Higher-risk MDS and AML: How new guidelines are changing diagnosis, classification and management

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities*
- *touchIME accepts no responsibility for errors or omissions*

touch HAEMATOLOGY

Presenting symptoms and the diagnostic process for MDS and AML

Prof. Andrew Wei
Peter MacCallum Cancer Centre,
Walter and Eliza Hall Institute of
Medical Research,
Melbourne, Australia

touch HAEMATOLOGY

Presenting symptoms of MDS and AML

MDS[1]

- Easy bruising
- Pallor
- Pale conjunctiva
- Mucosal bleeding
- Hypotension
- Tachycardia
- Emphysema
- Heart failure
- Epistaxis[1,2]
- Petechiae[1,2]
- Fatigue[1,2]
- Headache[1,2]
- Angina pectoris[1,2]
- Frequent infections[1,2]
- Exercise intolerance[1,2]
- Major bleeding[1,2]

AML[2]

- Gingival haemorrhage
- Fever
- Adenopathy
- Dyspnoea
- Confusion
- Palpitations
- Coma visual disturbances
- Hypoxia
- Organomegaly
- Respiratory failure
- Seizures
- Menorrhagia
- Claudication

AML, acute myeloid leukaemia; GI, gastrointestinal; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Barzi A, Sekeres MA. *Cleve Clin J Med*. 2010;77:37–44; 2. Smith M, et al. *Crit Rev Oncol Hemat*. 2004;50:197–222.

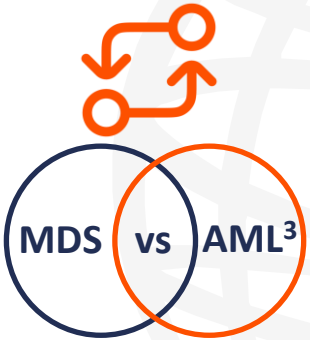
touch HAEMATOLOGY

Modes of presentation

Incidental cytopenia[1]

- ICUS[2]
- CCUS[2]

Prior cytotoxic therapy[3]



AML, acute myeloid leukaemia; CCUS, clonal cytopenia of undetermined significance; ICC, International Consensus Classification; ICUS, idiopathic cytopenia of undetermined significance; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Samiev D, et al. *Korean J Fam Med*. 2014;35:111–8; 2. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 3. Khoury JD, et al. *Leukemia*. 2022;36:1703–19.

touch HAEMATOLOGY

Diagnosing MDS or AML

Laboratory parameters (MDS only)[1]

- Ferritin
- Transferrin
- Transferrin saturation
- Reticulocyte counts
- Vitamin B12
- Folate concentrations
- Haptoglobin
- Creatinine levels

Blood counts (MDS only)[1]

Blood counts

- Evaluate cytopenia

Cytomorphology

- Dysplastic features

Bone marrow aspiration[1,2]

Cytomorphology

- Dysplastic features
- Blast counts

Cytogenetics

Molecular studies

Bone marrow biopsy[1,2]

Cellularity and fibrosis

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 2. Heuser M, et al. *Ann Oncol*. 2020;31:697–712.

