MDS

Myelodysplastische Syndrome inkl. MDS/MPN Overlap

Medizinische Leitlinie

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Diese Leitlinie ist eine Grundlage für die Diagnostik und Therapie innerhalb des Tumorzentrums Oberösterreich und erhebt nicht den Anspruch auf Vollständigkeit.
Darüberhinaus von den jeweiligen Fachgesellschaften festgelegte Qualitätsstandards sind dem Stand der Wissenschaft entsprechend enzubeziehen.

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1 Allgemeines

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2 Diagnostik und Scoring

2.1 Diagnostik bei Verdacht auf MDS

1 Blutbild, Differentialblutbild, Retikulozyten, Na, K, Krea, BUN, LDH, GOT, GPT, gGt, AP, Bili, CRP, Fe, EBK, Ferritin, Transferrinsättigung, PTZ, Fibrinogen, AT III, BZ, Albumin, Eiw.ges, Elektrophorese, Vitamin B12, Folsäure, Kupferspiegel, Haptoglobin, Coombstest, Blutgruppe, AK-Suchtest, Blutausstrich

2 **Knochenmark**

- **Zytologie** (Diagnostik nach Hausstandard, international empfohlen: Fe-Färbung, Esterase);
- **Histologie**
- **FACS** (Marker: verminderter SSC; CD45, CD13, CD33, CD34, CD117, HLA-DR, CD15; aberrantes Muster von CD11b/CD13 und CD13/CD16 auf ausreifenden Granulozyten; Lineage infidelity markers auf myeloischen Zellen: CD2, CD5, CD7, CD19, CD56, TdT; Monozytäres Kompartment: CD36, CD14, CD64, CD33; CD11b/HLA-DR Muster, CD56 Überexpression, Lineage infidelity markers: CD2, CD7, CD19), Optional: Ogata-Score
- **Konventionelle Zytogenetik; falls konventielle Zytogenetik nicht möglich (keine Mitosen) FISH** auf Chromosom 5, 7, 8 und 20. Bei normalem Karyotyp wird in der Regel kein FISH durchgeführt. Bei unklaren Fällen kann dieser nachgefordert werden.
- **Molekularbiologie**

  Next Generation Sequencing (NGS)

  - Eine Mutationsanalyse mittels NGS ist bei Patienten mit **MDS, CMML und aCML** indiziert, wenn daraus eine mögliche therapeutische Konsequenz resultiert (ECOG <=3). Zudem kann bei unklaren Fällen und normalem Karyotyp der klonale Charakter der Erkrankung nachgewiesen werden.
  - **Bemerkung zu aCML**: die Gene SETBP1 und ETNK1 sind im NGS- Panel enthalten.
  - Multiplex-PCR (notwendig für Nachweis einer Dupl. MLL), bei Blastenvermehrung: WT1, FLT3-ITD PCR
  - bei nicht fitten Patienten und Verdacht auf **MDS/MPN können isoliert** Untersuchungen auf JAK-2 und PDGFR-ß angefordert werden

3 Anamnese (Medikamentenanamnese, Infektionsanamnese, sek. MDS?), klinischer Status, ECOG Performancestatus, Dokumentation des Transfusionsbedarfes

4 Sonographie Abdomen, Thorax-Röntgen

2.2 Erweiterte Diagnostik bei gesichertem MDS

1 Epo-Spiegel, PNH- Marker

2 falls Kandidat für allogene Stammzelltransplantation: Familienanamnese (Geschwister, ev. Eltern und Kinder), HCT-CI Score (s.u.); HLA-Typisierung, CMV-Status, ev. HLA-DR 15-Bestimmung

2.3 Diagnosestellung MDS nach minimalen diagnostischen Kriterien

Consensus Conference Vienna 2017: Valent et al Oncotarget 2017

A. Prerequisite Criteria (both must be fulfilled)

- Persistent (4 months) peripheral blood cytopenia** in one or more of the following lineages: erythroid cells, neutrophils, platelets (exception: in the presence of a blast cell excess and MDS-related cytogenetic abnormalities the diagnosis of MDS can be established without delay)

- Exclusion of all other hematopoietic or non-hematopoietic disorders as primary reason for cytopenia/dysplasia***

B. MDS-Related (Major) Criteria (at least one must be fulfilled)

- Dysplasia in at least 10% of all cells in one of the following lineages in the bone marrow smear: erythroid; neutrophilic; megakaryocytic****

- ≥15% ring sideroblasts (iron stain) or ≥5% ring sideroblasts (iron stain) in the presence of *SF3B1* mutation

- 5-19% myeloblasts on bone marrow smears (or 2-19% myeloblasts on blood smears)

- Typical chromosome abnormality(ies) by conventional karyotyping or FISH*****

C. Co-Criteria (for patients fulfilling A but not B, and otherwise show typical clinical features, e.g. macrocytic transfusion-dependent anemia; two or more of these co-criteria must be fulfilled for considering a provisional diagnosis of MDS)

- Abnormal findings in histologic and/or immunohistochemical studies of bone marrow biopsy sections supporting the diagnosis of MDS****

- Abnormal immunophenotype of bone marrow cells by flow cytometry, with multiple MDS-associated phenotypic aberrancies indicating the presence of a monoclonal population of erythroid and/or myeloid cells

- Evidence of a clonal population of myeloid cells determined by molecular (sequencing) studies revealing MDS-related mutations******

*The diagnosis of MDS can be established when both prerequisite criteria (´A´) and at least one major criterion (´B´) are fulfilled. If no major criterion is fulfilled, but the patient is likely to suffer from a clonal myeloid disease, co-criteria (´C´) should be applied and may help in reaching the conclusion that the patient has a myloid neoplasm resembling MDS or will develop MDS. In this diagnostic setting, repeated bone marrow investigations during follow-up may be required to arrive at a final diagnosis of MDS.
**Cytopenia defined by local institutional reference values.
***As more and more patients with two co-existing bone marrow neoplasms are diagnosed, it is important to state that in rare cases, MDS can be diagnosed even if another co-existing disease potentially causing cytopenia is also detected.
****Examples: clusters of abnormally localized immature precursors (ALIP); clusters of CD34+ blast cells; dysplastic micromegakaryocytes detected by immunohistochemistry (≥10% dysplastic megakaryocytes).
*****Typical chromosome abnormalities are those recurrently and typically found in MDS patients (e.g. 5q-, -7) and considered as indicative of MDS by the WHO even in the absence of morphologic criteria of MDS.
******Detection of multiple mutations typically seen in MDS (e.g. SF3B1) increases the likelihood that the patient suffers from MDS or will develop MDS.
Abbreviations: MDS, myelodysplastic syndrome(s); FISH, fluorescence in situ hybridization; WHO, World Health Organization; Hb, hemoglobin; ANC, absolute neutrophil count.

