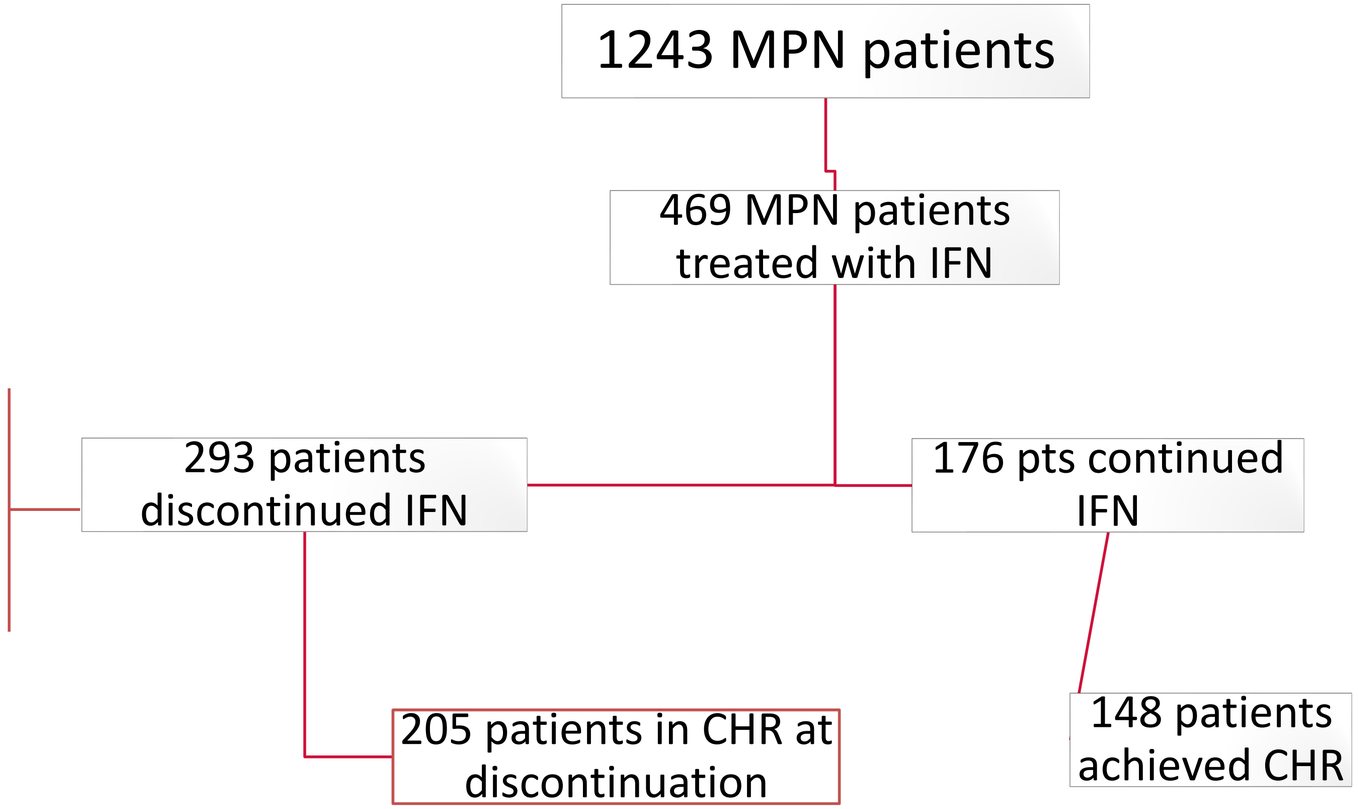


Interferon-alpha therapy discontinuation is feasible in MPN patients with complete hematological remission

Rafael Daltro de Oliveira MD, Juliette Soret-Dulphy MD, Lin-Pierre Zhao MD, Clémence Marcault MD, Nicolas Gauthier MD, Emmanuelle Verger PhD, Nabih Maslah PharmD, Nathalie Parquet MD , Emmanuel Raffoux MD , William Vainchenker MD, PhD , Christine Chomienne MD PhD , Stéphane Giraudier MD PhD, Bruno Cassinat PharmD, PhD , Lina Benajiba, MD, PhD and Jean-Jacques Kiladjian, MD, PhD

Hôpital Saint-Louis AP-HP
Université de Paris
INSTITUT DE RECHERCHE SAINT-LOUIS
Hématologie | Immunologie | Oncologie

