Proposals for Revised International Working Group-European LeukemiaNet Criteria for Anemia Response in Myelofibrosis

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Proposals for Revised International Working Group-European LeukemiaNet Criteria for Anemia Response in Myelofibrosis

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Ayalew Tefferi (Mayo Clinic, United States) Giovanni Barosi (IRCCS Policlinico S. Matteo, Italy) Francesco Passamonti (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy) Juan Carlos Hernandez-Boluda (Hospital Clínico Valencia, Spain) Prithviraj Bose (University of Texas MD Anderson Cancer Center, United States) Konstanze Döhner (University Hospital of Ulm, Germany) Martin Ellis (Meir Medical Center, Israel) Naseema Gangat (Mayo Clinic, United States) Jacqueline Garcia (Dana-Farber Cancer Institute, United States) Heinz Gisslinger (Medical University of Vienna, Austria) Jason Gotlib (Stanford Cancer Institute, United States) Paola Guglielmelli (Univ. of Florence and Azienda Ospedaliera Careggi, Italy) Vikas Gupta (The Princess Margaret Cancer Centre, Canada) Claire Harrison (Guy's and St Thomas' NHS Foundation Trust, United Kingdom) Elizabeth Hexner (University of Pennsylvania School of Medicine, United States) Gabriela Hobbs (Massachusetts General Hospital, United States) Jean-Jacques Kiladjian (HÃ'pital Saint-Louis AP-HP & UniversitÃ© Paris CitÃ©, France) Steffen Koschmieder (RWTH Aachen University, Germany) Nicolaus Kröger (University Medical Center Hamburg_Eppendorf, Germany) Andrew Kuykendall (Moffitt Cancer Center and Research Institute, United States) Giuseppe Gaetano Loscocco (University of Florence, Italy) John Mascarenhas (Icahn School of Medicine at Mount Sinai, United States) Lucia Masarova (The University of Texas MD Anderson Cancer Center, United States) Ruben Mesa (Wake Forest University School of Medicine, United States) Barbara Mora (Division of Hematology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy, Italy) Olatoyosi Odenike (The University of Chicago, United States) Stephen Oh (Washington University School of Medicine, United States) Animesh Pardanani (Mayo Clinic, United States) Anand Patel (University of Chicago, United States) Naveen Pemmaraju (The University of Texas MD Anderson Cancer Center, United States) Alessandro Rambaldi (Università degli Studi di Milano, Italy) Raajit Rampal (Memorial Sloan-Kettering Cancer Center, United States) Shireen Sirhan (Jewish General Hospital- McGill University, Canada) Natasha Szuber (University of Montreal, Canada) Moshe Talpaz (University of Michigan, United States) Pankit Vachhani (O'Neal Comprehensive Cancer Center at the University of Alabama at Birmingham, United States) Alessandro Vannucchi (Azienda Ospedaliero-Universitaria Careggi, Italy) Tiziano Barbui (FROM Research Foundation ASST Papa Giovanni XXIII Bergamo, Italy)

Abstract:
With emerging new drugs in myelofibrosis (MF), a robust and harmonized framework for defining the severity of anemia and response to treatment will enhance clinical investigation and facilitate inter-study comparisons. Accordingly, the lead authors on the 2013 edition of the International Working Group-European LeukemiaNet (IWG-ELN) response criteria in MF were summoned to revise their document with the intent to i) account for gender-specific differences in determining hemoglobin levels for eligibility criteria, ii) revise definition of transfusion-dependent anemia (TDA) based on current restrictive transfusion practices, and iii) provide a structurally simple and easy to apply response criteria that are sensitive enough to detect efficacy signals (minor response) and also account for major responses. The initial draft of the 2024 IWG-ELN proposed criteria was subsequently circulated around a wider group of international experts and their feedback incorporated. The proposed articles include new definitions for TDA ({greater than or equal to}3 units in the 12 weeks prior to study enrollment) and hemoglobin thresholds for eligibility criteria (<10 g/dL for women and <11 g/dL for men). The revised document also provides separate (TDA vs. non-TDA) and graded (major vs. minor response) response criteria while preserving the requirement for a 12-week period of screening and observation on treatment.