touch HAEMATOLOGY

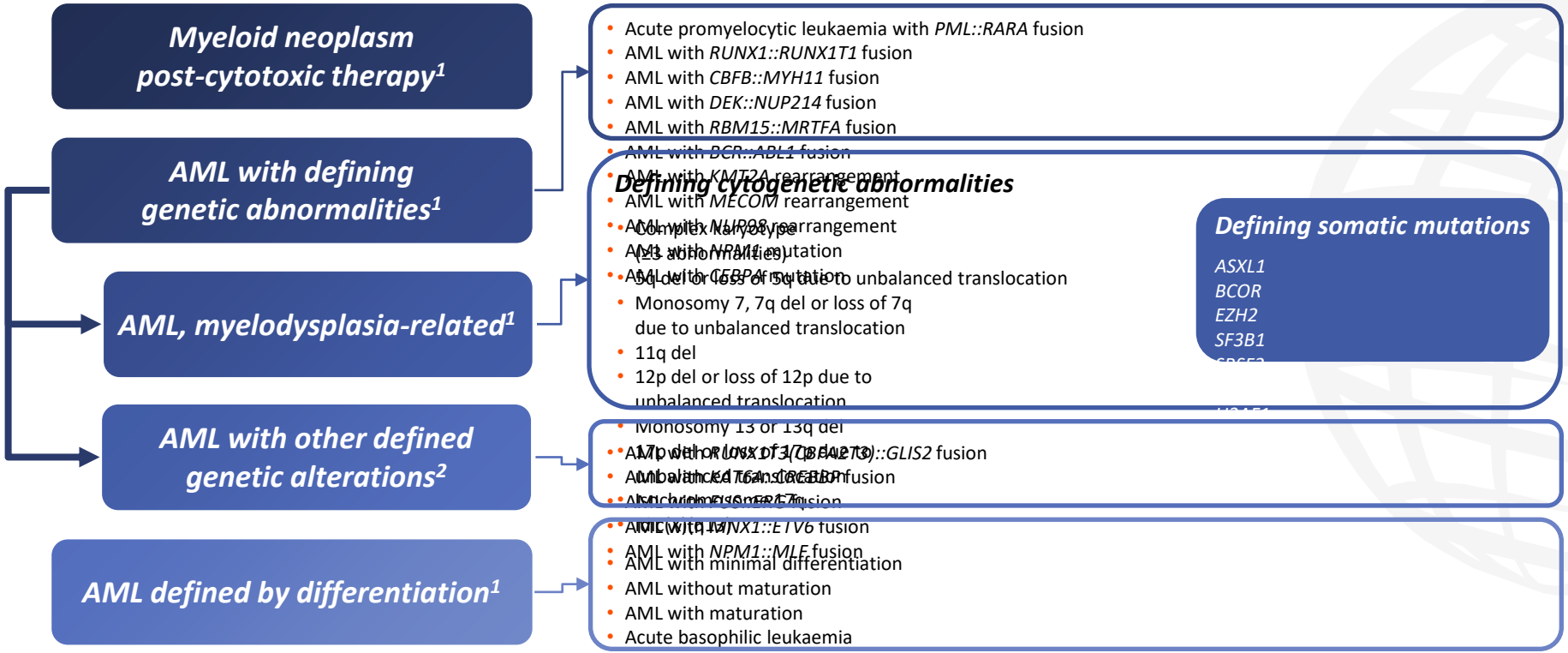
Categorization of MDS by WHO and ICC

<table>
<tr><th>Blast burden</th><th>Genetic</th><th colspan="4">WHO 2022[1]</th><th>ICC 2022[2]</th></tr>
<tr><td rowspan="3">BM blasts <5%
PB blasts <2%</td><td>del(5q)</td><td colspan="3">MDS-5q</td><td rowspan="5">AML with defining genetic abnormalities*</td><td>MDS-del(5q)</td></tr>
<tr><td>SF3B1</td><td colspan="3">MDS-SF3B1</td><td>MDS-SF3B1</td></tr>
<tr><td>Other</td><td colspan="2">MDS-LB</td><td rowspan="3">MDS-biTP53</td><td>MDS, NOS
Without dysplasia
or with SL/ML dysplasia</td></tr>
<tr><td colspan="2">BM blasts 5–9%
PB blasts 2–4%</td><td>MDS-IB1</td><td rowspan="2">MDS-f</td><td>MDS-EB†</td></tr>
<tr><td colspan="2">BM blasts 10–19%
PB blasts 5–19%
Auer rods</td><td>MDS-IB2</td><td>MDS/AML‡
Unless AML-defining cytogenetic or molecular abnormality*</td></tr>
</table>

*AML except *BCR::ABL* and *CEBPA* mut (≥20% blasts required). †PB blasts 2–9%. ‡PB blasts 5–19% and no requirement for auer rods.
AML, acute myeloid leukaemia; BM, bone marrow; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-EB, MDS with excess blasts; MDS-f, MDS with fibrosis; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-NOS, MDS not otherwise specified; ML, multilineage; PB, peripheral blood; SL, single lineage; WHO, World Health Organization.
1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Arber DA, et al. *Blood*. 2022;140:1200–28.

