EUROPEAN HEMATOLOGY ASSOCIATION

8th INTERNATIONAL SYMPOSIUM on ACUTE PROMYELOCYTIC LEUKEMIA - EHA Symposium, April 11 , 2024, Rome

# Classification and risk assessment of AML at diagnosis

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# DISCLOSURES OF COMMERCIAL SUPPORT

## Konstanze Döhner

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# Two new classifications of myeloid neoplasms in 2023

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

Daniel A. Arber,[1] Attilio Orazi,[2] Robert P. Hasserjian,[3] Michael J. Borowitz,[4] Katherine R. Calvo,[5] Hans-Michael Kvasnicka,[6] Sa A. Wang,[7] Adam Bagg,[8] Tiziano Barbui,[9] Susan Branford,[10] Carlos E. Bueso-Ramos,[7] Jorge E. Cortes,[11] Paola Dal Cin,[12] Courtney D. DiNardo,[7] Hervé Dombret,[13] Eric J. Duncavage,[14] Benjamin L. Ebert,[15] Elihu H. Estey,[16] Fabio Facchetti,[17] Kathryn Foucar,[18] Naseema Gangat,[19] Umberto Gianelli,[20] Lucy A. Godley,[1] Nicola Gökbuget,[21] Jason Gotlib,[22] Eva Hellström-Lindberg,[23] Gabriela S. Hobbs,[3] Ronald Hoffman,[24] Elias J. Jabbour,[7] Jean-Jacques Kiladjian,[13] Richard A. Larson,[1] Michelle M. Le Beau,[1] Mignon L.-C. Loh,[25] Bob Löwenberg,[26] Elizabeth Macintyre,[27] Luca Malcovati,[28] Charles G. Mullighan,[29] Charlotte Niemeyer,[30] Olatoyosi M. Odenike,[1] Seishi Ogawa,[31] Alberto Orfao,[32] Elli Papaemmanuil,[33] Francesco Passamonti,[28] Kimmo Porkka,[34] Ching-Hon Pui,[29] Jerald P. Radich,[35] Andreas Reiter,[36] Maria Rozman,[37] Martina Rudelius,[38] Michael R. Savona,[39] Charles A. Schiffer,[40] Annette Schmitt-Graeff,[41] Akiko Shimamura,[15,42] Jorge Sierra,[43] Wendy A. Stock,[1] Richard M. Stone,[15] Martin S. Tallman,[44] Jürgen Thiele,[45] Hwei-Fang Tien,[46] Alexandar Tzankov,[47] Alessandro M. Vannucchi,[48] Paresh Vyas,[49] Andrew H. Wei,[50] Olga K. Weinberg,[51] Agnieszka Wierzbowska,[52] Mario Cazzola,[28] Hartmut Döhner,[53] and Ayalew Tefferi[19]

Arber D, et al. Blood. 2022 Sep 15;140(11):1200-1228.

In its final version, further details published in series in Virchows Archiv, and a textbook to be published in early 2024

REVIEW ARTICLE OPEN

Check for updates

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

Joseph D. Khoury[1], Eric Solary[2], Oussama Abla[3], Yassmine Akkari[4], Rita Alaggio[5], Jane F. Apperley[6], Rafael Bejar[7], Emilio Berti[8], Lambert Busque[9], John K. C. Chan[10], Weina Chen[11], Xueyan Chen[12], Wee-Joo Chng[13], John K. Choi[14], Isabel Colmenero[15], Sarah E. Coupland[16], Nicholas C. P. Cross[17], Daphne De Jong[18], M. Tarek Elghetany[19], Emiko Takahashi[20], Jean-Francois Emile[21], Judith Ferry[22], Linda Fogelstrand[23], Michaela Fontenay[24], Ulrich Germing[25], Sumeet Gujral[26], Torsten Haferlach[27], Claire Harrison[28], Jennelle C. Hodge[29], Shimin Hu[1], Joop H. Jansen[30], Rashmi Kanagal-Shamanna[1], Hagop M. Kantarjian[31], Christian P. Kratz[32], Xiao-Qiu Li[33], Megan S. Lim[34], Keith Loeb[35], Sanam Loghavi[1], Andrea Marcogliese[19], Soheil Meshinchi[36], Phillip Michaels[37], Kikkeri N. Naresh[35], Yasodha Natkunam[38], Reza Nejati[39], German Ott[40], Eric Padron[41], Keyur P. Patel[1], Nikhil Patkar[42], Jennifer Picarsic[43], Uwe Platzbecker[44], Irene Roberts[45], Anna Schuh[46], William Sewell[47], Reiner Siebert[48], Prashant Tembhare[42], Jeffrey Tyner[49], Srdan Verstovsek[31], Wei Wang[1], Brent Wood[50], Wenbin Xiao[51], Cecilia Yeung[35] and Andreas Hochhaus[52]

Khoury JD, et al. Leukemia. 2022;36(7):1703-1719.

Currently beta version, to be published as WHO Blue Book in early 2024

# International Consensus Classification (ICC) - Major changes

**AML and related neoplams**

**AML with recurrent genetic abnormalities (requiring ≥10% blasts in BM or PB)**

- APL w
- AML w
- AML w
- AML w
- AML w
- AML w
- AML wi
- AML with mutated *NPM1*
- **AML with in-frame bZIP mutated *CEBPA*[c]**
- AML with t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*[a]

- ICC 2022 **sets blast cutoff at ≥10%** for most AML types with defining genetic alterations and **introduced MDS/AML** category with **10%-19% blast** cutoff for the other categories

- WHO 2022 **eliminates blast cutoffs** for most AML types with defining genetic alterations (except *CEBPA* mutations) but retains **20% blast** cutoff to **delineate MDS from AML**
- ***CEBPA*:** biallelic or single mutations in bZIP

**Categories designated AML (if ≥20% blasts in BM or PB) or MDS/AML (if 10-19% blasts)**

- AML with mutated *TP53*[d]
- AML with myelodysplasia-related gene mutations
  Defined by mutations in *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*
- AML with myelodysplasia-related cytogenetic abnormalities[e]
- AML not otherwise specified

Myeloid proliferations related to Down syndrome

The WHO 2022 adds "post cytotoxic therapy" and "associated with germline variant" as qualifiers

Blastic plasmacytoid dendritic cell neoplasm

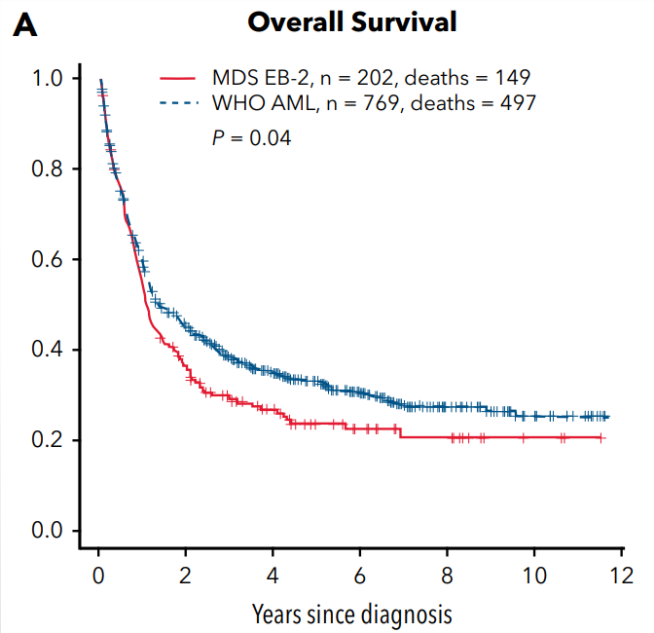
**Diagnostic qualifiers**

Therapy-related; progression from MDS; progression from MDS/MPN; germline predisposition (specify type)

[a] Bone marrow or peripheral blood blast count of ≥10% required, except for AML with t(9;22)(q34.1;q11.2); *BCR*::*ABL1*.
[b] Variant rearrangements involving *RARA*, *KMT2A*, or *MECOM* should be recorded accordingly.
[c] AML with in-frame mutation in the bZIP domain of the CEBPA gene, either monoallelic or biallelic.
[d] The presence of a pathogenic somatic *TP53* mutation (at a variant allele fraction of at least 10%, with or without loss of the wild-type TP53 allele) defines the entity AML with mutated *TP53*.
[e] Cytogenetic abnormalities sufficient for the diagnosis of AML with MDS-related cytogenetic abnormalities and the absence of other AML-defining disease categories.
- Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities.
- Unbalanced clonal 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)

Arber D, et al. Blood. 2022 Sep 15;140(11):1200-1228.

