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ORIGINAL ARTICLE

Which patients with myelofibrosis should receive ruxolitinib therapy? ELN-SIE evidence-based recommendations

M Marchetti[1], G Barosi[2], F Cervantes[3], G Birgegård[4], M Griesshammer[5], C Harrison[6], R Hehlmann[7], J-J Kiladjian[8], N Kröger[9], MF McMullin[10], F Passamonti[11], A Vannucchi[12] and T Barbui[13]

Ruxolitinib is an oral Janus-activated kinase 1 (JAK1)/JAK2 inhibitor approved for the treatment of patients with myelofibrosis based on the results of two randomized clinical trials. However, discordant indications were provided by regulatory agencies and scientific societies for selecting the most appropriate candidates to this drug. The European LeukemiaNet and the Italian Society of Hematology shared the aim of building evidence-based recommendations for the use of ruxolitinib according to the GRADE methodology. Eighteen patient-intervention-comparator-outcome profiles were listed, each of them comparing ruxolitinib to other therapies with the aim of improving one of the three clinical outcomes: (a) splenomegaly, (b) disease-related symptoms, and (c) survival. Ruxolitinib was strongly recommended for improving symptomatic or severe (>15 cm below the costal margin) splenomegaly in patients with an International Prognostic Scoring System (IPSS)/dynamic IPSS risk intermediate 2 or high. Ruxolitinib was also strongly recommended for improving systemic symptoms in patients with an MPN10 score >44, refractory severe itching, unintended weight loss not attributable to other causes or unexplained fever. Because of weak evidence, the panel does not recommend ruxolitinib therapy for improving survival. Also, the recommendations given above do not necessarily apply to patients who are candidates for allogeneic stem cell transplant.

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INTRODUCTION

In the past 20 years, the outcomes of blood cancers in Europe have significantly improved[1] proportionally to the number of newly approved agents.[2,3] In 2012, two randomized phase 3 clinical trials reported outcomes for myelofibrosis (MF) patients treated with ruxolitinib, a Janus-activated kinase 1/2 inhibitor.[4,5] Ruxolitinib therapy was associated with reduction in splenomegaly and improvement of MF-related symptoms, and on this basis, it was rapidly approved in the United States and European Union. Three years later, however, the Cochrane Collaboration cast doubts on the real efficacy of this drug as a systematic literature review based on a limited follow-up concluded that ruxolitinib did not demonstrate sufficient efficacy for the two principal outcomes.[6] Availability of ruxolitinib in clinical practice prompted the British Society of Haematology,[7] the European Society of Medical Oncology[8] and the Australian Hematology Association[9] to elaborate recommendations on its use, although they were not based on an explicit GRADE approach.[10] As a matter of fact, differences between marketing authorization for ruxolitinib and patient selection criteria for the COMFORT trials were reckoned as relevant hurdles by the National Institute for Clinical Excellence, which finally approved ruxolitinib in 2016 but within strict evidence-based stonemarks.[11] In August 2015, the Italian Society of Haematology (SIE) and the European LeukemiaNet (ELN) shared the common effort of providing clinicians with strictly evidence-based recommendations for the selection of MF patients suitable for ruxolitinib therapy. This paper reports the process for elaborating such statements according to the GRADE methodology and the final recommendations of the expert panel.

MATERIALS AND METHODS

A multi-country panel of 12 senior ELN members with expertise in MF management was convened. A hematologist with expertise in the development of clinical practice guideline led the group through the following steps, according to the GRADE methodology:[10]

1. Listing the three most relevant efficacy outcomes and the two most relevant risk outcomes
   a Efficacy outcomes: the panel chose splenomegaly, disease-related symptoms and overall survival
   b Risk outcomes: the panel chose bleeding and infection
2. Listing therapies to be compared with ruxolitinib for the achievement of each specific clinical outcome
   a Comparator therapies were hydroxycarbamide (HU) and interferon (IFN)
   b Prednisone was also considered a comparator therapy for the outcome 'disease-related symptoms'
3. Formulating an agreed definition for ambiguous terms
   a 'symptomatic' splenomegaly
   b 'severe' splenomegaly
   c 'relevant' disease-related symptoms

