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A paradigm shift in the treatment of patients with polycythemia vera. The initial early use of recombinant interferon-alpha

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During the past 35 years, single-arm studies documented the efficacy and safety of recombinant interferon alpha (rIFNα) for treating polycythemia vera (PV). In some patients, 2-5 years of disease-modifying treatment resulted in symptom relief, regression of splenomegaly, normalization of abnormal blood counts and marrow morphology, and sustained *JAK2V617F* molecular remission. The PROUD-CONTI study showed the superiority of rIFNα compared to hydroxyurea (HU), which led to the European Medicines Agency approval in 2019 of ropeginterferon alpha-2b ("ropegIFN") for ELN-defined high-risk PV patients. In 2021, the Food and Drug Administration (USA) gave unrestricted approval, except for pregnant PV patients. The Low-PV randomized trial established the superiority of ropegIFN compared to phlebotomy-only (PHLEB-O) in ELN-defined low-risk patients. Nevertheless, worldwide, HU remains the cytoreductive drug most often used; maintenance PHLEB-O is still endorsed as maintenance therapy by some hematologists. The National Comprehensive Cancer Network (NCCN, USA) approved ropegIFN as a II-A recommendation for ELN-defined low and high-risk disease; the ELN suggested criteria for using rIFNα in low-risk patients if certain issues developed after PHLEB-O, including more symptoms, progressive splenomegaly, significant leukocytosis, thrombocytosis, or inadequate hematocrit control. These issues are important because even low-risk patients are at increased thrombotic risk, estimated at 2 to 3 times that of the general population. Moreover, as PV progresses, the development of myelofibrosis is the leading cause of morbidity, perhaps abetted by PHLEB-O. Here, we review recent progress in the treatment of PV with rIFNα and discuss our rationales and perspectives for, and the endorsement of the initial treatment with rIFNα of both low and high-risk PV patients, unless a contraindication exists to its use.

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INTRODUCTION

The restricted approval of ropegIFN, a new form of recombinant interferon alpha-2b (Besremi®), for treating certain patients with PV by the European Medicines Agency (EMA) and its unrestricted approval (except for pregnant PV patients) by the U.S. Food and Drug Administration will likely lead to an increase in its use. This also holds true for the use of pegylated interferon alpha-2a (Pegasys®), which has been recently approved by the EMA for the treatment of all eligible adults with PV and essential thrombocythemia without any restrictions. This has been abetted by the demonstration that rIFNα is the only drug used in treating PV that specifically reduces the mutant *JAK2V617F* variant allele frequency (VAF) [1–4]. This occurs by a selective effect of rIFNα on the malignant clone as will be addressed below [5–9]. This biologic phenomenon may translate into important results: long-term molecular remissions resulting from "deep" or "complete" molecular responses in a minority of patients [1–4, 10–12], which may yield an improved disease-free and overall survival [13, 14] and longer periods without treatment [10–12]. Notwithstanding the aforementioned, in the United States and in Europe, hydroxyurea (Hydrea®) (HU) remains the most commonly used drug [15, 16] despite its nonselective cytotoxicity and concerns in regard to its potential leukemogenicity, if being used for decades [17]. Moreover, even when economic factors do not play a role in the selection of therapy, PHLEB-O is often recommended as a preferred method of treatment [16].

Most practitioners treating pts with PV classify them according to ELN and NCCN guidelines, which divide patients into low and high-risk groups based on age and thrombotic risk [18–20]. Low-risk patients are those under the age of 60 years (pts <60) with no history of thrombosis; high-risk pts are those over the age of 60 years (pts >60) and/or with a history of thrombosis. There are major issues with this risk categorization. Pts <60 also have a thrombotic risk 3 times that of the general population [21–23]. Furthermore, the risk of thrombosis continues throughout the course of PV, although at a decreased rate [13]. This classification ignores the fact that most PV patients have constitutional symptoms at disease onset [24]. Repeated phlebotomies accentuate iron deficiency, which also contributes to the symptom burden, and includes memory loss [25] and heart failure [26].

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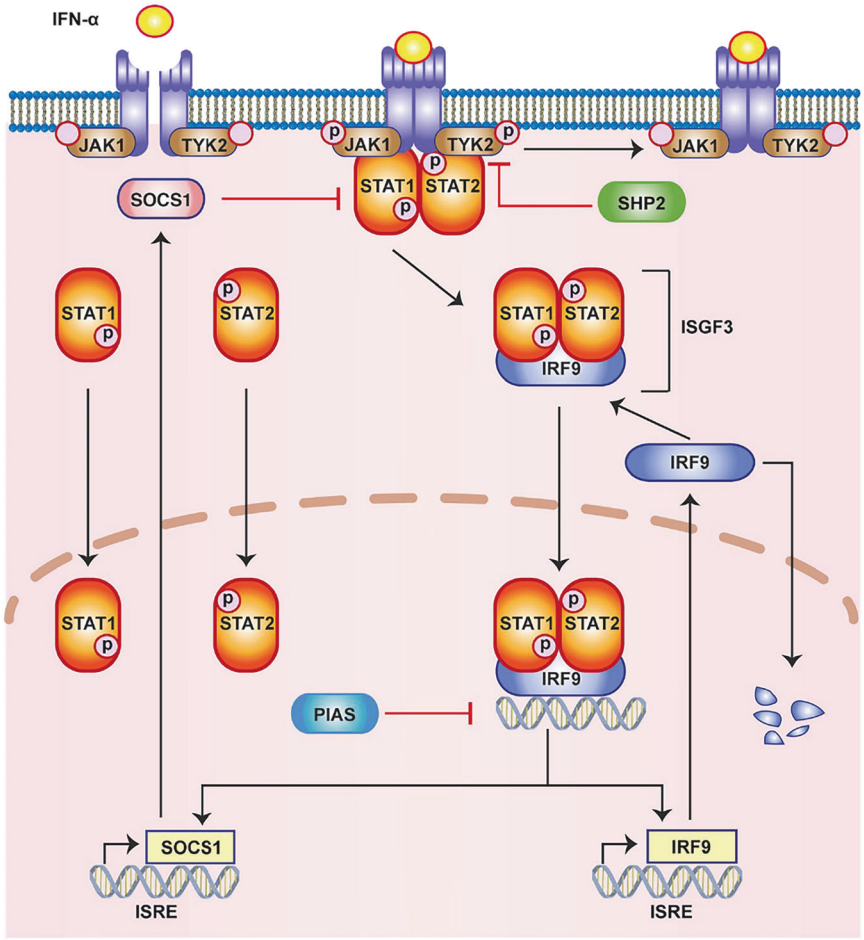

Fig. 1 The JAK/STAT pathway in response to IFN-α. IFN binds to the receptor and activates JAK1 and TYK2 with subsequent activation of the STATs by phosphorylation. The phosphorylated STATs and IRF9 form the transcription complex ISGF3, which after translocation to the nucleus activates hundreds of ISGs, including IRF9, Mx2 and SOCS1. *With permission from Kalra P,Brandl J, Gaub T, Niederalt C, Lippert JSahle S* et al. *Quantitative systems pharmacology of interferon alpha administration: A multi-scale approach. Plos One 2019, 14(2):e0209587.PMID:30759154, PMCID: PMC6374012.*

Thrombocytosis adds to the thrombotic risk of iron deficiency [27–29]. Leukocytosis, usually present at PV diagnosis, is probably an additional thrombotic risk factor [30–32]. An expert committee of the ELN recognized the importance of the recent LOW-PV study, which randomized low-risk patients to receive either ropegIFN + phlebotomy or PHLEB-O as initial treatment to maintain the hematocrit ≤45%. The superiority of ropegIFN, after only one year, was substantial [33]. Therefore, this ELN panel recently modified its recommendation by considering rIFNα for low-risk patients [18]. Likewise, the NCCN also modified its recommendations for treating low-risk PV patients by also allowing the use of rIFNα as a II-B ("soft") recommendation [19, 20]. For high-risk patients, both the NCCN and ELN recommendations include rIFNα [18, 19].

Based upon the results from randomized studies of safety and efficacy of rIFNα in PV, published within recent years, our purpose now is to detail our recommendations for treating all PV patients with rIFNα from early in the course of the disease, hopefully from the time of diagnosis, unless contraindicated. We believe this will reduce the initial risk of thrombosis and later, the risk of developing secondary post-polycythemic myelofibrosis (PPMF) [13, 14]. Thereby, a normal life expectancy may be possible for some patients with PV [34].

