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NewYork-Presbyterian

How do I identify and treat secondary AML?

SOHO Brazil
May 8, 2025

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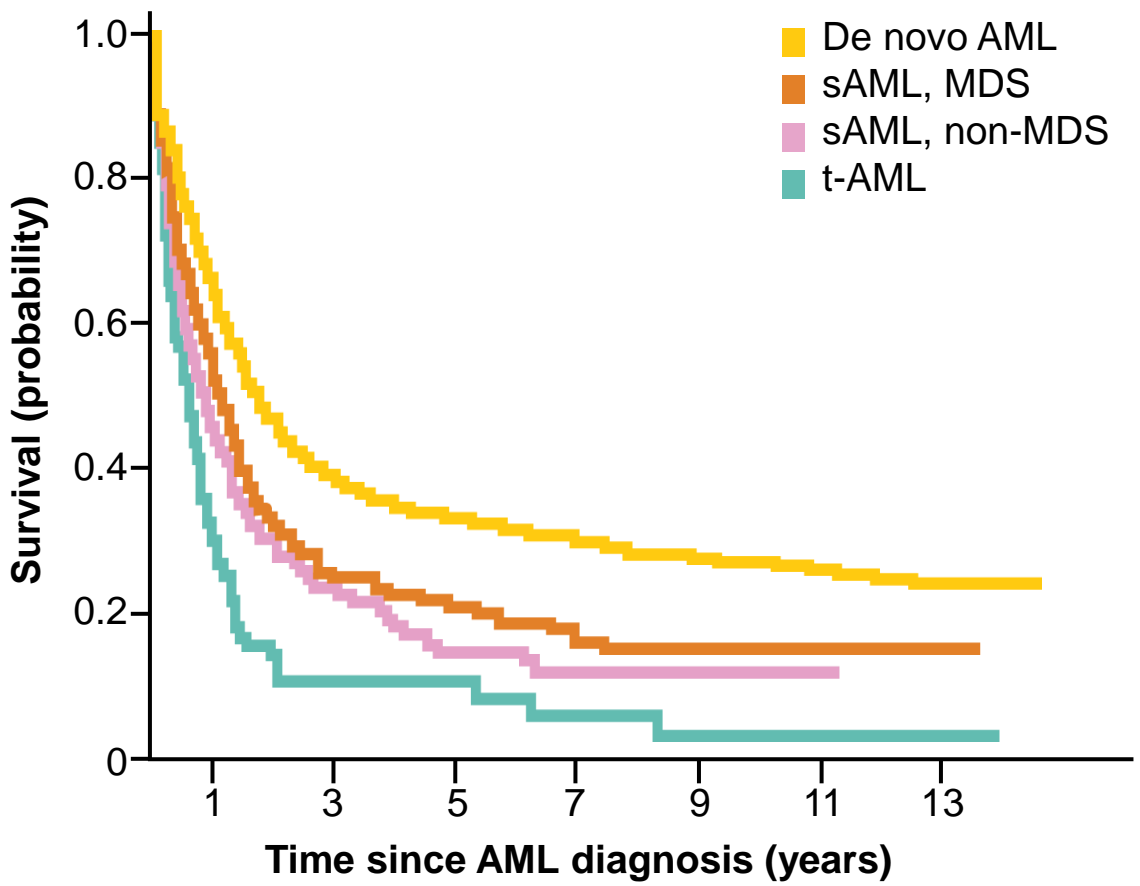
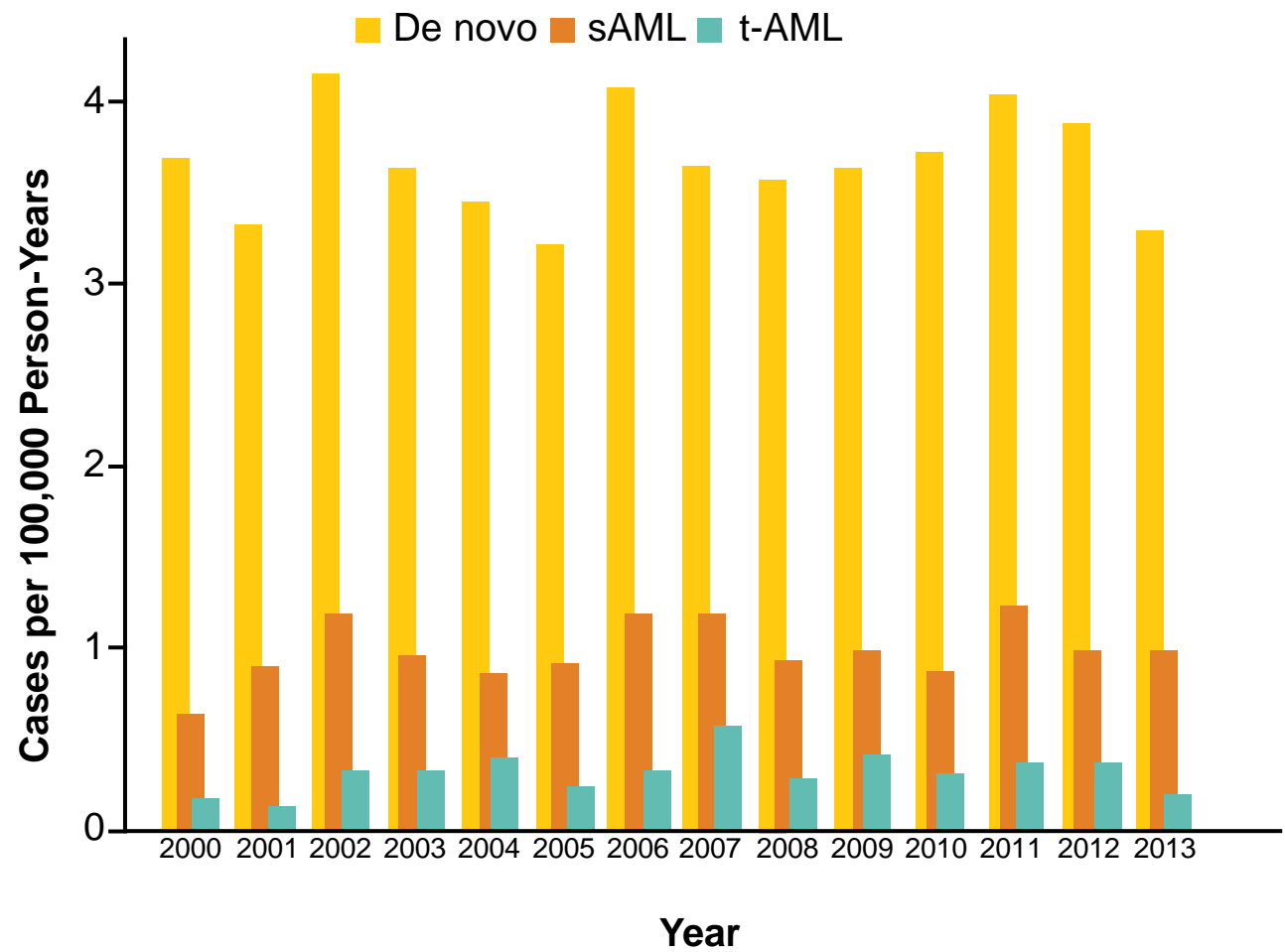
DISCLOSURES OF COMMERCIAL SUPPORT

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

Secondary AML

- 10–30% of all AML cases, prevalence increases with age
- 2022 WHO classification: secondary acute myeloid leukemia (sAML) is defined as AML that arises from an antecedent hematologic disorder (including MDS, MPN) or after prior cytotoxic or radiation therapy (t-AML).
- After MDS (60–85%) or MPN
- After cytotoxic chemotherapy, radiation, immunosuppression (t-AML, 15–40%)
- Inferior remission rates and overall survival

Secondary AML

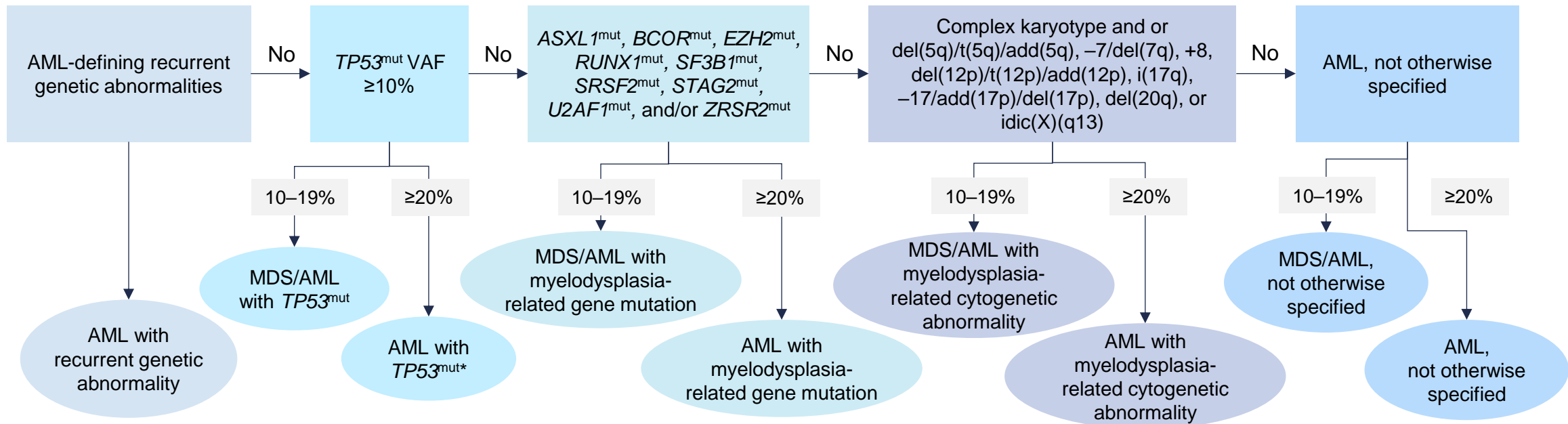


Diagnosing AML: A moving Target

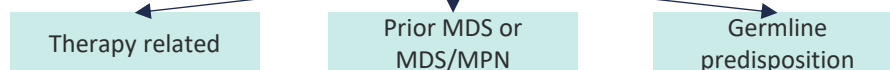
ICC 2022 and WHO 2022 classifications

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*³

WHO 2022 does not list *RUNX1*³

WHO 2022 does not list +8 or del(20q)³

WHO 2022 refers to as: AML, defined by differentiation³

* The presence of *TP53* mutation (VAF ≥10% with/without loss of *TP53*^{wt}) defines the entity AML with *TP53*^{mut}.
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.



