# URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Polycythaemia Vera)

## 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 polycythaemia vera (PV) or essential thrombocythaemia (ET) were randomly assigned to peginterferon alfa-2 (Peg-IFNa-2a) or hydroxyurea (HU). Paper 2 is a single arm trial (phase II; MPD-RC 111) 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 retrospective cohort study conducted in one centre in the USA. Patients (n=470) with PV were included and outcomes were compared between patients with low and high-risk PV treated with recombinant interferon-alpha (rIFNα), HU and phlebotomy-only (PHL-O).

### 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. 82% of patients with PV 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 PV 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 PV patients not reported) completed 12 months of therapy and 37 patients (23 PV patients) completed 24 months of therapy. In the HU group, 64 patients (n of PV patients not reported) completed 12 months of therapy and 31 patients (20 PV 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 (66.0% of PV patients were over 60 years). 48% of patients with PV were female. The median time from diagnosis was 54.8 months for patients with PV. 66% of patients with PV were classified as HU-intolerant and 34% were HU-resistant. Prior thrombosis was present in 22% of patients with PV. 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 82 weeks (range 4 to 209) for patients with PV. The mean weekly dose of Peg-IFNa-2a was 128.7 mg (standard deviation (SD) 46.4) for patients with PV. HU therapy was ongoing in 68% of patients with PV. 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: Abu-Zeinah et al 2021: Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival

This paper is a retrospective cohort study (n=470) including patients diagnosed with PV by either the PV Study Group (PVSG) criteria (1974 to 2007), Weill Cornell Medicine (WCM) criteria (2008 to 2016) or World Health Organization (WHO) criteria (2016 to 2019) (no further details provided). Patients were classified by the first cytoreductive treatment they received for at least one year. Treatment groups included rIFNα (n=93; including recombinant interferon alpha-2a, recombinant interferon alpha-2b or Peg-IFNa-2a[3]), HU (n=189), other cytoreductive drugs and combinations (n=55) or PHL-O (n=133; no cytoreductive treatment). Patients were identified by review of medical records of a single centre in the USA and included patients diagnosed with PV between 1966 and 2019. The median age at diagnosis was 54 years (range 20 to 94), 49% were female and 44% were deemed high-risk[4]. The median treatment duration was four years (range 0 to 28). Treatment cross-over occurred in 19% of rIFNα treated patients and 26% of HU treated patients. Excluding patients in the other cytoreductive drugs group, 199 patients received rIFNα at any time for a cumulative duration of 1,137 patient-years and 285 patient received HU at any time for cumulative duration of 1,671 years. The median follow-up was 10 years (range 0 to 45).

[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] The number of patients receiving Peg-IFNa-2a was not reported and results were not reported separately for these patients.

[4] The European LeukemiaNet (ELN) risk category at diagnosis was determined for each patient; high-risk patients included those who were 60 years of age or older and/or had a history of thrombosis at diagnosis; low-risk patients were younger than 60 years and had no prior history of thrombosis at diagnosis.

## 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[5] between Peg-IFNa-2a or HU at 12, 24 and 36 months for all patients (ET (n=81) and PV (n=87) patients) (Table 1). The proportions of PV 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) |
| | PV | 12 (28) | 13 (30) | NR | NR |
| | Overall response | | | | |
| | All patients | 64 (78) | 60 (70) | 8% (-5 to 21) | 1.12 (0.93 to 1.34) |
| | PV | 37 (86) | 30 (68) | 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) |
| | PV | 7 (25) | 5 (17) | NR | NR |
| | Overall response | | | | |
| | All patients | 31 (60) | 22 (41) | 19% (1 to 37) | 1.46 (1.00 to 2.16) |
| | PV | 17 (61) | 14 (47) | 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) |
| | PV | 5 (29) | 3 (17) | NR | NR |
| | Overall response | | | | |
| | All patients | 16 (59) | 14 (47) | 13% (-15 to 38) | 1.27 (0.77 to 2.08) |
| | PV | 10 (59) | 10 (56) | 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 ET 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 (Essential thrombocythaemia))