For a clinical perspective, we first review some basic aspects of interferons.

WHAT ARE INTERFERONS, AND HOW DO THEY EXERT THEIR EFFECTS?

Interferons (IFNs) are cytokines, signaling molecules, released by many cells involved with immune regulation. There are 3 types of IFNs of clinical interest. Type 1 interferons include α and β subtypes (also called "viral interferons"), type 2 or "immune interferons," and type 3 interferons (γ, 1, 2, and 3). Type 3 IFNs have similar activity to type 1 [35, 36]. Among IFNs, type I IFN-α is the principal interferon used in hematologic malignancies because of its broad immunomodulatory, antiproliferative, and anti-clonal effects. The mechanisms behind these beneficial effects will be addressed below.

MOLECULAR MECHANISMS OF TYPE I INTERFERON SIGNALING

Type I IFNs exert their effects through binding to the heterodimeric IFNAR1/IFNAR2 receptor complex, which activates JAK1 and TYK2, and to a lesser extent JAK2, initiating phosphorylation of STAT1 and STAT2 (Fig. 1). These form either STAT1 homodimers, which drive early pro-inflammatory transcription, or the ISGF3 complex (STAT1–STAT2–IRF9), which translocates to the nucleus and initiates the broad transcriptional program of interferon-stimulated genes (ISGs). The ISG response is dynamically regulated through negative feedback mechanisms, including SOCS1, SOCS3, and USP18, which modulate the duration and magnitude of

signaling [37, 38]. These regulatory layers shape the hematopoietic, immune, and antitumor effects central to interferon's clinical activity in PV.

ANTITUMOR AND IMMUNOREGULATORY EFFECTS OF IFN-A

The antitumor actions of IFN-α are multifaceted [35, 36]. Key mechanisms include activation of cytotoxic T cells and NK cells [39–41], upregulation of HLA class I expression, improving immune recognition of malignant clones, reversal of impaired tumor-surveillance pathways documented in PV and related MPNs [42], and modulation of inflammatory signaling cascades within the malignant microenvironment. Together, these effects enhance immune-mediated clearance of the neoplastic hematopoietic cells.

EFFECTS ON HEMATOPOIETIC STEM AND PROGENITOR CELLS

A defining feature of IFN-α is its direct activity on *JAK2V617F*-mutated HSCs. Interferon-α drives quiescent mutant HSCs into active cell cycle and depletes the malignant stem-cell reservoir [7–9]. This contributes to the progressive reduction in mutant allele burden observed in long-term clinical studies, which will be addressed below.

EFFECTS ON MEGAKARYOPOIESIS AND ERYTHROPOIESIS

In vitro, type I IFNs inhibit erythroid progenitor growth, erythroid burst-forming units, megakaryocyte proliferation and differentiation, and thrombopoietin receptor signaling [43]. They also induce morphologic and biochemical changes in megakaryocytes, contributing to their clinical effect on platelet and erythrocyte production [44].

POTENTIAL EFFECTS ON ADDITIONAL MUTATIONS OUTSIDE JAK2

Although interferon-α induces significant reductions in *JAK2V617F* VAF and, in some cases, near-complete molecular remissions in patients with PV and related MPNs [1–6, 10–12, 33], its effects on additional non-driver mutations such as *TET2*, *DNMT3A*, and *ASXL1* are less consistent [45]. However, post-hoc molecular analyses from the phase III PROUD-PV/CONTINUATION-PV program have convincingly demonstrated that long-term treatment with ropeginterferon-α2b not only reduces *JAK2V617F* VAF but also *TET2*-mutant VAF in patients with PV [46]. Importantly, this study also showed ropeginterferon-α2b to induce high hematological and molecular responses regardless of *TET2* mutational status. Indeed, in this study, the PV patients harboring *ASXL1* and *DNMT3A* also showed relevant ropeg responses with a reduction in allele burdens of these non-driver mutations [47]. In the study by Quintás-Cardama et al. PV and ET patients achieving complete molecular remission with undetectable *JAK2V617F* also exhibited clearance of concomitant non-driver mutations [3]. These findings suggest that rIFNα may exert broader clonal modulation beyond the *JAK2*-mutant clone. In contrast, previous clonal analysis studies of erythroid progenitors found that pegylated interferon-alpha2 treatment did not affect *TET2* mutant cells [48]. Furthermore, comprehensive NGS studies using pegylated interferon-α2a (Pegasys) in PV, ET and early myelofibrosis have demonstrated that coexistent mutations in *TET2, ASXL1*, and *DNMT3A* frequently persist during interferon therapy and are associated with lower rates of *JAK2V617F* molecular response, reduced likelihood of achieving complete molecular remission, and potential treatment resistance [45, 49, 50]. Notably, *DNMT3A*-mutant clones may even emerge or expand during interferon treatment, particularly in patients who fail to achieve a complete clinicohematologic response [51], although a negative impact of the *DNMT3A* mutation upon the response to interferon-α2 treatment has not been consistently recorded [52]. Taken together, these findings indicate that while ropeginterferon-α2b reduces *TET2* VAF in a subset of patients, current evidence does not support a generalizable effect of interferon-alpha on the eradication of additive mutations, particularly *ASXL1* or *DNMT3A*. Prospective molecular studies incorporating serial NGS and clonal tracking will be essential to define whether interferon can meaningfully modify the broader genomic landscape beyond the *JAK2*-mutated clone [53].

DISTINCTION BETWEEN INTERFERON-ALPHA AND JAK-INHIBITOR EFFECTS ON HEMATOPOIETIC STEM CELLS

Recent mechanistic studies have clarified crucial differences between interferon-alpha and JAK inhibitor effects on *JAK2V617F*-mutated HSCs. In essence, they have distinct cellular targets and exert differential activation of signaling pathways. Thus, as alluded to above, IFNα induces robust STAT1 phosphorylation in mutated HSCs along with activation of STAT2 and IRF9 signaling complexes (ISGF3), leading to interferon-stimulated gene expression. This mechanism—IFNα-induced STAT1 activation—is not suppressed by ruxolitinib, which primarily blocks STAT5, thereby reducing cytokine-driven myeloproliferation, but fails to inhibit the same pathway in HSCs, leaving the disease-initiating clone largely unaffected. Mathematical modeling studies of stem cell and progenitor cell dynamics during ruxolitinib treatment of patients with MPN have substantiated that ruxolitinib inhibits the myeloid progenitor population with no impact upon the stem cell pool [54]. In contrast, as previously alluded to, IFN-α has direct effects on dormant HSCs, driving them into active cycling and thereby exposing them to oxidative stress, DNA damage, and eventual stem cell exhaustion [7, 55, 56]. Importantly, ruxolitinib does not block IFN-α induced reactive oxygen species (ROS) generation and DNA damage in *JAK2V617F* murine HSCs, providing a biological rationale for combination strategies with rIFN-α and JAK 1-2 inhibitors due to their distinct cellular targets and mechanisms [57–59]. These findings support rIFNα as uniquely capable of engaging the disease-propagating stem cell compartment, unlike JAK inhibitors, which predominantly manage symptoms and cytokine-mediated inflammation without targeting the malignant HSC reservoir [38, 54, 57]. Table 1 summarizes major differences between IFN-α, ruxolitinib and hydroxyurea in terms of targeting the *JAK2V617F*-mutated stem cell, depleting the stem cell pool, potentially influencing non-driver mutations, reducing inflammation and collectively thereby being disease-modifying.

PEGYLATION OF INTERFERON ("PEGINTERFERON")

The term "pegylation" refers to the conjugation of interferon to polyethylene glycol (PEG), a nontoxic, nonimmunogenic polymer [60]. In general, pegylation changes the physical and chemical properties of a biochemical molecule, which improves the pharmacokinetic behavior of the drug and reduces toxicity. This results in improved stability, solubility, decreased immunogenicity, reduced proteolysis, and renal excretion [61]. Pegylated forms of rIFNα are more stable and allow longer intervals between dosing; thus, they are more convenient to use than non-pegylated forms [61].

