Università degli Studi di Modena e Reggio Emilia
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Scuola di Specializzazione in Ematologia
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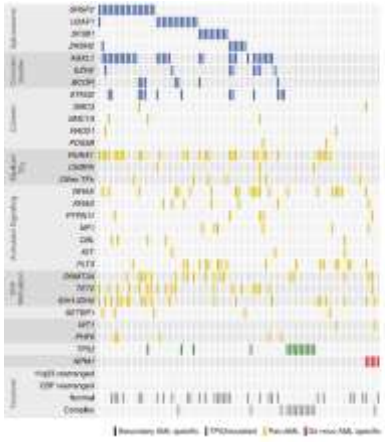
Journal club

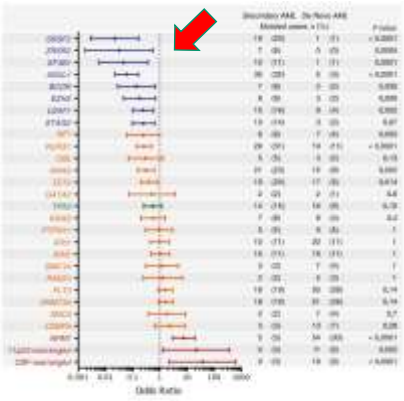
"Differential prognostic impact of MDS-related gene mutations in a European cohort of 4978 intensively treated AML patients"

Bill et al, Leukemia 2026;40:63-71

10 Marzo 2026

Dott. Fabio Forghieri

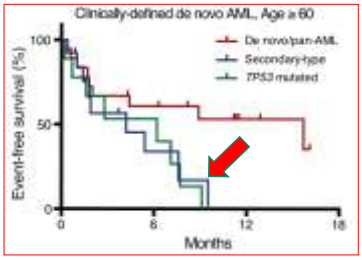


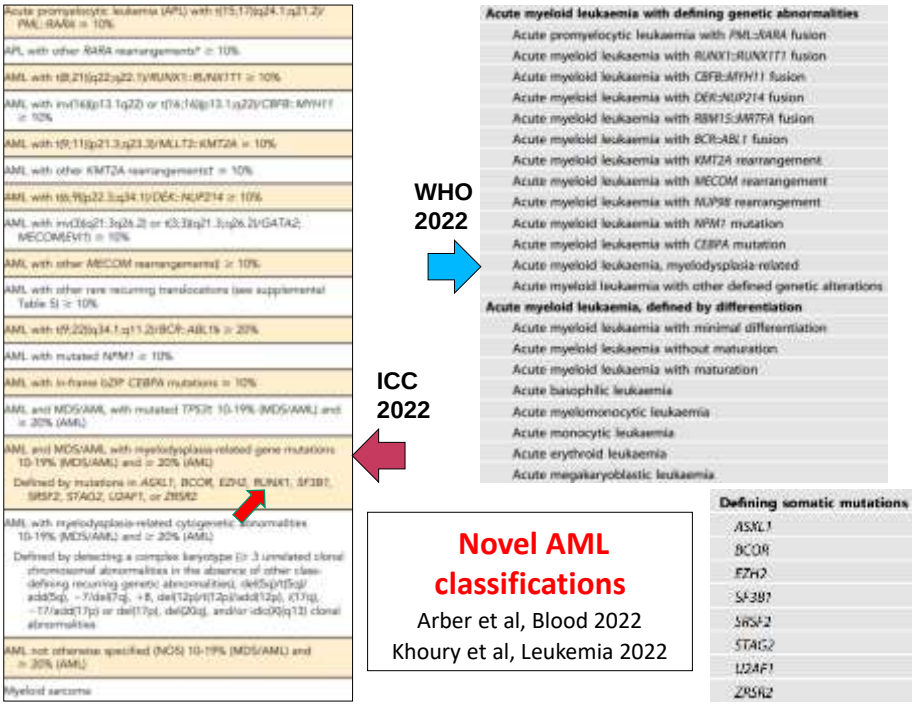


MDS-related gene mutations were >95% specific for the diagnosis of **secondary-AML.**

In **therapy-related AML** and **elderly de novo AML** populations, these alterations define a **distinct genetic subtype** that shares clinico-pathological properties with clinically confirmed s-AML and highlights a subset of patients **with worse clinical outcomes.**

Lindsley et al, Blood 2015

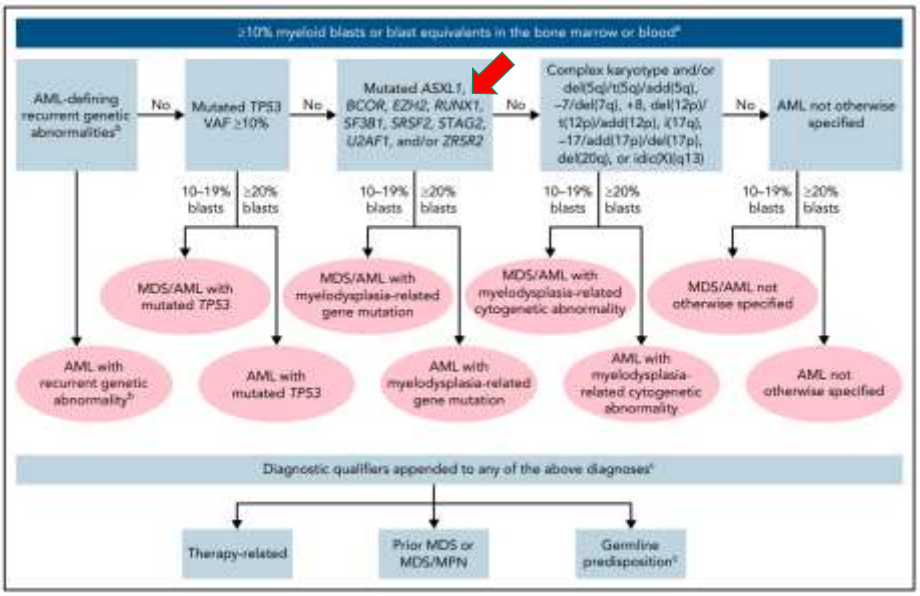




Novel AML classifications

Arber et al, Blood 2022

Khoury et al, Leukemia 2022



Hierarchical AML classification according to ICC (ELN 2022)

