POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

Policitemia Vera e Trombocitemia Essenziale

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DICHIARAZIONE

NOME COGNOME

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NOVARTIS, INCYTE, BLUEPRINT, ABBVIE, BMS, GSK, ROCHE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Topics:

- ''Very-low'' *JAK2* V617F Variant Allele Frequency in PV and ET
- Significance of *JAK2* V617F molecular response in PV patients treated with ruxolitinib and Ropeg-interferon
- Clinical studies in PV: *LOW-PV, MAGIC, RUXO-SVT*
- Clinical trials in ET: *RUXO-Beat, CTP-201* (LSD1i)

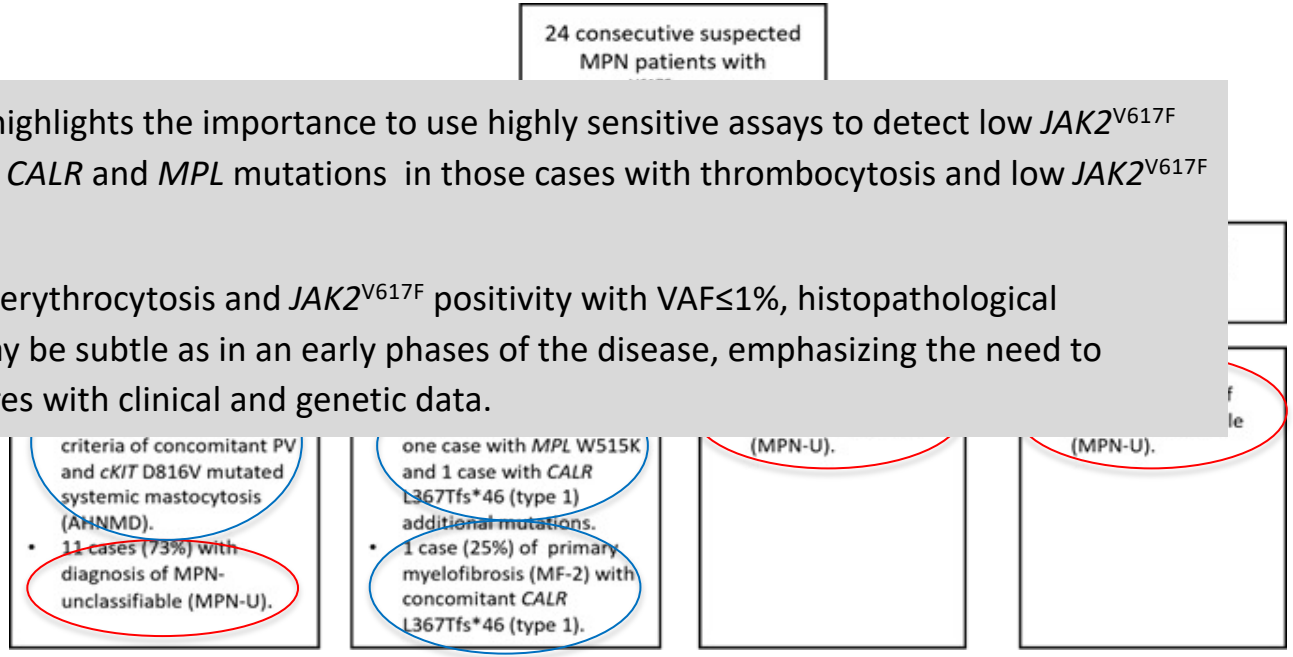
Clinical, Molecular and Histopathological correlates in a series of 24 consecutive cases of suspected myeloproliferative neoplasms with a *JAK2*V617F variant allele frequency ≤1%

Loscocco GG et al.

- **B'GROUND:** Use of highly

pathological correlates in 24 consecutive cases of suspected MPN with a *JAK2*^{V617F} VAF≤1% (from 2017 to 2022 at CRIMM).

- **CONCLUSIONS:** This study highlights the importance to use highly sensitive assays to detect low *JAK2*^{V617F} mutation, and to search for *CALR* and *MPL* mutations in those cases with thrombocytosis and low *JAK2*^{V617F} VAF.
- In patients presenting with erythrocytosis and *JAK2*^{V617F} positivity with VAF≤1%, histopathological diagnostic clues to MPN may be subtle as in an early phases of the disease, emphasizing the need to integrate histological features with clinical and genetic data.



REVIEW ARTICLE OPEN

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

blood Special Report

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

WHO 5th Edition	ICC
MPN, not otherwise specified (MPN-NOS)	**MPN, unclassifiable (MPN-U)**
• Reserved for cases with clinical, laboratory, morphologic and molecular features of MPN, but lacking diagnostic criteria of any specific MPN type or with overlapping features.	1. Clinical and hematological features of an MPN are present 2. *JAK2, CALR*, or *MPL* mutation [b]. ***or*** Presence of another clonal marker [c] 3. Diagnostic criteria for any other MPN, MDS, myelodysplastic/ myeloproliferative neoplasms, or B*CR::ABL1-pos* CML are not met
	The diagnosis of MPN-U requires all 3 criteria

- **Use highly sensitive assays for driver mutations,** consider searching for non-canonical *JAK2* and *MPL* mutations.

- MPN-U category is also appropriate **for patients in very early phase of disease** with not yet fully developed disease to meet threshold diagnostic criteria, that should be closely monitored.
- MPN-U is also used to capture **patients presenting with SVT or PVT** that fail to meet specific MPN subtype criteria.

