בסיס ביולוגי וטיפול קו ראשון ב- AML

Ofir Wolach, MD

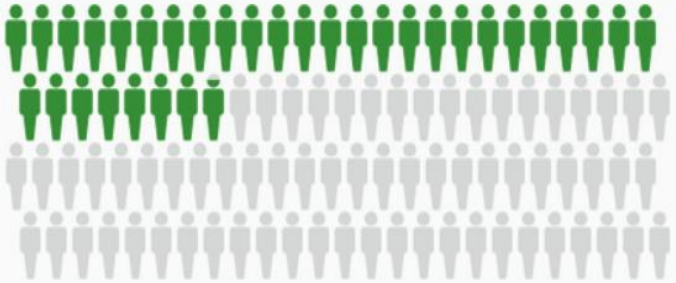
Davidoff Cancer Center

Rabin Medical Center

November 2025

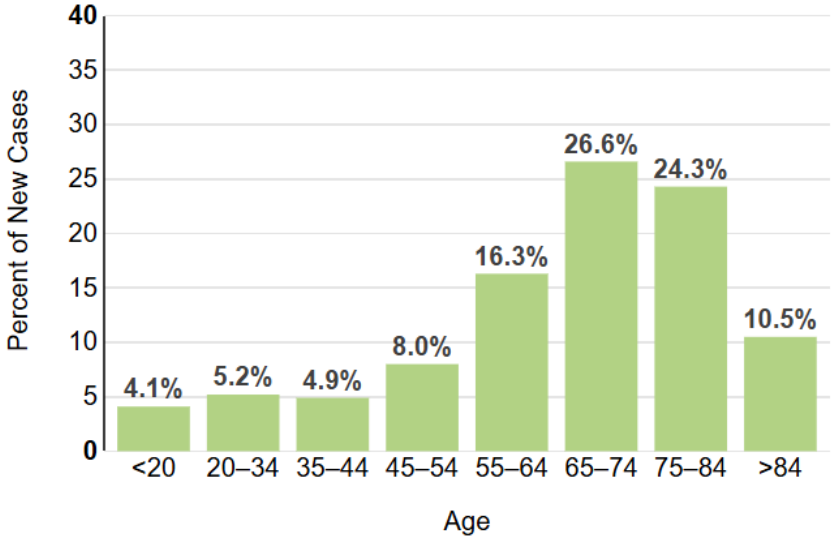
owolach@gmail.com

Acute Myeloid Leukemia (AML)



5-Year Relative Survival

32.9%



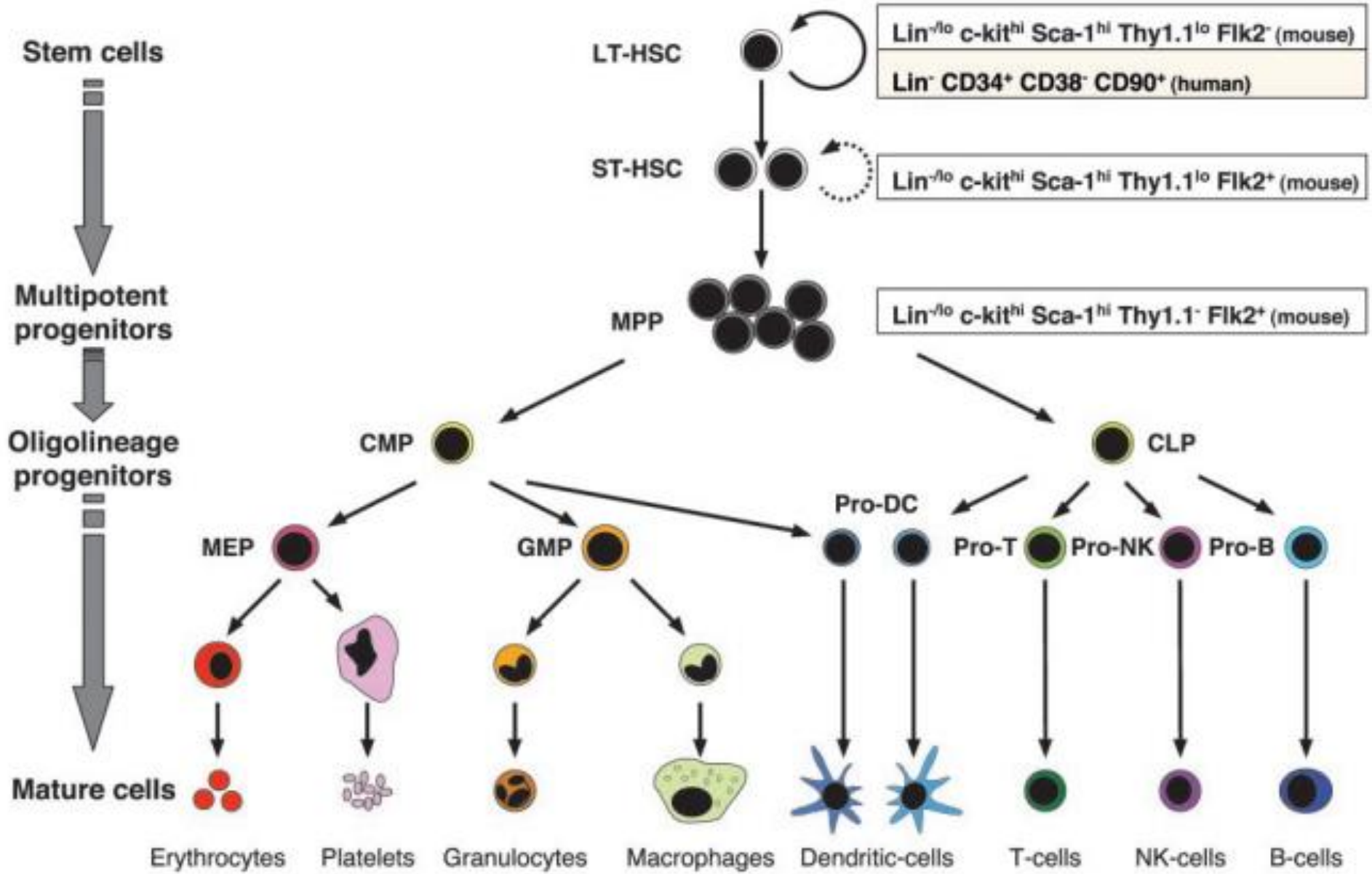
Acute myeloid leukemia is most frequently diagnosed among people aged 65–74.

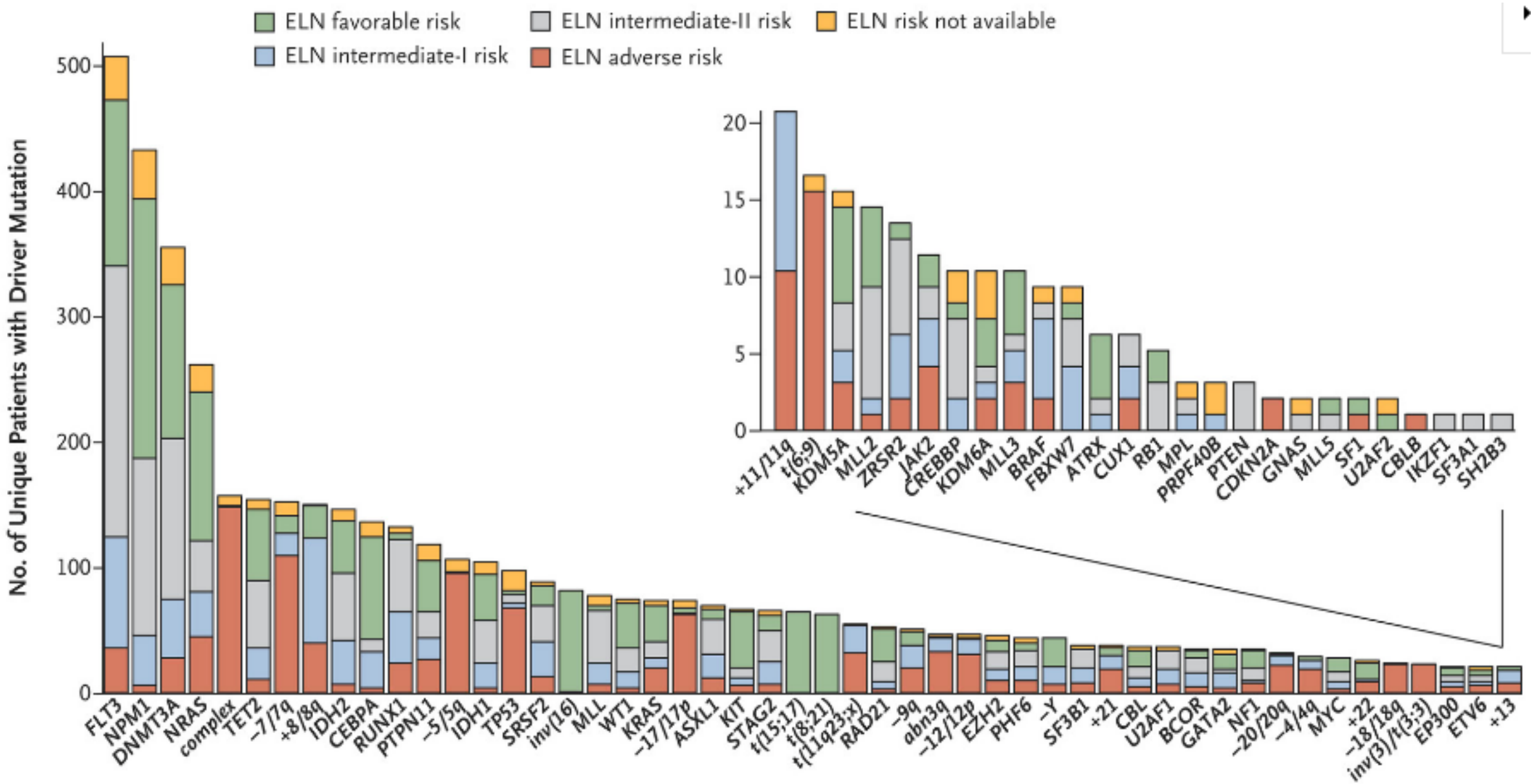
Median Age At Diagnosis

69

	Common Types of Cancer	Estimated New Cases 2025	Estimated Deaths 2025
1.	Breast Cancer (Female)	316,950	42,170
2.	Prostate Cancer	313,780	35,770
3.	Lung and Bronchus Cancer	226,650	124,730
4.	Colorectal Cancer	154,270	52,900
5.	Melanoma of the Skin	104,960	8,430
6.	Bladder Cancer	84,870	17,420
7.	Kidney and Renal Pelvis Cancer	80,980	14,510
8.	Non-Hodgkin Lymphoma	80,350	19,390
9.	Uterine Cancer	69,120	13,860
10.	Pancreatic Cancer	67,440	51,980
	-	-	-
	Acute Myeloid Leukemia	**22,010**	**11,090**

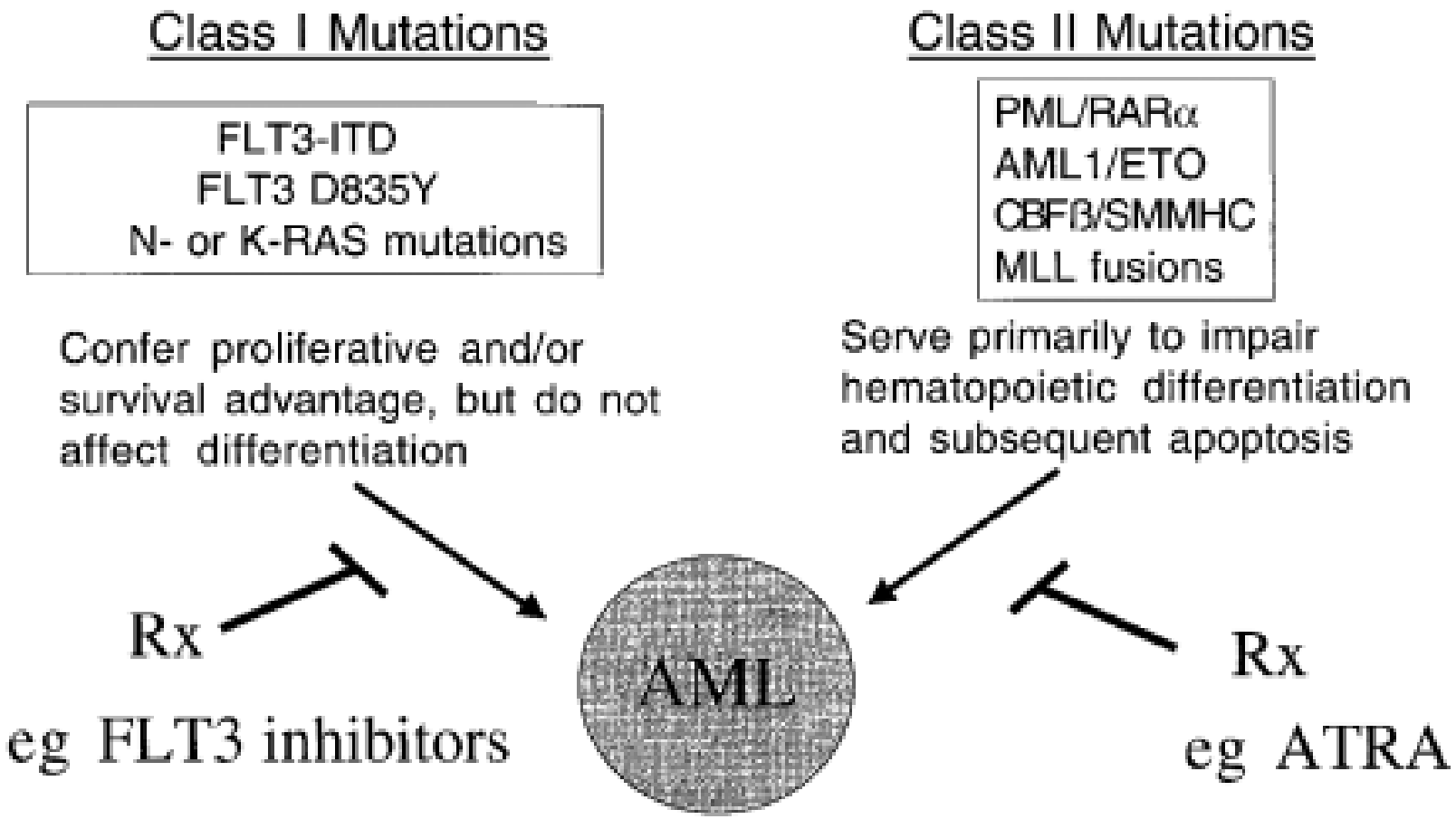
Source SEER data base
https://seer.cancer.gov/statfacts/html/amyl.html


Stem cells
Multipotent progenitors
Oligolineage progenitors
Mature cells
LT-HSC
ST-HSC
MPP
CMP
CLP
MEP
GMP
Pro-DC
Pro-T
Pro-NK
Pro-B
Lin-/lo c-kithi Sca-1hi Thy1.1lo Flk2- (mouse)
Lin- CD34+ CD38- CD90+ (human)
Lin-/lo c-kithi Sca-1hi Thy1.1lo Flk2+ (mouse)
Lin-/lo c-kithi Sca-1hi Thy1.1- Flk2+ (mouse)
Erythrocytes
Platelets
Granulocytes
Macrophages
Dendritic-cells
T-cells
NK-cells
B-cells

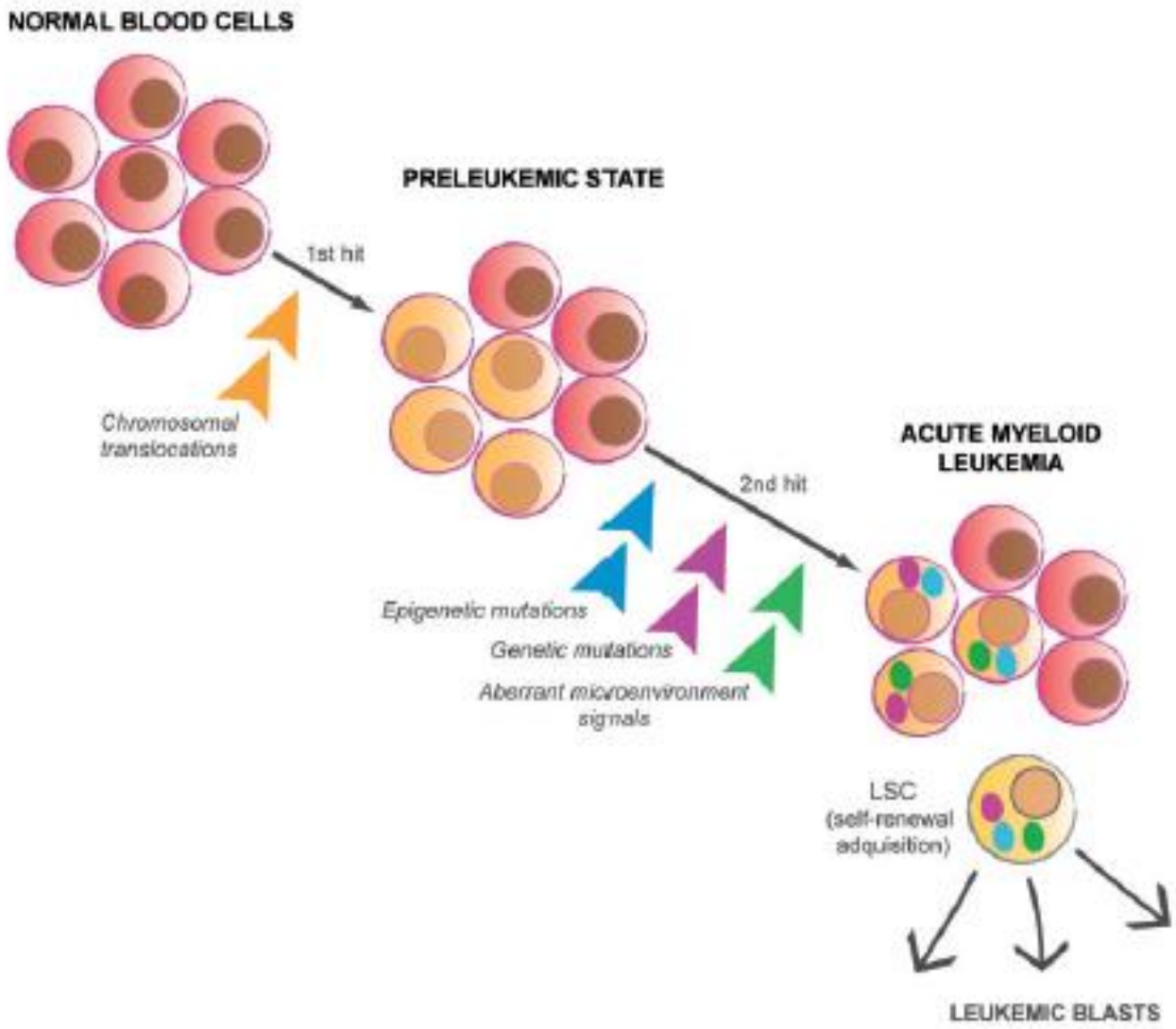


Papaemmanuil, NEJM 2016

Concepts in the evolution of AML

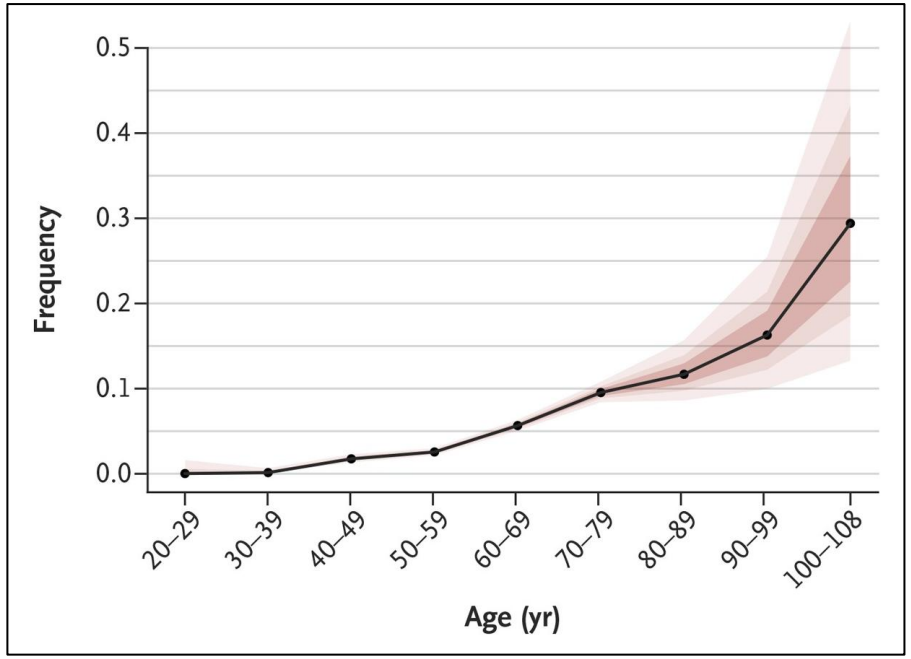


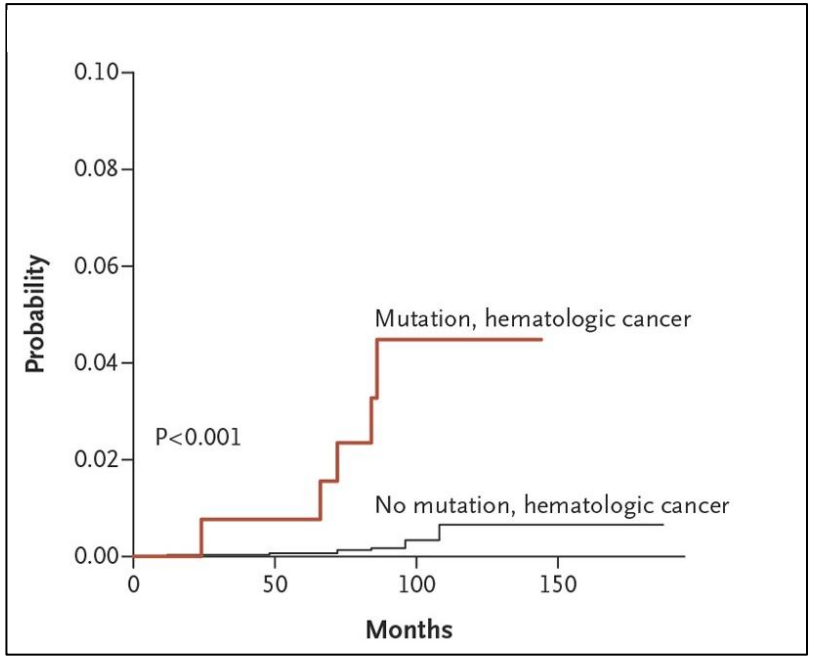
Gilliland & Griffin, Blood 2002



Uribesalgo & Di Croce, BRIEFINGS IN FUNCTIONAL GENOMICS 2011

Clonal hematopoiesis of indeterminate potential (CHIP)



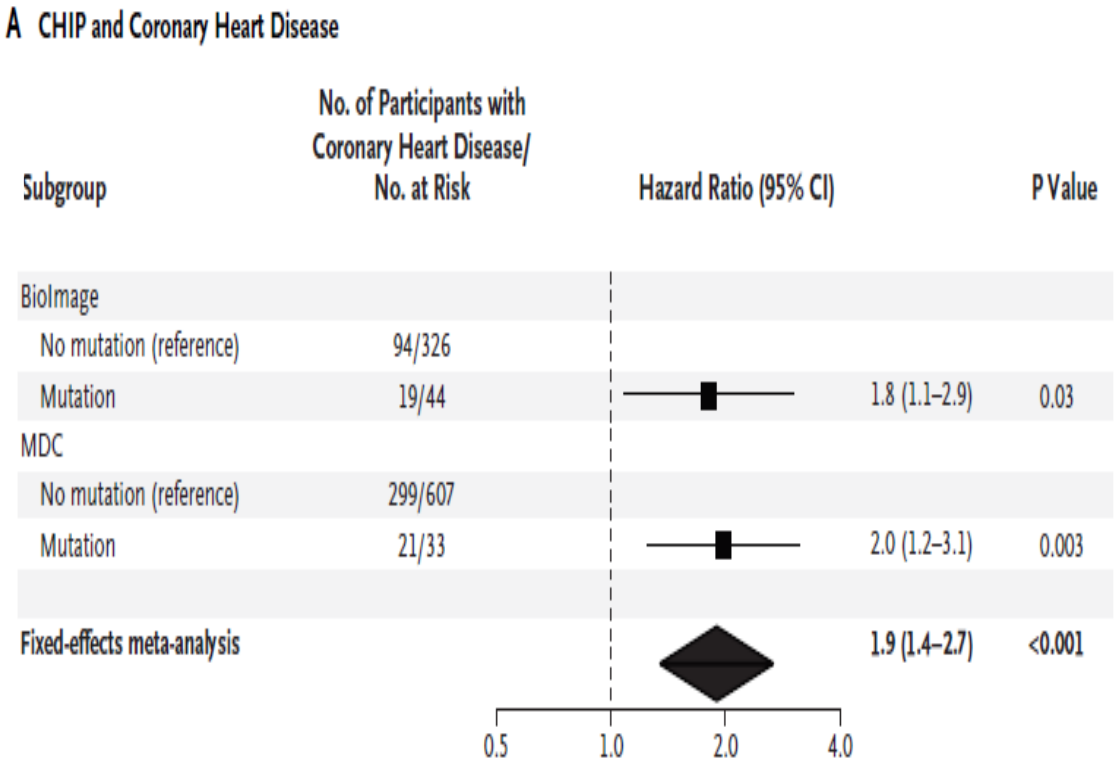


Acquired mutations in peripheral blood of healthy adults.
Associated with increased risk of hematologic malignancy (1%/yr).