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Brief Report:

Proposals for Revised International Working Group-European LeukemiaNet Criteria for Anemia Response in Myelofibrosis

Ayalew Tefferi,[1*] Giovanni Barosi, [2] Francesco Passamonti,[3] Juan-Carlos Hernandez-Boluda,[4] Prithviraj Bose,[5] Konstanze Döhner,[6] Martin Ellis,[7] Naseema Gangat,[1] Jacqueline S. Garcia,[8] Heinz Gisslinger,[9] Jason Gotlib,[10] Paola Guglielmelli,[11] Vikas Gupta,[12] Claire Harrison,[13] Elizabeth O. Hexner,[14] Gabriela S. Hobbs,[15] Jean-Jacques Kiladjian,[16] Steffen Koschmieder,[17] Nicolaus Kroger,[18] Andrew T. Kuykendall,[19] Giuseppe G. Loscocco,[11] John Mascarenhas,[20] Lucia Masarova,[5] Ruben Mesa,[21] Barbara Mora,[3] Olatoyosi Odenike,[22] Stephen T. Oh,[23] Animesh Pardanani,[1] Anand Patel,[22] Naveen Pemmaraju,[5] Alessandro Rambaldi,[24] Raajit Rampal,[25] Shireen Sirhan,[26] Natasha Szuber,[27] Moshe Talpaz,[28] Pankit J. Vachhani,[29] Alessandro M. Vannucchi,[11] Tiziano Barbui.[30]

[1]Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; [2]Center for the Study of Myelofibrosis, IRCCS Policlinico S Matteo Foundation, Pavia, Italy; [3]Dipartimento di Oncologia ed Onco-Ematologia, Università degli Studi di Milano; Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; [4]Haematology Department, Hospital Clínico Universitario, INCLIVA, Valencia, Spain; [5]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; [7]Hematology Institute, Meir Medical Center, Tel Aviv University, Tel Aviv, Israel; [8]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [9]Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Medical University of Vienna, Vienna Austria; [10]Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA; [11]CRIMM, Center Research and Innovation of Myeloproliferative Neoplasms, University of Florence; AOU Careggi, Florence, Italy; [12]Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, Canada; [13]Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK; [14]Cell Therapy and Transplant Program, Division of Hematology-Oncology, Department of Medicine, Philadelphia, PA; [15]Division of Hematology and Oncology, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; [16]Centre d'Investigations Cliniques Hôpital Saint-Louis, Université Paris Cité Paris France; [17]Department of Hematology, Oncology, Hemostaseology, and Stem Cell Transplantation, Faculty of Medicine, RWTH Aachen University and Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD), Aachen, Germany; [18]Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [19]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [20]Division of Hematology & Oncology, Department of Internal Medicine, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [21]Levine Cancer Institute, Charlotte, NC, USA; [22]Leukemia Program, University of Chicago Medicine and University of Chicago Comprehensive Cancer Center, Chicago, IL, USA; [23]Division of Hematology, Department of Pathology and Immunology, Washington University School of Medicine, St Louis, Missouri, USA; [24]Department of Oncology and Hematology, University of Milan and Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [25]Memorial Sloan Kettering Cancer Center, New York, NY; [26]Jewish General Hospital, McGill University, Montreal, QC, Canada; [27]Maisonneuve-Rosemont Hospital, University of Montreal, Quebec, QC, Canada; [28]Department of Hematology-Oncology, University of Michigan, Ann Arbor, MI, USA; [29]Department of Medicine, Division of Hematology and Oncology, The University of Alabama at Birmingham, Birmingham, AL; [30]FROM Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy

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*__Corresponding Author:__ Ayalew Tefferi, MD, Division of Hematology, Department of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 5590 Tel- 507-284-2511; tefferi.ayalew@mayo.edu.

Key points:

1. An international panel of 38 experts and clinical trialists in myelofibrosis participated in the preparation of the current document.
2. New definitions of transfusion status, gender-specific hemoglobin thresholds, and criteria for major and minor responses are submitted.

Abstract

With emerging new drugs in myelofibrosis (MF), a robust and harmonized framework for defining the severity of anemia and response to treatment will enhance clinical investigation and facilitate inter-study comparisons. Accordingly, the lead authors on the 2013 edition of the International Working Group-European LeukemiaNet (IWG-ELN) response criteria in MF were summoned to revise their document with the intent to i) account for gender-specific differences in determining hemoglobin levels for eligibility criteria, ii) revise definition of transfusion-dependent anemia (TDA) based on current restrictive transfusion practices, and iii) provide a structurally simple and easy to apply response criteria that are sensitive enough to detect efficacy signals (minor response) and also account for major responses. The initial draft of the 2024 IWG-ELN proposed criteria was subsequently circulated around a wider group of international experts and their feedback incorporated. The proposed articles include new definitions for TDA (≥3 units in the 12 weeks prior to study enrollment) and hemoglobin thresholds for eligibility criteria (<10 g/dL for women and <11 g/dL for men). The revised document also provides separate (TDA vs. non-TDA) and graded (major vs. minor response) response criteria while preserving the requirement for a 12-week period of screening and observation on treatment.