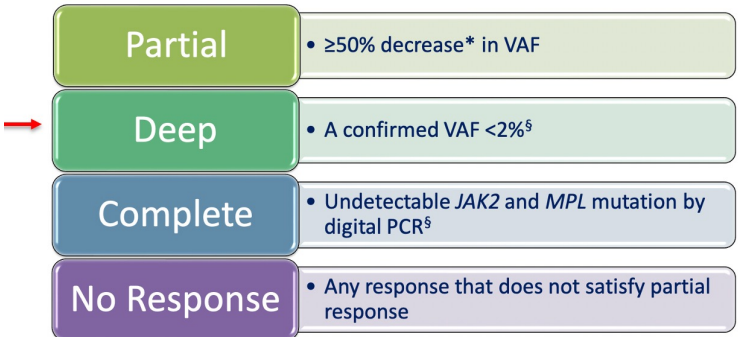
Khoury JD et al, Leukemia 2022; 36:1703-19. Arber DA et al, Blood 2022;140:1200-1227

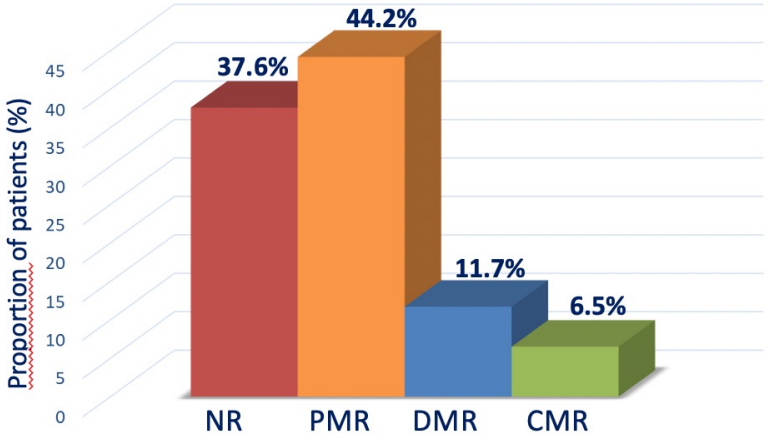
*JAK2*V617F Molecular Response to Ruxolitinib in Patients with PV and ET Is Associated with Lower Risk of Progression to Secondary Myelofibrosis

Guglielmelli P et al.

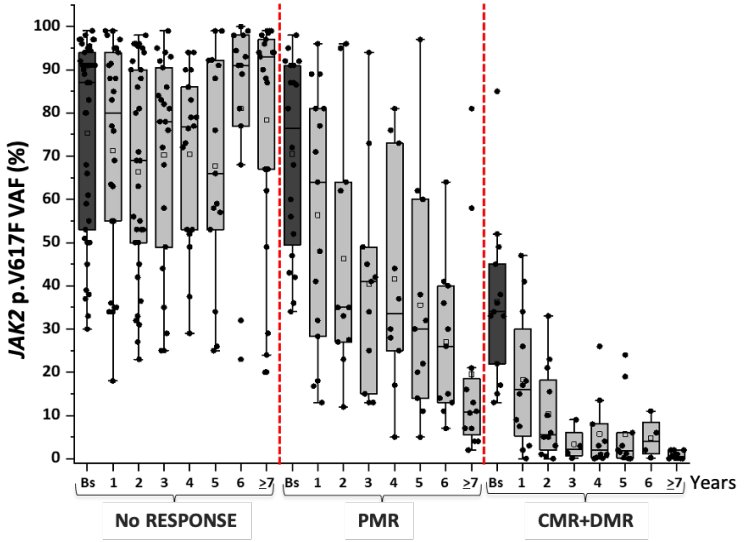
- **B'GROUND:** In Ph3 RESPONSE studies, RUX treatment for up to 4 years caused progressive reduction of *JAK2* V617F VAF, with 32.4% and 2% of the patients reaching IWG-MRT- defined Partial (PMR) and Complete (CMR) response, respectively.
- **AIM:** To serially analyze changes of *JAK2 V617F* VAF in patients with PV and ET who **were long-term treated (median, 8.8 years) with ruxolitinib.**
- To correlate changes of *JAK2* V617F VAF with clinical, molecular and hematology features at baseline, clinical and hematologic response to ruxolitinib, and with outcome.

- **PATIENTS & METHODS:** A total of 77 patients were included, 65 PV (84.4%) and 12 ET (12.6%).
- At circa-annual intervals, PB GN were analyzed for *JAK2* V617F VAF by digital PCR or high sensitive RTQ-PCR (lower detec limit, <0.01%).
- NGS panel for 42 myeloid genes was used at Baseline, at the time of confirmed CMR or DMR, and at last FU.