touch HAEMATOLOGY

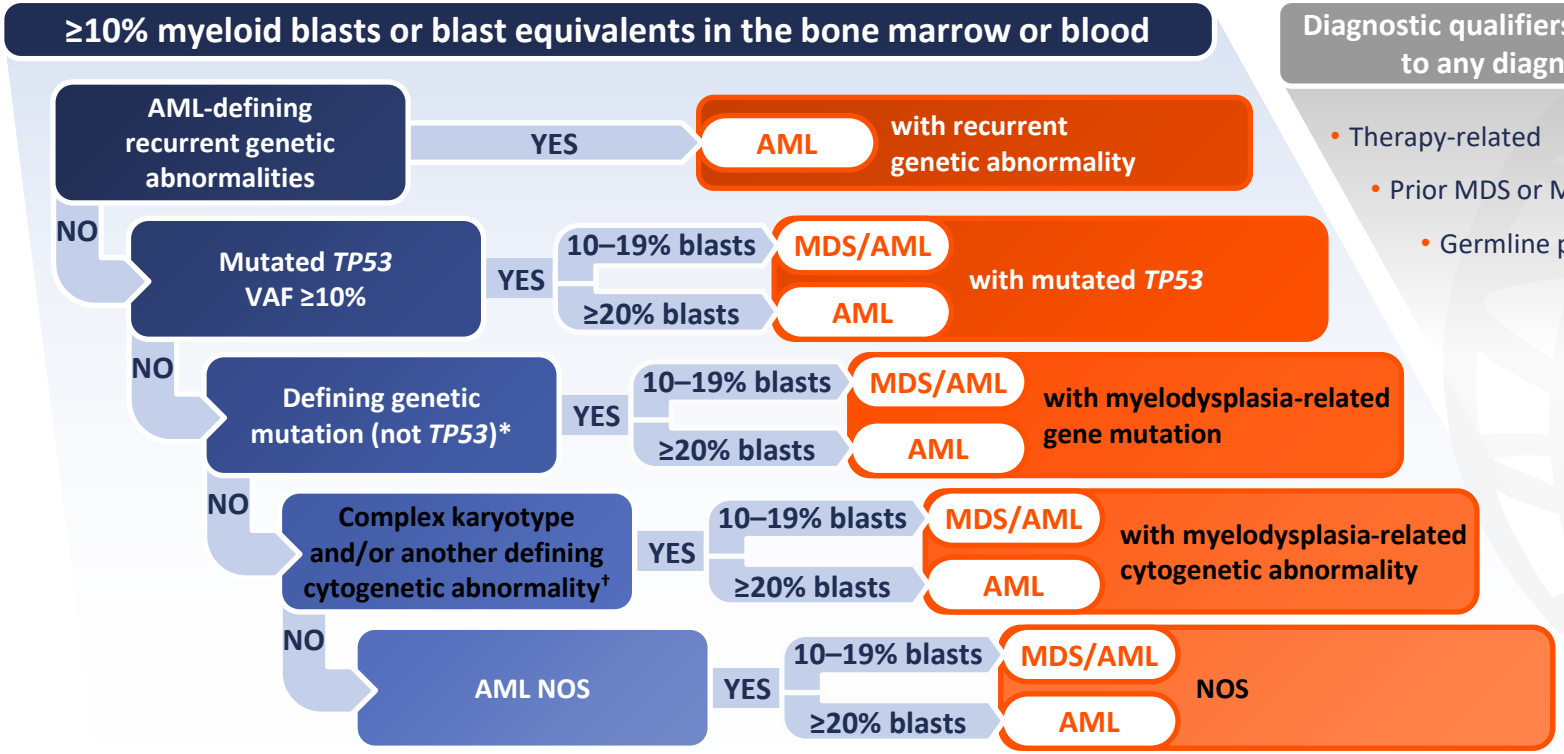
WHO 2022 classification of AML[1]



*Previously pure erythroid leukaemia. AML, acute myeloid leukaemia; WHO, World Health Organization.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Li W. In: Li W (ed). *Leukemia: Diagnosis and Therapy*. Exon Publications, 2022;1–21.