# Distinguishing AML from MDS: a fixed blast percentage may no longer be optimal



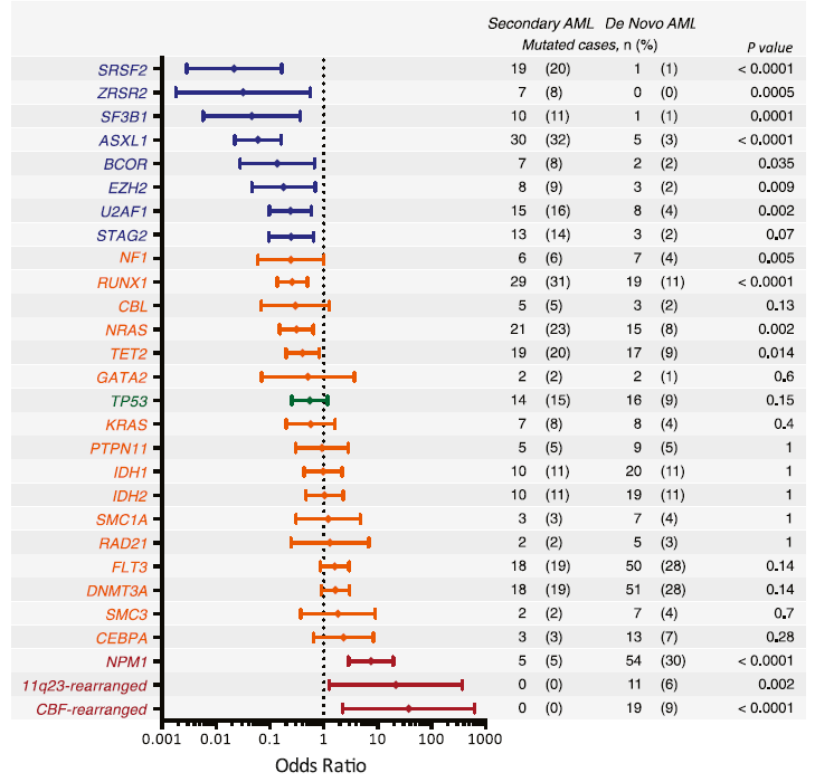

Multivariable Model

| Variable | OS HR (95% CI) | EFS HR (95% CI) | CR or CRi OR (95% CI) | RFS if CR/CRi HR (95%CI) |
|---|---|---|---|---|
| WHO AML (ref MDS-EB2) | 0.89 (0.74-1.07) | 0.89 (0.75-1.06) | 1.06 (0.99-1.13) | 0.66 (0.53-0.83) |
| *P* | .21 | .2 | .11 | <.001 |
| Age (per 10 y) | 1.3 (1.22-1.38) | 1.19 (1.13-1.26) | 0.98 (0.96-1) | 1.13 (1.05-1.2) |
| *P* | <.001 | <.001 | .02 | <.001 |
| PS 2-4 (ref PS 0-1) | 2 (1.68-2.37) | 1.68 (1.42-1.99) | 0.87 (0.82-0.93) | 1.21 (0.96-1.51) |
| *P* | <.001 | <.001 | <.001 | .11 |
| ELN 2017 intermediate risk (ref favorable risk) | 1.7 (1.34-2.15) | 1.72 (1.38-2.14) | 0.86 (0.8-0.93) | 2.15 (1.67-2.76) |
| *P* | <.001 | <.001 | <.001 | <.001 |
| ELN 2017 adverse risk (ref favorable risk) | 2.28 (1.8-2.88) | 2.29 (1.84-2.85) | 0.78 (0.73-0.84) | 3.07 (2.35-4) |
| *P* | <.001 | <.001 | <.001 | <.001 |
| Secondary (ref de novo) | 1.3 (1.1-1.55) *P* = 0.002 | 1.28 (1.08-1.5) *P* = 0.004 | 0.93 (0.87-0.99) *P* = 0.02 | 1.16 (0.93-1.43) *P* = 0.18 |
| *P* | .002 | .004 | .02 | .18 |
| Low-intensity induction (ref high intensity) | 1.3 (1.08-1.55) | 1.62 (1.36-1.93) | 0.7 (0.66-0.75) | 1.07 (0.82-1.38) |
| *P* | .004 | <.001 | <.001 | .63 |
| Allogeneic HCT (ref no allogeneic HCT) | 0.48 (0.39-0.6) | 0.39 (0.31-0.47) | Not applicable | 0.29 (0.23-0.36) |
| *P* | <.001 | <.001 | | <.001 |

- After accounting for age, performance status, genetic risk, and allogeneic HCT, patients with MDS-EB2 and AML have similar rates of survival and response to therapy, challenging the arbitrary 20% blast threshold
- Cases with 10-19% blasts lie on the border between MDS and AML in terms of their prognosis, but also their biology

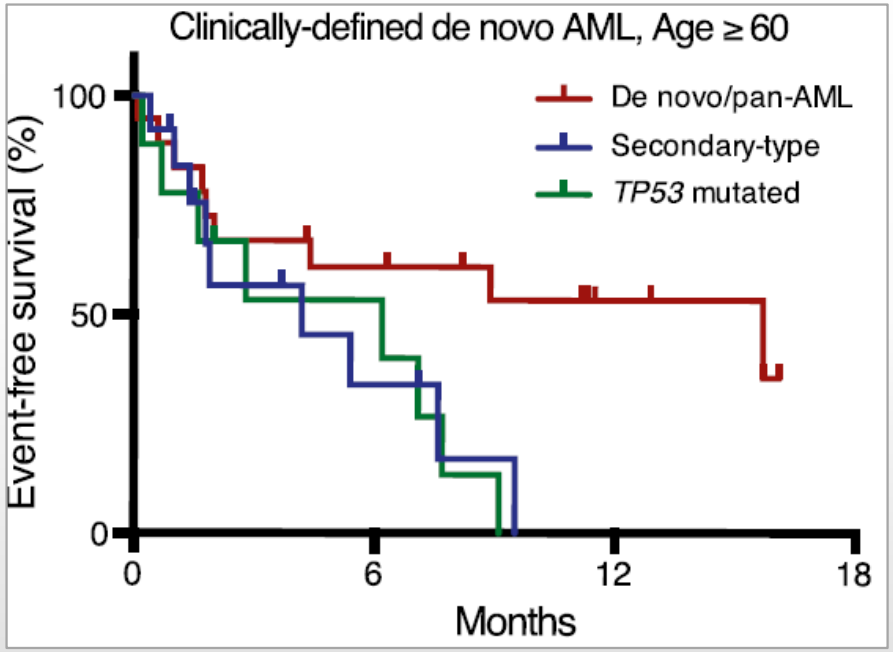
Estey E, Hasserjian RP, Döhner H. Blood. 2022;139(3):323-332.

# Antecedent AML history: genetic basis for secondary AML




- Comparison of the mutational profile of 93 clinically defined secondary AML (ACCEDE trial) with 180 *de novo* AML from the Cancer Genome Atlas
- Identification of a gene mutation signature characterized by mutations in *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *ASXL1*, *EZH2*, *BCOR*, or *STAG2* genes that was highly specific for the diagnosis of secondary AML

**Validation of the signature in 105 unselected AML (Dana-Farber Cancer Institute)**

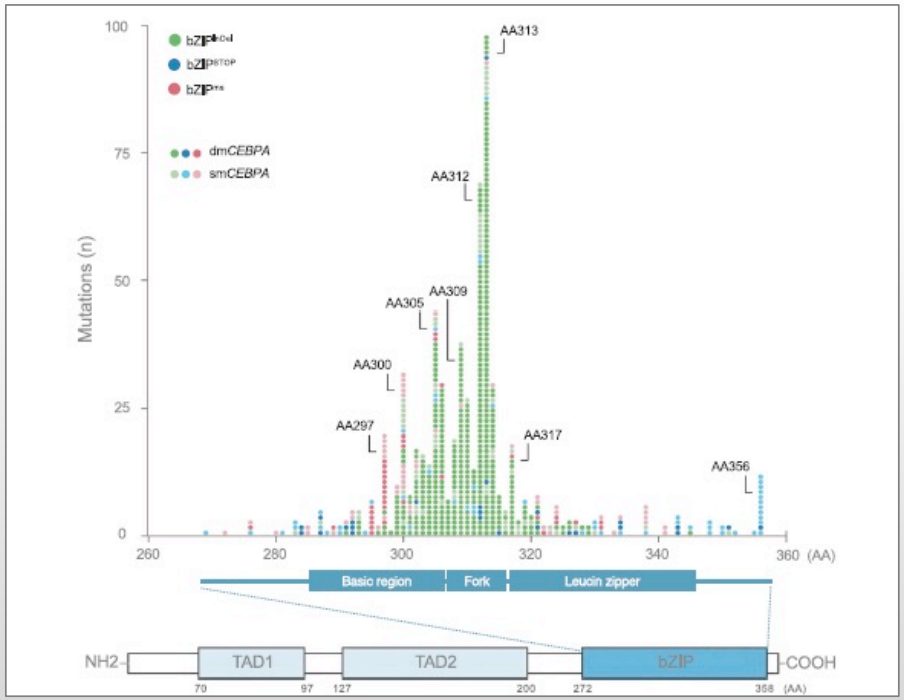



- In elderly clinically-defined *de novo* AML, 33% of patients had this secondary AML-type mutation signature, and these patients shared clinicopathologic characteristics with clinically confirmed secondary AML, and had worse clinical outcome

Lindsley RC, et al. Blood. 2015;125(9):1367–1376.