Introduction

Anemia in myelofibrosis (MF) is frequent, mechanistically multifactorial, and molecularly aligned with certain mutations, including *U2AF1*. In one large study,[1] approximately 86% of patients with primary MF presented with anemia, ranging in severity from mild (35%) to severe (37%), with respective lower limit hemoglobin (Hgb) values of ≥10 g/dl (35%) and <8 g/dL (37%).[1] Pathogenetic mechanisms include clone-intrinsic defects, splenic sequestration, and deregulated/iron-restricted erythropoiesis. Some of these abnormalities are mediated by an abnormal cytokine milieu involving inflammatory cytokines and hepcidin.[2] The prognostic relevance of anemia in MF is formally recognized by contemporary risk models.[3] A correlation between anemia response in MF and improved quality-of-life (QoL) has previously been reported.[4]

Allogeneic cell transplantation is currently the only curative treatment in MF.[5] Drug therapy is effective in alleviating disease-associated symptoms, including splenomegaly. JAK2 inhibitor (JAKi) therapy offers class-wide benefit in reducing spleen size and ameliorating constitutional symptoms.[6-9] However, management strategies for MF-associated anemia have limited and short-term benefit. The first two FDA-approved JAKi, including ruxolitinib[8] and fedratinib,[7] are more likely to exacerbate rather than improve anemia. More recently introduced JAKi, including momelotinib[6] and pacritinib,[9] were less detrimental to erythropoiesis with documentation of anemia response in some patients, attributed to an off-target inhibition of activin A receptor, type 1 (ACVR1)/activin receptor-like kinase-2 (ALK2).[10]

The recognition that the transforming growth factor beta (TGF-β)-bone morphogenic protein (BMP)-SMAD signaling pathway participates in the pathogenesis of ineffective and iron-restricted erythropoiesis in MF has led to a flurry of recent clinical trials with drugs directed at different components of the BMP-SMAD signaling pathway. Candidate drugs, in this regard, include TGF-β ligand traps (e.g., luspatercept,[11] sotatercept,[12] elritercept[13]), ACVR1/ALK2 inhibitors (e.g., momelotinib,[6] pacritinib,[14] zilurgisertib[15]), and inhibitors of SMAD 1/5/8 signaling, including monoclonal antibody

treatment targeting hemojuvelin, a co-receptor in the BMP-signaling pathway.[16] Another pathway of relevance involves the hypoxia-inducible factor-prolyl hydroxylase and its inhibition with roxadustat has also been reported to have potential value in the treatment of anemia associated with MDS.[17]

The above-outlined activities signaled the need to revisit anemia response criteria in MF, previously reported by members of an International Working Group and European LeukemiaNet (IWG-ELN) committee.[18] The current project was further inspired by the lack of uniformity among current clinical trial and working group definitions of transfusion status and anemia response in MF (Table 1).

Methods

Senior members of the 2013 IWG-ELN committee (TB, GB, AMV, FP, and AT) were summoned, with the objective to review current definitions of anemia and response criteria cited for MF and MDS (Tables 1 and 2) and prepare a set of proposals for a revised document. After securing 100% agreement among the 5 senior authors, the initial draft was circulated separately to i) authors of the 2013 edition of the IWG-ELN response criteria in MF (overseen by AT, who was the lead author of the project), ii) members of the ELN committee on myeloproliferative neoplasms (MPN; overseen by TB, who is the chair of the ELN MPN committee), and iii) a broader international panel of experts and clinical trialists in MF (overseen by AT). A second draft was then prepared based on discussions and feedback from each group and subsequently circulated to the entire panel for additional review before the final draft was prepared and once again circulated to secure unanimous agreement on the articles proposed (Table 3).