Mascarenhas et al 2022 (n=168; MPD-RC 112 RCT) reported that in patients with PV, 41 (47%) out of 87 (20 Peg-IFNa-2a and 21 HU) were receiving phlebotomy during six months prior to enrolment, with a median number of phlebotomies of 4.0 (1 to 13) for Peg-IFNa-2a and 3.0 (1 to 12) for HU. During the first year of treatment, 33 patients with PV (Peg-IFNa-

[5] Responses were assessed by a central review committee blinded to treatment using the ELN criteria. Complete response was defined for ET patients as a platelet count <400 x $10^9$/L, haematocrit <45% without phlebotomy for patients with PV only, 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.

2a: 18; HU: 15) received phlebotomy, with a median number of phlebotomies of 3.0 (1 to 6) for Peg-IFNa-2a and 2.0 (1 to 5) for HU.

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 PV[6] refractory and/or intolerant to HU treated with Peg-IFNa-2a (n=50) at 12 months:

- Complete response[7] was attained in 11 (22%) patients
- Partial response was observed in 19 (38%) patients
- Overall response rate was 60% (95% CI 45.2% to 73.6%) which differed significantly from the null hypothesis of 35% (p<0.001)
- The best overall response rate at any time point was 64.0% (95% CI 49.2 to 77.1%)
- 23 (46%) patients had achieved ≤45% haematocrit
- Of the 27 patients receiving phlebotomy at enrolment (with a median of 2.0 (range, 1 to 12) phlebotomies in the six months before enrolment), the median number of phlebotomies was 1.0 (range 0 to 6) and 10 (37%) were phlebotomy independent during the first six months of the study

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 28%, 25% and 29% and overall response rates were 86%, 61% and 59% at 12, 24 and 36 months respectively in patients with PV treated with Peg-IFNa-2a. A second included paper (n=65) reported a complete response rate of 22%, partial response rate of 38% and an overall response rate of 60% at 12 months in patients with high-risk PV 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[8] compared

[6] ET results reported in the three paper summary URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Essential thrombocythaemia).
[7] 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.
[8] Splenomegaly was assessed by ultrasound measurement of the craniocaudal axis and defined as >13 cm.

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 PV. 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[9]). Results were not reported separately for patients with PV.

**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, 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 PV.**

**Bone marrow response and fibrosis**

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).[10] 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 length 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 four PV 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).[11] 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.

Abu-Zeinah et al 2021 reported that among 242 patients with PV with bone marrow biopsies treated with rIFNα (n=64), HU (n=114) or PHL-O (n=64) bone marrow fibrosis (grade MF2-3) was observed in:

- 4% of rIFNα, 15% of HU and 0% of PHL-O patients at 0 to two years from the initial biopsy

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

- 24% of rIFNα, 37% of HU and 32% of PHL-O patients at two to eight years
- 16% of rIFNα, 49% of HU and 62% of PHL-O patients at eight to 14 years
- 38% of rIFNα, 55% of HU, and 74% of PHL-O patients at >14 years

The authors reported that percentage of patients with MF2-3 fibrosis was statistically significantly lower for the rIFNα group compared to the HU and PHL-O groups at eight to 14 years from the initial biopsy.

**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 PV receiving Peg-IFNa-2a or HU (n=63 for HPR and 66 for best response), HPR was 6% and best HPR was 12% at 12 months. A second included paper (n=74) reported a histopathologic remission rate of 12.2% (nine patients including four PV 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. A third included paper (n=242) reported that bone marrow fibrosis was observed in 4%, 24%, 16% and 38% of patients with PV on rIFNα at 0 to two, two to eight, eight to 14 and >14 years from initial biopsy.**

**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 PV.

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 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 PV.

**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 PV.**

**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

*JAK2*V617F 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 PV.

**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 PV.**

**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 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 PV.

**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**

[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).

