4th edition
Unmet challenges in high risk hematological malignancies: from benchside to clinical practice
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Biologic features of HR-AML

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Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X	X	
Astellas					X		
Daiichi Sankyo					X		
Janssen					X		
Jazz					X	X	
Novartis					X	X	
Otsuka			X		X	X	
Pfizer					X		
Servier					X		
Sobi					X		

High risk AML

RISK FACTORS	
Genetic abnormalities (12)	t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* t(v;11q23.3)/*KMT2A*-rearranged# t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM (EVI1)* t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged −5 or del(5q); −7; −17/abn(17p) Complex karyotype,** monosomal karyotype†† Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ Mutated *TP53*[a]
AML sub-type	Secondary type, after previous hematological diseases or previous cytotoxic therapies (t-AML, AML-MR)
Clinical factors	Age Comorbidities Performance Status
Quality or response	Refractoriness to anthracyclines and cytarabine or fludarabine-based regimens (2 cycles) MRD positivity after 2 cycles (induction/consolidation)

Excluding KMT2A partial tandem duplication (PTD).
**Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
[a]TP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

Palmieri R et al, Frontiers in Oncology, 2024

ELN2022 risk classification

Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)* • t(3q26.2;v)/*MECOM*(*EVI1*)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2*‡‡ • Mutated *TP53*[a]

*Frequencies, response rates and outcome measures should be reported by risk category, and, if sufficient numbers are available, by specific genetic lesions indicated.

†Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.

‡Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.

§AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.

‖Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA*, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.

¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

#Excluding *KMT2A* partial tandem duplication (PTD).

**Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.

††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).

‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.

[a]*TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.

Dohner H et al, Blood 2022

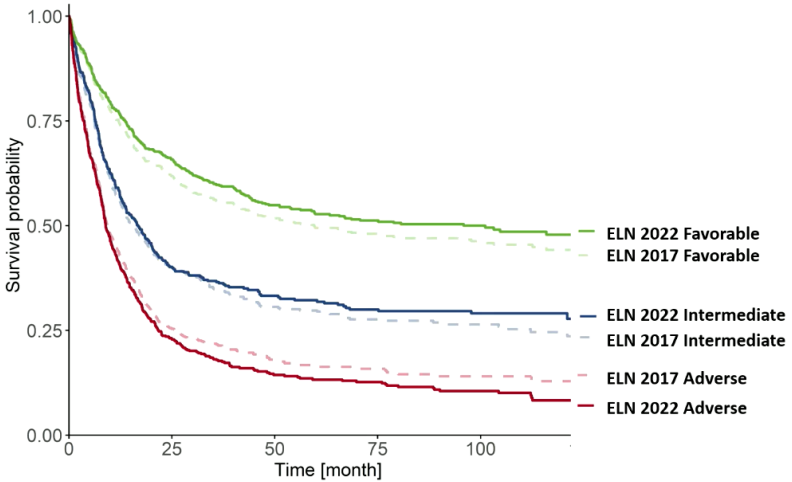
New classifications…but at what cost?

Genetic analysis	Results preferably within
Cytogenetics	5 – 7 days
Screening for gene mutations required for establishing the diagnosis and to identify actionable therapeutic targets	
✓ FLT3, IDH1, IDH2	3 – 5 days
✓ NPM1	3 – 5 days
✓ CEBPA, DDX41, TP53; ASXLI, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,	< 1st cycle
Screening for gene rearrangement	
✓ PML::RARA, CBFB::MVH11, RUNXI:RUNX1T1, KMT2A rearrangements, BCR:ABL1, other fusion genes (if available)	3 – 5 days
Additional genes recommended to test at diagnosis: ANKRD26, BCORL1, BRAF, CBL, CSF3R, DNMT3A, ETV6, GATA2, JAK2, KIT, KRAS, NRAS, NF1, PHF6, PPMID, TPN11, RAD21, SETBP1, TET2, WT1	

Dohner H et al, Blood 2022

Impact of novel risk classifications (ELN2022)