[1]Ospedale Cardinal Massaia, Asti, Italy; [2]IRCCS Policlinico San Matteo Foundation, Pavia, Italy; [3]Hospital Clinic, IDIBAPS, Barcelona, Spain; [4]Uppsala University Hospital, Uppsala, Sweden; [5]Johannes Wesling Klinikum Minden, Minden, Germany; [6]Guy's and St Thomas' NHS Foundation, London, UK; [7]Medizinische Fakultät Mannheim, Universität Heidelberg, Mannheim, Germany; [8]Centre d'Investigations Cliniques - CIC 1427, Paris, France; [9]University Hospital Hamburg-Eppendorf, Hamburg, Germany; [10]Queen's University Belfast, Belfast, UK; [11]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [12]Ospedale di Circolo e Fondazione Macchi, Varese, Italy and [13]Research Foundation, Ospedale Papa Giovanni XXIII, Bergamo, Italy. Correspondence: Dr M Monia, Ematologia DH, SOC Oncologia, Ospedale Cardinal Massaia, Corso Dante 202, Asti 14100, Italy.
E-mail: moniamarchettitamellini@gmail.com
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4. Listing patient-intervention-comparator-outcome (PICO) vignettes (Table 1)
5. Critical appraisal of available evidence for each of the PICOs
   a Available evidence was retrieved from the following sources: PubMed, ASH proceedings from 2013 ahead and EHA proceedings from 2013 ahead
   b Evidence was appraised according to the following hierarchy:
      i Comparative studies with appropriate directness, that is, control arm corresponding to the comparator treatment of the PICO
      ii Comparative studies without appropriate directness, that is, control arm does not correspond to the comparator treatment of the PICO
      iii Non-comparative studies
6. Assessing the net benefit of ruxolitinib versus the comparator treatment in each PICOs
7. Assessing the quality of evidence according to GRADE, namely, based on:
   a The study design (see hierarchy above)
   b The study directness, namely, the degree of similarity between the study and PICO population, intervention and outcome
8. Scoring 1 to 9 the preference of each panelist for ruxolitinib versus the comparator therapy within each PICO
9. Formulating final recommendations
10. Assessing the strength of approved recommendations, according to GRADE, namely, based on the following criteria:
   a Quality of evidence
   b Benefit-to-risk balance
   c Overall uncertainty

A Delphi panel method[12] was used for the steps 1, 2, 3 and 8. Final approval of definitions and recommendations was achieved informally during three meetings held in Orlando in December 2015, in Mannheim in February 2016 and in Milan in March 2016.

RESULTS

Splenomegaly

Summary of evidence. The body of evidence supporting PICOs 1–6 mainly consisted of the COMFORT II trial, randomizing intermediate-2- and high-risk MF patients to ruxolitinib or best-available therapy (BAT).[4] The clinical outcomes of patients assigned to BAT and receiving active treatments (mostly HU) was considered a proxy for the clinical outcomes of HU-treated control patients. The COMFORT II trial reported that in patients assigned to ruxolitinib spleen volume decreased, on average, by 29% in a median of 12 weeks.[4,13] The probability of maintaining a −35% reduction in spleen volume was 48% at 5 years, that is, a median time of response of 3.2 years.[13] Rather, palpable spleen size decreased for a few months and by no more than 10 cm in a small portion of actively treated patients assigned to BAT: in these patients spleen volume increased by 5% in a year.[14] The efficacy of ruxolitinib onto spleen size was also supported by the randomized trial COMFORT I,[5] the prospective study ROBUST[15] and the large phase IIIb study JUMP.[16] A definite dose–response was reported.

Owing to the scarce number of IFN-treated patients enrolled into the COMFORT-II control arm, evidence from phase II and retrospective studies was sought. One hundred and twenty-six patients reported by eight mainly retrospective studies were recently reviewed.[17] Spleen response rates reported by the largest studies ranged from 30% to 53%, and median time to response was >6 months.[17–20]

Finally, we scanned evidence for patients with intermediate-1-risk disease who were excluded from enrollment into the COMFORT trials: phase II[15] and phase IIIb[16] studies reported a similar efficacy of ruxolitinib onto splenomegaly in this subpopulation than in patients with intermediate-2- or high-risk disease.

