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Review

Classification, risk stratification and response assessment in myelodysplastic syndromes/neoplasms (MDS): A state-of-the-art report on behalf of the International Consortium for MDS (icMDS)

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ABSTRACT

The guidelines for classification, prognostication, and response assessment of myelodysplastic syndromes/neoplasms (MDS) have all recently been updated. In this report on behalf of the International Consortium for MDS (icMDS) we summarize these developments. We first critically examine the updated World Health Organization (WHO) classification and the International Consensus Classification (ICC) of MDS. We then compare traditional and molecularly based risk MDS risk assessment tools. Lastly, we discuss limitations of criteria in measuring therapeutic benefit and highlight how the International Working Group (IWG) 2018 and 2023 response criteria addressed these deficiencies and are endorsed by the icMDS. We also address the importance of patient centered care by discussing the value of quality-of-life assessment. We hope that the reader of this review will have a better understanding of how to classify MDS, predict clinical outcomes and evaluate therapeutic outcomes.

1. Introduction

In the last two years, significant changes in the diagnostic evaluation, prognostication, response assessment and therapeutic landscape of MDS have occurred.

First, the updated 2022 World Health Organization (WHO) [1] and the International Consensus Classification (ICC) [2] have been published (Fig. 1). One notable and clinically relevant difference between both classification systems is the creation of a novel entity of "MDS/AML" in the ICC but not the WHO classification. The incongruence between these systems should be taken into account in diagnosis and management to best promote clinical drug development and eventual drug approvals [3].

Second, several prognostic tools integrating information on recurrently found mutations in MDS into traditional prognostic scoring systems based on clinical information have been presented and are now increasingly included into clinical decision making such as the recently developed International Prognostic Scoring System-Molecular (IPSS-M) (Figs. 2 and 3) [4,5]. Yet, it remains unclear to what extent these new molecularly-based risk assessment tools can guide therapeutic decisions in clinical practice and how to address the reality that much of the world does not have access to large next generation sequencing (NGS) panels.

The 2006 International Working Group (IWG) MDS response criteria have been widely employed, guiding not only clinical practice but also as surrogate endpoints of clinical trials and informing regulatory reviews [6]. Nevertheless, they have multiple limitations that impact their ability to measure clinical benefits of investigational drugs and to be used as a surrogate for longer-term patient benefit (e.g., overall survival (OS)). To help overcome these limitations and to be more reflective of patient-centered and clinically relevant outcomes in HR-MDS, a new version of the IWG MDS response criteria was recently developed (Figs. 4, 5 and 6) [7].

During and in the year following the first international workshop on MDS (iwMDS) held in Miami, Florida in June 2022, members of the International Consortium for MDS (icMDS) discussed changes in the diagnostic classification, prognostication, and response assessment in MDS.

In this review, we summarize some of the lessons learned and provide practicing physicians with guidance in using the new diagnostic classification (Fig. 1), prognostication (Figs. 2 and 3) and response assessment systems (Figs. 4, 5 and 6) in clinical practice. We critically discuss potential issues and shortcomings of the updated diagnostic classifications of MDS and give readers an in-depth explanation of the rationale behind the new response criteria in MDS.

2. How should we classify MDS?

The WHO classification of Haematolymphoid Tumours replaced the French-American-British (FAB) classification in 2001 and was revised in 2008 and 2016 [8–10]. The WHO classification system has been widely used in MDS for diagnostic pathology reporting, clinical trial eligibility and disease registry reporting across the world. However, with the widespread use of genetic testing in MDS, a revised classification incorporating more of the genetic aspects of the disease was published in 2022 as part of the 5th edition of the WHO classification of diseases [1,11]. At the same time the ICC of myeloid neoplasms, which also emphasizes molecularly defined disease subtypes, was developed [12].

What unifies both classification systems, is the increased emphasis on molecularly defined subtypes of MDS [13,14]. Deletion of 5q and mutations in *SF3B1* and *TP53* now define unique MDS subtypes in both classifications, although with some minor differences in defining criteria of the latter two [1,12].

However, there are some discordances between the classifications which have the potential to confuse treating clinicians and patients and hence can affect clinical care, the design, conduct and interpretation of clinical trials as well as regulatory aspects of novel agent approval (Fig. 1). In the next paragraph we point out the most significant differences between the classification systems as they pertain to MDS.

The first example of differences between the classification systems is the definition of the term "MDS" itself, as the WHO adopted a new terminology of "myelodysplastic neoplasms" to emphasize the neoplastic nature of MDS (while at the same time retaining the abbreviation of MDS) whereas the ICC maintained the term "myelodysplastic syndromes" (Fig. 1). [1,12] This inconsistency in terminology may affect how data are entered into large publicly available disease registries (e.g., Surveillance, Epidemiology, and End Results [SEER]), and how drug reimbursement and medical billing codes are processed. To be consistent, it might be easiest to agree to code and reimburse MDS as a neoplasm.

The WHO 2022 classification also added hypoplastic MDS (MDS-h) and MDS with fibrosis (MDS-f) as distinct disease subtypes, but these are absent in the 2022 ICC (Fig. 1) [1,12]. These two disease categories have

unique clinical features, with hypoplastic MDS being associated with an increased likelihood of response to immunosuppressive therapy [15] and MDS with fibrosis being associated with a worse clinical prognosis [16]. Another difference in morphologic interpretation and classification is the retention of the single versus multilineage dysplasia distinction in the ICC, whereas this distinction is optional in the WHO classification.

The most clinically relevant difference between the 2022 WHO and ICC classification is the creation of a novel entity of "MDS/AML" in the ICC, defined as 10–19% blasts in the peripheral blood and/or bone marrow in the absence of AML-defining genetic abnormalities (Fig. 1) [12]. In contrast, the WHO classification retains the cut-off of 20% blasts to distinguish MDS from AML while renaming "MDS with excess blasts 2" (MDS-EB2) as "MDS with increased blasts 2" (MDS-IB2) [1]. Both classification systems present their rationale for how MDS with 10–19% blasts is defined. The WHO does however acknowledge that there are limitations of applying an arbitrary 10% blast cut-off when distinguishing MDS-IB2 from AML but ultimately advocated that a numeric blast cut-off regardless of the threshold is subject to the same challenges and may result in overtreatment or possibly undertreatment in a subset of patients.

The ICC classification argues that the prognosis of MDS patients with 10–19% blasts is comparable to patients with so-called oligoblastic AML defined by 20–30% blasts and that the historic threshold of 20% blasts is not supported by differences in disease biology [2,17,18]. The lack of survival difference for patients with 10%–19% vs. >20% blasts in the original International Prognostic Scoring System (IPSS) and its Revised version (IPSS-R) is consistent with these observations [19,20]. In addition, the decision of the ICC to abandon the arbitrary threshold of 20% blasts is a practical one: MDS patients with 10–19% blasts and oligoblastic AML are already frequently enrolled in the same clinical trial protocols. Therapeutic regimens approved for AML, such as DNMTi plus venetoclax or liposomal cytarabine-daunorubicin, are sometimes used off-label for MDS patients albeit differences in dosing schedules such as a 14-day instead of a 28-day dosing schedule of venetoclax for MDS patients compared to AML patients. [21–23] The ICC argues that the new

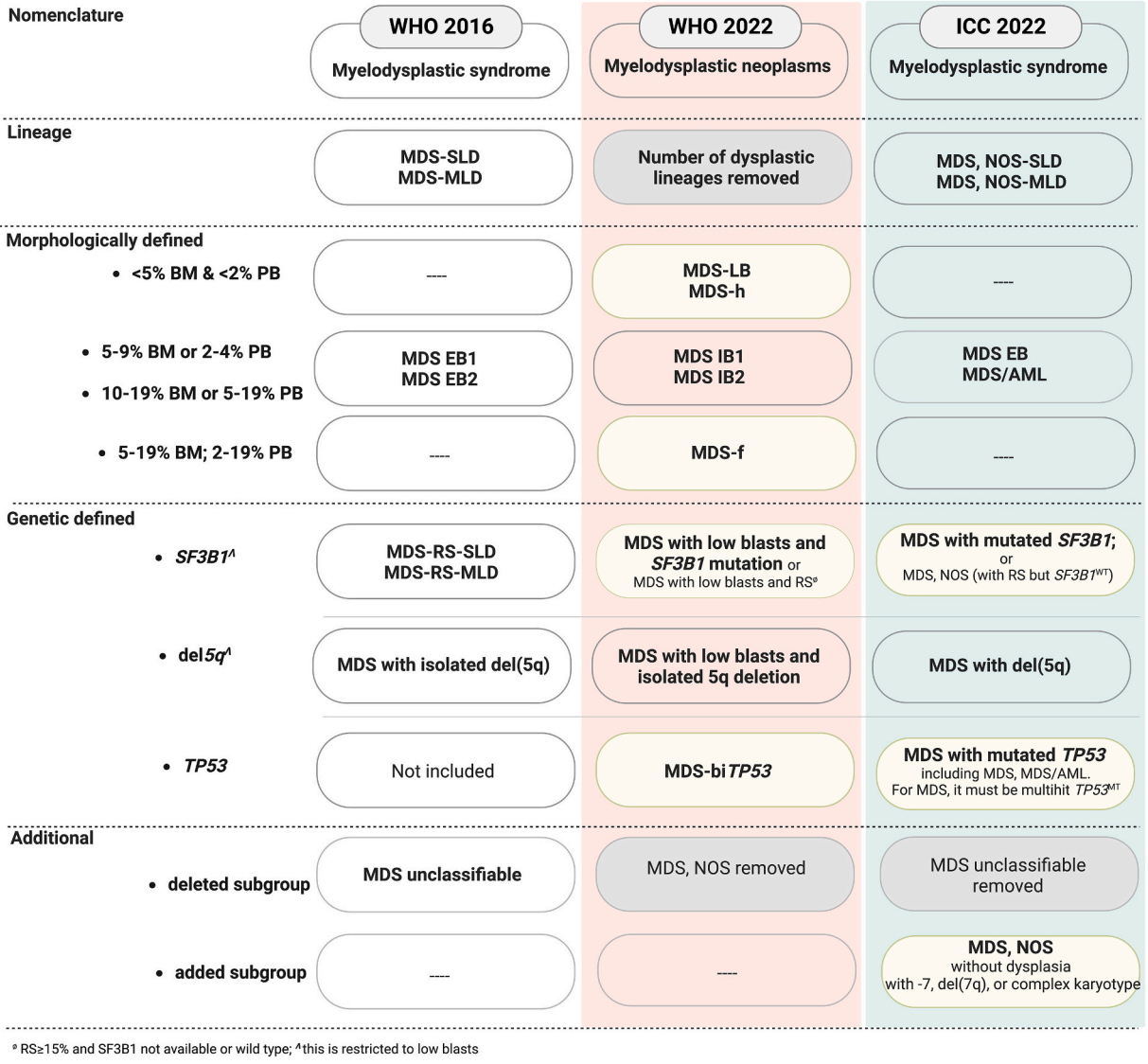
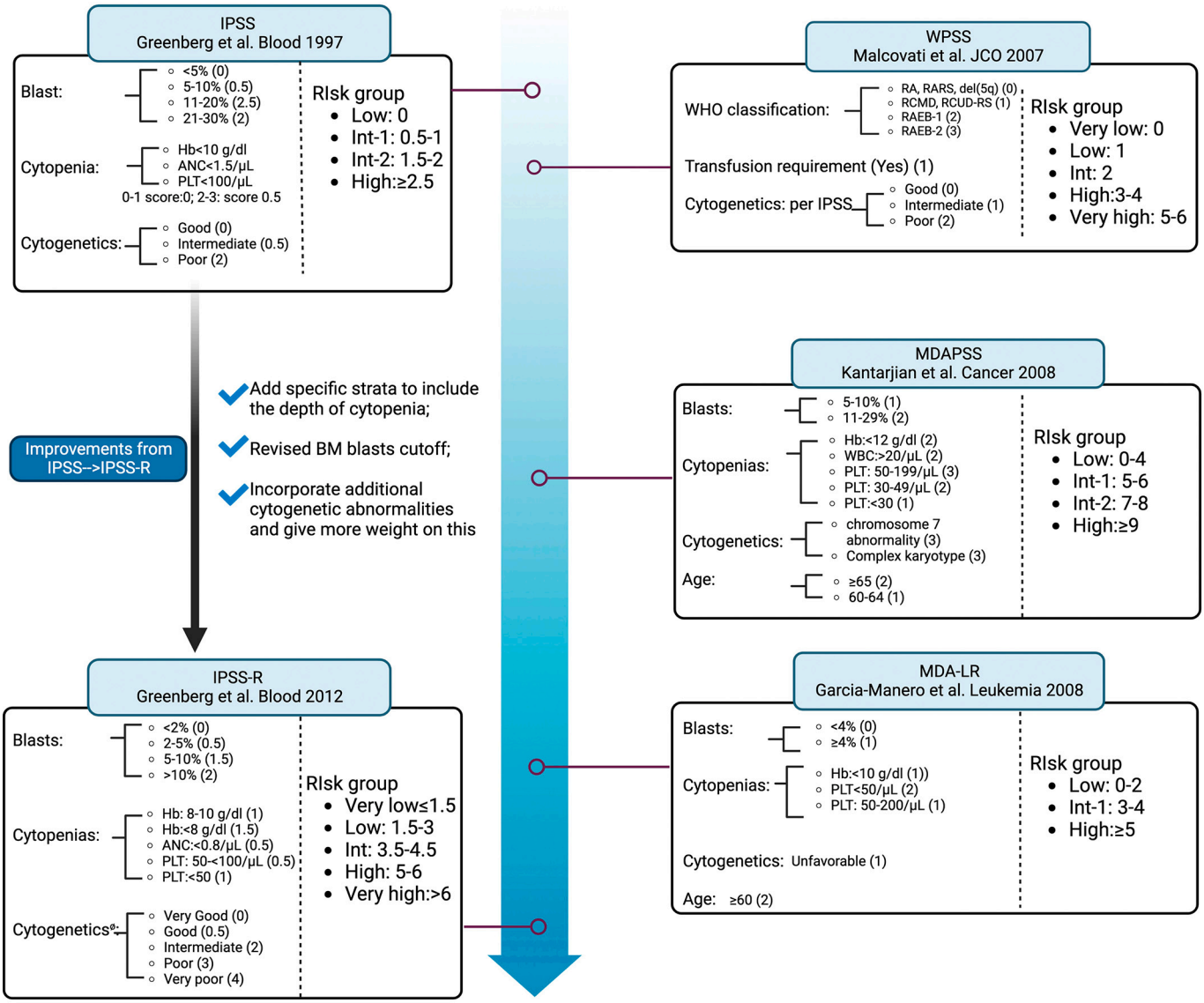