Methods



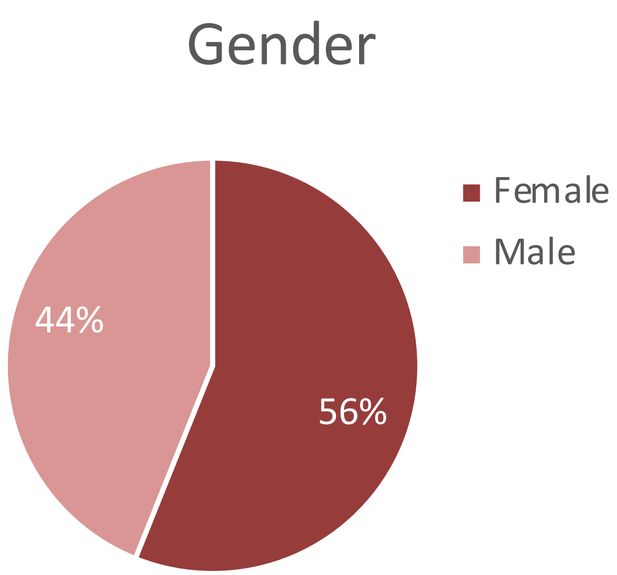
Reason for discontinuation:

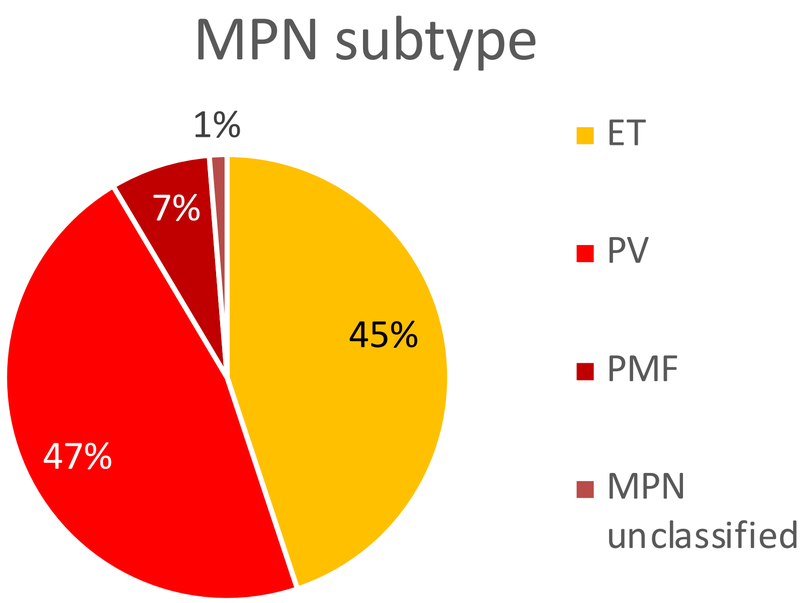
- 96 for CHR
- 138 for toxicity
- 28 failure/disease progression
- 31 other

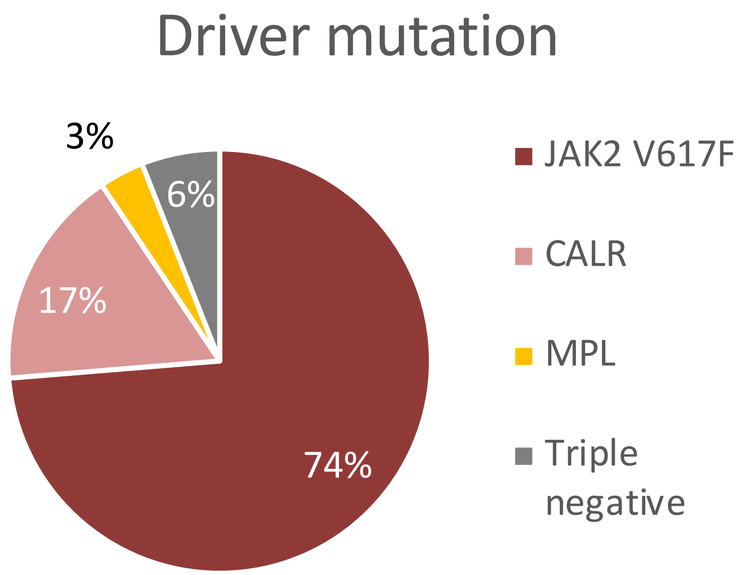
- **MPN patients diagnosed (WHO criteria) between January 2000 to August 2020**
- **All patients received at least 3 months of IFNα treatment.**
- **Discontinuation was defined as a minimum of 3 months of IFNα interruption.**

