FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

CONVEGNO FISiM

Firenze, CSF Montedomini
"Il Fuligno"
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Response criteria and measure of comorbidities in clinical trials

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EMSCO
MYELODYSPLASTIC SYNDROMES

MDS Foundation CENTER OF EXCELLENCE DESIGNATED 2024-25

Disclosure

- **Honoraria/Speaker: BMS, NOVARTIS, KEROS, ABBIE**
- **Advisory Board: BMS, NOVARTIS, BLUEPRINT MEDICINES, GSK, AGIOS, HEMAVANT, SYROS, KEROS, CURIS, ASTEX/OTSUKA, ASCENTAGE**

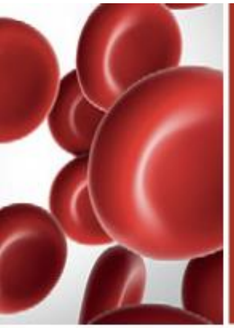
Outline

- LR-MDS 2018 criteria
- HR-MDS 2023 criteria
- Comorbidities?
- QoL and PRO?

➢LR-MDS 2018 criteria

Response criteria for clinical trials in Lower Risk MDS

Rationale



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Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials

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Response criteria for clinical trials in Lower Risk MDS

General topics

- Experts from EU & USA
- Procedures used for ELN guidelines
- Review of literature
- Different clinical scenarios
- Consensus: agreement by more than two-thirds of the experts

Hematological Improvement Erythroid

Response criteria for clinical trials in Lower Risk MDS

Hematological Improvement Erythroid major problems in IWG2006

- 8w period for screening and response
- TD criteria, 2 categories:
  - ✓ TID, no transfusion requirements
  - ✓ TD, >4 RBC/8w
  - ✓ patients receiving <4 RBC/8w?

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

HI-E: Procedures at baseline

Item	Suggested IWG 2018 procedures	IWG 2006 procedures
Baseline assessment procedures		
Screening period for the evaluation of transfusion burden and baseline Hb levels*	16 wk but only in lower-risk MDSs, when anemia is the predominant or only cytopenia; patients should be off any active treatment during this period Transfusions: Patients with unusual or abnormal changes of their transfusion rate during the 16-wk observation period should be evaluated carefully for confounding factors (ie, bleeding, hemolysis, EPO levels, iron metabolism), including a potential extension of the evaluation period Baseline Hb: For the determination of the baseline Hb level, we suggest using the mean of all available Hb measurements during the 16-wk screening period; to avoid bias, measurements prior to transfusions should be used in this calculation for TD patients and the measurements should be at least 7 d apart	8 wk
easurements prior	Hb measurements for the determination of baseline Hb values should be performed (or retrospective results should be available) at least every 2 wk, if possible, during the 16 wk screening period	NA
ethod and laboratory	Investigators should be aware of potential fluctuations in Hb measurements due to different blood count devices or laboratories To avoid any ambiguities in Hb levels, investigators should check when using several devices/methods or laboratories whether they yield similar Hb levels; in case of different values, baseline Hb level (as well as subsequent response and response duration) should be assessed based on measurements from only 1 device/method or laboratory, especially at key time points of a clinical trial	NA
Baseline Hb level	Hb < 10 g/dL as prerequisite for patients in need of therapy	Hb < 11 g/dL

- **16 weeks for screening**
- **Hb levels every 2w: mean value**
- **1 device/lab**
- **Hb level <10 g/dL for trial inclusion**

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

HI-E: Procedures at Response evaluation

Item	Suggested IWG 2018 procedures	IWG 2006 procedures
Response evaluation procedures Response evaluation period	24 wk	8 wk
No./frequency of Hb measurements	Hb measurement should be performed (or results be available) at least every 2 wk during the first 16 wk of therapy	NA
	Investigators should be aware of potential fluctuations in Hb measurements due to different blood count devices or laboratories To avoid any ambiguities in Hb levels, investigators should check when using several devices/methods or laboratories whether they yield similar Hb levels; in case of different values, baseline Hb level, response, and response duration should be assessed based on measurements from only 1 device/method or laboratory, especially at key time points of a clinical trial	NA
	Treatment should be continued at a lower dose level (ie, increased intervals between doses or administration of lower dose level) rather than stopped when 2 subsequent Hb measurements exceed a predefined threshold If the drug under investigation is being reduced in dose, stopped, or its administration delayed in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such, if reintroduction of the drug at the same or lower dose induces a new response If the reintroduction of the drug at a lower dose does not reinduce a response, this should be documented as such When the investigational drug is being reduced in dose, stopped, or its administration delayed, blood counts are required continuously to monitor subsequent blood levels	NA

- **16-24w weeks for evaluation**
- **Hb level every 2w for 1st 16w: mean Hb value**
- **1 device/lab**
- **Responding patients with dose modifications**

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

Response criteria for HI-E

- NTB (0U/16w)
- LTB (3-7U/16w)
- HTB (>8U/16w)
- 1-2 RBCs/16w?

Item	Suggested IWG 2018 criteria	IWG 2006 criteria
Baseline criteria		
Definition of transfusion-burden categories	3 groups: NTD (0 RBCs in 16 wk)* LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)* HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	2 groups: TD (at least 4 U of RBC with 8 wk for Hb < 9 g/dL) TID (<4 U of RBC with 8 wk for Hb < 9 g/dL)
Pretreatment RBC transfusion policy	Transfusion policy for the individual patient prior to therapy should be maintained on treatment†	Transfusion threshold of 9 g/dL, no exception for clinical indication

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

Response criteria for HI-E

- NTB: Hb ≥1.5 g/dL
- LTB: TI*
- HTB: Ma: TI*
  mi: ≥50% red TB*

- Transfusion policy
- 8w during 16-24w
- *Independent of Hb increase
- Clinically meaningful if >16w

