3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

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High-risk cytogenetic AML

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Disclosures of Pau Montesinos

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	x		x		x	x	
Jazz pharma	x		x		x	x	
Daiichi Sankyo	x		x		x	x	
BMS	x		x		x	x	
Pfizer	x		x		x	x	

Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel

Favourable

- 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 or with *FLT3*-ITD^{low}**
- Biallelic mutated *CEBPA*

Intermediate

- **Mutated *NPM1* and *FLT3*-ITD^{high}**
- **Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}** (without adverse-risk genetic lesions)
- t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*
- Cytogenetic abnormalities not classified as favourable or adverse

Adverse

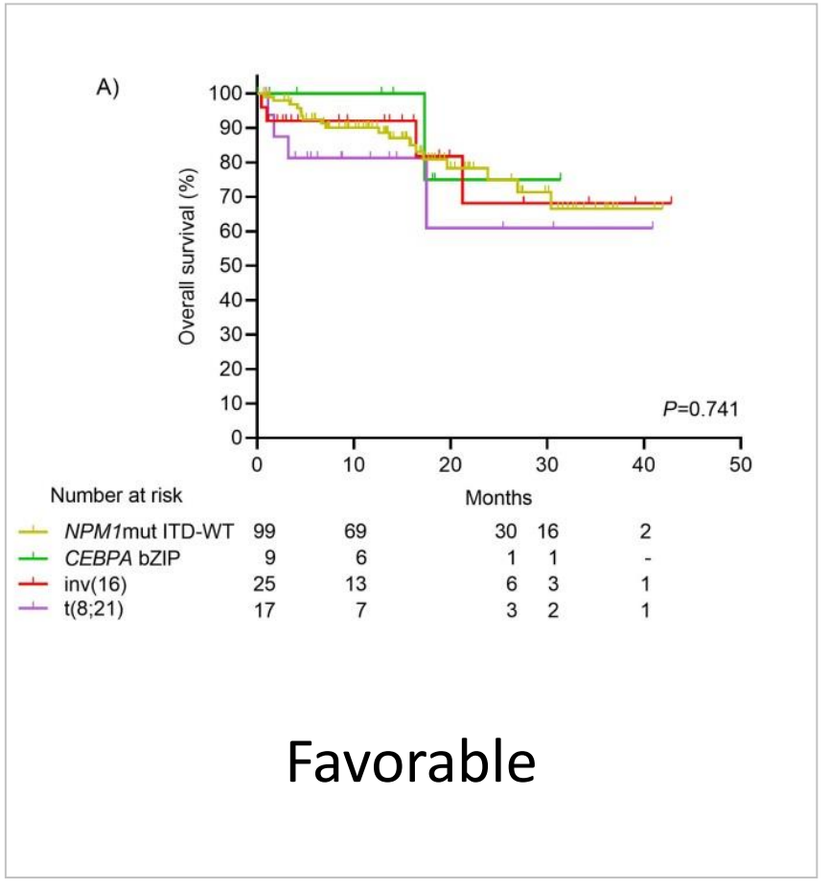
- t(6;9)(p23;q34.1); *DEK-NUP214*
- t(v;11q23.3); *KMT2A* rearranged
- t(9;22)(q34.1;q11.2); *BCR-ABL1*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)*
- −5 or del(5q); −7; −17/abn(17p)
- Complex karyotype, monosomal karyotype
- **Wild-type *NPM1* and *FLT3*-ITD^{high}**
- **Mutated *RUNX1*¶**
- **Mutated *ASXL1*¶**
- **Mutated *TP53***

HE-ES-2100380

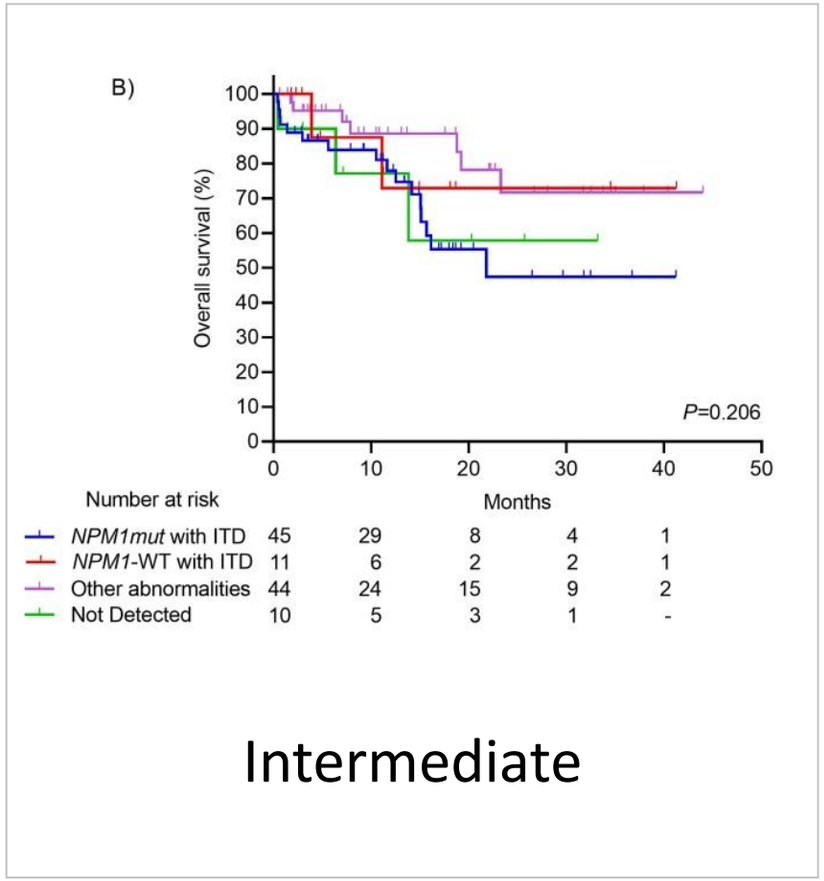
FLT3-ITD allelic ratio defined as: low, <0.5; high, ≥0.5. ¶These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes

Döhner H et al. *Blood* 2017;129:424–447

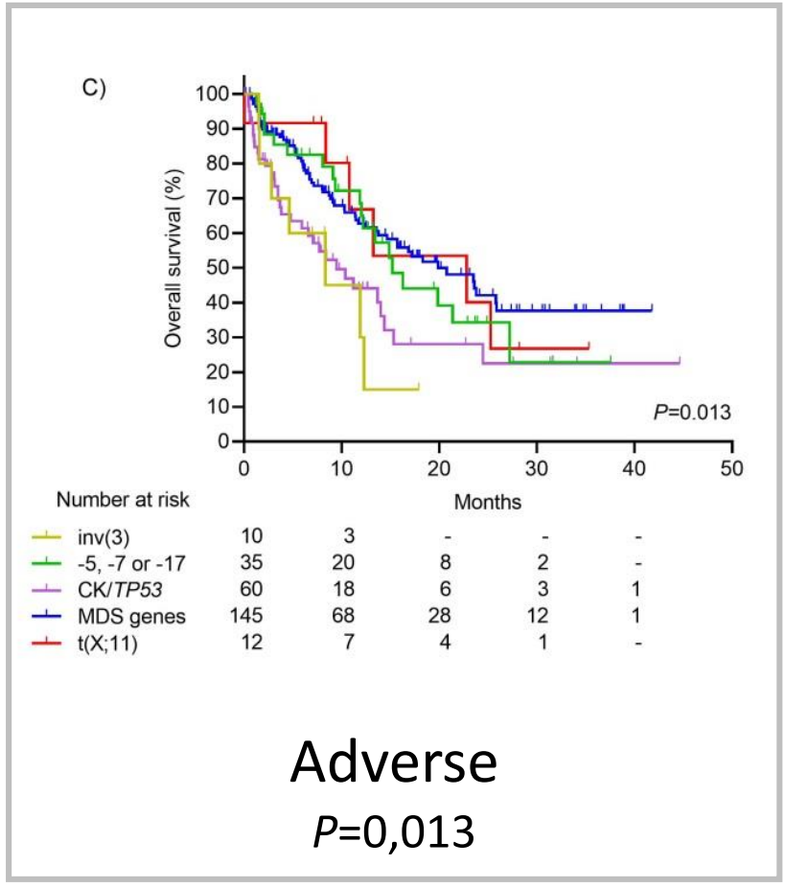
European LeukemiaNet 2022. Validation by PETHEMA group