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Molecular and Cytogenetic Characteristics of Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) in Patients Exposed to Chemotherapy (CT) and/or Radiation (XRT)

Pinkal Desai¹, Yasmin Abaza², Hetty E. Carraway³, Jason Chua¹, Jonathan Canaani¹, Michael Samuel¹, Gabriella Pereira¹, Dunay Bach¹, Cynthia Crispino, Bridget Foley, Sindhusa Veeraballi³, Nicole Vincek³, Peter Doukas², Oluwatobi Odetola², Justin D. Kaner¹, Michal Bar-Natan¹, Ellen K. Ritchie¹, and Gail J. Roboz¹

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Introduction

- Therapy related myeloid neoplasms (t-MN) have been traditionally defined as MDS/AML that occur after chemotherapy (CT) and/or radiation (XRT) exposure
- t-MN have poor survival and long term cure rates
- The impact of therapeutic radiation exposure alone as a cause of t-MN has been challenged (*Mukherjee et al JNCI 2014*)
- The recent ICC 2022 classification recommends therapy relatedness as a diagnostic qualifier for other pathologic subtypes rather than the designation t-MN
- We performed a retrospective chart review to characterize the clinical, molecular, and cytogenetic characteristics of MDS and AML in patients exposed to CT and/or XRT

Desai, P et al ASH Abstract # 821



Conclusions

Exposure to CT +/- XRT prior to t-MN diagnosis increases the risk of adverse cytogenetics and ELN 2022 adverse risk stratification, and TP53 mutations.

Prior exposure to platinum-based CT in patients with t-MN increases the risk of adverse cytogenetics and TP53 mutation.

t-MN patients who had chemotherapy for prior cancer had worse overall survival than those who had XRT alone or no chemo/XRT exposure as part of their cancer treatment.

Exposure to CT +/- XRT worsens OS in t-MN patients with intermediate risk cytogenetics, but not in patients with adverse cytogenetics

Mutated TP53 has an independent negative impact on survival in CT +/- XRT exposed t-MN patients with intermediate risk cytogenetics, but not in those with adverse cytogenetics

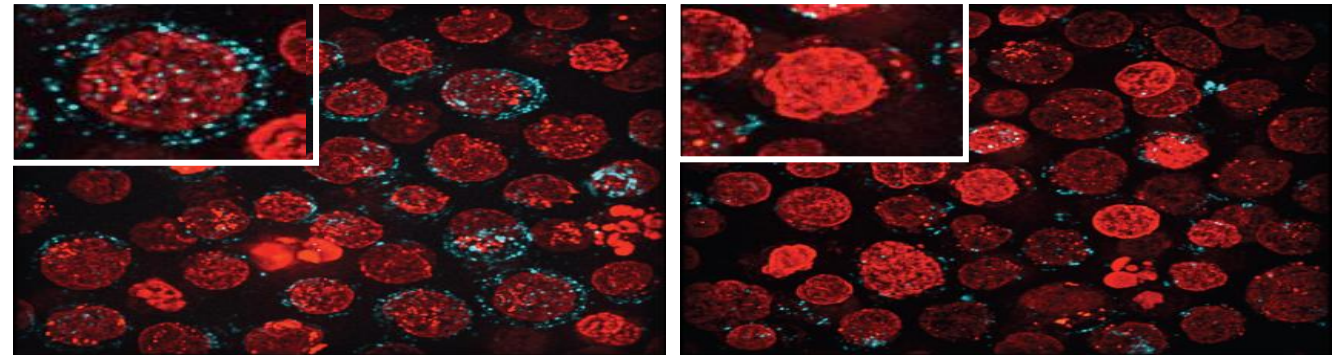
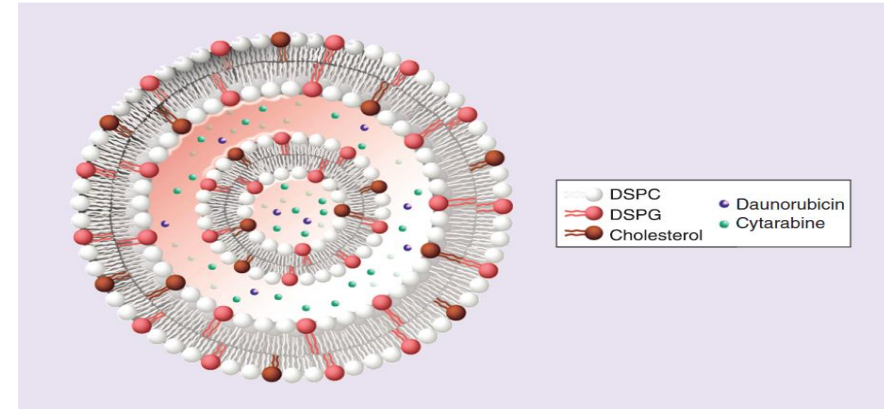
Having $\geq 10\%$ blasts at diagnosis significantly worsens OS in t-MN patients with non-adverse cytogenetics.

Blast count at t-MN diagnosis is not an independent predictor of OS in patients with TP53 mutation.

Among transplanted patients with t-MN, there was no difference in OS between those with and without prior CT +/- XRT exposure.

CPX-351 (daunorubicin and cytarabine liposome)

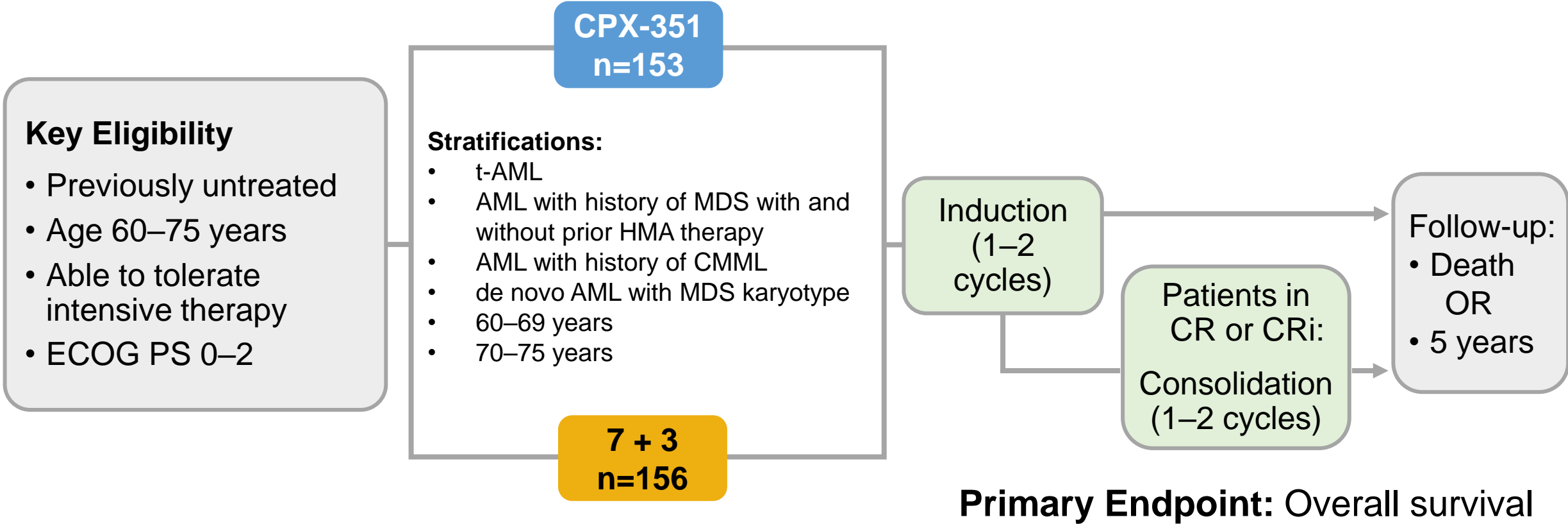
- Indicated for the treatment of adults with newly-diagnosed t-AML or AML-MRC
- 100 nm bilamellar liposomes
- 1:5 molar ratio of cytarabine to daunorubicin
- 1 unit = 0.44 mg daunorubicin plus 1.0 mg cytarabine



30 minutes

24 hours

Phase 3 Study of CPX-351 vs Standard Induction in Older Patients with Newly Diagnosed High-Risk AML*

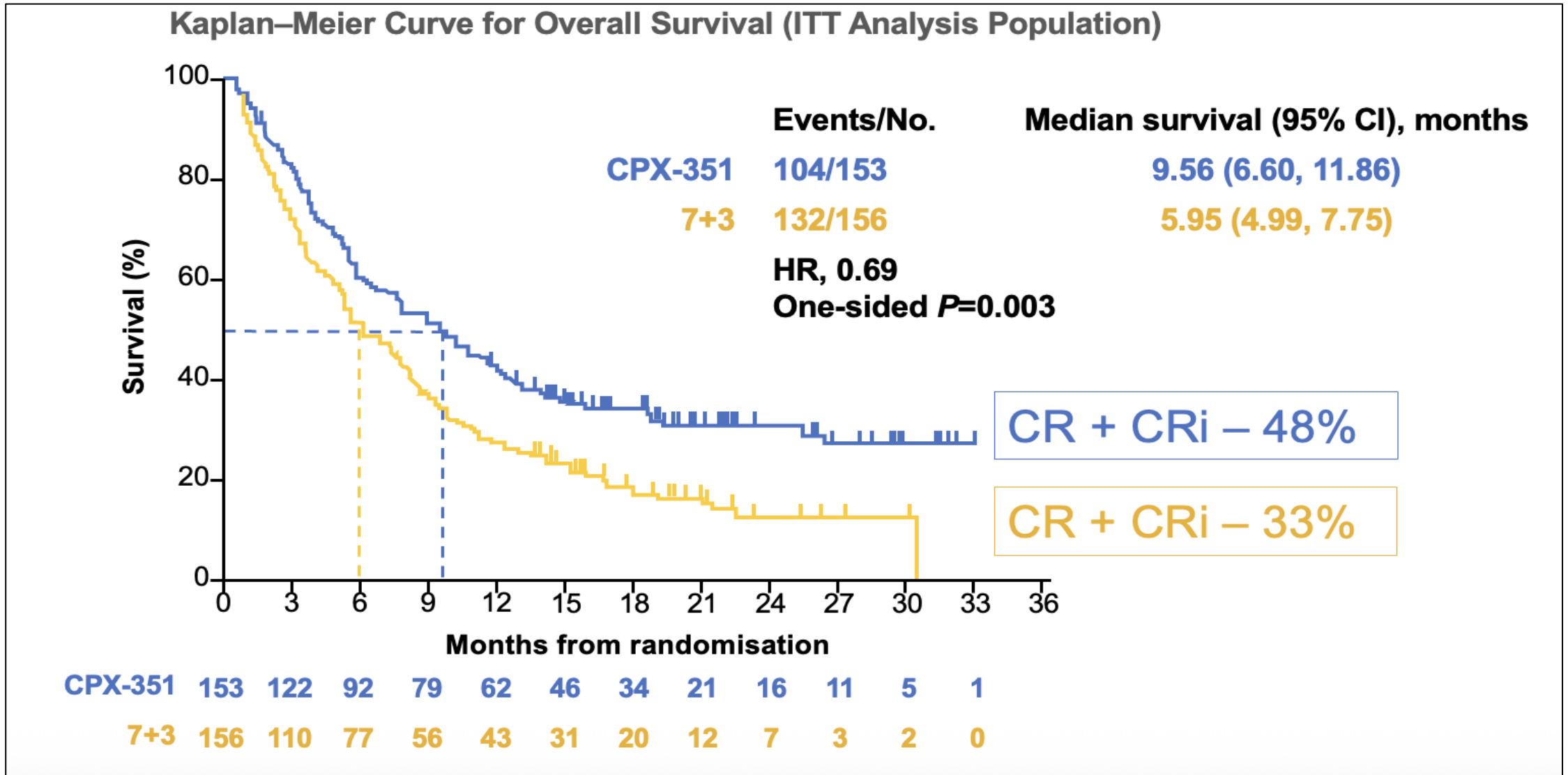


*Newly diagnosed t-AML, AML with antecedent MDS or CMML, or de novo AML with MDS-related cytogenetic abnormalities (per 2008 WHO criteria)
CMML, Chronic myelomonocytic leukaemia; HMA, hypomethylating agent