- Duration of TI
- Magnitude of Hb increase

Item	Suggested IWG 2018 criteria	IWG 2006 criteria
HTB (≥8 RBCs in 16 wk,	At least 2 consecutive Hb measurements ≥1.5 g/dL for a period of minimum 8 wk in an observation period of 16 to 24 wk compared with the lowest mean of 2 Hb measurements (apart from any transfusion) within 16 wk before treatment onset‡; only a response duration of at least 16 wk, however, is considered clinically meaningful	Hb increase by 1.5 g/dL and/or relevant reduction of U of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk; only RBC transfusions given for an Hb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
	HI-E in LTB patients corresponds to transfusion independence, defined by the absence of any transfusions for at least 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful	
	Major response: Major HI-E response in HTB patients corresponds to transfusion independence, defined by the absence of any transfusions over a period of minimum 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful	
	Minor response: Minor HI-E response in HTB patients is defined as a reduction by at least 50% of RBCs over a minimum of 16 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment	
	Transfusion policy for the individual patient prior to therapy should be maintained on treatment if not otherwise clinically indicated (documentation by the treating physician required); we suggest a maximum variation between pre- and on-study practice of 1 g/dL (or 0.6 mmol/L) in terms of transfusion threshold	Transfusion threshold of 9 g/dL, no exception for clinical indication
	If the drug under investigation is stopped or its dose reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such if reintroduction at the same or lower dose of the drug induces a new response; if reintroduction of the drug at a lower dose does not reinduce a response, this should be documented as such	NA

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

Response criteria for HI-P

- Counts and symptoms
- Any increment need to be reported

Newly suggested evaluations: IWG 2018		IWG 2006 criteria	
Type of response	**Criteria**	**Type of response**	**Criteria**
Platelet response (pretreatment, $<100 \times 10^9$/L), HI-P	• Absolute increase of 30×10^9/L for patients starting with $>20 \times 10^9$/L PLTs or • Increase from $<20 \times 10^9$/L to $>20 \times 10^9$/L and by at least 100% In addition, • Evolution of bleeding symptoms is to be taken into account • Increments of platelets also for patients with a pretreatment PLT count of $>100 \times 10^9$/L are to be reported	Platelet response (pretreatment, $<100 \times 10^9$/L), HI-P	• Absolute increase of 30×10^9/L for patients starting with $>20 \times 10^9$/L PLTs or • Increase from $<20 \times 10^9$/L to $>20 \times 10^9$/L and by at least 100%
Dose-adjustment policy for PLT counts on treatment	• If the drug under investigation is being stopped or its dose is being reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such, if reintroduction at the same or lower dose of the drug induces a new response • When the investigational drug is stopped or reduced in dose, weekly blood counts are required to monitor the PLT levels • 2 subsequent PLT counts $>450 \times 10^9$/L are a sufficient reason for treatment discontinuation in the case of treatment with TPO agonists		None

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

Response criteria for HI-N

- Counts and symptoms
- Any increment need to be reported

Newly suggested evaluations: IWG 2018		IWG 2006 criteria	
Type of response	**Criteria**	**Type of response**	**Criteria**
Neutrophil response (pretreatment, all patients), HI-N	At least 100% increase and an absolute increase >0.5 × 10^9/L (pretreatment, <1.0 × 10^9/L) Increments of neutrophils also for patients with a pretreatment ANC of >1.0 × 10^9/L are to be reported	Neutrophil response (pretreatment, <1.0 × 10^9/L), HI-N	At least 100% increase and an absolute increase >0.5 × 10^9/L

Platzbecker, Blood 2018

Response criteria for clinical trials in Lower Risk MDS

Response criteria for HI-E: loss response

- Loosing response
- But still beneficial for patient
- Treatment should be maintained

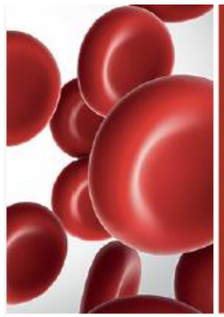
Panel recommendation

We suggest that the current definition of loss of response (at least a 50% decrement from maximum response levels in neutrophils or platelets) is amended by the wording that the patient should also not meet IWG response criteria anymore (eg, ANC response from 0.5 to 1.2 and loss of response to 0.6 or platelet response from 30 to 70 and loss of response to 35) all in the absence of dose interruptions and in the absence of any infection, hemorrhagic events, and concomitant medications. The loss of erythroid response is currently well defined but should be amended by the comment that, for example, a response from Hb 8.5 to 13 and a consecutive decline to 11.5 g/dL (ie, by >1.5 g/dL) is not a loss of response whereas a decline to 9.5 or transfusion dependence is a loss of response because the patient does not meet response criteria anymore when levels are compared with baseline. Furthermore, some HTB patients will not become completely TID (eg, just a reduction by 50% of transfusion burden). As a result, progression should be defined by an increase in transfusion burden by at least 50% (eg, prior therapy 16 U within 16 weeks, reduction to 8 U during therapy as a response, and subsequent increase to 12 U).

Platzbecker, Blood 2018

➢HR-MDS 2023 criteria

Response criteria for clinical trials in Higher Risk MDS



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Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes

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Response criteria for clinical trials in Higher Risk MDS

General topics

- 36 international Experts
- Delphi process
- Patient centered & relevant for outcomes
- Fully capture the clinical benefit of novel drugs
- Serve as valid surrogates for end points

Hb level for CR (≥10g/dL)
Complete Remission categories

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: CR

Response	IWG 2006	IWG 2023
CR	• BM: ≤5% myeloblasts; dysplasia may persist • PB: Hb ≥11 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%	• BM: <5% myeloblasts;* dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%†

- **<5% BM blasts**
- **Hb ≥ 10 g/dL**

*CR, mCR, CRL and CRh required ≥5% blast
CR equivalent for HR patients with <5% blast

