De Novo Acute Myeloid Leukemia

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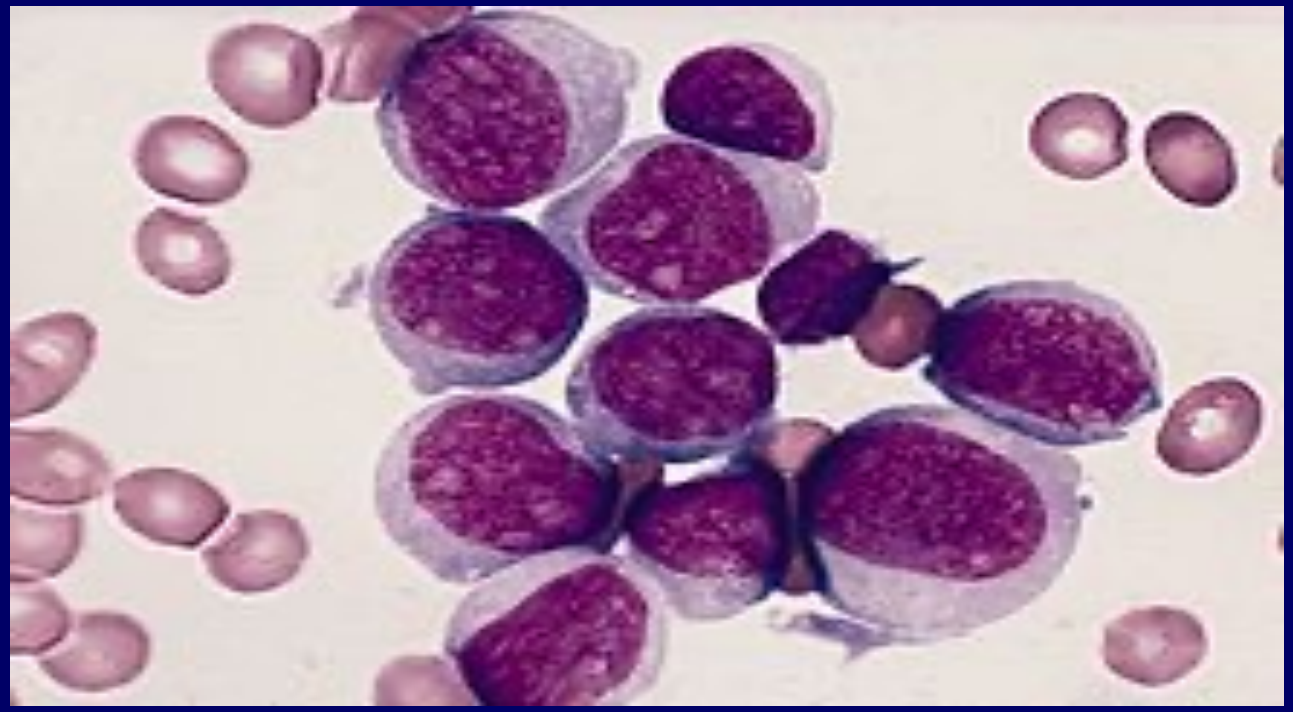
Dana-Farber
Cancer Institute

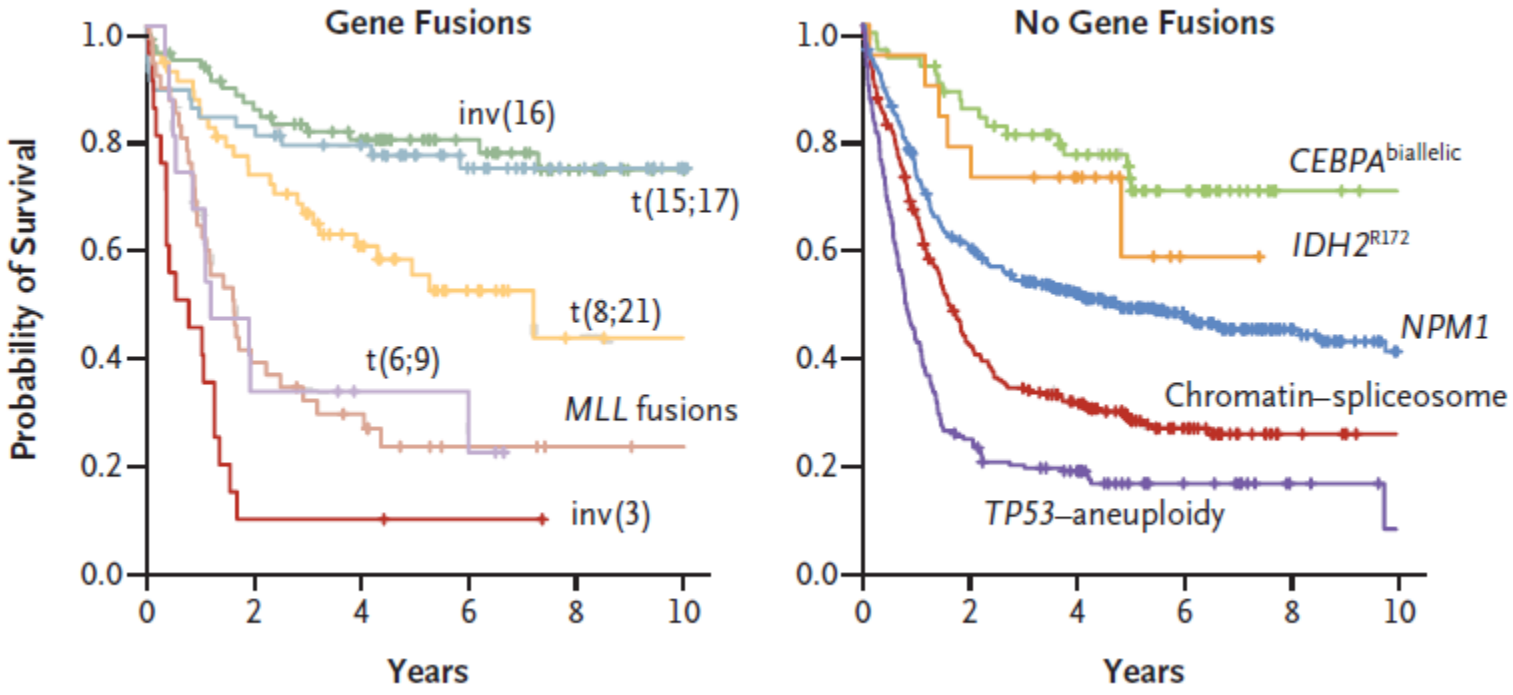
AML: What is it and how did it get there?

- Unbridled proliferation of hematopoietic stem cells (myeloid lineage) resulting in marrow failure and patient death unless successfully treated
- Risk factors: AGE, prior chemo for other cancers, ionizing radiation, industrial solvents (last 3 probably <10% of incidence=15K new US cases annually); unusual but kindreds exist w germ-line mutations in >10 genes*



*CEBPA, DDX41 (monocytosis) , MBD4, RUNX1 (t-penia) , ETV6 (t-penia. GATA1, SAMD9/SAMD9L (-7), TP53 (LFS) , TERC/TERT (lung and liver fibrosis; telemeropathy); Churpek J et al , UTD, 2022; Rio-MAchinA, et al , *Nat Commun* **11,** 1044 (2020). https://doi.org/10.1038/s41467-020-14829-5

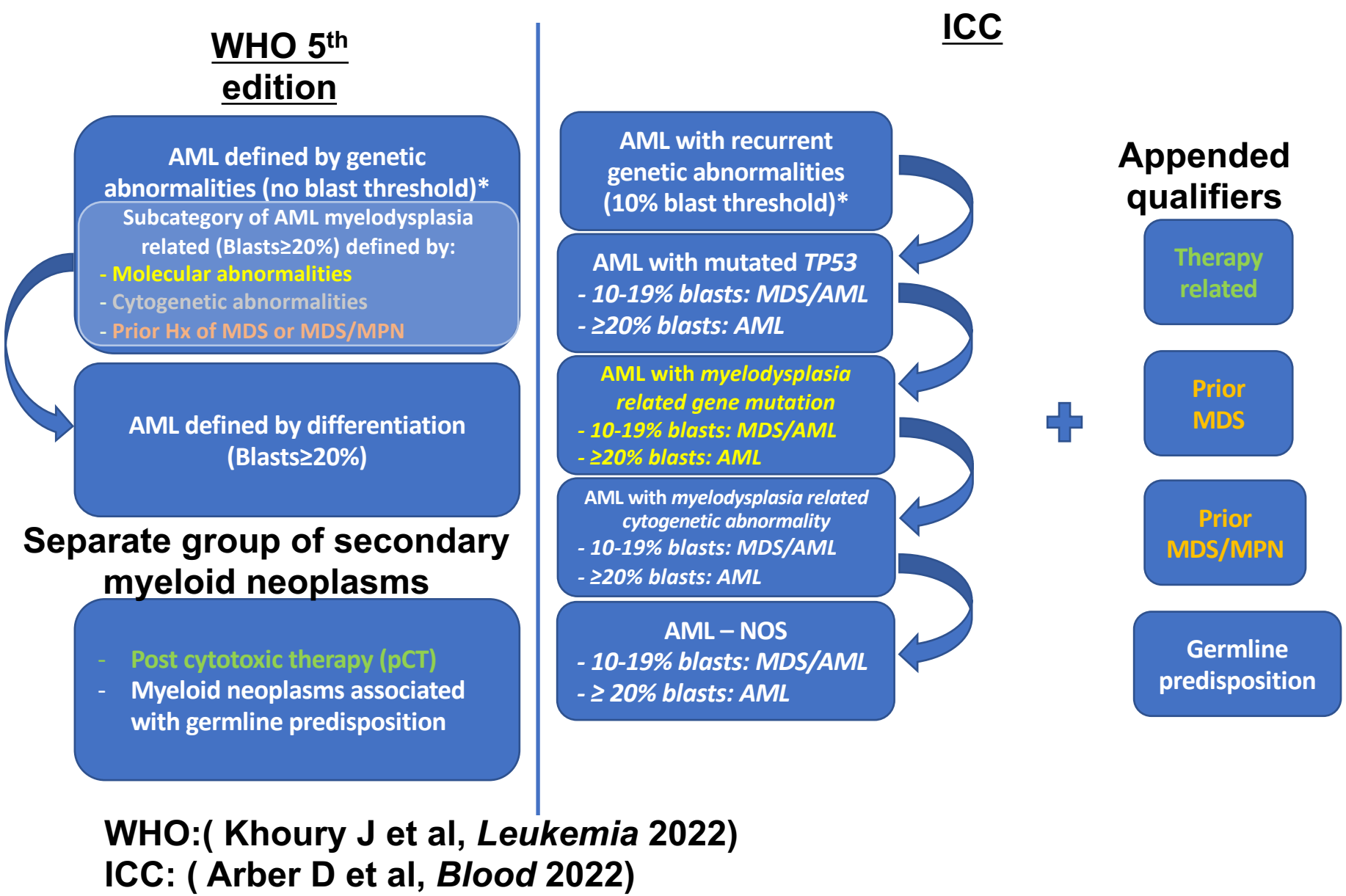
Genomic Classification and Prognosis in AML: Disease Heterogeneity



Dana-Farber Cancer Institute

Paparmmanuil E et al. *NEJM* 2016;374:2209-2221.

Rapid whole genome sequencing: more accurate and reliable than cytogenetics: Duncavage EJ, et al *NEJM* 2021; 384:924-935.