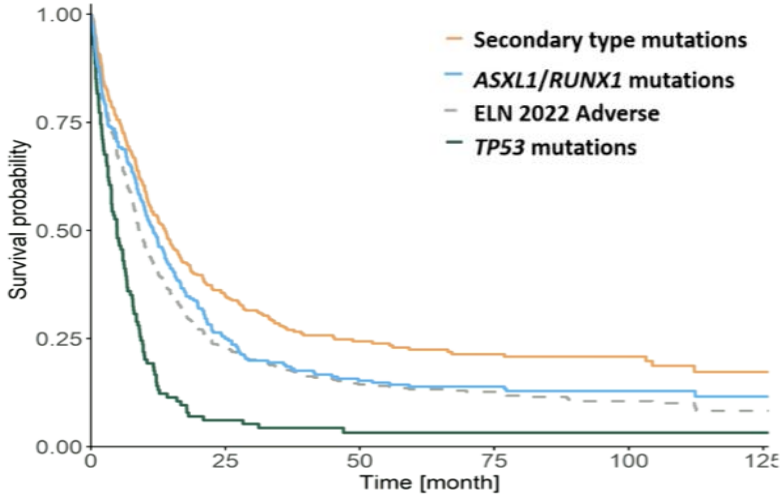
ELN2017 vs. 2022 (entire cohort)



C-statistics for 3-year OS:

- $AUC_{ELN2017}$=0.67
- $AUC_{ELN2022}$=0.71
- p=0.001

Only ELN2022 adverse pts



Bill M, et al. EHA 2023

TP53 overrides classification systems

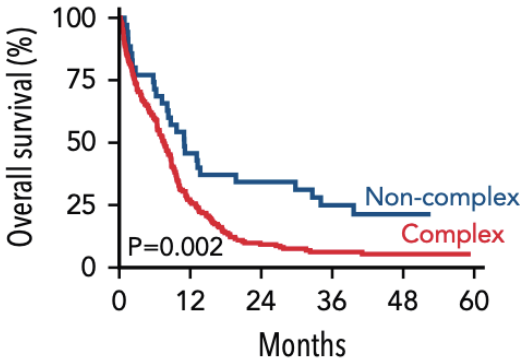
Type	Cytopenia	Blasts	Genetics
MDS with mutated *TP53*	Any	0-9% bone marrow and blood blasts	Multi-hit TP53 mutation* or *TP53* mutation (VAF > 10%) and complex karyotype often with loss of 17p†
MDS/AML with mutated *TP53*	Any	10-19% bone marrow or blood blasts	Any somatic *TP53* mutation (VAF > 10%)
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%)

«This mutation is typically associated with extraordinarily poor outcomes regardless of whether classified as AML or MDS» (Estey E, et al, Blood 2022)

Arber DA et al. Blood. 2022

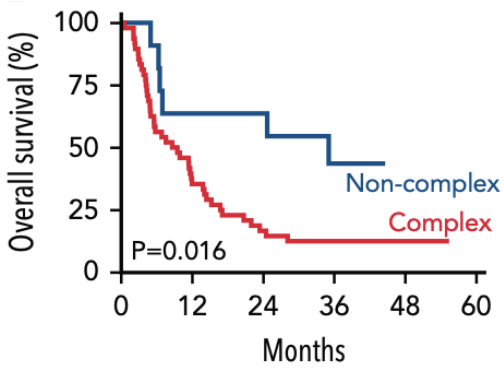
Tp53 and its world

A. Tp53+



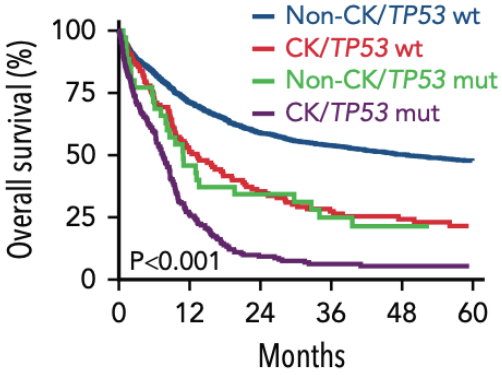
No. at risk:						
Non-complex	35	16	12	8	4	3
Complex	185	49	16	7	5	2

