URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Essential thrombocythaemia)

Narrative summary of papers presented for review

Three papers were presented for review by NHS England. Paper 1 is a randomised controlled trial (RCT; phase III; MPD-RC 112 RCT) conducted in 24 centres in Europe and the USA. Patients (n=168) with treatment naïve, high-risk essential thrombocythaemia (ET) or polycythaemia vera (PV) were randomly assigned to peginterferon alfa-2a (Peg-IFNa-2a) or hydroxyurea (HU). Paper 2 is a single arm trial (phase II; MPD-RC 111 Study) conducted in 17 centres in Italy and the USA. Patients (n=115) with high-risk ET or PV refractory and/or intolerant to HU were treated with Peg-IFNa-2a. Paper 3 is a post-hoc analysis of data from the MPD-RC 112 RCT and the MPD-RC 111 Study. This paper examined the association of symptom burden with clinical–haematological response at 12 months.

Paper 1: Mascarenhas et al 2022. A randomized phase 3 trial of interferon-a vs hydroxyurea in polycythemia vera and essential thrombocythemia

This paper reports on a multicentre phase III RCT (n=168; MPD-RC 112 RCT) comparing Peg-IFNa-2a (n=82) to HU (n=86) in adults diagnosed with treatment naïve, high-risk[1] ET (n=81) or PV (n=87) according to World Health Organization 2008 diagnostic criteria. Patients were enrolled between September 2011 and June 2016 from 24 centres in Europe and the USA. Mean patient age was 60 years (range 19 to 79) in the Peg-IFNa-2a group and 63 years (range 18 to 87) in the HU group. 40% were female in the Peg-IFNa-2a group and 44% in the HU group. Median disease duration was 2.6 months (range 0.4 to 41.7) in the Peg-IFNa-2a group and 3.1 months (1 to 84.2) in the HU group. 75% of patients with ET were deemed high risk due to age ≥60 years and/or a history of thrombosis. Peg-IFNa-2a was self-administered subcutaneously at 45 mg weekly and titrated in 45 mg increments monthly to a maximum of 180 mg weekly. HU was initiated at 500 mg twice daily. Dose modification occurred when criteria for complete response were not met or dose-limiting toxicity occurred. The median weekly dose of Peg-IFNa-2a was 89.4 mg and duration of treatment was 94.6 weeks (range 2.9 to 287.3). The median weekly dose of HU was 6,708 mg and duration of treatment was 81 weeks (range 0 to 268). Characteristics and dosing details were not reported separately for ET patients. Results were reported at 12, 24 and 36 months. Mean/median follow-up was not reported. In the Peg-IFNa-2a group, 71 patients (n of ET patients not reported) completed 12 months of therapy and 37 patients (14 ET patients) completed 24 months of therapy. In the HU group, 64 patients (n of ET patients not reported) completed 12 months of therapy and 31 patients (11 ET patients) completed 24 months of therapy. No information was reported on concomitant treatments. The trial was closed earlier than planned due to a lack of availability of Peg-IFNa-2a.

Paper 2: Yacoub et al 2019. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea

This paper reports on a single arm phase II trial (n=115; MPD-RC 111 Study) in adults diagnosed with high-risk[1] ET (n=65) or PV (n=50) according to World Health Organization

[1] High-risk disease was defined by one of the following factors: history of thrombosis, age >60 years, history of bleeding (ET only), platelet count >1500 x 10^9/L in ET and >1000 x 10^9/L in PV, vasomotor symptoms (erythromelalgia, severe migraine headaches), significant or symptomatic splenomegaly, and the presence of diabetes or hypertension requiring pharmacologic intervention.

2008 diagnostic criteria, who were refractory and/or intolerant[2] to HU and were treated with Peg-IFNa-2a. Patients were excluded if they had received previous therapy for ET or PV with an agent other than HU, had prior therapy with interferon or had contraindications to interferon. Patients were enrolled between February 2012 and December 2015 from 17 centres in Italy and the USA. The median patient age was 64.0 years for all patients (58.5% of patients with ET were over 60 years). 50.8% of patients with ET were female. The median time from diagnosis was 37.3 months for patients with ET. 68.8% of patients with ET were classified as HU-intolerant and 31.3% were HU-resistant. Prior thrombosis was present in 32.3% of patients with ET. Peg-IFNa-2a was administered subcutaneously at a starting dose of 45 µg weekly and titrated monthly in 45 µg increments up to a maximum of 180 µg weekly. Dose escalation occurred when the criteria for complete response and dose limiting toxicity were not met. The median duration of Peg-IFNa-2a was 78.5 weeks (range 1 to 245) for patients with ET. The mean weekly dose of Peg-IFNa-2a was 102.7 mg (standard deviation (SD) 52.3) for patients with ET. HU therapy was ongoing in 60% of patients with ET. No further details on concomitant treatments were reported. Patients were followed-up for a median of 19.6 months (range 0.6 to 56.6).