Patient Characteristics

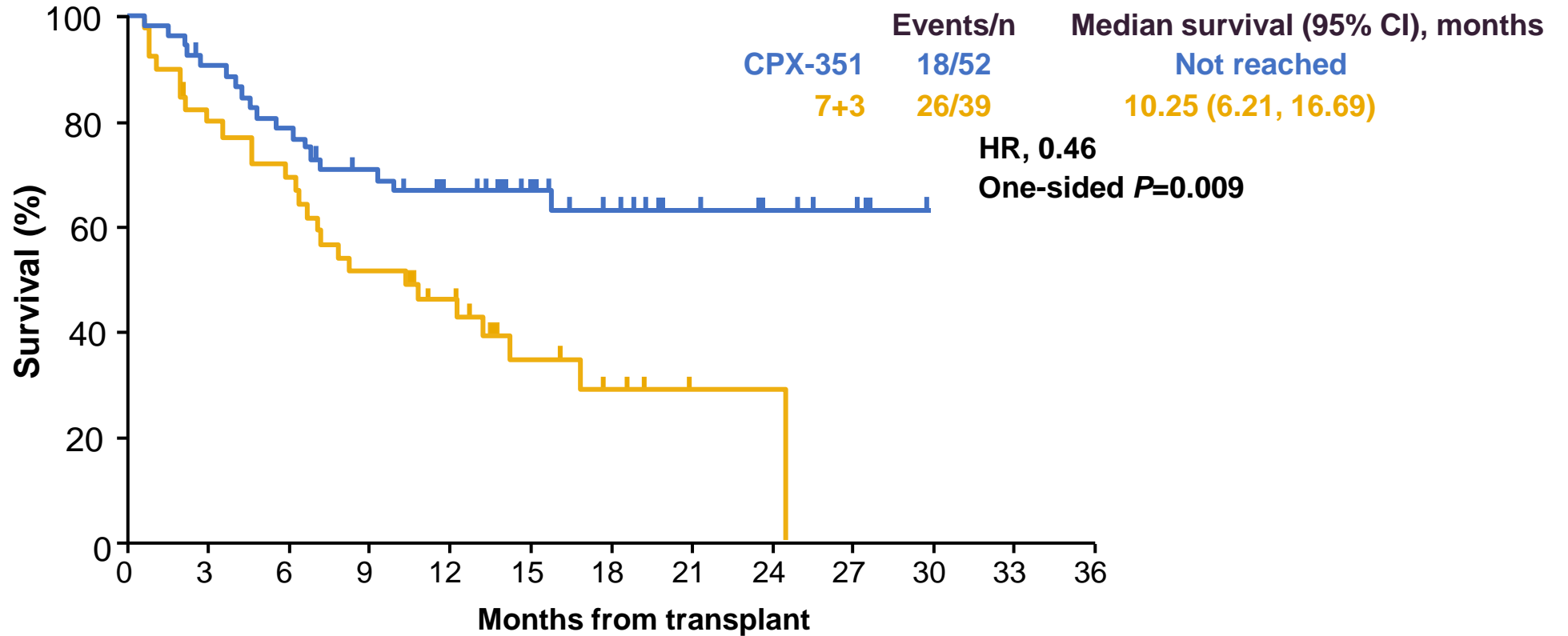
		CPX-351 n=153 (%)	7+3 n=156 (%)
Sex	Male	94 (61.4)	96 (61.5)
Race	Caucasian	128 (83.7)	139 (89.1)
Age group	≥70 years	57 (37.3)	54 (34.6)
	Mean	67.8	67.7
ECOG PS	0–1	138 (90.2)	134 (85.9)
	2	15 (9.8)	22 (14.1)
Cytogenetic risk by NCCN		143	146
	Favorable	7 (4.9)	5 (3.4)
	Intermediate	64 (44.8)	58 (39.7)
	Unfavorable	72 (50.3)	83 (56.8)
Strata:			
	Therapy-related	30 (19.6)	33 (21.2)
	MDS with prior HMA	50 (32.7)	55 (35.3)
	MDS without prior HMA	21 (13.7)	19 (12.2)
	CMML	11 (7.2)	12 (7.7)
	de novo with MDS karyotype	41 (26.8)	37 (23.7)

Randomized Phase 3 Trial of CPX-351 vs. 7+3 in Older Patients With t-AML/AML-MRC



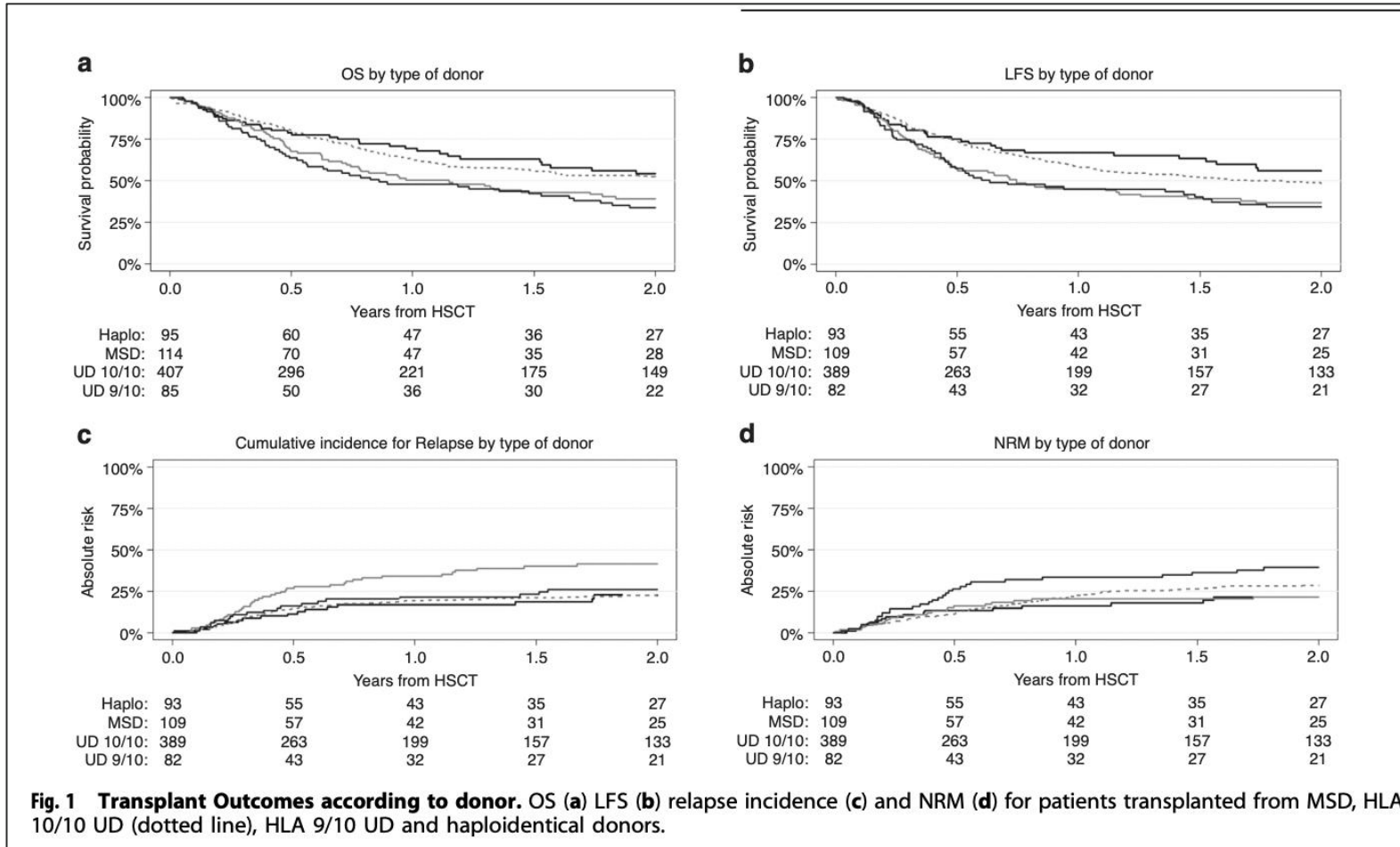
Landmark Survival Analysis at Time of Transplant

Kaplan–Meier Curve for Overall Survival Landmarked at Stem Cell Transplant – ITT Analysis Population



CPX-351	52	46	40	34	27	20	15	9	6	3	0	0
7 + 3	39	31	27	20	15	7	4	1	1	0	0	0

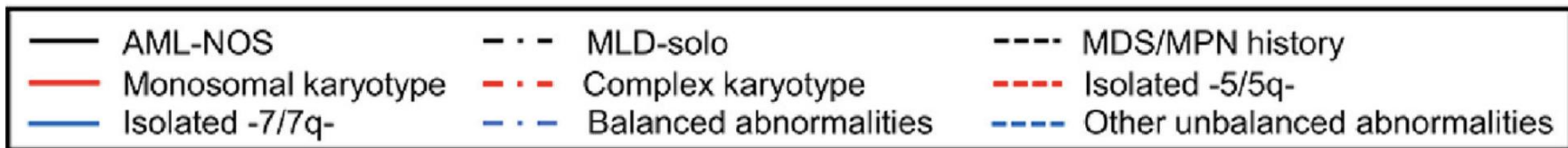
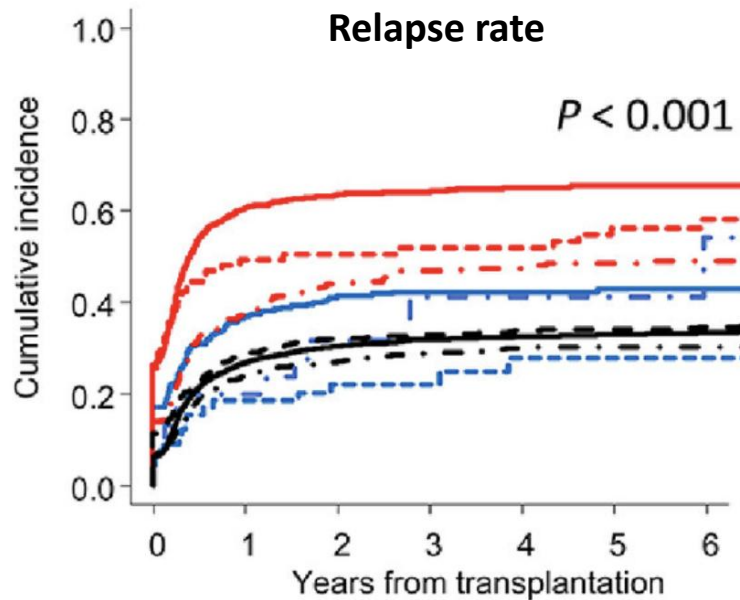
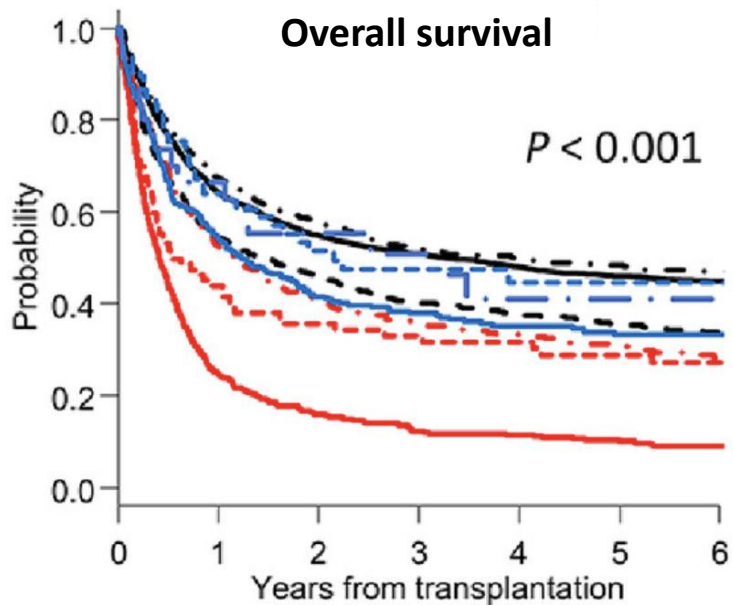
How effective is allogeneic stem cell transplantation in older AML patients?



