POLICITEMIA VERA NEL 2023:

qualcosa è cambiato

La nuova risorsa terapeutica nella PV – Ropeg IFN α2b

Mario Tiribelli - Udine

Disclosures of Mario Tiribelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

NONE

Agenda

- Mechanism of action IFN
- The symptomatic burden of PV (and MPNs)
- Ropeg-IFN in PV: data from clinical trials

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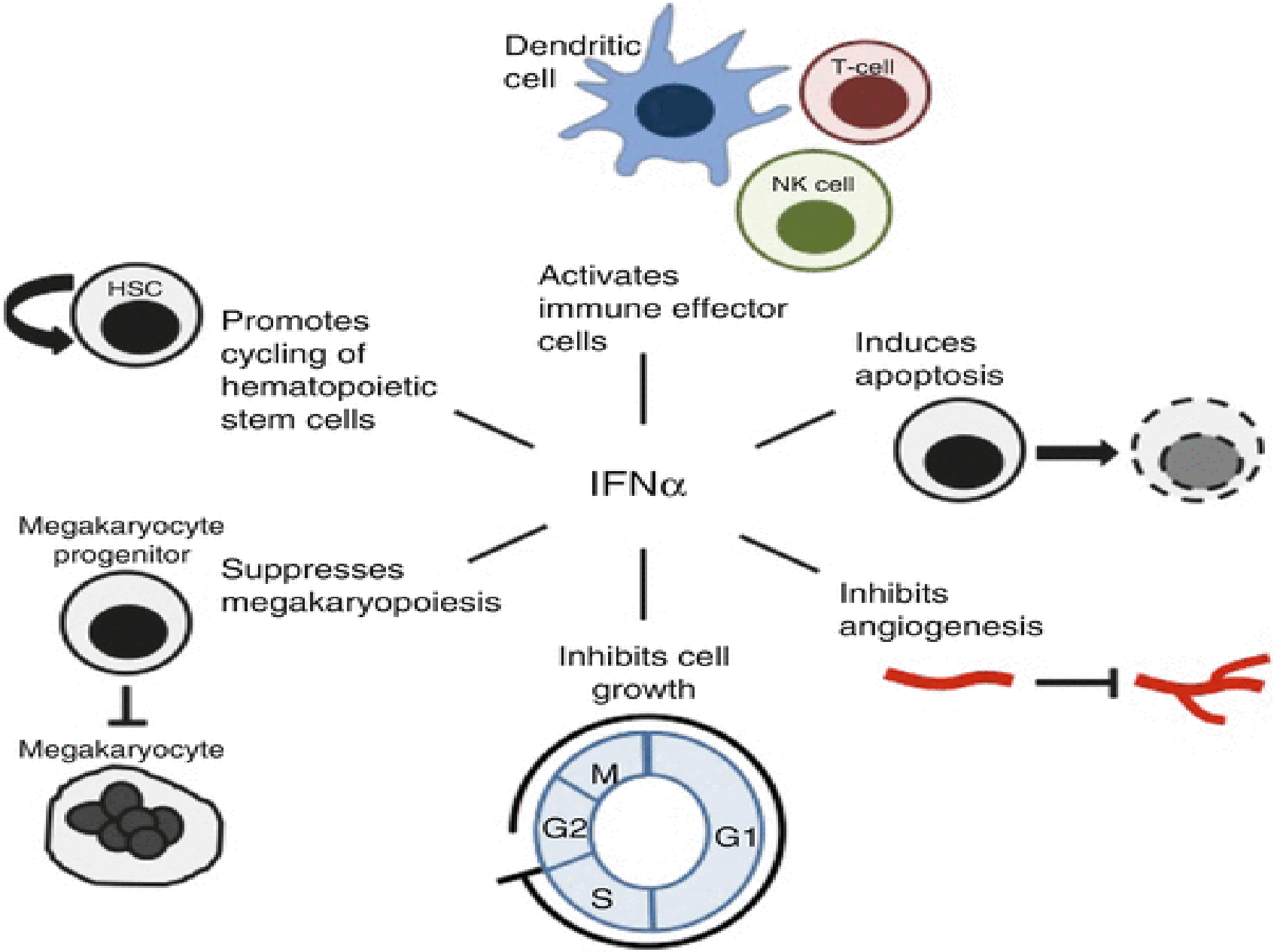
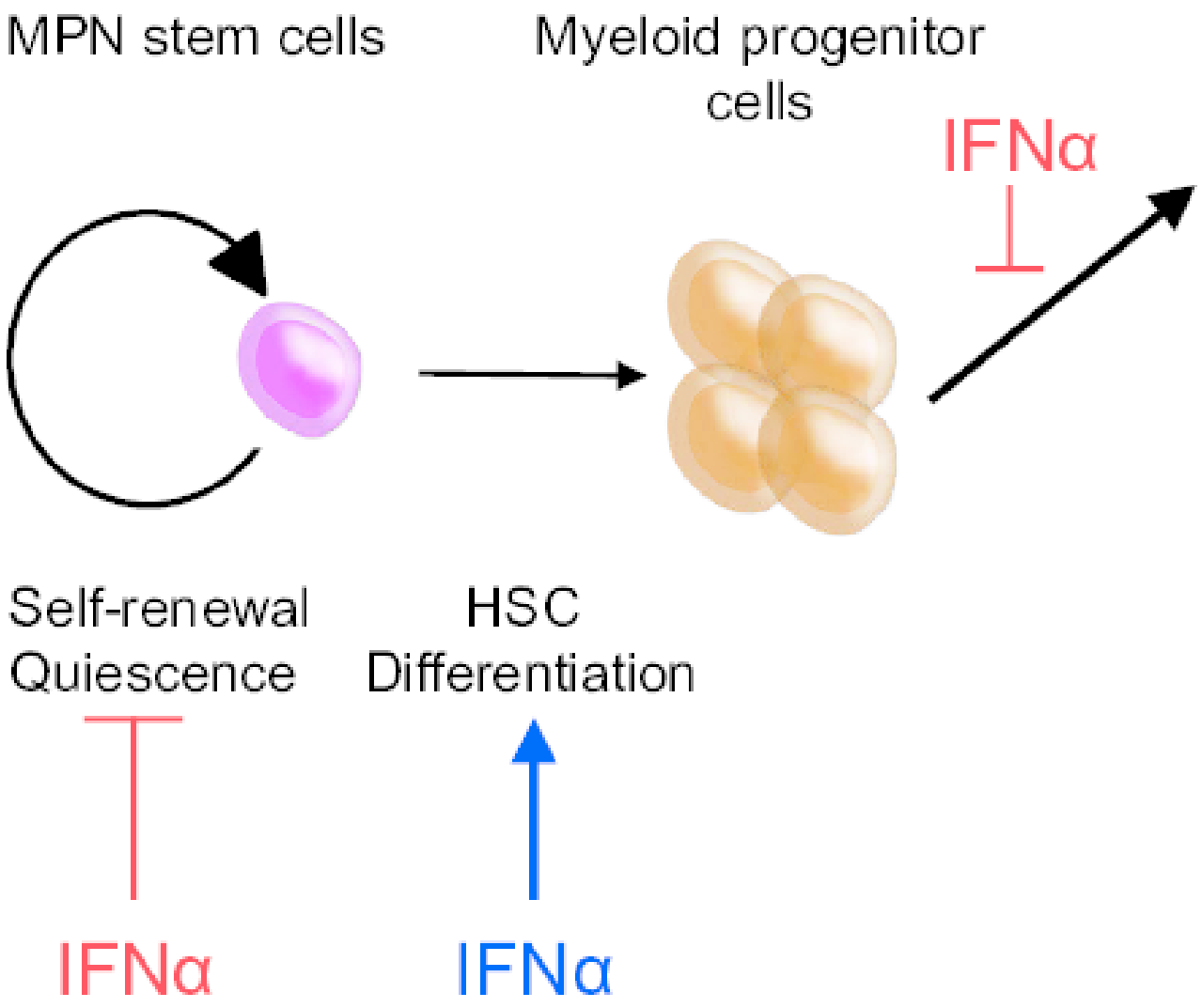


Lane 2013

Talpaz et al 2016



Myeloproliferation

Elevated blood counts

Extramedullary hematopoiesis

Thrombotic complications

IFNα ?

