International Working Group (IWG) Consensus Criteria for Treatment

Response in Myelofibrosis with Myeloid Metaplasia: On Behalf of the IWG for

Myelofibrosis Research and Treatment (IWG-MRT)

Ayalew Tefferi,1 Giovanni Barosi,2 Ruben A. Mesa,1 Francisco Cervantes,3 H. Joachim Deeg,4 John T. Reilly,5 Srdan Verstovsek,6 Brigitte Dupriez,7 Richard T. Silver,8 Olatoyosi Odenike,9 Jorge Cortes,6 Martha Wadleigh,10 Lawrence A. Solberg, Jr.,11 John K. Camoriano,12 Heinz Gisslinger,13 Pierre Noel,14 Juergen Thiele,15 James W. Vardiman,9 Ronald Hoffman,16 Nicholas C.P. Cross,17 D. Gary Gilliland,10 Hagop Kantarjian,6

1Mayo Clinic, Rochester, Minnesota, USA
2Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy
3Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain
4Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
5Royal Hallamshire Hospital, Sheffield, United Kingdom
6MD Anderson Cancer Center, Houston, Texas, USA
7Service d'Hématologie Clinique, Centre Hospitalier de Lens, France
8Cornell Medical Center, New York, New York, USA
9University of Chicago, Chicago, Illinois
10Dana Farber Cancer Institute, Boston, Massachusetts, USA
11Mayo Clinic, Jacksonville, Florida, USA
12Mayo Clinic, Scottsdale, Arizona, USA
13Department of Hematology and Blood Coagulation, Medical University of Vienna, Vienna, Austria
14National Institutes of Health, Bethesda, Maryland, USA
15Institute of Pathology, University of Cologne, Germany
16University of Illinois, Chicago, Illinois, USA
17Wessex Regional Genetics Laboratory, Salisbury, United Kingdom

The current study was jointly organized by the Mayo Clinic (Rochester, MN) and MD Anderson Cancer Center (Houston, TX) and supported by the Joe W. and Dorothy Dorsett Brown Foundation (Metairie, LA) and the William Waugh and Judy Olin Higgins Research Fund of the Cancer Research and Treatment Fund Inc. (New York, NY).
Abstract

Myelofibrosis with myeloid metaplasia (MMM) is a clinicopathologic entity characterized by stem cell-derived clonal myeloproliferation, ineffective erythropoiesis, extramedullary hematopoiesis, and bone marrow fibrosis and osteosclerosis. Patients with MMM have shortened survival and their quality of life is compromised by progressive anemia, marked hepatosplenomegaly, and severe constitutional symptoms including cachexia. After decades of frustration with ineffective therapy, patients are now being served by promising treatment approaches that include allogeneic hematopoietic stem cell transplantation and immunomodulatory drugs. Recent information regarding disease pathogenesis, including a contribution to the myeloproliferative disorder phenotype by a gain-of-function JAK2 mutation (JAK2V617F), has revived the prospect of targeted therapeutics as well as molecular monitoring of treatment response. Such progress calls for standardization of response criteria to accurately assess the value of new treatment modalities, to allow accurate comparison between studies, and to assure that the definition of “response” reflects meaningful health outcome. Accordingly, an international panel of experts recently convened and delineated three response categories; complete (CR) and partial (PR) remissions and “clinical improvement (CI)”. Bone marrow histological and hematological remissions characterize CR and CR/PR, respectively. The panel agreed that the CI response category is applicable only to patients with moderate to severe cytopenia or splenomegaly.
Introduction

Myelofibrosis with myeloid metaplasia (MMM) is classified with polycythemia vera (PV) and essential thrombocythemia (ET) as a BCR/ABL-negative, myeloproliferative disorder (MPD). Current diagnosis is based on morphological assessment of bone marrow histology, peripheral blood examination, and complementary information from cytogenetic and molecular studies. The term MMM, for the purposes of the current communication, includes both chronic idiopathic myelofibrosis (i.e. de novo presentation of the clinicopathologic phenotype, also known as agnogenic myeloid metaplasia) and cases in which the disease is preceded by either essential thrombocythemia (i.e. post-thrombocytemic myeloid metaplasia; PTMM) or polycythemia vera (i.e. post-polycythemic myeloid metaplasia; PPMM). It also includes cases with a cellular (a.k.a. prefibrotic) phase of the disease. Previous studies have shown clinical and laboratory similarities between de novo MMM, PPMM, and PTMM, including the types and distribution of bone marrow cytogenetic abnormalities. Furthermore, the three MMM variants are now known to harbor a common mutant allele (JAK2 V617F). Pathogenetically, MMM represents a stem cell-derived abnormal clonal myeloproliferation distinctly associated with reactive, cytokine-mediated marrow stromal changes including collagen fibrosis, osteosclerosis, and angiogenesis.

