THE FUTURE OF INTERFERON IN MPN

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CLINICAL TRIALS

1. First line therapy with IFN

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

Final results presented at EHA 2022

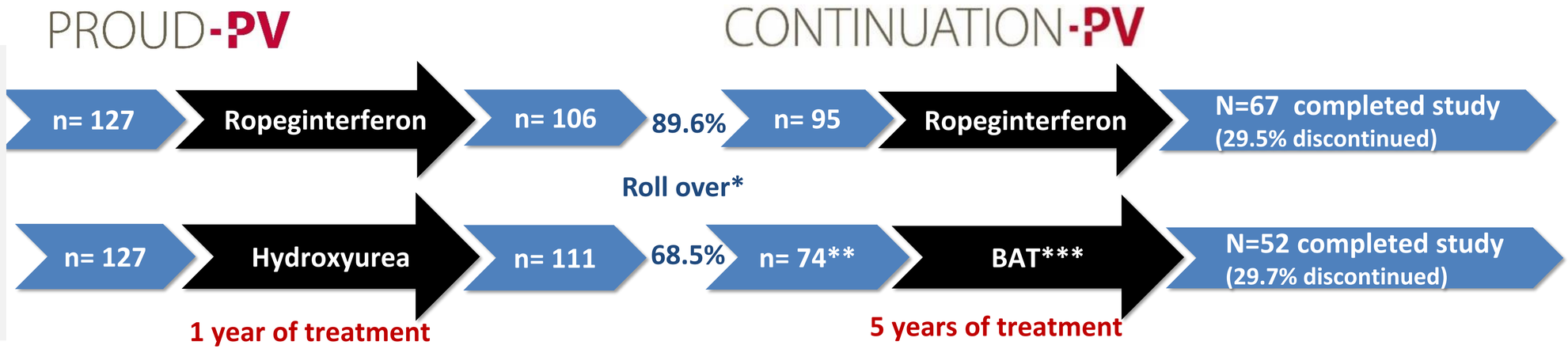
Kiladjian JJ et al. *Leukemia*. 2022;36(5):1408-1411

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

Patient disposition and dosing

- Patients were analyzed according to assigned treatment group. As of Year 6:
  - 88% of patients in the control arm remained on hydroxyurea as best available treatment, and 12% of patients had switched to an interferon therapy.
  - The median cumulative 4-weekly dose of ropeginterferon alfa-2b was 499 µg (IQR: ±268-782 µg); the median dose of hydroxyurea was 1000 mg/day (IQR: 750-1500 mg).

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

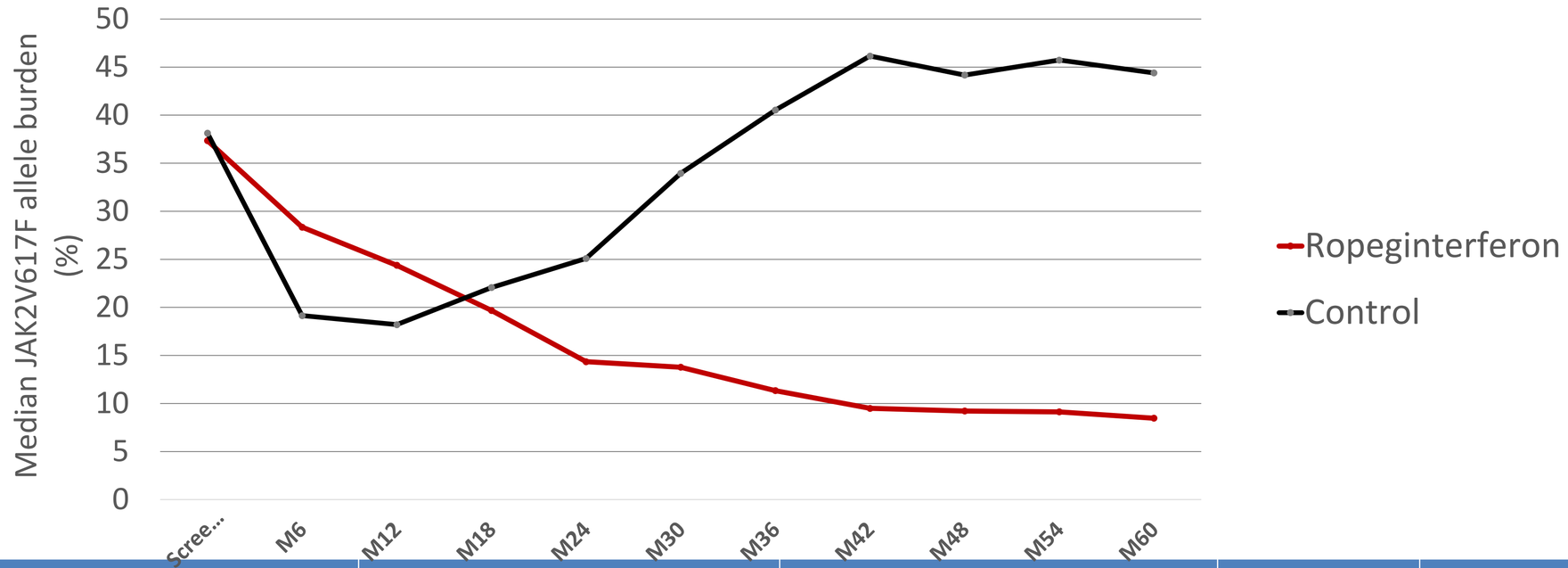
Results from CONTINUATION-PV at 6 years agreed with previously published interim analyses,[1,2] demonstrating higher rates of complete hematologic response (CHR) and molecular response (MR [partial/complete] using ELN criteria) among ropeginterferon alfa-2b treated patients compared to the control group

	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)



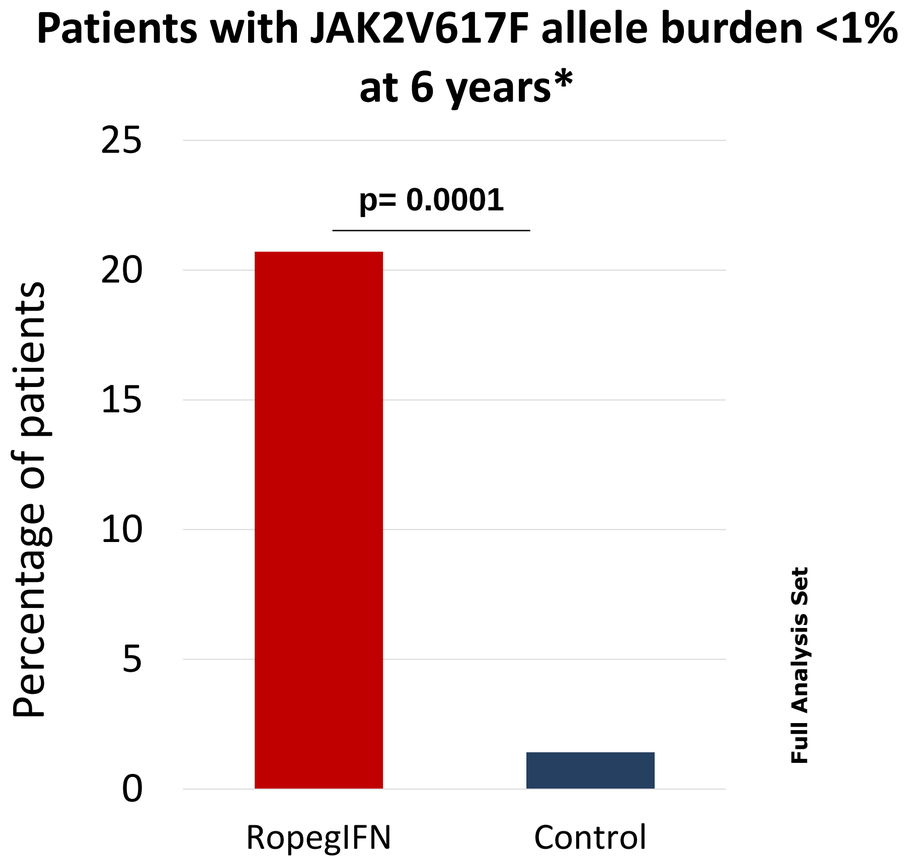
Study Month	Ropeg IFN (N=95)		Control (N=76)		p-value	RR [95% CI] (Ropeg IFN/Control)
	Mean	Median	Mean	Median		
Baseline	42.8	37.3	42.9	38.1	-	-
MONTH 12	30.2	24.4	24.4	18.2	0.0244	6.646 (0.86 to 12.43)
MONTH 24	20.9	14.3	32.4	25.1	0.0003	-10.745 (-16.50 to -4.98)
MONTH 36	19.7	11.3	39.3	40.5	<0.0001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