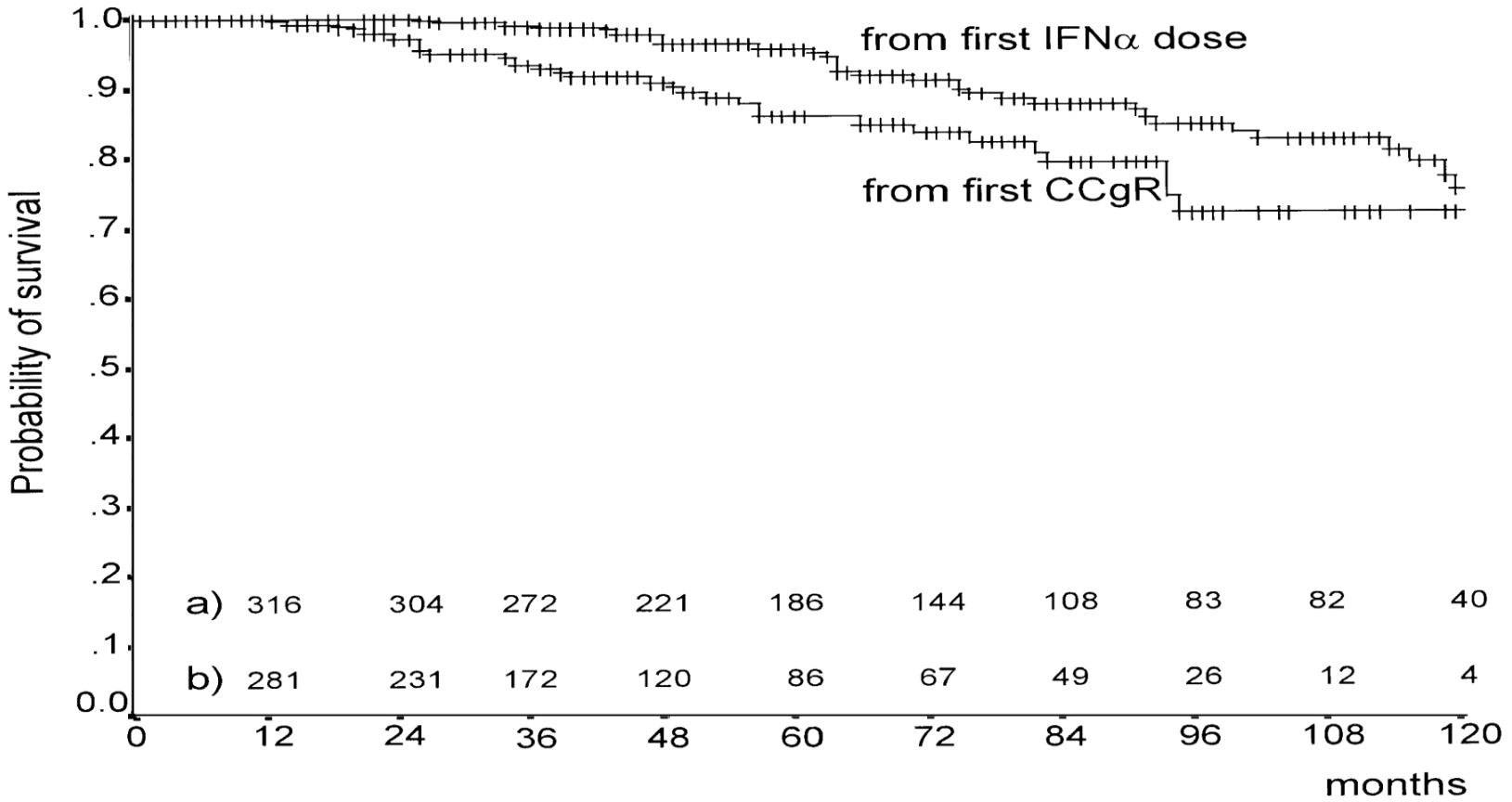
Transformation

Bone marrow fibrosis

Acute leukemia

Chronic myeloid leukemia and interferon-α: a study of complete cytogenetic responders

Francesca Bonifazi, Antonio de Vivo, Gianantonio Rosti, François Guilhot, Joëlle Guilhot, Elena Trabacchi, Rüdiger Hehlmann, Andreas Hochhaus, Patricia C. A. Shepherd, Juan Luis Steegmann, Hanneke C. Kluin-Nelemans, Josef Thaler, Bengt Simonsson, Andries Louwagie, Josy Reiffers, François Xavier Mahon, Enrico Montefusco, Giuliana Alimena, Joerg Hasford, Sue Richards, Giuseppe Saglio, Nicoletta Testoni, Giovanni Martinelli, Sante Tura, and Michele Baccarani, for the European Study Group on Interferon in Chronic Myeloid Leukemia

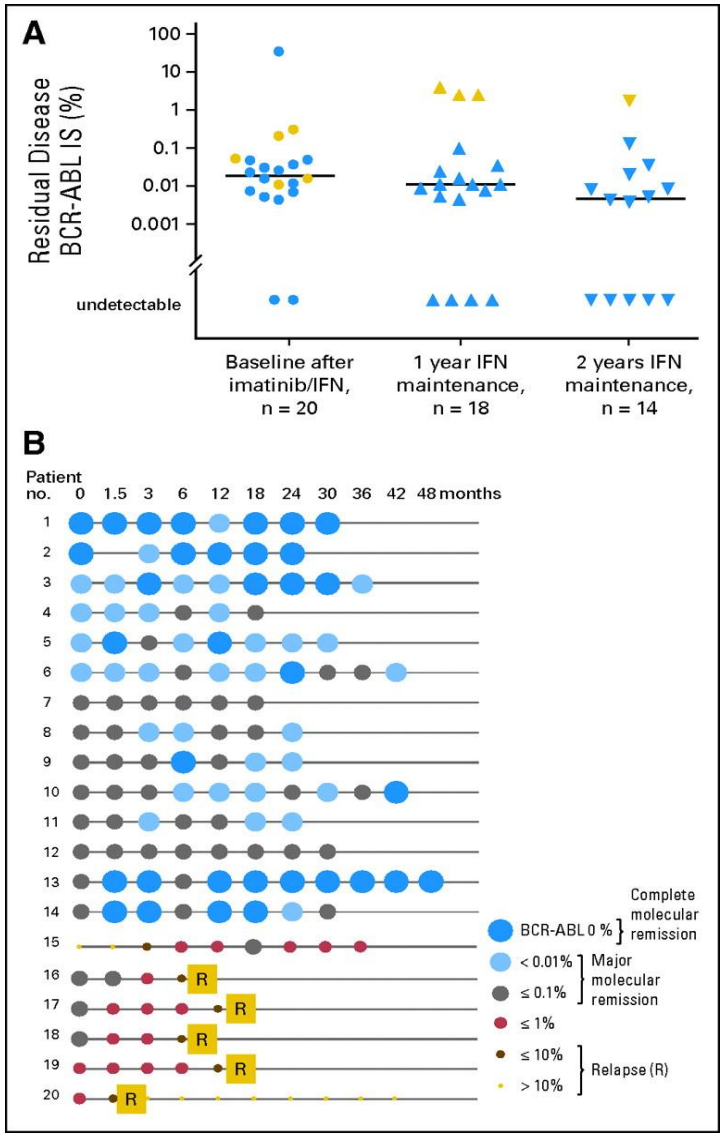


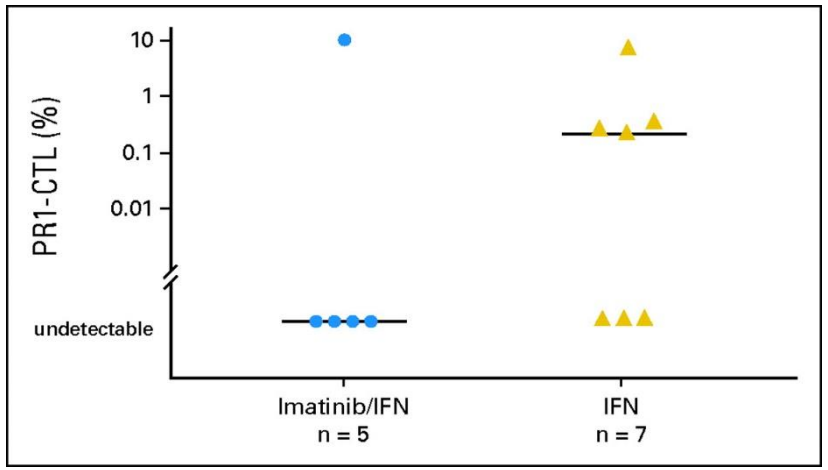
Bonifazi F et al. *Blood.* 2001;98(10):3074-3081