WHO:(Khoury J et al, *Leukemia* 2022)
ICC: (Arber D et al, *Blood* 2022)

Outline:
Myeloid neoplasms with mutated *TP53*

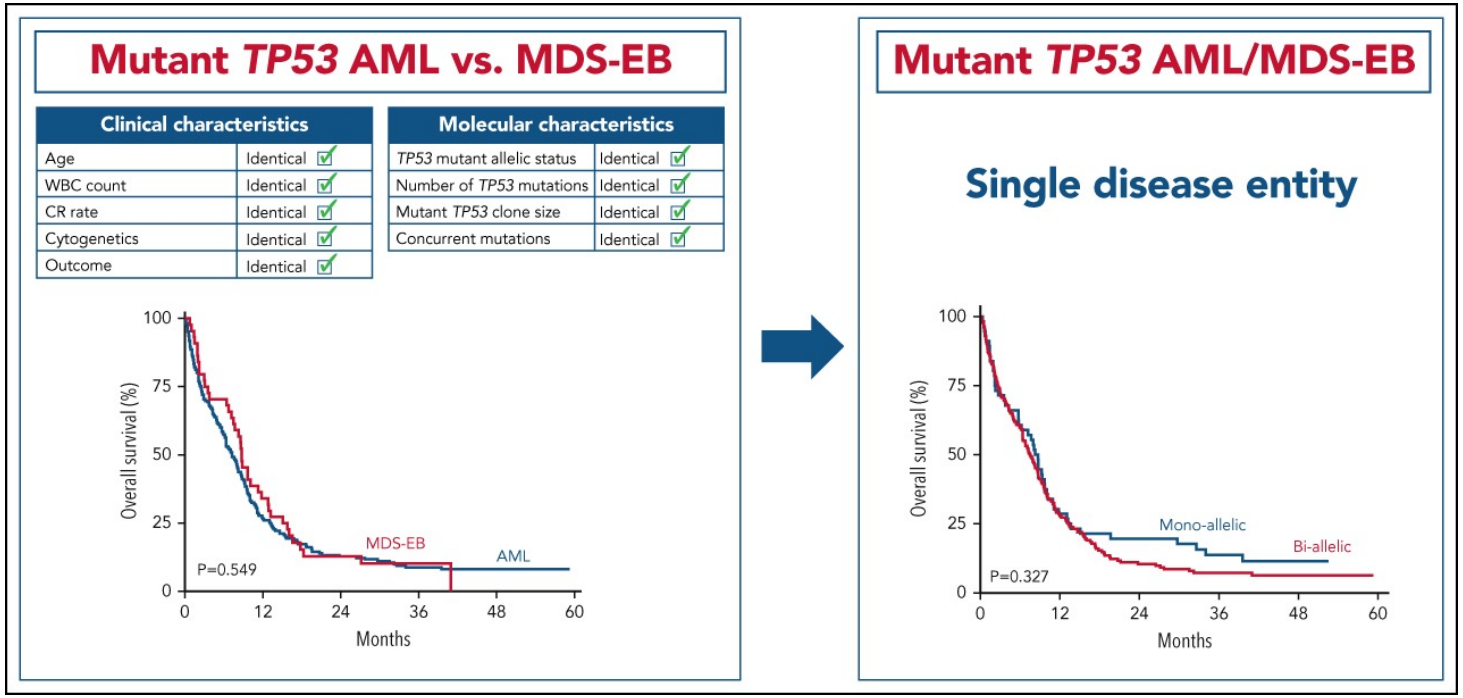
ICC 2022

- **MDS with mutated *TP53***
  - 0-9% blasts (marrow or blood)
  - Multi-hit *TP53* mutation
- **MDS/AML with mutated *TP53***
  - 10-19% blasts (marrow or blood)
  - Any *TP53* mutation (VAF >10%)
- **AML with mutated *TP53***
  - ≥20% blasts (marrow or blood)
  - Any *TP53* mutation (VAF >10%)

WHO 5th edition

- **Myelodysplastic neoplasm with biallelic *TP53* inactivation**
  - Myeloid neoplasm fulfilling diagnostic criteria for MDS
  - Detection of ≥2 *TP53* mutations
    - ≥2 SNVs / small indels
    - ≥1 SNV / small indel + *TP53* copy loss
    - ≥1 SNV / small indel + *TP53* copy neutral loss of heterozygosity

Mutant *TP53* AML vs. MDS-EB



Grob *et al., Blood, 2022*

Current Risk Assessment in AML

Key Prognostic Data in AML in 2023	
Patient **age** (FH, bleeding hx; **?Therapy related; ?Prior MDS**)	
Cytogenetics / fusion mRNA (screen for APL, MLL, Ph+, CBF)	
Multiparameter flow	
Molecular studies:	
• ***FLT3*** **ITD (internal tandem duplication) mutation**	*Unfavorable*
• ***NPM1*** **mutation or *CEBPα bZIP* mutation**	*Favorable*
• ***RUNX1, TP53, ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2***	*Unfavorable*

Importance for future rx: *IDH1/2*

Favorable	t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* (*FLT3* or *KIT* mut don't affect)
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11*(*FLT3*,*KIT* mut don't affect)
	Mutated *NPM1* without *FLT3*-ITD (adverse risk CG takes precedence)
	bZIP in-frame mutated *CEBPA* (mono- or bi-allelic)
Intermediate	*FLT3*-ITD (irrespective of allelic ratio or NPM1 mutation)
	t(9;11)(p21.3;q23.3)/MLLT3::KMT2A
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/*DEK::NUP214*
	t(v;11q23.3)/*KMT2A* rearranged (excluding *KMT2A*-PTD)
	t(9;22)(q34.1;q11.2)/*BCR::ABL1*
	(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 (3 or more, not hyerpdiploid) ; Monosomal Karyotype
	Mutated *ASXL1*, ***BCOR, EZH2,*** *RUNX1*, ***SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2***
	Mutated *TP53* **(Variant Allele Frequency ≥ 10%)**

(NEW) ELN 2022 classification

Dohner H, et al, Blood 2022.

AML: General Treatment Principles

- **Goal 1:** **Induction therapy to reduce gross leukemia to undetectable levels (2-3 log cell kill); to achieve CR (no AML, nl CBC)**

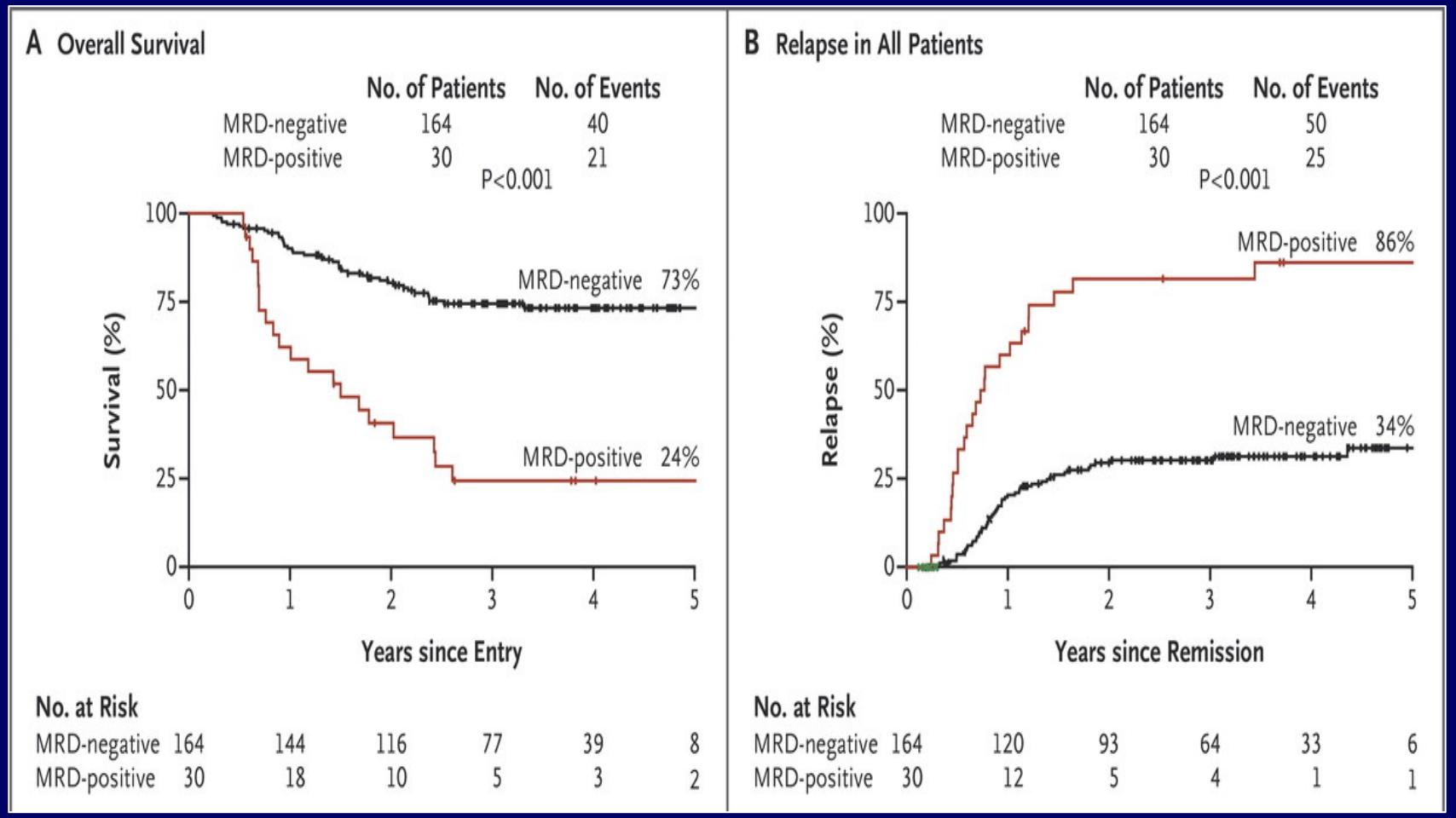
- **Goal 2:** **Reduce 10^9 - 10^{10} cells, undetectable by standard means, present at CR, to a level low enough to achieve prolonged disease-free survival (‘cure’)**

AML: Key Endpoints

- Overall survival (OS)
- Event-free survival (event= no CR, relapse, death)
  - Somewhat correlated with OS
  - Has intrinsic value to pts: when no event they are in CR with acceptable counts
- Complete remission (CR)
  - CR with incomplete plt (or ANC) recovery has value
  - CR at MRD negative level has most value !

MRD Based on PCR for Mutant NPM1 in Peripheral Blood After the Second Cycle of Chemotherapy Independently Predicts Clinical Outcomes

MP flow and PCR are currently sensitive in the 1 in 10,000 range c/w 1 in 20 for CG and morph

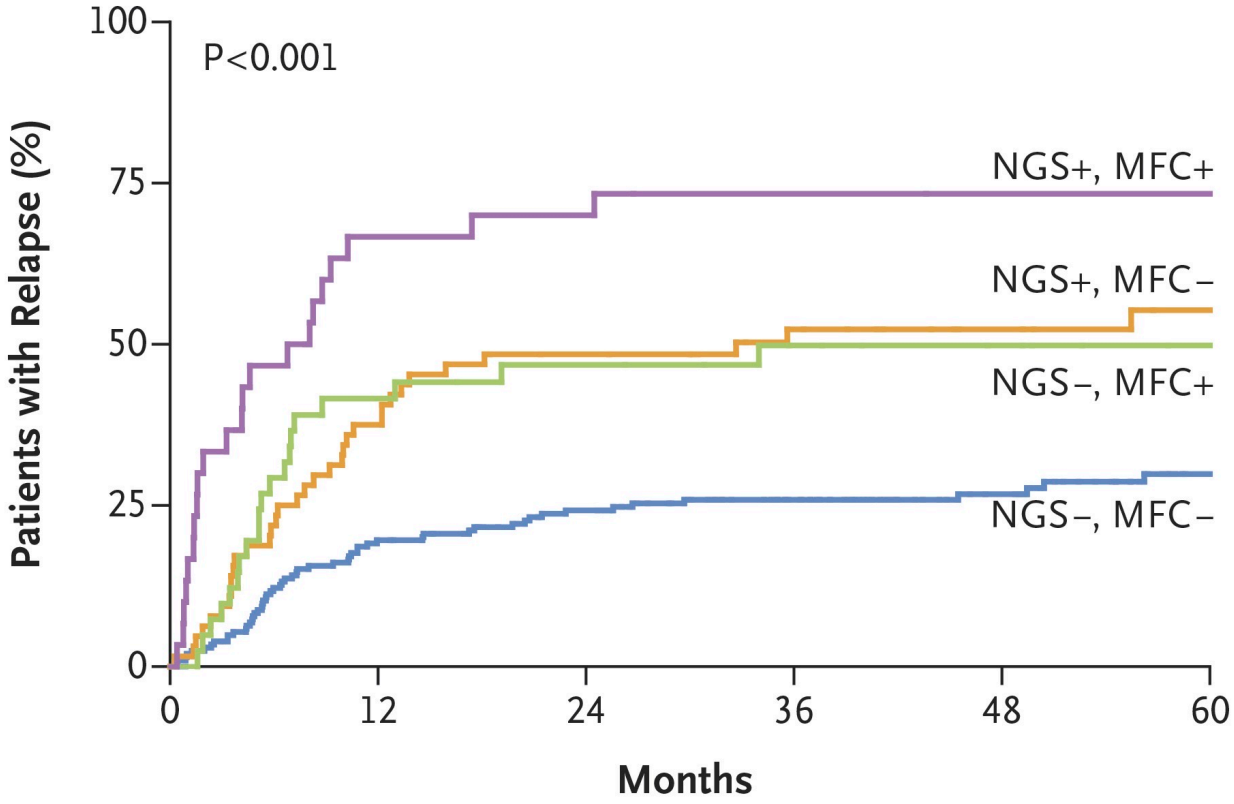


MRD = minimal residual disease; PCR = polymerase chain reaction.