Dohner et al, Blood 2022

Blood Cancer Journal

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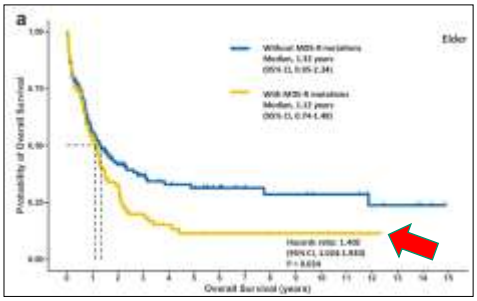
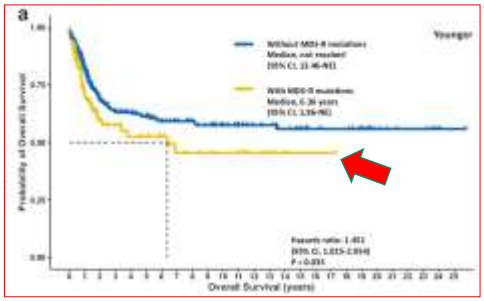
Poor prognostic implications of myelodysplasia-related mutations in both older and younger patients with *de novo* AML

Xavier Cheng-Hong Tsai[1,2,3], Kuo-Jui Sun[2,4], Min-Yen Lo[5], Feng-Ming Tien[6,7], Yuan-Yeh Kuo[8], Mei-Hsuan Tseng[9], Yen-Ling Peng[1], Yi-Kuang Chuang[10], Bor-Sheng Ko[2,3,4], Ming-Luh Tang[11,12], Hsuan-I Sun[13], Ming-Chih Liu[1], Chia-Wen Liu[1], Chien-Chin Lin[14], Ming Yao[1], Wen-Chien Chou[2,3,4], Hsin-An Hou[1,15] and Hwei-Fang Tien[1,2,15]

Adverse survival outcomes in intensively treated AML with MRG mutations **regardless of patient age.**





MRG mutations prevalence 44.9%

MRG mutations prevalence 23.4%

Genetic marker	Median overall survival (months)
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*[a] (*TP53*^{wt})	29
• Mutated *DDX41*	>24
• AML with myelodysplasia-related gene mutations (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})	23
Intermediate-risk group	
• AML with myelodysplasia-related 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

2024 ELN risk classification for AML patients receiving less-intensive therapies

Dohner et al, Blood 2024

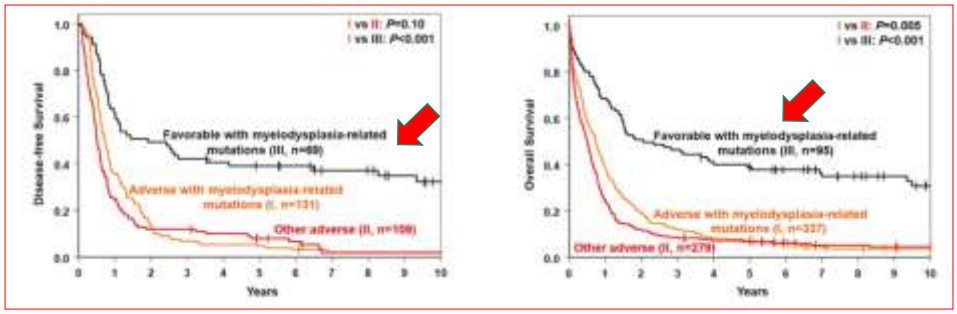
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (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*°

2022 ELN risk classification by genetics at initial AML diagnosis for intensively treated fit patients

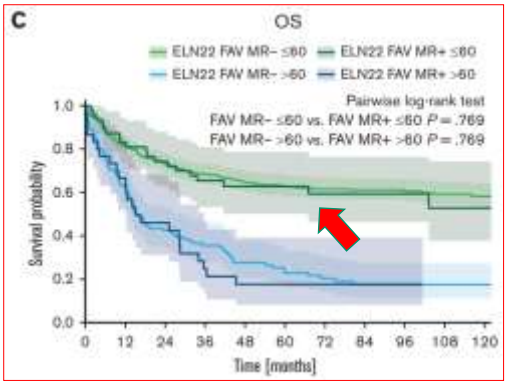
Dohner et al, Blood 2022

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

Heterogeneous clinical bevahior of AML with MDS-related gene mutations



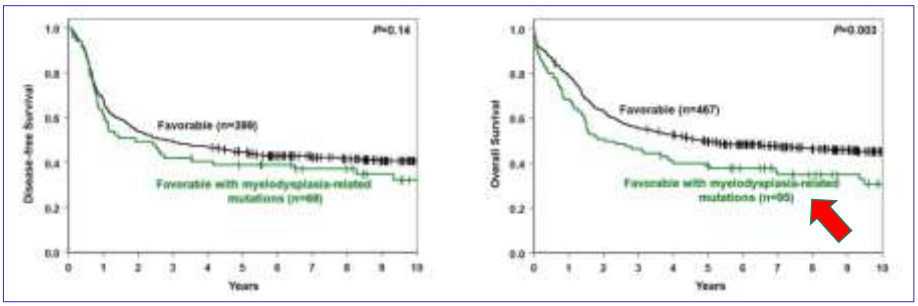
The outcomes of patients with MDS-related mutations **without favorable-risk features** were **worse** than the outcome of patients harboring MDS-related mutations together with favorable genetic-risk markers (Mrozek et al, Leukemia 2023)