Results

Median age at diagnosis: 44 years



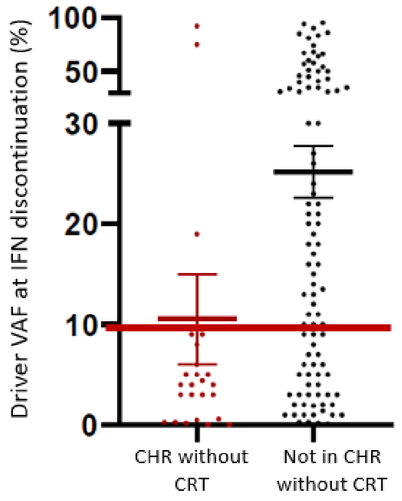


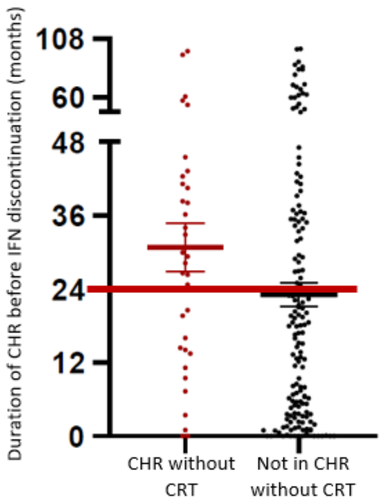


Results

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



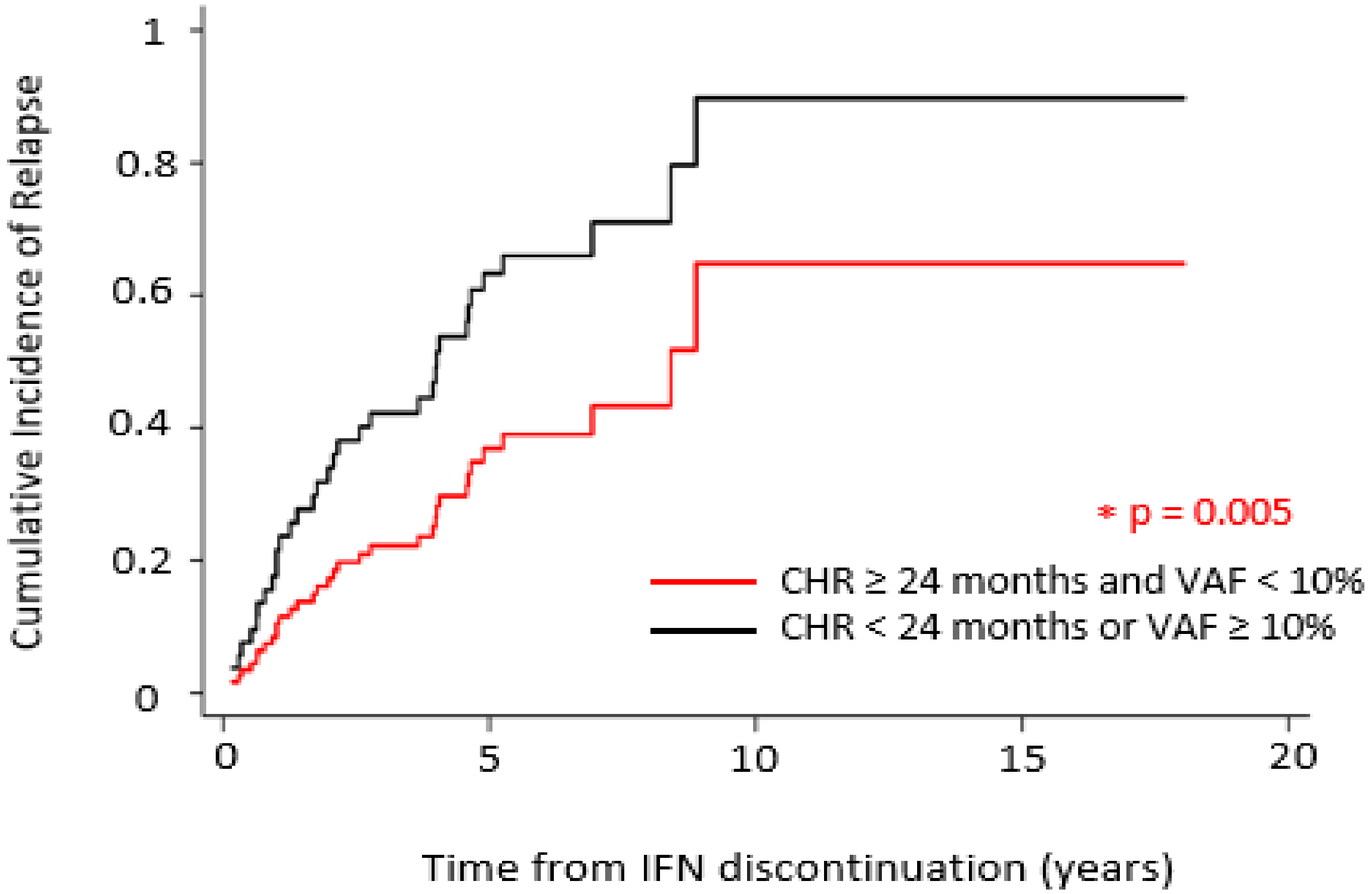


Variables	Multivariate analysis		
	OR	95% CI	pval
Driver VAF at time of IFN discontinuation ≥ 10%	0,128	[0.025; 0.638]	**0,012**
Duration of CR/CHR before IFN discontinuation ≥ 24 months	14,612	[1.765; 120.944]	**0,013**