Ivey A et al. *N Engl J Med*. 2016;374:422-433.

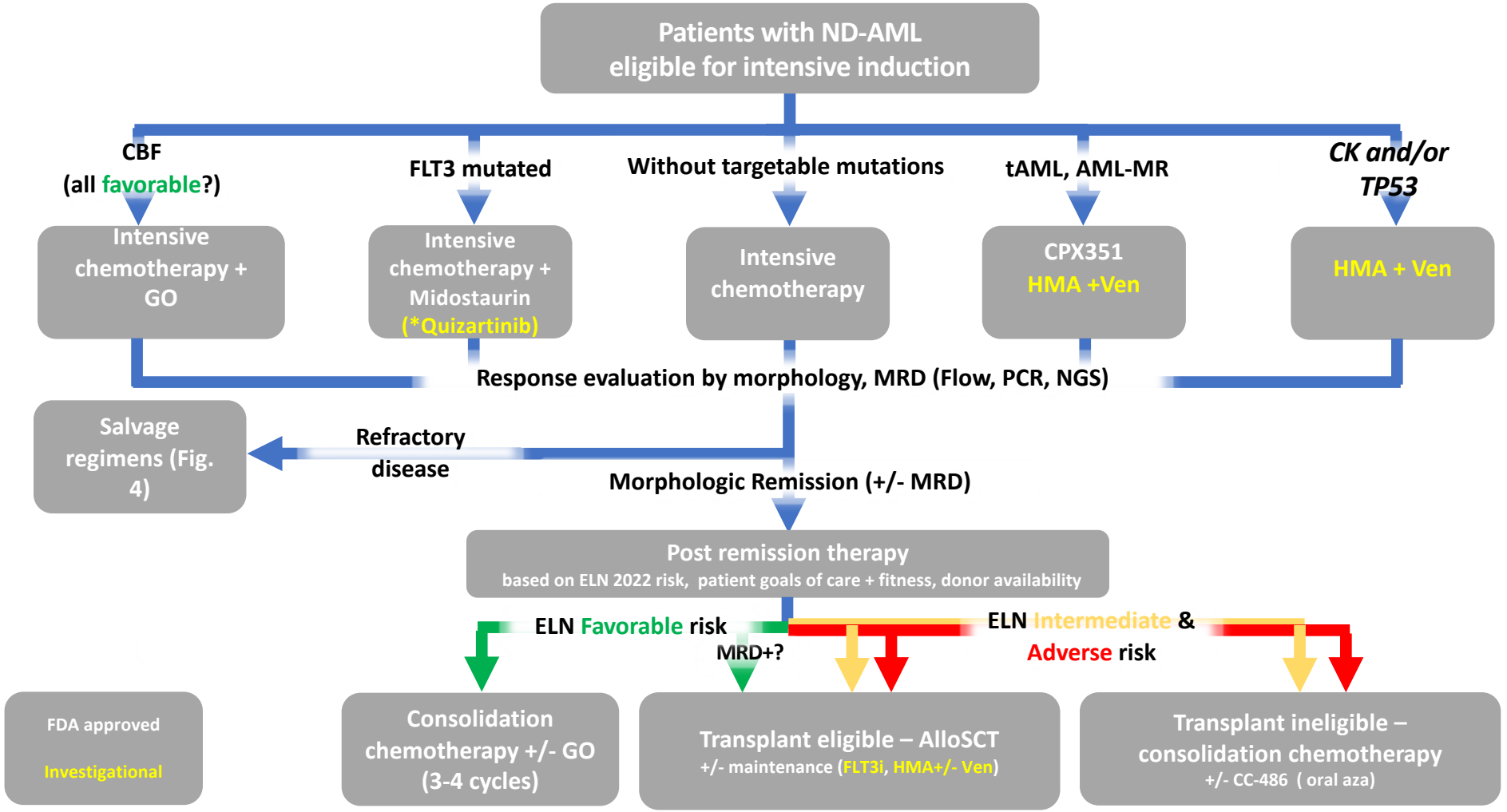
Rate of Relapse According to Results of Next-Generation Sequencing and Multiparameter Flow Cytometry.

Note: DNMT3A, TET2, ASXL1 mutaions do not ‘count’



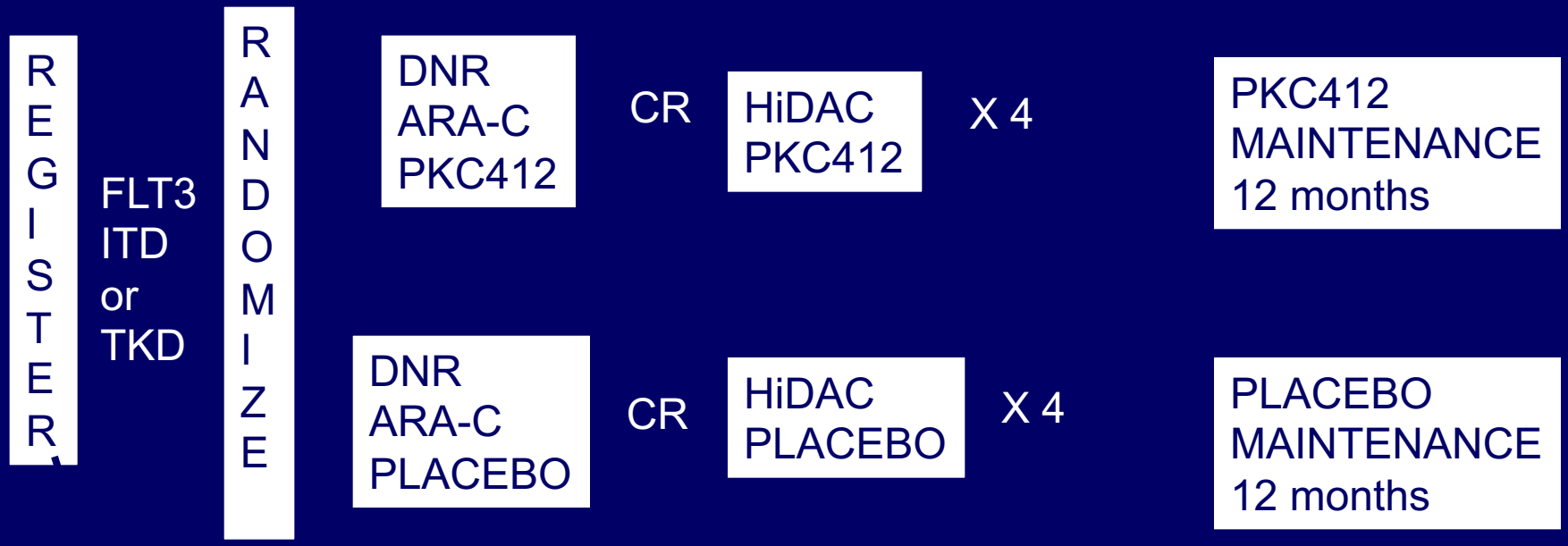
No. at Risk						
NGS+, MFC+	30	8	7	5	4	4
NGS–, MFC+	41	22	18	14	11	7
NGS+, MFC–	64	39	30	22	15	11
NGS–, MFC–	205	153	130	101	69	42

Jongen-Lavrencic M et al. N Engl J Med 2018;378:1189-1199



Shimony S, Stahl M, Stone R, Am J Hematol, 2023

CALGB 10603: Prospective Phase III, double-blinded randomized study of induction and consolidation +/- Midostaurin (PKC412) in newly diagnosed patients < 60 years old with FLT3 mutated AML

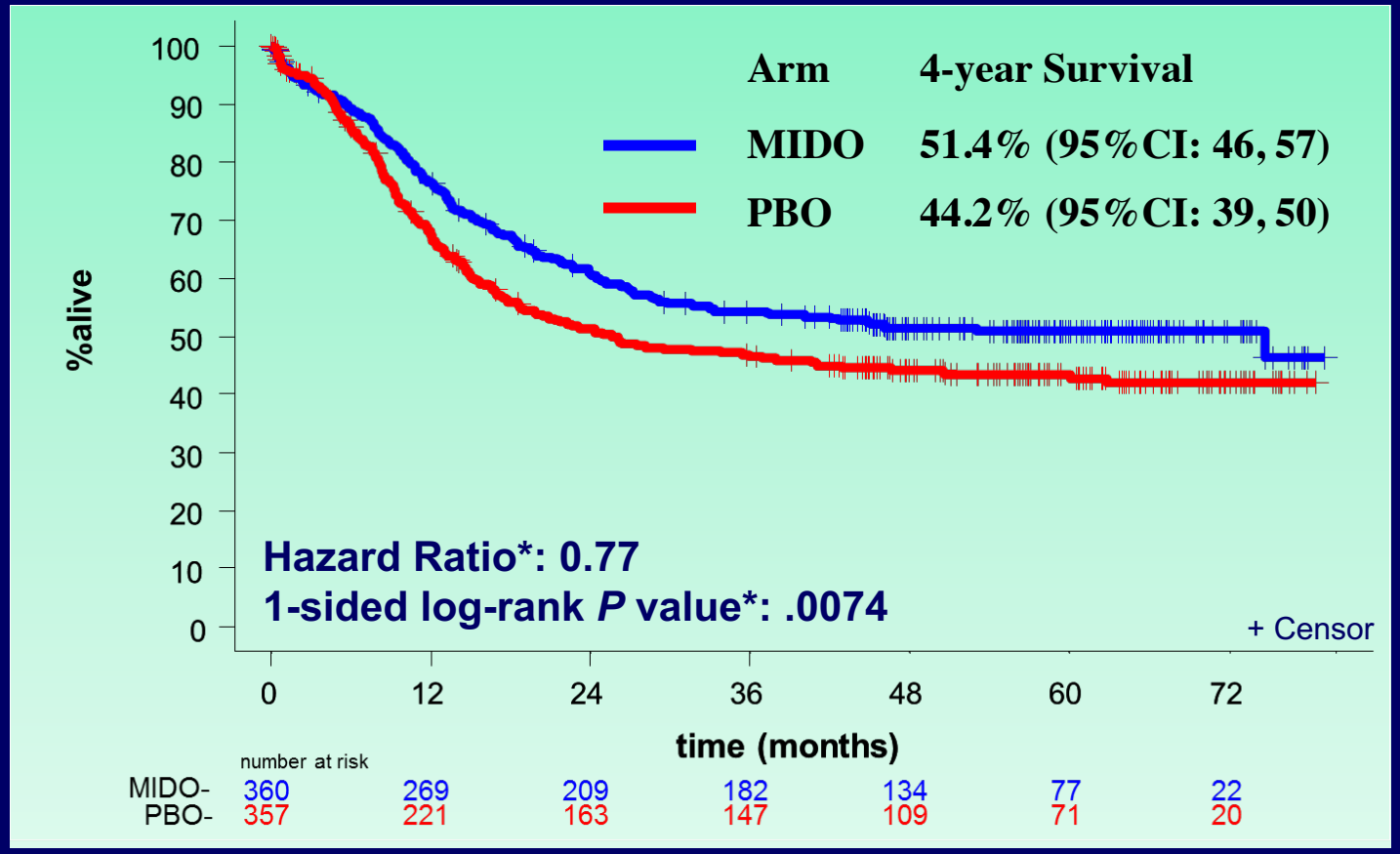


Not on STUDY:
FLT3 WILD TYPE

Study drug is given on Days 8-21 after each course of chemotherapy, and Days 1-28 (note change) of each 28 day Maintenance cycle.