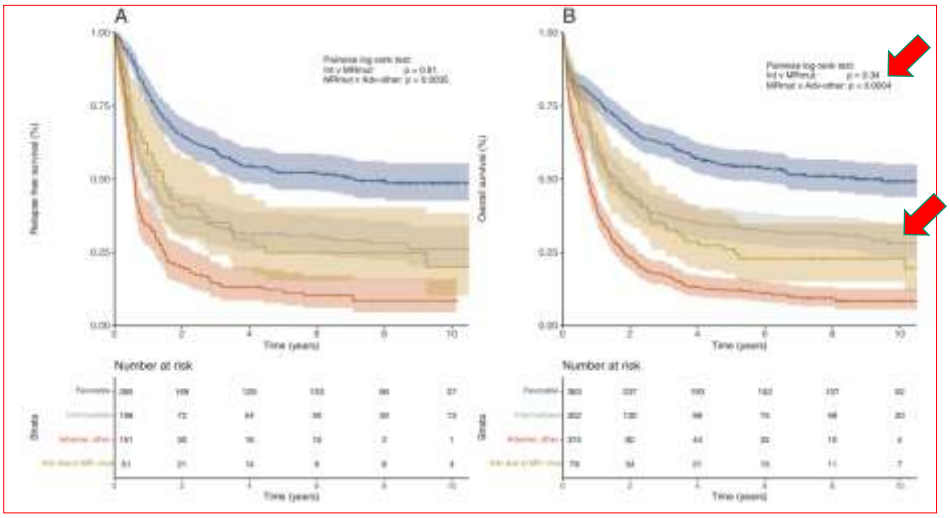


Discordant results on the impact of MRG mutations on clinical outcomes in ELN 2022 favorable-risk AML subgroup

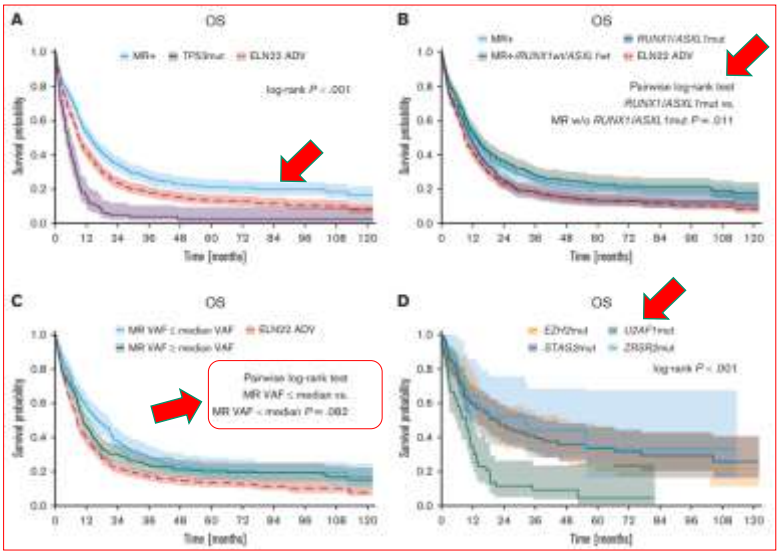
Ruhnke et al, Blood Adv 2025

Mrozek et al, Leukemia 2023



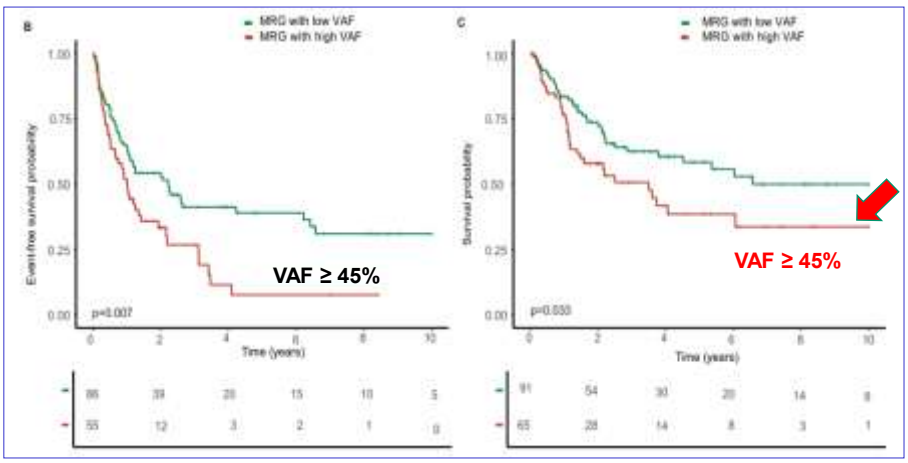


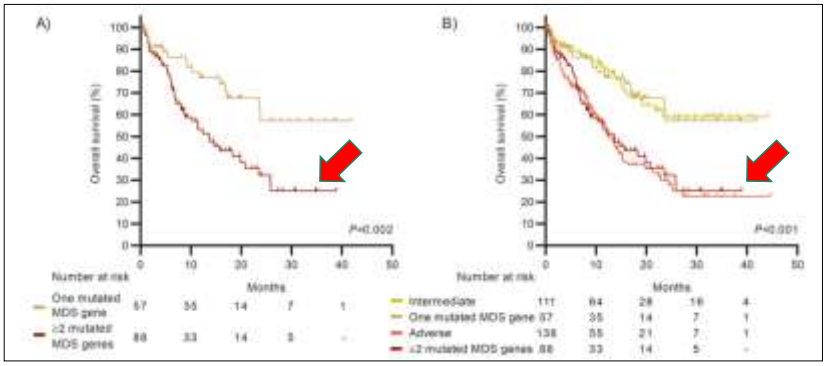
MRG-mutated AML had significantly **better outcomes** than patients with other adverse-risk genotypes (5-year OS, 26% vs. 12%) and **resembled the remaining intermediate-risk group** (Rausch et al, Leukemia 2023)