B. Tp53+ undergoing ASCT



No. at risk:						
Non-complex	11	7	7	4	1	1
Complex	48	17	8	4	3	2

C. Overall series

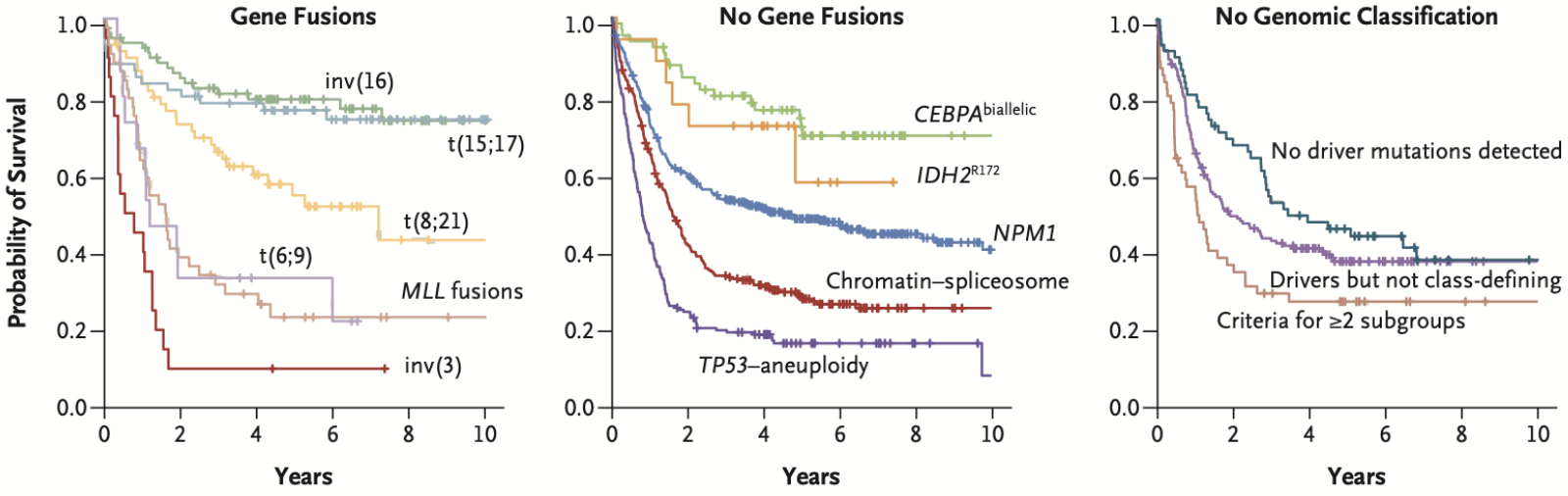


No. at risk:						
Non-CK/*TP53* wt	1764	1247	1011	802	566	398
CK/*TP53* wt	117	61	40	28	21	13
Non-CK/*TP53* mut	35	16	12	8	4	3
CK/*TP53* mut	185	49	16	7	5	2

2200 patients with AML and MDS-EB classified according to ELN2017. TP53 mutations were detected in 230 (10.5%).

