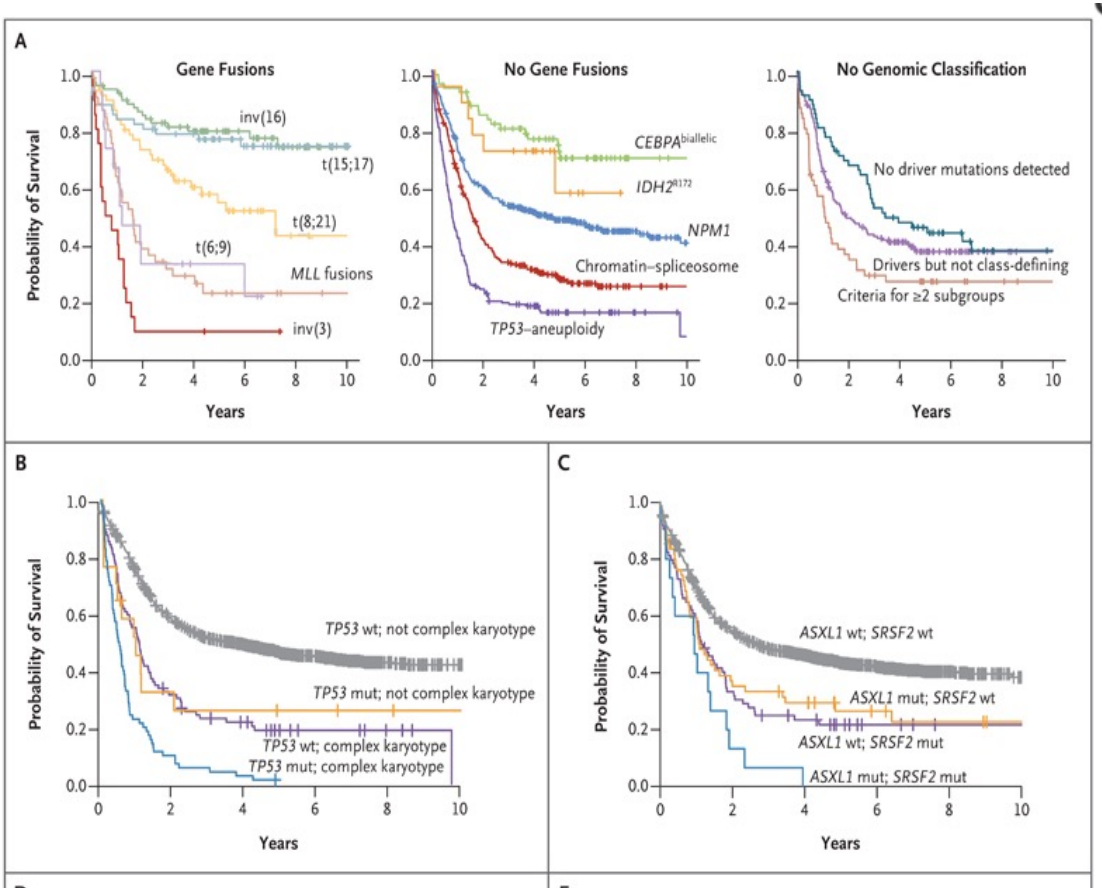
Dr. Fabio Guolo

Clinica Ematologica, Dipartimento di Medicina Interna (DiM
Università degli Studi di Genova
IRCCS Ospedale Policlinico San Martino
Genova

Guida all'uso delle nuove classificazioni nelle AML e MDS

Genomic Classification and Prognosis in Acute Myeloid Leukemia



With whole-genome sequencing, AML emerges as a **complex, dynamic disease.**

The disease evolves over time, with **multiple competing clones coexisting** at any time.

Patients typically have more than one driver mutation.

The structure of driver mutations identifies nonoverlapping subgroups of patients allowing a fully genomic classification of AML.

The prognostic effects of individual mutations were often significantly altered by the **presence or absence of other driver mutations**

Such **gene-gene interactions** were especially pronounced for NPM1-mutated AML, in which patterns of co-mutation identified groups with a favorable or adverse prognosis.

Papaemmanuil E, et al. The New England journal of medicine. 2016

- The old WHO 2016 classifications was partially genomic driven, however it did not reflect thelatest advances in the understanding of myeloproliferative neoplasms.

To address this issues two new classifications were developed:

The 5th edition of the **World Health Organization Classification** of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

Published: 22 June 2022 on *Leukemia* by Khoury JD et al.

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

Published: 15 September 2022 on *Blood* by Arber AD et al.

Khoury JD et al. Leukemia 2022
Arber AD et al. Blood 2022

AML: main changes in ICC 2022 from WHO 2016

2016 WHO CLASSIFICATION

Acute myeloid leukemia (AML) and related neoplasms

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS

2022 ICC CLASSIFICATION

- **Acute promyelocytic leukemia (APL) with t(15;17)(q24.1;q21.2)/*PML*::*RARA* ≥10%**
- **APL with other *RARA* rearrangements* ≥10%**
- **AML with t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* ≥10%**
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* ≥10%**
- **AML with t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* ≥10%**
- **AML with other *KMT2A* rearrangements** ≥10%**
- **AML with t(6;9)(p22.3;q34.1)/*DEK*::*NUP214* ≥10%**
- **AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*; *MECOM*(*EVI1*) ≥10%**
- **AML with other *MECOM* rearrangements*** ≥10%**
- **AML with other rare recurring translocations (see Supplemental Table 5) ≥10%**
- **AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*‡ ≥20%**
- **AML with mutated *NPM1* ≥10%**
- **AML with in-frame bZIP *CEBPA* mutations ≥10%**
- **AML and MDS/AML with mutated *TP53*† 10-19% (MDS/AML) and ≥20% (AML)**
- **AML and MDS/AML with myelodysplasia-related gene mutations 10-19% (MDS/AML) and ≥20% (AML)**
  - Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
- **AML with myelodysplasia-related cytogenetic abnormalities 10-19% (MDS/AML) and ≥20% (AML)**
  - Defined by detecting a complex karyotype (≥3 unrelated clonal chromosomal abnormalities in the absence of other class-defining recurring genetic abnormalities), del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) or del(17p), del(20q), and/or idic(X)(q13) clonal abnormalities
- **AML not otherwise specified (NOS) 10-19% (MDS/AML) and ≥20% (AML)**
- **Myeloid Sarcoma**

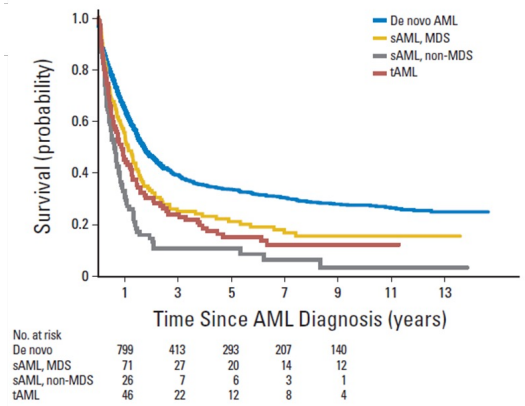
- New blast count to define AML: >10% for recurrent abnormalities
- t-MPNs and AML-MRC are elminated (now only noted as diagnostic qualifiers)
- AML with MDS related-gene mutations and cytogenetic abnormalities are introduced
- New MDS/AML introduced