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

**improvements at nine months and at 12 months. Results were not reported separately for patients with PV.**

### 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 PV.

**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. Results were not reported separately for patients with PV.**

### All-cause mortality

Abu-Zeinah et al 2021 (n=470) reported that in patients with PV, longer time on rIFNα was statistically significantly associated with a lower risk of all-cause mortality (hazard ratio (HR) 0.94 (95% CI 0.9 to 0.99); p=0.012) independent of age, sex, thrombosis history, cardiovascular risk factors, diagnosis year and PV fibrosis grade in a multivariable analysis at a median follow-up of 10 years (range 0 to 45). Longer time on HU was not associated with a significantly lower risk of all-cause mortality (HR 0.97 (95% CI 0.94 to 1.00); p=0.074).

**One included paper (n=470) reported a statistically significant lower risk of all-cause mortality with longer duration on rIFNα in patients with PV at a median follow-up of 10 years.**

### Overall survival

Abu-Zeinah et al 2021 (n=470) reported on overall survival (OS) in patients with PV for all patients, all patients by ELN risk, high-risk patients by treatment group[17] and low-risk patients by treatment group at a median follow-up was 10 years (range 0 to 45).

- Median OS for all patients was 26.3 years
- 20-year OS for all patients was 69%
- 20-year OS for low-risk patients (n=262) was 87% and for high-risk patients (n=208) was 34% (p<0.0001)

[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).

[17] The other cytoreductive drugs and combinations treatment group was excluded from the survival analyses by treatment. The authors reported that this was due to treatment heterogeneity disabling a clinically meaningful interpretation of results.

- 20-year OS for low-risk patients on rIFNα (n=71), HU (n=84) and PHL-O (n=77) was 100%, 85% and 80%, respectively (p=0.44)
- 20-year OS for high-risk patients on rIFNα (n=22), HU (n=105) and PHL-O (n=56) was 66%, 40% and 14%, respectively (p=0.016)

**One included paper (n=470) reported no statistically significant difference in 20-year OS for patients on rIFNα, HU and PHL-O with low-risk PV (100%, 85% and 80% respectively). For patients with high-risk PV, there was a statistically significant difference in 20-year OS between patients on rIFNα, HU and PHL-O (66%, 40% and 14% respectively).**

**Myelofibrosis-free survival**

Abu-Zeinah et al 2021 (n=470) reported on myelofibrosis-free survival (MFS)[18] in patients with PV for all patients, all patients by ELN risk, high-risk patients by treatment group[19] and low-risk patients by treatment group at a median follow-up was 10 years (range 0 to 45).

- Median MFS for all patients was 23.8 years
- 20-year MFS for all patients was 61%
- 20-year MFS for low-risk patients (n=262) was 66% and for high-risk patients (n=208) was 47% (p=0.021)
- 20-year MFS for low-risk patients on rIFNα (n=71), HU (n=84) and PHL-O (n=77) was 84%, 65% and 55%, respectively (p=0.0011)
- 20-year MFS for high-risk patients on rIFNα (n=22), HU (n=105) and PHL-O (n=56) was 89%, 41% and 36%, respectively (p=0.19)

**One included paper (n=470) reported a statistically significant difference in 20-year MFS for patients on rIFNα, HU and PHL-O with low-risk PV (84%, 65% and 55% respectively). For patients with high-risk PV there was no statistically significant difference in 20-year MFS between patients on rIFNα, HU and PHL-O (89%, 41% and 36% respectively).**

**Complication-free survival**

Mascarenhas et al 2022 (n=168; MPD-RC 112 RCT) reported on complication-free survival[20] 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. A statistically non-significant hazard ratio of 0.60 (95% CI 0.10 to 3.62) was reported, including two events in the Peg-IFNa-2a group and three events in the HU group. These included a bleeding event consisting 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 PV.