Results

Factors associated with post-discontinuation relapse: COX regression model

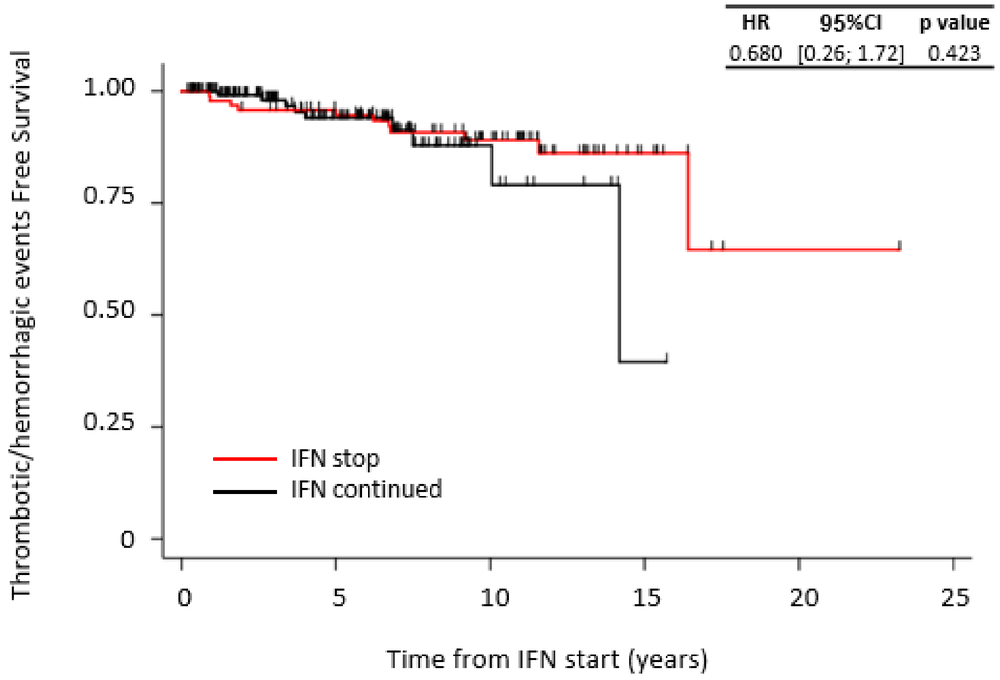
	Univariate analysis		
	OR	95% CI	pval
VAF < 10% and ≥ 24 months	0,459	[0.232; 0.908]	0,025



Results

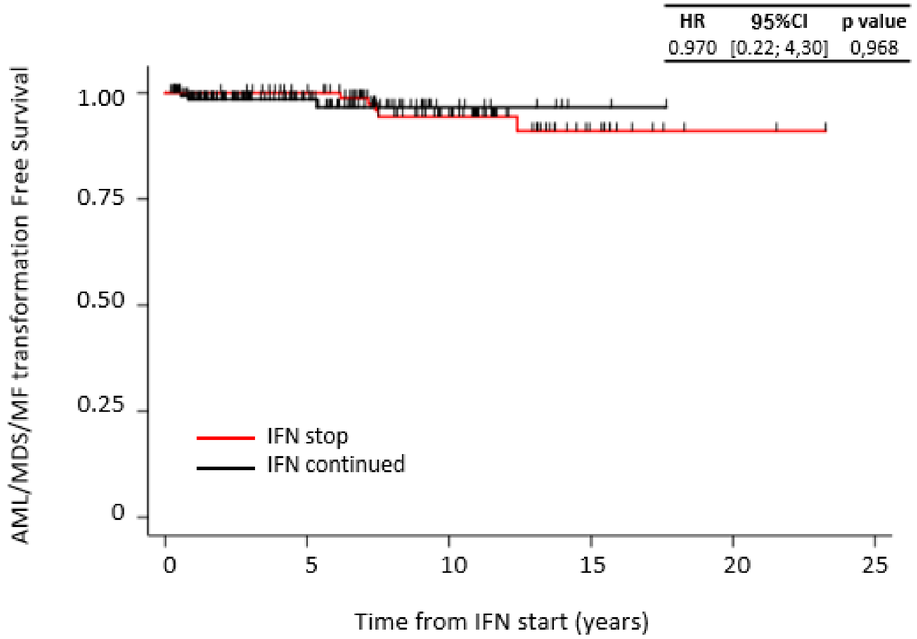
Post-discontinuation outcomes: event free survival

