ASH Draft Recommendations for Guidelines on Myelofibrosis

INTRODUCTION

American Society of Hematology (ASH) guidelines are based on a systematic review of available evidence. Through a structured process, a guideline panel makes judgements about the evidence and forms recommendations.

The public comment period occurs after recommendations are formed but before a manuscript report of the guidelines has been finalized and before ASH organizational approval of the guidelines. Comments collected during the open comment period are provided to the guideline panel for review prior to finalizing the guidelines.

These draft recommendations are not final and therefore are not intended for use or citation.

To submit comments on the draft recommendations, **please email guidelines@hematology.org.** Only comments submitted via email will be reviewed by the guideline panel.

Evidence Profiles and Evidence to Decision Frameworks are available via links below. If you are unable to access these links, please email Rachel Cohen at rcohen@hematology.org.

The public comment period for these draft recommendations is open until **November 24th, 2025**.

RECOMMENDATIONS

RISK ASSESSMENT

- **Question 1:** *Should extended molecular genetic testing (e.g. Next Generation Sequencing) or limited molecular genetic testing (JAK2/CALR/MPL) be used for all patients with Myelofibrosis?*
  - **Recommendation 1**: In all patients with myelofibrosis, we *suggest* extended molecular genetic testing compared to limited testing for MPN driver mutations (conditional recommendation based on moderate certainty in the evidence ⊕⊕⊕◯).
  - **Remarks:**
    - Extended molecular genetic testing should be performed at diagnosis. It may be repeated at key clinical decision points, such as disease progression, pre-transplant evaluation, or when making new treatment decisions, to identify acquisition of new mutations.
    - Extended testing is less compelling for patients that are transplant-ineligible with poor expected longevity, or among patients that did not want to know prognosis if there was no impact on their treatment.
  - Evidence Profile
  - Evidence to Decision Framework

NON-TRANSPLANT THERAPIES: PREFIBROTIC MYELOFIBROSIS

- **Question 2:** *Should pegylated interferon therapy be used or not in patients with prefibrotic myelofibrosis?*
  - **Recommendation 2:** In patients with prefibrotic myelofibrosis (MF) and no indication for cytoreduction, we *suggest against* routine use of pegylated interferons (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).
  - Evidence Profile
  - Evidence to Decision Framework

NON-TRANSPLANT THERAPIES: PRIMARY/POST-ET/PV MYELOFIBROSIS: JAK-INHIBITOR NAIVE

- **Question 3:** *Should JAK-inhibitor naïve, higher risk (DIPSS intermediate-2 and high, MIPSS70/plus high) myelofibrosis (primary and post-ET/PV MF) patients without symptomatic splenomegaly and/or disease-related symptoms be treated with JAK inhibitors vs not?*
  - **Recommendation 3:** In JAK-inhibitor naïve patients with higher risk (DIPSS intermediate-2 and high, MIPSS70/plus high) myelofibrosis (primary and post-ET/PV MF) without symptomatic splenomegaly and/or disease-related symptoms, we *suggest against* the initiation of JAK inhibitors (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).
  - Evidence Profile
  - Evidence to Decision Framework
  - **Good Practice Statement.** Panelists emphasize the need for dynamic, structured symptom assessment (noting that validated patient reported outcome tools are available) as higher risk patients under observation are increasingly likely to need treatment during their disease course.
- **Question 4:** *Should JAK inhibitor naïve, lower risk (DIPSS low, intermediate-1, MIPSS70/plus low, intermediate) myelofibrosis (primary and post-ET/PV MF) patients with symptomatic splenomegaly and/or disease-related symptoms be treated with JAK inhibitors vs not?*
  - **Recommendation 4:** In JAK inhibitor naïve patients with lower risk (DIPSS low, intermediate-1, MIPSS70/plus low, intermediate) myelofibrosis (primary and post-ET/PV MF) with symptomatic splenomegaly and/or disease-related symptoms, we *suggest* the use of JAK inhibitors (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).
  - Evidence Profile
  - Evidence to Decision Framework
- **Question 5:** *Should JAK inhibitor naïve, myelofibrosis (primary, post-ET/PV) patients whose primary symptom burden is disease-related anemia be treated with JAK inhibitor therapy or non-JAK inhibitor anemia-directed therapy?*
  - **Recommendation 5:** In patients who are JAK inhibitor naïve, with myelofibrosis (primary, post-ET/PV) whose primary indication for treatment is disease-related anemia, we *suggest either* JAK inhibitor therapy (momelotinib or pacritinib) or

non-JAK inhibitor anemia-directed therapies (conditional recommendation based on low certainty in the evidence ⊕⊕◯◯)