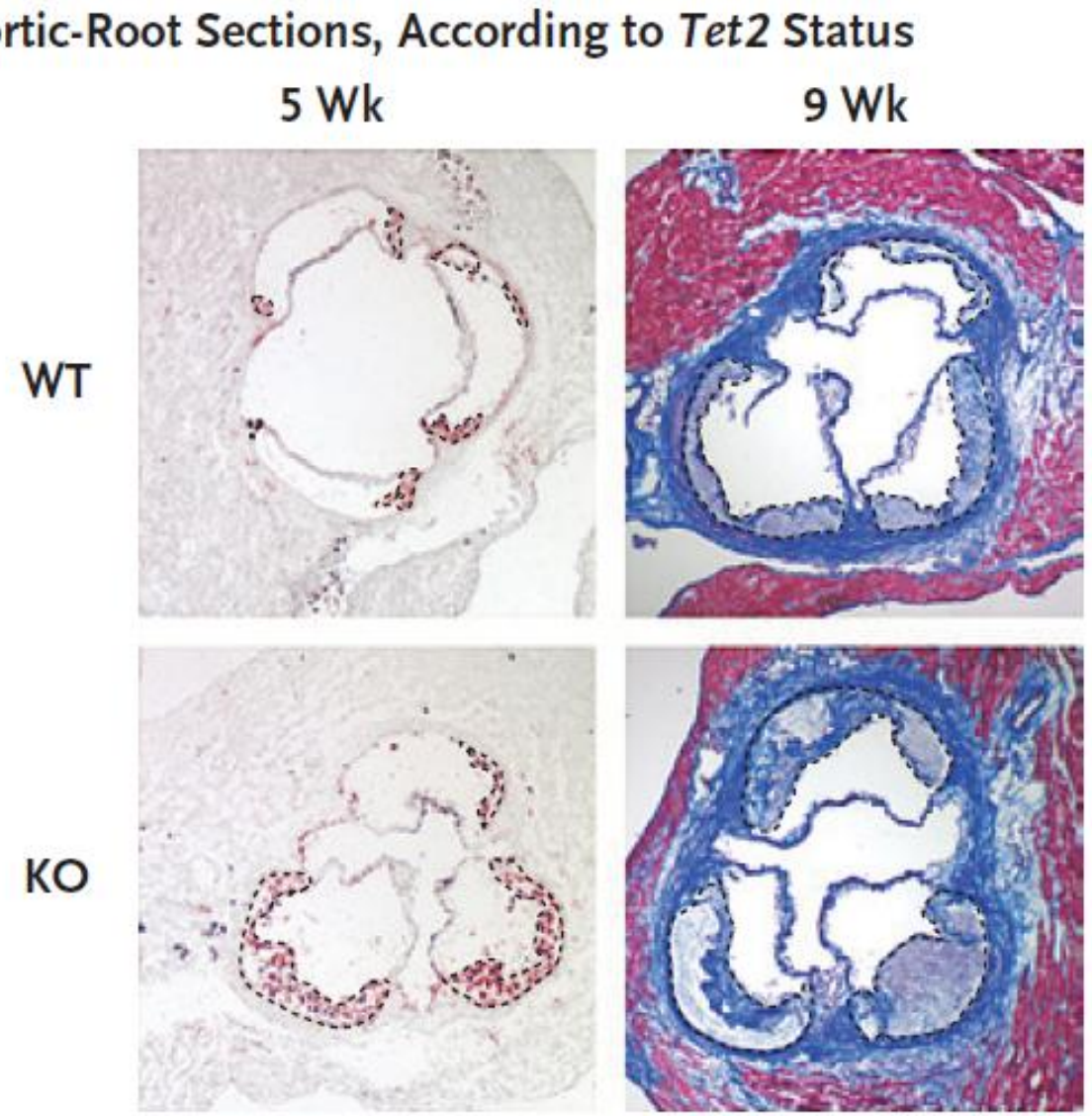
Jaiswal et al, NEJM 2014; Genovese et al, NEJM 2014
Xie et al, Nat Med 2014; Young et al, Nat Comm 2016

Curtesy of Chris Gibson, MD

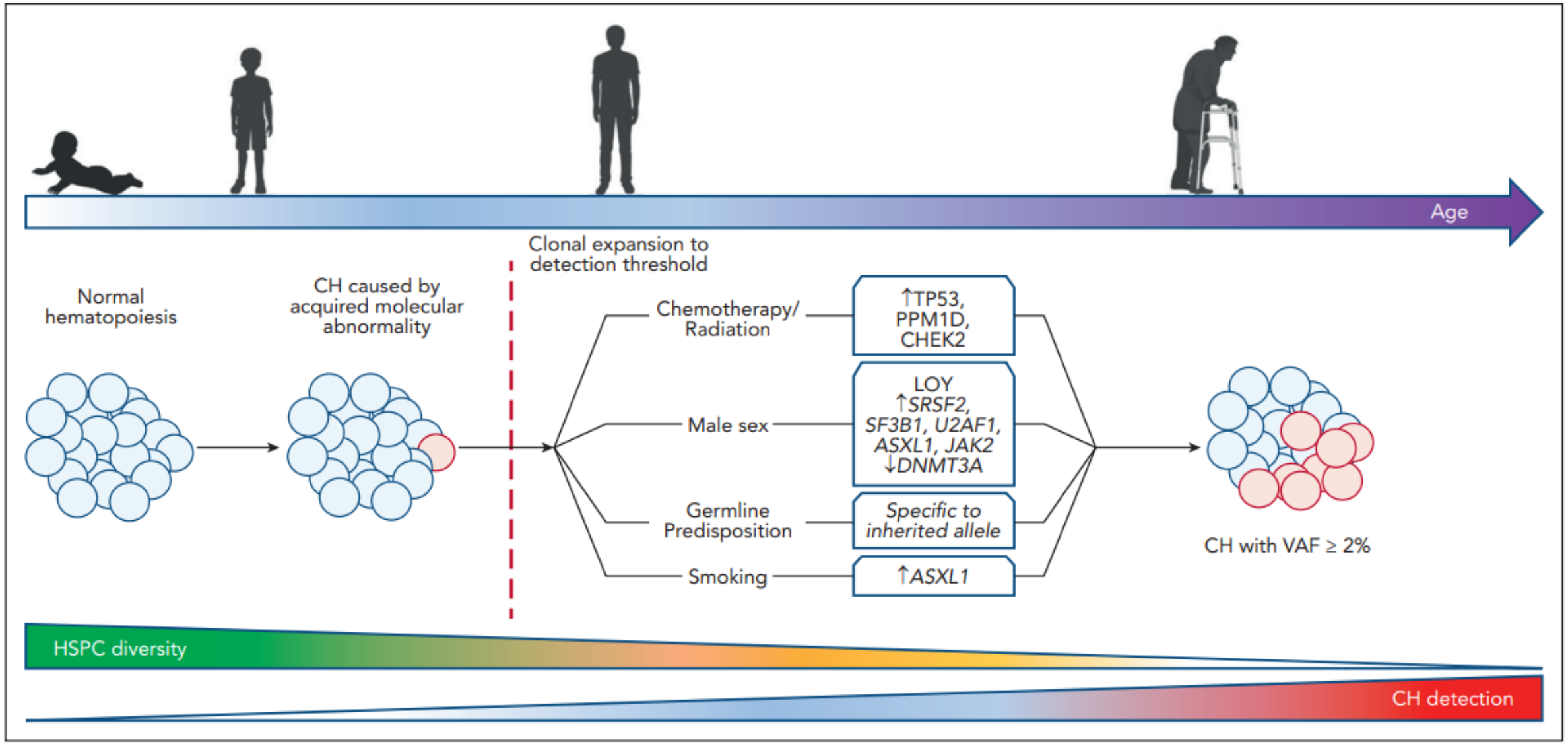
CHIP & Heart disease



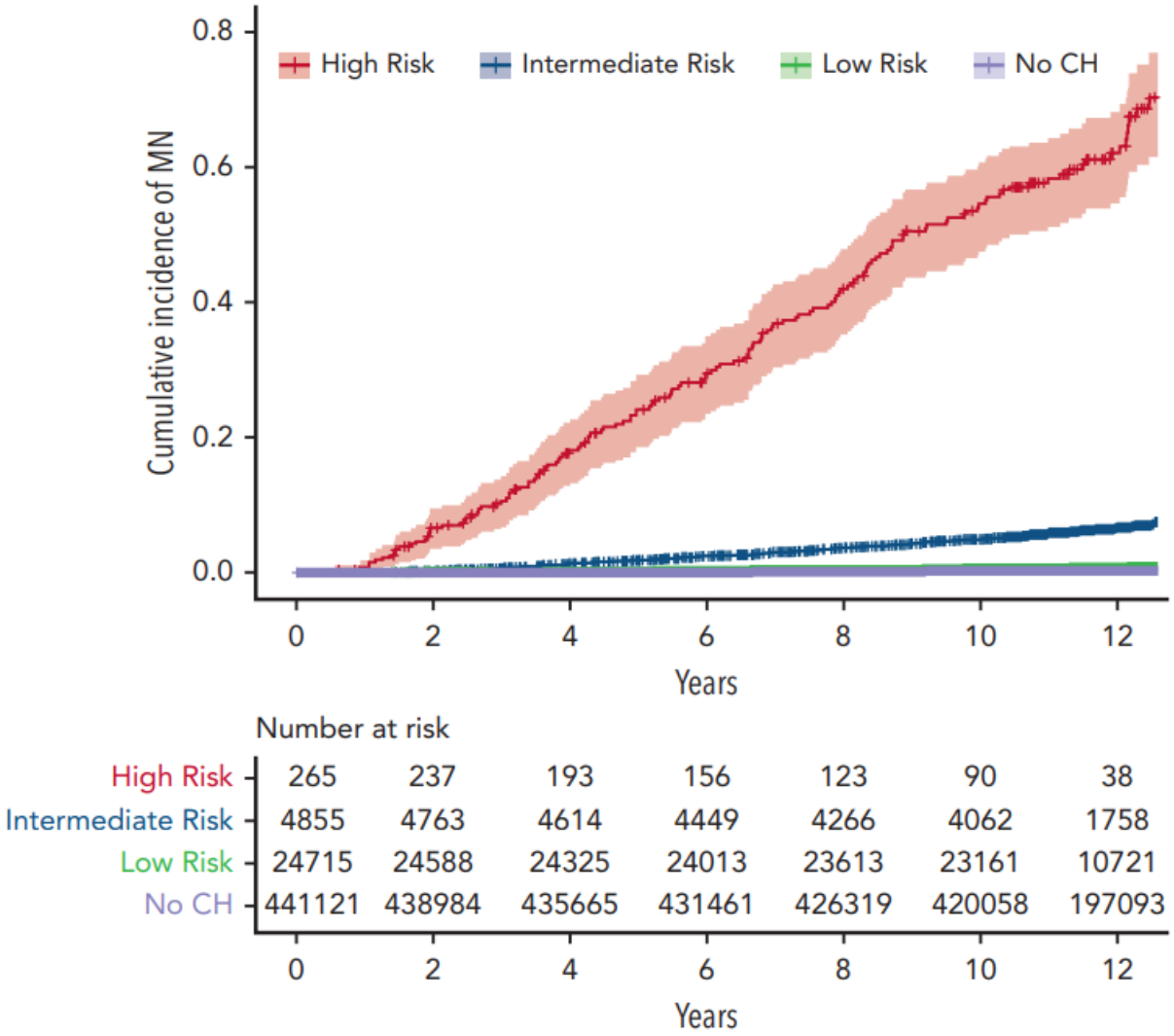
	Events	OR	P value
DNMT3A	31/46	1.4 (0.7–2.8)	0.29
TET2	12/13	8.3 (1.2–357.5)	0.02
ASXL1	8/8	Undefined	0.02
JAK2	16/16	Undefined	<0.001



Jaiswal, NEJM 2017



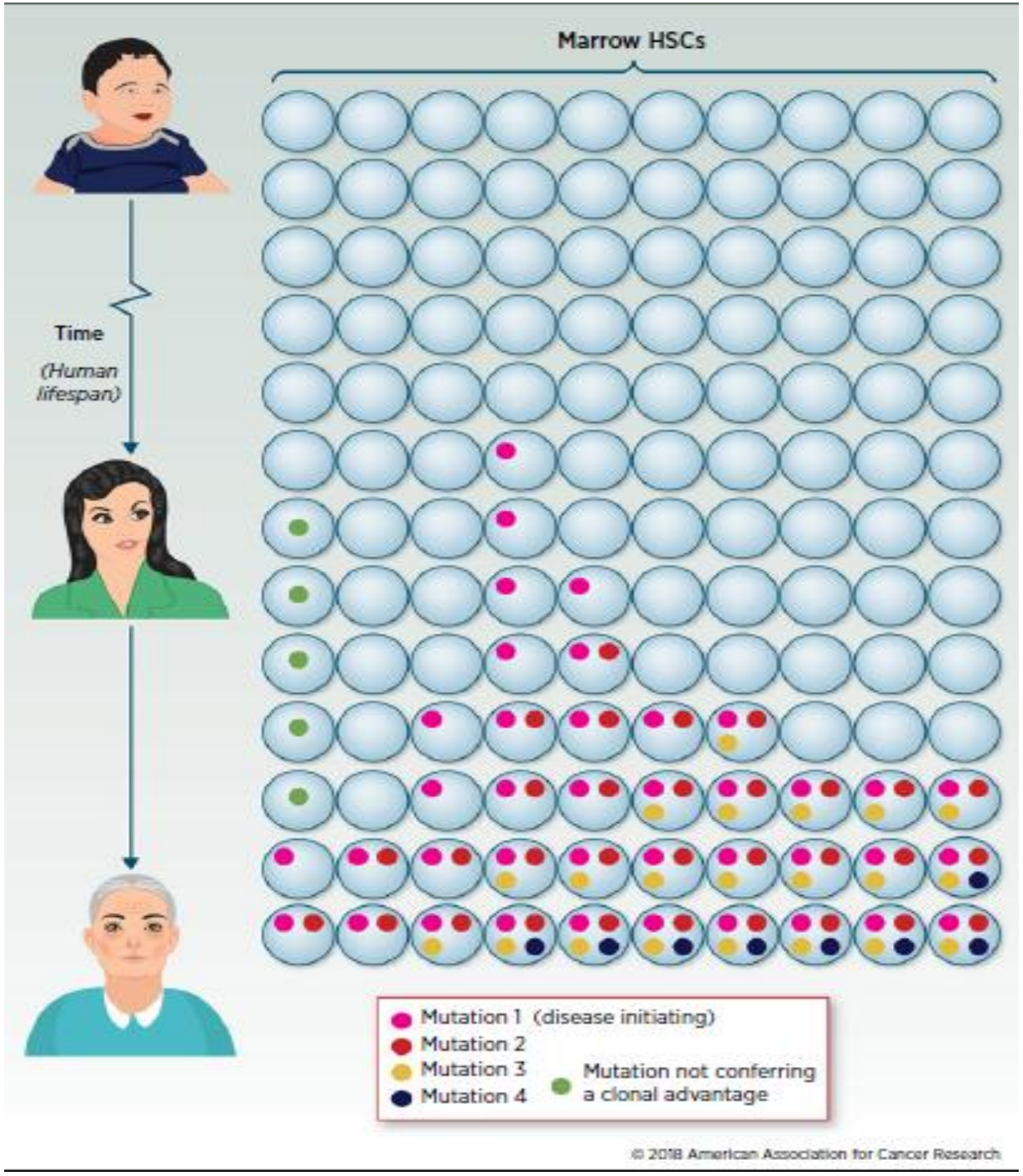
Weeks & Ebert. Blood 2023



CHRS Prognostic Variable Scores

Prognostic Variable	0.5	1	1.5	2	2.5
Single *DNMT3A*	present	absent	–	–	–
High Risk Mutation	–	absent	–	–	present
Mutation Number	–	1	–	≥ 2	–
Variant Allele Fraction	–	< 0.2	–	> 0.2	–
Red Cell Distribution Width	–	< 15	–	–	≥ 15
Mean Corpuscular Volume	–	< 100	–	–	> 100
Cytopenia	–	CHIP	CCUS	–	–
Age	–	< 65y	≥ 65y	–	–

Weeks & Ebert. Blood 2023

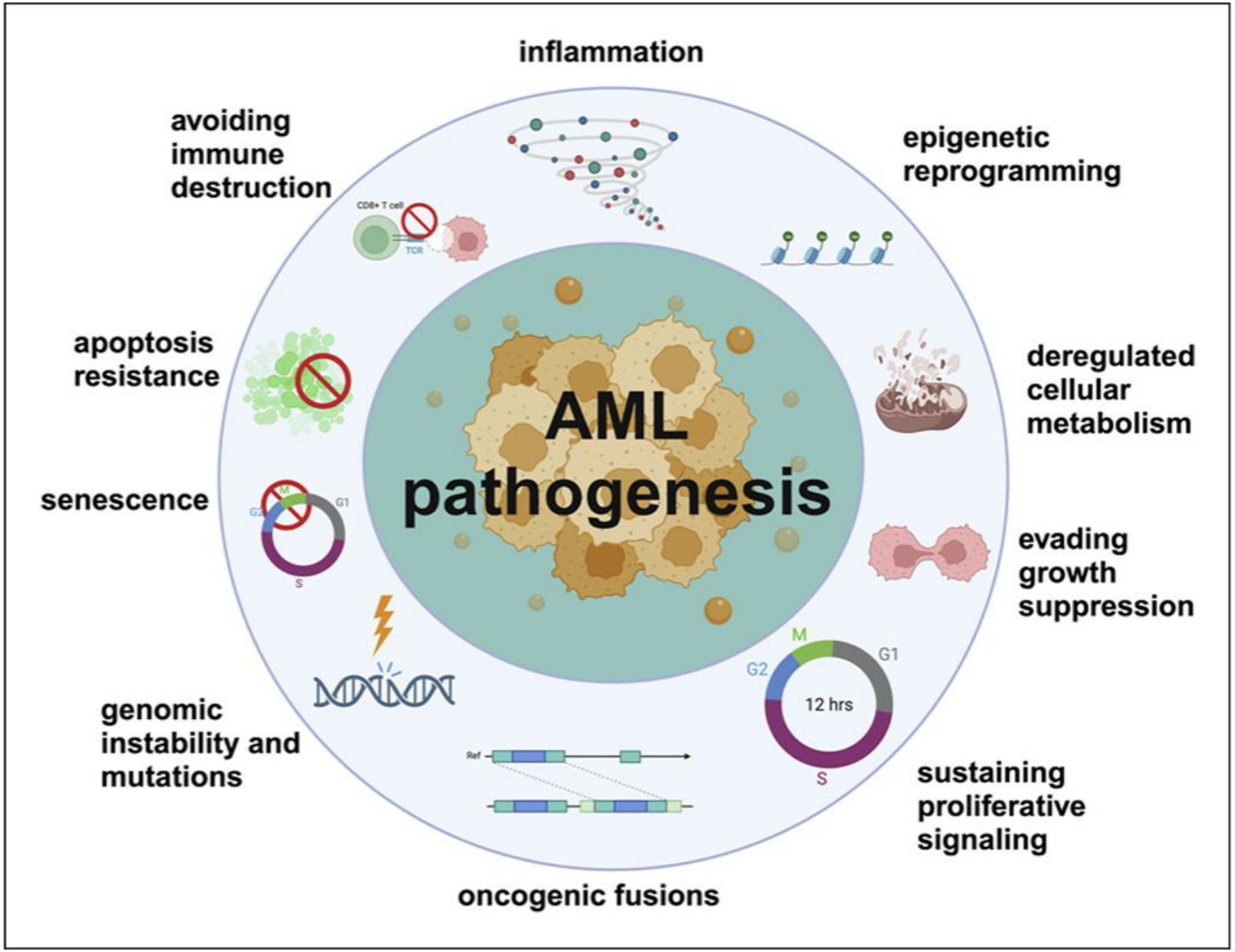


תאי אב תקינים
Normal hematopiesis

שינוי גנטי נרכש (סומטי)
Clonal hematopiesis

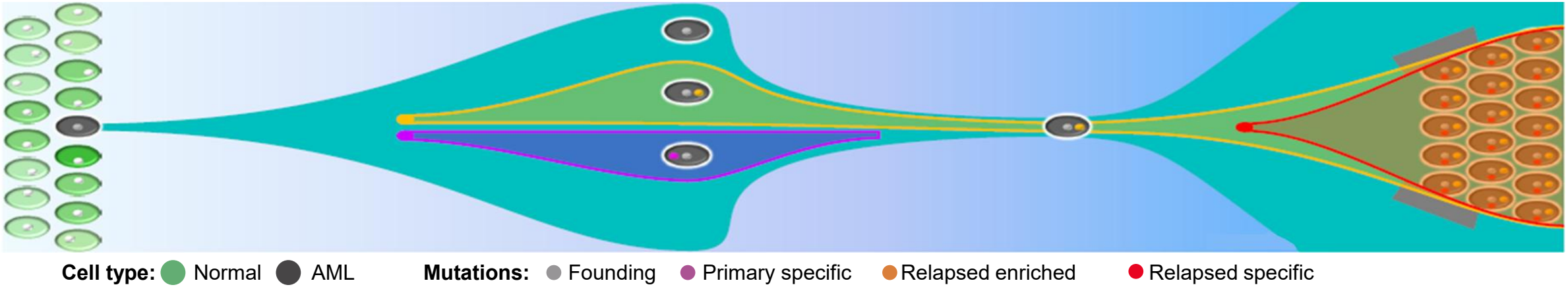
מחלה
MDS/AML

Gibson et al. Clin Can Res 2018

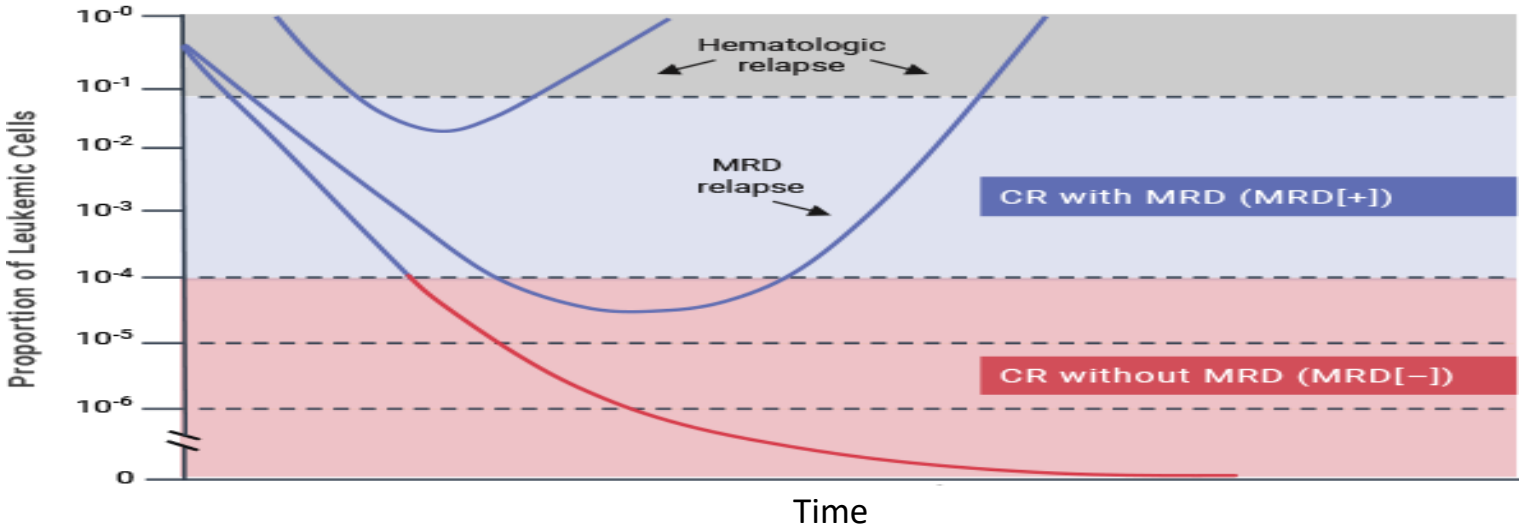


Wachter & Pikman,
Acta Haem 2024

AML is a heterogenous, clonally complex disease[1]

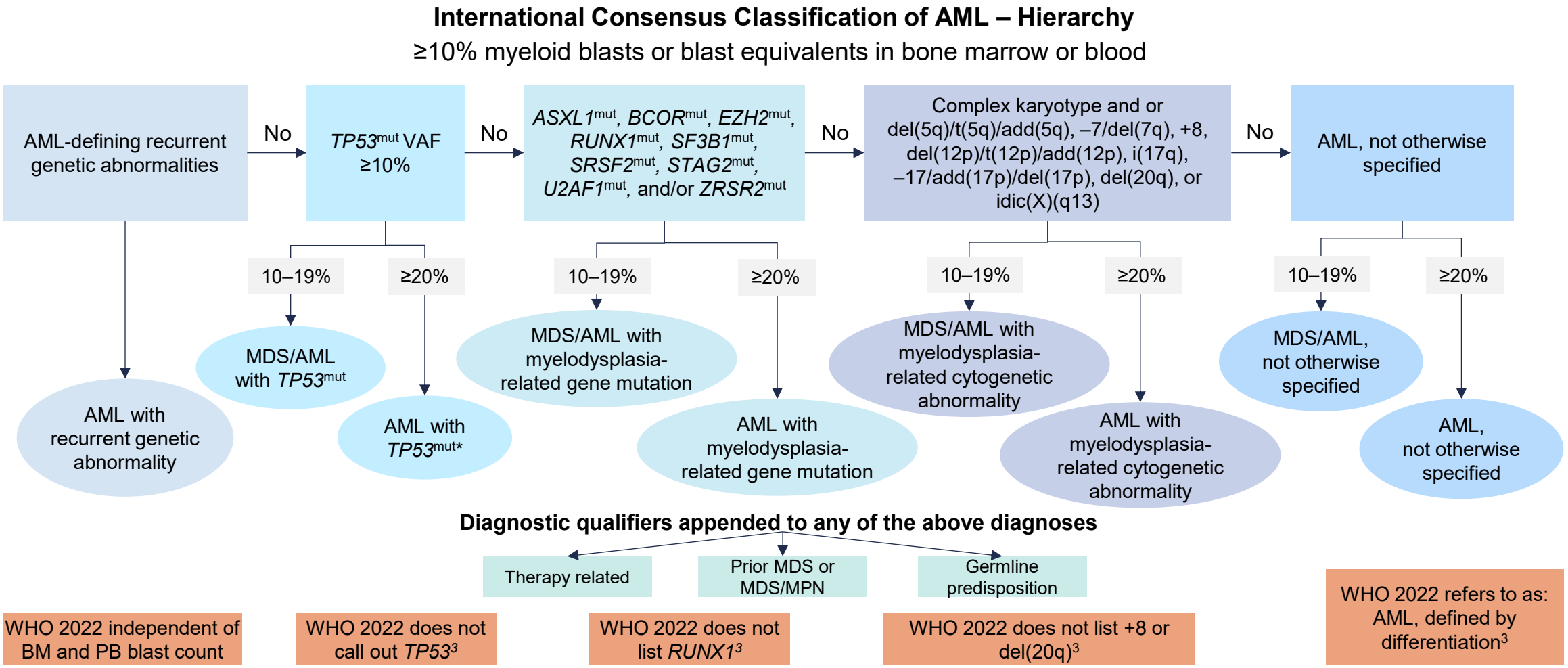


Genetic, epigenetic and metabolic insights inform therapeutic goals[2]



1. Ding L, *et al. Nature* 2012; **481:**506–510.
2. Short NJ, *et al. Am J Hematol* 2019; **94:**257–265.

ICC 2022 and WHO 2022 classification



* 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

ICC *vs.* *WHO*

Diagnosis of AML

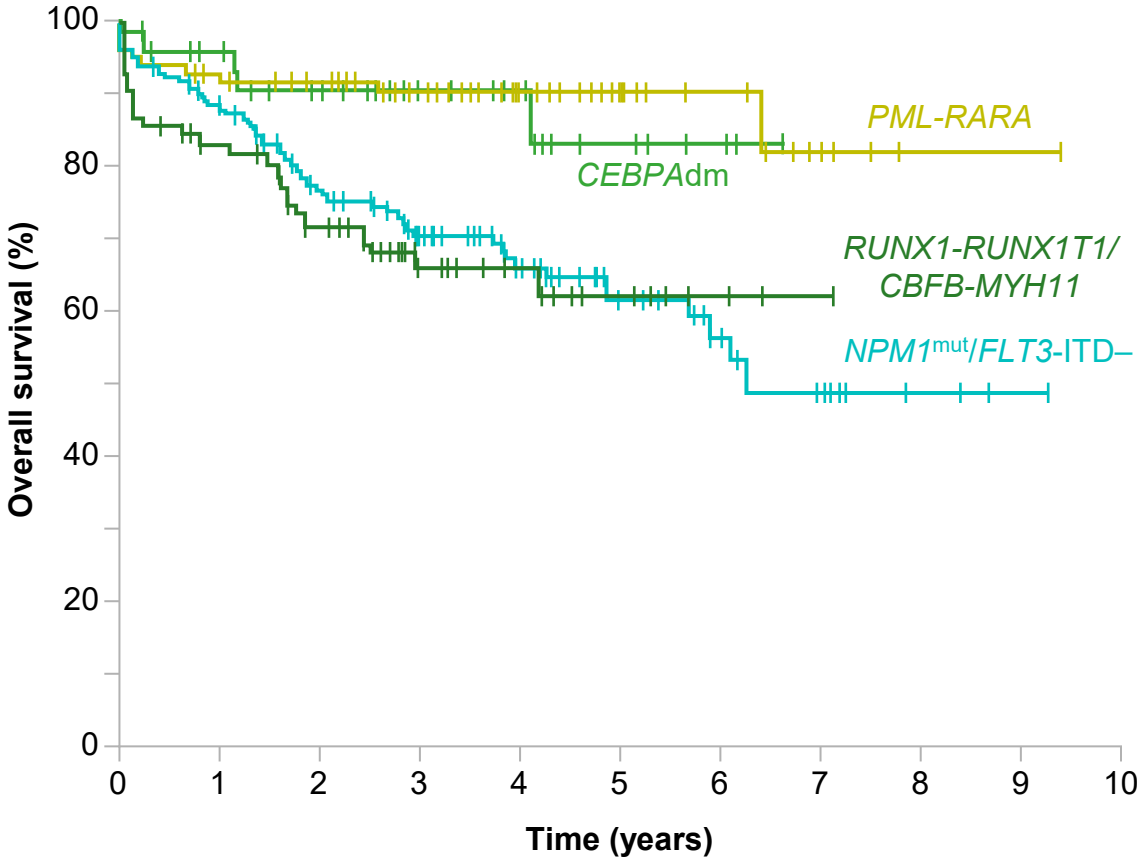
	ICC 2022[1]	WHO 5th Edition[2]
NPM1 mutation	**≥10% blasts**	**Regardless of blast count**
TP53 mutation	**≥20% blasts**	**Not a separate category**
CEBPA mutation	**≥10% blasts** *bZIP* mutation only	**≥20% blasts** Biallelic or *bZIP* mutation
AML-MR	**0-19% blasts: MDS/AML** **≥20% blasts**: AML	**≥20% blasts** *RUNX1*^{mut}, +8 not included

AML, acute myeloid leukemia; AML-MR, AML-myelodysplasia-related; HMA, hypomethylating agent; IC, intensive chemotherapy; ICC, International Consensus Classification; MDS, myelodysplastic syndrome; Tx, treatment; Ven, venetoclax; WHO, World Health Organization.