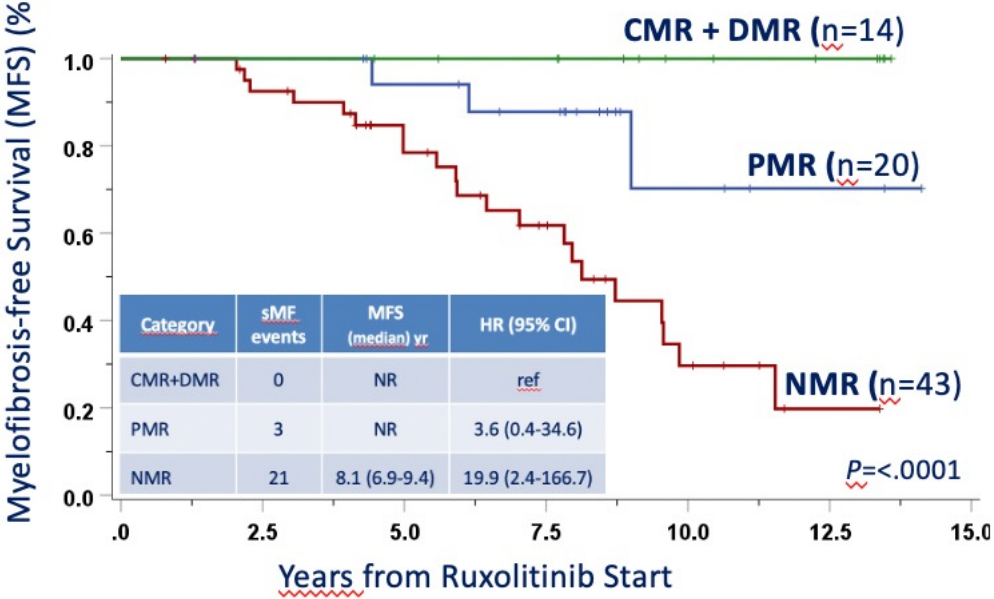


- **A CMR** was reached in 5 patients (6.5%), 3 (4.6%) and 2 (16%) with PV and ET; **a DMR** was reached in 9 patients (11.7%), 6 were PV (8.5%) and 3 ET (25%).
- There was no correlation between molecular response and response of Hct, platelets and spleen length reduction.
- **A baseline *JAK2*V617F VAF level of <60%** was associated with a significantly greater likelihood to obtain CMR+DMR (37.1% *vs* 2.4%; P<0.0001) as well as PMR (60% *vs* 38.2%, P=0.01).

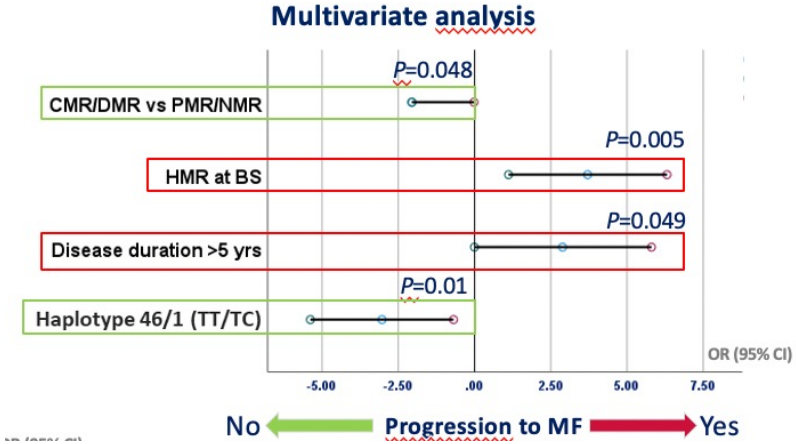


- Median time to CMR and DMR was 4.6y (1.1-7.6y) and 5.0y (2.1-12.1y), respectively.
- Median duration of CMR + DMR was 8y (7-12y).
- All CMR + DMR pts have ongoing molecular responses at data cutoff.

- **Molecular Response Is Associated with Longer Myelofibrosis-Free Survival**



Category	sMF events	MFS (median) yr	HR (95% CI)
CMR+DMR	0	NR	ref
PMR	3	NR	3.6 (0.4-34.6)
NMR	21	8.1 (6.9-9.4)	19.9 (2.4-166.7)



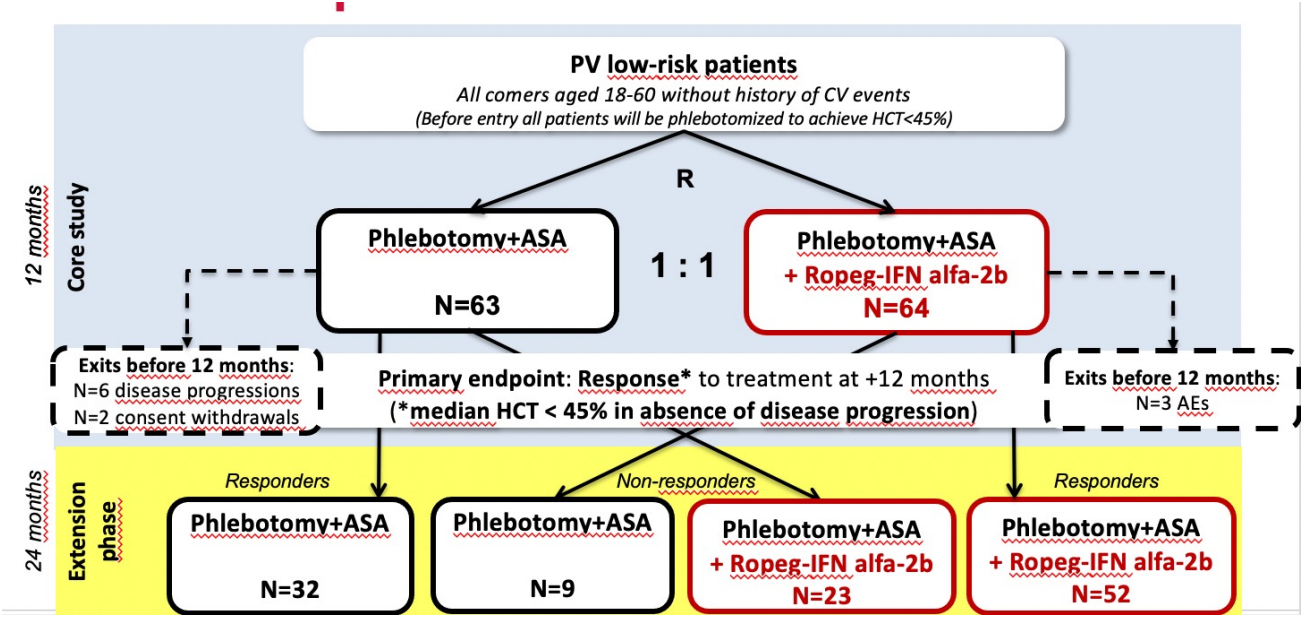
- 24 patients (31.1%) progressed to sMF after a median of 6.0y (2-11.5). 34% were PV and 16.6% ET.

