Treating Anemic Patients With Myelofibrosis in the New Janus Kinase Inhibitor Era: Current Evidence and Real-world Implications

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Anemia is a prevalent and burdensome clinical manifestation of myelofibrosis (MF) with a complex etiology. Most MF patients are anemic within 1 year of diagnosis, and nearly all become dependent on red blood cell transfusions over time. Anemia is associated with a reduced health-related quality of life (HRQoL) and shortened survival. Moreover, anemia and transfusion dependence are independent negative prognostic indicators incorporated into standard clinical MF risk scoring systems. While specific subsets of patients with MF may derive temporary anemia benefit from androgens (eg, danazol), corticosteroids (eg, prednisone), immunomodulators (eg, pomalidomide), or erythropoiesis-stimulating agents, the vast majority of patients will not achieve a prolonged response. The Janus kinase inhibitor (JAKi) ruxolitinib has been a decade-long standard of care for patients with intermediate- and high-risk MF due to its efficacy in reducing spleen size and improving disease-related symptoms; however, ruxolitinib is myelosuppressive and associated with dose-dependent worsening of anemia. More recently, the JAKi fedratinib and pacritinib have each been approved for the treatment of MF, having demonstrated spleen size and symptom improvements compared with placebo or best available therapy. Like ruxolitinib, new-onset or worsening anemia is commonly reported with fedratinib treatment, whereas pacritinib is relatively nonmyelosuppressive. Notably, the investigational agent momelotinib is the first and only JAKi to also target the iron regulator activin A receptor type 1/activin receptor-like kinase-2 (ACVR1/ALK2), addressing the unmet need of anemia in MF patients in addition to the traditional treatment goals of JAK inhibition: reducing splenomegaly and symptom burden.

Due to the lack of comparative information among these expanding treatment options, a systematic literature review and network meta-analysis (NMA) of 7 randomized controlled trials of JAKi in patients with MF (noted in Table 1) by Sureau et al evaluated the relative efficacy and tolerability of treatments, including endpoints of reduced spleen volume and adverse events due to hematologic toxicity, among others. This NMA demonstrated that ruxolitinib, momelotinib, and pacritinib were comparably efficacious in reducing spleen volume (with ruxolitinib and momelotinib providing significant improvements in achieving ≥35% spleen volume reduction at 24 weeks compared with pacritinib), while momelotinib was associated with significantly less grade 3/4 anemia compared with ruxolitinib, fedratinib, or pacritinib. However, this analysis did not include real-world studies, examine anemia-related benefits among treatments (such as decreased transfusion need), or evaluate the differential impact of therapies on the HRQoL and economic burden associated with anemia and transfusions in MF.

To address this, we conducted an expanded targeted literature review within the MEDLINE, Embase, Cochrane, NHS Economic Evaluation, and Health Technology Assessment databases to identify articles published between January 2011 and February 2021 reporting treatment outcomes of phase 2 and phase 3 clinical trials and real-world studies in MF in the United States, United Kingdom, France, Germany, Italy, or Spain, with at least 25 patients per arm or cohort. Both approved (ie, ruxolitinib, fedratinib, pacritinib) and investigational (ie, momelotinib, as well as the telomerase inhibitor imetelstat and the transforming growth factor beta trap luspatercept) MF treatments were assessed. A total of 52 publications were identified, including 29 real-world studies and 23 records covering 16 clinical trials (Table 1). No published study of luspatercept met the inclusion criteria.