VOLUME 28 · NUMBER 8 · MARCH 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Sustained Molecular Response With Interferon Alfa Maintenance After Induction Therapy With Imatinib Plus Interferon Alfa in Patients With Chronic Myeloid Leukemia

Andreas Burchert, Martin C. Müller, Philippe Kostrewa, Philipp Erben, Tilman Bostel, Simone Liebler, Rüdiger Hehlmann, Andreas Neubauer, and Andreas Hochhaus





-MMR at baseline: n=15

-Median *BCR-ABL* transcript level:
- **-0.02% at baseline**
- **-0.011% at 1 year**
- **-0.0048% at 2 years**

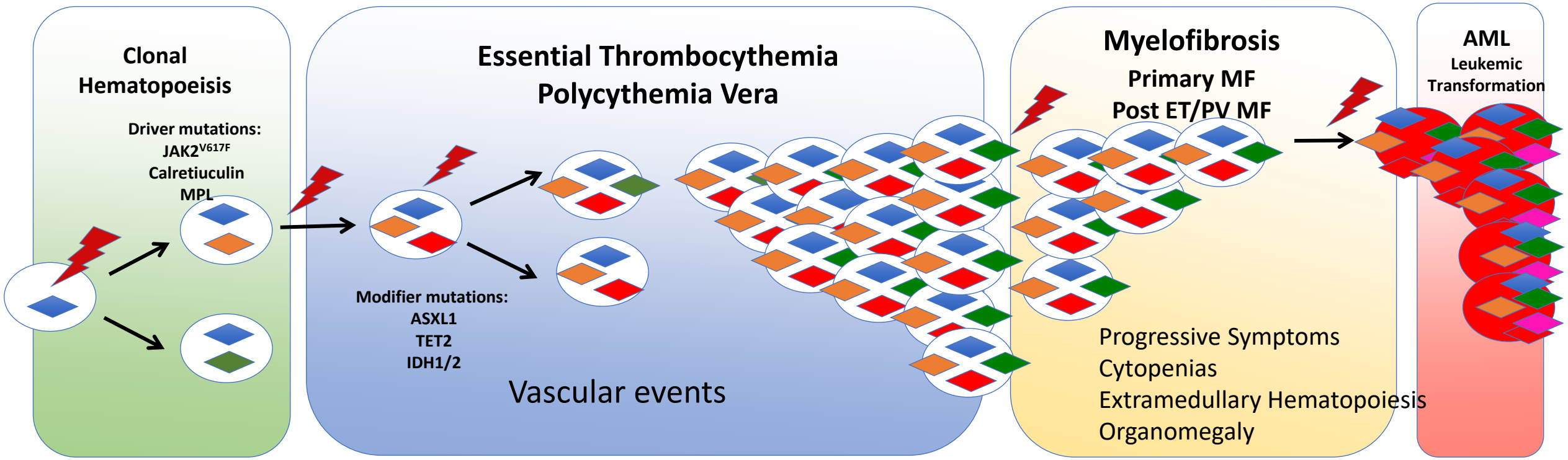
-After 2 years:
- **-5 patients had retained**
- **-10 had improved >1log the depth of their response**

-The number of patients in CMR increased from 2 to 5

Additional driver mutations promote rapid growth

Patient	Clade	% additional growth per yr	95% CI
PD5847	*JAK2* ^{V617F}, *9pUPD*, *TET2* ^{N281fs*1}	**233**	143-360
PD5182	*JAK2* ^{V617F}, 9pUPD	**142**	75-279
PD6646	*DNMT3A*$^{p?}$, *JAK2* ^{V617F}	**128**	92-266
PD4781	*JAK2* ^{V617F}, 9pUPD, *TET2* ^{Q1632*}, 7q-, 7p-	**119**	76-289
PD5179	*JAK2* ^{V617F}, 1q+	**115**	86-170
PD6629	*DNMT3A*^{R882H}, *JAK2* ^{V617F}, *TET2* ^{Q744fs*10}	**83**	36-166
PD9478	*JAK2* $^{Exon\ 12}$, *DNMT3A*^{Y908*}	**71**	54-96
PD6646	*DNMT3A*$^{p?}$, *CBL*^{C401S}	**70**	34-369
PD7271	*JAK2* ^{V617F}	**68**	41-95
PD5847	*JAK2* ^{V617F}, 9pUPD	**67**	6-246
PD5163	*JAK2* ^{V617F}	**43**	19-65
PD6629	*DNMT3A*^{R882H}, *JAK2* ^{V617F}	**40**	27-56
PD5163	*DNMT3A*^{T275fs*41}	**38**	22-61
PD6629	*DNMT3A*^{R882H}	**26**	19-35
PD5117	*JAK2* ^{V617F}	**18**	13-23
PD5847	*DNMT3A*^{Y660F}	**9**	5-25

Myeloproliferative Neoplasms



Lead time: Typically yrs (>10) to ∞

Time: Variable (3-5 yrs common)

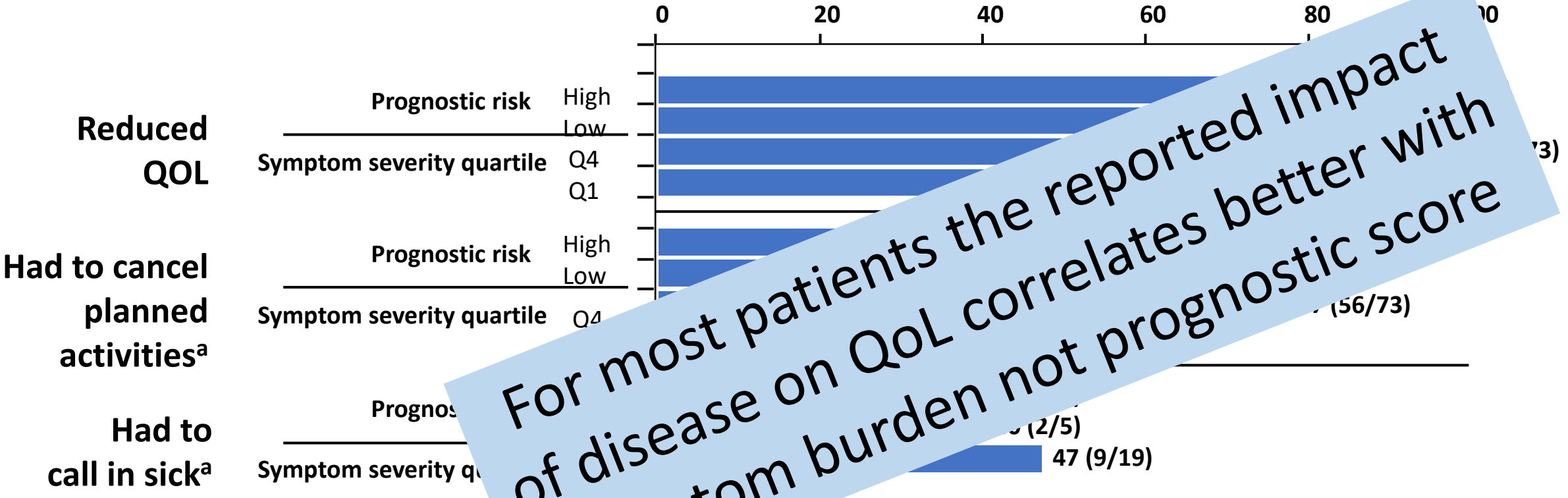
Normal Hematopoiesis

Bone Marrow Fibrosis
Premature Death

Agenda

- Mechanism of action IFN
- **The symptomatic burden of PV (and MPNs)**
- Ropeg-IFN in PV: data from clinical trials

QOL, activities of daily living, and work productivity stratified by calculated prognostic risk score and symptom severity quartile—MF



For most patients the reported impact of disease on QoL correlates better with symptom burden not prognostic score

81% of respondents with M… …ed that their symptoms reduced their QOL

Mesa R, et al. *BMC Cancer*. 2016;16:167.