2.4 Differentialdiagnose MDS-Vorläufererkrankungen und MDS

CCUS	Clonal cytopenia of unknown significance
CHIP	Clonal hematopoiesis of indeterminate potential
ICUS	Idiopathic cytopenia of unknown significance
IDUS	Idiopathic dysplasia of unknown significance
CMUS	Clonal monocytosis of undetermined significance (ICC 2022)
CCMUS	Clonal cytopenia and monocytosis of undetermined significance (ICC 2022)
VEXAS	VEXAS Syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic)
LR MDS	Low Risk Myelodysplastic syndrome
HR MDS	High Risk Myelodysplastic syndrome

	Pre-MDS Conditions and MDS					
Feature	ICUS	IDUS	CHIP	CCUS	LR MDS	HR MDS
Monoclonal/ Oligoclonal	-/+	+/-	+	+	+	+
Dysplasia*	-	+	-	-	+	+
Cytopenia(s)**	+	-	-	+	+	+
BM blasts	<5%	<5%	<5%	<5%	<5%	<20%
Flow abnormalities	+/-	+/-	+/-	+/-	++	+++
Cytogenetic abnormalities	-/+***	-/+***	+/-	-	+	++
Molecular aberration/s****	-	-	+	+	++	+++

*At least 10% of all cells in a given lineage (erythroid, neutrophil, or megakaryocyte) are dysplastic.
**Persistent cytopenia(s) recorded over a time-period of at least 4 months.
***In a subset of cases, a small-sized clone with MDS-related anomaly is detectable by FISH.
****A molecular aberration is defined by MDS-related mutations and an allele burden of ≥2%. The working definition for pre-MDS conditions is also ≥2% allele burden, whereas the minimal allele burden to count as a co-criterion of MDS should be higher (e.g. 10%). However, a high allele burden does not exclude the presence of CHIP or CCUS. It is also important to note that in most patients with MDS, multiple gene mutations/aberrations are found. When several co-criteria of MDS are present, the diagnosis MDS can be established in the absence of diagnostic dysplasia.
Abbreviations: MDS, myelodysplastic syndrome(s); ICUS, idiopathic cytopenia of undetermined significance; IDUS, idiopathic dysplasia of undetermined significance; CCUS, clonal cytopenia of undetermined significance; LR, low risk; HR, high risk; BM bone marrow, FISH, fluorescence in situ hybridization.

2.5 Definition der klinisch signifikanten Zytopenie (WHO 2022)

Cytopenia definitions are harmonized for CCUS, MDS, and MDS/MPN; they include Hb <13 g/dL in males and <12 g/dL in females for anaemia, absolute neutrophil count <1.8 ×109/L for leukopenia, and platelets <150 × 109/L for thrombocytopenia.

2.6 Klassifikation

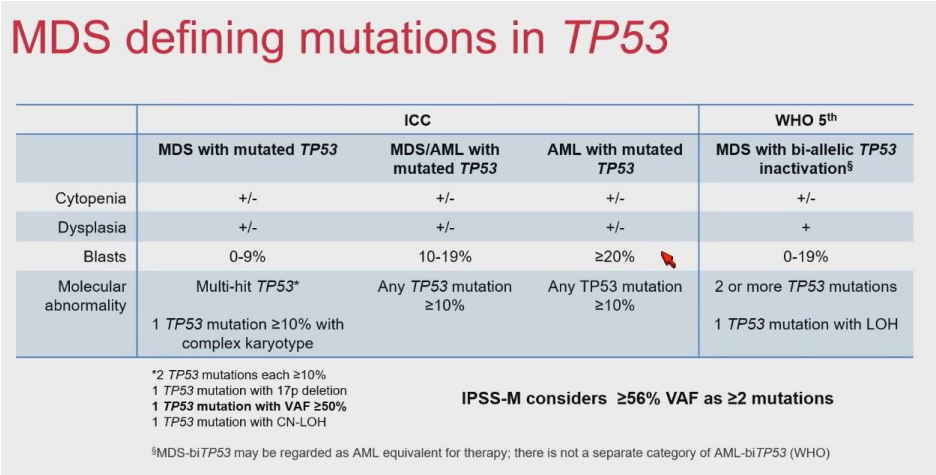
2.6.1 WHO Klassifikation 2022: MDS

Table 3. Classification and defining features of myelodysplastic neoplasms (MDS).

	Blasts	Cytogenetics	Mutations
MDS with defining genetic abnormalities			
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB	5q deletion alone, or with 1 other abnormality other than monosomy 7 or 7q deletion	
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)		Absence of 5q deletion, monosomy 7, or complex karyotype	*SF3B1*
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB	Usually complex	Two or more *TP53* mutations, or 1 mutation with evidence of *TP53* copy number loss or cnLOH
MDS, morphologically defined			
MDS with low blasts (MDS-LB)	<5% BM and <2% PB		
MDS, hypoplastic[b] (MDS-h)			
MDS with increased blasts (MDS-IB)			
MDS-IB1	5–9% BM or 2–4% PB		
MDS-IB2	10-19% BM or 5–19% PB or Auer rods		
MDS with fibrosis (MDS-f)	5–19% BM; 2–19% PB		

[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Khoury J. et al , Leukemia Jun 2022



2.6.2 MDS/MPN overlap: atypische CML, CMML, MDS/MPN mit Ringsideroblasten

Table 5. Myelodysplastic/myeloproliferative neoplasms.

Chronic myelomonocytic leukaemia
Myelodysplastic/myeloproliferative neoplasm with neutrophilia
Myelodysplastic/myeloproliferative neoplasm with *SF3B1* mutation and thrombocytosis
Myelodysplastic/myeloproliferative neoplasm, not otherwise specified

CMML:

- Proliferativer Typ: Leukozytenzahl > 13x109/ L
- Dysplastischer Typ: Leukozytenzahl < 13 x 109 / L
- Klonale zytogenetische Veränderungen bei 20–40% (ASXL1 (40%), TET2 (58%), SRSF2 (46%), RUNX1 (15%), NRAS (11%) CBL (10%); und andere)

Table 6. Diagnostic criteria of chronic myelomonocytic leukaemia.