Fig. 1. Comparison of MDS classification systems (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).
Grey color indicates the item was removed; light yellow color indicates the items were added. $^{\varphi}$ RS $\geq$ 15% and SF3B1 not available or wild type.
Abbreviations: EB: excess blasts; IB: increased blasts; ICC: International Consensus Classification; MDS: myelodysplastic neoplasms/syndromes; MLD: multilineage dysplasia; SLD: single lineage dysplasia; NOS, not otherwise specified; MDS-h: MDS, hypoplastic; MDS-f: MDS with fibrosis; MDS-LB: MDS with low blasts; RS: ring sideroblasts; WT: wild type; WHO: World Health Organization; MT: mutation.

MDS/AML subtype will allow enrollment of MDS patients with 10–19% blasts to either MDS or AML trials and thus possibly speed up drug approval in this subgroup of MDS patients. In addition, the ICC argues that the MDS/AML disease category could have important implications from a health system and payer perspective in allowing a broader utilization of novel therapies approved in AML.

In contrast, the WHO classification argues that lowering the blast cut-off to 10% ultimately replaces one arbitrary cut-off with another. In addition, treating MDS patients with 10–19% blasts as AML patients introduces the risks of overtreatment and excessive toxicity. At the time of diagnosis, MDS patients are almost a decade older than those with AML (median age 77 years vs. 68 years) and have lower bone marrow reserve and reduced ability to tolerate intensive treatments [24,25]. Furthermore, it is possible that therapeutic agents might not show the same efficacy in oligoblastic AML and MDS/AML, leading to issues in clinical trial design and interpretation. In addition, it should be mentioned that there could be negative psychological consequences about having confusing or conflicting diagnoses for the same patient. Lastly, if patients with AML with <30% blasts and AML/MDS patients are treated in the same clinical trial protocol, it is currently unclear whether the 2017/2022 European LeukemiaNet (ELN) AML [26,27] or the 2006 IWG MDS response criteria should be employed to measure



[ϕ]**IPSS-R cytogenetic prognostic subgroups**: **Very good**-Y, del(11q); **Good:** Normal, del(5q), del(12p), del(20q), double including del(5q); **Intermediate:** del(7q), +8, +19, i(17q), any other single or double independent clones; **Poor:** -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities; **Very poorComplex:** >3 abnormalities

Fig. 2. Conventional risk assessment tools in MDS.
[ϕ]IPSS-R cytogenetic prognostic subgroups: **Very good**-Y, del(11q); **Good:** Normal, del(5q), del(12p), del(20q), double including del(5q); **Intermediate:** del(7q), +8, +19, i(17q), any other single or double independent clones; **Poor:** -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities; **Very poor:** Complex: >3 abnormalities
Abbreviations: IPSS: International Prognostic Scoring System; IPSS-R: International Prognostic Scoring System- Revised; WPSS: WHO classification-based Prognostic Scoring System; RA: refractory anemia; RARS: refractory anemia with ring sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; RCUD-RS: refractory cytopenia with unilineage dysplasia and ring sideroblasts; RAEB-1: refractory anemia with excess blasts-1; RAEB-2: refractory anemia with excess blasts-2; MDAPSS: MD Anderson Prognostic Scoring System; MDA-LR: MD Anderson Lower Risk Prognostic Scoring System; int: intermediate; Hb: hemoglobin; ANC: absolute neutrophil count; PLT: platelets.

response [6]. One illustrative example of the importance of the specific response criteria employed to measure clinical benefit is the the phase II trial of CPX-351 in higher risk MDS [28,29]. In this trial, response assessment by the 2017 ELN response criteria resulted in a CR rate of 52% but CR rate was only 23% when assessed by 2006 IWG MDS response criteria [28,29].

In this context, members of the icMDS recently published the updated 2023 IWG MDS response criteria which specifically includes an effort to harmonize response criteria for higher risk MDS with the 2022 ELN response criteria for AML. A practical consideration for now is that patients with 10–19% blasts should be evaluated by the 2023 IWG MDS response criteria if treated on MDS trials, and with ELN 2022 criteria if treated on AML trials. However, future efforts are needed to carefully re-examine the distinction between AML and MDS, as it pertains to patients with oligoblastic AML and AML/MDS recognizing that the underlying disease biology should drive inclusion criteria for clinical trials rather than physicians' tendencies to lump according to titles, rather than biology.

In summary, both classification systems are reasonable proposals in isolation, however, the presence of two parallel and at times conflicting classifications creates confusion for physicians, researchers, regulators and most importantly our patients. Hence, harmonization of the dual classification systems would likely reduce ambiguity for physicians, researchers, regulators and most importantly patients.

An effort to propose a harmonization of both classification systems was recently initiated by the members of the icMDS by applying the 2022 WHO and ICC criteria to a cohort of 2231 USA-based MDS patients with extensive molecular annotation and examining clinical outcomes associated with each defined MDS entity [30]. For example, genetically defined entities (*SF3B1*-mutant, deletion 5q, and biallelic *TP53* loss) were clearly unique and validated as distinct disease categories, as proposed by both the WHO and ICC. This effort is now being expanded by adding data from >4000 patients from the European GenoMed4All database to create perhaps the largest molecularly annotated dataset of >7000 patients with MDS to inform the classification revision in an evidence-based fashion.

While the icMDS recognizes that there are other potential ways to unify both classification systems, and each new classification system has its own shortcomings, its members strongly agreed that development of a single classification system for MDS will minimize confusion among clinicians, regulatory agencies, and patients alike. The MDS field should note that conflicting classifications, such as occurred with the lymphoid malignancies (Kiel, Rappaport, Working Formulation, etc), were successfully resolved by the consensus 1994 Revised European-American Lymphoma (REAL) classification and subsequently improved as technological advances incorporated disease biology into the clinical system [31]. As it is unlikely that a unified classification system is developed in the near future, we leave the reader with our suggestions on how to best deal with the reality of two parallel classifications for the next several years. This has recently been concisely formulated by Robert Hasserjian, a member of the icMDS and President of the Society for Hematopathology, and by Stefan Dirnhofer, President of the European Association for Hematopathology in letters to Society members [32,33]. In these communications, hematopathologists are urged to become familiar with using both classifications and wherever possible to provide both the ICC and WHO diagnosis in pathology reports. While it is acknowledged that this might complicate workflows and pathology reports, it is stressed that this practice is essential to ensure patient safety and maintain transparency with clinicians, clinical researchers, and our patients. He advocates that the community come together in our shared objective to better understand hematologic diseases and help patients get the best treatments and outcomes [32]. We feel that ultimately a universally accepted single classification in its next iteration would help achieve this and that such a future classification will include further refinement of the different diagnostic groups based on the underlying MDS disease biology similar to what has already been done for 5q- and *SF3B1* and *TP53* mutated MDS in the current classification systems.

