THE FUTURE OF INTERFERON IN MYELOPROLIFERATIVE NEOPLASMS

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Besremi

ropeginterferon alfa-2b

On 13 December 2018, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Besremi, intended for the treatment of polycythaemia vera without symptomatic splenomegaly. Besremi was designated as an orphan medicinal product on 9 December 2011. The applicant for this medicinal product is AOP Orphan Pharmaceuticals AG.

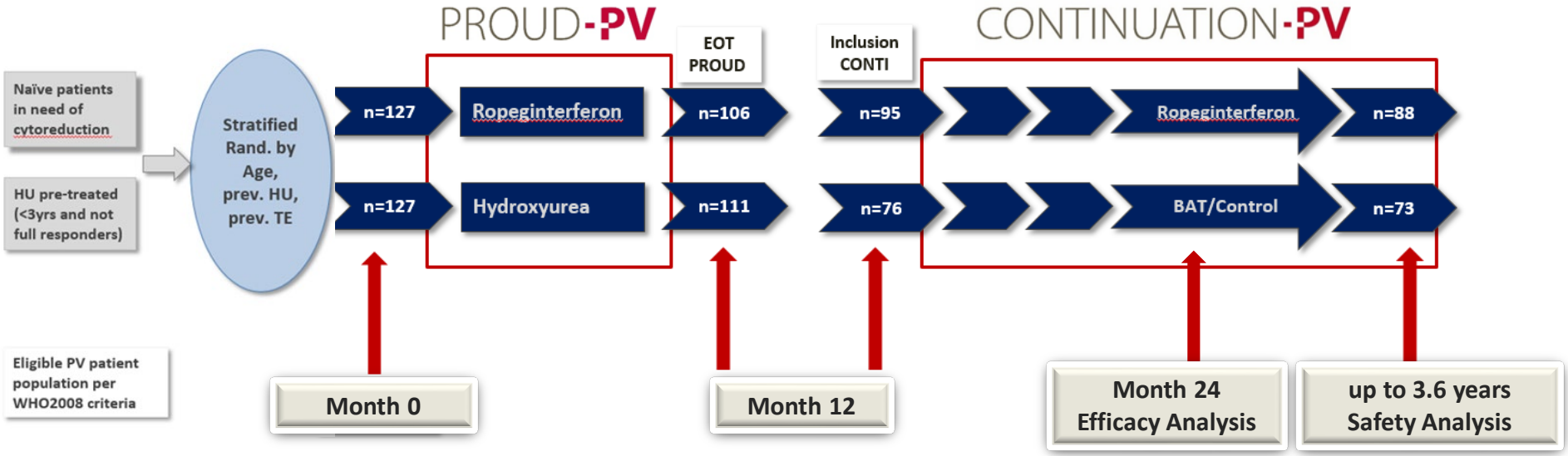
The full indication is: "Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly." It is proposed that Besremi is prescribed by physicians experienced in the management of the disease.

EVIDENCE FOR SUPERIOR EFFICACY AND DISEASE MODIFICATION AFTER THREE YEARS OF PROSPECTIVE RANDOMIZED CONTROLLED TREATMENT OF POLYCYTHEMIA VERA PATIENTS WITH *ROPEGINTERFERON ALFA-2B* VS. *HYDROXYUREA/BEST AVAILABLE TREATMENT*

HEINZ GISSLINGER, CHRISTOPH KLADE, PENCHO GEORGIEV, DOROTA KROCHMALCZYK, LIANA GERCHEVA-KYUCHUKOVA, MIKLOS EGYED, VIKTOR ROSSIEV, PETR DULICEK, ARPAD ILLES, HALYNA PYLYPENKO, LYLIA SIVCHEVA, JIRI MAYER, VERA YABLOKOVA, KURT KREJCY, BARBARA GROHMANN-IZAY, HANS C. HASSELBALCH, ROBERT KRALOVICS, AND JEAN-JACQUES KILADJIAN

ASH 2018

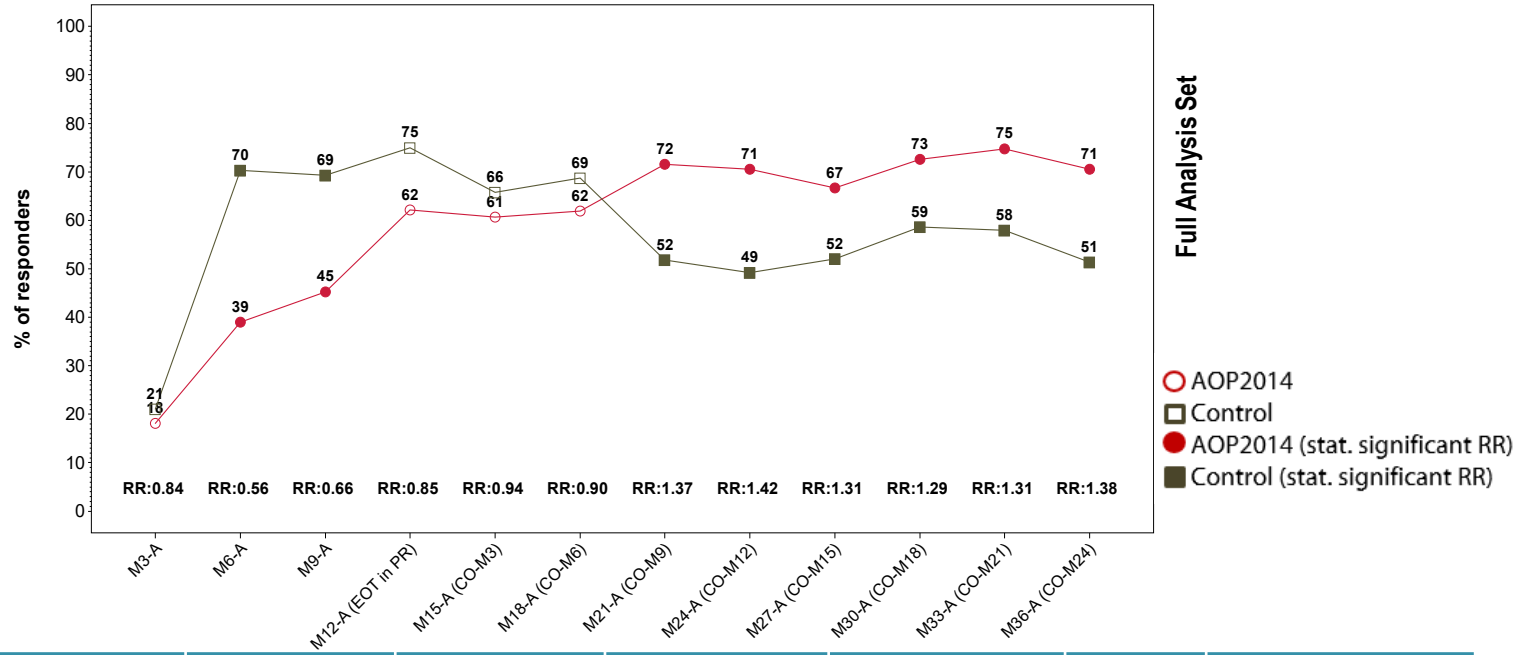
Ropeginterferon alfa-2b phase III development in PV: PROUD-PV and CONTINUATION-PV Studies