Quality of evidence. The overall quality of evidence supporting the net benefit of ruxolitinib in PICOs 1–6 was judged to be high in principle, owing to the randomized design of the COMFORT II trial, but it was necessarily reduced to low or very low owing to unblindness and serious indirectness of the study. Serious indirectness was caused by a limited portion (47%) of the control arm patients being treated with HU (the comparator therapy in PICOs 1 and 2) and by a very small portion of cytoreduction-naive patients (population of PICOs 1–4). The quality of evidence supporting PICOs 2–6 was limited by the very few patients receiving IFN in the BAT arm of the COMFORT II trial and by the scarcity of evidence supporting IFN efficacy in prospective or comparative studies. Indirectness was also supported by the lack of information regarding spleen size kinetics before enrollment (population of PICOs 2, 4 and 6) and of subanalyses for patients with symptomatic splenomegaly at enrollment (population of PICOs 1, 3 and 5). The quality of evidence was increased by a clear

Table 1. List of PICOs

PICO	*Patient*	*Outcome*	*Comparator*	*Quality of evidence*
1	Cytoreduction-naive symptomatic splenomegaly	Splenomegaly	Hydroxyurea	Moderate
3	Cytoreduction-naive asymptomatic progressive splenomegaly	Splenomegaly	Hydroxyurea	Low
2	Cytoreduction-naive symptomatic splenomegaly	Splenomegaly	Interferon	Very low
4	Cytoreduction-naive asymptomatic progressive splenomegaly	Splenomegaly	Interferon	—
5	HU-refractory/intolerant symptomatic splenomegaly	Splenomegaly	Interferon	Low
6	HU-refractory/intolerant asymptomatic progressive splenomegaly	Splenomegaly	Interferon	Very low
7	Naive patients	Disease-associated symptoms	Prednisone	Very low
8	Refractory to prednisone	Disease-associated symptoms	Hydroxyurea	Low
9	Refractory to prednisone	Disease-associated symptoms	Interferon	Very low
10	High risk	Survival	Hydroxyurea	Very low
11	INT2 risk	Survival	Hydroxyurea	Very low
12	INT1 risk	Survival	Hydroxyurea	—
13	High risk	Survival	Interferon	—
14	INT2 risk	Survival	Interferon	—
15	INT1 risk	Survival	Interferon	—
16	High risk—HU-refractory	Survival	Interferon	Very low
17	INT2 risk—HU-refractory	Survival	Interferon	Very low
18	INT1 risk—HU-refractory	Survival	Interferon	—

Abbreviations: HU, hydroxycarbamide; INT, intermediate; PICO, Patient Intervention Comparator Outcome. INT1 and INT2 according to the IPSS and DIPSS scoring systems.[44,45]

demonstration of a dose–response relationship between ruxolitinib dose and spleen volume reduction.

Finally, the quality of evidence of ruxolitinib as compared with HU for patients with intermediate-1-risk disease was judged to be very low owing to the non-randomized design of the studies supporting the safety and efficacy of ruxolitinib in this setting.

Panel discussion. The panel agreed that patients with symptomatic and/or severe splenomegaly not responding to prior treatment should receive ruxolitinib, based on the rapid and durable reduction of spleen size reported by the COMFORT trials.[4,5,13] The panel deemed that cytoreduction-naive patients with symptomatic or severe splenomegaly, who also need a rapid and sustained spleen reduction, were expected to get from ruxolitinib a similar incremental benefit as pretreated patients.

Despite the lack of comparative evidence, the panel also recommended ruxolitinib in a limited subset of patients with intermediate-1-risk disease whose quality of life is severely impaired by huge symptomatic spleens or splenomegaly-related symptoms not responsive to prior therapies.

Finally, the panel did not provide any operative definition for 'progressive splenomegaly'; however, it deemed that treatments aimed at preventing severe or symptomatic splenomegaly might be effectively implemented in patients with progressive increase of spleen size, although no evidence from clinical trials supports a specific treatment pathway.

Recommendations. Although evidence suggests that ruxolitinib is effective in reducing splenomegaly in any patient risk category, the benefit/risk profile of the drug favors its use for improving splenomegaly in selected patients.

Ruxolitinib is recommended for improving splenomegaly in:

- Patients with intermediate-2- or high-risk disease and either symptomatic or severe splenomegaly (strong recommendation)
- Patients with intermediate-1-risk disease and either symptomatic or severe splenomegaly not responsive or intolerant to HU or IFN (weak recommendation)
- Patients with intermediate-1-risk disease and both symptomatic and severe splenomegaly not previously treated with any cytoreductive agent (weak recommendation)

'Severe' splenomegaly refers to splenomegaly palpable 15 cm below the costal margin.

'Symptomatic' splenomegaly refers to the concurrent presence of a splenomegaly and local symptoms not attributable to other causes, such as pain in the left upper quadrant of the abdomen or impairment of food intake owing to early satiety.