A detailed review of the 15 clinical trial publications that reported anemia- or transfusion-related outcomes in MF confirmed that momelotinib not only had the lowest grade 3/4 anemia rates among JAKi but also showed the greatest improvement in transfusion independence rates (Table 1). Specifically, reported rates of treatment-emergent grade 3/4 anemia ranged from 6% to 14% for momelotinib, 20% to 42% for ruxolitinib, 38% to 60% for fedratinib, 7% to 27% for pacritinib, and 30% for imetelstat. Overall, the proportion of transfusion-independent patients from baseline to week 24 or end of the treatment period decreased by 13% to 21% for ruxolitinib, decreased by 9% for fedratinib, remained stable with a 1% increase for...
### Table 1
Summary of the Impact of JAKi and Imetelstat on Transfusion Burden in Clinical and Real-world Studies of MF

| Treatment | Publication Source | Trial name/Data | Number of Patients | Measurement | Results | Impact on Transfusion Burden | Overall Change in %TI Patients From BL to W24 or End of Treatment |
|-----------|-------------------|-----------------|-------------------|-------------|----------|-----------------------------|---------------------------------------------------------------|
| **Phase 3 clinical trials** |                    |                 |                   |             |          |                             |                                                              |
| Ruxolitinib | Varstoske et al. N Engl J Med. 2012;366:799–807. | COMFORT-1*       | Ruxolitinib (n = 155) Placebo (n = 154) | Proportion of patients with grade 3 anemia during month 0–6 | 26.4% (ruxolitinib) 10.7% (placebo) | Proportion of patients who were TD at baseline who achieved TI during the study | 41.2% (ruxolitinib) vs 46.9% (placebo) P = NR |
| Harrison et al. N Engl J Med. 2012;366:787–798. | COMFORT-2*       | Ruxolitinib (n = 146) BAT (n = 73) | Exposure-adjusted rate (event per 100 patient-years) of grade 3/4 anemia | 5 (7.5) (BAT) | 21 (12.3) (ruxolitinib) | Proportion of patients who received ≥1 RBC transfusion during the treatment period | 51% (ruxolitinib) vs 38% (BAT) P = NR |
| Al-Ali et al. haematologica 2016;101:1065. | JUMP             | Ruxolitinib (n = 1144) | Proportion of patients with grade 3/4 anemia | 27% (ruxolitinib) 14% (placebo) | 33.0% | Proportion of patients who were TD at baseline who had reduced transfusion burden at W24 | +1.3% (ruxolitinib 400 mg) +1.4% (ruxolitinib 500 mg) |
| Fedratinib | Pardanani et al. JAMA Oncol. 2015;1:643–651. | JAKARTA-1*       | Fedratinib 400 mg daily (n = 96) Fedratinib 500 mg daily (n = 97) Placebo (n = 96) | Proportion of patients with grade 3/4 anemia | 43% (fedratinib 400 mg) 60% (fedratinib 500 mg) 25% (placebo) | Proportion of patients who were TD at baseline who achieved TI during follow-up | 92.3% (fedratinib 400 mg and 500 mg pooled) vs 50% (placebo) P = NR |
| Pacritinib | Mesa et al. Lancet Hematol. 2017;4:e225–e236. | PERSIST-1*       | Pacritinib 400 mg (n = 220) BAT excluding JAKI (n = 107) | Proportion of patients with grade 3/4 anemia through W24 | 17% (pacritinib 400 mg) 15% (BAT) | Proportion of patients who were TD at baseline who achieved TI during follow-up | 25% (pacritinib 400 mg) vs 0% (BAT) P = 0.043 |
| Mascarenhas et al. JAMA Oncol. 2018;4:652–659. | PERSIST-2*       | Pacritinib 400 mg once daily (n = 75) Pacritinib 200 mg twice daily (n = 74) | Proportion of patients with grade 3/4 anemia | 27% (pacritinib 400 mg) 22% (pacritinib 200 mg) 14% (placebo) | Proportion of patients who were TI during the study | +0.5% (pacritinib 200 mg) +6.6% (pacritinib 400 mg) 0% change (placebo) P = NR |
| Momeletinib | Mesa et al. J Clin Oncol. 2017;35:3844–3850. | SIMPLIFY-1*      | Momeletinib (n = 215) Ruxolitinib (n = 217) | Proportion of patients with grade 3/4 treatment-emergent anemia | 5.6% (momeletinib) 23.1% (ruxolitinib) | Proportion of patients who were TI at W24 | 66.5% (momeletinib) vs 49.3% (ruxolitinib) P < 0.001 |
| Harrison et al. Lancet Haematol. 2018;5:e73–e81. | SIMPLIFY-2*      | Momeletinib (n = 104) BAT (n = 52) | Proportion of patients with grade 3/4 treatment-emergent anemia | 13.5% (momeletinib) 13.5% (BAT) | Proportion of patients who were TI at W24 | 0% (momeletinib) vs 0.4% (ruxolitinib) P < 0.001 |
| **Phase 2 clinical trials** |                    |                 |                   |             |          |                             |                                                              |
| Ruxolitinib | Mead et al. Br J haematol. 2015;170:29–39. | ROBUST           | Ruxolitinib (n = 48) | Proportion of patients with grade 3/4 anemia | 20.8% | Proportion of patients who were TD at baseline achieved TI by the end of the study | 17% (1 out of 6 evaluable patients) P = NR |
| Talpaz et al. J Hematol Oncol. 2018;11:1–0. | NCT01445769      | Ruxolitinib (n = 45) | Proportion of patients with grade 3/4 treatment-emergent anemia | 20.0% | Proportion of patients who were TI | 66.7% (baseline) 53.3% (by the end of treatment phase) |
| Talpaz et al. J Hematol Oncol. 2013;6:1–0. | NCT01348490      | Ruxolitinib (n = 50) | Proportion of patients with grade 3/4 anemia | 42.2% | Proportion of patients who required RBC transfusion | 40.0% (12 W before baseline) 60.0% (during the treatment phase of the study) P = NR |