*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: CR & subcategories

Response	IWG 2006	IWG 2023
CR	• BM: ≤5% myeloblasts; dysplasia may persist • PB: Hb ≥11 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%	• BM: <5% myeloblasts;* dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%†
CR equivalent*	Not included	Patients with <5% BM blasts at baseline • BM: <5% myeloblasts*; dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%† • Full cytogenetic clearance of baseline abnormalities (complete cytogenetic response)
mCR	• BM: ≤5% blasts and decrease by ≥50% over pretreatment • No PB responses required	Eliminated as a response criterion‡

- **CR equivalent, CR for entities <5% BM blasts**
- **Eliminated marrow CR, no OS benefit**

*CR, mCR, CRL and CRh required ≥5% blast
CR equivalent for HR patients with <5% blast
*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: CR & subcategories

Response	IWG 2006	IWG 2023
CR	• BM: ≤5% myeloblasts; dysplasia may persist • PB: Hb ≥11 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%	• BM: <5% myeloblasts;* dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%†
CR equivalent*	Not included	Patients with <5% BM blasts at baseline • BM: <5% myeloblasts*; dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%† • Full cytogenetic clearance of baseline abnormalities (complete cytogenetic response)
mCR	• BM: ≤5% blasts and decrease by ≥50% over pretreatment • No PB responses required	Eliminated as a response criterion‡
CR_L§ (CR_{uni} and CR_{bi})	Not included	• BM: <5% myeloblasts;* dysplasia may persist • PB: blasts 0%† • CR_{uni}: PB, not meeting CR but only 1 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L • CR_{bi}: PB, not meeting CR but only 2 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L

➢ **CR limited count recovery: uni or bilineage**

(CR_L, CRuni, Crbi)

*CR, mCR, CRL and CRh required ≥5% blast
CR equivalent for HR patients with <5% blast
*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: CR & subcategories

Response	IWG 2006	IWG 2023
CR	• BM: ≤5% myeloblasts; dysplasia may persist • PB: Hb ≥11 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%	• BM: <5% myeloblasts;* dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%†
CR equivalent*	Not included	Patients with <5% BM blasts at baseline • BM: <5% myeloblasts*; dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%† • Full cytogenetic clearance of baseline abnormalities (complete cytogenetic response)
mCR	• BM: ≤5% blasts and decrease by ≥50% over pretreatment • No PB responses required	Eliminated as a response criterion‡
CR_L§ (CR_{uni} and CR_{bi})	Not included	• BM: <5% myeloblasts;* dysplasia may persist • PB: blasts 0%† • CR_{uni}: PB, not meeting CR but only 1 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L • CR_{bi}: PB, not meeting CR but only 2 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L
CRh§	Not included	• BM: <5% myeloblasts;* dysplasia may persist • PB: Not meeting criteria for CR or CR_L, no Hb threshold required, platelets ≥50 × 10^9/L; neutrophils ≥0.5 × 10^9/L; blasts 0%†

➢ **CR with partial hematology recovery (CRh)**

*CR, mCR, CRL and CRh required ≥5% blast
CR equivalent for HR patients with <5% blast
*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: CR & PR

Response	IWG 2006	IWG 2023
CR	• BM: ≤5% myeloblasts; dysplasia may persist • PB: Hb ≥11 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%	• BM: <5% myeloblasts;* dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%†
CR equivalent*	Not included	Patients with <5% BM blasts at baseline • BM: <5% myeloblasts*; dysplasia may persist • PB: Hb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%† • Full cytogenetic clearance of baseline abnormalities (complete cytogenetic response)
mCR	• BM: ≤5% blasts and decrease by ≥50% over pretreatment • No PB responses required	Eliminated as a response criterion‡
CR_L§ (CR_{uni} and CR_{bi})	Not included	• BM: <5% myeloblasts;* dysplasia may persist • PB: blasts 0%† • CR_{uni}: PB, not meeting CR but only 1 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L • CR_{bi}: PB, not meeting CR but only 2 of the following: Hb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L
CRh§	Not included	• BM: <5% myeloblasts;* dysplasia may persist • PB: Not meeting criteria for CR or CR_L, no Hb threshold required, platelets ≥50 × 10^9/L; neutrophils ≥0.5 × 10^9/L; blasts 0%†
PR	All CR criteria except: • BM blasts decreased by ≥50% over pretreatment but still >5% • Cellularity and morphology not relevant	All CR criteria except: • BM blasts decreased by ≥50% over pretreatment but still ≥5% • Cellularity and morphology not relevant

*CR, mCR, CRL and CRh required ≥5% blast
CR equivalent for HR patients with <5% blast
*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: HI, ORR & No response

Response	IWG 2006	IWG 2023
HI	HI (responses >8 wk): • Erythroid response (pretreatment, <11 g/dL):Hb increase by ≥1.5 g/dL and 50% reduction of RBC transfusions. • Platelet response (pretreatment, <100 × 10^9/L):absolute increase of ≥30 × 10^9/L for patients starting with >20 × 10^9/L platelets or increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%. • Neutrophil response (pretreatment, <1.0 × 10^9/L): at least 100% increase and an absolute increase >0.5 × 10^9/L.	HI defined according to IWG 2018 response criteria:‖ • Not meeting criteria for CR (or CR equivalent) or CRuni or CR_L • $HI_{erythroid}$ (HI-E) • $HI_{platelets}$ (HI-P) • $HI_{neutrophils}$ (HI-N)
ORR	Not defined	ORR = CR (or CR equivalent)* + PR + CR_L + CRh + HI
No response	Not defined	Not meeting criteria for CR (or CR equivalent)*, PR, CR_L, CRh, or HI‡
SD	Failure to achieve at least PR, but no evidence of progression for >8 wk	Eliminated as a response criterion‡

➢ **ORR= CR (or equivalent) + CR_L + CRh + PR + HI**

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Response criteria for clinical trials in Higher Risk MDS

Response criteria: other relevant ”responses”

Response	IWG 2006	IWG 2023
Not evaluable	Not included	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.