Currently, there are two types of pegylated rIFNα (pegIFNα) available in clinical practice, Pegasys® (pegIFNα-2a), and Besremi® (ropegIFNα-2b). PegIFNα-2a is composed of several isoforms of interferon and is administered weekly. Ropeginterferon α-2b is monopegylated, composed of only one interferon isoform linked via an additional proline [61]. It is clinically attractive because it is administered once every 14 or 28 days [60]. As yet, no substantive differences have been reported between the two types except for the time differences in administration [62].

Table 1. Major differences between IFN-α, ruxolitinib and hydroxyurea in terms of targeting the *JAK2V617F*-mutated stem cell, depleting the stem cell pool, potentially influencing non-driver mutations, reducing inflammation and collectively thereby being disease-modifying.

Feature	IFN-α	Ruxolitinib	Hydroxyurea
Targets *JAK2V617F*-mutated HSCs	✔ Yes	✘ No	✘ No
Depletes malignant stem cell pool	✔ Yes	✘ No	✘ No
Affects additional mutations (e.g., DTA)	⚠ *	✘ No	✘ No
Reduces inflammatory signaling	✔ Yes	✔ Yes	⚠ Limited
Disease-modifying potential	★ High	⚠ Moderate	✘ Low

Hydroxyurea may give rise to skin cancer; there is concern that long-term treatment (10-15-20 years) may predispose to the development of acute myelogenous leukemia.
* : emerging evidence, DTA : *DNMT3A*, *TET2*, *ASXL1*.

TOXICITY OF rIFN-α IN POLYCYTHEMIA VERA

When properly used, rIFN-α probably has no greater frequency of toxicity than HU, and probably in the order of ~10–20%. In fact, the toxicity of rIFN-α may be far less than HU when considering the results from a German study, showing that long-term treatment with HU was associated with multiple side effects leading to discontinuation in half of the patients [63]. Toxicity to rIFN-α can be categorized into 5 subgroups: (1) viral-like, (2) hepatic, (3) endocrine, (4) autoimmune, and (5) neurologic and psychiatric [64–69].

PegIFN and ropegIFN have never been compared on a head-to-head basis with respect to side effects. We tend to continue the same dose of rIFN-α if viral-like symptoms develop, or temporarily interrupt medication to allow the symptoms to clear, supporting the patient with paracetamol. Abnormal liver tests may develop during rIFN-α treatment, with, in particular, elevated alanine aminotransferase (ALAT) levels. These elevations are usually transient, reversible, and clinically insignificant.

We allow a 2× rise in ALAT/ASAT and increase in two times the bilirubin value. This does not preclude continuation of treatment, but should be monitored closely at least monthly to ensure that the increase in ALAT levels does not continue. In some patients, discontinuation of rIFN-α may be necessary until abnormal liver tests have normalized. Reexposition to rIFN-α is recommended before the definitive decision is taken that the patient does not tolerate rIFN-α. The reasons for abnormal liver tests in some patients during exposure to rIFN-α are elusive. However, it is intriguing to speculate whether *JAK2V617F*-induced liver disease—e.g., inflammation-driven liver steatosis—might play a role, taking into consideration that CHIP-*JAK2V617F* associates with a 16-fold increased risk of liver disease [70]. Secondary hypothyroidism is not considered a contra-indication, since thyroid hormone replacement is easy. Hyperthyroidism, however, is considered a contraindication for continuation. The rarer co-occurrence of autoimmune disease, such as rheumatoid arthritis, requires discussion with a rheumatoid disease consultant. Significant neurologic disorders require careful thought and neurologic consultation before the use of rIFN-α. On the other hand, many patients who are depressed when initially seen may have symptoms because of their disease, and may well profit by rIFN-α therapy. Obviously, psychiatric consultation is required. In our experience, most patients have decreased symptoms of depression following institution of overall therapy, including rIFN-α. Toxicity issues during treatment with rIFN-α have been thoroughly described in several previous comprehensive reviews [35, 68, 69, 71–73].

PRACTICAL DOSING OF RECOMBINANT INTERFERON-A IN POLYCYTHEMIA VERA

An important and often underappreciated aspect of rIFN-α therapy in PV concerns dosing strategy. We recommend using low initial doses (e.g., 50–100 µg for ropeginterferon; 45 µg weekly for Pegasys) with slow intrapatient titration. Durable hematologic and molecular responses are commonly maintained at 45–90 µg weekly, with many patients later extended to every 2–4 weeks dosing in deep remission. We believe that the individualized "start-low–go-slow" approach minimizes toxicity and discontinuation while maximizing the long-term disease-modifying benefits of interferon therapy. However, studies are ongoing, which successfully use a higher initial dose of RopegIFN (250 µg every second week) with stepwise increases up to 500 µg every second week [74]. The rationales for this approach are, among others, that a higher initial dose with faster dose titration may lead to earlier complete hematological remission and lowering of the *JAK2V617F* VAF, thereby reducing the increased risk of thromboembolic events, which are highest immediately before and in the first months after the diagnosis of PV [23, 75, 76]. This increased risk may not be adequately addressed by a low starting dose and slow titration regimen, since the time to normalization of blood cell counts may be delayed. Adding to this, a more rapid decline in the *JAK2V617F* VAF may also be favorable, taking into account the thrombogenic potential of the *JAK2V617F* mutation and its association with a high leukocyte count [74, 77–81], which has been shown to be an independent risk factor for thromboembolic events [82, 83]. A recent excellent overview comprehensively addresses the alternative dosing strategy for ropegIFN [74]. Most importantly, the treatment should be patient-tailored, the goals being to maximize tolerability, preserve adherence, and to allow patients to remain on rIFN-α therapy long enough to realize its unique disease-modifying benefits, including *JAK2V617F* reduction, suppression of clonal evolution, and potential restoration of polyclonal hematopoiesis. Table 2 summarizes key differences between pegIFNα-2a and ropegIFNα-2b.

THE NEW GOALS OF THERAPY IN PV

A prerequisite for a favorable outcome for most types of cancer is its earliest diagnosis and treatment when the tumor burden is low. We believe this concept also applies to the MPNs. The conventional goals of therapy in PV are to relieve symptoms (e.g., fatigue, pruritus, night sweats, and microvascular disturbances), eliminate or minimize the risk of thrombosis and the much less frequent hemorrhagic complications, and to reduce the risk of evolution to myelofibrosis and leukemic transformation. In this context, retrospective long-term studies of the course of PV patients suggest that PHLEB-O-treated PV pts compared to those treated with HU or rIFN progress sooner to PPMF [13]. This is accompanied by clonal evolution and the acquisition of additional mutations [53]. The notion that "younger" patients have a more benign course than "older" patients belies the fact that younger patients may have a more aggressive disease phenotype [84], although this is still controversial [85]. Thus, we believe that

Table 2. Comparison of Peginterferon alfa-2a (Pegasys) and Ropeginterferon alfa-2b (Besremi) in Polycythemia Vera.

Feature	Peginterferon alfa-2a (Pegasys®)	Ropeginterferon alfa-2b (Besremi®)
Molecular structure	Standard pegylated IFN alfa-2a (40 kDa branched PEG)	Monopegylated IFN alfa-2b (single-site 40 kDa PEG)
Dosing frequency	Weekly or biweekly	Every 2 weeks during titration, then every 4 weeks (maintenance)
Regulatory approvals in PV	EMA approval 2024 (generic Pegasys also available)	EMA approval 2019; FDA approval 2021 for PV
Typical starting dose	45–90 µg weekly (variable real-world practice)	50 µg every 2 weeks (EMA); 100 µg every 2 weeks (FDA)
Dose titration	Increase by 45–90 µg every 4–6 weeks	Increase by 50 µg increments every 2 weeks
Usual maintenance dose	45–180 µg weekly or biweekly	250–350 µg every 2–4 weeks
Half-life	~80–90 h	~120 h (longer due to monopegylation)
Mechanism of action	Type I IFN signaling; hematopoietic and immunomodulatory effects	Same pathway; prolonged and more stable exposure may improve tolerability
Molecular response data	High rates of partial and complete molecular remissions over 3–5 years; CMR in a subset of patients*	High rates of partial and complete molecular remissions over 3–5 years; CMR in a subset of patients *
Hematologic response	High and sustained CHR rates	High and sustained CHR rates
Pregnancy	Historically preferred IFN for pregnancy (long safety record)	Not approved for pregnancy; limited data
Tolerability	Flu-like symptoms, mood changes, and thyroid dysfunction are more common	Generally better tolerated; fewer neuropsychiatric events reported
Liver toxicity	Transaminase elevations are possible; reversible with dose adjustment	Similarly, EMA recommends caution at ALT/AST > 5× ULN
Stem cell targeting	Demonstrated suppression of the malignant HSC clone with normal bone marrow in a subset of patients	Strong suppression of MPN HSC with long-term allele burden decline
Long-term disease modification	Established but variable	Strong evidence for sustained molecular remission, low progression to MF or AML
Practical considerations	Widely available; familiar to clinicians; generic reduces cost	Longer dosing interval; consistent pharmacokinetics; preferred by many for long-term therapy