(Continued)
### Table 1 (Continued)

| Treatment | Publication | Trial name/Data Source | Number of Patients | Measurement | Results | Measurement | Results | Overall Change in %TI Patients From BL to W24 or End of Treatment |
|-----------|-------------|------------------------|--------------------|-------------|----------|-------------|----------|---------------------------------------------------------------|
| Ruxolitinib + lenalidomide | Daver et al. Haematologica. 2015;100:1058 | NCT01375140 | Ruxolitinib and lenalidomide (n = 31) | NR | NR | NR | NR |
| Fedratinib | Harrison et al. Am J Hematol. 2020;95:594–603. | JAKARTA-2 | Fedratinib 400 mg (n = 97) | Proportion of patients with grade 3/4 treatment-emergent anemia | 38% | Proportion of patients who had treatment-emergent TD | 8% | NR |
| Pacritinib | Gerds et al. Blood adv. 2020;4:5825–35. | PACIFICA | Pacritinib 100 mg QD (n = 52) Pacritinib 200 mg QD (n = 54) | Proportion of patients with grade 3/4 anemia | 9.6% (pacritinib 100 mg QD) 7.3% (pacritinib 100 mg BID) 20.4% (pacritinib 200 mg BID) | Proportion of patients with reduction in transfusion burden by 50% or greater | 17.9% (pacritinib 100 mg QD) 35.5% (pacritinib 100 mg BID) 14.7% (pacritinib 200 mg BID) | NR |
| Momelotinib | Oh et al. Blood adv. 2020;4:4282–91. | NCT02515630 | Momelotinib (n = 41) | Proportion of patients with grade 3 or above anemia | 12% | Proportion of patients achieved TI by W24 | 34% | +34% |
| Imetelstat | Tefferi et al. N Engl J Med. 2015 Sep 3;373:908–19. | NCT01731951 | Imetelstat (n = 33) | Proportion of patients with grade 3/4 treatment-emergent anemia | 30% | Proportion of patients who TD and who achieved TI | 31% (4/13) | NR |
| Real-world studies | | | | Proportion of patients with anemia (hemoglobin < 10 g/dL) at baseline | 43% (overall) 38% (patients with platelet count > 100 × 10^9/L) 52% (patients with platelet count 50–100 × 10^9/L) 68% (patients with platelet count 43% (PMF) 38% (PET/MF) 41% (PPV/MF) 26% (overall) 18% (patients with platelet count > 100 × 10^9/L) 38% (patients with platelet count 50–100 × 10^9/L) 62% (patients with platelet count < 50 × 10^9/L) | Proportion of patients with TD at baseline | 29% (PMF) 17% (PET/MF) 20% (PPV/MF) | NR |
| NR‡ | Masarova et al. Eur J haematol. 2018;100:257–63. | University of Texas MD Anderson Cancer Center | Overall (n = 1,269) Patients with platelet count > 100 × 10^9/L (n = 948) Patients with platelet count 50–100 × 10^9/L (n = 178) Patients with platelet count < 50 × 10^9/L (n = 145) | Proportion of patients with anemia (hemoglobin < 10 g/dL) at baseline | 43% (PMF) 38% (PET/MF) 41% (PPV/MF) | Proportion of patients with TD at baseline | 29% (PMF) 17% (PET/MF) 20% (PPV/MF) | NR |
| NR‡ | Masarova et al. Leuk Res. 2017;59:110–6. | University of Texas MD Anderson Cancer Center | PMF (n = 755) PET/MF/N (n = 163) PPV/MF (n = 181) PMF (n = 24) PET/MF (n = 4) PPV/MF (n = 7) | Proportion of patients with anemia (hemoglobin < 10 g/dL) at baseline | 43% (PMF) 38% (PET/MF) 41% (PPV/MF) | Proportion of patients with TD at baseline | 29% (PMF) 17% (PET/MF) 20% (PPV/MF) | NR |
| NR‡ | Naqvi et al. Leuk Lymphoma. 2017;58:866–71. | University of Texas MD Anderson Cancer Center | PMF (n = 24) PPV/MF (n = 4) PET/MF (n = 7) | Proportion of patients with anemia (hemoglobin < 10 g/dL) at baseline | NR | Proportion of patients with TD at baseline | NR | NR |
| All patients treated with ruxolitinib | Kuykendall et al. Ann hematology. 2018;97:435–41. | Lee Moffitt Cancer Center | 64 | Proportion of patients with anemia (hemoglobin < 10 g/dL) prior to ruxolitinib | 51% | Proportion of patients with anemia (hemoglobin < 10 g/dL) post ruxolitinib | 70% | NR |
| All patients treated with ruxolitinib | Kuykendall et al. Clin Lymphoma Myeloma Leuk. 2017;17:e45–53. | Lee Moffitt Cancer Center | 309 | Proportion of patients with anemia (hemoglobin < 10 g/dL) prior to ruxolitinib | 55% | Proportion of patients with anemia OR TD at baseline | 55% | NR |
| | Gerds et al. ASCO Ann meeting. 2020; e19539–e19539. | Chart review | 104 | | NR | Proportion of patients with anemia OR TD at baseline | NR | NR |
| Treatment | Publication | trial name/data source | Number of Patients | Measurement                                                                 | Results | Measurement                                                                 | Results | overall change in % перевода | Impact on Transfusion Burden |
|-----------|-------------|------------------------|--------------------|----------------------------------------------------------------------------|---------|----------------------------------------------------------------------------|---------|-----------------------------|-----------------------------|
| NR‡       | Vallapureddy et al. Blood Cancer J. 2019;9:1–8. | Mayo Clinic | 1,306              | Proportion of patients with moderate/severe anemia at first referral        | 54%     | Proportion of patients with TD at first referral                           | NR      |                             |                            |
| NR‡       | Szuber et al. Am J Hematol. 2018;93:1474–84 | Mayo Clinic | PMF, age ≤ 40 (n = 63) PMF, age 41–60 (n = 388) PMF, age >60 (n = 831) | Proportion of patients with anemia (hemoglobin < 10g/dL) at first referral | 47% (all PMF patients) 23% (PMF, age ≤ 40) 37% (PMF, age 41–60) 54% (PMF, age >60) | Proportion of patients with TD at first referral | 13% (PMF, age ≤ 40) 24% (PMF, age 41–60) 38% (PMF, age >60) | NR                           |                            |