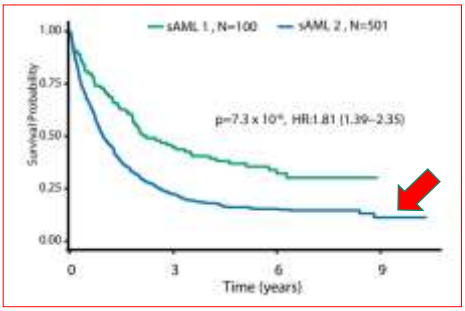
Marked **survival differences** across **mutational subgroups** (**5-year OS rate of 21%** and 3% in patients with MRG mutations and TP53 mutations, respectively). **Adverse** outcome **for *RUNX1/ASXL1*-mutated cases**. ***EZH2, STAG2* and *ZRSR2*-mutated** patients showed an **intermediate-like OS** (Ruhnke et al, Blood Adv 2025)

Clonal representation: prognostic **impact of the size of MRG-mutated clone** in adverse risk AML harboring at least one MRG mutation (Mecklenbrauck et al, Leukemia 2025)



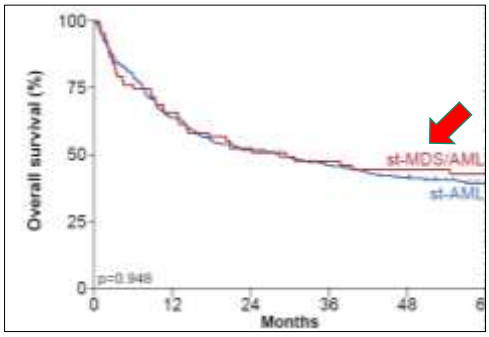


Sargas et al, Blood Cancer J 2023



The association with **adverse survival outcomes** was specific to AML patients with **>2 MRG mutations**

et al, Nat Comm 2022

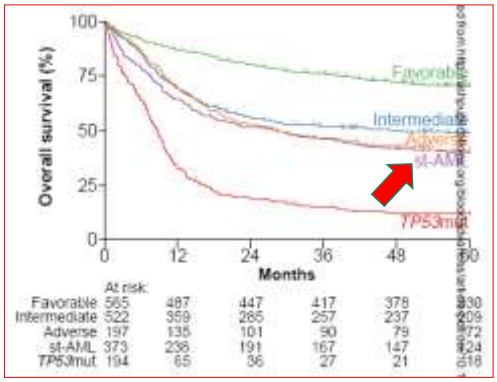


Impact of BM blast percentage

OS was **comparable** between patients with **secondary-type AML and st-MDS/AML**

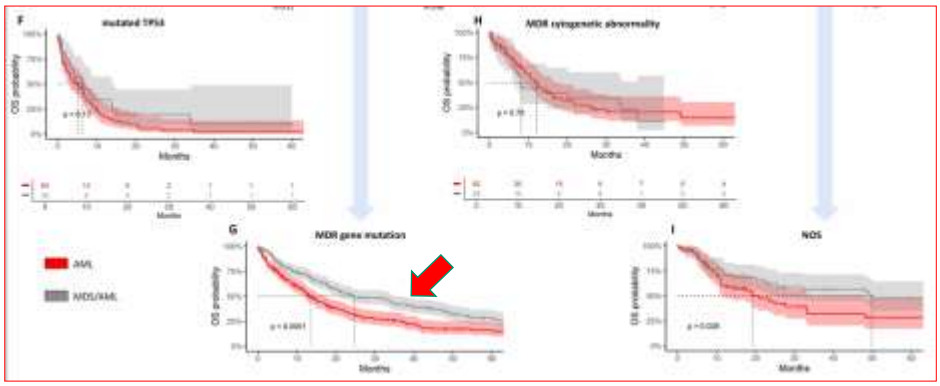
Boertjes et al, Blood Adv 2026

Patients with **st-AML** had a significantly **reduced OS** compared to ELN2022 **favorable risk and intermediate risk** AML patients **but significantly better OS compared to TP53 mutant** AML and **comparable OS** to all other **adverse AML** patients



Impact of BM blast percentage

-*TP53*-mutated and MR-cytogenetic abnormality AML and MDS/AML categories presented similar biology and prognosis, irrespective of blast counts.
-Conversely, in **MDS/AML with "MR gene mutations"** and NOS, profiles significantly differed from AML and were characterized by a **higher number of mutations in *STAG2, SRSF2, ASXL1* and *TET2***.
-**Improved OS in MDS/AML** vs AML with **MRG-mutations** (median OS 24.8 vs 13.6 months)
Attardi et al, Blood Adv 2026



Leukemia 2026 www.nature.com/leu

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Acute Myeloid Leukemia

Differential prognostic impact of myelodysplasia-related gene mutations in a European cohort of 4978 intensively treated AML patients