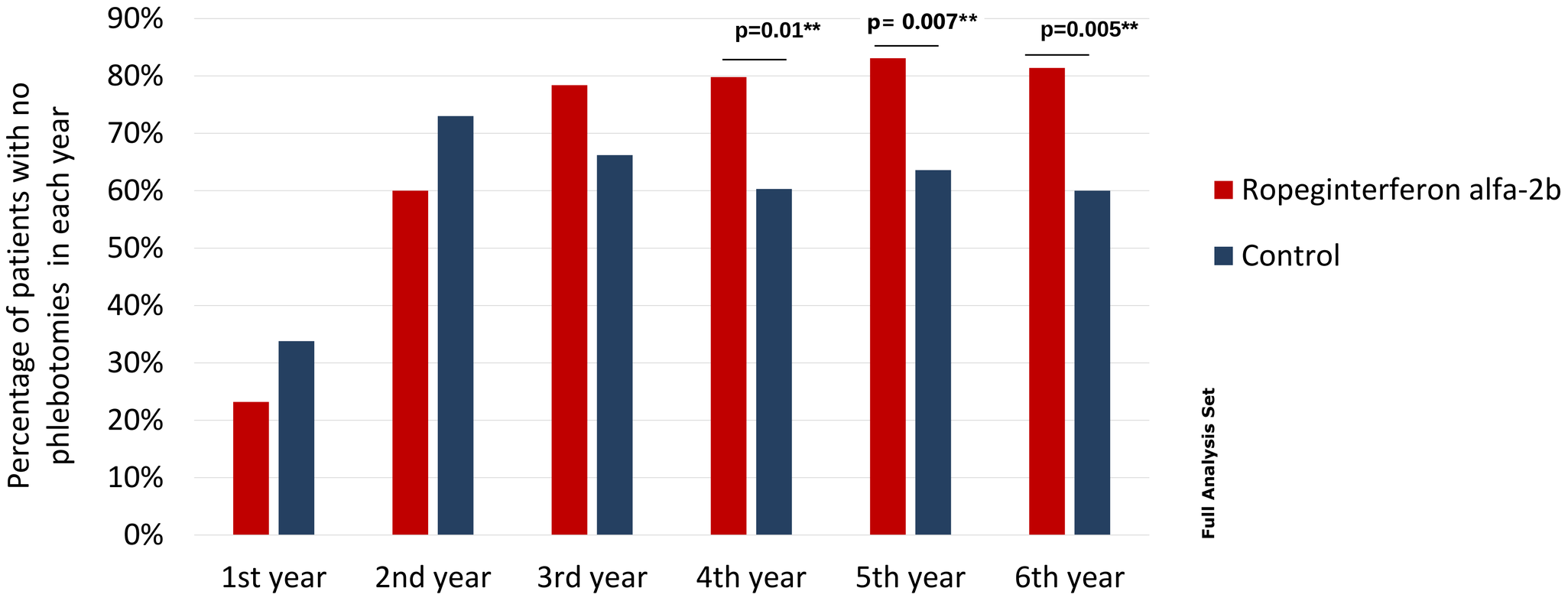
- Depletion of the *JAK2*V617F allele burden may lower the risk of progression of PV to secondary myelofibrosis.[1,2]
- After 6 years of treatment, the *JAK2*V617F allele burden decreased to <1% in **20.7%** of patients in the ropeginterferon alfa-2b arm.
- In contrast, only **1.4%** of patients in the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

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)**

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	5	5
Number of patients (%)	**4 (3.1%)**	**5 (3.9%)**

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)
Number of patients (%)	**1 (0.8%)**	**4 (3.1%)**

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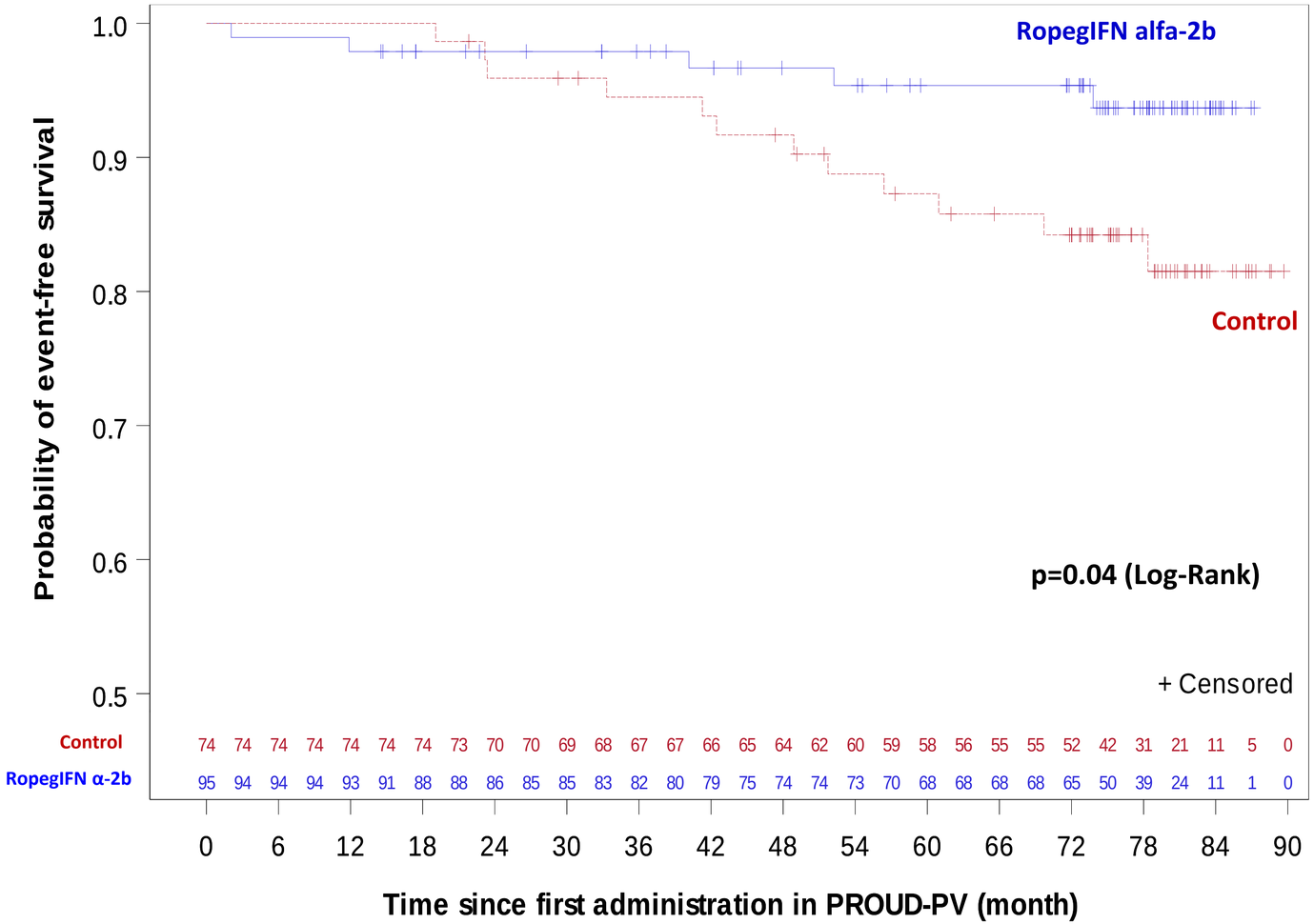
Event-free survival

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)

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

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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.

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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

Conclusions

Long-term ropeginterferon alfa-2b therapy fulfils treatment goals important to patients with PV:

- Good quality of life as indicated by a low symptom burden and low phlebotomy requirement
- Potential to influence disease progression
- Higher probability of event-free survival compared with best available treatment

Low-PV

- *The benefit/risk profile of Pegylated proline-Interferon alpha-2b (AOP2014) added to the best available strategy based on phlebotomies in low-risk patients with Polycythemia Vera (PV).*
- **The Low-PV randomized trial**

Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study): a multicentre, randomised phase 2 trial