# Prognostic impact of *CEBPA* mutational subgroups

| Subgroup | dmCEBPA bZIP$^{InDel}$ | dmCEBPA bZIP$^{STOP}$ | dmCEBPA bZIP$^{ms}$ | dmCEBPA TAD | smCEBPA bZIP$^{InDel}$ | smCEBPA bZIP$^{STOP}$ | smCEBPA bZIP$^{ms}$ | smCEBPA TAD |
|---|---|---|---|---|---|---|---|---|
| | Group1 n=435 | Group n=26 | Group3 n=35 | Group4 n=60 | Group5 n=66 | Group6 n=55 | Group7 n=54 | Group n=289 |




- Significant differences in outcome and molecular profile in pts with in-frame *CEBPA* bZIP mutations and pts with frameshift or nonsense mutations

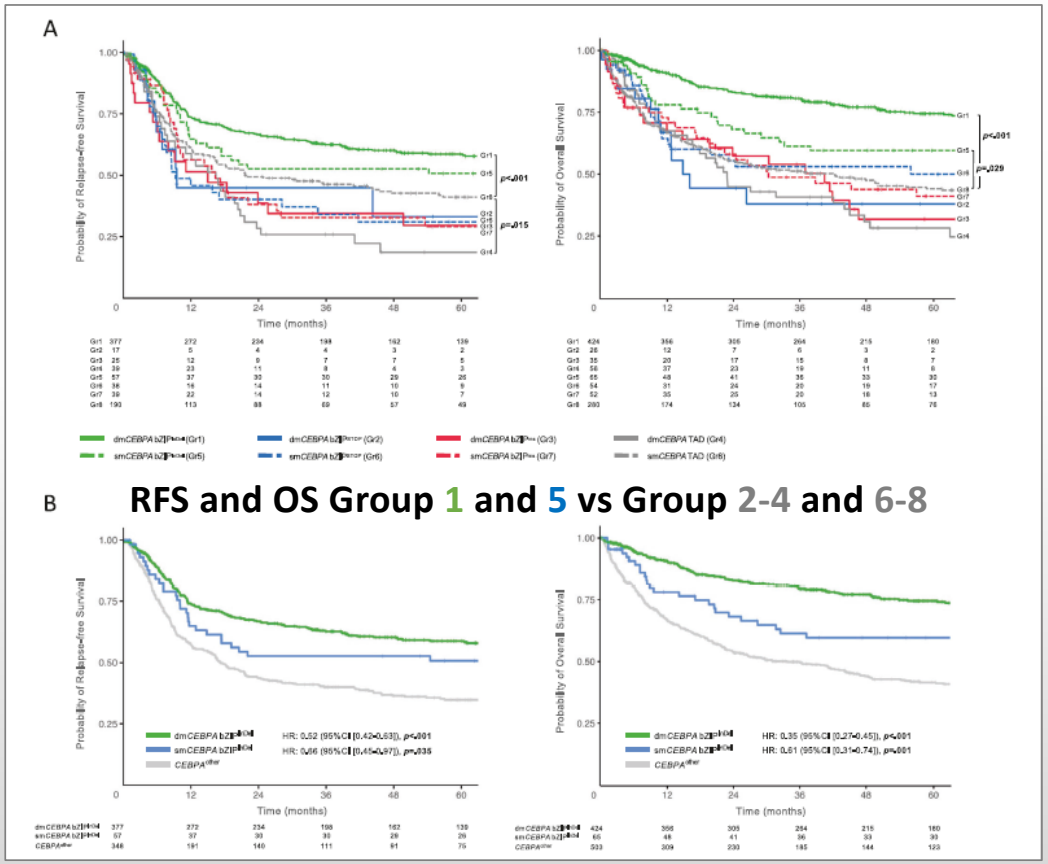
Taube F, et al. Blood. 2022;139(1):87-103.

- Further insights on the impact of different *CEBPA* mutation subtypes, in particular *CEBPA* bZIP mutations
- Meta-analysis of 1010 adult AML pts from 6 European AML study groups/registries
- Definition of 8 subgroups considering type and allelic status of the mutation
- Correlation with clinical characteristics, molecular data, and outcome

Georgi JA, et al. Leukemia. 2024 Feb;38(2):281-290.

# Prognostic impact of *CEBPA* mutational subgroups

**RFS and OS Group 1-8**




- Pts with bZIP$^{InDel}$ in-frame mutations were significantly younger, had a higher prevalence of de novo AML and a specific co-mutational pattern
- Co-mutations (e.g. *GATA2, FLT3, WT1*) in bZIP$^{InDel}$ pts had no impact on OS whereas in non-bZIP$^{InDel}$ pts grouping according to ELN 2022 added prognostic information
- Only pts with bZIP$^{InDel}$ in-frame mutations had significantly higher CR rates and longer RFS and OS compared to all other mutational subgroups

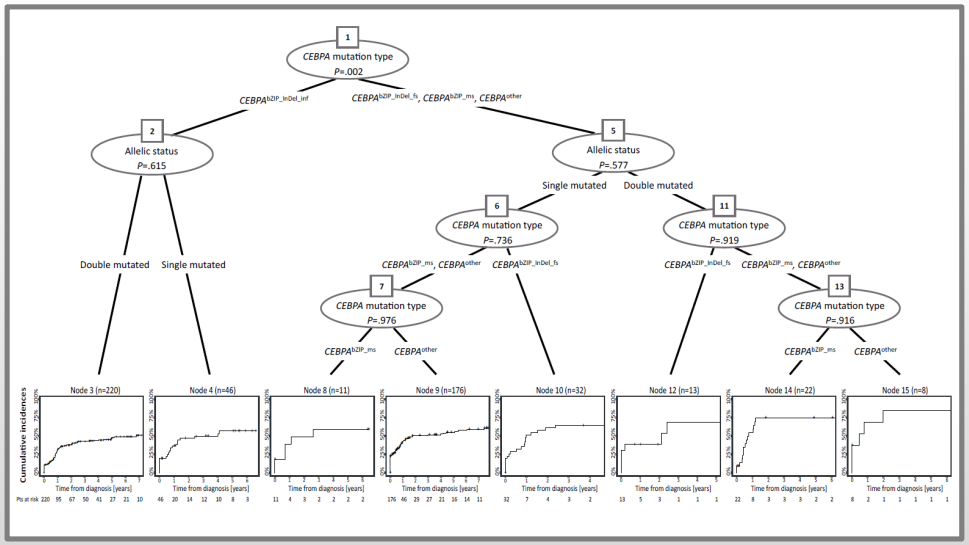
- ➢ *CEBPA* bZIP$^{InDel}$ in-frame mutations represent a subset of AML with distinct disease biology and clinical outcomes
- ➢ Further refinement of *CEBPA* bZIP mutations as listed in the current WHO, ICC and ELN

Georgi JA, et al. Leukemia. 2024 Feb;38(2):281-290.

# Refinement of the prognostic impact of *CEBPA* bZIP mutations in AML: Results of the AML Study Group (AMLSG)

| Subgroup | dmCEBPA bZIP$^{InDel}$ | dmCEBPA bZIP$^{InDel-fs}$ | dmCEBPA bZIP$^{ms}$ | dmCEBPA$^{other}$ | smCEBPA bZIP$^{InDel}$ | smCEBPA bZIP$^{InDel-fs}$ | smCEBPA bZIP$^{ms}$ | smCEBPA$^{other}$ |
|---|---|---|---|---|---|---|---|---|
| | Group1 n=220 | Group n=13 | Group3 n=22 | Group4 n=8 | Group5 n=46 | Group6 n=32 | Group7 n=11 | Group 8 n=176 |

Conditional interference tree model on EFS and OS

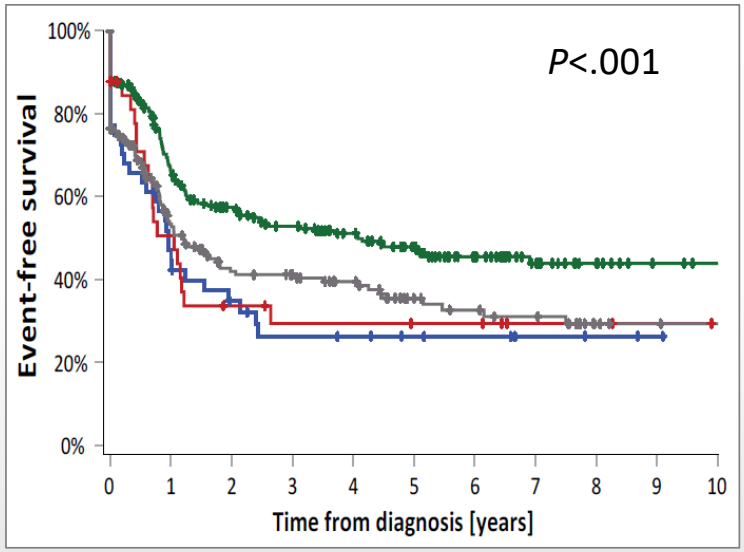



- To evaluate the prognostic impact of *CEBPA* bZIP in-frame mutations, 528 intensively treated adult *CEBPA*$^{mut}$ AML patients were analyzed
- Median follow-up time: 55.5 months
- Patients were categorized in eight subgroups based on allelic status and mutation type
- Conditional interference tree models for EFS and OS separated *CEBPA* bZIP$^{InDel}$ in-frame mutated pts from bZIP$^{InDel-fs,}$ bZIP$^{ms}$ and *CEBPA*$^{other}$