Clinical course in MMM is characterized by progressive anemia, marked hepatosplenomegaly, profound constitutional symptoms including cachexia, and occasionally the development of non-hepatosplenic extramedullary hematopoiesis (EMH). Median survival ranges from less than 3 years to more than 10 years depending on the presence or absence of adverse risk factors; anemia, thrombocytopenia, leucopenia, leukocytosis, circulating blasts, constitutional symptoms, and poor-risk cytogenetic abnormalities. Causes of death include leukemic transformation, infections, bleeding, thrombosis, heart failure, liver failure, solid tumor, respiratory failure, and portal hypertension. Conventional treatment modalities, which include drugs,
splenectomy,\textsuperscript{17} and involved field irradiation of an EMH site,\textsuperscript{18,19} neither alter the natural history of MMM nor provide durable symptom relief. The \textit{status quo} is fortunately changing in the face of encouraging preliminary results from both allogeneic hematopoietic stem cell transplantation (HSCT)\textsuperscript{20-22} and novel drugs,\textsuperscript{23-25} Further progress is expected from the development and/or application of new agents that target disease-specific molecular abnormalities.\textsuperscript{26-28} It is therefore essential to establish uniform response criteria that allow valid inter-study comparisons and accurate assessment of the efficacy of newer therapies.

\textbf{Methods}

The current document was compiled by an international panel of clinical and laboratory experts in MMM. The initial process involved review of response criteria used in i) recent collaborative group\textsuperscript{29} or cell-based\textsuperscript{20,30} treatment trials, ii) a recent proposal by the European Myelofibrosis Network (EUMNET),\textsuperscript{31} and iii) published response criteria for myelodysplastic syndrome (MDS),\textsuperscript{32} which is a related chronic myeloid disorder. The strengths and limitations of each one of the aforementioned documents were discussed and new recommendations were proposed with the intent to; i) preserve some similarity to response categories in MDS,\textsuperscript{32} ii) assure that a defined response has relevance to quality of life (QOL), and iii) incorporate treatment effects on bone marrow histology.\textsuperscript{33}

\textbf{Panel Consensus Regarding Treatment Objectives and Definition of \textquotedblleft Response\textquotedblright}

Two primary objectives in the treatment of cancer are to prolong survival and to improve QOL. Among myeloid disorders, randomized studies have confirmed treatment-associated improvement in survival in both acute (AML)\textsuperscript{34-36} and chronic (CML)\textsuperscript{37,38} myeloid leukemias. The same has not yet been definitively documented for either MDS or MMM, although this possibility exists in the context of modern therapeutic regimens, including allogeneic HSCT.\textsuperscript{20,21,39} The achievement of a strictly-defined complete remission (CR) state has been shown to be a prerequisite
for improvement in survival in many hematological malignancies including AML and CML. Similarly, treatment-induced CR and partial remission (PR) in MDS have been associated with significantly longer survival. Therefore, the panel endorsed the inclusion of CR and PR categories in MMM that are similar but not identical to those utilized in MDS, with the intention to prove their validity in future studies (Tables 1 and 2). In so doing, the CR designation in MMM fulfilled the requirement of bone marrow histological remission, which distinguishes such a response category from those that imply clinical benefit without the potential to alter the natural history of the underlying disease. In contrast, CR and PR categories were not part of the MMM response criteria published by either the European Myelofibrosis Network (EUMNET) or previously published collaborative group clinical trials. Furthermore, the latter groups considered histologic remissions as a separate response category and not part of the major clinical response categories (Table 3). On the other hand, histological remission has been an integral component of response criteria in the context of allogeneic HSCT.