In the meantime, we feel that advocating the use of one or the other

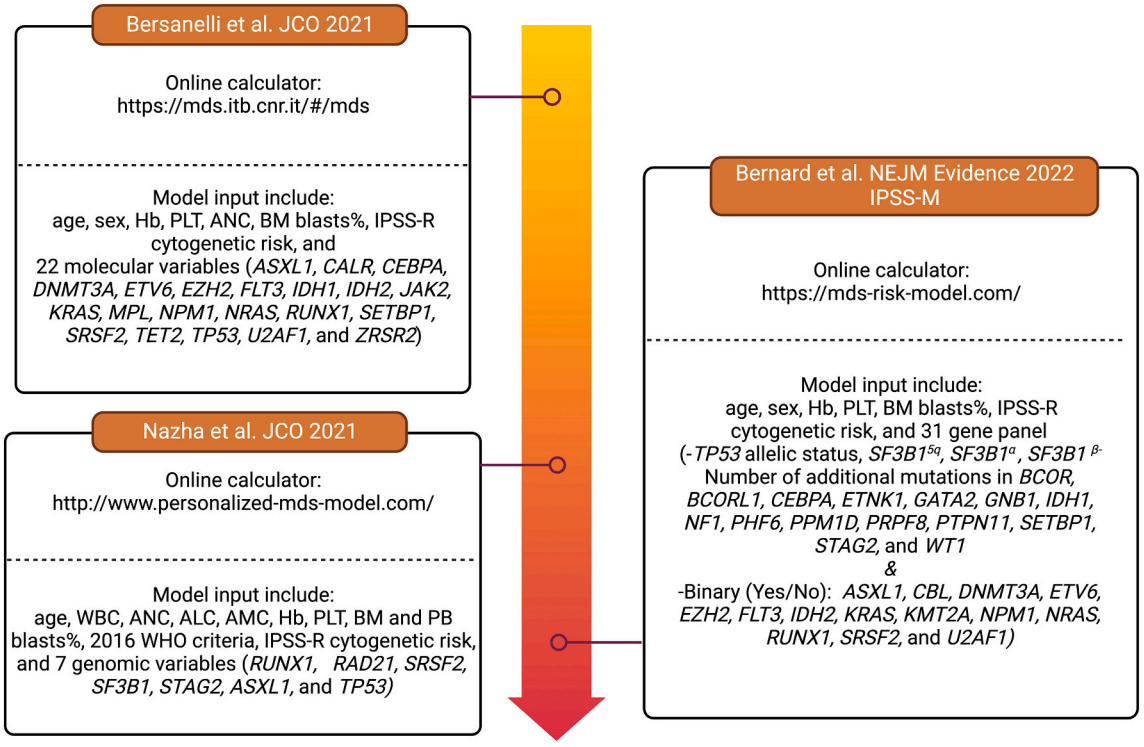
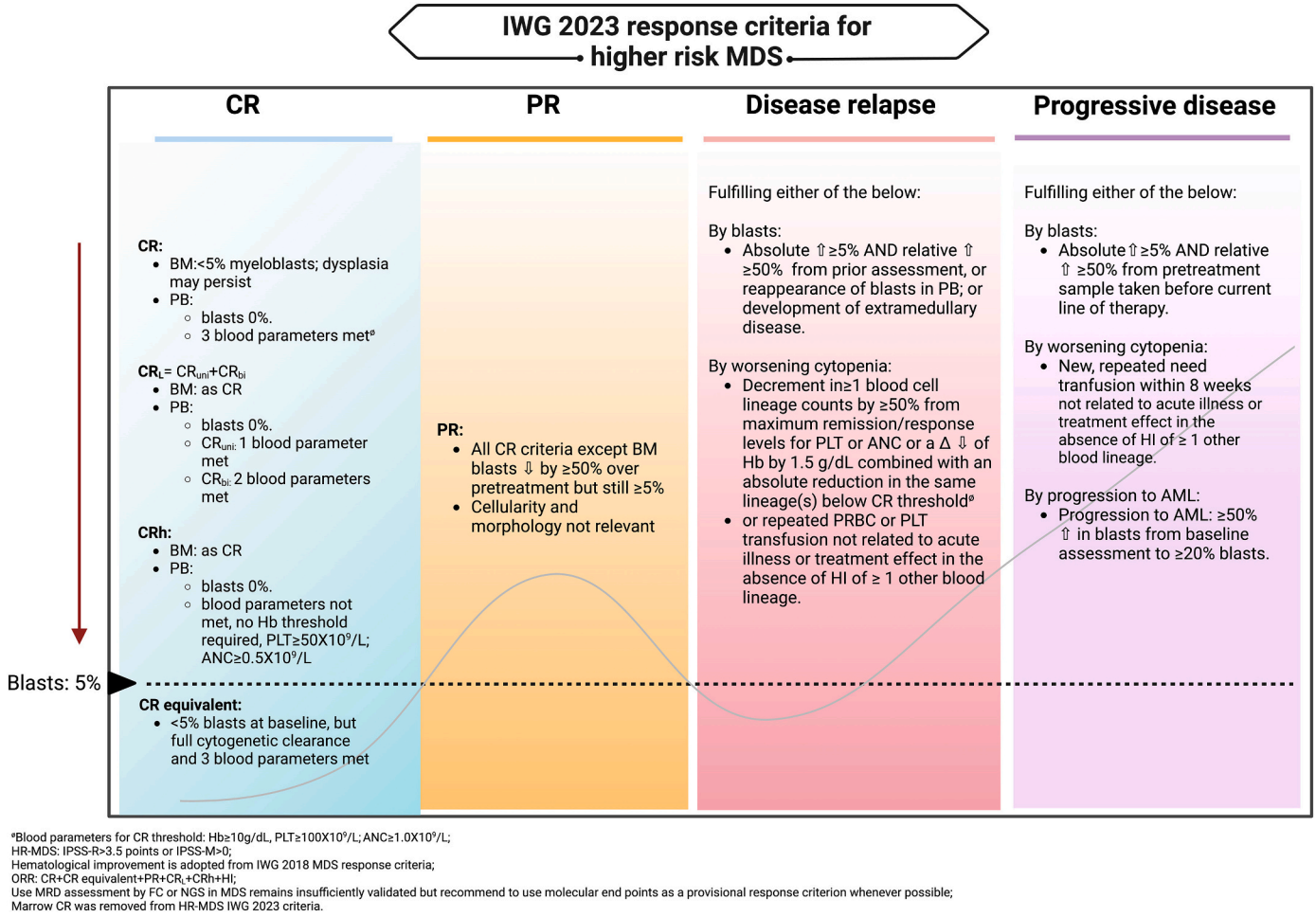


Fig. 3. Molecular risk assessment tools in MDS.
Abbreviations: WBC: white blood cell count; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; AMC: absolute monocyte count; Hb: hemoglobin; PLT: platelets; BM: bone marrow; PR: peripheral blood.



⁰Blood parameters for CR threshold: Hb≥10g/dL, PLT≥100X10⁹/L; ANC≥1.0X10⁹/L;
HR-MDS: IPSS-R>3.5 points or IPSS-M>0;
Hematological improvement is adopted from IWG 2018 MDS response criteria;
ORR: CR+CR equivalent+PR+CRL+CRh+HI;
Use MRD assessment by FC or NGS in MDS remains insufficiently validated but recommend to use molecular end points as a provisional response criterion whenever possible;
Marrow CR was removed from HR-MDS IWG 2023 criteria.

Fig. 4. 2023 IWG MDS response criteria.
øBlood parameters for complete remission: Hb $\geq$ 10 g/dL, PLT $\geq$ 100 $\times$ 10^9/L; ANC $\geq$ 1.0 $\times$ 10^9/L; Repeated blood transfusion means needing blood transfusion (RBC or platelet) more than once and separated by at least 7 days. Marrow CR and stable disease were removed from HR-MDS IWG 2023 criteria. Hematological improvement is adopted from IWG 2018 MDS response criteria; ORR = CR (or CR equivalent) + PR+ CRL + CRh + HI; Use MRD assessment by FC or NGS in MDS remains insufficiently validated but recommend using molecular end points as a provisional response criterion whenever possible.
Abbreviations: BM: bone marrow; CBC: complete blood count; CR: complete remission; CRL: CR with limited count recovery; CRbi: CR bilineage; CRh: CR with partial hematologic recovery; CRuni: CR with unilineage; Hg: hemoglobin; HI: hematologic improvement; PB: peripheral blood; PD: progressive disease; PR: partial remission; PLT: platelet; ANC: absolute neutrophil count.

classification system alone would further divide the hematopathology community and would likely lessen the chances of arriving at universally accepted single classification.

3. How should we assess risk in MDS?

Treatment intensity in MDS ranges from observation and erythropoiesis stimulating agents (ESA) for patients with lower-risk MDS to DNMTi-based therapy and allogeneic stem cell transplantation for higher-risk disease. Accurate risk assessment is essential in matching the correct treatment intensity to the right patient. Both "undertreatment" (e.g., delaying allogeneic stem cell transplant in patients who would benefit from it) as well as "overtreatment" (e.g., starting DNMTi-based therapy in patients with low risk MDS and cytopenias not requiring transfusions) should be avoided. Multiple risk-stratification models have been developed and more recently, our ever-improving understanding of the impact of mutations in MDS prognosis has resulted in novel new molecular-based prognostication tools (Figs. 2 and 3) [34].

The initial prognostic models of MDS included the International Prognostic Scoring System (IPSS) [35] published in 1997 and the Revised IPSS (IPSS-R) [20] published in 2012. Several other models have been published, including the WHO Classification-based Prognostic Scoring System (WPSS) [36], the MD Anderson Prognostic Scoring System (MDAPSS) [37] and the MD Anderson Lower Risk MDS model (MDA-LR) [38](Fig. 2). These early prognostic models share major variables to calculate disease risk including number and depth of cytopenias, the bone marrow blast percentage and a variety of prognostically important cytogenetic abnormalities. While the IPSS and IPSS-R were initially only designed to produce a risk estimate at the time of diagnosis, the WPSS and MDAPSS were developed as time-dependent models that can accommodate a patient's changing disease risk over time. It is important to note that the IPSS-R was subsequently shown to retain prognostic power for patients receiving disease-modifying therapy [39] or at the time of stem cell transplant [40] hence demonstrating its validity at other timepoints apart from the timepoint of first diagnosis.

A leap forward in developing prognostic models came following large scale sequencing efforts which led to the identification of recurring genetic mutations in MDS and other myeloid neoplasms [41–43]. At least one mutation is detectable in approximately 90% of cases of MDS, using standard NGS multigene panels; MDS is quite heterogeneous, however, with only four to six genes are found to be recurrently mutated in $\geq$10% of patients, while over 40 genes are mutated less frequently [41–43].