1. Arber DA, et al. *Blood*. 2022;140(11):1200-1228. 2. Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719. 3. Chandra DJ, et al. *Blood Rev*. 2024 Mar:64:101156. doi: 10.1016/j.blre.2023.101156. Epub 2023 Nov 25.

Risk stratification can inform outcomes

OS in patients aged <60 years with *de novo* AML* (N=867)[1]



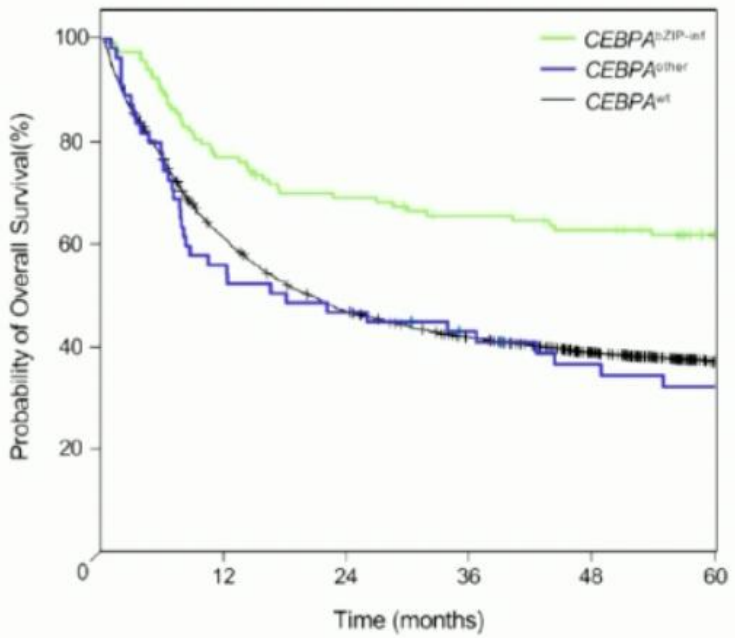
	ELN 2017[2]	ELN 2022[3]
Favorable	• t(8;21); *RUNX1-RUNX1T1* • inv(16) or t(16;16); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low†} • Biallelic-mutated *CEBPA*	• bZIP in-frame mutated *CEBPA*

* This population of patients had been previously treated with intensive chemotherapy; † Low allelic ratio (<0.5) vs high allelic ratio (≥0.5).

1. Haferlach C, *et al. Blood* 2016; **128:**286; 2. Döhner H, *et al. Blood* 2017; **129:**424–447; 3. Döhner H, *et al. Blood* 2022; doi: 10.1182/blood.2022016867.

Survival analysis by *CEBPA* mutation status

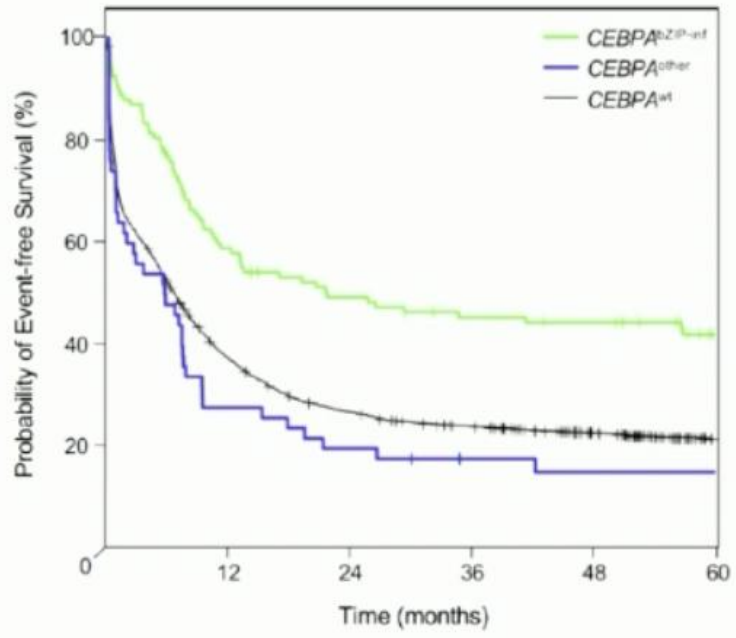
Overall survival



CEBPA^{wt}	4225	2472	1777	1461	1169	921
CEBPA$^{bZIP-inf}$	154	117	102	93	77	66
CEBPA^{other}	82	42	30	25	20	15

	CEBPA^{wt}	*CEBPA*^{other}
CEBPA^{other}	0.480	-
CEBPA$^{bZIP-inf}$	<0.001	<0.001

Event-free survival



CEBPA^{wt}	4225	1593	1100	926	768	625
CEBPA$^{bZIP-inf}$	154	92	75	68	60	49
CEBPA^{other}	82	22	15	11	9	8

	CEBPA^{wt}	*CEBPA*^{other}
CEBPA^{other}	0.160	-
CEBPA$^{bZIP-inf}$	<0.001	<0.001

➢ Favorable outcome is confined to AML with bZIP in-frame *CEBPA* mutations, irrespective of mono- or biallelic

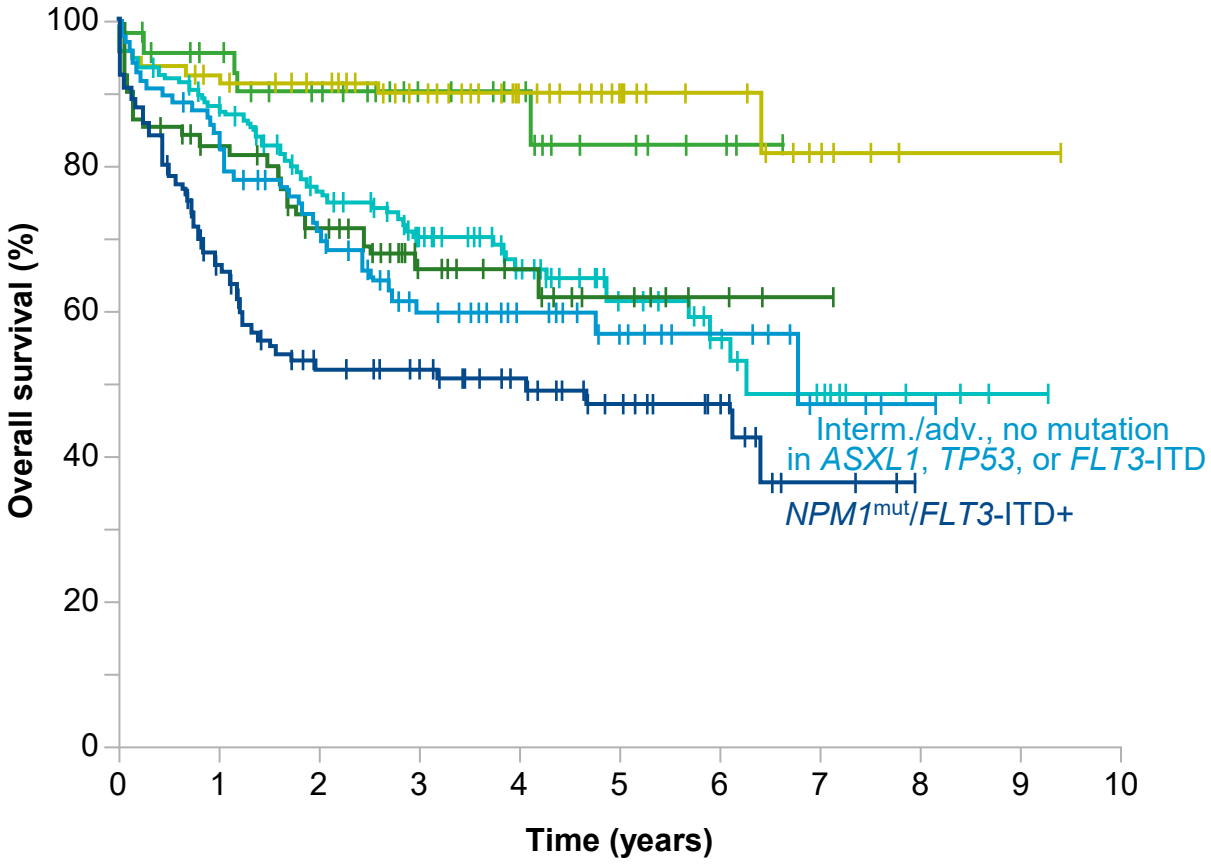
Similar data:

Tarlock K, et al. Blood 2021;138(13):1137; Wakita S, et al. Blood Advances 2021;6(1):238; Rücker F, et al. EHA 2022

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

Risk stratification can inform outcomes

OS in patients aged <60 years with *de novo* AML* (N=867)[1]



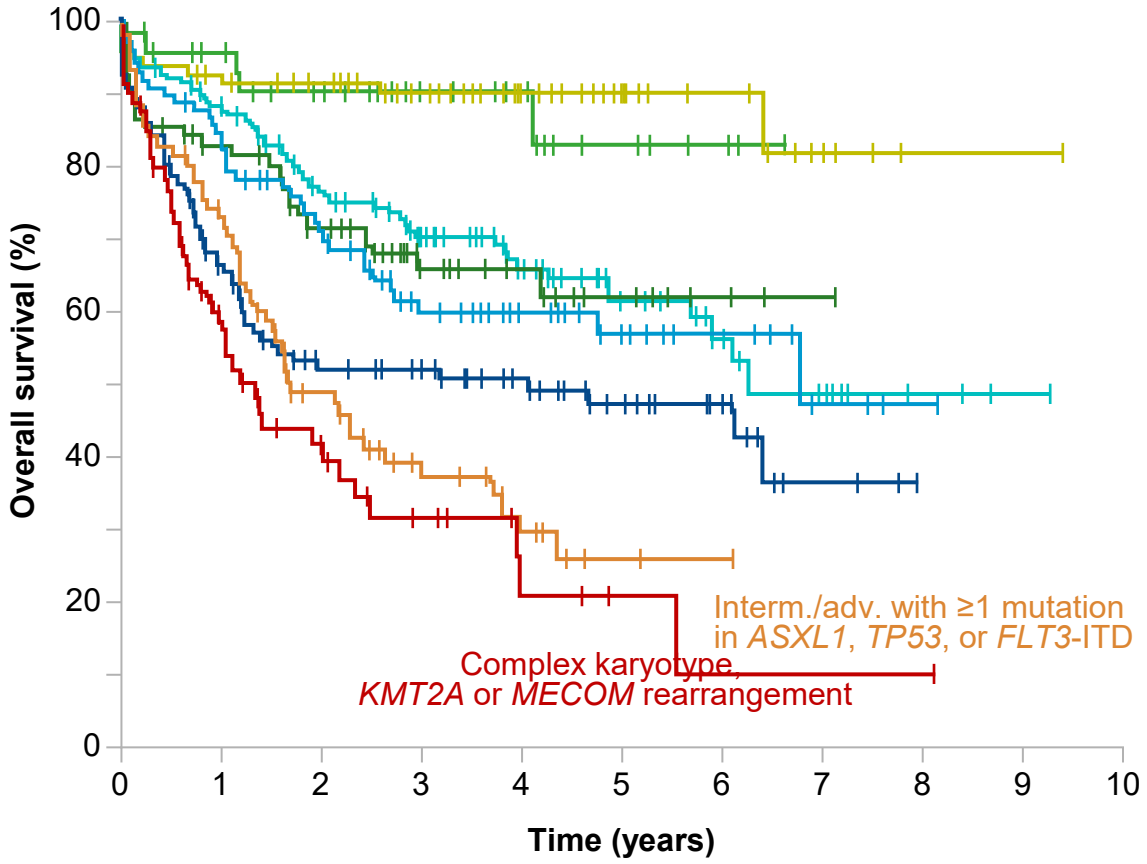
	ELN 2017[2]	ELN 2022[3]
Favorable	• t(8;21); *RUNX1-RUNX1T1* • inv(16) or t(16;16); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low}† • Biallelic-mutated *CEBPA*	• bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1* and *FLT3*-ITD^{high}† • Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low}*,† • t(9;11); *MLLT3-KMT2A* • Abnormalities not classified as favorable/adverse	• *Any FLT3*-ITD

* This population of patients had been previously treated with intensive chemotherapy; † Low allelic ratio (<0.5) vs high allelic ratio (≥0.5).

1. Haferlach C, *et al. Blood* 2016; **128:**286; 2. Döhner H, *et al. Blood* 2017; **129:**424–447; 3. Döhner H, *et al. Blood* 2022; doi: 10.1182/blood.2022016867.

Risk stratification can inform outcomes

OS in patients aged <60 years with *de novo* AML* (N=867)[1]



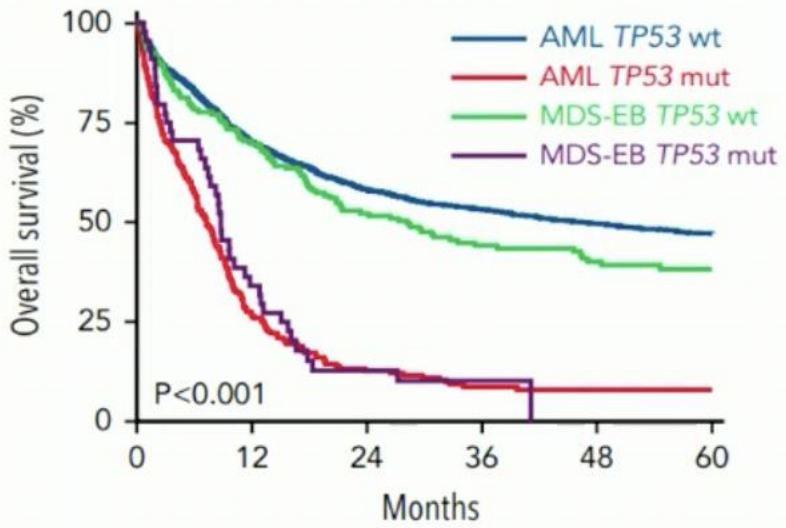
	ELN 2017[2]	ELN 2022[3]
Favorable	• t(8;21); *RUNX1-RUNX1T1* • inv(16) or t(16;16); *CBFB-MYH11* • Mutated *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low†} • Biallelic-mutated *CEBPA*	• bZIP in-frame mutated CEBPA
Intermediate	• Mutated *NPM1* and *FLT3*-ITD^{high†} • Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low*,†} • t(9;11); *MLLT3-KMT2A* • Abnormalities not classified as favorable/adverse	• *Any FLT3*-ITD
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 or monosomal karyotype • Wild-type *NPM1* and *FLT3*-ITD^{high†} • Mutated *RUNX1*, *ASXL1*, or *TP53*	• Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2* • Mutated *TP53*

* This population of patients had been previously treated with intensive chemotherapy; † Low allelic ratio (<0.5) vs high allelic ratio (≥0.5).

1. Haferlach C, *et al. Blood* 2016; **128:**286; 2. Döhner H, *et al. Blood* 2017; **129:**424–447; 3. Döhner H, *et al. Blood* 2022; doi: 10.1182/blood.2022016867.

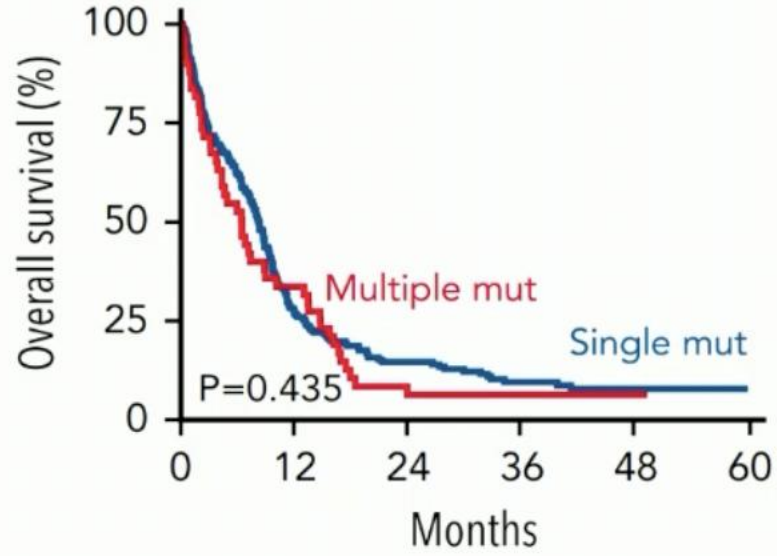
TP53 mutation in AML and MDS with excess blasts

- Accumulating evidence from both a clinical and molecular perspective that AML and MDS with mutated *TP53* represent a distinct molecular disease entity



No. at risk:

AML *TP53* wt	1805	1255	1014	807	572	397
AML *TP53* mut	186	50	23	14	9	5
MDS-EB *TP53* wt	165	114	81	62	45	35
MDS-EB *TP53* mut	44	15	5	1	0	0



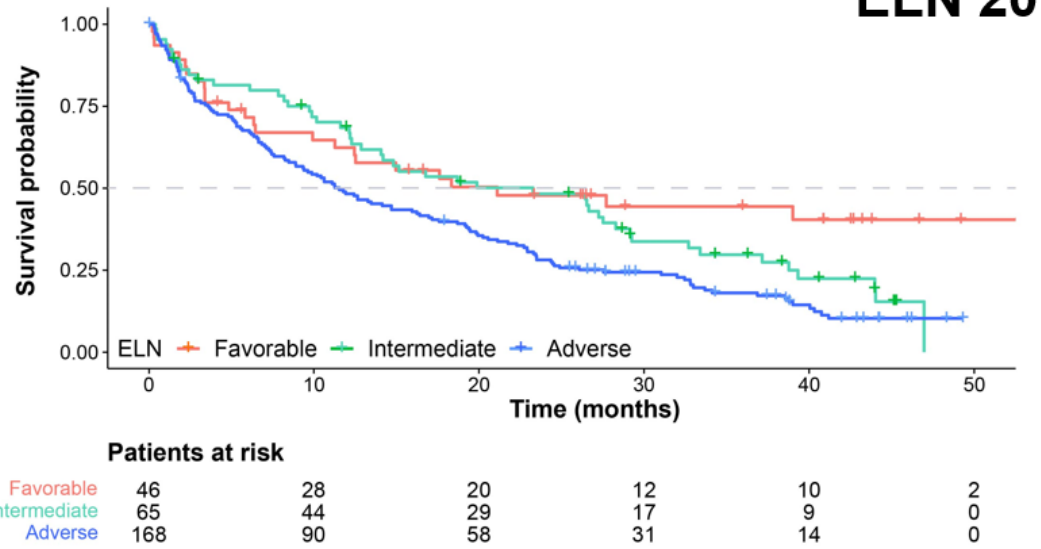
No. at risk:

Single mut	181	49	25	12	6	3
Multiple mut	49	16	3	3	3	2

Grob T, et al. Blood. 2022;139(15):2347-2354.

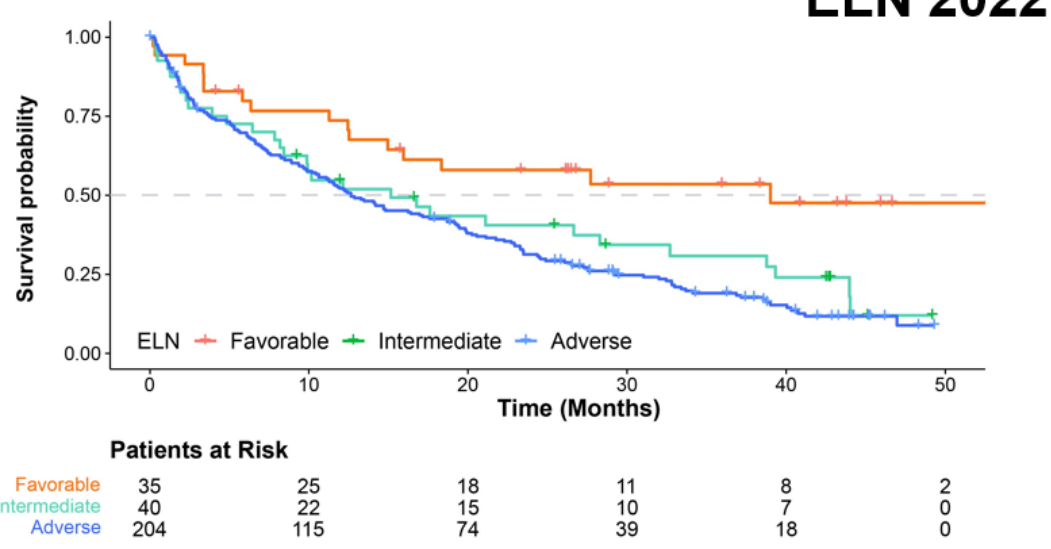
ELN risk stratification perform poorly in lower-intensity treated patients

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)

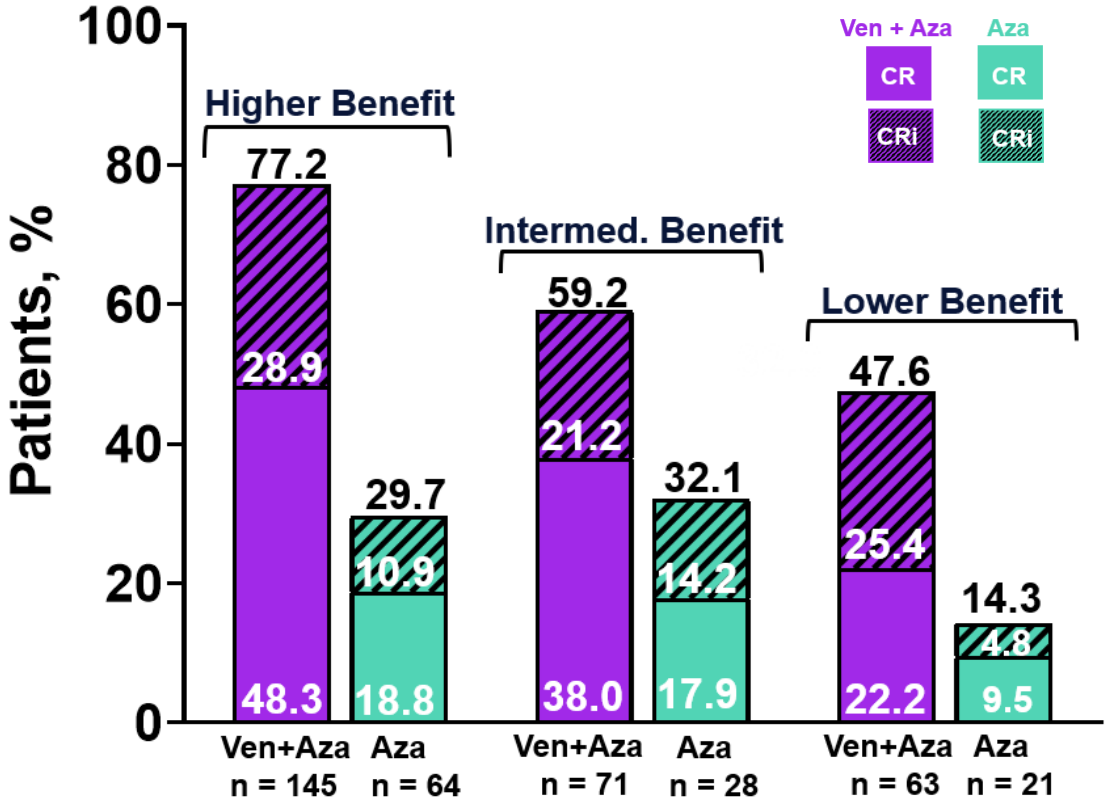
ELN 2022

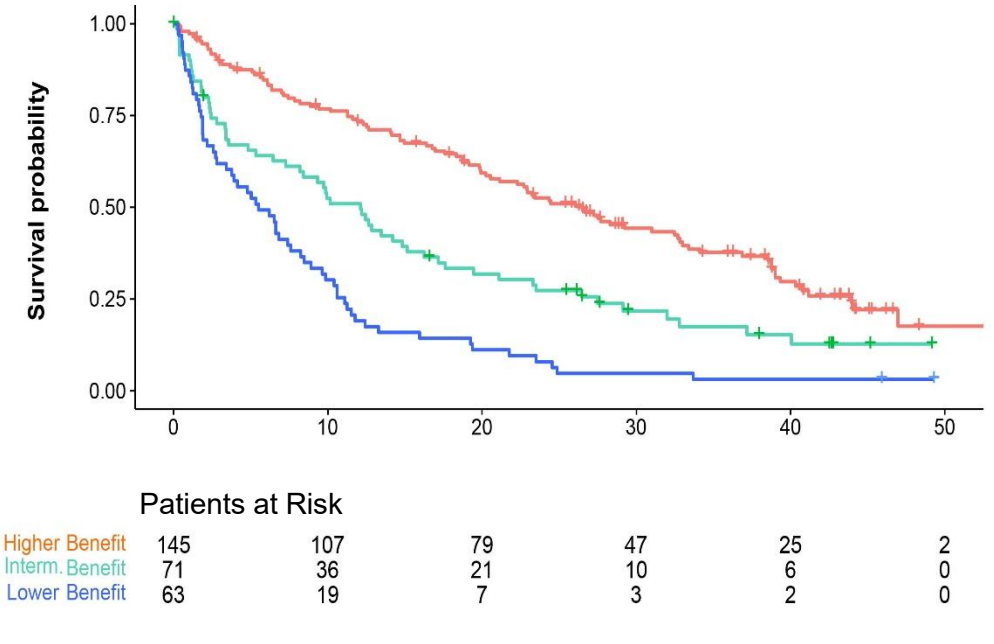


ELN 2022	n	Events	Median OS, mo (95% CI)
Favorable	35	16	39.0 (12.52 – NE)
Intermediate	40	30	15.15 (8.18 – 28.29)
Adverse	204	168	12.65 (10.41 – 17.15)

Döhner et al, Blood. 2024 :blood.2024025409. doi: 10.1182/blood.2024025409
Döhner et al, Blood. 2024 blood.2024024944. doi: 10.1182/blood.2024024944.