Prerequisite criteria
1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]
Supporting criteria
1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]
Requirements for diagnosis
- Pre-requisite criteria must be present in all cases.
- If monocytosis is ≥ 1 × 10^9/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and <1 × 10^9/L: supporting criteria 1 and 2 must be met.
Subtyping criteria
- Myelodysplastic CMML (MD-CMML): WBC < 13 × 10^9/L
- Myeloproliferative CMML (MP-CMML): WBC ≥ 13 × 10^9/L
Subgrouping criteria (based on percentage of blasts and promonocytes)
CMML-1: <5% in peripheral blood and <10% in bone marrow
CMML-2: 5–19% in peripheral blood and 10-19% in bone marrow

[a]Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes.
[b]Myeloproliferative neoplasms (MPN) can be associated with monocytosis at presentation or during the course of the disease; such cases can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or high burden of MPN-associated mutations (*JAK2*, *CALR* or *MPL*) tends to support MPN with monocytosis rather than CMML.
[c]Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.
[d]Morphologic dysplasia should be present in ≥10% of cells of a haematopoietic lineage in the bone marrow.
[e]Based on detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

2.7 Risikoscoring

2.7.1 IPSS-Risikoscoring von de novo MDS

Greenberg et al , Blood 1997

Punkte:	0	0,5	1	1,5	2
Knochenmarkblasten	**<5**	**5-10**	**-**	**11-20**	**21-30**
Karyotyp	**Good***	**intermediate****	**poor*****		
Zytopenie	**0/1**	**2/3**			

* Good: Normal, 5q-,20q-, -Y,
** Intermediate: alle anderen
*** Poor: Chromosom 7 Aberr., komplex>=3Aberrationen

Risikokategorie:	**Punktezahl**	**Gesamtüberleben median**
Low	0	5,7 y
Intermediate I	0,5 – 1,0	3,5 y
Intermediate II	1,5 – 2,0	1,1 y
High	>= 2,5	0,4 y

2.7.2 WHO classification-based scoring system (WPSS)

Malcovati et al J Clin Onc2005

Scores	**0**	**1**	**2**	**3**
WHO Subtype	RA, RARS,del 5q	RCMD	RAEB 1	RAEB 2
Transfusionrequirement	None	regular		
Cytogenetic category	Low	Intermediate	High	

RISK GROUPS	**SUM OF SCORES**	**Gesamtüberleben median**
Very Low	0	141 mo.
Low	1	66 mo.
Intermediate	2	48 mo.
High	3 – 4	26 mo.
Very High	5 – 6	9 mo.

2.7.3 IPSS-R (revised)

Greenberg et al, Blood 20 September 2012

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable.

Table 2. MDS Cytogenetic Scoring System

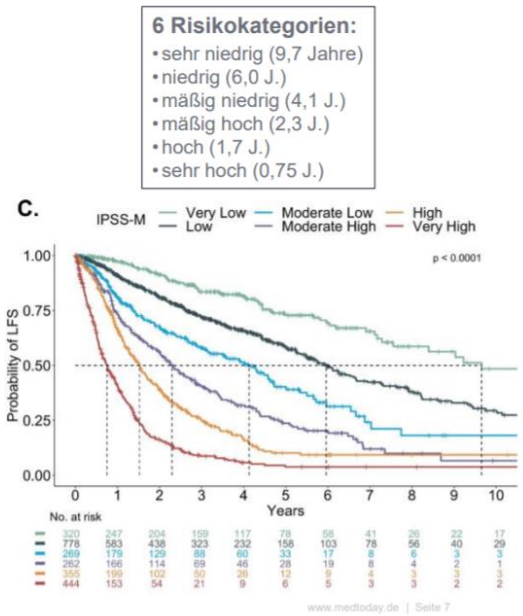
Prognostic subgroups, % of patients	Cytogenetic abnormalities
Very good (4%*/3%†)	−Y, del(11q)
Good (72%*/66%†)	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate (13%*/19%†)	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor (4%*/5%†)	−7, inv(3)/t(3q)/del(3q), double including −7/del(7q), complex: 3 abnormalities
Very poor (7%*/7%†)	Complex: > 3 abnormalities

Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

2.7.4 IPSS-M (molecular)

Online Calculator: https://mds-risk-model.com



Laut einer retrospektiven Auswertung transplantierter Patienten mit Integration genomischer Daten (Tentori et al ASH 2023 ,#197) profitieren MDS Patienten ab dem Stadium IPSS-M moderate-high von einer früheren allogenen Stammzell-Transplantation im Vergleich zu einem späteren Zeitpunkt der TX. Diese Patienten sollen daher frühzeitig zur Evaluierung für eine allogene SZT vorgestellt werden.

2.7.5 Für Stammzelltransplantationskandidaten - Comorbidity score (HCT-CI, Sorror)

Sorror et al Blood 2005

Table 4. Definitions of comorbidities included in the HCT-CI and HCT-CI scores compared with original CCI scores