In addition to reporting CR and PR, the current panel of experts strongly recommends the gathering and reporting of baseline and follow up cytogenetic/molecular and other biological information during clinical trials, as has been the case in CML and AML. Because many patients with MMM do not display a specific molecular or cytogenetic marker, and furthermore it is unclear whether these abnormalities are primary or secondary events, the panel felt that it was premature, at the present time, to incorporate such information in formal response categories. However, the panel underscores the fact that none of the previously published or currently proposed response criteria in MMM have been validated in a prospective fashion and the current lack of effective drug therapy limits one’s ability to retrospectively examine the issue at hand. Accordingly, our main goal in the current proposal was not to undermine the potential value of cytogenetic/molecular responses but to establish widely applicable uniform response criteria that
bear some similarity to those currently in use for MDS and AML (Table 2). Nevertheless, we would like to reiterate that monitoring disease status by cytogenetic and molecular analysis provides important supplementary information and should be clearly communicated along with other responses.

In addition to strictly-defined CR and PR categories, and as has been the case with the designation of “hematologic improvement”, as a response category in MDS, the panel recommended the inclusion of an additional response category that reflected a measurable effect on QOL. The major parameters of relevance in MMM, in this regard, include symptomatic anemia (hemoglobin < 10 g/dL; frequency of 35%-45%), marked splenomegaly (palpable at > 5 cm from left costal margin (LCM); frequency of > 50%), and constitutional symptoms/cachexia (e.g. fatigue, fever, night sweats, loss of lean body mass; frequency of approximately 20%). The panel felt that a suitable designation for this symptom-directed response in MMM would be “clinical improvement (CI)” rather than “hematological improvement” because it includes splenomegaly response in addition to response in other hematological parameters. It is to be noted that such responses have in the past been assigned a myriad of response categories that have not been uniform, across different groups of investigators, in both nomenclature and the levels of change that were required to constitute a response. Furthermore, previous response categories of clinical improvement did not always reflect an associated QOL benefit (Table 3).

Other disease manifestations with the potential to affect QOL include severe to moderate thrombocytopenia (platelet count < 50 x 10^9/L) or neutropenia (absolute neutrophil count < 1 x 10^9/L), painful hepatomegaly, and clinically overt non-hepatosplenic EMH (e.g. pleural effusion, ascites, pulmonary hypertension, and spinal cord and nerve root compression). The choice of a relatively higher platelet count threshold for clinically-relevant thrombocytopenia was based on the fact that MPD platelets are often qualitatively defective. On the other hand, a treatment effect on
mild anemia (hemoglobin level $\geq 10$ g/dL), mild asymptomatic splenomegaly (spleen palpable at $\leq 5$ cm below LCM), non-blastic leukocytosis, asymptomatic thrombocytosis, mild leukopenia or thrombocytopenia, serum lactate dehydrogenase level, circulating myeloblasts, CD34-positive cells, or endothelial progenitor cells, rarely translates into meaningful health outcome, and may not warrant consideration for definition of “response” outside the context of CR and PR.\textsuperscript{9,15,48-52} Similarly, the panel felt that symptomatic thrombocytosis in MMM was too infrequent to warrant its inclusion as a parameter of response.

**Discussion and Recommendations**

Until very recently,\textsuperscript{31} published response criteria in MMM did not exist. Both ongoing and recently completed clinical trials utilized “in-house” versions with little uniformity among different studies. The recent effort from EUMNET\textsuperscript{31} to standardize response criteria in MMM is useful but may not have addressed the complexity and assignment of QOL relevance to “response” and did not incorporate histological remission as part of the major clinical response categories, as has been the tradition in other myeloid disorders including MDS and AML (Table 3). The current panel of experts, which includes the lead authors from the EUMNET publication,\textsuperscript{31} proposes new recommendations with the specific intent to simplify response definitions, assure that “response” is linked to meaningful health outcome and QOL, and preserve some similarity with response criteria used for MDS, a related chronic myeloid disorder.\textsuperscript{32}