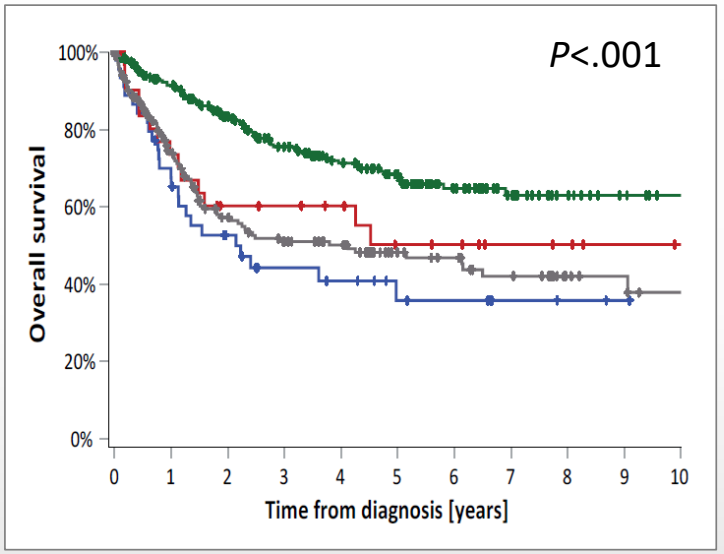
Rücker F,…….Döhner K, in preparation

# Refinement of the prognostic impact of *CEBPA* bZIP mutations in AML: Results of the AML Study Group (AMLSG)

Event-free survival




Overall survival




- EFS: 49.8 months for ***CEBPA* bZIP$^{InDel}$** vs 11.5 for ***CEBPA* bZIP$^{InDel\text{-}fs}$** vs 12.6 for ***CEBPA* bZIP$^{ms}$** vs 14.6 for ***CEBPA*$^{other}$**
- OS: NA for ***CEBPA* bZIP$^{InDel}$** vs 25.7 months for ***CEBPA* bZIP$^{InDel\text{-}fs}$** vs 54.3 for ***CEBPA* bZIP$^{ms}$** vs 45.5 for ***CEBPA*$^{other}$**
- Beneficial effect of bZIP is restricted to bZIP$^{InDel}$ in-frame mutations, irrespective of the allelic status
- Further refinement of *CEBPA*$^{mut}$ AML within the current ICC and WHO classifications as well as for ELN risk-stratification

Rücker F,…….Döhner K, in preparation

# The new ICC impacts the initial genetic work-up

| Genetic test | |
|---|---|
| **Cytogenetics**[a] | *Results preferably obtained within 5-7 d* |
| **Screening for gene mutations including (to establish diagnosis)**<br>• *FLT3*,[b] *IDH1*, *IDH2 (actionable therapeutic targets)*<br>• *NPM1*<br>• *CEBPA*,[c] *DDX41*, *TP53; ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, *ZRSR2* | *within 3-5 d*<br>*within 1st treatment cycle* |
| **Screening for gene rearrangements**[d]<br>*PML*::*RARA*, *CBFB*::*MYH11*, *RUNX1*::*RUNX1T1*, *KMT2A*-R, *BCR*::*ABL1*, other fusion genes (if available) | *within 3-5 d* |

| | |
|---|---|
| **Additional genes recommended to test at diagnosis**<br>*ANKRD26*, *BCORL1*, *BRAF*, *CBL*, *CSF3R*, *DNMT3A*, *ETV6*, *GATA2*, *JAK2*, *KIT*, *KRAS*, *NRAS*, *NF1*, *PHF6*, *PPM1D*, *PTPN11*, *RAD21*, *SETBP1*, *TET2*, *WT1* | *Information can be used to monitor the disease by NGS-based MRD analyses (except mutations consistent with pre-malignant clonal hematopoiesis)* |

[a] In case of no analyzable metaphases, fluorescence in-situ hybridization is an alternative method to detect genetic abnormalities like *RUNX1*::*RUNX1T1*, *CBFB*::*MYH11*, *KMT2A*::R, and *MECOM*::R, or myelodysplasia-related chromosome abnormalities, eg, loss of chromosome 5q, 7q, or 17p material.

[b] *FLT3* mutational screening should include the analysis of internal tandem duplications (ITD) and of tyrosine kinase domain (TKD) mutations.

[c] The report should specify type of mutation: 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.

[d] Screening for gene rearrangements should be performed if rapid information is needed for recommendation of suitable therapy, if chromosome morphology is of poor quality, or if there is typical morphology but the suspected cytogenetic abnormality is not present.

Döhner H, et al. Blood. 2022 Sep 22;140(12):1345-1377.

# AMLSG: Algorithm of central diagnostics and trial portfolio*

## Central Diagnostics

**Molecular screening**

- *FLT3*
- *IDH1/2*
- *NPM1*
- *PML-RARA*
- *RUNX1-RUNX1T1*
- *CBFB-MYH11*
- *MLLT3-KMT2A*
- *BCR-ABL1*
- *CEBPA*

within 24-48 hrs

- *DDX41, TP53; ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, ZRSR2*

within 1st cycle

**Cytogenetics** within 5-7 days

**MFC (LAIP)**

AMLSG-BiO Registry [NCT01252485]

## Genotype

## Clinical Trial

| Genotype | Clinical Trial | |
|---|---|---|
| *PML-RARA* (high-risk) | APOLLO +/- ATO-ATRA-Ida | ✓ |
| Core-binding factor AML | AMLSG 21-13 (n=203) ‚3+7' +/- Dasatinib | ✓ |
| AML with *NPM1* mutations | AMLSG 09-09 (n=588) ‚3+7' + ATRA +/- GO | ✓ |
| AML with *FLT3* mutations | AMLSG 16-10 (n=440) ‚3+7' + Midostaurin | ✓ |
| | HOVON 156/ AMLSG 28-18 ‚3+7' + Mido. vs Gilt. | ✓ |
| AML with *IDH1/IDH2* mutations | HOVON 150/ AMLSG 29-18 ‚3+7' +/- Ena. / Ivo. | ● |
| AML – ELN intermediate-/high-risk | AMLSG 30-18 ‚3+7' vs CPX-351 | ● |
| AML | AMLSG 31-19/HOVON 501 ‚3+7' +/- Venetoclax | ● |

✓ Completed ● Active

STUDY AML GROUP

* Intensive first-line trials only; trial portfolio for older, unfit patients currently in progress
≥18 years, eligible for intensive chemotherapy

# 2022 ELN genetic risk classification

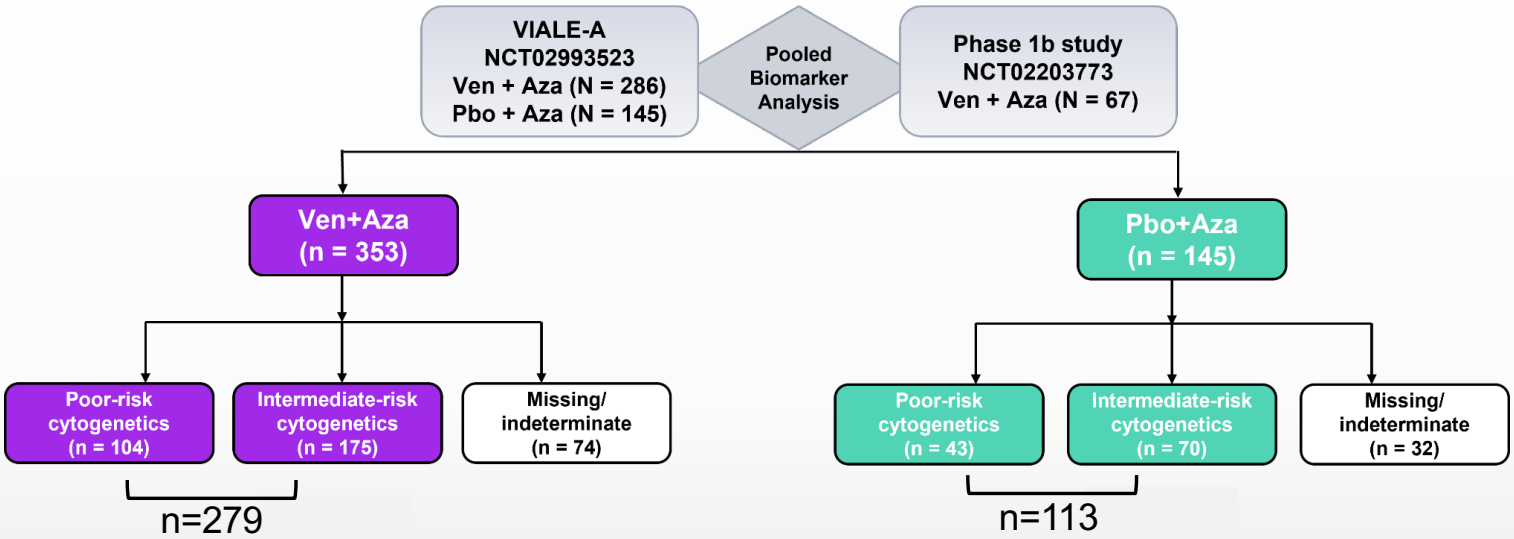
| Risk category | Genetic abnormality |
|---|---|
| **Favorable** | • t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*<br>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*<br>• Mutated *NPM1* without *FLT3*-ITD<br>• bZIP in-frame mutated *CEBPA* |
| **Intermediate** | • Mutated *NPM1*[a] with *FLT3*-ITD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

*Note*:

- Initial risk assignment may change during the treatment course based on the results from MRD analyses
- The ELN AML risk classification has been developed based on data from intensively treated patients and it does not apply to patients receiving less intensive therapies

Döhner H, et al. Blood. 2022 Sep 22;140(12):1345-1377.