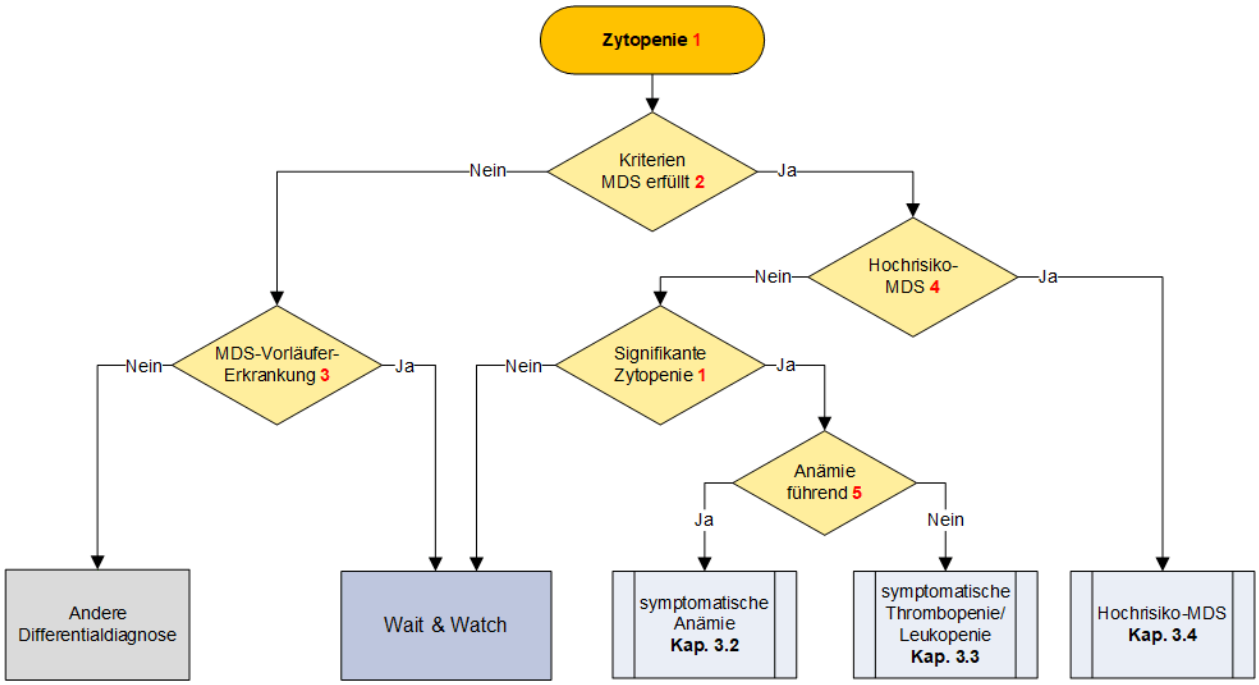
Comorbidity	Definitions of comorbidities included in the new HCT-CI	HCT-CI weighted scores	Original CCI scores*
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1	0
Cardiac‡	Coronary artery disease,§ congestive heart failure, myocardial infarction, or EF ≤ 50%	1	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1	0
Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone	1	1
Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident	1	1
Psychiatric disturbance†	Depression or anxiety requiring psychiatric consult or treatment	1	Not included
Hepatic, mild‡	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1	1
Obesity†	Patients with a body mass index > 35 kg/m^2	1	Not included
Infection†	Requiring continuation of antimicrobial treatment after day 0	1	Not included
Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica	2	1
Peptic ulcer	Requiring treatment	2	1
Moderate/severe renal‡	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2	2
Moderate pulmonary‡	DLco and/or FEV$_1$ 66%-80% or dyspnea on slight activity	2	1
Prior solid tumor‡	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer	3	2
Heart valve disease	Except mitral valve prolapse	3	0
Severe pulmonary‡	DLco and/or FEV$_1$ ≤ 65% or dyspnea at rest or requiring oxygen	3	1
Moderate/severe hepatic‡	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3	3

To convert creatinine from milligrams per deciliter to micromoles per liter, multiply milligrams per deciliter by 88.4.
EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.
*Definitions of comorbidities included in the original CCI are defined in the appendix of a prior publication.[8]
†Newly investigated comorbidities.
‡Comorbidities with modified definitions compared with the original CCI.
§One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.

HCT-CI Online-Calculators

3 Behandlungsplan

3.1 Übersichtsplan



1 Definition Zytopenie gemäß WHO siehe Kapitel 2.5
2 Minimal diagnostische Kriterien des MDS siehe Kapitel 2.3
3 MDS-Vorläufererkrankungen siehe Kapitel 2.4
4 Hochrisiko-MDS: definiert als IPSS-R high oder IPSS-R very high **oder** Hochrisiko-Molekularbiologie (siehe 2.7.4)
5 Anämie ist Hauptsymptom und es besteht keine signifikante Thrombo- oder Leukozytopenie

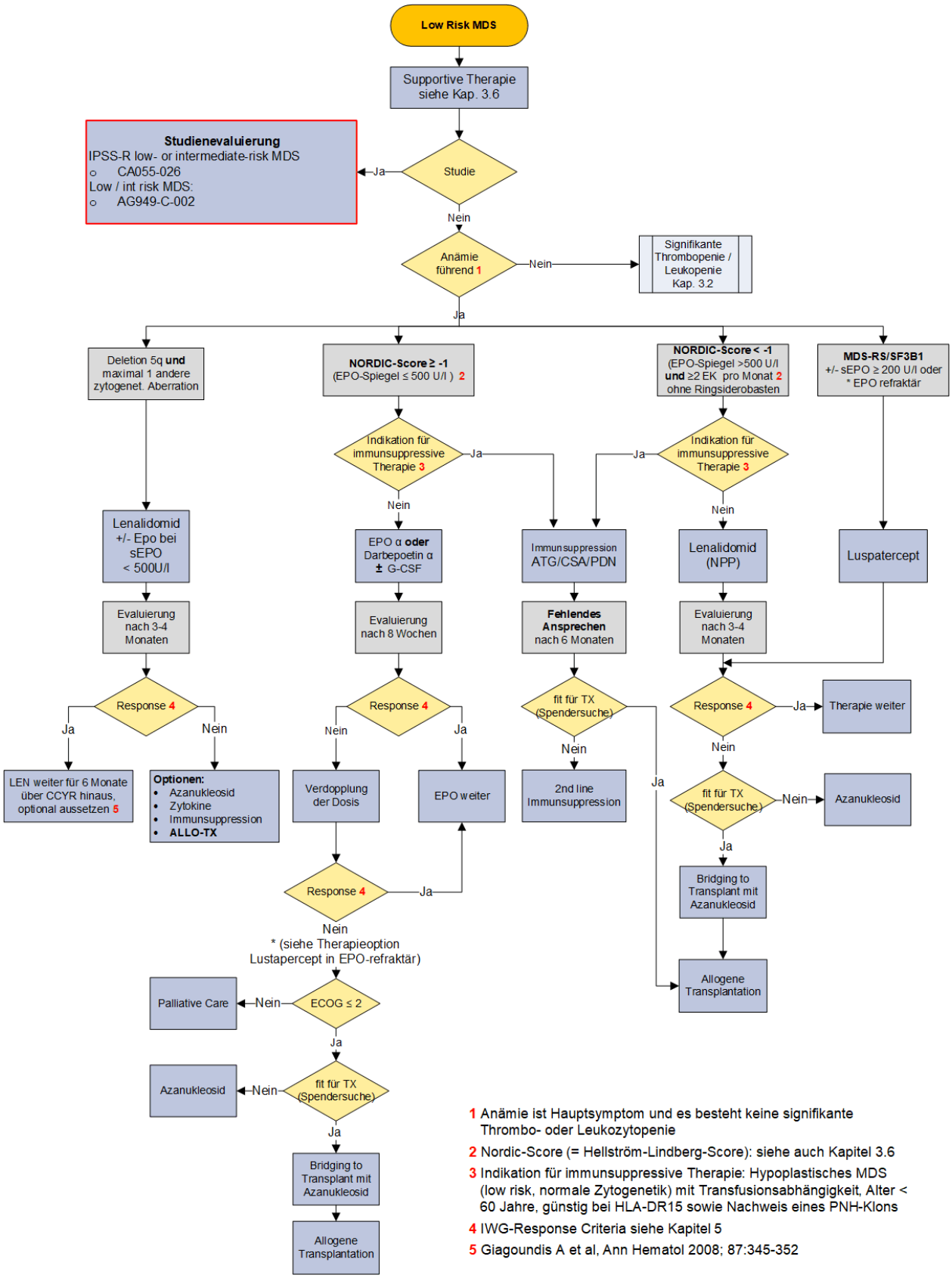
Anmerkung: Eine Hochrisiko-Molekularbiologie ist ein möglicher Faktor zur Entscheidung bezüglich Transplantationsindikation.