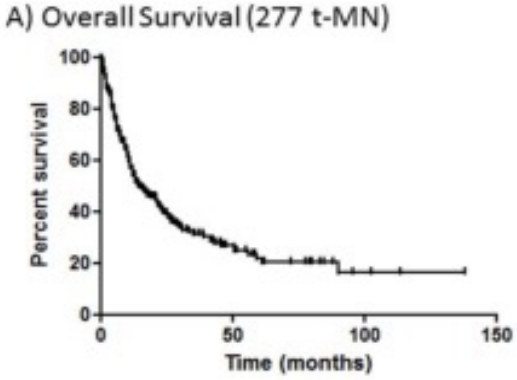
Arber AD et al. Blood 2016
Arber AD et al. Blood 2022

Diagnostic qualifiers

Diagnostic qualifiers that should be used following a specific MDS, AML (or MDS/AML) diagnosis
Therapy-related • prior chemotherapy, radiotherapy, immune interventions
Progressing from myelodysplastic syndrome • MDS should be confirmed by standard diagnostics
Progressing from myelodysplastic/myeloproliferative neoplasm (specify) • MDS/MPN should be confirmed by standard diagnostics

Although the importance of **prior therapy**, **antecedent myeloid neoplasms** (ie, MDS or MDS/MPN), the classification now identifies such associations as **qualifiers** to the diagnosis rather than as specific disease categories





Arber DA, et al. Am J Hematol. 2022 Granfeldt-Øsgtård, LS et al. J Clin Oncol. 2015 Fianchi L, et al. Am J Hematol. 2015

AML with MDS-related changes has been eliminated in ICC 2022

while introducing three new categories:

- **AML with MDS-related cytogenetic** abnormalities defined by detecting a **complex karyotype** (≥ 3 unrelated clonal chromosomal abnormalities **in the absence of other class-defining recurring genetic abnormalities**), **del(5q)/t(5q)/add(5q), −7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), −17/add(17p) or del(17p), del(20q), and/or idic(X)(q13)** clonal abnormalities

- **AML with mutated *TP53***

- AML with **MDS-related gene** mutations: ***ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2***

Arber AD et al. Blood 2022

New category of *TP53* mutated MPNs

- This disease category encompasses separate diagnoses of MDS, MDS/AML, and AML with mutated TP53 (including pure erythroid leukemia), according to the blast percentage.

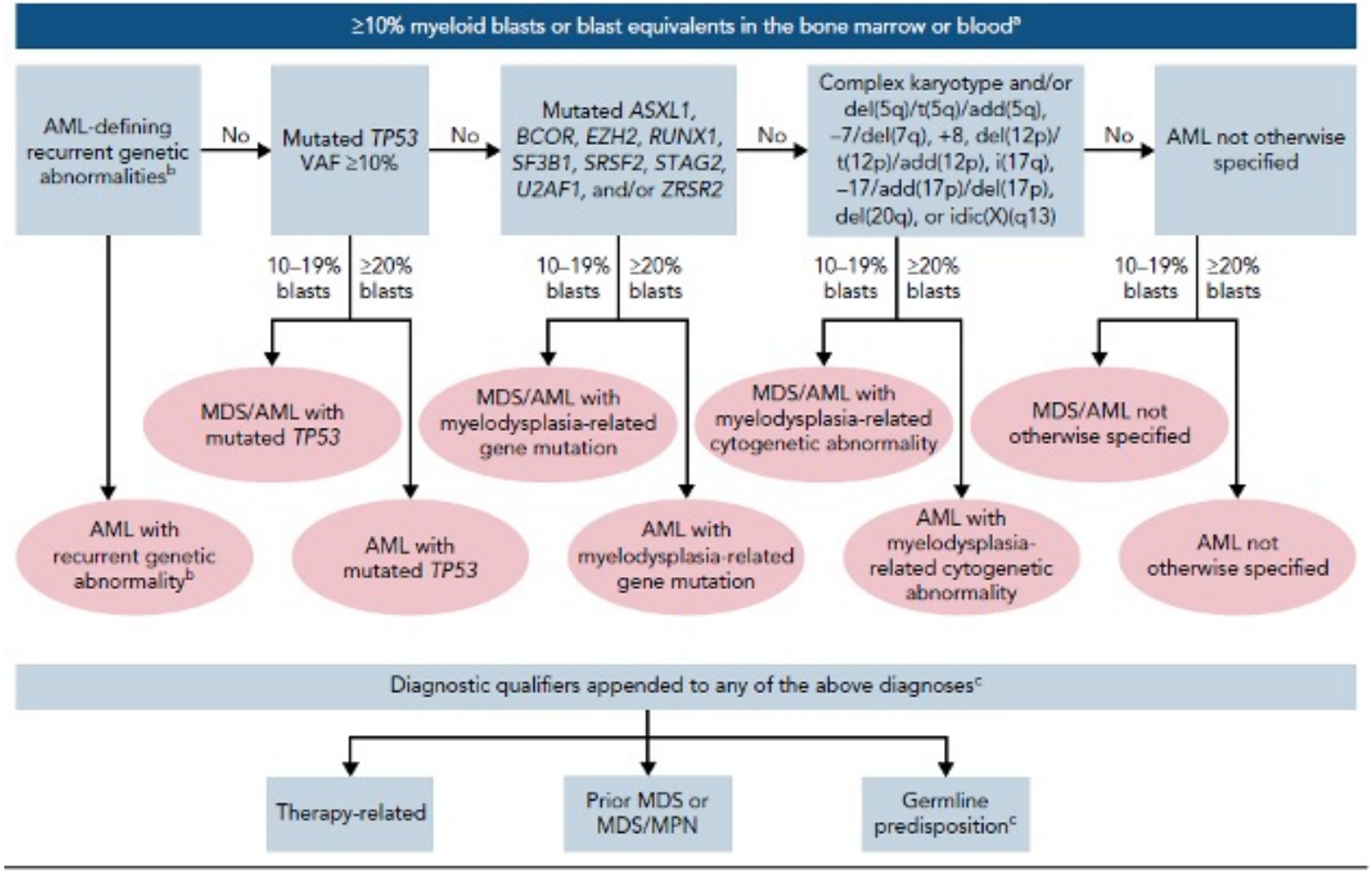
- These diseases are grouped together because of their overall similar aggressive behavior irrespective of the blast percentage, warranting a more unified treatment strategy across the blast spectrum.

Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
AML with mutated *TP53*	Not required	≥20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia	Any somatic *TP53* mutation (VAF > 10%)

- The presence of multihit TP53 mutations in cytopenic myeloid neoplasms corresponds to a highly aggressive disease with short survival.

