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Pegylated Interferon Alfa 2a Therapy in Patients with Myeloproliferative Disorders: A Review of Clinical Effectiveness and Cost-Effectiveness

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Authors: Yan Li, Caitlyn Ford

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Abbreviations

CHCR	Clinicohematologic complete responses
CML	Chronic myeloid leukemia
CR	Complete response
ET	Essential thrombocythemia
HU	Hydroxyurea
MF	Myelofibrosis
Peg-IFNα-2a	Pegylated interferon alfa 2a
PR	Partial response
PV	Polycythemia vera
QOL	Quality of life
SPIRIT	STI571 ProspectIve RandomIzed Trial
ULN	Upper limit of normal range

Context and Policy Issues

Myeloproliferative disorders, also known as myeloproliferative neoplasms, are stem cell disorders, which encompass a heterogenous group of blood cancers such as chronic myeloid leukemia (CML), essential thrombocythemia (ET), myelofibrosis (MF), polycythemia vera (PV), chronic neutrophilic leukemia, and chronic eosinophilic leukemia.[1,2] Myeloproliferative disorders are chronic conditions characterized by an abnormal overproduction of white cells, red cells, or platelets in the bone marrow.[2] Patients living with myeloproliferative disorders may experience stable or slowly progressing disease, and clinical manifestations may include fatigue, weakness, shortness of breath, splenomegaly, bone pain, bleeding disorders, and stroke.[2] In 2016, the prevalence of Canadians living with or who were in remission from leukemia (all types), PV, ET, and MF was estimated to be 22,510, 14,300, 8,700, and 1,800, respectively.[3]

With various treatment options for CML depending on factors such as patient age, phase of disease, blood cell counts, and availability of stem cell donors, targeted therapy with tyrosine kinase inhibitors (e.g., imatinib) may be used for most patients with CML as first-line therapy.[4] For patients with resistant CML or who are intolerant to targeted therapy, biological therapy with interferon alfa may be considered.[4] Treatment options for PV, ET, and MF may include chemotherapy (e.g., hydroxyurea [HU]), targeted therapy (e.g., ruxolitinib), or biological therapy (e.g., interferon alfa).[5]

Currently, various pegylated interferons are approved in Canada for the treatment of chronic hepatitis B and C and for the treatment of relapsing remitting multiple sclerosis. None has received a Health Canada Notice of Compliance for an oncology indication. In spite of this, pegylated interferon has been used off-label in Canadian jurisdictions for the treatment of some cancers and some hospitals may choose to provide funding for this treatment. The aim of this report is to summarize and critically appraise the relevant evidence regarding the clinical effectiveness and cost-effectiveness of pegylated interferon alfa 2a (Peg-IFNα-2a) therapy in patients with myeloproliferative disorders.

Research Questions

1. What is the clinical effectiveness of pegylated interferon alfa 2a therapy in patients with myeloproliferative disorders?
2. What is the cost-effectiveness of pegylated interferon alfa 2a therapy in patients with myeloproliferative disorders?

Key Findings

Two primary studies regarding the clinical effectiveness of pegylated interferon alfa 2a therapy in patients with myeloproliferative disorders were included in this report. No economic evaluations regarding the cost-effectiveness of pegylated interferon alfa 2a therapy in this population were identified. Overall, the body of evidence was limited in quantity and was moderate in quality.

The identified literature revealed varied conclusions regarding the clinical effectiveness of pegylated interferon alfa 2a therapy in patients with myeloproliferative disorders depending on the specific population, comparator treatment, and assessed outcome. Specifically, for patients with chronic-phase chronic myeloid leukemia included in the randomized controlled trial, there were no significant differences in complete hematologic or cytogenetic response amongst four treatment groups (i.e., imatinib plus pegylated interferon alfa 2a, imatinib plus cytarabine, imatinib 400 mg, imatinib 600 mg). Imatinib plus pegylated interferon alfa 2a resulted in significantly greater rates of major and superior molecular response, but also significantly higher rates of grade 3-4 neutropenia and thrombocytopenia, compared to imatinib 400 mg monotherapy. Information on survival outcomes was not reported in this randomized controlled trial.

In patients with polycythemia vera and myelofibrosis included in the non-randomized study, no significant differences in partial or complete response were detected amongst the three treatment groups (i.e., pegylated interferon alfa 2a, ruxolitinib, hydroxyurea ± anagrelide). However, in patients with essential thrombocythemia included in the non-randomized study, pegylated interferon alfa 2a resulted in significantly greater rates of complete response compared to ruxolitinib and hydroxyurea ± anagrelide. In the total cohort of patients with polycythemia vera, myelofibrosis, and essential thrombocythemia, pegylated interferon alfa 2a and hydroxyurea ± anagrelide resulted in significantly less improvement in quality of life compared to ruxolitinib. In the total cohort of patients, grade 1-2 adverse events were seen in 62%, 44%, and 20%, and grade 3-4 adverse events were seen in 7%, 0%, and 9% of participants receiving pegylated interferon alfa 2a, hydroxyurea ± anagrelide, and ruxolitinib, respectively (statistical analysis not reported).

