



**Weill Cornell Medicine**

**NewYork-Presbyterian**

**Deciphering DNA in AML:  
How do molecular data influence the  
choice of first- and second-line treatment?**

SOHO Brazil  
May 8, 2025

**Gail J. Roboz, M.D.**

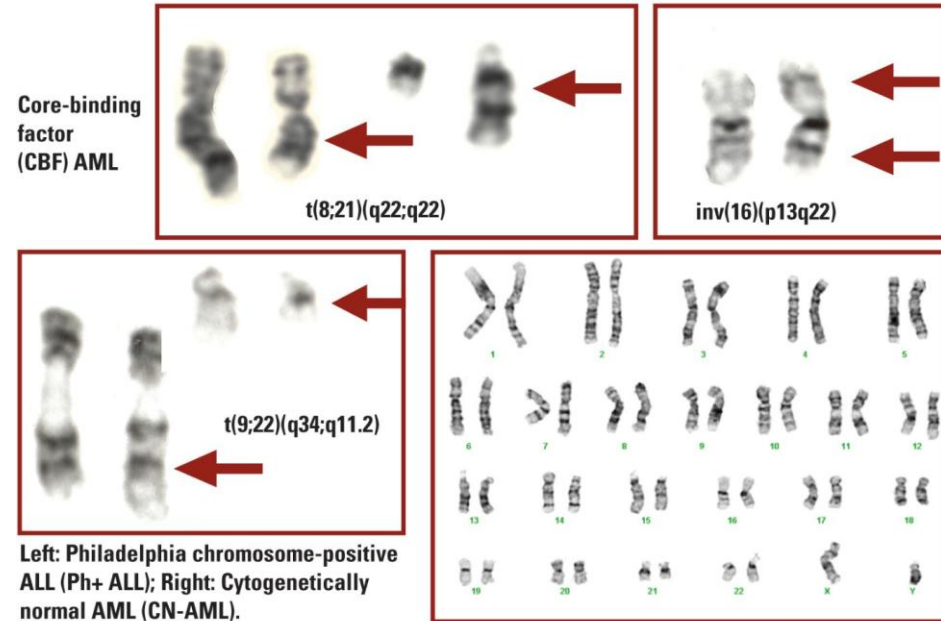
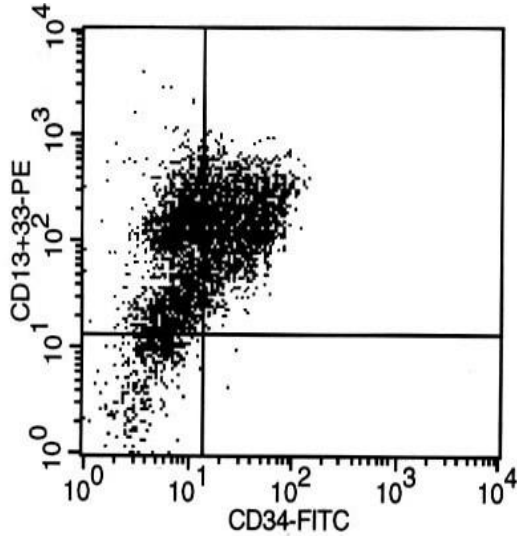
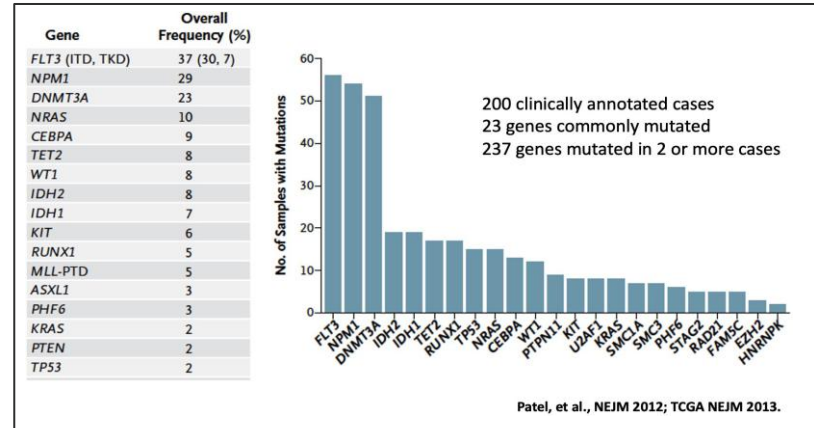
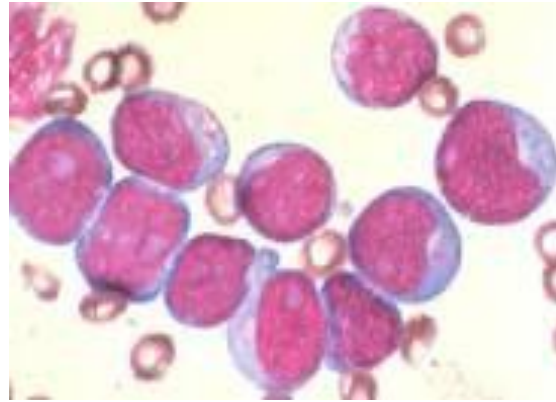
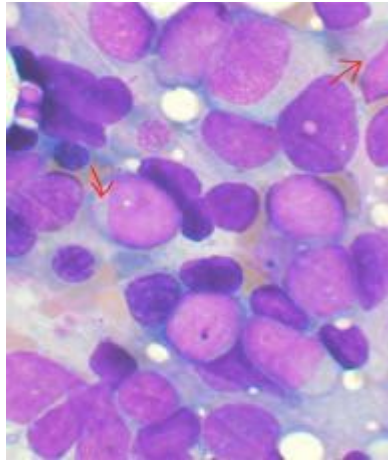
William S. Paley Professor of Medicine

Director, Clinical and Translational Leukemia Programs

# DISCLOSURES OF COMMERCIAL SUPPORT

Consultancy – AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, GlaxoSmithKline, Geron, Glycomimetics, Janssen, Jasper Pharmaceuticals, Jazz Pharmaceuticals, Molecular Partners, Morphosys, Novartis, Oncoprecision, Oncoverity, Pfizer, Rigel, Roche, Syndax  
Research Support – Janssen

# Components of an AML Diagnosis

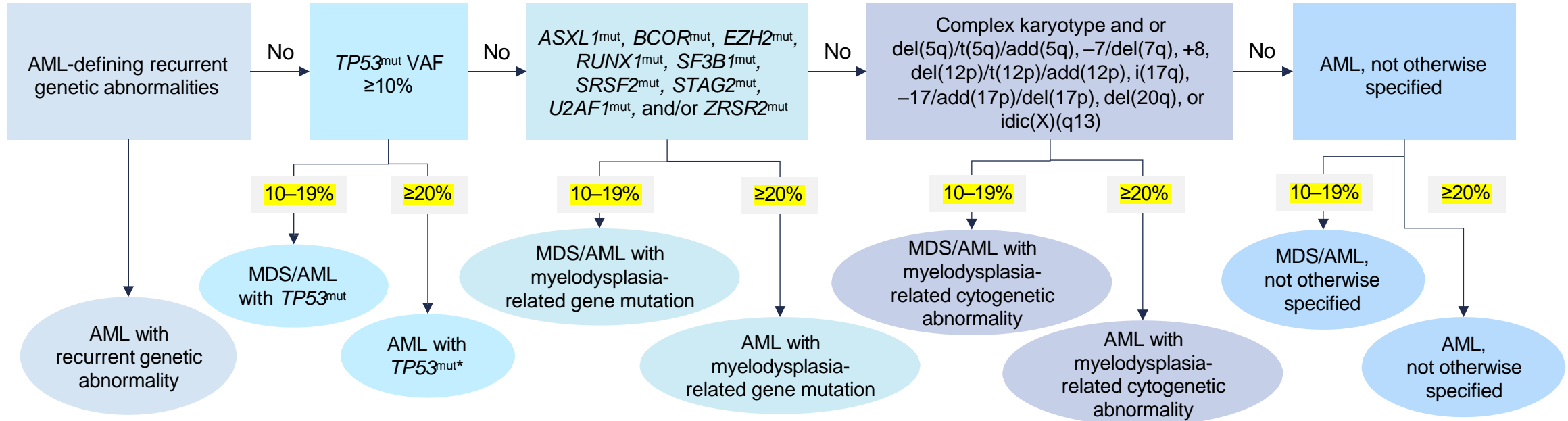


- Morphology: fast, but tricky
- Flow cytometry: fast, essential
- Cytogenetics: often slow
- FISH - fast
- PCR -fast
- NGS -variable timing
- Emerging:
  - Array CGH
  - RNA fusion panels

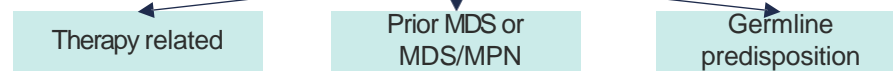
# Diagnosing AML: ICC 2022 and WHO 2022 classifications

## International Consensus Classification of AML – Hierarchy

≥10% myeloid blasts or blast equivalents in bone marrow or blood



### Diagnostic qualifiers appended to any of the above diagnoses



WHO 2022 independent of BM and PB blast count

WHO 2022 does not call out *TP53*<sup>3</sup>

WHO 2022 does not list *RUNX1*<sup>3</sup>

WHO 2022 does not list +8 or del(20q)<sup>3</sup>

WHO 2022 refers to as: AML, defined by differentiation<sup>3</sup>

\* The presence of *TP53* mutation (VAF ≥10% with/without loss of *TP53*<sup>wt</sup>) defines the entity AML with *TP53*<sup>mut</sup>.  
mut, mutated; VAF, variant allelic frequency; wt, wild type.

1. Adapted from Döhner H, et al. *Blood* 2022; **140**:1345–1377; 2. Arber DA, et al. *Blood* 2022; **140**:1200–1228; 3. Khoury JD, et al. *Leukemia* 2022; **36**:1703–1719.

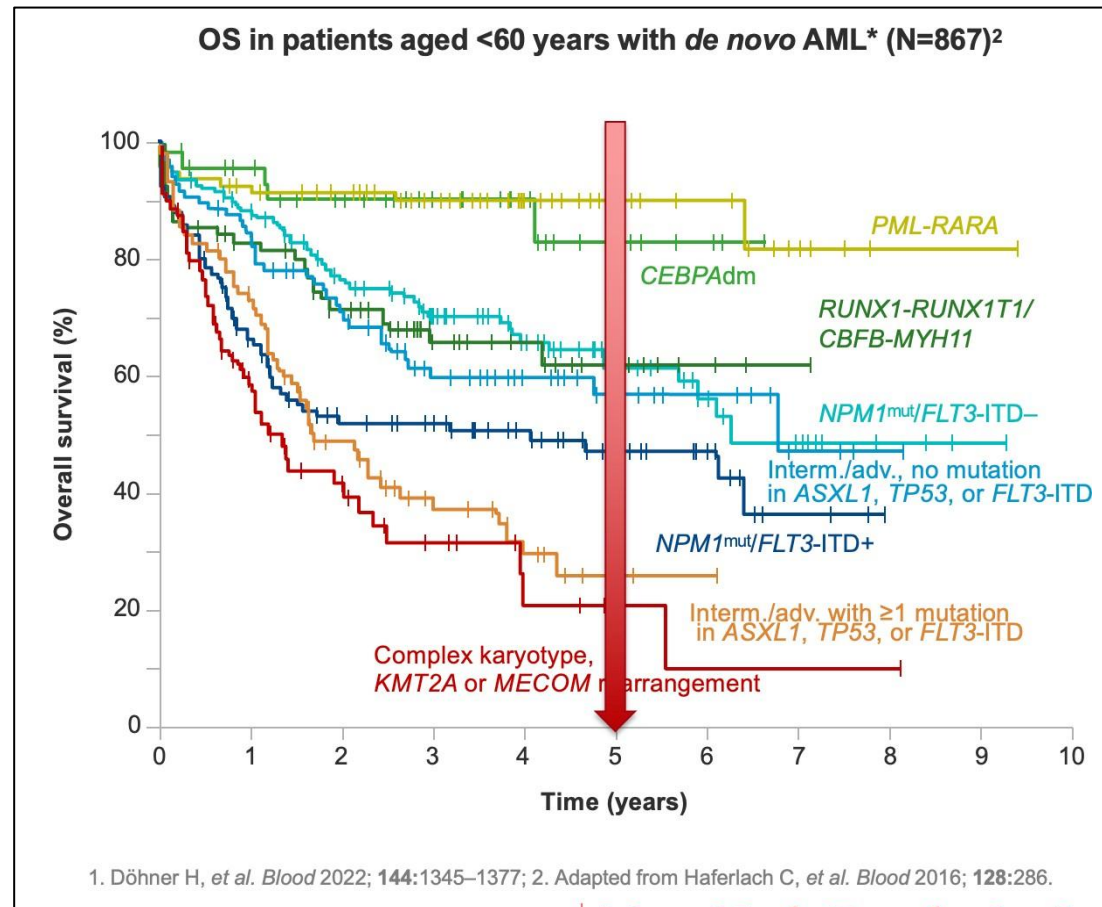
# 2022 European LeukemiaNet (ELN) risk classification by genetics at initial diagnosis

## ELN 2022<sup>1</sup>

- Favorable**
- t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1*
  - inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*
  - Mut *NPM1* w/o *FLT3*-ITD
  - bZIP in-frame mut *CEBPA*

- Intermediate**
- Mut *NPM1* with *FLT3*-ITD
  - Wt *NPM1* with *FLT3*-ITD
  - t(9;11)(p21.3;q23.3)/*MLL3::KMT2A*
  - Cytogenetic and/or molecular