Grob T et al, Blood, 2022

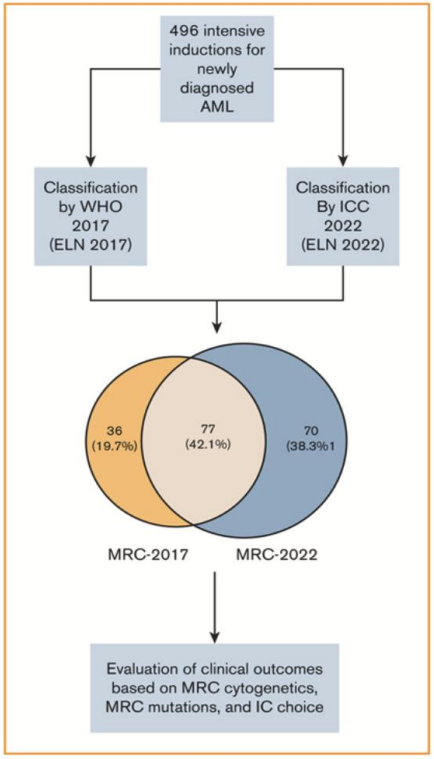
Genomic classification of AML

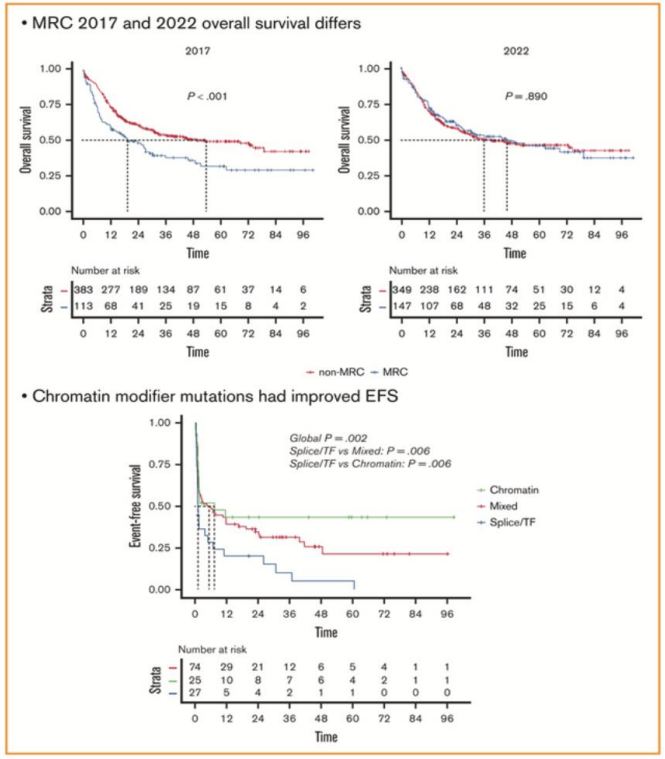


Chromatin: ASXL1, STAG2,BCOR, MLLPTD, EZH2, and PHF6
Splicesoome: SRSF2, SF3B1, U2AF1, and ZRSR2
Transcriptome: RUNX1

Papaemmanuil E et al, NEJM 2016

MRC nowadays



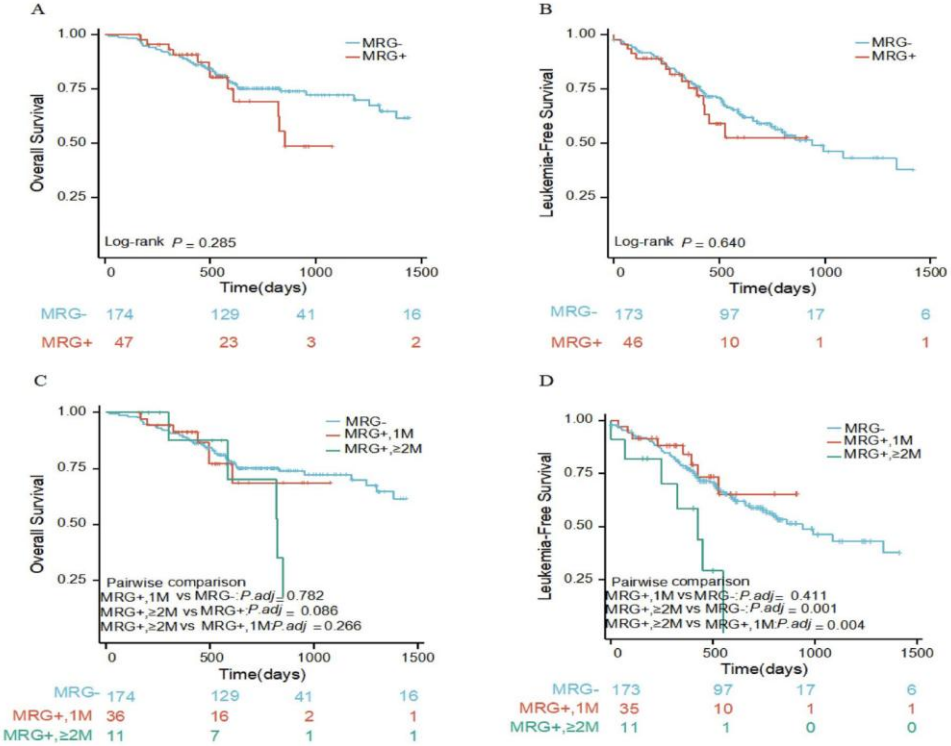


Survival outcomes in AML-MRC defined by ICC 2022 vary by mutation type, revealing significant heterogeneity in this adverse-risk group.