Favorable



Intermediate

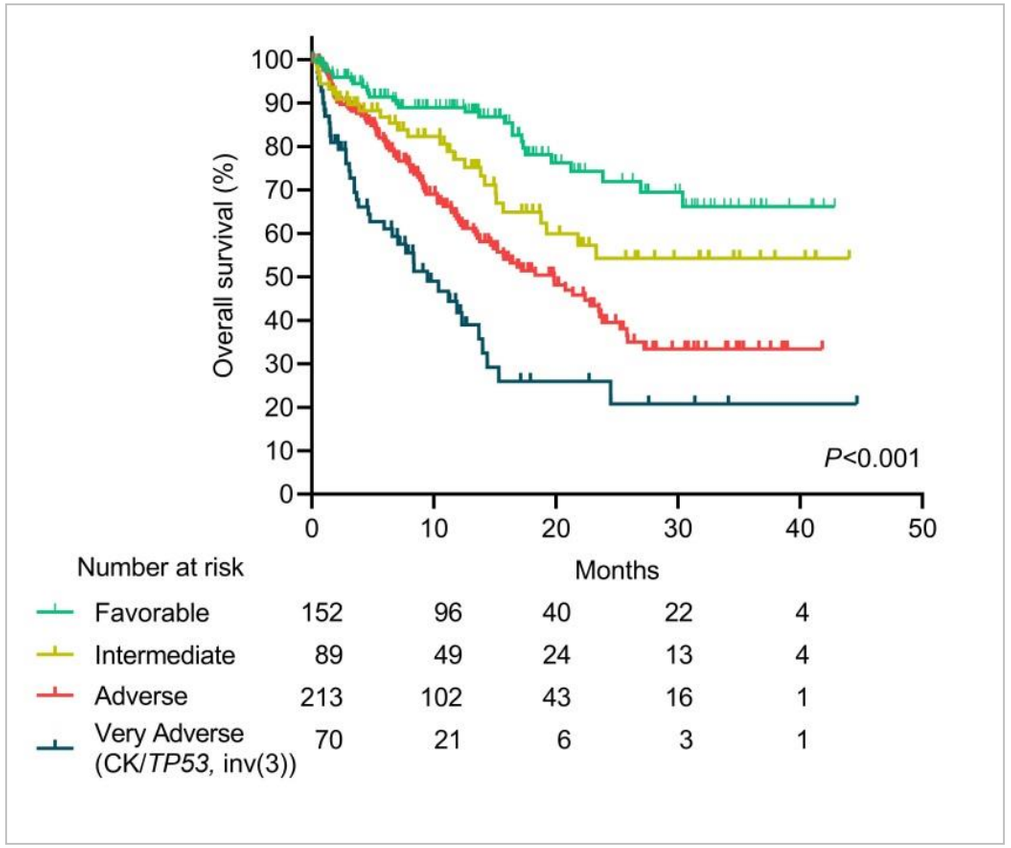


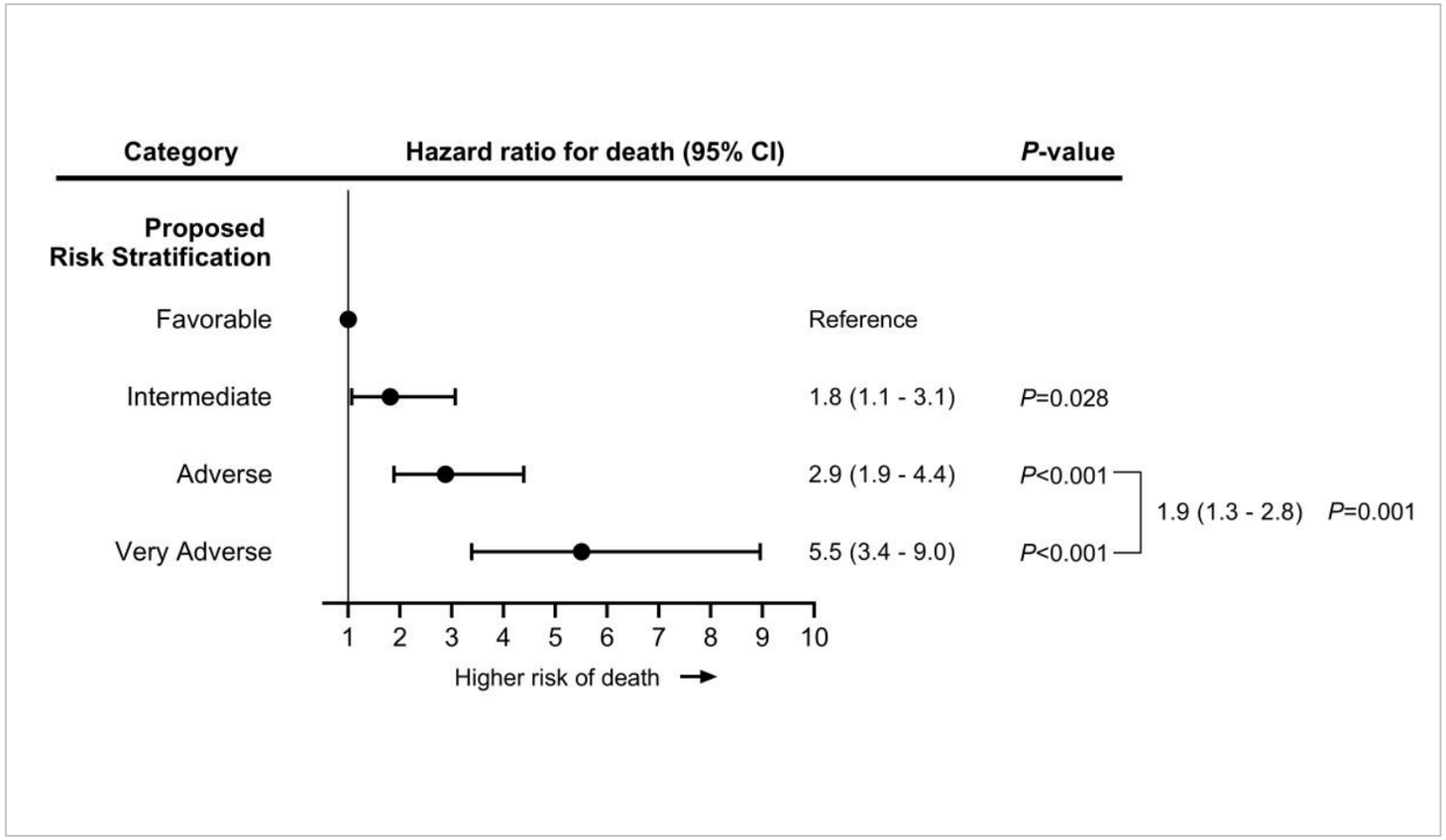
Adverse

P=0,013

Claudia Sargas, Blood Cancer Journal, 2023

European LeukemiaNet 2022 refinement → Very adverse group



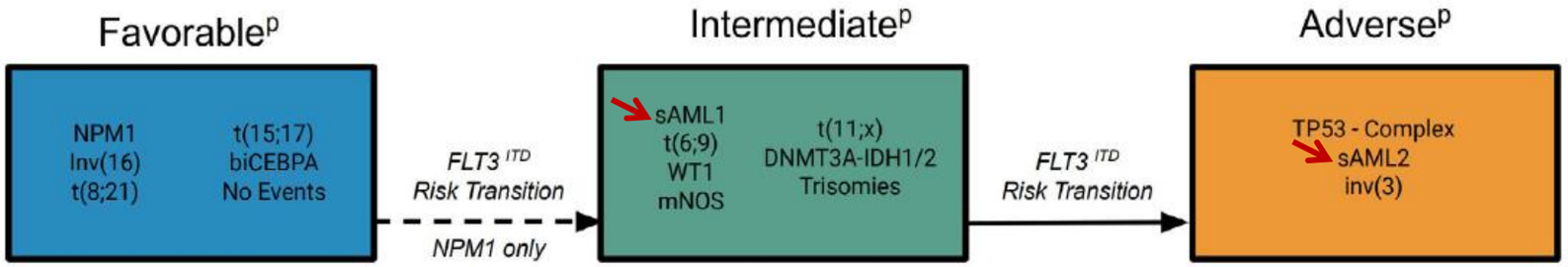


Claudia Sargas, Blood Cancer Journal, 2023

European LeukemiaNet 2022. The issue of MDS-genes

sAML: *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, STAG2, RUNX1, SETBP1*

Tazi *et al*., Nature Communications (2022) 13:4622

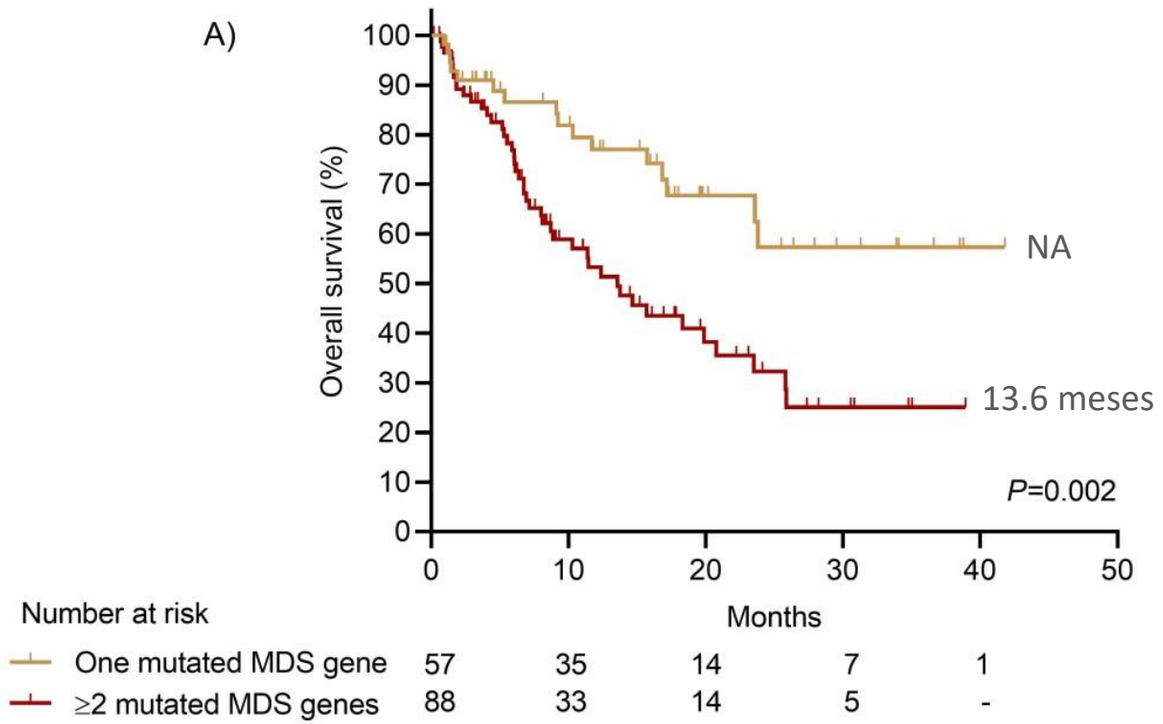


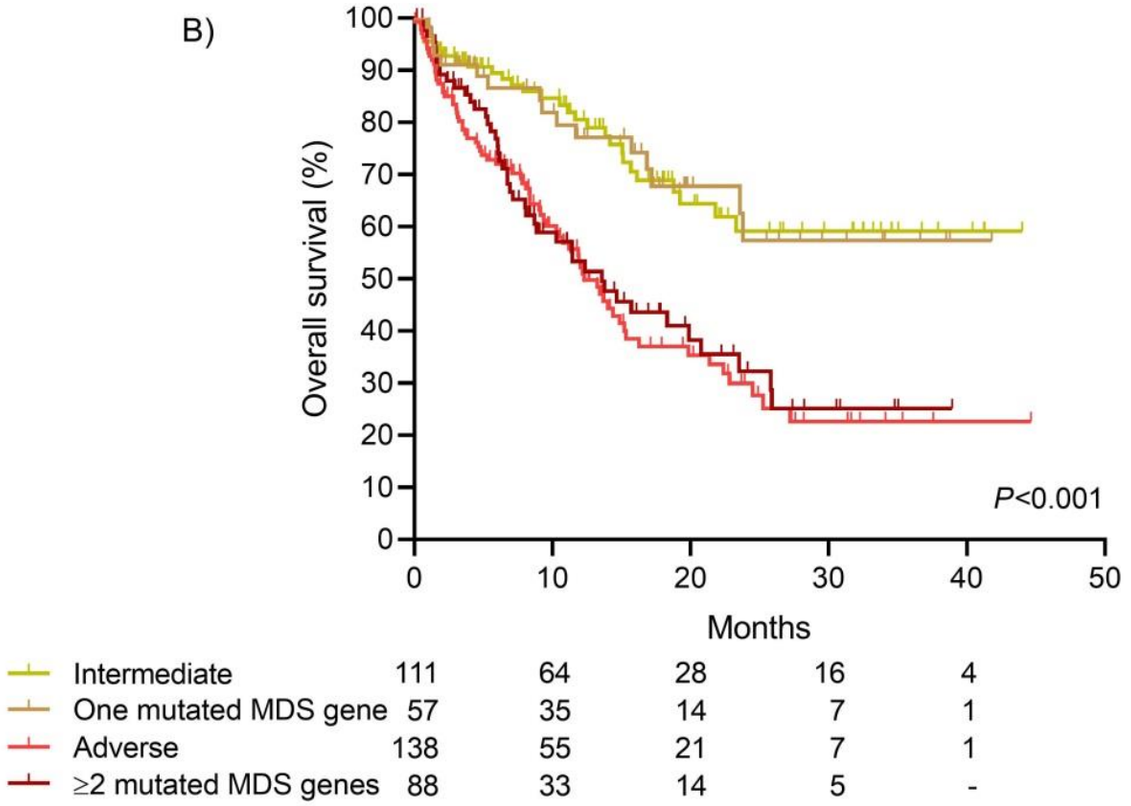
European LeukemiaNet Döhner H *et al*., Blood (2022) 140 (12): 1345–1377.

Risk Category[b]	Genetic Abnormality
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged[g] • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*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,[h] monosomal karyotype[i] • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2*[j] • Mutated *TP53*[k]

European LeukemiaNet 2022. Validation by PETHEMA group

Genes MDS: *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1 Y ZRSR2*





Claudia Sargas, Blood Cancer Journal, 2023

Use of biomarkers to refine risk-adapted algorithms

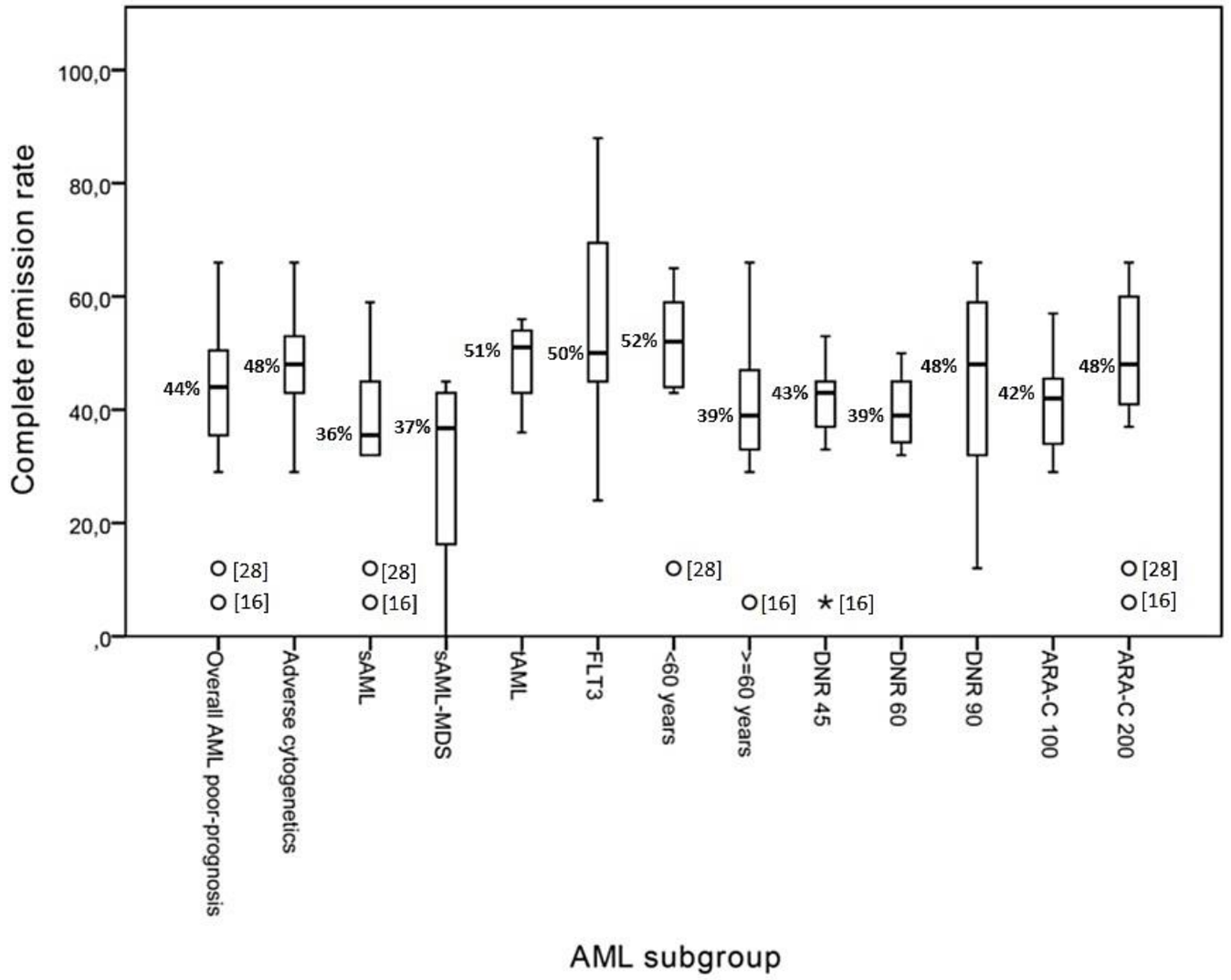
"One-size-fits-all" therapy: AML as a single entity