Genetic Risk Stratification and Outcomes for Ven-HMA Treated patients





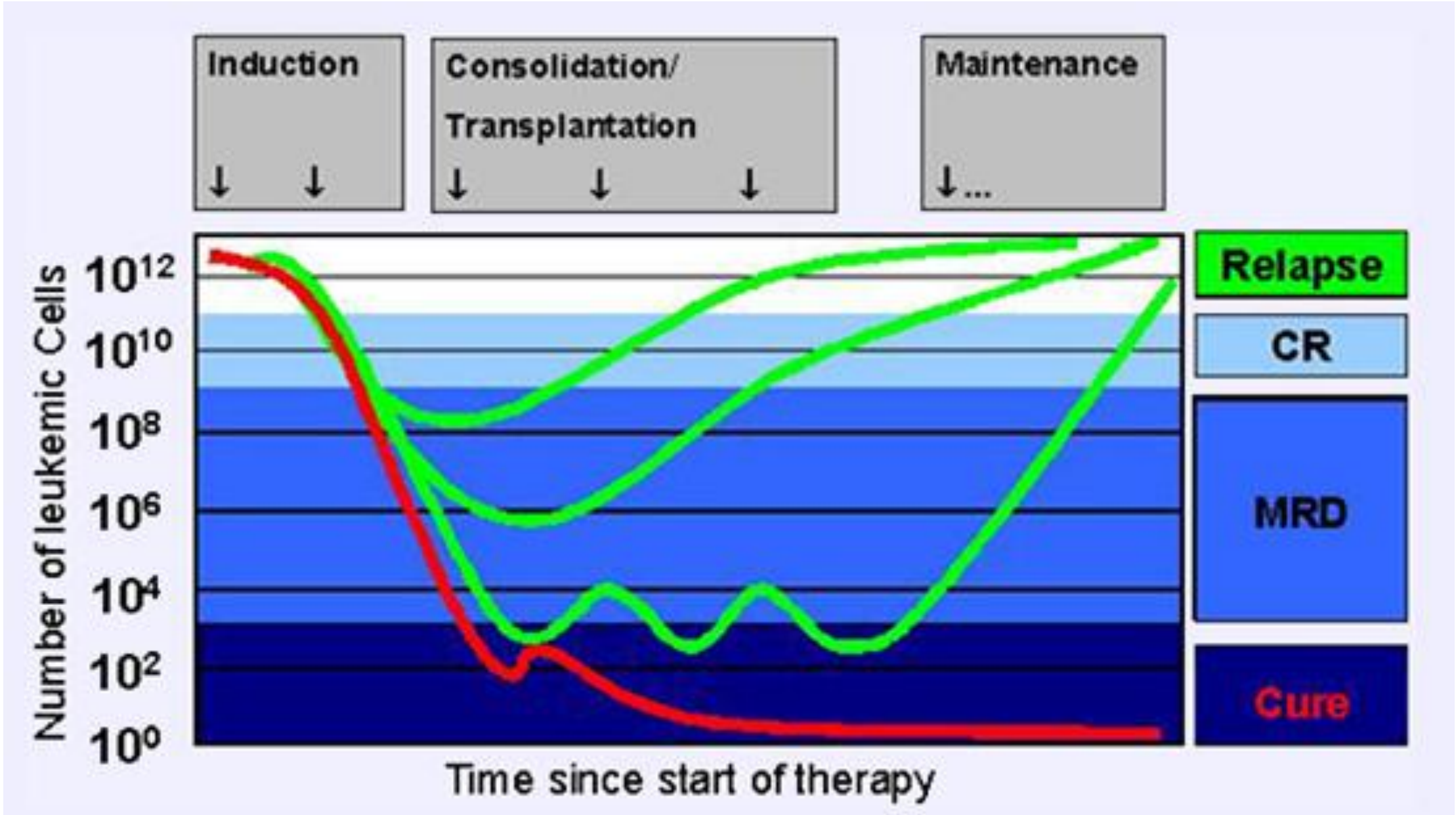
Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	26.51 (20.24, 32.69)
Intermediate Benefit	71	57	12.12 (7.26 - 15.15)
Lower Benefit	63	61	5.52 (2.79 - 7.59)

Döhner et al, Blood. 2024 :blood.2024025409. doi: 10.1182/blood.2024025409
Döhner et al, Bood. 2024 blood.2024024944. doi: 10.1182/blood.2024024944.

ELN risk classification for patients receiving less-intensive therapies

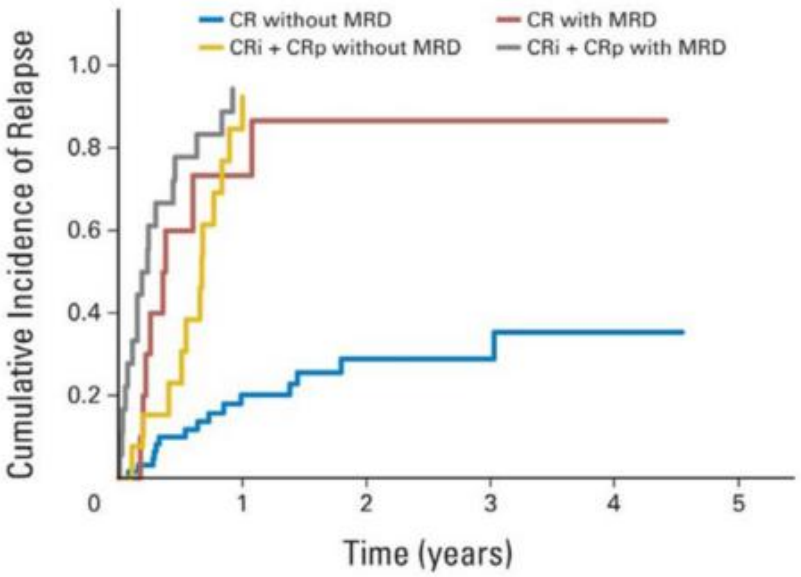
Risk category	Genetic abnormality
Favorable	• Mutated *NPM1* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH2* (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt}) • Mutated *IDH1*[b] (*TP53*^{wt}) • Mutated *DDX41*[c] • Other cytogenetic and/or molecular abnormalities[d] (*FLT3*-ITD^{neg}, *NRAS*^{wt}, *KRAS*^{wt}, *TP53*^{wt})
Intermediate	• Other cytogenetic and molecular abnormalities[d] (*FLT3*-ITD^{pos} and/or *NRAS*^{mut} and/or *KRAS*^{mut}; *TP53*^{wt})
Adverse	• Mutated *TP53*

Döhner et al, Blood. 2024 :blood.2024025409. doi: 10.1182/blood.2024025409
Döhner et al, Bood. 2024 blood.2024024944. doi: 10.1182/blood.2024024944.


Induction
Consolidation/
Transplantation
Maintenance
Number of leukemic Cells
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
Relapse
CR
MRD
Cure
Time since start of therapy

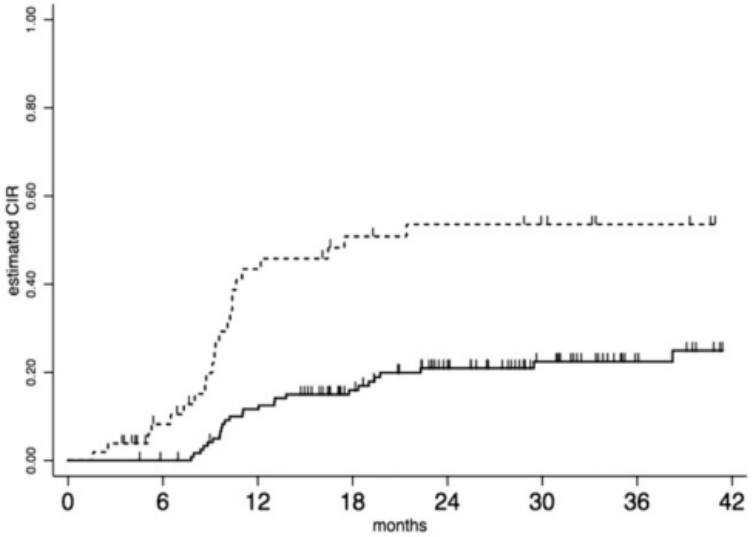
Minimal Residual Disease

Flow-based



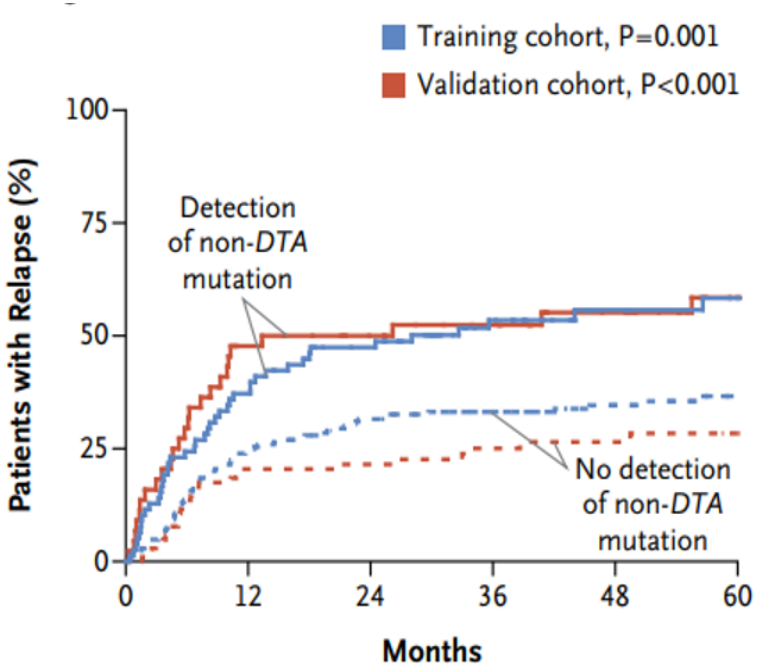
Chen et al. JCO 2015

RT-PCR



Jourdan Blood 2013; Yin Blood 2012

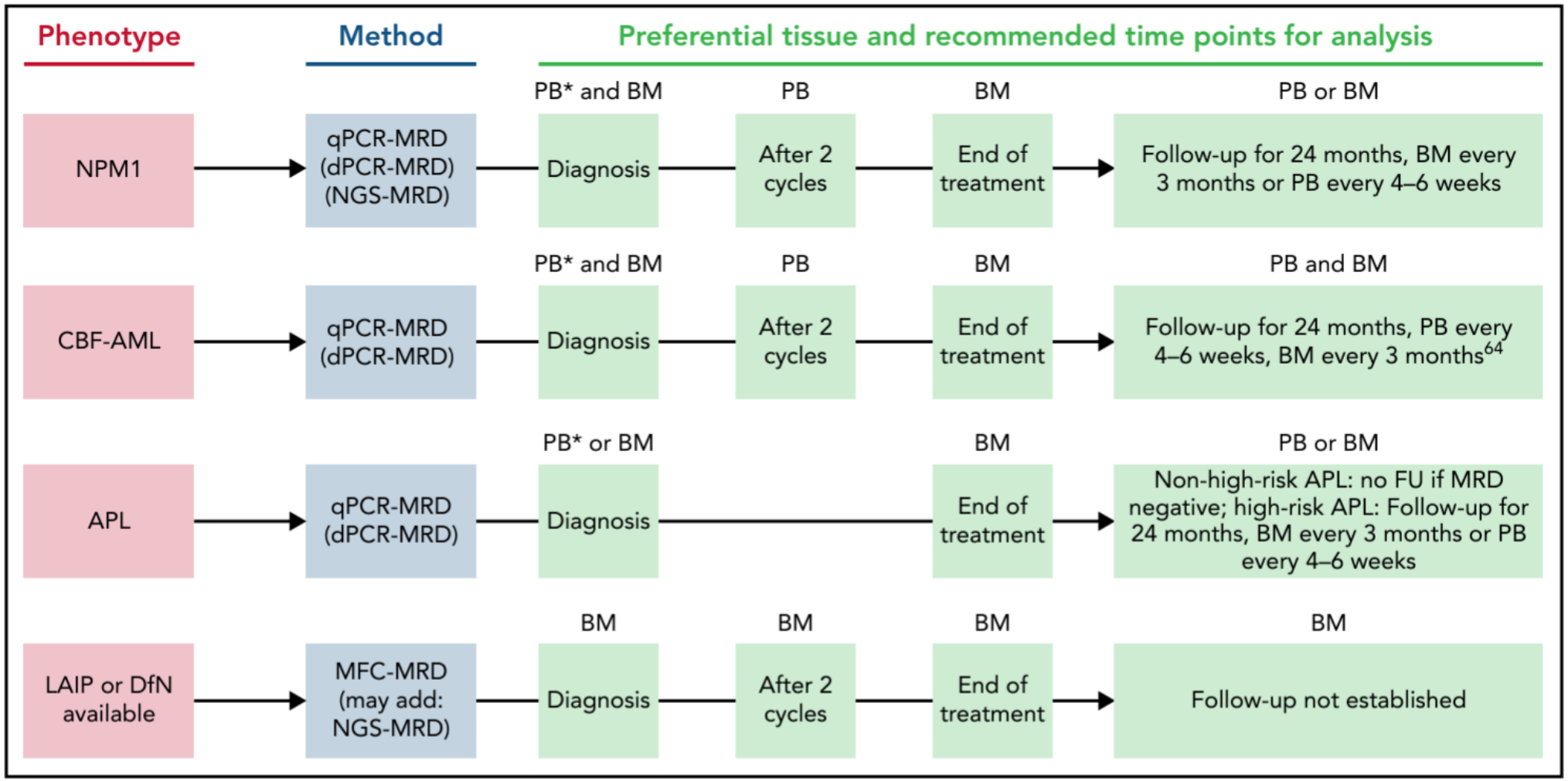
NGS



Jongen-Lavrencic et al, NEJM 2018

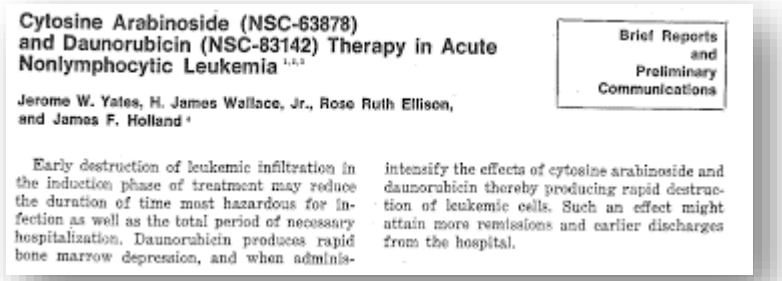
blood Special Report

2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party



Heuser et al. Blood 2021

The historical AML “dogma”

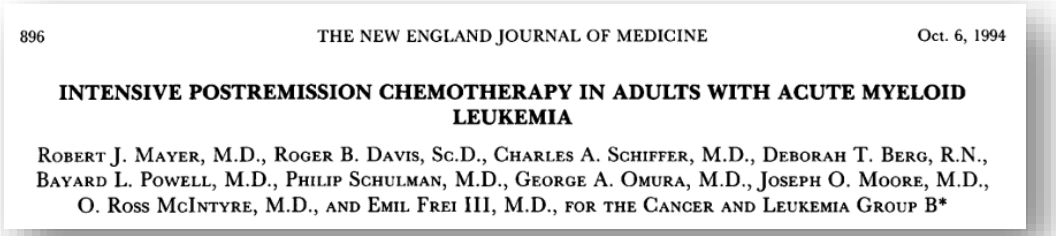


Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia [1,2,3]

Brief Reports and Preliminary Communications

Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison, and James F. Holland [4]

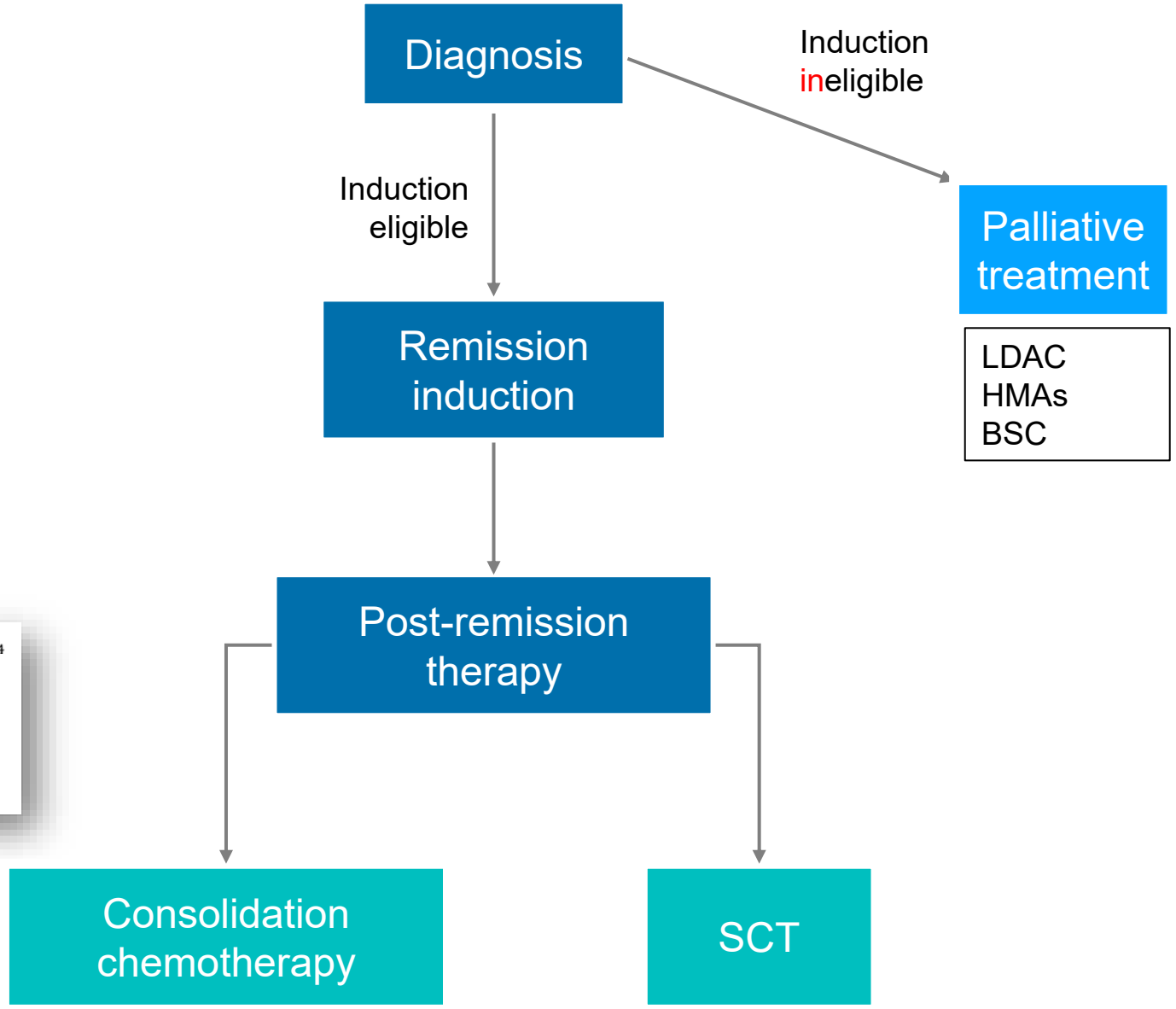
Early destruction of leukemic infiltration in the induction phase of treatment may reduce the duration of time most hazardous for infection as well as the total period of necessary hospitalization. Daunorubicin produces rapid bone marrow depression, and when administered intensify the effects of cytosine arabinoside and daunorubicin thereby producing rapid destruction of leukemic cells. Such an effect might attain more remissions and earlier discharges from the hospital.



896 THE NEW ENGLAND JOURNAL OF MEDICINE Oct. 6, 1994

INTENSIVE POSTREMISSION CHEMOTHERAPY IN ADULTS WITH ACUTE MYELOID LEUKEMIA

Robert J. Mayer, M.D., Roger B. Davis, Sc.D., Charles A. Schiffer, M.D., Deborah T. Berg, R.N., Bayard L. Powell, M.D., Philip Schulman, M.D., George A. Omura, M.D., Joseph O. Moore, M.D., O. Ross McIntyre, M.D., and Emil Frei III, M.D., for the Cancer and Leukemia Group B*



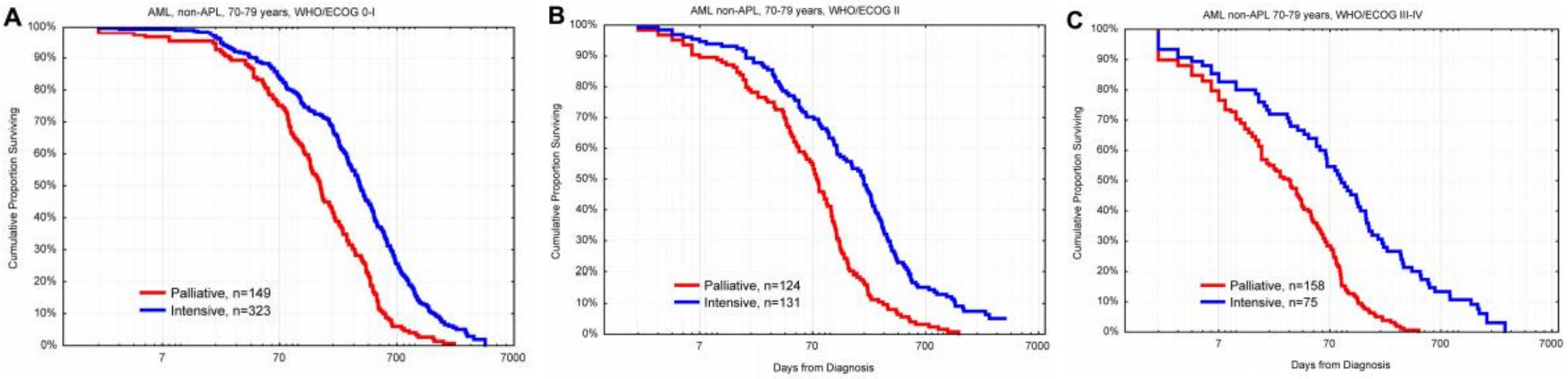
Yates JW, *et al. Cancer Chemother Rep* 1973; **57:**485–488; Mayer RJ, *et al. N Engl J Med* 1994; **331:**896–903.

Resistance to therapy, **not** TRM – the leading cause of death in older AML

Resistance vs treatment-related mortality (TRM)[a]

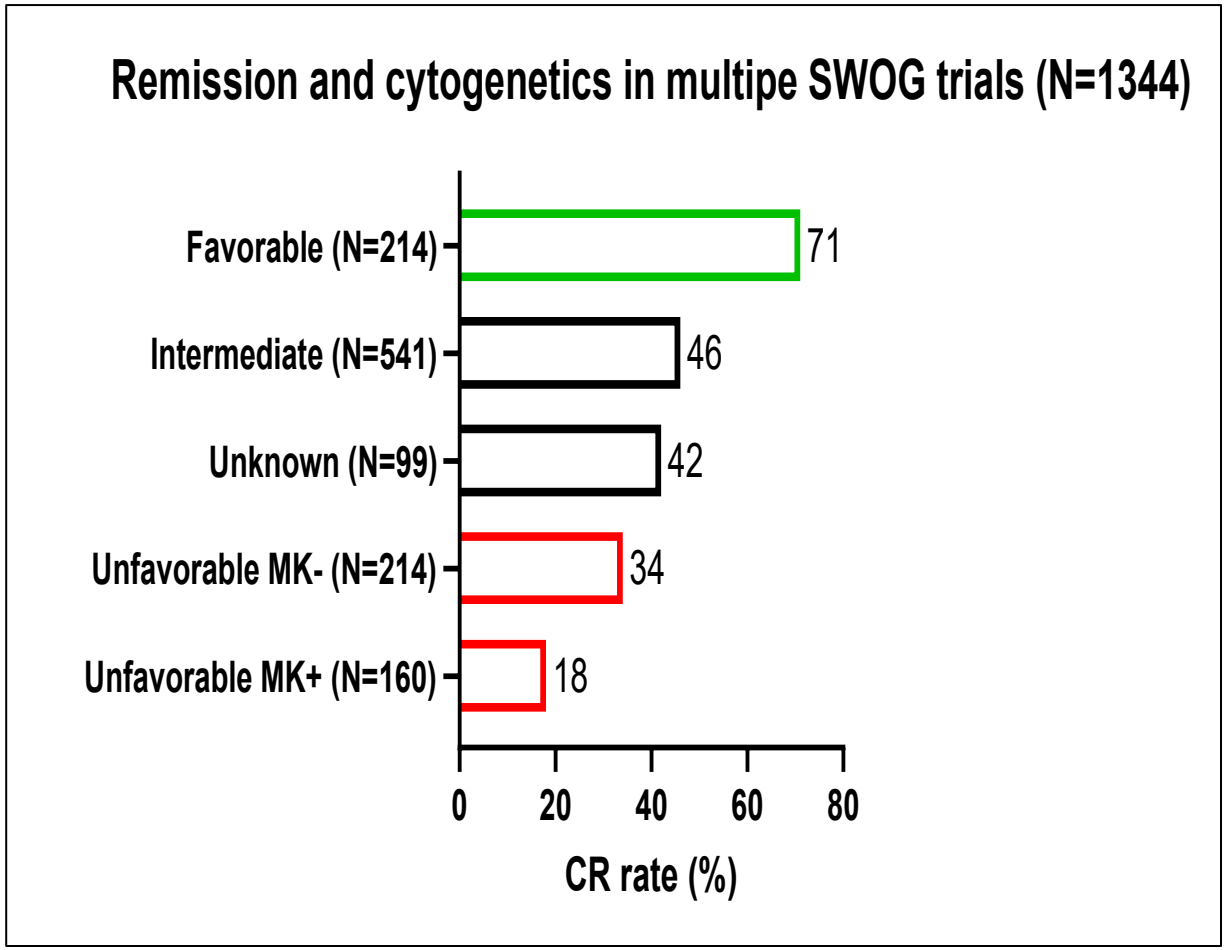
Age	Patients (N)	Complete remission	TRM	Resistant
<56 years	368	64%	9%	27%
56–65 years	246	46%	17%	37%
66–75 years	274	39%	24%	37%
>75 years	80	33%	31%	36%

Based on Appelbaum et al. Blood 2006; 107:3481–3485. [10].