Results and Discussion

Hemoglobin cutoffs used for study inclusion criteria

In principle, the authors find the commonly used Hgb level of <10 g/dL, as a key inclusion criterion for clinical trials targeting anemia in MF, to be reasonable and in line with what has often been

applied in previous studies in MF and MDS (Tables 1 and 2). However, the specific threshold overlooks physiological differences between men and women;[19] in a Mayo Clinic study of anemia in MF,[1] the prognostic contribution of moderate or severe anemia (Hgb <10 g/dL) was apparent in both men and women whereas that of mild anemia (Hgb ≥10 g/dl and less than sex-adjusted lower limit of normal) was apparent only in men. In other words, the severity of anemia in men was under-estimated when using a Hgb cutoff level of 10 g/dL. The specific concern has since been addressed in the context of contemporary risk models in PMF[3] and MDS,[20] where gender-specified Hgb levels are used for risk stratification. It is therefore reasonable to do the same in the setting of clinical trials and earlier intervention for Hgb levels below 11 g/dL might also provide protection from the risk of cardiac remodelling and QoL.[21]

Definitions of transfusion status

The 2013 IWG-ELN definition of transfusion-dependent anemia (TDA) and response criteria were purposefully stringent, in prospect of disease-modifying targeted therapies; other definitions were either similar or more lenient and often inconsistent (Table 1). A similar pattern is apparent regarding TDA definitions in MDS (Table 2). Transfusion practices in the US have significantly changed over the last few years with more restrictive transfusion trigger and limitation of units transfused per episode.[22] The authors considered all of the above and agreed on ≥3 units/12 weeks to define TDA, in line with definitions used in pivotal studies leading to recent drug approvals in MDS;[23,24] the 12-week observation period would also be consistent with the required time interval for response assessment (Table 3). Patients requiring ≥6 units, within the 12-week pre-enrolment period constitute a high transfusion burden subcategory (Table 3). The panel voted to dispense with the requirement for Hgb to be <8.5 g/dL in order to trigger transfusion considering the current state of restrictive transfusion practices and the requirement for a concomitant increase in hgb level from baseline, in order to qualify as a response in TDA (Table 3).

Response criteria specified by transfusion status

For TDA, the 2013 IWG-ELN response criteria included a 12-week transfusion-free period, capped by a Hgb level of ≥8.5 g/dL (Table 3).[18] The authors agreed on preserving the 12-week transfusion-free period for "major" response (Table 1). In addition, in order to minimize overcalling responses stemming from variable transfusion practices, a concomitant and durable (12 weeks) increase in Hgb level, by an average of ≥1.5 g/dL, from pre-treatment baseline, is required to confirm major response (Table 3). Furthermore, the panel underscores the need for transfusion policy for the individual patient to remain the same before and after study enrollment. In non-TDA, major response requires a rolling 12-week average of ≥1.5 g/dL increase in Hgb from pre-treatment baseline; the latter is defined as the average of the lowest 3 Hgb levels in the 12 weeks prior to enrollment, including one reading collected in the 28 days prior to enrollment. The rationale for decreasing the required margin of Hgb increase from 2 g/dL to 1.5 g/dL, for major anemia response, includes increasing awareness on the existence of multiple causes for MF-associated anemia, which makes it difficult for a single anemia-targeting drug, by itself, to produce a robust response. Furthermore, anemia response criteria used in the most recent study in MDS that led to approval of luspatercept (Table 2) was consistent with the proposals herein set forth for MF (Table 1). Responses that do not meet the above-outlined criteria for major response are categorized as "minor" and include a ≥50% reduction in transfusion burden or, in non-TDA, an increase in Hgb of ≥1 g/dL but <1.5 g/dL (Table 3).

Definitions of response duration and loss of response

The 2013 IWG response criteria did not include details regarding loss of anemia response.[18] In MDS, loss of anemia response is considered in patients who lose transfusion-free status or experience a ≥1.5 g/dL decline in Hgb level.[25] In the revised IWG-MDS proposal,[26] non-TD patients who no longer meet response criteria for anemia (i.e., ≥1.5 g/dL increase in Hgb level from baseline) but nevertheless maintain a ≥1.0 g/dL increase from baseline, would still count as a responder. The authors of the current project find these propositions reasonable and applicable to MF (Table 1). The current panel has also recommended definitions for "progressive" anemia, which include a ≥50% increase in transfusion

requirement in TDA and, in non-TDA, either meeting criteria for TDA or a decrease in Hgb by >1.5 g/dL, from the baseline established at study entry, with a 12-week period of assessment required in both instances (Table 3).