- ***These findings reinforce that attainment of molecular response may be a surrogate of disease modification, as inferred also in studies with interferons in PV.***

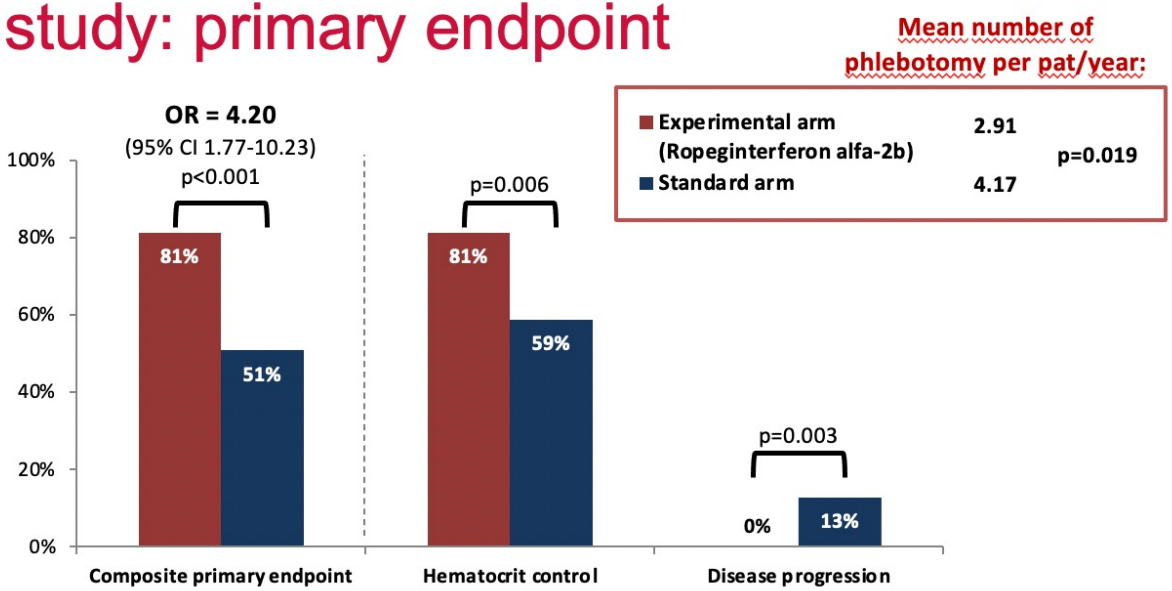
Ropeginterferon Alfa-2b Versus Standard Therapy for Low-Risk Patients with Polycythemia Vera. Final Results of Low-PV Randomized Phase II Trial

Tiziano Barbui, MD

- Low-PV is an investigator driven clinical trial (supported by AOP Orphan Pharmaceuticals).
- The **adaptive design** included 2 interim analyses
- 2nd interim analysis: 2020 (100 patients) → Stop for **overwhelming efficacy. DSMB** decided to stop the enrollment of new patients yet continuing the 2-years follow-up, as for protocol.*
- **Final analysis of the core and extensive phases: June 2022 (127 patients)**



Core study: primary endpoint

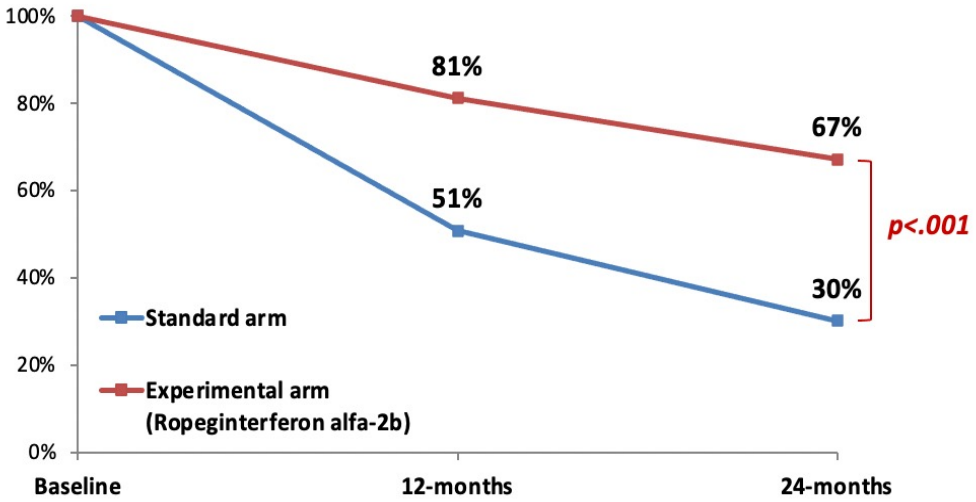


Disease progression was observed in **8 patients** (all in standard arm):