Hierarchical classification of AML: ICC

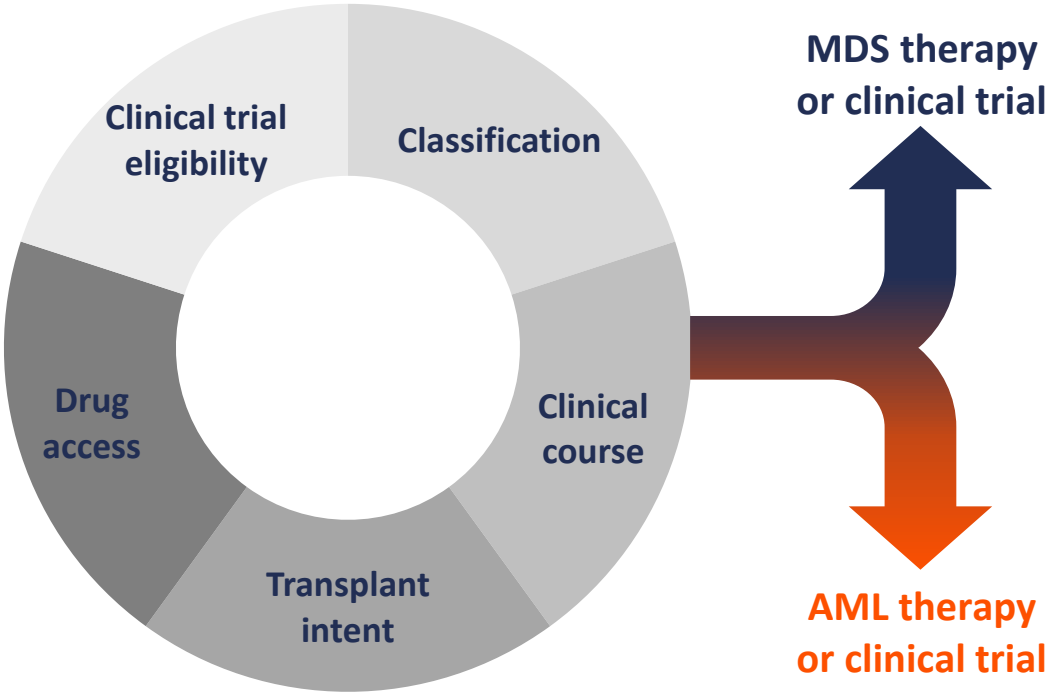


**ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1* and/or *ZRSR2*. †del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/(add(12p), i(17q), -17/add(17p)/del(17p), del(20q) or idic(X)(q13). AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MPN, myeloproliferative neoplasms; NOS, not otherwise specified; VAF, variant allele frequency; WHO, World Health Organization.

Döhner H, et al. *Blood*. 2022;140:1345–77.

touch HAEMATOLOGY

MDS vs AML: Treatment considerations[1–3]



AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Fenaux P, et al. *Ann Oncol.* 2021;32:142–56; 2. Heuser M, et al. *Ann Oncol*. 2020;31:697–712; 3. Döhner H, et al. *Blood*. 2022;140:1345–77.

touch HAEMATOLOGY

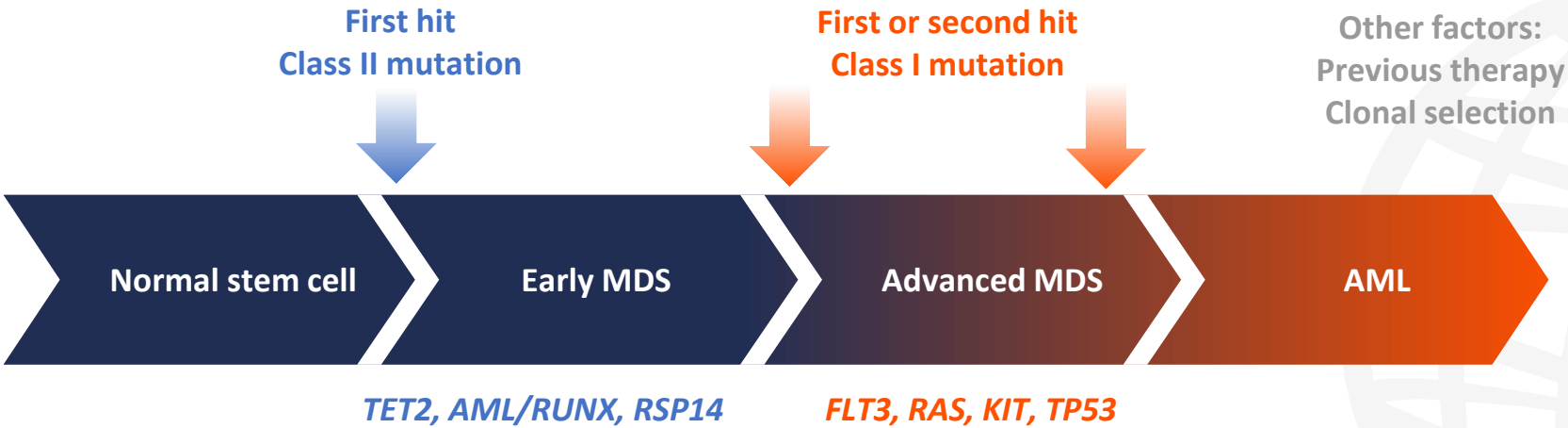
Pathophysiology of MDS and AML and how it relates to disease classification