Overall Survival (Primary Endpoint)

23% Reduced Risk of Death in the MIDO Arm



- **Median OS**: MIDO 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

Controlled for *FLT3* subtype (TKD, ITD-Low, ITD-High)

Stone RM, et al. NEJM 2017.

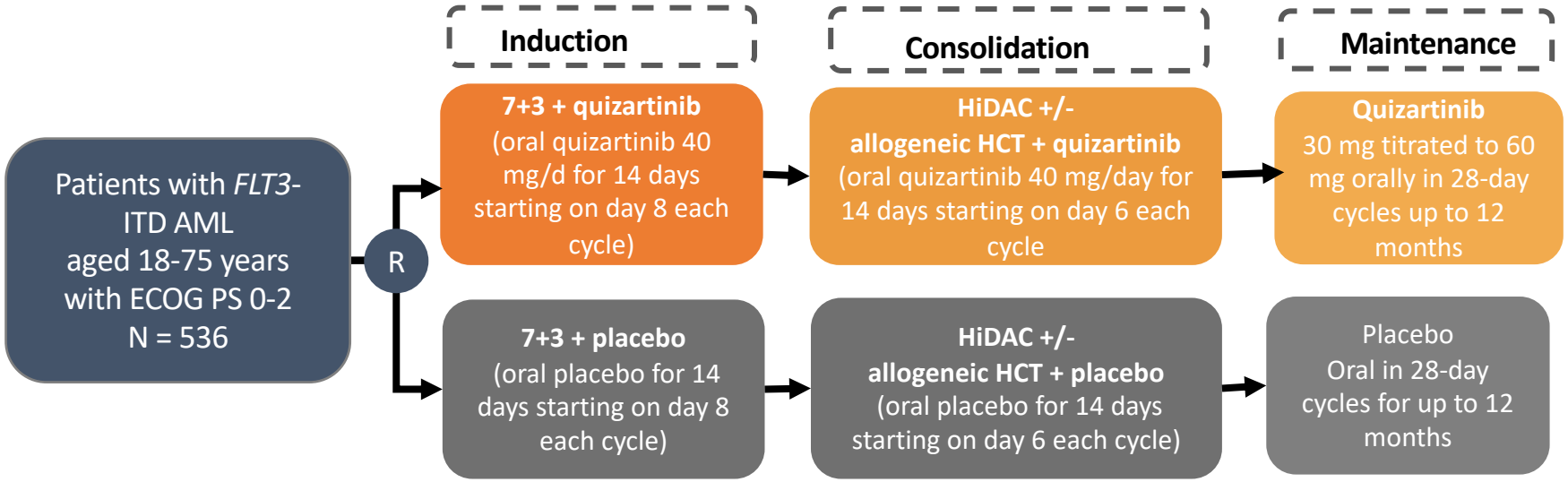
Multivariate Analysis for OS

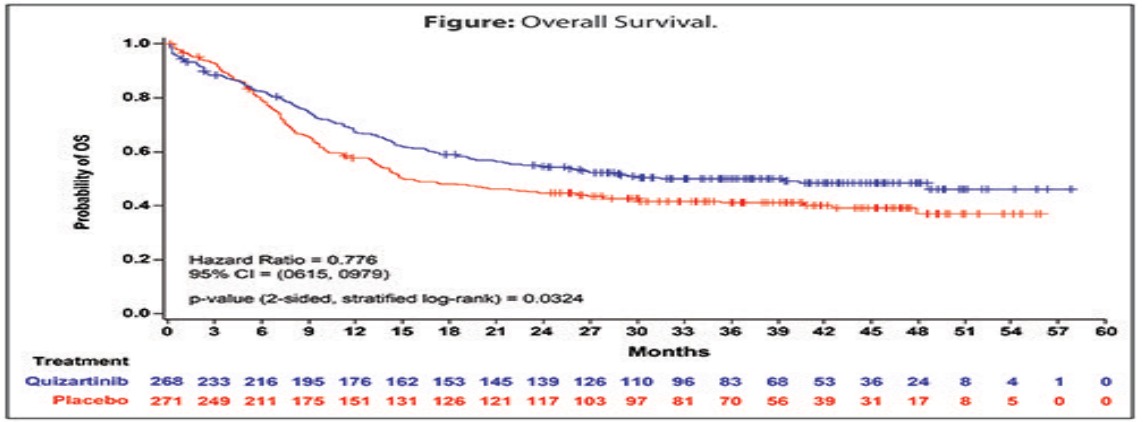
Factor	2-sided *P* value
ELN subgroups (*NPM1*/*FLT3*-ITD)	<.001
Treatment (midostaurin vs placebo)	.012
Allogeneic HCT	<.001
WBC (≥ vs <50 x10^9/L)	.028
Age (difference of 10 years)	.335
Sex	.689

- Döhner K, et al. *Blood.* 2017;130:467.

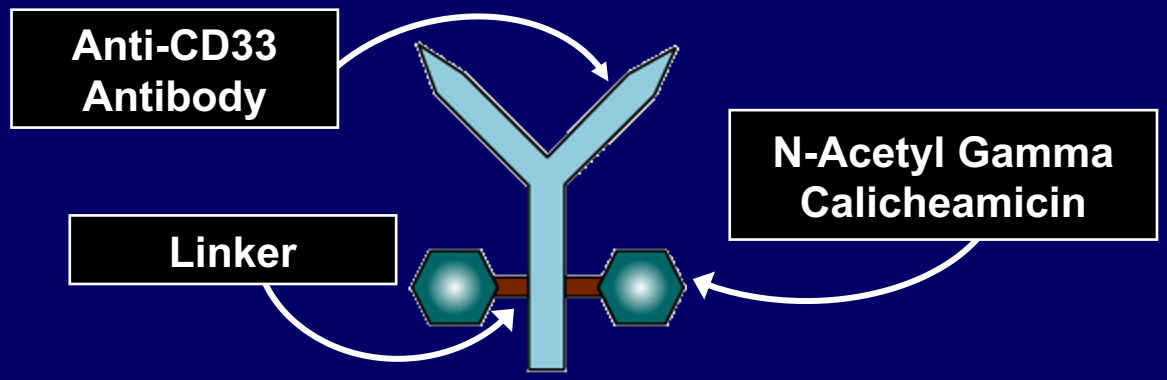
QUANTUM-FIRST: Quizartinib in Induction, Consolidation, and as Maintenance in *FLT3*-ITD+ AML

Erba H, et al; *Lancet* 401; 1571-1583, 2023





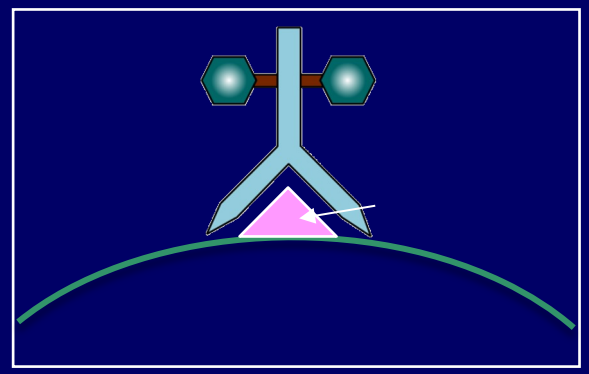
(Gemtuzumab Ozogamicin)