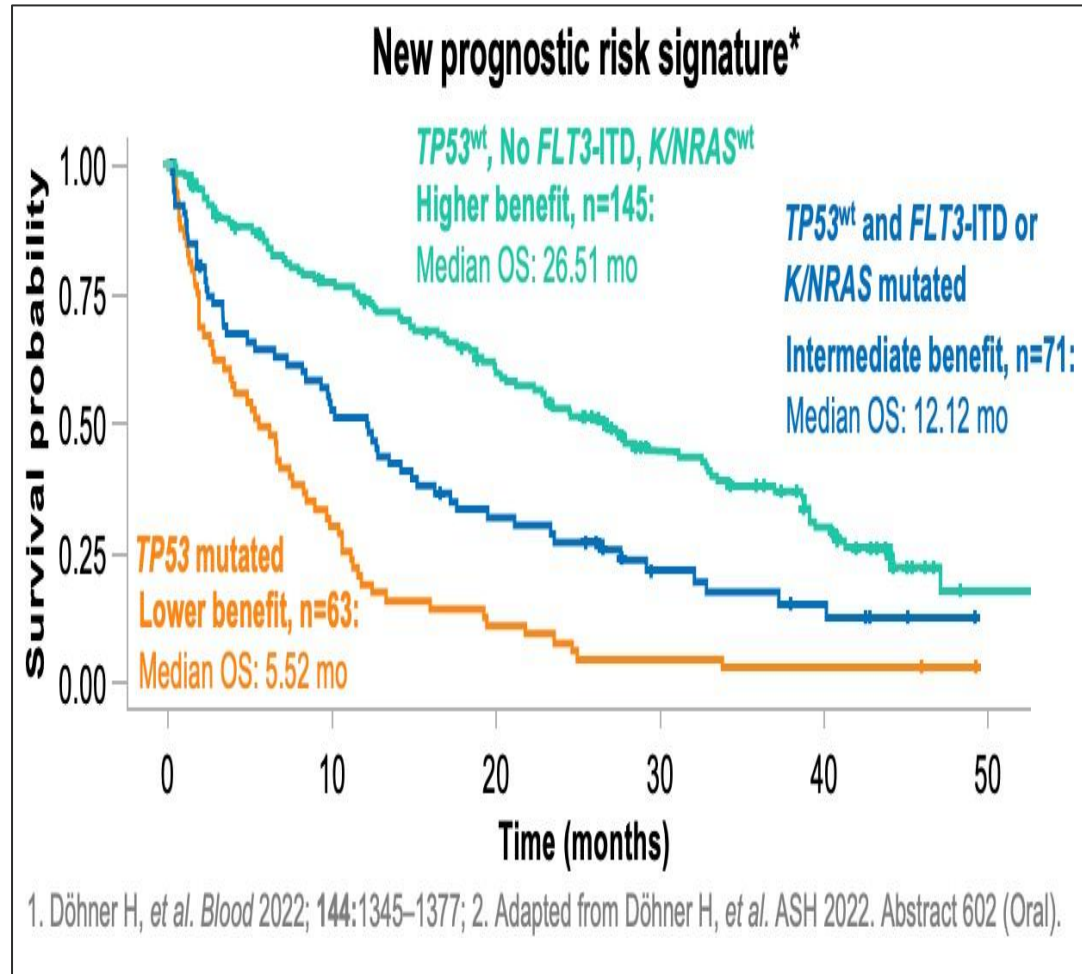
- Adverse**
- t(6;9)(p23.3;q34.1)/*DEK::NUP214*
  - t(v;11q23.3)/*KMT2A*-rearr
  - t(9;22)(q34.1;q11.2)/*BCR::ABL1*
  - t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP*
  - inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2, MECOM(EVI1)*
  - t(3q26.2;v)/*MECOM(EVI1)*-rearr
  - -5 or del(5q); -7; -17/abn(17p)
  - Complex/monosomal karyotype
  - Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*
  - Mut *TP53*



\* This population of patients had been previously treated with intensive chemotherapy. ELN, European LeukemiaNet; mut, mutated; rearr, rearranged; wt, wild type.

1. Döhner H, et al. *Blood* 2022; **144**:1345–1377; 2. Adapted from Haferlach C, et al. *Blood* 2016; **128**:286.





















# The New ELN 2024 for AML patients treated with low-intensity induction



Genetic marker	Median overall survival (months)	Reference
<b>Favorable-risk group</b>		
• Mutated <i>NPM1</i> ( <i>FLT3-ITD<sup>neg</sup></i> , <i>NRAS<sup>wt</sup></i> , <i>KRAS<sup>wt</sup></i> , <i>TP53<sup>wt</sup></i> )	39	4
• Mutated <i>IDH2</i> ( <i>FLT3-ITD<sup>neg</sup></i> , <i>NRAS<sup>wt</sup></i> , <i>KRAS<sup>wt</sup></i> , <i>TP53<sup>wt</sup></i> )	37	4
• Mutated <i>IDH1<sup>a</sup></i> ( <i>TP53<sup>wt</sup></i> )	29	6,17
• Mutated <i>DDX41</i>	>24	3,13
• AML with myelodysplasia-related gene mutations ( <i>FLT3-ITD<sup>neg</sup></i> , <i>NRAS<sup>wt</sup></i> , <i>KRAS<sup>wt</sup></i> , <i>TP53<sup>wt</sup></i> )	23	4
<b>Intermediate-risk group</b>		
• AML with myelodysplasia-related gene mutations ( <i>FLT3-ITD<sup>pos</sup></i> and/or <i>NRAS<sup>mut</sup></i> and/or <i>KRAS<sup>mut</sup></i> ; <i>TP53<sup>wt</sup></i> )	13	4
• Other cytogenetic and molecular abnormalities ( <i>FLT3-ITD<sup>pos</sup></i> and/or <i>NRAS<sup>mut</sup></i> and/or <i>KRAS<sup>mut</sup></i> ; <i>TP53<sup>wt</sup></i> )	12	4
<b>Adverse-risk group</b>		
• Mutated <i>TP53</i>	5-8	3,4,7,10,14-16

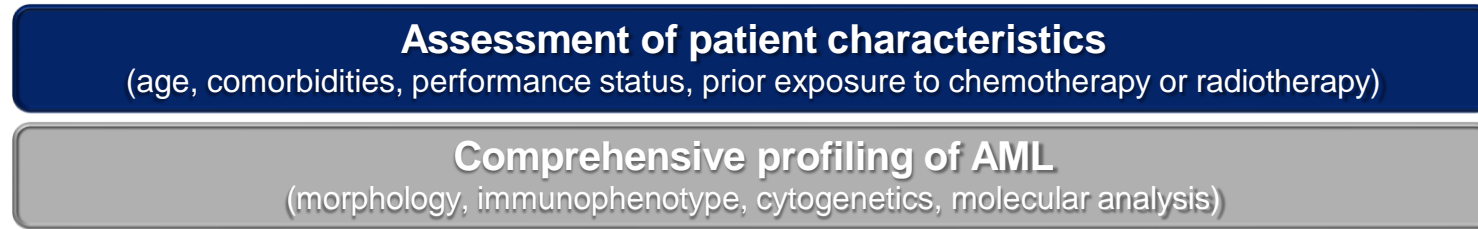
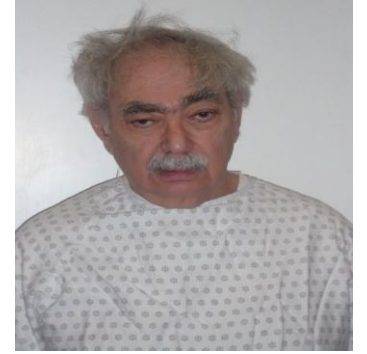
Dohner et al. *Blood*.2024025409.

# US and EU Drug Approvals for AML 2017-2024

	Target	Approval	EU	US
Midostaurin (+IC)	FLT3	ND		
CPX-351	t-AML, AML-MRC	ND		
Enasidenib	IDH2	R/R		
Gemtuzumab ozogamicin	CD33	ND and R/R		
Ivosidenib	IDH1	ND and R/R		
Glasdegib (+LDAC)	Sonic hedgehog pathway	ND		
Gilteritinib	FLT3	R/R		
Venetoclax (+Aza/Dec/LDAC) <sup>†</sup>	BCL-2	ND		
CC-486 (oral azacitidine)	Hypermethylation	Maintenance		
Olutasidenib	IDH1	R/R		
Quizartinib	FLT3	ND		
Revumenib	KMT2A-R	R/R		