Because of underlying pathogenetic heterogeneity, it is unlikely that drugs currently under investigation for the treatment of anemia in MF would result in complete correction of anemia; a more effective approach might require comination therapy using drugs with non-overlapping mechanisms of action. Drug trials that target anemia in MF should include QoL assessment and laboratory correlative studies, in order to identify suitable drug candidates. Our proposed changes in Hgb thresholds for eligibility criteria represent a paradigm shift in our perception of treatment-requiring anemia in men. This might influence current practice in the use of erythropoiesis stimulating agents and brings attention to QoL issues in men with Hgb levels between 10 and 11 g/dL, who might now be offered a chance to participate in clinical trials.

Table 1. Definition of red cell transfusion-dependence and anemia response criteria in myelofibrosis

Clinical trial	Transfusion-dependent anemia (TDA)	Transfusion-requiring anemia (TRA)	Non-TDA	Response criteria for TDA	Response criteria for non-TDA
SIMPLIFY-1 **Phase 3 study** **Momelotinib** **vs** **Ruxolitinib** **in JAKi-naïve MF** Mesa *JCO*, 2017[27]	≥4 units or Hgb <8 g/dL in the 8 weeks prior to randomization	Not defined	Not meeting criteria for TDA	TD rate at week 24 (Proportion of patients who were TD) Transfusion rate (average number of units per subject-month)	TI rate at week 24 (Proportion of patients who were TI) No transfusions and all Hgb ≥ 8 g/dL in the prior 12 weeks leading up to week 24
SIMPLIFY-2 **Phase 3 study** **Momelotinib** **vs** **Best available therapy** **in JAKi-treated MF** Harrison *Lancet Haematol*, 2018[28]					
MOMENTUM **Phase 3 study** **Momelotinib** **vs** **Danazol in JAKi-treated MF** Verstovsek *Lancet*, 2023[29]	≥ 4 units in the 8 weeks prior to randomization with each transfusion trigger of Hgb ≤9·5 g/dL	1–3 units in the 8 weeks prior to randomization	Hgb <10 g/dl without transfusions in the 8 weeks prior to randomization	TI rate at week 24 No transfusion and all Hgb ≥ 8 g/dl in the prior 12 weeks Transfusion rate (average number of units per subject-month)	≥2 g/dL increase in Hgb over a rolling ≥12 consecutive weeks
PERSIST-2 **Phase 3 study** **Pacritinib** **vs** **Best available therapy** **in JAKi-treated MF** Mascarenhas *JAMA Oncology*, 2018[30]	≥ 2 units/month in the 12 weeks prior to cycle 1 day 1	Not defined	Hgb < 10 g/dl without transfusions in the 12 weeks prior to cycle 1 day 1	TI rate at week 24 Absence of transfusions in the prior 12 weeks	≥2 g/dL increase in Hgb for ≥8 weeks prior to week 24 Applicable to patients with baseline Hgb < 10 g/dl

ACE-536-MF-001 Phase 2 study Luspatercept in anemia-related to MF Gerds *Blood Advances*, 2024[11]	4 -12 units in 12 weeks prior to cycle 1 day 1 Transfusion threshold Symptomatic anemia (Hgb ≤ 9.5 g/dL)	Not defined	Hgb ≤ 9.5 g/dl on ≥3 different days and without transfusions in 12 weeks prior to cycle 1 day 1	Absence of transfusions for ≥12 weeks	≥1.5 g/dL increase in baseline Hgb for ≥12 weeks without transfusion
Established anemia response criteria					
GALE Gale et al. *Leuk Res*, 2011[31]	≥ 2 units /month in the prior 12 weeks	Not defined	No transfusions in the prior 12 weeks	No transfusions over any 12-week interval with no minimum Hgb requirement	No transfusions over any 12-week interval with no minimum Hgb requirement
IWG-MRT Tefferi et al. *Blood*, 2013[18]	≥6 units for Hgb <8.5 g/dL in the 12 weeks prior to screening most recent transfusion within 28 days prior to screening	Not defined	Not meeting criteria for TDA	No transfusions over a rolling ≥12 consecutive weeks, + Hgb ≥ 8.5 g	≥2 g/dL increase in baseline Hgb If transfused in prior month, pre-transfusion Hgb used as baseline Applicable to patients with baseline Hgb <10 g/dl