CD33 expressed on blasts in 90% of pts

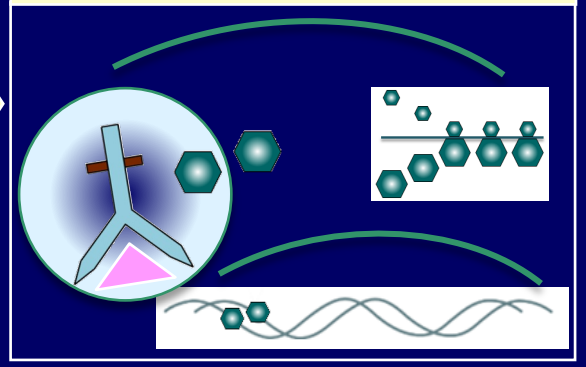
Mechanism of Action

Gemtuzumab Ozogamicin recognizes and binds to CD33, expressed on AML cells



Gemtuzumab Ozogamicin /CD33 complex is internalized

Calicheamicin is released causing DNA double-strand breaks/cell death



The Return of Gemtuzomab Ozogamycin

MRC AML 15
1,099 patients
5-year OS of all patients: GO 43%, no GO 41%

SWOG-0106
595 patients
5-year OS of all patients: GO 46%, no GO 50%

NCRI AML 16
1,115 patients
4-year OS of all patients: GO 20%, no GO 15%

GOELAMS AML2006IR
238 patients
5-year OS of all patients: GO 53%, no GO 46%

ALFA-0701
278 patients
2-year OS of all patients: GO 53%, no GO 41%

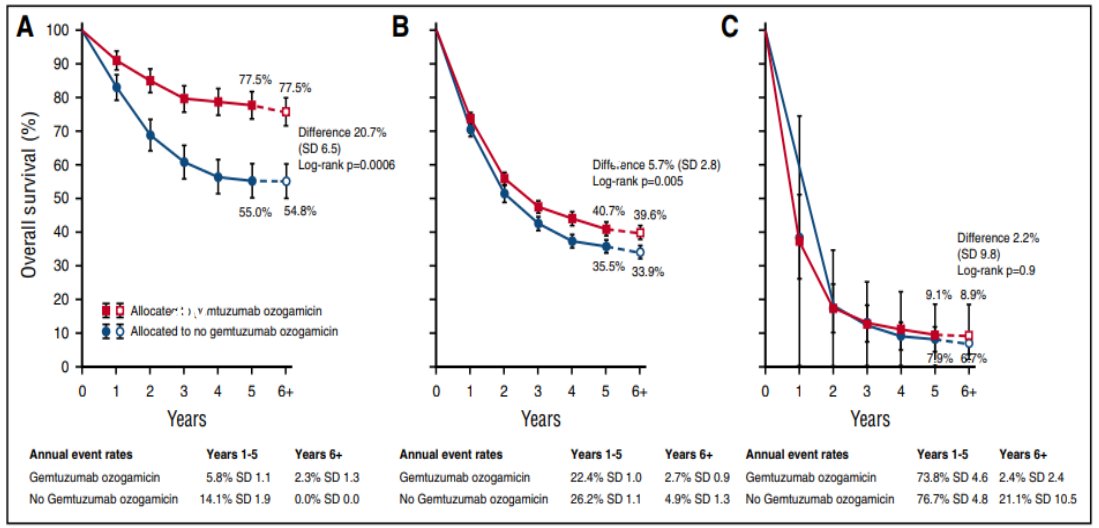
Meta-analysis

5-year OS of all patients
GO 34.6%
No GO 30.7%

5-year OS favorable risk
GO 77.5%
No GO 55%

5-year OS intermediate risk
GO 40.7%
No GO 35.5%

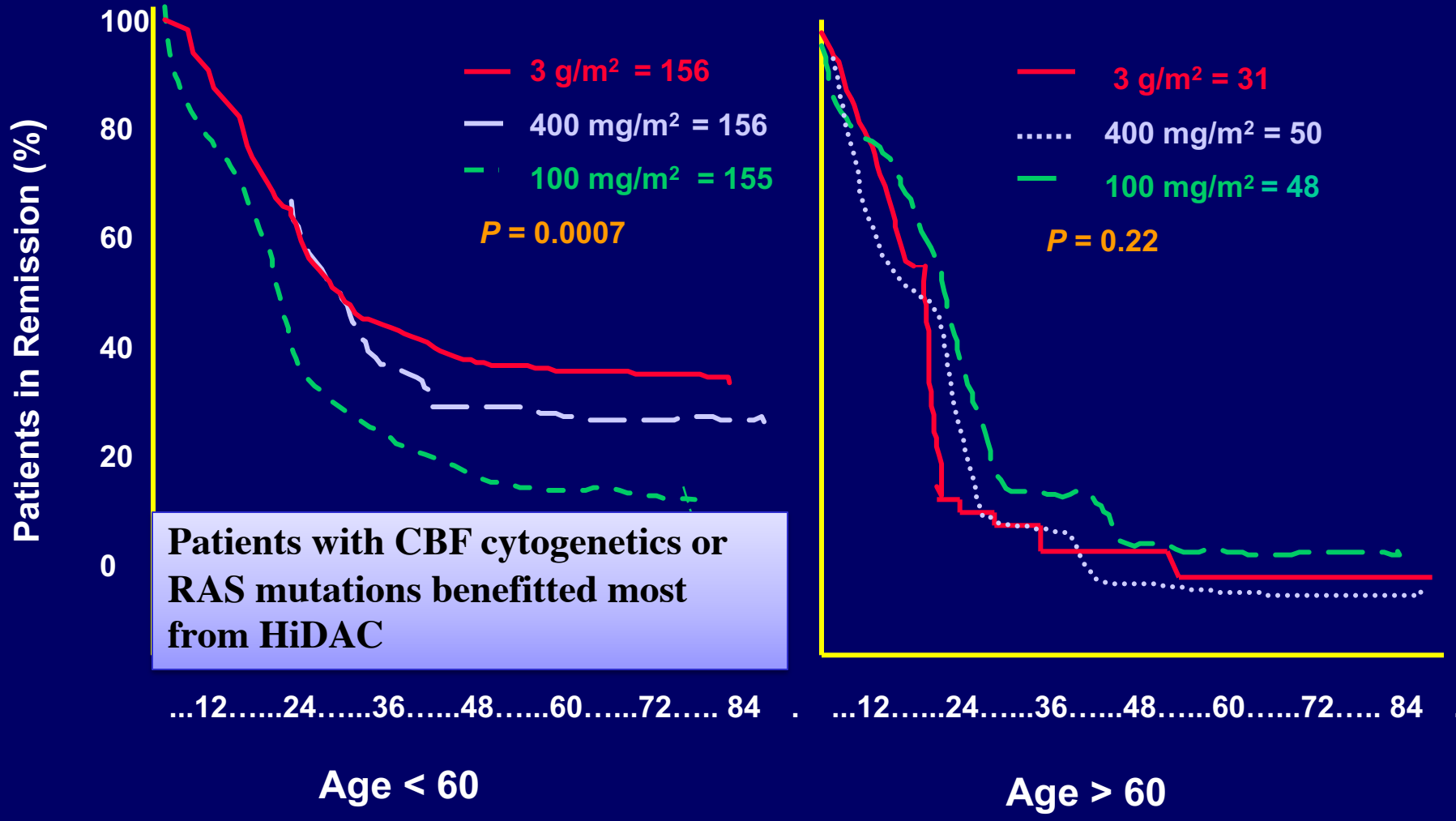
5-year OS unfavorable risk
GO 9.1%
No GO 7.9%



FAV INT UNFAV
Karytoype-based risk

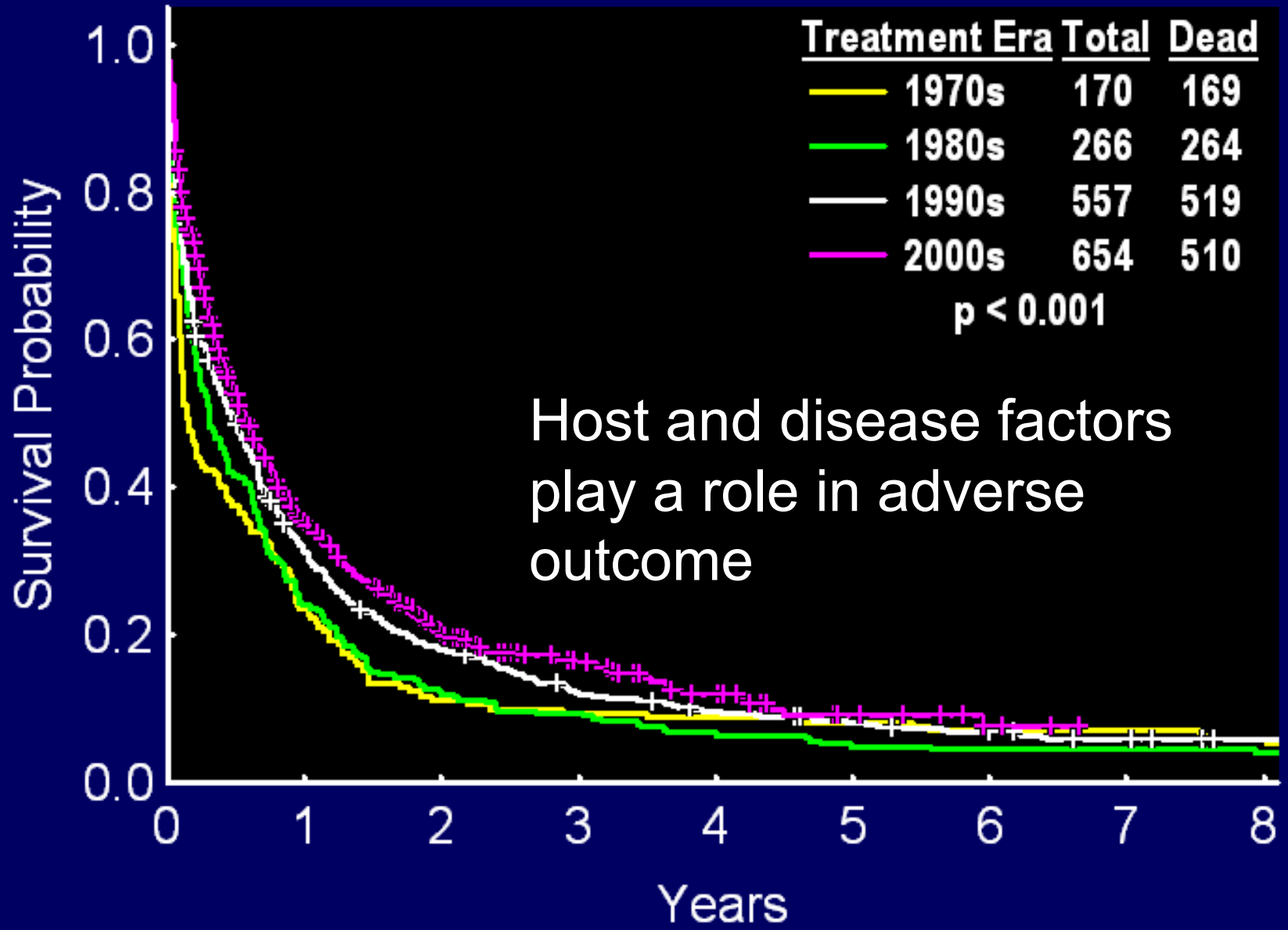
Hills RT, et al, *Lancet Oncol* 15: 986-996, 2014

Consolidation: DFS (and OS) Benefit Only in Patients < 60 Years Receiving High-Dose Ara-C

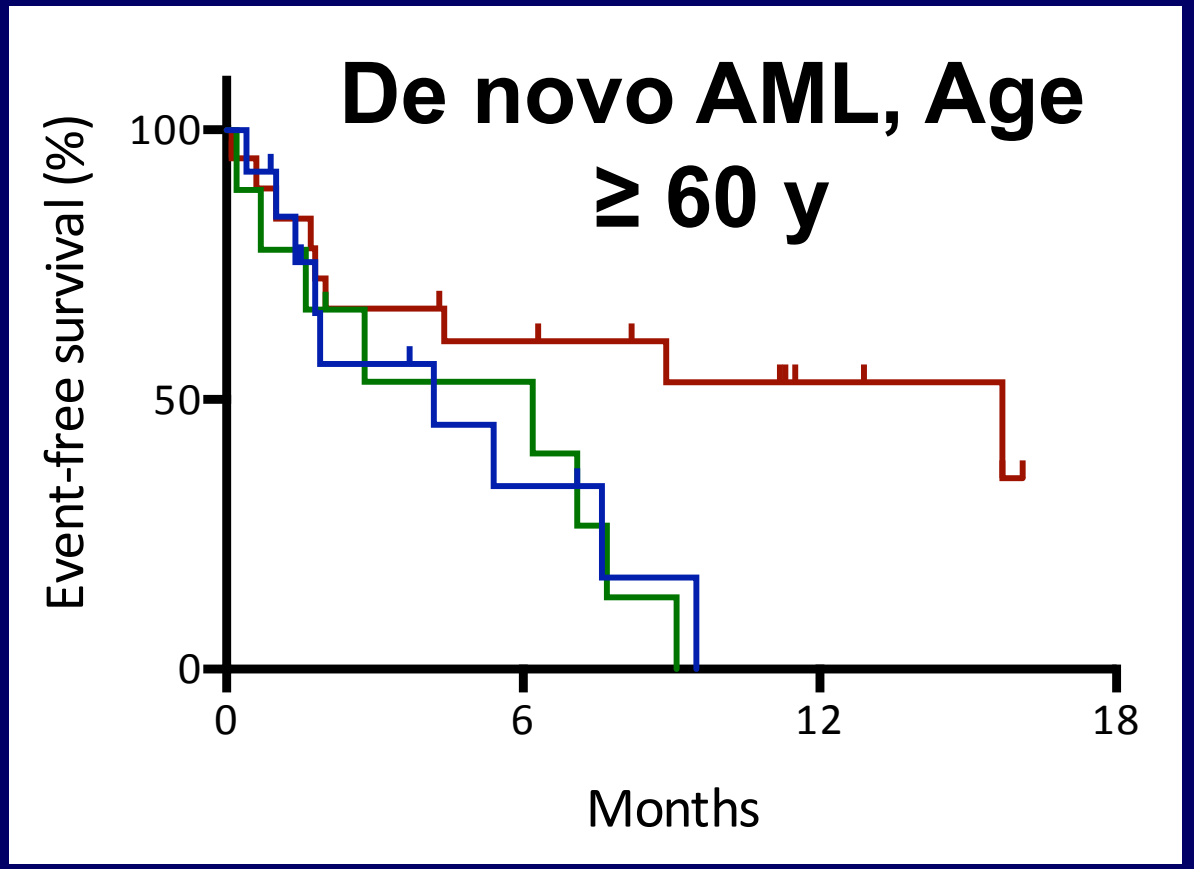


Bloomfield CD, et al. *Cancer Res.*1998;58(18):4173-4179; Neubauer A, et al. *J Clin Oncol.* 2008; 26(28):4603-4609; Mayer RJ, et al. *N Engl J Med*. 1994;33(1):896-903.