Prof. Agnieszka Wierzbowska

Medical University of Łódź,
Copernicus Memorial Hospital,
Łódź, Poland

touch HAEMATOLOGY

Model of progression from MDS to AML[1]



MDS[2]

- Cytopenia
- Inefficient haematopoiesis
- Dysplasia in one or more myeloid cell lineages
- Increased risk of development of AML

AML[3]

- Clonal expansion of myeloid blasts in the bone marrow, peripheral blood or other tissues

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022).

1. Porwit A, Saft L. *J Hematop.* 2011;4:69–79; 2. Visconte V, et al. *Blood Res*. 2014;49:216–27; 3. He GL, et al. *Cancer Cell Int*. 2014;14:111.

touch HAEMATOLOGY

WHO and ICC classification comparison

WHO[1]

MDS = myelodysplastic neoplasms

MDS with defining genetic abnormalities

- MDS with low blasts and isolated 5q deletion
- MDS with low blasts and *SF3B1* mutation
- MDS with biallelic *TP53* inactivation

MDS, morphologically defined

- MDS with low blasts (MDS-LB)
- MDS, hypoplastic (MDS-h)
- MDS with increased blasts (MDS-IB)
  - MDS-IB1
  - MDS-IB2
  - MDS with fibrosis (MDS-f)

ICC[2]

MDS = myelodysplastic syndromes

- MDS with del(5q)
- MDS with mutated *SF3B1*
- MDS with mutated *TP53*
- MDS, not otherwise specified (MDS, NOS)
  - MDS, NOS without dysplasia
  - MDS, NOS with single lineage dysplasia
  - MDS, NOS with multilineage dysplasia
- MDS with excess blasts (MDS-EB)
- MDS/AML
  - MDS/AML with mutated *TP53*
  - MDS/AML with myelodysplasia-related gene mutations
  - MDS/AML with myelodysplasia-related cytogenetic abnormalities
  - MDS/AML, not otherwise specified

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); WHO, World Health Organization.

1. Khoury JD, et al. *Leukemia*. 2022;36:1703–19; 2. Arber DA, et al. *Blood*. 2022;140:1200–28.

Validation of MDS guideline updates (1/3)

Retrospective, single-centred cohort study of patients with MDS

Validation of WHO 2022 guidelines

Jan 2018 – Dec 2021

N=118

WHO 2022 classification	% lower-risk patients	Median OS
Genetically defined		
• MDS-*SF3B1*	91 (IPSS-R/IPSS-M)	7.0 years
• MDS-bi*TP53*	14 (IPSS-R/IPSS-M)	0.8 years
Morphologically defined		
• MDS-LB	71 (IPSS-R/IPSS-M)	NR
• MDS-IB1	21 (IPSS-R); 16 (IPSS-M)	NR
• MDS-IB2	0 (IPSS-R); 7 (IPSS-M)	1.5 years

- Differing mutational features were prominently associated with both morphologically and genetically defined subgroups
- OS differed between the defined subgroups

IPSS-M, international prognostic scoring system – molecular; IPSS-R, IPSS – revised; MDS, myelodysplastic neoplasms; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; NR, not reached; OS, overall survival; WHO, World Health Organization.