Marius Bill[1,2,3,4,34], Jan-Niklas Eckardt[1,34], Konstanze Döhner[5], Maximillian-Alexander Röhnert[1], Christian Rausch[6], Klaus H. Metzeler[7], Karsten Spiekermann[8], Sebastian Stasik[1], Alexander A. Wurm[1,2,3,4], Tim Sauer[8], Sebastian Scholl[9], Ulf Schnetzke[9], Andreas Hochhaus[9], Martina Crysandt[10], Tim H. Brümmendorf[10], Utz Krug[11], Bernhard Wörmann[12], Hermann Einsele[13], Wolfgang Hiddemann[6], Dennis Görlich[14], Cristina Sauerland[14], Björn Steffen[15], Andreas Neubauer[16], Andreas Burchert[16], Kerstin Schäfer-Eckart[17], Wolfgang E. Berdel[18], Christoph Schliemann[18], Stefan W. Krause[19], Mathias Hänel[20], Maher Hanoun[21], Martin Kaufmann[22], Lars Fransecky[23], Jan Braess[24], Johannes Schetelig[1], Jan Moritz Middeke[1], Lars Bullinger[12], Michael Heuser[25,26], Felicitas Thol[26], Hubert Serve[15], Claudia D. Baldus[27], Uwe Platzbecker[7], Carsten Müller-Tidow[8], Jan Válka[27], Jiří Šrámek[28,29], Barbora Weinbergerova[30], Jiri Mayer[30], Pierre-Yves Dumas[31], Sarah Bertoli[32], Eric Delabesse[32], Christian Récher[32], Arnaud Pigneux[31], Tobias Herold[6,33], Arnold Ganser[20], Hartmut Döhner[5], Martin Bornhäuser[1,2,3,4], Christian Thiede[1] and Christoph Röllig[1,35]

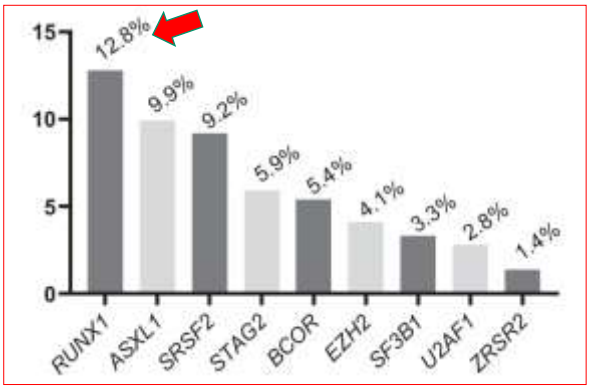
Explorative analyses of **individual MR gene mutations** revealed **distinct differential survival outcomes** among individual MR gene mutations, raising **the question whether grouping all MR gene mutations in the adverse risk group is justified.**

Variable	MR gene mutation	No MR gene mutation	p
n/N (%)	1698/4978 (34.1)	3280/4978 (65.9)	
Age (years), median (IQR)	59 (50–67)	52 (42–61)	<0.001
Sex, n (%)			<0.001
female	660 (38.9)	1703 (51.9)	
male	1038 (61.1)	1577 (48.1)	
Disease status, n (%)			
de novo	1287 (75.8)	2896 (88.3)	<0.001
sAML	326 (19.2)	208 (6.3)	<0.001
tAML	71 (4.2)	151 (4.6)	0.515
missing	14 (0.8)	25 (0.8)	
Complex karyotype, n (%)			<0.001
Yes	131 (7.7)	383 (11.7)	
No	1513 (89.1)	2799 (85.3)	
missing	54 (3.2)	98 (3.0)	
Normal karyotype, n (%)			0.285
Yes	893 (52.6)	1781 (54.3)	
No	751 (44.2)	1401 (42.7)	
missing	54 (3.2)	98 (3.0)	
Laboratory, median (IQR)			
WBC (10^9/l)	10.7 (2.9–39.6)	23.3 (5.8–66.0)	<0.001
Hb (mmol/l)	5.7 (4.9–6.6)	5.8 (5.0–6.7)	0.160
PLT (10^9/l)	55 (30–105)	55 (30–100)	0.570
PB blasts (%)	26 (6–63)	43 (13–76)	<0.001
BM blasts (%)	60 (39–80)	72 (50–88)	<0.001

4978 intensively treated AML patients, enrolled in clinical trials between 1998 and 2021 **(34.1% harboring MRG mutations)**

Patients were retrospectively **assigned to risk groups** according to ELN 2022 recommendations

Bill et al, Leukemia 2026

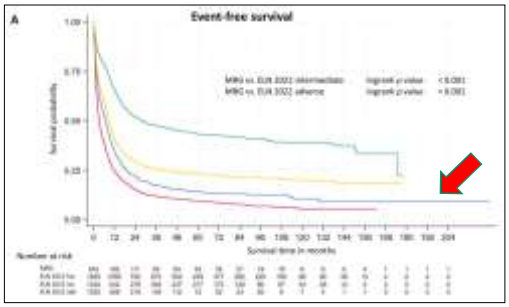


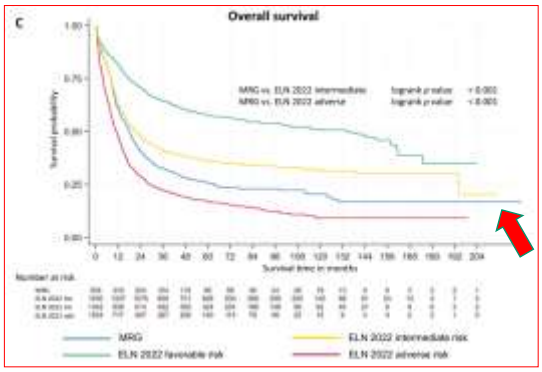
Prevalence of MR gene mutations and **patient outcomes** with respect to MR gene mutations for the entire cohort.