Arber AD et al. Blood 2022

ICC 2022 requires a hierarchycal classification of AML



Arber AD et al. Blood 2022

MDS: main changes in ICC 2022 from WHO 2016

2016 WHO CLASSIFICATION

MDS with single lineage dysplasia	MDS with excess blasts in transformation
MDS with ring sideroblasts	Chronic myelomonocytic leukemia (CMML-1)
MDS with multilineage dysplasia	CMML-2
MDS with excess blasts-1	Atypical chronic myeloid leukemia, *BCRABL1* negative
MDS with excess blasts-2	Chronic neutrophilic leukemia
MDS, unclassifiable	Juvenile myelomonocytic leukemia
MDS with isolated del(5q)	MDS/MPN unclassifiable
Refractory cytopenias of childhood	MDS/MPN with ring sideroblast and thrombocytosis

2022 ICC CLASSIFICATION

	Dysplastic lineages	Cytopenias	Cytoses*	BM and PB Blasts	Cytogenetics†	Mutations
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1	0	<5% BM <2% PB	Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex	*SF3B1* (≥ 10% VAF), without multi-hit *TP53*, or *RUNX1*
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1	Thrombocytosis allowed	<5% BM <2% PB§	del(5q), with up to 1 additional, except −7/del(7q)	Any, except multi-hit *TP53*
MDS, NOS without dysplasia	0	≥1	0	<5% BM <2% PB§	−7/del(7q) or complex	Any, except multi-hit *TP53* or *SF3B1* (≥ 10% VAF)
MDS, NOS with single lineage dysplasia	1	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*;not meeting criteria for MDS-*SF3B1*
MDS, NOS with multilineage dysplasia	≥2	≥1	0	<5% BM <2% PB§	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit *TP53*,; not meeting criteria for MDS-*SF3B1*
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1	0	5-9% BM, 2-9% PB§	Any	Any, except multi-hit *TP53*
MDS/AML	Typically ≥1‡	≥1	0	10-19% BM or PB‖	Any, except AML-defining¶	Any, except *NPM1*, bZIP *CEBPA* or *TP53*

- MDS/AML introduced in substitution of previous MDS-EB2
- New MDS without displasia but with del(7) or del(7q) or complex karyotypeintroduced
- MDS with mutated *SFR3B1* introduced
- MDS with ring sideroblasts removed

Arber et al. Blood 2016
Arber AD et al. Blood 2022

AML: main changes in WHO 2022 from WHO 2016

2016 WHO CLASSIFICATION

Acute myeloid leukemia (AML) and related neoplasms

- AML with recurrent genetic abnormalities
  - AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
  - AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
  - APL with *PML-RARA*
  - AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
  - AML with t(6;9)(p23;q34.1);*DEK-NUP214*
  - AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
  - AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
  - *Provisional entity: AML with BCR-ABL1*
  - AML with mutated *NPM1*
  - AML with biallelic mutations of *CEBPA*
  - *Provisional entity: AML with mutated RUNX1*
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, NOS

2022 WHO CLASSIFICATION

AML with defining genetic abnormalities

- Acute promyelocytic leukemia with *PML::RARA* fusion
- AML with *RUNX1::RUNX1T1* fusion
- AML with *CBFB::MYH11* fusion
- AML with *DEK::NUP214* fusion
- AML with *RBM15::MRTFA* fusion
- AML with *BCR::ABL1* fusion
- AML with *KMT2A* rearrangement
- AML with *MECOM* rearrangement
- AML with *NUP98* rearrangement
- AML with *NPM1* mutation
- AML with *CEBPA* mutation
- AML, myelodysplasia-related
- AML with other defined genetic alterations
  - AML with *RUNX1T3::GLIS2* fusion
  - AML with *KAT6A::CREBBP* fusion
  - AML with *FUS::ERG* fusion
  - AML with *MNX1::ETV6* fusion
  - AML with *NPM1::MLF1* fusion

AML defined by differentiation

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute basophilic leukemia
- Acute myelomonocytic leukemia
- Acute monocytic leukemia
- Acute erythroid leukemia*
- Acute megakaryoblastic leukemia

- No blast cell count required for AML with defining genetic abnormalities
- More recurrent genetic abnormalities introduced
- AML with mutated *RUNX1* eliminated
- AML-MRC has been eliminated and AML MDS-related has been introduced (requires previous diagnosis of MDS or MDS-related cytogenetics)
- t-AML retained but as a qualifier

Khoury JD et al. Leukemia 2022

Myelodisplasia related AML

Requires (at least one of the following):

- **Previous history of MDS or MPN** :

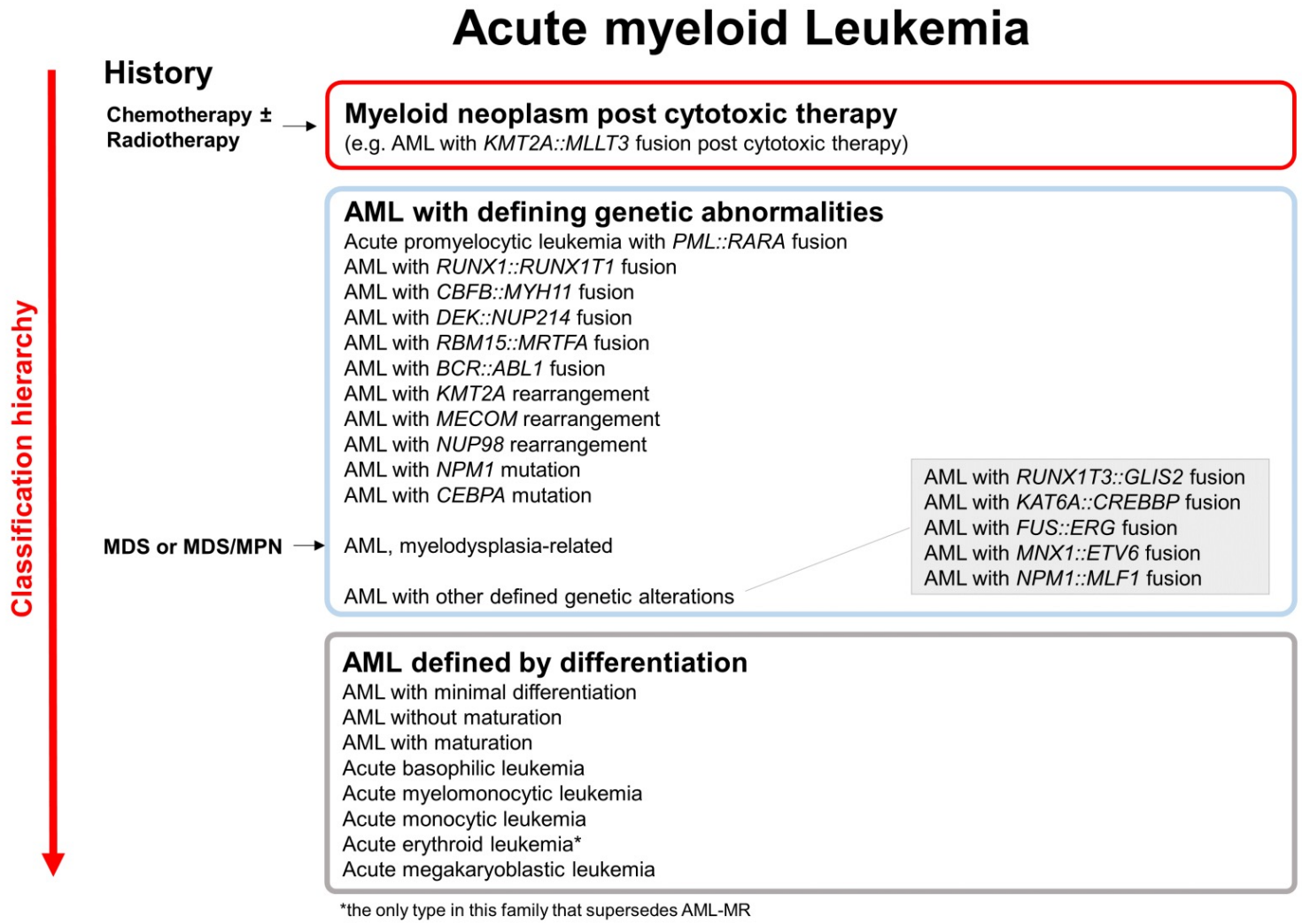
- **MDS-related Cytogenetic abnormalities:** complex karyotipe, 5q deletions, 7 or 7q deletion, 11q deletion, 12p deletion, 13 or 13q deletion, 17p deletion, iso17q and idic(X)(q13)