Table 1. Definition of HR-MDS based on currently used prognostic models

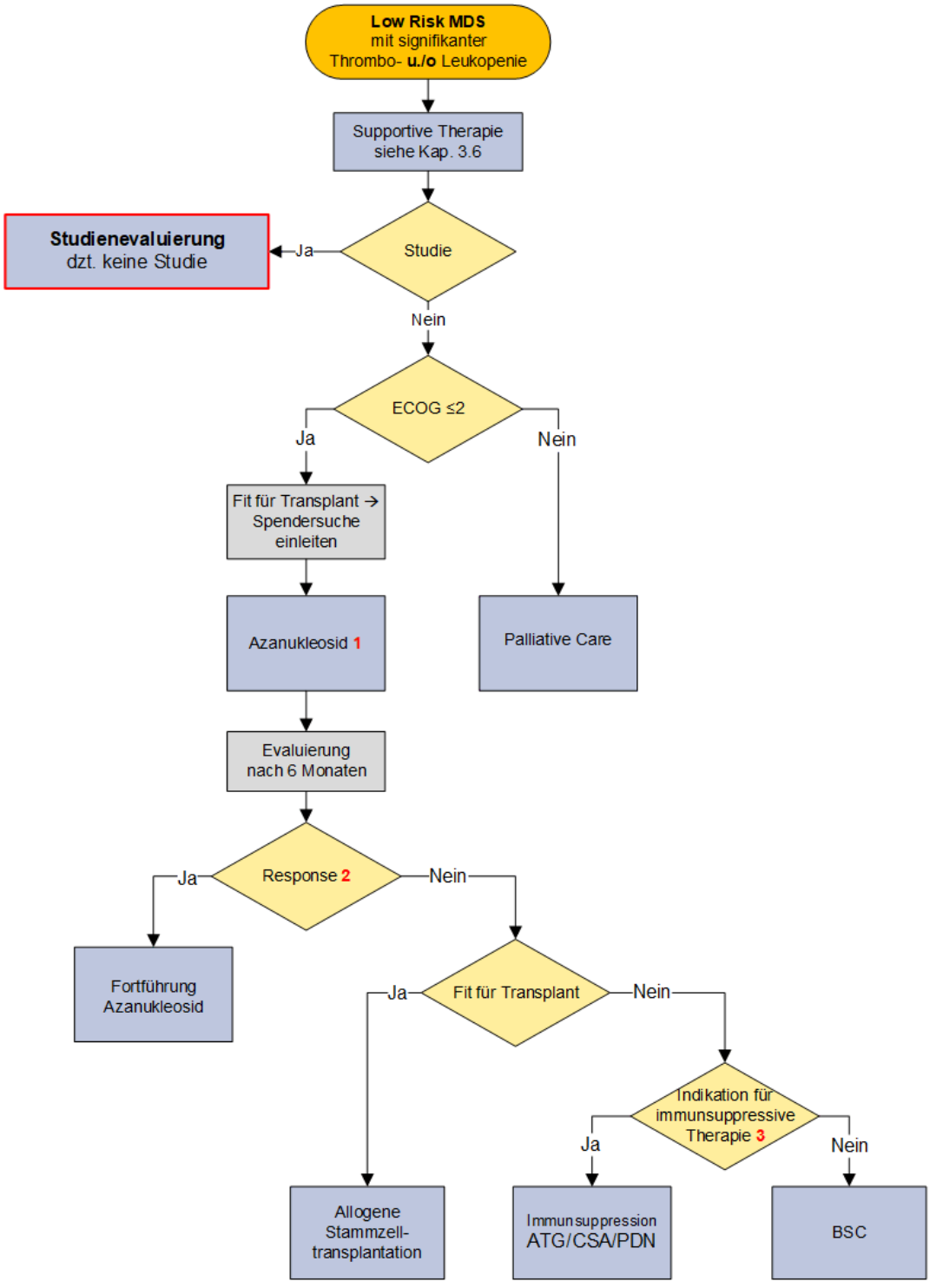
Prognostic model	Threshold to define HR-MDS
IPSS-R	>3.5 points
IPSS-M	>0 (ie, any positive score; risk categories of moderate-high, high, and very high)