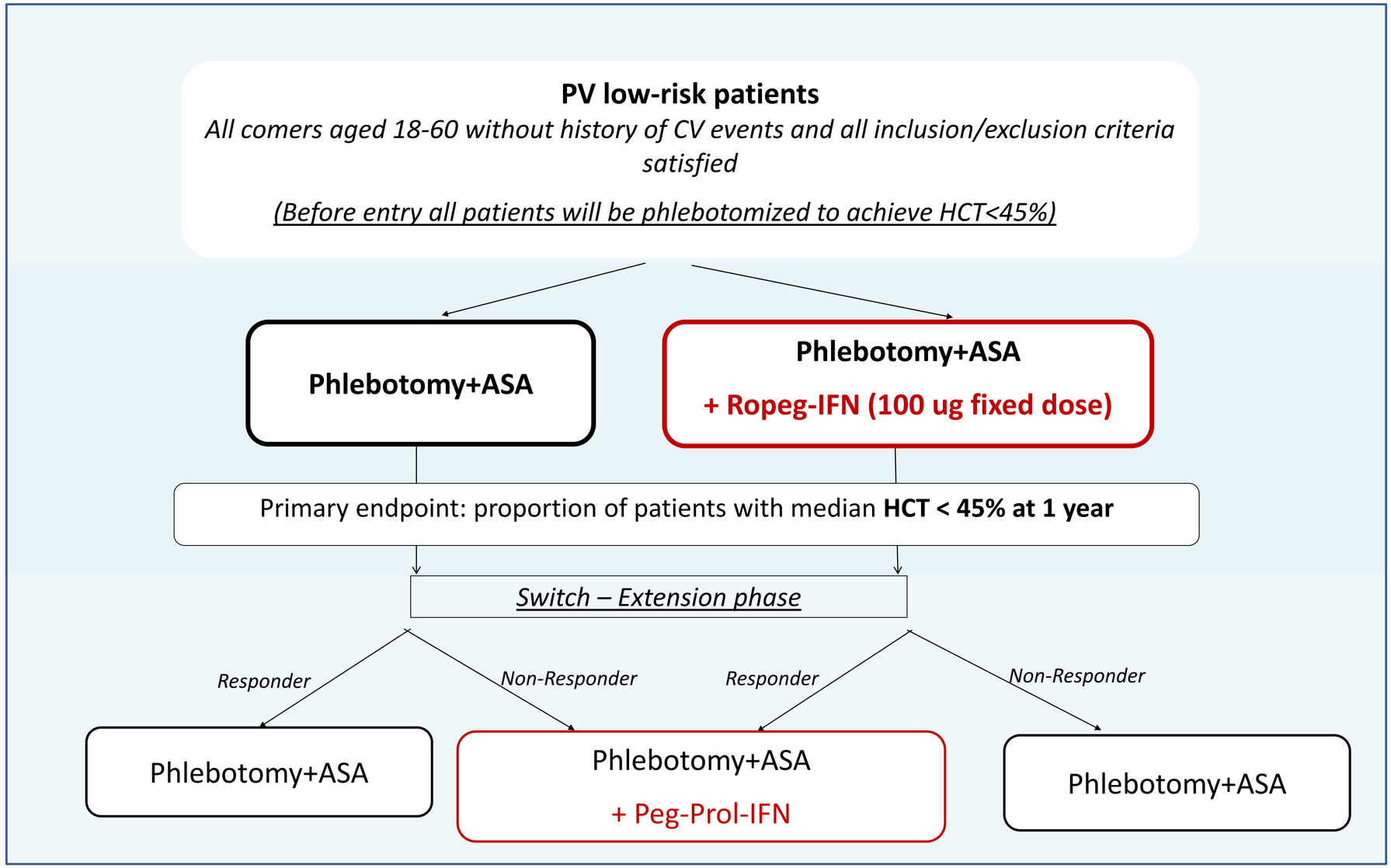
Tiziano Barbui, Alessandro Maria Vannucchi, Valerio De Stefano, Arianna Masciulli, Alessandra Carobbio, Alberto Ferrari, Arianna Ghirardi, Elena Rossi, Fabio Ciceri, Massimiliano Bonifacio, Alessandra Iurlo, Francesca Palandri, Giulia Benevolo, Fabrizio Pane, Alessandra Ricco, Giuseppe Carli, Marianna Caramella, Davide Rapezzi, Caterina Musolino, Sergio Siragusa, Elisa Rumi, Andrea Patriarca, Nicola Cascavilla, Barbara Mora, Emma Cacciola, Carmela Mannarelli, Giuseppe Gaetano Loscocco, Paola Guglielmelli, Silvia Betti, Francesca Lunghi, Luigi Scaffidi, Cristina Bucelli, Nicola Vianelli, Marta Bellini, Maria Chiara Finazzi, Gianni Tognoni, Alessandro Rambaldi

Lancet Haematol 2021

This online publication has been corrected. The corrected version first appeared at thelancet.com/haematology on January 27, 2021

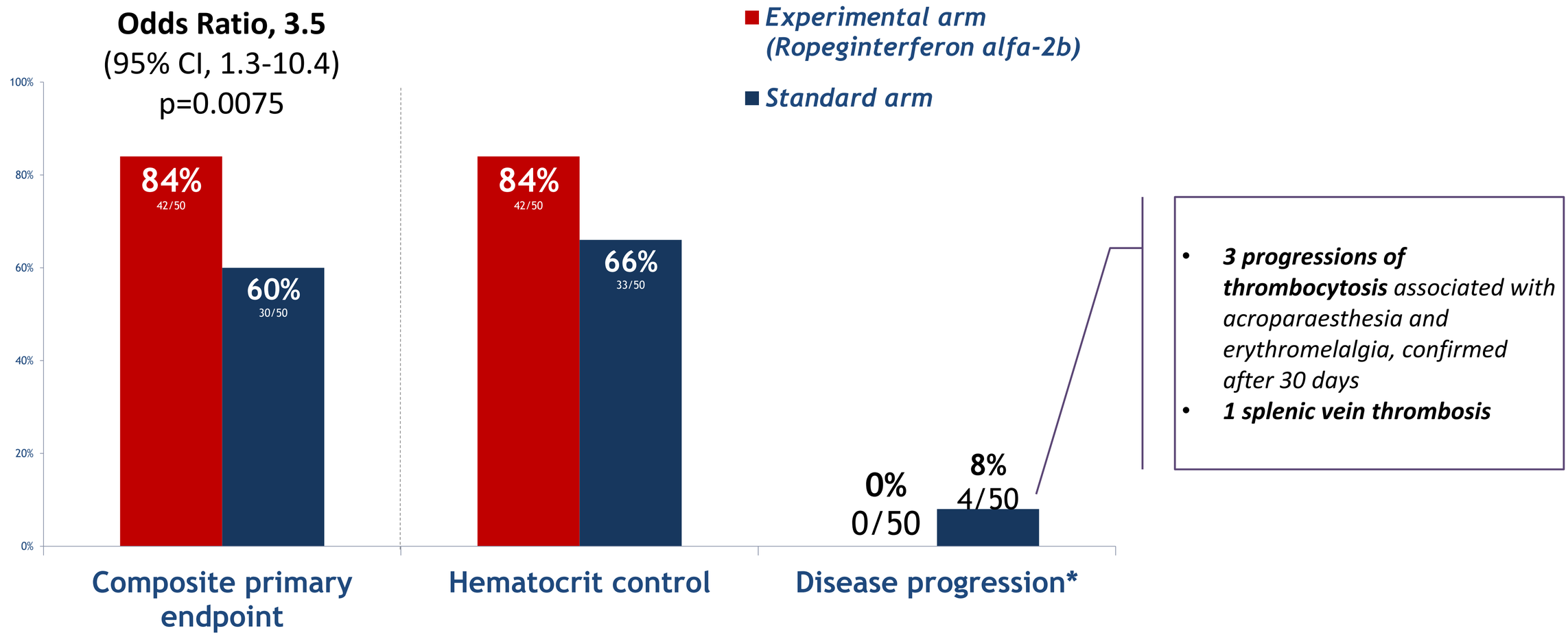
Published Online
January 18, 2021
https://doi.org/10.1016/S2352-3026(20)30373-2

Low-PV phase II RCT



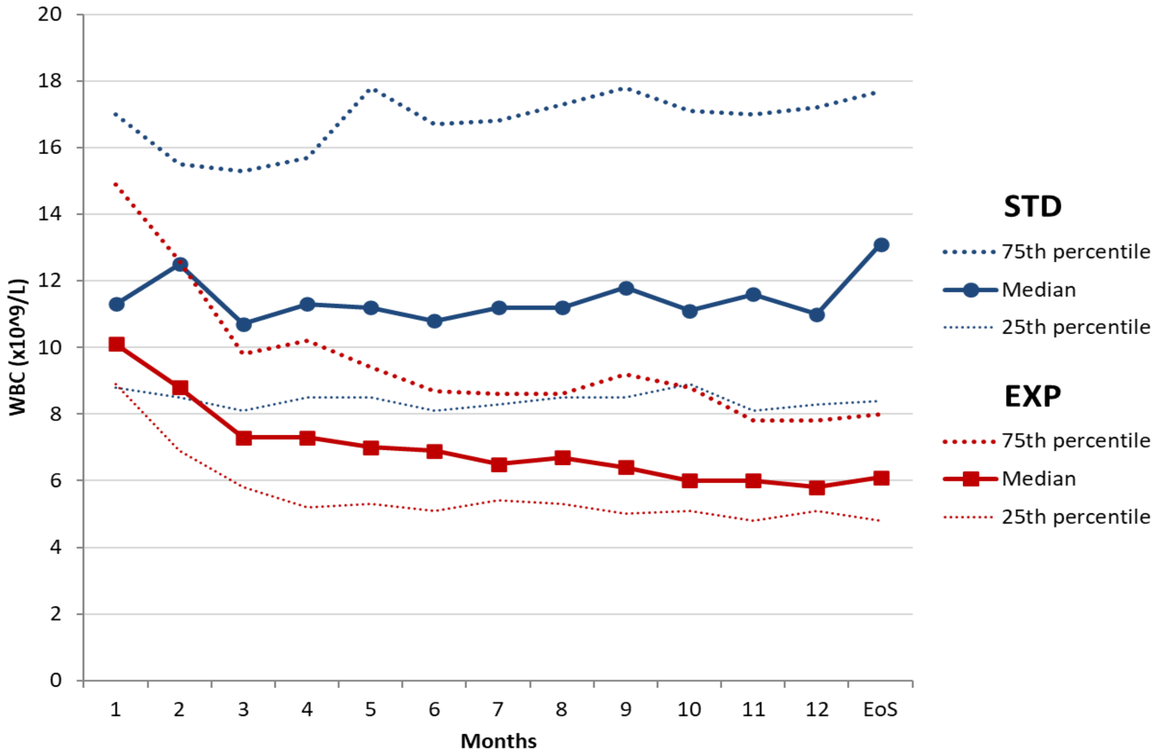
Primary Endpoint

Definition: patients maintaining the median HCT values <45% during 12 months in the absence of progressive disease*