Statistical tests in the randomized controlled trial and non-randomized study were mainly conducted for differences across all treatment groups, with additional post hoc tests to determine between-group differences for only select outcomes.[5,6] Furthermore, the small sample size (N = 125) in the non-randomized study should also be taken into consideration when interpreting these results.[5] Additionally, since the sample populations consisted of patients living in France and Hong Kong, these findings may not be generalizable to the Canadian setting.[5,6]

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Embase and Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were pegylated interferon alfa 2a and myeloproliferative disorders. No filters were applied to

limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and July 2, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients diagnosed with myeloproliferative disorders (e.g., polycythemia vera, myelofibrosis [also known as primary myelofibrosis or chronic idiopathic myelofibrosis], essential thrombocythemia [also known as essential thrombocytosis] chronic neutrophilic leukemia, chronic myelogenous leukemia, and chronic eosinophilic leukemia)
Intervention	Q1-2: Pegylated-interferon alfa-2a therapy also known as Peginterferon alfa-2a or peg-IFN alpha-2a (brand name: Pegasys) administered alone or in combination with another agent .
Comparator	Q1-2: Imatinib mesylate, dasatinib, ruxolitinib, nilotinib, glucocorticoids, cytarabine, hydroxyurea, interferon therapy (e.g., non-pegylated interferon therapy), anagrelide, or busulfan (oral)
Outcomes	Q1: Clinical-effectiveness (e.g., progression-free survival, overall survival, quality of life, response to treatment [e.g., complete response, partial response], duration of response); Adverse events (e.g., treatment discontinuation, infection) Q2: Cost-effectiveness
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the Downs and Black checklist[7] for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 465 citations were identified in the literature search. Following screening of titles and abstracts, 455 citations were excluded and ten potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, nine publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These comprised one randomized controlled trial[6] and one non-randomized study.[5] Appendix 1 presents the PRISMA[8] flowchart of the study selection. A study comparing two different doses of Peg-IFNα-2a (i.e.,

90 mcg versus 45 mcg weekly) was excluded as it was beyond the scope of this report.[9] Additional references of potential interest are provided in Appendix 5, including single-arm studies published after 2017.

Summary of Study Characteristics

One relevant randomized controlled trial[6] and one non-randomized study[5] were identified for inclusion in this review. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Two primary studies were included in this report.[5,6] Preudhomme et al. (2010)[6] conducted a randomized controlled trial, while Gill et al. (2020)[5] conducted a prospective non-randomized cohort study.

Country of Origin

The first authors of the primary clinical studies by Preudhomme et al.[6] and Gill et al.[5] were from France and the People's Republic of China, respectively.

Patient Population

In the randomized controlled trial (the STI571 ProspectIve RandomIzed Trial [SPIRIT] study), 636 participants aged 18 years or older with untreated chronic-phase, Philadelphia chromosome–positive or negative, BCR-ABL-positive CML were recruited from 69 centres.[6] The median age ranged from 50 to 55 years old across treatment groups.[6] Patients were excluded from the trial if they had received treatment for CML in the past, with the exception of HU or anagrelide.[6]

In the non-randomized cohort study, real-world data for 125 adult patients with myeloproliferative disorders were included.[5] The number of patients with PV, ET, and MF were 23, 56, and 46, respectively.[5] The overall median age was 48.4 years old.[5] Unlike in the randomized controlled trial, patients were not excluded if they received HU or anagrelide before this study.[5]

Interventions and Comparators

In the randomized controlled trial, all study participants started with a two week treatment of imatinib 400 mg daily.[6] Thereafter, 159 patients received imatinib 400 mg daily plus Peg-IFNα-2a 90 mcg weekly, 159 patients received imatinib 400 mg daily, 160 patients received imatinib 600 mg daily, and 158 patients received imatinib 400 mg daily plus cytarabine (20 mg per square meter of body surface area daily on days 15 through 28 of each 28-day cycle).[6] At the time of data analysis, the median treatment duration was 44, 44, 46, and 43 months for imatinib plus Peg-IFNα-2a, imatinib 400 mg daily, imatinib 600 mg daily, and imatinib plus cytarabine, respectively.[6]

In the non-randomized study, 55, 35, and 35 patients received Peg-IFNα-2a, ruxolitinib, and HU ± anagrelide, respectively.[5] Peg-IFNα-2a was initially administered at 135 mcg every 2 weeks and escalated to weekly, while ruxolitinib was initially administered at 10 mg twice daily and escalated by 10 mg/day every 4 weeks to a maximum of 25 mg twice daily.[5] The dosing for HU ± anagrelide was not reported. The median treatment duration was 16, 12, and 20 months for Peg-IFNα-2a, ruxolitinib, and HU ± anagrelide, respectively.[5] All 125 participants received aspirin 80 mg/day or clopidogrel 75 mg/day for anti-platelet therapy.[5]

Outcomes

Authors of both included studies investigated clinical effectiveness and safety outcomes.[5,6] In the randomized controlled trial, primary endpoints of the SPIRIT study were event-free survival, survival without disease progression, and overall survival. However, these survival outcomes were planned for the second part of this trial and were not reported in this article.[6] The following were classified as other endpoints: rate of complete hematologic response at 3 months, rate of complete cytogenetic response at 1 year, and rates and duration of molecular responses at 12, 18, and 24 months.[6] Complete definitions of outcomes measures are contained within Appendix 2. Adverse events were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) with scores ranging from 1 (i.e., mild adverse event) to 5 (death related to adverse event).[6]

In the non-randomized study, relevant effectiveness outcomes included clinicohematologic response, spleen size reduction, and quality of life (QOL).[5] Clinicohematologic complete response (CHCR) or complete response (CR) and partial response (PR) for PV, ET, and MF was defined as per the European Leukemia Net and International Working Group-Myeloproliferative Neoplasms Research and Treatment criteria.[10,11] Complete definitions of outcomes measures are contained within Appendix 2. Confirmed by two clinicians, spleen size was measured from the costal margin to the spleen tip.[5] QOL was assessed using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score, which included questions on symptoms such as fatigue night sweats, and weight loss.[12] The scoring ranged from 0 (i.e., absent) to 10 (i.e., worst imaginable) for each item, with a total possible score of 100.[12] Adverse events were graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).[5]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Randomized Controlled Trial