Median EFS : 169,7 months IFN continued *vs* NR IFN discontinued



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

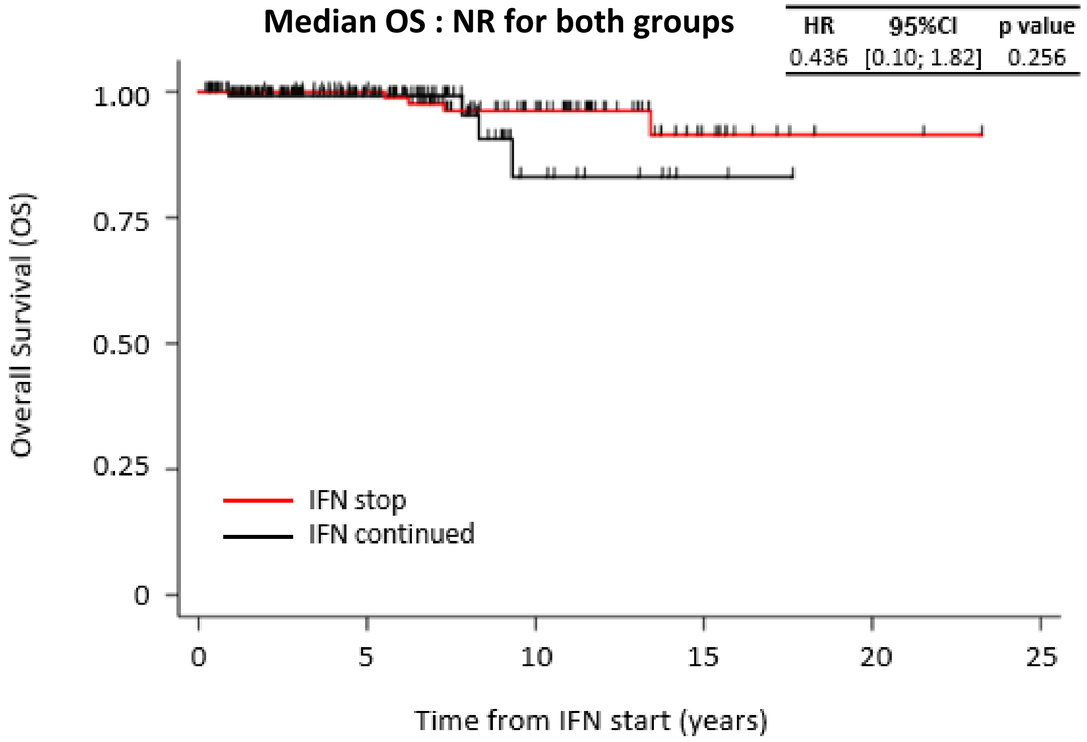
Median EFS : NR for both groups



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

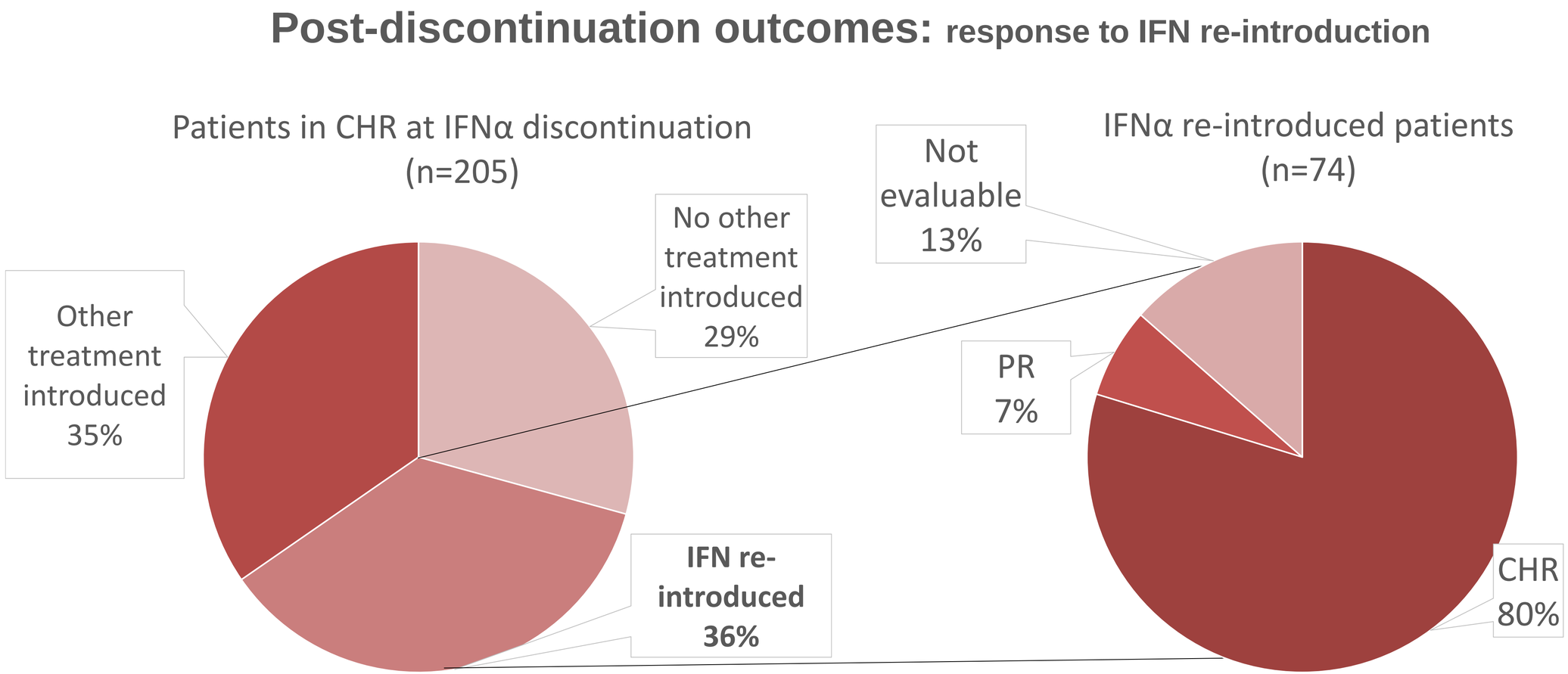
Results

Post-discontinuation outcomes: overall survival



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
Patients in CHR at IFNα discontinuation (n=205)
IFNα re-introduced patients (n=74)
No other treatment introduced 29%
Other treatment introduced 35%
IFN re-introduced 36%
Not evaluable 13%
PR 7%
CHR 80%

Phase II randomized clinical trial comparing Ropeginterferon *versus* phlebotomy in low-risk patients with polycythemia vera. Results of the pre-planned interim analysis of LOW-PV trial