Paper 3: Mazza et al 2022. Symptom burden and quality of life in patients with high-risk essential thrombocythaemia and polycythaemia vera receiving hydroxyurea or pegylated interferon alfa-2a: a post-hoc analysis of the MPN-RC 111 and 112 trials

Paper 3 reports on a post-hoc analysis of data (n=280) from the majority of patients included in Paper 1 (MPD-RC 112 RCT; n=166) and Paper 2 (MPD-RC 111 Study; n=114) assessing the change in symptom burden and quality of life over 12 months in patients with high-risk ET (n=143) or PV (n=137) treated with Peg-IFNa-2a or HU. Three patients were excluded for not completing the symptom and quality of life questionnaires. Across the two studies, patients self-reported on disease-related symptoms, functioning, quality of life and symptoms specifically related to Peg-IFNa-2a (if applicable) in clinic via paper booklets at baseline and at three, six, nine and 12 months. Mixed models were used to examine the association of symptom burden with the clinical–haematological response at 12 months and the effect of baseline symptom burden on subsequent changes in symptoms.

Effectiveness

Clinical–haematological response

Mascarenhas et al 2022 (n=168; MPD-RC 112 RCT) reported that no statistically significant differences were observed in complete response or overall response[3] between Peg-IFNa-2a and HU at 12, 24 and 36 months for all patients (ET (n=81) and PV (n=87) patients) (Table

[2] Resistance to and/or intolerance of HU was assessed according to the following criteria: failure to achieve adequate cytoreduction (platelet count ≥600 x 10^9/L; haematocrit >45% or continued need for therapeutic phlebotomy; or white blood cell count >10 x 10^9/L), the development of or progression of splenomegaly, development of major thrombotic episodes despite the maximum tolerated dose of HU, or development of haematologic or non-haematologic toxicities at any dose of HU.

[3] Responses were assessed by a central review committee blinded to treatment using the European LeukemiaNet (ELN) criteria. Complete response was defined for ET patients as a platelet count <400 x 10^9/L, white blood cell count <10 x 10^9/L, resolution of splenomegaly, and resolution of disease-related symptoms (microvascular disturbances, headache and pruritus) and the same for PV patients plus haematocrit <45% without phlebotomy. Overall response rate was patients who had either a complete or partial response.

1). The proportions of ET patients achieving a complete or overall response are also reported in Table 1.

Table 1: Response by treatment arm at 12, 24 and 36 months reported by Mascarenhas et al 2022

		Peg-IFNa-2a n (%)	HU n (%)	Difference in proportions, (95% CI) (Peg-IFNa-2a – HU)	Rate ratio (95% CI)
12 months (Peg-IFNa-2a: n=82 & HU: n=86)	*Complete response*				
	All patients	29 (35)	32 (37)	-2% (-16 to 13)	0.95 (0.64 to 1.42)
	ET	17 (44)	19 (45)	NR	NR
	Overall response				
	All patients	64 (78)	60 (70)	8% (-5 to 21)	1.12 (0.93 to 1.34)
	ET	27 (69)	30 (71)	NR	NR
24 months (Peg-IFNa-2a: n=52 & HU: n=54)	*Complete response*				
	All patients	15 (29)	11 (20)	9% (-9 to 26)	1.42 (0.72 to 2.79)
	ET	9 (38)	6 (25)	NR	NR
	Overall response				
	All patients	31 (60)	22 (41)	19% (1 to 37)	1.46 (1.00 to 2.16)
	ET	14 (58)	8 (33)	NR	NR
36 months (Peg-IFNa-2a: n=27 & HU: n=30)	*Complete response*				
	All patients	9 (33)	5 (17)	17% (-8 to 40)	2.0 (0.76 to 5.23)
	ET	4 (40)	2 (17)	NR	NR
	Overall response				
	All patients	16 (59)	14 (47)	13% (-15 to 38)	1.27 (0.77 to 2.08)
	ET	6 (60)	4 (33)	NR	NR

Abbreviations: CI; confidence intervals; ET: essential thrombocythaemia; HU: hydroxyurea; n: number; NR: not reported; Peg-IFNa-2a: peginterferon alfa-2a; PV: polycythaemia vera

Proportions of PV patients achieving a complete or overall response are reported in the three paper summary URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Polycythaemia Vera)

Mascarenhas et al 2022 (n=168; MPD-RC 112 RCT) also reported that the median weekly dose of Peg-IFNa-2a was 76.4 µg (interquartile range (IQR) 46.7 to 104.4) for patients with ET or PV with complete response compared to 89.2 µg (IQR 59.7 to 131.2) for patients without complete response (p=0.27; non-significant difference).

Yacoub et al 2019 (MPD-RC 111 Study) reported that among patients with high-risk ET[4] refractory and/or intolerant to HU treated with Peg-IFNa-2a (n=65):

- Complete response[5] was attained in 28 (43.1%) patients at 12 months
- Partial response was attained in 17 (26.2%) patients at 12 months

[4] PV results reported in the three paper summary URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Polycythaemia Vera).