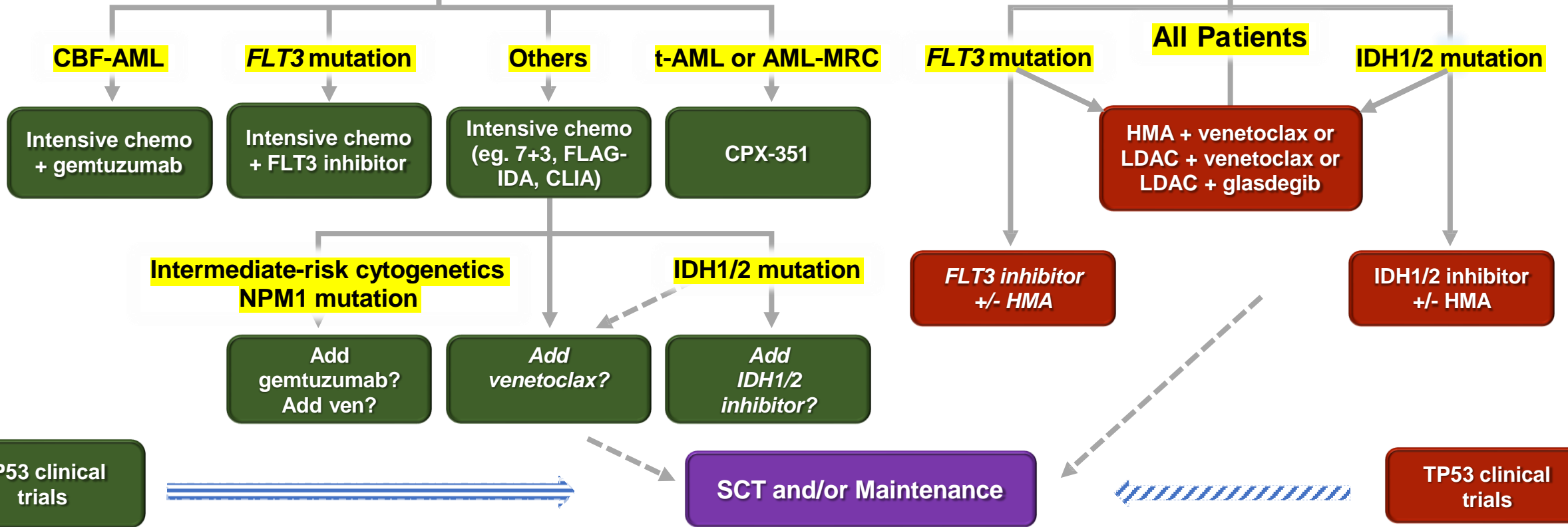


# Evolving diagnostic and treatment paradigm for Newly Diagnosed AML

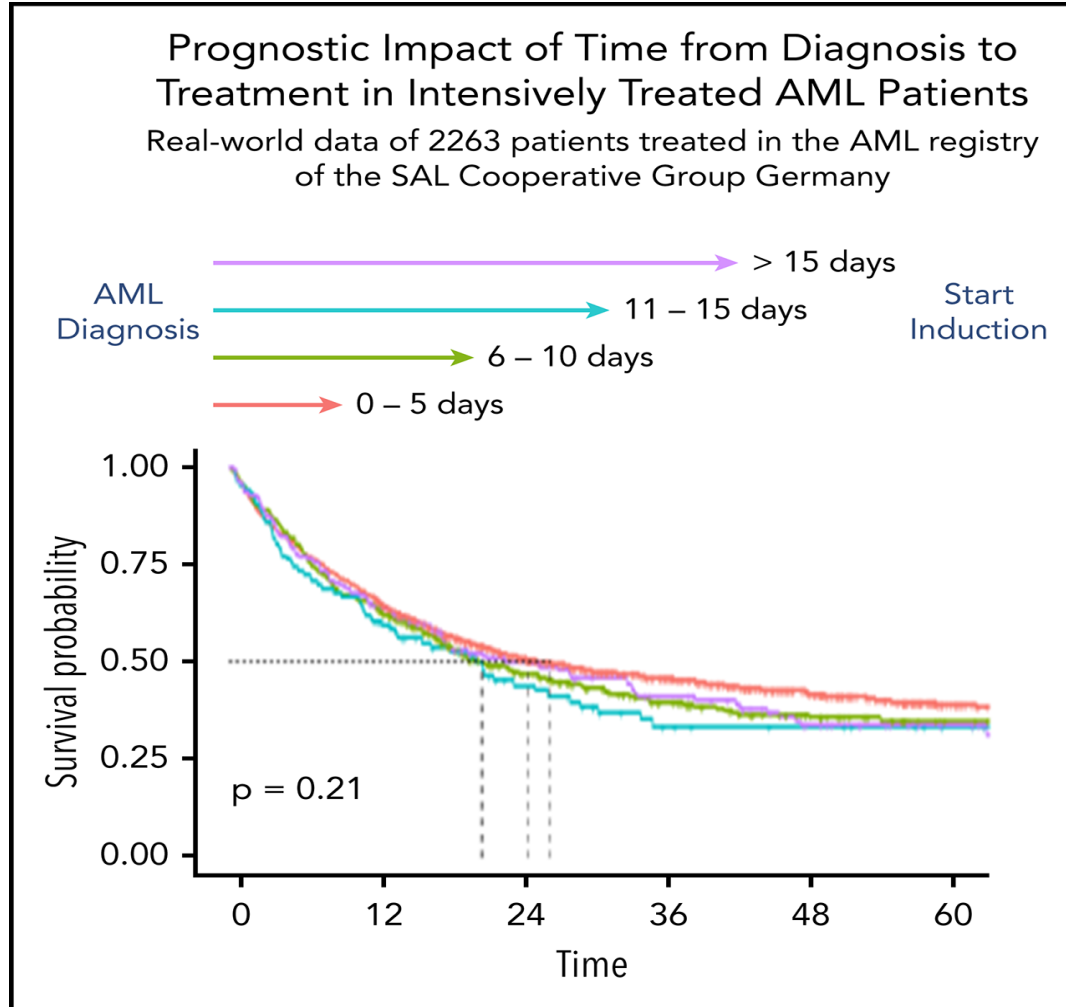


**Patient ELIGIBLE for intensive chemotherapy**

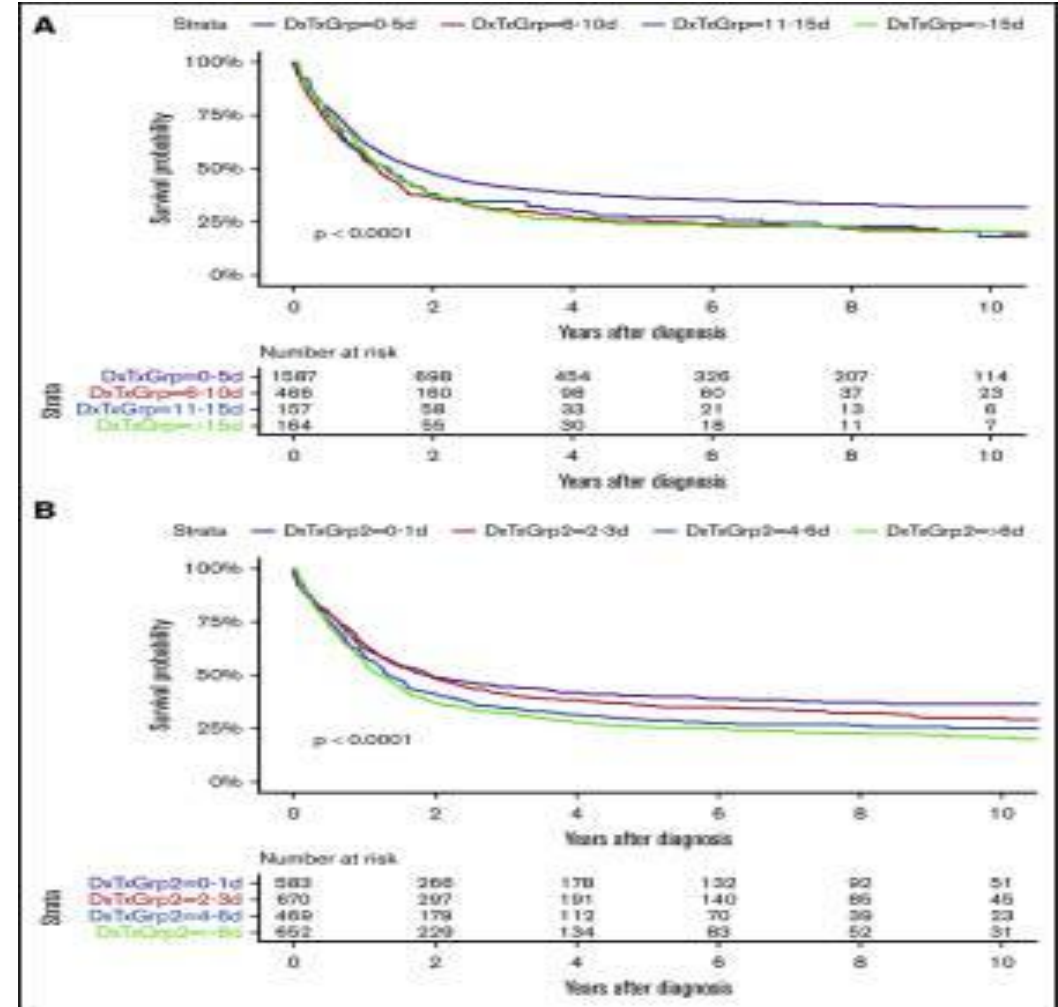
**Patient INELIGIBLE for intensive chemotherapy**



# How long can you wait before starting AML treatment?

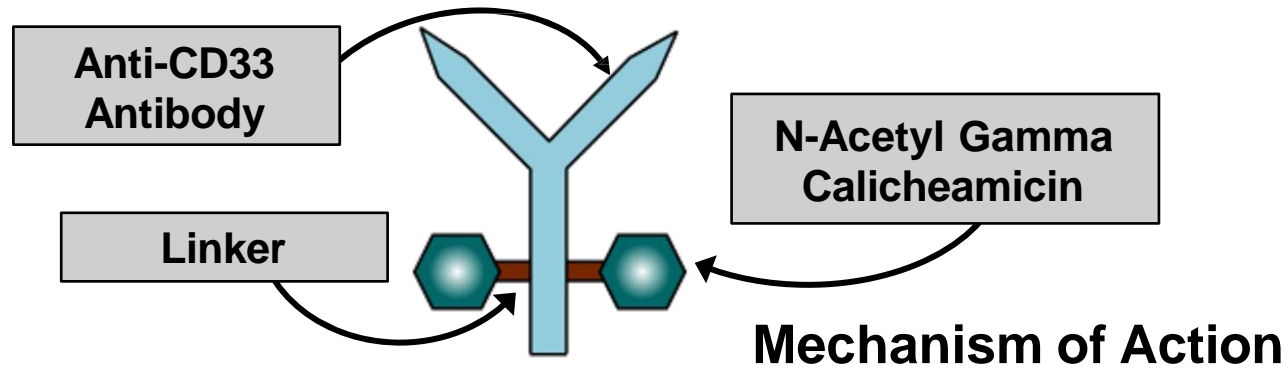


Rollig et al. *Blood* (2020) 136 (7): 823–830.

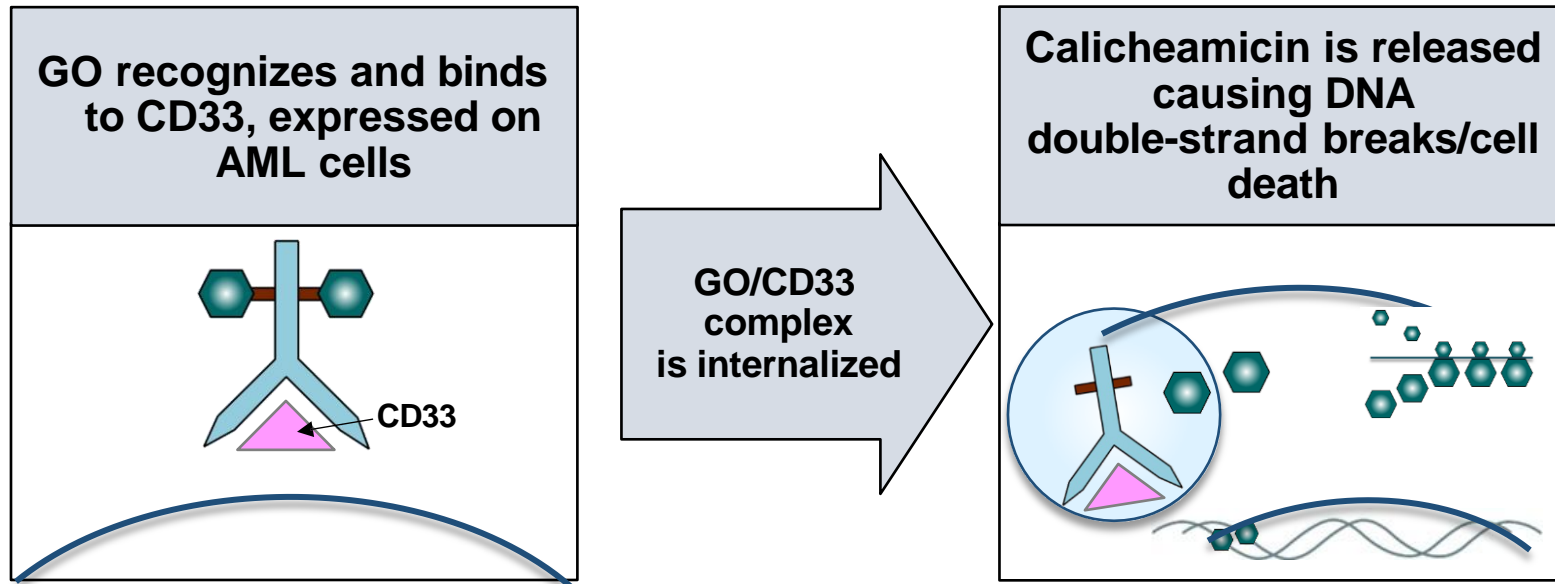


Juliusson et al. *Blood Adv* . 2021 Feb 3;5(3):787–790.

# Gemtuzumab Ozogamicin



- In 2000 approved for CD33+ AML in first relapse  $\geq 60$  years<sup>1\*</sup>
- In 2017 approved for adults with newly diagnosed CD33+ AML, and adults and children 2 years and older with relapsed or refractory CD33+ AML<sup>2\*</sup>

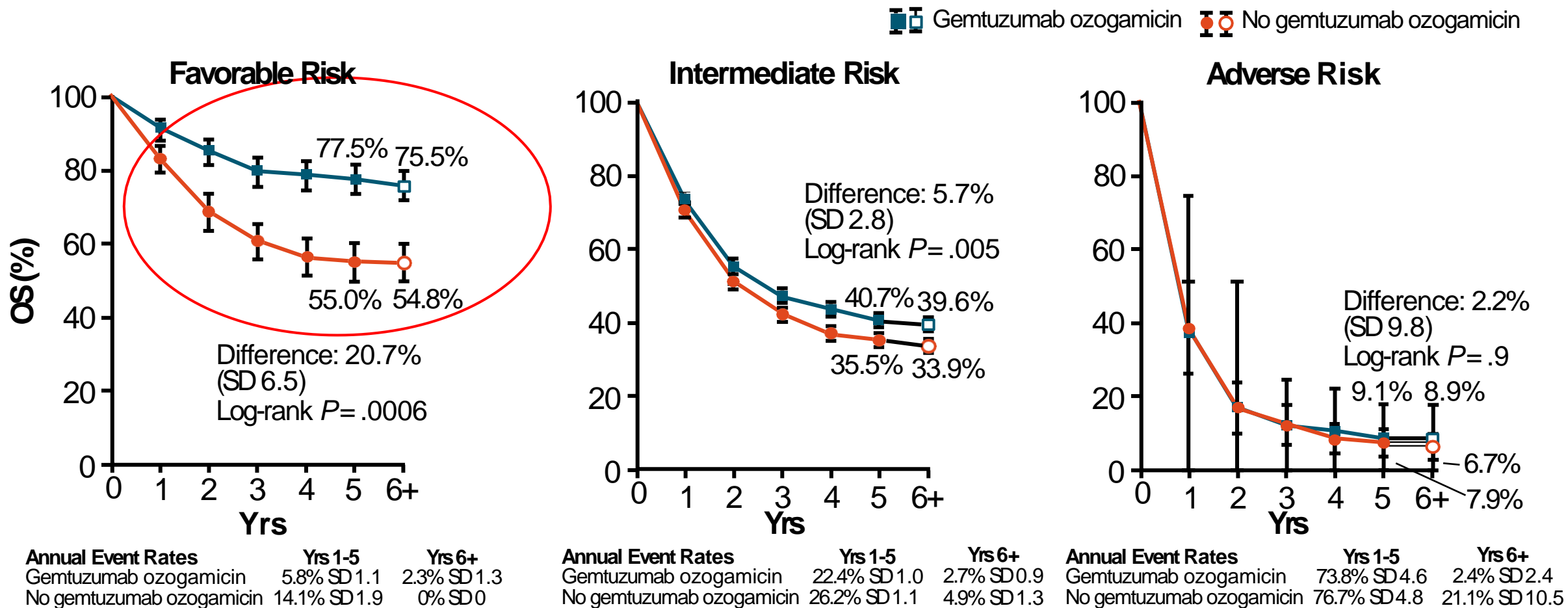


FDA. MYLOTARG® (gemtuzumab ozogamicin). Available from: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM567370.pdf> Accessed 13 May 2020