701 pts > 70 yrs
2 yr OS 48.1%
 LFS 45.3%
 Relapse 25.2%
 NRM 30%
 GRFS 33.4%

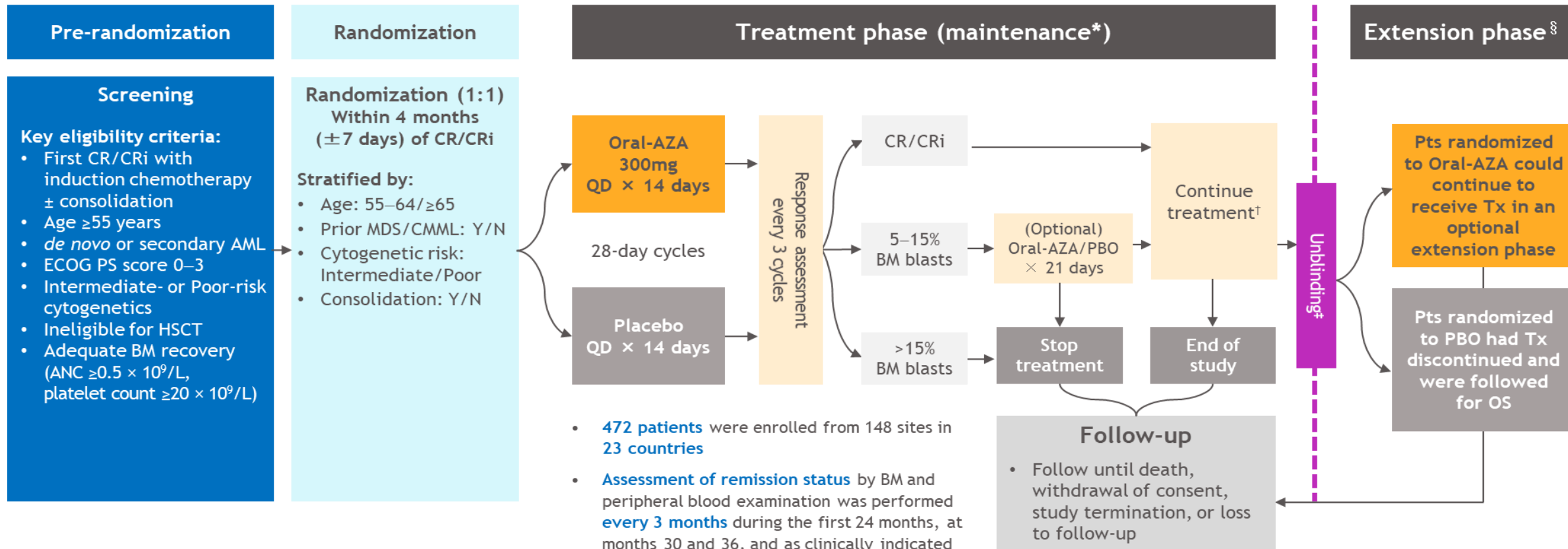
Maffini et al. Bone Marrow Transplant, 2023 Jun 29.
 doi: 10.1038/s41409-023-02027-y. Online ahead of print

Survival of patients with AML with Myelodysplasia-Related Changes Undergoing Allogeneic Stem Cell Transplantation: Retrospective Study of the Japan Society for Hematopoietic Cell Transplantation



QUAZAR[®] AML-001: Study design and eligibility criteria

International, multicenter, placebo-controlled, double-blind, randomized, Phase III trial of Oral-AZA as maintenance in patients with AML in first CR/Ri post-IC and ineligible for HSCT (NCT01757535)^{1,2}



*Termed 'continued treatment' in the USA, according to FDA label

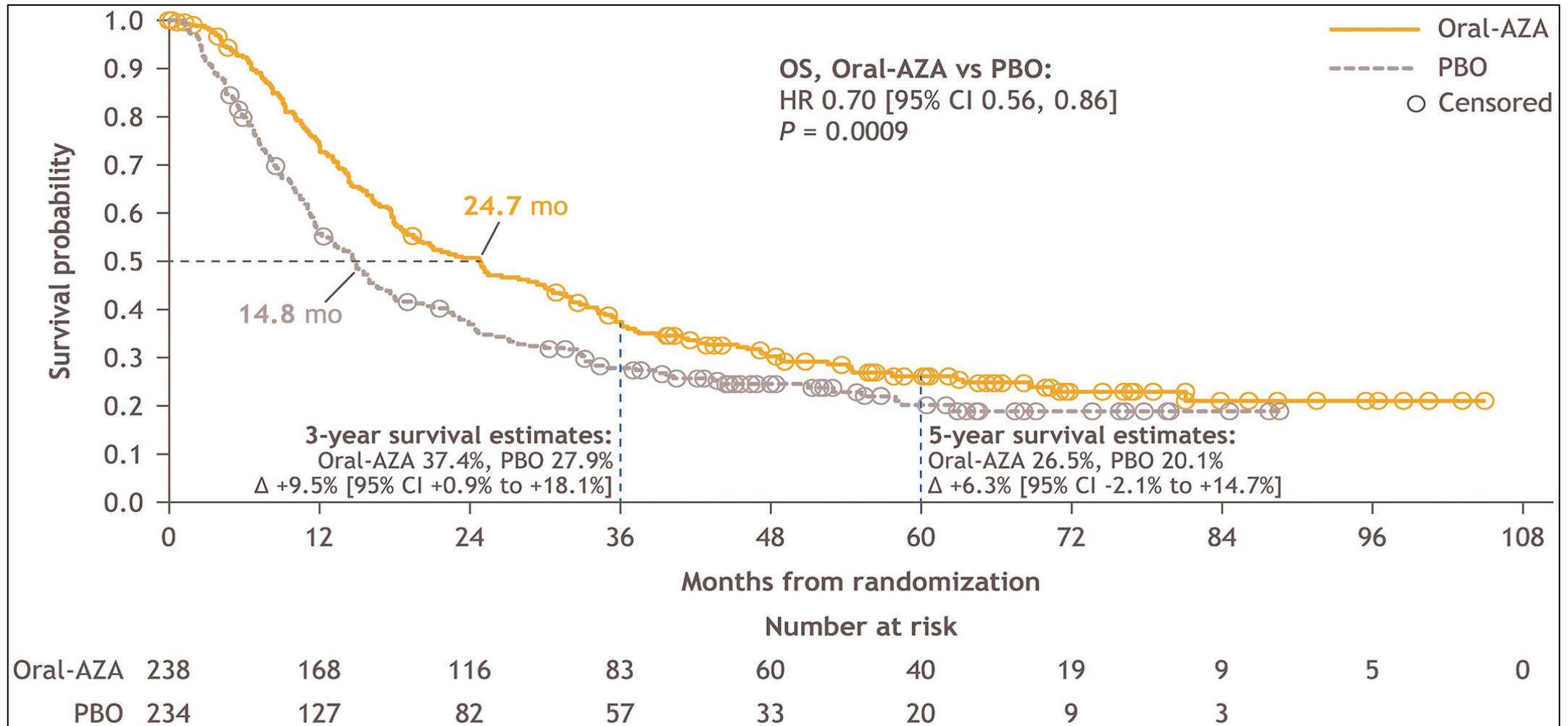
†Treatment continued until the presence of >15% blasts or unacceptable toxicity

‡Unblinding occurred in August, 2019

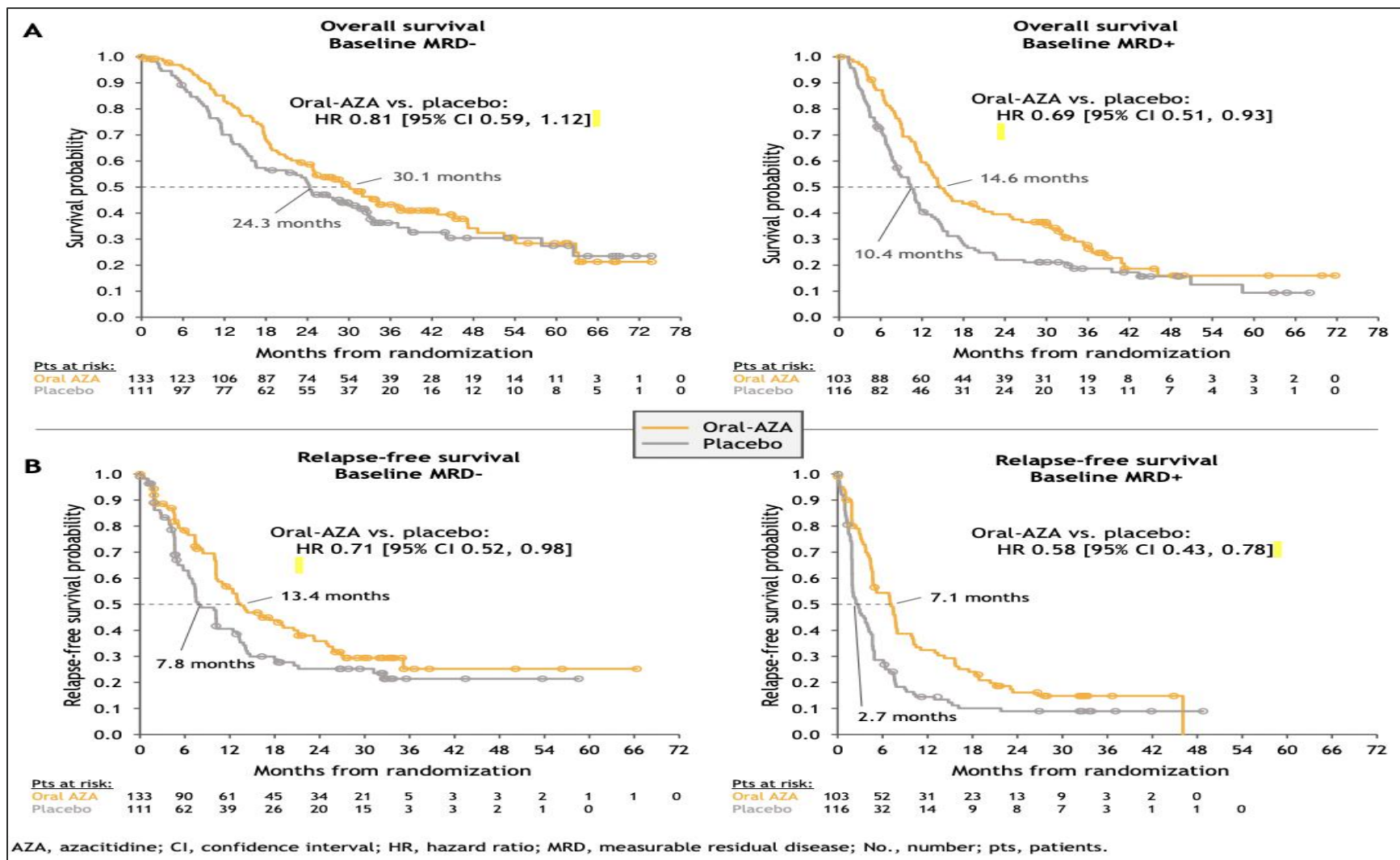
§After unblinding, 39 patients receiving Oral-AZA entered the extension phase and continued treatment