Treatment-related adverse events in >10% of patients

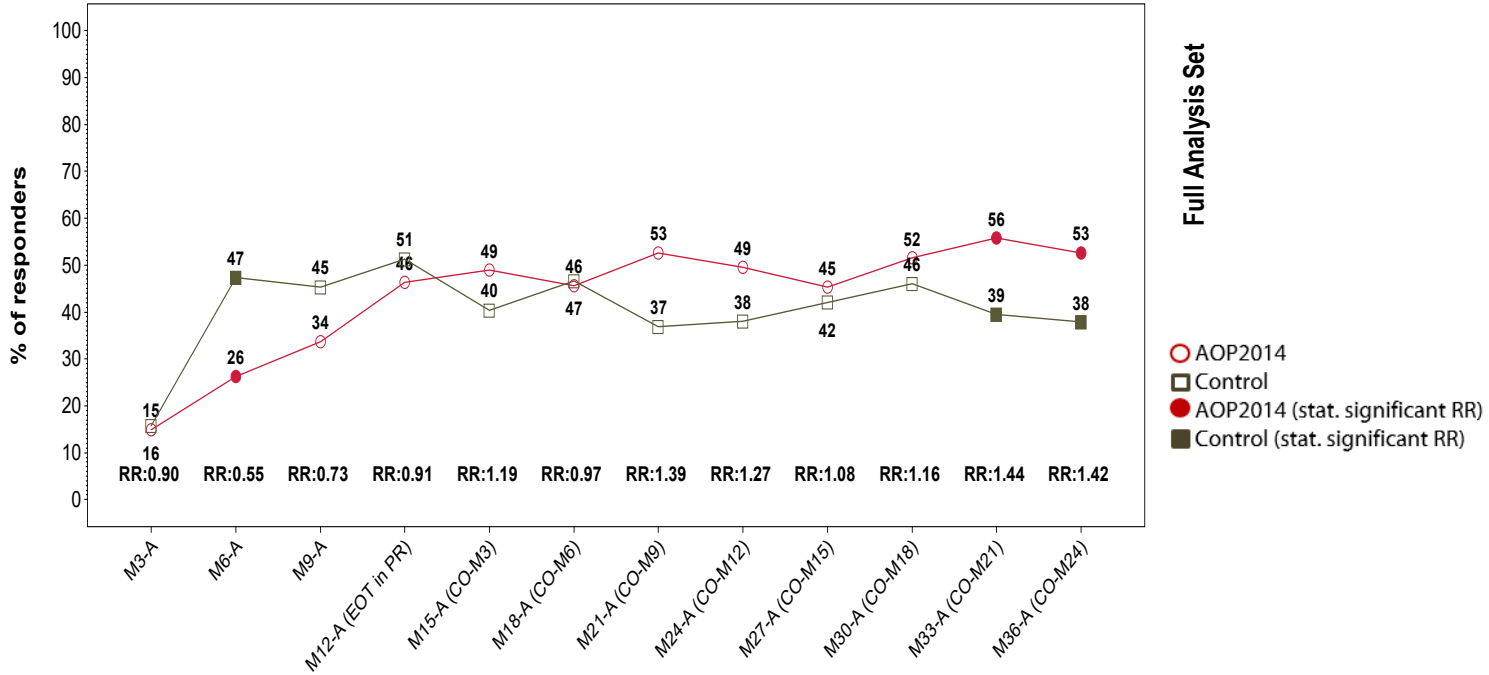
Treatment-related AE	Ropeg (n=95) n (%)	Control (n=76) n (%)
Thrombocytopenia	24 (25.3%)	**25 (32.9%)**
Leukopenia	21 (22.1%)	**23 (30.3%)**
Anaemia	10 (10.5%)	**22 (28.9%)**
Increased gamma-GT	**11 (11.6%)**	2 (2.6%)
Alanine aminotransferase increased	**10 (10.5%)**	-
Platelet count decreased	-	**8 (10.5%)**
Myalgia	**10 (10.5%)**	3 (3.9%)

Complete hematologic response (CHR)



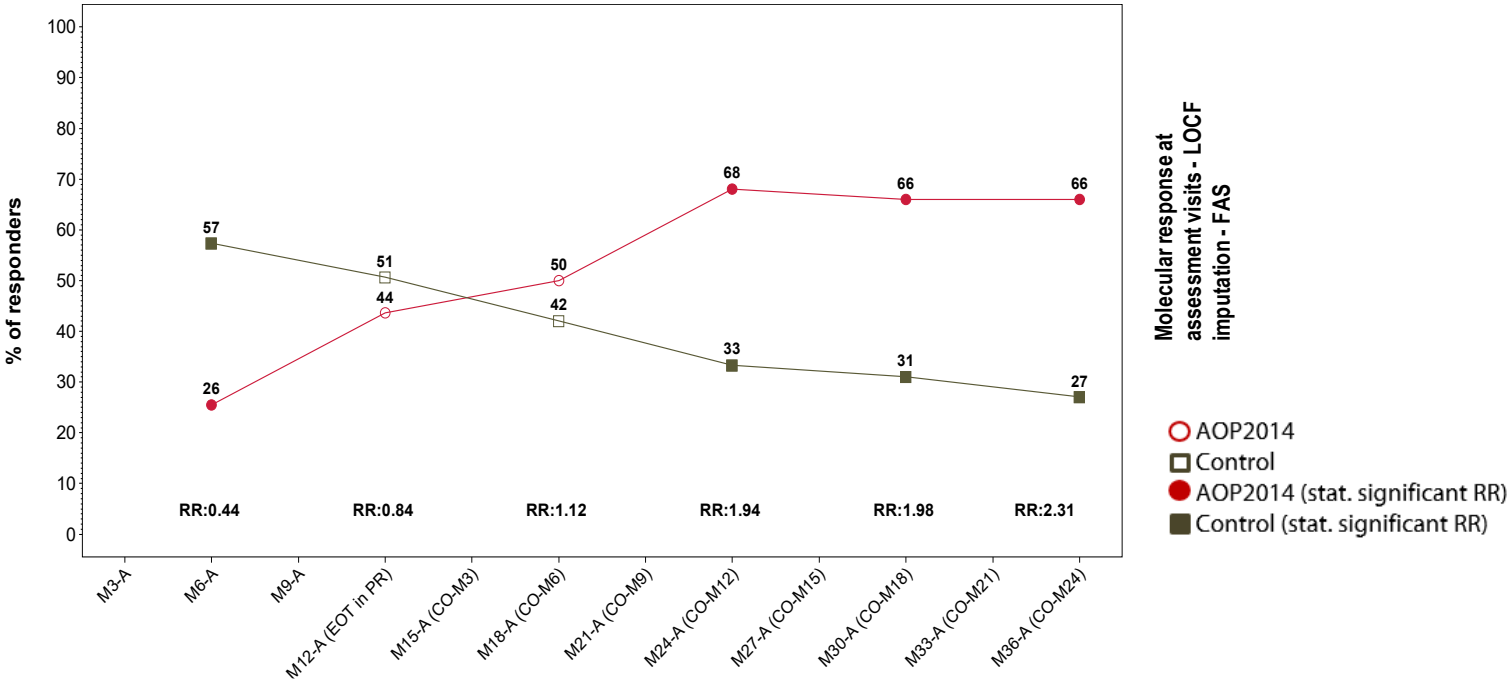
Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1201	0.85 [0.70-1.04]
MONTH 24	67/95	70.5	33/67	49.3	0.0111	1.42 [1.08-1.87]
MONTH 36	67/95	**70.5**	38/74	**51.4**	0.0122	1.38 [1.07-1.79]

CHR + improvement in disease burden



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	44/95	46.3	39/76	51.3	0.5245	0.91 [0.67-1.23]
MONTH 24	47/95	49.5	27/71	38.0	0.1832	1.27 [0.89-1.81]
MONTH 36	50/95	**52.6**	28/74	**37.8**	0.0437	1.42 [1.01-2.00]

JAK2 (V617F) - Molecular response



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	41/94	43.6	38/75	50.7	0.5001	0.84 [0.62-1.15]
MONTH 24 (LOCF)	64/94	68.1	25/75	33.3	0.0001	1.99 [1.40-2.84]
MONTH 36 (LOCF)	62/94	**66.0**	20/74	**27.0**	<0.0001	2.31 [1.56-3.42]

Conclusions

- Results from three years of treatment in this large, prospective, controlled trial in PV confirm the previously reported efficacy and safety of ropeginterferon alfa-2b
- Ropeg showed high and **durable hematologic responses** and **symptom control** with **good tolerability**
- Ropeg reduced not only *JAK2*V617F but also additional mutations and cytogenetic aberrations confirming **disease modification** capability of IFNa
- Ropeginterferon alfa-2b will provide a valuable and safe new long-term treatment option with features clearly **distinct from other treatment modalities** including HU

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COMPARISON OF LONG-TERM EFFICACY AND SAFETY OF ROPEGINTERFERON ALFA-2B VS. HU IN POLYCYTHEMIA VERA PATIENTS AGED BELOW OR ABOVE 60 YEARS: TWO-YEAR ANALYSIS FROM THE PROUD/CONTINUATION PHASE III TRIALS

Heinz Gisslinger, Christoph Klade, Pencho Georgiev, Dorota Krochmalczyk, Liana Gercheva-Kyuchukova, Miklos Egyed, Viktor Rossiev, Petr Dulicek, Arpad Illes, Halyna Pylypenko, Lylia Sivcheva, Jiri Mayer, Vera Yablokova, Barbara Grohmann-Izay, Gabriele Maurer, Hans Hasselbalch, Robert Kralovics and Jean-Jacques Kiladjian

Background

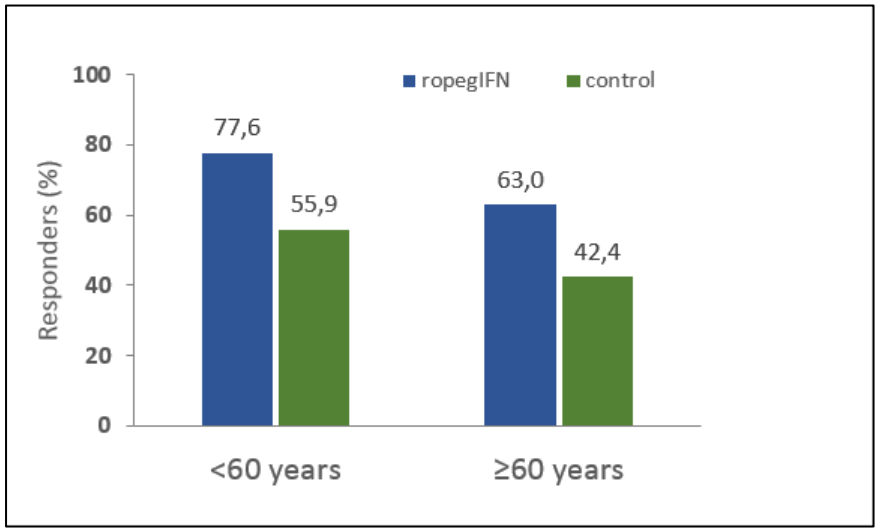
Off-label IFNα as first-line therapy is primarily used in patients of younger age, partly because of the misconception that the risk-benefit ratio is not so favorable in elderly patients.