[5] Response was assessed by a central review committee. Complete and partial responses were defined by ELN criteria and overall response rate was patients who had either a complete or partial response.

- Overall response rate was 69.2% (95% CI 56.6% to 80.0%) at 12 months, which differed significantly from the null hypothesis of 35% (p<0.001)
- The best overall response rate at any time point was 70.8% (95% CI 58.2% to 81.4%)
- 45 (69.2%) had achieved a platelet count ≤400 x 10^9/L

Yacoub et al 2019 also reported that patients with ET had higher complete response rates than those with PV (43% vs 22%; odds ratio (OR) 2.68 (95% CI 1.17 to 6.15)) and *CALR*-mutated patients had higher complete response rates than patients without a *CALR* mutation (56% vs 28%; OR 3.34 (95% CI 1.28 to 8.67). HU resistance vs intolerance, maximum dose of Peg-IFNa-2a and disease duration were not found to be predictors of attaining complete response.

One included paper (n=168) reported no statistically significant differences in complete response or overall response between Peg-IFNa-2a and HU at 12, 24 and 36 months in patients with treatment naïve, high-risk ET or PV. Complete response rates were 44%, 38% and 33% and overall response rates were 69%, 58% and 60% at 12, 24 and 36 months respectively in patients with ET treated with Peg-IFNa-2a. A second included paper (n=65) reported a complete response rate of 43.1%, partial response rate of 26.2%, and an overall response rate of 69.2% at 12 months in patients with high-risk ET refractory and/or intolerant to HU treated with Peg-IFNa-2a.

Spleen response

Mascarenhas et al 2022 (MPD-RC 112 RCT) reported that among 109 patients with treatment naïve, high-risk ET or PV receiving post-baseline imaging for spleen response, the median spleen reduction (best response on treatment) was -6% (range -37% to 54%) in 58 patients treated with Peg-IFNa-2a compared to -5% (range -24% to 17%) in 51 patients treated with HU. In patients with a spleen size ≥13 cm by imaging at baseline, six (17%) out of 36 patients receiving Peg-IFNa-2a were reported to attain a normalised spleen[6] compared with four (11%) out of 37 patients receiving HU at any time on treatment. Statistical comparison of the two groups was not reported. Results were not reported separately for patients with ET. Mean/median follow-up was not reported.

Yacoub et al 2019 (MPD-RC 111 Study) reported that among 52 patients with high-risk ET or PV refractory and/or intolerant to HU and a baseline spleen size of >13 cm by imaging, 17 (32.7%) attained a normalised spleen (decrease to 13 cm) with Peg-IFNa-2a at a median follow-up of 19.6 months (range 0.6 to 56.6). The median absolute change in spleen size was reported to be 2% (no further details reported[7]). Results were not reported separately for patients with ET.

One included paper (n=109) reported a median spleen reduction of -6% with Peg-IFNa-2a and -5% with HU in patients with treatment naïve, high-risk ET or PV. In patients with a spleen size ≥13 cm at baseline, 17% of patients receiving Peg-IFNa-2a and 11% of patients receiving HU attained a normalised spleen (mean/median follow-up not reported). A second included paper (n=52) reported that among 52 patients with high-risk ET or PV refractory and/or intolerant to HU and a baseline spleen size of >13 cm,

[6] Splenomegaly was assessed by ultrasound measurement of the craniocaudal axis and defined as >13 cm.
[7] It is not clear if this result is in patients with a baseline spleen size of >13cm or in all patients with imaging for spleen response.

32.7% attained a normalised spleen with Peg-IFNa-2a at a median follow-up of 19.6 months. Results were not reported separately for patients with ET.

Bone marrow response

Mascarenhas et al 2022 (MPD-RC 112 RCT) reported that among 109 patients with treatment naïve, high-risk ET or PV and pre- and post-treatment biopsies, three (5%) out of 57 patients on Peg-IFNa-2a had a histopathologic response (HPR; not defined) compared to 12 (23%) out of 52 patients on HU (p=0.01).[8] Best HPR was observed in 10 (17%) out of 59 patients on Peg-IFNa-2a compared to 18 (33%) out of 54 patients on HU (p=0.05). HPR was more frequent in the ET group compared with the PV group in patients receiving Peg-IFNa-2a or HU (13 (24%) out of 46 ET patients vs four (6%) out of 63 PV patients) as well as best HPR (20 (42%) out of 48 ET patients vs eight (12%) out of 66 PV patients) at 12 months (no p-value reported). The authors reported that a dose-dependent effect on achieving HPR was observed with HU (p=0.04) but was not observed with Peg-IFNa-2a (p=0.6). Mean/median follow-up was not reported.

Yacoub et al 2019 (MPD-RC 111 Study) reported that among 74 patients evaluated for bone marrow response, histopathologic remission with Peg-IFNa-2a was observed in nine patients (12.2%; including five ET patients) with high-risk ET or PV refractory and/or intolerant to HU at a median follow-up of 19.6 months (range 0.6 to 56.6).[9] The authors reported that bone marrow fibrosis progressed to grade 2+ (scale 0 to 3+) in seven patients while receiving Peg-IFNa-2a but only one patient met clinical criteria for transformation to myelofibrosis. The remaining patients had stable degrees of bone marrow fibrosis.