The randomized controlled trial had numerous methodological strengths, including: 1) clearly stated objectives, inclusion/exclusion criteria, interventions, outcome measures, and main findings; 2) reported estimates of random variability; 3) planned data analysis at the outset of the study; and 4) disclosure of funding sources and completed disclosure forms by authors.[6] Furthermore, assessed clinical and safety outcomes seem consistent with routine clinical practice.[13,14] However, this study had some methodological limitations such as lack of reporting on the sample size calculation.[6] Although common reasons (e.g., toxic effects, treatment failure) for participant drop out were described, the characteristics of patients lost to follow-up or who did not complete the treatment were not reported.[6] Furthermore, treatment discontinuation rates were not balanced across the four treatment groups, with 133,148, 55, and 58 patients stopping Peg-IFNα-2a, cytarabine, imatinib 400 mg, and imatinib 600 mg, respectively.[6] Overall, 159 of 160 and 158 of 159 participants randomized to receive imatinib plus Peg-IFNα-2a and imatinib plus cytarabine, respectively, were included in the intention-to-treat analysis, while all participants randomized to receive imatinib 400 mg or imatinib 600 mg were included.[6] Although statistical tests were performed for differences amongst all four treatment groups, statistical comparison between specific treatment groups was only reported for select outcomes.[6] Overall survival and event-free survival were planned outcomes for the second part of this study and were not

reported in this article.[6]. Thus, it was unclear if the higher rate of molecular response achieved in participants receiving imatinib plus Peg-IFNα-2a compared to imatinib monotherapy may result in an improvement in long-term overall survival.[6] For the second part of the trial, enrolled participants were only randomized to receive imatinib 400 mg or imatinib plus Peg-IFNα-2a due to the toxicity profile of cytarabine and superiority of imatinib plus Peg-IFNα-2a.[6] Lastly, the generalizability of findings to the Canadian setting was unclear since the study was conducted in France.[6]

Non-Randomized Study

The non-randomized study had methodological strengths such as: 1) clearly stated objectives, inclusion criteria, interventions, outcome measures, and main findings; 2) reported estimates of random variability; 3) planned data analysis at the outset of the study; 4) calculated the sample size a priori; and 5) disclosed that there were no conflicts of interest.[5] However, this study had methodological limitations such as the lack randomization, lack of patient and clinician blinding, and not reporting the exclusion criteria and funding support.[5] Baseline patient characteristics such as median age (i.e., 50.5 years [PV], 44.1 years [ET], 58.9 years [MF]) varied amongst patients with PV, ET, and MF.[5] Furthermore, it was unclear if the sampled population was representative of the population of interest as the details of patient data retrieval were not reported.[5] Since statistical tests were performed for differences across all three treatment groups, and no post hoc tests to identify individual between-group differences were conducted, the relative effectiveness and safety between treatment groups was unclear.[5] Due to adverse events, five of 55 and three of 35 patients stopped Peg-IFNα-2a and ruxolitinib, respectively (therapy discontinuation not reported for HU ± anagrelide.[5]) However, the characteristics of patients lost to follow-up or who did not complete the treatment were not reported.[5] Lastly, the generalizability of findings to the Canadian setting was unclear since the study was conducted in Hong Kong.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Clinical Effectiveness of Peg-IFNα-2a in Patients with Myeloproliferative Disorders

Chronic Myeloid Leukemia

Evidence regarding the clinical effectiveness of Peg-IFNα-2a in patients with chronic-phase CML was available from one randomized controlled trial.[6] At 3 months, there was no significant difference in complete hematologic response (ranging from 89% to 95%) across the four treatment arms (i.e., imatinib 400 mg plus Peg-IFNα-2a, imatinib 400 mg plus cytarabine, imatinib 400 mg alone, imatinib 600 mg alone).[6] Furthermore, at 12 months, there was no significant difference in complete cytogenetic response (ranging from 58% to 70%) across the four groups.[6] However, at 12 and 24 months, the rates of major and superior molecular response were significantly greater in the imatinib 400 mg plus Peg-IFNα-2a group (major/superior: 57%/30% [12 months]; 64%/38% [24 months]) compared to the imatinib 400 mg monotherapy group (major/superior: 38%/14% [12 months]; 43%/21% [24 months]), imatinib 600 mg monotherapy group (major/superior: 49%/17% [12 months]; 53%/26% [24 months]), and imatinib 400 mg plus cytarabine (major/superior: 46%/15% [12 months]; 54%/26% [24 months]) (adjusted $P \leq 0.007$).[6] At 24 months, imatinib plus Peg-IFNα-2a resulted in a significantly greater rate (16%) of undetectable residual disease compared to imatinib 400 mg plus cytarabine (8%), imatinib 400 mg alone (9%), and imatinib 600 mg alone (8%) (adjusted $P = 0.01$).[6] Survival outcomes were planned for the second part of this trial and were not reported in this article.[6]

Compared to the other three study groups, participants in the imatinib plus Peg-IFNα-2a group experienced numerically greater rates of adverse events (rates of grade 3-4 rash, depression, asthenia, edema, and hypophosphatemia) (statistical analysis not reported).[6] Additionally, imatinib plus Peg-IFNα-2a resulted in significantly higher rates of grade 3-4 neutropenia (49%) compared to imatinib 400 mg monotherapy (7%) ($P < 0.001$).[6] Furthermore, 44% and 12% of patients receiving imatinib plus cytarabine and imatinib 600 mg monotherapy, respectively, experienced grade 3-4 neutropenia (statistical analysis not reported).[6] Imatinib plus Peg-IFNα-2a and imatinib plus cytarabine resulted in significantly higher rates of grade 3-4 thrombocytopenia (11% and 28%, respectively) compared to imatinib 400 mg monotherapy (2%) ($P = 0.002$ and $P < 0.001$, respectively).[6] Additionally, 6% of patients receiving imatinib 600 mg monotherapy experienced grade 3-4 thrombocytopenia (statistical analysis not reported).[6]