Response criteria for clinical trials in Higher Risk MDS

Response criteria: other relevant ”responses”

Response	IWG 2006	IWG 2023
Not evaluable	Not included	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.
Cytogenetic response¶*	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.

*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: other relevant ”responses”

Response	IWG 2006	IWG 2023
Not evaluable	Not included	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.
Cytogenetic response¶*	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.
PD	For patients with: • <5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to >10% blasts • 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hb by ≥2 g/dL • Transfusion dependence	Fulfilling any of the criteria below:#,**,†† • Disease progression by blasts: ≥50% relative increase in blasts and absolute increase of blast percentage by at least 5% from pretreatment sample taken before current line of therapy. • Disease progression by worsening cytopenia: new, repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions within 8 weeks, not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect, in the absence of HI of at least one other blood lineage as defined above. • Progression to AML: ≥50% increase in blasts from baseline assessment to ≥20% blasts.

- **Progression Disease (PD)**
  - **Rising of PB blasts**
  - **Worsening cytopenia/tx requirements**
  - **Progression to AML**

***molecular clearance not included**

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Response criteria for clinical trials in Higher Risk MDS

Response criteria: other relevant ”responses”

Response	IWG 2006	IWG 2023
Not evaluable	Not included	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.
Cytogenetic response¶*	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.
PD	For patients with: • <5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to >10% blasts • 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hb by ≥2 g/dL • Transfusion dependence	Fulfilling any of the criteria below:#,**,†† • Disease progression by blasts: ≥50% relative increase in blasts and absolute increase of blast percentage by at least 5% from pretreatment sample taken before current line of therapy. • Disease progression by worsening cytopenia: new, repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions within 8 weeks, not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect, in the absence of HI of at least one other blood lineage as defined above. • Progression to AML: ≥50% increase in blasts from baseline assessment to ≥20% blasts.
Disease relapse	Any of the following: • Return to pretreatment BM blast percentage. • Decrement of 50% from maximum remission/response levels in granulocytes or platelets. • Reduction in Hb concentration by 1.5 g/dL or transfusion dependence.	Fulfilling any of the criteria below:# • Disease relapse by blasts: absolute and relative increase in BM blasts by at least 5% and ≥50%, respectively, from prior assessment, or reappearance of blasts in the blood, or development of extramedullary disease (myeloid sarcoma). • Disease relapse by worsening cytopenias: decrement in one or more blood cell lineage counts by ≥50% from maximum remission/response levels for platelets or absolute neutrophil count or a reduction of Hb by 1.5 g/dL combined with an absolute reduction in the same lineage(s) as follows: Hb <10 g/dL, platelets <100 × 10^9/L, or absolute neutrophils <1.0 × 10^9/L or repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions which are not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect; in the absence of HI of at least one other blood lineage as defined above.

*molecular clearance not included

Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Response criteria: other relevant ”responses”

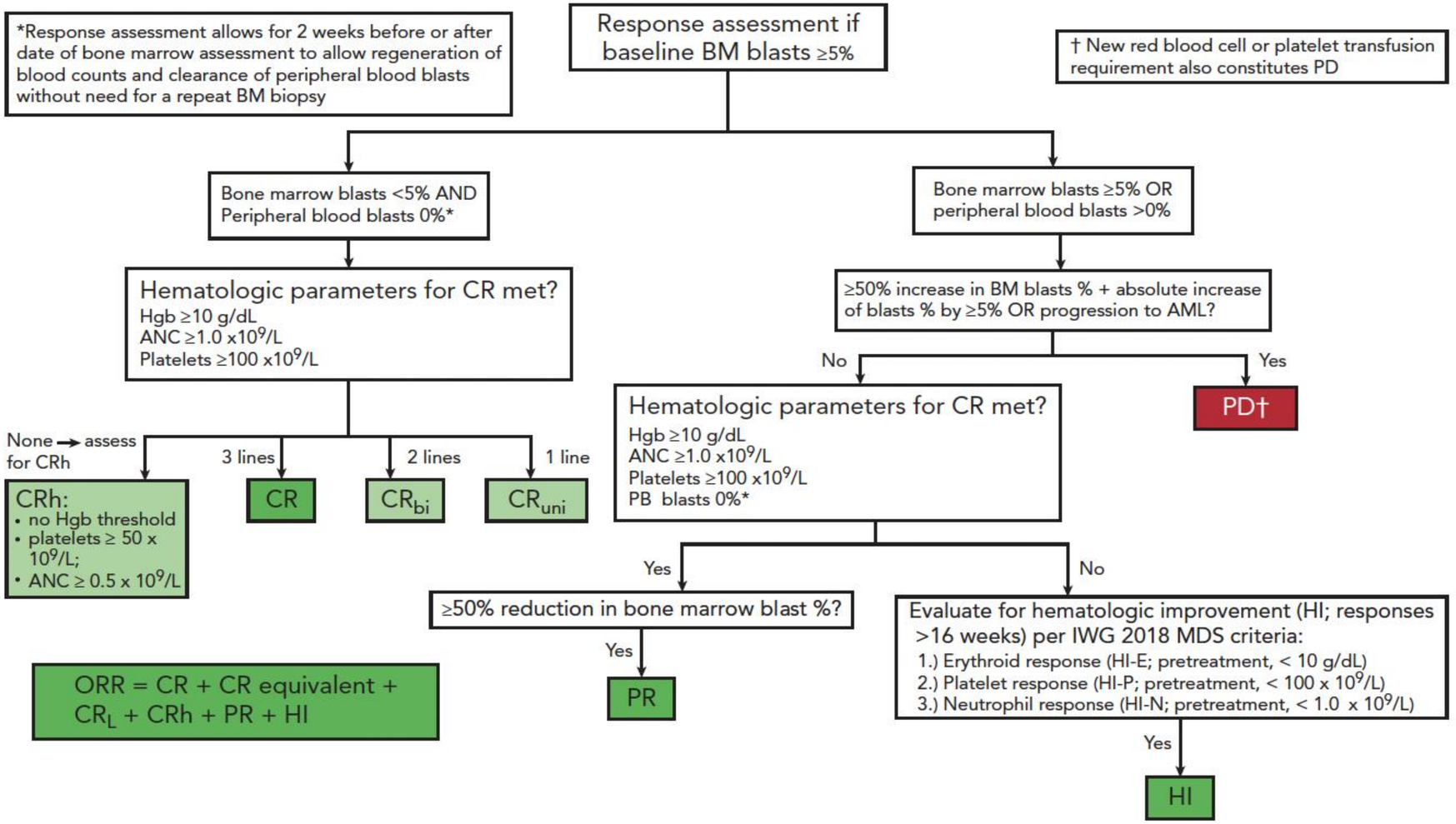
Response	IWG 2006	IWG 2023
Not evaluable	Not included	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.
Cytogenetic response¶*	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.	• Complete: disappearance of the chromosomal abnormality without appearance of new ones. • Partial: ≥50% reduction of the chromosomal abnormality.
PD	For patients with: • <5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase to >10% blasts • 10%-20% blasts: ≥50% increase to >20% blasts • 20%-30% blasts: ≥50% increase to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response in granulocytes or platelets • Reduction in Hb by ≥2 g/dL • Transfusion dependence	Fulfilling any of the criteria below:#,**,†† • Disease progression by blasts: ≥50% relative increase in blasts and absolute increase of blast percentage by at least 5% from pretreatment sample taken before current line of therapy. • Disease progression by worsening cytopenia: new, repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions within 8 weeks, not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect, in the absence of HI of at least one other blood lineage as defined above. • Progression to AML: ≥50% increase in blasts from baseline assessment to ≥20% blasts.
Disease relapse	Any of the following: • Return to pretreatment BM blast percentage. • Decrement of 50% from maximum remission/response levels in granulocytes or platelets. • Reduction in Hb concentration by 1.5 g/dL or transfusion dependence.	Fulfilling any of the criteria below:# • Disease relapse by blasts: absolute and relative increase in BM blasts by at least 5% and ≥50%, respectively, from prior assessment, or reappearance of blasts in the blood, or development of extramedullary disease (myeloid sarcoma). • Disease relapse by worsening cytopenias: decrement in one or more blood cell lineage counts by ≥50% from maximum remission/response levels for platelets or absolute neutrophil count or a reduction of Hb by 1.5 g/dL combined with an absolute reduction in the same lineage(s) as follows: Hb <10 g/dL, platelets <100 × 10^9/L, or absolute neutrophils <1.0 × 10^9/L or repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions which are not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect; in the absence of HI of at least one other blood lineage as defined above.
Patient reported outcomes (PROs)	Not included	Reporting by means of a validated assessment tool is encouraged‡‡