Survival in AML in Age ≥ 60 Years (MDACC, 1973-Present, n=1647)



In Elderly de novo AML, Secondary-Type Mutations Are Associated With Adverse Outcomes



Genetic Subtype

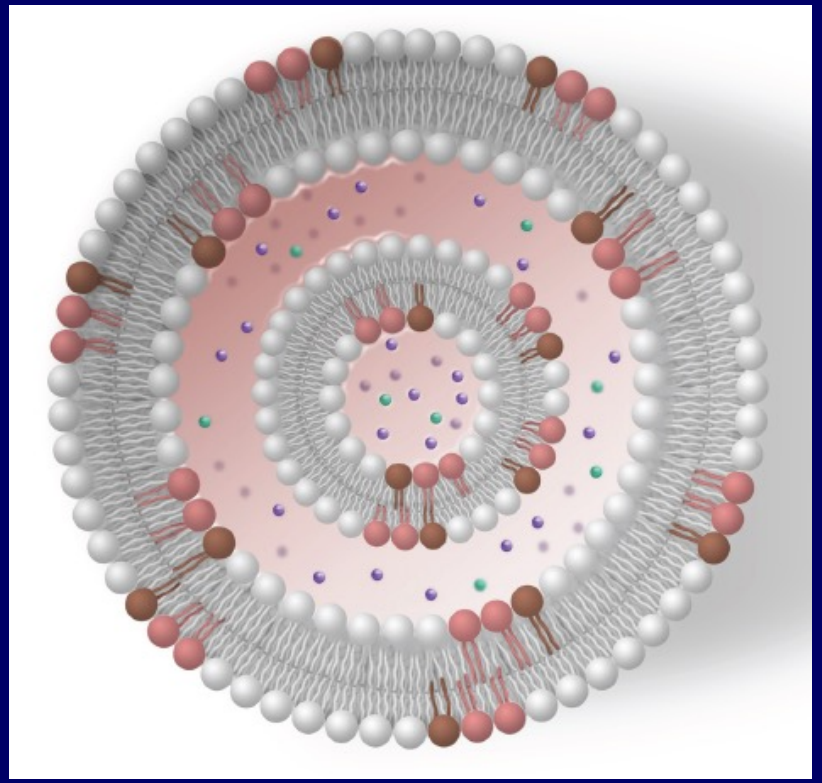
- De novo/pan-AML
- Secondary-type
- *TP53* mutated

Secondary type:ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2

Lindsley RC et al. Blood. 2015;125:1367-1376.

CPX-351

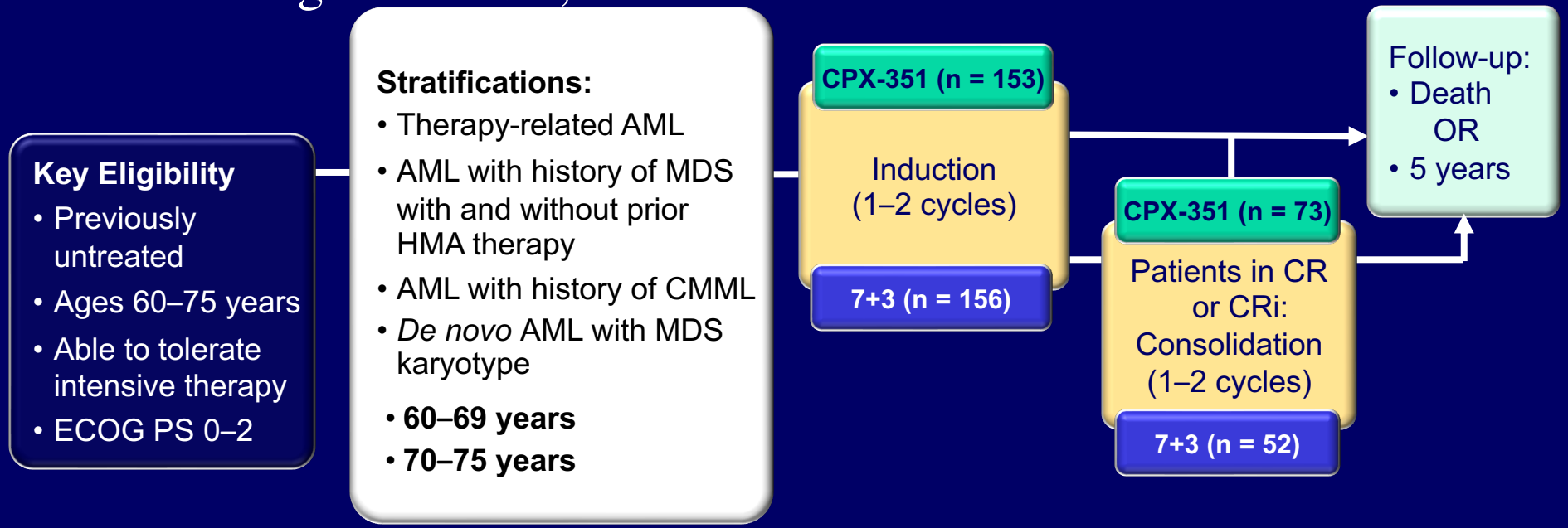
- CPX-351 is a liposomal co-formulation of cytarabine and daunorubicin designed to achieve synergistic antileukemia activity
  - 5:1 molar ratio of cytarabine:daunorubicin provides synergistic leukemia cell killing *in vitro*[1]
  - In patients, CPX-351 preserved delivery of the 5:1 drug ratio for over 24 hours, with drug exposure maintained for 7 days[2]
  - Selective uptake of liposomes by bone marrow leukemia cells in xenograft models[3]



. Tardi P et al. *Leuk Res.* 2009;33(1):129–139.
2. Feldman EJ et al. *J Clin Oncol.* 2011;29(8):979–985;
3. Lim WS et al. *Leuk Res.* 2010;34(9):1245–1223.

CPX-351 Phase III Study Design

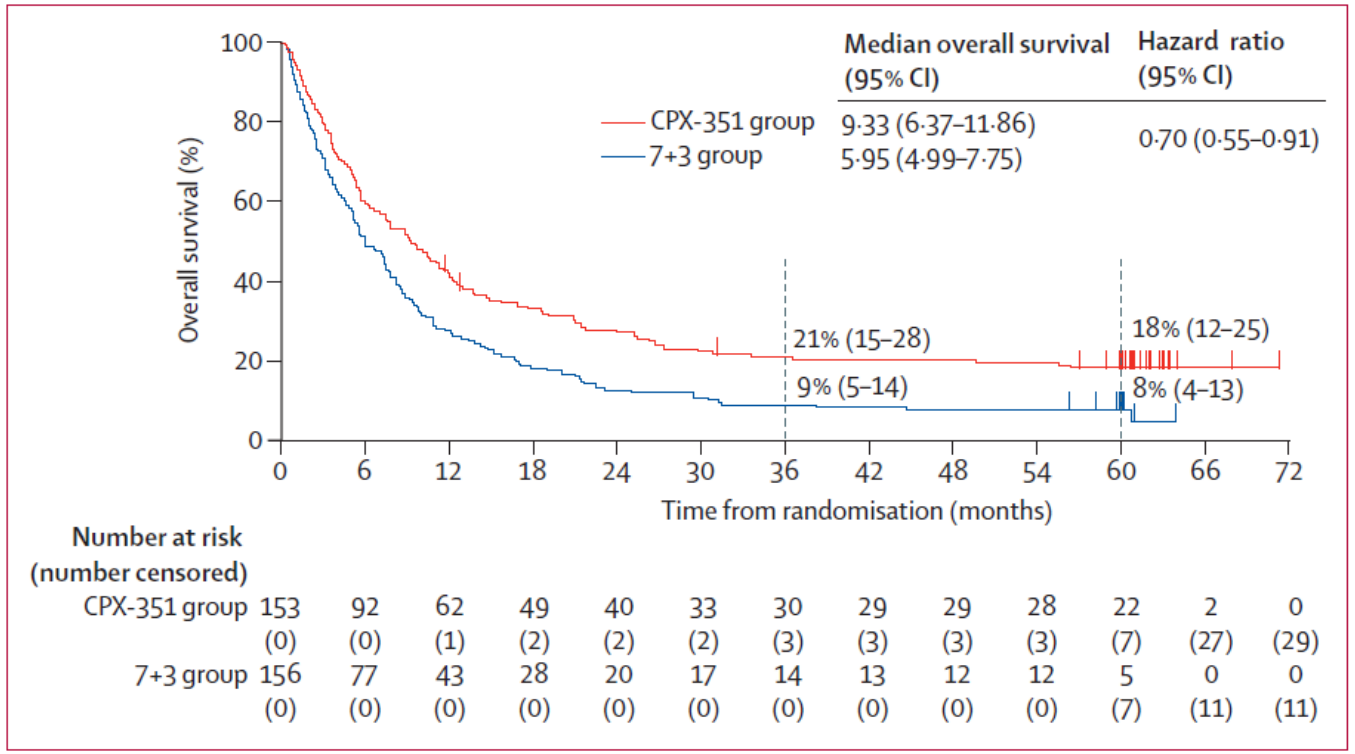
- Randomized, open-label, parallel-arm, standard therapy–controlled
  - 1:1 randomization, enrolled from December 2012 to November 2014
  - Patients with CR or CRi could be considered for allogeneic HCT, based on institutional criteria



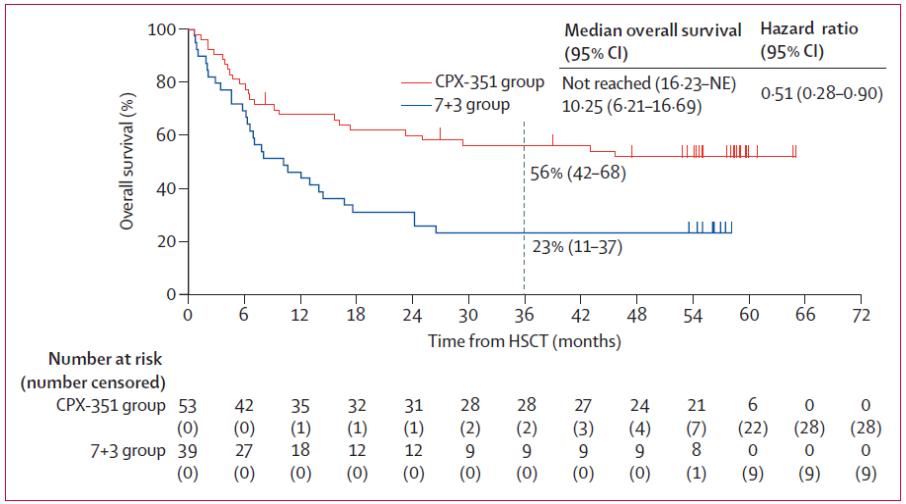
recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; HMA, hypomethylating agents; MDS, myelodysplastic syndrome.

1. World Health Organization. *WHO Classification of Tumours of Haematopoitic and Lymphoid Tissues*. Swerdlow S et al (ed). Lyon, IRAC Press, 2008.