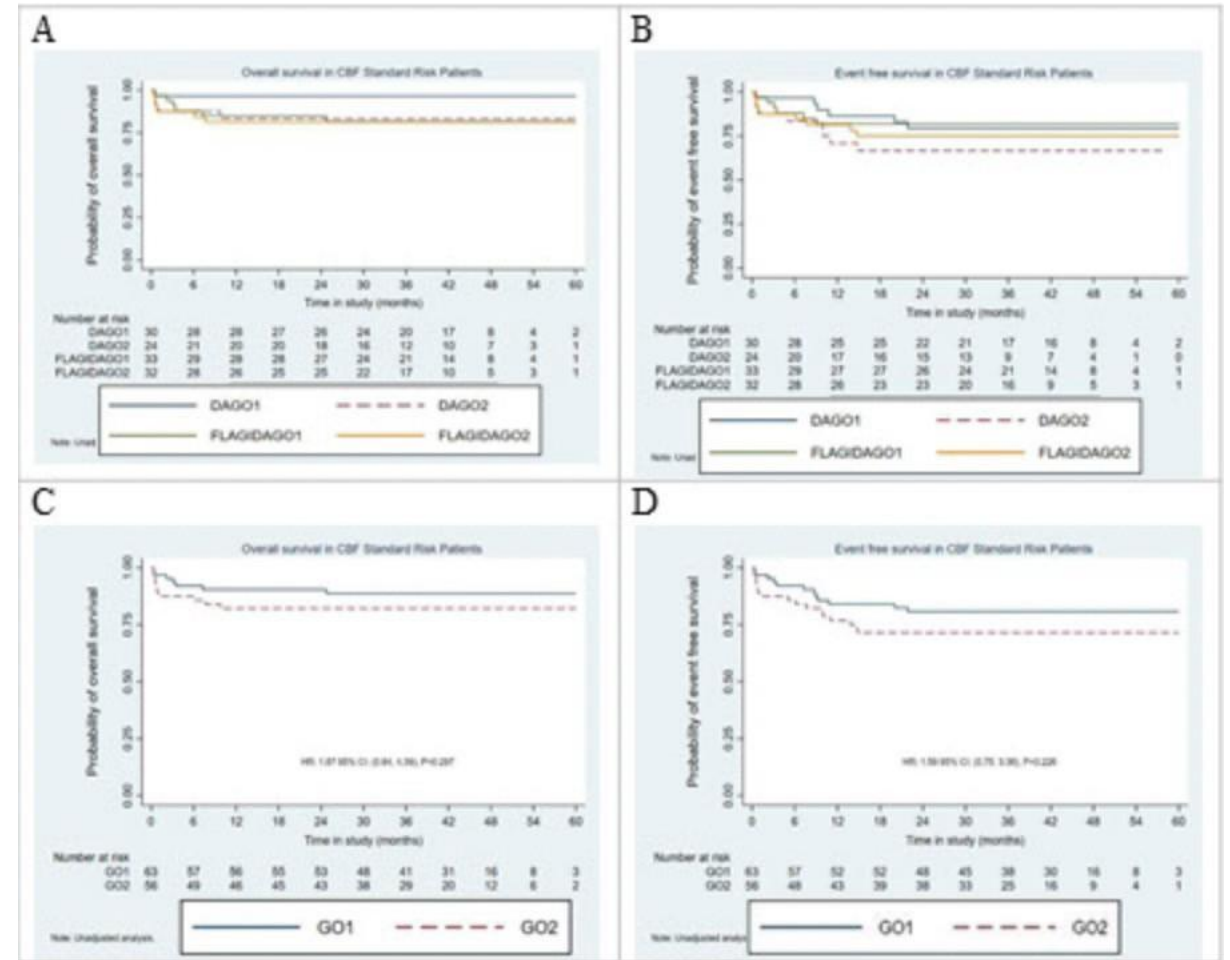
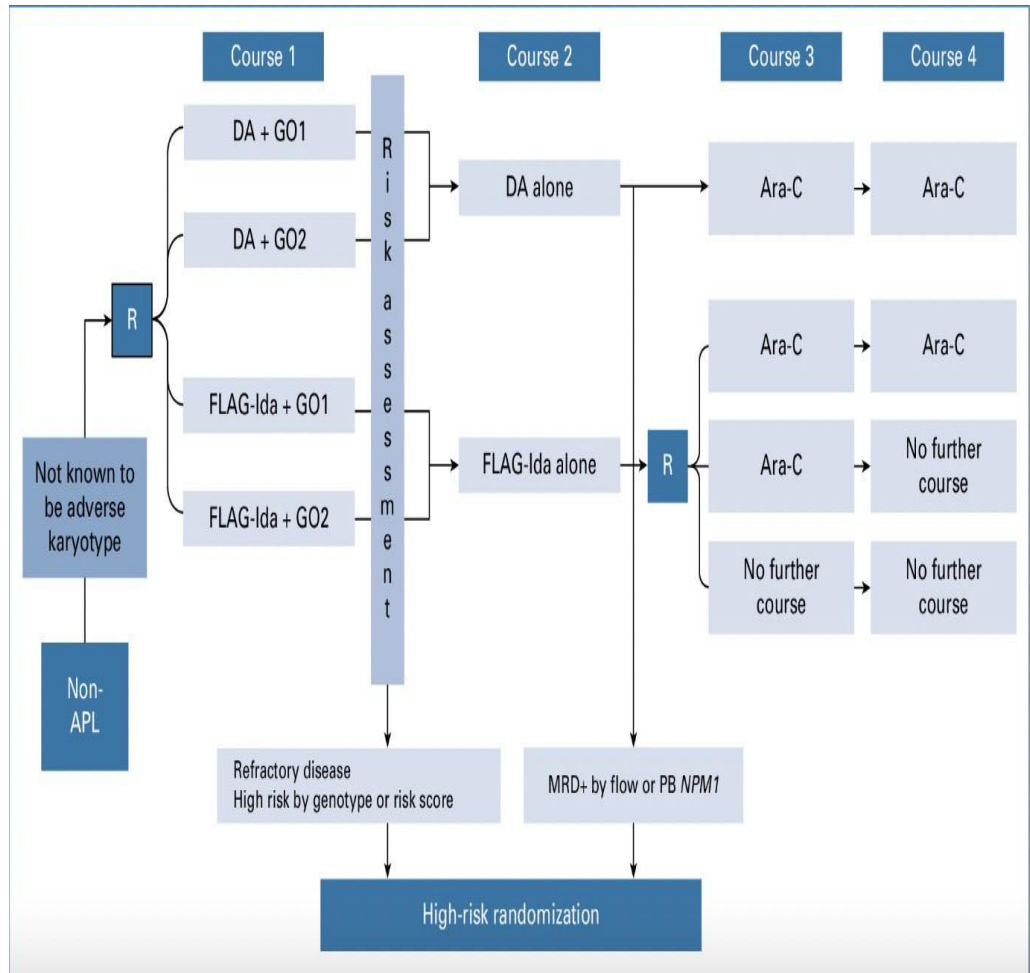
2. FDA. FDA Approves Gemtuzumab Ozogamicin for CD33-positive AML. Available from: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-gemtuzumab-ozogamicin-cd33-positive-aml> Accessed 13 May 2020

\*This does not include the full indication or risk profile

# Gemtuzumab Ozogamicin in AML Induction Therapy: Meta-analysis of 5 Randomized Trials



# UK NCRI AML19 Study: Fludarabine, Cytarabine, Granulocyte Colony-Stimulating Factor, and Idarubicin With Gemtuzumab Ozogamicin Improves Event-Free Survival in Younger Patients With Newly Diagnosed AML and Overall Survival in Patients With *NPM1* and *FLT3* Mutations n=1045 Randomized patients

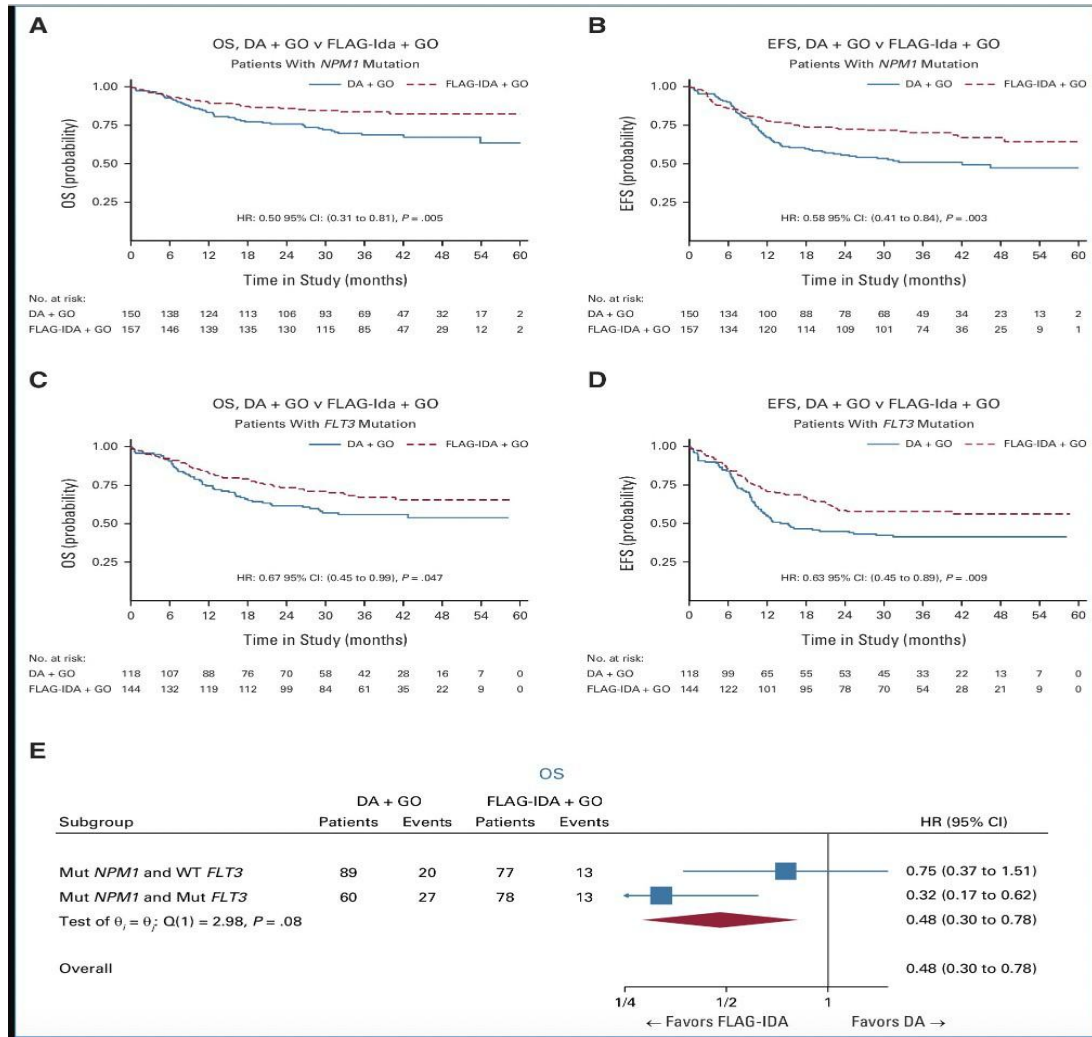


**CBF AML treated with DA and one dose of GO: 3-yr OS of 96%**

**with no survival benefit from FLAG-Ida + GO.**

Russell et al. Journal of Clinical Oncology  
Volume 42, Number 10  
<https://doi.org/10.1200/JCO.23.00943>

# UK NCRI AML19 Study: Fludarabine, Cytarabine, Granulocyte Colony-Stimulating Factor, and Idarubicin With Gemtuzumab Ozogamicin Improves Event-Free Survival in Younger Patients With Newly Diagnosed AML and Overall Survival in Patients With *NPM1* and *FLT3* Mutations n=1045 Randomized patients



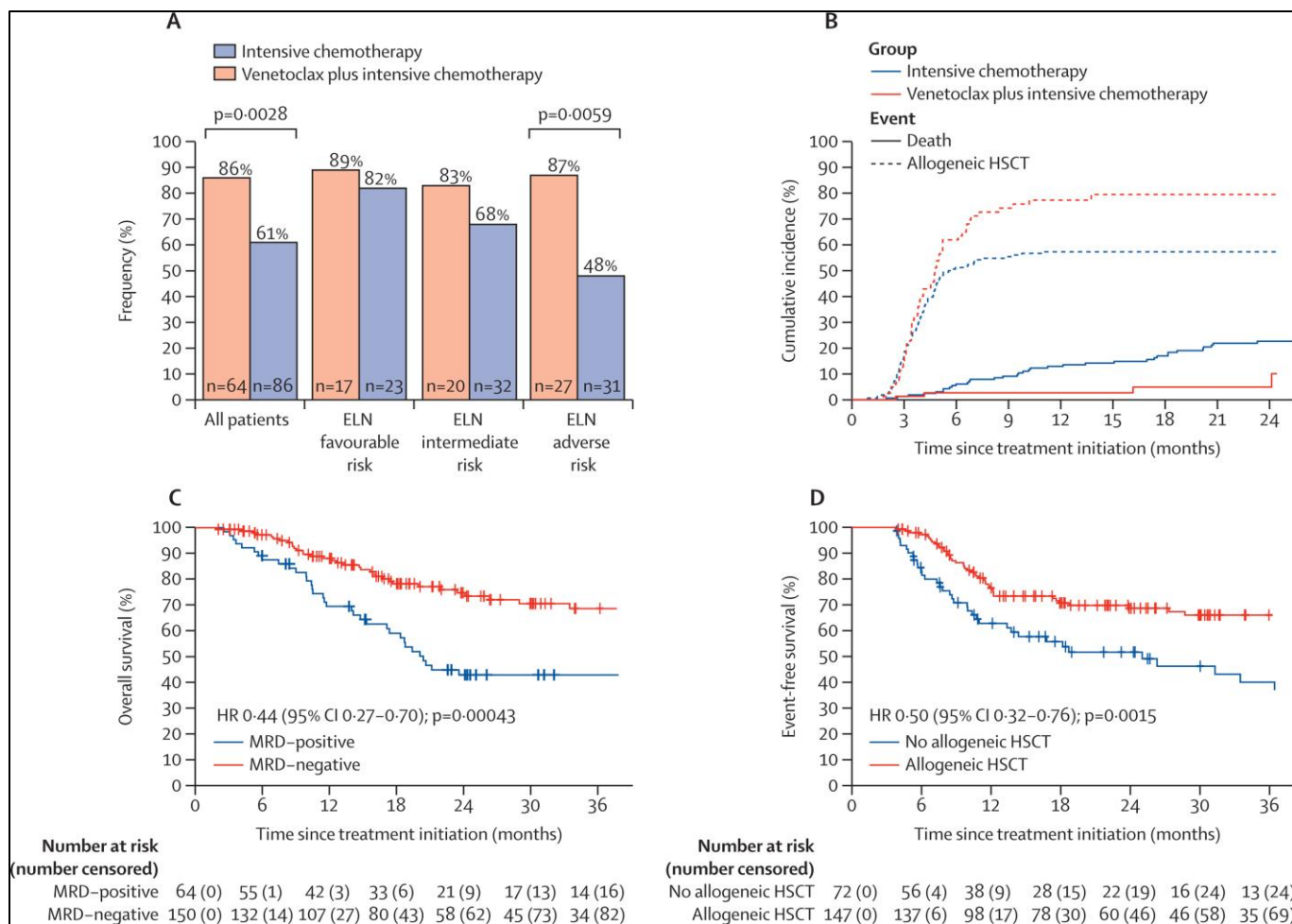
**OS at 3 years for FLAG-Ida + GO:**

86% *NPM1*<sup>mut</sup> and 62% *FLT3*<sup>mut</sup>

**OS at 3 years for DA + GO:**

64% *NPM1*<sup>mut</sup> and 54% *FLT3*<sup>mut</sup>

# Investigational Venetoclax combinations: FLAG/CLIA +/- Venetoclax



	Venetoclax plus intensive chemotherapy n (%)	Intensive chemotherapy n (%)	Hazard ratio (95% CI)	p value
Secondary acute myeloid leukaemia or therapy-related acute myeloid leukaemia	15 (18)	18 (9)	0.34 (0.1-1.1)	0.065
Aged 60 years or older	13 (15)	24 (12)	0.93 (0.1-5.8)	0.94
Adverse or complex cytogenetics	22 (26)	58 (30)	0.34 (0.1-1.2)	0.098
Diploid or other intermediate cytogenetics	58 (68)	128 (66)	0.93 (0.4-2.0)	0.85
ELN favourable risk	21 (25)	32 (16)	1.40 (0.5-4.2)	0.58
ELN intermediate risk	29 (34)	67 (35)	0.39 (0.04-3.8)	0.42
ELN adverse risk	35 (41)	95 (49)	0.31 (0.1-0.9)	0.029

← Favours venetoclax plus intensive chemotherapy | Favours intensive chemotherapy →

Lachowicz et al. Lancet Haematol. 2022 May;9(5):e350-e360.