Khanna V, et al. *Blood*. 2022;140(Suppl. 1):6955–7.

touch HAEMATOLOGY

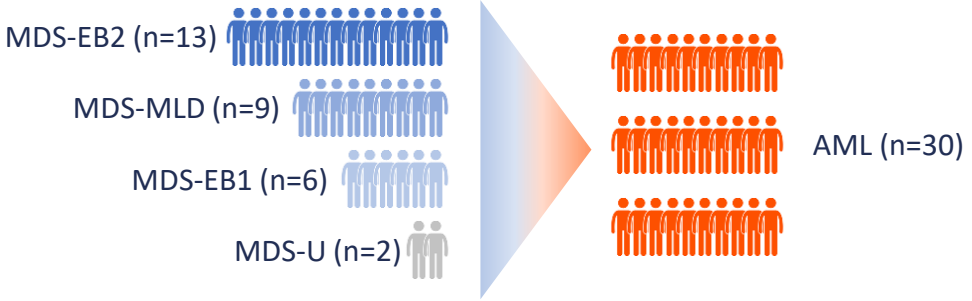
Validation of MDS guideline updates (2/3)

Patients with newly diagnosed MDS based on WHO 2016 criteria → **Reclassified according to WHO 2022 guidelines**

N=852

Aug 2016 – Sep 2021

30 subjects with *NPM1* mutation were reclassified as AML



WHO 2022 classification	Median OS
MDS-5q	24 months
MDS-*SF3B1*	58 months
MDS-bi*TP53*	10 months
MDS-LB	Unreached
MDS-h	Unreached
MDS-IB1	24 months
MDS-IB2	26 months
MDS-f	15 months

AML, acute myeloid leukaemia; MDS, myelodysplastic neoplasms; MDS-bi*TP53*, MDS with biallelic *TP53* inactivation; MDS-EB, myelodysplastic syndromes with excess blasts; MDS-f, MDS with fibrosis; MDS-h, MDS, hypoplastic; MDS-IB, MDS with increased blasts; MDS-LB, MDS with low blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia; MDS-*SF3B1*, MDS with low blasts and *SF3B1* mutation; MDS-U, myelodysplastic syndromes, unclassifiable; OS, overall survival; WHO, World Health Organization. Zhang Y, et al. *Blood*. 2022;140(Suppl. 1):1343–5.

touch HAEMATOLOGY

Validation of MDS guideline updates (3/3)

Retrospective, single-centred cohort study of patients with MDS

N=2,231

Reclassified by WHO 2022 and ICC 2022 proposed criteria

WHO 2022

- MDS-IB1 and MDS-IB2 had similar mOS (p=0.726)

WHO 2022 and ICC 2022

- MDS with mutated *SF3B1* had best mOS across all subtypes
- Categories for MDS-m*TP53* had worst survival of all subtypes

ICC 2022

- MDS-MLD had significantly worse mOS compared with MDS-SLD (49.6 months vs 79.4 months; p<0.001)

ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-IB, MDS with increased blasts; MDS-MLD, myelodysplastic syndromes with multilineage dysplasia; MDS-m*TP53*, MDS with mutated *TP53*; MDS-SLD, MDS with single lineage dysplasia; mOS, median overall survival; WHO, World Health Organization.

Ball S, et al. *Blood*. 2022;140(Suppl. 1):1118–20.

touch HAEMATOLOGY

Impact of WHO and ICC 2022 on AML diagnosis

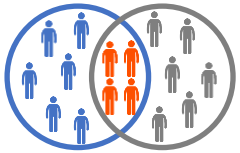
1,451 non-therapy-related cases with MDS or AML according to 2017 revised 4th edition WHO guidelines

WHO 2022 guidelines

- 746 patients diagnosed with AML
- **<1%** of cases were **upgraded from MDS to AML** compared with the revised 4th edition WHO guidelines

ICC 2022 guidelines

- 742 patients diagnosed with AML
- 137 patients diagnosed with MDS/AML
- **10%** of cases were **upgraded from MDS to AML** compared to the revised 4th edition WHO guidelines, **mainly due to the introduction of the MDS/AML class**



4/16 patients with **MDS-EB2 according to the revised 4th edition WHO** guidelines were **upgraded to AML using both the WHO 2022 and ICC 2022 guidelines**

AML, acute myeloid leukaemia; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); MDS-EB, myelodysplastic syndrome with excess blasts; WHO, World Health Organization.