Results: Activities of Daily Living

MPN Impact on Activities, n (%)	MF (n = 207)	PV (n = 380)	ET (n = 226)
Interfered with daily activities (ever)			
At all[a]	110 (53)	181 (48)	84 (37)
A great deal[b]	43 (21)	36 (10)	15 (7)
Interfered with family or social life (ever)			
At all[a]	163 (79)	241 (63)	125 (55)
A great deal[b]	35 (17)	43 (11)	18 (8)
Activities limited by pain/discomfort (ever)			
At all[a]	127 (61)	197 (52)	101 (45)
A great deal[b]	25 (12)	36 (10)	15 (7)
Days canceling planned activities[c]			
1-3	44 (21)	68 (18)	41 (18)
4-6	22 (11)	26 (7)	14 (6)
7-9	2 (1)	0	3 (1)
10-12	7 (3)	9 (2)	4 (2)
13-15	3 (1)	2 (1)	1 (< 1)
≥ 16	8 (4)	6 (2)	1 (< 1)
Days spent in bed (all or most of the day)[c]			
1-3	38 (18)	54 (14)	30 (13)
4-6	13 (6)	15 (4)	10 (4)
7-9	1 (< 1)	4 (1)	5 (2)
10-12	4 (2)	2 (1)	5 (2)
13-15	4 (2)	5 (1)	1 (< 1)
≥ 16	7 (3)	9 (2)	5 (2)

Results: Work Productivity

MPN Impact on Work Productivity, n/N (%)[a,b]	MF (n = 207)	PV (n = 380)	ET (n = 226)
Reduced work hours (ever)	70/119 (59)	91/246 (37)	51/169 (30)
Days sick from work (preceding 30 days)			
1-3	11/52 (21)	19/127 (15)	18/88 (20)
4-6	3/52 (6)	4/127 (3)	2/88 (2)
7-9	0	0	0
≥ 10	1/52 (2)	1/127 (1)	0
Voluntarily terminated job (ever)	39/125 (31)	54/254 (21)	19/169 (11)
Involuntarily terminated job (ever)	6/120 (5)	11/242 (5)	7/168 (4)
Medical disability (ever)	38/134 (28)	37/253 (15)	12/177 (7)
Early retirement (ever)	38/125 (30)	54/253 (21)	24/169 (14)

Symptoms (patient perspective)

When asked which symptom patients would most like to have resolved:

- most patients referred to improvement in **fatigue/tiredness** across all disease subtypes (44% MF, **35% PV**, and 45% ET)
- other symptoms most patients wanted to resolve included bone pain in patients with MF (59%), **pruritus in patients with PV (63%)**, and strokes or headaches in patients with ET (67% or 58% respectively)

Harrison, Ann Hematol 2017

Agenda

- Mechanism of action IFN
- The symptomatic burden of PV (and MPNs)
- **Ropeg-IFN in PV: data from clinical trials**

Il Ropeg-IFNα-2b è un coniugato covalente dell'interferone alfa-2b proteico, prodotto nelle cellule di Escherichia coli mediante tecnologia da DNA ricombinante, con una frazione metossipolietilenglicole (mPEG).

Ropeg-IFNα-2b è indicato come monoterapia negli adulti per il trattamento della PV senza splenomegalia sintomatica.

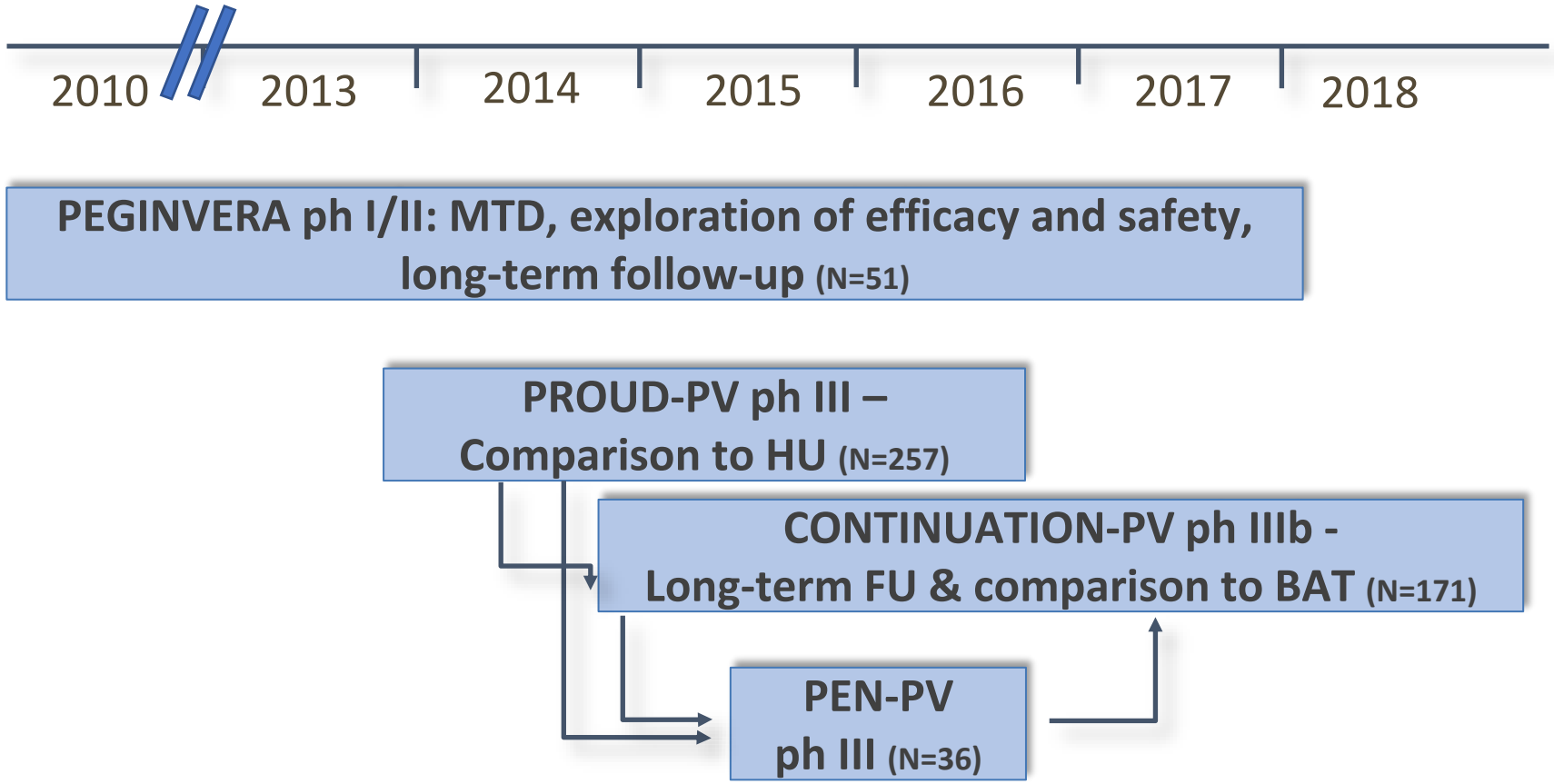
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Indicazione ammessa alla rimborsabilità

trattamento di soggetti con PV e senza splenomegalia sintomatica che:

- **siano risultati intolleranti al trattamento con idrossiurea secondo i criteri della ELN (Barbui et al., J Clin Oncol 2011)**
- **delle donne in età fertile che intendano intraprendere una gravidanza**
- **dei soggetti con storia di tumori cutanei**

Ropeginterferon alfa-2b: clinical development in PV



European Marketing authorisation 15th February 2019

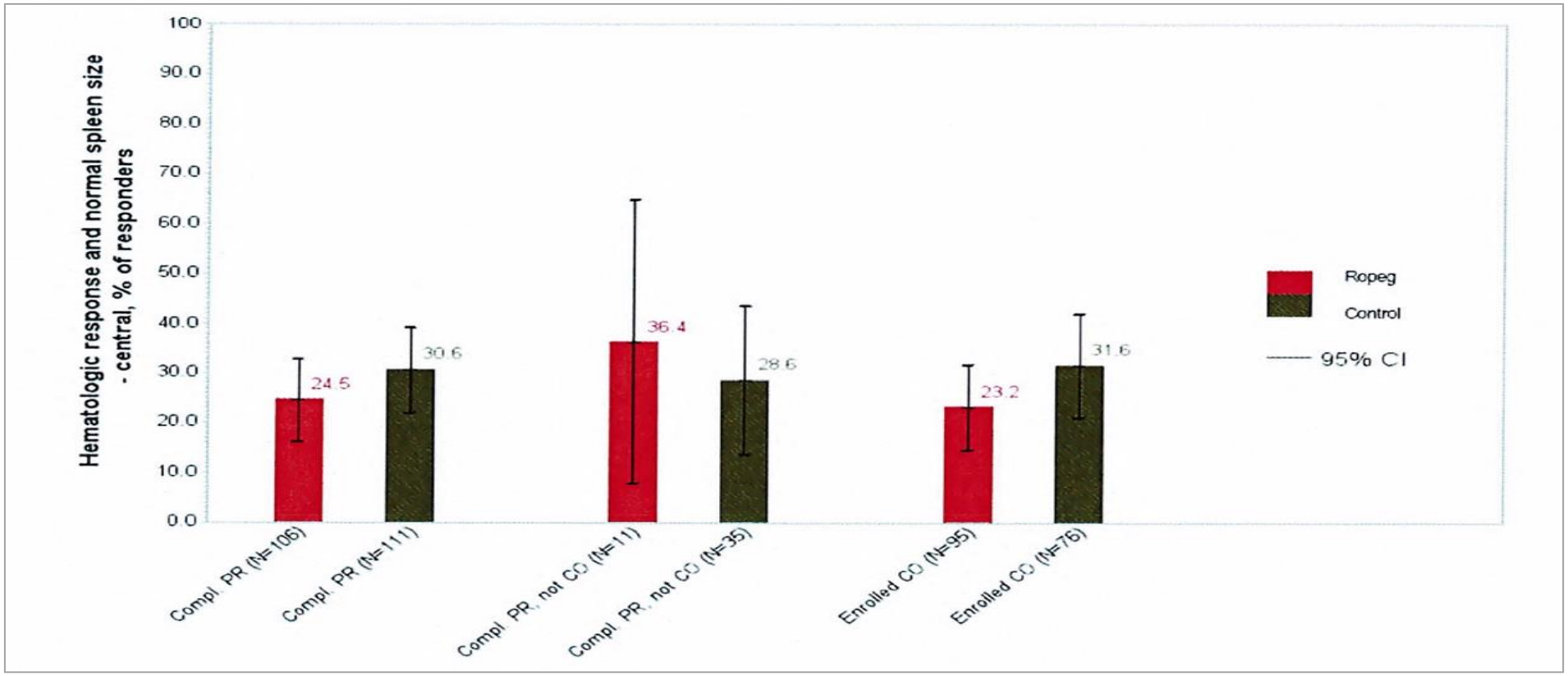
PEGINVERA-PV

- **PEGINVERA-PV è uno studio di *dose escalation* di fase I/II *open-label*, prospettico, multicentrico, condotto in Austria in 6 centri, su 51 pazienti con PV.**
- **La durata del trattamento è stata di 5 anni per il 52.9% dei pazienti e di 6 anni per 31.4%.**
- **Lo studio PEGINVERA-PV ha permesso di individuare l'MTD (Massima Dose Tollerata) di Ropeg-IFNα-2b che è risultata di 540 µg.**

PROUD-PV

- **PROUD-PV è uno studio di fase III *open-label*, randomizzato, multicentrico, controllato, a bracci paralleli.**
- **In totale 257 pazienti arruolati in 48 centri (127 Ropeg-IFNα-2b e 127 HU)**
- **Obiettivo dello studio è stato dimostrare la non-inferiorità di Ropeg-IFNα-2b *vs*. HU in termini di tasso di risposta alla malattia, in pazienti con diagnosi di PV V617F JAK2 mutati, sia naïve all'HU che trattati con HU.**

PROUD-PV



Il tasso di risposta alla malattia al Mese 12 è risultato del **21.3%** (26/122 pazienti) per il braccio ropegIFNα-2b *vs*. **27.6%** (34/123 pazienti) per il braccio HU p=0.23).

La non-inferiorità di ropegIFNα-2b *vs*. HU al mese 12 non è stata, quindi, dimostrata.

Gisslinger et al. Blood 2020;136:33

PROUD-PV

La causa del “fallimento” dell’endpoint primario è verosimilmente imputabile alla scarsità di pazienti con splenomegalia al baseline.

L’analisi post-hoc sulla CHR *senza il criterio “dimensione normale della milza”*, al 12° mese, ha confermato l’attività biologica di ropegIFNα-2b nel controllo della malattia, con tassi di risposta ematologica di **43.1%** per il braccio ropegIFNα-2b vs **45.6%** per il braccio HU (p = 0.63).

Tale analisi ha mostrato una significativa non-inferiorità di ropegIFNα-2b vs. HU (p=0.0028).

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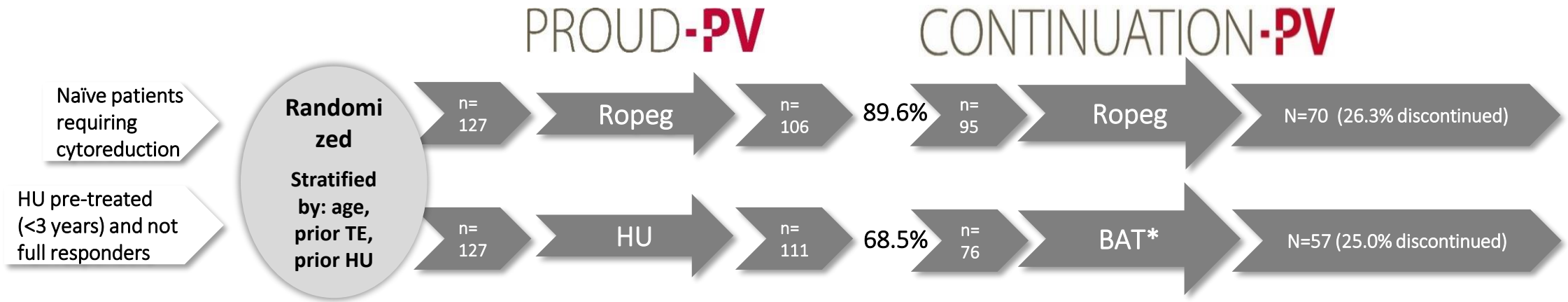
Phase III studies PROUD-PV and CONTINUATION-PV: design and patient disposition



* 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 DB lock on 29.05.2020
(up to 6.3 years of treatment overall)

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CONTINUATION-PV

Assess long-term efficacy of ropegIFNα-2b compared to BAT (HU or other) in patients with PV who completed the PROUD-PV Study, with respect to:

- **Hematologic response rate**
- **Long-term safety, quality of life, and change of JAK2 allelic burden**
- **Changes in disease burden (i.e. splenomegaly, microvascular disturbances, pruritus or headache) as assessed by investigator**

Gisslinger et al. Lancet Haematol 2020;7:196–208

Complete hematologic response (CHR)

Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (Ropeg/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]

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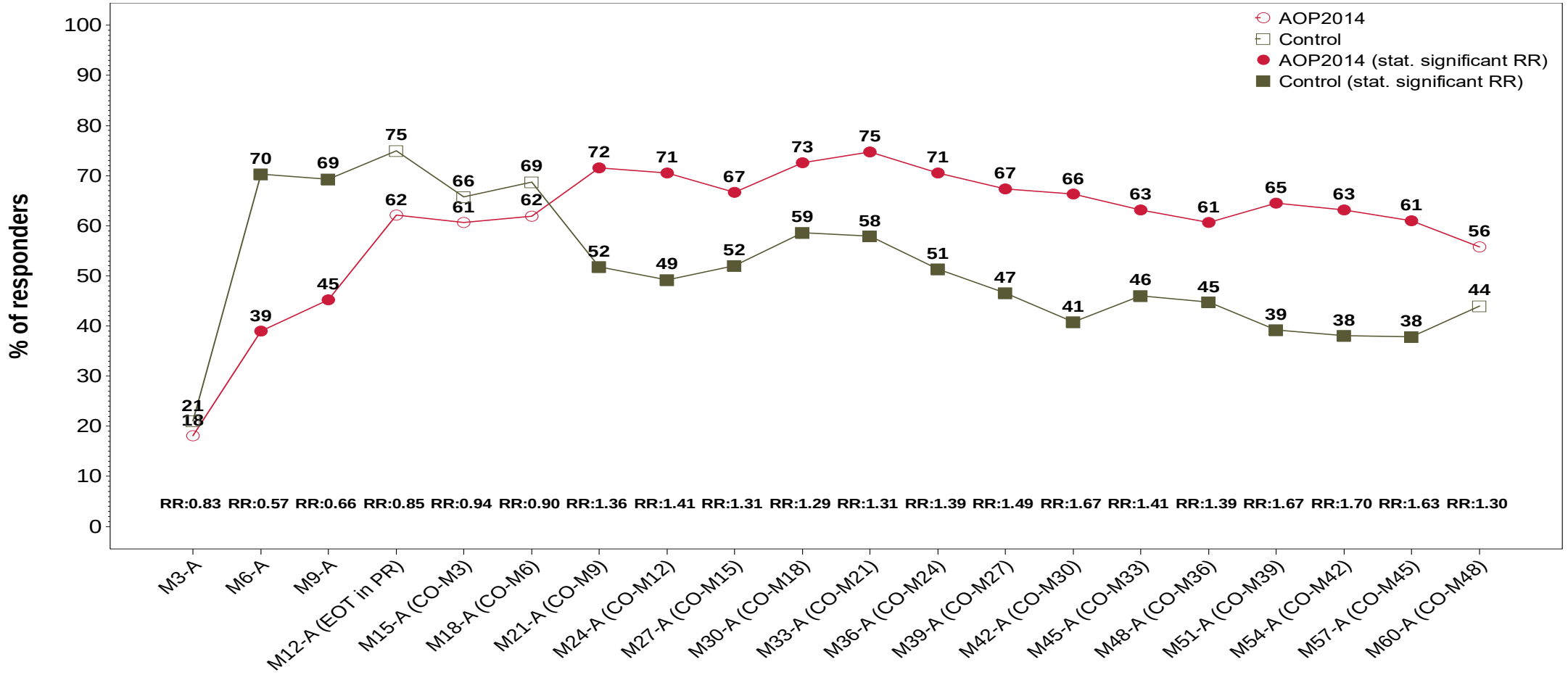
Complete hematologic response (CHR)



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Events: Thromboembolic - Disease Progression

Thromboembolic adverse events

	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

	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**

Gisslinger et al. Blood 2020;136:33

Molecular response

Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg/control)
	Responder/N	Responder %	Responder/N	Responder %		
MONTH 12 (EOT in PR)	41/94	43.6	36/73	49.3	0.3744	0.87 [0.63-1.19]
MONTH 24	64/94	**68.1**	24/74	**32.4**	**0.0001**	2.00 [1.41-2.84]
MONTH 36	62/94	**66.0**	20/74	**27.0**	**<0.0001**	2.31 [1.56-3.43]
MONTH 48	63/94	**67.0**	19/74	**25.7**	**<0.0001**	2.50 [1.67-3.73]
MONTH 60	65/94	**69.1**	16/74	**21.6**	**<0.0001**	3.04 [1.96-4.71]

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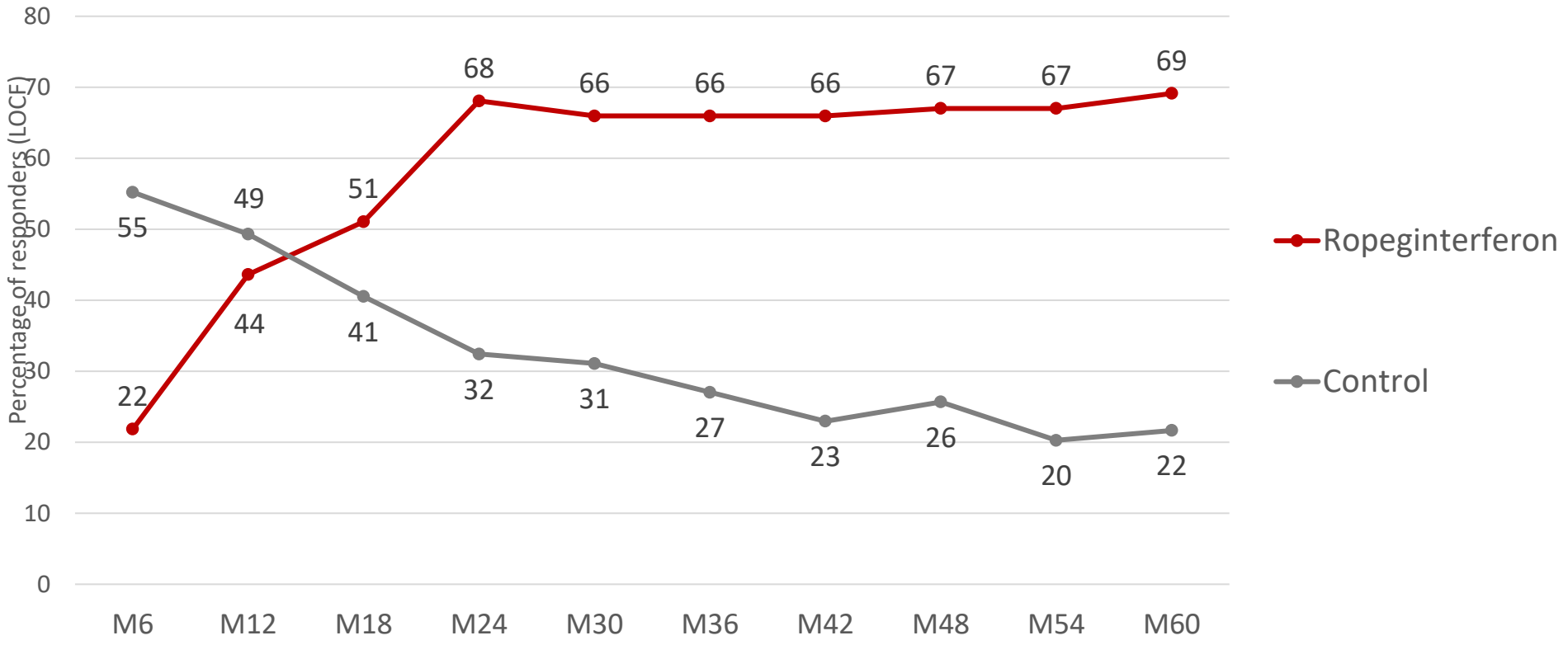
Molecular response