Aim:

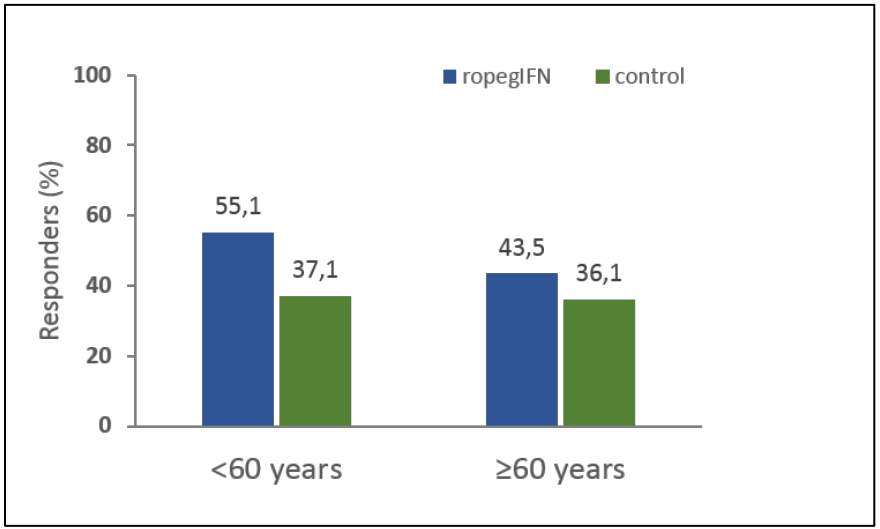
To analyze the efficacy and safety of Ropeginterferon alfa-2b and HU in two age cohorts (<60 years and ≥60 years).

Efficacy Results 24 Months – by age group

CHR



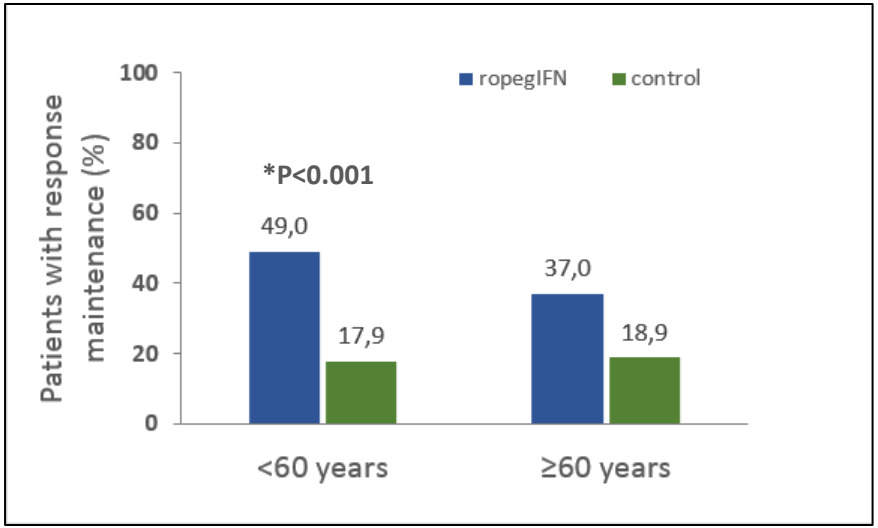
CHR & improvement in disease burden



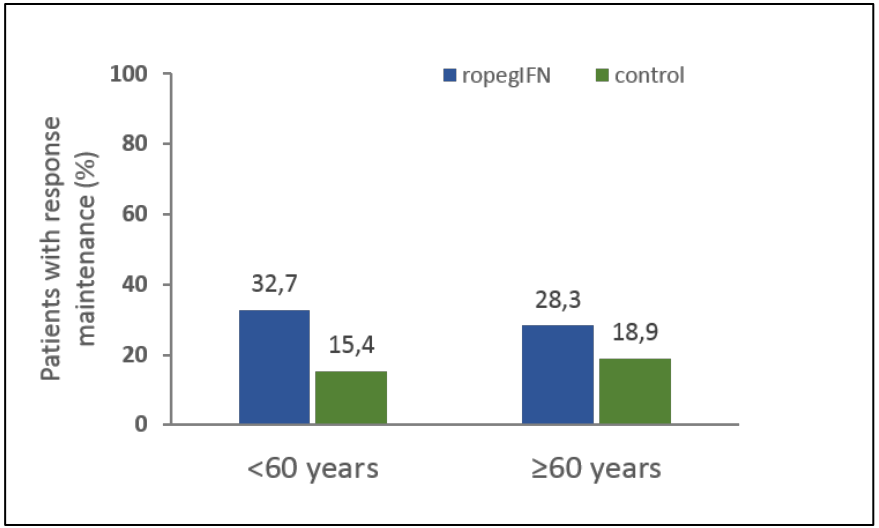
Ropeginterferon alfa-2b induced higher CHR rates compared to control, irrespective of age.

Efficacy Results 24 Months – by age group

Maintenance of CHR



Maintenance of CHR & improvement in disease burden

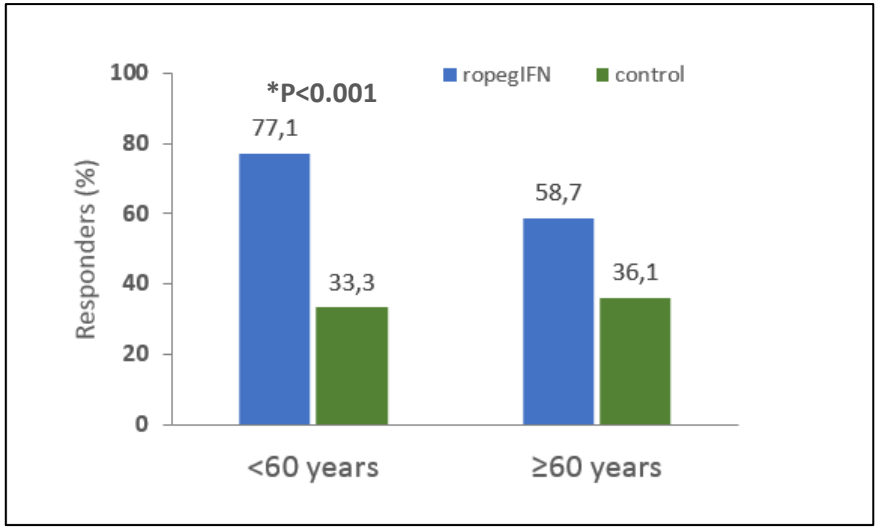


*RR Ropeg/control [95% CI]: 2.82 [1.37-5.79]

Ropeginterferon alfa-2b induced higher maintenance rates of CHR compared to control, irrespective of age.

Efficacy Results 24 Months – by age group

Molecular response (LOCF)



*RR Ropeg/control [95% CI]: 2.17 [1.38 to 3.42]

Ropeginterferon alfa-2b induced a higher molecular response compared to control, irrespective of age

Long-term Safety: up to 3.6 years of treatment; mean 2.7 years

	Ropeg		Control	
	<60 years N=49	≥60 years N=46	<60 years N=39	≥60 years N=37
Patients with AE	44 (89.8%)	43 (93.5%)	36 (92.3%)	34 (91.9%)
Patients with serious AE	3 (6.1%)	10 (21.7%)	4 (10.3%)	9 (24.3%)
Patients with adverse drug reaction (ADR)	38 (77.6%)	29 (63.0%)	29 (74.4%)	33 (89.2%)
Patients with serious ADR	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (10.8%)*
Patients with ≥ Grade 3 AE	10 (20.4%)	16 (34.8%)	10 (25.6%)	14 (37.8%)

- Comparable numbers of AEs and serious AEs in the treatment arms, irrespective of age.
- Number of ADRs was comparable in the patients <60 years but a trend towards a lower number of ADRs (serious and non-serious) was evident for Ropeginterferon alfa-2b vs. control in patients ≥60 ys

*Acute Leukemia, Anemia, Leukopenia, Granulocytopenia

Summary - Conclusion

- A high CHR, symptom improvement and molecular response (*JAK2*V617F) as well as maintenance of response achieved by long-term treatment with Ropeginterferon alfa-2b was shown, with an advantage over HU independent of age