Juliusson Blood 2012

Response *versus* Early death



Adapted from
Medeiros et al. Blood 2010, Sep 30;116(13):2224-8

analysis by number of adverse prognostic factors

No. of adverse factors	No. of patients (%)	8-wk mortality, %	CR, %	Survival		
				Median, mo	2-y, %	3-y, %
0	122 (28)	16	57	11.3	30	22
1	170 (40)	31	52	5.3	15	7
2	100 (23)	55	29	1.5	7	6
≥ 3	38 (9)	71	16	0.5	0	0

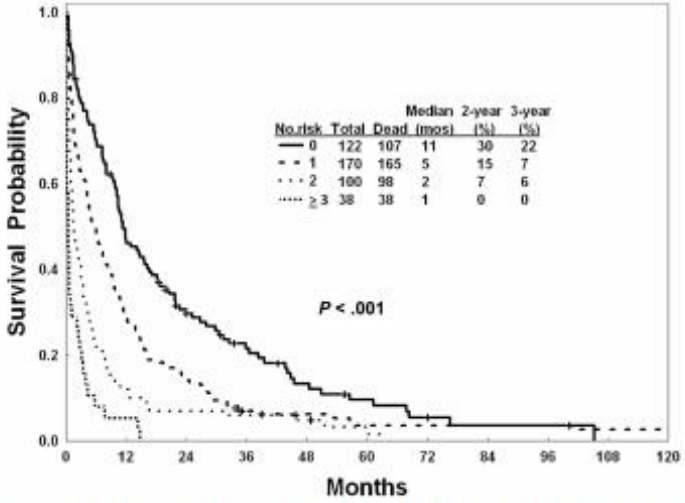
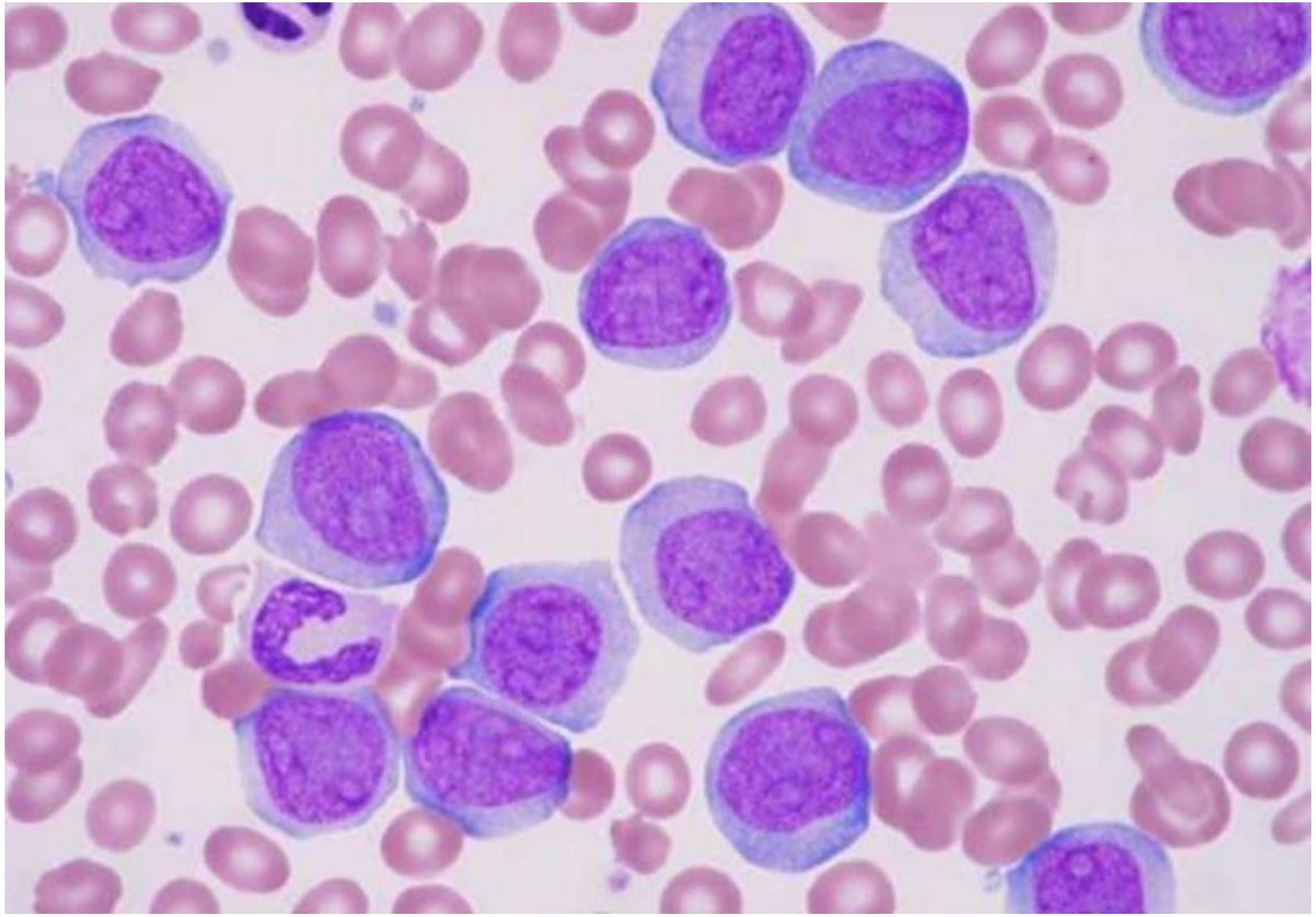
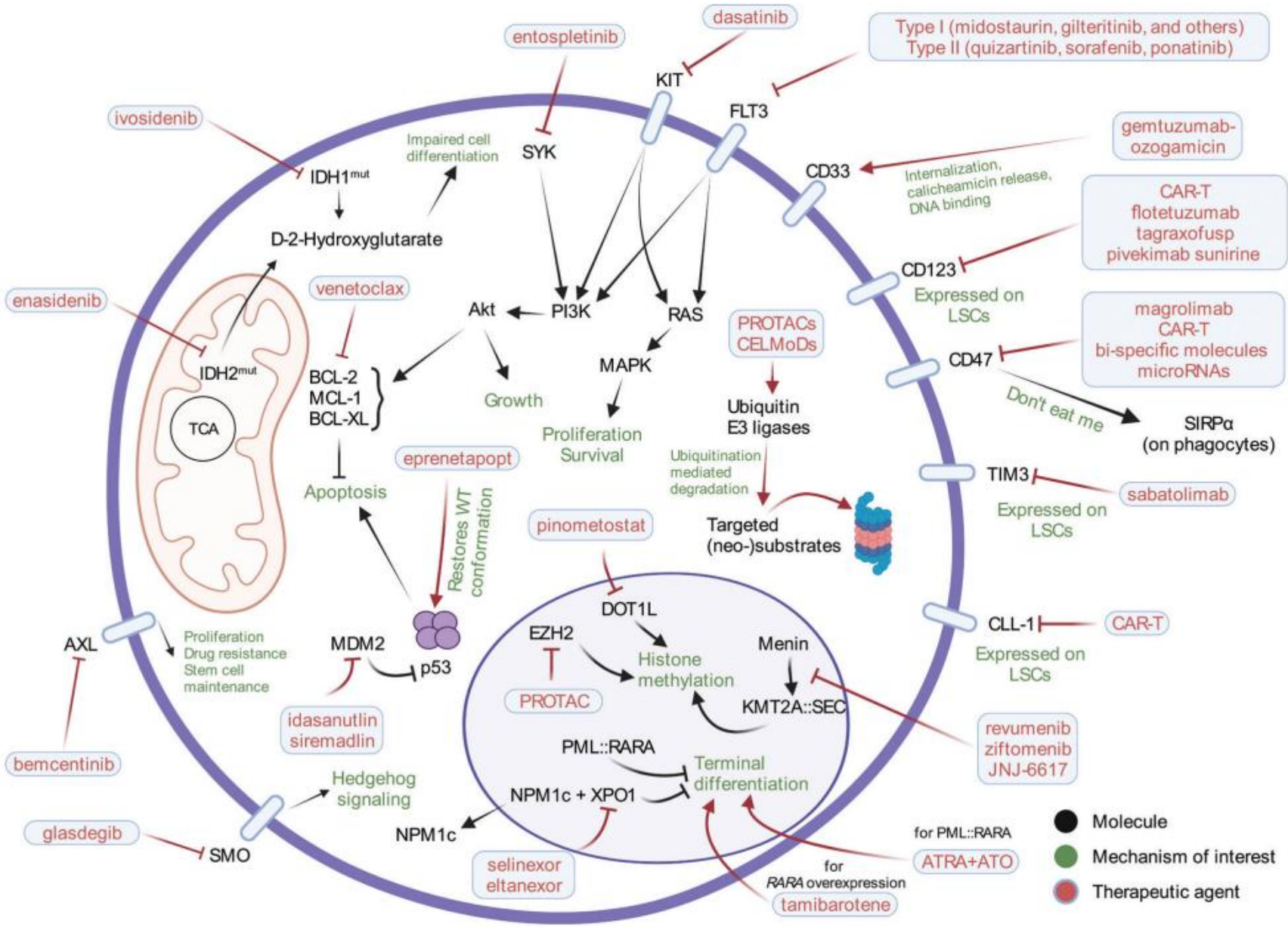


Figure 4. Survival of 430 elderly patients with AML by number of independent risk factors for 8-week mortality.

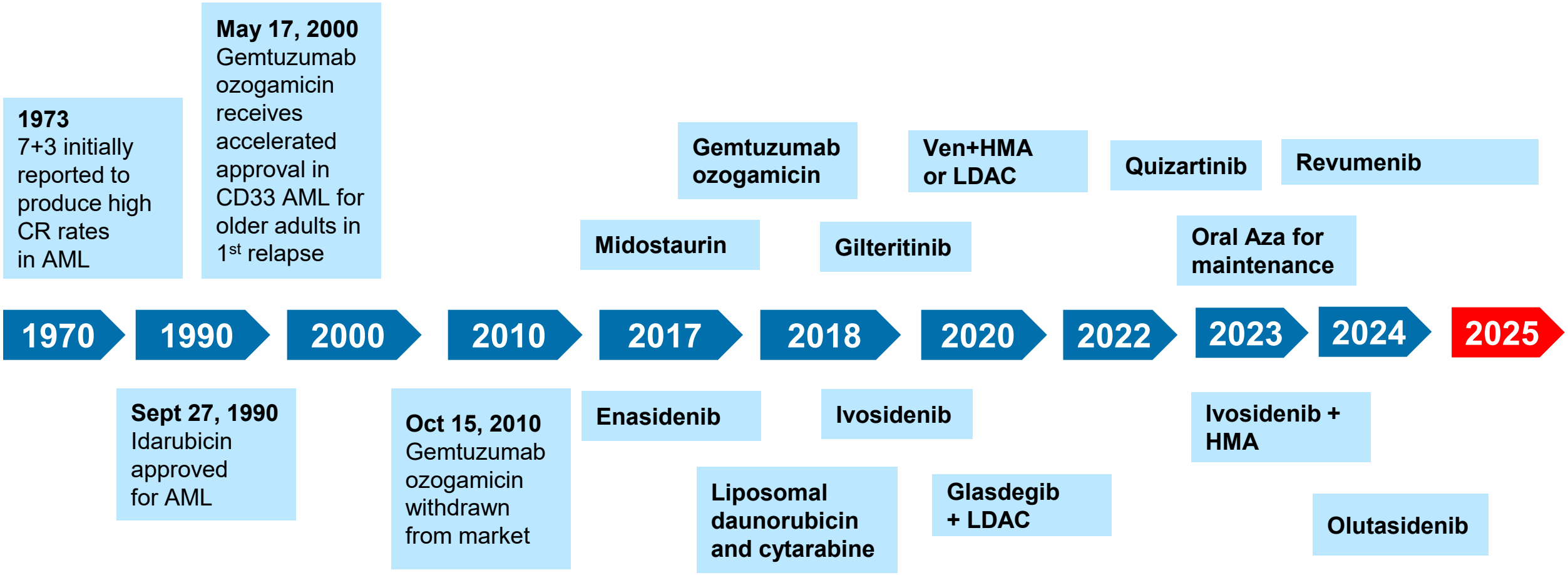
Kantarjian Blood 2010, Nov 25;116(22):4422-9



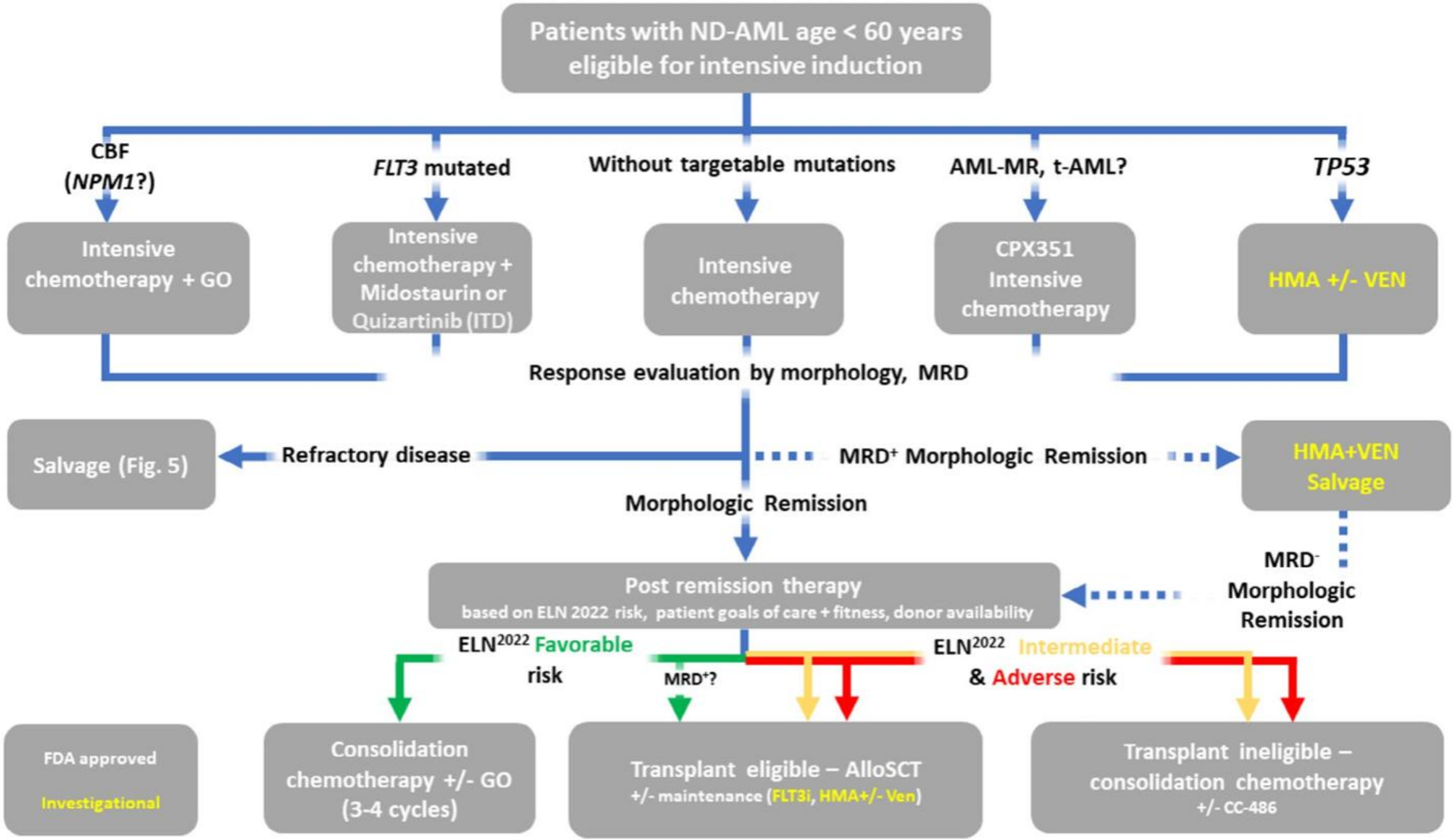


Turkalj et al. HemaSphere 2023

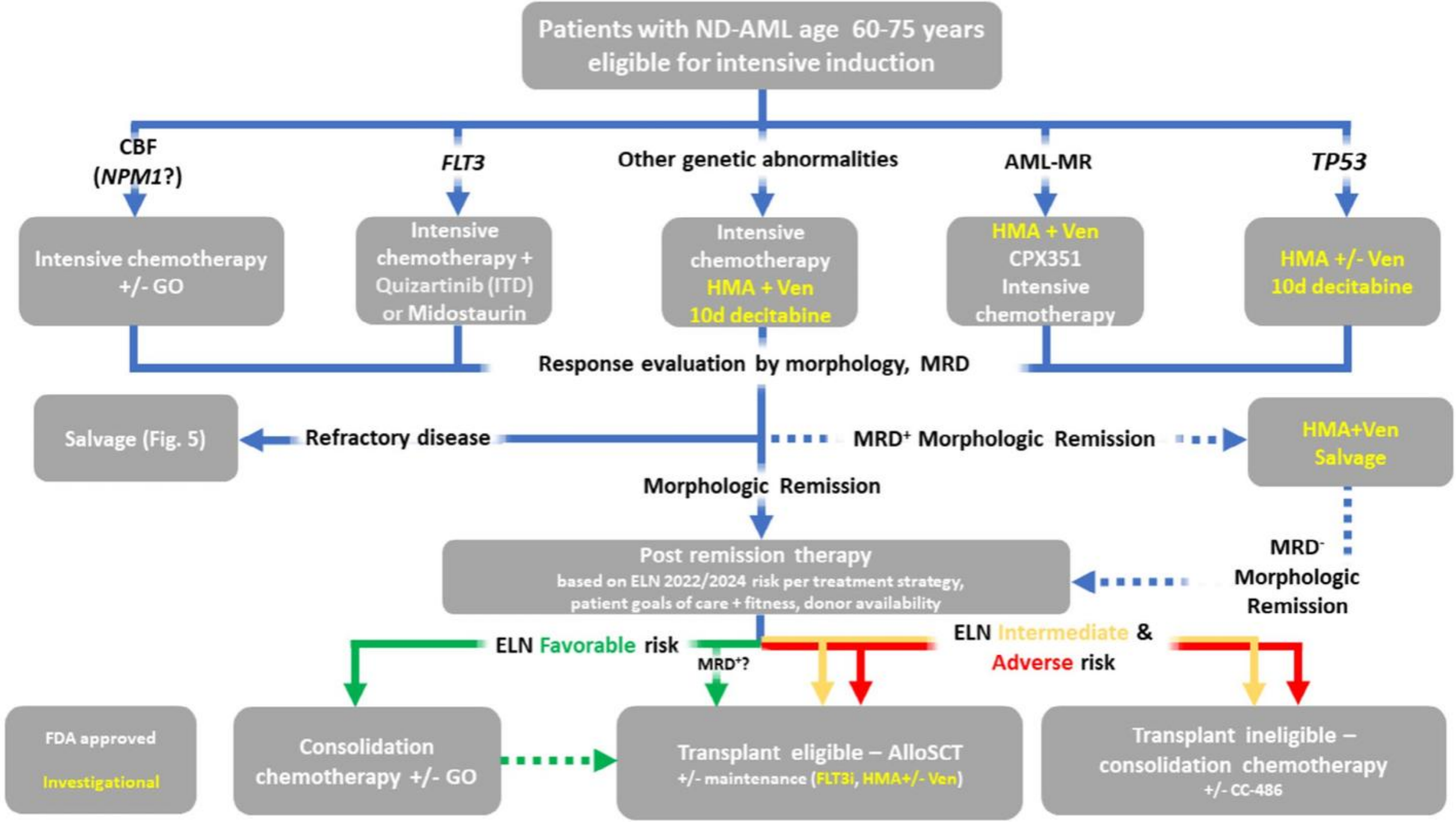
The ‘era’ of targeted therapy – recent FDA approvals



Differentiation and Combination therapies…



Shimony et al. AJH 2025



Shimony et al. AJH 2025

Goals of Care

Intensive induction

Lower-intensity approach

Fitness

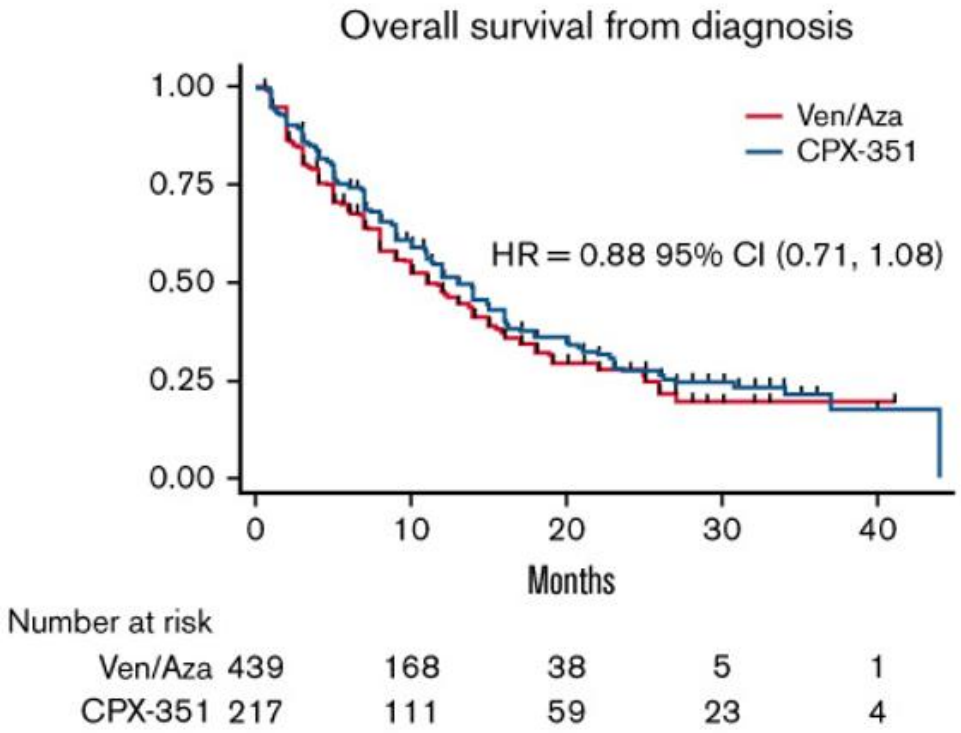
Efficacy

Toxicity

Quality of Life

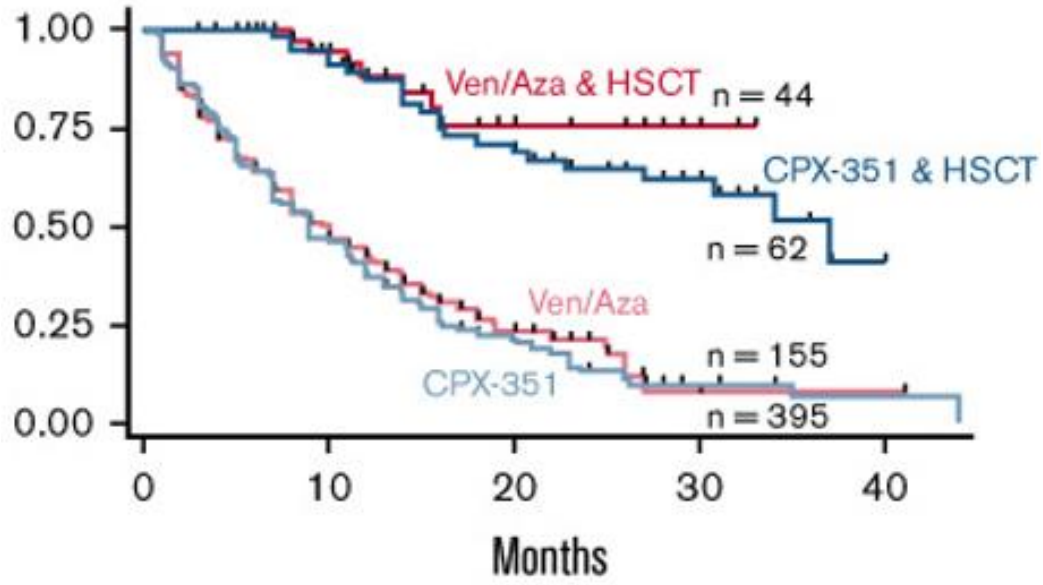
CPX-351 *vs.* HMA-Ven

Retrospective comparative study (FLATIRON & University of Pennsylvania)



Median OS	13 months	11 months
Median OS w/ allogeneic transplant	Not reached	37 months
Median OS w/o allogeneic transplant	10 months	9 months

Transplant critical for long-term benefit

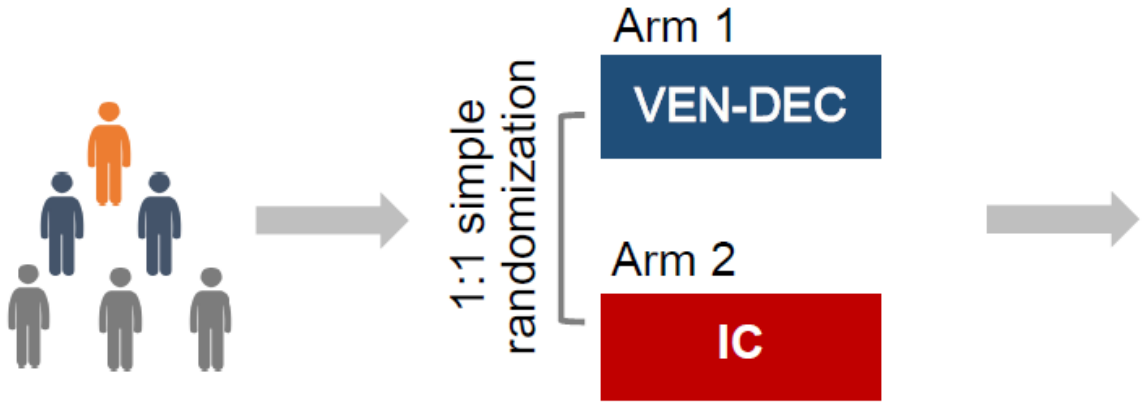


Flatiron & UPHS	CPX-351 n = 217	Venetoclax & azacitidine n = 439
Median cycles (range)	2 (1–5)	4 (1–28)
30 day mortality % (95% CI)	5% (2%–8%)	5% (3%–7%)
60 day mortality % (95% CI)	10% (6%–14%)	13% (10%–16%)
Diagnosis of infection[1] % (95% CI)	51% (42%–61%)	20% (15%–25%)

Matthews AH et al Blood Adv 2022 Jul 12;6(13):3997-4005.