Disease-related symptoms

Summary of evidence. Only one study provided direct evidence of ruxolitinib relative efficacy in improving disease-related symptoms as compared with other therapies in patients with intermediate-2- or high-risk disease: COMFORT II trial reported a similar mean improvement of EORTC Q-C30 score at week 24 in patients assigned to ruxolitinib or BAT, provided that the latter were receiving an active treatment.[14] Moreover, no dose–response relationship was proved by any comparative or non-comparative study. Nevertheless, a rapid, relevant and sustained improvement of fatigue, appetite loss and itching was consistently reported with ruxolitinib treatment by the COMFORT I and ROBUST trials.[5,15] Appetite and dyspnea, on the contrary, significantly worsened in BAT-treated patients.[14] Despite the universal use of EORTC Q-C30, the questionnaire is not disease specific and includes 30 items, therefore it cannot be feasible outside a clinical trial setting. Rather, MPN10 (Table 2) is a brief disease-specific tool applied longitudinally in the COMFORT-I trial and validated in several languages, showing a good feasibility. Moreover, MPN10 score should be recorded in order to assess response according to IWG-MRT criteria. Despite no 'clinically meaningful' threshold score for MPN10 has been validated, one-third of MF patients enrolled in a cross-sectional study reported a MPN10 score >44, which can be considered a good cutoff for selecting patients with 'relevant' disease-related symptoms, in that it corresponds to the mean value plus one s.d.[21]

No study longitudinally assessed quality of life in patients receiving IFN or prednisone.

Patients with intermediate-1-risk disease enrolled into the ROBUST phase II trial achieved similar symptom improvement during ruxolitinib therapy than intermediate-2- and high-risk patients.[15]

Quality of evidence. The overall quality of evidence was judged to be low. Despite the randomized design of the COMFORT II trial, several limitations hamper its quality in supporting PICOs 7–9: limited size, unblindness, high rate of missing data, and indirectness add up with lack of a clear-cut improvement in quality of life of patients assigned to ruxolitinib as compared with those assigned to active BAT. However, the consistency of the data reported by COMFORT II and other studies, namely, COMFORT I and ROBUST, supports a potentially relevant effect of ruxolitinib in the patients' quality of life.

Panel discussion. The panel deemed that a systematic and quantitative assessment of MF-associated symptoms with MPN10 was feasible and necessary prior to treatment decisions. The panel also considered the structured summary of evidence and the poor quality of the evidence supporting a benefit of ruxolitinib as compared with BAT, mainly HU. However, the rapid and sustained action of ruxolitinib upon itching, appetite and fatigue was considered to be sufficient to strongly recommend it

Table 2. MPN10 questionnaire

Symptom	*1 to 10 ranking (0 if absent; 1 most favorable; 10 least favorable)*
Early satiety	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Problems with concentration	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Itching	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Bone pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Fever	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Unintentional weight loss past 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)

Adapted from Scherber *et al*.[46]

in patients carrying a high burden of symptoms, that is to say, with a MPN10 score >44. The panel also deemed that ruxolitinib could be recommended for controlling some specific severe symptoms, such as itching, relevant weight loss or fever, irrespectively of the overall MPN10 score. The recommendation was judged to be valid also in patients with intermediate-1-risk disease, while no exclusion criterion for low-risk patients was required, as disease-related symptoms are very rare in this setting and would often mean that patient risk category is increasing.

Recommendations. Accurate assessment by the tools such as MPN10 should be performed before any clinical decision regarding the use of ruxolitinib for improving disease-associated symptoms.

Ruxolitinib is recommended for improving disease-related symptoms in patients with a MPN10 score >44 or refractory severe itching (score >6) or unintended weight loss ($>10\%$ in the past 6 months) not attributable to other causes or unexplained fever (strong recommendation).

Survival

Summary of evidence. Search for evidence supporting PICOs 10–18 could retrieve only one study comparing the survival of ruxolitinib-treated patients with the survival of patients assigned to other active treatments. The COMFORT II trial reported a significant and relevant increase of 5-year survival from 44% (BAT) to 56% (ruxolitinib), despite crossover, in patients with intermediate-2- or high-risk disease. Spleen response predicted a major improvement of survival.[22] A survival benefit in favor of ruxolitinib versus other therapies, consisting mainly of HU, was also reported by two case–control studies.[23,24]

No evidence compared the overall survival of ruxolitinib-treated with IFN-treated patients.