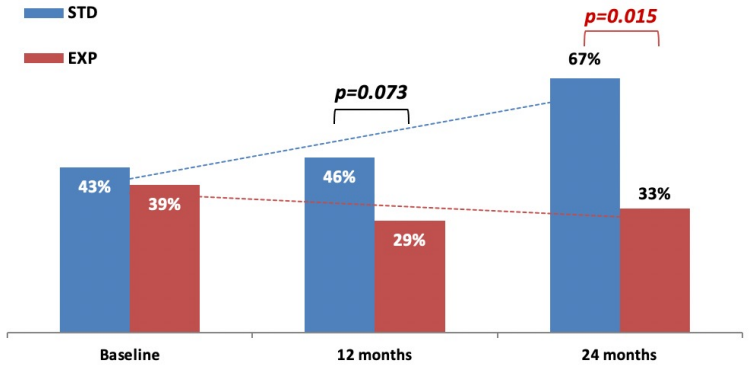
- **In 6**, platelet count progression to >1000x10^9/L in pts with baseline values lower than 600x10^9/L.
- **In 2,** splenic infarction and transient ischemic attack, respectively

* Barbui T et al, Lancet Haematology 2021

Responders: treatment response maintenance

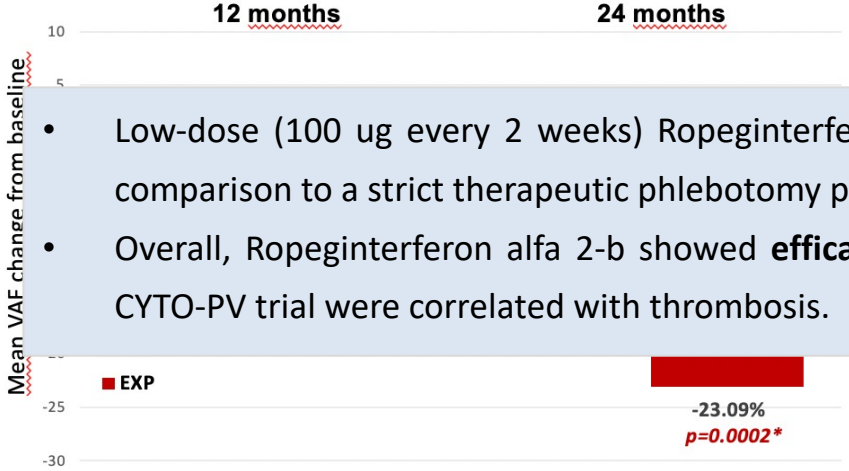


Responders: overall quality of life*

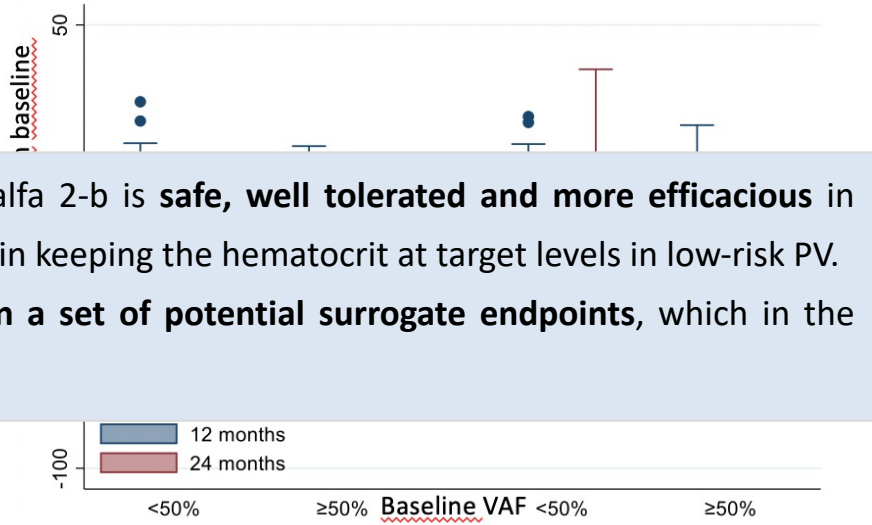


	Ropeg	Phlebotomy	p
	*N=87**	*N=72**	
Patients with AE	73 (84%)	36 (50%)	<.001
Patients with treatment-related AE	48 (55%)	4 (6%)	<.001
Patients with grade 3 or 4§ AE	8 (9%)	6 (8%)	0.948
AE that caused therapy discontinuation	7 (8%)	0 (0%)	0.016

Responders: *JAK2*V617F VAF



Responders: *JAK2*V617F VAF by baseline allele burden

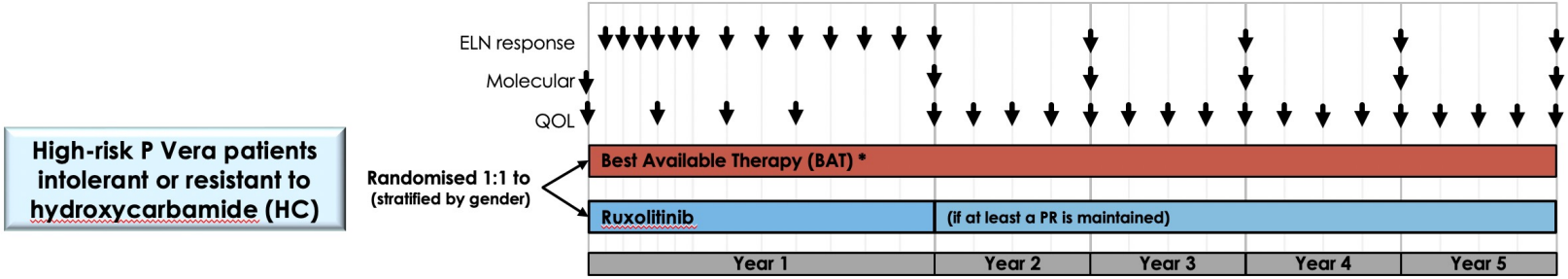


- Low-dose (100 ug every 2 weeks) Ropeginterferon alfa 2-b is **safe, well tolerated and more efficacious** in comparison to a strict therapeutic phlebotomy policy in keeping the hematocrit at target levels in low-risk PV.
- Overall, Ropeginterferon alfa 2-b showed **efficacy on a set of potential surrogate endpoints**, which in the CYTO-PV trial were correlated with thrombosis.