Tailored therapy—Risk-adapted therapy:
Distinct subtypes of AML (prognostic factors)

Targeted therapy: Acknowledgment of molecular targets

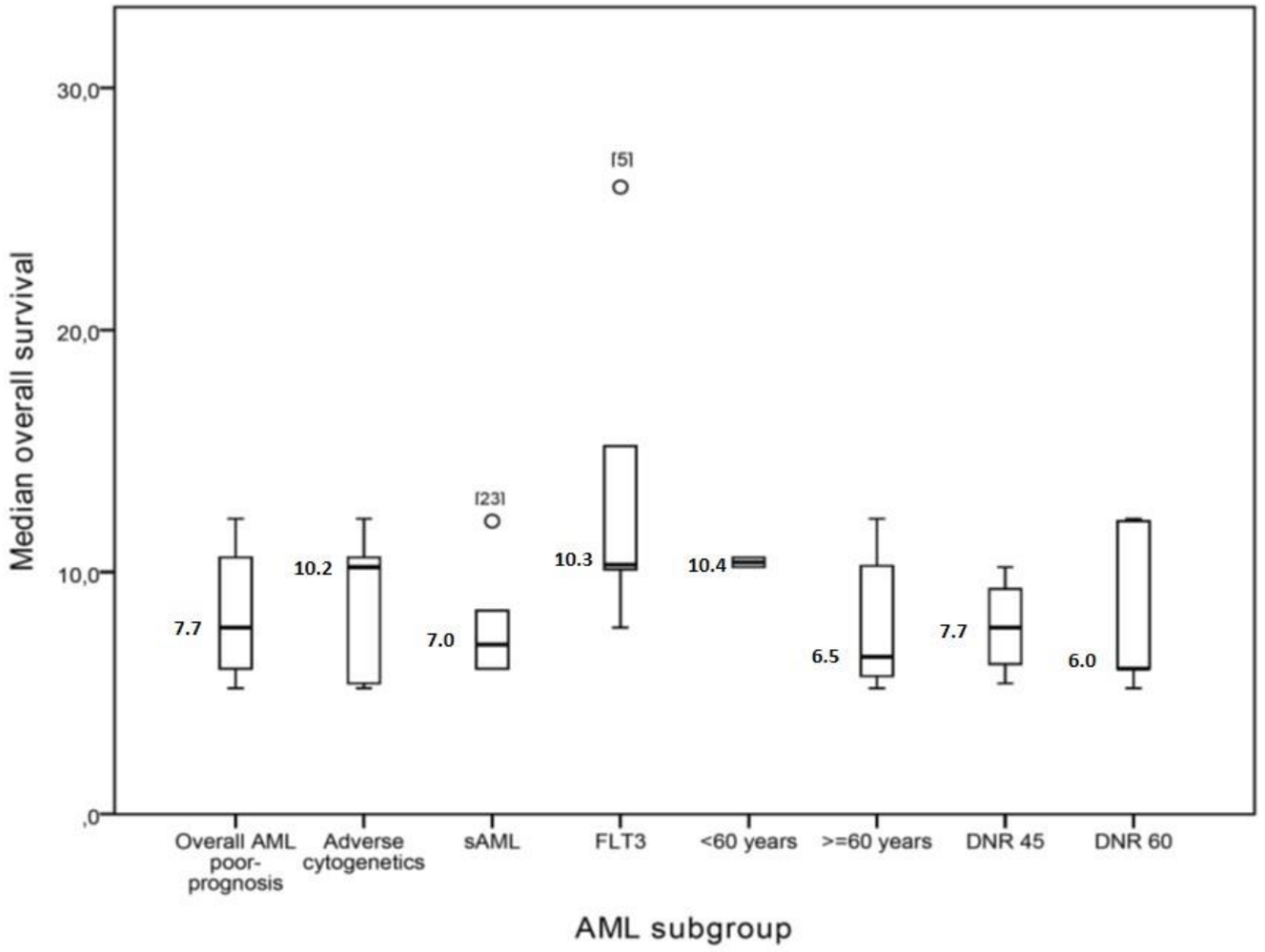
Courtesy by Dr. Miguel A. Sanz

Boxplot diagram of the complete remission (CR) rate of the different subgroups of AML with poor prognosis



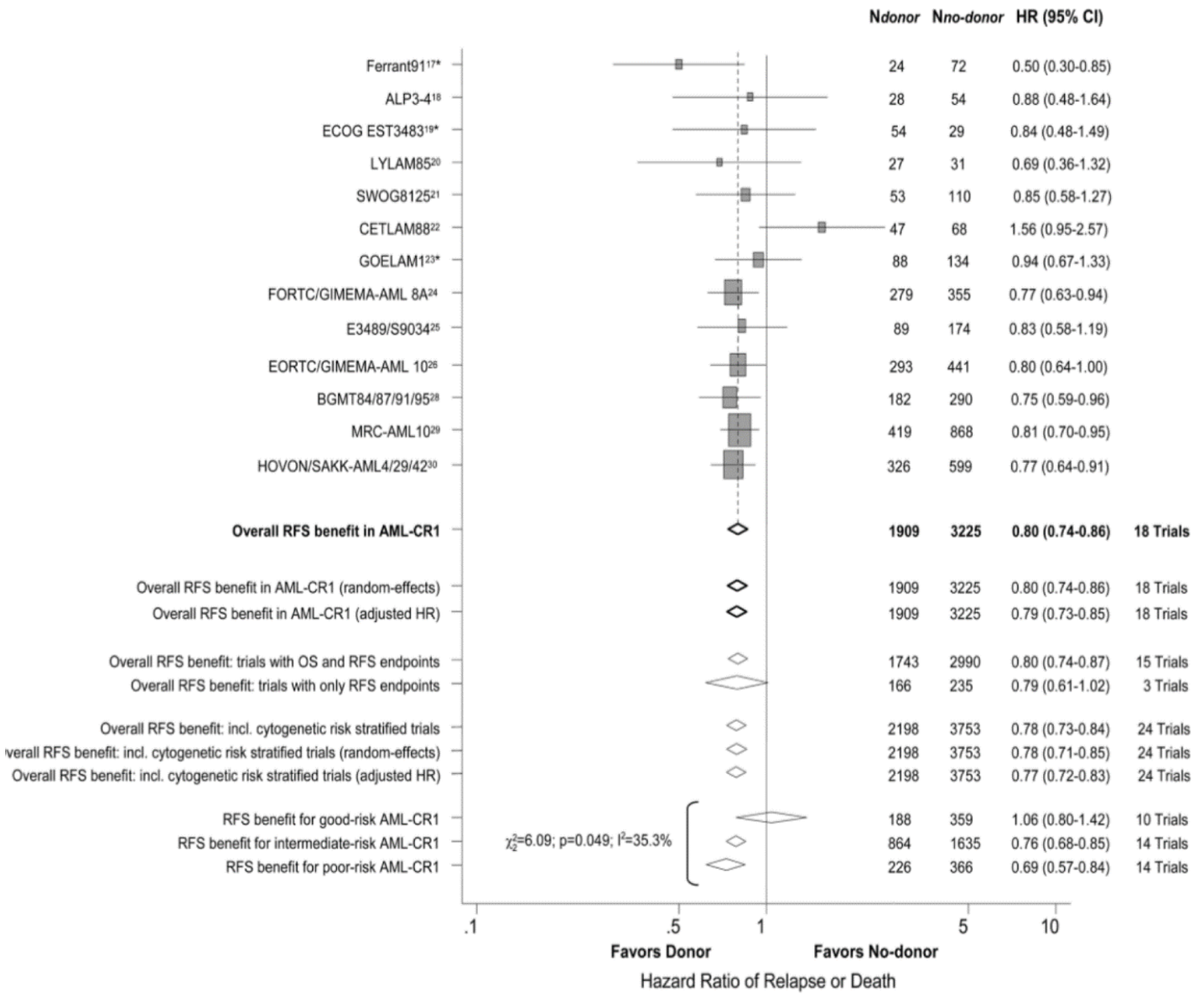
Juan Eduardo Megías-Vericat, Expert Review of Clinical Pharmacology, 2018

Boxplot diagram of the median overall survival (OS) rate of the different subgroups of AML with poor prognosis



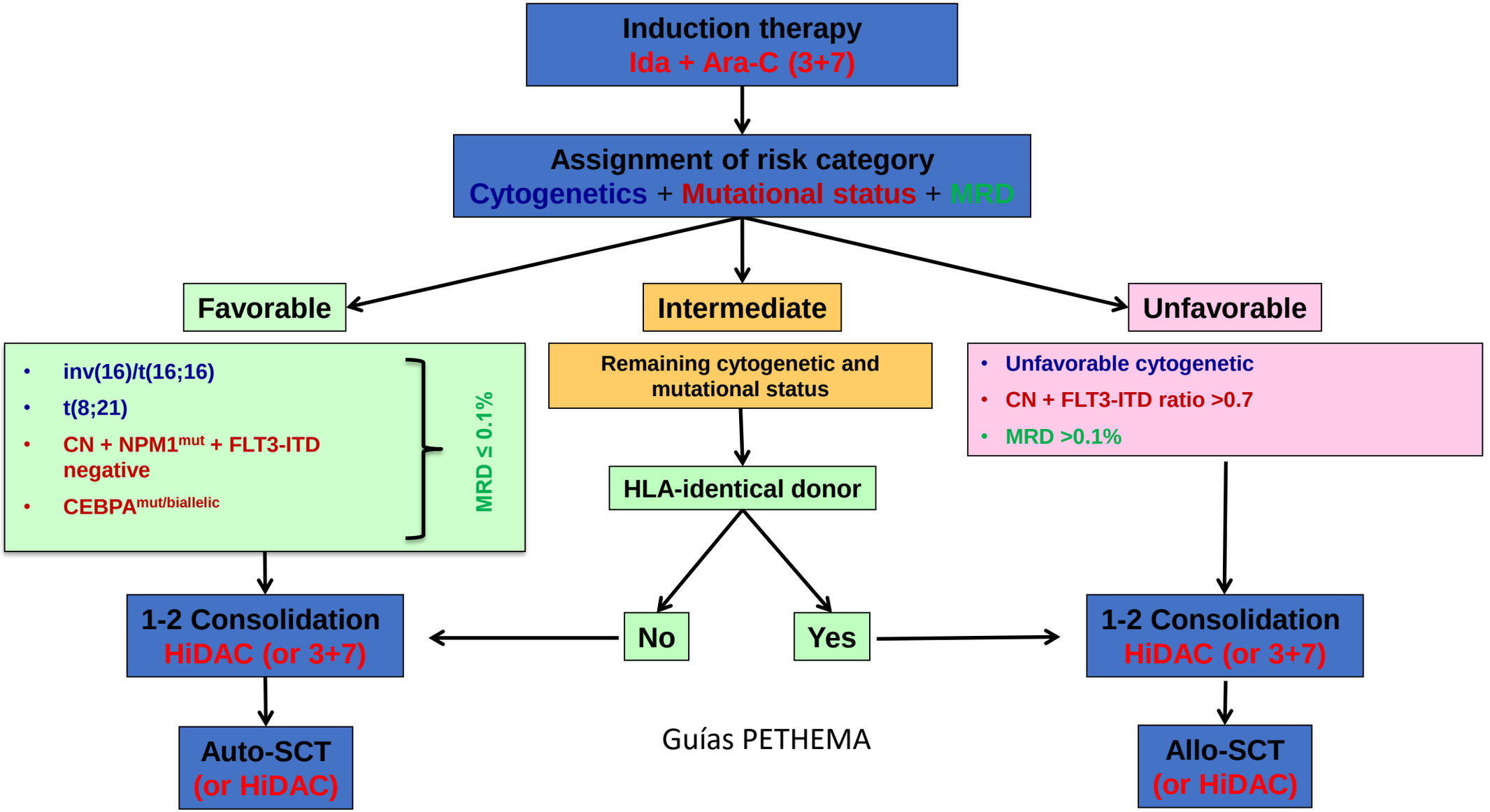
Juan Eduardo Megías-Vericat, Expert Review of Clinical Pharmacology, 2018