A unique position within prognostication is occupied by mutations in

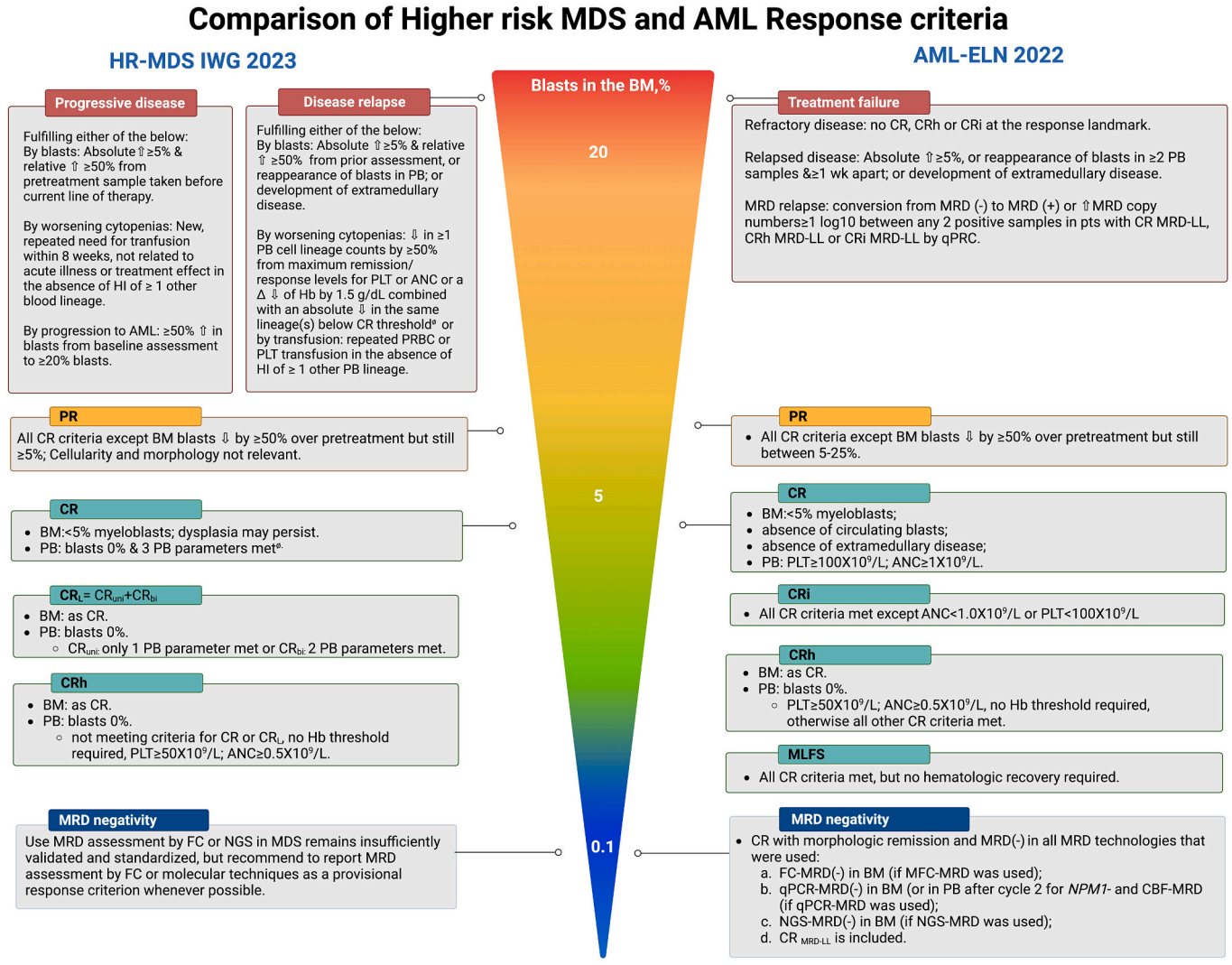


Fig. 5. Comparison for higher-risk MDS and AML response criteria.
[a]Blood parameters for CR threshold: Hb $\geq$ 10 g/dL, PLT $\geq$ 100 $\times$ 10^9/L; ANC $\geq$ 1.0 $\times$ 10^9/L.
If patients meet criteria for both CRL and CRh, they should be reported as having achieved CRL for the ORR.
Marrow CR was removed from IWG 2023, but it is an equivalent of MLFS in AML ELN 2022.
Abbreviations: AML: acute myeloid leukemia; ANC: absolute neutrophil count; BM: bone marrow; CR: complete remission; PR: partial remission; CR_L: CR with limited count recovery; CRh: CR with partial hematologic recovery; CR_{MRD-LL}: MRD detection at low level; HHI: hematological improvement; FC: flow cytometry; Hb: hemoglobin; HR-MDS: higher risk myelodysplastic syndrome/neoplasm; MLFS: morphology leukemia-free state; MRD: measurable residual disease; NGS: next generation sequencing; PB: peripheral blood; PLT: platelet

TP53. *TP53* gene mutations are encountered in 5–10% of patients with MDS and portend a poor prognosis, with lower response to therapy, higher rates of progression to AML, and significantly shortened OS. [44] However, it is becoming increasingly understood that not all *TP53* mutations carry equal prognostic weight and that distinct patient subpopulations exist even within the cohort of *TP53*-mutated MDS [45]. Patients with multi-hit *TP53* mutations, defined as either two separate *TP53* mutations or loss of the remaining wild type allele, have significantly worse outcomes compared to patients with only one single-hit *TP53* mutation [45]. This finding is crucial to distinguish in clinical practice, as patients with a multi-hit state of *TP53* mutations should be referred to innovative clinical trials early in their disease course [46].

A first attempt at integrating mutation data into prognostic models demonstrated that a model that included age, IPSS-R risk, *EZH2*, *SF3B1*, and *TP53* mutations exhibited a superior C-index for predicting OS compared to the IPSS-R [43,47]. A follow-up study demonstrated similar improvements by including genetic information into the IPSS, WPSS, and MDAPSS, which upstaged a significant proportion of patients compared to the original models [48]. Since then, three separate molecular based models have published by Bersanelli et al [14], Nazha et al. [5] and Bernard et al. (IPSS-M) [49] (Fig. 3).

There are both overlap and differences between these models (Fig. 3). All three models included primarily patients with de novo MDS (although the model by Nazha et al. and Bernard et al. also contained patients with secondary MDS), included patients who had received disease modifying therapy, and used age, cytogenetics, and gene mutations as co-variables [48]. An important difference between the models is the number of mutations included in the models. Bersanelli et al. included 22 genes and another 24 optional genes in the prediction model [14]. In contrast, the model from Nazha et al. reduced a larger

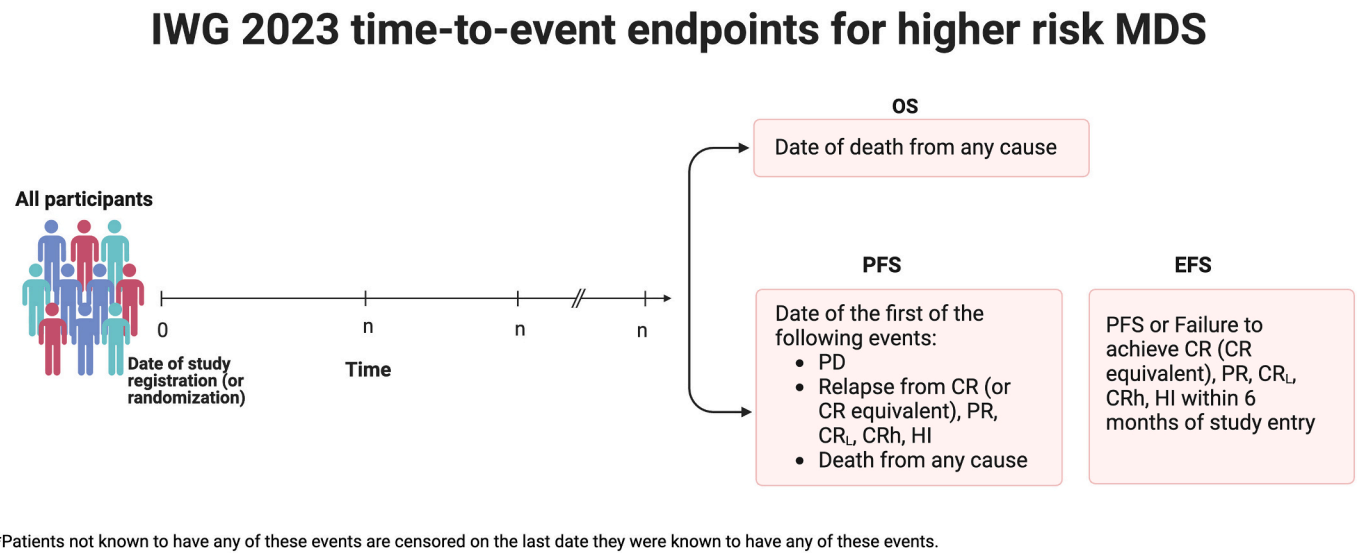


Fig. 6. 2023 IWG MDS response criteria time-to-events assessment.
OS: Overall survival; PFS: Progression free survival; EFS: Event free survival.

mutation dataset to the most impactful seven mutations along with the mutation number, as a broader capture of mutations did not have an impact on the model accuracy [5]. Lastly, the IPSS-M includes a total of 16 genes which independently correlated with outcomes.

However, with the ever-increasing popularity of molecularly based assessment methods, several open questions remain:

First, which one of these prognostic models should be used in clinical practice? The tools have not been directly compared to each other and have been derived from different populations of MDS patients. The IPSS-M provides an easy online calculator tool. However, one important limitation of the IPSS-M is that many laboratories (even when they are based in large academic centers) do not routinely assess for *TP53* loss of heterozygosity (LOH) and *MLL* partial tandem duplication (PTD) in their NGS panels, despite these two genetic lesions having the most significant impact on risk in the IPSS-M. Several studies validating the IPSS-M and comparing its predictive power in comparison to less resource intensive risk stratification methods are under way under the auspices of the icMDS.

Second, not all physicians taking care of MDS patients, in particular outside of the U.S. and European Union, have ready access to multi-gene NGS tools. In addition, even in countries in which NGS tools are readily available, their use is not always reimbursed by insurance limiting the access to this technology for some MDS patients. While the IPSS-M requires information on 31 genes, the risk assessment score developed by Nazha et al only requires information on the mutational status of seven genes and might be easier to incorporate in more resource restricted settings [5,49]. Thus, important questions in a setting, in which NGS is either not available or not reimbursed, are which patients truly require mutational based risk assessment and which risk assessment is the most practical to employ in these patients. The icMDS is planning to study these questions in a large cohort of patients with MDS from around the U.S. and the European Union.

Third, how should these new molecularly based risk assessment tools guide therapeutic decisions? The use of DNMTi and allo-SCT therapies have all been studied using traditional risk assessment tools such as the IPSS and the IPSS-R. The landmark AZA-001 trial demonstrated an improved median OS in patients with IPSS intermediate-2 or high-risk MDS compared to patients receiving conventional care [50]. Whether this survival advantage achieved with DNMTi therapy can be extended to patients with low or intermediate-1 risk per IPSS who are upstaged to a higher risk employing molecularly based risk assessment tools is not entirely clear. Similarly, for the decision on whether to proceed to an allo-SCT, a Markov model showed that IPSS intermediate-2 or high-risk patients experienced longer survival if they received transplantation at diagnosis compared to delayed transplantation, which should be reserved for MDS patients with IPSS low and intermediate-1 risk [51]. Similar conclusions were reached employing the IPSS-R in a continuous-time Markov model with survival maximized when allo-SCT was delayed for IPSS-R very low and low-risk patients but not for those with higher risk [64]. An open question is whether all patients with lower-risk MDS based on IPSS and IPSS-R, but high molecular risk should be preferentially transplanted upfront. Another open question relates to how the timing of DNMTi therapy initiation and the decision to proceed with allo-SCT differ for patients with higher-risk disease assessed using traditional variables (cytopenias, blast percentage) versus for those with high-risk mutations in the absence of abnormal blood counts/increased bone marrow blasts. Lastly, it is important to remember that a key component of determining the best treatment for a patient cannot be encompassed in any classification system, namely the tempo of the disease and the presence of disease complications, or threatening complications, that may affect patient outcomes. These features should be considered, for proper clinical decision making for all patients with myeloid malignancies. In other words, clinical judgement should not be replaced by any rigid classification scheme.