Polycythemia Vera, Essential Thrombocythemia, and Myelofibrosis

Evidence regarding the clinical effectiveness of Peg-IFNα-2a in patients with PV, ET, or MF was available from one non-randomized study.[5] In patients with PV, no significant differences in CHCR and PR were detected amongst the three treatment arms (i.e., Peg-IFNα-2a, ruxolitinib, HU ± anagrelide) at a median treatment duration of 6 months.[5] In those with ET, Peg-IFNα-2a resulted in significantly greater CHCR compared to HU ± anagrelide or ruxolitinib (89% versus 77% versus 43%) ($P = 0.045$).[5] In participants with MF, although rates of partial and complete response were comparable amongst three treatment groups, ruxolitinib resulted in significantly greater rates of clinical improvement compared to Peg-IFNα-2a and HU ± anagrelide (70% versus 32% versus 0%) ($P = 0.018$).[5]

Outcomes pertaining to spleen size reduction, QOL, and adverse events were assessed for the total cohort of myeloproliferative disorder patients (combining those with PV, ET, and MF).[5] At baseline, there was a significant difference in mean spleen size amongst three treatment groups (ruxolitinib: 5.81 cm, Peg-IFNα-2a: 1.71 cm, HU ± anagrelide: 0.32) ($P = 0.000$).[5] From 6 to 24 months, there was no significant difference in mean spleen size amongst the three treatment groups.[5] Compared to Peg-IFNα-2a and HU ± anagrelide, ruxolitinib also resulted in significantly greater improvement in QOL at 3 months and every 3 months thereafter through to 24 months ($P < 0.001$).[5] Overall, 62% and 7% of patients treated with Peg-IFNα-2a and 20% and 9% of patients treated with ruxolitinib experienced grade 1-2 and 3-4 adverse events, respectively (statistical analysis not reported).[5] HU ± anagrelide accounted for 44% and 0% of grade 1-2 and 3-4 adverse events (statistical analysis not reported).[5] Typical adverse events experienced by patients who were treated with Peg-IFNα-2a included neutropenia (24%), fatigue (24%), liver dysfunction (24%), rash (13%) and anemia (11%).[5]

Cost-Effectiveness

No relevant economic evaluations regarding the cost-effectiveness of Peg-IFNα-2a therapy in patients with myeloproliferative disorders were identified; therefore, no summary can be provided.

Limitations

Limitations were identified in the critical appraisal (details in Appendix 3); however, additional limitations exist. Imatinib has been shown to cause high prevalence of platelet dysfunction in patients with CML.[15] However, the authors of the randomized controlled trial did not report if participants were taking anti-platelet therapy such as aspirin or clopidogrel, which would have affected patient outcomes.[6] Albeit statistical tests were performed for

differences across all treatment groups within each primary study, post hoc tests to assess specific between-group differences were not conducted for all outcomes.[5,6] Thus, the clinical effectiveness and safety amongst treatment groups was unclear.[5,6] No economic evaluations regarding the cost-effectiveness of Peg-IFNα-2a therapy in patients with myeloproliferative disorders were identified. Furthermore, no relevant literature was identified regarding the clinical effectiveness and cost-effectiveness of Peg-IFNα-2a therapy in patients with other types of myeloproliferative disorders such as chronic neutrophilic leukemia and chronic eosinophilic leukemia.

Conclusions and Implications for Decision or Policy Making

This review was comprised of one randomized control trial[6] and one non-randomized study[5] regarding the clinical effectiveness of Peg-IFNα-2a therapy in patients with myeloproliferative disorders. No economic evaluations regarding the cost-effectiveness of Peg-IFNα-2a therapy in patients with myeloproliferative disorders were identified.

For patients diagnosed with chronic-phase CML, no significant differences in complete hematologic or cytogenetic response were detected amongst participants randomized to receive imatinib 400 mg plus Peg-IFNα-2a, imatinib 400 mg plus cytarabine, imatinib 400 mg alone, or imatinib 600 mg alone.[6] Nonetheless, compared to imatinib 400 mg monotherapy, imatinib plus Peg-IFNα-2a resulted in significantly higher rates of major and superior molecular response.[6] In terms of adverse events, imatinib plus Peg-IFNα-2a resulted in significantly greater rates of grade 3-4 neutropenia and thrombocytopenia compared to imatinib 400 mg monotherapy.[6]

For patients with PV and MF, no significant differences in partial or complete response were detected amongst the three treatment groups (i.e., Peg-IFNα-2a, ruxolitinib, HU ± anagrelide).[5] While Peg-IFNα-2a resulted in significantly higher rates of complete response compared to HU ± anagrelide or ruxolitinib in participants with ET, ruxolitinib resulted in significantly higher rates of clinical improvement compared to Peg-IFNα-2a and HU ± anagrelide in participants with MF.[5] In the total cohort of study participants, ruxolitinib resulted in significantly greater improvement in QOL compared to Peg-IFNα-2a and HU ± anagrelide.[5] Grade 1-2 or 3-4 adverse events were seen in 62% or 7%, 44% or 0%, and 20% or 9% of participants receiving pegylated interferon alfa 2a, hydroxyurea ± anagrelide, and ruxolitinib, respectively (statistical analysis not reported).[5]

Overall, the body of evidence was limited and the relevant studies in this report were considered to be of moderate quality. In the randomized controlled study evaluating patients with CML, survival outcomes were not reported, and it was unclear if improvements in molecular response would result in improved overall survival.[6] In the non-randomized study evaluating patients with PV, ET, and MF, the lack of randomization may have biased the findings if patients were systematically different across treatment groups, and the small sample size within each disorder (i.e., N = 23 [PV], 56 [ET], 46 [MF]) may make the study underpowered.[5] Additionally, since the studies were conducted in France and Hong Kong, the findings may not be generalizable to the Canadian setting.[5,6]

Further research investigating the clinical effectiveness of Peg-IFNα-2a therapy, especially with multinational clinical trials with Canadian representation, long-term follow-up, and survival outcomes, would provide additional knowledge base for clinicians providing care to adults living with myeloproliferative disorders. Additionally, economic evaluations investigating the cost-effectiveness of Peg-IFNα-2a therapy versus other treatment options

in patients with myeloproliferative disorders would help stakeholders in decision-making on the use of Peg-IFNα-2a.