- Ropeginterferon alfa-2b was well tolerated in all age groups. The safety analysis in patients ≥60 years showed a positive trend regarding less ADRs and less serious ADRs for Ropeginterferon alfa-2b vs. HU

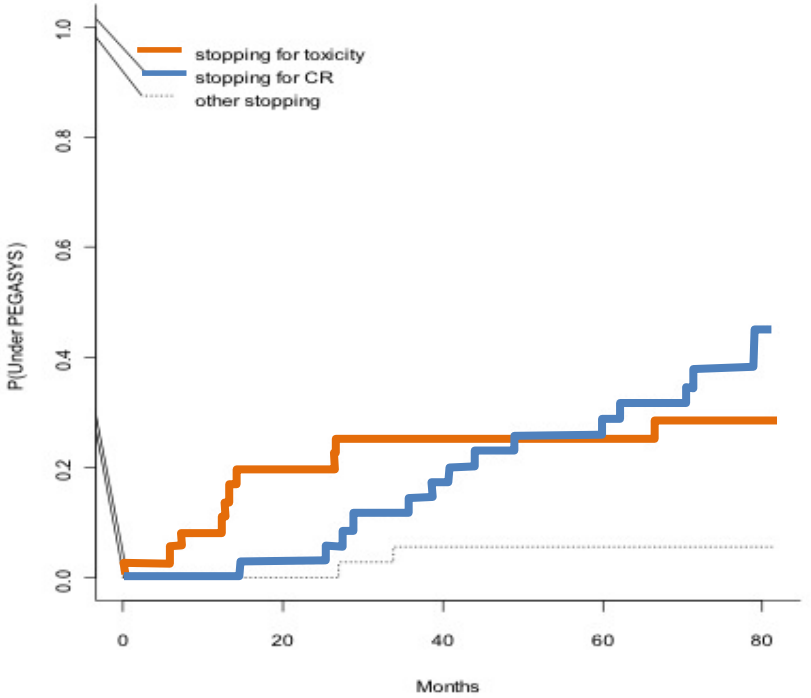
- **Ropeginterferon alfa-2b provides a valuable, efficacious and safe new treatment option for PV patients of all ages, including those older than 60**

IFN TREATMENT DISCONTINUATION

PVN1 study – *peg-IFNα-2a discontinuation*

- Causes of peg-IFNα-2a discontinuation
  - 38% for hematol. CR
  - 27% for toxicity

Fatigue (n= 2)
Depression (n= 1)
Auto-antibodies (n=2)
Thyroiditis (n= 1)
Arthralgia (n= 1)
Neutropenia (n= 1)
Neuropathy gr. 2 (n= 1)
LFTs elevation gr. 2 (n=1)



OUTCOME OF PATIENTS AFTER DISCONTINUATION?

Objectives

- Single center study of outcome of MPN patients treated with IFN after discontinuation (whichever the cause)
- Endpoints (competing risk) :
  - hematological relapse
  - thrombosis
  - hematological transformation
  - EFS (thrombosis, transformation, death)
- Predictive factors

Results

- Since 2000 in St-Louis hospital, 333 MPN patients received IFNa
- 149 stops
  - 78 PV, 61 ET, 10 MF
- Reasons for stopping:
  - Toxicity : 79 (53%)
  - Prolonged CHR: 52 (35%)
- Median time on IFN : 28.3 months

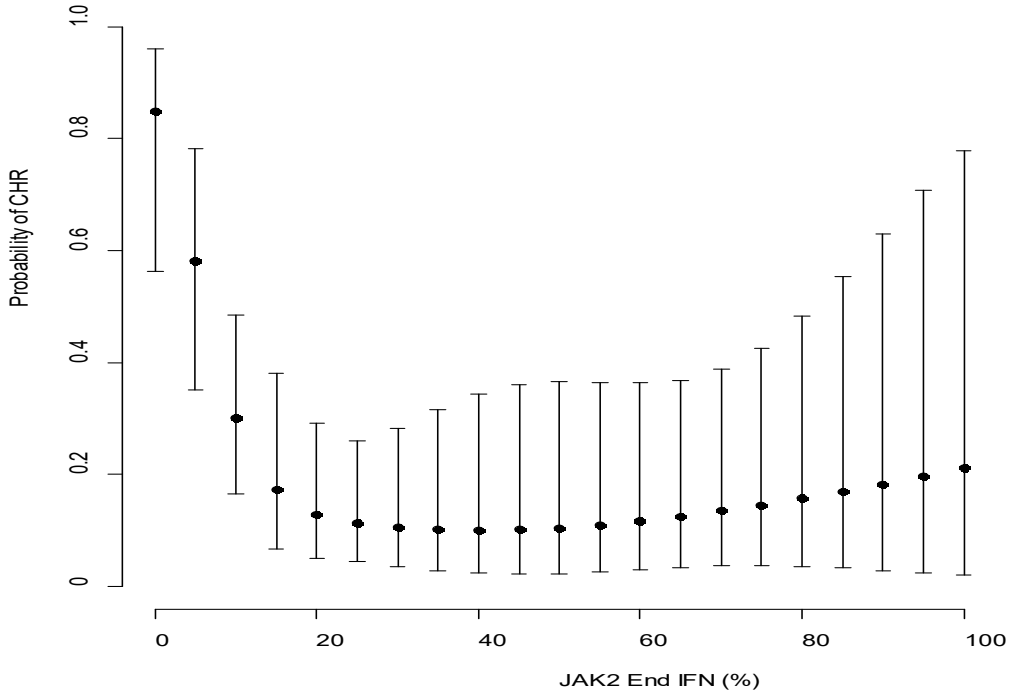
Results

- Last follow-up:
  - 109 (73%) patients were in CHR for a median time after IFN discontinuation of 42 months [23-58]
  - including 46 (42%) without cytoreductive therapy after 33 months [19-53]

Impact of molecular response on clinical outcomes

Influence of JAK2V617 allele burden on the predicted probability of

persistent complete hematological response without cytoreductive therapy



Kiladjian et al., ASH 2016

COMBINATION THERAPY WITH IFN

RUXOPEG, a Multi-Center Bayesian Phase 1/2 Adaptive Randomized Trial of the Combination of Ruxolitinib and Pegylated Interferon Alpha 2a in Patients with MPN-Associated Myelofibrosis

Phase 1: a Bayesian dose finding study to assess the safety of the combination of different doses of ruxolitinib and peg-IFN alpha-2a

Phase 2: a secondary randomized evaluation of the 2 optimal doses found in the first part of the study

FIM FRENCH INTERGROUP MYELOPROLIFERATIVE DISORDERS

ClinicalTrials.gov Identifier: NCT02742324

FIL FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

RUXOPEG study design - phase 1

Primary tolerance criterion: occurrence of dose limiting toxicity within 45 days

Ruxolitinib (started D1)	**10 mg BID**	**15 mg BID**	**20 mg BID**
Peg-IFN 45 mcg/w (started D15)	n= 3	n= 3	n= 3
Peg-IFN 90 mcg/w			n= 3
Peg-IFN 135 mcg/w		n= 3	n= 3

18 patients enrolled from Sept 2017 to Nov 2018

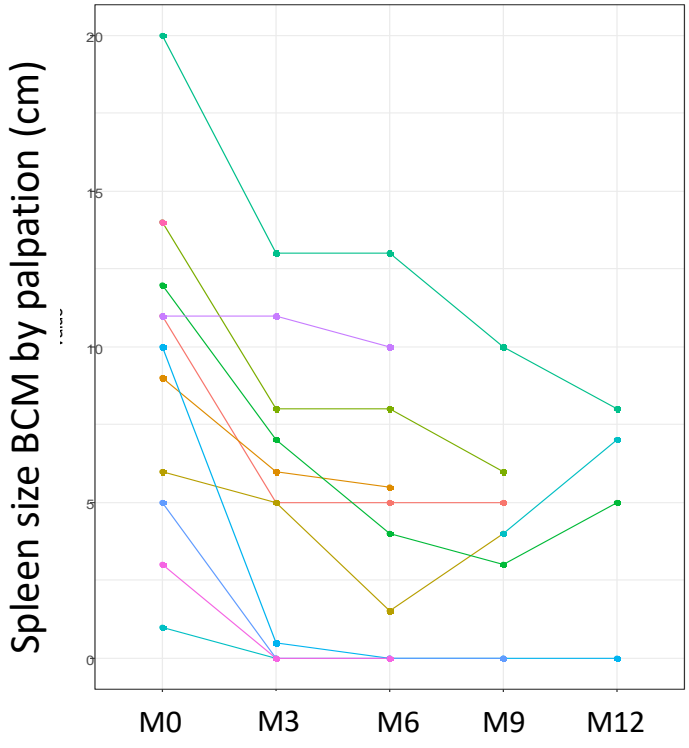
Analysis on the first 16 patients allowing for DLT assessment