Zeidan et al Blood 2023

3.2 Low-Risk-MDS - Klinisch signifikante Anämie (IPSS-R very low / low / int)



3.3 Low-Risk-MDS - Symptomatische Thrombopenie / Leukopenie

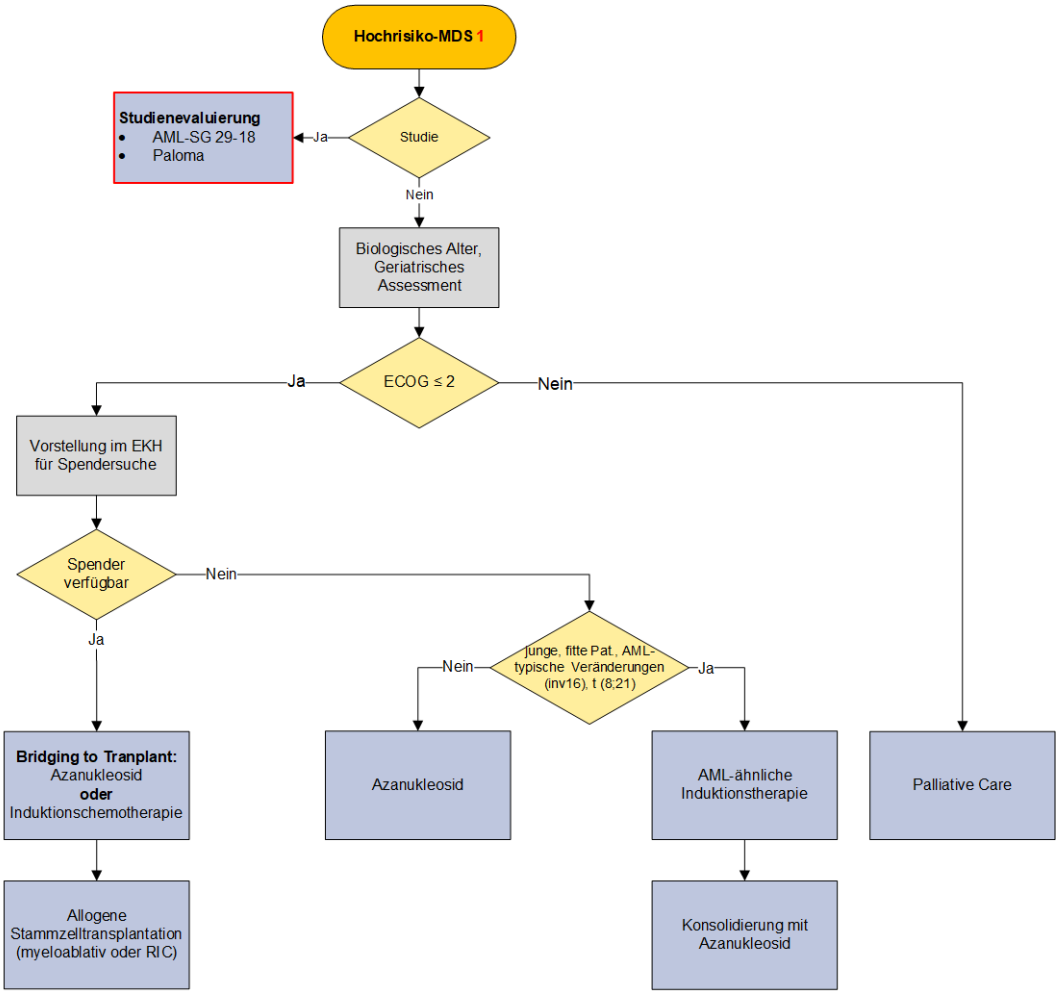


1 evt. Named Patient Program mit TPO-R-Agonisten

2 IWG-Response Criteria siehe Kapitel 5

3 Indikation für immunsuppressive Therapie: Hypoplastisches MDS (low risk, normale Zytogenetik) mit Transfusionsabhängigkeit, Alter < 60 Jahre, günstig bei HLA-DR15 sowie Nachweis eines PNH-Klons

3.4 Hochrisiko-MDS (IPSS-R high / very high)



1 HR MDS definiert als IPSS-R high und IPSS-R very high risk

Anmerkung: Eine Hochrisiko-Molekularbiologie ist ein möglicher Faktor zur Entscheidung bezüglich Transplantationsindikation.

Table 1. Definition of HR-MDS based on currently used prognostic models

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Zeidan et al, Blood 2023

Sowohl bei Bridging to transplant, als auch ohne geplante Transplantation besteht nach Meinung der Leitlinienautoren neben einer Induktionschemotherapie auch die Therapieoption mit Venetoclax und Azacitidin bei MDS mit 10-19% Blasten, da diese nach der ICC-Klassifikation als MDS/AML klassifiziert werden.
Die Ergebnisse der randomisierten Phase 3 Studie (Verona Studie) mit Aza +- Venetoclax für HR MDS sind jedoch noch ausstehend. Cave: Bei MDS wurde Venetoclax nur Tag 1-14 verabreicht!
Inaqovi (Decitabine/Cedazuridine) wurde für die AML, nicht fit für intensive Therapie zugelassen und könnte bei MDS/AML nach ICC eine (orale) Therapieoption darstellen.

3.5 Therapie der CMML (adaptiert von Germing et al/ Düsseldorf)

CMML Dysplastische Form I:

- Hämatopoietische Insuffizienz:
- BSC, Transfusionen, EPO, ggf. Studien, Evaluierung für allogene Transplantation

CMML Dysplastische Form II:

- Hämatopoietische Insuffizienz, Progress:
- BSC, Vidaza, Evaluierung für allogene allogene Transplantation

CMML Proliferative Form:

- Leukozytose, Organomegalie, konstit. Symptome
- Zytoreduktion (Hydroxyurea etc), demethylierende Sustanzen, Evaluierung für ggf. allogene Transplantation

Bzgl. Risikoscores und Therapie der CMML siehe aktuelle Leitlinie der DGHO/Onkopedia.

3.6 Supportive Therapie

- Erythrozytenkonzentrate bei symptomatischer Anämie (gefiltert, bestrahlt bei Patienten mit immunmodulierender oder zytostatischer Therapie)
- Thrombozytenkonzentrate bei PLT <10 G/l u.o. Blutung (gefiltert, bestrahlt); bei Kandidaten für allogene Stammzelltransplantation und/ oder CMV-negativen Empfängern → CMV-negative Konzentrate
- Antibiotika für bakterielle Infekte
- G-CSF wird für die Routineprophylaxe nicht empfohlen, nur bei resistenten oder rezidivierenden Infekten oder in Kombination mit Epo bei sympt. Anämie (s.u.)
- Antifibrinolytika (Aminokapronsäure) für Blutungen, die refraktär auf Thrombozytenkonzentrate sind
- Eisenchelation s.u.
- Erythropoietine s.u.

3.7 Indikationen für Eisenchelation

Eisenchelation basierend auf folgenden Parametern zu überlegen:

- Transfusionsabhängige Anämie
- **Serumferritin** >2.000 ng/mL (ohne Zeichen einer aktiven Inflammation oder Lebererkrankung)
- Bei **hohem Transfusionsbedarf** (>2 EK/Monat) und stark steigendem Ferritin bereits frühzeitiger Beginn
- **Lebenserwartung** von >2 Jahren
- **Organopathie** durch Eisenüberladung
- Geplante **Stammzelltransplantation**

Auswahl des Eisenchelators

(1. Desferoxamine (Desferal®) → nicht praktikabel)

2. Deferasirox, ICL670 (Exjade®) → Indikation: sek. Eisenüberladung, Intoleranz von Desferoxamin

→ Fortsetzung der Eisenchelation bis CR

→ bei kontinuierlicher Transfusion weiter, ev. Dosisreduktion

Beurteilung des Therapieansprechens auf Eisenchelation

(Valent et al, Eur.J Clin Invest 2008)

CR:	Ferritin < 2000 ng/ml und eine Senkung um mind. 500 ng/ml
MR:	Ferritin < 2000 ng/ml, aber Senkung um weniger als 500 ng/ml
SIL (stable iron load):	Ferritin bleibt < 4000 ng/ml
NR:	Anstieg von Ferritin unter Therapie

3.8 Erythropoietine

Modifizierter Nordic Score (= Hellström-Lindberg-Score)