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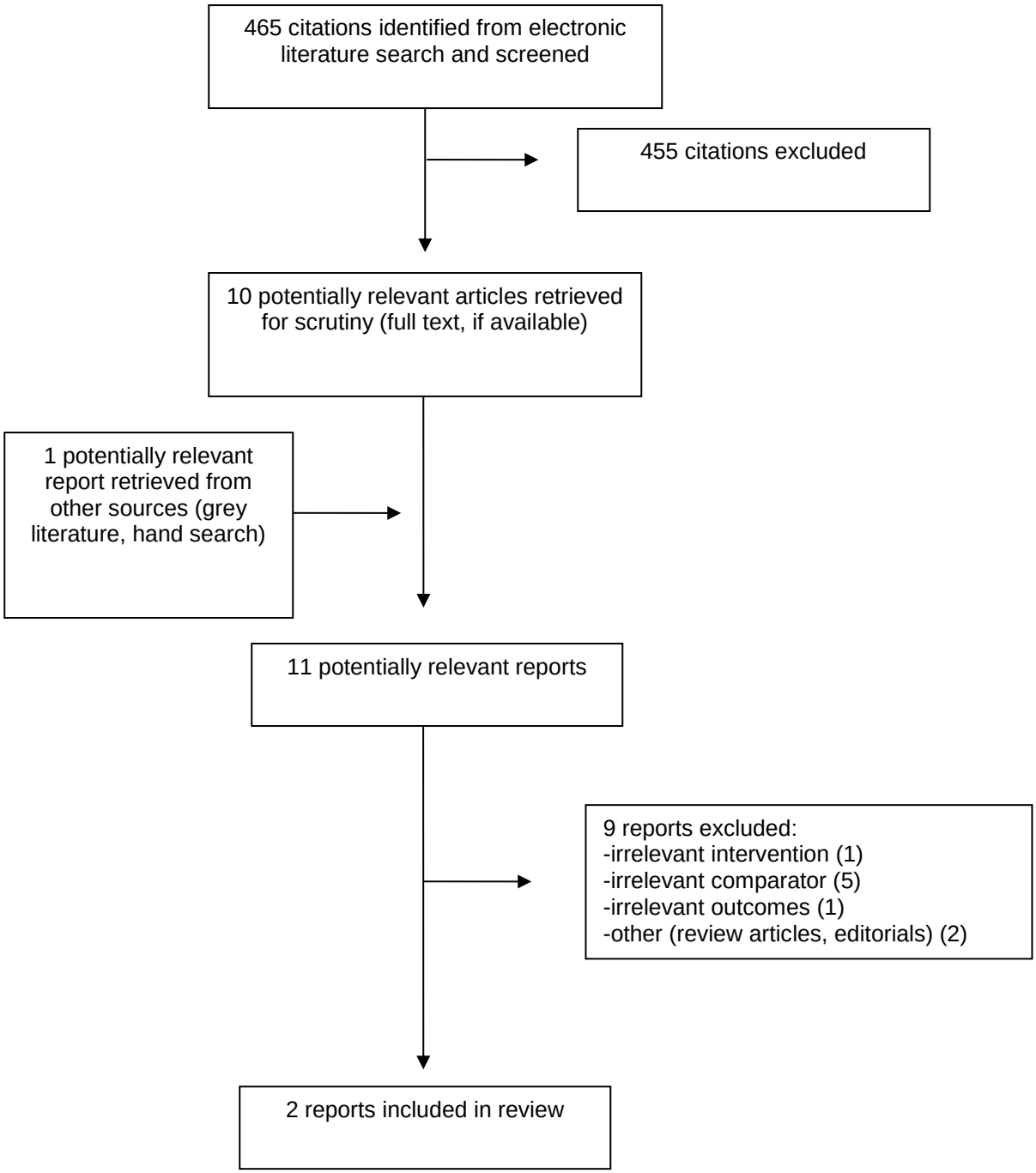
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Randomized Controlled Trial				
Preudhomme et al. (2010)[6] France Funding Source: Primarily the French Ministry of Health	**Study design:** Randomized controlled trial **Setting:** 69 centres in France **Objective:** To assess and compare the efficacy and safety of imatinib, imatinib plus Peg-IFNα-2a, and imatinib plus cytarabine	Adult patients with untreated chronic-phase CML **Number of patients:** N = 636 **Median age (years):** - Imatinib 400 mg plus Peg-IFNα-2a (51) - Imatinib 400 mg (50) - Imatinib 600 mg (51) - Imatinib 400 mg plus cytarabine (55) **% female:** - Imatinib 400 mg plus Peg-IFNα-2a (35%) - Imatinib 400 mg (31%) - Imatinib 600 mg (44%) - Imatinib 400 mg plus cytarabine (42%)	**Intervention:** - Imatinib 400 mg daily plus Peg-IFNα-2a 90 mcg weekly (N = 159) **Comparator:** - Imatinib 400 mg daily (N = 159) - Imatinib 600 mg daily (N = 160) - Imatinib 400 mg daily plus cytarabine (20 mg per square meter of body surface area daily on days 15 through 28 of each 28-day cycle) (N = 158)	**Relevant Outcomes:**[a] - Primary endpoints (to be reported in a subsequent publication): event-free survival, survival without disease progression, and overall survival - Other endpoints: hematologic, cytogenetic, and molecular responses (complete definitions contained within footnotes below) - Adverse events **Follow-up:** - Median duration of follow-up of 47 months (range: 3 to 73)
Non-Randomized Study				
Gill et al. (2020)[5] People's Republic of China Funding Source: Not reported	**Study design:** Prospective non-randomized cohort study **Setting:** Real-world practice settings in Hong Kong (specific hospitals/clinics not reported) **Objective:** To assess and compare the efficacy and safety of Peg-IFNα-2a, ruxolitinib, and hydroxyurea ± anagrelide	Adult patients with PV, ET, or MF **Number of patients:** PV (N = 23), ET (N = 56), MF (N = 46) **Median age (years):** 48.4 (range: 22.7 to 88.6) **% female:** 44%	**Intervention:** - Peg-IFNα-2a initially administered at 135 mcg every 2 weeks and escalated to 135 mcg weekly (N = 55) **Comparator:** - Ruxolitinib initially administered orally at 10 mg twice daily and escalated by 10 mg/day every 4 weeks (maximum = 25 mg twice daily) (N = 35) - Hydroxyurea ± anagrelide (dose not reported) (N = 35) All participants received anti-platelet	**Relevant Outcomes:**[b] - Clinicohematologic response according to ELN and IWG-MRT criteria (complete definitions contained within footnotes below) - Spleen size reduction - QOL (measured by MPN-SAF TSS) - Adverse events **Follow-up:** - Median duration of follow-up of 36.1 months (range: 19 to 42)