- **MDS-related genetic abnormalities:** *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*

Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

Khoury JD et al. Leukemia 2022

Also WHO 2022 requires a hierarchycal classification of AML



Khoury JD et al. Leukemia 2022

MDS: main changes in WHO 2022 from WHO 2016

2016 WHO CLASSIFICATION

MDS with single lineage dysplasia	MDS with excess blasts in transformation
MDS with ring sideroblasts	Chronic myelomonocytic leukemia (CMML-1)
MDS with multilineage dysplasia	CMML-2
MDS with excess blasts-1	Atypical chronic myeloid leukemia, *BCRABL1* negative
MDS with excess blasts-2	Chronic neutrophilic leukemia
MDS, unclassifiable	Juvenile myelomonocytic leukemia
MDS with isolated del(5q)	MDS/MPN unclassifiable
Refractory cytopenias of childhood	MDS/MPN with ring sideroblast and thrombocytosis

2022 WHO CLASSIFICATION

	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		

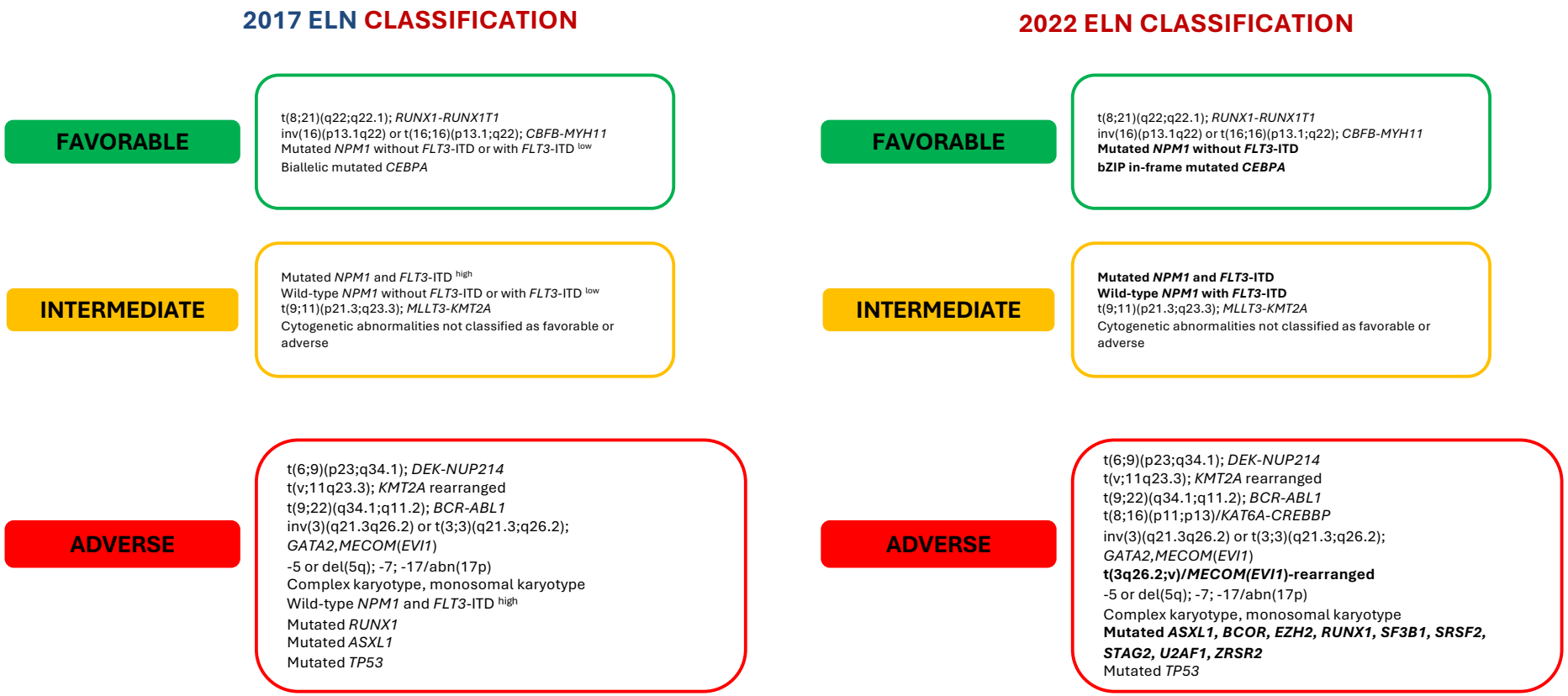
[a]Detection of ≥15% ring sideroblasts may substitute for *SF3B1* mutation. Acceptable related terminology: MDS with low blasts and ring sideroblasts.
[b]By definition, ≤25% bone marrow cellularity, age adjusted.
BM bone marrow, *PB* peripheral blood, *cnLOH* copy neutral loss of heterozygosity.

Denomination of Myelodisplastic Syndromes has been changed to Myelodisplastic Neoplasm (still abbreviated MDS though…)

- Distinction between MDS genetic defined and morphologically defined
- Introduced MDS with biallelic *TP53* inactivation
- Introduced hypoplastic MDS
- Introduced MDS with fibrosis

Arber et al. Blood 2016
Khoury JD et al. Leukemia 2022

AML risk-stratification has been changed by ELN as well



Döhner H, et al. Blood. 2017
Döhner H, et al. Blood. 2022

AML: main differences between ICC 2022 and WHO 2022

	ELN 2022 & ICC 2022	WHO 5th edition
MDS/AML (without AML defining genetic alterations)	10-19% blasts	Designated as MDS-IB2 (10-19% BM or 5-19% PB or Auer rods
AML with antecedent MDS, MDS/MPN, or prior exposure to therapy	Myelodysplasia added as a diagnostic qualifier	Included as a separate entity "AML-MR"
AML with *NPM1* mutations, *KMT2A* rearrangement, *MECOM* rearrangement, and *NUP98* rearrangement	Requires ≥10% blasts in BM or PB	Can be diagnosed irrespective of blast count
AML with *CEBPA* mutation	Requires ≥10% blasts in BM or PB Includes only bzip mutations	Requires ≥20% blasts in BM or PB Includes bi-allelic and bzip mutations
***TP53* mutation**	Included separately in the hierarchical classification	Not included as a separate entity for AML
Therapy related	Added as a diagnostic qualifier	Included as separate entity "AML-pCT"