*: *CMR* Complete Molecular Remission has not yet been documented if a highly sensitive droplet digital PCR is being used.

therapy with rIFNα should be initiated at the time of diagnosis, inducing complete hematologic and deep molecular remission, and accordingly leading to a state of "minimal residual disease" (MRD) [2, 10–12, 58, 86]. This is the antithesis of the "watch and wait" approach espoused by those favoring PHLEB-O and aspirin as the only initial treatment in low-risk PV-patients [87]. The harmful consequences of such a strategy are summarized in Table 3.

THE EARLY INTERVENTION CONCEPT IN THE INTERFERON ERA

It has been known for decades that rIFNα can induce a complete hematologic remission in PV [1–5, 10, 12, 64–67]. Several studies have shown accompanying "complete" or "major" molecular remission, the latter most often being associated with a decrease in the *JAK2V617F* VAF to less than 5% [1–4, 10, 58, 86], which in a subset of patients is accompanied by sustained normalization of marrow morphology after discontinuation of rIFN. This MRD state can be considered an "operational biologic cure" [2, 10, 12, 58] [to be discussed below].

Despite these results, rIFNα use in PV has been limited until recently by the relative lack of phase 3 studies. Therefore, rIFNα has been recommended only in selected patients, for example, those resistant or intolerant to HU [18, 71]. Since rIFNα treatment remains extremely heterogeneous worldwide, the recommendations for its use are influenced by local experience [16]. It is, therefore, not surprising that several expert reviews and recommendations for treating PV pts have failed to recognize the beneficial effects of early treatment with rIFNα [71, 87–89]. However, a new era is fortunately emerging, in which the rationales and perspectives of the early use of rIFNα, also in low-risk patients, are highlighted and increasingly being recognized [12, 67, 68, 72, 73, 90, 91], supporting our previous reports and others on the benefits of early intervention with rIFNα [2, 10, 12, 33, 34, 51, 58, 66, 92–98]. This paradigm shift from a "watch and wait strategy" to "early rIFNα-treatment" has been partly based upon results from the recent randomized trials, substantiating and providing further evidence for its efficacy and safety. We describe this now.

RANDOMIZED STUDIES OF INTERFERON IN PV INDICATE ITS SAFETY AND EFFICACY

Historically, the first randomized trial of interferon versus PHLEB-O occurred about 30 years ago using lymphoblastoid IFNα, 3.0×10^6 U/day sc. PVSG criteria were used for diagnosing 22 patients younger than 70 years [99]. Treatment in each arm lasted for 5 months only, and then treatment was crossed over. The symptoms of PV in all the interferon-treated patients were "greatly reduced" and the need for phlebotomy was eliminated. Spleen size decreased in 6 of 14 patients. One chromosome analysis pretreatment showed i(17q) in 3 of 50 cells, which normalized after 3 months of IFN therapy. Correction of iron deficiency and replacement of marrow iron stores were noted. Mild flu-like symptoms in 18 of the 22 patients did not lead to any patient discontinuation. The authors believed their results "unequivocally demonstrated IFN was superior to PHLEB-O in controlling all clinical aspects of the myeloproliferative process and of the disease." There are obvious gross limitations to this study, but nevertheless, based on a randomized trial, it suggested the

Table 3. Consequences of "watch and wait strategy" treatment with only phlebotomy and aspirin in low-risk PV patients.

Aggravation of the iron-deficient state :	**Explanations /Mechanisms**	**References**
a. Learning and memory impairment	Iron deficiency induces impairment of cognitive function	[25]
b. Heart failure (HF)	Iron deficiency pathophysiology in HF is poorly understood—chronic inflammation likely plays a prominent role	[26]
c. Increased risk of thrombosis	Iron-induced thrombocytosis	[22, 86]
	Increased coagulopathy and platelet activation	[28, 29]
Inadequate reduction in the number of phlebotomies and accordingly increased risk of thrombosis	Lowering of MCV and thereby hematocrit despite erythrocytosis: Hematocrit = erythrocyte count x MCV/10	[69]
Persistent and increasing leukocytosis and thrombocytosis	Uncontrolled myeloproliferation	[31]
a. Increased risk of thrombosis	Uncontrolled myeloproliferation, chronic inflammation /oxidative stress	[31]
b. Increased risk of post-PV- MF	Uncontrolled myeloproliferation, chronic inflammation /oxidative stress with ensuing DNA-damage; post-PV MF in about 10–20% after approx. 10–20 years	[31, 112, 115–117, 126, 127]
c. Increased risk of leukemic transformation	Uncontrolled myeloproliferation, chronic inflammation, and increasing genomic instability	[31, 78, 80, 113, 126]
d. Increased metastatic potential of second cancer	Uncontrolled myeloproliferation and inflammation, which favor increased cancer invasiveness	[154, 155]
Increasing *JAK2V617F* mutation load	Clonal expansion	
a. Increased risk of genomic instability	Chronic inflammation /oxidative stress with ensuing DNA damage	[79, 115–117, 126, 127]
b. Increased risk of thrombosis risk	Induction of PADI4	[77, 140]
c. Increased risk of post-PV MF	Chronic inflammation /oxidative stress with ensuing DNA damage	[112]
d. Increased risk of CVD (e.g., stroke, coronary disease, pulmonary hypertension and aneurysms	In vivo activation of leukocytes, platelets and endothelial cells; formation of aggregates, which block the circulation, giving rise to thrombosis, organ dysfunction and organ failure.	[112, 119–123, 128–130]
e. Increased risk of second cancers	Chronic inflammation /oxidative stress with ensuing DNA-damage? Defective "tumor immune Surveillance"/"tumor immune escape"?	[115, 116, 151–153]
f. Early atherosclerosis development?	Chronic inflammation /oxidative stress?	[115–117, 139]
g. Early immune-aging?	Chronic inflammation /oxidative stress?	[115, 147]
h. Early development of drusen and age-related macular degeneration	Chronic inflammation /oxidative stress?	[165]
Increase in platelet - CD8 + T cell aggregates giving rise to jeopardized CD8 T cell responses	Clonal myeloproliferation	[166]
a. Increased risk of disease progression?	Impaired immune cell function?	[166]

superiority of IFN compared to PHLEB-O, even in the short term [99].

Other randomized trials, unfortunately, could not be organized until recently. In the ensuing 20 years, more than 2000 PV patients have been treated with various types of interferons in approximately 20 phase 2 studies [for reviews 5, 12, 35, 58, 64–68].

Recently, four large randomized studies pertaining to the efficacy and safety of rIFNα in PV have been conducted: the phase 3 randomized PROUD and CONTINUATION- PV trial [86, 92–94], the DALIAH-trial [51, 95], the MPN-Consortium trial [100] and the ropegIFN trial in low-risk PV patients [33, 96, 97].