One included paper (n=109) reported that 5% of patients with treatment naïve, high-risk ET or PV on Peg-IFNa-2a achieved a bone marrow HPR and 17% achieved best HPR compared to 23% and 33% respectively of patients on HU (statistically significant differences). In patients with ET receiving Peg-IFNa-2a or HU (n=46 for HPR and 48 for best response), HPR was 24% and best HPR was 42% at 12 months. A second included paper (n=74) reported a histopathologic remission rate of 12.2% (nine patients including five ET patients) in patients with high-risk ET or PV refractory and/or intolerant to HU treated with Peg-IFNa-2a at a median follow-up of 19.6 months.

Cytogenetic response

Mascarenhas et al 2022 (MPD-RC 112 RCT) reported that among 144 patients with treatment naïve, high-risk ET or PV with baseline cytogenetics, abnormalities were observed in eight (11%) out of 73 patients on Peg-IFNa-2a and 14 (20%) out of 71 patients on HU. A chromosomal abnormality (trisomy 9, del(20q), t(14;21)(q24;q22), trisomy 8, and loss of Y chromosome) was observed in three (38%) out of eight patients on Peg-IFNa-2a and three (21%) out of 14 patients on HU (p=0.62). After 24 to 36 months follow-up, one (1%) out of 73 patients on Peg-IFNa-2a and three (4%) out of 71 patients on HU developed new abnormalities including a gain of del(20q), loss of Y and del(16q). The authors reported that there was no association between cytogenetic response and complete or partial response. Results were not reported separately for patients with ET.

Yacoub et al 2019 (MPD-RC 111 Study) reported that among 110 patients with high-risk ET or PV refractory and/or intolerant to HU treated with Peg-IFNa-2a and baseline sequencing data, four of 17 patients with abnormal baseline karyotypes, showed changes in their

[8] Bone marrow biopsies were examined by a single blinded expert haematopathologist.
[9] Bone marrow biopsies were examined by an expert haematopathologist without knowledge of the clinical or molecular responses.

chromosomal abnormalities during treatment with Peg-IFNa-2a at a median follow-up of 19.6 months (range 0.6 to 56.6). Results were not reported separately for patients with ET.

One included paper (n=144) reported that after 24 to 36 months follow-up of patients with treatment naïve, high-risk ET or PV, new cytogenetic abnormalities developed in 1% of 73 patients on Peg-IFNa-2a and 4% of 71 patients on HU. A second included paper (n=110) reported four of 17 patients with high-risk ET or PV refractory and/or intolerant to HU and abnormal baseline karyotypes showed changes in their chromosomal abnormalities during treatment with Peg-IFNa-2a at a median follow-up of 19.6 months. Results were not reported separately for patients with ET.

Molecular response

Mascarenhas et al 2022 (n=144; MPD-RC 112 RCT) reported that in patients with treatment naïve, high-risk ET or PV, the median greatest change from baseline in *JAK2*V617F variant allele frequencies (VAF) was -10.7% in patients on Peg-IFNa-2a and -5.3% in patients on HU (p-value not reported). The authors reported that reductions in *JAK*2V617F, *CALR* and *TET2* VAF were observed in most patients treated with Peg-IFNa-2a or HU and results for *JAK*2V617F VAF were similar for ET and PV groups (no further details provided). In a mixed-model including 117 allele burden values at baseline, 97 values at 12 months and 52 values at 24 months, estimates of *JAK2*V617F VAF reduction were statistically significantly greater for Peg-IFNa-2a (-0.16 (95% CI -0.23 to -0.10)) than for HU (-0.004 (95% CI -0.08 to 0.08)) at 24 months (p=0.002). The authors reported that the median *JAK2*V617F VAF decreased consistently from baseline to 24 months in the Peg-IFNa-2a group but increased in the HU group after 12 months.

Yacoub et al 2019 (n=110; MPD-RC 111 Study) reported that in patients with high-risk ET or PV refractory and/or intolerant to HU, the median absolute change in *JAK2*V617F VAF was -6% (range -84% to 47%) in patients achieving complete response with Peg-IFNa-2a compared to +4% (range -18% to 56%) in patients with partial response or no response at a median follow-up of 19.6 months (range 0.6 to 56.6). The authors reported that patients with complete response had a significantly lower VAF at baseline compared with those who achieved no response. Results were not reported separately for patients with ET.

One included paper (n=144) reported a median greatest change from baseline in *JAK2*V617F VAF of -10.7% with Peg-IFNa-2a and -5.3% with HU, for patients with treatment naïve, high-risk ET or PV (mean/median follow-up not reported). Estimates of *JAK2*V617F VAF reduction were statistically significantly greater for Peg-IFNa-2a (-0.16) than HU (-0.004) at 24 months. A second included paper (n=110) reported a median absolute change in *JAK2*V617F VAF of -6% (range -84% to 47%) in patients achieving complete response compared to +4% (range -18% to 56%) in patients with partial response or no response at a median follow-up of 19.6 months. Results were not reported separately for patients with ET.