Arber et al. Blood 2022
Khoury JD et al. Leukemia 2022

Differences in definitions of MR-AML

ICC 2022	WHO 2022
Complex Karyotype	Complex Karyotype
del(5q)/t(5q)/**add(5q)**	del(5q)/t(5q)
-7/del(7q)	-7/del(7q)/**t(7q)**
del(12p)/t(12p)/**add(12p)**	del(12p)/t(12p)
i(17q), -17/**add(17p)**, del(17p)	i(17q), -17, del(17p)
idic(X)(q13)	idic(X)(q13)
+8	**del(11q)**
del(20q)	**Previous history of MDS**
TP53 mutated AML	
ASXL1, BCOR, EZH2, ***RUNX1****, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*	*SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2*

Khoury JD et al. Leukemia 2022
Arber AD et al. Blood 2022

MDS: main differences between WHO 2022 and ICC 2022

ICC 2022 CLASSIFICATION

	Dysplastic lineages	Cytopenias
MDS with mutated *SF3B1* (MDS-*SF3B1*)	Typically ≥1‡	≥1
MDS with del(5q) [MDS-del(5q)]	Typically ≥1‡	≥1
MDS, NOS without dysplasia	0	≥1
MDS, NOS with single lineage dysplasia	1	≥1
MDS, NOS with multilineage dysplasia	≥2	≥1
MDS with excess blasts (MDS-EB)	Typically ≥1‡	≥1
MDS/AML	Typically ≥1‡	≥1

2022 WHO CLASSIFICATION

	Blasts
MDS with defining genetic abnormalities	
MDS with low blasts and isolated 5q deletion (MDS-5q)	<5% BM and <2% PB
MDS with low blasts and *SF3B1* mutation[a] (MDS-*SF3B1*)	
MDS with biallelic *TP53* inactivation (MDS-bi*TP53*)	<20% BM and PB
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

- No EB2 in ICC
- No MDS with hypoplasia or fibrosis in ICC
- No distinction in number of cytopenias in WHO
- Different approach to distinction of morphologically and genetically defined MDS

Arber et al. Blood 2022
Khoury JD et al. Leukemia 2022

Italian guidelines from Italian Society of Hematology

Società Italiana di Ematologia

Tabella 1: Classificazione delle LAM secondo International Consensus Classification con la indicazione della percentuale di blasti necessaria per la diagnosi (da Arber DA, et al. Blood 2022)

Leucemia acuta a promielociti con t(15;17)(q24.1;q21.2)/PML::RARA ≥10%
Leucemia acuta a promielociti con altri riarrangiamenti RARA * ≥10%
LAM con t(8;21)(q22;q22.1)/RUNX1::RUNX1T1 ≥10%
LAM con inv(16)(p13.1q22) o t(16;16)(p13.1;q22)/CBFB::MYH11 ≥10%
LAM con t(9;11)(p21.3;q23.3)/MLLT3::KMT2A ≥10%
LAM con altri riarrangiamenti KMT2A ** ≥10%
LAM con t(6;9)(p22.3;q34.1)/DEK::NUP214 ≥10%
LAM con inv(3)(q21.3q26.2) o t(3;3)(q21.3;q26.2)/GATA2; MECOM(EVI1) ≥10%
LAM con altri riarrangiamenti MECOM *** ≥10%
LAM con altre rare traslocazioni ≥10%
LAM con t(9;22)(q34.1;q11.2)/BCR::ABL1‡ ≥20%
LAM con mutazione di NPM1 ≥10%
LAM con mutazioni in-frame bZIP di CEBPA ≥10%
LAM e SMD/LAM con mutazione di TP53† 10-19% (SMD/LAM) e ≥20% (LAM)
LAM e SMD/LAM con mutazione di geni mielodisplasia-relati 10-19% (SMD/LAM) e ≥20% (LAM) • Definita da mutazione di ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, o ZRSR2
LAM con alterazioni citogenetiche geni mielodisplasia-relate 10-19% (SMD/LAM) e ≥20% (LAM) • Definita da: riscontri di cariotipo complesso (≥3 alterazioni citogenetiche clonali non correlate in assenza di altre alterazioni genetiche ricorrenti caratteristiche); alterazioni citogenetiche del(5q)/t(5q)/add(5q), -7/del(7q), +8, del(12p)/t(12p)/add(12p), i(17q), -17/add(17p) o del(17p), del(20q), e/o idic(X)(q13)
LAM non altrimenti specificata 10-19% (SMD/LAM) e ≥20% (LAM) • LAM con minima differenziazione • LAM senza maturazione • LAM con maturazione • LAM basofilica • LAM mielomonocitica
• LAM monocitica • LAM eritroide • LAM megacarioblastica
Sarcoma mieloide

- **Only ICC 2022** classifications is **considered**
- No clues on if MDS/AML should be treated as AML or MDS (but AML-like treatment historically has always been an option for EB2-MDS)

ARTICLE OPEN

Check for updates

ACUTE MYELOID LEUKEMIA

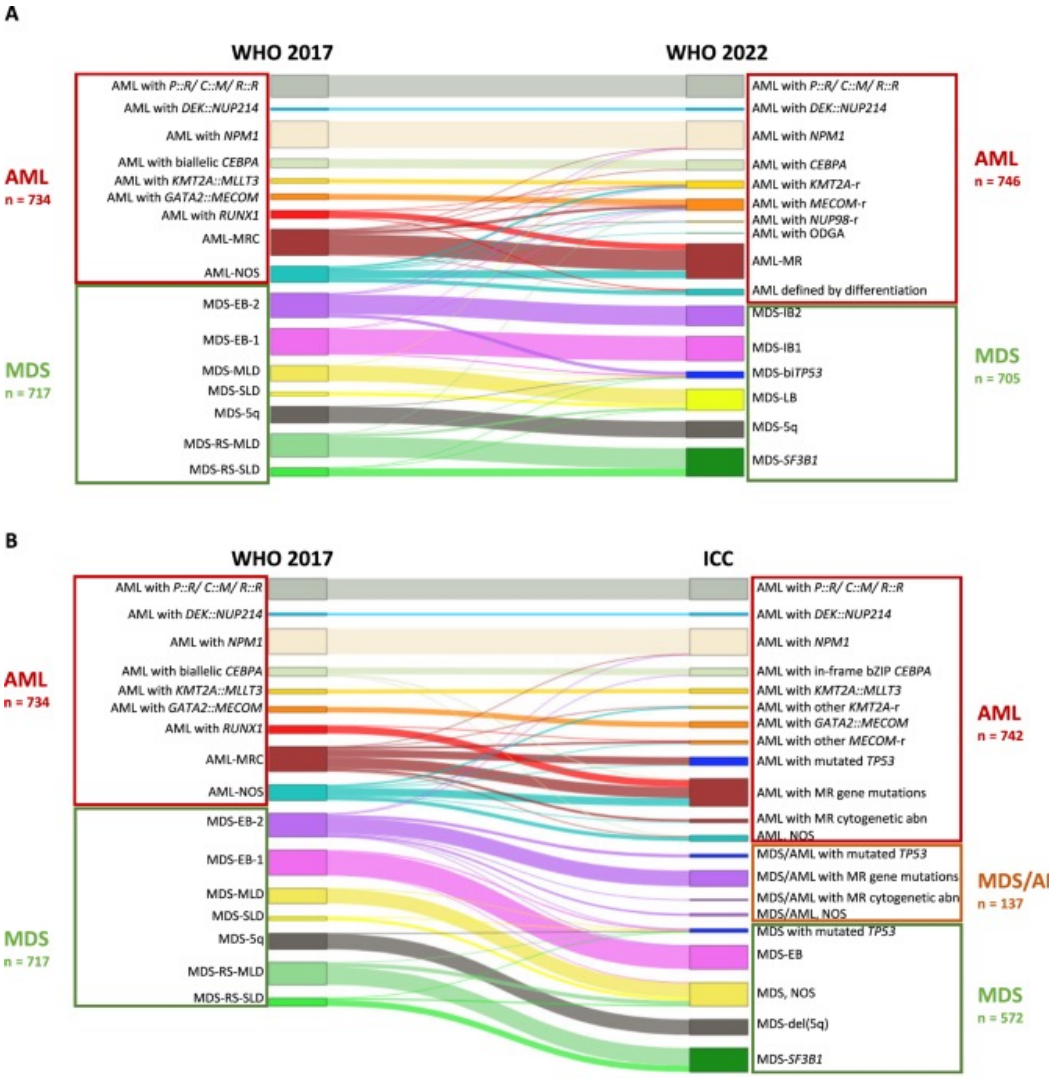
AML classification in the year 2023: How to avoid a Babylonian confusion of languages