# Pooled analysis of chemotherapy-ineligible patients in the phase 3 (VIALE-A) and the phase 1b study




**Objectives:**

- To apply the ELN 2017 and 2022 risk categories to patients receiving Ven+Aza vs Aza monotherapy
- To develop a prognostic genetic signature from the data itself

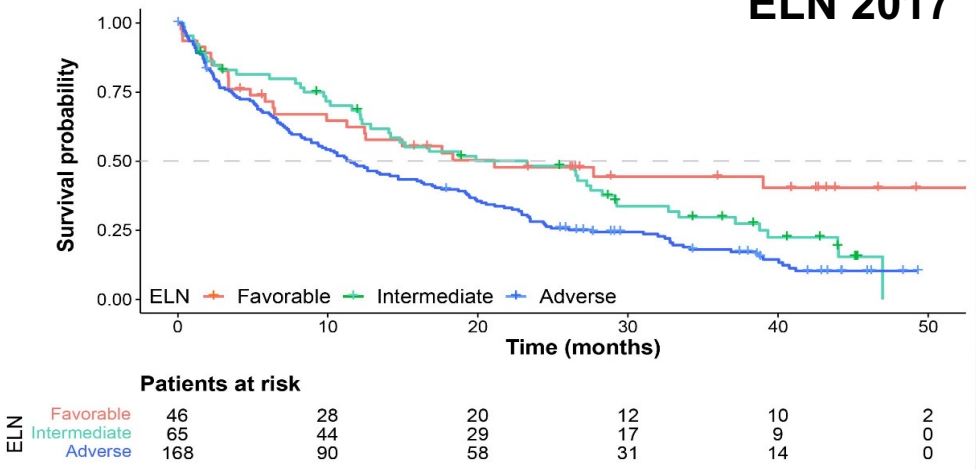
**Analysis of genetic features:**

- Cytogenetics analyzed locally and categorized per NCCN criteria
- Mutations analyzed from BM aspirate at baseline using the MyAML assay (194 genes; central lab)

Data cut-off: VIALE-A, 01 Dec 2021; Phase 1b, 19 Jul 2019; Median follow-up duration for patients included in the pooled analysis was 42.7 months (40.8-44.2);
Abbreviations: Aza, azacitidine; BM, bone marrow; ELN, European LeukemiaNet; Pbo, placebo; NCCN, National Comprehensive Cancer Network; Ven, venetoclax (400 mg)

# ELN risk groups do not provide clinically meaningful outcome stratification for patients treated with Ven+Aza

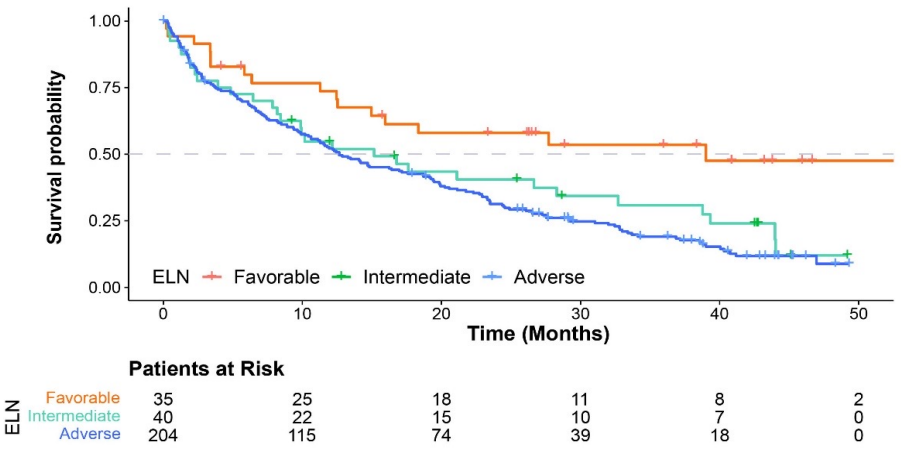
## ELN 2017




| ELN 2017 | n | Events | Median OS, mo (95% CI) |
|---|---|---|---|
| Favorable | 46 | 25 | 21.09 (9.92 – NE) |
| Intermediate | 65 | 48 | 23.26 (12.85 – 28.29) |
| Adverse | 168 | 141 | 11.53 (8.87 – 16.23) |

- Overlapping outcomes to Ven+Aza for favorable and intermediate-risk patients

## ELN 2022




| ELN 2022 | n | Events | Median OS, mo (95% CI) |
|---|---|---|---|
| Favorable | 35 | 16 | 39.0 (12.52 – NE) |
| Intermediate | 40 | 30 | 15.15 (8.18 – 28.29) |
| Adverse | 204 | 168 | 12.65 (10.41 – 17.15) |

- Overlapping outcomes to Ven+Aza for intermediate and adverse-risk pts;
- A small population of favorable-risk pts, primarily with *NPM1* mutations, show prolonged mOS of 39 months

Abbreviations: Aza, azacitidine; CI, confidence interval; ELN, European LeukemiaNet; HR, hazard ratio; mo, months; Pbo, placebo; NCCN, National Comprehensive Cancer Network; Ven, venetoclax

# To develop a prognostic genetic signature for response to VEN + AZA treatment

## Objective

Divide patients treated with Ven+Aza into three distinct groups based on OS, and then determine how these groups differ with respect to baseline cytogenetic/molecular data

## Approach

**Sequential-BATTing method[1] to derive algorithm**

- Subgroup identification method to define subgroups as distinctive as possible from the remainder of the population.
- Minimize the *P* value of HR between the selected subgroup versus the remainder of the population

**30 genetic markers as candidate predictors**

- Included in the ELN 2022 recommendations and/or
- Genes with prevalence ≥ 10% in the analysis poplation of patients in the Ven+Aza arm

Limitation: 11 of the genetic markers have prevalence < 10% and may be too small to identify a signal

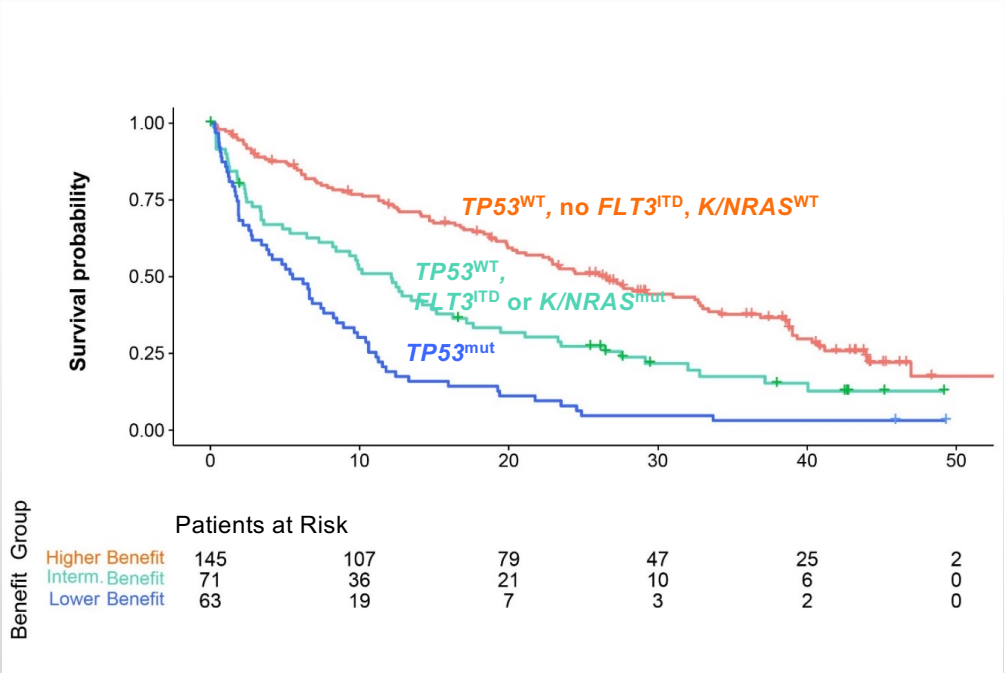
| Cytogenetics | Ven+Aza (N=279) | Prev. (%) |
|---|---|---|
| Com. karyotype | 72 | 25.8 |
| del(5q) | 49 | 17.6 |
| del(7q) | 48 | 17.2 |
| del(17p) | 15 | 5.4 |
| t(v;11q23) | 7 | 2.5 |
| inv(3) | 6 | 2.1 |

| Mol. mutations detected | Ven+Aza (N=279) | Prevalence (%) |
|---|---|---|
| *TET2* | 81 | 29.0 |
| *IDH1/2* | 77 | 27.6 |
| *DNMT3A* | 72 | 25.8 |
| *RUNX1* | 70 | 25.1 |
| *TP53* | 63 | 22.6 |
| *SRSF2* | 62 | 22.2 |
| *FLT3*-TKD | 59 | 21.1 |
| *IDH2* | 47 | 16.8 |
| *NPM1* | 46 | 16.5 |
| *FLT3*-ITD | 43 | 15.4 |
| *N/KRAS* | 42 | 15.0 |
| *ASXL1* | 35 | 12.5 |
| *STAG2* | 34 | 12.2 |
| *IDH1* | 32 | 11.5 |
| *BCOR* | 29 | 10.4 |
| *EZH2* | 16 | 5.7 |
| *SF3B1* | 23 | 8.2 |
| *U2AF1* | 26 | 9.3 |
| *CEBPA* | 13 | 4.7 |
| *ZRSR2* | 6 | 2.1 |
| *CEBPA*-bZip | 4 | 1.4 |