MAJIC

Ruxolitinib Versus Best Available Therapy for Polycythaemia Vera Intolerant or Resistant to Hydroxycarbamide in a Randomised Trial

Harrison C et al.



*in common with the RESPONSE trials patients could receive HC on the BAT arm

BAT (n=87) RUXO (n=93)

- **B'ground:** Ruxolitinib is approved for HC resistant/intolerant PV ***but trials included cross-over of the control arm*** limiting knowledge of benefits over longer term clinically-relevant events.

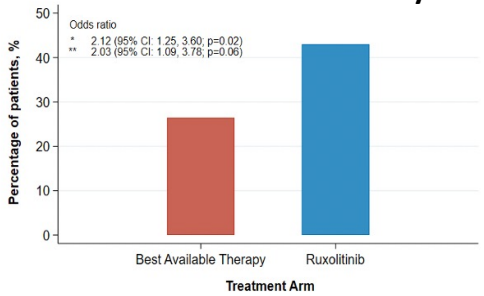
Primary outcome

Complete response per ELN (WBC ≤10, HCT ≤0.45, Plt ≤400) rate within 1 year.

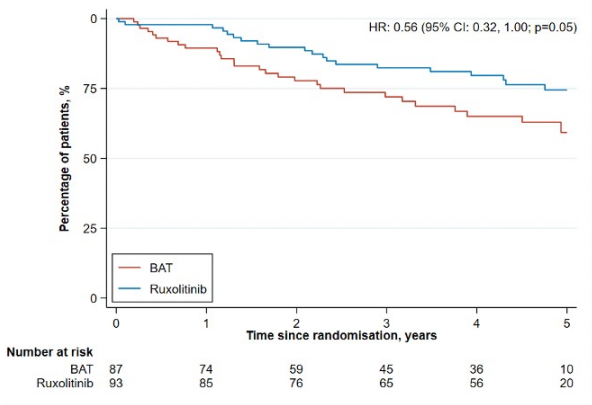
Secondary outcomes

Duration of complete response
Haemorrhagic and thromboembolic event rates
Progression free and overall survival
Responses (Histological, Molecular)
Quality of life and disease symptom burden
Safety and toxicity

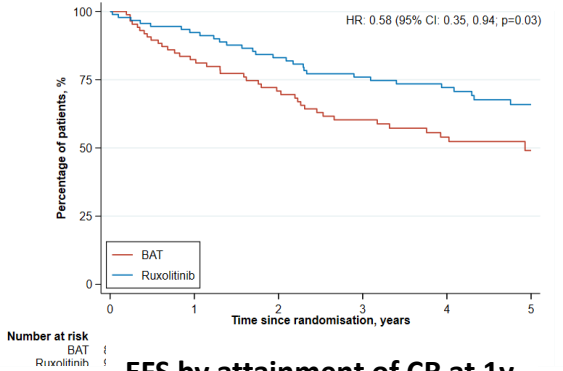
Achievement of CR at 1y



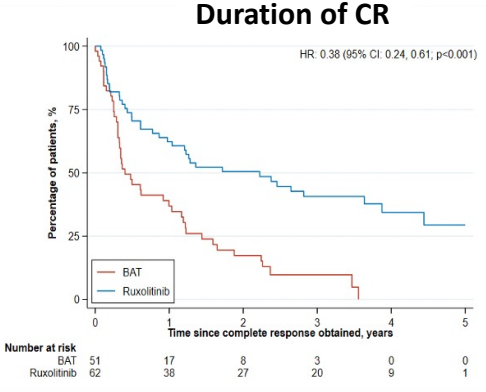
Thrombosis event-free survival



Event free survival (major haemorrhage thrombosis, transformation or death)

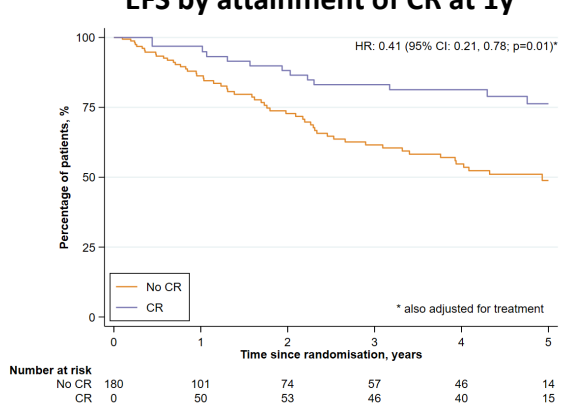


Duration of CR

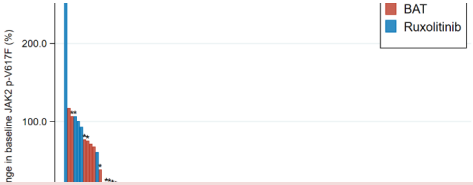


- Ruxolitinib treated patients had fewer venesections 84 vs 307 (BAT)
- 52% BAT had ≥1 venesection Vs 29% ruxolitinib
- **Time to first thrombotic event correlated with mean no. of venesections per year (p <0.001)**

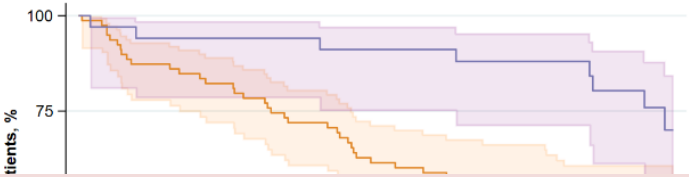
EFS by attainment of CR at 1y



Change in JAK2 VAF at latest timepoint



EFS by molecular response at 1y.