| NR‡       | Pardanani et al. Am J Hematol. 2013;88:312–6. | Mayo Clinic | 203                | Proportion of patients with anemia (hemoglobin < 10g/dL) at first referral  | 59%     | Proportion of patients with TD at first referral                           | NR      |                             |                            |
| NR‡       | Tefferi et al. Mayo Clin Proc. 2012;vol. 87, No. 1, pp. 25–33 | Mayo Clinic | 1,000              | Proportion of patients with anemia (hemoglobin < 10g/dL) at first referral  | 54%     | Proportion of patients with TD at first referral                           | NR      |                             |                            |
| All patients treated with ruxolitinib | Mascarenhas et al. J Med Econ. 2020;23:721–7. | Optum, MarketScan, and SEER | 290 | Proportion of patients with anemia                                           | 36% (30 days after ruxolitinib initiation) 53% (60 days after ruxolitinib initiation) 60% (90 days after ruxolitinib initiation) 66% (180 days after ruxolitinib initiation) 53% (30 days after ruxolitinib discontinuation) 65% (60 days after ruxolitinib discontinuation) 69% (90 days after ruxolitinib discontinuation) 77% (180 days after ruxolitinib discontinuation) | NR      | Months from first MF diagnosis to TD, median (range): 2.9 (0.03, 33.80) (TD patients with iron chelation therapy) 4.3 (0.03, 60.23) (TD patients with iron chelation therapy) 13% (no therapy) 25% (first-line therapy) 32% (second-line therapy) 35% (third-line therapy) | NR |                            |
| NR‡       | Vekeman et al. Leuk Lymphoma. 2015;56:2803–11. | MarketScan and IMS PharMetrics | TD patients with iron chelation therapy (n = 103) TD patients with iron chelation therapy (n = 468) | Proportion of patients with anemia                                         | 86.4% (TD patients with iron chelation therapy) 77.4% (TD patients with iron chelation therapy) | Months from first MF diagnosis to TD, median (range): | 2.9 (0.03, 33.80) (TD patients with iron chelation therapy) 4.3 (0.03, 60.23) (TD patients with iron chelation therapy) 13% (no therapy) 25% (first-line therapy) 32% (second-line therapy) 35% (third-line therapy) | NR |                            |
| NR‡       | Yang et al. ASCO Ann meeting. 2016:e18556–e18556. | Markerscan | 1,658              | NR                                                                            | NR      | Proportion of patients with RBC transfusion by line of therapy            | NR      |                             |                            |
| All patients treated with ruxolitinib | Pemmaraju et al. ASCO Ann meeting. 2020:e19535–e19535. | Cardinal Health (chart review) | 26 | NR                                                                            | NR      | NR                                                                        | NR      |                             |                            |
| Treatment | Publication | Trial name/Data Source | Number of Patients | Measurement | Results | Impact on Transfusion Burden | Measurement | Results |
|-----------|-------------|------------------------|--------------------|-------------|---------|-------------------------------|-------------|---------|
| NR‡ | Gimenez et al. J Med Econ. 2014;17:435–41. | Three hospitals in Spain | 33 | NR | NR | Proportion of patients who needed transfusion | Among splenomegaly symptomatic patients: 33% (patients with constitutional symptoms and anemia) 0% (patients with constitutional symptoms without anemia) 21% (patients without constitutional symptoms with anemia) 0% (patients without constitutional symptoms and anemia) | | |
| | | | | | | Among splenomegaly asymptomatic patients: 16% (patients with constitutional symptoms and anemia) 2% (patients with constitutional symptoms without anemia) 32% (patients without constitutional symptoms with anemia) 0% (patients without constitutional symptoms and anemia) | | | |
| NR‡ | Pastor-Galan et al. Med Clin. 2020;155:152–8. | Spanish Registry of Myelofibrosis (GEM-MIE-2014-01) | 1,000 | Proportion of patients with anemia | 36% | NR | | | |
| NR‡ | Palandri et al. Hematol Oncol. 2020;38:372–80. | European Hematology centers | 589 | Proportion of patients with ruxolitinib induced anemia | 76% (any grade, any time) 67% (any grade, at month 3) 53% (any grade, at month 3) | NR | | | |
| NR‡ | Breccia et al. Ann Hematol. 2019;98:889–96. | European Hematology centers | 462 | Proportion of patients with ruxolitinib induced anemia | 93.3% | NR | | | |
| NR‡ | Palandri et al. Br J Haematol. 2018;183:35–46. | European Hematology centers | 291 | Proportion of patients developed anemia of any grade during ruxolitinib therapy | NR | NR | | | |
| NR‡ | Palandri et al. Oncotarget. 2017;8:79073. | European Hematology centers | 408 | Proportion of patients with anemia (hemoglobin <10g/dL) | 51.5% (at the start of ruxolitinib) 69.9% (at discontinuation of ruxolitinib) | NR | | | |
| NR‡ | Palandri et al. Cancer. 2020;126:1243–52. | European Hematology centers | 268 | Proportion of patients with anemia (hemoglobin <10g/dL) | 51.5% (at the start of ruxolitinib) 69.9% (at discontinuation of ruxolitinib) | NR | | | |