[1]Huang et. al. Stat. Med., 2017; Favorable-risk pts with CBF-AML [inv(16), t(8;21)] were excluded from the trials, except for one patient who was enrolled with poor cytogenetic risk; inv(6) and t(8;21) were included in the thirty genetic markers that were analyzed; Abbreviations: Aza, azacitidine; ELN, European LeukemiaNet; HR, hazard ratio; OS, overall survival; Ven, venetoclax

# Patients receiving Ven+Aza are distinguishable into three efficacy subgroups by OS benefit

- Higher benefit group: ***TP53$^{WT}$*, no *FLT3*-ITD, *K/NRAS$^{WT}$***, median OS > 24 months
- Lower benefit group: ***TP53* mutated,** median OS < 6 months
- Intermediate benefit group: Patients fitting neither criteria (***TP53$^{WT}$* and *FLT3*-ITD or *K/NRAS* mutated)**, median OS 12 months



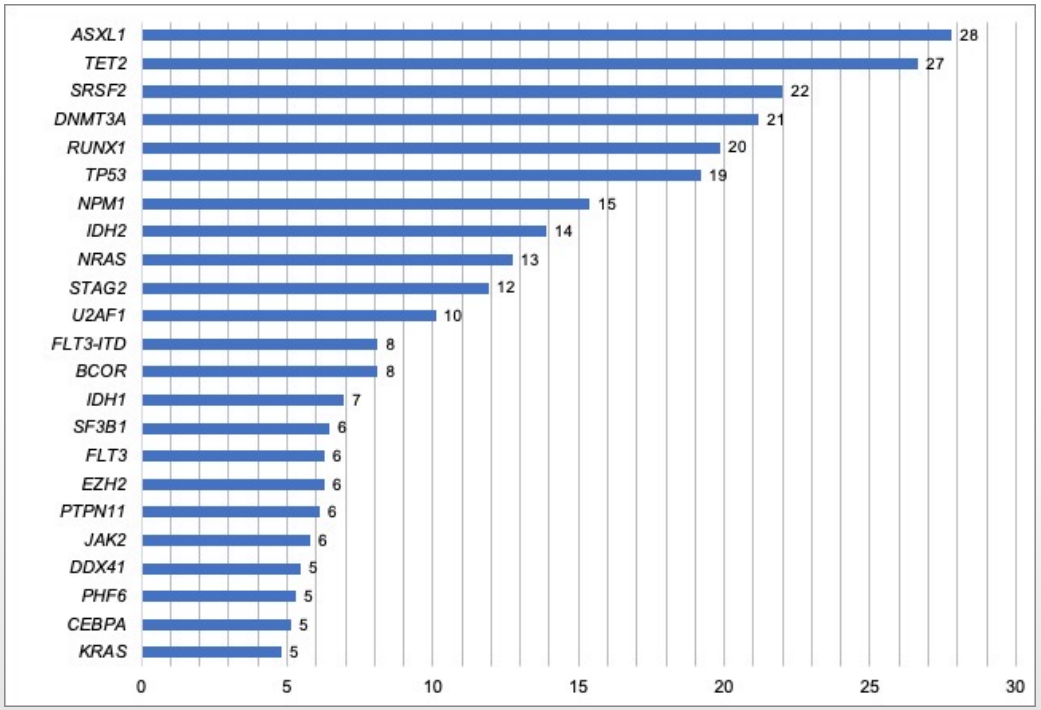

| Ven + Aza (N = 279) | n | Events | Median OS, months (95% CI) |
|---|---|---|---|
| Higher Benefit | 145 | 96 | 26.51 (20.24, 32.69) |
| Intermediate Benefit | 71 | 57 | 12.12 (7.26 – 15.15) |
| Lower Benefit | 63 | 61 | 5.52 (2.79 – 7.59) |

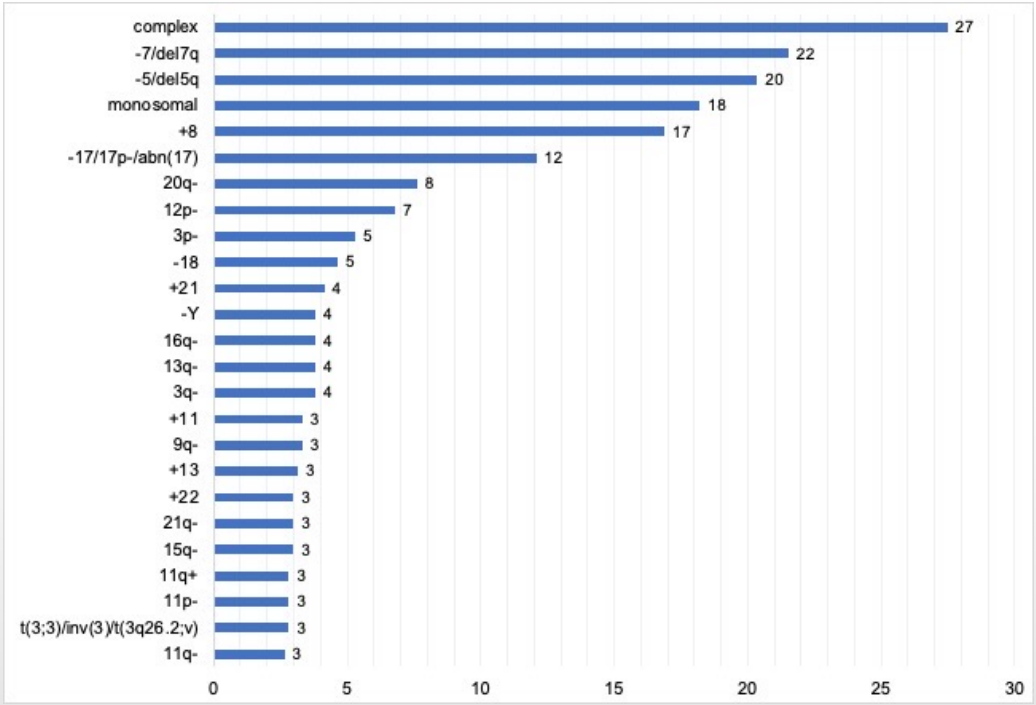
- Majority of patients in the Ven+Aza arm are in the higher benefit group: 52% (145/279)
- The remainder of the patients are distributed equally between the intermediate and lower benefit groups: 25.4% (71/279) and 22.6% (63/279), respectively
- The prognostic signatures of the three groups were derived based on the mutational status of 4 genes only

Döhner H et al., ASH meeting 2022, oral presentation, #602

. 2023 Sep 12;7(17):5027-5037.
. 2023 Sep 12;7(17):5027-5037.