- MAJIC-PV confirms benefits of targeted therapy and molecular monitoring in PV.
- **Ruxolitinib improves thrombosis-free and event free survival** in patients with high risk PV who are intolerant or resistant to hydroxycarbamide.
- **Complete response, regardless of treatment allocation, correlated with improved event free survival.**
- Attaining a **50% reduction in *JAK2* V617F VAF, was associated with important clinical benefits (improved PFS, EFS, OS) and clearance of MPN stem cells. Suggestive of disease modification**.
- **No new adverse events** emerged in these patients but skin cancer and infection remain of note

- N
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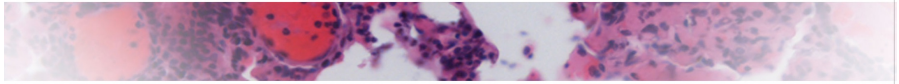
  - **<u>>50% reduction</u> in 56% RUX and 25% BAT**
- Median time to molecular response was 36 months for ruxolitinib & not reached for BAT.
- Single cell based analysis of 3 responders indicates changes in HSPC compartment 72-100% reductions

- Those with durable molecular response at last time point

had significant improvements in EFS, PFS and OS regardless of treatment arm

- **Additional mutations** (independent of age) were associated with less likelihood of molecular response and worse *EFS.*
- ***ASXL1* mutations had an independent effect upon EFS**



Long Term Follow-up of an Investigator-Initiated Phase 2 Study of Ruxolitinib in MPN-Associated Splancnic Vein Thrombosis

Paoli C et al. Poster

- **B'ground:** The SVT-RUXO is a Phase 2 investigator initiated trial of ruxolitinib in 21 pts with MPN-associated SVT.
- Primary results showed therapy safety and efficacy in SVR ≥35% by MRI at 24weeks (w) in 29% of the pts.
- Pts who succesfully completed the 24w core studywere allowed to enter an extension phase up to w72, then entered a long-term FU.
- **AIM:** To provide information about long-term safety and efficacy of ruxolitinib in pts enrolled in the SVT-RUXO who were treated in the extension phase at a median of 8.6y (range 6.2-9.8y).

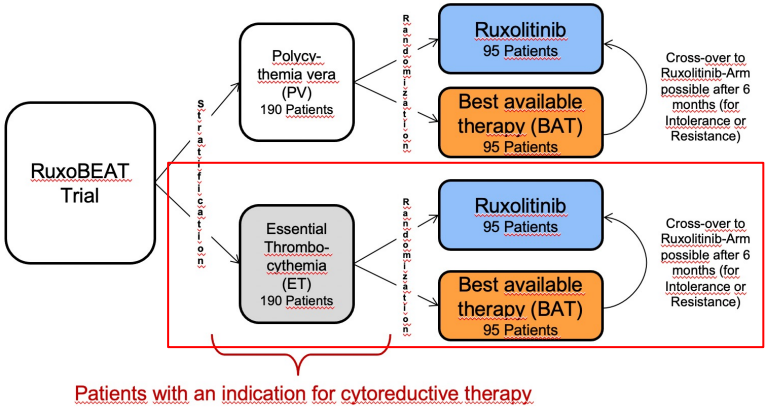
RESULTS:

- After a median follow-up of 8.6 years, **71% of pts continue to be on ruxolitinib.**
- Treatment continues to be **safe with no major AE**. No patient stopped because of toxicity.
- At last FU, ruxolitinib maintained efficacy on splenomegaly in 61% of pts, with stable disease in 22%.
- **No event of recurrent thrombosis nor gastrointestinal bleeding events were recorded**.

Ruxolitinib versus Best Available Therapy in Patients with Essential Thrombocythemia

Pre-Specified Interim Analysis of the Randomized Phase 2b RuxoBEAT Clinical Trial of the German Study Group for Myeloproliferative Neoplasms (GSG-MPN)

Koschmieder S.



Primary endpoint

Clinico-hematologic complete response (CR) rate at month 6 (ELN)

Secondary and exploratory endpoints

Overall response rate (CR+PR), changes in blood counts, spleen size, PROM

Ruxolitinib versus Best Available Therapy in Patients with Essential Thrombocythemia

Pre-Specified Interim Analysis of the Randomized Phase 2b RuxoBEAT Clinical Trial of the German Study Group for Myeloproliferative Neoplasms (GSG-MPN)

Koschmieder S.

1°EP: Complete Remission at Month 6 **2°EP: Overall Remission (CR + PR) at Month 6**

CONCLUSIONS:

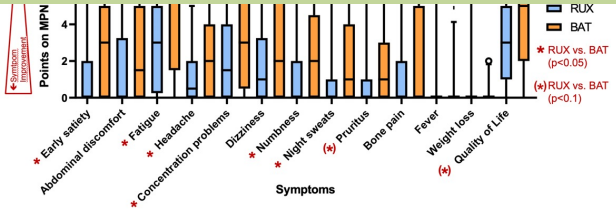
- In this **pre-specified interim analysis**, treatment with **ruxolitinib was not superior over BAT** to induce **complete response** (using strict criteria for symptoms)
  - in high-risk ET pts that were either untreated or pre-treated (but not intolerant/resistant to prior therapy)
- However, **RUX was more effective in reducing ET-associated spleen size and symptoms**
  - including headache and concentration problems, numbness, night sweats, early satiety, and fatigue
- Overall, **none of the treatment regimens was better** than the other