Complication-free survival

Mascarenhas et al 2022 (n=168; MPD-RC 112 RCT) reported on complication-free survival[10] in patients with treatment naïve, high-risk ET or PV randomised to Peg-IFNa-2a (n=82) or HU (n=86). There was no statistically significant difference between the Peg-IFNa-2a group (two events) and the HU group (three events) (hazard ratio 0.60 (95% CI 0.10 to 3.62)). Mean/median follow-up length was not reported. Events included a bleeding event consisting

[10] Defined as free of major thrombotic event, major haemorrhagic complications, progression to myelofibrosis, progression to acute leukaemia or death.

of macroscopic haematuria that required red cell transfusions and a cerebral vascular accident in the Peg-IFNa-2a group and a bilateral vertebral artery blockage noted on imaging but without clinical consequences, progression to myelofibrosis after 46 months and death due to lung cancer at nine months in the HU group. Cumulative incidence of thrombosis was reported to be 2% (95% CI 0.3 to 15) for Peg-IFNa-2a and 2% (95% CI 0.3 to 13) for HU at 24 months. Results were not reported separately for patients with ET.

One included paper (n=168) reported no statistically significant difference in complication-free survival between Peg-IFNa-2a (two events) and HU (three events) in patients with treatment naïve, high-risk ET or PV (mean/median follow-up not reported). Results were not reported separately for patients with ET.

Symptoms related to Peg-IFNa-2a

Mazza et al 2022 (n=280) reported on average changes in symptoms related to Peg-IFNa-2a[11] in patients treated with Peg-IFNa-2a with high-risk ET or PV from baseline to 12 months using data from the Peg-IFNa-2a group of the MPN-RC 112 RCT (Paper 1) and the MPN-RC 111 Study (Paper 2). In the MPN-RC 112 RCT, statistically significant mean worsening was observed in: influenza-like symptoms (1.0 (95% CI 0.6 to 1.5); p<0.0001), injection site irritation (1.1 (95% CI 0.7 to 1.4); p<0.0001), blurry vision (0.5 (95% CI 0.3 to 0.8); p=0.0002), vision change (0.6 (95% CI 0.4 to 0.9; p<0.0001) and flushing (0.3 (95% CI 0.1 to 0.5; p=0.011). In the MPN-RC 111 Study, statistically significant mean worsening was observed in: influenza-like symptoms (0.6 (95% CI 0.2 to 0.9); p=0.0040), injection site irritation (0.8 (95% CI 0.4 to 1.3); p=0.0004), blurry vision (0.5 (95% CI 0.2 to 0.9); p=0.0059) and vision change (0.5 (95% CI 0.1 to 0.8); p=0.010). Results were not reported separately for patients with ET.

One included paper (n=280) reported statistically significant worsening of symptoms related to Peg-IFNa-2a (influenza-like symptoms, injection site irritation, blurry vision, vision change and flushing) from baseline to 12 months in patients treated with Peg-IFNa-2a with high-risk ET or PV. Results were not reported separately for patients with ET.

Myeloproliferative neoplasm symptoms

Yacoub et al 2019 (n=109; MPD-RC 111 Study) reported on mean changes from baseline in myeloproliferative neoplasm (MPN) symptoms during Peg-IFNa-2a treatment in patients with high-risk ET or PV refractory and/or intolerant to HU as measured by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)[12] at a median follow-up of 19.6 months (range 0.6 to 56.6). Mean Total Symptom Score (TSS)[13] at baseline was 19.5 (SD 18.4, range 0 to 95). Statistically significant mean improvements from baseline in TSS were

[11] Patients treated with pegylated interferon alfa-2a reported the severity of their treatment-related symptoms—influenza-like symptoms, injection site irritation, blurry vision, vision change, and flushing—in the previous week on a scale ranging from 0 (absent) to 10 (worst imaginable).
[12] The MPN-SAF2 consists of 19 items assessing fatigue, early satiety, abdominal pain, abdominal discomfort, inactivity, headache, concentration problems, dizziness, numbness, insomnia, sad mood, problems with sexual desire or function, cough, night sweats, itching, bone pain, fever, unintentional weight loss, and overall quality of life in the previous week on a scale ranging from 0 (absent or as good as it can be) to 10 (the worst imaginable or as bad as it can be).
[13] Ten items of the MPN-SAF (fatigue, early satiety, abdominal discomfort, inactivity, concentration problems, night sweats, itching, bone pain, fever, and unintentional weight loss) are included in the TSS. The TSS is calculated for patients who complete at least six of these items by calculating the mean of the available items and multiplying by 10 to achieve a scale ranging from 0 to 100 (taken from Mazza et al 2022).

observed at three months (-0.4 (SE 0.1); n=104) and six months (-0.5 (SE 0.1); n=92) and non-significant mean improvements at nine months (-0.3 (SE 0.2); n=81) and 12 months (-0.3 (SE 0.2); n=74).[14] Results were not reported separately for patients with ET.