Role of allogeneic stem cell transplantation in acute myeloid leukemia



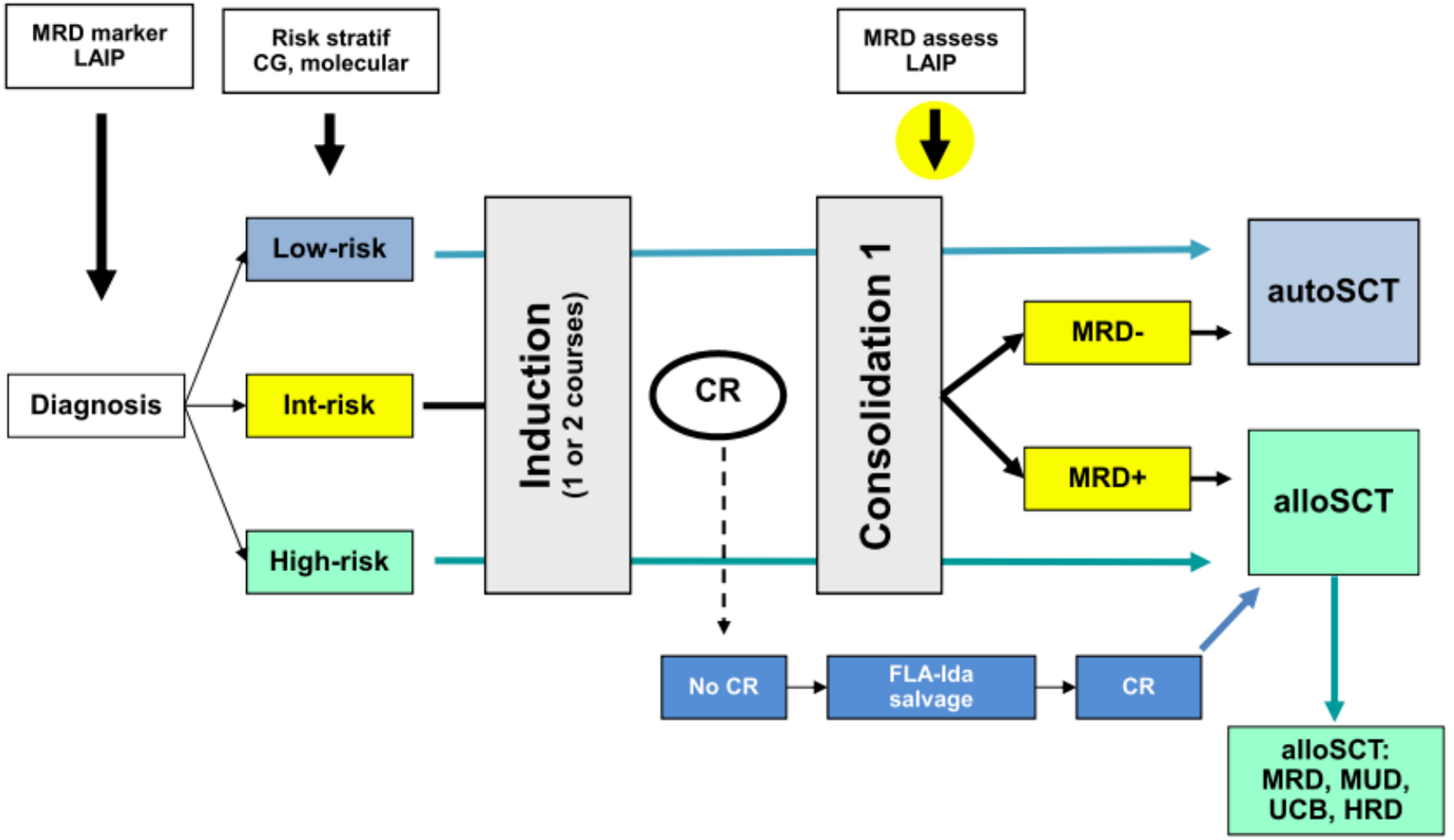
Koreth, JAMA 2009

PETHEMA LMA2007/2010 protocol



Guías PETHEMA

GIMEMA AML1310 trial – Schedule

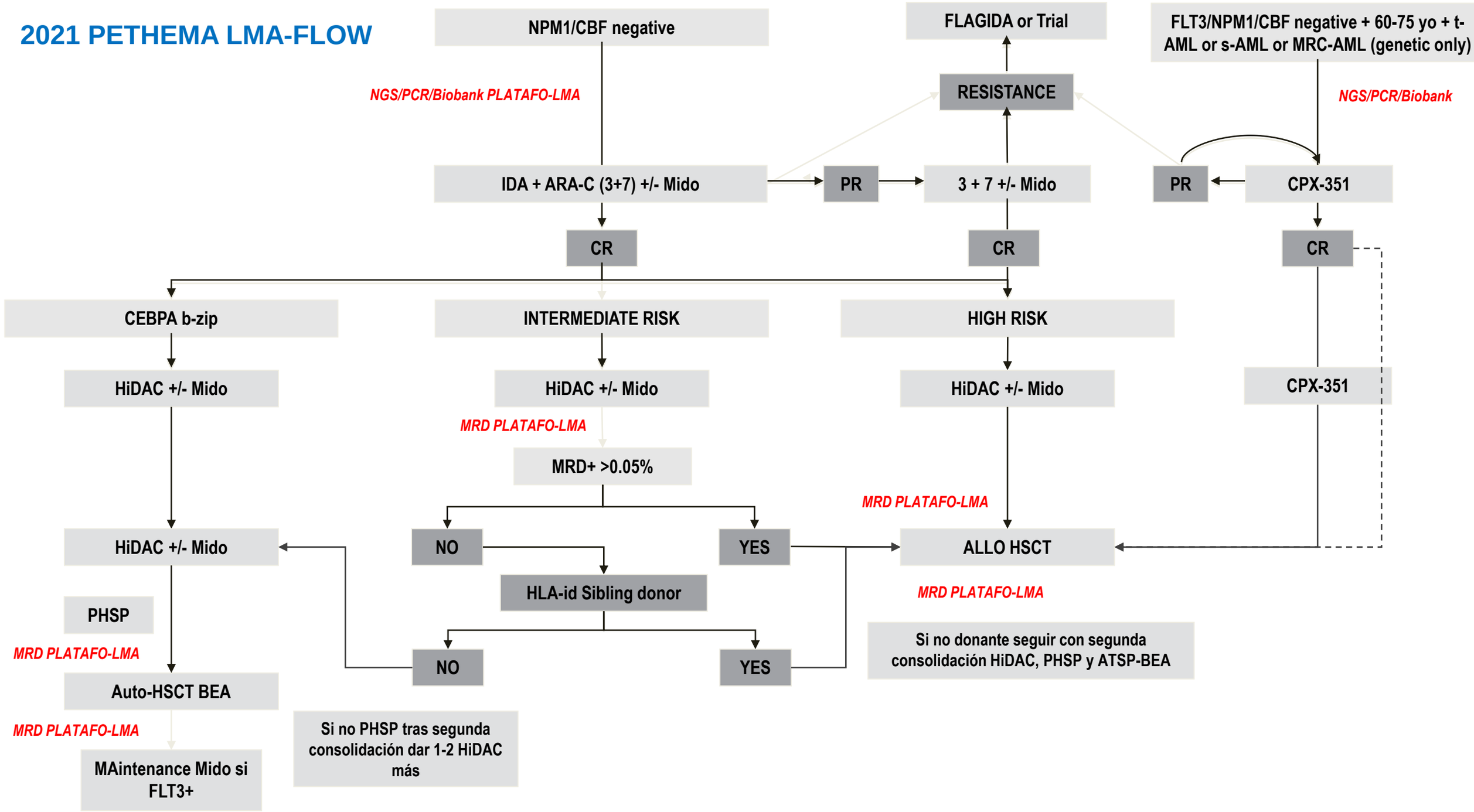


Low-risk: CBF/Kit^{wt}; NPM1+/FLT3-
Int-risk: all others
High-risk: Adverse K; FLT3-ITD

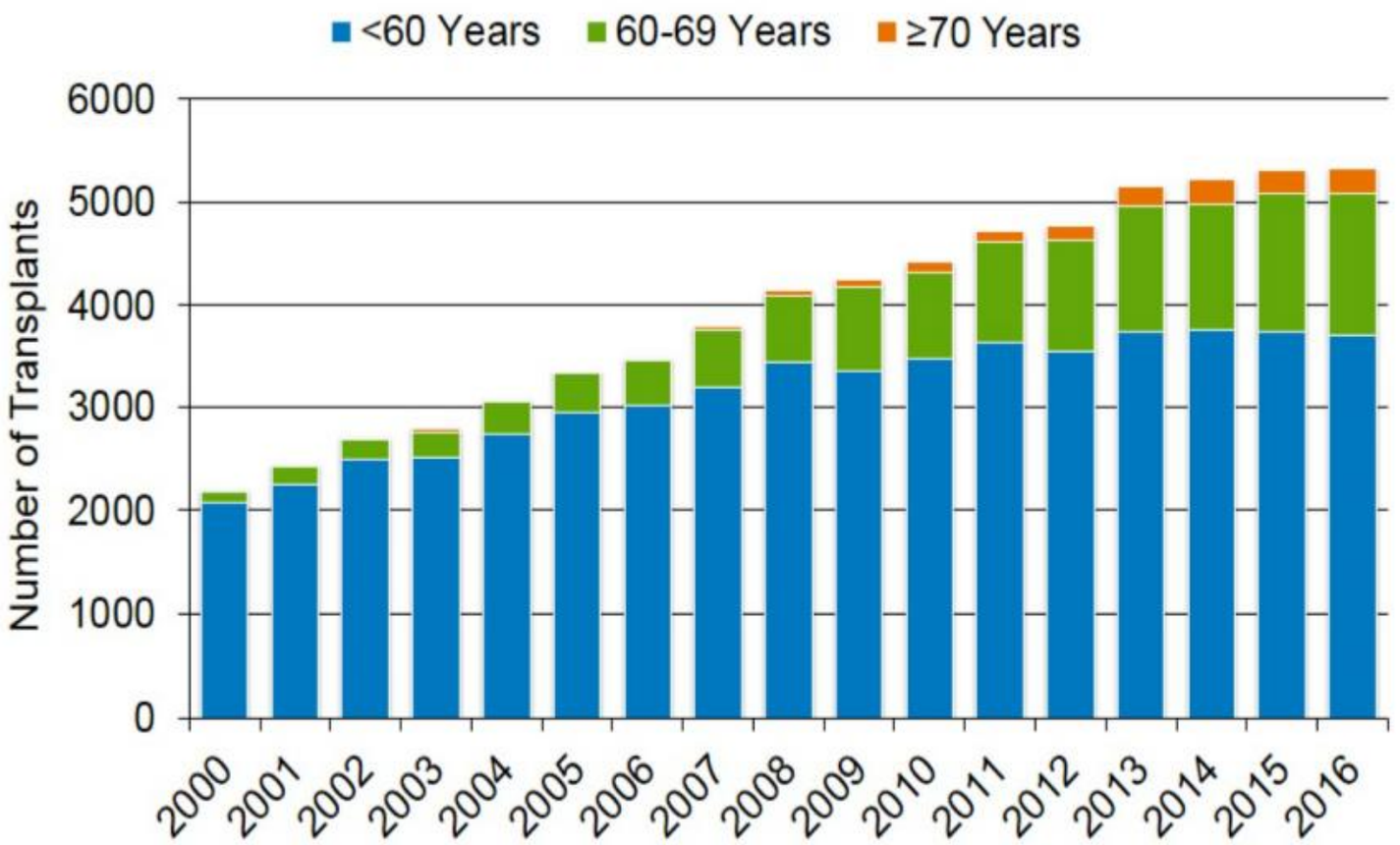
- *INDUCTION*
  - *Daunorubicin : 50 mg/m2 iv D 1,3,5*
  - *SD-Ara-C: 100 mg/m2 c.i. D 1-10,*
  - *Etoposide: 100 mg/m2 iv D 1-5*
- *CONSOLIDATION*
  - *Daunorubicin : 50 mg/m2 iv D 4-6*
  - *ID-Ara-C : 500 mg/m2/q12 hrs, over 2 hrs, D 1-6*