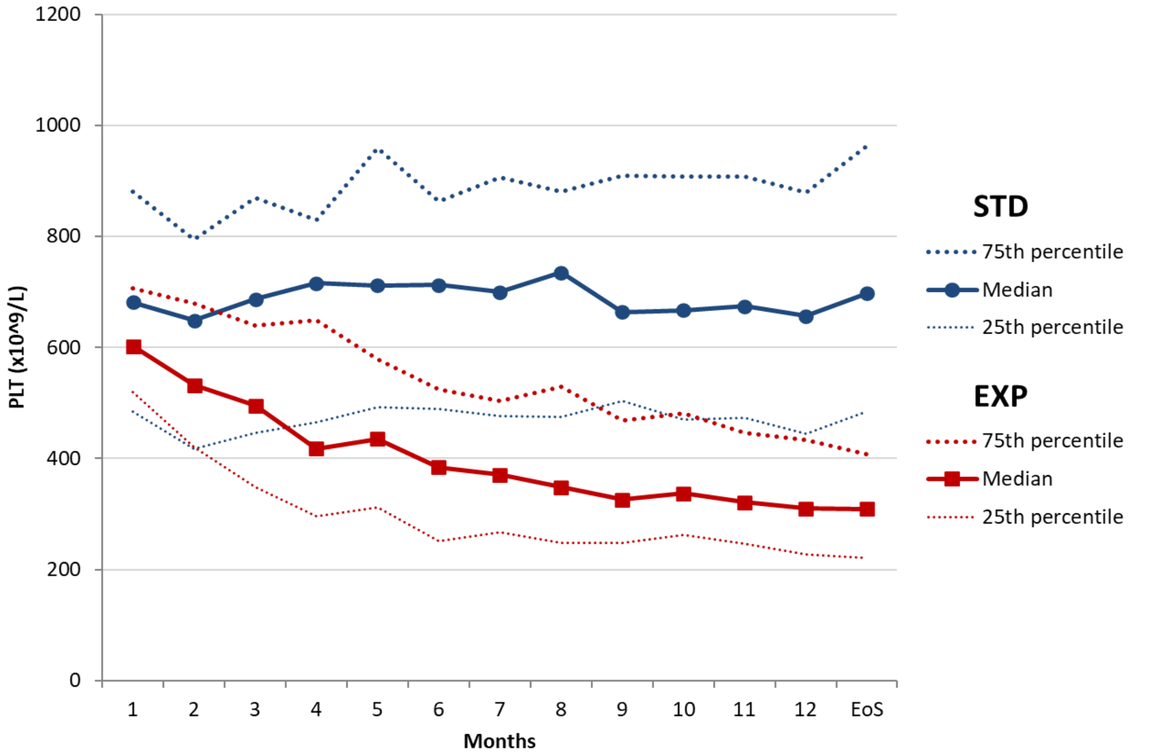


Secondary endpoint: White-Cell and Platelet Counts

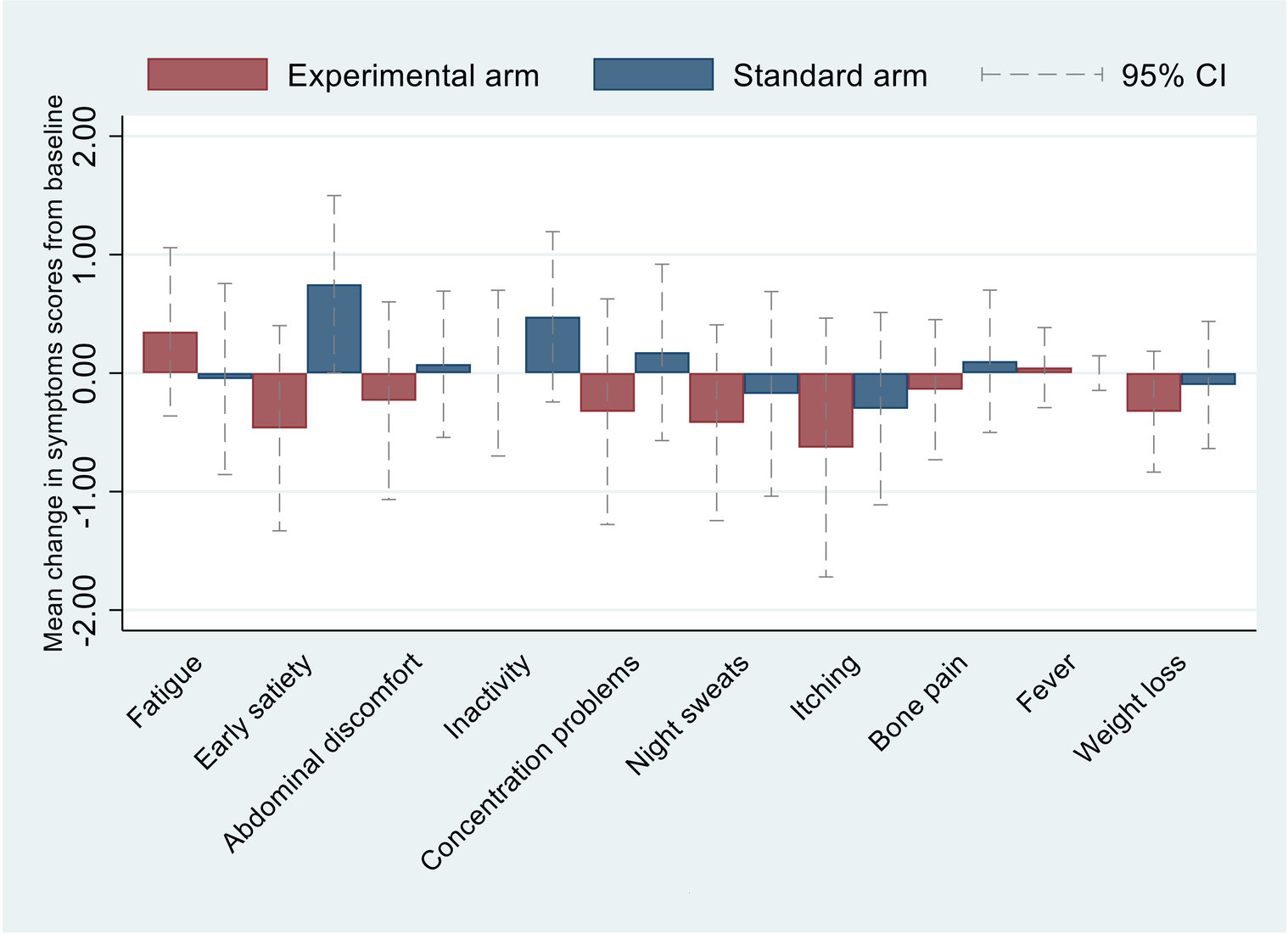
White Blood Cells



Platelets



Secondary endpoint: Quality of life (MPN-SAF items)



Mean change

p=0.033

EXP *STD*

+10%

-21%

Negative values indicate a reduction in the severity of symptoms

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Efficacy and Safety of Ropeginterferon Alfa-2b for Pre-Fibrotic Primary Myelofibrosis and DIPSS Low/Intermediate-1 Risk Myelofibrosis

Harinder Gill*[1], Lester Au[1], Dorothy Tsai[1], Rita Yim[1], Lynn Chin[1], Vivian Li[1], Paul Lee[1], Chantelle Wong[1], Garret MK Leung[1], Carmen Lee[1], Tony KY Wu[1], Cheong Ngai[1], Ryan Ho[1], Albert CF Sin[2], Hsin-An Hou[3], Chih-Cheng Chen[4], and Yok-Lam Kwong[1]

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Results – Haematological responses at 24 weeks