THE PHASE 3 RANDOMIZED PROUD AND CONTINUATION- PV STUDY. TREATMENT RESULTS AFTER 5 TO 7.3 YEARS

The regulatory approval by the European Medicines Agency in 2019 of ropegIFN for ELN-defined high-risk PV pts stipulated the absence of symptomatic splenomegaly. Of note, symptomatic splenomegaly in PV is a curious criterion for exclusion since, in fact, previous studies and a recent systematic one indicate it is a rare event at diagnosis, and it is infrequent in the absence of progression to PPMF, where the drug would likely be helpful [69, 98, 101]. PROUD-PV was the first study comparing HU to rIFNα as initial therapy in European LeukemiaNet (ELN) defined high-risk PV patients requiring cytoreductive therapy. After one year, it showed the non-inferiority of ropegIFN treatment. The follow-up CONTINUATION-PV trial showed an unambiguous advantage for ropegIFN for achieving a complete hematologic response and for inducing molecular responses [92]. The 5-year results showed the superiority of ropegIFN compared to HU therapy for achieving and maintaining both complete hematologic and deep molecular responses. Thus, the molecular response rate was significantly higher in the ropegIFN arm than in the control arm (65/94 [69.1%] versus 16/74 [21.6%], respectively; $p < 0.0001$). Importantly, the median *JAK2V617F* VAF declined continuously during ropegIFN treatment, from 37.3% at baseline (before treatment in PROUD-PV) to 8.5% at 60 months. In the control arm, the median *JAK2V617F* VAF decreased from 38.1% at baseline to 18.2% at 12 months but rebounded to 44.4% by 60 months (comparison of treatment

arms: $p < 0.0001$). A *JAK2V617F* VAF < 10% was achieved in 50/92 (54.3%) of the ropegIFN-treated patients at month 60, but this occurred in patients at a lower age and lower *JAK2V617F* VAF at baseline. Furthermore, a *JAK2V617F* VAF < 10% was associated with a higher complete hematologic response rate at month 60. The *JAK2V617F* VAF decreased to <1% in 18/92 patients (19.6%), who received ropegIFN. Only 1 patient (1.4%) in the control arm achieved a VAF < 1% at 60 months ($p = 0.0002$) [92].

RopegIFN was well-tolerated at a maintenance dose of 350–500 µg administered every 2 to 4 weeks; side effects, although of different types, occurred at approximately the same frequency in both arms: HU, 79%; ropegIFN, 79% [92]. Moreover, no new signs of toxicity appeared. One case of myelofibrosis (MF) occurred in the ropegIFN arm compared to 2 cases of MF and 2 of acute leukemia in the HU arm. These early findings are suggestive and are consistent with a long-term single-center retrospective study, showing a superiority of myelofibrosis-free survival in ELN-defined low-risk rIFNα-treated PV patients compared with those treated with either HU or PHLEB-O [13]; superior overall survival occurred in ELN-defined high-risk rIFN-treated patients compared to either HU or PHLEB-O [13]. An update of safety data of the ropegIFN arm for pts treated for as long as 7.3 years has shown continued superiority in event-free survival [93]. Only 14/127 (11.0%) of patients in the ropegIFN arm and 3/127 (2.4%) in the HU/BAT arm discontinued therapy due to drug-related toxicity. It was suggested that the higher discontinuation rate in the ropegIFN arm might reflect more intensive monitoring for potential side effects [93], but this obviously could be drug-related. The clinical relevance of a molecular response (MR) (a reduction in *JAK2V617F* VAF) has been debated. Therefore, the most recent results from PROUD and CONTINUATION-PV are highly interesting, showing for the first time that MR correlates with improved event-free survival (EFS) in patients with early-stage PV [94]. A correlation between MR and EFS has been previously demonstrated in the MAJIC-PV study, which included high-risk PV patients resistant/intolerant to hydroxyurea, being treated with ruxolitinib [102] and in a cohort of 77 patients with PV and ET, treated with ruxolitinib for a median of 8 years and prospectively followed with serial measurements of *JAK2V617F* VAF [103].

THE DALIAH-TRIAL

The DALIAH-trial was an open-label, randomized, phase III trial comparing the efficacy and safety of two different rIFNα formulations (pegIFNα-2b and pegIFNα-2a) compared to HU in 202 newly-diagnosed patients with MPNs, of whom 89 had PV. To decrease toxicity and discontinuation, rIFNα was initially administered in low doses (pegIFNα-2a : 45 µg/week and pegIFNα-2b : 35 µg/week). Doses were increased in a response-driven manner at prespecified time-points to achieve a complete hematologic response at 4 and 12 months [51, 95]. Those patients with CHR had a significantly greater reduction in the *JAK2V617F* VAF than those who did not achieve CHR [51, 95]. Importantly, in patients treated with rIFNα, the *JAK2V617F* VAF displayed a slow but continuous reduction with no evidence of plateau at 60 months [95]. By contrast, in the HU-group, the initial rapid decline in *JAK2V617F* VAF was transient, implying a greater reduction in the *JAK2V617F* VAF from baseline in the pegIFNα group at 60 months [95]. Next-generation sequencing (NGS) was assessed for 120 genes [51]. Of note, mutations in *DNMT3A* occurred more commonly in patients treated with rIFNα than with HU; it was also significantly more common in rIFNα-treated patients not attaining CHR [51, 95]. This might be explained either by treatment-resistant subclones or genetically unrelated clones that developed in parallel with the *JAK2V617F* clone. Since many adults older than 50 years have evidence of clonal hematopoiesis, most commonly involving mutations in *DNMT3A* [104], it is reasonable to conclude that treatment-emerging *DNMT3A* mutations are pre-existing at baseline and are selected by rIFNα therapy. An association between the *DNMT3A* mutation and failure to achieve a CHR and major molecular remission has been previously reported [3]. This phenomenon has also been demonstrated in *JAK2V617F* mice, in which genetic loss of *DNMT3A* conferred resistance to rIFNα [105]. The mechanism underlying the association between the *DNMT3A* mutation and resistance of stem cells and progenitors to rIFNα might be aberrant self-renewal of *JAK2V617F*-mutant hematopoietic stem and progenitor cells and increased pro-inflammatory signaling [106, 107]. Importantly, however, a recent retrospective single-center study of 247 PV patients, in whom NGS testing was available out of the total PV cohort of 646 patients, reported no association between *DNMT3A* and rIFNα treatment outcomes [108]. In this large cohort, a total of 37 *DNMT3A* mutations were identified in 34 patients who had similar outcomes as those without *DNMT3A* in terms of the likelihood of achieving CHR, the time to achieve CHR and molecular response defined as a relative decrease in *JAK2V617F* alle burden >20% from baseline. No difference in overall survival or event-free survival, defined as survival free of thrombosis, myelofibrosis or leukemia, was recorded between patients having the *DNMT3A* mutation as compared to the IFN-PV subgroup without this mutation. These results strongly indicate that the existence of the *DNMT3A* mutation should not impact the decision to start rIFNα treatment or its discontinuation, if *DNMT3A* emerges during treatment [108].

Despite a low-dose regimen, 28 (37%) of the rIFNα-treated PV patients in the DALIAH trial discontinued treatment because of toxicity. This contrasts with the ropegIFNα-2b studies, in which rIFNα was relatively well-tolerated [33, 92–94, 96, 97], even in elderly patients [109]. The diverging discontinuation rates due to toxicity between the DALIAH trial and other pegIFNα-2a trials are surprising and need to be further investigated. The high discontinuation rate in the DALIAH trial may have been physician-dependent.

THE MPD-RC 112 CONSORTIUM TRIAL

This randomized pegrIFNα-2a versus HU trial included 87 high-risk PV patients. At 12 months, the complete response (CR) rate was 28% for pegIFNα-2a and 30% for HU; hematocrit control without phlebotomy was achieved in 65% of the pegIFNα-2a-treated group and 43% of the HU group. More rIFN-treated patients achieved a reduction in the *JAK2V617F* VAF with a consistent decrease from baseline through 24 months, whereas *JAK2V617F* increased after month 12 with HU. No differences were noted regarding thrombotic events or disease progression. It was concluded that, at 1 year, pegIFNα-2a and HU are both effective for treating PV [100]. Based upon many phase 2 trials, the PROUD-CONTINUATION study, and the DALIAH trials, 1 year of therapy is insufficient to determine the drug superiority of HU compared to pegIFNα [51, 92, 93, 95].