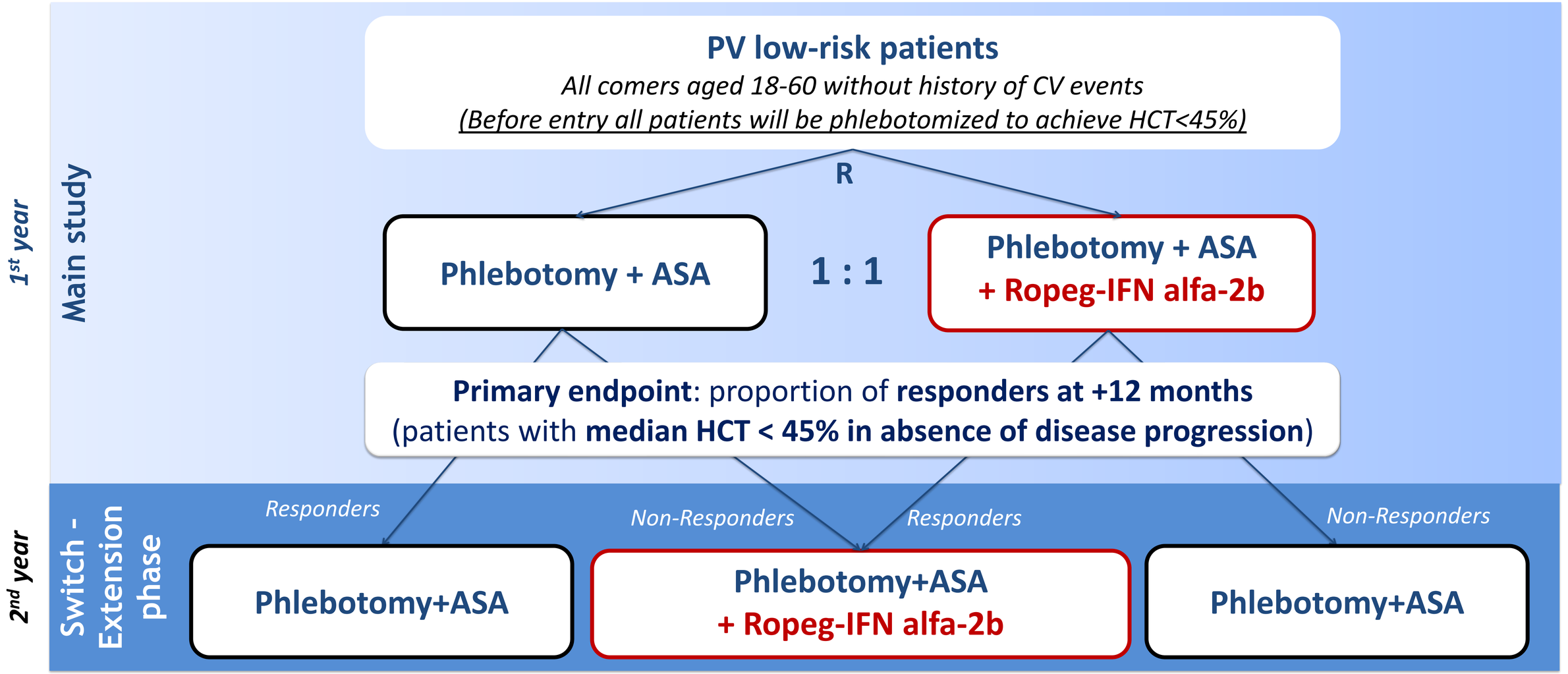
Tiziano Barbui

FROM Research Foundation, Papa Giovanni XXIII hospital, Bergamo, ITALY

June, 14th 2020
Late-Breaking Oral Session

Low-PV phase II RCT (*NCT03003325*)