Outcome	MR gene mutation	No MR gene mutation	OR/HR	p
n/N (%)	1698/4978 (34.1)	3280/4978 (65.9)		
CR rate, n (%)	1116/1698 (65.7)	2549/3280 (77.7)	0.55 [0.50–0.63]	<0.001
EFS	6.3 [5.4–7.0]	10.5 [9.8–11.3]	1.45 [1.36–1.55]	<0.001
RFS	14.3 [12.7–16.3]	20.3 [17.9–23.3]	1.33 [1.22–1.45]	<0.001
OS	16.6 [15.2–17.8]	26.5 [24.3–30.2]	1.45 [1.35–1.56]	<0.001

Patients with an MRG mutation had a significantly **shorter OS** than patients without an MRG mutation **after allo-HCT in CR1** (Bill et al, Leukemia 2026)

Prognostic impact of grouped MR gene mutations in relation to ELN 2022





For survival analyses in the context of ELN 2022 classification, **patients carrying an MR mutation, in the absence of other unfavorable risk features, were excluded from the adverse group** and analyzed separately, while those with co-occurring favorable or intermediate features remained in their respective prognostic groups.

MRG-mutated patients without favorable or intermediate genetics had **a longer median OS (14.7 months)** compared to **non-MR gene mutation ELN 2022 adverse risk patients** (median OS 8.3 months)

Prognostic impact of individual MR gene mutations in relation to ELN 2022

	Event-free survival		Relapse-free survival		Overall survival	
	ELN 2022 intermediate	ELN 2022 adverse	ELN 2022 intermediate	ELN 2022 adverse	ELN 2022 intermediate	ELN 2022 adverse
ASXL1	0.019[#]	n.s.[#]	n.s.	n.s.	n.s.	n.s.
BCOR	n.s.	n.s.	0.011[#]	n.s.[#]	n.s.[$]	0.026[$]
EZH2	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
RUNX1	<0.001[#]	n.s.[#]	0.014[#]	n.s.[#]	0.003[#]	n.s.[#]
SF3B1	0.003[#]	n.s.[#]	0.046[#]	n.s.[#]	0.045[#]	n.s.[#]
SRSF2	n.s.[$]	<0.001[$]	n.s.	n.s.	n.s.[$]	0.01[$]
STAG2	n.s.[$]	<0.001[$]	n.s.[$]	<0.001[$]	n.s.[$]	<0.001[$]
U2AF1	0.003[#]	n.s.[#]	n.s.	n.s.	0.003[#]	n.s.[#]
ZRSR2	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

In summary:

-MR gene mutations in ***ASXL1, RUNX1, SF3B1*, and *U2AF1*** were associated with outcomes significantly worse than those of intermediate risk patients but **similar to adverse risk patients** for at least one clinical endpoint.

-Mutations in ***EZH2* and *ZRSR2*** were associated with outcomes neither significantly worse than those of intermediate risk patients nor significantly better than those of adverse risk patients.

-Mutations in ***SRSF2* and *STAG2*** were found to be linked to significantly **better outcomes**, **comparable** to those classified as **intermediate risk** rather than adverse risk (Bill et al, Leukemia 2026)

While most MR gene mutations are associated with dismal outcomes, these recent data suggest **that mutations in *SRSF2* and *STAG2* should probably not be classified as adverse,** aligning these genetic lesions to ELN 2022 **AML intermediate risk category.**

Limitations of the study (Bill et al, Leukemia 2026)

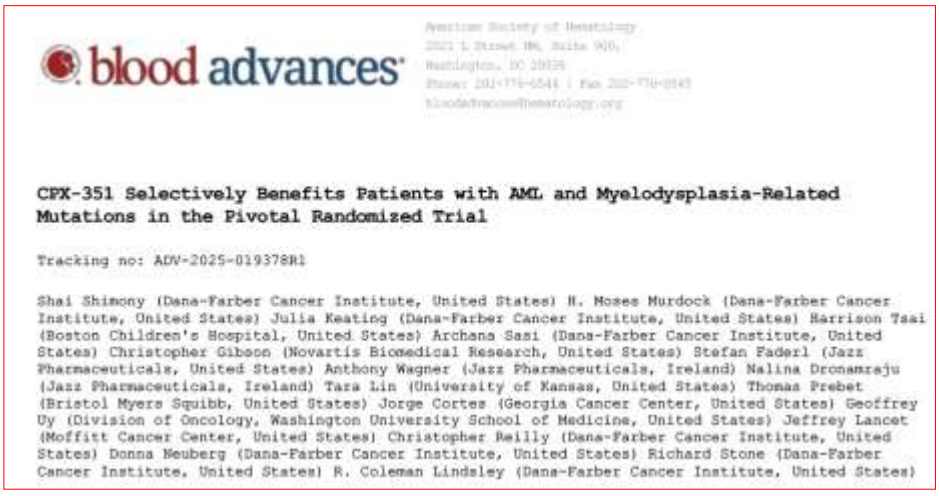
- Retrospective nature of the analysis, with drawbacks such as patient selection, heterogeneity in chemotherapeutic treatments and supportive care

- Novel therapies, such as **GO, FLT3 inhibitors and CPX-351** were not necessarily available or standard of care during the period data collection.

- No detailed data were available on ***NPM1* and *FLT3*** mutational status

- Lack of **measurable residual disease (MRD)** monitoring at clinically significant timepoints

- **Prospective validation** of distinct prognostic significance of different individual MR gene mutations is warranted