JAKi- JAK inhibitor, MF- myelofibrosis, IWG-MRT International Working Group for Myelofibrosis Research and Treatment

Table 2. Definitions of transfusion-dependence and anemia response criteria in myelodysplastic syndromes

Clinical trial	Transfusion-dependent anemia (TDA)	Transfusion-requiring anemia (TRA)	Non-TDA	Response criteria for TDA	Response criteria for non-TDA
Epoetin alpha Phase 3 study in low-risk MDS Fenaux *Leukemia*, 2018[32]	1-4 units in 8 weeks prior to baseline visit	Not applicable	Hgb ≤10 g/dl without transfusions in the prior 8 weeks	TI per IWG-2006 No transfusions for ≥8 consecutive weeks + increase in Hgb by ≥1.5 g/dL Baseline Hgb value taken before the last transfusion preceding enrollment	IWG-2006 ≥1.5 g/dL increase in Hgb for ≥8 weeks Modified IWG-2006 Increase in Hgb ≥1.5 g/dL lasting <8 weeks was considered a response if epoetin-α was discontinued and when restarting at lower dose, Hgb increased by ≥1.5 g/dl
Darbepoetin alpha Phase 3 study in low-risk MDS Platzbecker *Leukemia*, 2017[33]	1-4 units in each of two consecutive 8-week periods before randomization	Not applicable	Not applicable	TI per IWG-2006 No transfusions over ≥8 consecutive weeks + increase in Hgb by ≥1.5 g/dL	Not applicable
MEDALIST Phase 3 study Luspatercept vs Placebo in MDS with ring sideroblasts Fenaux *NEJM*, 2020[24]	≥2 units in 8 weeks during the 16 weeks before randomization	Not applicable	Not applicable	TI rate at week 24 No transfusions over ≥8 consecutive weeks	Not applicable

COMMANDS Phase 3 study Luspatercept vs Epoetin alpha in low-risk MDS Platzbecker *Lancet*, 2023[23]	2-6 units in 8 weeks for ≥8 weeks before randomization	Not applicable	Not applicable	TI rate at week 24 No transfusions over ≥12 consecutive weeks + concurrent mean Hgb increase ≥1.5 g/dL	Not applicable
Established anemia response criteria	**Definitions**		**Erythroid response**		
IWG-2006 Cheson *Blood*, 2006[25]	Screening period, 8 weeks for evaluation of transfusion burden and baseline Hgb Pre-treatment Hgb < 11 g/dl TDA (≥4 units in 8 weeks for Hgb < 9 g/dL) TI (<4 units in 8 weeks for Hgb < 9 g/dL)		≥1.5 g/dL increase in Hgb for ≥8 weeks Reduction of ≥4 units transfusions/8 weeks compared with the pretreatment transfusion in the prior 8 weeks		
Revised IWG-2018 Platzbecker *Blood*, 2019[26]	Screening period, 16 weeks for evaluation of transfusion burden and baseline Hgb **Baseline Hgb:** -Mean of all available Hgb values during 16-week screening period. -Values prior to transfusion should be used for TD patients and should be ≥7 days apart **Pre-treatment Hgb < 10 g/dl** NTD (0 units in 16 weeks) LTB (3-7 units in 16 weeks in at least two transfusion episodes, maximum three in 8 weeks) HTB (≥8 units in 16 weeks, ≥4 in 8 weeks)		**NTD** Hgb ≥1.5 g/dL for ≥8 weeks over 16-24 weeks compared with the lowest mean of two Hgb values within 16 weeks prior to treatment **LTB** TI, defined by the absence of transfusions for ≥8 weeks over 16-24 weeks **HTB** -Major response: TI, defined by the absence of transfusions for ≥8 weeks over 16-24 weeks -Minor response: Transfusion reduction by ≥ 50% over a minimum of 16 weeks *Same transfusion policy should be applied compared with 16 weeks prior to treatment*		

MDS- myelodysplastic syndrome, TI- transfusion independent, IWG- International Working Group, NTD- non-transfusion dependent, LTB- low transfusion burden, HTB- high transfusion burden

Table 3: Proposals for revised International Working Group-European LeukemiaNet (IWG-ELN) response criteria for anemia in myelofibrosis