Huber S, et al. *Blood*. 2022;140(Suppl. 1):555–6.

touch HAEMATOLOGY

Updated prognostic risk stratification and its impact on patient management

Prof. Gert Ossenkoppele

Vrije Universiteit University Medical Center, Amsterdam, Netherlands

touch HAEMATOLOGY

Comparison between IPSS-R and IPSS-M

IPSS-R

Risk based on haematologic and cytogenetic features

- 5 cytogenetic risk categories
- Haemoglobin level
- Marrow blast percentage
- Platelet count

Factors from IPSS-R conserved in IPSS-M

IPSS-M

Risk based on haematologic parameters, cytogenetic abnormalities and somatic mutations

Additional factors in IPSS-M

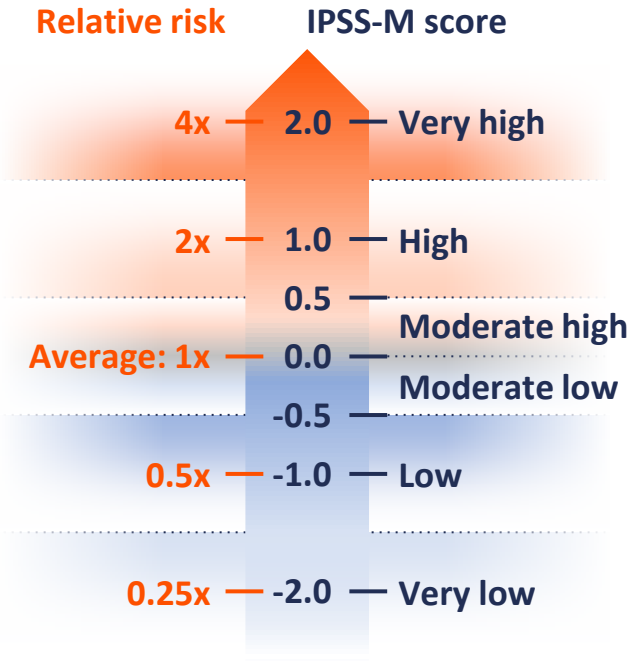
- 16 main effect genes
- 15 residual genes
- Mutations associated with worse outcome:
  - *TP53*$^{\text{multihit}}$
  - *FLT3*
  - *MLL*$^{\text{PTD}}$

IPSS, International Prognostic Scoring System; M, Molecular; R, Revised.

Bernard E, et al. *NEJM Evidence*. 2022;1:EVIDoa2200008.

IPSS-M risk categories

The IPSS-M score corresponds to the relative risk compared with an ‘average’ patient



A patient’s IPSS-M score can be calculated using the IPSS-M web calculator*

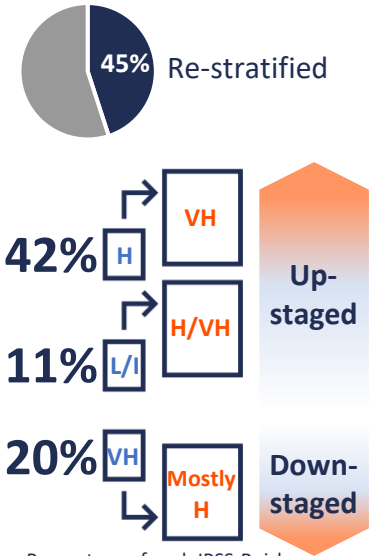
*www.mds-risk-model.com
IPSS-M, Molecular International Prognostic Scoring System.
Bernard E, et al. *NEJM Evidence*. 2022;1:EVIDoa2200008.

touch HAEMATOLOGY

Validation of the IPSS-M: Data from ASH 2022

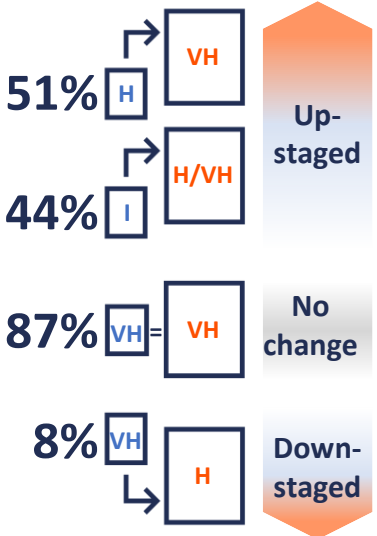
Aguirre LEE, et al.[1]