In the setting of two diagnostic classifications and multiple risk stratification systems with ever increasing complexity, it is an important question what clinical and molecular information is essential for basic classification, prognostication, and therapeutic implication in particular in resource limited settings. A recent study analyzed of a total of 7017 MDS in the icMDS, genetically defined entities (*SF3B1*-mutant, del5q, and bi-*TP53*) were clearly unique in terms of prognosis and therapeutic decisions and hence a chromosomal analysis and assessment for mutations in *SF3B1* and *TP53* are essential [52]. Among morphologic categories, outcome of patients with MDS-RS *SF3B1* wild type (WT) was not different from MDS low blasts (LB) and hence assessment of ring sideroblasts does not seem to be equally important if sequencing for *SF3B1* mutation is available. MDS with fibrosis (MDS-f) should potentially be reported as it portends worse survival outcomes compared to MDS-LB without fibrosis. While in this analysis the WHO hypoplastic MDS group (MDS-h) had similar median OS compared to the LB group and was hence not prognostic, we would recommend reporting it as it has been associated with responsiveness to immunosuppressive therapy. The specific blast percentage cutoff that defines MDS with excess blasts remains debated, and there are ongoing analyses to address this

question, including within the icMDS.

4. How should we measure therapeutic success in MDS?

During the iwMDS meeting thoughtful discussions were held regarding the shortcomings of the 2006 IWG diagnostic criteria [6,53]. Out of these discussions, consensus was established that novel response criteria are needed [53]. Concurrently, a parallel effort by an international panel of 36 MDS experts resulted in a proposal for the 2023 IWG MDS response criteria (Fig. 4) [7,53]. In this section, we discuss shortcomings of our measures of success in lower- and higher-risk MDS, and how the updated 2018 response criteria for lower-risk MDS [54] and the 2023 response criteria for higher-risk MDS address these issues [7]. Therefore, the icMDS members endorse the IWG 2018 and 2023 criteria as the recommended methods of measurement of therapeutic success in clinical trials and routine practice for lower- and higher-risk MDS, respectively.

4.1. Measurement of response in lower-risk MDS

The predominant issue in lower-risk MDS is anemia which is present in approximately 85% of MDS patients at the time of diagnosis [55]. In lower-risk MDS patients, the main priority is usually the treatment of cytopenias, mainly anemia, and the improvement in quality of life [55–58]. The standard of care for lower-risk MDS is supportive treatment with RBC transfusions, ESAs and luspatercept and lenalidomide in certain subtypes of lower-risk MDS [55].

Accordingly, primary endpoints of trials for patients with lower-risk MDS are hematologic improvement (HI) including erythroid (HI-E), neutrophil (HI-N) and platelet (HI-P) response rate and RBC transfusion independence (RBC-TI). Unfortunately, the durability of response to current standard of care therapies is limited as these agents do not generally have a significant disease modifying effect. For instance, the median duration of response to ESAs is only approximately 15–18 months [59,60].

Accordingly, past clinical trials have been designed with endpoints reflecting rather modest goals. In the phase III MEDALIST trial, which tested luspatercept in patients with MDS with ring sideroblasts (defined as either ≥15% ring sideroblasts or ≥ 5% ring sideroblasts plus an *SF3B1* mutation), the primary endpoint was ≥8 weeks of RBC-TI during the first 24 weeks of therapy [61]. The trial showed superiority of luspatercept with 38% (95% CI 30–46%) of patients who received luspatercept achieving ≥8 week RBC-TI during weeks 1–24, versus 13% (95% CI 6–23%) of those receiving placebo ($p < 0.001$), for an absolute difference of 25% [61]. However, keeping the patient's perspective in mind, one wonders whether choosing an endpoint of ≥8 weeks of RBC-TI is aiming too low for our patients. In the United States, luspatercept for example is administered in the clinic and subsequently a significant burden is put on a patient to achieve the ≥8-week RBC-TI. Moreover, in the MEDALIST trial the RBC-TI is achieved in less than half of patients, the median duration of the longest single episode of RBC-TI was 30.6 weeks (95% CI 20.6–30.6) with luspatercept, and only 19% of patients achieved ≥16-week RBC-TI. Is this significant effort from the patient truly worthwhile to a patient considering that they must repeat this procedure every 3 weeks? Do we as the treating physicians need to be more critical of what constitutes a meaningful response in lower-risk MDS? In addition, this case example illustrates that a meaningful benefit derived from a novel therapy depends not only on the response to the drug, but also on side effects and the organization of care in a given country health system. Similar concerns exist for ESA which in the case of epoetin alfa are administered weekly.

The members of the iwMDS believe that future trials in lower-risk MDS should be more ambitious in what they are trying to achieve and how they measure success while at the same time remaining realistic to not prevent the development of promising therapeutic agents. An imperative should be to adjust the endpoints of clinical trials and demand a longer durability of HI and RBC-TI to ensure a clinical benefit that is aligned with the patient's perspective. The updated 2018 IWG response criteria updated response assessment specifically for patients with lower-risk MDS [54]. The 2018 IWG response criteria adjusted the time frames for the screening and observation periods for measuring RBC transfusion dependence and achievement of RBC-TI. While the screening period before initiation of treatment was not explicitly described in the 2006 IWG MDS response criteria it was generally accepted to be 8 weeks; the 2018 IWG MDS response criteria recommend a longer period of 16 weeks prior to initiation of treatment. Furthermore, the observation period for achievement of RBC-TI was extended from 8 weeks to 16–24 weeks [62,63].

The recently presented phase III COMMANDS trial, which demonstrated the superiority of luspatercept over ESA in the frontline management of lower-risk RBC transfusion dependent MDS, used RBC-TI for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL (weeks 1–24), assessed in the intention-to-treat population as the primary endpoint[64]. In contrast, the phase III IMerge trial, which showed superiority of imetelstat over placebo in patients with lower-risk MDS refractory or ineligible for ESA, still used a shorter 8-week transfusion independence period similar to the previously published MEDALIST trial as the primary endpoint of the trial. However, it is important to note that a longer 24-week transfusion independence period was a key secondary endpoint of the IMerge trial which was met along the primary endpoint of only an 8-week transfusion independence period. These trials are good examples that in evaluating therapeutic options for patients with lower risk MDS trials are starting to use longer transfusion independence periods to assess the efficacy of novel agents.

The icMDS believes that future investigation should go one step further in better defining meaningful endpoints in clinical trials for patients with lower-risk MDS: while transfusion independence will remain an important endpoint, endpoints measuring disease modification such as clonal eradication will require prospective evaluation in clinical trials [65].

4.2. Measurement of response in higher-risk MDS

Given the increased risk of progression to AML compared to lower-risk MDS, the goal in higher-risk MDS is to alter the natural course of MDS, delay the progression to AML, and prolong survival [66]. Phase II trials in higher-risk MDS frequently use the standardized response criteria in MDS initially developed by the IWG in 2000 and updated in 2006 as primary endpoints [6,67]. If a new investigational agent is considered promising based on a high response rate (ideally identified from randomized phase 2 data), it is then compared to the current standard of care (which is DNMTi monotherapy) in either randomized phase II or phase III clinical trials to assess and compare event-based outcome measures including OS as well as event- and progression-free survival (EFS, PFS, respectively). However, single arm trials using a variety of different response definitions that seemed promising, have failed to demonstrate in randomized testing EFS or OS benefit for multiple agents. [68,69] This emphasizes the necessity for well-designed randomized trials so that phase III testing can be rationally prioritized.

Hence, at the first iwMDS meeting, icMDS members spent significant time discussing what constitutes meaningful response criteria with the goal to better predict event-based outcomes. A concurrent effort by the IWG resulted in the publication of the 2023 MDS response criteria (Fig. 4) [7]. Below, we summarize the shortcomings of the 2006 IWG response criteria [6] and how these were specifically addressed in the updated 2023 IWG response criteria [7], which the icMDS formally endorses.

Phase II trials frequently include the response criterion of so-called marrow CR (mCR) which only requires a marrow blast reduction to ≤5% and decrease by ≥50% blasts, but does not mandate any hematological improvement [6]. As a response criterion mCR is problematic as mCR without HI does not correlate with OS [70]. In contrast, CR and

mCR with HI are associated with a benefit in OS in MDS patients [70]. In another study using a patient-level analysis of eight higher risk MDS clinical trials, CR, partial remission (PR) and HI were associated with longer OS and EFS, again emphasizing the need for responses to be associated with appropriate hematological improvement in order to predict improvement in survival outcomes [71]. If non-randomized phase II trials include mCR in their ORR definition (as many ongoing trials do), the perceived benefit is inflated. Thus, if a randomized phase II or phase III trial is designed based on this potentially flawed endpoint, it will likely be negative if the endpoint is OS given that mCR does not correlate with OS. Hence, in the 2023 IWG response criteria, mCR without HI was eliminated as a formal response criterion (Fig. 4). [7] While it can be reported, in particular for patients proceeding to a subsequent allo-SCT, it should not be included in assessing the overall response rate (ORR) in a clinical trial [7].

While CR as defined by the 2006 IWG MDS criteria is the most rigorous endpoint in terms of its consistent association with an OS benefit [70,71], its definition is not without controversy either. CR in MDS has been defined as bone marrow blasts $\leq$5% with hemoglobin $\geq$11 g/dL, platelets $\geq 100 \times 10^9$/L, neutrophils $\geq 1.0 \times 10^9$/L. However, CR in AML is defined as bone marrow blasts <5% with the same platelet and neutrophil thresholds as for MDS but importantly no requirement for hemoglobin recovery [27,72]. This important difference in how CR is defined in AML and MDS, makes it significantly more difficult in MDS to reach the definition of CR compared to AML. An illustrative example are the clinical trials which tested the use of CPX-351, a liposomal combination of cytarabine and daunorubicin, in AML and higher-risk MDS. CPX-351 is already approved for the treatment of secondary AML but not MDS. In a phase II trial, which tested CPX-351 in higher-risk MDS, the CR rate was 52% when response was assessed by 2017 ELN AML response criteria but only 23% when assessed by 2006 IWG MDS response criteria [29]. This example underlines the concern that the approval of some therapies, which are already approved for the treatment of AML, might be delayed for higher-risk MDS because different measures of response are used.