	2013 IWG-ELN criteria	2024 proposed IWG-ELN criteria
Definitions		
Hemoglobin (Hgb) cutoffs for clinical trial inclusion or response adjudication	<10 g/dL	Men <11 g/dL[∞¶] Women <10 g/dL[∞]
Transfusion-dependent anemia (TDA)	≥6 units in the 12 weeks prior to enrollment* *(only transfusions for Hgb <8.5 g/dL are counted)*	≥3 units in the 12 weeks prior to enrollment*[£] *(High transfusion burden defined as ≥6 units in the 12 weeks prior to enrollment)*
Baseline Hgb for TDA	Not clearly defined	Average of pre-transfusion Hgb levels in the 12 weeks prior to enrollment/first dose[£]
Non-TDA	Not meeting criteria for TDA	Not meeting criteria for TDA
Baseline Hgb for non-TDA	Hgb level at time of screening	Average of the lowest three Hgb levels in the 12 weeks prior to enrollment/first dose, including one obtained in the 28 days prior to enrollment/first dose[£¥]
Anemia Response Criteria		
Major response for TDA	No transfusions during any rolling 12-week period + a documented Hgb level of ≥8.5 g/dL	No transfusions x 12 weeks[ŧ] and rolling 12-week average Hgb increase of ≥1.5 g/dL from pre-treatment baseline
Major response for non-TDA	Rolling 12-week average Hgb increase of ≥2.0 g/dL from pre-treatment baseline**	Rolling 12-week average Hgb increase of ≥1.5 g/dL from pre-treatment baseline *(also requires no transfusions)*
Minor response for TDA	Not included	A ≥50% reduction in transfusions[€] (*and not meeting criteria for major response*)
Minor response for non-TDA	Not included	Rolling 12-week average Hgb increase of ≥1.0 g/dL from pre-treatment baseline[€] *(Also requires no transfusions and not meeting criteria for major response)*
Loss of response	Loss of anemia response persisting for ≥1 month	No longer meeting criteria for even minor response[♣]
Duration of anemia response	Not defined	Interval between first time point of response to first time point of loss of response
Progressive anemia	Not defined	TDA: ≥50% increase in transfusion requirement[€] Non-TDA: Hgb decrease of >1.5 g/dL from baseline or meeting criteria for TDA[€]
Stable anemia	Not defined	Not meeting criteria for response or progression

[∝]In the absence of nutritional anemia including iron or vitamin B12 deficiency. In patients receiving replacement therapy, an observation period of 3 months is required before establishing a baseline hemoglobin level.

[◐]For clinical trial purposes, it is equally reasonable to use a hemoglobin threshold of <10 g/dL, in both men and women, as an inclusion criterion

*Most recent transfusion episode must have occurred in the 28 days prior to enrollment

[£]Transfusions or hemoglobin measurements considered are only those obtained after completion of drug washout period

[¥]If transfused in the 28 days before enrollment, baseline should include pre-transfusion but not post-transfusion hemoglobin levels

[€]12-week period of assessment required before and after enrollment

[♣]Short periods of decline in hemoglobin level, which are attributed to a clear alternative cause, such as bleeding or surgery, should not qualify as “loss of response”

[ﬦ]Transfusion policy before enrollment should be the same as after enrollment

**Applicable only for patients with baseline hemoglobin of <10 g/dL

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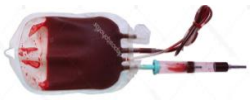
International Working Group-European LeukemiaNet (IWG-ELN) Response Criteria for Anemia in Myelofibrosis: 2024 Edition

Transfusion-dependent

(≥3 units in the 12 weeks prior to enrollment)



Baseline for response assessment

- 12-week average of pre-transfusion hemoglobin levels

Major response

- No transfusions x 12 weeks and
- Rolling 12-week average hemoglobin increase by ≥1.5 g/dL

Minor response

- A >50% reduction in transfusions

Non-transfusion-dependent

(Not meeting criteria for transfusion-dependent)

Baseline for response assessment

- 12-week average of the 3 lowest hemoglobin levels, including one obtained in the 28 days before enrollment

Major response

- Rolling 12-week average hemoglobin increase by ≥1.5 g/dL

Minor response

- Rolling 12-week average hemoglobin increase by ≥1.0 g/dL

Conclusion: The 2024 IWG-ELN response criteria provide a uniform framework for defining the severity of anemia, as well as criteria for major and minor responses in transfusion-dependent and –independent patients with myelofibrosis.