Mazza et al 2022 reported on average changes from baseline in MPN symptoms across 12 months using data from the MPN-RC 112 RCT (Paper 1) and the MPN-RC 111 Study (Paper 2). In the MPN-RC 112 RCT, no statistically significant improvements were observed in TSS or individual MPN-SAF items in patients on Peg-IFNa-2a or HU with high-risk ET or PV but statistically significant worsening of fever was observed in patients on Peg-IFNa-2a (0.2 (95% CI 0.0 to 0.4); p=0.020). In the MPN-RC 111 Study, statistically significant mean improvement was observed in: TSS (mean -3.6 (95% CI -6.3 to -0.9); p=0.0098), fatigue (-0.7 (95%CI -1.2 to -0.2; p=0.0039), abdominal pain (-0.4 (95% CI -0.8 to -0.1); p=0.024), abdominal discomfort (-0.5 (95% CI -0.9 to -0.1); p=0.011), dizziness (-0.5 (95% CI -0.9 to 0.0); p=0.040), numbness (-0.7 (95% CI -1.2 to -0·3; p=0.0026), night sweats (-0.5 (95% CI -1.0 to -0.1); p=0.022) and fever (-0.4 (95% CI -0.6 to -0.1); p=0.011) in patients with high-risk ET or PV refractory and/or intolerant to HU treated with Peg-IFNa-2a. Results were not reported separately for patients with ET.

Mazza et al 2022 examined the association between symptom burden and clinical–haematological response at 12 months for patients with ET or PV using data from the MPN-RC 112 RCT (n= 166; Paper 1) and the MPN-RC 111 Study (n=114; Paper 2). The authors reported that clinical–haematological response was statistically significantly associated with a clinically significant improvement in symptom burden at 12 months in the full sample (p=0.00047), in patients with high baseline symptom burden (p=0.050), and in patients with low baseline symptom burden (p=0.0043). Note this includes patients treated with HU from the MPN-RC 112 RCT. In patients treated with Peg-IFNa-2a, a clinically significant improvement in symptom burden was reported by five (19%) of 27 complete responders and six (18%) of 34 partial responders treated with Peg-IFNa-2a in the MPN-112 RCT, and by 12 (32%) of 38 complete responders and seven (20%) of 35 partial responders treated with Peg-IFNa-2a in the MPN-RC 111 Study. Results were not reported separately for patients with ET.

Mazza et al 2022 also examined the association between the effect of baseline symptom burden (high burden TSS ≥20 vs low burden TSS<20) on subsequent change for patients with ET or PV using data from the MPN-RC 112 RCT (n=166; Paper 1) and the MPN-RC 111 Study (n=114; Paper 2). The authors reported that on average, patients treated with Peg-IFNa-2a with high baseline symptom burden had significant improvement in the TSS (mean -10.2 (95% CI -13.2 to -7.2; p<0.0001) and quality of life (mean -0.7 (95% CI -1.2 to -0.2); p=0·0086) from baseline between three and 12 months whereas those with low baseline symptom burden had significant worsening in the TSS (3.2 (95% CI 0.9 to 5.4); p=0.0057). Results were not reported separately for patients with ET.

One included paper (n=109) reported statistically significant mean improvements in MPN symptoms in patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a at three months and at six months and non-significant improvements at nine months and at 12 months. A second included paper (n=280) reported no statistically significant mean improvements in TSS or individual MPN-SAF items across 12 months in patients with high-risk ET or PV receiving Peg-IFNa-2a or HU. For patients with high-risk ET or PV refractory and/or intolerant to HU treated with Peg-IFNa-2a, there were statistically significant mean improvements in TSS, fatigue,

[14] Results were transformed to a 0 to 10 scale where 10 represents the worst outcome and 10 (worst imaginable).

abdominal pain, abdominal discomfort, dizziness, numbness, night sweats and fever. Results were not reported separately for patients with ET. Clinical–haematological response was found to be statistically significantly associated with a clinically significant improvement in symptom burden at 12 months. Patients with ET or PV with high baseline symptom burden receiving Peg-IFNa-2a had statistically significant improvement in the TSS and quality of life from baseline to three and 12 months whereas those with low baseline symptom burden had significant worsening in the TSS. Results were not reported separately for patients with ET.

Quality of life

Yacoub et al 2019 (n=109; MPD-RC 111 Study) reported on global health status/quality of life (GHS/QoL) as measured by the European Organisation for the Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)[15] at a median follow-up of 19.6 months (range 0.6 to 56.6) in patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a. The mean QLQ-C30 score at baseline was 71.6 (SD 20.1). GHS/QoL scores[16] did not change significantly over time (mean changes from baseline ranged from -0.1 to 0.2 up to 12 months, p>0.05). Results were not reported separately for patients with ET.