Parameter	Pre-PMF (N=32)	Overt PMF (N=3)	SMF (N=12)	All (N=47)
Hb response, no.(%)	26 (81.3)	2 (66.7)	8 (66.7)	36 (76.6)
WBC response, no.(%)	29 (90.6)	2(66.7)	10 (83.3)	41 (87.2)
Platelet response, no.(%)	26 (81.3)	3 (100)	8 (66.7)	37 (78.7)

Hb: haemoglobin; WBC: white blood cell; Pre-PMF: pre-fibrotic primary myelofibrosis; Overt primary myelofibrosis; SMF: Secondary (post-PV and post-ET) MF

Hb response is defined as 10 g/dL to ULN
WBC response is defined as less than 10 x 10^9/L
Platelet response is defined as <= 400 x 10^9/L

Results – Common adverse events

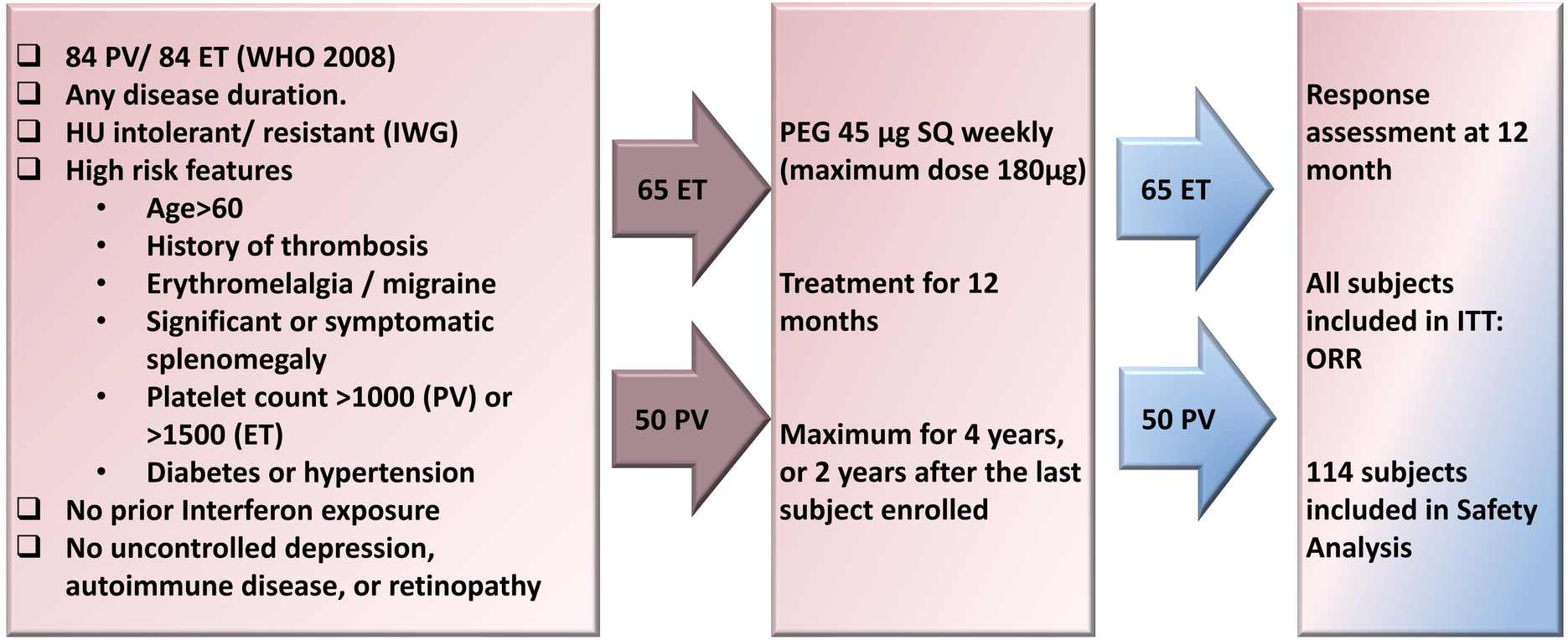
Adverse event	Grade 1/2	Grade 3/4	Total
Haematological			
Anaemia	14 (23.3)	5 (8.3)	19 (31.6)
Leucopenia	1 (1.7)	0	1 (1.7)
Neutropenia	4 (6.7)	2 (3.3)	6 (10)
Thrombocytopenia	9 (15)	0	9 (15)
Non-haematological			
Hair loss	20 (33.3)	0	20 (33.3)
Bone pain	10 (10)	0	10 (10)
Fever	2 (3.3)	0	2 (3.3)
Malaise	24 (40)	1 (1.7)	25 (41.7)
Muscle pain	11 (18.3)	0	11 (18.3)
Transaminitis (ALT/AST)	7 (11.7)	1 (1.7)	8 (13.4)
Thyroid dysfunction	1 (1.7)	0	1
Depression/Mood disorders	0	0	0

ONLY 8.3% of patients required dose reduction due to anaemia

CLINICAL TRIALS

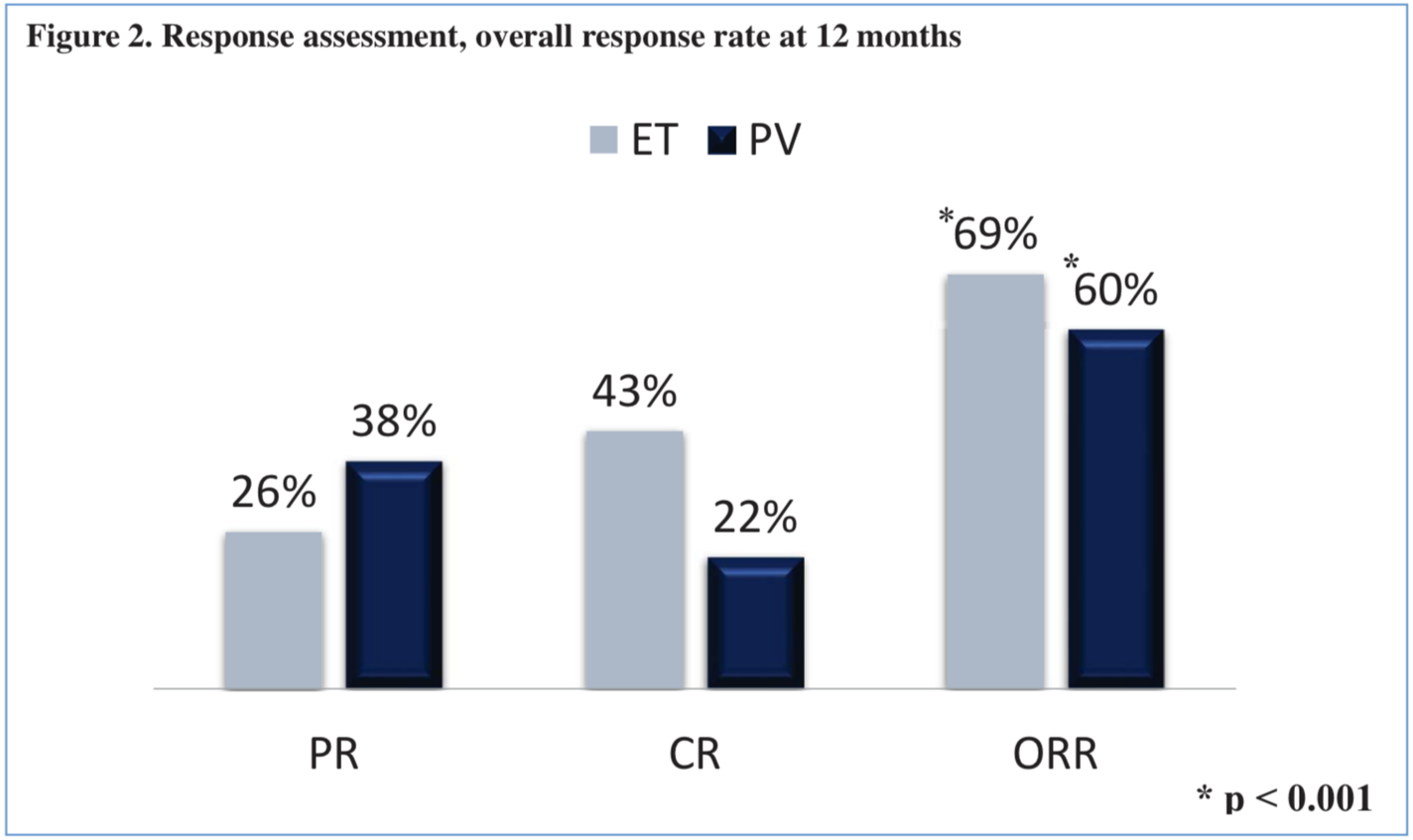
1. First line therapy with IFN
2. Second line therapy with IFN

Pegylated Interferon Alfa-2a for Polycythemia Vera or Essential Thrombocythemia Resistant or Intolerant to Hydroxyurea.



Yacoub et al. Blood, 2019. pii: blood.2019000428. doi: 10.1182/blood.2019000428.