As elaborated in the previous section, the new set of recommendations is based on three response categories; CR, PR, and “clinical improvement (CI)” (Table 1). Both CR and PR designations require trilineage peripheral blood count remission, leukocyte differential including the absence of nucleated red blood cells, circulating blasts, and immature myeloid progenitor cells (in the absence of splenectomy), and complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly. In addition, CR requires the attainment of an operationally-
defined complete bone marrow histological remission in terms of cellularity (normocellular for age), myeloblast percentage (≤ 5%), and osteomyelofibrosis (grade of ≤ 1; Table 4). Because of a high degree of subjectivity and lack of standardization in peripheral blood and bone marrow smear interpretation, the panel favored not including demonstration of normal erythrocyte or megakaryocyte morphology as a CR requirement. The requirements for PR are similar to CR but without the need to demonstrate bone marrow histological remission. In this regard, the panel considers resolution of leukoerythroblastosis, a PR requirement, as a reflection of a favorable effect on bone marrow histology. However, the panel strongly recommends a repeat (i.e. post-treatment) bone marrow biopsy in PR patients and recognizes the possibility that less than complete histological remission might occur in some of these patients. Accordingly, the MMM-relevant CR and PR response categories encompass the requirements needed for MDS-relevant CR or PR categories without being identical to them (Table 2). The “CI” response category in MMM (Table 1) is linked to positive experience in symptom relief and is therefore applicable only in the presence of symptomatic anemia (hemoglobin < 10 g/dL), marked splenomegaly (palpable spleen size > 5 cm from LCM), or either severe to moderate thrombocytopenia (platelet count < 50 x 10^9/L) or neutropenia (absolute neutrophil count < 1 x 10^9/L). The panel fully recognizes the fact that the current response criteria do not capture all treatment effects. Multiple factors were discussed as the basis for this decision. For example, the measurement of “constitutional symptoms” is not always accurate because it involves subjective interpretation of a non-standardized patient report. Furthermore, constitutional symptoms are closely linked to the presence of marked hepatosplenomegaly and display a similar direction of response to treatment. Similarly, symptomatic non-hepatosplenic EMH is an infrequent complication with exquisite response to low-dose involved field irradiation. On the other hand, it is unusual for either mild thrombocytopenia/neutropenia or thrombocytosis/leukocytosis to directly
affect QOL in MMM. Therefore, such parameters along with serum LDH, leukoerythroblastosis, and circulating CD34-positive cell count should be monitored during clinical trials but not used to define formal response categories outside the context of CR and PR. In this regard, the new IWG criteria differ from those prescribed by the EUMNET, which are outlined in Table 3. Similarly, unlike both the EUMNET and the IWG for MDS, the current IWG for MMM does not consider “reduction in transfusion requirement” as constituting “a response” that is significant enough to be included in any of the major response categories. The reason for this decision concerns the difficulty in acquiring accurate quantification of baseline and post-treatment transfusion requirements. On the other hand, whereas both IWG and EUMNET for MMM require a minimum of 2 g/dL increase in hemoglobin for an erythroid response, the corresponding hemoglobin increment level used by the IWG for MDS is 1.5 g/dL. It is also important to note that the three sets of response criteria differ in the parameters they use in defining platelet and neutrophil responses as well as disease progression.

The panel also recommends baseline and follow up evaluation of either bone marrow or peripheral blood cytogenetic and molecular studies (e.g. JAK2 V617F mutation analysis) to further define quality/depth of “CR”, clarify equivocal histological remissions, and obtain preliminary information on the value of minimal residual disease monitoring. Our cytogenetic response criteria are similar to those used by the IWG for MDS and differ from the EUMNET criteria, which use the terms major and minor instead of complete and partial (Table 3); a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality and a partial cytogenetic response should be defined as 50% or greater reduction in abnormal metaphases, with at least 20 bone marrow-derived metaphases being analyzed in both cases. Molecular response is currently only applicable to cases that are JAK2 V617F-positive, and we suggest that major molecular response be defined as the absence of the mutation in peripheral
blood granulocytes of previously positive cases using the most sensitive methods currently available (allele-specific PCR, real time PCR, or pyrosequencing, all of which have sensitivity of approximately 2-5%). The sensitivity of the assay employed should be established in each center and stated as a percentage. Finally, while it is appropriate to incorporate QOL assessment in clinical trials, such practice is unlikely to enrich the experience from phase I/II studies and is best reserved for large phase III studies. In this regard, a recent QOL study in MPD involving 1179 patients is being analyzed and will be utilized to construct guidelines for assessing QOL in MMM.