1. Wei AH...Roboz GJ. *N Engl J Med* 2020;383:2526–37
2. Wei AH, et al. Oral presentation at ASH 2021. Abstract #871

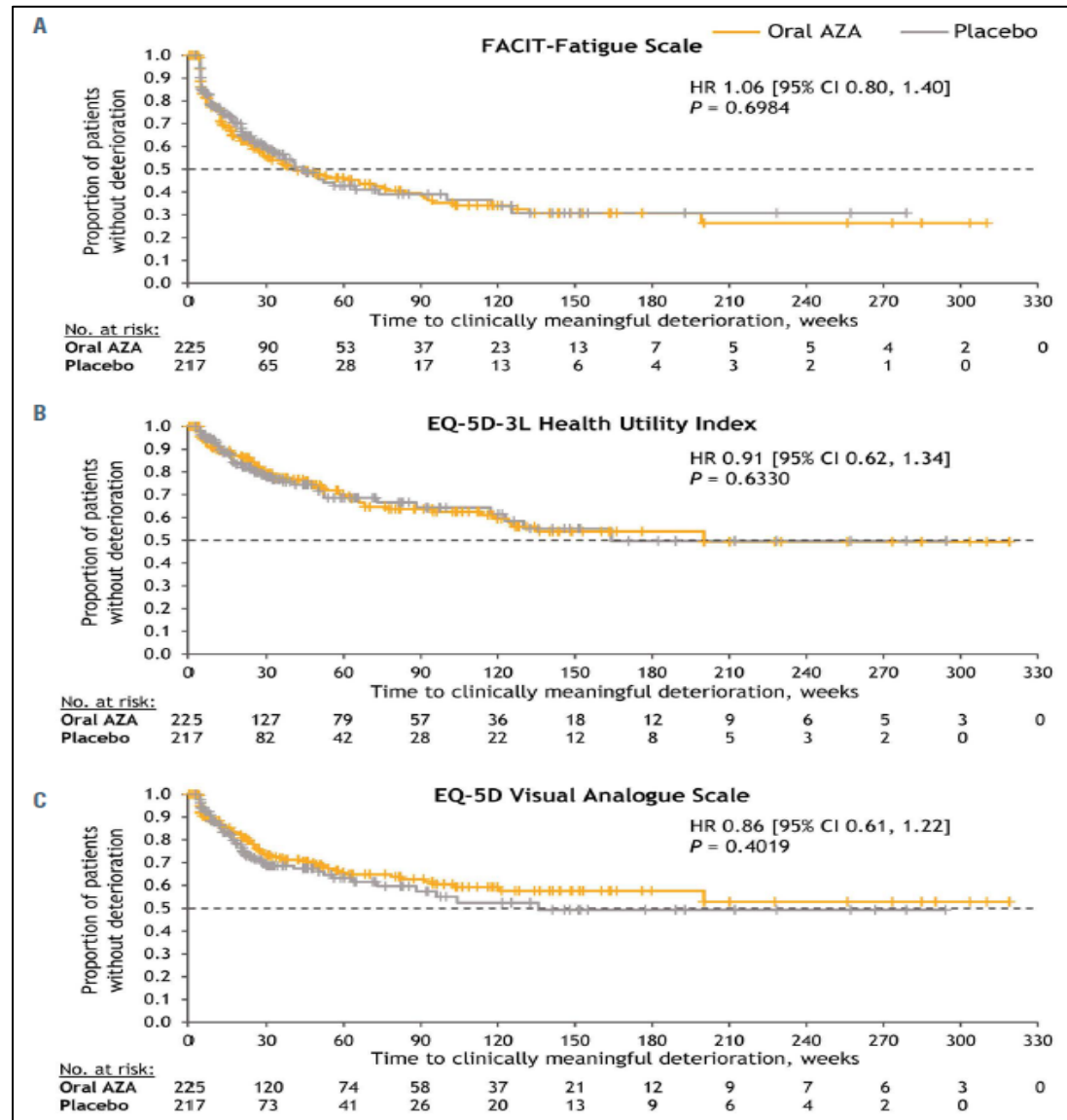
QUAZAR AML-001: Long-term Survival



Oral azacitidine prolongs survival of patients with AML in remission independent of measurable residual disease status



Health-related quality of life with oral azacitidine



- HRQoL preserved in pts receiving Oral-AZA
- No Clinically meaningful differences between treatment arms
- Longitudinal analyses supported the non-inferior HRQoL in the Oral-AZA arm
- Oral AZA significantly improved OS and RFS while maintaining HRQoL comparable to placebo

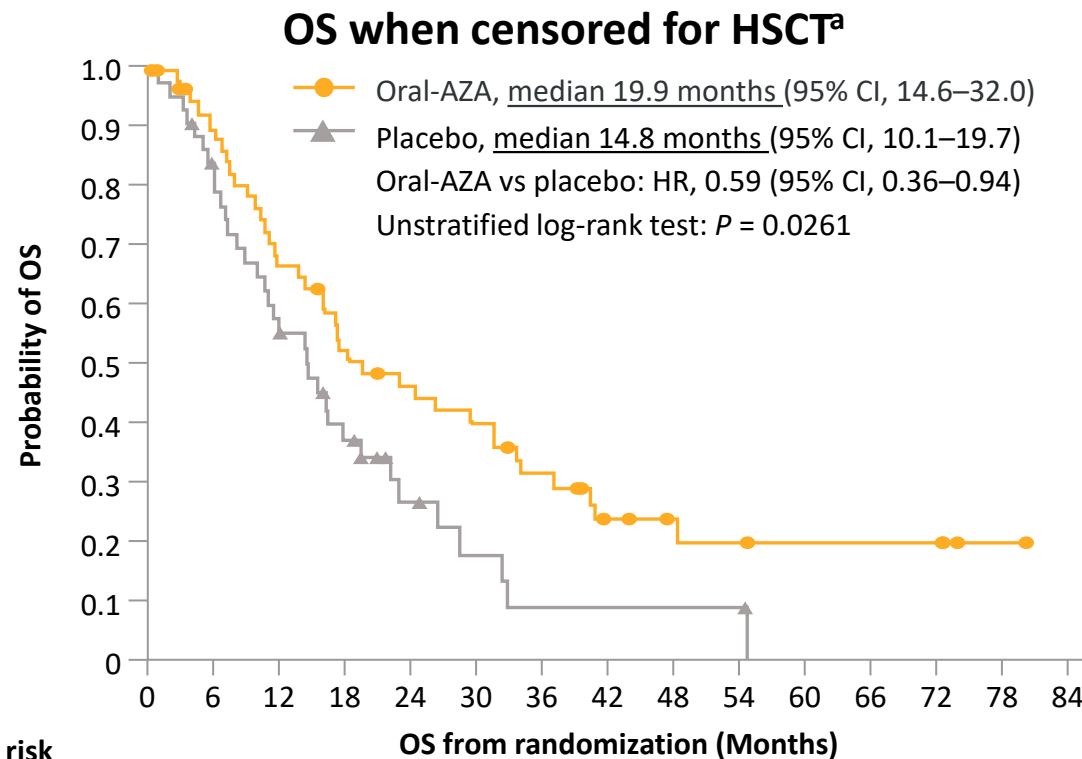
A post-hoc analysis of outcomes of patients with acute myeloid leukemia with myelodysplasia-related changes who received oral azacitidine maintenance therapy in the QUAZAR AML-001 study

[Maria Teresa Voso](#),¹ Stéphane de Botton,² Michael Pfeilstöcker,^{3,4} Angela Figuera Alvarez,⁵ Kefeng Wang,⁶ Wendy L. See,⁷ Manuel Ugidos Guerrero,⁸ Daniel Lopes de Menezes,⁷ Erica Petrlik,⁶ Thomas Prebet,⁹ Gail J. Roboz¹⁰

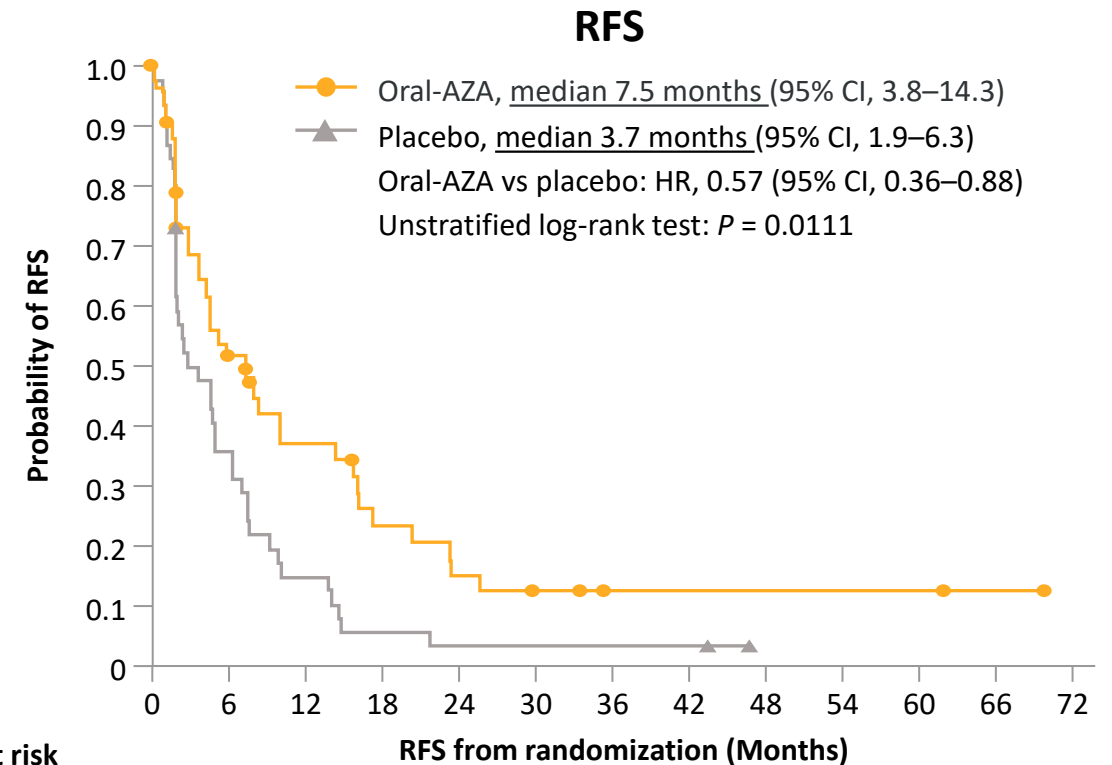
¹Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy; ²Institut Gustave Roussy, Villejuif, France; ³Third Medical Department for Hematology and Oncology, Hanusch Hospital, Vienna, Austria; ⁴Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria; ⁵Hospital Universitario de La Princesa, Madrid, Spain; ⁶Bristol Myers Squibb, Princeton, NJ, USA; ⁷Bristol Myers Squibb, San Francisco, CA, USA; ⁸BMS Center for Innovation and Translational Research Europe (CITRE), Seville, Spain; ⁹Bristol Myers Squibb, Summit, NJ, USA; ¹⁰Weill Cornell Medicine, New York, NY, USA