# Classification of FLT3 Inhibitors

## Summary of Type I vs Type II

		First Generation	Second Generation
		Lack specificity for FLT3	More specific and potent
Type I	<ul style="list-style-type: none"> <li>Pure ATP-competitive*</li> <li>Active on ITD+ and TKD+ cells</li> </ul>	Sunitinib Lestaurtinib Midostaurin	Gilteritinib Crenolanib
Type II	<ul style="list-style-type: none"> <li>Maintain the inactive conformation†</li> <li>Active on ITD+ cells only</li> </ul>	Sorafenib Tandutinib	Quizartinib Ponatinib Pacritinib Ibrutinib

\*Bind to the ATP-binding site when the receptor is in the active conformation.

†Interact with a hydrophobic region immediately adjacent to the ATP binding site that is only accessible when the receptor is in the inactive conformation; prevent receptor activation. As most TKD (D835) mutations favor the active conformation, Type II inhibitors are usually ineffective on TKD-positive cells.

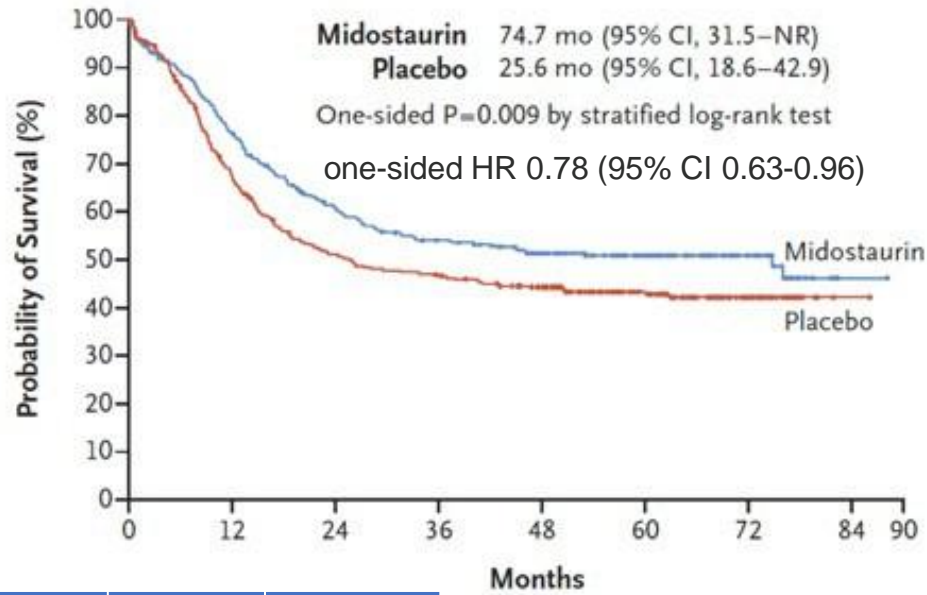
Modified from Larrosa-Garcia M, et al. Mol Cancer Ther. 2017;16:991-1001.



# Induction for *FLT3*<sup>mut+</sup> AML

## RATIFY

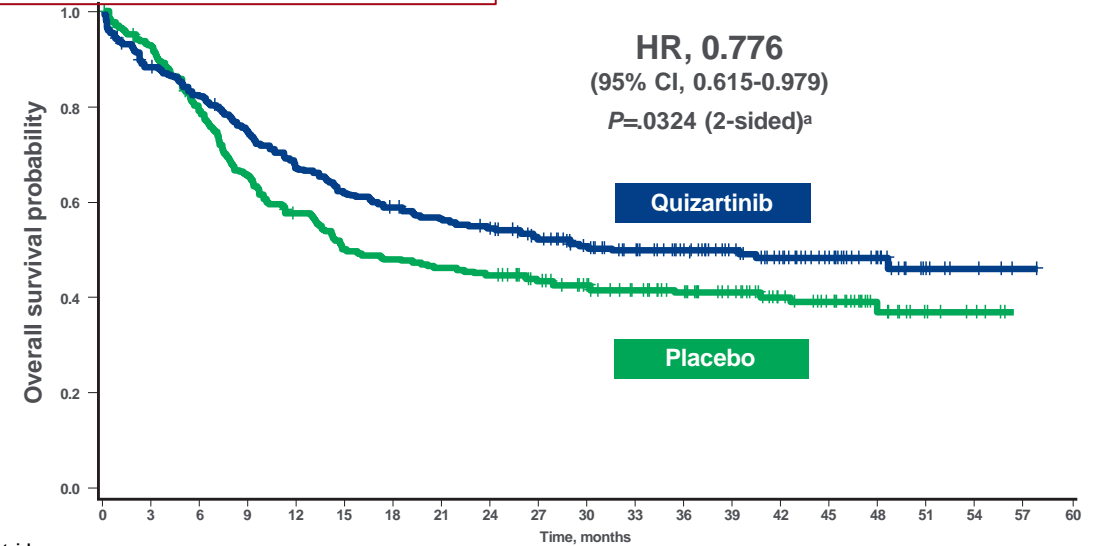
*FLT3*-ITD or *FLT3*-TKD, age 18-60



	CR by day 60	CR at any time
Midostaurin	58.9%	68%
Placebo	53.5%	61%

## QuANTUM-First

*FLT3*-ITD, age 18-75



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	97	81	70	56	39	31	17	8	5	0	0

	CR	CR/CRi
Quizartinib	54.9%	71.6%
Placebo	55.4%	64.9%

**Two FLT3 inhibitors have beaten placebo when added to frontline intensive chemotherapy**

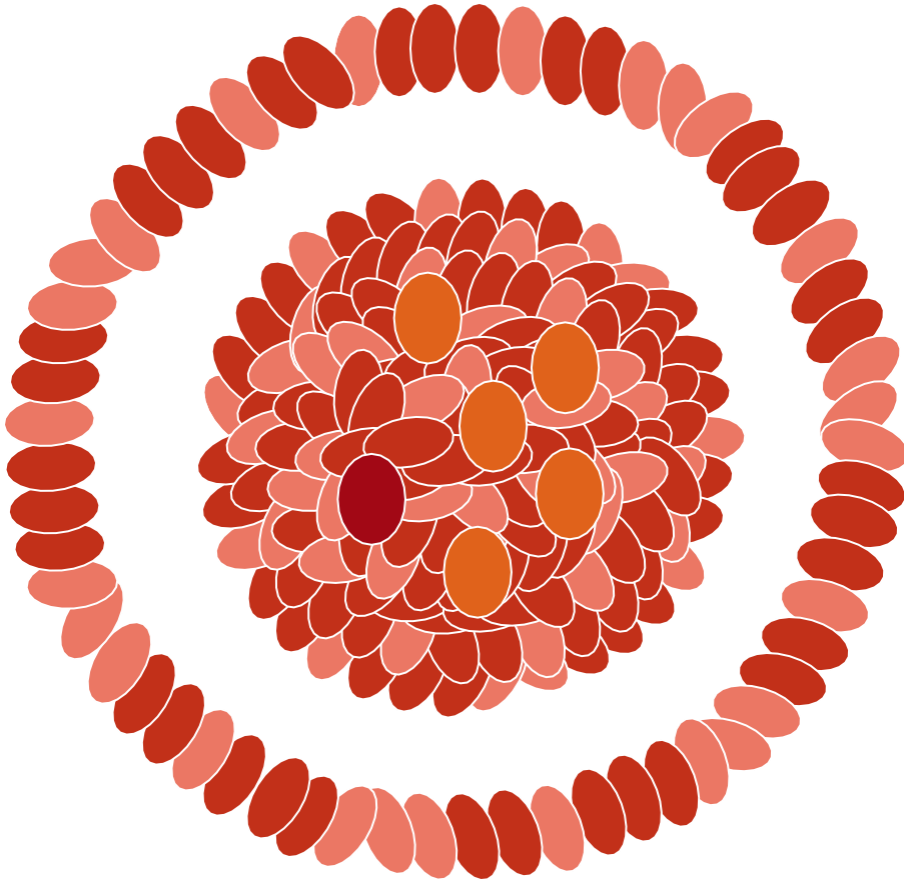
Similar design of 7+3 +/- TKI followed by HiDAC +/- TKI, with TKI given on days 8-21 of each chemo cycle

Maintenance given after consolidation on both studies, also after HSCT on QuANTUM-First

Stone RM et al. *N Engl J Med.* 2017;377(5):454-464.

Erba H et al. 2022 EHA Annual Congress. Abstract S100.

# Liposomal Cytarabine and Daunorubicin (CPX-351)

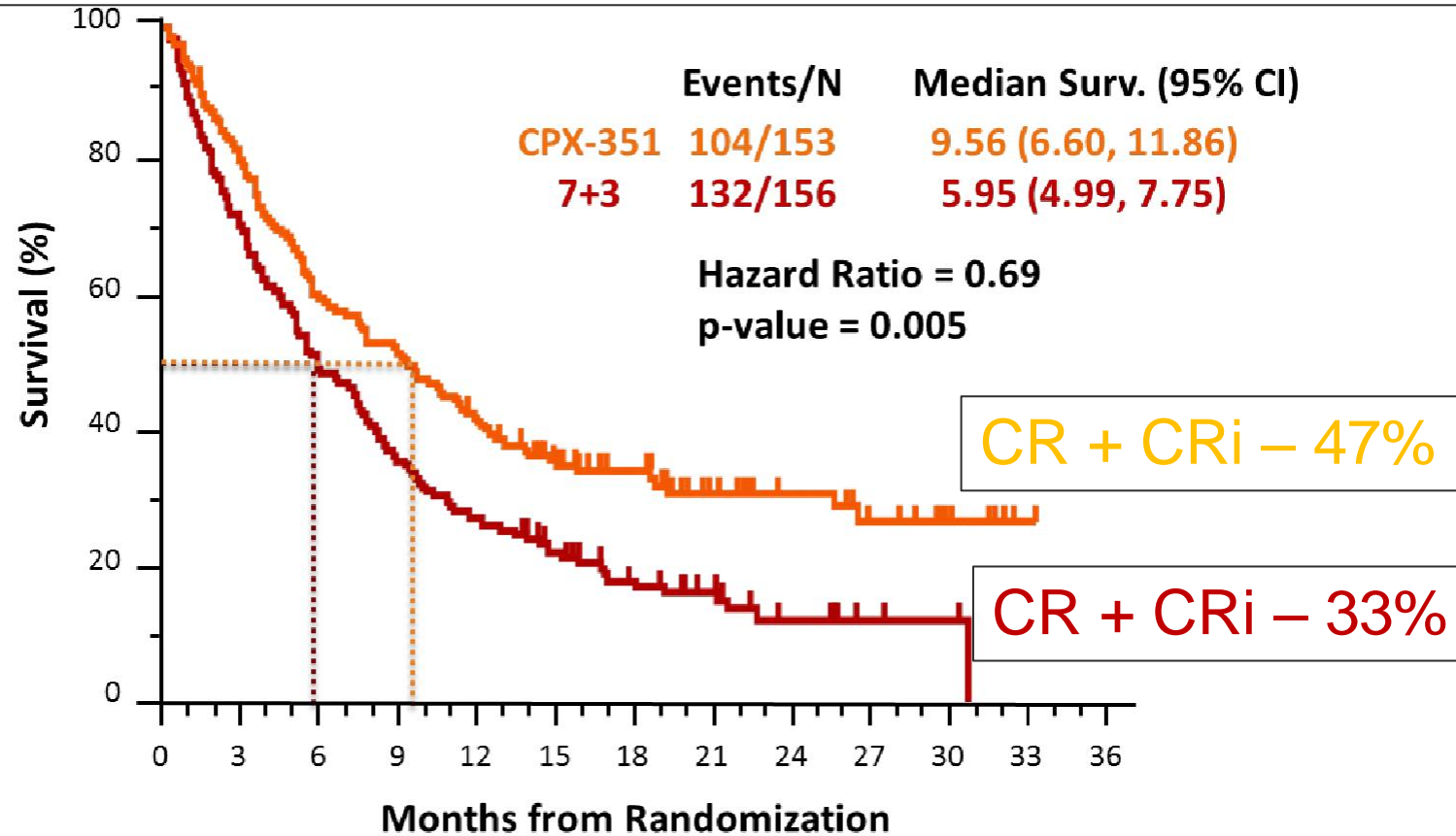


- CPX-351 a 5:1 molar ratio of cytarabine:daunorubicin
- Formulation provides synergistic leukemia cell killing in vitro<sup>[1]</sup>
- Indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