THE ROPEGrIFNα-2B LOW-RISK PV TRIAL

The ELN/NCCN recommendations for maintenance treatment of low-risk PV patients with phlebotomy and low-dose aspirin have been noted already [18–20]. In 2025, the NCCN recommendations were updated to include ropegIFN as a category 2A treatment option for patients with symptomatic low-risk disease; it remained a treatment option for high-risk patients [20]. As mentioned, we believe a disease-modifying drug should be administered initially or early in the course of the disease since it may affect survival. In this perspective, the randomized PHLEB-O versus ropegIFN study in ELN defined low-risk PV patients [33, 96, 97] has convincingly confirmed prior data obtained during the last 30 years, that rIFNα is safe and more effective than phlebotomy PHLEB-O

[1–4, 10, 12, 13]. In this trial, a fixed dose of ropegIFN, 100 ug every 2 weeks, was compared to PHLEB-O plus aspirin in ELN-defined low-risk PV patients [33, 96, 97]. The primary endpoint was the proportion of patients maintaining a median hematocrit value of 45% or lower without disease progression for 12 months. A preplanned interim analysis at 12 months after enrollment of the first 100 patients, corresponding to 2/3 of the expected sample size, showed the superiority of the ropegIFN arm with 84% of patients (42 of 50 patients) reaching the primary endpoint, compared to 66% (33 of 50 patients) in the PHLEB-O arm. In this group, 42% of the patients reported at least one adverse event compared with 78% in the experimental group ($p < 0{\cdot}0001$), in which adverse events were attributed to ropegIFN in 48% of the 50 patients, whereas adverse events were attributed to treatment (PHLEB-O) in only 6% of the 50 patients in the standard group. Importantly, the addition of ropegIFN did not increase the frequency of serious adverse events (Grade 3) (6%) in comparison to the PHLEB-O group (5%). Therapy withdrawals were not recorded in the patients in the standard group but occurred in 6% of patients in the ropegIFN arm [33]. Because of the convincing efficacy of ropegIFN, the data safety monitoring board decided to stop patient accrual and to continue follow-up of enrolled patients for 2 years, when ropegIFN was still superior to phlebotomy alone in maintaining hematocrit on target. Ropeg responders less frequently experienced moderate/severe symptoms (33% vs. 67% in the standard group arm) and palpable splenomegaly (14% vs. 37%) and showed normalization of ferritin levels and blood counts. No dose-limiting side effects or toxicities were noted.

Final analysis after 5 years of follow-up [97] confirmed the initial favorable reports [33, 96]. Of note, ropegIFN was discontinued in 33% of patients during the first 2 years due to "lack of response" (12 pts), adverse events (6 pts), or withdrawal of consent (3 pts) [97]. The two main reasons for discontinuation were failure to control the HCT on target and the occurrence of adverse events in 19% and 14% of the patients, respectively [97]. It was speculated that the fixed dose of 100 µg in this low-risk PV study might be the reason for failure to control the HCT on target. Accordingly, a higher dose might have yielded higher response rates without increased toxicity as shown in the PROUD-CONTINUATION Study, in which the average dose of ropegIFNα-2b was four to five times higher than in the low-risk PV trial and yet with a drug discontinuation due to adverse events of only 13% [86, 92]. These results are important because they confirm early disease control with rIFNα in PV [10, 12, 13, 34, 58]. Importantly, in their 5-year follow-up ropegIFNα study in low-risk PV patients, "drug-survival " as defined by a proxy measure for the effectiveness, safety, adherence, and tolerability of the drug was only 58%, meaning that it had been discontinued in 42% of the patients. The main reasons for discontinuation were failure to control HCT on target in 19% and adverse events in 14% of the patients, and accordingly very similar to the incidence of 13%, recorded in the PROUD CONTINUATION study [97]. Table 4 provides an overview of key registration-enabling trials of conventional IFN and pegylated IFN in polycythemia vera.

DO THE RECOMMENDATIONS OF AN EXPERT PANEL OF THE ELN FOR TREATING PV DIFFER FROM OURS?

Some hematologists continue to treat low-risk patients with PHLEB-O despite the results of the low-risk PV trial. In 2022, the ELN published criteria for the use of cytoreductive therapy if low risk, developing certain symptoms, signs, or laboratory abnormalities. An expert panel of ELN PV investigators promulgated recommendations for treating PV with rIFNα [18]. It recommended cytoreductive therapy with ropegIFN or pegIFNα-2a for ELN defined low risk PV patients, if at least one of the following criteria were fulfilled: strictly defined intolerance to phlebotomy, symptomatic progressive splenomegaly, persistent leukocytosis (WBC > 15×10^9/L), progressive leukocytosis (at least 100% increase if the baseline count was $<10 \times 10^9$/L or at least a 50% increase if the WBC was $>10 \times 10^9$/L), "extreme" thrombocytosis (platelets $>1500 \times 10^9$/L), inadequate hematocrit control despite phlebotomies, a high cardiovascular risk, and a persistently high symptom burden. The panel also suggested either rIFNα or ruxolitinib for patients resistant or intolerant to HU, if that drug had been administered [18].

Since rIFNα induces complete hematologic and molecular remission in a significant number of PV patients, as we have discussed, the recommendations of the expert panel are challenging. We believe that the encouraging results from the final reports of the low-risk PV phase 2 trial and continuation studies, providing definite evidence that ropegIFN is superior to PHLEB-O, are strongly supportive of the initial use of rIFNα in all eligible low-risk patients to prohibit thrombotic events and disease progression in terms of increasing leukocytosis, thrombocytosis and increasing splenomegaly [96, 97]. These results align with the large number of studies and our clinical experience during the last 30 years that the early use of rIFNα in PV is highly effective in controlling elevated blood cell counts [12, 13, 69, 98]. Importantly, long-term treatment with rIFNα improves myelofibrosis-free survival in low-risk PV patients [13]. In addition, data-driven analysis of *JAK2V617F* kinetics suggests that early use of rIFNα shortens the time required to obtain molecular response [110]. Finally, younger patients may have more aggressive disease [84, 85, 111], implying a need for earlier treatment with rIFNα.

Prior studies of correlations between leukocytosis, thrombosis, leukemic transformation, and survival have demonstrated conflicting results [31, 80, 83, 112, 113]. A Swedish-French study showed leukocytosis associated with impaired survival [31], and a recent large retrospective study of 520 PV patients showed that persistent leukocytosis is associated with disease evolution to myelofibrosis, myelodysplastic syndrome, and acute leukemia. The hematocrit value and the platelet count were not associated with disease evolution or thrombosis. Persistent leukocytosis either associated with thrombosis [113]. On the other hand, in the REVEAL Study, persistent leukocytosis increased the risk of thrombotic events, even with a normal hematocrit and suggested that white blood cell count control was important in reducing thrombotic complications [83]. More evidence is accumulating that leukocytosis in PV is associated with an increased risk of both arterial and venous thrombosis [32, 77–79, 83]. Noteworthy, in PV, neutrophils are not only a pathogenic link to thrombosis, but in PV also contribute to chronic inflammation [114].

Because of this strong suggestive evidence, we recommend normalizing elevated leukocyte counts in PV because it is probably a risk factor for thrombosis [83], but also since it is a biomarker of chronic inflammation [77–79, 114] - a driving force for disease progression [115–117]. Therefore, we strongly support the above recommendations to normalize the elevated leukocyte count and platelet count in PV by the initial use of rIFNα. We envisage these recommendations to be included in the next revision of the ELN recommendations.

Virtually all PV patients have constitutional symptoms of varying severity at disease onset, which interfere with quality of life [24, 101, 118]. The development of severe iron deficiency due to repeated phlebotomies accentuates the symptom complex (Table 3). Symptomatic splenomegaly at the onset of disease is rare [101]. When progressive splenomegaly occurs, it frequently signals the onset of post-polycythemic myelofibrosis (PPMF) [101]. Considering that rIFNα efficiently normalizes elevated leukocyte- and platelet counts in concert with a reduction in the *JAK2V617F* VAF in the majority of PV patients, it is important to note, that the *JAK2V617F* mutation is associated with an increased risk of cardiovascular diseases, including coronary artery calcifications,

Table 4. Overview of key registration-enabling trials of conventional IFN and pegylated IFN in polycythemia vera.