(Continued)
| Treatment | Publication | Trial name/Data Source | Number of Patients | Anemia Rate | Impact on Transfusion Burden | Overall Change in %TI Patients From BL to W24 or End of Treatment |
|-----------|-------------|------------------------|--------------------|-------------|-----------------------------|---------------------------------------------------------------|
| All patients treated with ruxolitinib | Palandri et al. *Hematol Oncol.* 2018 Feb;36:285–90. | European Hematology centers | 70 | Proportion of patients with ruxolitinib-induced anemia 45.7% | Proportion of patients requiring occasional transfusion support 21.4% | NR |
| All patients treated with ruxolitinib | Mazza et al. *Leuk Lymphoma.* 2017;58:138–44. | Six institutions from the Apulia region in the south of Italy | 65 | Proportion of patients with mild anemia during ruxolitinib treatment 5% | Proportion of patients who needed RBC transfusion 23% (before ruxolitinib) 37% (during ruxolitinib) 15% (after ruxolitinib) | NR |
| All patients treated with ruxolitinib | Breccia et al. *Ann Hematol.* 2018;98:1933–6. | Nine Italian hematological centers | 53 | Proportion of patients with grade 2 or above anemia during ruxolitinib treatment 45% | NR | NR |
| All patients treated with ruxolitinib | Breccia et al. *Ann Hematol.* 2017;96:387–91. | Nine Italian hematological centers | 98 | Proportion of patients experienced anemia of any grade 39.7% | NR | NR |
| All patients treated with ruxolitinib | Guglielmelli et al. *Ann J Hematol.* 2016;91:918–922. | Six Italian centers of the AGMM consortium | 490 | Proportion of patients with anemia stratified by fibrosis grade 28.0% (overall) 17.2% (grade 1 fibrosis) 29.1% (grade 2 fibrosis) 43.0% (grade 3 fibrosis) | NR | NR |
| All patients treated with ruxolitinib | Caocci et al. *Int J Hematol.* 2020;111:614–8. | One Italian medical center | 106 | NR | Median number of RBC units received 24 (TD patients with infection complication) 15 (TD patients without infection complication) | NR |
| All patients treated with ruxolitinib | Beauverd et al. *Br J Haematol.* 2016;175:37–42. | Guy’s and St Thomas’ NHS Foundation Trust (UK) | 43 | Proportion of patients with anemia (hemoglobin < 10g/dL) at referral 7.5% | Proportion of patients with TD at referral 7% | NR |
| All patients treated with ruxolitinib | Barraco et al. *Br J Haematol.* 2020;191:764–74. | The PASS (post-authorization safety study) study | 259 | Proportion of patients who developed anemia during follow-up 17.6% | Treatment-emergent anemia per 100 patient-years 3.8 | NR |