Mazza et al 2022 reported that in the MPN-RC 112 RCT (Paper 1), patients with treatment naïve, high-risk ET or PV treated with either Peg-IFNa-2a or HU showed no statistically significant improvement from baseline in GHS/QoL (no further results reported). Results for the MPD-RC 111 Study (Paper 2) were only reported in a bar chart. Results were not reported separately for patients with ET.

One included paper (n=109) reported no statistically significant changes in quality of life from baseline up to 12 months in patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a. A second included paper (n=280) reported no statistically significant improvement from baseline in quality of life in patients with treatment naïve, high-risk ET or PV treated with either Peg-IFNa-2a or HU. Results were not reported separately for patients with ET.

Vascular events

Yacoub et al 2019 (n=115; MPD-RC 111 Study) reported a cumulative incidence of major vascular events at one year of 2% (95% CI 1% to 8%) and at two years of 5% (95% CI 2% to 15%) in patients with high-risk ET or PV refractory and/or intolerant to HU treated with Peg-IFNa-2a. Events were a grade 3 severity venous thromboembolic event, grade 3 cardiovascular disease and two coronary artery occlusions (grade 2 and 3 myocardial infarction). Results were not reported separately for patients with ET.

One included paper (n=115) reported a cumulative incidence of major vascular events of 2% at one year and 5% at two years in patients with high-risk ET or PV refractory

[15] The 30-item EORTC QLQ-C30 12 assesses five functioning domains (physical, role, emotional, cognitive, and social), eight symptoms (fatigue, nausea or vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), financial difficulties, and global health status/ quality of life (GHS/QoL) in the previous week. The GHS/QoL scale consists of two items answered on a scale ranging from 1 (very poor) to 7 (excellent) and serves as an overall summary of the EORTC QLQ-C30.12 The GHS/QoL scale was calculated by averaging these two items and transforming the means to achieve a scale ranging from 0 to 100.

[16] Results were transformed to a 0 to 10 scale where 10 represents the worst outcome and 10 (worst imaginable).

and/or intolerant to HU treated with Peg-IFNa-2a. Results were not reported separately for patients with ET.

Acute myeloid leukaemia

Yacoub et al 2019 (n=115; MPD-RC 111 Study) reported that one patient with ET[17] transformed to acute myeloid leukaemia within eight weeks of Peg-IFNa-2a.

One included paper (n=115) reported that one patient with ET transformed to acute myeloid leukaemia within eight weeks of Peg-IFNa-2a.

Second cancer

Yacoub et al 2019 (n=115; MPD-RC 111 Study) reported a cumulative incidence of a second cancer (excluding non-melanoma skin cancers) of 4% (95% CI 1% to 10%) at two years in patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a at a median follow-up of 19.6 months (range 0.6 to 56.6). The authors reported that one patient with ET developed a spindle cell sarcoma. Four patients with ET or PV discontinued treatment because of secondary cancer.

One included paper (n=115) reported a cumulative incidence of a second cancer (excluding non-melanoma skin cancers) of 4% at two years in patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a at a median follow-up of 19.6 months. The authors reported that one patient with ET developed a spindle cell sarcoma.

Safety

Adverse events

Mascarenhas et al 2022 (MPD-RC 112 RCT) reported on adverse events (AEs) in 162 patients with treatment naïve, high-risk ET or PV (82 Peg-IFNa-2a and 80 HU patients). Mean/median follow-up length was not reported. Results were not reported separately for patients with ET.[18] The authors reported that:

- The proportion of grade 3-4 AEs was statistically significantly greater in the Peg-IFNa-2a group (38 (46%)) compared to the HU group (22 (28%)) (p=0.01).
- Leukopaenia, flu-like symptoms, pruritus, injection site reactions, increased alanine aminotransferase and depression (any grade) were statistically significantly more common in the Peg-IFNa-2a group (p<0.05)
- Anorexia and oral mucositis (any grade) were statistically significantly more common in the HU group (p<0.05)

Yacoub et al 2019 (MPD-RC 111 Study) reported on AEs in 114 patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a at a median follow-up of 19.6 months (range 0.6 to 56.6). The authors reported that:

- AEs of any grade were observed in 90.4% of patients with ET or PV
- Grade ≥3 AEs were observed in 43.8% of patients with ET or PV

[17] The authors noted that the baseline BM biopsy favoured a diagnosis of pre-fibrotic myelofibrosis rather than ET.
[18] Table 3 in the paper reports on AEs. It appears that the table provides separate AE results for ET and PV patients, but the column headings are missing, making it unclear which results correspond to ET and PV patients.

- The most common AEs (all grade) in patients with ET were fatigue (43.8%), headache (31.3%), anaemia (25.0%), nausea (23.4%), pruritus (23.4%), leukopaenia (20.3%) and injection site reaction (20.3%)
- Grade 3+ AEs in patients with ET were neutropaenia (7.8%), anaemia (6.3%), headache (3.1%), lymphocytopaenia (1.6%), leukopaenia (1.6%), pain (1.6%), rash (1.6%), diarrhoea (1.6%) and dyspnoea (1.6%).