Pegylated Interferon Alfa-2a for Polycythemia Vera or Essential Thrombocythemia Resistant or Intolerant to Hydroxyurea.



Yacoub et al. Blood, 2019. pii: blood.2019000428. doi: 10.1182/blood.2019000428.

CLINICAL TRIALS

1. First line therapy with IFN
2. Second line therapy with IFN
3. Combination therapy with IFN

American Society *of* Hematology

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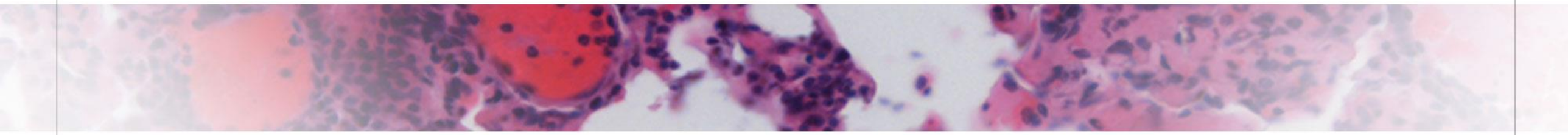


Final Results of Ruxopeg, a Phase 1/2 Adaptive Randomized Trial of Ruxolitinib and Pegylated Interferon Alpha 2a in Patients with Myelofibrosis

Jean-Jacques Kiladjian,

J.C. Ianotto, J. Soret, N. Maslah, C. Chaffaut, F. Boyer Perrard, F. Barraco, V. Dubruille, C. Capron, A. Tisserand, V. Rolland-Neyret, Z. Ghrieb, S. Chevret, I. Plo, M.H. Schlageter, V. Meignin, M. Resche-Rigon, and B. Cassinat

FIM FRENCH INTERGROUP MYELOPROLIFERATIVE DISORDERS

filo FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

RUXOPEG study design

Key inclusion criteria:

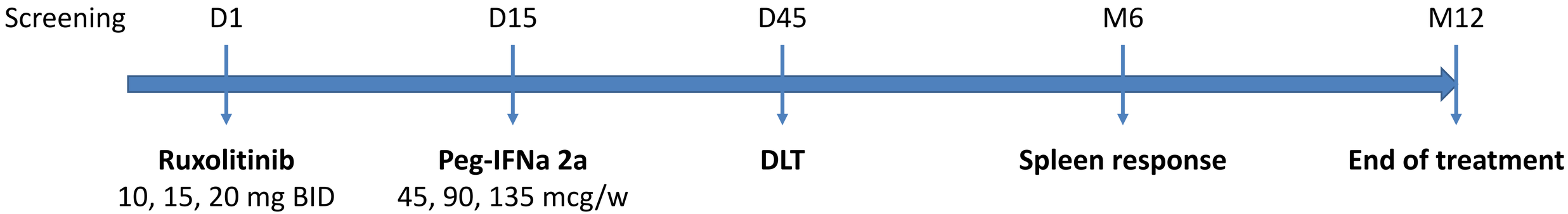
- diagnosis of MF (WHO criteria)
- Int or HR (IPSS)
- need of active therapy
- presence of a driver mutation

Key exclusion criteria:

- prior treatment (or contra-indication) with Rux or IFNa
- eligibility for stem cell transplantation
- inadequate liver, cardiac or renal function,
- autoimmune disease
- history of depression

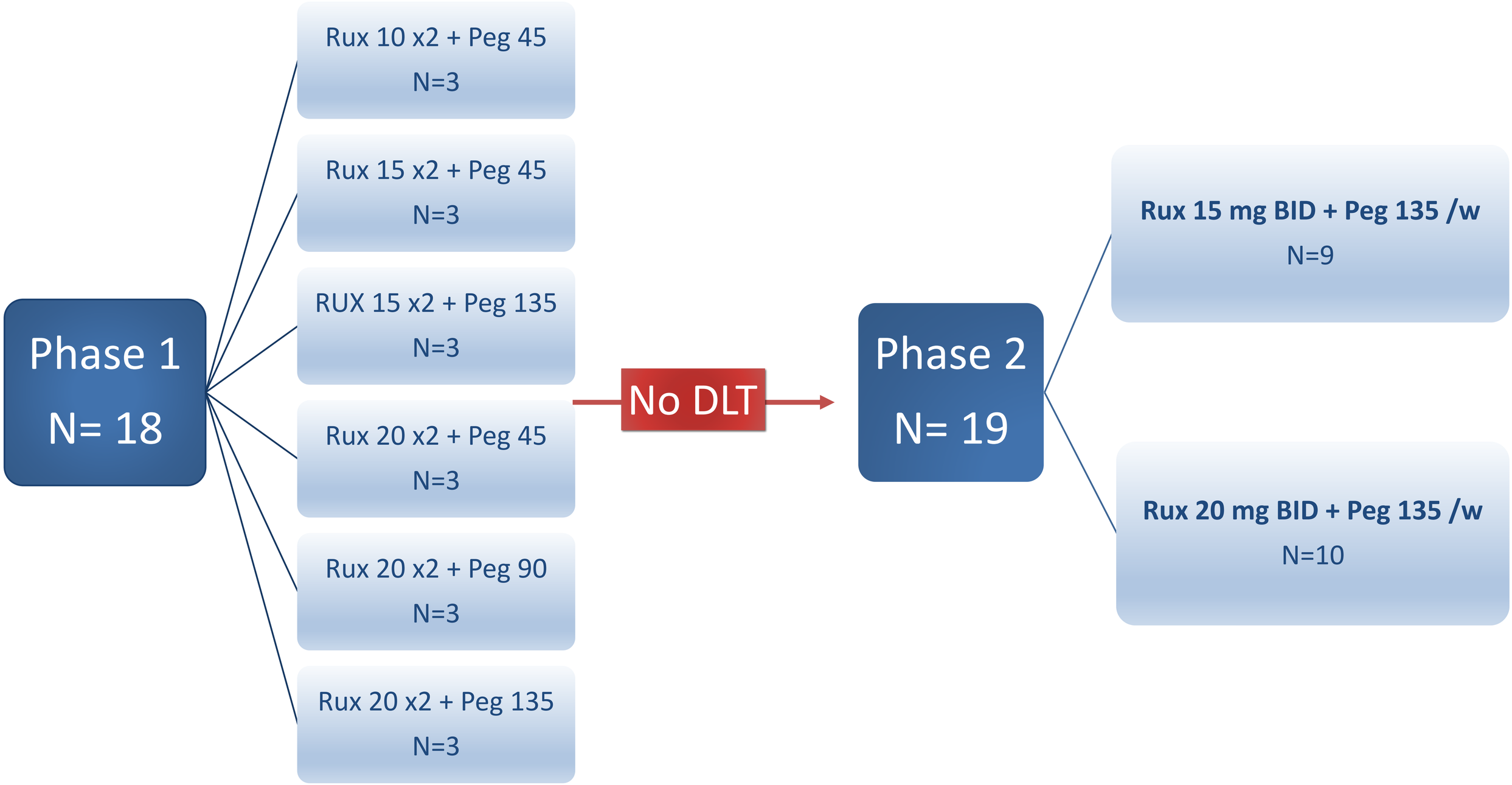
ClinicalTrials.gov Identifier: NCT02742324

RUXOPEG study design



BM Biopsy				BM Biopsy
Mutations	Mutations	Mutations	Mutations	Mutations
HSPC assay				HSPC assay
Cytokines	Cytokines	Cytokines		Cytokines
Immune effectors	Immune effectors	Immune effectors		Immune effectors

Patient disposition



Results – Spleen response (50% reduction)

Primary endpoint (W24)	N included	N success	Success rate (ITT) [IC95%]
Phase 1	18	12	67% [41;87]
Phase 2	19	14	74% [49;91]
Total	**37**	**26**	**70% [53;84]**

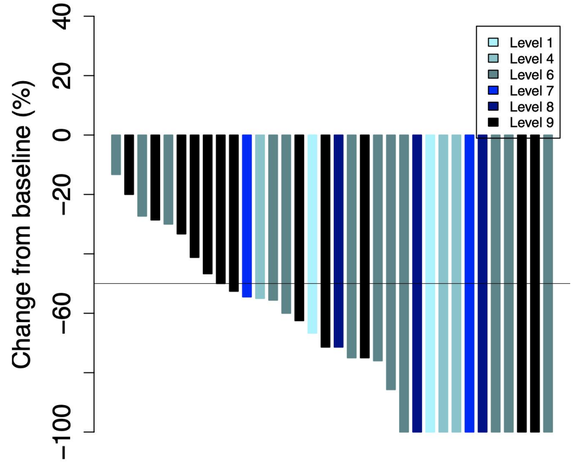


Figure 1 - Waterfall plot of percent change in spleen length at week 24 according to dose levels