Prädiktives Modell zur Vorhersage der Wirksamkeit einer Therapie mit r-EPO +- G-CSF bei Patienten mit MDS (RA, RARS, RAEB)

Kriterium	Wert	Punktzahl
Transfusionsbedarf	< 2 EK/ Monat	+2
Transfusionsbedarf	≥ 2 EK/ Monat	-2
Serum EPO-Spiegel	<100 U/l	+2
Serum EPO-Spiegel	100 - 500 U/l	+1
Serum EPO-Spiegel	>500 U/l	-3

Definition des Ansprechens

- CR Stable hemoglobin > 11,5 g/dL
- PR Increase in Hb with >1,5 g/dL or total stop in RBC transfusion

Summe (Punktzahl)

Score >1	74 % Ansprechwahrscheinlichkeit (CR, PR)
Score -1 bis +1:	23 % Ansprechwahrscheinlichkeit (CR, PR)
Score <-1:	7 % Ansprechwahrscheinlichkeit (CR, PR)

Indikation für Erythropoietine:

1. Alle MDS Patienten, welche rein supportiv behandelt werden
2. **Hellström Lindberg-Score** ≥-1 bzw. Epo-Spiegel ≤500 U/l
3. **Initiale Dosis:** rHuEpo 40.000 – 60.000 IE s.c./ Woche
   oder Darbepoetin alpha 150 – 300 µg s.c./Woche
4. **Zusätzliche Zytokine optional** (G-CSF):
   bei Nicht-Ansprechen unter Epo 1 -2 mcg/kg 1-3x/Wo,
   bei RARS 1 - 3x/Wo ab Beginn der Epo-Therapie

Evaluation nach 6-8 Wochen:

- Bei fehlendem Ansprechen Verdopplung der Epo-Dosis

Nach weiteren 6-8 Wochen Evaluation:

zumindest **minor erythroid response** gefordert, d.h. mind. 50% Reduktion des Transfusionsbedarfes oder bei Hb <11 g/dl ohne Transfusionen ein Anstieg des Hb von 1g/dl

→ Fortführung EPO (Dauertherapie = solange EPO wirkt, d.h. zumindest minor response hält;
EPO-Dosierung nach Hb -> Erhaltungstherapie)

Falls nicht wirksam → EPO - STOP !

4 Besondere klinische Situationen

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5 Verlaufskontrolle und Nachsorge

IWG response criteria

Platzbecker U et al. Blood 2019

Table 2. Suggested modified IWG 2018 HI-E criteria for response evaluation

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
Response evaluation criteria: HI-E		
NTD (0 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
LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)*	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	
HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	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	
On-treatment RBC transfusion policy§	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
Dose adjustment thresholds for high Hb levels	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

Table 3. Suggested modified IWG 2018 HI-N and HI-P criteria for response evaluation

Newly suggested evaluations: IWG 2018		IWG 2006 criteria	
Type of response	**Criteria**	**Type of response**	**Criteria**
Platelet response (pretreatment, <100 × 10⁹/L), HI-P	• Absolute increase of 30 × 10⁹/L for patients starting with >20 × 10⁹/L PLTs or • Increase from <20 × 10⁹/L to >20 × 10⁹/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 × 10⁹/L are to be reported	Platelet response (pretreatment, <100 × 10⁹/L), HI-P	• Absolute increase of 30 × 10⁹/L for patients starting with >20 × 10⁹/L PLTs or • Increase from <20 × 10⁹/L to >20 × 10⁹/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 × 10⁹/L are a sufficient reason for treatment discontinuation in the case of treatment with TPO agonists		None
Neutrophil response (pretreatment, all patients), HI-N	At least 100% increase and an absolute increase >0.5 × 10⁹/L (pretreatment, <1.0 × 10⁹/L) Increments of neutrophils also for patients with a pretreatment ANC of >1.0 × 10⁹/L are to be reported	Neutrophil response (pretreatment, <1.0 × 10⁹/L), HI-N	At least 100% increase and an absolute increase >0.5 × 10⁹/L

Zeidan AM et al Blood 2023

Table 2. IWG 2023 response criteria for HR-MDS

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‡
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
SD	Failure to achieve at least PR, but no evidence of progression for >8 wk	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%†
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‡

CR_{bi}, CR bilineage; CR_{uni}, CR unilineage; CR_L, CR with limited count recovery; CRh, CR with partial hematologic recovery; wk, weeks.

*Patients require ≥5% blasts before treatment initiation to be considered evaluable for CR, PR, CRh, or CR_L. For time window of response assessment by PB counts, refer to Table 5. For patients with <5% blasts who have HR-MDS owing to adverse cytogenetics and/or severe cytopenias, full cytogenetic clearance (complete cytogenetic response) and blood counts that meet CR criteria are considered CR equivalent but should be reported separately. Full trilineage count recovery is defined as Hb ≥10 g/dL, platelets ≥100 × 10^9/L, and ANC ≥1.0 × 10^9/L independent of baseline PB. Given that molecular clearance has not been validated prospectively, it was not used for CR definition.

Table 2 (continued)