[18] MFS was determined from the date of PV diagnosis to the date of progression to post-polycythaemia vera myelofibrosis or censored at the date of death or last follow-up.
[19] The other cytoreductive drugs and combinations treatment group was excluded from the survival analyses by treatment. The authors reported that this was due to treatment heterogeneity disabling a clinically meaningful interpretation of results.
[20] Defined as free of major thrombotic event, major haemorrhagic complications, progression to myelofibrosis, progression to acute leukaemia or death.

**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 PV.**

**Post-polycythaemia vera myelofibrosis**

Abu-Zeinah et al 2021 (n=470) reported that in patients with PV, longer time on rIFNα was statistically significantly associated with a lower risk of post-polycythaemia vera myelofibrosis (HR 0.91 (95% CI 0.87 to 0.95); p<0.001) independent of age, sex, thrombosis history, cardiovascular risk factors, diagnosis year and PV fibrosis grade in a multivariable analysis at a median follow-up of 10 years (range 0 to 45). Longer time on HU was not associated with a significantly lower risk of post-polycythaemia vera myelofibrosis (HR 0.98 (95% CI 0.95 to 1.01); p=0.250).

**One included paper (n=470) reported a statistically significant lower risk of post-polycythaemia vera myelofibrosis with longer duration on rIFNα in patients with PV at a median follow-up of 10 years.**

**Acute myeloid leukaemia**

Abu-Zeinah et al 2021 (n=470) reported that transformation to acute myeloid leukaemia (AML) occurred in 18 (4%) patients at a rate of 0.34 per 100 patient-years in all patients with PV, and two (2%) patients on rIFNα, seven (4%) on HU and six (5%) on PHL-O. The authors reported that the number of events were too few to identify statistically significant group differences.

**One included paper (n=470) reported a transformation to AML rate of 0.34 per 100 patient-years in all patients with PV. Transformation to AML occurred in two (2%) patients on rIFNα, seven (4%) on HU and six (5%) on PHL-O.**

**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 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 PV.

**One included paper (n=115) reported a cumulative incidence of major vascular events at one year of 2% and at two years of 5% 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 PV.**

**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 two patients with PV developed lung adenocarcinoma and one patient with PV developed melanoma. 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 two patients with PV developed lung adenocarcinoma and one patient with PV developed melanoma.**

## 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 PV.[21] 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
- The most common AEs (all grade) in patients with PV were fatigue (40%), diarrhoea (40%), injection site reaction (34%), pain (30%), headache (26%), nausea (24%), pruritus (22%) and leukopaenia (22%)
- Grade 3+ AEs in patients with PV were lymphocytopaenia (6.0%), leukopaenia (4.0%), neutropaenia (4.0%), arthralgia (4.0%), headache (2.0%), pain (2.0%), rash (2.0%), dyspnoea (2%) and depression (2%)

**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 PV. 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 PV were fatigue (40%), diarrhoea (40%), injection site reaction (34%), pain (30%), headache (26%), nausea (24%), pruritus (22%) and leukopaenia (22%). Grade 3+ AEs in patients with PV were lymphocytopaenia (6.0%), leukopaenia (4.0%), neutropaenia (4.0%), arthralgia (4.0%), headache (2.0%), pain (2.0%), rash (2.0%), dyspnoea (2%) and depression (2%).**

[21] 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.

**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 PV 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 PV.

Abu-Zeinah et al 2021 reported that among 199 patients with PV on rIFNα at any time, 25 (13%) discontinued treatment due to toxicity over a follow-up of 1,137 patient-years (discontinuation rate of 2.2 per 100 patient-years). In the 285 patients treated with HU at any time, 46 (16%) discontinued treatment due to toxicity over 1,671 patient-years of follow-up (discontinuation rate of 2.8 per 100 patient-years). The most common toxicities leading to discontinuation of treatment were fatigue and malaise, arthralgia, peripheral neuropathy and myalgia in patients on rIFNα and skin ulceration, thrombocytopaenia and nausea and vomiting in patients on HU.

**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 PV in either paper. A third included paper reported that 25 (13%) patients with PV on rIFNα at any time discontinued treatment due to toxicity over a follow-up of 1,137 patient-years.**

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