# ASTRAL1- trial: Genomic landscape in older AML patients

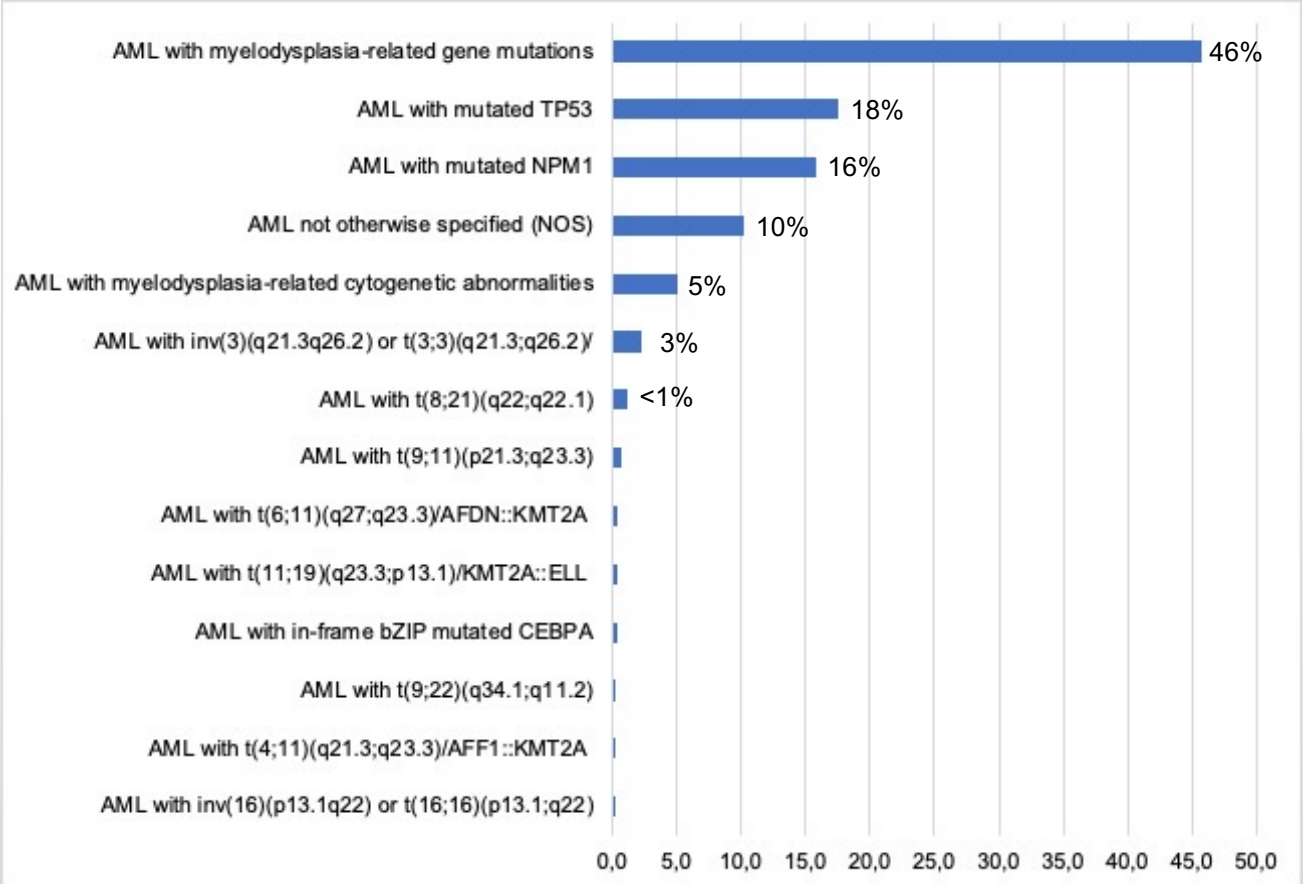



- Targeted DNA sequencing of 263 genes in 604 patients (median age 77 yrs) enrolled in the international ASTRAL-1 trial
- Cytogenetic analysis and/or fluorescence in situ hybridization performed decentrally; data retrieved from electronic case report forms
- Data on CNVs based on conventional cytogenetics complemented by data from methylation EPIC array data analysis performed in 477 patients

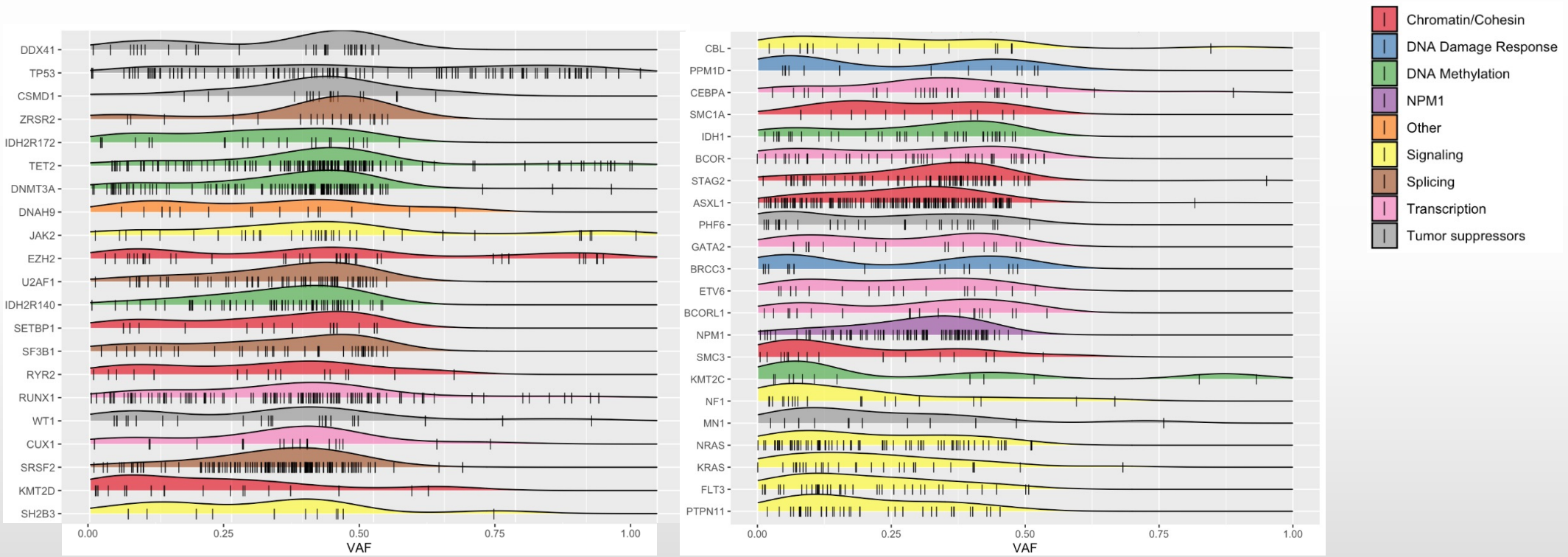
Jahn E, Saadati M, et al. Leukemia. 2023; 37:2336–2337.
Clinical data of ASTRAL-1 trial: Fenaux P, et al. Blood Adv. 2023;17:5027-5037.

# Distribution of AML by the International Consensus Classification




Jahn E, Saadati M, et al. Leukemia. 2023; 37:2336–2337; clinical data of ASTRAL-1 trial: Fenaux P, et al. Blood Adv. 2023;17:5027-5037.

# Temporal acquisition of mutations (Bradley-Terry model)




- Order of temporal acquisition of mutations based on pairwise relationships of variant allele frequencies (VAFs)
- In line with previous reports, genes that have been associated with clonal hematopoiesis of indeterminate potential such as *TP53*, *IDH2*$^{R172}$, *TET2*, *DNMT3A*, and *JAK2* occurred early during leukemogenesis suggesting disease initiating events; of note, *DDX41* mutations also occurred very early
- Mutations in signaling genes such as *NF1*, *NRAS*, *KRAS*, *FLT3*, and *PTPN11* were late events

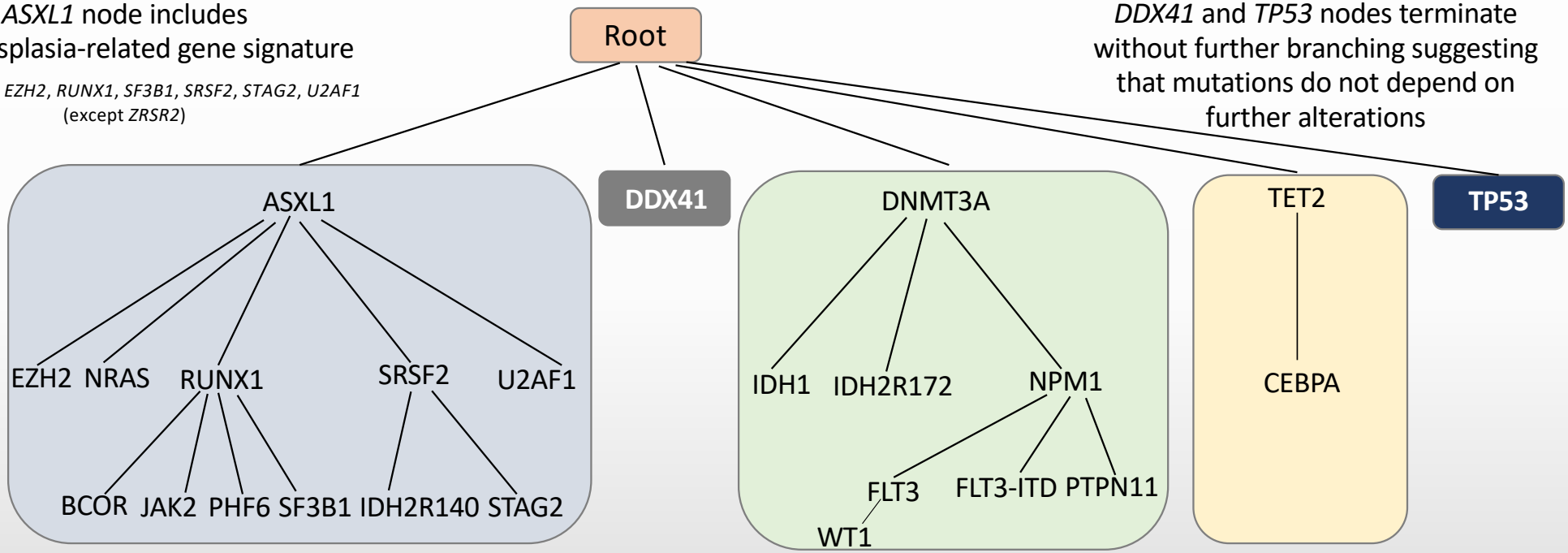
Jahn E, Saadati M, et al. Leukemia. 2023; 37:2336–2337.