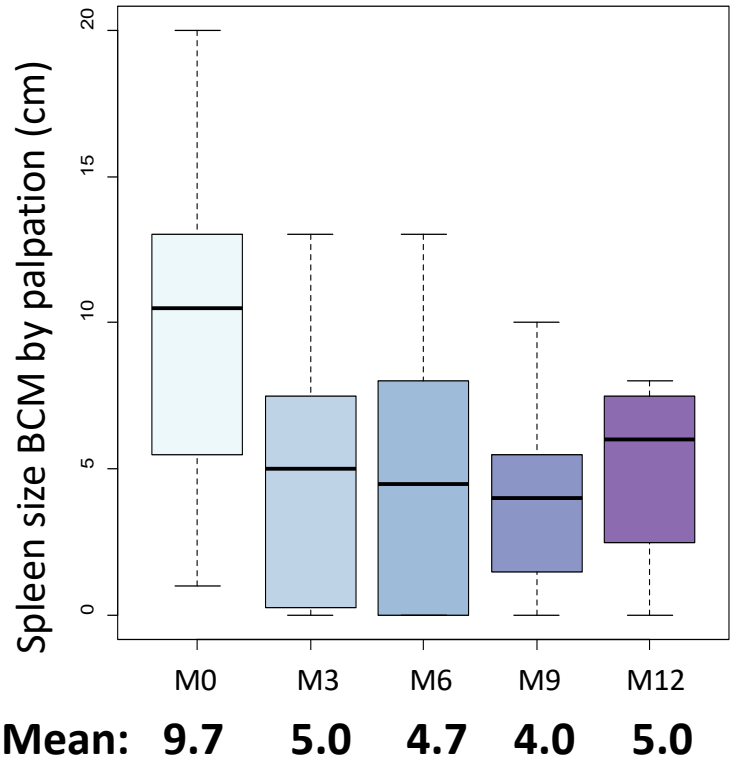
Phase 1 - Conclusion

- **No DLT was observed among the 18 enrolled patients**
- **Starting Phase 2**: a secondary randomized evaluation of the 2 optimal doses found in the first part of the study
  - **Ruxolitinib 15 mg BID + Peg-IFN 135 mcg/w**
  - **Ruxolitinib 20 mg BID + Peg-IFN 135 mcg/w**
- **Primary efficacy criterion**: > 50% reduction in spleen length within 6 months
- **Will include up to a total of 42 patients** (24 additional patients)

RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing the **spleen size**

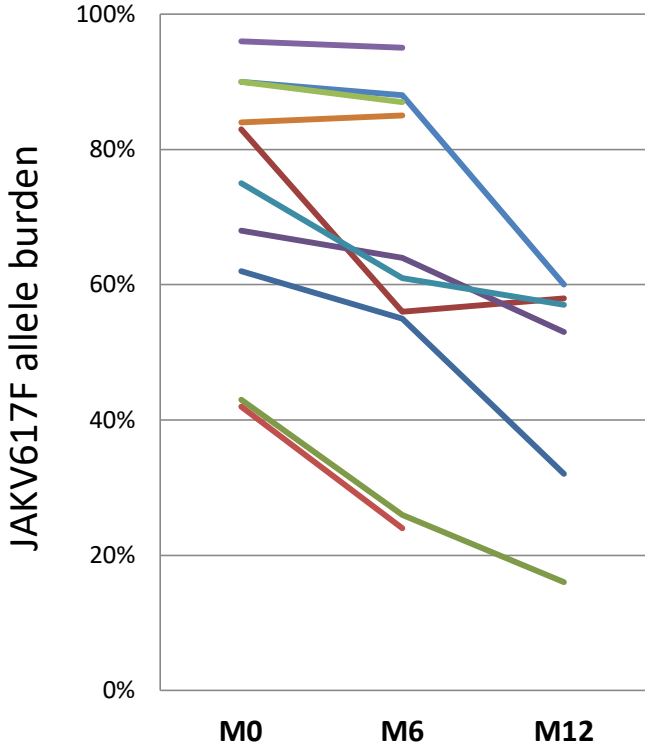


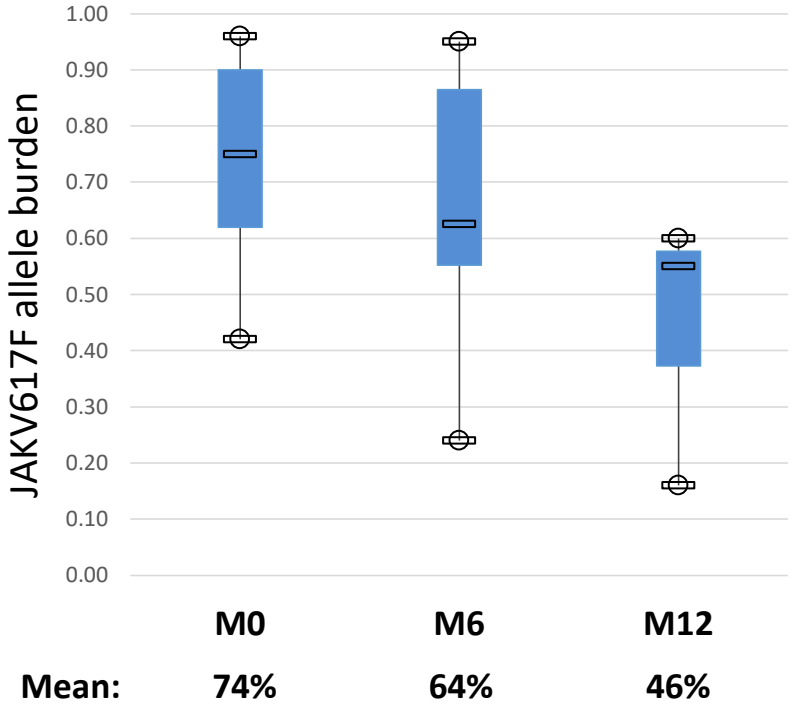


Mean: 9.7 5.0 4.7 4.0 5.0

RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing the **MPN clone**



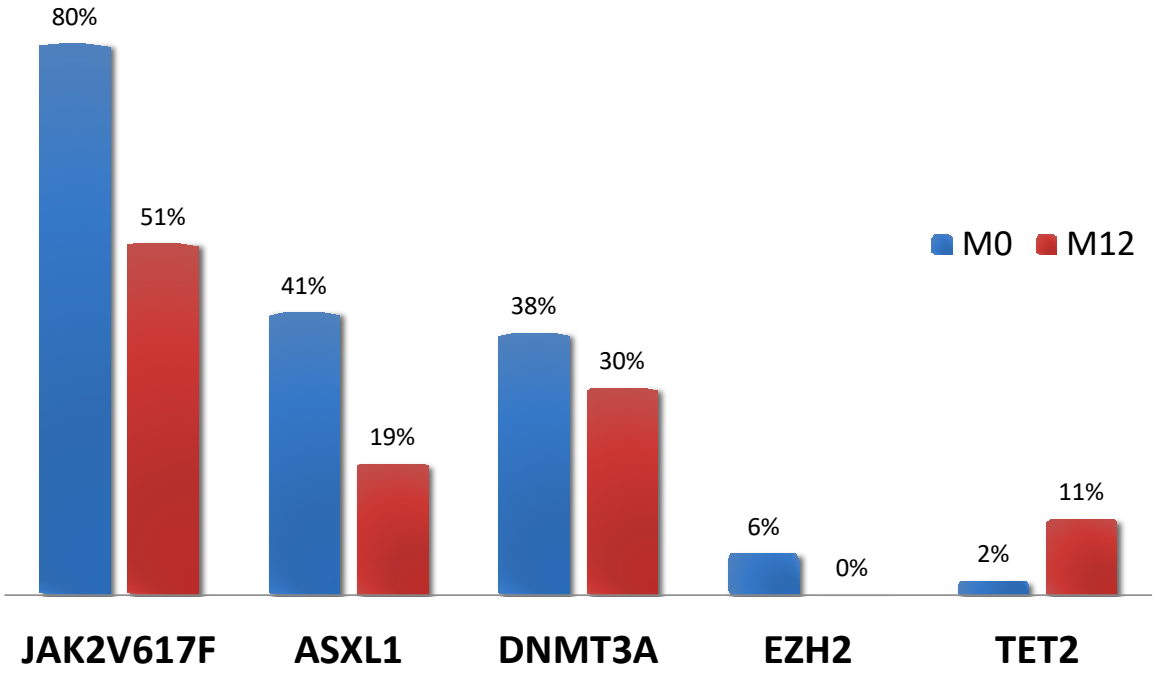


RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing the **MPN clones**

Patient #110-002
5 mutations at baseline

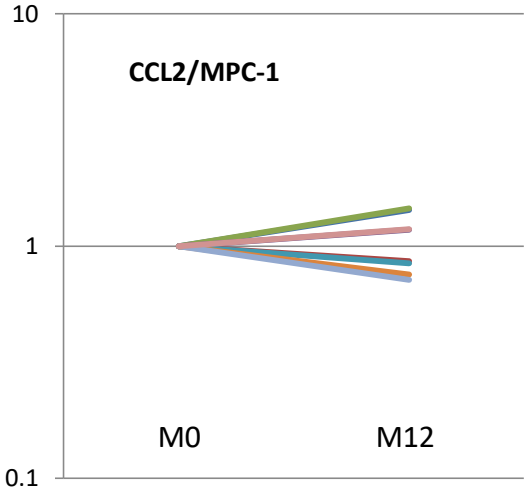
Dose level 1:
Rux 10 mg BID
Peg 45 mcg/w