Sandra Huber[1], Constance Baer[1], Stephan Hutter[1], Frank Dicker[1], Manja Meggendorfer[1], Christian Pohlkamp[1], Wolfgang Kern[1], Torsten Haferlach[1], Claudia Haferlach[1] and Gregor Hoermann[1]

- To evaluate the **impact of the new classifications** on AML diagnoses and ELN-based risk classification, 717 MDS and 734 AML non-therapy-related patients diagnosed according to the revised 4th WHO edition (WHO 2017) by whole genome and transcriptome sequencing were **analysed and stratified by ICC 2022 and WHO 2022**
- The **incidence** of **re-stratification** from old **WHO 2016 to** new **ICC 2022** and **WHO 2022** was evaluated
- The classification **differences** between **ICC 2022** and **WHO 2022** were analysed
- The prognostic relevance was evaluated in order to **disclose the impact in a real life scenario**

Huber S., et al. Leukemia 2023

From old to new



WHO 2022

- **Myelodysplasia-related AML** substantially **increased** from 22% (158/734) AML-MRC to 28% (208/746) AML-MR, mainly **due to mutations** in defining genes (44%, 92/208)
- **23%** (36/158) former **AML-MRC** patients were **not re-classified** as AML-MR, mostly (**96%**) because of **defining genetic abnormalit**ies
- For **MDS** reclassification was a **rare** event (2% of patients)
- **AML defined by morphology** only was **reduced** from 13% (99/734) AML-NOS **to 5%** (36/746)

ICC 2022

- The new category of **MDS/AML** overlap was the **largest change** from WHO 2017 to ICC affecting **9% of all patients** (most of the former EB-2 patients)
- **Myelodisplasia related AML** increased to a total of 193/746 (**26%** of AML cases). AML with **MR gene** mutations **mainly composed** former AML-MRC (n = 69), AML-NOS (n = 52) and **AML-RUNX1** (n = 46).
- **AML-NOS** was **reduced** from 99 to 34 cases **(5%)**

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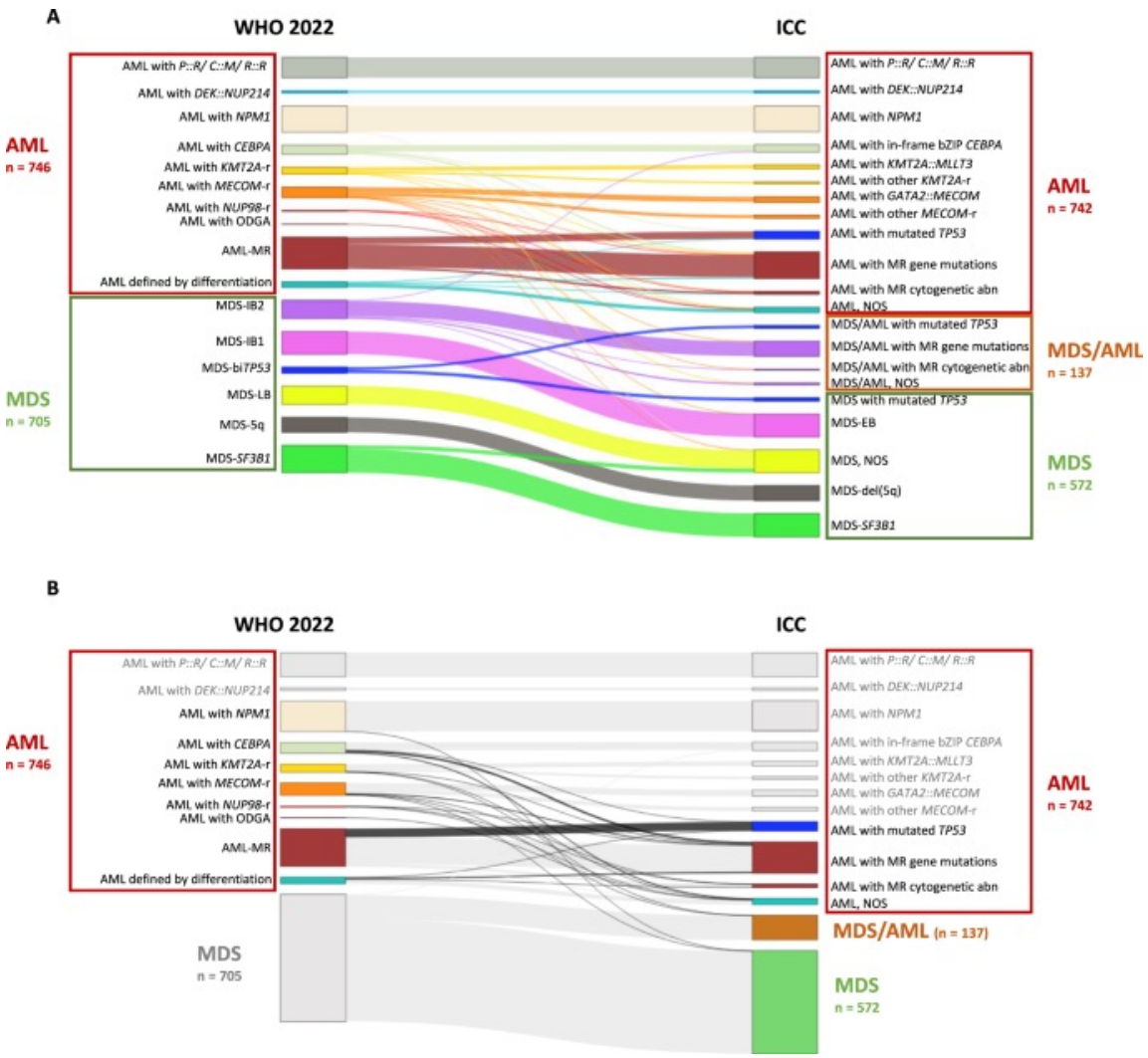
Differences between ICC and WHO 2022



Overall, there was a **large degree of agreement** between the WHO 2022 and the ICC classification **with 86%** (643/750) AML cases being assigned to **corresponding subgroups**.