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
			therapy (aspirin 80 mg/day or clopidogrel 75mg/day)	

CML = chronic myeloid leukemia; ELN = European Leukemia Net; ET = essential thrombocythemia; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; MPN = myeloproliferative neoplasms; MF = myelofibrosis; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; Peg-IFNα-2a = Pegylated-interferon alfa-2a; PV = polycythemia vera; QOL = quality of life.

[a] Complete definitions of outcome measures from randomized controlled trial:

In the SPIRIT study, a complete hematologic response in patients with chronic-phase CML was achieved if white cell count < 10,000/mm^3, platelet count < 450,000×10^9/L, combined myelocytes and metamyelocytes < 5%, lack of blasts and promyelocytes in peripheral blood, and lack of extramedullary involvement. A complete cytogenetic response was defined as 0% Philadelphia chromosome-positive cells in metaphase from a bone marrow specimen. A major or superior molecular response (used as the molecular end point at 1 year) was achieved if there was a reduction in the ratio of BCR-ABL to ABL transcripts of < 0.1% and ≤ 0.01%, respectively. A complete molecular response (i.e., undetectable molecular residual disease) was achieved if there was a lack of BCR-ABL transcripts in high-quality RNA assays.

[b] Complete definitions of outcome measures from non-randomized study:

For PV, CHCR was achieved if hematocrit was < 0.45, platelet count ≤ 400x10^9/L, white cell count ≤ 10x10^9/L, and there was an absence of disease-related symptoms and hepatosplenomegaly, while PR was achieved if hematocrit was < 0.45 or ≥ three other CHCR criteria were met. For ET, CHCR was achieved if platelet count was ≤ 400x10^9/L, white cell count ≤ 10x10^9/L, and there was an absence of disease-related symptoms and hepatosplenomegaly, while PR was achieved if platelet count was ≤ 600x10^9/L or ≥ 50% reduction from baseline but not meeting CHCR criteria. For MF, CR was achieved upon bone marrow morphological remission and fulfilling CHCR criteria (hemoglobin ≥ 10 g/dL and < upper limit of normal range [ULN], neutrophil count ≥ 1x10^9/L and < ULN, platelet count ≥ 100x10^9/L and < ULN, < 2% immature myeloid cells, absence of disease-related symptoms and hepatosplenomegaly, and no evidence of extramedullary hematopoiesis), while PR was achieved upon bone marrow morphological remission or fulfilling CHCR criteria. Furthermore, clinical improvement for MF was defined as anemia, spleen, or symptoms response in the absence of progressive disease or worsening of anemia, thrombocytopenia, or neutropenia.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Study Using the Downs and Black checklist[7]

Strengths	Limitations
Randomized Controlled Trial	
Preudhomme et al. (2010)[6]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section, and were valid and reliable • The inclusion and exclusion criteria were clearly described • The time period over which patients were recruited was specified • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and are appropriate • Exact P values were reported for outcomes • The participants were recruited from 69 French centres, which would be representative of the population of interest • Data analyses were planned at the outset of the study • Potential adverse events relating to the interventions were discussed • The authors completed disclosure forms available with the full text • Funding support for this study was disclosed	• A sample size calculation was not reported • Although statistical tests were performed for differences amongst all four treatment groups, statistical comparison between specific treatment groups was only reported for select outcomes • Characteristics of patients lost to follow-up or who did not complete the program were not reported, although common reasons of drop out were described • Study was conducted in France; findings may not be generalizable to the Canadian setting
Non-Randomized Study	
Gill et al. (2020)5	
• The study's objective, intervention, and main findings were clearly stated • The use of real-world data reflects patient outcomes from routine clinical practice • The main outcomes to be measured were clearly described in the Methods section, and were valid and reliable • The inclusion criteria were clearly described • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and appropriate • Exact P values were reported for outcomes • A sample size calculation was conducted a priori • Data analyses were planned at the outset of the study • Potential adverse events relating to the interventions were discussed • The authors disclosed no conflicts of interest	• This was not a randomized controlled trial, but a prospective cohort study using real-world data • There was a lack of patient and clinician blinding • The exclusion criteria were not reported • Details of patient data retrieval were not reported; hence, it was unclear if the data were representative of the population of interest • The time period over which patients were recruited was not specified • Characteristics of patients lost to follow-up were not described • Since statistical tests were performed for differences across all three treatment groups, and no post hoc tests to identify individual between-group differences were conducted • Study was conducted in Hong Kong; findings may not be generalizable to the Canadian setting • Funding support for this study was not reported