Survival outcomes in patients with AML-MRC: Oral-AZA versus placebo

→ Oral-AZA significantly prolonged median OS and RFS, for patients with AML-MRC compared with placebo



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Oral-AZA events: 38/56	56	46	34	26	22	19	14	9	7	5	4	4	4	1	0
Placebo events: 34/45	45	35	23	14	7	4	2	2	2	2	0	0	0	0	0

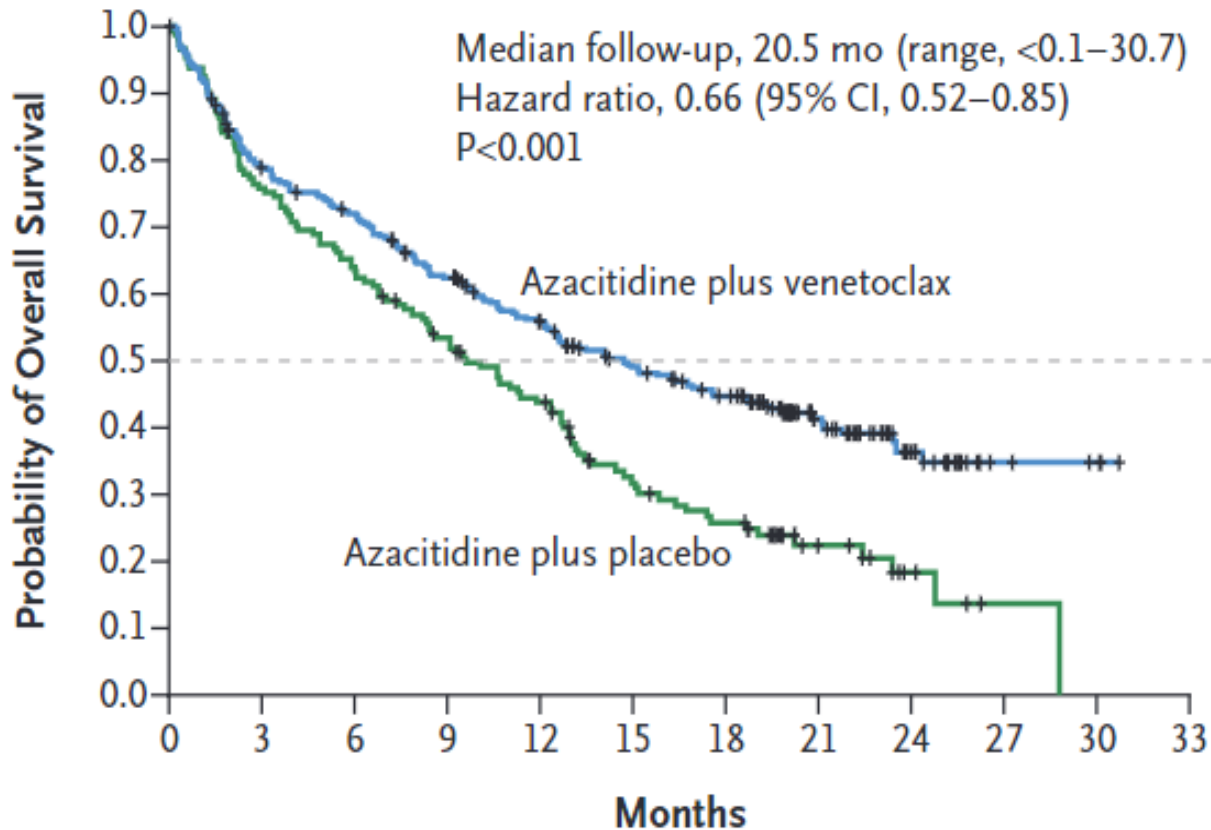


No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Oral-AZA events: 39/56	56	24	15	9	6	4	2	2	2	2	2	1	0
Placebo events: 42/45	45	16	7	3	2	2	2	2	0	0	0	0	0

^aCensoring for HSCT was done after study drug discontinuation; HSCT was received by 5 patients with AML-MRC in the Oral-AZA and 8 patients with AML-MRC in the placebo arm. HE-GL-2400068
 CI, confidence interval; HR, hazard ratio.

Results of VIALE-A : Azacitidine + venetoclax

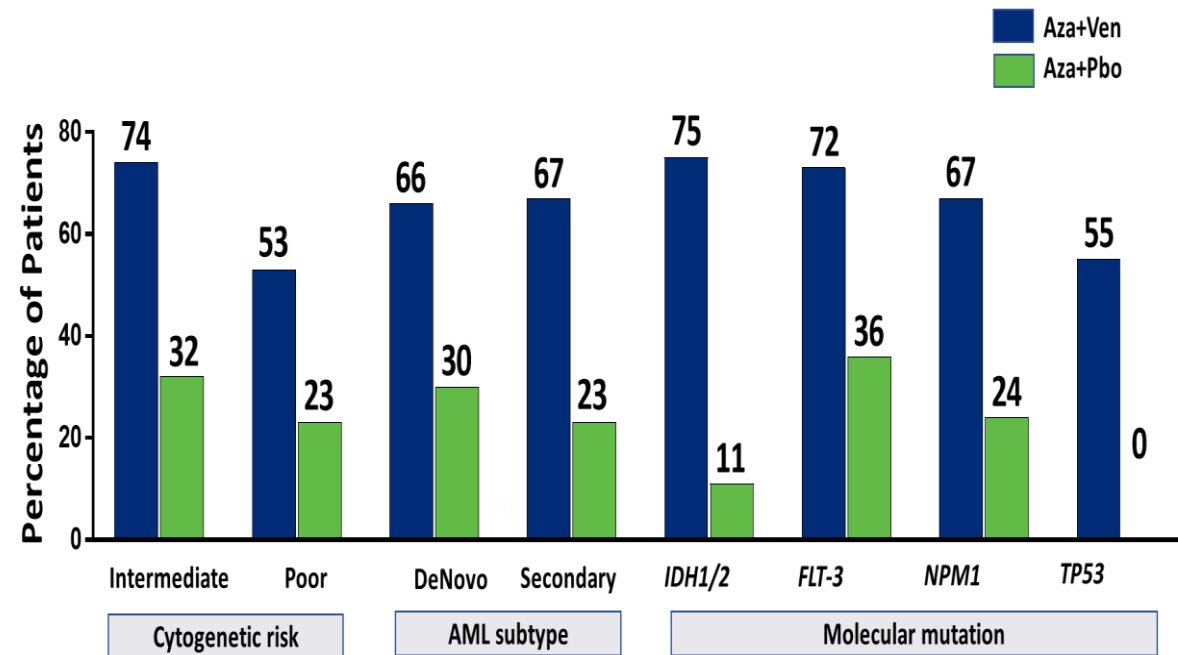
Significant OS improvement with
azacitidine + venetoclax
(Med OS 14.7 vs 9.6 mos)



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

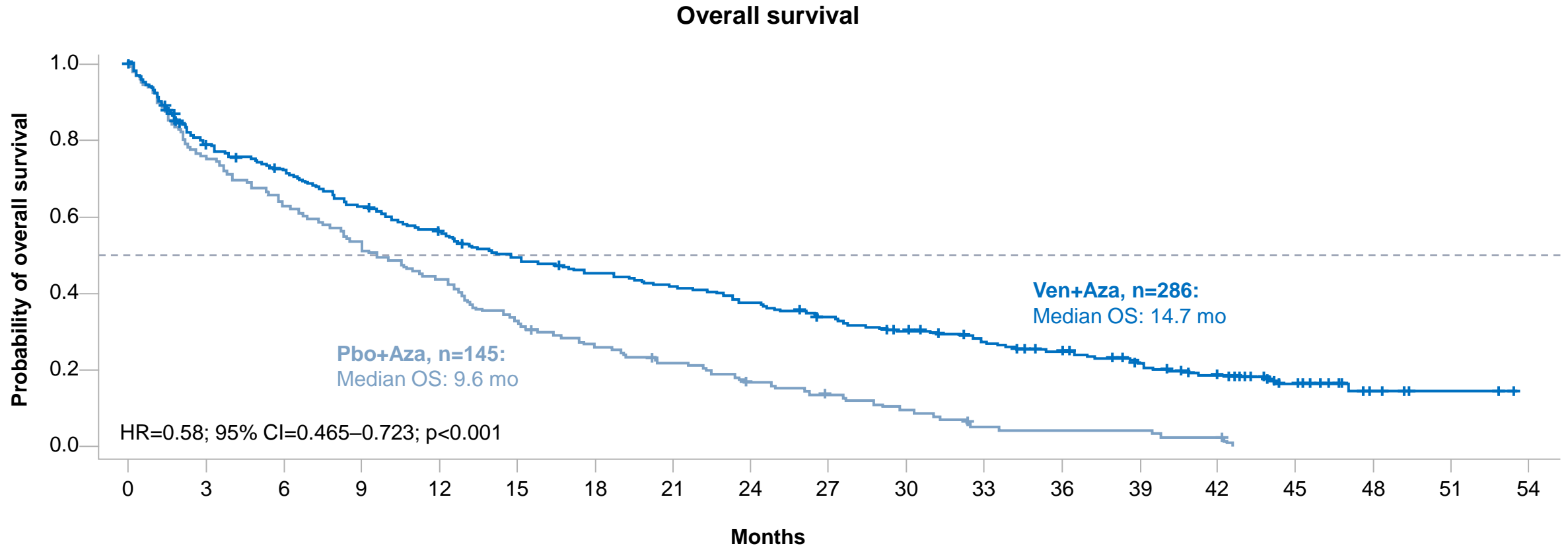
CR/CRi rate: 66.4% vs 28.3% ($P < .001$)

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 ≥ 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, ≥ 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).