N=2,333



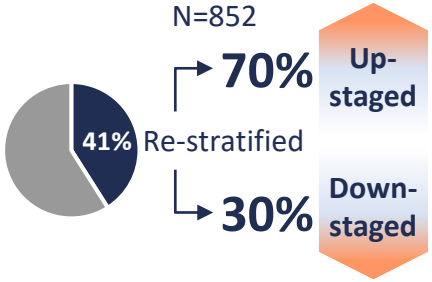
Santini V, et al.[2]

N=512



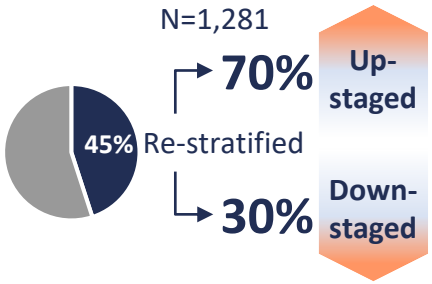
Wu J, et al.[3]

N=852



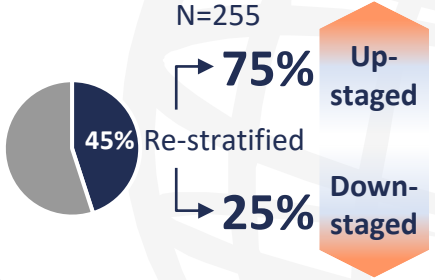
Kewan T, et al.[4]

N=1,281



Ma J, et al.[5]

N=255



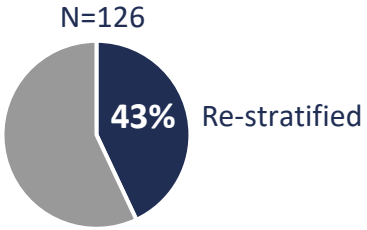
ASH, American Society of Hematology; H, high risk; I, intermediate risk; IPSS, International Prognostic Scoring System; L, low risk; M, Molecular; R, Revised. sig, significant; VH, very high risk. 1. Aguirre LEE, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 465; 2. Santini V, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 559; 3. Wu J, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 1780; 4. Kewan T, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 3087; 5. Ma J, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 4400.

touch HAEMATOLOGY

Real-world use of IPSS-R vs IPSS-M: Data from ASH 2022

Jáuregui SN, et al.

Patients with MDS from a single centre



17.4% of re-stratifications of patients had a potential impact on therapeutic choices

- Of these, 11.9% of patients were up-staged, 5.6% were down-staged

9.5% would have actually been treated differently if IPSS-M was initially applied

- Some of the higher-risk patients were not candidates for intensive care due to age and comorbidities

ASH, American Society of Hematology; IPSS, International Prognostic Scoring System; M, Molecular; ICC, International Consensus Classification; MDS, myelodysplastic neoplasms (WHO 2022)/myelodysplastic syndromes (ICC 2022); R, Revised; WHO, World Health Organization.

Jáuregui SN, et al. Presented at: 64th ASH Annual Meeting, New Orleans, LA, USA. 10–13 December 2022. Abstr 3096.

touch HAEMATOLOGY

ELN 2022: Genetic risk classification changes

- ***FLT3*-ITD allelic ratio is no longer considered in the risk classification**
  - AML with *FLT3*-ITD (without adverse-risk genetic lesions) is categorized in the intermediate-risk group, irrespective of allelic ratio or concurrent presence of an *NPM1* mutation
- **AML with myelodysplasia-related gene mutations are now in the adverse-risk group**
  - Mutations include pathologic variants in at least one of the following:
    - *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- **In-frame mutations in the leucine zipper region of *CEBPA* are now classified in the favourable-risk group**
  - Classification is irrespective of biallelic or monoallelic mutations
- **The presence of adverse-risk cytogenetic abnormalities in *NPM1*-mutated AML are now classified as adverse risk**
- **Additional disease-defining, recurring cytogenetic abnormalities are now in the adverse-risk group**
  - Include mutations in t(3q26.2;v) involving the *MECOM* gene, or t(8;16)(p11.2;p13.3) associated with *KAT6A::CREBBP* gene fusion
- **Hyperdiploid karyotypes with multiple trisomies are no longer on the list of complex karyotypes or in the adverse risk group**

AML, acute myeloid leukaemia; ELN, European LeukemiaNet; ITD, internal tandem duplication.

Döhner H, et al. *Blood*. 2022;140:1345–77.

touch HAEMATOLOGY