# Oncogenic tree model using a modeling algorithm by Szabo

*ASXL1* node includes myelodysplasia-related gene signature

*ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1* (except *ZRSR2*)

*DDX41* and *TP53* nodes terminate without further branching suggesting that mutations do not depend on further alterations

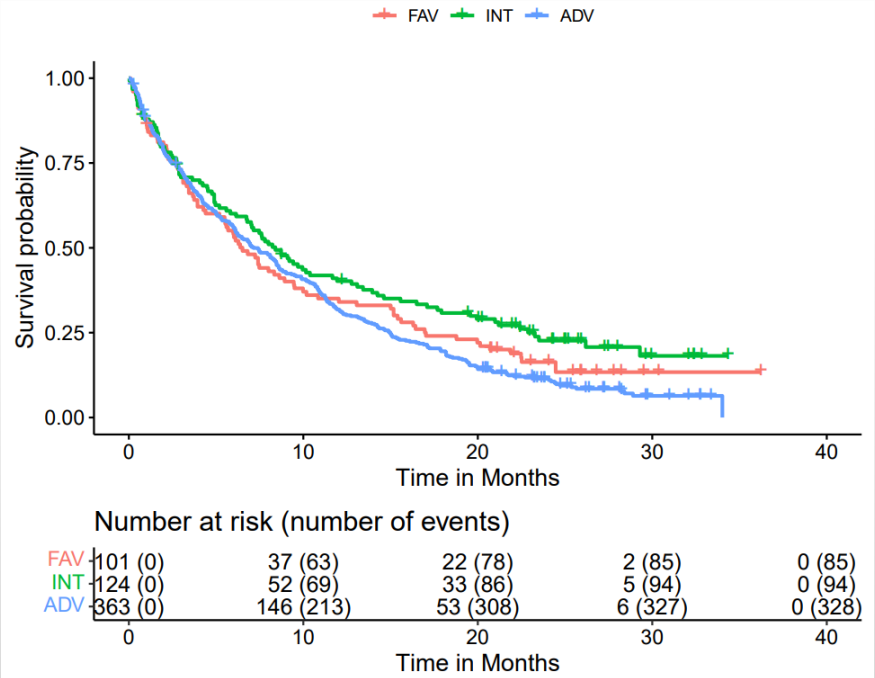



- Each node represents a gene mutation and each branch describes the evolution of different possible pathways of leukemogenesis by inferring the sequence of mutation acquisition
- The algorithm yielded a stable and reproducible oncogenic tree with five main branches with *ASXL1*, *DDX41*, *DNMT3A*, *TET2*, and *TP53* emanating from the root. The data suggests that these mutations represent the initiating events predisposing to additional events with further branches

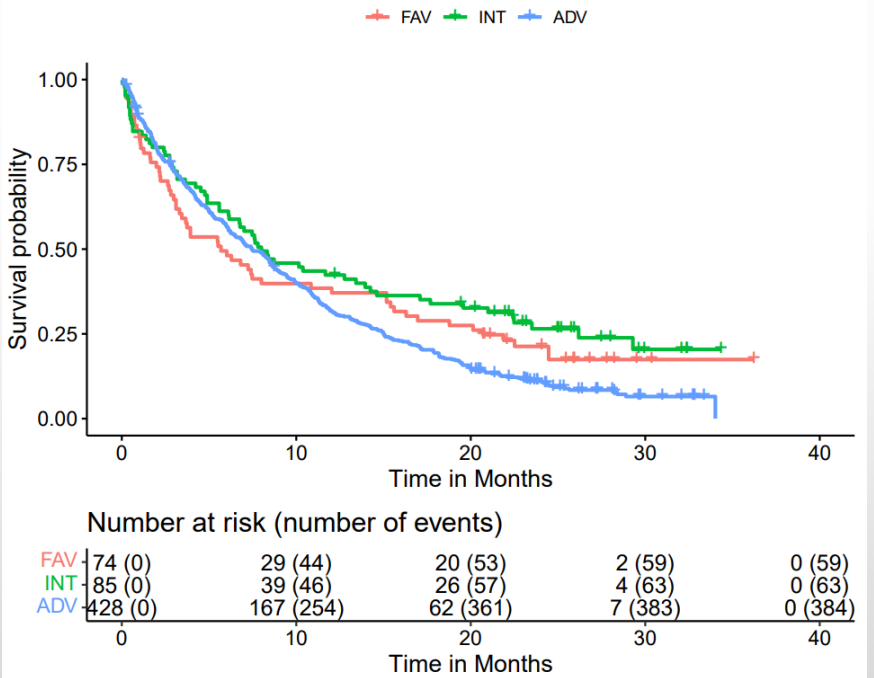
Jahn E, Saadati M, et al. Leukemia. 2023; 37:2336–2337.

# 2017 and 2022 ELN genetic risk classifications do not provide clinically meaningful outcome stratification for older, unfit patients

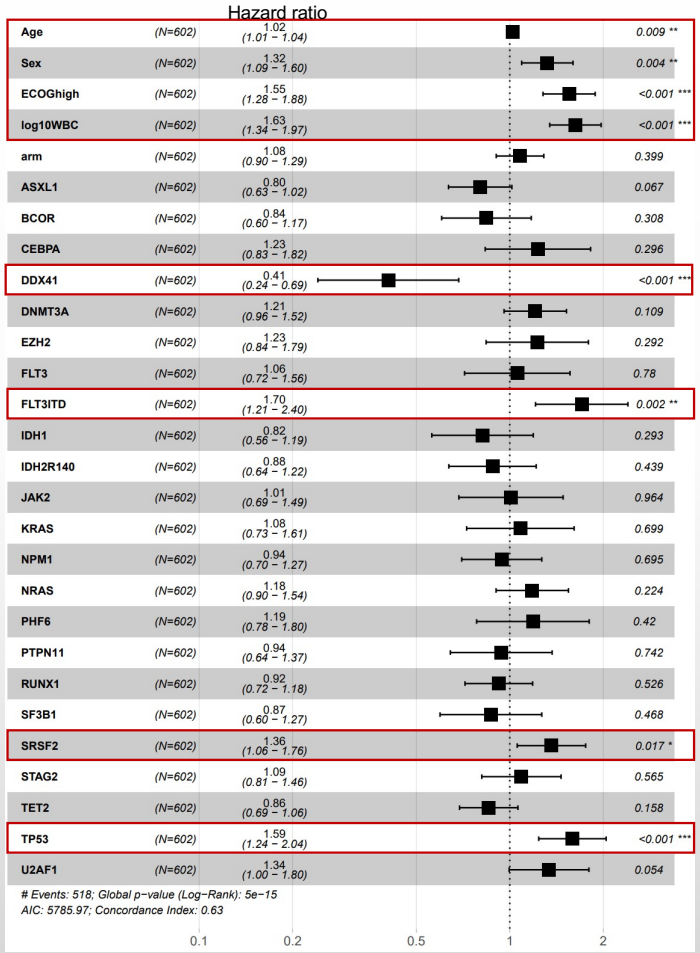
## 2017 ELN



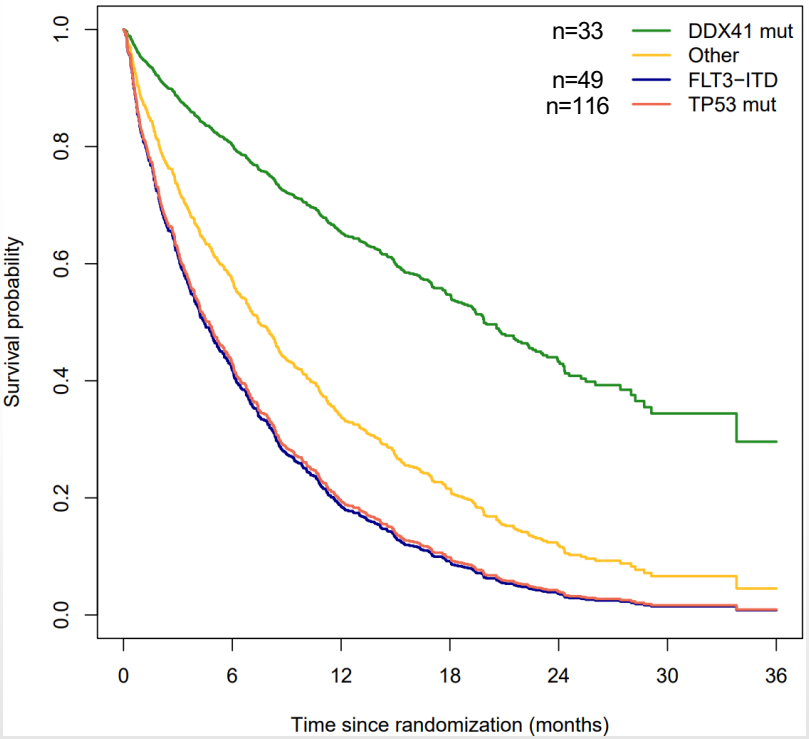

## 2022 ELN



# Genetic risk classification using multivariate Cox models




- Comprehensive model for OS including clinical variables (age, gender, ECOG PS, WBC, treatment arm) and gene mutations (with a frequency ≥4%)




- A backward selection procedure resulted in a reduced model that included only *DDX41* mutations as favorable factor, and *FLT3*-ITD and *TP53* mutations as unfavorable factors – WBC and ECOG PS remained significant clinical variables (fixed at the median [WBC] or mode [ECOG])
- Predicted survival probabilities visualizing the most important prognostic genetic factors

# Summary

- There have been major advances in our understanding of AML, including
  - new knowledge about the genomic landscape of AML, leading to an update of the disease classification, a refined risk classification, and the identification of predictive factors
  - technological progress in genomic diagnostics and assessment of measurable residual disease
- Data on the mutational landscape and its clinical significance in older patients ineligible for intensive therapies are emerging
- Recent advances are reflected in the new International Consensus Classification of AML, as well as in the 2022 ELN recommendations

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SFB 1074

SFB 1074 Experimental Models and Clinical Translation in Leukemia

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