IC *vs.* HMA-Ven

Prospective randomized phase II study



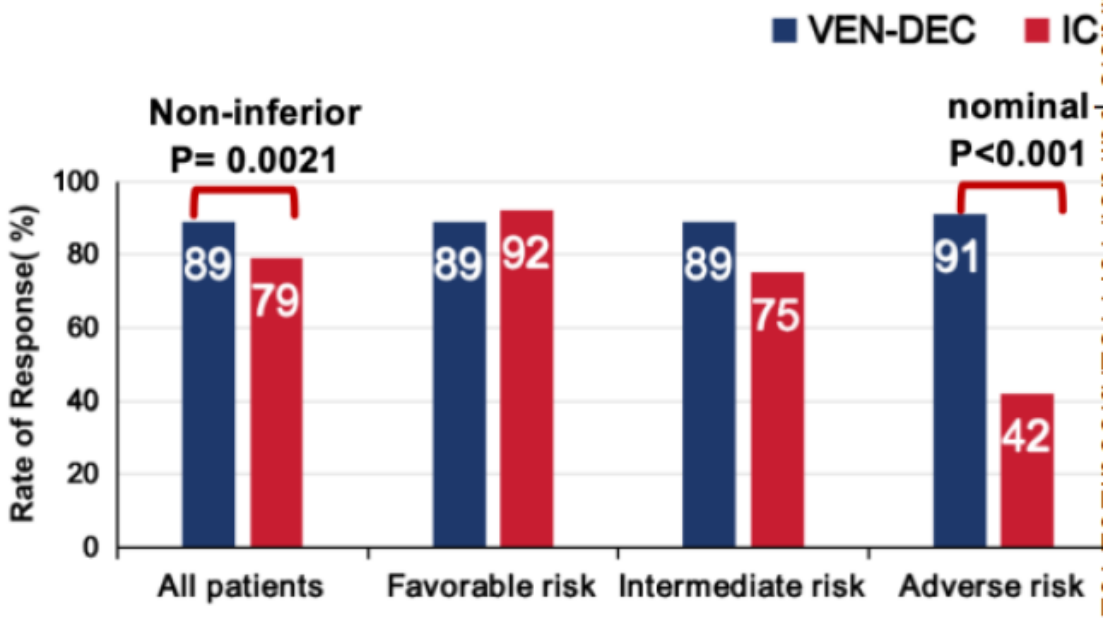
188 Patients

Induction/Re-induction

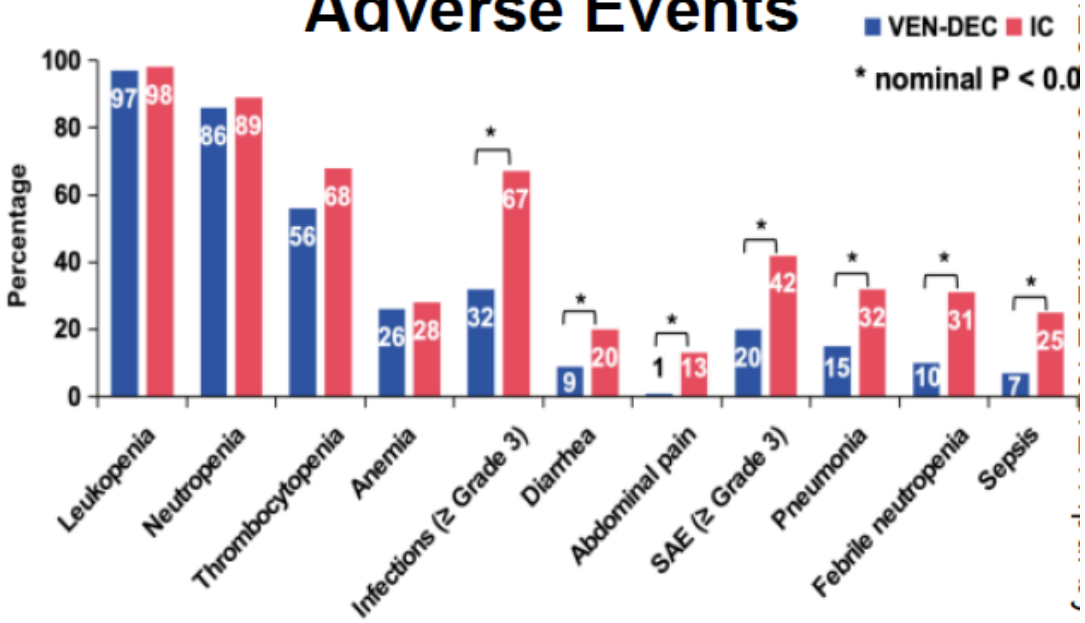
- Untreated AML
- 18-59 years old
- No extramedullary disease
- No prior Venetoclax / HMA use

- VEN-DEC:
  Venetoclax (target 400 mg/d)× 28d
  Decitabine (20 mg/m²/d)× 5d
- IC:
  Idarubicin (12 mg/m²/d)× 3d
  Cytarabine (100 mg/m²/d)× 7d

CR/CRi for Induction



Adverse Events



Jing Lu et al Blood 2025.

Decitabine is not approved in Japan and is used in combination with Azacitidine. Please refer to the Venclexta package insert for further details.

Abstract Number : abs25-8236

Abstract Title : Results from paradigm - a phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with acute myeloid leukemia

Category: 600s - Hematologic Malignancy

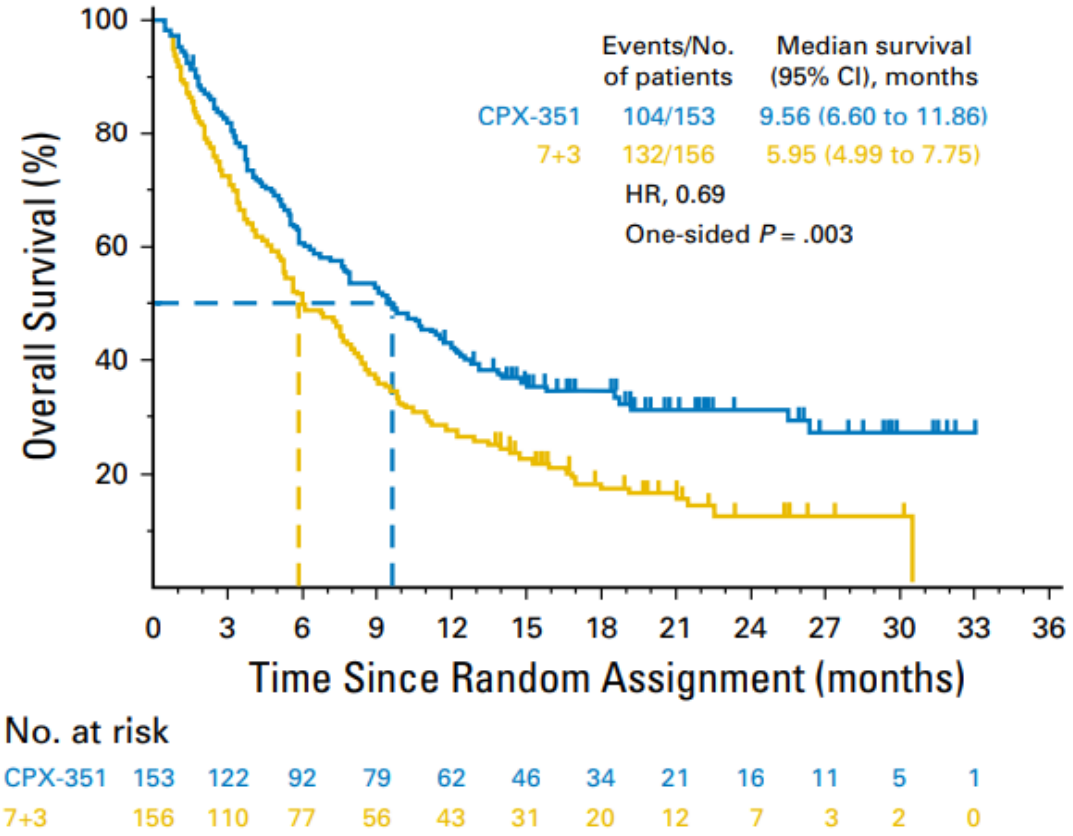
Review Category: 617. Acute Myeloid Leukemias: Commercially Available Therapies

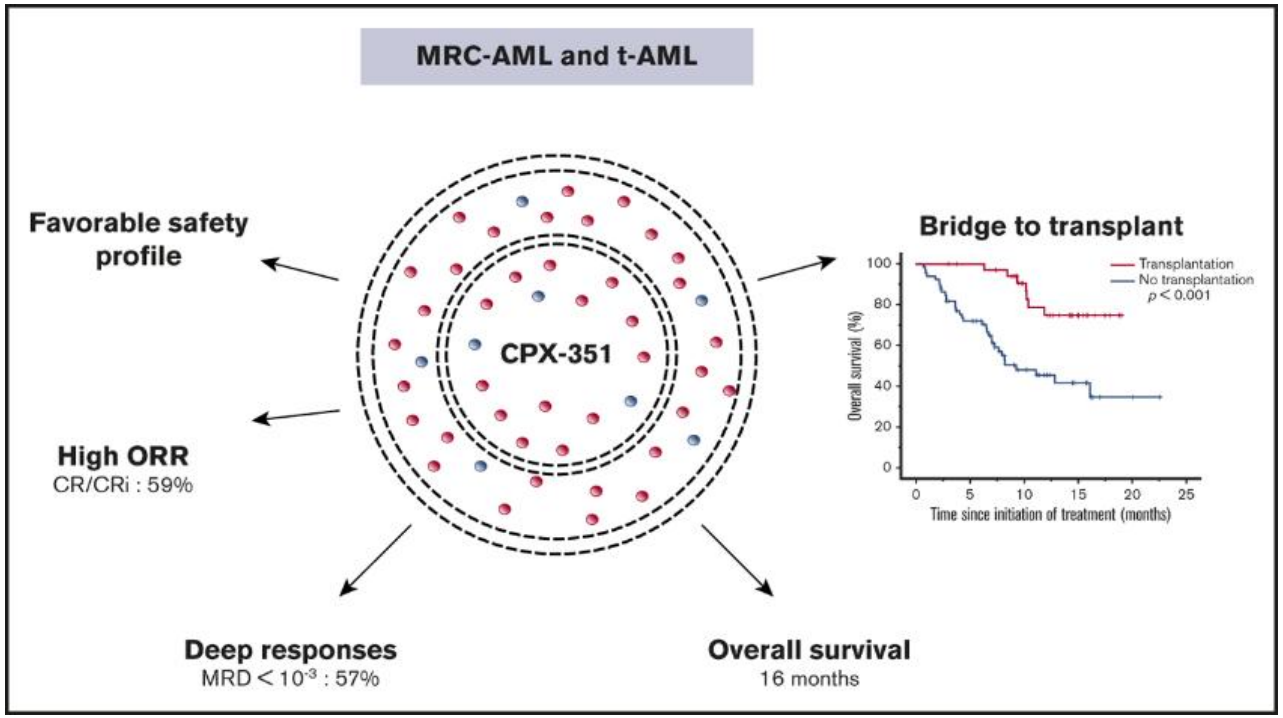
Authors

Amir Fathi[1], Alexander Perl[2], Geoffrey Fell[3], Brian Jonas[4], Brittany Ragon[5], Alice Mims[6], Uma Borate[6], Gabriel Mannis[7], Karen Quillen[8], Max Stahl[3, 9], Paul Koller[10], Andrew Artz[10], Monzr M. Al Malki[10], Guido Marcucci[10], Mary Linton Peters[8], Timothy Graubert[1], Peter Westervelt[11, 12], Philip Amrein[1], Hanno Hock[1], Andrew Brunner[1], Gabriela Hobbs[1], Rupa Narayan[1], Michelle Lee[1], Brandon Aubrey[1], Alyssa Watson[11], Richard Hao[11], Shilton Dhaver[11], Michael Grunwald[5], Yi-Bin Chen[1], Andrew Matthews[2], Christopher Hourigan[13], Brent Wood[14], Donna Neuberg[3], Areej El-Jawahri[1], Ibrahim Aldoss[10]

[1] Massachusetts General Hospital / Harvard Medical School, Boston, MA, United States, [2] Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, United States, [3] Dana Farber Cancer Institute, Boston, MA, United States, [4] University of California Davis Comprehensive Cancer Center, Sacramento, CA, United States, [5] Levine Cancer Institute, Atrium Health, Charlotte, NC, United States, [6] The Ohio State University, Columbus, OH, United States, [7] Stanford University School of Medicine, Stanford, CA, United States, [8] Beth Israel Deaconess Medical Center, Boston, MA, United States, [9] Yale School of Medicine, New Haven, CT, United States, [10] City of Hope, Duarte, CA, United States, [11] Massachusetts General Hospital, Boston, MA, United States, [12] MaineHealth, Brunswick, ME, United States, [13] Fralin biomedical research institute, Virgina Tech University, Roanoke, VA, United States, [14] Children's Hospital Los Angeles, University of Southern California, Los Angeles, MA, United States