*Randomized controlled trial included in network meta-analysis by Sureau et al.† Only patients who completed at least 22 weeks of follow-up after randomization and before clinical hold were considered.‡ Treatment information was not extracted for real-world studies where patients used various types of treatment or where treatment use was not reported. BAT = best available therapy; BD = twice per day; BL = baseline; JAKi = Janus kinase inhibitor; MF = myelofibrosis; NR = not reported; PET = postessential thrombocythemia; PMF = primary myelofibrosis; PPV = postpolycythemia vera; QD = once per day; RBC = red blood cell; TD = transfusion dependent; TI = transfusion independent; UK = United Kingdom; W = week.
pacritinib, and ranged from a 2% decrease to a 12% increase for momelotinib. Notably, momelotinib-treated patients experienced a higher rate of transfusion independence at week 24 compared with those treated with ruxolitinib in the head-to-head phase 3 SIMPLIFY-1 trial (66.5% versus 49.3%, nominal \( P < 0.001 \)) and those treated with best available therapy (88.5% compared with 72% to 93.3% of patients were anemic and 7% to 62% were transfusion dependent. Reported rates of ruxolitinib treatment discontinuation due to anemia ranged from 8% to 36%, and rates of ruxolitinib discontinuation due to anemia ranged from 5% to 33%.