AML-MRC by ICC 2022 had worse EFS but better posttransplant OS vs non-MRC, highlighting distinct treatment responses in this group

Chornenki et al. Blood Neoplasia 2026

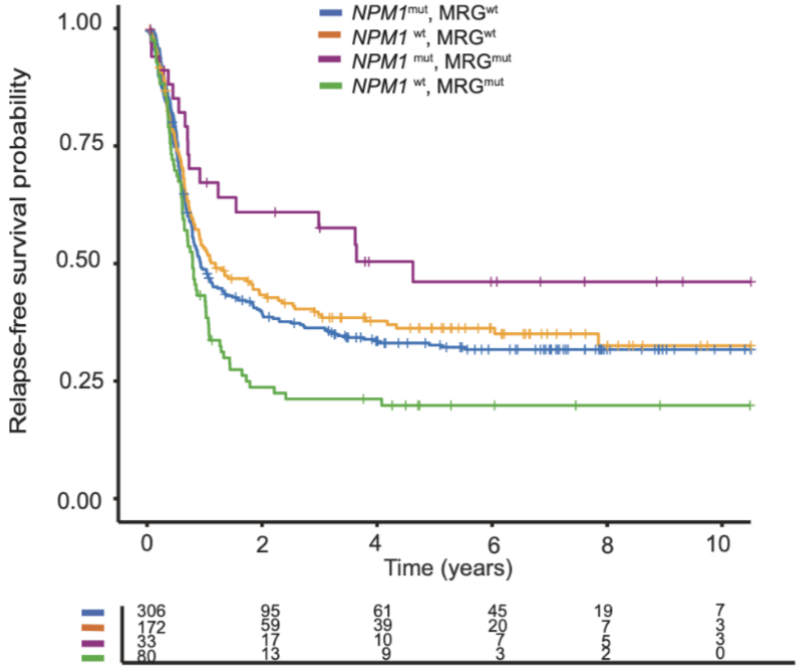
What about MRG in favorable risk?

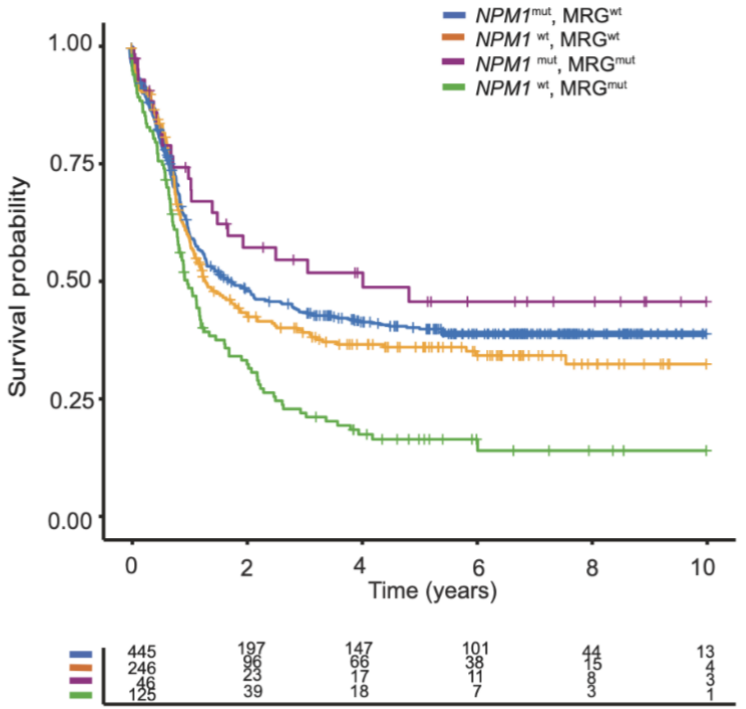


221 adult patients with de novo Favorable-risk AML (ELN2022), 21.5% of which carrying myelodysplasia-related genes mutations