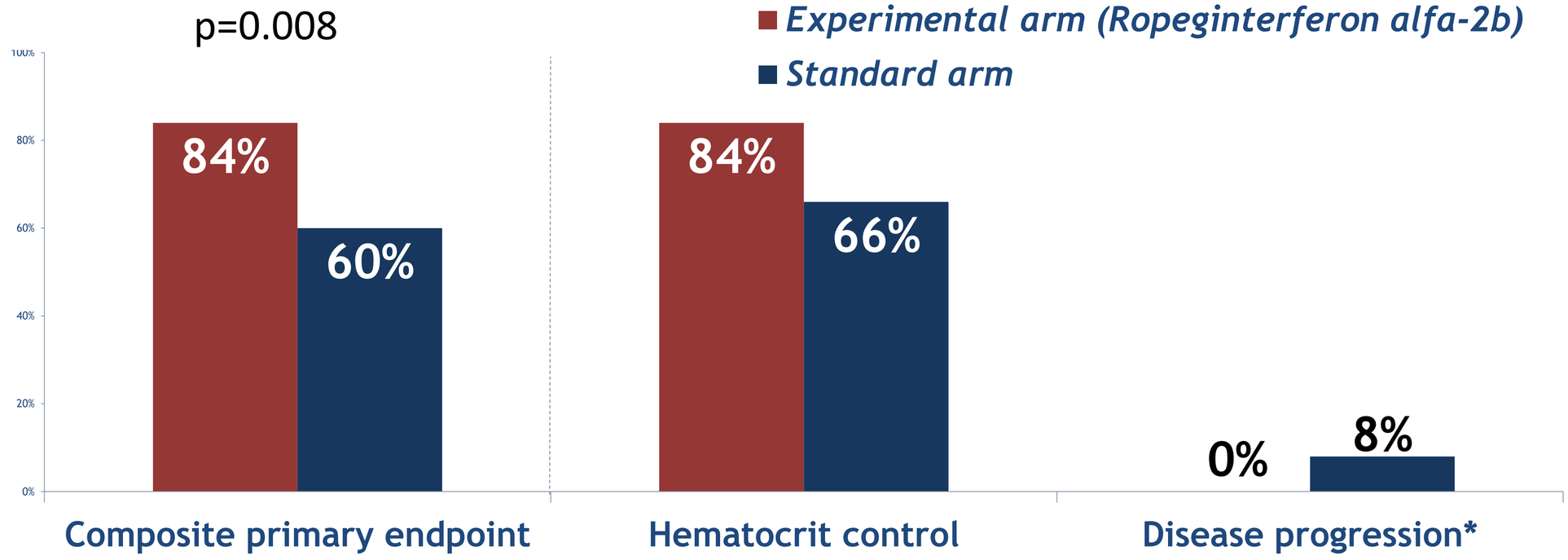
Low-PV



Low-PV RCT – Interim analysis

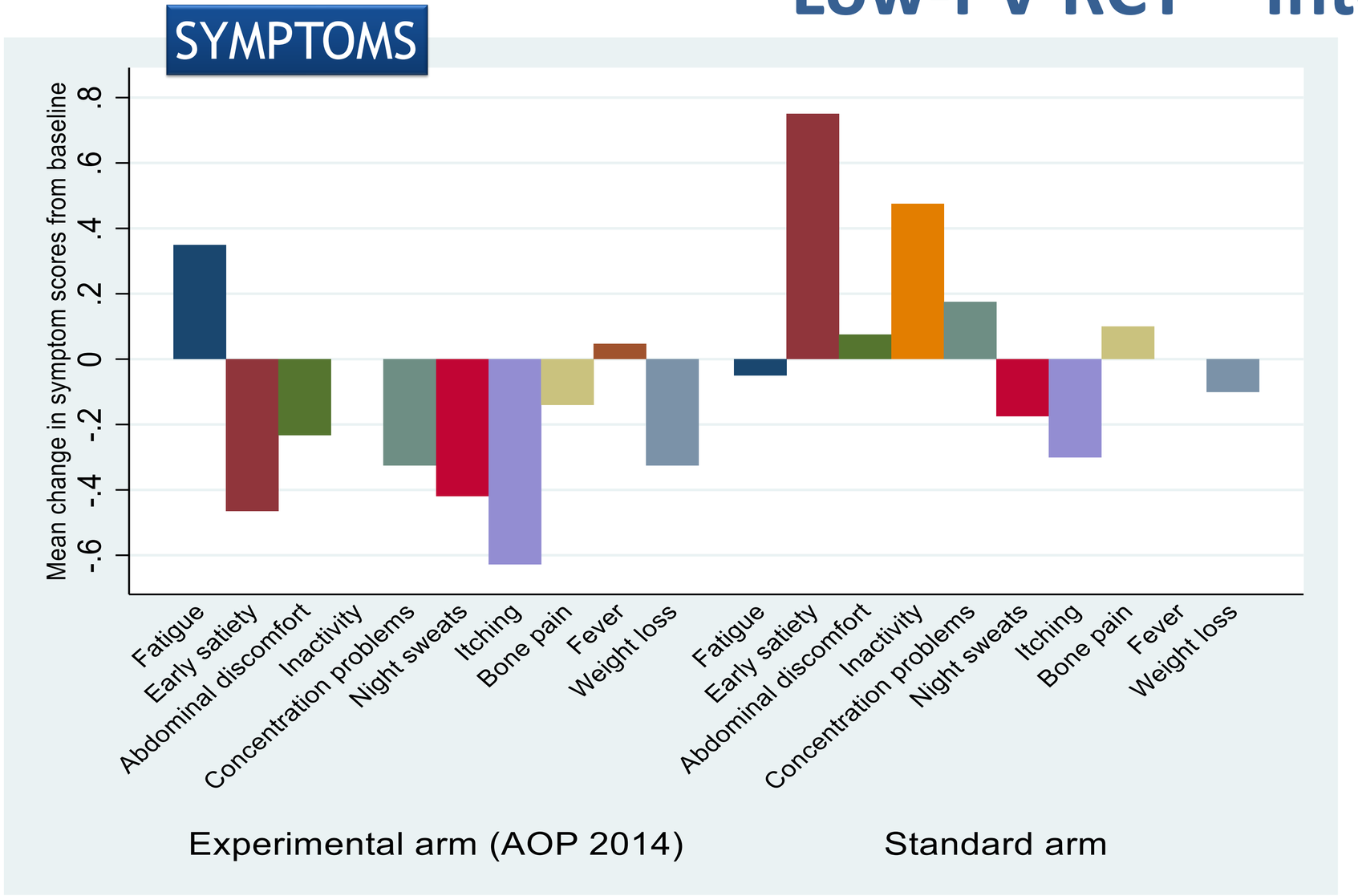
PRIMARY ENDPOINT

Odds Ratio, 3.5 (95% CI, 1.3-10.4)
p=0.008



**Disease progression* was observed in 4 patients (all in standard arm), as platelet count progression >1500x10^9/L or >1000x10^9/L according to baseline values (higher or lower than 600x10^9/L, respectively, confirmed after 30 days). In one patient progression was due to splenic infarction.*

Low-PV RCT – Interim analysis



Mean change

p=0.033

EXP *STD*

+10%

-21%

Negative values indicate a reduction in the severity of symptoms

Conclusions

- CONTINUATION-PV study shows that ropeginterferon provides long-term control of hematocrit, minimizes occurrence of thrombo-embolic events and transformation, with a well-known and favorable benefit-risk profile.

- In MPN patients achieving at least 2 years of complete hematological response, and in deep molecular response (i.e. reduction of the JAK2V617F allele burden below 10%), discontinuation of IFN therapy is feasible and safe.

- Results of the LOW-PV study provide new evidence challenging the current management of patients with “low-risk” PV.