Additionally, we identified 5 real-world studies and 1 pooled clinical trial analysis that evaluated the association between anemia and overall survival in patients with MF, which include a range of treatments (Table 2). Among these, 5 of the 6 studies demonstrated an association between anemia and shortened overall survival (univariate hazard ratio range: 1.20–3.28; multivariate hazard ratio range: 1.27–1.92), and a similar trend was observed in the sixth study (Table 2), consistent with the known negative prognostic value of anemia in MF.

Although the substantial clinical burden associated with anemia and transfusion dependence has been well documented in patients with MF, our review sought to quantify the impact of anemia and transfusions on HRQoL and economic outcomes in this specific patient population. Overall, we found that data from adequately sized MF patient populations is lacking in these areas.
An investigation from the Nordic MPN Study Group found that transfusion-dependent patients with MF had significantly worse QoL scores than nontransfusion dependent patients; however, this study did not meet our review inclusion criteria for sample size per cohort, and it did not address economic implications. In patients with myelodysplastic syndromes, myeloid neoplasms with many features in common with MF including anemia, transfusion burden is associated with significant HRQoL and economic burden, with transfusion-dependent patients incurring 53% higher total costs over 2 years. Future investigation is needed to quantify the full HRQoL and economic impact attributable to anemia and transfusion dependence in MF to assess the true value of current treatments as well as emerging treatments that have the potential to address all key hallmarks of MF, including anemia, splenomegaly, and symptoms.

Consistent with findings from Sureau et al., our expanded targeted literature review corroborates the inadequacy of ruxolitinib in addressing the unmet need among anemic patients with MF in real-world clinical practice. Anemic MF patients receiving ruxolitinib may require dose reductions, treatment interruptions, or early treatment discontinuation, which can reduce treatment efficacy, or red blood cell transfusions throughout the course of therapy. Furthermore, nearly 50% of MF patients treated with ruxolitinib require add-on agents to treat anemia, such as androgens, corticosteroids, or erythropoiesis-stimulating agents. Despite the use of supportive measures, the median duration of ruxolitinib treatment in the real-world setting is shorter than in clinical trials. While the reasons for this short duration of treatment may be multifaceted, evidence suggests that adverse events (including anemia) and loss of treatment response are important contributing factors.