**Confounders of Response and Study Eligibility**

The panel favors a treatment-free period of at least 4 weeks for patient participation in a clinical trial in order to minimize the confounding effect of previous therapy on study drug response. For example, a patient receiving hydroxyurea therapy might experience an improvement in anemia and other cytopenia as well as worsening of splenomegaly, cytosis, and constitutional symptoms as a result of drug discontinuation. This effect might be inaccurately attributed to the study drug unless an adequate period of time has elapsed between the discontinuation of hydroxyurea and initiation of protocol therapy. A similar scenario is possible in patients in whom growth factor treatment is discontinued close to study accrual. The panel recognizes the difficulty in withholding therapy for 4 weeks in the presence of active disease, in some patients who are otherwise fit for investigational therapies. The alternative possibility of allowing study participation without altering baseline disease-directed therapy might undermine accurate assessment of both drug effect and toxicity. However, because the aforementioned issues are unlikely to be a factor in the context of CR or PR, the panel was comfortable in considering, in some instances, patient participation in clinical trials regardless of the presence or absence of active therapy. Clinical trials that allow patients to continue pre-existing drug therapy should require the use of stable drug doses.
for at least 3 months prior to protocol entry and should include patient stratification that would allow assessment of “CI” based on baseline treatment status.

Another issue during clinical trials in MMM involves the distinction between potentially reversible drug-induced myelosuppression and disease progression. This is highlighted by the experience in CML with imatinib\(^{53,54}\) and in MDS with either lenalidomide\(^{55}\) or hypomethylating agents,\(^{40,41}\) where drug-associated myelosuppression often preceded response. It is therefore conceivable that an effective drug might be discontinued prematurely if its effect on blood counts is spuriously attributed to disease progression. This is the basis for not including anemia and cytopenias as markers of disease progression during protocol therapy. Instead, study drug-associated alterations in blood count should be utilized primarily for purposes of dose modification. However, a decrease in hemoglobin level of \(\geq 2\) g/dL, acquiring transfusion dependency, or a 100% increase in transfusion requirement, each persisting for \(> 3\) months after drug discontinuation, should ultimately be considered as a marker of disease progression unless proven otherwise. On the other hand, the on-protocol criteria for disease progression include progressive splenomegaly, bone marrow biopsy-proven leukemic transformation per WHO criteria, or a persistent (i.e. \(\geq 8\) weeks duration) increase in circulating blasts to \(\geq 20\%\) (Table 2). Finally, as elaborated before, the current recommendations for response criteria do not include measurements of drug effect on constitutional symptoms and asymptomatic splenomegaly that is palpable at \(\leq 5\) cm from LCM; this minimizes inaccuracies stemming from subjective interpretations and avoids the need for objective confirmation by ultrasound.
Table 1. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia.

1. Complete remission (CR): Requires all of the following in the absence of both transfusion and growth factor support;
   i) Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
   ii) Peripheral blood count remission defined as hemoglobin ≥ 11 g/dL, platelet count ≥ 100 x 10^9/L, and absolute neutrophil count ≥ 1.0 x 10^9/L. In addition, all three blood counts should be ≤ the upper normal limit.
   iii) Normal leukocyte differential including disappearance of nucleated red blood cells, blasts and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*
   iv) Bone marrow histological remission defined as the presence of age-adjusted normocellularity, ≤ 5% myeloblasts, and an osteomyelofibrosis grade of ≤ 1.**

2. Partial remission (PR): Requires all of the above criteria for CR except the requirement for bone marrow histological remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

3. Clinical improvement (CI): Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for ≥ 8 weeks).
   i) A ≥ 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of < 10 g/dL).§
   ii) Either a ≥ 50% reduction in palpable splenomegaly of a spleen that is ≥ 10 cm at baseline or a spleen that is palpable at > 5 cm at baseline becomes not palpable.¶
   iii) A ≥ 100% increase in platelet count and an absolute platelet count of ≥ 50,000 x 10^9/L. (applicable only for patients with baseline platelet count of < 50 x 10^9/L).
   iv) A ≥ 100% increase in ANC and an ANC of ≥ 0.5 x 10^9/L. (applicable only for patients with baseline absolute neutrophil count of < 1 x 10^9/L).