Venditti, Blood 2019

2021 PETHEMA LMA-FLOW



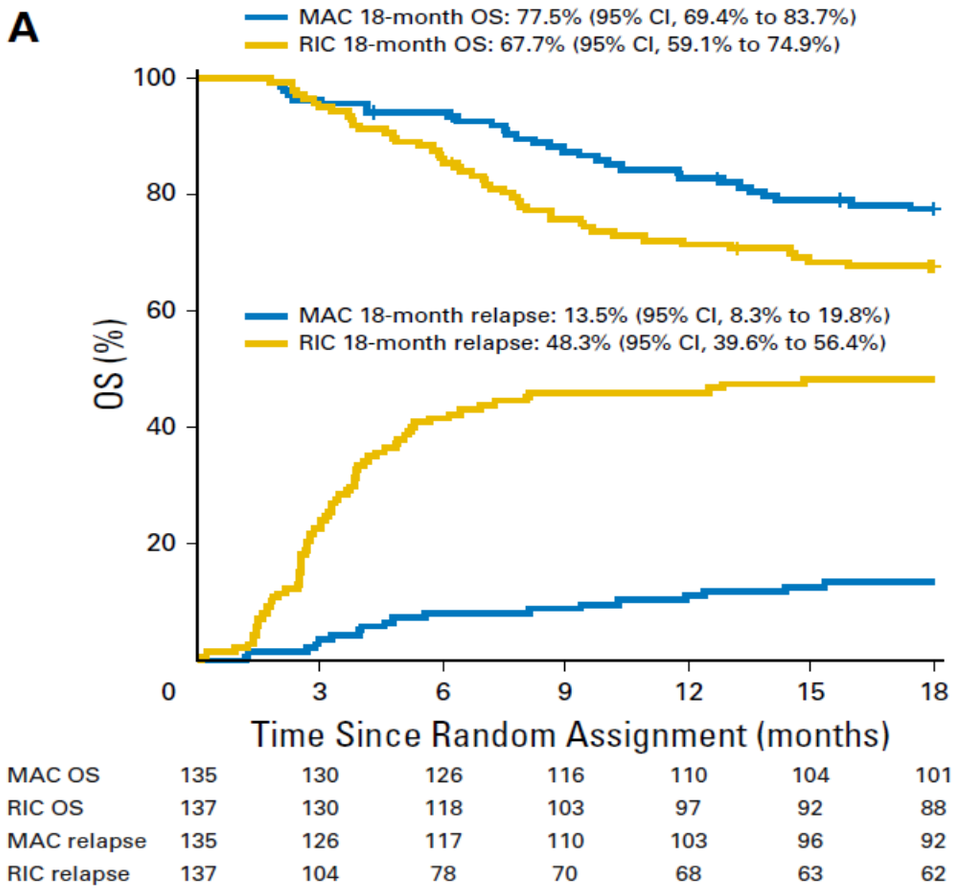
Trends in allogeneic HCT in the US by recipient age*

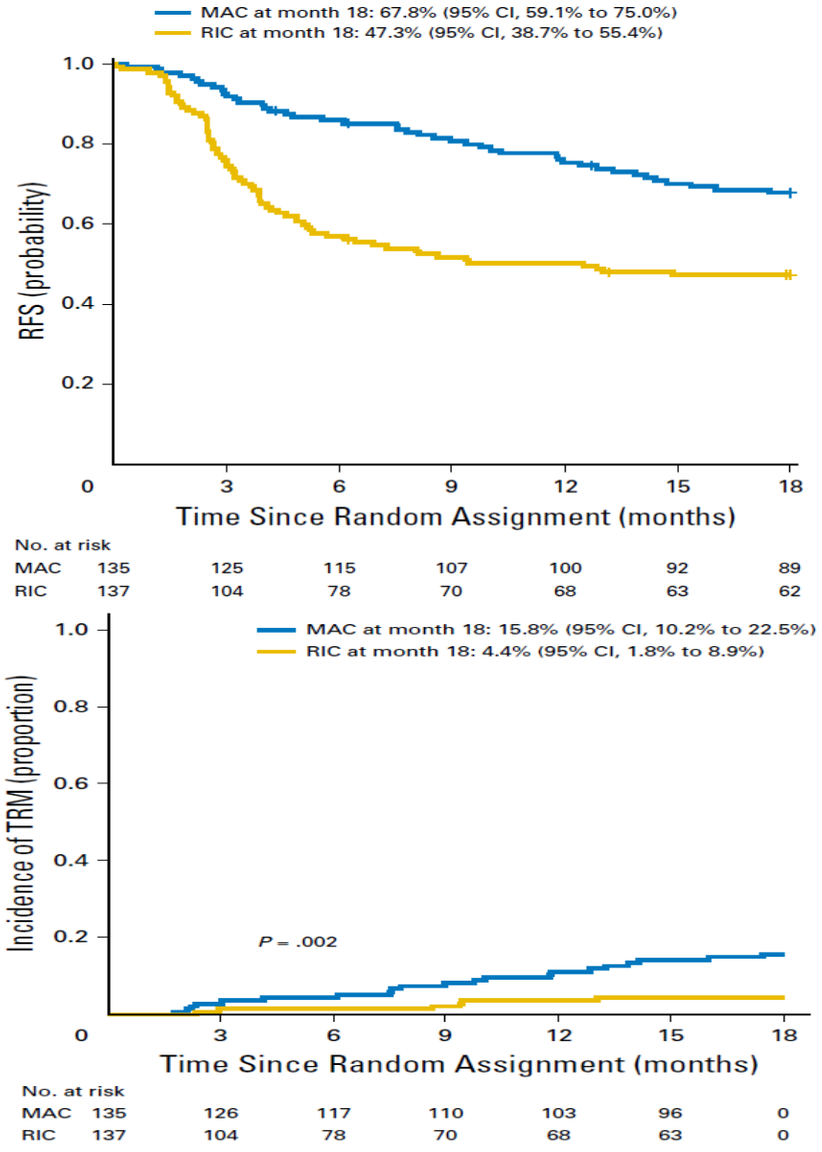


*Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2018. Available at http://www.cibmtr.org

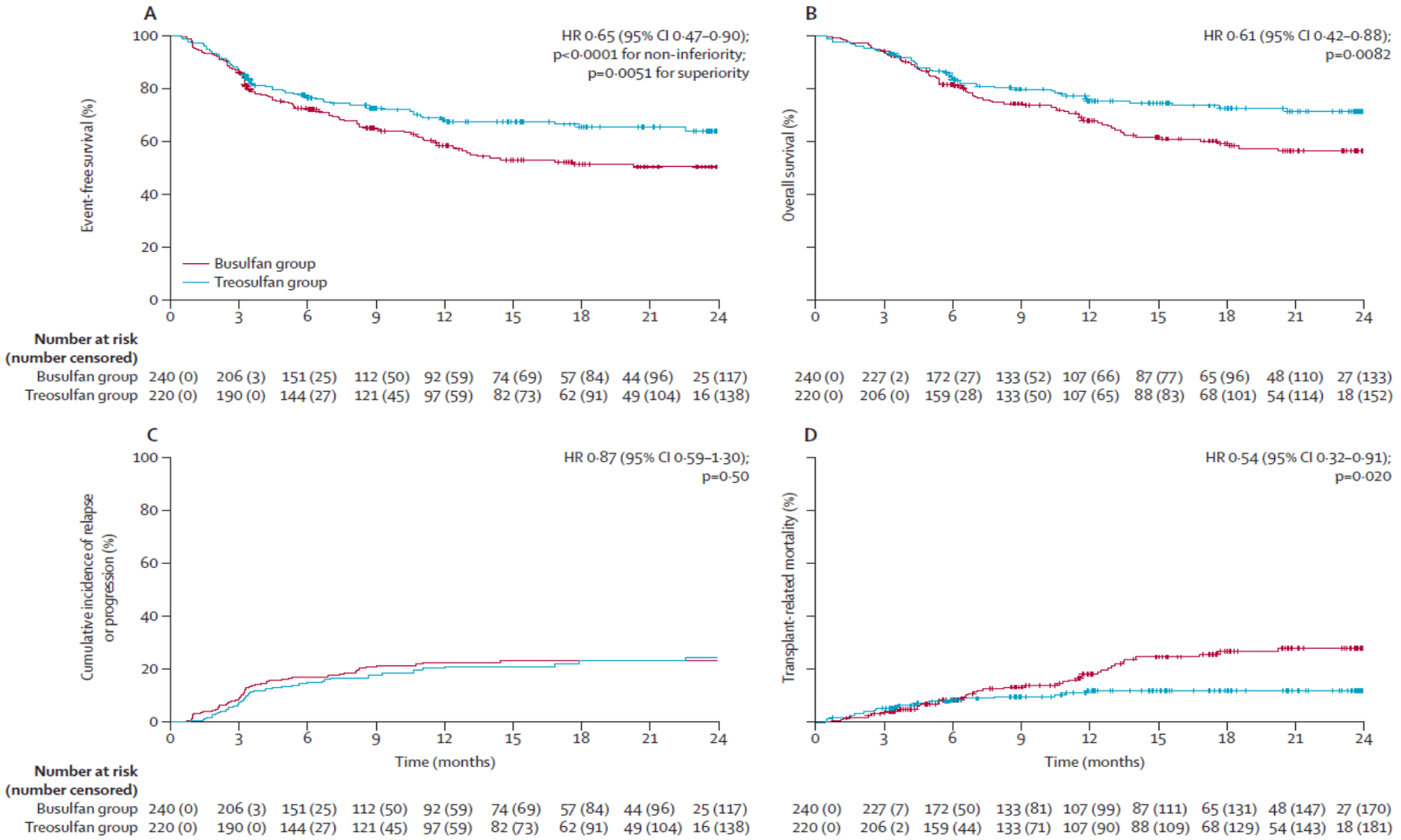
Randomized trial: RIC vs MAC in AML and MDS patients: Age 18-65 and comorbidity index < 4





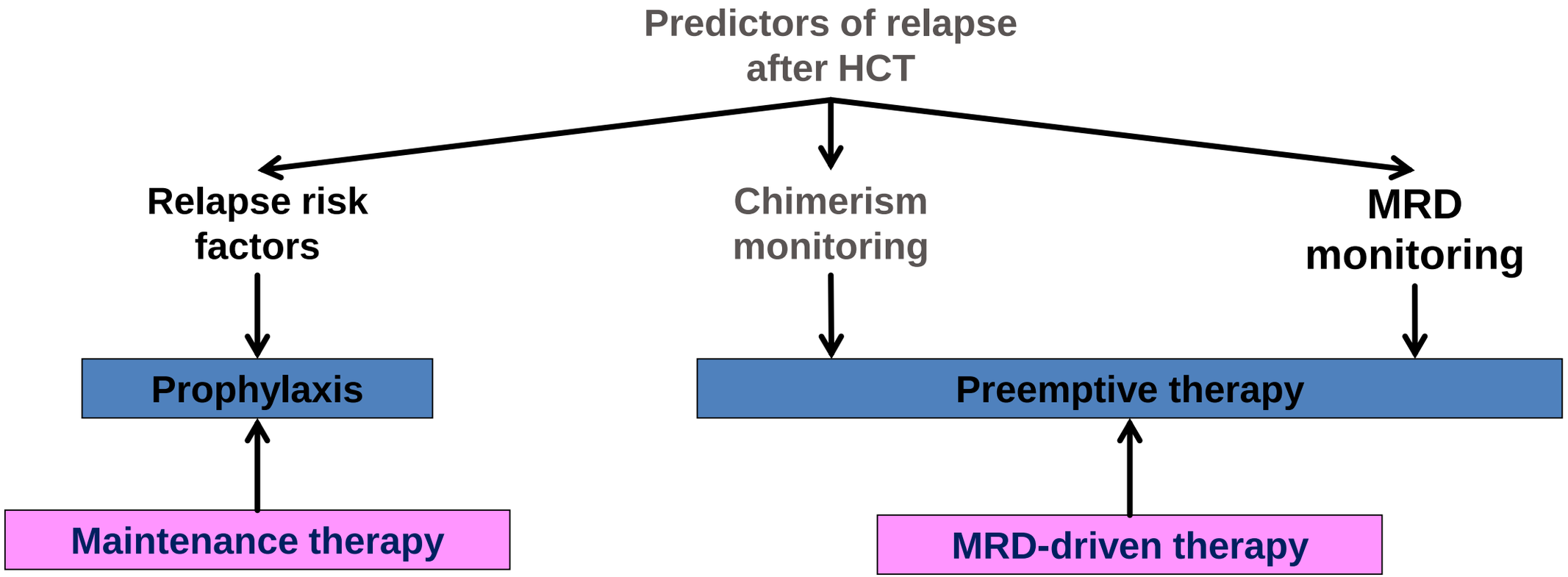
Scott B, JCO 2017

Randomized trial: Treosulfan or busulfan plus fludarabine as RIC before allo-HSCT for older patients with AML or MDS



Beelen Lancet Hematol 2020

Strategies to control relapse in AML
Maintenance vs. preemptive therapy



Personal opinion from P. Montesinos

Phase 3 trial of 10-day decitabine versus 7+3 followed by transplantation in fit AML patients aged ≥ 60 years: HRQoL