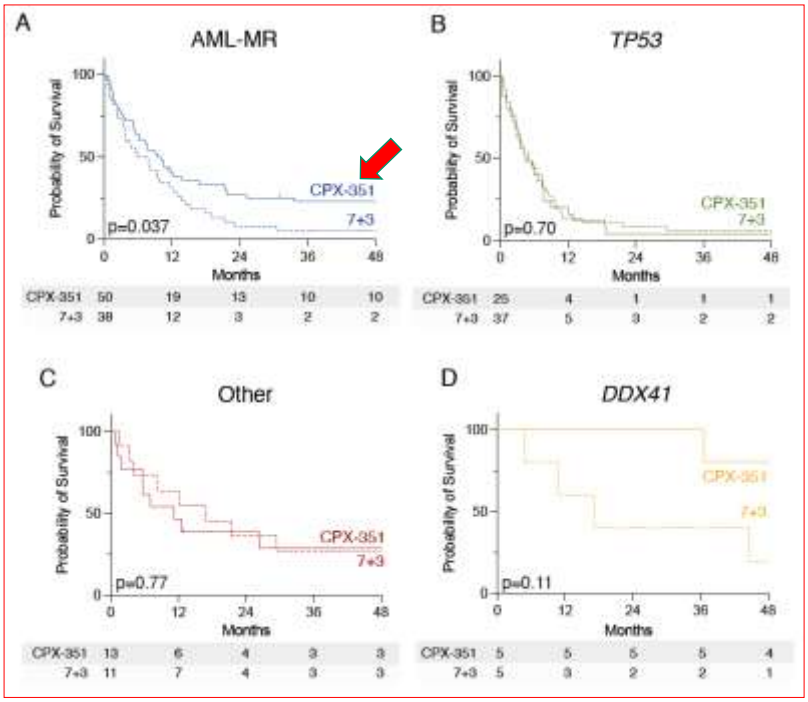
blood advances

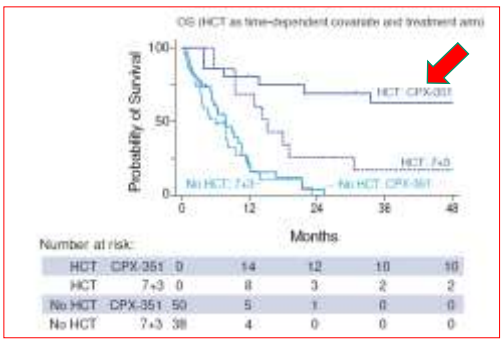
CPX-351 Selectively Benefits Patients with AML and Myelodysplasia-Related Mutations in the Pivotal Randomized Trial

Tracking no: ADV-2025-019378R1

Shai Shimony (Dana-Farber Cancer Institute, United States) N. Moses Murdock (Dana-Farber Cancer Institute, United States) Julia Keating (Dana-Farber Cancer Institute, United States) Harrison Tsai (Boston Children's Hospital, United States) Archana Sasi (Dana-Farber Cancer Institute, United States) Christopher Gibson (Novartis Biomedical Research, United States) Stefan Faderl (Jazz Pharmaceuticals, United States) Anthony Wagner (Jazz Pharmaceuticals, Ireland) Nalina Dronamraju (Jazz Pharmaceuticals, Ireland) Tara Lin (University of Kansas, United States) Thomas Prebet (Bristol Myers Squibb, United States) Jorge Cortes (Georgia Cancer Center, United States) Geoffrey Uy (Division of Oncology, Washington University School of Medicine, United States) Jeffrey Lancet (Moffitt Cancer Center, United States) Christopher Reilly (Dana-Farber Cancer Institute, United States) Donna Neuberg (Dana-Farber Cancer Institute, United States) Richard Stone (Dana-Farber Cancer Institute, United States) R. Coleman Lindsley (Dana-Farber Cancer Institute, United States)

In this **post-hoc analysis**, **184 patients** enrolled in the pivotal phase 3 randomized trial were **categorized hierarchically** based on gene mutations: (1) *TP53*-AML, (2) *DDX41*-AML, (3) myelodysplasia-related AML (AML-MR) defined by WHO 5th edition, or (4) other-AML.

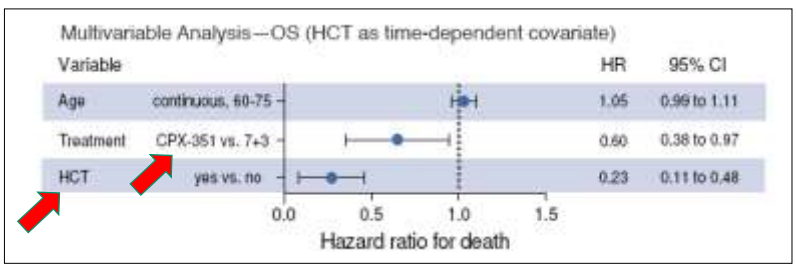




For patients undergoing **allo-HCT**, **CPX-351 improved 2-year OS**, an effect primarily observed in AML-MR.

Multivariable analysis confirmed the independent association with OS of both CPX-351 and HCT in AML-MR.

The **OS benefit of CPX-351 was driven by AML-MR** with no benefit of CPX-351 in *TP53*-AML.



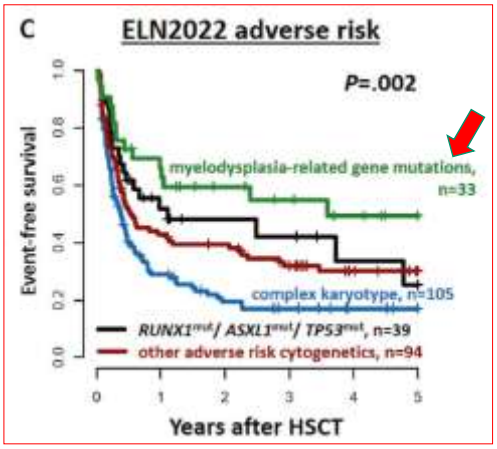
Shimony et al, Blood Adv 2026

Blood Cancer Journal

ARTICLE OPEN

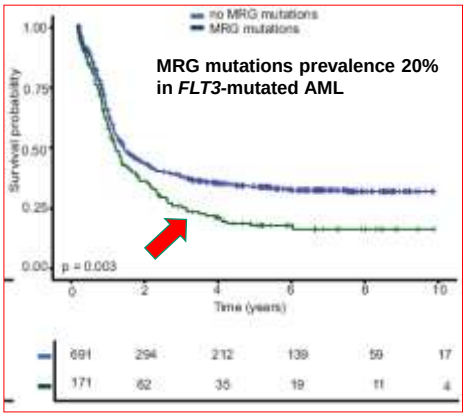
Prognostic impact of the AML ELN2022 risk classification in patients undergoing allogeneic stem cell transplantation

Madlen Jentzsch, Lara Bischof, Jyle Ussmann, Donata Backhaus, Dominic Brauer, Klaus H. Metzeler, Maximilian Merz, Vladan Vucinic, Georg-Nikolaus Franke, Marco Hetling, Uwe Platzbecker and Sebastian Schwind



In **transplanted AML** patient population, **MRG mutations did not associate with adverse outcomes** when no other adverse risk characteristics were present.