*molecular clearance not included

Zeidan, Blood 2023

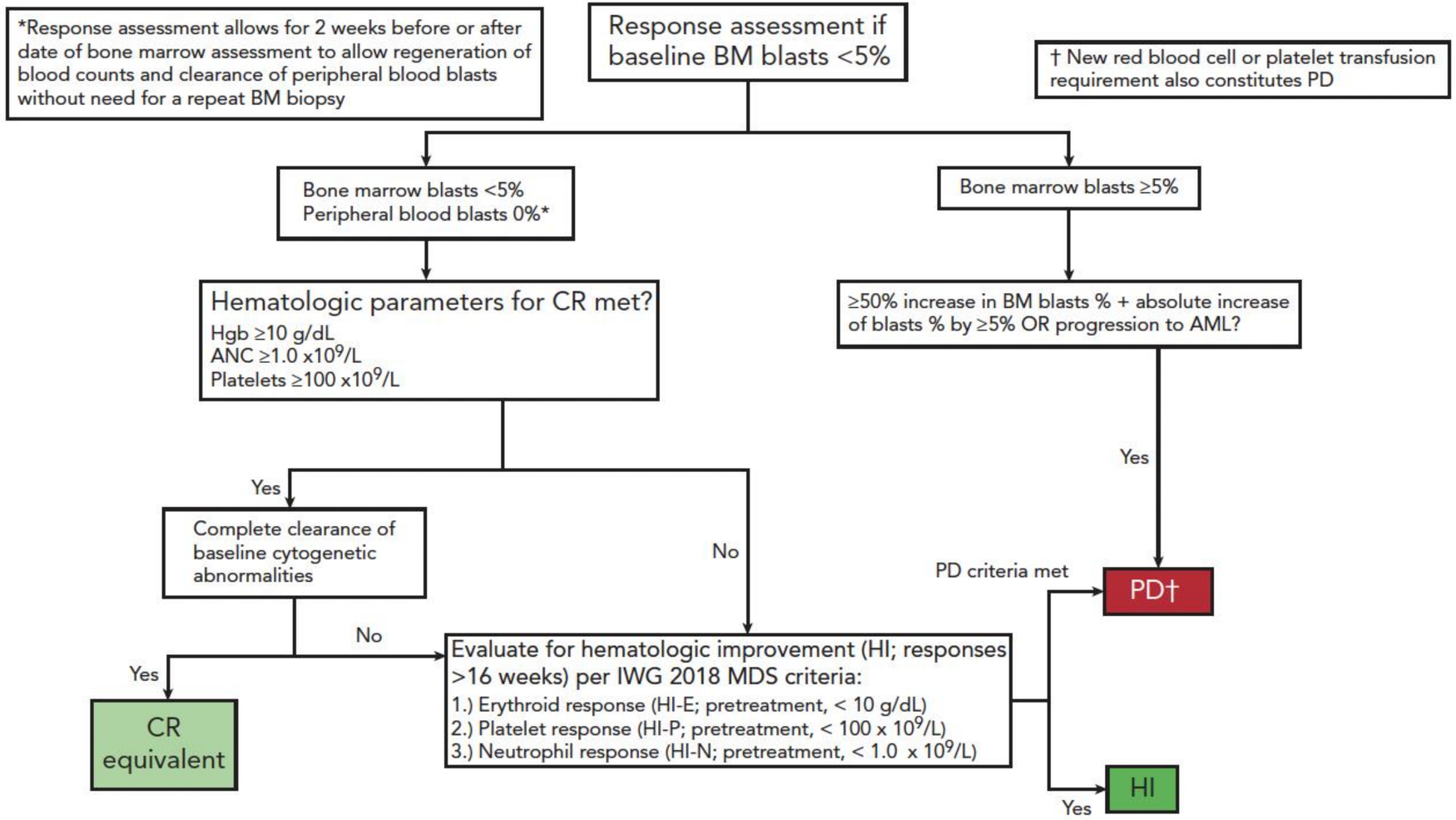
Response criteria for clinical trials in Higher Risk MDS