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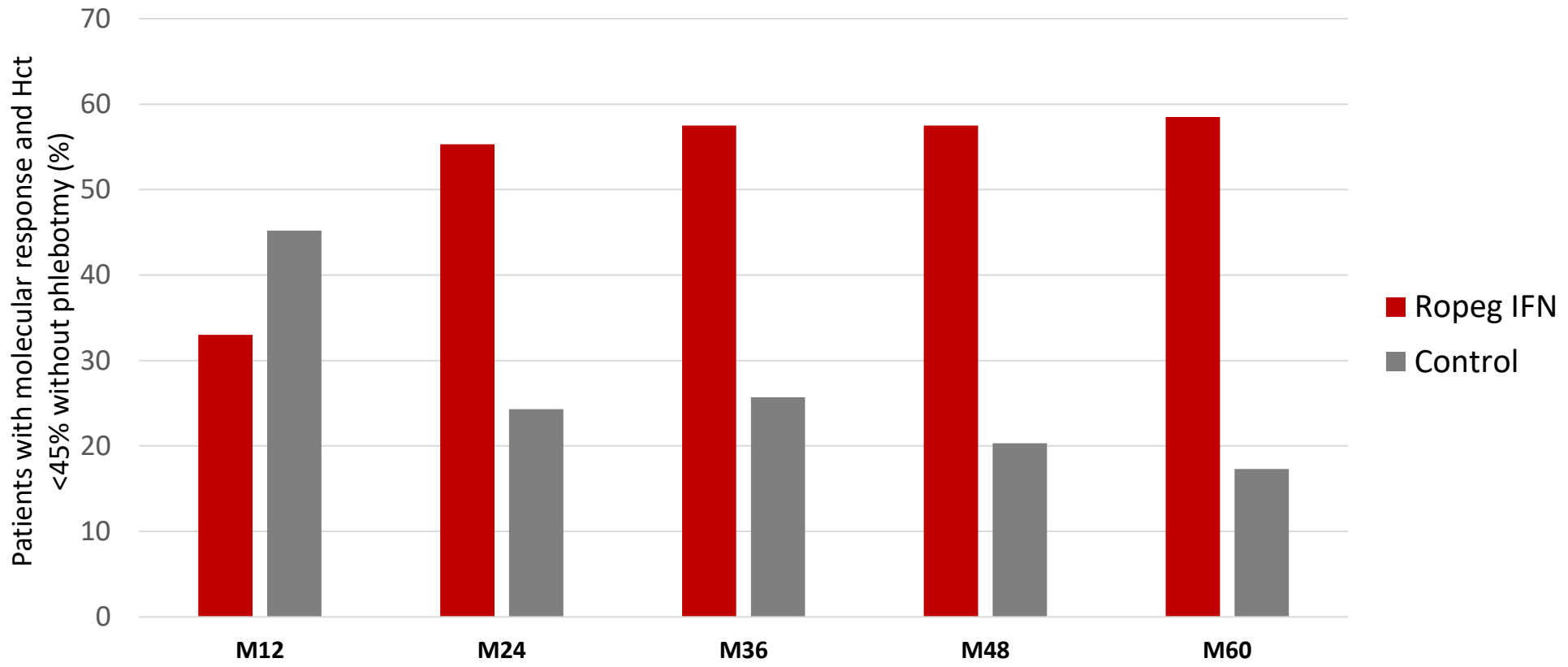
Combined analysis of Hct <45% without phlebotomy AND molecular response



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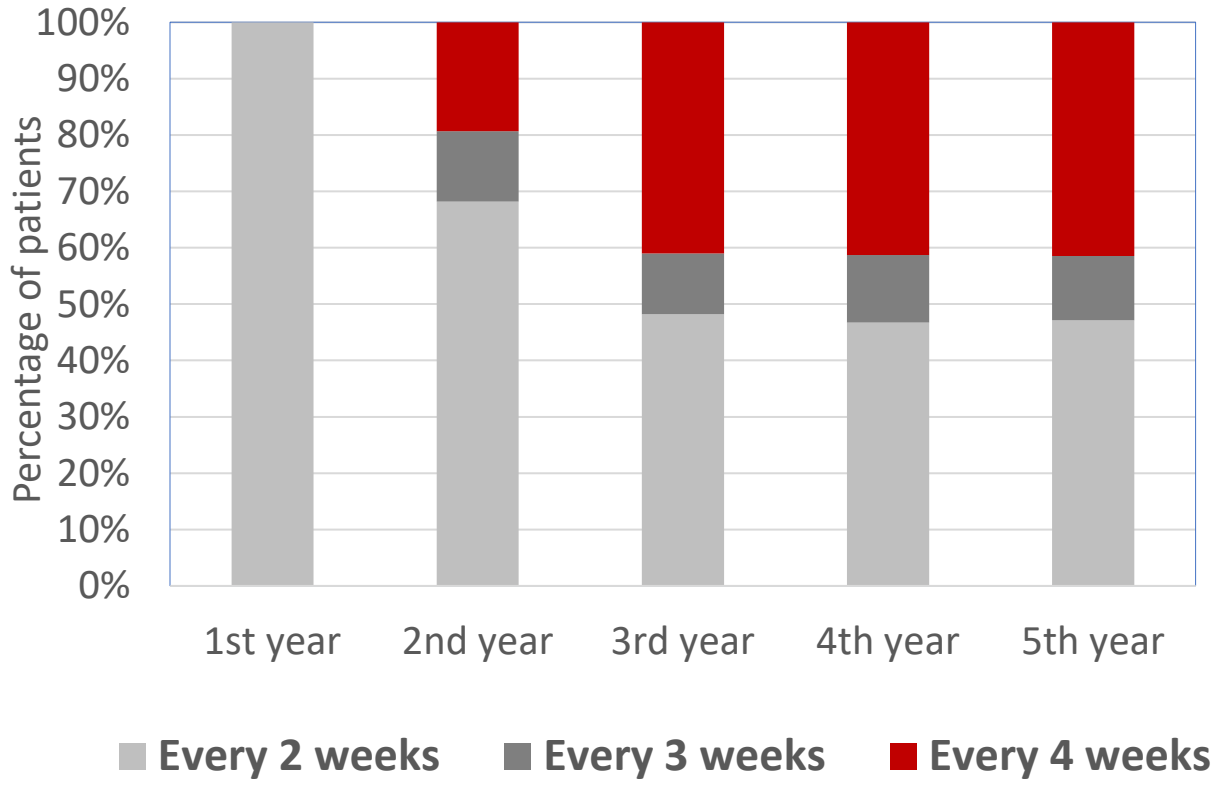
Dose of ropeginterferon alfa-2b



- 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%)

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Safety profile overview

	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

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Skin toxicity

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%)	-	-

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Adverse drug reactions of special interest to IFN

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%)

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Conclusions after 60 months treatment

- ✓ In a randomized controlled setting, ropegIFN-treated patients were significantly **more likely to be phlebotomy-free** in the 4th and 5th year of treatment
- ✓ RopegIFN controlled hematocrit and minimized the occurrence of thromboembolic events
- ✓ Disease progression was rare during long-term ropegIFN treatment, which might reflect **a change in the natural history of PV** due to durable molecular responses
- ✓ No new safety signals were detected in the 5th year of treatment, confirming the **good tolerability** of this novel pegylated interferon over long-term treatment.