Zhang L et al, Ann of Medicine, 2026

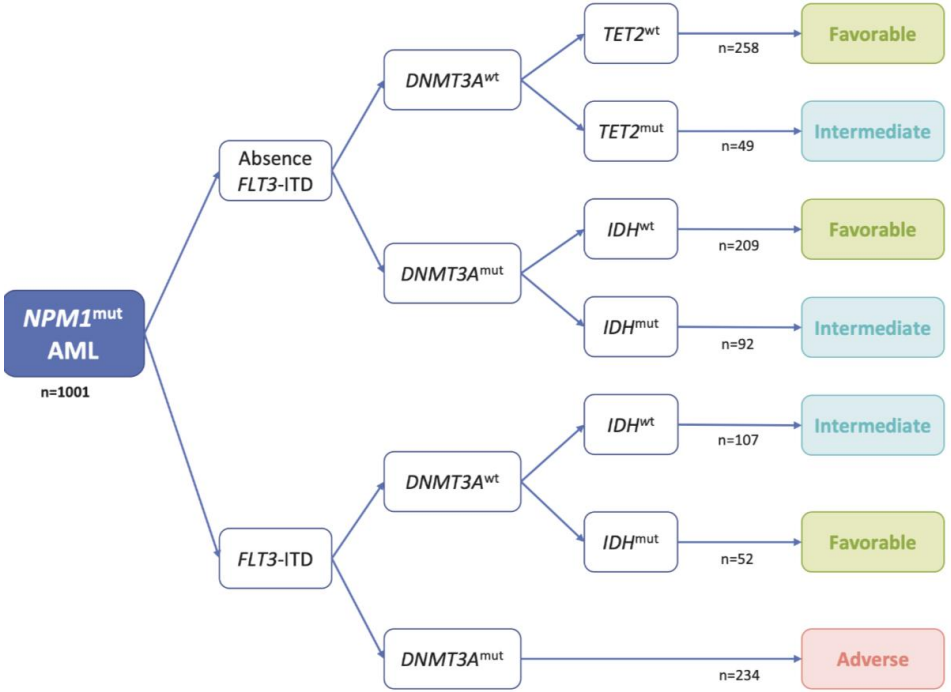
FLT3/NPM1/MRG





Mecklenbrauck R et al, Hemasphere, 2025

NPM1, is all that glitters gold?



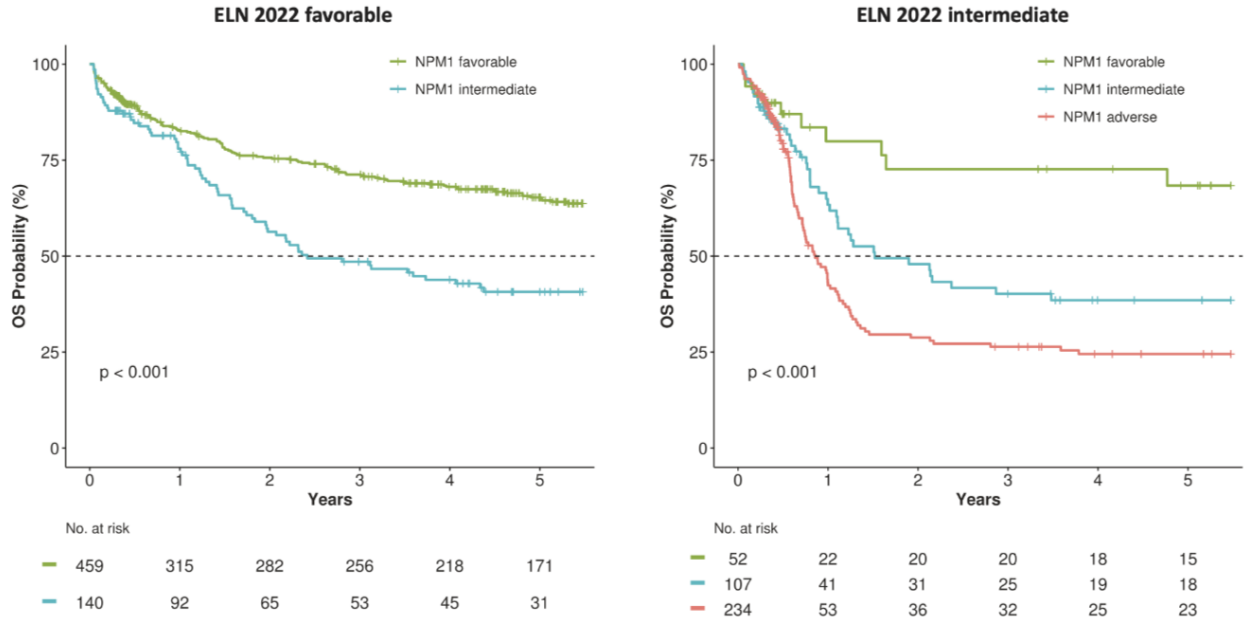
NPM1^{mut}FLT3^{wt}DNMT3A^{wt}TET2^{wt}
NPM1^{mut}FLT3^{wt}DNMT3A^{mut}IDH1^{wt}
NPM1^{mut}FLT3^{mut}DNMT3A^{wt}IDH1^{mut}