Response assessment flowchart ≥ 5% blasts



Response criteria for clinical trials in Higher Risk MDS

Response assessment flowchart <5% blasts



Zeidan, Blood 2023

Response criteria for clinical trials in Higher Risk MDS

Time to event end-points

Time-to-event–[illegible]	[illegible]	[illegible]

Recommendations OS should remain the primary end point for phase 3 clinical trials in MDS. EFS and PFS can potentially serve as surrogate outcomes for OS but require additional pro-spective validation. In general, time-to-event–based outcomes should be defined for all patients in a trial and measured from the date of study entry (or randomization) to the date of the event.

Disease-free survival	Time to relapse	Eliminated

- **Comorbidities in clinical trials?**

Measure of comorbidities for clinical trials in MDS

Comorbidities are frequent in MDS patients and impact on outcomes

Sorror comorbidities after review

Comorbidity	Definition	Prevalence	
Cardiac	Arrhythmia* Heart valve disease** Coronary artery disease *** or myocardial infarction Congestive heart failure or ejection fraction ≤50%	7% 2% 8% 19%	25%
Cerebrovascular	Transient ischemic attack and/or ischemic or hemorrhagic cerebrovascular accident	5%	
Mild to moderate pulmonary	DLCO and/or FEV1 66%-80% or dyspnea on moderate or slight activity	3%	
Severe pulmonary	DLCO and/or FEV1 ≤65% or dyspnea at rest or requires oxygen	2%	
Mild hepatic ****	Chronic hepatitis, persistent bilirubin > ULN to 1.5 x ULN or AST/ALT > ULN to 2.5 x ULN	14%	
Moderate to severe hepatic ****	Cirrhosis, fibrosis, persistent bilirubin > 1.5 x ULN or AST/ALT > 2.5 x ULN	3%	
Renal	Persistent creatinine > 2 mg/dL, renal dialysis, or renal transplant	4%	
Solid tumor	Malignancy at any time point in the patient's history, excluding non-melanoma skin cancer	10%	
Rheumatological	One or more of the following conditions: systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, polymyalgia rheumatica	2%	
Gastrointestinal	One or more of the following conditions: Crohn's disease, ulcerative colitis, or peptic ulcer requiring treatment	6%	
Diabetes	Diabetes requiring treatment with insulin or oral hypoglycemics	11%	
Endocrine	One or more of the following conditions: thyroid disorders, adrenal disorders, parathyroid gland disorders, pituitary gland disorders, or hypogonadism	5%	
Obesity	Body mass index >35 kg/m²	2%	
Psychiatric	Depression or anxiety requiring psychiatric counseling or treatment	2%	

MDS-CI

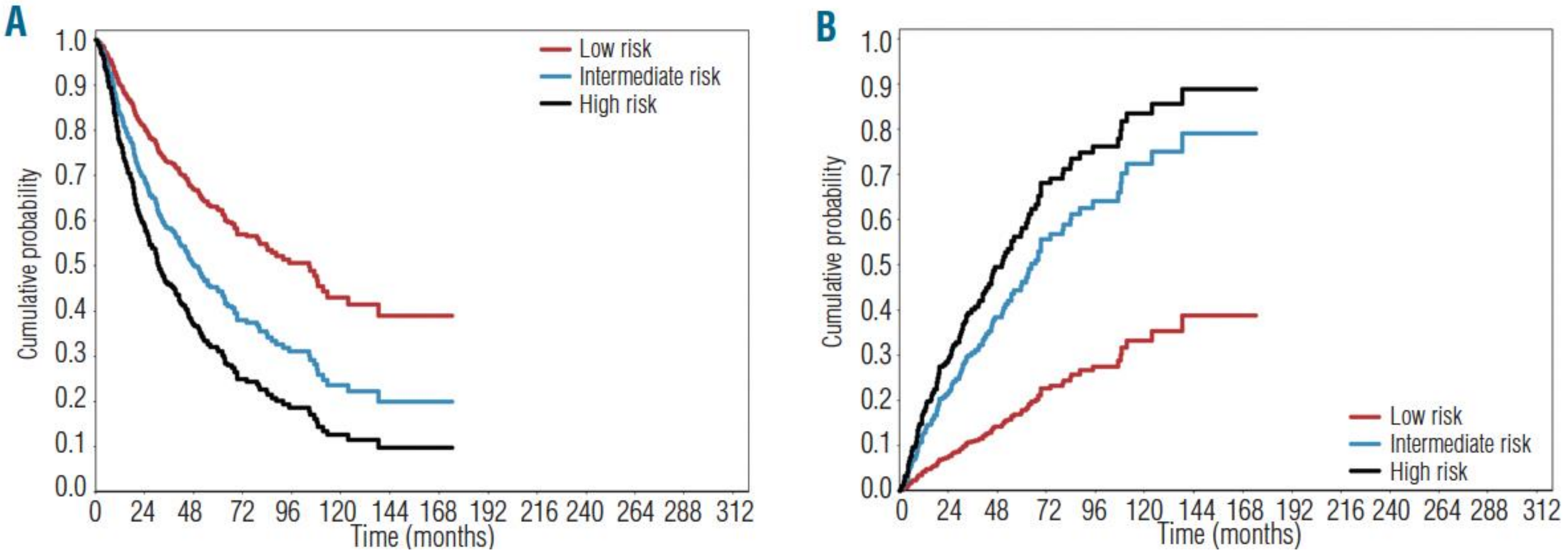
Comorbidity	HR obtained through a multivariable Cox's survival analysis with NLD as an outcome	Variable weighted score (to be taken into account if the specific comorbidity is present)
Cardiac disease	3.57 (P<0.001)	2
Moderate-to-severe hepatic disease	2.55 (P=0.01)	1
Severe pulmonary disease	2.44 (P=0.005)	1
Renal disease	1.97 (P=0.04)	1
Solid tumor	2.61 (P<0.001)	1