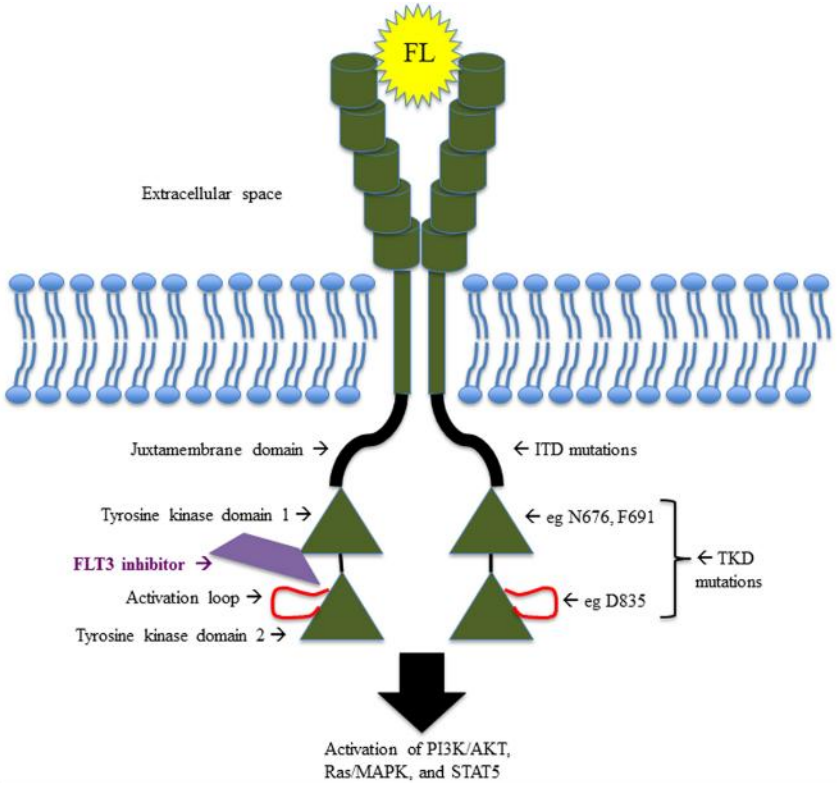
CPX-351 for Secondary AML

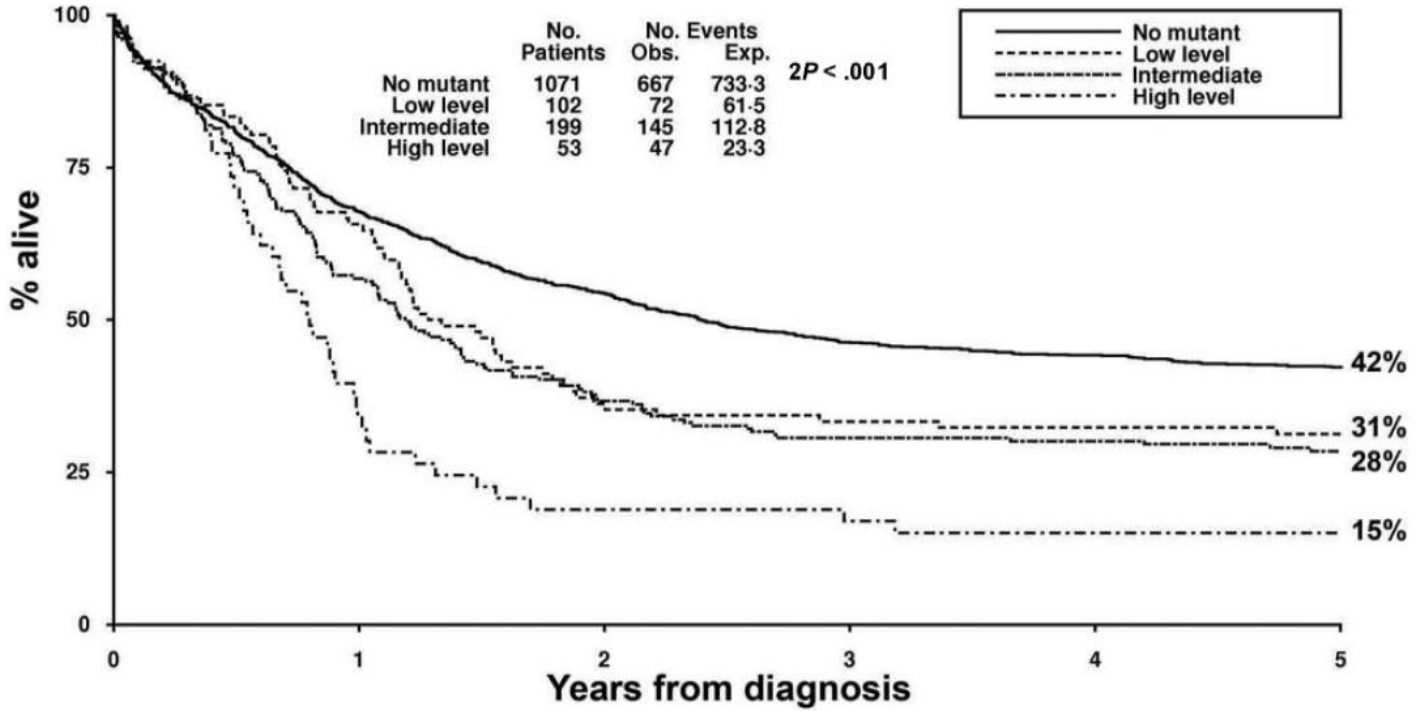




Lancet et al. JCO 2018

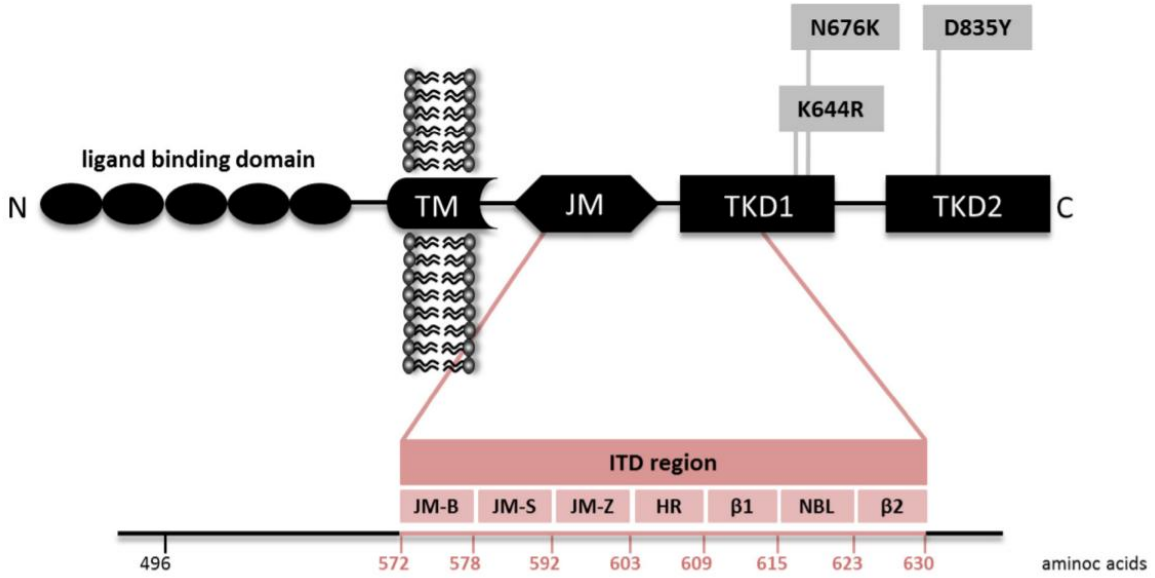
Fms-like Tyrosine Kinase 3

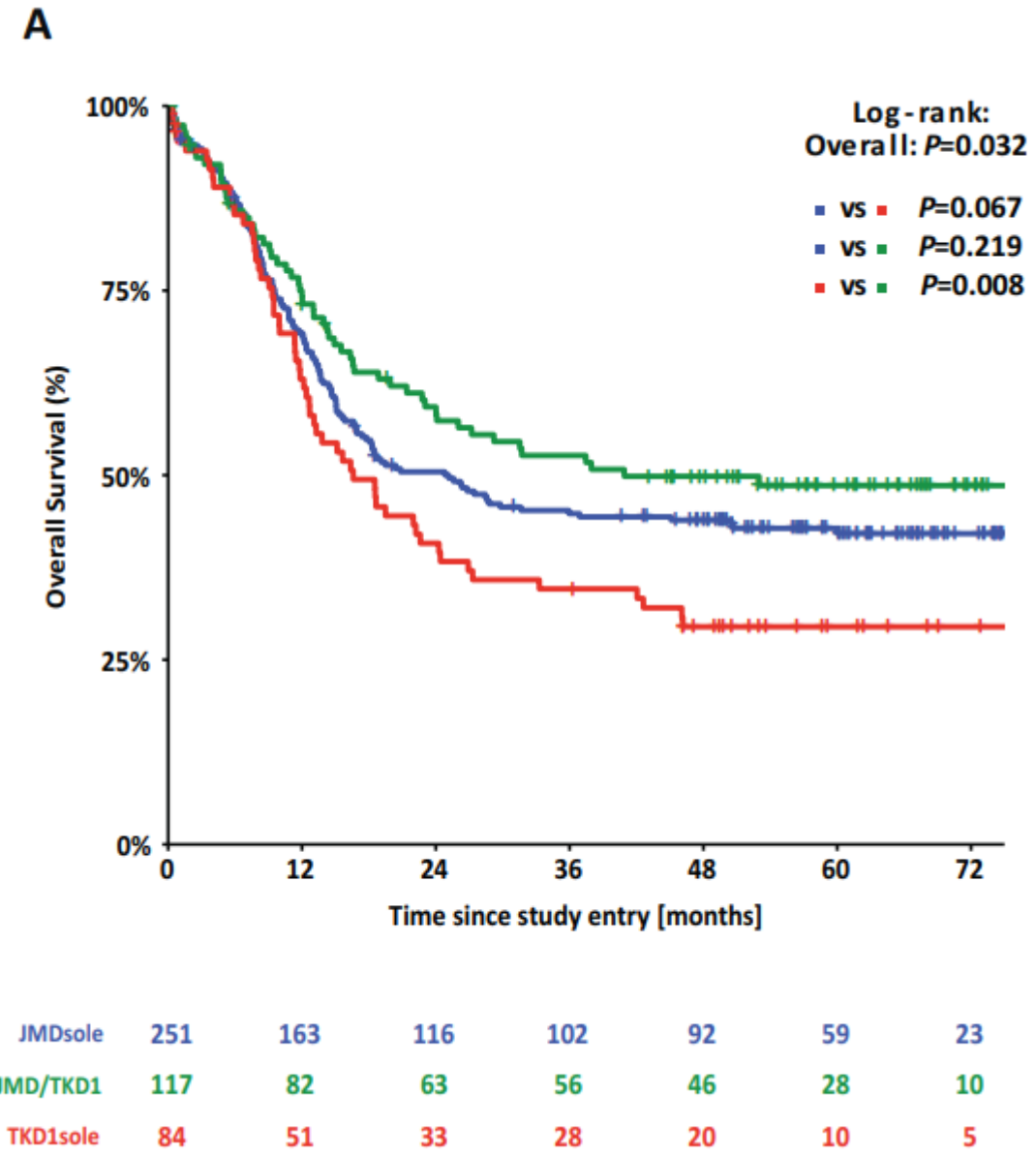




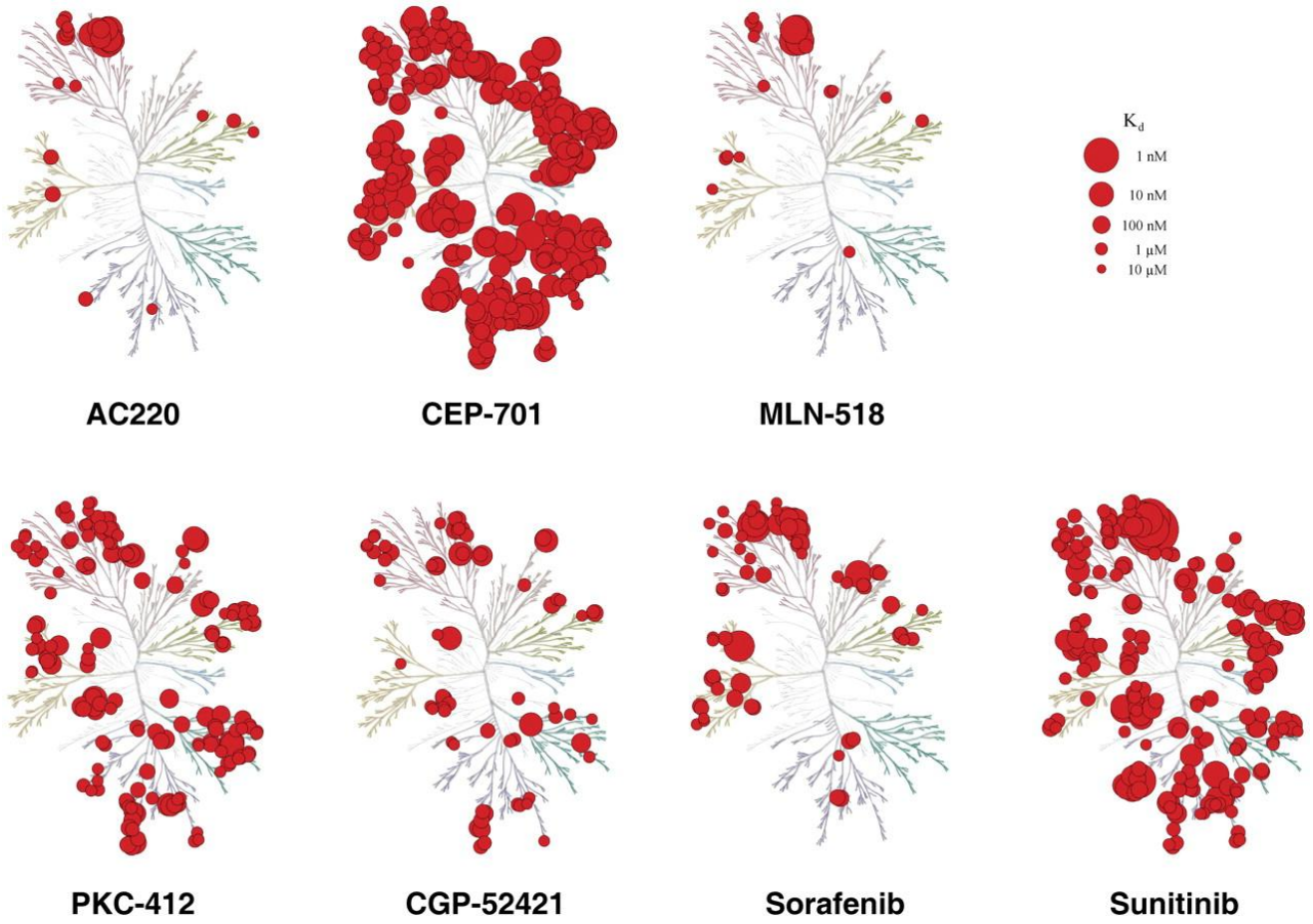
Gale blood 2008

ITD insertion site





Schranz et al, Oncotarget 2018; Rucker et al. Leukemia 2022

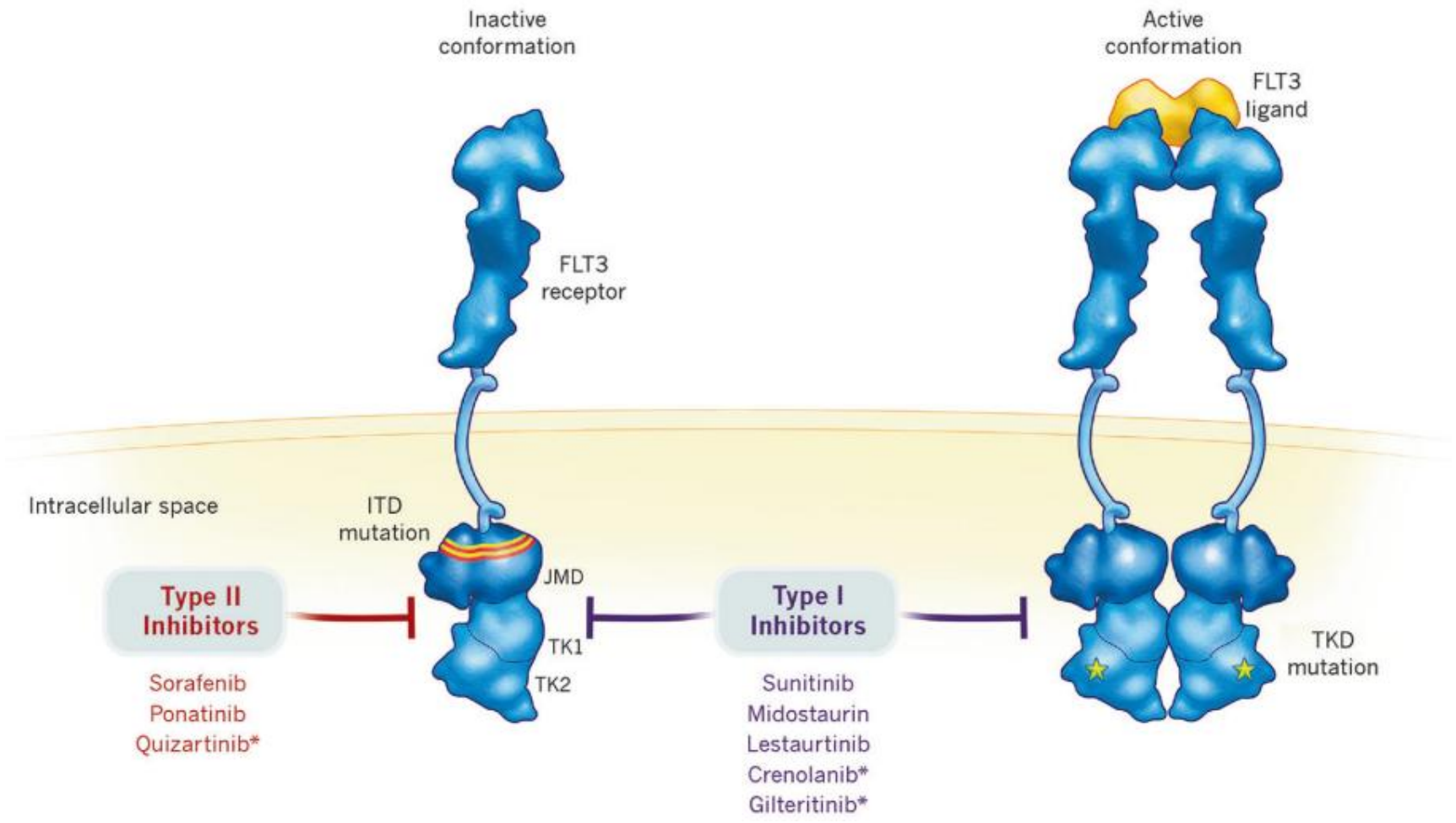


Potency (IC_{50})	
Lestaurtinib (CEP-701)	700nM
Midostaurin (PKC-412)	1000nM

Potency (IC_{50})	
Sorafenib	265nM
Quizartinib (AC220)	18nM

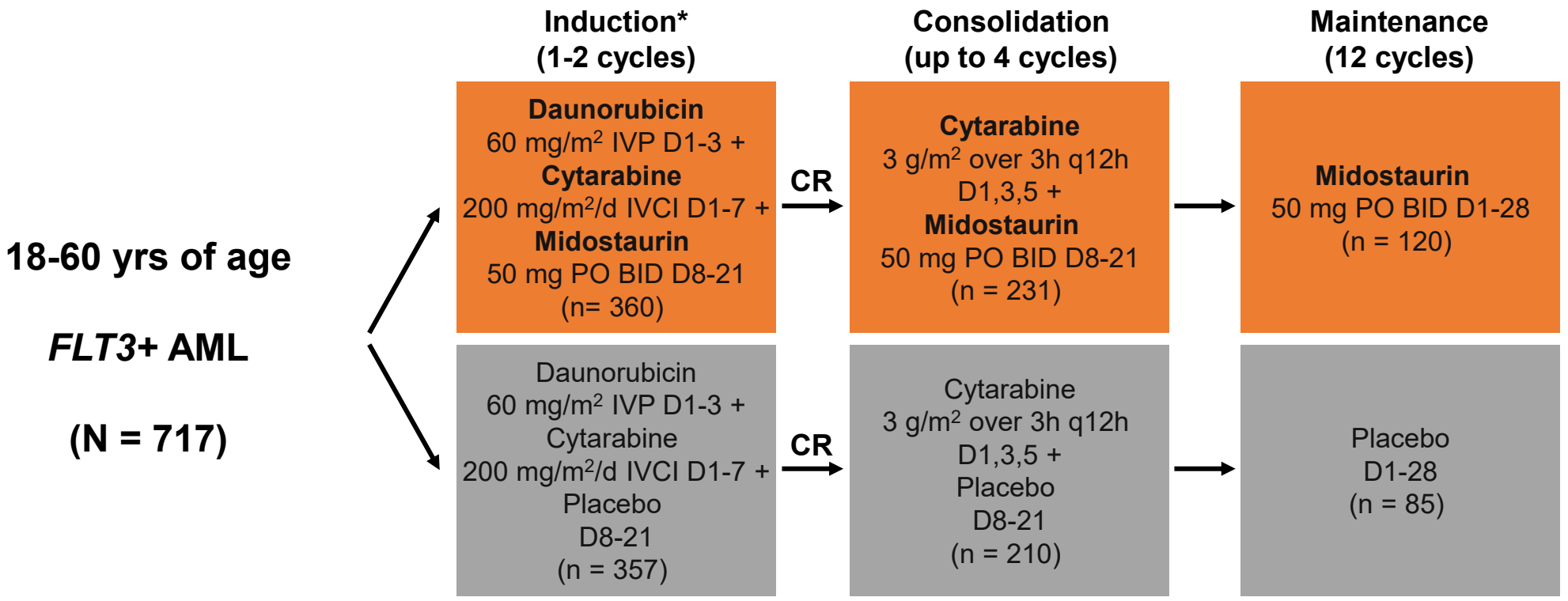
Zarrinkar et al. Blood 2009; Weisberg et al. BJH 2019

Summary of first- and next-generation *FLT3* inhibitors



Davet *al. Leukemia* 2019; **33**:299–312.

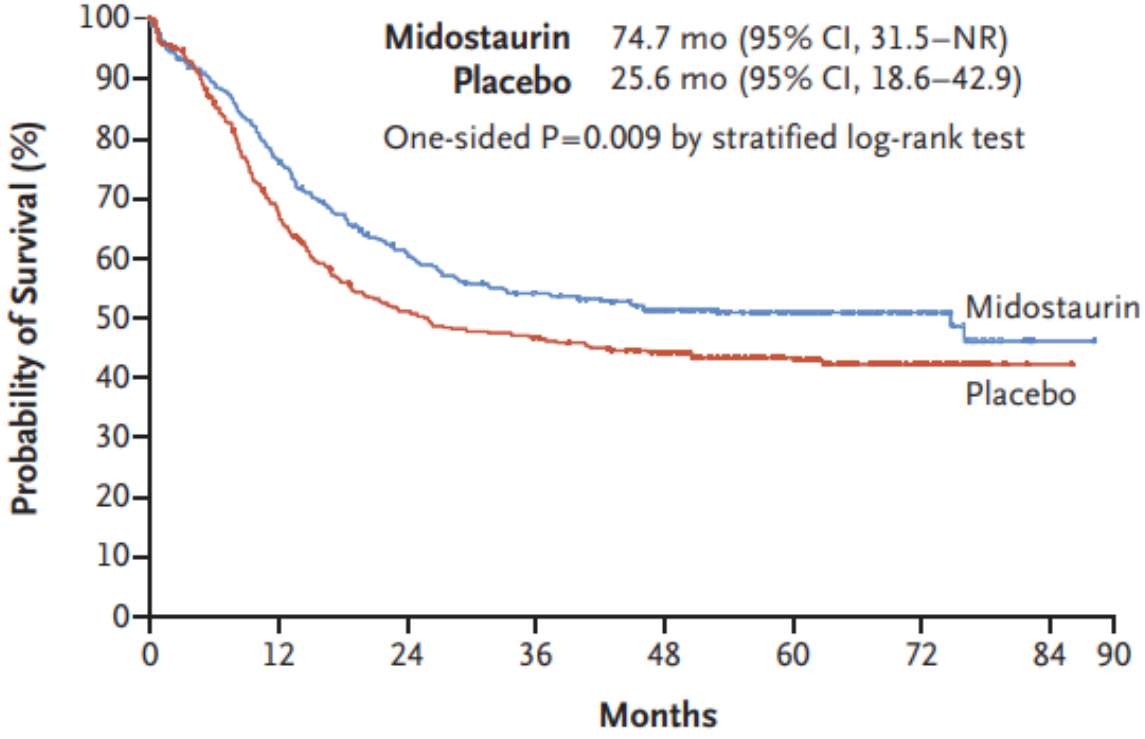
RATIFY: Midostaurin in FLT3-Positive AML



*Hydroxyurea allowed for ≤ 5 days prior to induction therapy.

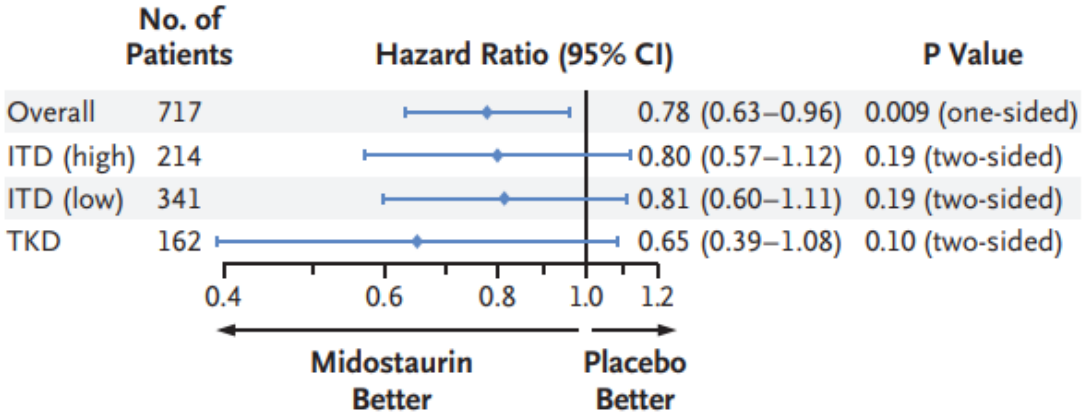
Stone et al, ASH 2016

RATIFY: Midostaurin in FLT3-Positive AML



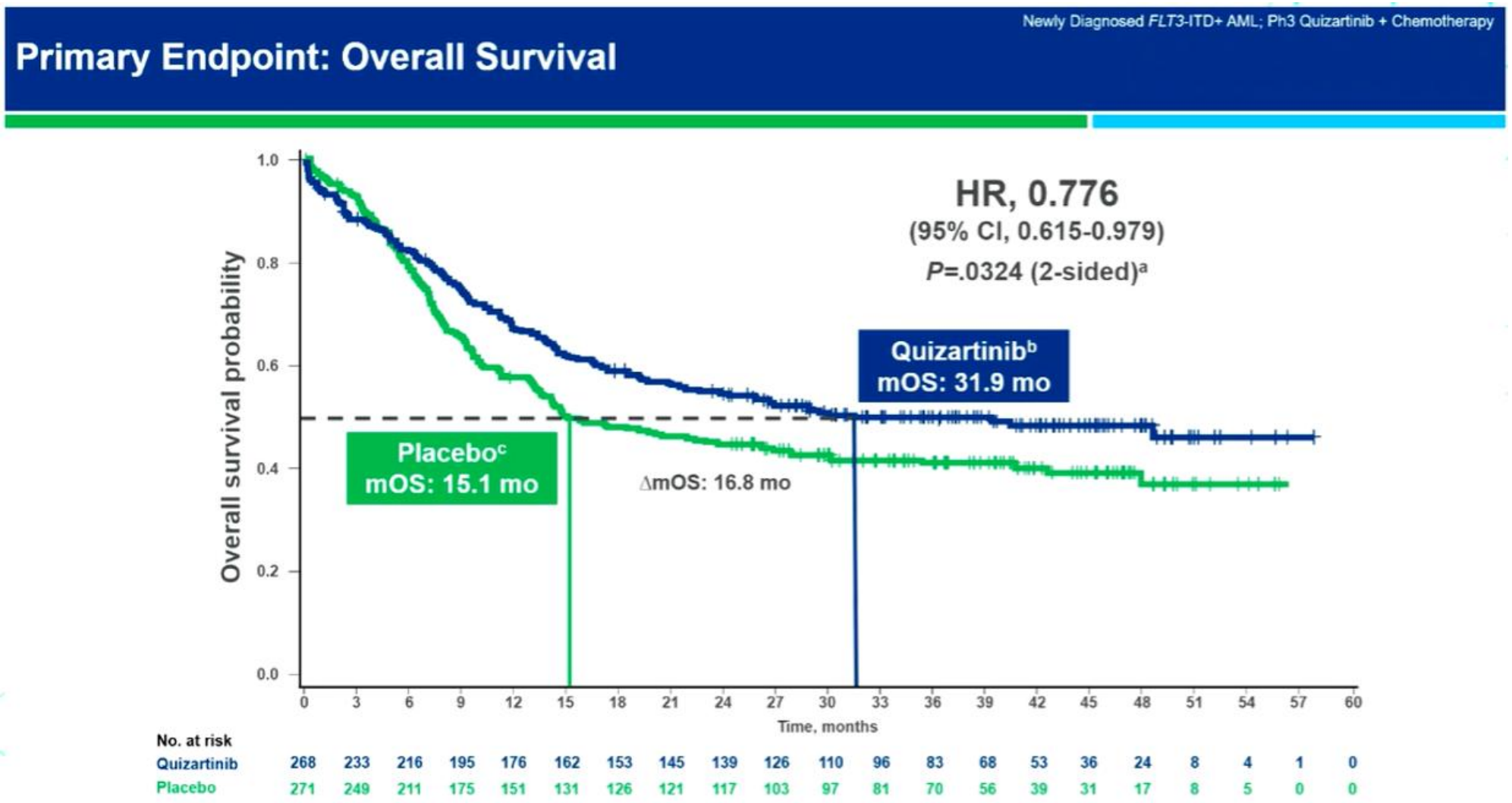
No. at Risk

Midostaurin	360	269	208	181	151	97	37	1
Placebo	357	221	163	147	129	80	30	1



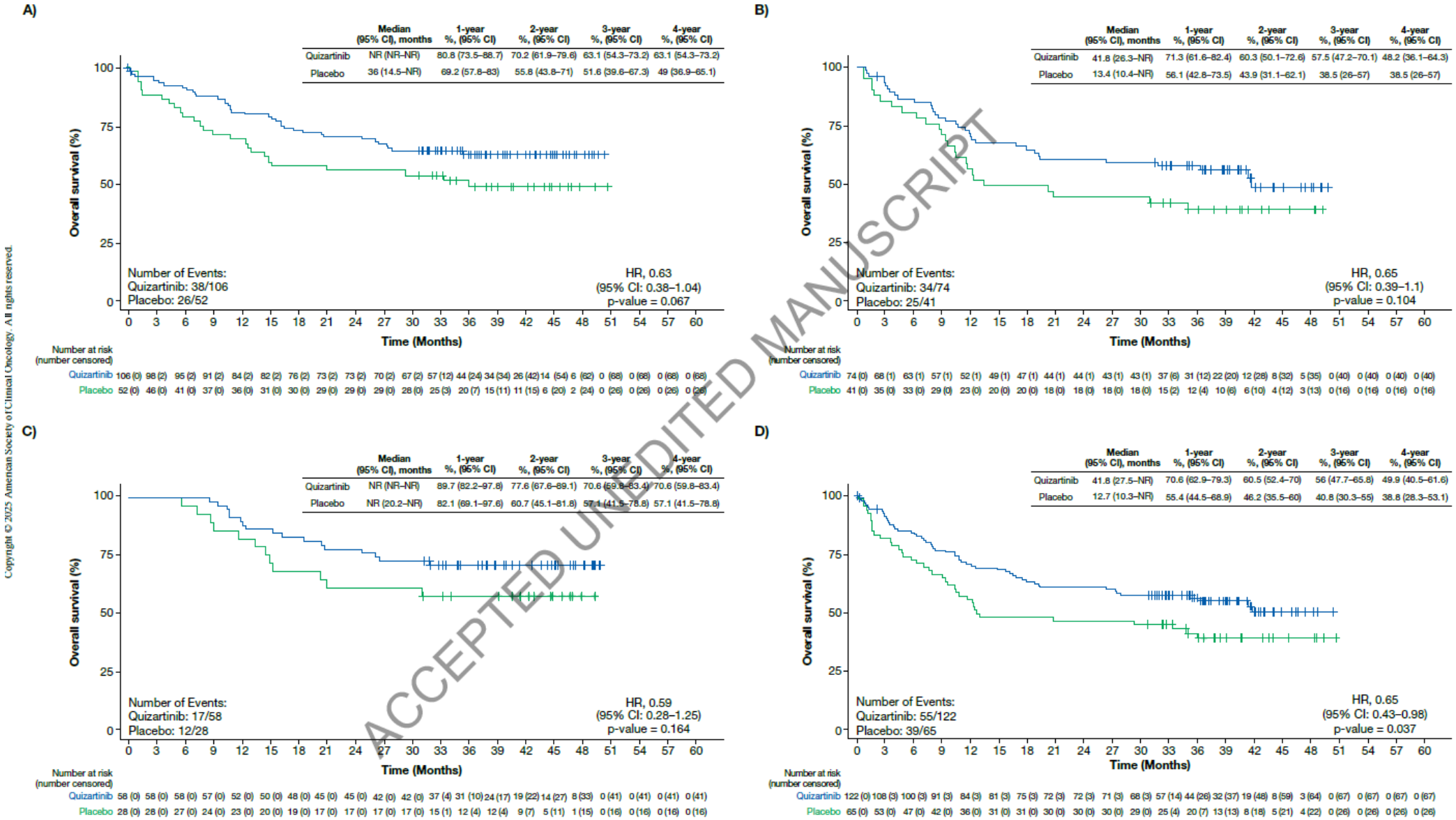
Stone et al, NEJM 2017

Quantum-First study



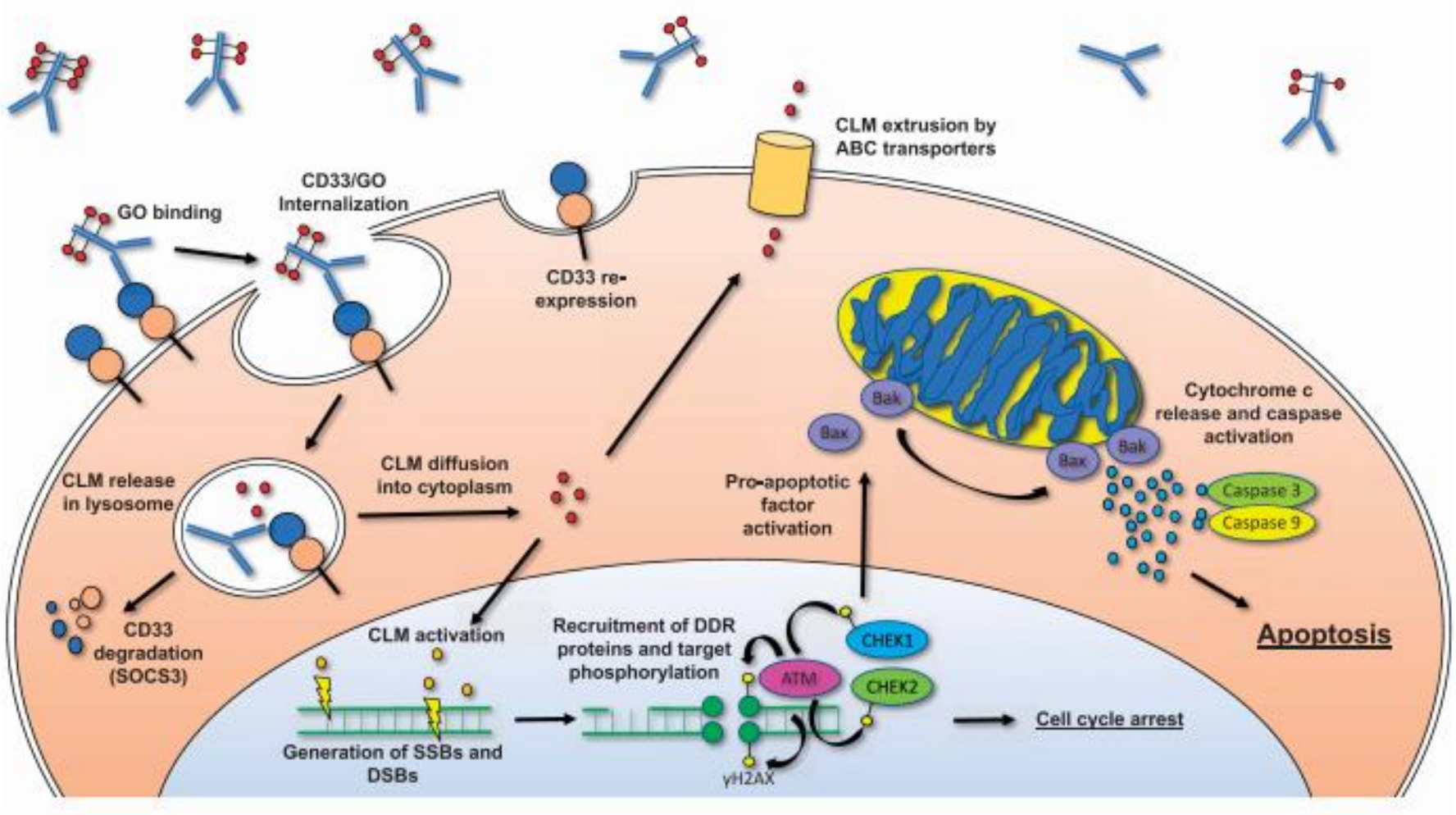
Erba et al. Lancet 2023

Quizartinib for FLT3—ITD negative AML – Quiwi trial



Montesinos et al. JCO 2025

Gemtuzumab Ozogamicin (GO, Mylotarg®)



Godwin, Leukemia 2017

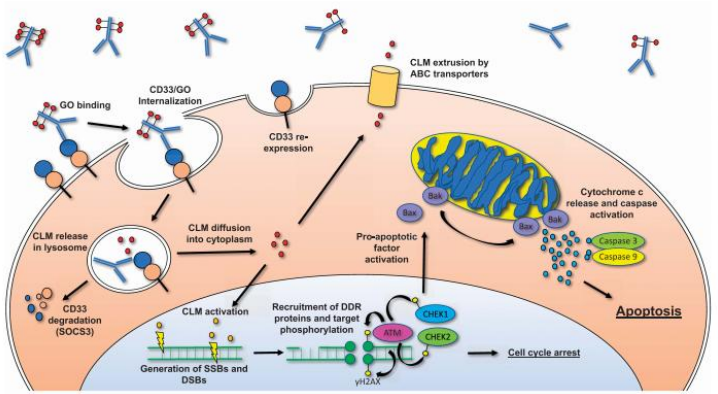
Blood Forum

Gemtuzumab ozogamicin in acute myeloid leukemia: a remarkable saga about an active drug

Jacob M. Rowe[1,2] and Bob Löwenberg[3]

[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Technion, Israel Institute of Technology, Haifa, Israel; and [3]Department of Hematology, Erasmus University Medical Center, Rotterdam, The Netherlands

Improving patient outcome gemtuzumab ozogamicin



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%

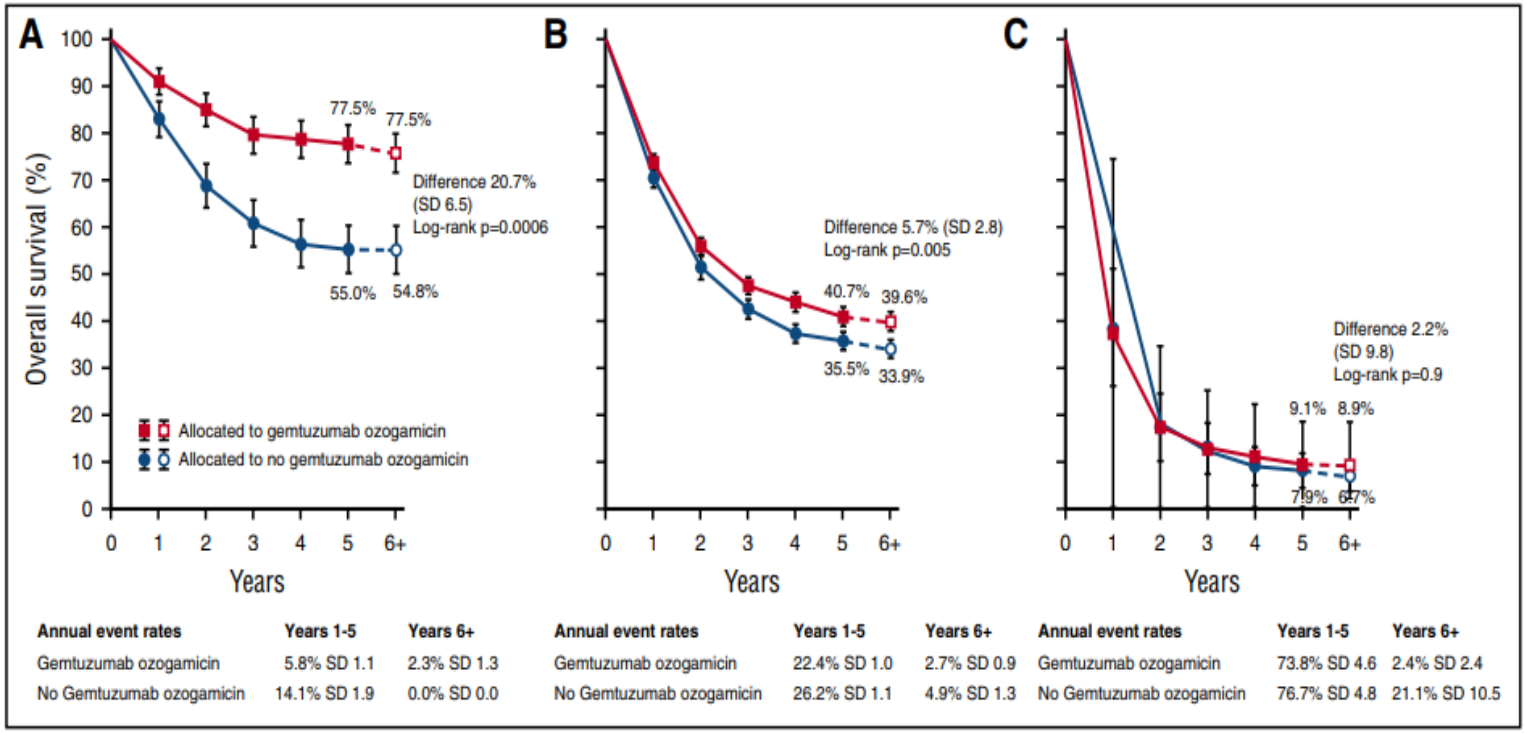
Meta-analysis

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%



Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	5.8% SD 1.1	2.3% SD 1.3
No Gemtuzumab ozogamicin	14.1% SD 1.9	0.0% SD 0.0