Trial/Year	Interferon Formulation	Design/Population (*n*)	Primary Endpoint(s)	Key Findings	Regulatory Relevance
PROUD-PV (2013–2015) and CONTINUATION-PV (extension EudraCT 2014-001357-17); Lancet Hematology 2020)	Ropeginterferon alfa-2b (mono-pegylated IFN-α2b; Q2W titration)	Phase 3, randomized; non-inferiority; early PV; (no prior cytoreduction or <3y HU), mostly without splenomegaly; $N = 257$ randomized; 171 rolled over to extension; Comparator : Hydroxyurea (year 1); standard /BAT in extension	PROUD-PV: CHR with normal spleen size at 12 mo (non-inferiority). CONTINUATION-PV: CHR with improved disease burden at 36 mo.	Non-inferiority not met at 12 months; progressively higher CHR and molecular responses with longer therapy; acceptable safety	Pivotal safety/efficacy program supporting EMA (2019) and FDA (2021) approvals for PV
PEGINVERA (P1101) (NCT01193699)	Ropeginterferon alfa-2b (mono-pegylated IFN-α2b; Q2W)	Prospective, open-label Phase 1,2 trial; PV (new and pre-treated); Comparator: Single-arm (no active comparator	Safety, hematologic response, durability	High and durable hematologic responses; sustained allele-burden reduction; favorable long-term tolerability	Foundation trial for dose and safety data contributing to regulatory approvals
MPN-RC 112 (NCT01259856); Blood 2022	Pegylated interferon-α (PEG-IFN-α2a)	Phase 3, randomized;open-label; high-risk, treatment naïve ET/PV $n = 168$;comparator: hydroxyurea	CHR at 12 months	Similar CHR to HU at 12 months; deeper molecular responses with PEG-IFN; at later timepoints; grade 3/4 AEs more frequent with PEG-IFN; thrombotic events infrequent and similar	Supportive randomized evidence informing guidelines and, in 2025, UK MHRA approval of peg-IFN-α2a (Pegasys) for PV/ET.
DALIAH-Trial (NCT01387763). Presented as an abstract at ASH 2023	Pegylated interferon-α (PEG-IFN-α; predominantly peg-IFN-α2a bu also peg-IFN-α2b)	Phase 3, randomized; open-label; newly diagnosed ET,PV and myelofibrosis; comparator : hydroxyurea	The JAK2V617F molecular response (MR; partial or complete) at 18, 36, and 60 months, according to European LeukemiaNet (ELN) 2009 criteria.	HU and pegIFNα display distinct response kinetics. Among patients who tolerated therapy, pegIFNα achieved superior long-term molecular responses.	Supportive randomized evidence of the safety and efficacy of pegIFN-α
Early recombinant IFN-α studies (1980s–1990s)	rIFN-α2a/α2b	Open-label phase 2; small cohorts	Hematologic response	Demonstrated activity of IFN in PV and the basis for the development of pegylated formulations	Historical foundation; not part of modern regulatory filings

BAT best available therapy, *CHR* complete hematologic response, *HU* hydroxyurea, *IFN* interferon, *MHRA* UK Medicines and Healthcare products Regulatory Agency, *Q2W* every 2 weeks. Mediators.
The PROUD-PV/CONTINUATION-PV program is the pivotal randomized dataset for ropeginterferon alfa-2b, leading to FDA approval (Nov 2021) for adults with PV (FDA medical review/label dossier). PEGINVERA provides the foundational long-term safety/efficacy and molecular-response signal that complements phase 3 evidence for registration. MPN-RC 112 is not PV-only but is the largest phase 3 randomized head-to-head trial of peg-IFN vs HU across ET/PV, its findings were influential for practice recommendations and the 2025 MHRA decision on peg-IFN-α2a (Pegasys) in the UK.

ischemic stroke, and aortic aneurysms [77–79, 119–122] and with pulmonary hypertension (PH) as well [123–125]. Adding to this, the *JAK2V617F* mutation induces genomic instability [79, 126, 127] and provides the genetic background for emerging additional somatic mutations, especially *TET2* and *DNMT3A* mutations [53], which are also associated with an increased risk of cardiovascular disease [128–130].

According to ELN recommendations [18], high-risk patients should be treated first with HU and then with either rIFNα or ruxolitinib, if a refractory or resistant phase develops. These recommendations are not evidence-based, and there are no randomized trials comparing these 2 drugs in the HU refractory resistant stage.

Ruxolitinib is a potent immunosuppressive agent, which is associated with an increased risk of infections, especially of the urinary tract, and varicella zoster [131], and an increased risk of skin cancer [132] and malignant lymphoma [133]. Although ruxolitinib treatment of PV patients refractory or intolerant to HU results in a decrease in the *JAK2V617F* VAF and increased event-free and overall survival [102] which has also been confirmed in another study, demonstrating profound and durable MR in 20% of ruxolitinib treated patients with PV and ET, including a VAF stably ≤2%, and complete MR in 8%[103], we are less likely to use ruxolitinib before rIFNα in this setting because it is not disease-modifying, as is rIFNα. Recently, there has been confirmation of this viewpoint [134].

MINIMAL RESIDUAL DISEASE IN POLYCYTHEMIA VERA. IS IT ATTAINABLE AFTER LONG-TERM TREATMENT WITH rIFNα?

Sustained normal blood cell counts and low *JAK2V617F* VAF (< 5%) are attainable in a subset of PV patients after being treated with rIFNα for at least 3–5 years, in some even with a normal or virtually normal marrow histology (implying persistent, slightly abnormal megakaryocyte morphology) [10, 12, 58]. After discontinuation of rIFNα, normal blood cell counts and low *JAK2V617F* VAF may be maintained for 2-3 years [10, 12, 58]. These encouraging outcomes of long-term treatment with rIFNα may be described as minimal residual disease (MRD). We emphasize the urgent need for studies to characterize this subset of patients, likely thereby also modifying the MRD definition [12, 58]. Preliminary data suggest that patients achieving MRD are also non-smokers and do not have significant inflammation-driven comorbidities. This is consistent with the observation that smoking is a highly potent systemic inflammatory stimulus that impairs the rIFNα response in treating the MPNs [135]. The unresolved issues are whether MRD correlates with increased survival and whether rIFNα treatment should be continued or not when this state is achieved. The findings that long-term rIFNα treatment convincingly associates not only with durable hematologic and deep molecular responses but also improved event-free survival lend support to the viewpoint that these findings may also translate into an improved overall survival [93, 94].

Complete molecular remission (CMR) without detectable *JAK2V617F* has been reported in several studies [1, 3, 4, 93], but in our experience, CMR never occurs if a highly sensitive digital droplet PCR is used [136]. Moreover, a concurrent marrow biopsy was not reported in the patients achieving CMR [1, 3, 4, 93]; this is important since marrow abnormalities may persist in these patients, as alluded to below [137, 138].

DISCONTINUATION OF rIFNα IN POLYCYTHEMIA VERA?

Although prospective studies are lacking, our experience suggests that patients treated for only 2-3 years will eventually relapse after 3–6 months with rising blood cell counts and a rising *JAK2V617F* VAF. However, well-designed "STOP-Interferon" studies are urgently needed to assess the optimal time point for discontinuation and restarting rIFNα. Until now, we recommend treating with rIFNα for at least 5 years [10]. Importantly, using the *JAK2V617F* VAF, e.g., <5% and sustained normal blood cell counts as the only other criteria for discontinuation of therapy may be problematic, since - as alluded to above - persistent marrow abnormalities of PV, including hypercellularity, megakaryocytic hyperplasia and atypia, and reticulin fibrosis may persist [137, 138]. Thus, molecular and marrow findings are not always synchronous. In the case where the marrow remains abnormal, we have recommended continuing treatment, since we presume that these patients are destined to relapse. When this occurs, the patient is again "at risk" and will eventually require phlebotomy, and presumably resumption of rIFN at an "induction" dose. Patient preferences, however, remain important. After discussion, some patients may elect to discontinue therapy regardless and seek a drug respite. Overall, current experience suggests there are no adverse consequences for discontinuing treatment for an unspecified time, as marked by the low *JAK2V617F* VAF, per se. Clearly, careful follow-up is required.