- **Remarks:**
  - Severity of anemia influences decision-making. Some transfusion-dependent patients can become transfusion-independent when treated with momelotinib or pacritinib; in this context, these JAK-inhibitors would be the preferred strategy compared to non-JAK inhibitor anemia-directed therapies. Pacritinib can be considered in patients with concurrent anemia and thrombocytopenia.
  - Alternatively, non-transfusion dependent patients may start with a non-JAK inhibitor directed therapy such as an erythropoiesis-stimulating agent (if eligible) and/or another non-JAK inhibitor anemia-directed therapy
- Evidence Profile
- Evidence to Decision Framework

NON-TRANSPLANT THERAPIES: PRIMARY/POST-ET/PV MYELOFIBROSIS: JAK-INHIBITOR EXPERIENCED

- **Question 6:** *Should patients with myelofibrosis who experience JAK inhibitor-associated anemia with ruxolitinib or fedratinib be switched to momelotinib or pacritinib, compared to optimization strategies to maintain their therapy?*
  - **Recommendation 6a:** In myelofibrosis patients who experience JAK inhibitor–associated anemia that prevents the use of an optimal dose of ruxolitinib or fedratinib to control symptomatic splenomegaly and/or disease-related symptoms, we *suggest* switching to momelotinib or pacritinib (conditional recommendation based on low certainty in the evidence ⊕⊕◯◯).
  - **Recommendation 6b:** In myelofibrosis patients who experience JAK inhibitor-associated anemia but maintain adequate control of symptomatic splenomegaly and/or disease-related symptoms, on the current dose of ruxolitinib or fedratinib, we *suggest* implementing non-JAK inhibitor anemia-directed therapies compared to switching to momelotinib or pacritinib (conditional recommendation based on low certainty in the evidence ⊕⊕◯◯).
  - **Remarks:**
    - Non-JAK inhibitor anemia-directed therapies include erythropoiesis-stimulating agents, luspatercept and androgens.
    - Pacritinib, based on indirect evidence, can be considered in patients with concurrent anemia and thrombocytopenia.
    - Panelists emphasized that clinicians take the timing of anemia into account. Early onset anemia can be drug-related and may improve within 3 months whereas late onset anemia can indicate disease progression.
  - Evidence Profile
  - Evidence to Decision Framework

TRANSPLANTATION

- **Question 7:** *Should patients with higher-risk myelofibrosis (DIPSS int-2/high, MIPSS70/plus high) responding to first-line JAK inhibitor therapy be referred for early*

transplantation consultation, compared to delayed transplantation consultation after failure of response to JAK inhibitor therapy?

- **Recommendation 7:** In patients with higher-risk myelofibrosis (DIPSS int-2/high, MIPSS70/plus high) receiving JAK inhibitor therapy, and responding to therapy, we *suggest* early referral for allogeneic hematopoietic cell transplantation consultation compared to delayed referral after failure of response to JAK inhibitor therapy (conditional recommendation based on low certainty in the evidence ⊕⊕◯◯)
- **Remarks:**
  - Patients with high-risk molecular or cytogenetic features should be prioritized for early transplantation consultation, even in the presence of optimal JAK inhibitor response.
  - The decision to ultimately proceed with transplantation should be individualized, weighing the risks, benefits, patient preferences, and values.
- Evidence Profile
- Evidence to Decision Framework

➢ **Question 8:** *Among JAK inhibitor naïve myelofibrosis patients scheduled for transplantation, should JAK inhibitor therapy be initiated prior to transplantation or not?*

- **Recommendation 8:** In JAK inhibitor–naïve myelofibrosis patients planned for transplantation we *suggest against* the routine use of pre-transplant JAK inhibitors, except in those with marked splenomegaly or disease-related symptoms (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).
  - **Remark:** Patients who may benefit from spleen reduction prior to transplant include those with splenomegaly measuring ≥5 cm below the left costal margin, and especially if exceeding 15 cm below the left costal margin, or with splenomegaly-related symptoms.
- Evidence Profile
- Evidence to Decision Framework

Special Situations

➢ **Question 9:** *Should aspirin therapy be used (or not) in all patients with myelofibrosis?*

- **Recommendation 9:** In patients with *JAK2* V617F positive myelofibrosis (MF), we *suggest* primary prevention with low dose aspirin in the absence of contraindications. In all other MF patients, we suggest a shared decision-making process that incorporates MF subtype, thrombotic risk factors (age > 60, cardiovascular risk factors) and bleeding risk factors [extreme thrombocytosis, acquired von Willebrand disease, thrombocytopenia (platelets <50 x 10^9/L),prior bleeding history] (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).
- Evidence Profile
- Evidence to Decision Framework

- **Question 10:** *Should myelofibrosis patients with transfusional iron overload be treated with iron chelators or not?*
  - **Recommendation 10:** In patients with myelofibrosis and transfusional iron overload, we *suggest against* routine iron chelation therapy (conditional recommendation based on very low certainty in the evidence ⊕◯◯◯).
  - Evidence Profile
  - Evidence to Decision Framework