Study design	International, open-label, Phase 3 randomized controlled trial comparing 10-day decitabine followed by HSCT versus intensive chemotherapy (7+3) followed by HSCT*
Eligibility	Age ≥ 60 years; newly diagnosed AML (de novo or secondary); eligible for induction chemotherapy; ECOG PS ≤ 2
Enrolment	606 patients (303 per arm); around a third were aged ≥ 70 years
Clinical outcomes	*Presented at EHA 2022:* Similar survival with decitabine versus 7+3; comparable alloHSCT rates; more favorable safety profile with decitabine[1]
HRQoL	• Assessed using EORTC QLQ-C30 and its module for older patients (EORTC QLQ-ELD14), specifically based on 5 *a priori*-selected primary scales: physical functioning, role functioning, fatigue, pain, and illness burden • Assessments were performed at baseline and then short-term (2 months from randomization) and long-term (6 and 12 months) • For patients undergoing HSCT, HRQoL was assessed prior to the procedure and at day 100 after transplant • QoL deterioration was defined as any of the following: death; progression; or clinically meaningful deterioration from baseline in at least one of the primary HRQoL scales

**Decitabine was administered for 10 days consecutively in cycle 1 (20 mg/m^2), 10 or 5 days in subsequent cycles (depending on bone marrow blast clearance at day 28); intensive chemotherapy was daunorubicin 60 mg/m^2 x 3 days, cytarabine 200 mg/m^2 x 7 days, followed by 1–3 additional chemotherapy cycles.*

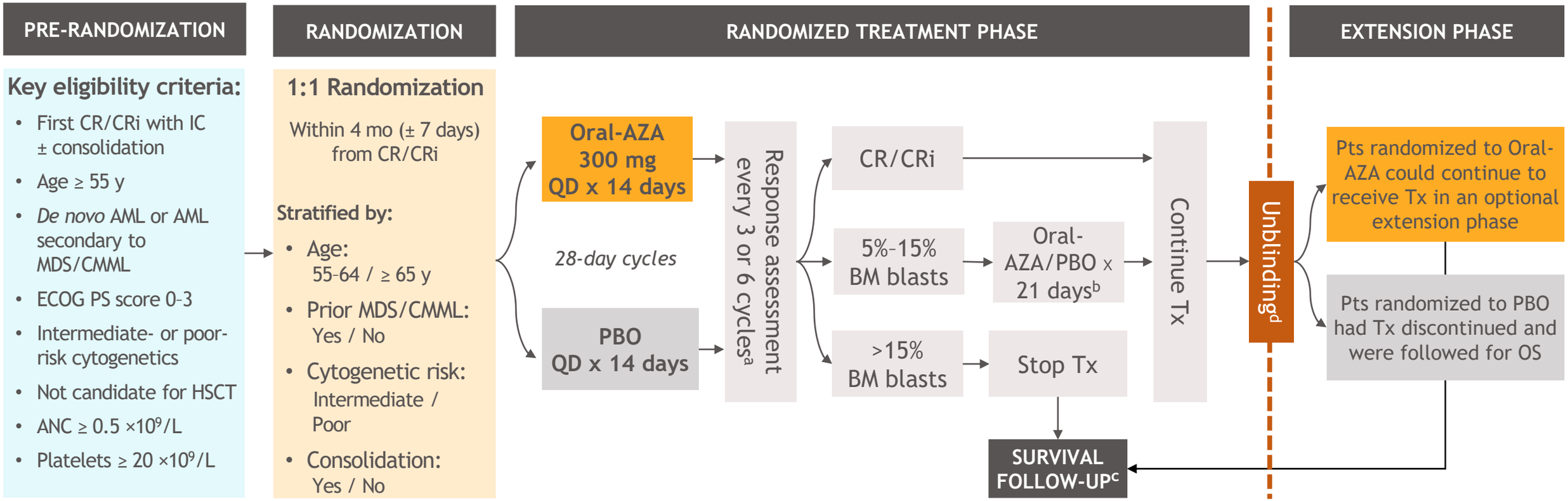
AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; EHA, European Hematology Association; EORTC, European Organisation for Research and Treatment of Cancer; HRQoL, health-related QoL; HSCT, hematopoietic stem cell transplant; QLQ, QoL questionnaire; QoL, quality of life.

1. Lübbert M et al. HemaSphere 2022;6:26–27.

Efficace F et al., ASH 2022; abstract 535 (oral presentation)

QUAZAR AML-001: Study design and key eligibility criteria

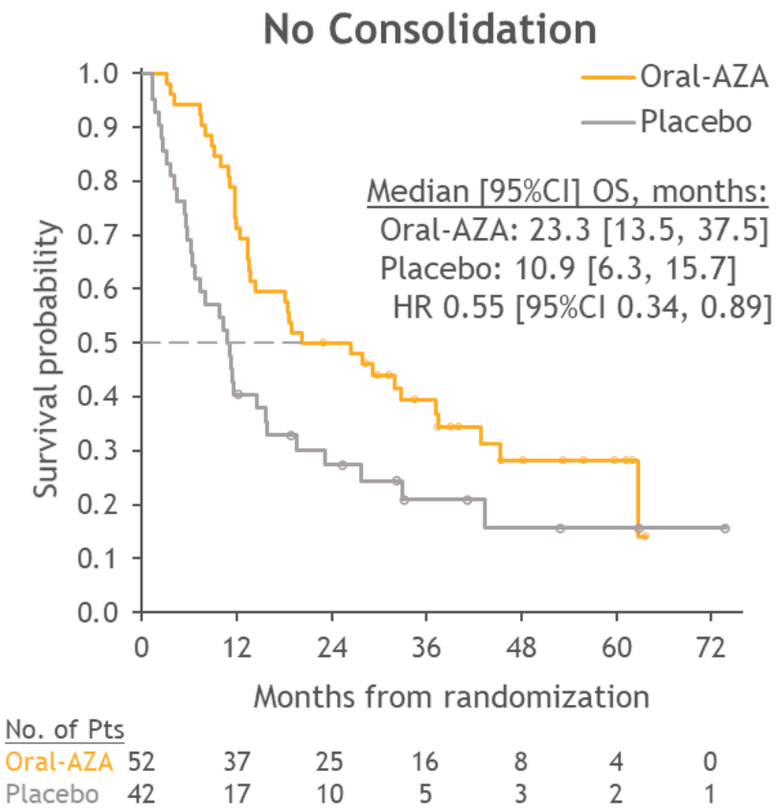
International, multicenter, PBO-controlled, double-blind, randomized, phase 3 trial

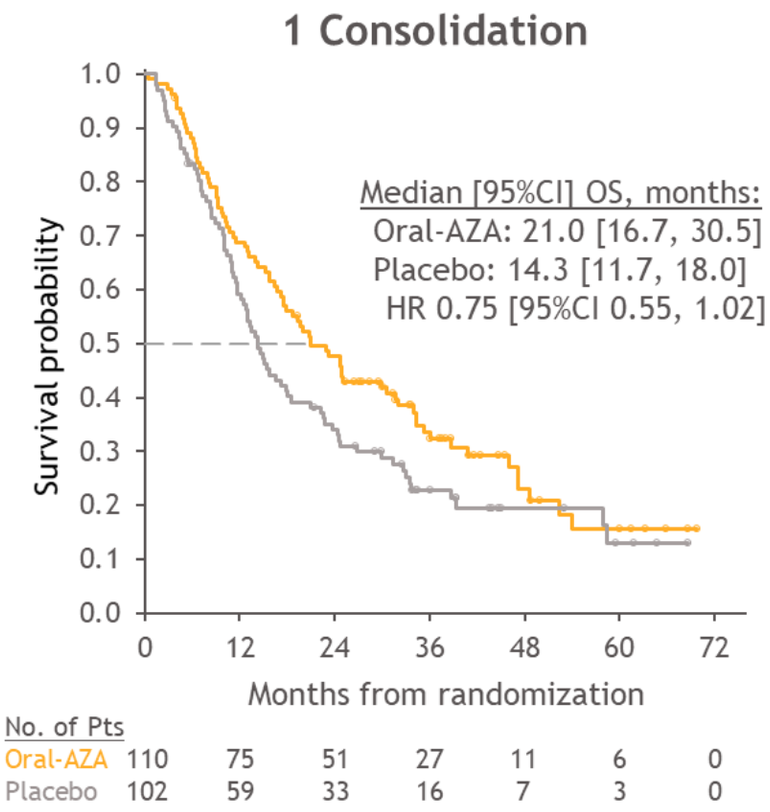


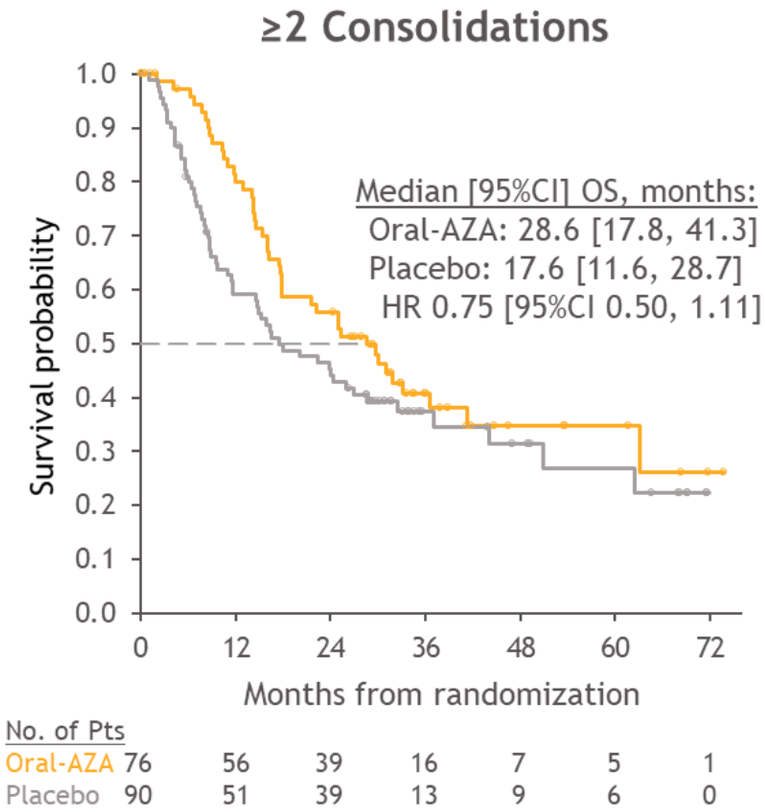
Wei et al. Long-term survival with oral azacitidine for patients with acute myeloid leukemia in first remission after chemotherapy: updated results from the randomized, placebo-controlled, phase 3 QUAZAR AML-001 trial. *Am J Hematol*. 2023. doi.org/10.1002/ajh.26847

QUAZAR: Overall survival by number of consolidations

- OS was also prolonged with Oral-AZA within each consolidation cohort
- Median OS ranged from 21.0–28.6 months in the Oral-AZA arm and 10.9–17.6 months in the placebo arm





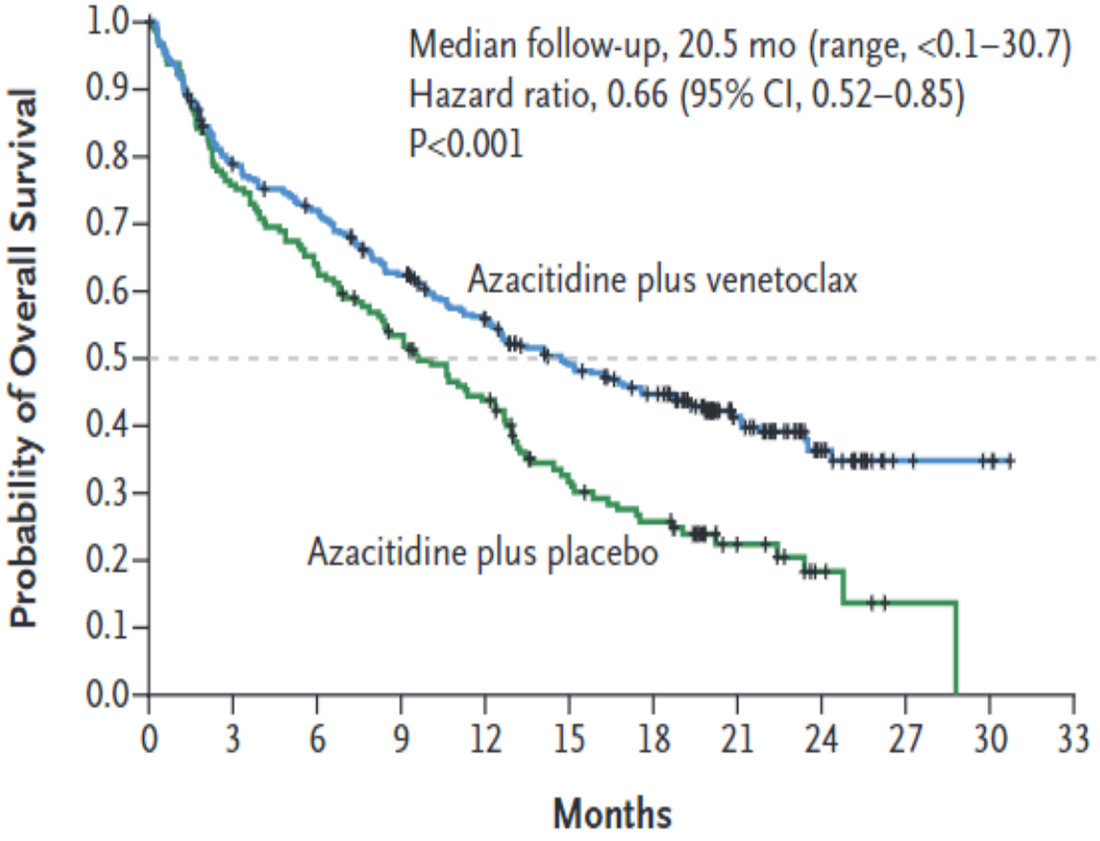


OS estimates were derived using Kaplan-Meier methods and compared for Oral-AZA vs. placebo using log-rank test. Hazard ratios (HRs) and 95% CIs were generated using a stratified Cox proportional hazards model.