Secondary endpoint (M12)	N included	N success	Success rate (ITT) [IC95%]
Phase 1	18	12	67% [41;87]
Phase 2	19	16	84% [60;97]
Total	**37**	**28**	**76% [59;88]**

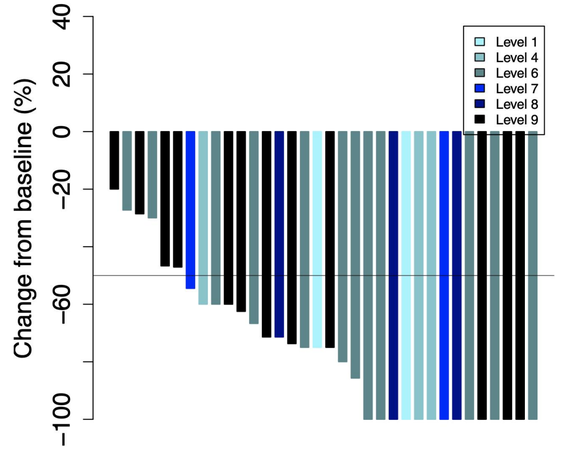


Figure 2 - Waterfall plot of percent change in spleen length at 12 months according to dose levels

Results – Safety

Adverse Events N= 363	
Grade 1	59%
Grade 2	33%
Grade 3	7.5%
Grade 4	0.5%

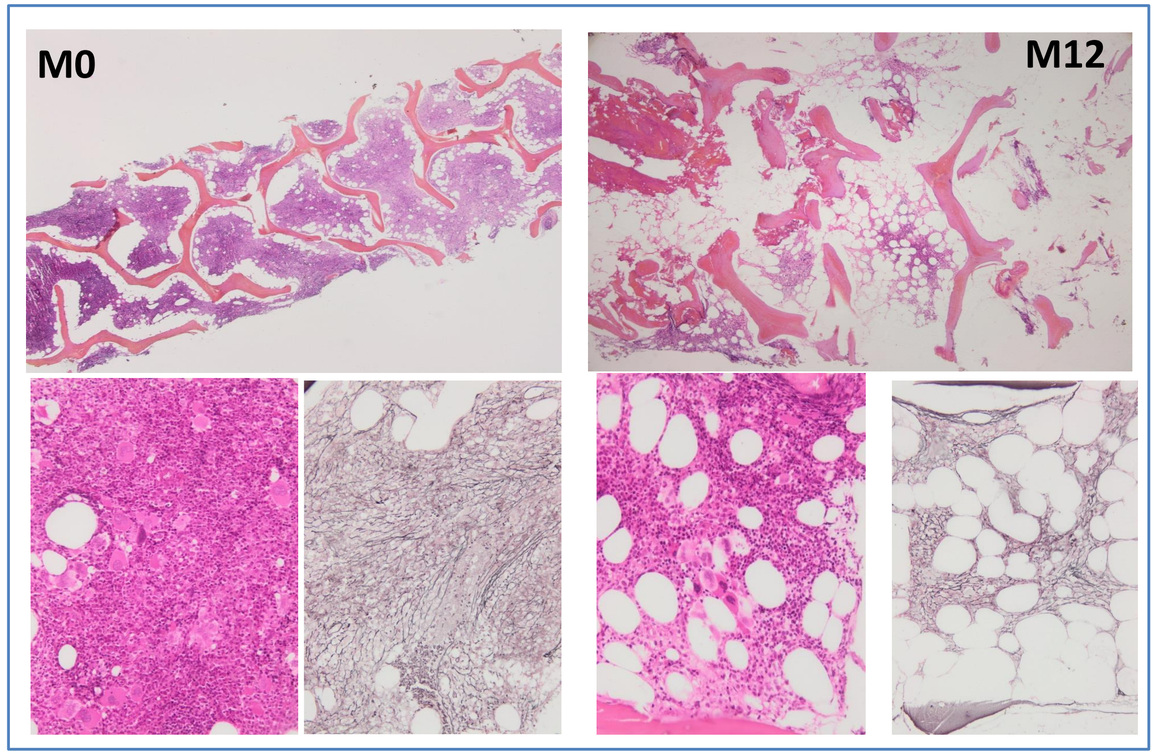
Most frequent AEs	
Anemia	18.7%
Thrombocytopenia	13.7%
GI	7%
Musculoskeletal	6.8%
Asthenia	6.6%

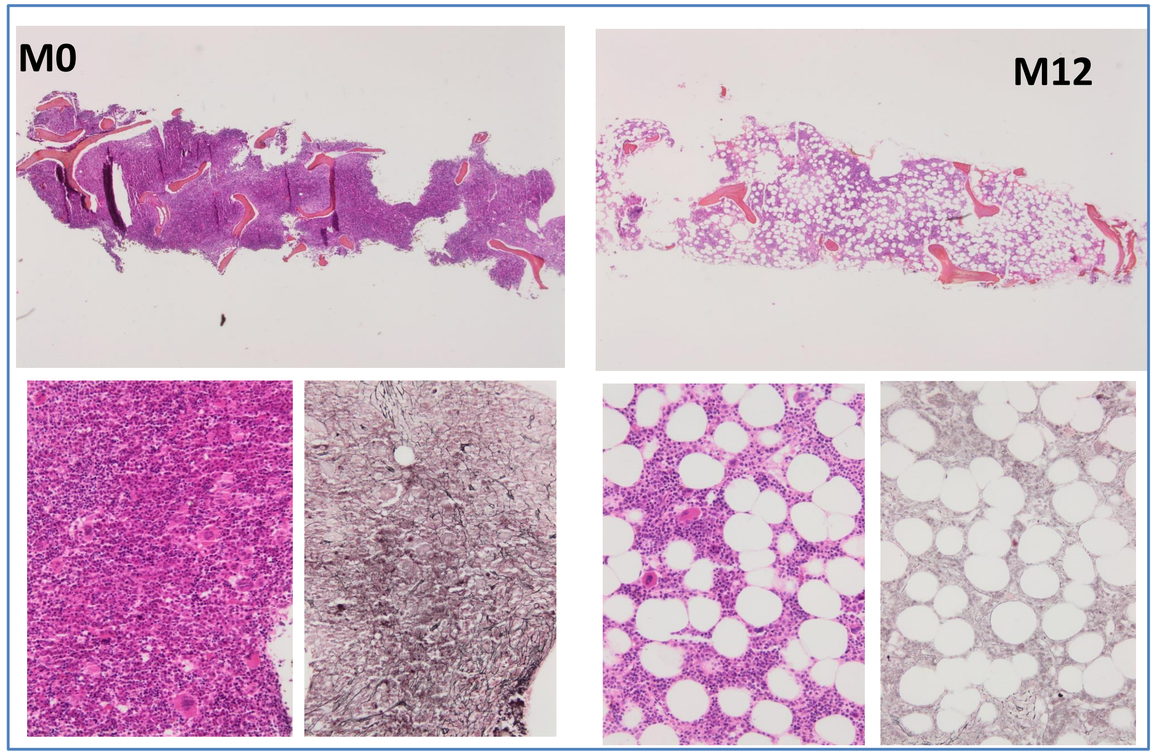
SAE N= 6	
Skin cancer	2
Anemia	2
Urinary infection	1
Raynaud's phenomenon	1