1. Tardi. *Leuk Res.* 2009;33:129. 2. Feldman. *JClin Oncol.* 2011;29:979. 3. Lim. *Leuk Res.* 2010;34:1214.

# Randomized Phase 3 Trial of CPX-351 vs 7+3 in Patients 60-75 yrs with Secondary AML

Kaplan-Meier Curve for Overall Survival (ITT Analysis Population)

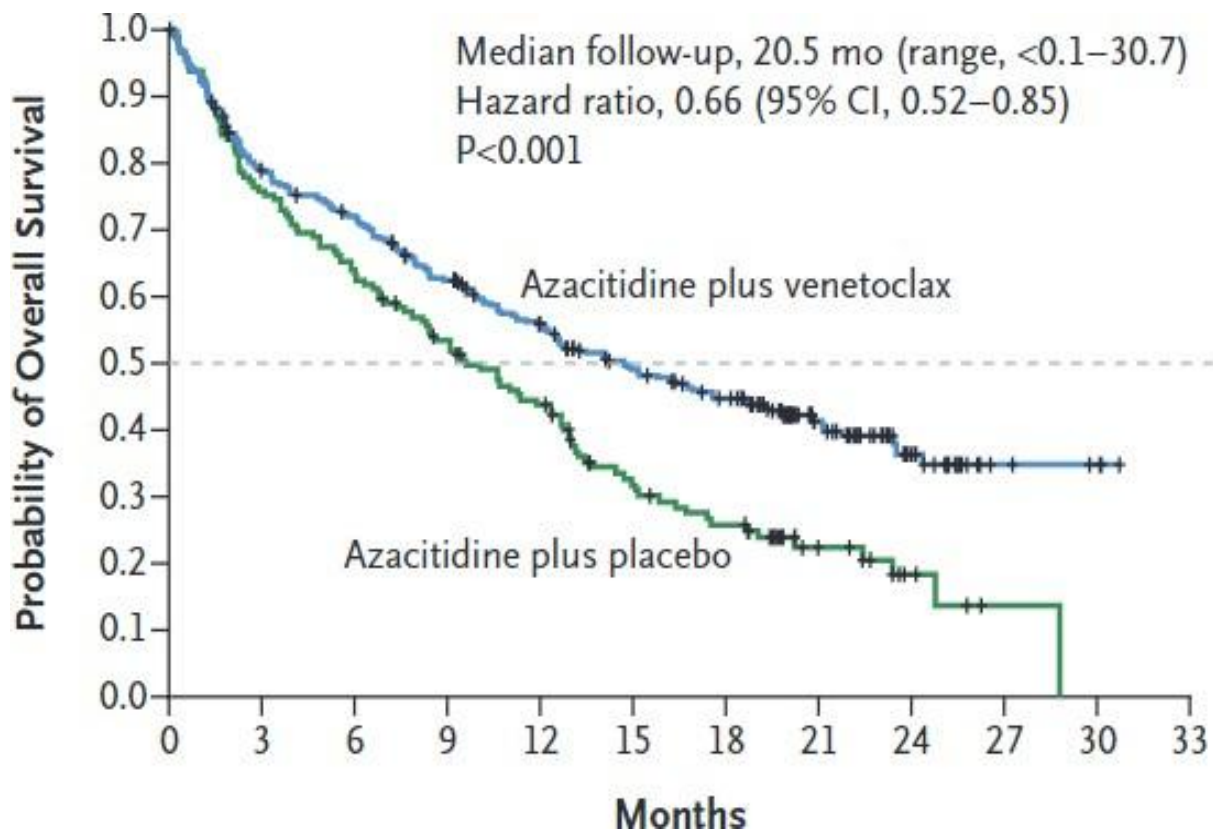


CPX-351	153	122	92	79	62	46	34	21	16	11	5	1
7+3	156	110	77	56	43	31	20	12	7	3	2	0

Lancet. *J Clin Oncol*. 2018;36:261

# Results of VIALE-A : Azacitidine ± venetoclax

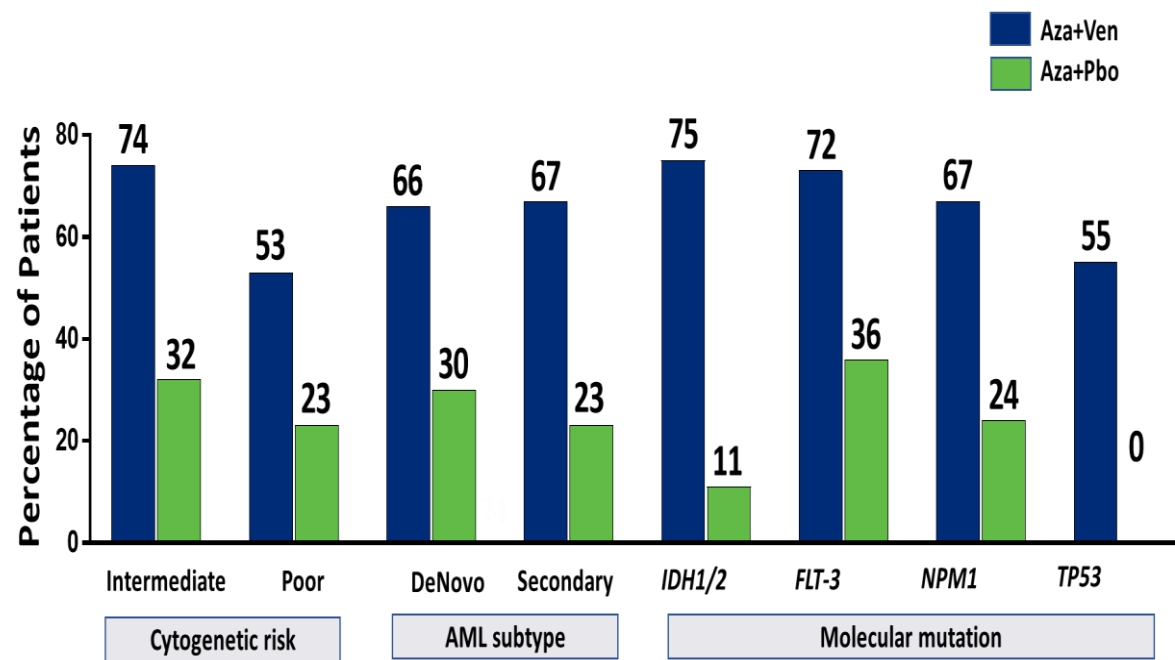
Significant OS improvement with  
azacitidine + venetoclax  
(Med OS 14.7 vs 9.6 mos)



CR rate: 36.7% vs 17.9% ( $P < .001$ )

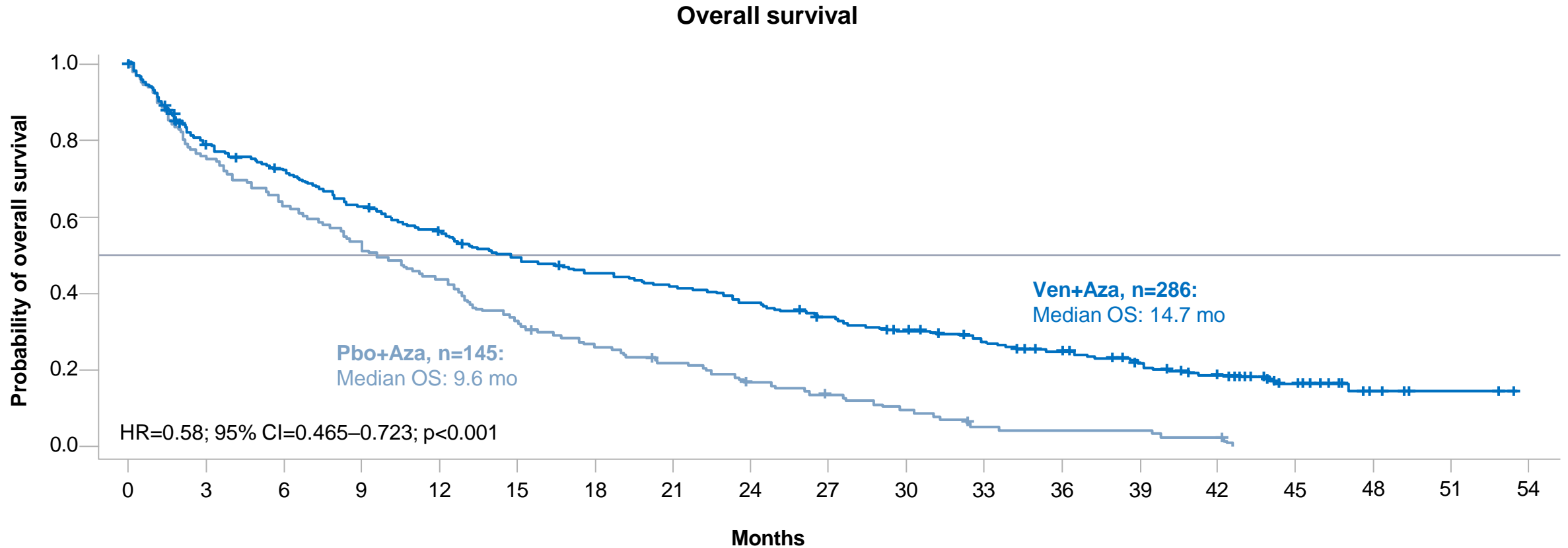
CR/CRi rate: 66.4% vs 28.3% ( $P < .001$ )

Improved responses occurred *independent* of high-risk biology



# VIALE-A: Continued OS benefit with Ven+Aza vs Pbo+Aza

Randomized, Ph3 trial in IC-ineligible patients (N=431); median follow-up: 43.2 months



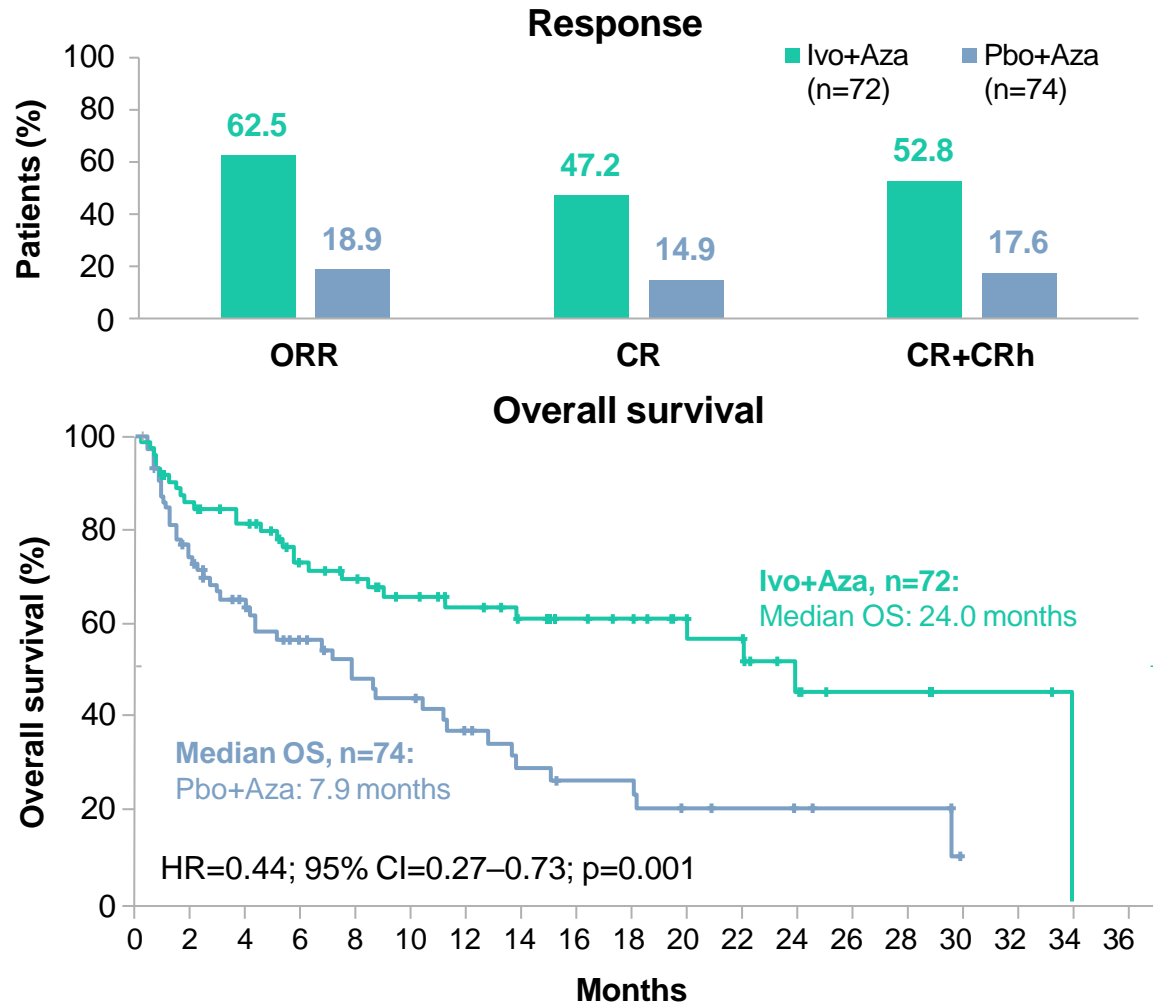
Grade  $\geq 3$  TEAEs  $\geq 10\%$  were slightly higher than in 75% interim analysis. Overall, AE rates were similar between arms; higher rates of hematologic events reported with Ven+Aza

Distributions were estimated for each treatment arm using Kaplan–Meier methodology and compared using the log-rank test stratified by age (18–<75,  $\geq 75$  years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms was estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test. Data cutoff: December 01, 2021.