MDS-CI risk	Sum of individual variable scores	Proportion of patients in the learning cohort belonging to the risk group (%)
Low risk	0	546/840 (65%)
Intermediate risk	1-2	244/840 (29%)
High risk	>2	50/840 (6%)

Della Porta, Haematologica 2011

Measure of comorbidities for clinical trials in MDS

Comorbidities are frequent in MDS patients and impact on outcomes



Della Porta, Haematologica 2011

Measure of comorbidities for clinical trials in MDS

Are comorbidities be measured in clinical trials?

- **Recorded in personal history at baseline**
  - **-Generally, not graded**
  - **-No information about evolution during clinical trial: AE/TEAS**
- **Exclusion criteria focus on specific toxicity profile of the drug**
  - **-uncontrolled HT, deep venous thrombosis… (Luspa)**
  - **-uncontrolled HT (KER-050)**
  - **-LVEF<45%, clinically significant CV disease, neumonitis (aCD123)**

Measure of comorbidities for clinical trials in MDS

Are comorbidities relevant in clinical trials?

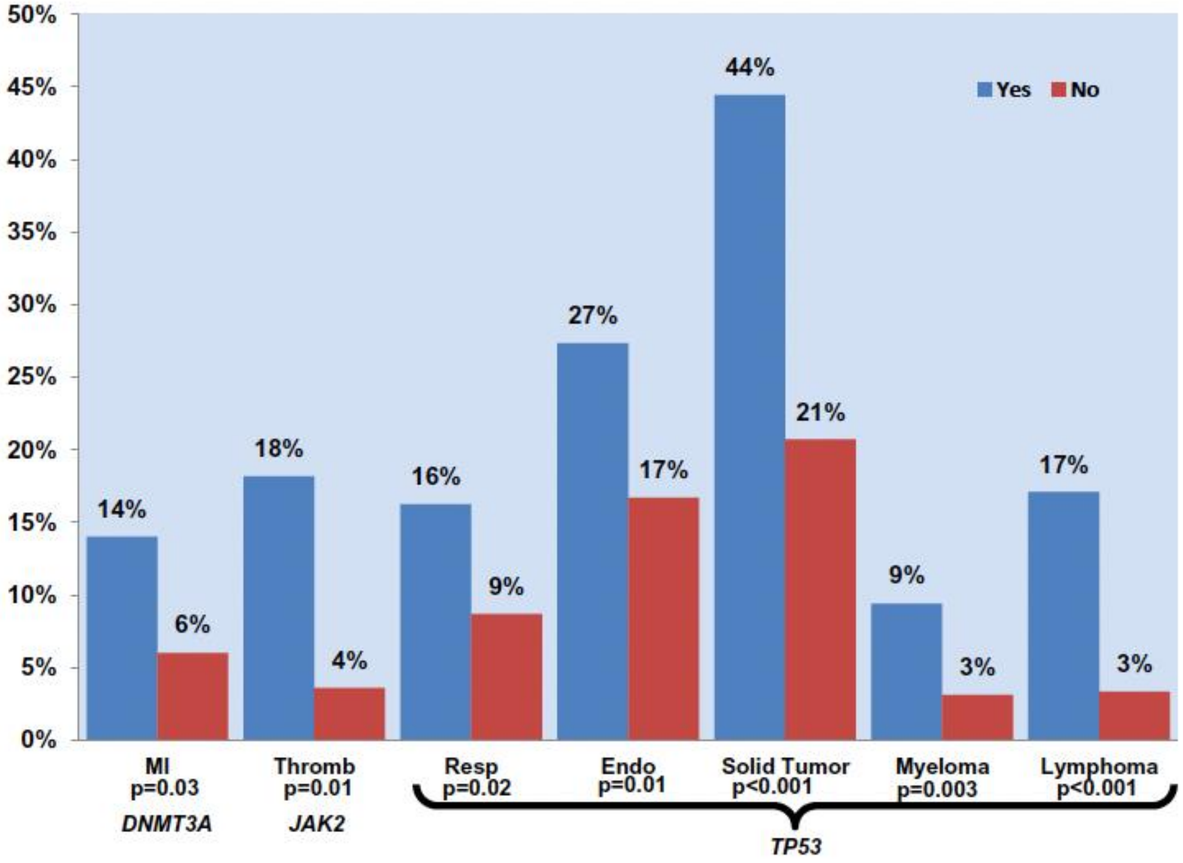
- **AEs/TEAEs**
  - **-impact on severity, incidence**
- **Treatment discontinuations/stopped**
  - **-Lower efficacy**
- **Impact on outcome**
  - **-Death, lower OS**