No study longitudinally compared the overall survival of intermediate-1 patients receiving ruxolitinib rather than other treatments.

Quality of evidence. The quality of evidence for PICOs 10 and 11 was judged to be very low despite the randomized design of the COMFORT II trial, owing to the limited size and lack of blindness of the study but even more owing to the severe indirectness provided by the low portion of actively treated patients in the BAT arm. No comparative evidence supporting a survival prolongation with ruxolitinib as compared with HU was available for patients with intermediate-1 disease (PICO 12). Similarly, no evidence supported a longer survival in patients treated with ruxolitinib versus IFN (PICOs 13–18).

Panel discussion. The panel judges that the universal prescription of a drug should be based on solid evidence supporting amelioration of one of the most relevant end point, which is survival. The panel therefore deemed that the quality of available evidence for a survival benefit of ruxolitinib versus HU or IFN was not sufficient to support a recommendation.

Recommendations. The evidence supports a survival benefit associated with ruxolitinib but its quality according to GRADE was judged to be very low. Therefore, ruxolitinib should not be recommended uniquely for improving survival (weak recommendation).

Safety: bleeding and infection

Comparative safety of ruxolitinib and HU or IFN was available in the COMFORT II trial: 35 out of the 146 (24%) patients assigned to ruxolitinib discontinued the therapy owing to adverse events, as compared with only 4 out of the 73 (5%) patients assigned to BAT.[13] Safety outcomes were not judged to counterbalance the expected ruxolitinib benefit; however, the panel deemed that the reported safety could be reproduced in the clinical practice only if a proactive prevention of bleeding and infection was implemented.

Bleeding. Direct evidence of the relative safety of ruxolitinib versus HU was derived only from the COMFORT II trial: treatment interruptions owing to adverse events were more frequent in patients assigned to ruxolitinib (8% versus 3%) as well as grades 3–4 thrombocythopenia (15% versus 5%) and overall bleeding events (odds ratio 2.2; 95% confidence interval 1.3–2.7).[4,13] Thanks to ruxolitinib dose adjustment according to baseline and follow-up platelet count, severe bleeding was rarely reported (2–3%) either in the COMFORT trials or in the JUMP study, enrolling almost only patients with baseline platelet count $>100\times10^9$/l.[4,5,13,16] Severe hemorrhages were also rare ($<3\%$) in studies specifically enrolling patients with baseline platelet counts $50–100\times10^9$/l: 5–10 mg BID ruxolitinib were administered.[25–27]

The reported risk of bleeding related to ruxolitinib-induced thrombocytopenia prompted the panel to list the principal bleeding risk factors: Table 3 lists such factors and the panel recommends a systematic assessment of these items before assigning any patient to ruxolitinib therapy. Moreover, the panel suggests periodical reassessment of these factors in treated patients. Physicians are advised to ensure patient awareness of his/her bleeding risk during the treatment. The panel did not provide any further suggestion on starting and continuation dose, which should be titrated based on platelet count, as reported by the product information.

Infection. The panel listed the most relevant issues to be considered in assessing infection risk (Table 4) and deemed that ruxolitinib could not be contraindicated in any specific subset of high-infective risk patients but that caution, specific monitoring or prophylactic measures are recommended in patients with at least one risk factor. Screening for hepatitis viruses was deemed mandatory in order to implement monitoring and/or prevention measures for potentially fatal reactivations. Specific antiviral or antimycobacterial preventive measures have been proposed.[9,28–29] The panel recommends the infection risk to be systematically assessed before administering ruxolitinib and caution in the prescription for patients carrying infection risk

Table 3. Risk factors for bleeding

Host	*History*	*Disease*	*Ongoing therapy*
Old age	Prior stroke	Low platelet count ($<100\times10^9$/l)	Antiplatelet therapy
Poor functional status	Prior bleeding events	High platelet count ($>1000\times10^9$/l)	Anticoagulant therapy
Severe comorbidity		Anemia	
Active solid cancer			
Hemorrhagic signs or symptoms			

Table 4. Risk factors for infection

History	*Ongoing therapy*	*Screening tests*
Mycobacteria infection Recurrent or severe infections Herpes (HSV, HZV) infections Opportunistic or parasite infections Known HCV, HBV or HIV infection	Immunosuppressive therapy	HBV serology HCV serology

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; HZV, herpes zoster virus.

factors (Table 4). Prophylaxis for patients at high risk of viral or mycobacterial infections should be considered on a case to case basis. Moreover, physicians are advised to pursue patient awareness of his/her infective risk during the treatment.