68/107 (64%) patients reclassifed are due to the substitution in the ICC 2022 of **MDS EB2** present in WHO 2022 in favour of the new **MDS/AML**

The remaining 39 patients were constituted mostly by:

- ***TP53* mutated** patients
- AML patients with a leukemia defining abnormalities but blast cells <10%

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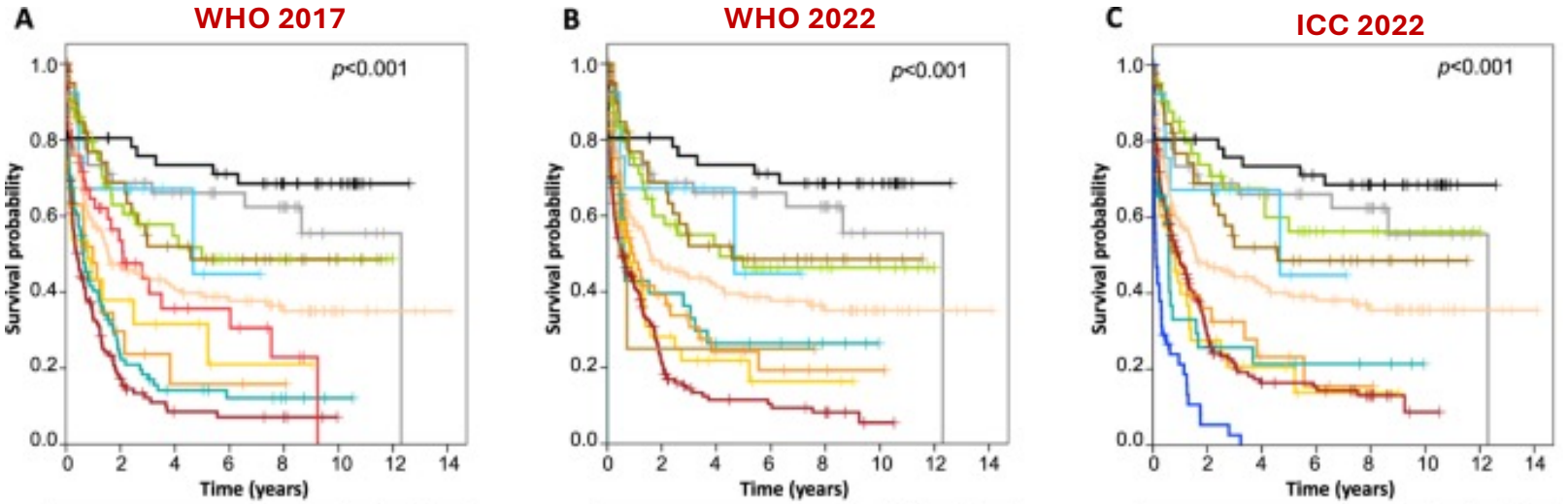

WHO 2017	n	Median OS (years)
PML::RARA	48	Not reached
CBFB::MYH11	45	12.3
CEBPA	56	5.0
DEK::NUP214	15	4.7
RUNX1::RUNX1T1	41	4.6
RUNX1	48	2.1
NPM1	162	1.6
GATA2::MECOM	36	1.0
KMT2A::MLLT3	26	0.8
NOS	99	0.6
MRC	158	0.4
Total	**734**	**1.4**

WHO 2022	n	Median OS (years)
PML::RARA	48	Not reached
CBFB::MYH11	45	12.3
DEK::NUP214	15	4.7
RUNX1::RUNX1T1	41	4.6
CEBPA	61	4.1
NPM1	172	1.6
MECOM-r	69	0.9
KMT2A-r	45	0.8
Differentiation	36	0.6
MR	208	0.5
NUP98-r	5	0.4
ODGA	1	0.0
Total	**746**	**1.5**

ICC 2022	n	Median OS (years)
PML::RARA	48	Not reached
CEBPA	47	Not reached
CBFB::MYH11	45	12.3
DEK::NUP214	15	4.7
RUNX1::RUNX1T1	41	4.6
NPM1	170	1.6
MR*	193	1.0
*MECOM-r***	57	1.0
*KMT2A-r****	40	0.8
NOS	34	0.6
TP53	52	0.1
Total	**742**	**1.5**

- The **prognostic value** of the old WHO 2017 was **similar** to the new WHO 2022 and ICC 2022
- **AML MRC** in **WHO 2017** (which included also morphology-only defined displasia) **had not a better outcome** than **AML-MR** (which was genetically or citogenetically defined) **in the newer classifications**

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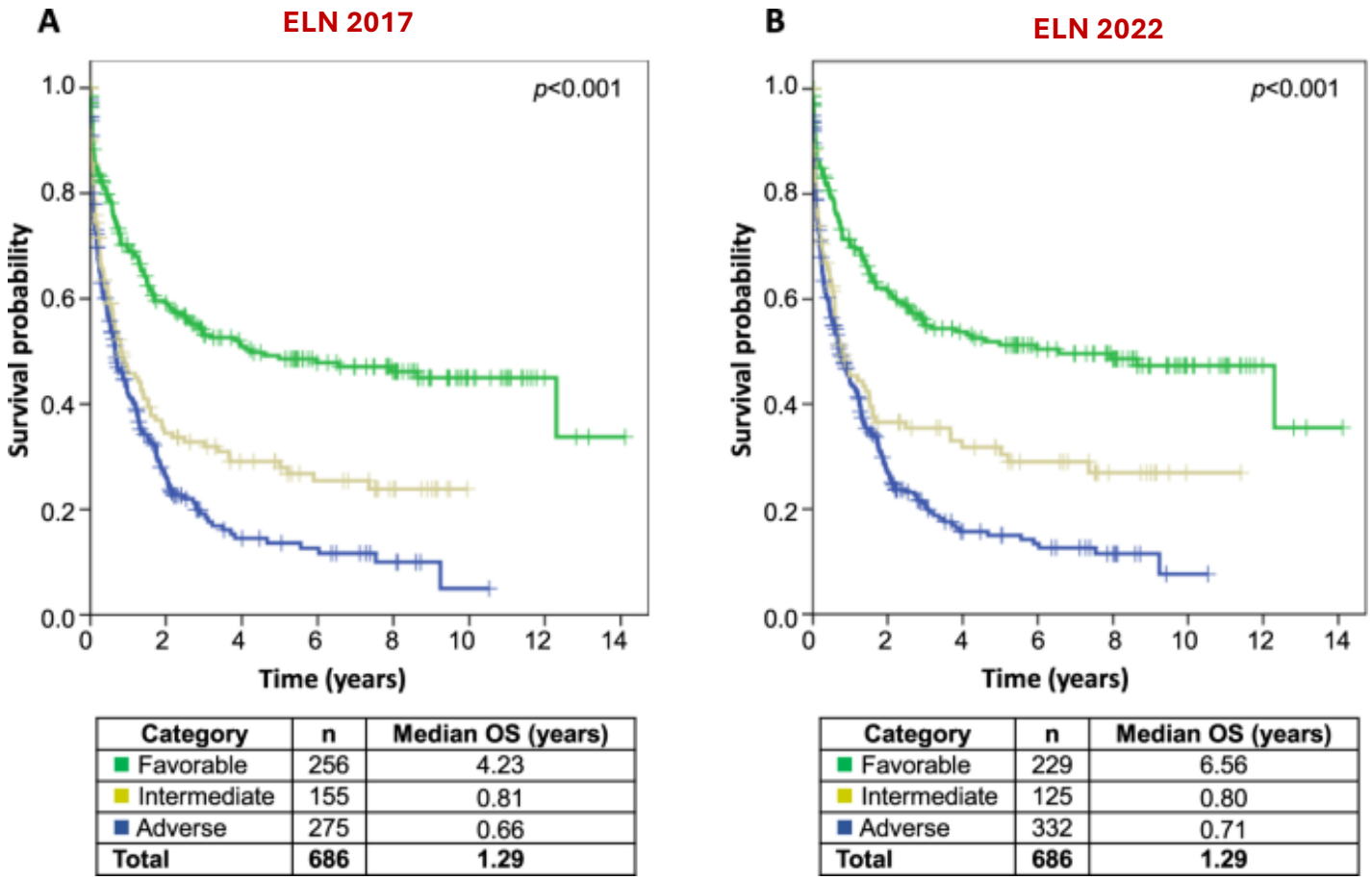