→ **No differential analysis**
Categorization
Cardiac disease

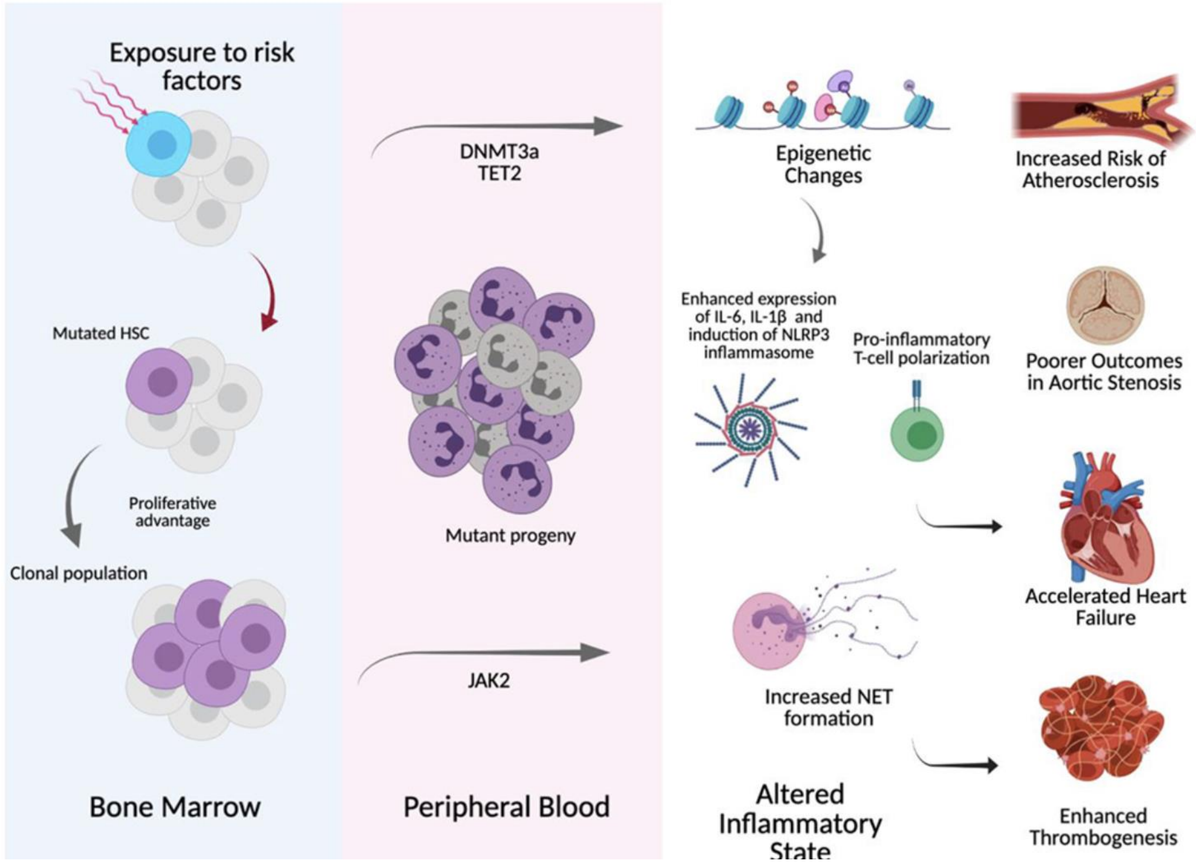
Measure of comorbidities for clinical trials in MDS

Are comorbidities relevant in clinical trials?

In patients with MDS, the presence of CHIP-associated mutations is associated with comorbidities



CHIP associates with an altered inflammatory state, elevating cardiovascular risk



Quavid, Cancer 2019
Marnell, J Mol Cell Cardiol. 2021

➢QoL and PRO in clinical trials?

Measure of QoL for clinical trials in MDS

General topics

- Impaired HRQoL in MDS at diagnosis
- PROs impact on prognosis
- New therapies for patients to live longer and better
- Important to determine value of novel treatments in improving patient´s well-being

Generation of rigorous PRO data
Support treatment decision-making

Measure of QoL for clinical trials in MDS

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Review

Do anemia treatments improve quality of life and physical function in patients with myelodysplastic syndromes (MDS)? A systematic review

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Physical function

ABSTRACT

Anemia is common in Myelodysplastic Syndromes (MDS). Different anemia treatments have been tested in clinical studies, but the full impact on patients' health-related quality of life (HRQoL) and physical function is unknown. The main aim of this review was to assess whether improvements in anemia are associated with changes in HRQoL/physical function.

Twenty-six full-text publications were identified, enrolling 2211 patients: nine randomized trials (RCTs), fourteen non-randomized studies of interventions and three cross-sectional studies. Interventions included: growth factors/erythropoiesis-stimulating agents ($n = 14$), red cell transfusion ($n = 9$), erythroid maturation agents ($n = 1$), or a combination ($n = 2$). Five RCTs reported no changes in HRQoL despite erythroid response to the intervention, raising the question of whether anemia treatment alone can effectively improve HRQoL. Many studies were considered at high risk of bias for assessing HRQoL. There is a pressing need for future clinical trials to better define the nature of the relationship between anemia and HRQoL/functional outcomes.

Response criteria for clinical trials in Lower Risk MDS

Summary

- Overcome pitfalls in some of IWG 2006 criteria
- Baseline assessments
- Response evaluation
- Progression or relapse after HI
- More accurate results of response evaluation
- Integration of PRO (QoL & fatigue) in response evaluation

Platzbecker, Blood 2018

Response criteria for clinical trials in Higher Risk MDS

Summary

- Better capture clinically relevant outcomes
- Reduce discrepancies with AML response criteria
- Improve applicability to novel therapies
- Future research focus on:

  - Standardization and validation of MRD assessment
  - Molecular responses
  - Less-than CR responses
  - Other surrogate end points that predict OS
  - Other scenarios different than frontline: Allo-SCT

Comorbidities, QoL & PROs should be incorporated in clinical trials

Summary

- Impact on response, outcome
- Categorization and graduation recommended
- Results based on comorbidities
- Standardized QoL and PRO assessments
- Confirm the benefit is not only numerical
- Patient lives more and better

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