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‡‡

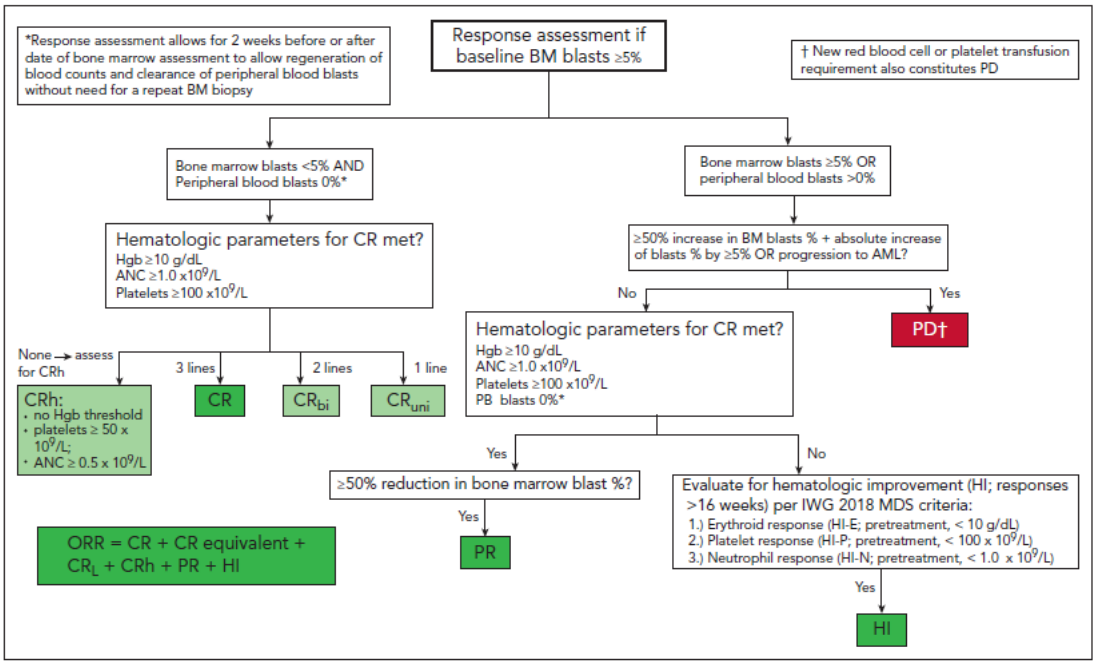

Figure 1. Response assessment flowchart for patients with ≥5% BM blasts at baseline. A flowchart for response assessment per the IWG 2023 response criteria is

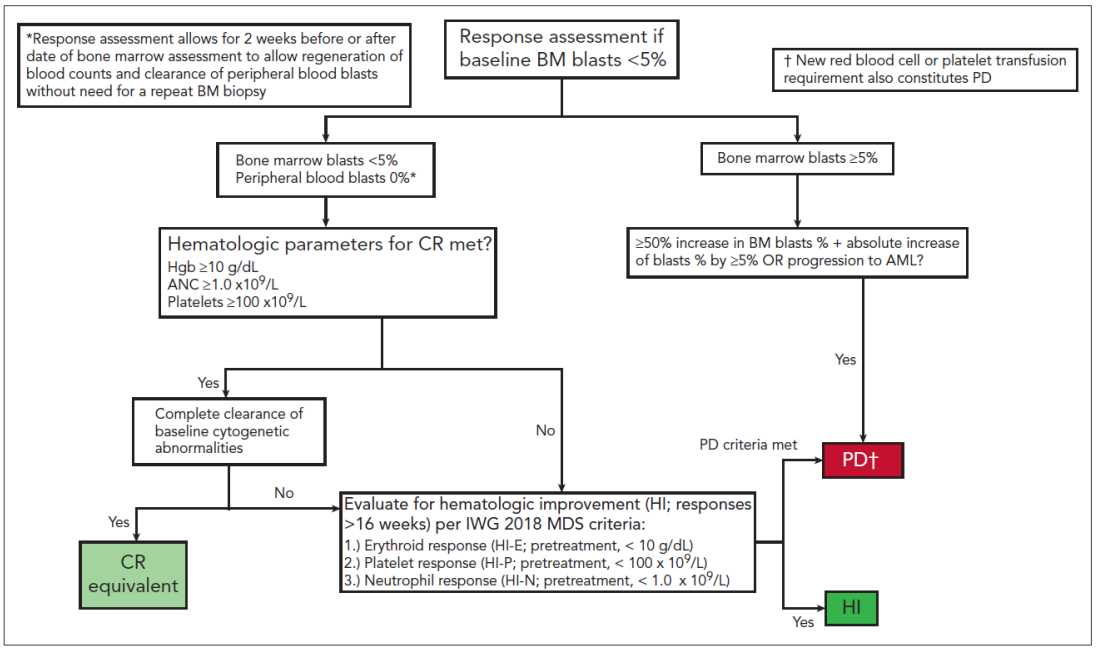

Figure 2. Response assessment flowchart for patients with <5% BM blasts at baseline (ie, prior to the current line of therapy). A response assessment flowchart for

6 Dokumentation und Qualitätsparameter

- Transfusionsfrequenz
- Toxizität/ Infektionen
- Overall- Survival
- AML-Progression
- Quality of life

7 Literatur/Quellenangaben

Grundlage der Empfehlungen der vorliegenden Leitlinie sind die zum Zeitpunkt der Freigabe aktuell gültigen internationalen Empfehlungen von Onkopedia und NCCN sowie Übersichtsarbeiten, u.a. aus UpToDate. Die nachfolgenden Quellenangaben zur Leitlinie stellen nur eine Auswahl der Literaturquellen dar, die für die Erkrankung bedeutsam sind. Weitere Literaturquellen sind den internationalen Leitlinien zu entnehmen.

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Anhang: Therapieprotokolle

Lenalidomid:	10mg/d, Anpassung der Dosis abhängig von der Kreatininclearance und den Thrombozytenwerten (Pause bei TC< 25 G/l, Wiederbeginn mit 5 mg/d nach Erholung >50G)
Azacitidine (Vidaza):	75 mg/m2 s.c. Tag 1-7 oder i.v. Tag 1-7 bei schwerer Thrombopenie
Induktionschemotherapie:	3+7-Schema: (Daunorubicin: 60 mg/m² (30 min LZ) Tag 1-3, ARA-C: 200 mg/m² (24 Std. LZ) Tag 1-7)
Luspatercept (Reblozyl):	Beginn mit 1 mg/kg alle 21 Tage s.c., bei fehlendem Hämoglobinanstieg Steigerung auf 1,33 mg/kg bei der 3. Dosis, bei weiterhin fehlendem Anstieg Steigerung auf 1,75 mg/kg (Maximaldosis). Behandlungsabbruch nach 9 Wochen (3 Verabreichungen) der höchsten Dosis, wenn kein klinischer Nutzen zu verzeichnen ist.

Anhang: Studienblatt

- **AMLSG 29-18**
  Ansprechpartnerin OÄ Dr. Sigrid Machherndl-Spandl (Ordensklinikum Linz Elisabethinen)
  A phase 3, multicenter, double-blind, randomized, placebo-controlled study of AG-120 or AG-221 in combination with induction therapy and consolidation therapy followed by maintenance therapy in patients with newly diagnosed acute myeloid leukemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation, eligible for intensive chemotherapy
  Inclusion Criteria: Hochrisiko-MDS (und AML) bei Patienten, die fit für eine Induktionschemotherapie oder allogene SZTX sind

- **AG946-C-002**
  Ansprechpartnerin OÄ Dr. Sigrid Machherndl-Spandl (Ordensklinikum Linz Elisabethinen)
  A Phase 2a/2b, Open label, proof of concept (Phase 2a) and double blind ramdomized placebo controlled (Phase 2b), Multicenter, Efficacy and Safety study of AG 946 in Participants with Anemia Due to lower risk MDS (Initiierung Q2/2024)

Anhang: Wirtschaftliche Analyse (optional)