The goal of the IWG 2023 criteria was to emphasize the importance of a meaningful count recovery but to also not limit provisional or accelerated drug approval in MDS with an overly strict definition of CR, which has been rarely achieved in MDS clinical trials. To address this, the definition of CR was maintained but slightly modified and the provisional response criterion of CR with limited count recovery (CR_L) was added (Fig. 4) [7]. For CR, the hemoglobin threshold was lowered from $\geq$11 g/dL to $\geq$10 g/dL [7]. The hemoglobin threshold of 11 g/dL is arbitrary and the IPSS and IPSS-R use a hemoglobin cut-off of <10 g/dL as an adverse prognostic factor [19]. Bone marrow blasts <5% are required instead of $\leq$5% to be consistent with ELN AML response criteria as well as ICC and WHO cutoffs for MDS with excess/increased blasts [7]. In addition, CR_L was introduced as a provisional new response criterion. Unlike CR, CR_L does not require count recovery in all three lineages but only two lineages ($CR_{bilineage}$) or one lineage ($CR_{unilineage}$). The hope is that it will more accurately reflect responses below CR but with adequate count recovery in one or two lineages. Response rate definitions that reasonably reflect meaningful clinical impact of a drug can be utilized in clinical trials and may assist pharma companies in gaining accelerated approval for their products. This type of strategy will allow marketing of the agent, but also allow additional time to conduct definitive trials to demonstrate clear clinical benefit in OS or EFS to gain full approval.

This is particularly relevant as higher-risk MDS and in particular MDS with excess blasts has been found to be biologically similar to AML [73,74]. This in part stimulated the ICC renaming of MDS-EB2 to MDS/AML (retained as MDS-IB2 in WHO 2022), as discussed above [75].

In a practical sense if patients with AML and MDS-IB2 (or MDS/AML) should be able to enroll in the same clinical trial, harmonization of AML and higher-risk MDS response criteria is needed whenever possible. In this context, it is pertinent to point out that the 2022 ELN response criteria in AML now include CR with partial hematologic recovery (CRh), defined as BM blasts <5%, platelets $\geq 50 \times 10^9$/L, and neutrophils $\geq 0.5 \times 10^9$/L (Fig. 5) [27]. Interestingly, CRh might also be of value in defining response in MDS. In a retrospective analysis of 311 patients with MDS who received DNMTi therapy, CRh as defined by ELN 2022 resulted in a similar OS (25 months) compared to CR (23.3 months) and was associated with a significantly longer OS compared to mCR (17.2 month) [76]. In contrast to mCR, CRh requires presence of count recovery (platelets $\geq 50 \times 10^9$/L, and neutrophils $\geq 0.5 \times 10^9$/L) but it uses thresholds that are less strict than CR (hemoglobin $\geq$10 g/dL, platelets $\geq 100 \times 10^9$/L, neutrophils $\geq 1.0 \times 10^9$/L). In the 2023 IWG MDS response criteria, CRh (with the definition equivalent to CRh in AML) was introduced as a provisional response criterion.

The new MDS response categories CR_L and CRh will require prospective validation as relative survival differences between CR_L, CRh and CR are not yet established, and survival might be dependent on the specific treatment context (e.g., full platelet recovery might not be present in venetoclax based combination therapy). While the icMDS believes that including CRh is a step into the right direction to harmonize AML and MDS response criteria, it also emphasizes that a systematic and prospective evaluation of different cut-offs for count recovery and their association with survival outcomes will be critical (Fig. 5).

The ORR which is frequently used in phase II trials as the primary endpoint is a summation of different types of response which unfortunately are not consistently defined in phase II clinical trials. The 2006 MDS response criteria did not specifically define which responses should or should not be included in assessing the ORR. This has led to heterogeneous definitions of the ORR between clinical trials and made it difficult to easily compare outcomes between different trials. In addition, mCR without HI was frequently included in the ORR assessment which raises the concern of overestimating the clinical benefit achieved with a drug. In this context the 2023 IWG MDS response criteria, clearly defined what constitutes an ORR: CR/CRequivalent, PR, CR_L, CRh and HI, but not mCR or stable disease (SD).

4.3. Survival and other event-driven endpoints in higher-risk MDS

The primary need in higher-risk MDS has been to improve upon the OS of 24.4 months achieved with single agent azacitidine in the AZA-001 trial [77]. The issue with using this benchmark in all future trials of DNMTi-based combination therapies in higher-risk MDS is that multiple other trials and real-world outcome studies have not replicated the extent of the survival benefit observed in AZA-001 [68,69,78,79]. This argues that using AZA-001 as our benchmark for improvement of survival is “aiming too high”. Unfortunately, the other large phase III trial leading to the approval of decitabine is probably also not helpful in providing an accurate estimation of survival time benefit achieved with DNMTi therapy [80]. In contrast to the AZA-001 trial, the median OS of only 10.1 months in this trial seemed rather pessimistic. The icMDS members believe that a more accurate reflection of survival benefit of DNMTi monotherapy in higher-risk MDS comes from a range of OS times achieved with azacitidine in the North American Intergroup Study SWOG S1117 [68], the PANTHER trial [81], and the MDS STIMULUS-1 trial [82] which resulted in median OS times with azacitidine of 15, 17.5 and 18 months in the SWOG S1117, PANTHER and the MDS STIMULUS-1 trial, respectively [68,81,82]. In the collective experience of members of the icMDS, a median OS of 15–18 months is a better benchmark for azacitidine monotherapy than the 24.4 months achieved in the AZA-001 study. However, it is important to mention that by selecting a shorter median OS than observed in the AZA-001 trial, there is a risk of overestimating the efficacy of a treatment in a study without a control arm as the median OS achieved with azacitidine is highly dependent on trial inclusion criteria including classic inclusion criteria such as the IPSS, IPSS-R, and oligoblastic AML as well as prognostic criteria usually not taken into account in trials yet such as the specific mutation profile of the patients. Hence, only randomized trials are able to assess with

confidence a survival advantage in MDS clinical trials.

Although OS is the benchmark of therapeutic efficacy, its assessment requires a longer follow-up period; moreover, cross-over, or sequential therapies (including allogeneic stem cell transplant) in clinical trials can complicate assessment of the impact of an MDS-specific intervention. For these reasons, other surrogate time-to-event outcomes have been explored in MDS clinical trials [83]. Event-free survival (EFS) and relapse-free survival (RFS) have been used as time to event endpoints in MDS clinical trials.

Importantly, the definition of disease progression in these event-driven endpoints is not fully standardized. While progression could refer to worsening cytopenias, increase in BM blasts, or progression to a more advanced subtype of MDS (or AML), the degree of cytopenias, percentage of BM blast increase or timeline for this development are not standardized and open to interpretation, limiting the implementation of a strict definition of EFS and RFS into clinical trials examining new agents in MDS.

The randomized phase II study of azacitidine plus pevonedistat versus azacitidine alone in patients with higher-risk MDS, chronic myelomonocytic leukemia (CMML) and oligoblastic AML showed a benefit in EFS (time to death or transformation to AML in the MDS cohort) of 20.2 months vs 14.8 months (HR: 0.539, $p = 0.045$), however the OS advantage of 4 months was not statistically significant between both arms [84]. The subsequent phase III PANTHER trials comparing azacitidine plus pevonedistat versus azacitidine alone in higher-risk MDS did not meet the endpoint of EFS, and the addition of pevonedistat to azacitidine did also not confer an OS advantage [81]. In both trials, the OS advantage for the combination vs. monotherapy was 4 months (as was EFS in the second trial) – yet the trial only had power to detect an OS advantage of 10–12 months. Moving forward, careful consideration of effect size and hazard ratios in randomized trials should consider the balance between making incremental progress in the treatment of HR-MDS and definitive patient benefit.

The 2023 IWG MDS response criteria now clearly define what constitutes an event in EFS and PFS (Fig. 6).

An event in EFS is defined as either progressive disease (PD) or a failure to achieve a response (CR/CR equivalent, PR, CR_L CRh, and HI within 6 months of study entry) or relapse from a prior response (CR/CR equivalent, PR, CR_L CRh, or HI) or death from any cause. In turn, a patient meets the definition of PD by either an increase in blasts ($\geq$50% relative increase in blasts and absolute increase of blast percentage by at least 5% from pretreatment sample taken before current line of therapy) or worsening cytopenia (continued requirement of RBC or platelet transfusions within 8 weeks not related to acute intercurrent illness or treatment effect), or progression to AML ($\geq$50% increase in blasts from baseline assessment to $\geq$20% blasts).

An event for the PFS analysis in the 2023 IWG MDS response criteria is defined as progressive disease (PD), or relapse from a prior response (CR/CR equivalent, PR, CRL CRh, and HI) or death from any cause.

Members of the icMDS hope that these clear definitions of event-driven endpoints will support clinical researchers in accurately and uniformly reporting these in clinical trials which will in turn help prospectively validating them as surrogate endpoints for overall survival.

Importantly, PFS and EFS measure different outcomes. Beyond PFS, EFS also includes failure to achieve a primary response (with the following responses being proposed by the IWG 2023 as events: CR/CR equivalent, PR, CR_L CRh, and HI within 6 months of study entry). PFS focuses on events that demonstrate worsening of disease (progressive disease and relapse after initial response, death). We believe that both metrics are important to report in phase 2 and phase 3 clinical trials. Both EFS and PFS should be measured from the date of study registration (for trials that are nonrandomized) or from the time of randomization (for trials that are randomized) to the date of death from any cause or last follow up.

In addition, other response endpoints such as reduction in the variant allele fraction (VAF) of MDS driver mutations and eradication of measurable residual disease (MRD) may be possible early readouts for clinical benefit in the future but require rigorous prospective evaluation [65].

Lastly, it is important as well to consider whether novel therapeutics may have benefits outside of median survival – for instance, an improved "tail" of long-term survivors may be seen with immune-based therapies as well as allogeneic transplant; such endpoints require different study design and rely on appropriate correlatives to characterize best-responders.

4.4. Patient reported outcomes in MDS risk scoring systems and clinical trials

During the iwMDS meeting the importance of patient-reported outcomes (PROs) in redefining MDS risk assessment and as valuable endpoints in the care of patients with MDS was discussed. PROs provide unique and clinically relevant information outside of classical risk assessment tools and established endpoints such as response and survival [85]. Apart from generic cancer PROs measurement tools such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), MDS specific PRO measures including the Quality of Life in Myelodysplasia Scale (QUALMS) and the QOL-E, are available [86–88].

In addition to, or in place of, the use of standard PRO measures which are "static" (i.e., present the same set of items), we note that more flexible approaches also exist which allow making more customized choices depending on the specific settings. Indeed, "PRO item libraries" typically include a large set of single items (or multi-item scales) addressing specific symptoms or functional aspects that can be selected ad-hoc by the investigators. In the context of MDS patients, who are often frail and older, this flexible PRO assessment approach can be instrumental, for example, to minimize patient burden by only including a few selected items relevant for the specific population and/or the type of treatment being considered in the given research setting. Recommendations for using PRO item libraries have been recently published and could help in the setting up of future MDS trials [89].

Importantly, PROs such as fatigue add independent prognostic information and additional value to established MDS risk scoring systems such as the International Prognostic Scoring System (IPSS) [90]. Based on this observation, the FA-IPSS(h), abbreviated for fatigue (FA) in higher risk (h) IPSS, was developed and externally validated [91],.To illustrate, rather than distinguishing between two higher-risk groups as in the IPSS, the FA-IPSS(h) was able to identify three higher-risk groups, that is: risk-1, risk-2 and risk-3, with a median OS of 23, 16 and 10 months, respectively. Importantly, the predictive accuracy of the FA-IPSS(h) was higher than that of the IPSS alone [91]. Further additional validation studies have also confirmed the clinical value of this patient-centered prognostic index [92]. A strength of this prognostic score that can be used in higher-risk patients, is its pragmatic approach which does not require any additional laboratory or clinical exam, rather, just a self-assessment of fatigue by patients themselves (completing only three PRO items).