Adapted from Pratz K, *et al.* ASH 2022. Abstract 219 (Oral).

# AGILE: Ivosidenib+Aza vs Pbo+Aza in ND *IDH1*<sup>mut</sup> AML

Randomized, Ph 3 trial in patients with untreated AML and an *IDH1* mutation (N=146)

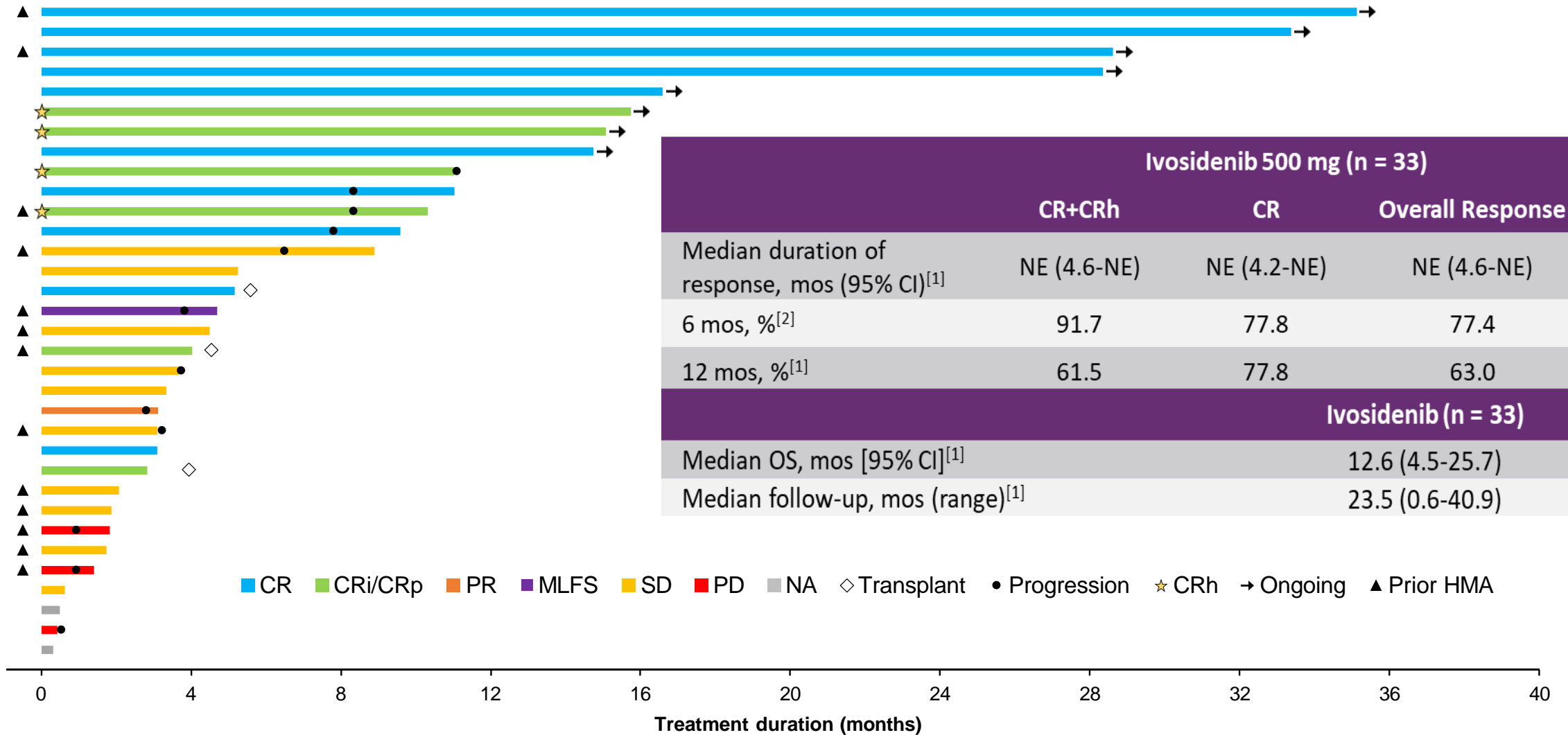


Grade ≥3 AEs in ≥20% of patients in either arm, n (%)	Ivo+Aza (n=71)	Pbo+Aza (n=73)
Hematologic AEs	50 (70)	47 (64)
Anemia	18 (25)	19 (26)
Febrile neutropenia	20 (28)	25 (34)
Neutropenia	19 (27)	12 (16)
Thrombocytopenia	17 (24)	15 (21)
Non-hematologic AEs		
Pneumonia	16 (23)	21 (29)
Infections	15 (21)	22 (30)
Other safety events, n (%)	Ivo+Aza (n=71)	Pbo+Aza (n=73)
Differentiation syndrome (any grade)	10 (14)	6 (8)
Grade ≥3	3 (4)	3 (4)
QT interval prolonged on ECG (any grade)	14 (20)	5 (7)
Grade ≥3	7 (10)	2 (3)
Discontinuation as a result of AEs	19 (27)	19 (26)

Aza, azacitidine; ECG, electrocardiography; Ivo, ivosidenib; mut, mutated; ND, newly diagnosed.

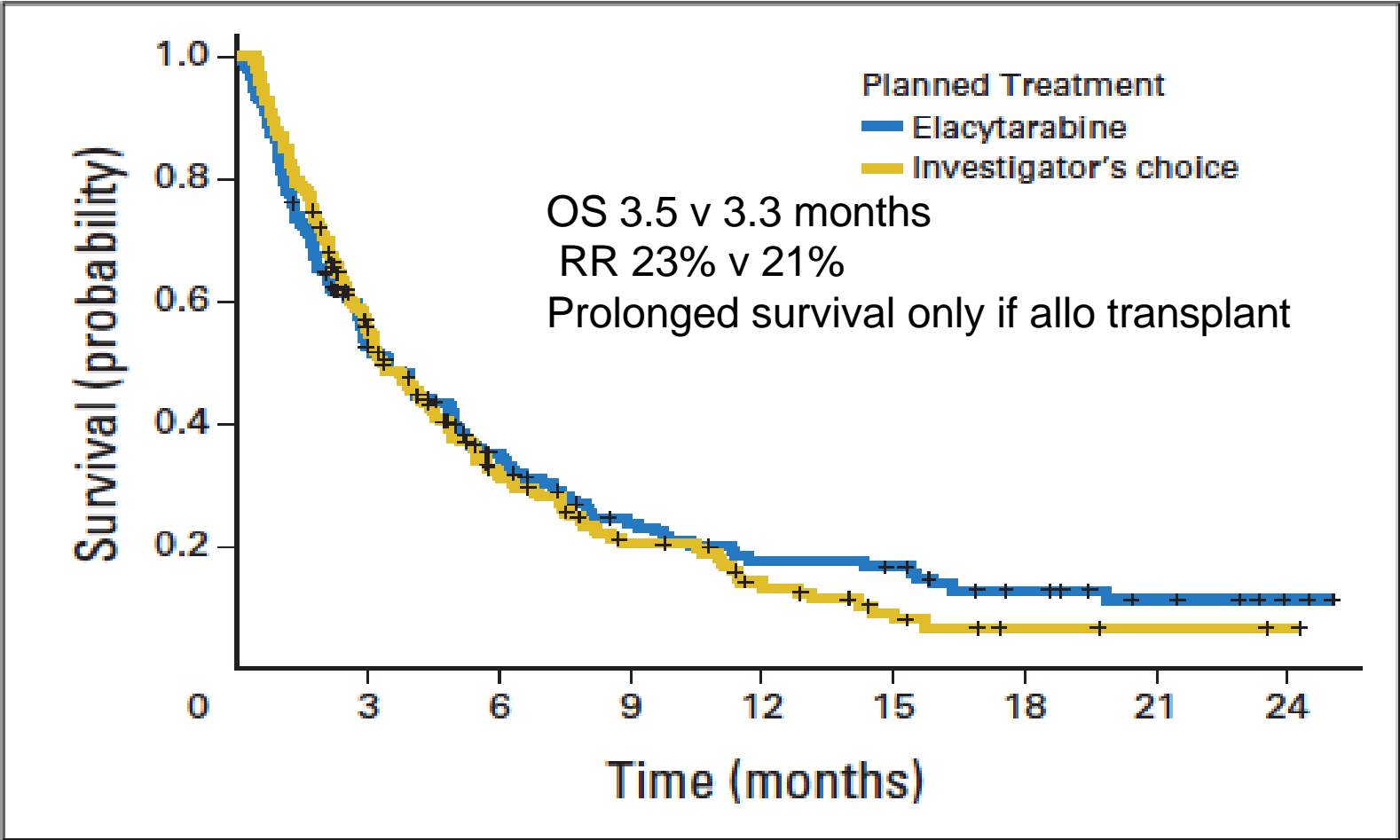
Adapted from Montesinos P, et al. *N Engl J Med* 2022; **386**:1519–1531.

# Ivosidenib in Untreated *IDH1*-Mutated AML: Duration of Treatment and Best Overall Response



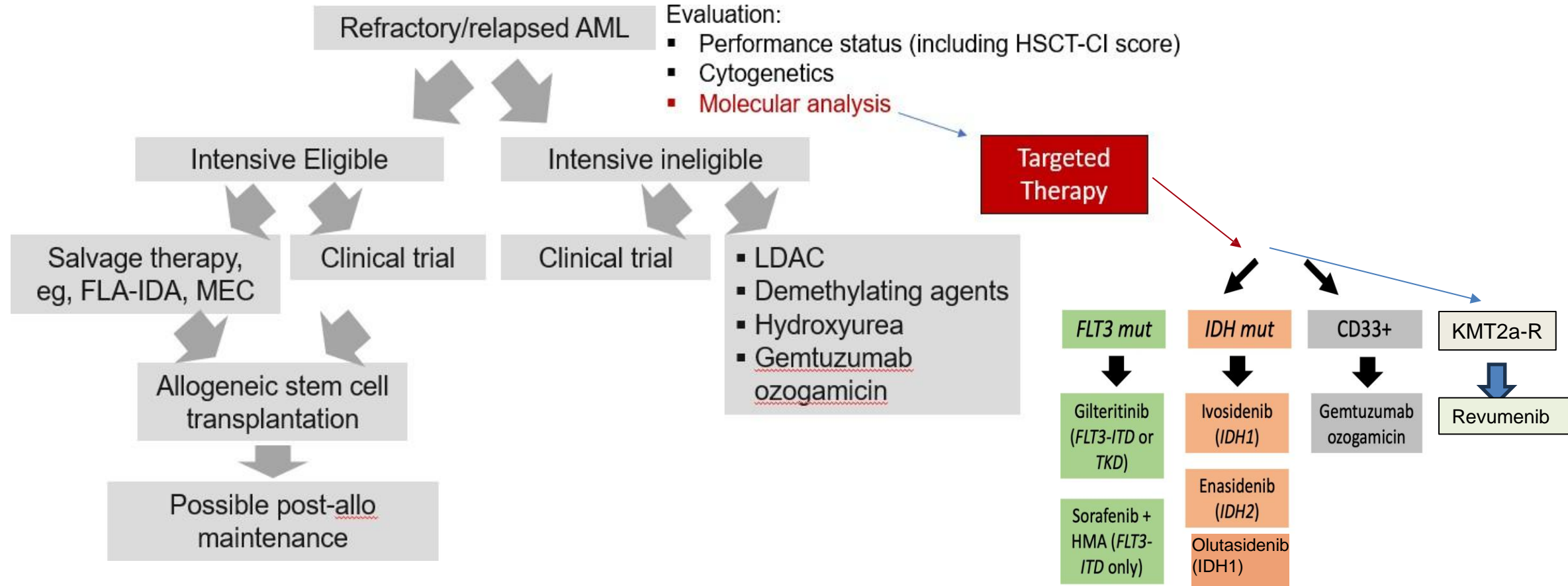
1. Roboz GJ. *Blood*. 2020;135:463. 2. Roboz GJ. ASH 2018. Abstr 561. Slide credit: [clinicaloptions.com](http://clinicaloptions.com)