The French MPN-Group has addressed the dynamics of blood cell counts and *JAK2V617F* VAF in MPN patients after rIFNα-discontinuation, including 171 PV patients [11]. This study confirmed that the *JAK2V617F* VAF at the time of discontinuation was important. A value ≥10% at the time of rIFNα discontinuation was associated with lower long-term CHR, reinforcing previous remarks about the importance of the *JAK2V617F* VAF at the time of discontinuation. This suggests that the *JAK2V617F* VAF should be decreased to at least < 10% before pausing rIFNα [11] and preferentially < 5% as alluded to above, but confirmatory studies are needed. Adding to this, we would recommend a bone marrow biopsy in all patients before rIFNα discontinuation. Importantly, in this study, event-free and overall survival were not significantly different between those patients who discontinued and those who continued rIFNα [11]. Thus, according to this study, rIFNα discontinuation or pausing represents a safe strategy in PV patients who achieve CHR, and *JAK2V617 F* VAF less than 10% at the time of discontinuation, regardless of marrow status. Of note, rIFNα resistance did not develop in relapsed patients.

DISCUSSION OF RATIONALES FOR EARLY TREATMENT WITH rIFNα

We believe that rIFNα treatment from the time of diagnosis is preferable to maintenance PHLEB-O, a "watch and wait strategy", which allows clonal expansion and, in low-risk PV patients, the risk of a major thrombosis and increased risk of developing myelofibrosis. By reducing the *JAK2V617F* VAF, rIFNα also reduces an important risk factor associated with thrombosis [77–79, 120, 139–142] and likely also several *JAK2V617F*-driven inflammation-associated comorbidities in PV, such as cardiovascular diseases, including coronary artery calcification [119], aortic aneurysms [121, 122], and pulmonary hypertension as well [123–125]. The potential for rIFNα inducing CHR and molecular response is superior when the disease is "early," and when phenotypic myelofibrosis has not developed.

A particularly compelling argument for early initiation of rIFN-α therapy in PV concerns young women who anticipate future pregnancy. Interferon-α is the only disease-modifying cytoreductive therapy with a long-standing, well-documented safety profile during conception, pregnancy, and lactation. Initiating interferon therapy early - before pregnancy is attempted - allows women to achieve stable hematologic control, reduce *JAK2V617F* allele burden, and thereby ameliorate the inflammatory and prothrombotic state characteristic of PV. These effects are clinically relevant because poorly controlled hematocrit, leukocytosis, and thrombocytosis are associated with increased risks of miscarriage, placental insufficiency, intrauterine growth restriction, preterm delivery, and maternal thrombosis. Unlike hydroxyurea, other cytoreductive

agents or ruxolitinib, which are contraindicated in pregnancy, rIFN-α therapy can be safely continued throughout gestation, ensuring uninterrupted disease control. Thus, early initiation of rIFN-α therapy in young women with PV is not only biologically rational but also represents an important strategy for optimizing maternal and fetal outcomes and supporting safe family planning [68, 143–145].

Chronic inflammation and immune deregulation are considered major driving forces for the increased risk of myelofibrotic and leukemic transformation [12, 58, 77, 115–117, 146–148], likely consequent to inflammation-mediated (*JAK2V617F*-driven) increased genomic instability [79, 126, 127]. In this perspective, it seems reasonable to interrupt the vicious self-perpetuating inflammation cycle [12, 58, 77, 115–117, 147] as early as possible, and at this time, rIFNα is the best candidate to induce major molecular remission with *JAK2V617F* VAF reduction and a MRD state [12, 58] and - as the only agent - being able to rescue normal dormant stem cells and restoring polyclonal hematopoiesis [149]. The capability of rIFNα to restore polyclonal hematopoiesis is intuitively much better in the early PV-stage than later in the transitional stage towards development of post-PV myelofibrosis, when the *JAK2V617F* VAF is much higher and accordingly the chronic inflammatory state as well. By instituting rIFNα in the early PV-stage, the response may also be enhanced, taking into account that chronic inflammation may impair the response to rIFNα [12]. This association between the chronic inflammatory state and response to rIFNα is supported by the favorable impact of combination therapy with ruxolitinib or statins in patients treated with Pegasys, which is likely explained by ruxolitinib and statins having potent anti-inflammatory capabilities [59, 150]. The role of chronic inflammation in PV and its impact upon response to rIFNα has been further substantiated by the most recent findings, that the presence of an Andean-enriched NFKB1 haplotype in PV decreases inflammation, HIF-activity, deregulation of prothombotic genes and increases ropeg-induced PV remission [151]. Lastly, PV and related MPNs associate with an increased risk of second cancers [152], which entail an inferior prognosis as compared to the same cancer in the background population [153]. In this context, it is intriguing to speculate that early treatment with rIFN might decrease the risk of second cancers and improve overall survival by improving defective tumor immune surveillance [42, 154], since uncontrolled myeloproliferation with leukocytosis and thrombocytosis also increases cancer-invasiveness [155].

CONCLUSION AND PERSPECTIVES

European LeukemiaNet (ELN) recommendations of 2022 [18] emphasized lowering the risk of thrombosis in PV while minimizing attention to symptoms and the risk of evolution to post-PV myelofibrosis and leukemic transformation. We provided reasons for the early treatment of PV patients with rIFNα, especially those "younger" than 60 years [156]. We also emphasized that some patients may achieve complete hematologic and major molecular remission sustained for more than 24 months after discontinuing rIFNα [10, 156]. We believe that the randomized trials completed during the last 5 years support the early use of rIFNα in all PV patients, unless there is a contraindication for its use.

We look into a future with a paradigm shift in treatment goals, which not only constitute a reduction in symptom burden and risk of major thrombosis but also long-term remissions with MRD and discontinuation of therapy in a subset of patients [12, 58, 115–117, 147]. Taking into account the important role of chronic inflammation as the driving force for disease progression in MPN, this outlook may entail the future treatment of PV to be a combination therapy with rIFNα and treatment targeting the chronic inflammatory state, such as statins [12, 77, 115–117, 147, 150, 157, 158], which may also decrease the cancer-related mortality associated with second cancers in MPNs [159]. A combination therapy of rIFNα and a statin and/or potent JAK 1-2 inhibitor treatment may be a highly efficacious triplet to obtain a much faster reduction in the inflammation - and thrombosis-promoting *JAK2V617F* mutation and normalization of the bone marrow - even after 2 years [12, 58, 59, 77, 115–117].

The observation that interferon-alpha selectively targets the JAK2-mutated clone but largely spares or even permits expansion of at least the *DNMT3A*- and *ASXL1*-mutant clones, but also targets *TET2* clones in a subset of PV patients, highlights an important therapeutic boundary [46, 47]. These passenger mutations represent potential reservoirs for clonal expansion and evolution both in the CHIP-stage towards MPNs as well as in the biological continuum towards myelofibrosis and leukemic transformation. This underscores a key conceptual shift: interferon-alpha may be most effective early, before clonal diversification occurs, supporting intervention at the CHIP/early MPN stage—when the disease remains genetically simple and biologically reversible. Future efforts should focus on mutation-specific monitoring, clonal interception strategies, and rational interferon-based combination therapies aimed at preventing clonal escape and malignant progression, as well as preventing common inflammation-driven diseases in MPNs, such as cardiovascular diseases, which associate tightly with both the *JAK2V617F* mutation and the non-driver *DNMT3A*, *TET2* and *ASXL1* (DTA) mutations. Based upon most recent Danish studies, which demonstrate CHIP-*JAK2V617F* to increase all-cause mortality, even with VAF < 1% and vascular diseases at VAF > 1% and CHIP-*JAK2V617F* to associate with a markedly increased risk of developing overt MPNs within 7–10 years [160] we envisage in the horizon the launching of prospective studies, which explore whether targeting the *JAK2V617* mutation with rIFNα in the CHIP-stage may actually eradicate the clone, thereby prohibiting major thrombosis and other *JAK2V617F*-driven complications and comorbidities to occur, herein also the development of overt MPNs [12, 148, 160]. Since the *JAK2V617F* mutation is much more prevalent in the background population than previously recognized [136] and associates with cardiovascular diseases [77–79, 115, 119–122, 161] novel strategies with screening of patients at risk of harboring the *JAK2V617F* mutation [120, 122] may also unravel the large number of unrecognized MPN-patients, which undiagnosed are at an increased risk of suffering potentially life-threatening or life-invalidating thrombosis in the brain, heart, lungs and elsewhere [77, 136]. By much earlier diagnosis, we have the opportunity to offer these patients treatment with rIFNα, which may be much more effective, better tolerated and cost-effective when instituted at the earliest time point possible [12, 110, 162, 163]. The power house for this innovative strategy is the CHIP clinic—the catalyst of preventive medicine [164].

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