Primary endpoint

Clinico-hematologic complete response (CR) rate at month 6 (ELN)

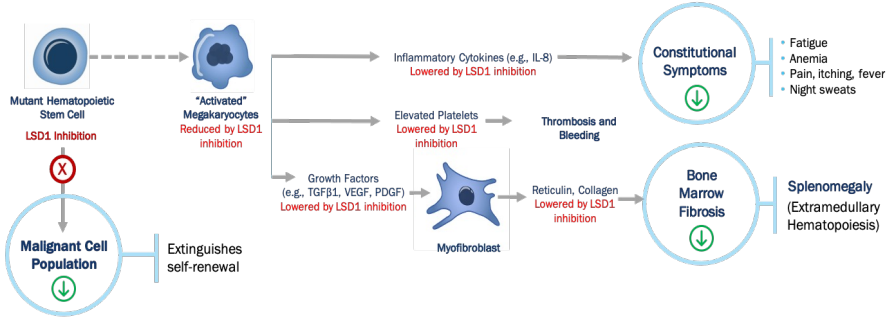
Secondary and exploratory endpoints

Overall response rate (CR+PR), changes in blood counts, spleen size, PROM



Phase 2 Study of the LSD1 Inhibitor Bomedemstat (IMG-7289) for the Treatment of Essential Thrombocythemia. Gills H

- LSD1 (Lysine-specific demethylase 1) demethylates histone H3K4 and other chromatin-associated proteins, *e.g.*, p53
- Loss of LSD1 activity is associated with loss of self-renewal in malignant HSCs
- LSD1 is required for the differentiation of megakaryocyte-erythroid progenitors to mature megakaryocytes
- Overexpressed in MPNs



CTP-201 Study Design

IMG-7289-CTP-201 is an *ongoing*, 24-week, Phase 2 global study to assess the safety, efficacy and pharmacodynamics of bomedemstat (IMG-7289) in patients with ET who have failed at least one standard of care

Primary Endpoints:
- Safety and tolerability
- Platelet count reduction (≤400 x 10^9/L) in the absence of thromboembolic events

Exploratory Endpoints:
- Symptom reduction (MPN-SAF TSS)
- Durability of platelet and WBC count reduction
- Changes in mutant allele frequencies (MAF)

Key Eligibility Criteria:
- Diagnosis of ET by WHO 2016 Criteria
- Failed at least one standard therapy
- Platelet count >450 x 10^9/L
- Hemoglobin ≥10 g/dL
- Peripheral blasts <1%
- Fibrosis Score <2 per protocol criteria (modified from Arber *et al.*, 2016)

73 treated with 53 on study

60 (82%) patients reached 24 weeks

Median Time on Treatment: 32 weeks

- Bomedemstat PO once daily
- Each patient dose-titrated to platelet count *per* dosing rules
- Starting dose is 0.6 mg/kg once daily
- Titrations may occur every 4 weeks to target platelet range of 200-400 x 10^9/L

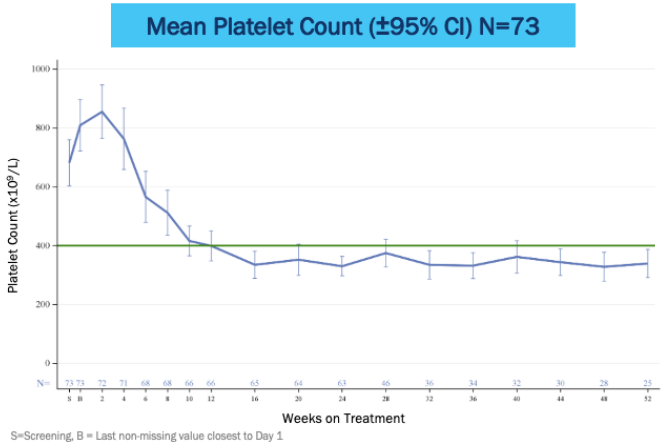
Safety and Tolerability Profile

Preferred Term (N=73)	Any Grade AEs	Grade 3/4 AEs
Dysgeusia	40 (55%)	N/A
Constipation	25 (34%)	1 (1%)
Thrombocytopenia	20 (27%)	6 (8%)
Arthralgia	20 (27%)	4 (6%)
Fatigue	17 (23%)	0
Contusion	15 (21%)	1 (1%)
Diarrhoea	15 (21%)	1 (1%)
Pruritus	13 (18%)	0
Anaemia	12 (16%)	5 (7%)
COVID-19	12 (16%)	0
Headache	11 (15%)	1 (1%)
Peripheral oedema	11 (15%)	1 (1%)

Any grade of AE occurring at a frequency of ≥15% of patients included regardless of relatedness; N/A = Gr 3/4 events do not exist per CTCAE criteria

- Bomedemstat is generally well-tolerated
- Most common AE was dysgeusia, **majority were Grade 1**
- 22/73 (30%) reported 38 SAEs, 7 SAEs DR in 4 pts
- One patient experienced thrombotic event – pulmonary embolism - unrelated to bomedemstat

Primary Objective: Reduction in Platelet Count



S=Screening, B = Last non-missing value closest to Day 1

Of 62 patients treated for **≥24 weeks:**

- 100% achieved a platelet count of ≤400 x 10^9/L
- Median time to ≤400 x 10^9/L is 10 weeks

Of 28 patients treated for **48 weeks:**

- 89% achieved a durable (≥12 weeks) platelet count of ≤400 x 10^9/L by week 48

Grazie per l'attenzione!