Overall survival CPX 351 v 3+7 in sec AML, age 60-75: 5-year results[1]



Overall survival from date of HSCT: 5-year results[1]



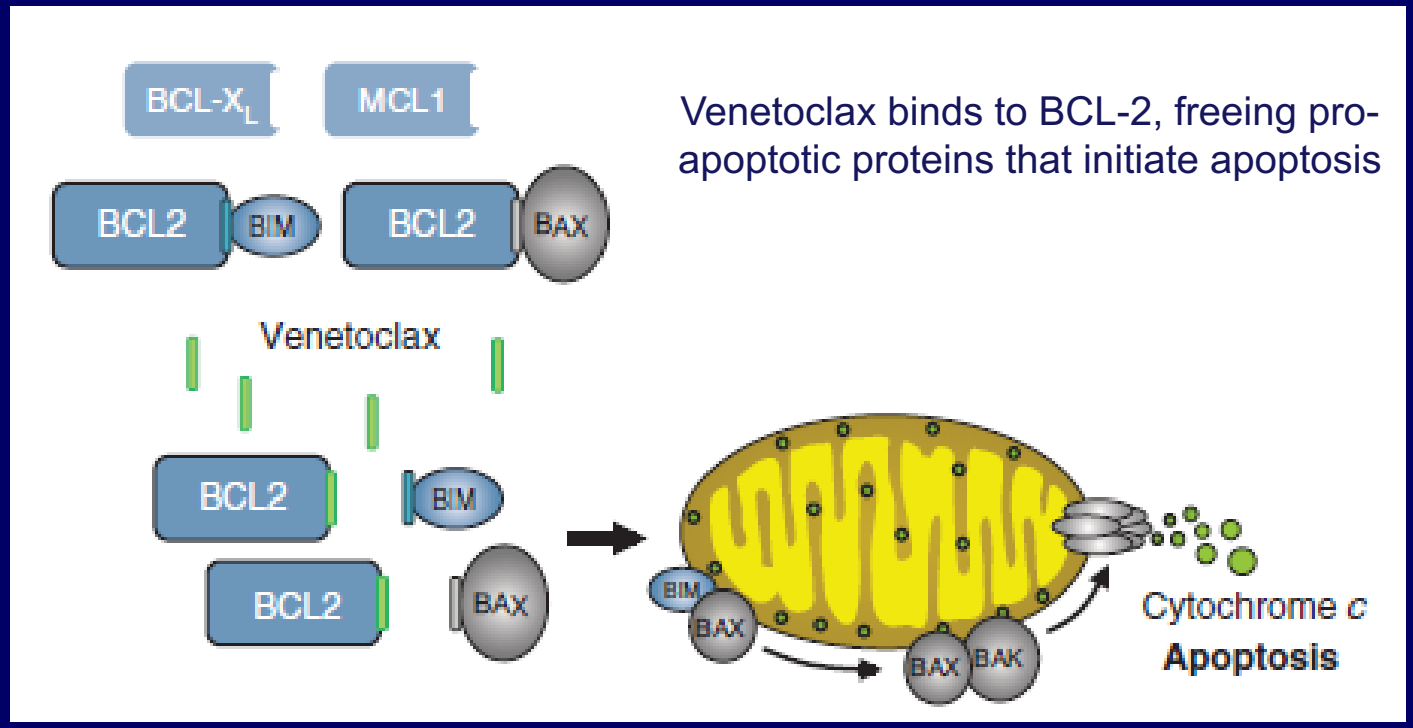
3-year and 5-year Kaplan-Meier-estimated survival rates are shown with 95% CI. 7+3=cytarabine and daunorubicin.

	CPX-351 (n = 153)	7+3 (n = 156)	Odds ratio	*P* value
CR+CRi	47.7%	33.3%	1.77 (1.11, 2.81)	0.016
HSCT rate	34.0%	25.0%	1.54 (0.92, 2.56)	0.098
Deaths ≤30 days*	5.9%	10.3%		
Deaths ≤60 days*	13.7%	21.2%		

1. Lancet JE, et al. *Lancet Hematol* 2021;8:e481–91. **2.** Lancet JE, et al. *J Clin Oncol* 2018;36(26):2684-2692.

Venetoclax: BCL-2 Selective Inhibitor

BCL-2 overexpression allows cancer cells to evade apoptosis by sequestering pro-apoptotic proteins



Venetoclax binds to BCL-2, freeing pro-apoptotic proteins that initiate apoptosis

Konopleva M, et al. *Cancer Discov*. 2016. Epub ahead of print. Lin T, et al. ASCO 2016. Abstract 7007.

Azacitidine ± Venetoclax (VIALE-A) Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ≥75 years of age
  - 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV_1 ≤65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N = 433*

Venetoclax + Azacitidine
(n = 286)
Venetoclax 400 mg PO, daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine
(n = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

Secondary

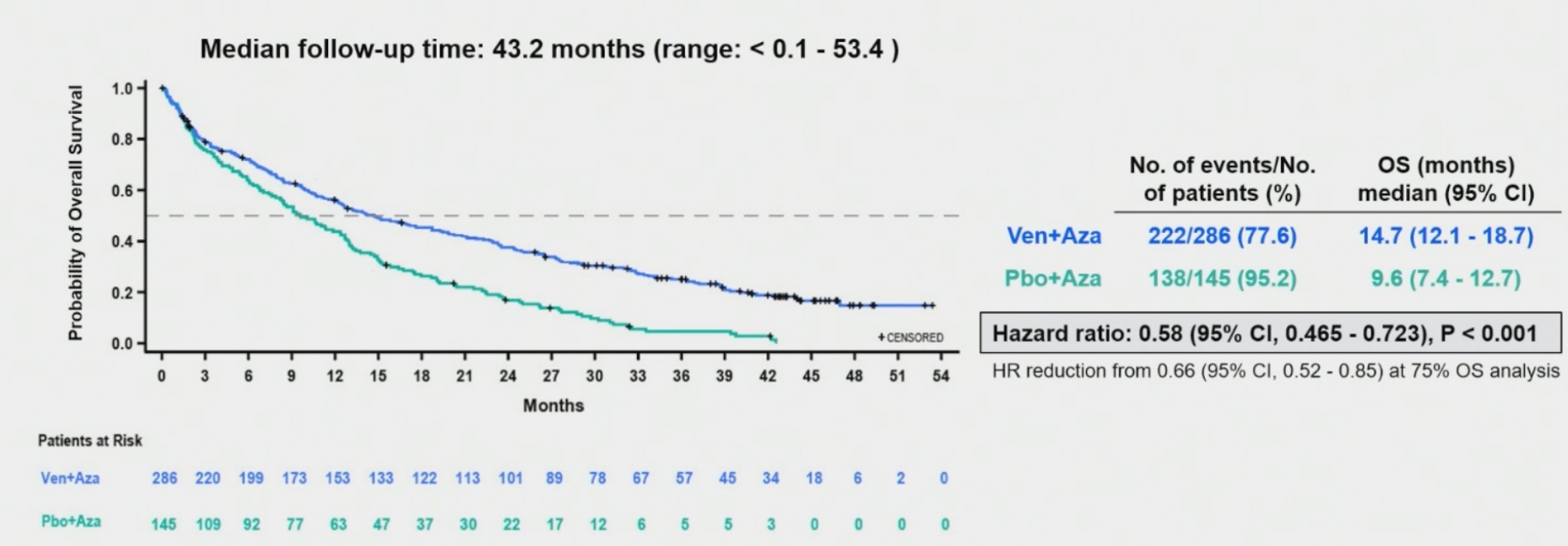
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

Randomization Stratification Factors: Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

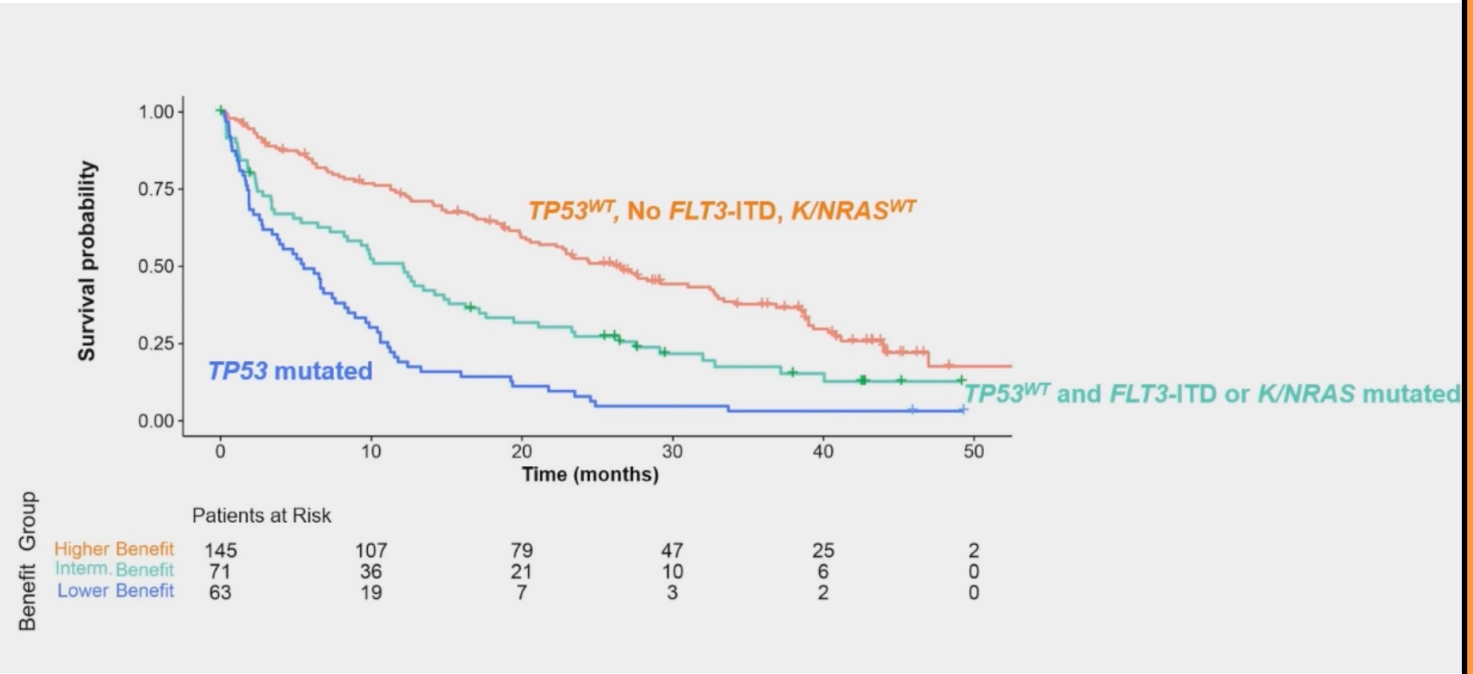
Venetoclax dosing ramp-up: **Cycle 1 ramp-up** Day 1: 100 mg, Day 2: 200 mg, Day 3 - 28: 400 mg; **Cycle 2** → Day 1-28: 400 mg

DiNardo CD et al. NEJM 2020

219:Long-Term Follow-up of the Phase 3 Viale-a Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

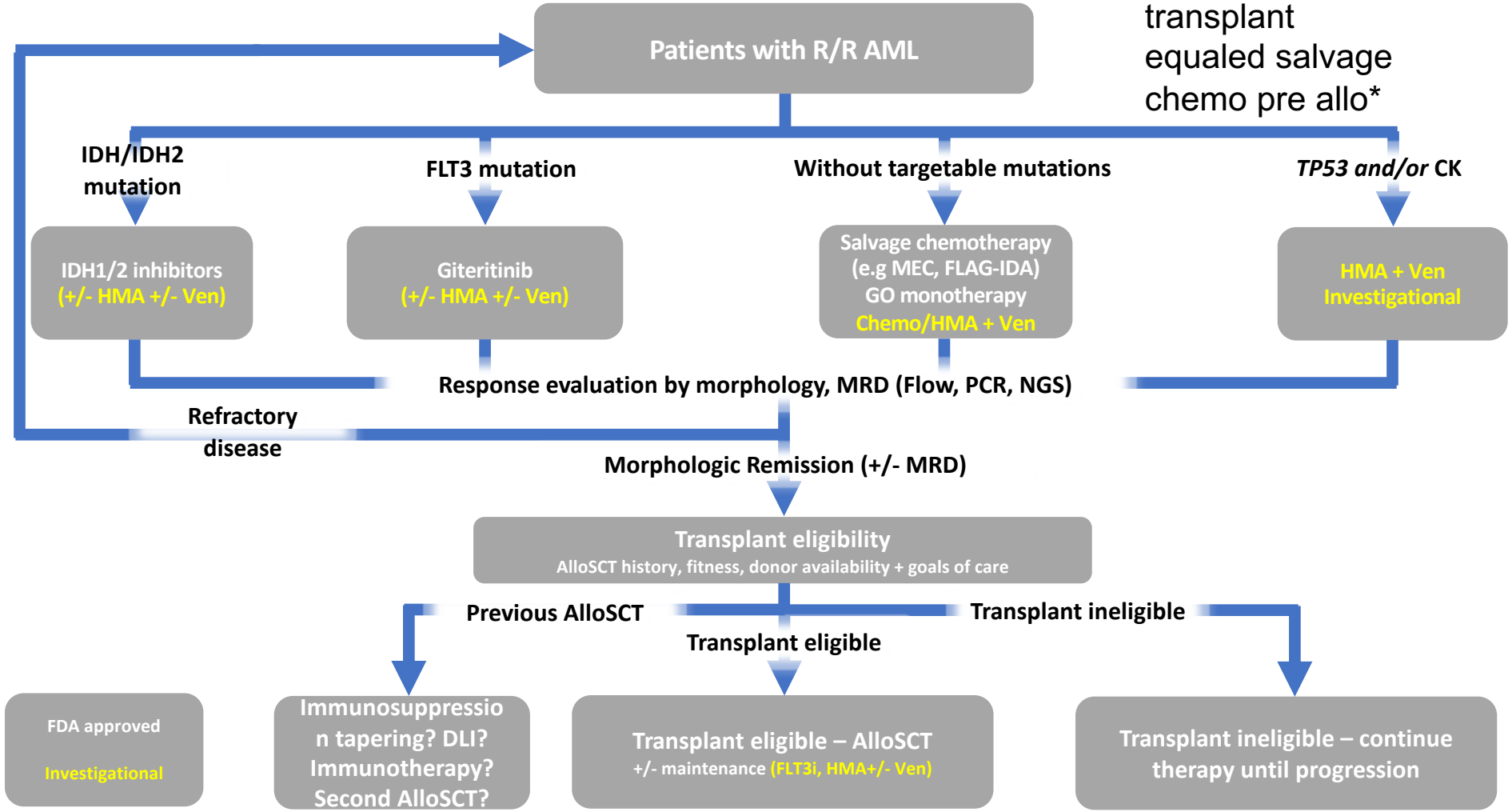


602: ELN Risk Stratification Is Not Predictive of Outcomes for Treatment-Naïve Patients with Acute Myeloid Leukemia Treated with Venetoclax and Azacitidine



- Simple 4 gene signature predicts patient outcomes better for aza + ven than ELN 2017/2022
- None of the patients were transplanted
- Adverse group had higher response but same survival -> avoid venetoclax if not going for allo-SCT
- Role for FLT3 inhibitor upfront for FLT3 ITD?