95%CI, 95% confidence interval; AZA, azacitidine; HR, hazard ratio; No., number; OS, overall survival; pts, patients.

Results of VIALE-A : Azacitidine +/- Venetoclax

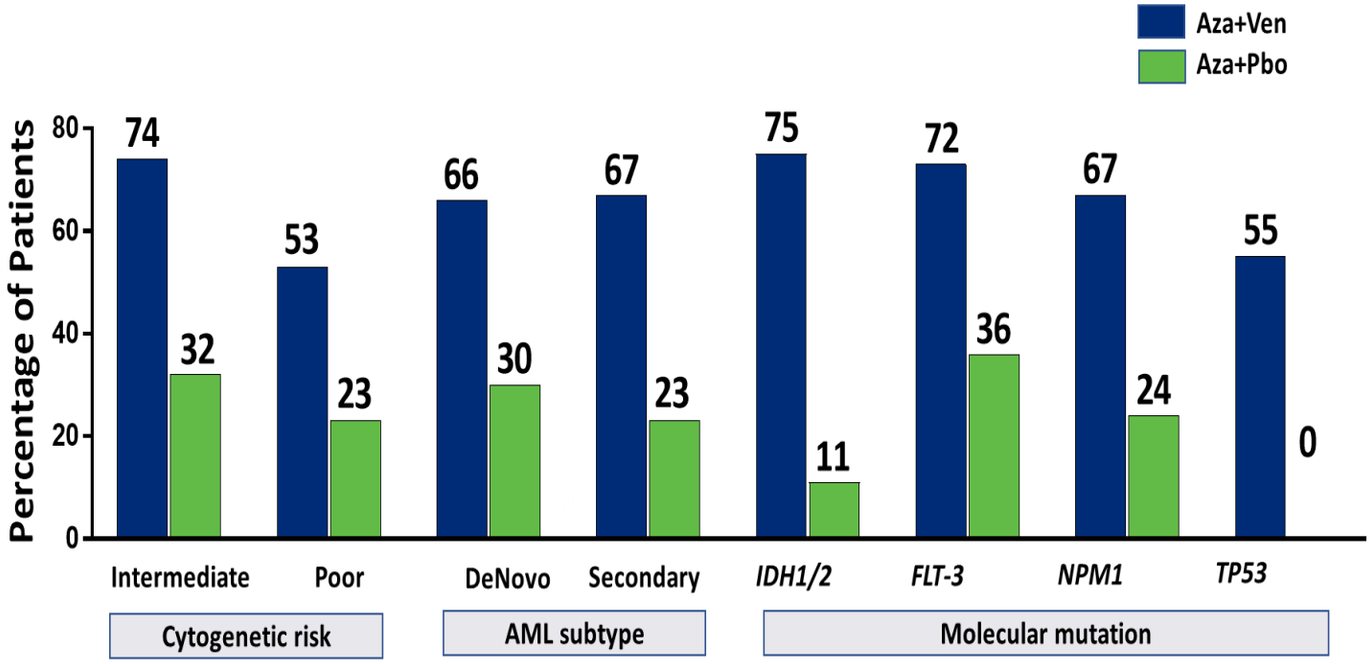
Significant OS improvement with azacitidine + venetoclax



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

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

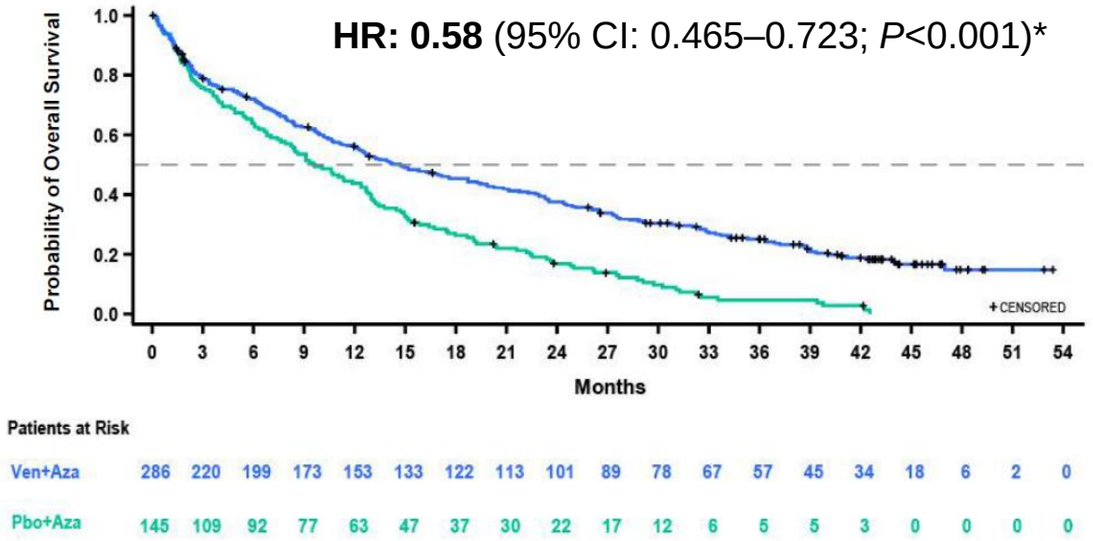
Improved responses occurred *<u>independent</u>* of high risk genomics



DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

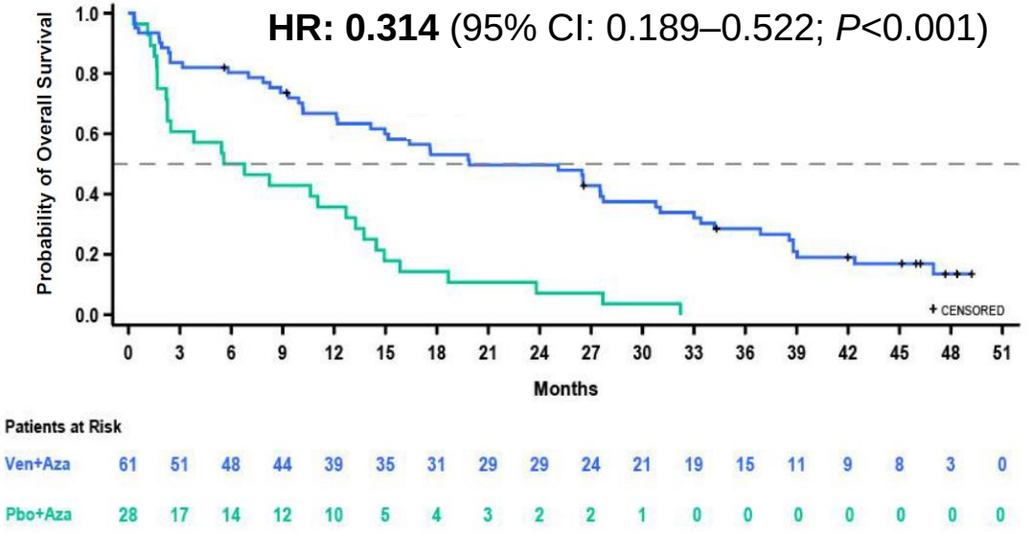
Long-term follow-up from VIALE-A: Overall survival

All patients (median follow up: 43.2 months)



	Events / patients (%)	Median OS, months (95% CI)
Ven + aza	222/286 (77.6)	14.7 (12.1–18.7)
Pbo + aza	138/145 (95.2)	9.8 (7.4–12.7)

Patients with *IDH1/2* mutations



	Events / patients (%)	Median OS, months (95% CI)
Ven + aza	49/61 (80.3	19.9 (12.2–27.7)
Pbo + aza	28/28 (100)	6.2 (2.3–12.7)

**Compared with HR of 0.66 at 75% OS analysis.*
Aza, azacitidine; CI, confidence interval; HR, hazard ratio; IDH, isocitrate dehydrogenase; OS, overall survival; pbo, placebo; ven, venetoclax.

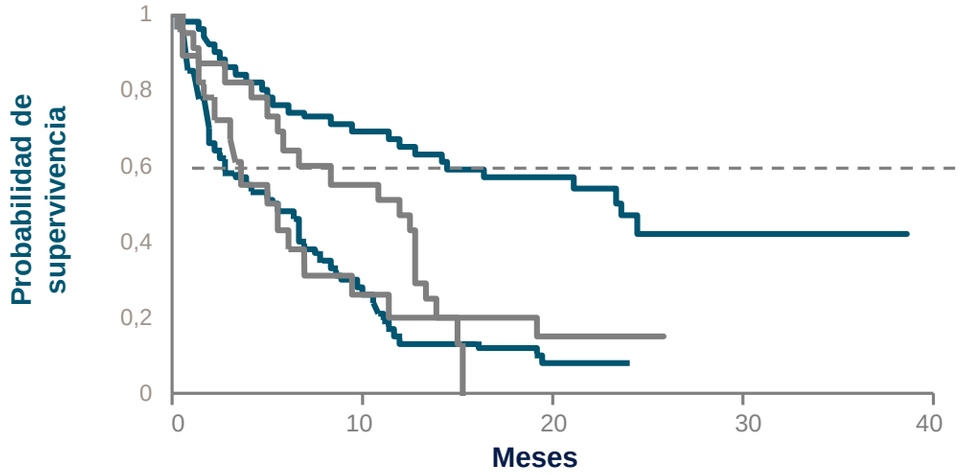
Pratz KW et al., ASH 2022; abstract 219 (oral presentation)

Real life results of HMA+VEN in high-risk Genetic AML

Reference	n	genetics	schedule	Response	Response %	mOS
Winters 2019 - Single center (USA)[1]	5	TP53+	AZA+VEN	CR/CRi	40	NA
Grenet ASH 2021 - Multicentric (USA)[2]	57	TP53+	HMA+VEN	CR/CRi	48	6.4
Johnson EHA 2022 - Single center (USA)[3]	ND (103*)	TP53+	HMA+VEN	CR/CRi	32	NA
Venugopal 2022 A - Single center (USA)[4]	53	TP53+	HMA+VEN LDAC+VEN	CR/CRi	56	6.4
Daver 2023 - Multicenter (USA)[5]	94	TP53+ or 17p deletion	HMA+VEN	NA	NA	7.6
Winters 2019 - Single center (USA)[1]	10	Unfavorable cytogenetic	AZA+VEN	CR/CRi	60	NA
De Bellis 2022 - Multicentric (Italy)[7]	23	Adverse karyotype	HMA+VEN	CR/CRi	61	10.5
Johnson EHA 2022 - Single center (USA)[3]	ND (103*)	Adverse karyotype	HMA+VEN	CR/CRi	49	NA
Lam EHA 2022 - Single center (UK)[8]	5	Adverse risk	AZA+VEN	CR/CRi	65	NA
Gherson 2023 - Multicentric (USA)[9]	136	Adverse ELN	HMA+VEN	NA	NA	7.9
Grenet ASH 2021 - Multicentric (USA)[2]	162	Adverse ELN	HMA+VEN	CR/CRi	52	9.7
Kale ASH 2022 - Single center (USA)[10]	ND (28*)	Adverse ELN	HMA+VEN	NA	NA	11.7
Vachhani 2022 - Multicenter (USA)[11]	65	Adverse ELN	HMA+VEN	CRc	45	NA

OS in TP53 AML in phase 3 RCT (VIALE-A & CPX351)