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Place video here

Comparing Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and Hypomethylating agent+Venetoclax (HMA+V) As Frontline Therapy in Acute Myeloid Leukemia

Justin Grenet, MD¹, Akriti G Jain, MD², Madelyn Burkart, MD^{3*}, Julian Waksal, MD⁴, Christopher Famulare, MS^{5*}, Yazan Numan, MD³, Maximilian Stahl, MD⁴, Zoe Mckinnell, MD^{4*}, Brian Ball, MD⁴, Xiaoyue Ma, MS^{6*}, Paul J Christos, Dr.P.H., M.S.^{6*}, Ellen Ritchie, MD⁷, Michael B. Samuel, MD^{8*}, Justin D. Kaner, MD⁸, Sangmin Lee, MD⁹, Aaron D Goldberg, MD, PhD⁴, Shira Dinner, MD³, Kendra Sweet, MD², Gail J. Roboz, MD⁸ and **Pinkal Desai, MD, MPH⁹**

¹New York-Presbyterian/Weill Cornell Medical Center, New York, NY

²H. Lee Moffitt Cancer Center, Tampa, FL

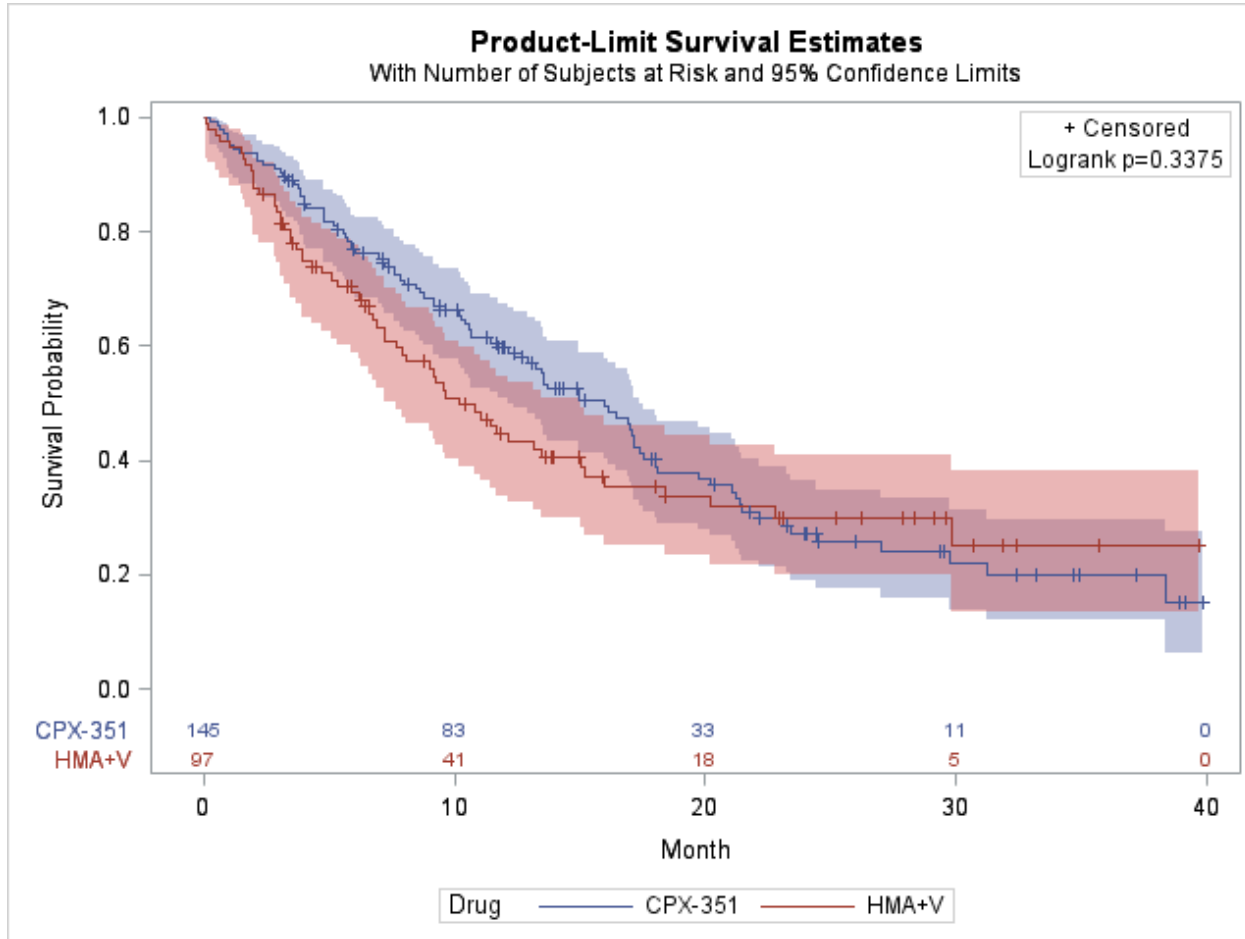
³Division of Hematology Oncology, Northwestern University, Chicago, IL

⁴Memorial Sloan Kettering Cancer Center, New York, NY

⁵Department of Population Health Sciences, Weill Cornell Medical College, New York, NY

⁶Division of Hematology and Oncology, Weill Cornell Medical College, New York, NY

60-75 yrs: No significant difference in OS between CPX-351 and HMA+venetoclax



CR+CRi, 60-75yo

CPX-351: 59.2%

HMA+V: 54.0%

p = 0.41

Total "n" and HSCT rates, 60-75yo

CPX-351: n = 152 (47.7% underwent HSCT)

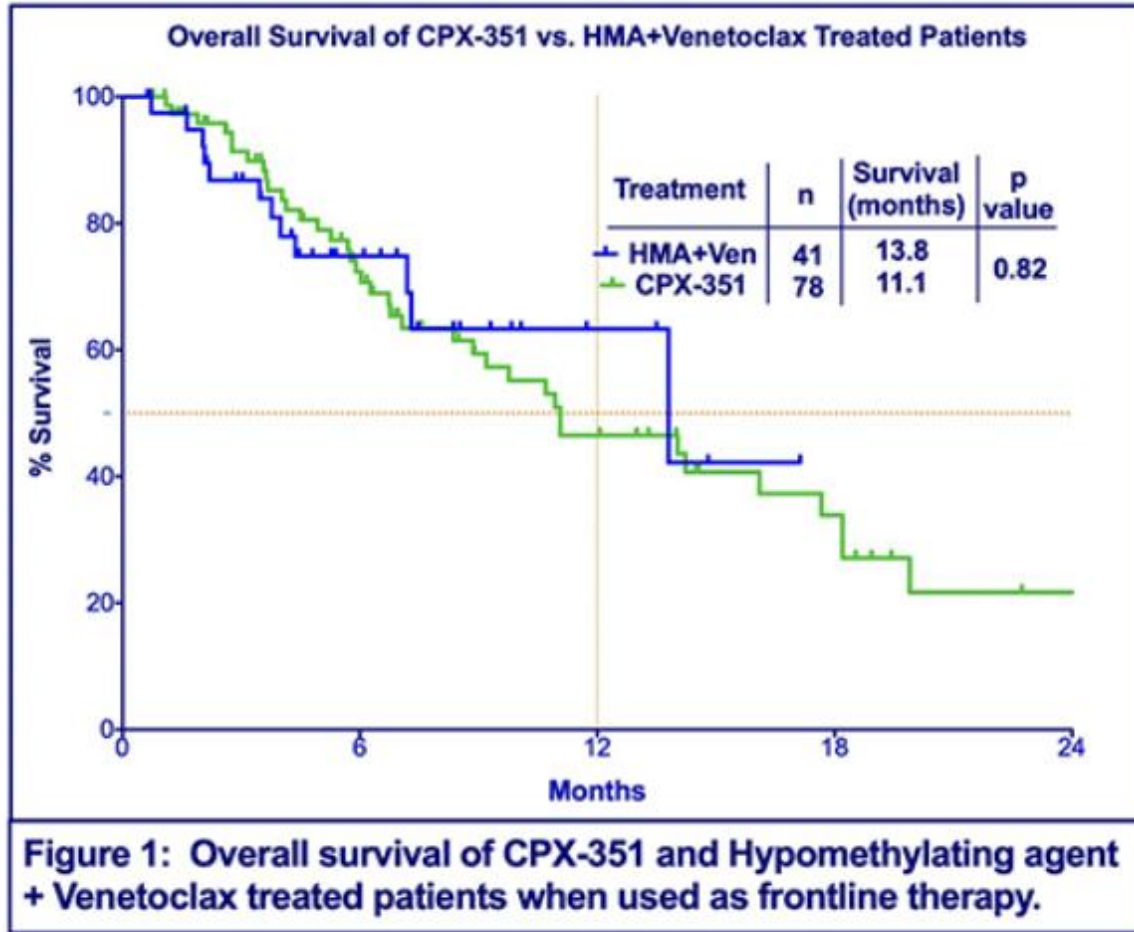
HMA+V: n = 100 (19% underwent HSCT)

p < 0.001

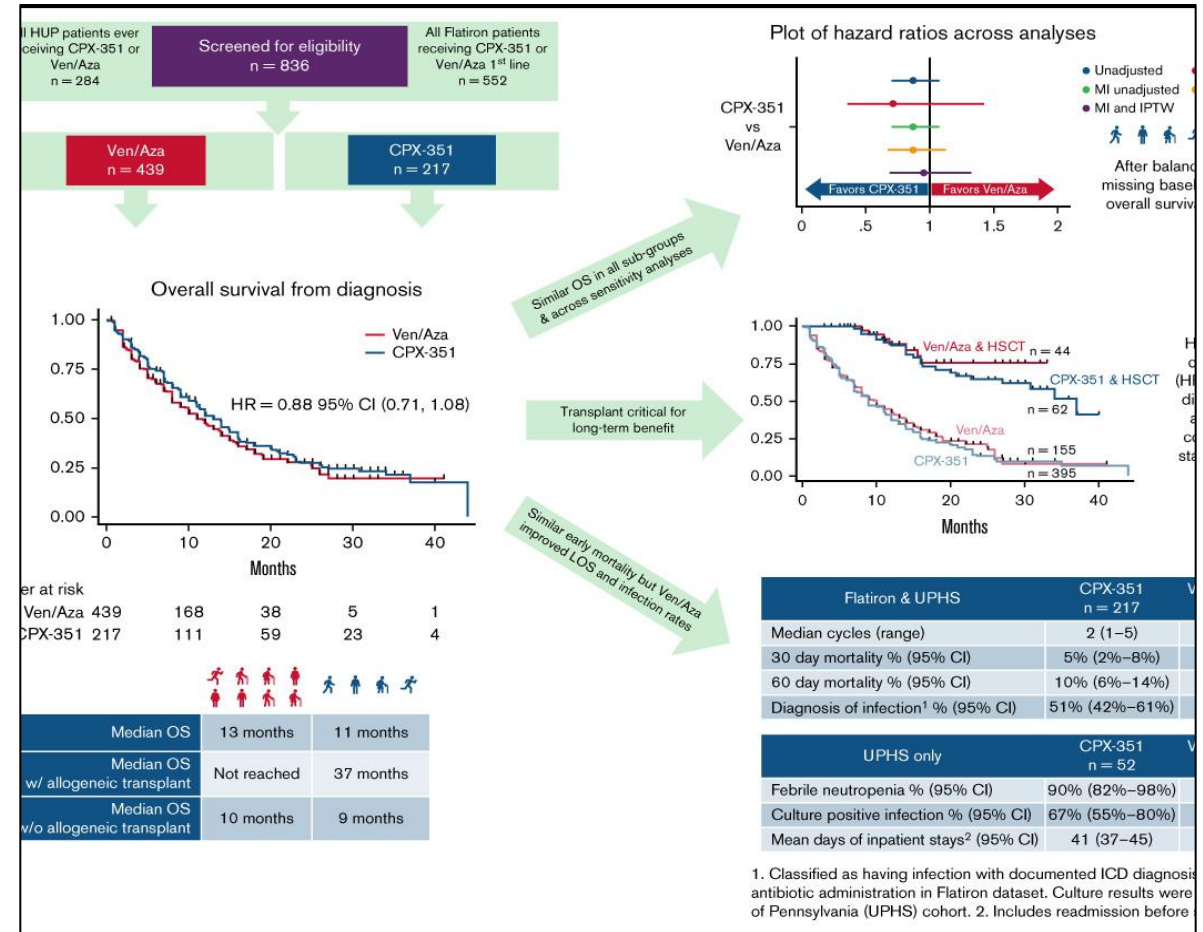
- ❖ Kaplan Meier curve for OS in 60-75yo (excluded 7 patients from CPX-351 group due to long follow up >40mo; excluded 3 from HMA+V group due to missing dates)



Other groups concur...