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

Main study findings	Authors' conclusion
Randomized Controlled Trial	
Preudhomme et al. (2010)[6]	
Randomized controlled trial of adult patients with chronic-phase CML receiving imatinib, imatinib plus Peg-IFNα-2a, or imatinib plus cytarabine. **Complete Hematologic Response at 3 Months:** • **Imatinib 400 mg (N = 159): 89% (95% CI, 83 to 93%)** • **Imatinib 600 mg (N = 160): 89% (95% CI, 83 to 93%)** • **Imatinib 400 mg plus cytarabine (N = 158): 95% (95% CI, 90 to 98%)** • **Imatinib 400 mg plus Peg-IFNα-2a (N = 159): 91% (95% CI, 87 to 96%)** • P (unadjusted) > 0.05; P (adjusted) not reported **Complete Cytogenetic Response at 12 Months:** • Imatinib 400 mg: 58% (95% CI, 50 to 66%) • Imatinib 600 mg: 65% (95% CI, 57 to 72%) • **Imatinib 400 mg plus cytarabine: 70% (95% CI, 62 to 77%)** • **Imatinib 400 mg plus Peg-IFNα-2a: 66% (95% CI, 58 to 73%)** • P (unadjusted) > 0.05; P (adjusted) not reported **Molecular Response:** **At 12 Months** **Major Response** • Imatinib 400 mg: 38% (95% CI, 30 to 46%) • Imatinib 600 mg: 49% (95% CI, 41 to 57%) • **Imatinib 400 mg plus cytarabine: 46% (95% CI, 38 to 54%)** • **Imatinib 400 mg plus Peg-IFNα-2a: 57% (95% CI, 49 to 65%)** • P (unadjusted) < 0.001; P (adjusted) = 0.005 **Superior Response** • Imatinib 400 mg: 14% (95% CI, 9 to 21%) • Imatinib 600 mg: 17% (95% CI, 11 to 24%) • **Imatinib 400 mg plus cytarabine: 15% (95% CI, 10 to 22%)** • **Imatinib 400 mg plus Peg-IFNα-2a: 30% (95% CI, 23 to 37%)** • P (unadjusted) = 0.001; P (adjusted) = 0.001 **At 24 Months** **Major Response** • Imatinib 400 mg: 43% (95% CI, 35 to 50%) • Imatinib 600 mg: 53% (95% CI, 45 to 60%) • **Imatinib 400 mg plus cytarabine: 54% (95% CI, 46 to 62%)** • **Imatinib 400 mg plus Peg-IFNα-2a: 64% (95% CI, 56 to 71%)** • P (unadjusted) = 0.006; P (adjusted) = 0.003 **Superior Response** • Imatinib 400 mg: 21% (95% CI, 15 to 28%) • Imatinib 600 mg: 26% (95% CI, 20 to 34%) • **Imatinib 400 mg plus cytarabine: 26% (95% CI, 19 to 34%)**	"At 12 months, the rates of cytogenetic response were similar among the four groups. The rate of a superior molecular response was significantly higher among patients receiving imatinib and peginterferon alfa-2a (30%) than among patients receiving 400 mg of imatinib alone (14%) (P = 0.001). The rate was significantly higher among patients treated for more than 12 months than among those treated for 12 months or less. Gastrointestinal events were more frequent among patients receiving cytarabine, whereas rash and depression were more frequent among patients receiving peginterferon alfa-2a (p. 2511)."[6]

Main study findings	Authors' conclusion
• **Imatinib 400 mg plus Peg-IFNα-2a: 38% (95% CI, 30 to 46%)** • P (unadjusted) = 0.001; P (adjusted) = 0.007 **Undetectable Residual Disease** • Imatinib 400 mg: 9% (95% CI, 5 to 14%) • Imatinib 600 mg: 8% (95% CI, 4 to 13%) • **Imatinib 400 mg plus cytarabine: 8% (95% CI, 4 to 13%)** • **Imatinib 400 mg plus Peg-IFNα-2a: 16% (95% CI, 12 to 24%)** • P (unadjusted) = 0.01; P (adjusted) = 0.01 **Adverse events** • Imatinib plus Peg-IFNα-2a resulted in higher rates of grade 3-4 rash, depression, asthenia, edema, and hypophosphatemia compared to the other three groups (statistical analysis not reported) • Imatinib plus Peg-IFNα-2a resulted in significantly higher rates of grade 3-4 neutropenia (49%) compared to imatinib 400 mg monotherapy (7%) (P < 0.001) • 44% and 12% of patients receiving imatinib plus cytarabine and imatinib 600 mg monotherapy, respectively, experienced grade 3-4 neutropenia (statistical analysis not reported) • Imatinib plus Peg-IFNα-2a and imatinib plus cytarabine resulted in significantly higher rates of grade 3-4 thrombocytopenia (11% and 28%, respectively) compared to imatinib 400 mg monotherapy (2%) (P = 0.002 and P < 0.001, respectively) • 6% of patients receiving imatinib 600 mg monotherapy experienced grade 3-4 thrombocytopenia (statistical analysis not reported)	
Non-Randomized Study	
Gill et al. (2020)[5]	
Non-randomized prospective cohort study of adult patients with PV, ET, or MF receiving Peg-IFNα-2a, ruxolitinib, or HU ± anagrelide. **Clinicohematologic response** **PV (N = 23):** • **HU ± anagrelide (N = 9):** CHCR (N = 6), PR (N = 2), NR (N = 0), PD (N = 1) • **Peg-IFNα-2a (N = 9):** CHCR (N = 5), PR (N = 3), NR (N = 1), PD (N = 0) • **Ruxolitinib (N = 5):** CHCR (N = 1), PR (N = 2), NR (N = 1), PD (N = 1) **ET (N = 56):** • **HU ± anagrelide (N = 22):** CHCR (N = 17), PR (N = 5), NR (N = 0), PD (N = 0) • **Peg-IFNα-2a (N = 27):** CHCR (N = 24), PR (N = 2), NR (N = 1), PD (N = 0) • **Ruxolitinib (N = 7):** CHCR (N = 3), PR (N = 4), NR (N = 0), PD (N = 0) **MF (N = 46):** • **HU ± anagrelide (N = 4):** CR (N = 0), PR (N = 0), clinical improvement (N = 0), SD (N = 4), PD (N = 0) • **Peg-IFNα-2a (N = 19):** CR (N = 0), PR (N = 2), clinical improvement (N = 6), SD (N = 10), PD (N = 1) • **Ruxolitinib (N = 23):** CR (N = 0), PR (N = 0), clinical improvement (N = 16), SD (N = 6), PD (N = 1) • Statistical analysis not reported for all comparisons. Where available, statistical comparisons were described in the Summary of Findings of this report. **Spleen size reduction (total cohort)** • At baseline, there was a significant difference in mean spleen size amongst three treatment groups (ruxolitinib: 5.81 cm, Peg-IFNα-2a: 1.71 cm, HU ± anagrelide: 0.32) (P = 0.000) • From 6 to 24 months, there was no significant difference in mean spleen size reduction amongst the three treatment groups (i.e., ruxolitinib, Peg-IFNα-2a, HU ± anagrelide) **QOL (total cohort)**	"In PV, responses were comparable for different modalities. CREBBP mutations were associated with inferior responses. In ET, PEG-IFNα-2A resulted in superior clinicohematologic complete responses (CHCR) (P = 0.045). In MF, superior overall response rates (ORR) were associated with ruxolitinib (P = 0.018) and JAK2V617F mutation (P = 0.04). For the whole cohort, ruxolitinib led to rapid and sustained reduction in spleen