One included paper (n=162) reported a statistically significant greater proportion of grade 3-4 AEs in the Peg-IFNa-2a group (46%) compared to the HU group (28%) in patients with treatment naïve, high-risk ET or PV (mean/median follow-up not reported). Results were not reported separately for patients with ET. A second included paper (n=114) reported that AEs of any grade were observed in 90.4% of patients and grade ≥3 AEs were observed in 43.8% of patients with high-risk ET or PV refractory and/or intolerant to HU receiving Peg-IFNa-2a at a median follow-up of 19.6 months. The most common AEs (all grade) in patients with ET were fatigue (43.8%), headache (31.3%), anaemia (25.0%), nausea (23.4%), pruritus (23.4%), leukopaenia (20.3%), and injection site reaction (20.3%). Grade 3+ AEs in patients with ET were neutropaenia (7.8%), anaemia (6.3%), headache (3.1%), lymphocytopaenia (1.6%), leukopaenia (1.6%), pain (1.6%), rash (1.6%), diarrhoea (1.6%) and dyspnoea (1.6%).

Therapy discontinuation due to adverse events

Mascarenhas et al 2022 (n=168; MPD-RC 112 RCT) reported on therapy discontinuation due to adverse events in patients with treatment naïve, high-risk ET or PV randomised to Peg-IFNa-2a (n=82) or HU (n=86). Mean/median follow-up length was not reported. In the Peg-IFNa-2a group, 12 (15%) patients discontinued therapy due to adverse events compared to nine (11%) in the HU group. Results were not reported separately for ET patients.

Yacoub et al 2019 (n=115; MPD-RC 111 Study) reported that discontinuation of Peg-IFNa-2a due to AEs occurred in 13.9% of patient with high-risk ET or PV refractory and/or intolerant to HU at a median follow-up of 19.6 months (range 0.6 to 56.6). Results were not reported separately for patients with ET.

One included paper (n=162) reported that 15% of patients with treatment naïve, high-risk ET or PV discontinued therapy due to adverse events in the Peg-IFNa-2a group compared to 11% in the HU group (mean/median follow-up not reported). A second included paper (n=115) reported that discontinuation of Peg-IFNa-2a due to AEs occurred in 13.9% of patients with high-risk ET or PV refractory and/or intolerant to HU at a median follow-up of 19.6 months. Results were not reported separately for patients with ET.

References

- Mascarenhas J, Kosiorek HE, Prchal JT, Rambaldi A, Berenzon D, Yacoub A, Harrison CN, McMullin MF, Vannucchi AM, Ewing J, O'Connell CL, Kiladjian JJ, Mead AJ, Winton EF, Leibowitz DS, De Stefano V, Arcasoy MO, Kessler CM, Catchatourian R, Rondelli D, Silver RT, Bacigalupo A, Nagler A, Kremyanskaya M, Levine MF, Arango Ossa JE, McGovern E, Sandy L, Salama ME, Najfeld V, Tripodi J, Farnoud N, Penson AV, Weinberg RS, Price L, Goldberg JD, Barbui T, Marchioli R, Tognoni G, Rampal RK, Mesa RA, Dueck AC, Hoffman R. A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia. Blood. 2022;139(19):2931-2941. Available from

A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia - PubMed (nih.gov)

- Mazza GL, Mead-Harvey C, Mascarenhas J, Yacoub A, Kosiorek HE, Hoffman R, Dueck AC, Mesa RA; Myeloproliferative Neoplasms Research Consortium (MPN-RC) 111 and 112 trial teams. Symptom burden and quality of life in patients with high-risk essential thrombocythaemia and polycythaemia vera receiving hydroxyurea or pegylated interferon alfa-2a: a post-hoc analysis of the MPN-RC 111 and 112 trials. Lancet Haematol. 2022;9(1):e38-e48. Available from Symptom Burden and Quality of Life in Patients With High-Risk Essential Thrombocythemia and Polycythemia Vera Receiving Hydroxyurea or Pegylated Interferon Alfa-2a: A Post-Hoc Analysis of the MPN-RC 111 and 112 Trials - PMC (nih.gov)
- Yacoub A, Mascarenhas J, Kosiorek H, Prchal JT, Berenzon D, Baer MR, Ritchie E, Silver RT, Kessler C, Winton E, Finazzi MC, Rambaldi A, Vannucchi AM, Leibowitz D, Rondelli D, Arcasoy MO, Catchatourian R, Vadakara J, Rosti V, Hexner E, Kremyanskaya M, Sandy L, Tripodi J, Najfeld V, Farnoud N, Papaemmanuil E, Salama M, Singer-Weinberg R, Rampal R, Goldberg JD, Barbui T, Mesa R, Dueck AC, Hoffman R. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood. 2019;134(18):1498-1509. Available from Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea - PubMed (nih.gov)