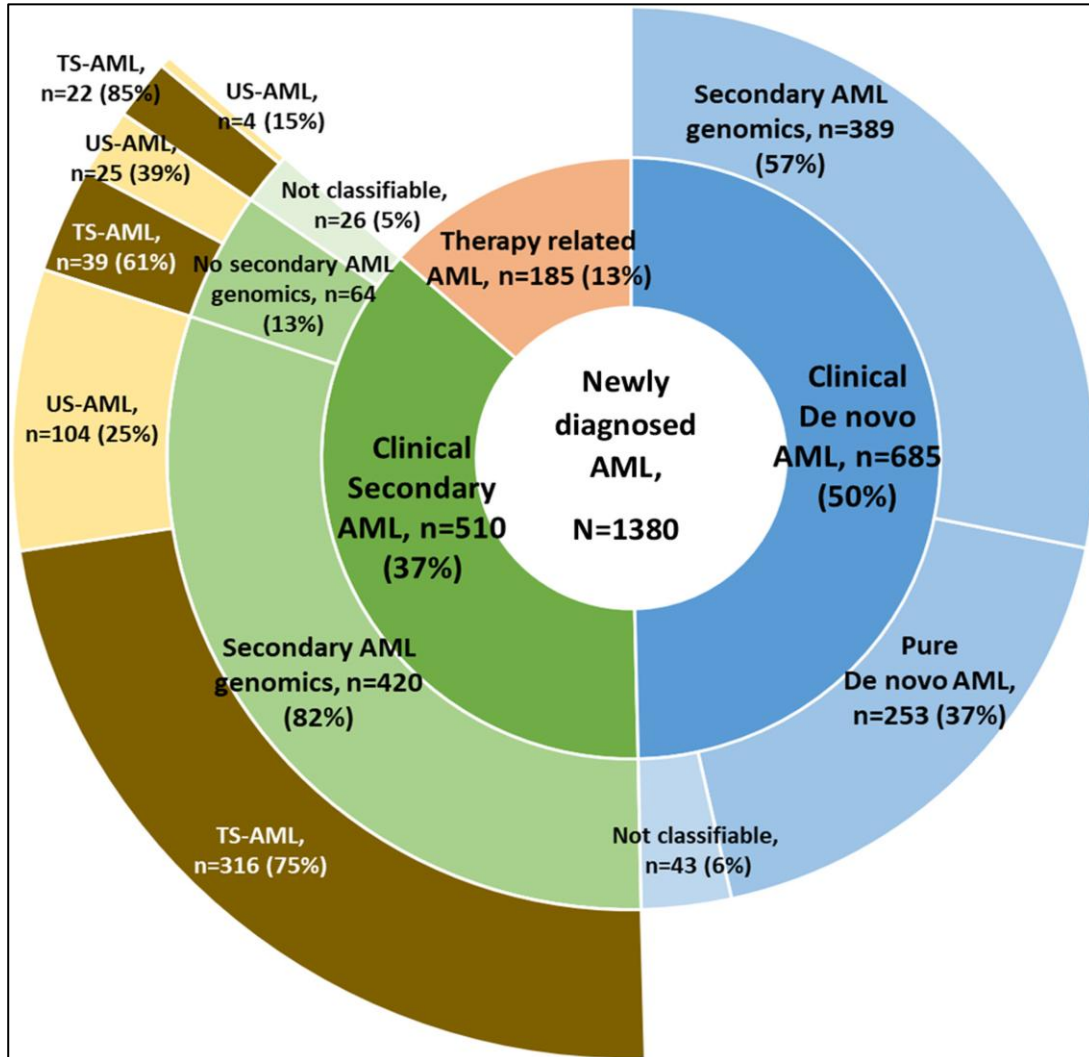


Asghari et al. *bloodjournal Blood* (2019) 134 (Supplement_1) : 3895.
<http://doi.org/10.1182/blood-2019-130379>



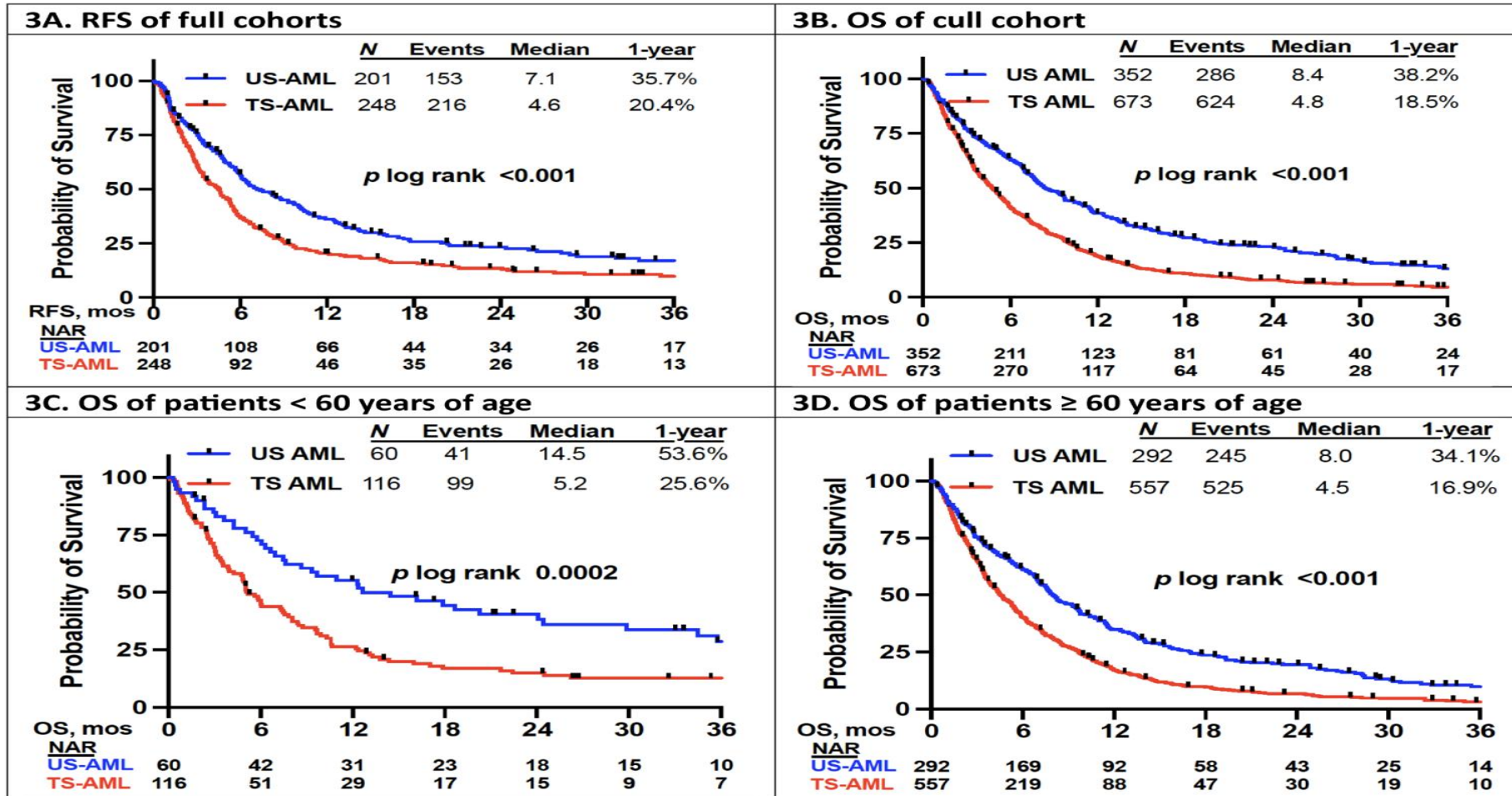
Matthews et al. *Blood Adv* (2022) 6 (13): 3997-4005.

Clinico-Genomic Interrogation of Secondary-Type Acute Myeloid Leukemia: Response and Outcomes to Contemporary Therapies



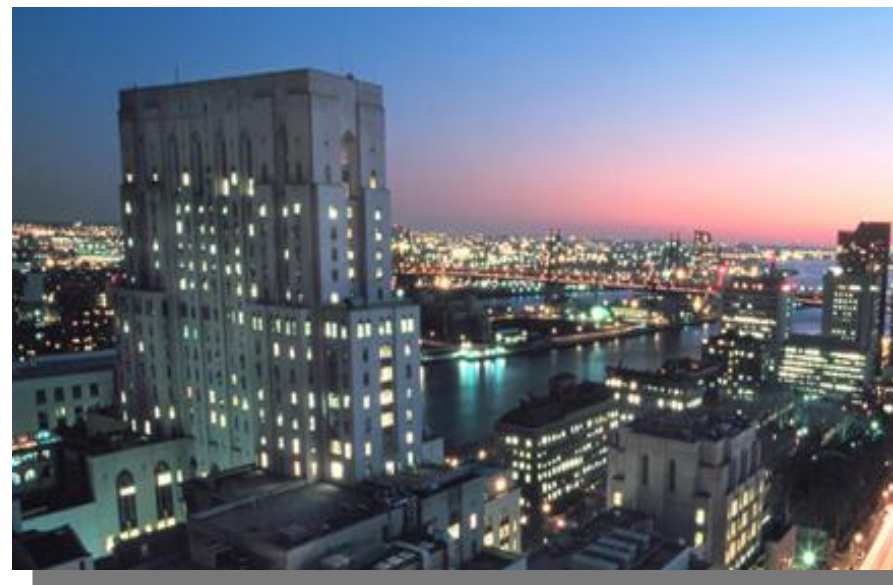
- Outcomes for un-treated CS-AML similar to GS-AML
- Outcomes for GS-AML worse if MRM+MRC
- Ven-based outcomes similar for GS-AML/MRM and DN-AML
- Ven-based outcomes worse in GS-AML with MRC
- Adverse cytogenetics remains an independent risk factor

Outcomes of Patients With Treated Secondary Acute Myeloid Leukemia



The Weill Cornell – NY Presbyterian Leukemia Program

- Gail J. Roboz, M.D.
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- Michael Samuel, M.D.
- Justin Kaner, M.D.
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- Christopher Mason, Ph.D.
- Ari Melnick, M.D.



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