The emergence of treatment options that directly address anemia in addition to the other key hallmarks of MF may lead to improved patient outcomes. Momelotinib inhibition of ACVR1/ALK2 in addition to JAK1 and JAK2 leads to decreased hepcidin, the master regulator of iron metabolism that is elevated in MF patients, and subsequent increased serum iron availability for erythropoiesis. Momelotinib may be a valuable first- or second-line JAKi option for anemic patients with MF, as its ability to reduce rates of anemia and transfusion dependence in addition to spleen volume and symptoms has been demonstrated in phase 3 trials and further confirmed by Sureau et al. In addition, several combination therapies are in advanced clinical development that have demonstrated clinical activity against anemia and other key hallmarks of MF, including ruxolitinib plus luspatercept, an activin receptor IIB ligand trap/erythroid maturation agent, ruxolitinib plus palbocarb, a bromodomain and extra-terminal protein (BET) inhibitor, and ruxolitinib plus navitoclax, a antiapoptotic B-cell lymphoma protein (BCL-X, BCL-2, BCL-w) inhibitor. Studies to address the substantial evidence gap identified in our targeted literature review surrounding quantification of the HRQoL and economic burden of anemia and transfusions in MF to the substantial evidence gap identified in our targeted literature review surrounding quantification of the HRQoL and economic burden of anemia and transfusions in MF to

**AUTHOR CONTRIBUTIONS**

JS and BK designed the study. JS conducted the search. ATG, PB, GH, AK, LMN, JS, BK, and CH analyzed the data and interpreted the findings. LMN wrote and edited the manuscript with input from ATG, PB, GH, AK, JS, BK, and CH.

**DISCLOSURES**

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8. An investigation from the Nordic MPN Study Group found that transfusion-dependent patients with MF had significantly worse QoL scores than nontransfusion dependent patients; however, this study did not meet our review inclusion criteria for sample size per cohort, and it did not address economic implications. In patients with myelodysplastic syndromes, myeloid neoplasms with many features in common with MF including anemia, transfusion burden is associated with significant HRQoL and economic burden, with transfusion-dependent patients incurring 53% higher total costs over 2 years. Future investigation is needed to quantify the full HRQoL and economic impact attributable to anemia and transfusion dependence in MF to assess the true value of current treatments as well as emerging treatments that have the potential to address all key hallmarks of MF, including anemia, splenomegaly, and symptoms.

Consistent with findings from Sureau et al., our expanded targeted literature review corroborates the inadequacy of ruxolitinib in addressing the unmet need among anemic patients with MF in real-world clinical practice. Anemic MF patients receiving ruxolitinib may require dose reductions, treatment interruptions, or early treatment discontinuation, which can reduce treatment efficacy, or red blood cell transfusions throughout the course of therapy. Furthermore, nearly 50% of MF patients treated with ruxolitinib require add-on agents to treat anemia, such as androgens, corticosteroids, or erythropoiesis-stimulating agents. Despite the use of supportive measures, the median duration of ruxolitinib treatment in the real-world setting is shorter than in clinical trials. While the reasons for this short duration of treatment may be multifaceted, evidence suggests that adverse events (including anemia) and loss of treatment response are important contributing factors.

The emergence of treatment options that directly address anemia in addition to the other key hallmarks of MF may lead to improved patient outcomes. Momelotinib inhibition of ACVR1/ALK2 in addition to JAK1 and JAK2 leads to decreased hepcidin, the master regulator of iron metabolism that is elevated in MF patients, and subsequent increased serum iron availability for erythropoiesis. Momelotinib may be a valuable first- or second-line JAKi option for anemic patients with MF, as its ability to reduce rates of anemia and transfusion dependence in addition to spleen volume and symptoms has been demonstrated in phase 3 trials and further confirmed by Sureau et al. In addition, several combination therapies are in advanced clinical development that have demonstrated clinical activity against anemia and other key hallmarks of MF, including ruxolitinib plus luspatercept, an activin receptor IIB ligand trap/erythroid maturation agent, ruxolitinib plus palbocarb, a bromodomain and extra-terminal protein (BET) inhibitor, and ruxolitinib plus navitoclax, a antiapoptotic B-cell lymphoma protein (BCL-X, BCL-2, BCL-w) inhibitor. Studies to address the substantial evidence gap identified in our targeted literature review surrounding quantification of the HRQoL and economic burden of anemia and transfusions in MF will be imperative to assessing therapeutic value among the growing number of currently available and new agents entering the MF treatment landscape.

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**DATA AVAILABILITY STATEMENT**

All data generated or analyzed during this study are included in this published article.