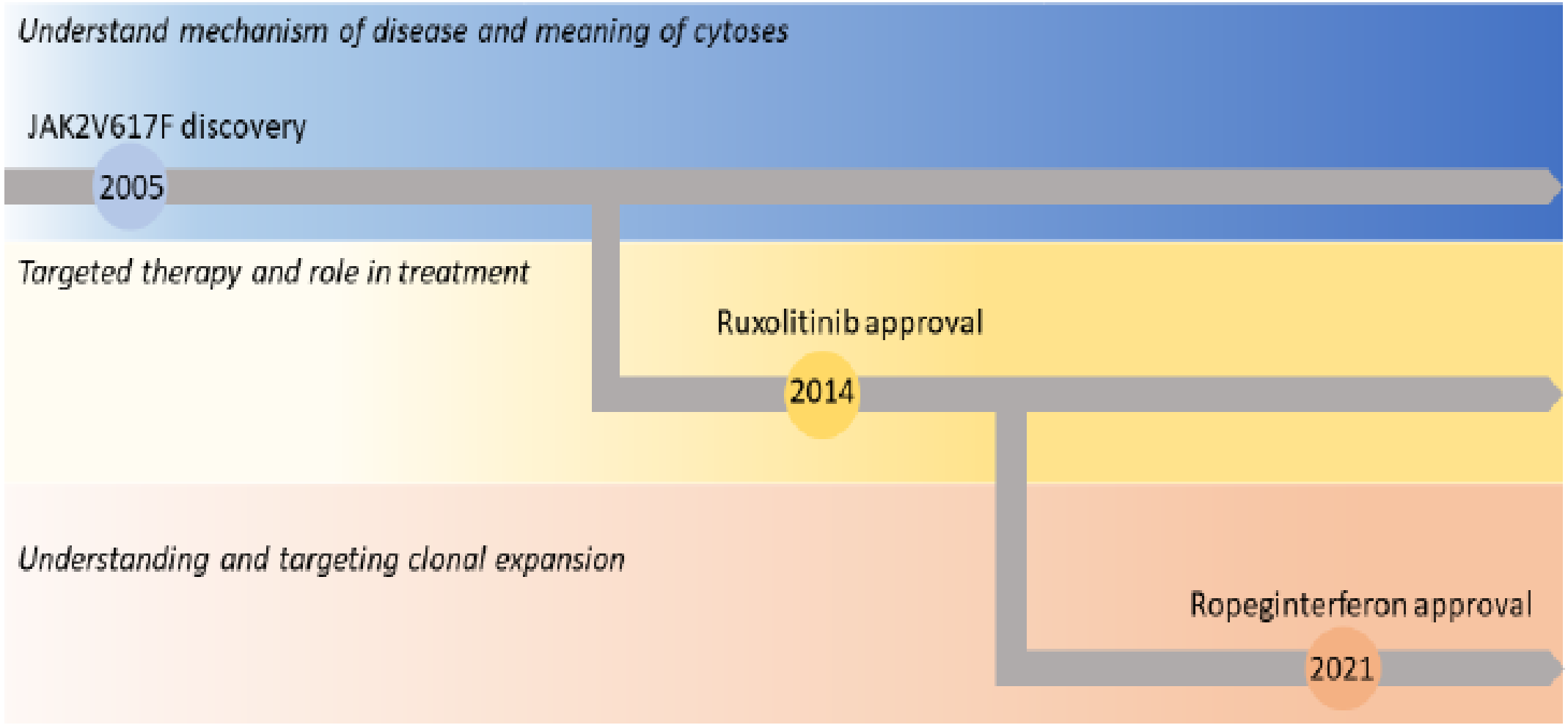
Gisslinger et al. Blood 2020;136:33

Effects of therapy on *JAK2*$_{V617F}$ cell quantity, quality, and clonal expansion

	Phlebotomy	Hydroxyurea	Ruxolitinib	Ropeginterferon
Quantity	+	++	+++	+++
Comments	Rapid reduction of red cells and blood volume	Control of WBC, RBC, and platelets	Control of WBC, RBC, and platelets. Most reliable hematocrit control	Control of WBC, RBC, and platelets, sustained with molecular responses
Quality	-	-	+	+
Comments	Reinforces iron deficiency, activates HIF[40,44]	Selection stress on bone marrow HSC[89]	Reduced intracellular signaling[45]	Targets and extinguishes JAK2V617F positive HSC[81]
Clonal suppression	-	-	+	+++
Comments	VAF increases ~1% per year[61]	Transient reduction in first year, then rebounds VAF increases~1% per year[60,72]	Mild to moderate, but highly variable VAF reduction[3,67,68]	Consistent reduction in VAF VAF decreases ~1% per month over 36 months[60,61,76,86]

Moliterno et al. Blood 2023; in press

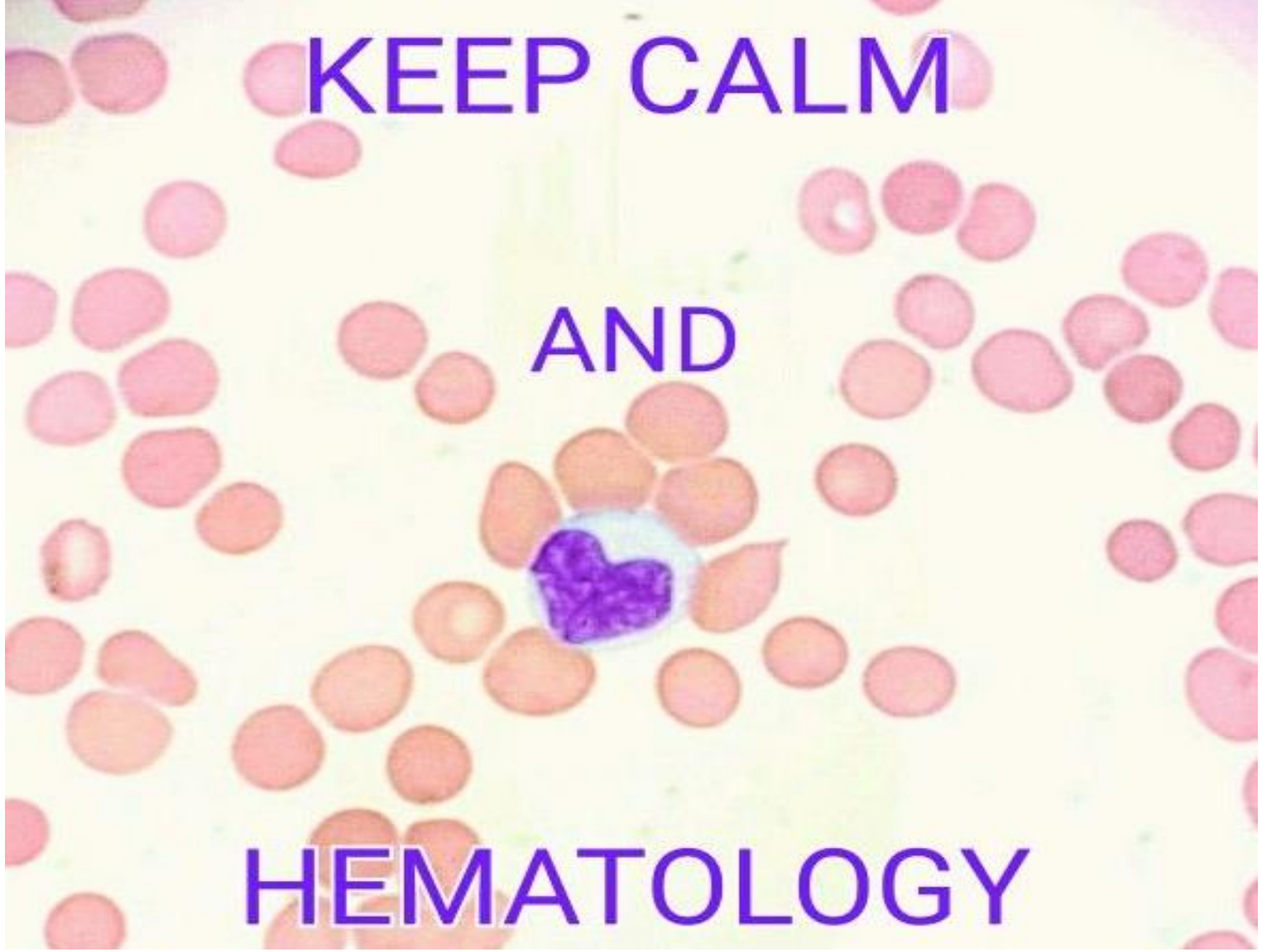
PV clinical and research goals



Moliterno et al. Blood 2023; in press

SUMMARY

- PV is a progressive disease, driven by V617F JAK2 mutation
- Disease burden significantly affect QoL in PV patients
- Interferons may act on various aspects of cellular proliferation and immune system… though mainly in still unknown ways
- Solid data on ropeg IFN α2b on disease control and potentially molecular responses
- Possibile use in early phases of disease (M. Bonifacio will tell…)
- Indications still limited



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