It could be speculated that an **allogeneic HCT might have the potential to overcome the adverse prognostic impact of MRG mutations.**



Impact of other common gene mutations

In MVA, MR gene mutations had **no independent prognostic impact** on RFS and OS in the overall cohort of ***FLT3*-ITD AML** patients.
However, among *FLT3*-ITD positive and ***NPM1*wt** patients, MRG mutations were independently associated with **inferior RFS and OS**.
MRG mutations with **concurrent *NPM1*** mutation **did not confer adverse prognostic significance**.

Mecklenbrauck et al, Leukemia 2026

	Univariate				Multivariable			
Variable	HR*	95% CI LL	95% CI UL	p	HR*	95%CI LL	95% CI UL	p
MRG mutant vs. wildtype	1.36	1.11	1.66	0.003	1.14	0.92	1.42	0.2
WBC at diagnosis (increase of 1, $\log_2$, x10^9/L)	1.12	1.07	1.18	<0.001	1.13	1.08	1.18	<0.001
Age (increase by 10)	1.22	1.14	1.30	<0.001	1.22	1.14	1.30	<0.001
TP53 mutant vs. wildtype	2.03	1.01	4.08	0.047	1.54	0.76	3.12	0.2
NPM1 mutant vs. wildtype	0.75	0.63	0.89	<0.001	0.66	0.55	0.80	<0.001
Favorable risk cytogenetics yes vs. no	0.69	0.44	1.06	0.09	0.66	0.42	1.04	0.075
Adverse risk cytogenetics yes vs. no	1.25	0.87	1.81	0.2	-	-	-	-

Another controversial issue

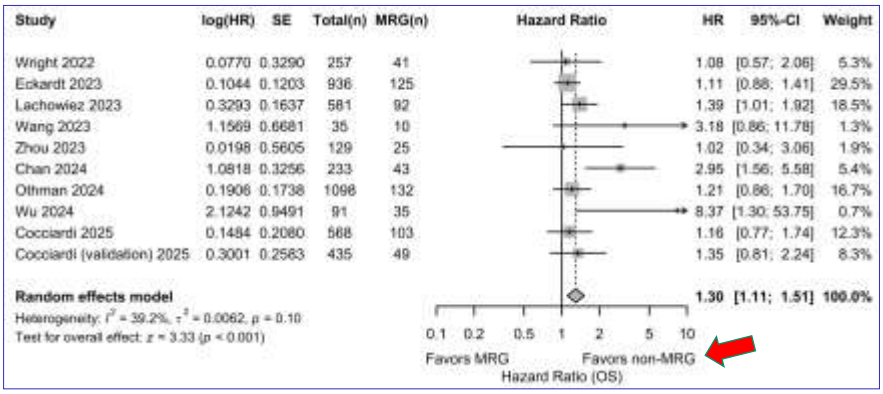
haematologica

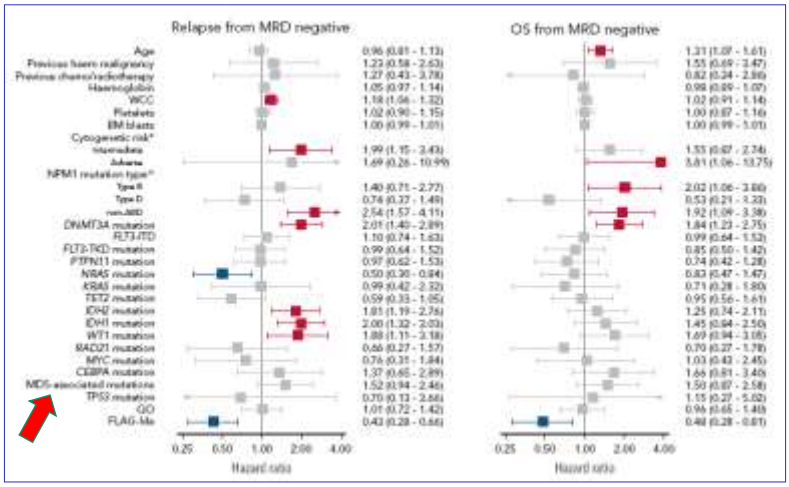
Chang et al, 2026

Prognostic implications of myelodysplasia-related gene mutations in *NPM1*-mutated acute myeloid leukemia: a systematic review and meta-analysis

Concurrent MRG mutations (15% of cases) are globally associated with significantly **worse survival and lower CR rates** in patients with ***NPM1*-mutated AML**, challenging the assumption that this genetic subtype uniformly portends a favorable prognosis.

However, MRG mutations may function as **moderate risk-modifying factors**.





The **unfavorable effect** was **no longer present** when including RQ-PCR for *NPM1*-mutated **MRD status in PB post cycle 2** in the survival model.

It could be proposed **not to consider MRG co-mutations** for risk stratification in *NPM1*-mutated AML if molecular **MRD negativity** post cycle 2 is achieved.

Cocciardi et al, Hemasphere 2025; Othman et al, Blood 2024

Discussion

Several open questions and fewer definitive answers on the prognostic significance of myelodysplasia-related gene mutations in AML patients.

Thank you for Your attention!