Special subpopulations

Owing to an overall lack of direct evidence of safety and efficacy, no evidence-based recommendations could be elaborated for the following specific subsets of patients.

Splanchnic vein thrombosis and/or portal hypertension. MF patients with a history of splanchnic vein thrombosis often have splenomegaly and also have a risk of portal hypertension with risk of variceal bleeding. They were identified as a special subpopulation. The panel elaborated safety recommendations based on eligibility criteria of a small phase II trial enrolling 21 patients with myeloproliferative neoplasms (including 12 MF) actively treated with anticoagulants or antiplatelet drugs and both showing a platelet count 100×10^9/l at baseline and esophageal varices of grade $\leqslant 2$.[30] Ruxolitinib was administered at reduced doses for patients with a baseline platelet count $< 200 \times 10^9$/l: 10 mg BID for polycythemia vera, 15 mg BID for MF, and 25 mg BID for essential thrombocythemia. Despite the occurrence of grades 3–4 thrombocytopenia in 14.3% of the patients, accurate dose reductions limited bleeding events and only one episode of grade 2 upper gastrointestinal bleeding occurred during the study period. However, the reported background rate of major hemorrhage in this setting is quite low, that is, 3.6/100 patient-years.[31,32] However, owing to the large unmet needs of this patient subpopulation, the panel deemed not to recommend against ruxolitinib in this setting but to use ruxolitinib with caution and to carefully titrate the dose with careful monitoring and management of portal hypertension. If ruxolitinib is used in these patients, patient awareness of bleeding risk is required.

Hepatomegaly. Some splenectomized patients have been reported as achieving a reduction of hepatomegaly during ruxolitinib treatment.[33,34] The panel could not provide specific recommendations in favor or against the use of ruxolitinib in this subset of patients. However, the panel agreed that ruxolitinib can be considered in this clinical situation.

Comorbidities and limited lifespan. The use of ruxolitinib was also questioned in patients with severe comorbidities, which are expected to limit lifespan by themselves. Only a few patients aged >80 years were enrolled into randomized COMFORT trials and the JUMP studies.[4,5,16] Moreover, only 13% and 8% of patients assigned to ruxolitinib and BAT, respectively, showed a performance score ECOG $\geqslant 2$.[4] Comorbidities were not systematically reported by the COMFORT and the JUMP studies, but half of MF patients have a significant comorbidity burden in routine care.[35] No evidence of a clear benefit-to-risk ratio of ruxolitinib as compared with other available treatments has been reported in patients with limited lifespan or severe comorbidities. Therefore, the panel recommended avoidance of this drug in such patients, until favorable evidence is available.

Low-risk disease. The panel could not formulate any specific recommendation for the use of ruxolitinib in patients with low-risk disease owing to insufficient evidence.

DISCUSSION

Ruxolitinib represents a novel therapeutic opportunity for patients with MF. However, conflicting indications to its use in the clinical practice have been provided, some being based on disease risk and others on symptoms.[7–9,36,37] In comparison with other published statements, the ELN-SIE panel chose to adopt the GRADE methodology to formulate evidence-based recommendation for an appropriate use of ruxolitinib. Evidence was retrieved and appraised for 18 PICOs (Table 1) and the panel subsequently formulated recommendations based on the benefit-to-risk profile of ruxolitinib, as compared with other available treatments. Six evidence-based recommendations were therefore formulated suggesting to use ruxolitinib for improving symptomatic or severe splenomegaly in patients with intermediate- or high-risk disease not responsive to cytoreductive agents. Ruxolitinib was also strongly recommended in patients with relevant disease-associated symptoms, provided that symptoms were adequately quantified and classified. Therefore, a strong suggestion to ruxolitinib use was formulated only for patients scoring >44 points by the MPN10 or suffering severe itching not responsive to standard therapy or with either unexplained fever or unintended weight loss. Owing to the urgent need for treatment, despite the scarce evidence, ruxolitinib was also recommended upfront for those patients with intermediate-1-risk disease suffering from both symptomatic and severe splenomegaly. The panel, however, chose not to recommend ruxolitinib uniquely aimed at survival prolongation as no study has been designed and powered sufficiently to provide definite evidence. This finally suggests to target therapeutic decisions on symptoms and splenomegaly and not on survival. Such recommendations, however, also need to be timely revised according to newly coming evidence.