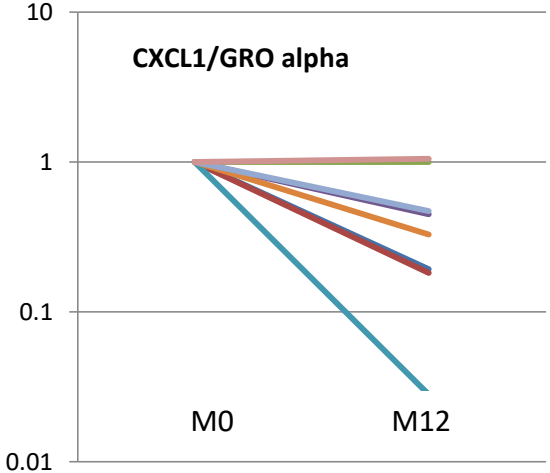


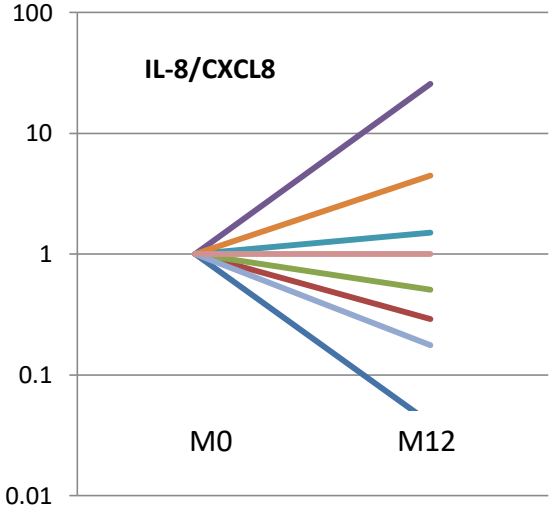
RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for reducing **cytokine levels**

  Multiplex assay of 45 cytokines at different time points







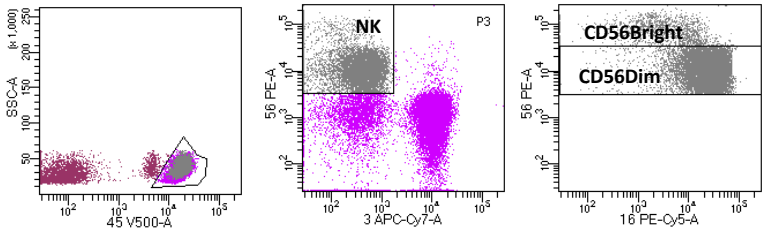
Different Cytokine Profiles : screening/end of treatment (n=8 first patients)

Marie-Hélène Schlageter

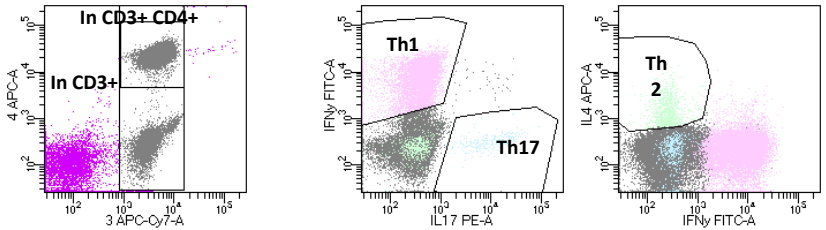
Ancillary study of immune cells

Phenotype evolution during treatment

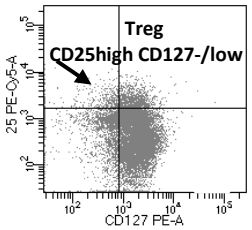
- *At baseline*
- *After Rux alone*
- *After Rux + Peg IFN*
- *At 12 months*



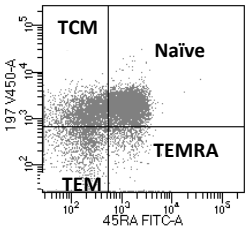
Cytokine expression in T lymphocytes



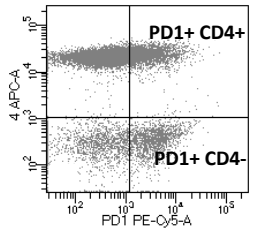
Population of Treg



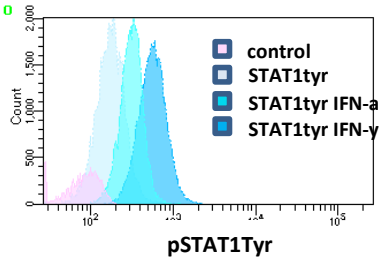
Population of naïve and memory T lymphocytes