Most importantly, measures of PROs should be used in assessing our daily practice patterns and should be employed as endpoints in prospective clinical trials. This is important as commonly used clinical assessments such as improvement in hemoglobin or reduction in RBC transfusion burden do not necessarily comprehensively reflect how a patient feels while receiving treatment. The goal of treatment in MDS must be to help patients live longer and with better quality of life; assessing PROs in clinical trials systematically will help us ensure that novel therapeutic agents do achieve these goals prior to formal approval by regulatory agencies. Indeed, inclusion of high-quality PRO data is highly relevant to the regulatory decision-making process [93]. As is the case with MDS response definitions, tools for QOL and PROs must be validated to have meaningful impact on advancing therapeutics.

5. Future considerations

These are exciting and dynamic times in MDS clinical care and research. Much is happening in the field of MDS all at once: we now have two new classifications of MDS, three molecular risk assessment tools and a new set of response criteria for higher-risk MDS. Future efforts need to focus on developing a unified MDS classification system with the goal to overcome differences between WHO and ICC criteria. Furthermore, investigating how molecularly based prognostication systems can better guide therapeutic decisions will be an important area of future investigation. Lastly, studies are needed to prospectively validate and further improve the IWG 2023 MDS response criteria to accurately measure success or the lack of it more accurately in higher-risk MDS therapy. Certainly, all these efforts are important, but the most critical part of MDS clinical research is the development of better therapies for our patients. Fortunately, multiple agents are in late-stage development for both lower- and higher-risk MDS patients and are poised to change the therapeutic landscape over the next couple of years [94].

5.1. Research agenda

- To develop unified MDS diagnostic and classification criteria
- To prospectively validate the new 2023 IWG response criteria
- To facilitate a patient centered care approach by more consistently implementing high quality validated PRO assessments.

5.2. Practice points

- The 2022 WHO and ICC classifications of MDS have several key differences. The ICC classification introduced a new disease category of AML/MDS whereas the WHO classification still labels these patients as MDS.
- New MDS risk-stratification tools, including the IPSS-M, are now available that incorporate mutations in predicting patient outcomes.
- The 2023 IWG response criteria made several recommendations for outcome measurement in higher risk MDS including to how a CR with full count recovery and limited count recovery (e.g. introducing CR_L and eliminating marrow CR) are defined and how to standardize the definition of time-to-event end points. The icMDS encourages the use of the 2023 IWG HR-MDS criteria in clinical trials and routine practice, as well as efforts to prospectively validate them.

Author contributions

MS, JPB and AMZ wrote the initial draft of the manuscript. ZX created figures. All authors reviewed and provided edits to subsequent versions of the manuscript.

Declaration of Competing Interest

Maximilian Stahl consulted for Curis Oncology and Boston Consulting; served on the advisory board for Novartis and Kymera, GSK, Rigel, Sierra Oncology; and participated in GME activity for Novartis, Curis Oncology, Haymarket Media and Clinical care options (CCO). Elizabeth A. Griffiths has received honoraria for advisory board membership from AbbVie, Alexion Pharmaceuticals, Apellis, Celgene/BMS, CTI Biopharma, Genentech, Novartis, Picnic Health, Takeda Oncology, Taiho Oncology. EAG has received research funding from Astex Pharmaceuticals, AstraZeneca Rare Disease, Alexion Pharmaceuticals, Apellis Pharmaceuticals, Blueprint Medicines, Genentech Inc., and honoraria for CME activities from Physicians Educational Resource, MediComWorldwide, American Society of Hematology, AAMDS International Foundation. Ravindra Majeti is on the Advisory Boards of Kodikaz Therapeutic Solutions, Syros Pharmaceuticals, TenSixteen Bio, Roche, and Cullgen Inc. and is an inventor on several patents related to CD47 cancer immunotherapy licensed to Gilead Sciences. R.M. receives research support from Gilead Sciences. Ravindra Majeti. is a co-founder and equity holder of Pheast Therapeutics, MyeloGene, and Orbital Therapeutics. Stephanie Halene consulted for Forma Therapeutics. Daniel T. Starczynowski is a consultant and received research funding from Kymera Therapeutics, Kurome Therapeutics, Captor Therapeutics, and Tolero Therapeutics. Daniel T. Starczynowski has equity in Kurome Therapeutics.

Gail Roboz: Consultancy: Abbvie, Amgen, Argenx, Astra Zeneca, Bluebird Bio, Blueprint Medicines, Bristol-Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, GlaxoSmithKline, Janssen, Jasper Pharmaceuticals, Jazz Pharmaceuticals, Molecular Partners, Novartis, Pfizer, Rigel, Roche, Syndax, Takeda (IRC Chair), Telix Pharma Research support: Janssen. David A. Sallman served on the advisory board of Aprea, AvenCell, BlueBird Bio, BMS, Intellia, Kite, Novartis, Shattuck Labs, Servier, Syndax. David A. Sallman served as a consultant for AbbVie, Magenta, Molecular Partners AG, Takeda and on the speakers' bureau for BMS, Incyte, Servier; David A. Sallman received research funding from Aprea, Jazz. Mrinal Patnaik received research funding from Kura Oncology and StemLine Pharmaceuticals. Andrew Brunner received consulting or advisory board honoraria from Novartis, Acceleron, Agios, Abbvie, Takeda, Celgene/BMS, Keros Therapeutics, Taiho, Gilead. Andrew Brunner has research support from the NIH SPORE in Myeloid Malignancies, and from the Edward P. Evans Foundation. Tae Kon Kim received research funding from Nextcure and is a consultant for Agenus. Alan List is employed by and has equity in Precision BioSciences, and has served as a consultant for Halia Therapeutics, CTI Biopharma, Aileron. Naval Daver has received research funding from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, Gilead, Sevier, Genentech, Astellas, Daiichi-Sankyo, Abbvie, Hanmi, Trovagene, FATE therapeutics, Amgen, Novimmune, Glycomimetics, Trillium, and ImmunoGen and has served in a consulting or advisory role for Daiichi-Sankyo, Bristol-Myers Squibb, Arog, Pfizer, Novartis, Jazz, Celgene, AbbVie, Astellas, Genentech, Immunogen, Servier, Syndax, Trillium, Gilead, Amgen, Shattuck labs, and Agios. Guillermo Sanz received honoraria, advisory board membership or consultation fees from AbbVie, BMS, ExCellThera, Novartis, Roche, and Takeda and participated in sponsored speaker's bureau for BMS, Novartis, and Takeda. Mikkael A. Sekeres has served on advisory boards for BMS, Novartis, Kurome, and Gilead. Pierre Fenaux received research funding from BMS, Abbvie, Jazz Pharmaceuticals, Novartis, and Janssen. Pierre Fenaux had a consultancy with and received honoraria from BMS, Abbvie, Jazz Pharmaceuticals, and Novartis. Fabio Efficace had a consultancy or advisory role for AbbVie, Incyte, Janssen, and Syros, outside the submitted work. Omar Abdel-Wahab has served as a consultant for H3B Biomedicine, Foundation Medicine Inc., Merck, Prelude Therapeutics, and Janssen, and is on the Scientific Advisory Board of Envisagenics Inc., AIChemy, Harmonic Discovery Inc., and Pfizer Boulder; Omar Abdel-Wahab has received prior research funding from H3B Biomedicine and LOXO Oncology unrelated to the current manuscript. Andrew H.Wei has served on advisory boards for Novartis, Astra Zeneca, Astellas, Janssen, Jazz, Amgen, Roche, Pfizer, Abbvie, Servier, Gilead, BMS, Shoreline, Macrogenics, Novartis and Agios; receives research funding to the Institution from Novartis, Abbvie, Servier, Janssen, BMS, Syndax, Astex, Astra Zeneca, Amgen; serves on speaker's bureaus for Abbvie, Novartis, BMS, Servier, Astellas; Andrew H.Wei is an employee of the Walter and Eliza Hall Institute (WEHI). WEHI receives milestone and royalty payments related to the development of Venetoclax. Current and past employees of Walter and Eliza Hall Institute may be eligible for financial benefits related to these payments. Andrew H. Wei receives such a financial benefit. Amer M. Zeidan received research funding (institutional) from Celgene/BMS, Abbvie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Cardiff oncology, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics. AMZ participated in advisory boards, and/or had a consultancy with and received honoraria from AbbVie, Otsuka, Pfizer, Celgene/BMS, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal

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References

[1] Khoury JD, Solary E, Abla O, et al. The 5th edition of the world health organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703–19.
[2] Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. Blood 2022;140(11):1200–28.
[3] Zeidan AM, Bewersdorf JP, Buckstein R, et al. Finding consistency in classifications of myeloid neoplasms: a perspective on behalf of the international workshop for myelodysplastic syndromes. Leukemia. 2022;36(12):2939–46.
[4] Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evidence 2022;1(7).
[5] Nazha A, Komrokji R, Meggendorfer M, et al. Personalized prediction model to risk stratify patients with myelodysplastic syndromes. J Clin Oncol 2021;39(33):3737–46.
[6] Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the international working group (IWG) response criteria in myelodysplasia. Blood. 2006;108(2):419–25.
[7] Zeidan AM, Platzbecker U, Bewersdorf JP, et al. Consensus proposal for revised international working group response criteria for higher risk myelodysplastic syndromes. Blood 2023;141(17):2047–61.
[8] Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
[9] Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51(2):189–99.
[10] Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937–51.
[11] Zheng G, Li P, Zhang X, Pan Z. The fifth edition of the World Health Organization classification and the international consensus classification of myeloid neoplasms: evolving guidelines in the molecular era with practical implications. Curr Opin Hematol 2023;30(2):53–63.
[12] Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. Blood 2022;140(11):1200–28.
[13] Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616–27. quiz 3699.
[14] Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and personalized prognostic assessment on the basis of clinical and genomic features in myelodysplastic syndromes. J Clin Oncol 2021;39(11):1223–33.
[15] Stahl M, DeVeaux M, de Witte T, et al. The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. Blood Adv 2018;2(14):1765–72.
[16] Jain AG, Zhang L, Bennett JM, Komrokji R. Myelodysplastic syndromes with bone marrow fibrosis: an update. Ann Lab Med 2022;42(3):299–305.
[17] Estey E, Hasserjian RP, Döhner H. Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal. Blood. 2022;139(3):323–32.
[18] Chen X, Othus M, Wood BL, et al. Comparison of myeloid blast counts and variant allele frequencies of gene mutations in myelodysplastic syndrome with excess blasts and secondary acute myeloid leukemia. Leuk Lymphoma 2021;62(5):1226–33.
[19] Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079–88.
[20] Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–65.
[21] Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and Azacitidine in TP53-mutant myelodysplastic syndromes. J Clin Oncol 2021;39(14):1584–94.
[22] Peterlin P, Turlure P, Chevallier P, et al. CPX 351 as first line treatment in higher risk MDS. A phase II trial by the GFM. Blood. 2021;138(Supplement 1):243.
[23] Garcia JS, Wei AH, Borate U, et al. Safety, efficacy, and patient-reported outcomes of venetoclax in combination with azacitidine for the treatment of patients with higher-risk myelodysplastic syndrome: a phase 1b study. Blood. 2020;136(Supplement 1):55–7.
[24] Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. Blood Rev 2019;36:70–87.
[25] Zeidan AM, Shallis RM, Wang R, Davidoff A, Ma X. Epidemiology of myelodysplastic syndromes: why characterizing the beast is a prerequisite to taming it. Blood Rev 2019;34:1–15.
[26] Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.
[27] Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–77.
[28] Peterlin P, Le Bris Y, Turlure P, et al. CPX-351 in higher risk myelodysplastic syndrome and chronic myelomonocytic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Haematol 2023;10(7):e521–9.
[29] Peterlin P, Turlure P, Chevallier P, et al. CPX 351 as first line treatment in higher risk MDS. A phase II trial by the GFM. ASH annual meeting. Blood 2021:243.
[30] Ball S. A product of "clash of titans" or true reflection of disease biology? Validation of 2022 WHO and ICC classifications in a large dataset of patients with myelodysplastic syndrome. American Society of Hematology Annual Meeting; 2022.
[31] Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood. 1994;84(5):1361–92.
[32] Hasserjian R. Message from the president to members of the Society for Hematopathology. 2023.
[33] community PsMfDRHfaith. 2023.
[34] Xie Z, Chen EC, Stahl M, Zeidan AM. Prognostication in myelodysplastic syndromes (neoplasms): molecular risk stratification finally coming of age. Blood Rev 2022;59:101033.
[35] Greenberg P, Cox C, LeBeau MM. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079–88.
[36] Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol 2007;25(23):3503–10.
[37] Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original international prognostic scoring system. Cancer. 2008;113(6):1351–61.
[38] Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia. 2008;22(3):538–43.
[39] Mishra A, Corrales-Yepez M, Ali NA, et al. Validation of the revised international prognostic scoring system in treated patients with myelodysplastic syndromes. Am J Hematol 2013;88(7):566–70.
[40] Scheid C, de Wreede L, van Biezen A, et al. Validation of the revised IPSS at transplant in patients with myelodysplastic syndrome/transformed acute myelogenous leukemia receiving allogeneic stem cell transplantation: a retrospective analysis of the EBMT chronic malignancies working party. Bone Marrow Transplant 2017;52(11):1519–25.
[41] Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616–27. quiz 3699.
[42] Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. Leukemia. 2014;28(2):241–7.
[43] Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med 2011;364(26):2496–506.
[44] Sallman DA, Komrokji R, Vaupel C, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. Leukemia. 2016;30(3):666–73.
[45] Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat Med 2020;26(10):1549–56.
[46] Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med 2017;376(6):536–47.
[47] Nazha A, Narkhede M, Radivoyevitch T, et al. Incorporation of molecular data into the revised international prognostic scoring system in treated patients with myelodysplastic syndromes. Leukemia. 2016;30(11):2214–20.
[48] Nazha A, Al-Issa K, Hamilton BK, et al. Adding molecular data to prognostic models can improve predictive power in treated patients with myelodysplastic syndromes. Leukemia. 2017;31(12):2848–50.
[49] Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndromes. NEJM Evidence 2022;1(7). EVIDoa2200008.
[50] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol 2009;10(3):223–32.
[51] Della Porta MG, Jackson CH, Alessandrino EP, et al. Decision analysis of allogeneic hematopoietic stem cell transplantation for patients with myelodysplastic

syndrome stratified according to the revised international prognostic scoring system. Leukemia. 2017;31(11):2449–57.
[52] Rami S, Komrokji SB, Maggioni Giulia, et al. MYELODYSPLASTIC NEOPLASMS (MDS) CLASSIFICATION FROM WHO 2017 TO WHO 2022 AND ICC 2022: AN EXPANDED ANALYSIS OF 7017 PATIENTS ON BEHALF OF THE INTERNATIONAL CONSORTIUM FOR MDS (ICMDS). EHA Meeting. 2023.
[53] Stempel JM, Xie Z, Bewersdorf JP, Stahl M, Zeidan AM. Evolution of therapeutic benefit measurement criteria in myelodysplastic syndromes/neoplasms. Cancer J 2023;29(3):203–11.
[54] Platzbecker U, Fenaux P, Ades L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood. 2019;133(10):1020–30.
[55] Fenaux P, Ades L. How we treat lower-risk myelodysplastic syndromes. Blood. 2013;121(21):4280–6.
[56] Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med 2020;382(2):140–51.
[57] Toma A, Kosmider O, Chevret S, et al. Lenalidomide with or without erythropoietin in transfusion-dependent erythropoiesis-stimulating agent-refractory lower-risk MDS without 5q deletion. Leukemia. 2016;30(4):897–905.
[58] Platzbecker U, Symeonidis A, Oliva EN, et al. A phase 3 randomized placebo-controlled trial of darbepoetin alfa in patients with anemia and lower-risk myelodysplastic syndromes. Leukemia. 2017;31(9):1944–50.
[59] Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol 2003;120(6):1037–46.
[60] Fenaux P, Santini V, Spiriti MAA, et al. A phase 3 randomized, placebo-controlled study assessing the efficacy and safety of epoetin-alpha in anemic patients with low-risk MDS. Leukemia. 2018;32(12):2648–58.
[61] Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. N Engl J Med 2020;382(2):140–51.
[62] Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. Blood. 2019;133(10):1020–30.
[63] Bejar R. How can we improve response assessments in MDS? Strategies to improve response assessment in MDS treatment paradigms. Best Pract Res Clin Haematol 2022;35(4):101405.
[64] Platzbecker U, Della Porta MG, Santini V, et al. Efficacy and safety of luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): interim analysis of a phase 3, open-label, randomised controlled trial. Lancet 2023;402(10399):373–85.
[65] Nannya Y, Tobiasson M, Sato S, et al. Post-azacitidine clone size predicts outcome of patients with myelodysplastic syndromes and related myeloid neoplasms. Blood Adv 2023;7(14):3624–36.
[66] National Comprehensive Cancer Network Practice Guidelines in Oncology. Myelodysplastic Syndromes Version 1. 2023.
[67] Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000;96(12):3671–4.
[68] Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: north American intergroup study SWOG S1117. J Clin Oncol 2017;35(24):2745–53.
[69] Adès L, Girshova L, Doronin VA, et al. Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast-percentage AML. Blood Adv 2022;6(17):5132–45.
[70] Komrokji RS, Al Ali NH, Sallman D, et al. Validation of international working group response criteria in higher-risk myelodysplastic syndromes: a report on behalf of the MDS clinical research Consortium. Cancer Med 2021;10(2):447–53.
[71] Kim N, Vallejo J, Herz J, et al. Response rate, event-free survival (EFS) and overall survival (OS) in higher-risk myelodysplastic syndromes (HR-MDS): U.S. food and drug administration (FDA) patient-level analyses. ASH Ann Meet: Blood 2021:2604.
[72] Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47.
[73] DiNardo CD, Garcia-Manero G, Pierce S, et al. Interactions and relevance of blast percentage and treatment strategy among younger and older patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Am J Hematol 2016;91(2):227–32.
[74] Estey E, Hasserjian RP, Dohner H. Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal. Blood. 2022;139(3):323–32.
[75] Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200–28.
[76] Brunner AM, Gavralidis A, Ali NA, et al. Evaluating complete remission with partial hematologic recovery (CRh) as a response criterion in myelodysplastic syndromes (MDS). Blood Cancer J 2022;12(11):153.
[77] Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002;20(10):2429–40.
[78] Zeidan AM, Stahl M, Sekeres MA, Steensma DP, Komrokji RS, Gore SD. A call for action: increasing enrollment of untreated patients with higher-risk myelodysplastic syndromes in first-line clinical trials. Cancer. 2017;123(19):3662–72.
[79] Zeidan AM, Salimi T, Epstein RS. Real-world use and outcomes of hypomethylating agent therapy in higher-risk myelodysplastic syndromes: why are we not achieving the promise of clinical trials? Future Oncol 2021;17(36):5163–75.
[80] Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS study group. J Clin Oncol 2011;29(15):1987–96.
[81] Ades L, Girshova L, Doronin VA, et al. Pevonedistat plus azacitidine vs azacitidine alone in higher-risk MDS/chronic myelomonocytic leukemia or low-blast-percentage AML. Blood Adv 2022;6(17):5132–45.
[82] AZe al. Primary results of Stimulus-MDS1: A randomized, double-blind, placebo-controlled phase II study of TIM-3 inhibition with Sabatolimab added to hypomethylating agents (HMAs). In: Adult patients with higher-risk myelodysplastic syndromes (MDS). American Society of Hematology Annual Meeting; 2022.
[83] Beaver JA, Howie LJ, Pelosof L, et al. A 25-year experience of US Food and Drug Administration accelerated approval of malignant hematology and oncology drugs and biologics. JAMA Oncol 2018;4(6):849.
[84] Sekeres MA, Watts J, Radinoff A, et al. Randomized phase 2 trial of pevonedistat plus azacitidine versus azacitidine for higher-risk MDS/CMML or low-blast AML. Leukemia. 2021;35(7):2119–24.
[85] Sekeres MA, Steensma DP. Rethinking clinical trial endpoints in myelodysplastic syndromes. Leukemia. 2019;33(3):570–5.
[86] Abel GA, Klaassen R, Lee SJ, et al. Patient-reported outcomes for the myelodysplastic syndromes: a new MDS-specific measure of quality of life. Blood. 2014;123(3):451–2.
[87] Abel GA, Efficace F, Buckstein RJ, et al. Prospective international validation of the quality of life in myelodysplasia scale (QUALMS). Haematologica. 2016;101(6):781–8.
[88] Oliva E, Nobile F, Dimitrov BD. Development and validation of QOL-E© instrument for the assessment of health-related quality of life in myelodysplastic syndromes. Central Eur J Med 2013;8.
[89] Piccinin C, Basch E, Bhatnagar V, et al. Recommendations on the use of item libraries for patient-reported outcome measurement in oncology trials: findings from an international, multidisciplinary working group. Lancet Oncol 2023;24(2):e86–95.
[90] Efficace F, Gaidano G, Breccia M, et al. Prognostic value of self-reported fatigue on overall survival in patients with myelodysplastic syndromes: a multicentre, prospective, observational, cohort study. Lancet Oncol 2015;16(15):1506–14.
[91] Efficace F, Cottone F, Abel G, et al. Patient-reported outcomes enhance the survival prediction of traditional disease risk classifications: an international study in patients with myelodysplastic syndromes. Cancer. 2018;124(6):1251–9.
[92] Amitai I, Geddes M, Zhu N, et al. Patient-reported fatigue refines prognosis in higher-risk myelodysplastic syndromes (MDS): a MDS-CAN study. Br J Haematol 2021;194(2):319–24.
[93] Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. Lancet Oncol 2018;19(5):e267–74.
[94] Bewersdorf JP, Xie Z, Bejar R, et al. Current landscape of translational and clinical research in myelodysplastic syndromes/neoplasms (MDS): proceedings from the 1 (st) International Workshop on MDS (iwMDS) of the International Consortium for MDS (icMDS). Blood Rev 2023;101072.