# Randomized Trial of Elacytarabine vs. Investigator's Choice in Relapsed/Refractory AML

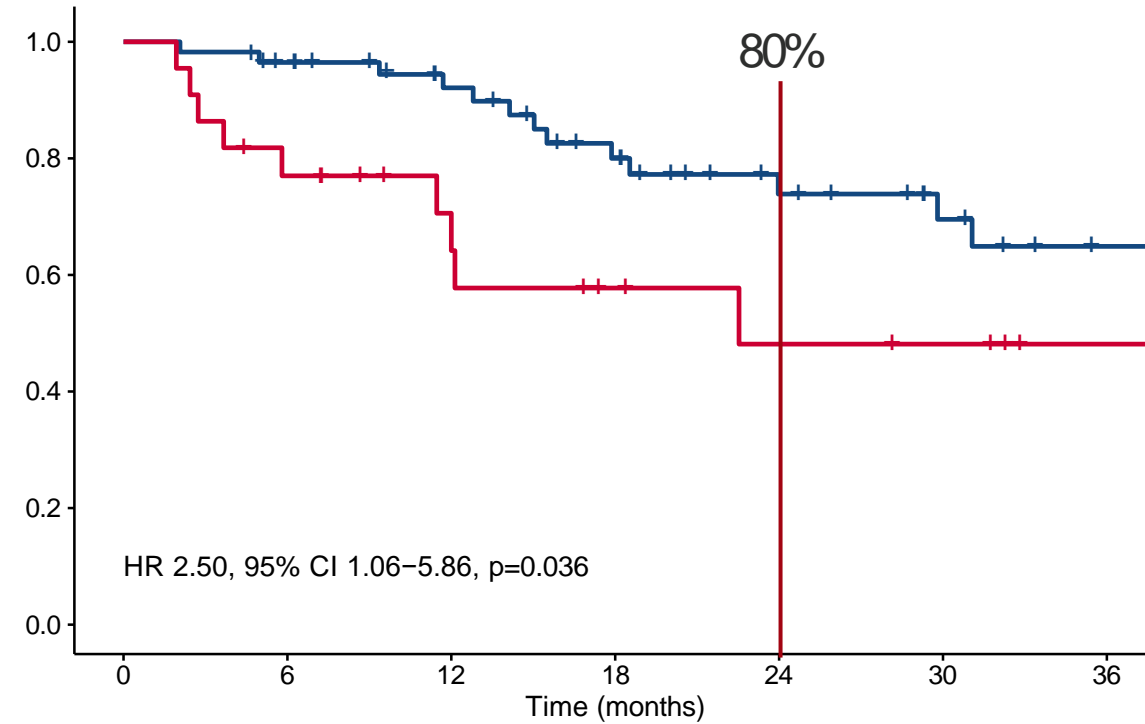
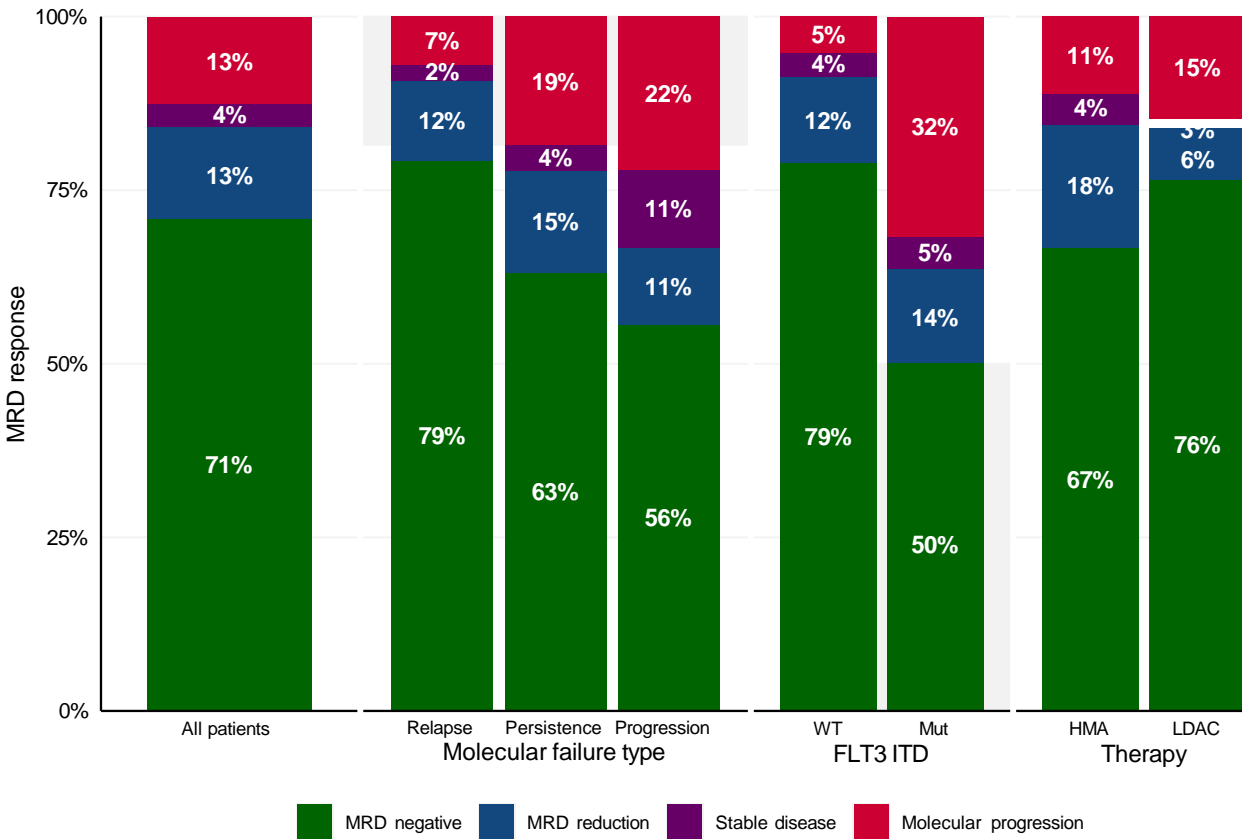


Roboz GJ et al. *J Clin Oncol.* 2014;32:1919-1926.

# Treatment Algorithm for Relapsed/Refractory Acute Myeloid Leukemia



# Venetoclax for *NPM1*<sup>mut</sup> molecular relapse



At risk

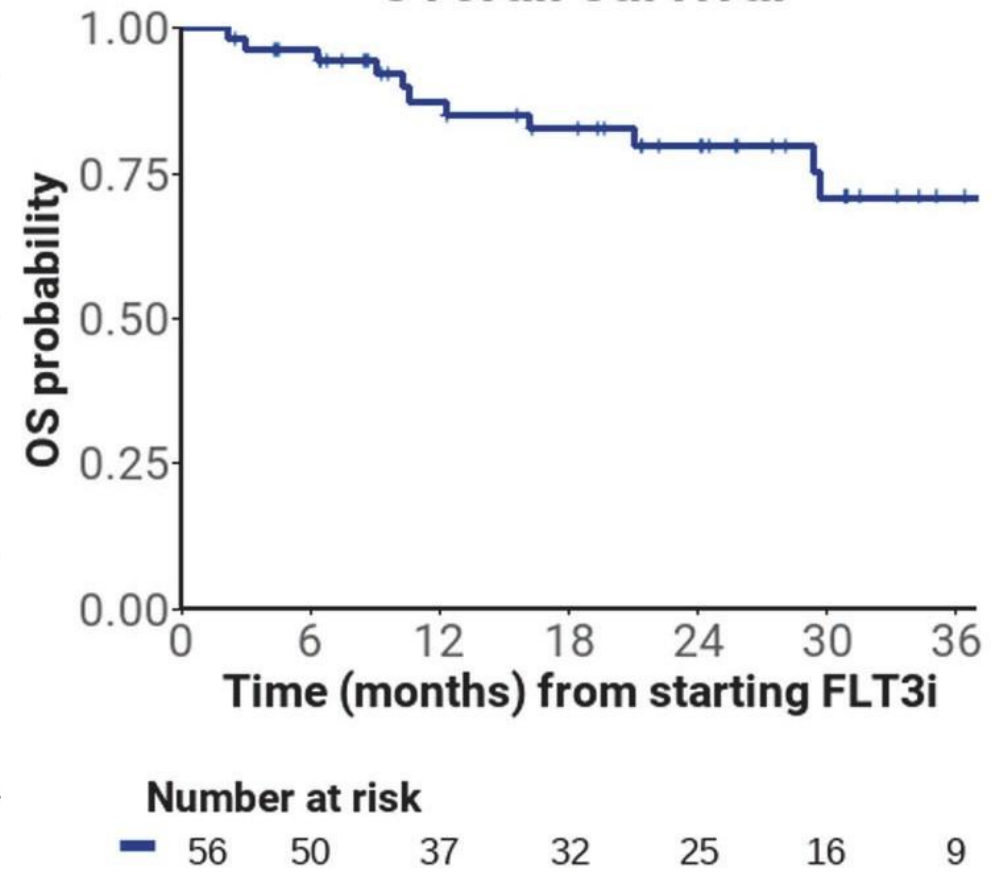
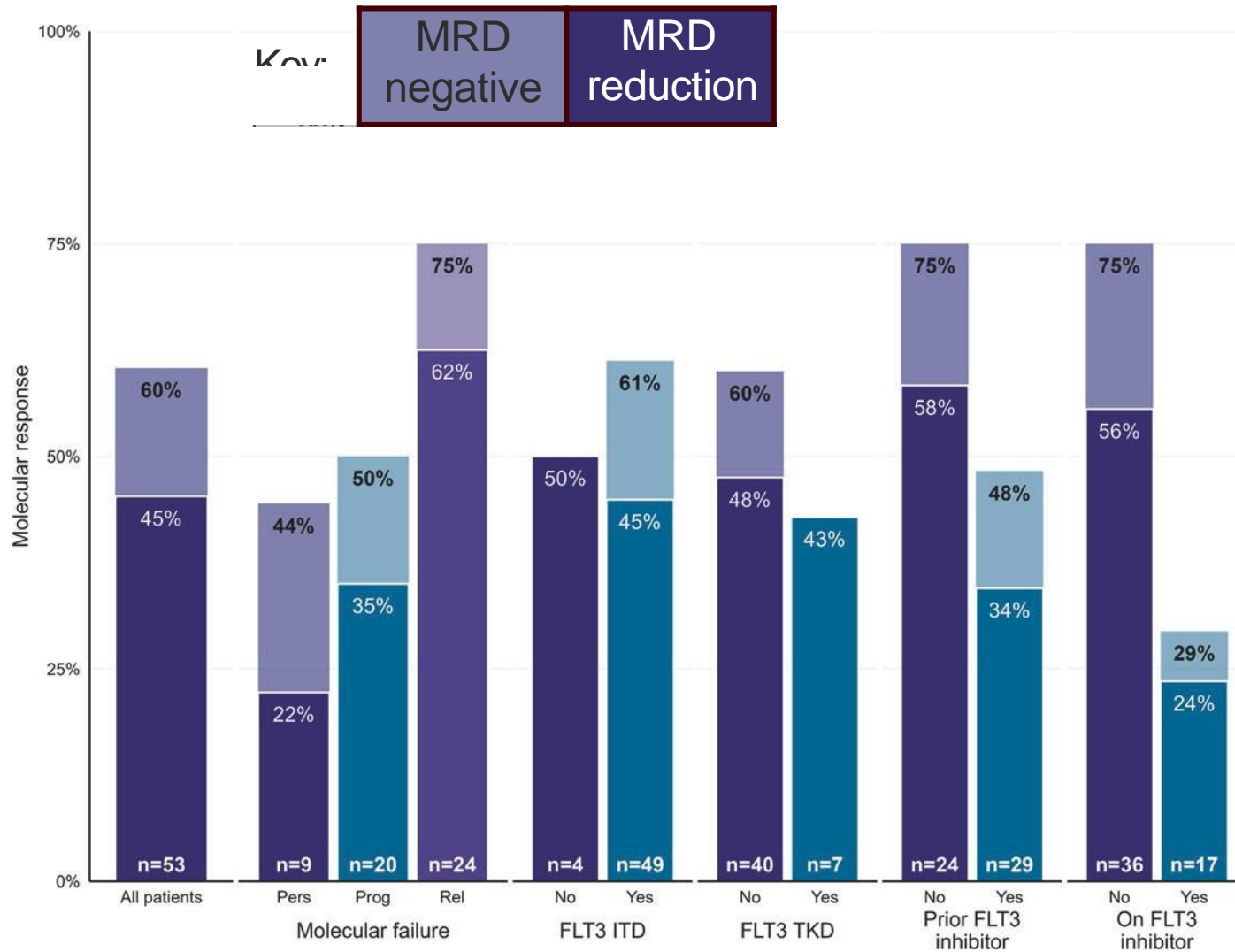
	0	6	12	18	24	30	36
FLT3-ITD wt	57	51	40	31	22	16	11
FLT3-ITD mut	22	16	11	7	5	4	1

Response

- Molecular progression
- Stable disease
- MRD reduction
- MRD negative

n=73

# FLT3 inhibitors for *FLT3*<sup>mut</sup> MRD relapse

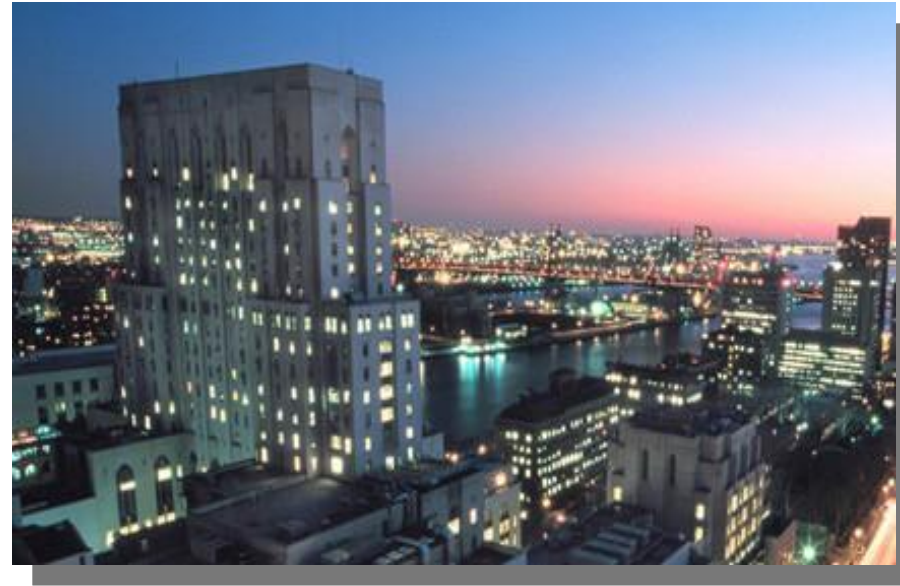


Othman et al. Leukemia. 2023 Oct;37(10):2066-2072.

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