Deaths:
1 patient died of AML transformation after 10.4 months

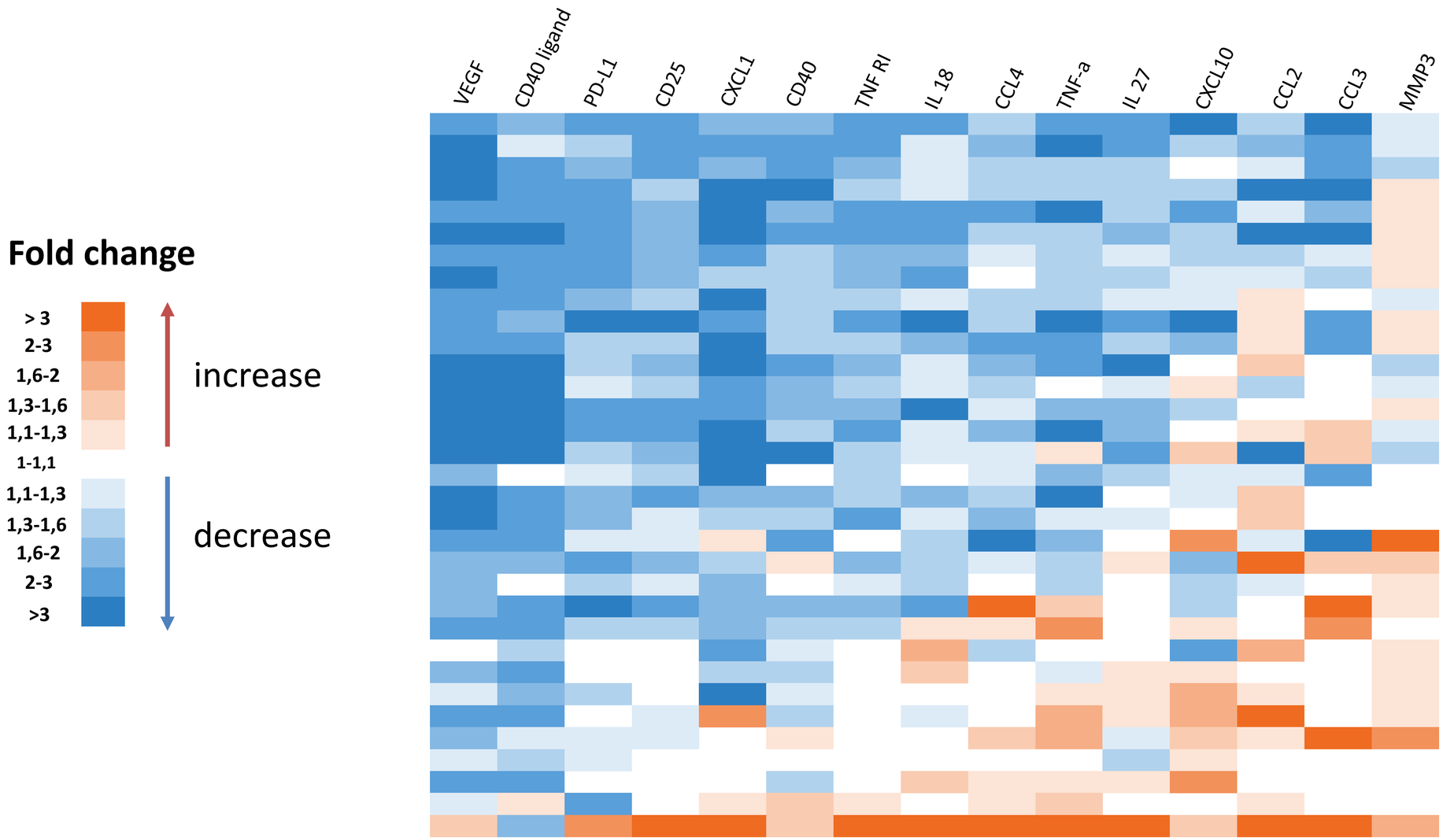
Results – Bone marrow biopsy (centralized blinded review)

Parameter (n evaluable)	Cellularity (n=21)	MK morphology N=24)	Fibrosis grade (n=20)
Improved	57%	25%	5%
No change	43%	75%	90%
Worsened	0	0	5%



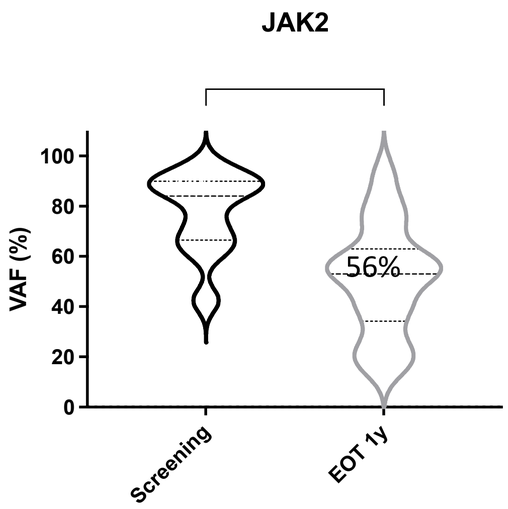


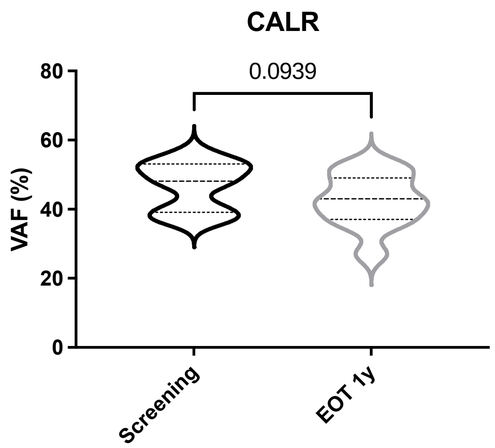
Results – Cytokines

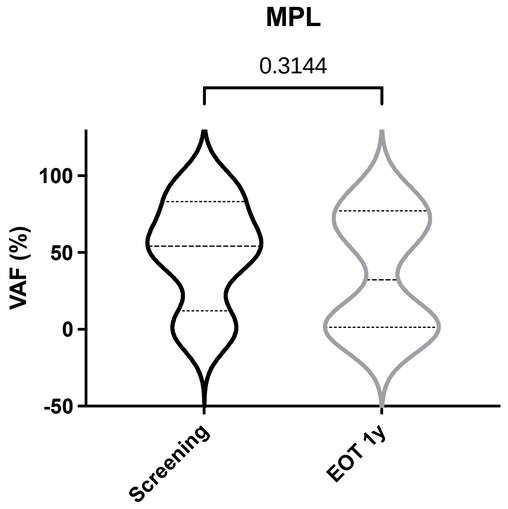


Results – Molecular response

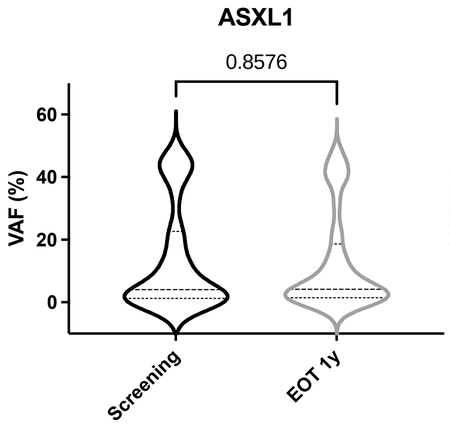
Driver mutations

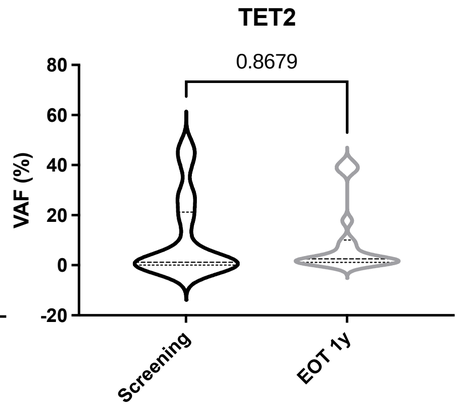


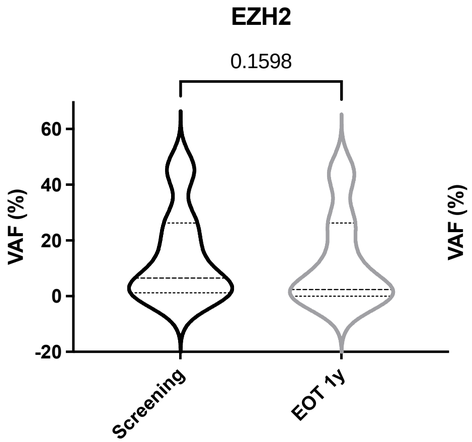


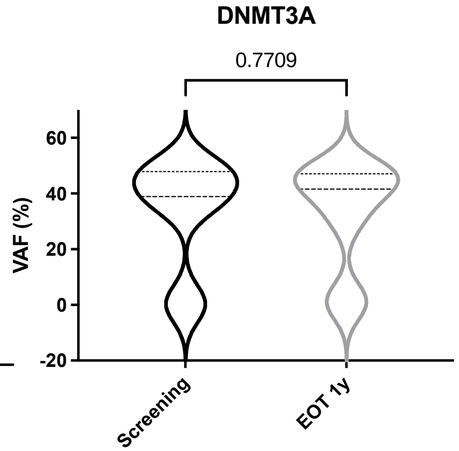


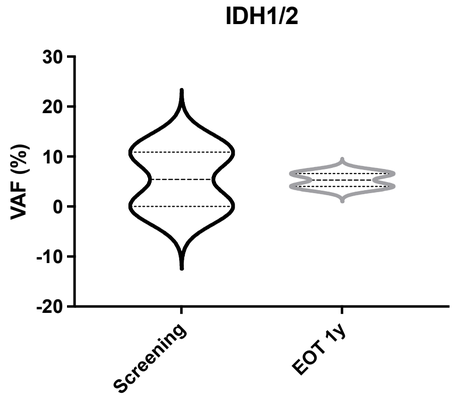
Non-Driver mutations











Conclusion

- The combination of ruxolitinib and peg-IFNa 2a is safe in patients with MF and seems to improve IFN tolerance
- We observed high rates of profound decreases in spleen length and JAK2V617F allele burden
- Presence of additional mutations in ASXL1 (but not in TET2 or DNMT3A) reduces JAK2V617F molecular response
- Ruxolitinib doesn’t impair the targeted effect of IFN on MPN HSPC
- This treatment may improve after 12 months the inflammatory cytokine profile and bone marrow histopathology, important biomarkers of disease severity