Category	n	Median OS (years)
Favorable	256	4.23
Intermediate	155	0.81
Adverse	275	0.66
Total	**686**	**1.29**

Category	n	Median OS (years)
Favorable	229	6.56
Intermediate	125	0.80
Adverse	332	0.71
Total	**686**	**1.29**

There was **no significant improvment** in prognostic stratification from applying the new **ELN 2022**

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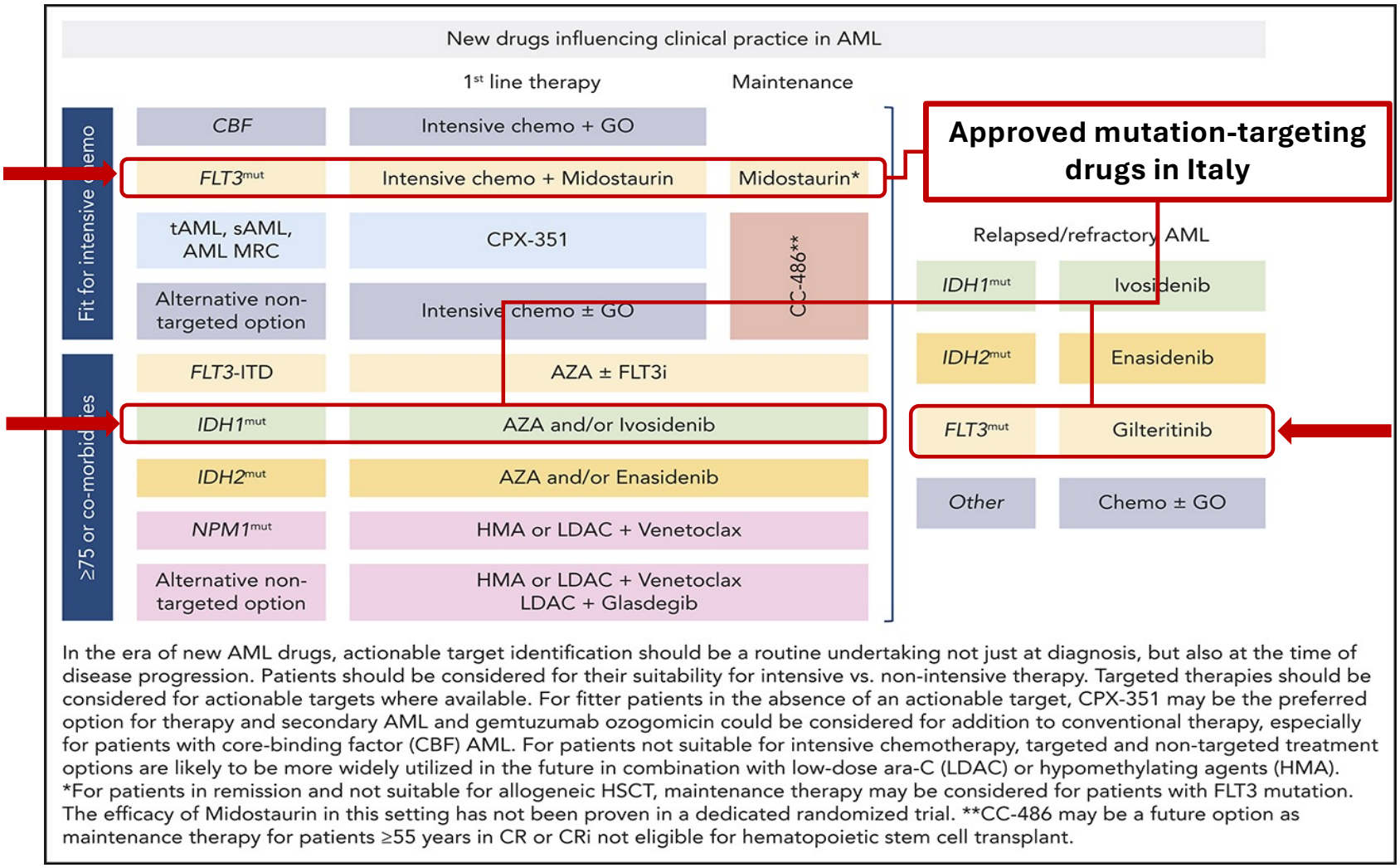

In the era of new AML drugs, actionable target identification should be a routine undertaking not just at diagnosis, but also at the time of disease progression. Patients should be considered for their suitability for intensive vs. non-intensive therapy. Targeted therapies should be considered for actionable targets where available. For fitter patients in the absence of an actionable target, CPX-351 may be the preferred option for therapy and secondary AML and gemtuzumab ozogomicin could be considered for addition to conventional therapy, especially for patients with core-binding factor (CBF) AML. For patients not suitable for intensive chemotherapy, targeted and non-targeted treatment options are likely to be more widely utilized in the future in combination with low-dose ara-C (LDAC) or hypomethylating agents (HMA). *For patients in remission and not suitable for allogeneic HSCT, maintenance therapy may be considered for patients with FLT3 mutation. The efficacy of Midostaurin in this setting has not been proven in a dedicated randomized trial. **CC-486 may be a future option as maintenance therapy for patients ≥55 years in CR or CRi not eligible for hematopoietic stem cell transplant.

Di Nardo CD, Wei AH. Blood. 2020.

Conclusions

- Both the new ICC 2022 and WHO 2022 classification of AML recognize the **importance** of **genome-level diagnosis** in AML and MDS
- The importance of blast count is reduced in both classifications
- t-AML and MRC-AML became qualifiers in both classifications
- **AML workup** becomes **more challenging** for small centers
- Albeit there are **some differences** between **classifications**, but the **real clinical impact** is unlikely to be relevant (with the possibile exception of MDS/AML)
- **A more complex risk** assessment **did not** result into a **better** stratifications
- Given the availability of **targeted drugs**, probably the **assessment** of **actionable mutations** should be priorityzed

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Clinic Of Hematology, Department of Internal Medicine (DiMI), University of Genoa
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Head: Prof. R. M. Lemoli

Acute Leukemia Unit

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Dr. F. Guolo
Dr. C. Riva
Dr. E. Maio
Dr. M. Chies
Dr. G. Zecchetti
Dr. Y. Azzanelli

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Dr. E. Carminati
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