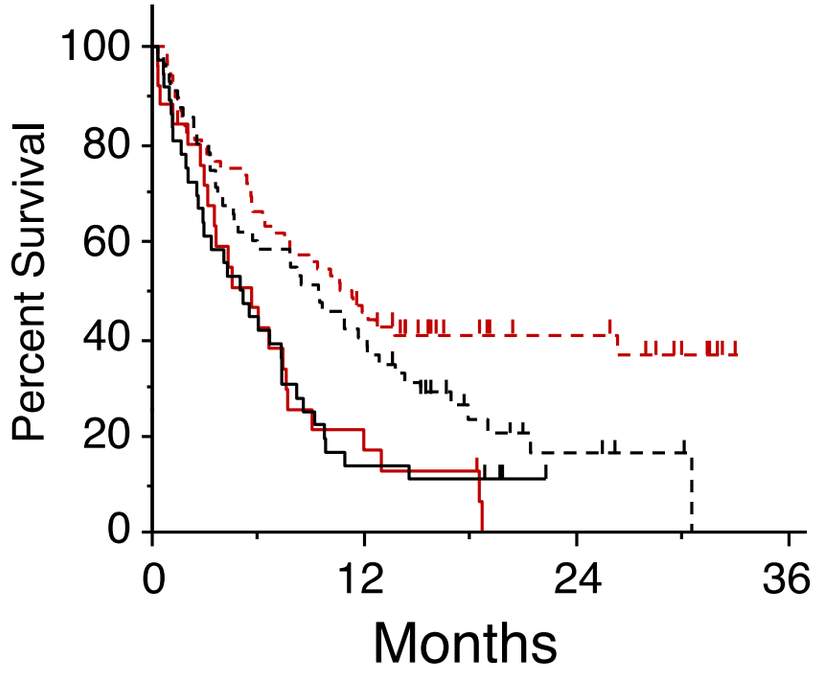
VENAZA

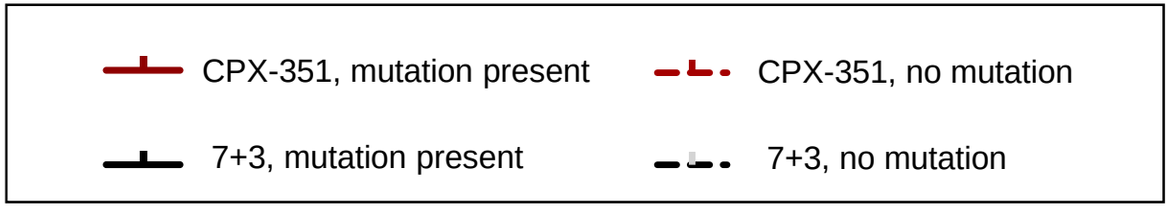


VEN+AZA, *TP53* wt	50	34	24	1	0
VEN+AZA, *TP53* mut	54	13	3	0	0
AZA, *TP53* wt	22	12	2	0	0
AZA, *TP53* mut	18	4	0	0	0

	mOS, months (IC 95%)
VEN+AZA *TP53* wt:	23,43 (11,93 - NR)
VEN+AZA *TP53* mut:	5,17 (2,17 - 6,83)
AZA *TP53* wt:	11,29 (4,9 - 12,78)
AZA *TP53* mut:	4,90 (2,14 - 9,30)

7+3 / CPX-351





Pollyea et al. Clin Cancer Res 2022
Lindsley RC, et al. ASH 2019

OS in TP53 AML (MDACC USA)

Table: Median overall survival (95% CI) and adjusted hazard ratio by allo-SCT status

Allo-SCT status	Overall (N=370)	Cohort A Ven+HMA (N=94)	Cohort B Intensive Chemo (N=135)	Cohort C HMA only (N=141)
No, n (%)	340 (92)	89 (95)	114 (84)	137 (97)
Deceased, yes, n (%)	279 (82)	65 (73)	89 (78)	125 (91)
Median OS, mos (95% CI)	**7.0 (6.0, 7.8)**	**7.2 (5.7, 8.4)**	**7.3 (6.5, 9.8)**	**5.7 (4.2, 7.0)**
Yes, n (%)	30 (8)	5 (5)	21 (16)	4 (3)
Deceased, yes, n (%)	15 (50)	1 (20)	12 (57)	2 (50)
Median OS, mos (95% CI)	**33.7 (13.0, 44.1)**	**NA (10.7, NA)**	**28.9 (12.8, 36.5)**	**45.5 (44.1, 46.9)**

Allo-SCT (yes vs no)*	aHR (95% CI)	*P*-value
In overall model (Cohort A, B, and C)	0.4 (0.2, 0.6)	<0.001

*Adjusted in Cox model for baseline covariates including age at baseline, time to 1L start, number of comorbidities, TP53m/cytogenetic risk level, 17p del status, bone marrow blast percentage at baseline, secondary AML, therapy-related AML, and healthcare practice type. 1L, initial therapy; aHR, adjusted hazard ratio; allo-SCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; CI, confidence interval; HMA, hypomethylating agents; mos, months; NA, not applicable; OS, overall survival; Ven, venetoclax.

Daver et al. ASH 2022 #615

Magrolimab + Aza in Patients With MDS and AML: Response in Patients With TP53 Mutation

Outcome	MDS *TP53* Mutant (n = 12)	AML *TP53* Mutant (n = 4)
ORR, n (%)	9 (75)	3 (75)
CR, n (%)	5 (42)	2 (50)
CRi/marrow CR, n (%)	4 (33)	1 (25)
Complete cytogenetic response, n/N (%)*	4/8 (50)	3/3 (100)
MRD negativity in responders, n/N (%)	4/9 (44)	0
Median DoR, mos	NR (0.03+ to 15.1)	NR (0.03+ to 5.2+)
6-mo survival probability, %	91	100
Median follow-up, mos (range)	8.8 (1.9 to 16.9)	7 (4.2 to 12.2)

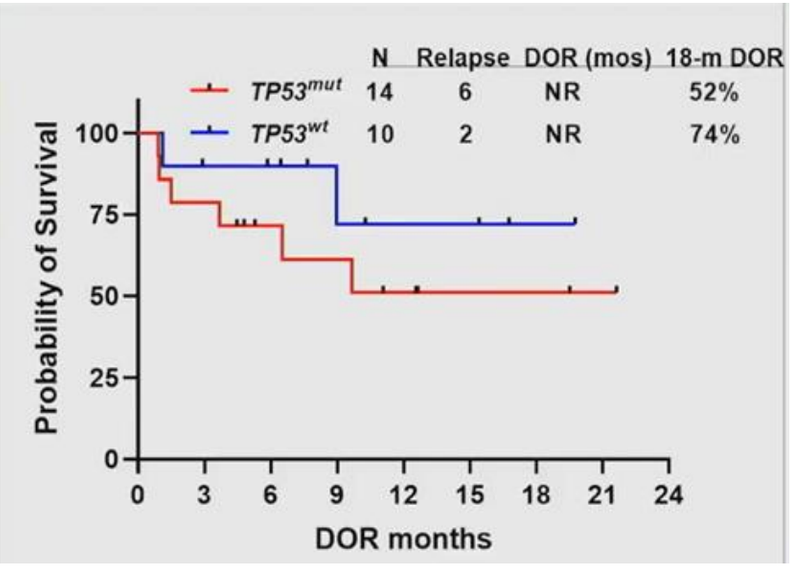
*Responders with cytogenetic abnormalities at baseline.

Sallman ASCO 2020. Abstract 7507

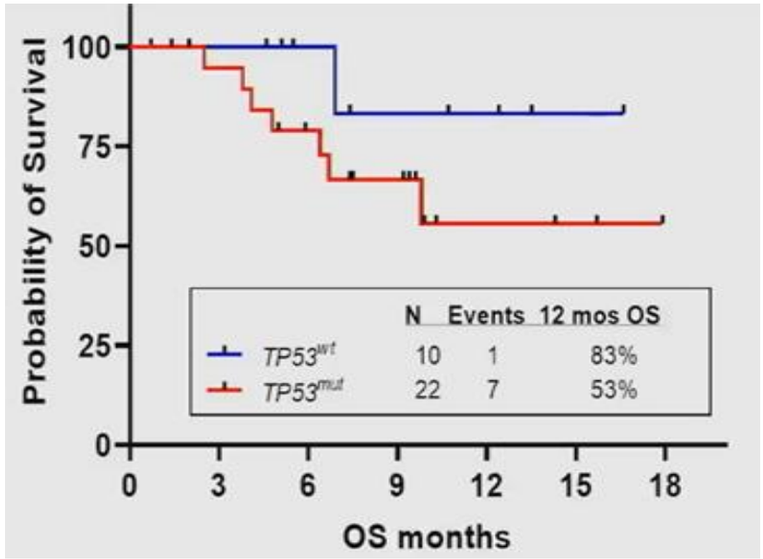
Phase 1/2 study of azacitidine with venetoclax and magrolimab: Frontline response and survival

- **Frontline cohort, N=43** (n=33 de novo AML; n=10 secondary AML)
  - Median age: 70 years, 37% female; 91% had adverse ELN 2017 risk stratification; 65% had adverse cytogenetics*
  - *TP53*^{mut}: n=27 (63%); *TP53*^{WT}: n=16 (37%)
- **Response rates:**
  - CR: n=21/43 (49%); CR+CRi: n=31/43 (72%)
  - MRD-negative best response: n=16/28 (67%)†

DOR (frontline de novo patients, n=33):‡



OS (frontline de novo patients, n=33):‡



Frontline secondary AML (n=10):

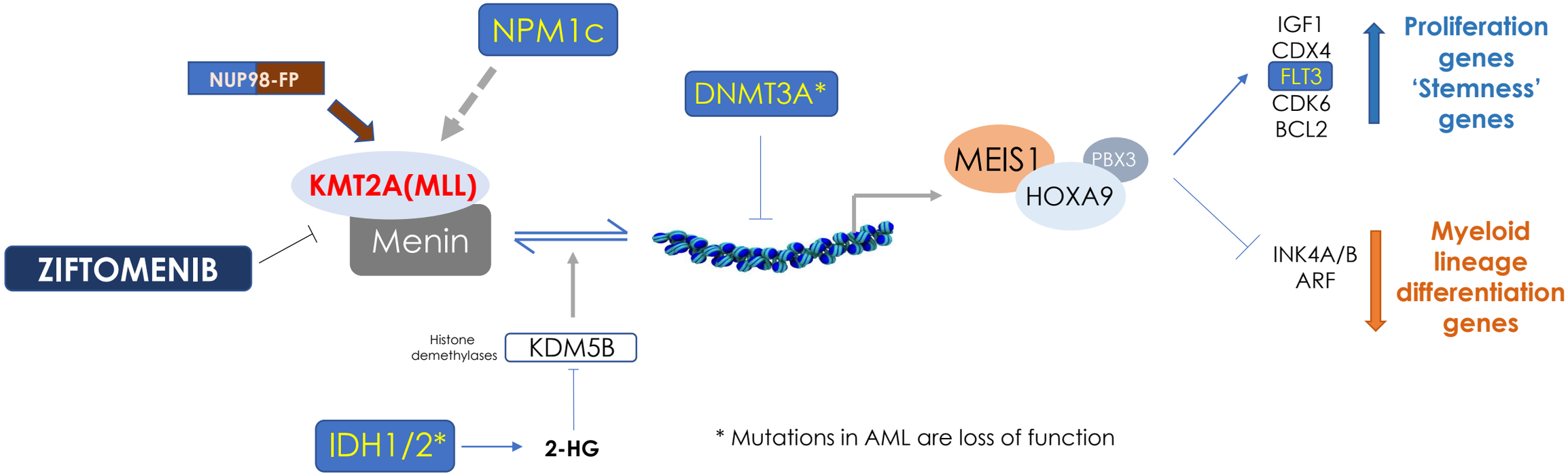
- Median DOR
  - *TP53*^{mut}: 5.9 months
  - *TP53*^{WT}: 2.2 months
- Median OS
  - *TP53*^{mut}: 7.6 months
  - *TP53*^{WT}: 9.6 months

**Per ELN 2017. †Among CR/CRi patients with longitudinally MRD-evaluable samples. ‡Median follow-up 14.5 months.*
AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete count recovery; DOR, duration of response; ELN, European LeukemiaNet; MRD, minimal residual disease; mut, mutated; NR, not reached; OS, overall survival; WT, wild type.

Daver N et al., ASH 2022; abstract 61 (oral presentation)

Menin-KMT2A Pathway Represents a Foundational Target for Ziftomenib

- *NPM1*-m and *KMT2A*-r drive overexpression of *HOXA9/MEIS1* genes, critical for transformation to AML
- KMT2A(MLL) sits upstream from major AML targets (ie, *FLT3*, *IDH1/2*, *DNMT3A*)
- KMT2A(MLL)-dependent genes contribute to therapeutic resistance and relapse to current SOC
- Menin inhibition down regulates HOXA9/MEIS1, leading to differentiation of leukemic blasts



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