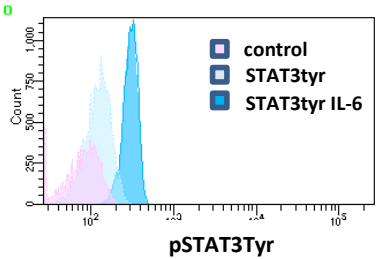


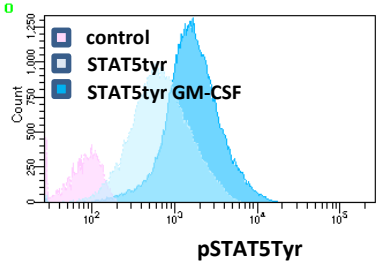
Checkpoint expression in T lymphocytes



Activation of immune cells during treatment



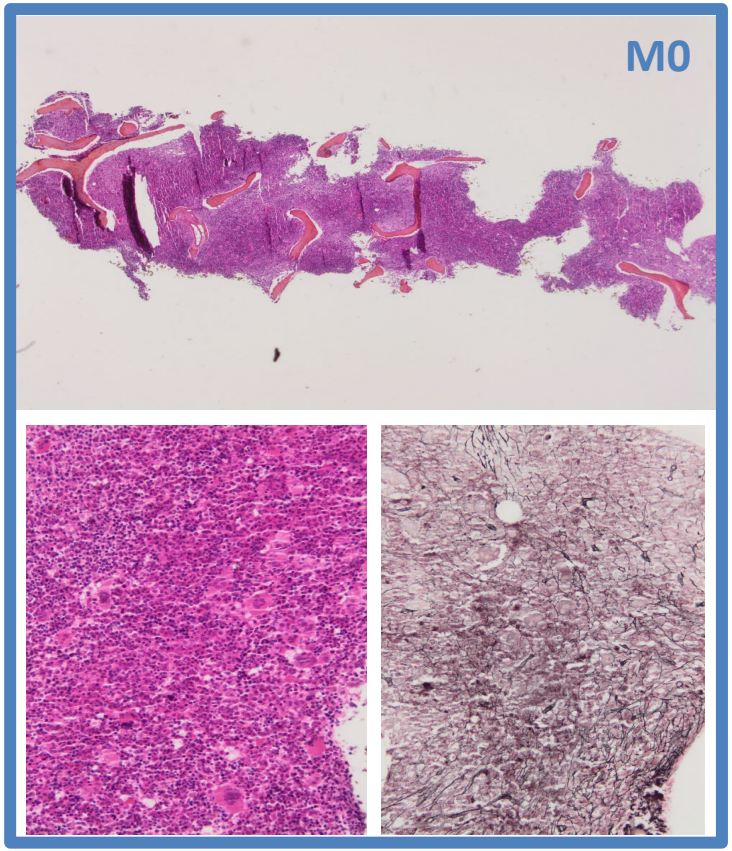




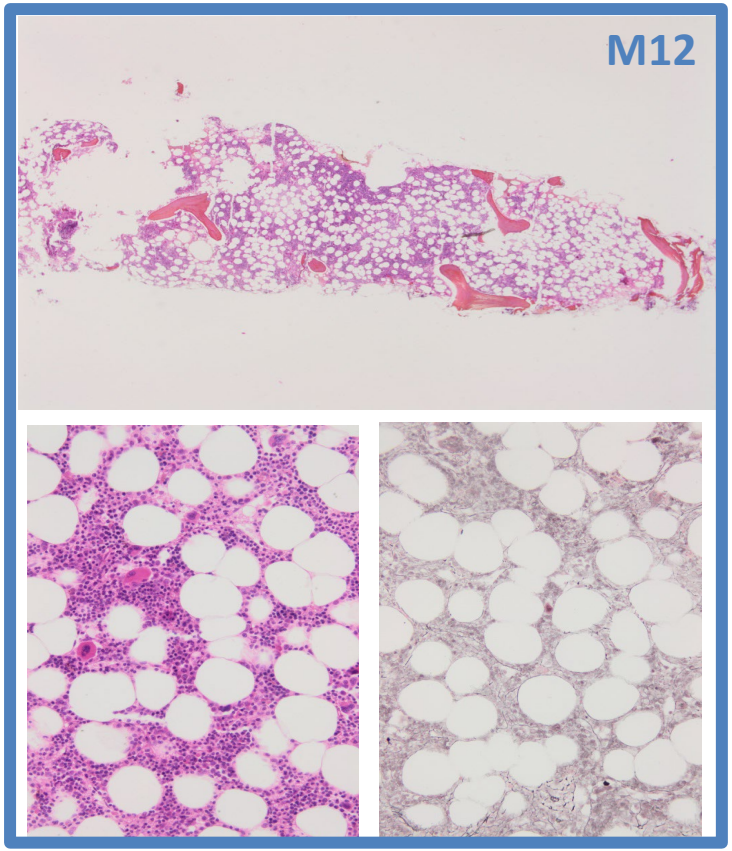
Claude Capron

RUXOPEG study - phase 1 preliminary efficacy results

- Efficacy of the combination for improving **bone marrow histology**



UPN #110-009

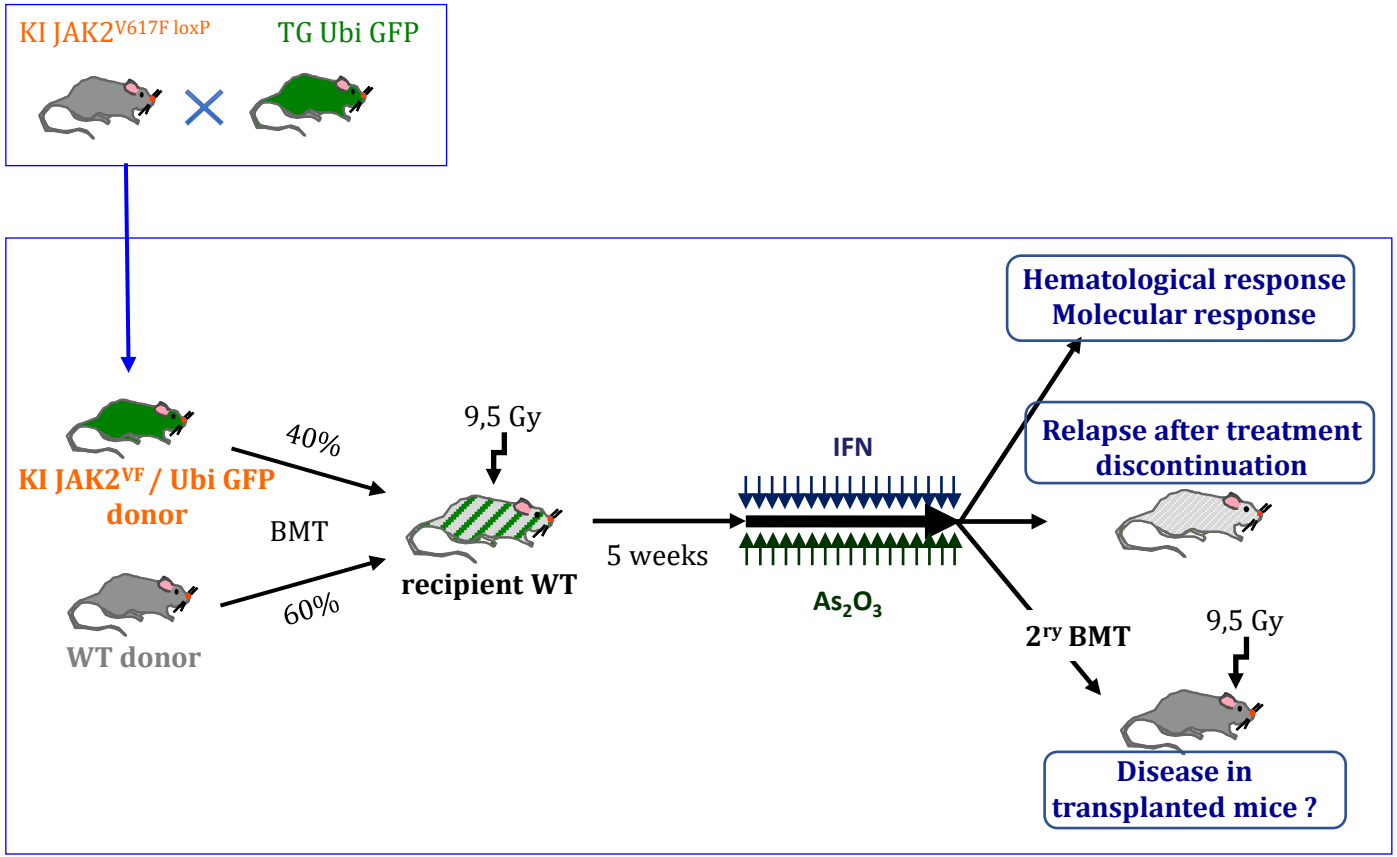


Specific and Synergistic Targeting of JAK2^{V617F} Cells by Interferon Alpha (IFN) and Arsenic (As_2O_3) in Myeloproliferative Neoplasms (MPNs)

Nabih Maslah, Tracy Dagher, Valérie Edmond, Bruno Cassinat, Valérie Lallemand-Breitenbach, Emmanuelle Verger, Isabelle Plo, Jean-Jacques Kiladjian, Jean-Luc Villeval, and Hugues de Thé

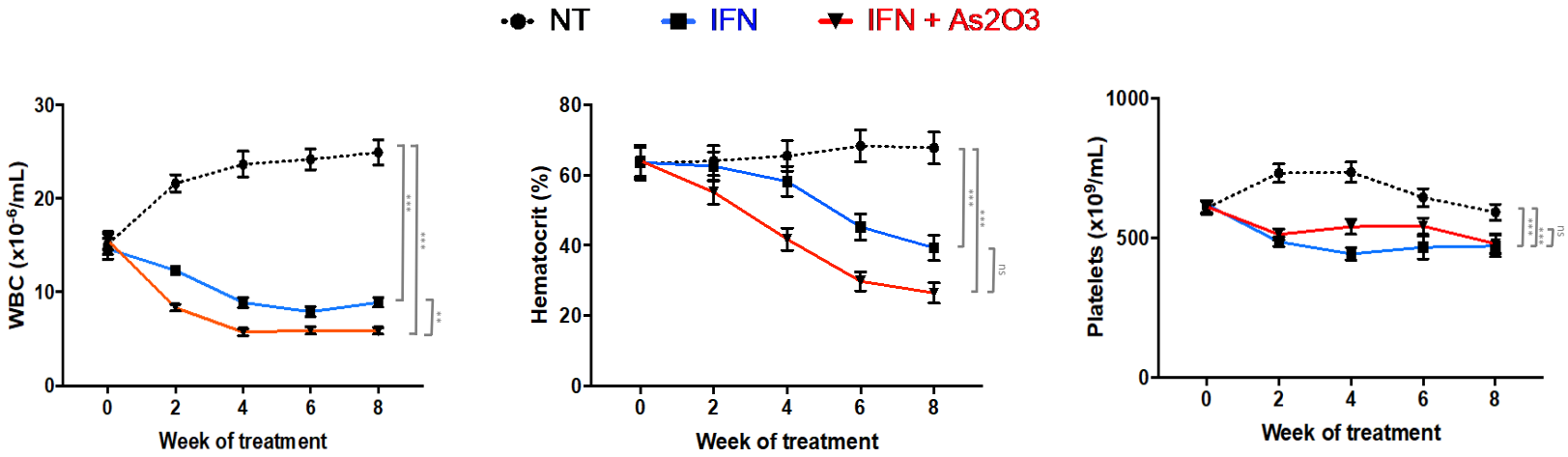
ASH 2018

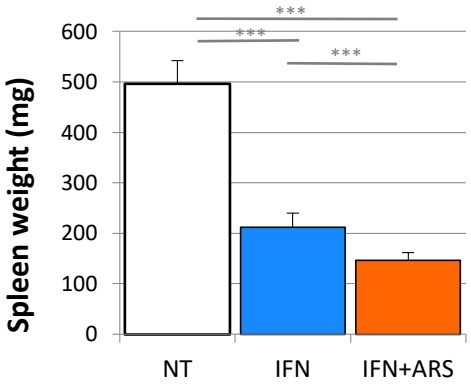
Preclinical model: Chimeric KI JAK2^{V617F} / JAK2^{WT} grafted model