4. Progressive disease: Requires one of the following:¶
   i) Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a ≥ 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a ≥ 50% increase in palpable distance for baseline splenomegaly of > 10 cm.
   ii) Leukemic transformation confirmed by either a bone marrow blast count of ≥ 20% or the occurrence of a histological documented granulocytic sarcoma.
   iii) A peripheral blood blast percentage value of ≥ 20% that lasts for ≥ 8 weeks.

5. Stable disease: None of the above.

6. Relapse: Loss of CR, PR, or CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for even CI. However, changes from either CR to PR or CR/PR to CI should be documented and reported.

*Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphological abnormalities of red cells, platelets, and neutrophils.
** In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

§ Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin of < 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin of ≥ 8.5 g/dL is discouraged unless it is clinically indicated.

§§ In splenectomized patients, palpable hepatomegaly is substituted with the same measurements. For both splenomegaly and hepatomegaly, palpable organ size is measured from the left or right costal margins, respectively, and represents the longest distance to the lowest palpable edge of the organ during deep inspiration.

¶ It is acknowledged that worsening cytopenia might represent progressive disease but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin of ≥ 2 g/dL, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy can be considered disease progression.
Table 2. Peripheral blood and bone marrow requirements for complete (CR) and partial (PR) remissions as well as other remission categories in myelofibrosis with myeloid metaplasia (MMM) and myelodysplastic syndrome (MDS). The International Working Group (IWG) response criteria for MMM and MDS are compared to each other as well as to the criteria set by the European Myelofibrosis Network (EUMNET) for MMM.

<table>
<thead>
<tr>
<th>Response Category</th>
<th>IWG-MMM</th>
<th>IWG-MDS</th>
<th>EUMNET-MMM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peripheral blood</td>
<td>Bone marrow</td>
<td>Peripheral blood</td>
</tr>
<tr>
<td>Complete Remission (CR)</td>
<td>Hgb ≥ 11 g/dL</td>
<td>Blasts ≤ 5%</td>
<td>Hgb ≥ 11 g/dL</td>
</tr>
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<td></td>
<td>Platelets ≥ 100 x 10^9/L</td>
<td>Normocellular</td>
<td>Platelets ≥ 100 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>Neutrophils ≥ 1.0 x 10^9/L</td>
<td>No blasts or immature cells</td>
<td>Neutrophils ≥ 1.0 x 10^9/L</td>
</tr>
<tr>
<td></td>
<td>All counts ≤ upper normal limit</td>
<td>Not relevant</td>
<td>All counts ≤ upper normal limit</td>
</tr>
<tr>
<td></td>
<td>No blasts or immature cells</td>
<td>Not relevant</td>
<td>No blasts or immature cells</td>
</tr>
<tr>
<td>Partial Remission (PR)</td>
<td>Hgb ≥ 11 g/dL</td>
<td>Blasts &gt; 5% but ≥ 50% ↓ in number</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Platelets ≥ 100 x 10^9/L</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Neutrophils ≥ 1.0 x 10^9/L</td>
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<td>N/A</td>
</tr>
<tr>
<td></td>
<td>All counts ≤ upper normal limit</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>No blasts or immature cells</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical improvement</td>
<td>See table 1</td>
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<td>N/A</td>
</tr>
<tr>
<td>Hematologic improvement</td>
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<td>See reference # 32</td>
<td>Not relevant</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Major response</td>
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<td>N/A</td>
</tr>
<tr>
<td>Moderate response</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Minor response</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A, not applicable; Hgb, hemoglobin level
Table 3. Response criteria for myelofibrosis with myeloid metaplasia, which was recently proposed by the European Myelofibrosis Network (EUMNET).

i. Clinicohematologic response.