ELN-SIE recommendations differ from those provided by the British Committee for Standards in Hematology[7] and by ESMO.[8] Both suggested ruxolitinib for patients with symptomatic splenomegaly or constitutional symptoms but did not provide the physician with a detailed support for interpreting the intensity and specificity of symptoms. ELN-SIE also struggled with using a solid methodology for evidence appraisal. The whole decision process was tracked and summarized in the paper in order to get the best transparency and to provide the best evidence-to-recommendation adherence.

Despite the rigid GRADE methodology imposes a comparison between intervention and comparator treatments, the huge and rapid improvement of symptoms reported during ruxolitinib treatment led the panel to provide recommendations despite the scarce availability or poor quality of comparative evidence.

Rather, a strict comparison-based high-quality evidence was requested by the panel for considering ruxolitinib with the unique aim of improving survival. Therefore, the major result of this project was a definite distinction between the enrollment criteria of the registration trials and the decisional criteria for ruxolitinib prescription in clinical practice. Moreover, systematic and stringent definitions of 'relevant' symptoms or splenomegaly were provided, favoring a homogenous and non-subjective assignment of the most suitable patients to ruxolitinib.

Some issues were not addressed, however, by the present project, such as the rules for treatment discontinuation. IWG-MRT and ELN classified as 'responsive' those patients achieving a 50% reduction of disease-related symptoms as assessed with MPN10 or a 50% reduction of spleen size from left costal margin.[38] A list of practical issues are faced in assessing the clinical response to ruxolitinib, such as appropriate timing of response assessment in patients receiving full dose or suboptimal doses.[39] The panel chose not to provide specific recommendations on the modality and timing of response assessment or drug tapering before interruption. However, this was considered to be a relevant issue. Furthermore, we did not include recommendations for ruxolitinib in patients who are candidates for allogeneic stem cell transplantation, as an EBMT/ELN consensus conference recently provided specific indications on transplantation and peri-transplant therapies.[40] To be definitive on the role of ruxolitinib as bridge to transplant, we decided to wait for results from ongoing prospective trials. However, we have to mention that the vast majority of patients with indications to allogeneic stem cell transplantation are on ruxolitinib treatment. Nor does this paper address combination therapies including ruxolitinib as only preliminary data are available from phase 1/2 studies. Finally, decision models estimated that ruxolitinib might reduce disease-related costs in responders, but the overall value-for-cost of the drugs has not been completely ascertained yet. Therefore, the present recommendations did not consider cost among the relevant GRADE outcomes. However, the panel deemed that an appropriate clinical use of ruxolitinib should assure a favorable value-for-cost.[41–43]

CONFLICT OF INTEREST

Dr Barosi participated in speakers' bureau for Novartis. Dr Kiladjian's research was funded by Novartis and AOP Orphan; he also participated in speakers' bureau for Novartis and AOP Orphan. Dr Passamonti participated in speakers' bureau for Novartis. Dr Griesshammer received travel reimbursement from Novartis and Shire, participated in speakers' bureaus for Baxalta, AOP Orphan, Novartis and Shire and received honoraria from Baxalta, AOP Orphan, Novartis and Shire. Dr Vannucchi participated in advisory boards and speakers' bureaus for Novartis. Dr Kröeger received honorarium and research funding from Novartis. Dr McMullin received speaker fee from Novartis and Shire. Dr Harrison received research support from Novartis and honoraria from Baxalta, Novartis, Sanofi and Shire; she joined speakers' bureaus for Baxalta, Incyte, CTI, Novartis, Sanofi and Shire. Dr Barbui received research grants and speaker fees from Novartis. Dr Marchetti's research was funded by Janssen, Shire and Celgene; she received travel reimbursements from Janssen, Baxalta, Celgene and Shire and consultant or speaker fees from Gilead and Celgene. Dr Cervantes was a member of advisory boards for Novartis, Baxalta and AOP; he also joined speakers' bureaus for Novartis, Baxalta and AOP. Dr Birgegård received research funding and speaker fees from Shire.

AUTHOR CONTRIBUTIONS

BT and MM conceived the project. All the authors contributed to the discussion on the PICOs and approved final recommendations. MM conducted the critical appraisal of the literature, tracked the feedbacks from the panelists and drafted the paper. All the authors revised the manuscript and approved the final version.

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