IFN+As_2O_3 in vivo treatment in chimeric KI $JAK2^{V617F}$ / $JAK2^{WT}$ mice:

Improvement of Hematological response





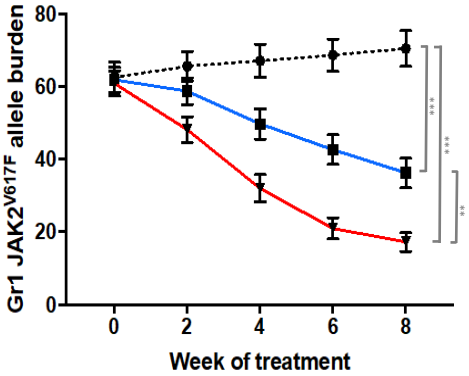
* *4 independent experiments*
N-14-19 animals

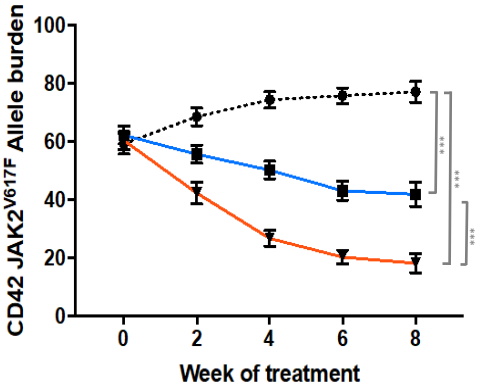
Arsenic increases the hematological response induced by IFN in blood and tissues

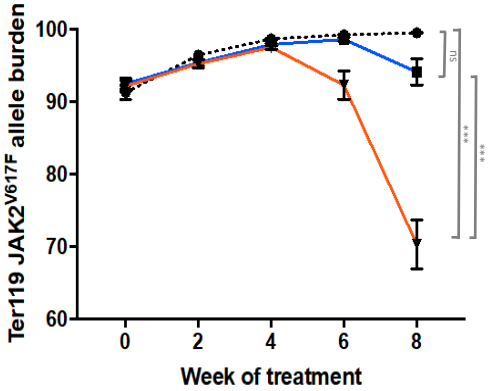
4 independent experiments
n-25-28 animals
ANOVA Dunnet test

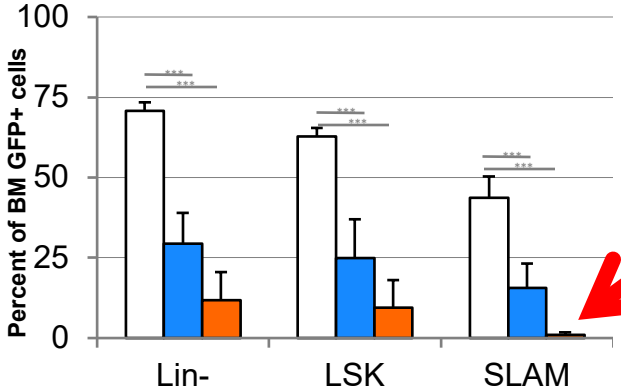
IFN+As_2O_3 in vivo treatment in chimeric KI $JAK2^{V617F}$ / $JAK2^{WT}$ mice:

Improvement of Molecular response









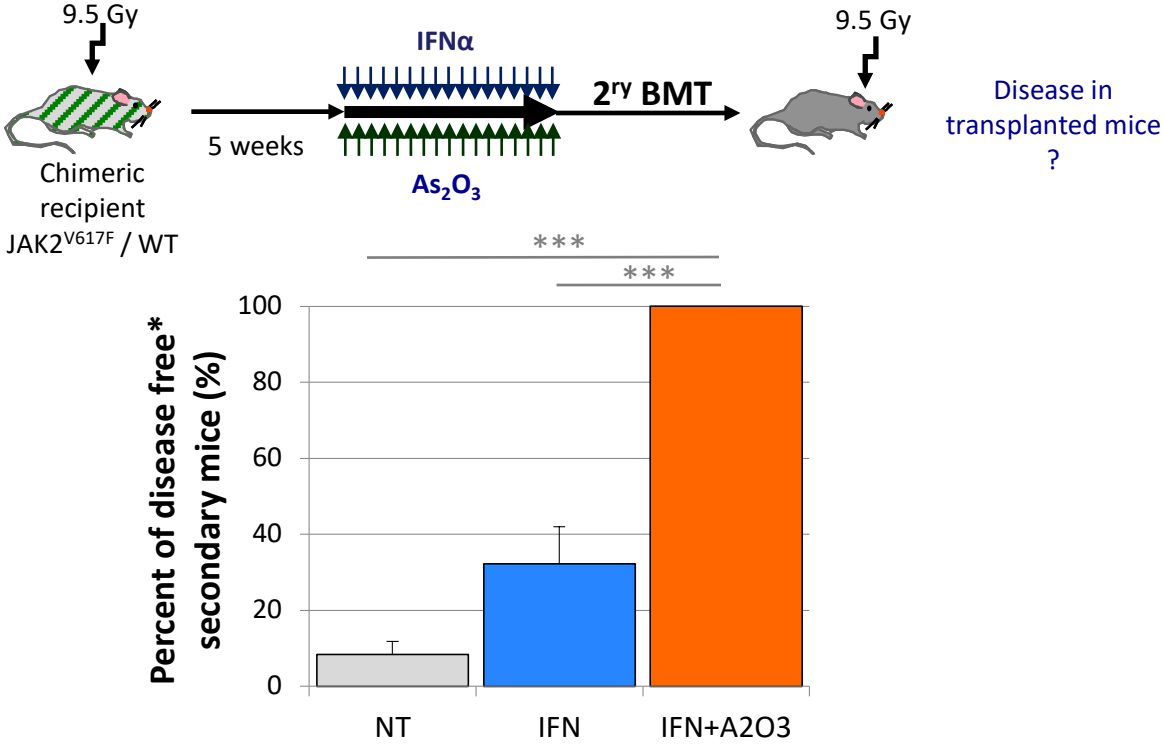
Addition of Arsenic to Interferon eradicates $JAK2^{V617F}$ leukemic stem cells?

1 out of 2 *experiments*
n=3 animals

4 independent experiments
n-25-28 animals
ANOVA Dunnet test

IFN+As_2O_3 in vivo treatment in chimeric KI $JAK2^{V617F}$ / $JAK2^{WT}$ mice:

Eradication of disease-initiating cells in secondary transplants

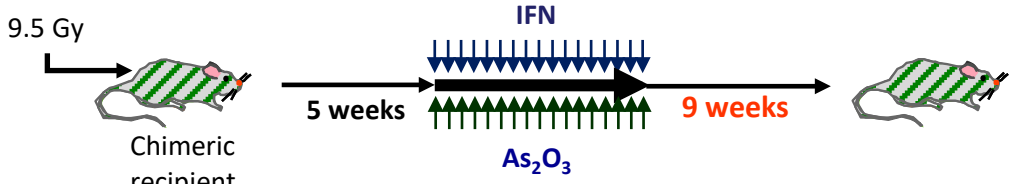


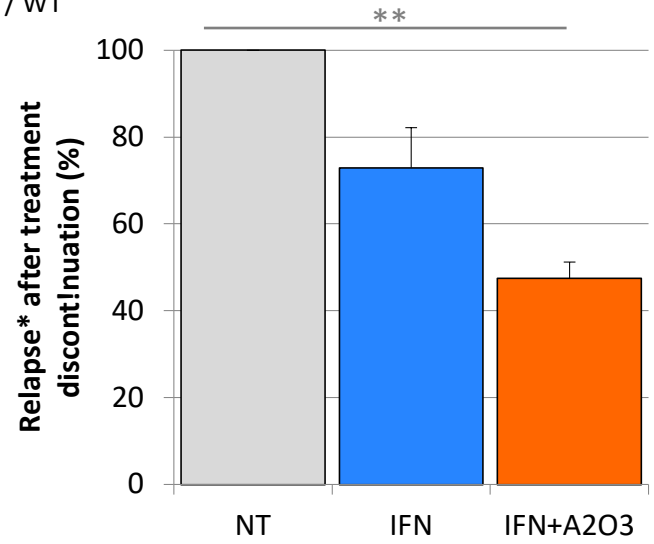
Arsenic greatly increases the suppression of disease-initiating cells induced by IFN

* from hematocrit and allele burden.
4 independent experiments
n-12-15 animals
ANOVA Dunnet test

IFN+As_2O_3 in vivo treatment in chimeric KI $JAK2^{V617F}$ / $JAK2^{WT}$ mice:

Lower risk of disease recurrence after treatment discontinuation





Arsenic decreases the percentage of disease relapse observed after discontinuation of the IFN treatment

* from hematocrit and allele burden.
4 independent experiments
n-12-15 animals
ANOVA Dunnet test

Conclusion