*Response or disease progression is validated only if it lasts for ≥ 1 month

   - Complete response in anemia: Hemoglobin ≥ 12 g/dL for transfusion-independent patients or ≥ 11 g/dL for transfusion-dependent patients (applicable only for patients with baseline hemoglobin level of < 10 g/dL).
   - Complete response in splenomegaly: Spleen not palpable
   - Complete response in constitutional symptoms: Absence of constitutional symptoms (fever, drenching night sweats, or ≥ 10% weight loss).
   - Complete response in platelet count: Platelet count 150-400 x 10⁹/L.
   - Complete response in leukocyte count: Leukocyte count 4-10 x 10⁹/L.

2. Major response: Any response in both anemia and splenomegaly without progression in constitutional symptoms or complete response in anemia without progression in splenomegaly or partial response in anemia in a baseline transfusion-dependent patient combined with response in constitutional symptoms without progression in splenomegaly or any response in splenomegaly combined with response in constitutional symptoms without progression in anemia.
   - Partial response in anemia: Either a ≥ 2 g/dL increase in hemoglobin level or > 50% decrease in transfusion requirement.
   - Partial response in splenomegaly: Either ≥ 50% decrease in spleen size if baseline ≤ 10 cm from LCM or ≥ 30% decrease if baseline ≥ 10 cm from LCM.
   - Partial response in platelet count: A ≥ 50% decrease in platelet count if baseline > 800 x 10⁹/L or platelet count increase by ≥ 50 x 10⁹/L if baseline < 100 x 10⁹/L.
   - Partial response in leukocyte count: A ≥ 50% decrease in leukocyte count if baseline > 20 x 10⁹/L or leukocyte count increase by ≥ 1 x 10⁹/L if baseline < 4 x 10⁹/L.
   - Progression in anemia: A hemoglobin decrease of ≥ 2 g/dL or ≥ 50% increase in transfusion requirement or becoming transfusion dependent.
   - Progression in splenomegaly: A ≥ 50% increase in spleen size if baseline ≤ 10 cm from LCM or ≥ 30% increase if baseline > 10 cm from LCM.
   - Progression in constitutional symptoms: Appearance of constitutional symptoms.

3. Moderate response: Complete response in anemia with progression in splenomegaly or partial response in anemia without progression in splenomegaly or any response in splenomegaly without progression in anemia and constitutional symptoms.

4. Minor response: Any leukocyte- or platelet-based response without progression in anemia, splenomegaly, or constitutional symptoms.

5. No response: None of the above.
**ii. Histologic response.**

The panel of experts recommended that a histologic response should include assessment of both age-adjusted bone marrow cellularity and fibrosis. The need for both adequate biopsy specimen and good quality reticulin/collagen staining was underscored. Furthermore, general assessment and scoring of grades of fibrosis is to be done in areas of hematopoiesis after assessing the quality of the reticulin stain by detection of normal staining in vessel walls as internal controls.

**iii. Cytogenetic response.**

1. **Major cytogenetic response:** Failure to detect a cytogenetic abnormality in cases with a preexisting abnormality.

2. **Minor cytogenetic response:** A 50% or greater reduction in abnormal metaphases.
**Table 4. European consensus on grading bone marrow fibrosis (fiber density should be assessed in hematopoietic cellular areas).**

<table>
<thead>
<tr>
<th>Fibrosis grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Scattered linear reticulin with no intersections corresponding to normal bone marrow</td>
</tr>
<tr>
<td>1</td>
<td>Loose network of reticulin with many intersections, especially in perivascular areas</td>
</tr>
<tr>
<td>2</td>
<td>Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis</td>
</tr>
</tbody>
</table>
References.


with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. Blood. 1999;93:4116-4124.


International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia: On behalf of the IWG for myelofibrosis research and treatment (IWG-MRT)

Ayalew Tefferi, Giovanni Barosi, Ruben A Mesa, Francisco Cervantes, H J Deeg, John T Reilly, Srdan Verstovsek, Brigitte Dupriez, Richard T Silver, Olatoyosi Odenike, Jorge Cortes, Martha Wadleigh, Lawrence A Solberg Jr., John K Camoriano, Heinz Gisslinger, Pierre Noel, Juergen Thiele, James W Vardiman, Ronald Hoffman, Nicholas C Cross, D G Gilliland and Hagop Kantarjian

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