ASH 2022 plenary suggest going 'straight' to transplant equaled salvage chemo pre allo*



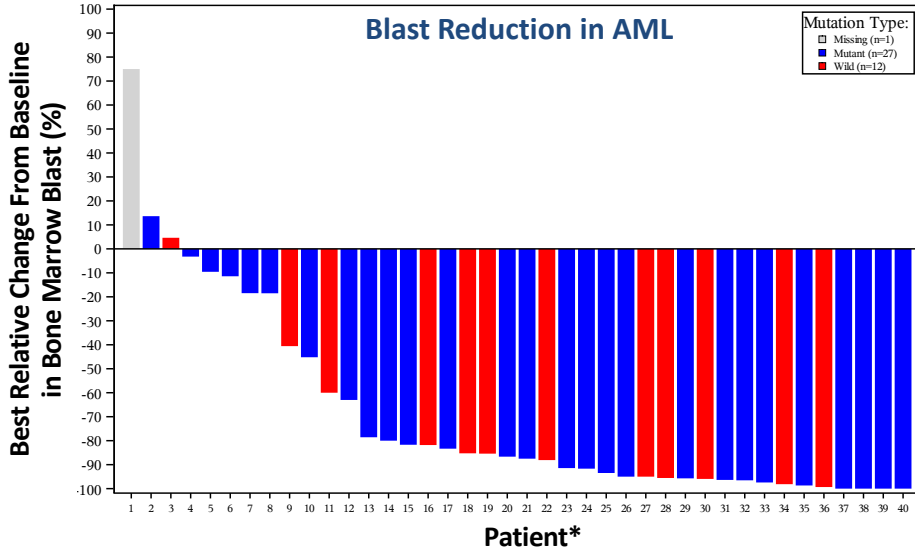
*Schetelig J, et al , ASh 2022.

Shimony S, Stahl M, Stone R, Am J Hematol, 2023

Magrolimab (Anti-CD47 (‘Don’t eat me’ signal) Ab + AZA Induces High Response Rates in AML (Sallman et al, ASH 2020)

Also promising outcomes in HR MDS; Sallman et al; *JCO* 2023

Best Overall Response	All AML (N=43)	*TP53*-mutant AML (29)
ORR	27 (63%)	20 (69%)
CR	18 (42%)	13 (45%)
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients

Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy

9.6% of patients proceeded to bone marrow stem cell transplantation

Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)[1,2]

- **Ongoing ENANCE -2: AZA/ven v AZA/magro in *TP 53* mut**
- **Ongoing ENHANCE 3: aza/ven v AVM in all ND unfit AML**

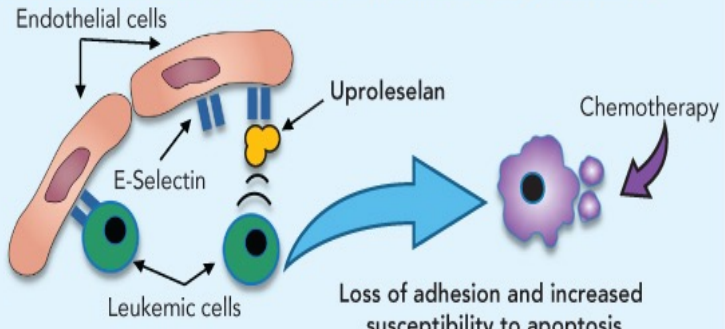
Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569. 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Phase 1/2 study of uproleselan added to chemotherapy in patients with relapsed or refractory AML and in newly diagnosed patients with AML

Mechanism of action

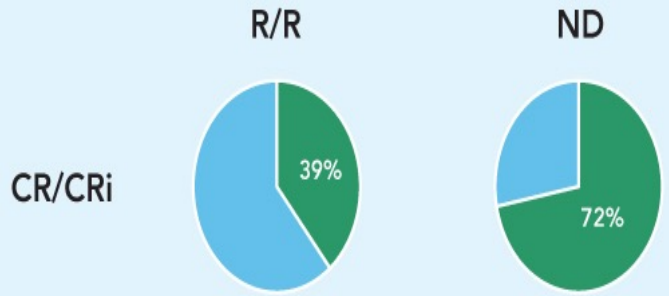
Uproleselan disrupts cell adhesion–mediated drug resistance



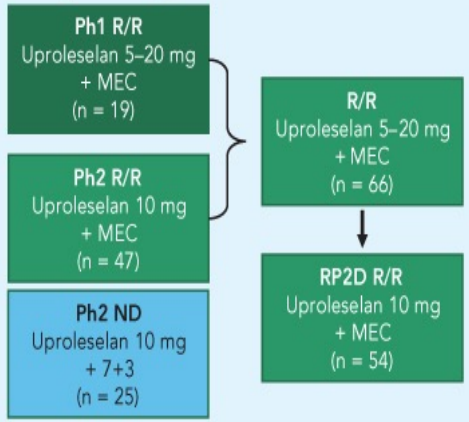
Safety

- Uproleselan at doses ranging from 5–20 mg/kg was well tolerated with an adverse event profile similar to that for background chemotherapy
- Just 2% of patients treated with uproleselan + MEC experienced severe mucositis, a percentage that is substantially lower than historically reported with MEC alone

Clinical response



Study design



- Phase 1/2 study
- Multicenter, open-label, conducted at 8 study sites
- R/R patients were ≥ 18 years of age and had either primary refractory AML or to be in their first or second relapse
- ND patients were ≥ 60 years of age, regarded as candidates for intensive chemotherapy, and had received no prior treatment for AML

Conclusion

The addition of uproleselan to chemotherapy was well tolerated with high remission rates, low-induction mortality, and low rates of mucositis.

7+3 = combination regimen cytarabine/darubicin; AML = acute myeloid leukemia; CR = complete response; CRi = complete response with incomplete blood count recovery; MEC = mitoxantrone, etoposide, cytarabine; ND = newly diagnosed; Ph1 = phase 1; Ph2 = phase 2; R/R = relapsed/refractory.

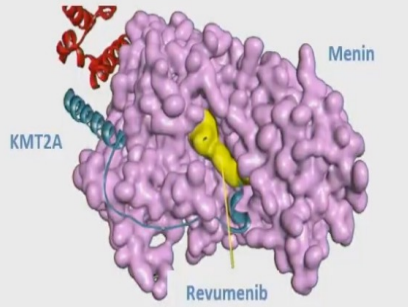
DeAngelo, DJ et al , Blood 2022; 139: 1139-1146

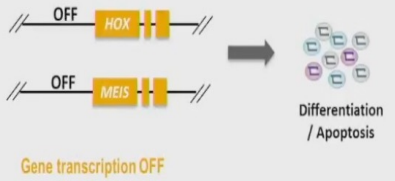
The Menin Inhibitor SNDX-5613 (revumenib) Leads to Durable Responses in Patients (Pts) with KMT2A-Rearranged or NPM1 Mutant AML: Updated Results of a Phase (Ph) 1 Study

Revumenib (SNDX-5613) is a potent, selective menin-KMT2A interaction inhibitor

- The menin-KMT2A interaction is a critical dependency in *KMT2Ar* (*MLL1r*) and *mNPM1* leukemias responsible for the leukemogenic gene expression
  - *KMT2Ar*: ~ 10% AML or ALL (~ 80% infant ALL)[1]
  - *mNPM1*: ~ 30% AML[2]
- Revumenib competitively binds a discrete, well-defined pocket within menin, where both wild-type KMT2A (MLL1) and KMT2A fusion proteins bind

  → disassembling abnormal transcription complexes in *KMT2Ar*, *mNPM1*, and other leukemia subtypes[3]





1. Issa GC, et al. *Leukemia*. 2021;35:2482–2495; 2. Papaemmanuil, E. *et al. N Engl J Med*. 2016;374: 2209-2221; 3. Krivtsov A, et al. Cancer Cell. 2019;36(6):660-673.
ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; *KMT2Ar*, lysine methyltransferase 2A rearrangements; *MLLr*, mixed lineage leukemia rearranged; *mNPM1*, mutated nucleophosmin 1.

American Society of Hematology

esponse	Efficacy population (*n* = 60)	*KMT2Ar* (*n* = 46)	Mutated *NPM1* (*n* = 14)
Overall response*	32 (53%)	27 (59%)	5 (36%)
Median time to first morphologic response (range), months	0.95 (0.9–3.7)	0.95 (0.9–3.7)	0.99 (1.0–1.9)
Best response*			
CR/CRh	18 (30%)	15 (33%)	3 (21%)
CR	12 (20%)	9 (20%)	3 (21%)
CRh	6 (10%)	6 (13%)	0
Median time to CR or CRh (range), months	1.9 (0.9–4.9)	2.0 (0.9–4.9)	1.9 (1.0–1.9)
CRi	0	0	0
CRp	5 (8%)	5 (11%)	0
MLFS	9 (15%)	7 (15%)	2 (14%)
Partial remission	0	0	0
No response	19 (32%)	12 (26%)	7 (50)
Progressive disease	7 (12%)	6 (13%)	1 (7%)
Missing	2 (3%)	1 (2%)	1 (7%)
MRD† neg. rate within CR/CRh	14/18 (78%)	11/15 (73%)	3/3 (100%)
Median time to MRD† neg. among patients with CR/CRh (range), months	1.9 (0.9–4.9)	1.9 (0.9–4.9)	1.9 (1.0–2.8)

GR 3 QT and DS in 10-15%

Issa, G, et al, *Nature* 615: 920-924, 2023


ERK, BET. SYK, inhibitors
Anti CD123, antiCD33 ADC/BiTe/CAR
Checkpoint inhibitors
New FLT3 inhibitors (e.g., quizartinib)
Anti CD47 (e.g., magrolimab)
Menin inhibitors
E-selectin inhibitors (e.g., uproleselan)

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* In memorium

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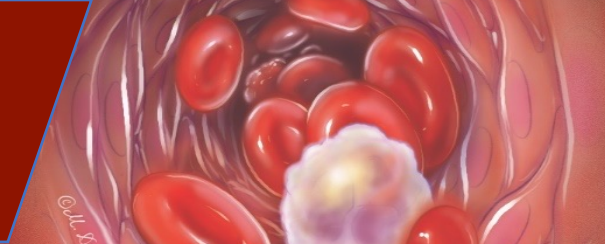

The End

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