NPM1^{mut}FLT3^{wt}DNMT3A^{wt}TET2^{mut}
NPM1^{mut}FLT3^{wt}DNMT3A^{mut}IDH1^{mut}
NPM1^{mut}FLT3^{mut}DNMT3A^{wt}IDH1^{wt}

NPM1^{mut}FLT3^{mut}DNMT3A^{mut}

Hernández-Sánchez A et al, Leukemia, 2026

Co-mutations redefine favorable AML



Hernández-Sánchez A et al, Leukemia, 2026

ELN classication in pts receiving less-intensive therapies

Genetic marker	Median OS, mo
Favorable-risk group	
Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	39
Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	37
Mutated *IDH1** (*TP53*^{wt})	29
Mutated *DDX41*	>24
AML with MR gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23
Intermediate-risk group	
AML with MR gene mutations (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	13
Other cytogenetic and molecular abnormalities (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})	12
Adverse-risk group	
Mutated *TP53*	5-8

Dohner H et al, Blood 2024

Genetic risk in non-intensively treated patients

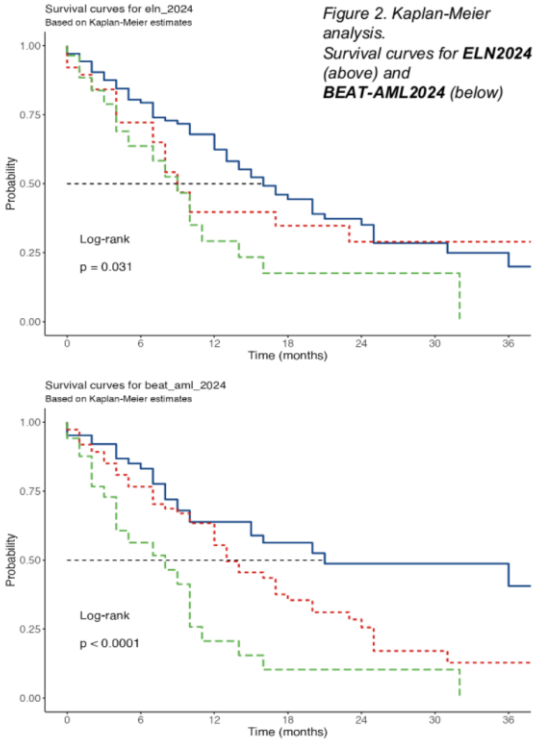


*Figure 2. Kaplan-Meier analysis. Survival curves for **ELN2024** (above) and **BEAT-AML2024** (below)*

Table 1. Pairwise Comparisons		
Levels	Levels	P-value
ELN 2022		
Intermediate	Favorable	0.694
Adeverse	Favorable	0.028
Adverse	Intermediate	0.058
ELN 2024		
Intermediate	Favorable	0.502
Adeverse	Favorable	0.015
Adverse	Intermediate	0.502
Beat-AML 2024		
Intermediate	Favorable	0.032
Adeverse	Favorable	<.001
Adverse	Intermediate	0.006

*Table1. Pairwise Comparison **BEAT-AML 2024 Demonstrates Superior Discrimination Between All Risk Categories.** Only the BEAT-AML 2024 model achieved statistical significance in distinguishing all three risk groups.*

171 unfit AML patients from 8 Italian centers

The C-index was highest for BEAT-AML 2024 (**0.603,**), as compared to ELN 2024 (**0.573**).

Savi A et al, Poster presentation, 2025 ASH meeting

Take home messages

- AML risk is biologically driven and highly heterogeneous
  Single genomic lesions (e.g. TP53) may outweigh standard classifications
- ELN2022 improves prognostic stratification, but remains incomplete
  Limited ability to fully capture outcome variability within risk groups
- So-called “favorable” AML is not uniformly favorable
  Co-mutations (MRG, DNMT3A, FLT3) significantly reshape prognosis
- Risk must be interpreted in the context of treatment strategy
  Need for therapy-adapted risk models

Hematology
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GIMEMA Foundation

Laboratory team

Clinical team