<table>
<tr><th>Main study findings</th><th>Authors' conclusion</th></tr>
<tr><td>

Participants receiving ruxolitinib exhibited significant improvements in QOL (measured by MPN-SAF TSS) (P < 0.001) compared to those receiving HU ± anagrelide or Peg-IFNα-2a at 3 months and at 3-month intervals thereafter through to 24 months

Adverse events (total cohort)
<table>
<tr><th>Adverse events</th><th>HU ± anagrelide, # of patients (%) (N = 35)</th><th>Peg-IFNα-2a, # of patients (%) (N = 55)</th><th>Ruxolitinib, # of patients (%) (N = 35)</th></tr>
<tr><td>Grade 1-2 adverse events</td><td>15 (44)</td><td>34 (62)</td><td>7 (20)</td></tr>
<tr><td>Grade 3-4 adverse events</td><td>0 (0)</td><td>4 (7)</td><td>3 (9)</td></tr>
</table>

Adverse events in participants receiving Peg-IFNα-2a included neutropenia (24%), anemia (11%), fatigue (24%), liver dysfunction (24%), rash (13%), myalgia (5%), alopecia (4%), diarrhea (4%), mucositis (4%), dyspepsia (2%), thrombocytopenia (2%), fluid retention (2%), anorexia (2%), pericarditis (2%), and myasthenia gravis (2%)
Five patients stopped Peg-IFNα-2a due to adverse events: cytopenia (three) and autoimmune phenomena (two), while three patients stopped ruxolitinib all due to grade 3-4 infections (therapy discontinuation not reported for HU ± anagrelide)
Statistical analysis not reported for comparison of adverse events between treatment groups

</td><td>size within the first 6 months, and significant improvement of QOL as reflected by reduction in MPN-SAF TSS (P < 0.001). Adverse events of grades 1–2 were observed in 44%, 62% and 20% of patients receiving conventional therapy, PEG-IFNα-2A and ruxolitinib respectively; and of grade 3–4 in 7% and 9% of patients receiving PEG-IFNα-2A and ruxolitinib (p. 247)."[5]</td></tr>
</table>

CHCR = clinicohematologic complete responses; CI = confidence interval; CML = chronic myeloid leukemia; CR = complete response; ET = essential thrombocythemia; MPN = myeloproliferative neoplasms; MF = myelofibrosis; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; NR = no response; PD = progressive disease; Peg-IFNα-2a = Pegylated-interferon alfa-2a; PR = partial response; PV = polycythemia vera; QOL = quality of life; SD = stable disease.

Appendix 5: Further Information

Randomized Controlled Trial – Alternative Outcome

Legros L, Guilhot J, Huault S, et al. Interferon decreases VEGF levels in patients with chronic myeloid leukemia treated with imatinib. *Leuk Res*. 2014 June;38(6):662-665.

Non-Randomized Study – Mixed Intervention

Hansen IO, Sorensen AL, Hasselbalch HC. Second malignancies in hydroxyurea and interferon-treated Philadelphia-negative myeloproliferative neoplasms. *Eur J Haematol*. 2017 01 Jan;98(1):75-84.

Non-Randomized Study – Alternative Comparator

Johnson-Ansah H, Guilhot J, Rousselot P, et al. Tolerability and efficacy of pegylated interferon-alpha-2a in combination with imatinib for patients with chronic-phase chronic myeloid leukemia. *Cancer*. 2013 Dec 15;119(24):4284-4289.
PubMed: PM24105694

Stauffer Larsen T, Iversen KF, Hansen E, et al. Long term molecular responses in a cohort of Danish patients with essential thrombocythemia, polycythemia vera and myelofibrosis treated with recombinant interferon alpha. *Leuk Res*. 2013 September;37(9):1041-1045.

Non-Randomized Studies – Single-Arm Studies Published After 2017

Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood*. 2019 10 31;134(18):1498-1509.
PubMed: PM31515250

Gowin K, Jain T, Kosiorek H, et al. Pegylated interferon alpha - 2a is clinically effective and tolerable in myeloproliferative neoplasm patients treated off clinical trial. *Leuk Res*. 2017 03;54:73-77.
PubMed: PM28113109

Masarova L, Patel KP, Newberry KJ, et al. Pegylated interferon alfa-2a in patients with essential thrombocythaemia or polycythaemia vera: a post-hoc, median 83 month follow-up of an open-label, phase 2 trial. *Lancet Haematol*. 2017 Apr;4(4):e165-e175.
PubMed: PM28291640

Additional Reference – Abstract

Mascarenhas, et al. Results of the Myeloproliferative Neoplasms - Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea (HU) Therapy for the Treatment of High Risk Polycythemia Vera (PV) and High Risk Essential Thrombocythemia (ET). *Blood* (2018) 132 (Supplement 1): 577.