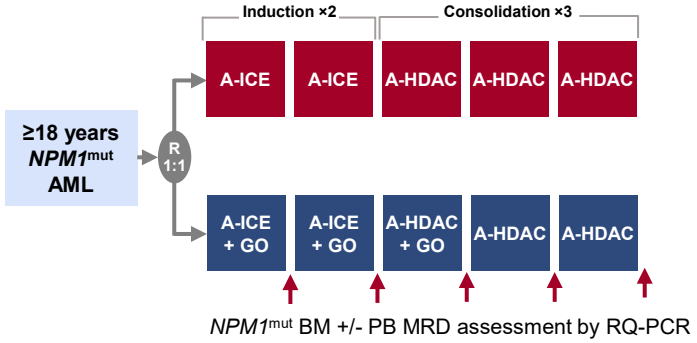
Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	22.4% SD 1.0	2.7% SD 0.9
No Gemtuzumab ozogamicin	26.2% SD 1.1	4.9% SD 1.3

Annual event rates	Years 1-5	Years 6+
Gemtuzumab ozogamicin	73.8% SD 4.6	2.4% SD 2.4
No Gemtuzumab ozogamicin	76.7% SD 4.8	21.1% SD 10.5

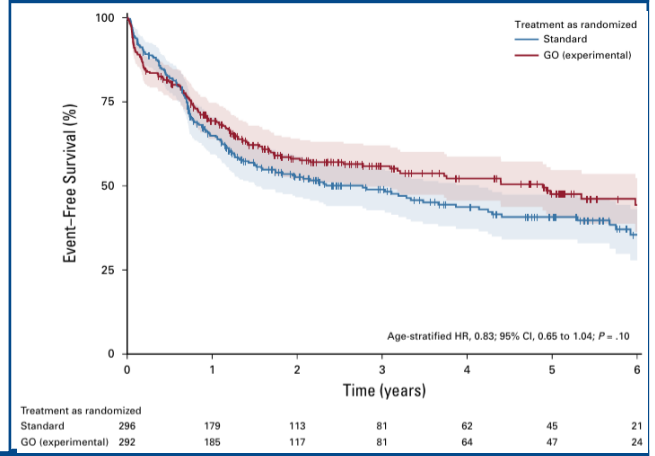
; Hills Lancet oncology 2014; 15(9):986-996; Godwin et al. Leukemia 2017

Gemtuzumab ozogamicin in *NPM1*-mutated AML: Results from prospective AMLSG 09-09 phase 3 study

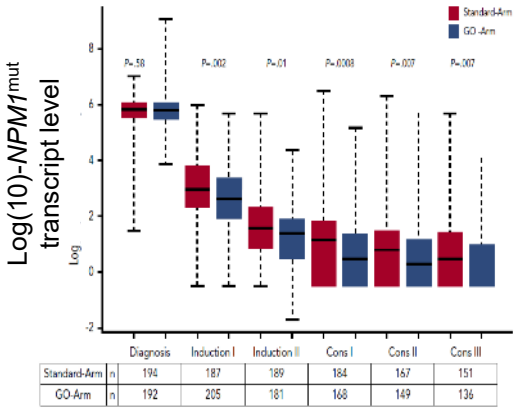
Study design



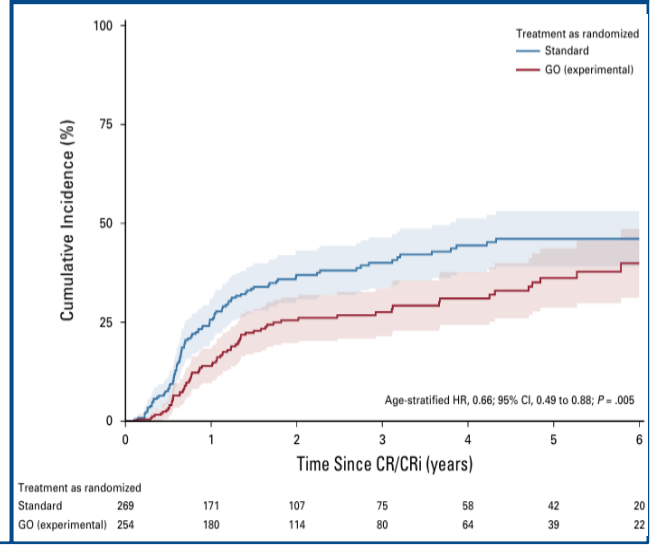
EFS



Kinetics of *NPM1*^{mut} transcript levels in BM

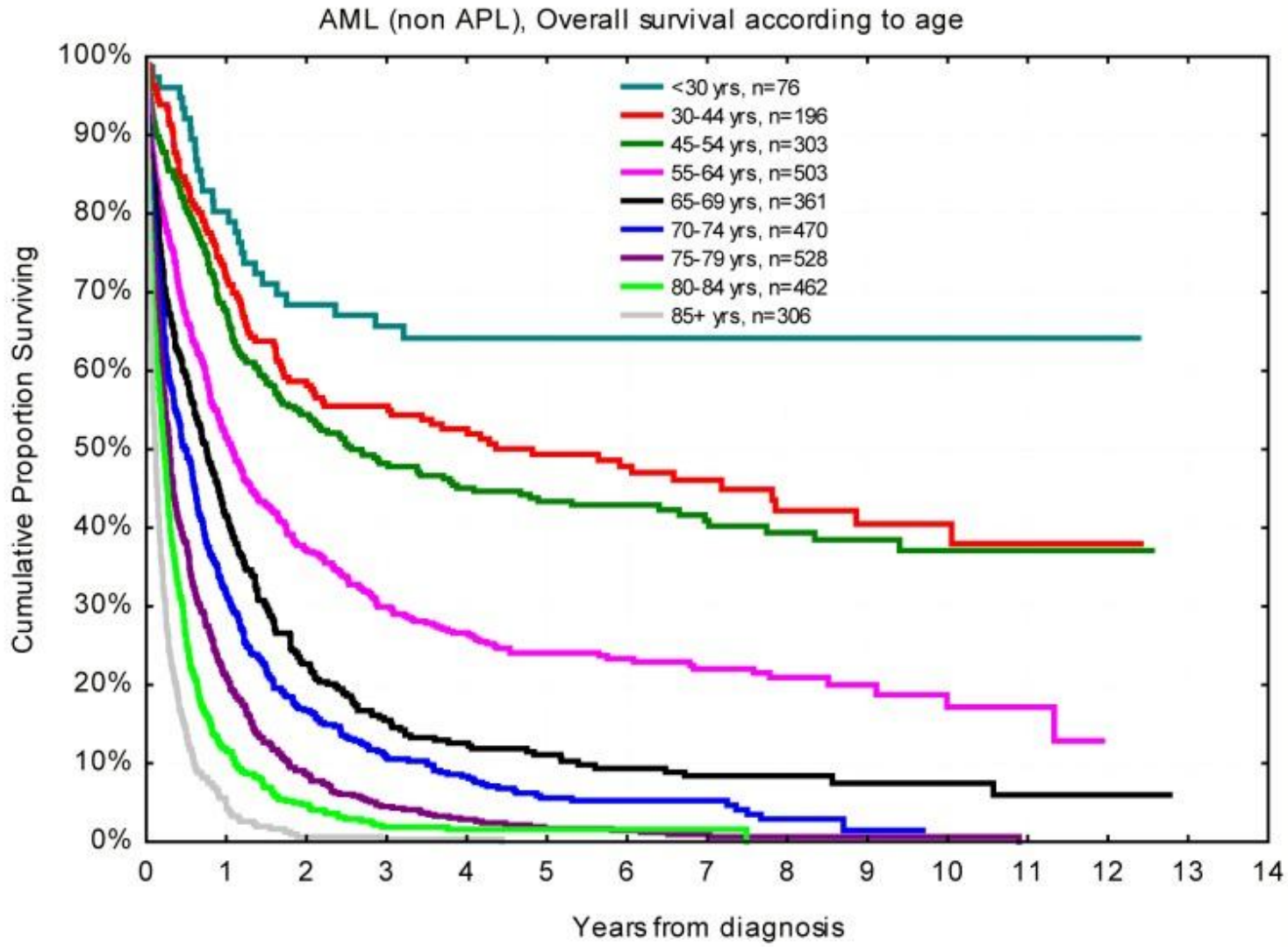


CIR

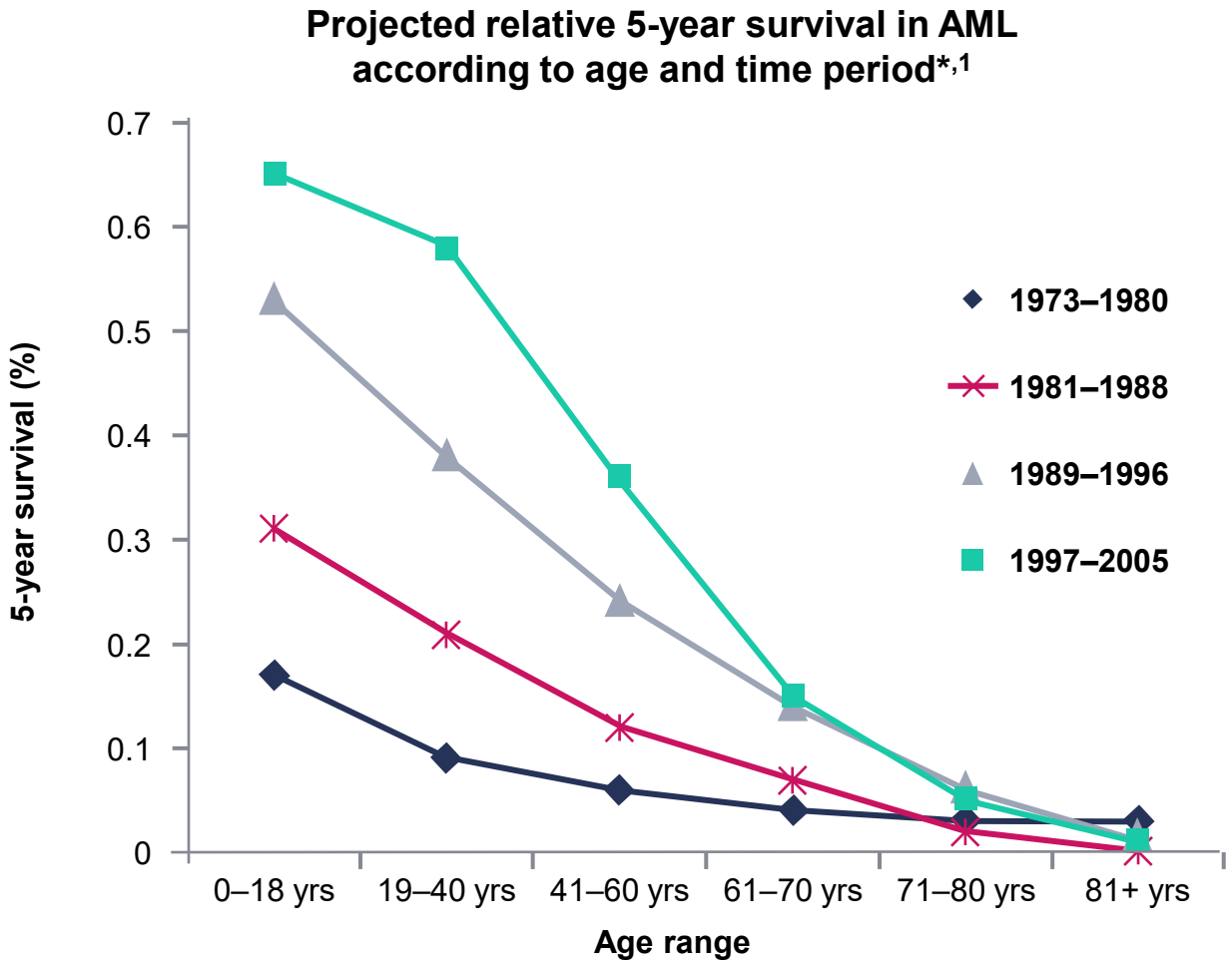


Schlenk RF, *et al. J Clin Oncol* 2020; **38:**623–632.; Kapp-Schwoerer S, *et al. Blood* 2020; **136:**3041–3050.

Age and outcome in AML



The challenge of treating AML



* Point estimates are from Derolf, *et al.*[2]

1. Juliusson G, *et al*. *Blood* 2012; **119:**3890–3899;
2. Derolf AR, *et al*. *Blood* 2009; **113:**3666–3672.

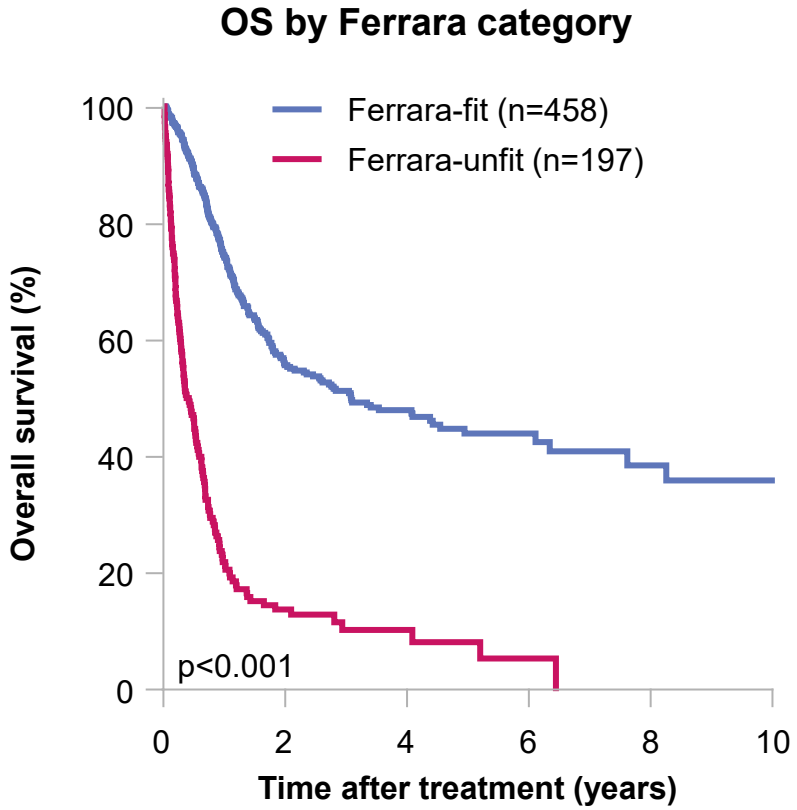
Treatment decision-making remains complex

Lack of consensus on the definition of eligibility for intensive chemotherapy

Ferrara criteria[1]

Consensus criteria of SIE-SIES-GITMO for defining fit/unfit for IC[1,3]

- Advanced age (>75 years)
- Severe organ comorbidities*
- Active infection resistant to anti-infective therapy
- Cognitive impairment
- Low performance score (ECOG PS ≥3)

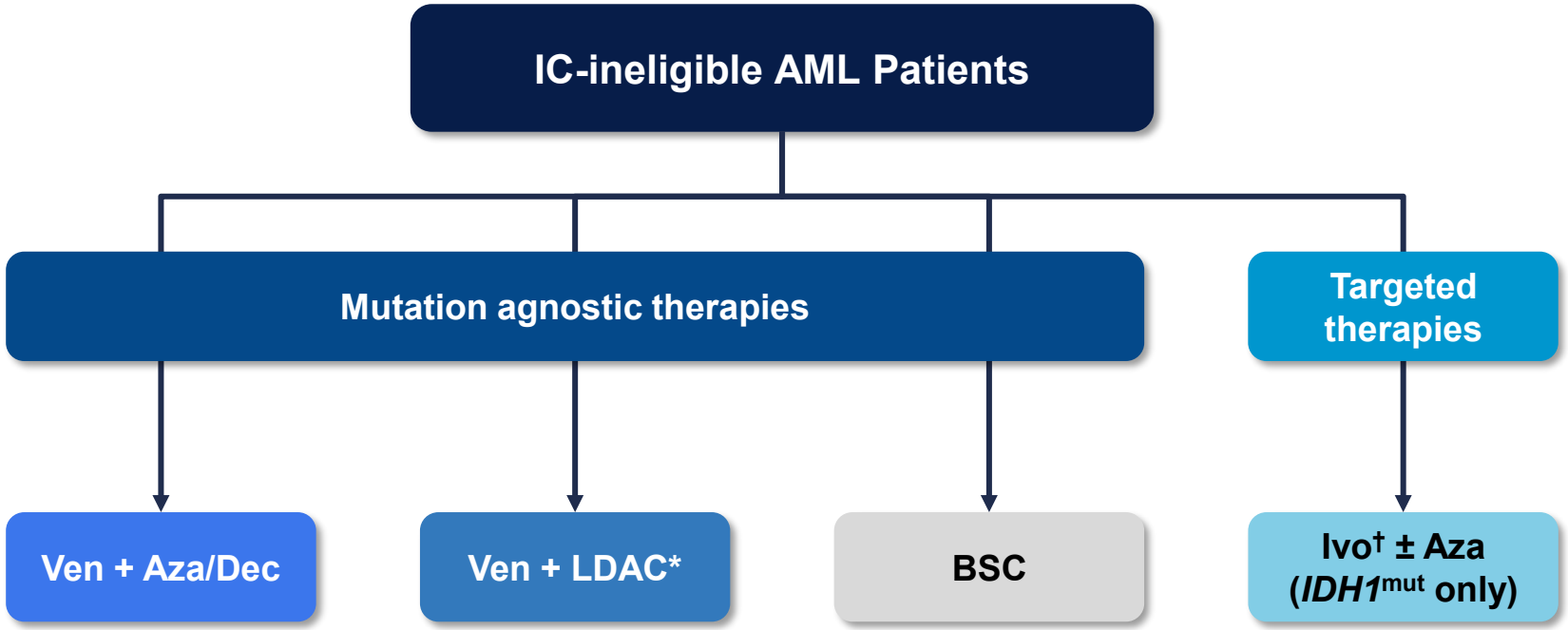


* And any other comorbidity that the physician judges to be incompatible with IC.
GITMO, Italian Group for Bone Marrow Transplantation;
IC, intensive chemotherapy; ND, newly diagnosed; SIE, Italian Society of Hematology;
SIES, Italian Society of Experimental Hematology; TRM, treatment-related mortality.

1. Ferrara F, *et al*. *Leukemia* 2013; **27:**997–999;
2. Walter RB, *et al. J Clin Oncol* 2011; **29:**4417–4423;
3. Chen EC & Garcia JS. *Hematology Am Soc Hematol Educ Program* 2020; **2020:**41–50.

Selected treatment options according to ELN:

IC-ineligible patients with AML



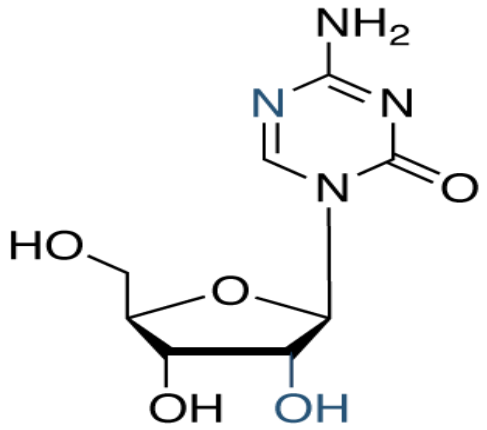
Mutations in *IDH1* occur in ~8-14% of patients with AML[2,3]

*LDAC + venetoclax is not approved by the EMA for use in patients with AML. †Ivosidenib monotherapy is currently not approved by the EMA.
AML, acute myeloid leukemia; Aza, azacitidine; BSC, best supportive care; Dec, decitabine; ELN, European LeukemiaNet;
IC, intensive chemotherapy; Ivo, ivosidenib; LDAC, low-dose cytarabine; Ven, venetoclax.

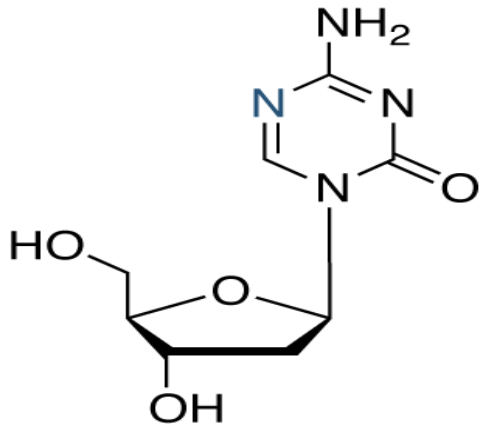
1. Döhner H et al. *Blood.* 2022;140(12):1345-1377. 2. Medeiros BC et al. *Leukemia.* 2017;31:272-281. 3. Issa GC et al. *Blood Cancer J.* 2021;11:107.

Hypomethylating Agents

Inhibitors of DNA methyl transferases:



5-azacytidine
(azacitibine)



5-aza-2'-deoxycytidine
(decitabine)

Both incorporate into DNA and cause hypomethylation (DEC > AZA)

AZA preferentially causes DNA damage and induces apoptosis

Monotherapy with AZA

Study design of the phase III randomised AZA-AML-001 trial

Phase III, randomised, multicentre, open-label, controlled study of
AZA vs conventional care regimen (CCR) in elderly patients with AML (NCT01074047)

N=488

Key eligibility criteria
- Aged ≥65 years, ineligible for allo-HSCT
- Newly diagnosed *de novo* or secondary AML (BM blasts >30%)
- ECOG PS 0–2, or poor-/intermediate-risk cytogenetics

Screening

Investigator pre-selection of CCR

Randomisation

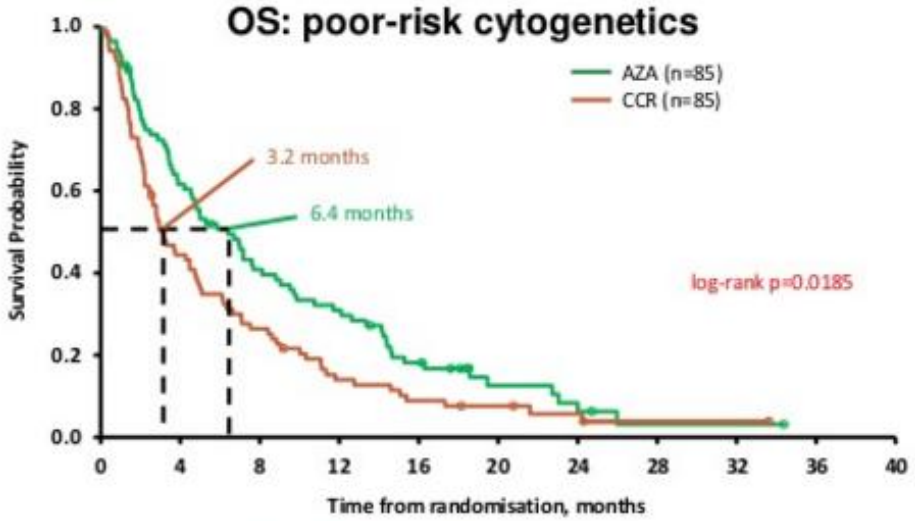
AZA (n=241)
75mg/m² SC x7 days every 28 days

CCR (n=247)
- IC (n=44): 7+3
- LDAC (n=158): 20mg SC BID for 10 days every 28 days
- BSC only (n=45)

- **Primary endpoint:** OS (including a pre-specified sensitivity analysis that censored patients at the start of subsequent AML therapy)
- **Secondary endpoints:** 1-year OS, response, safety

Subanalysis of AZA-AML-001 trial

Outcomes according to cytogenetic risk



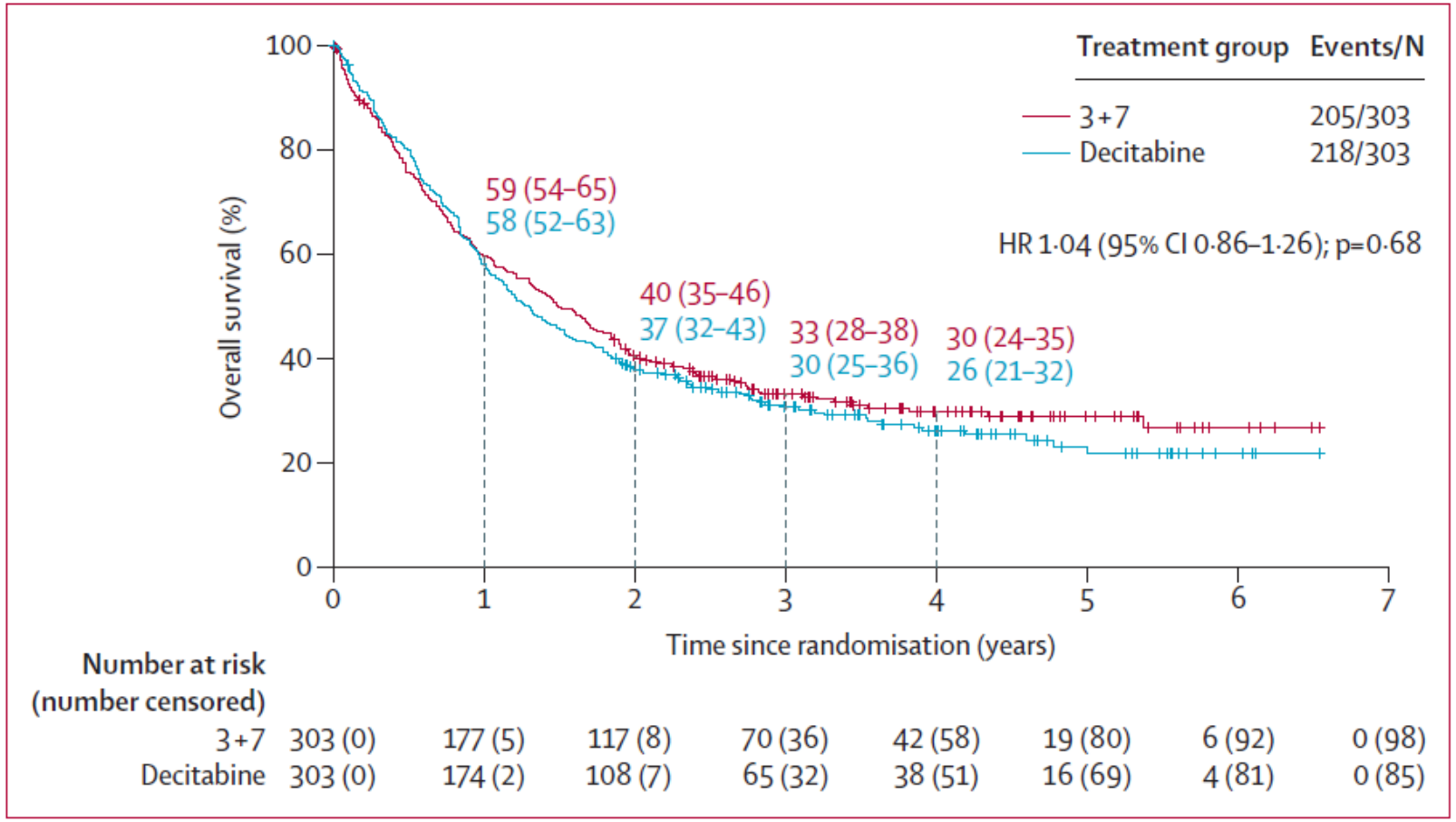
- 1-year OS: AZA: 30.9%; CCR: 14.0% (Δ16.9%; 95% CI: 4.4%, 29.5%)

Patients with poor-risk cytogenetics treated with AZA had significantly longer median OS than those treated with **CCR**

Dombret, Blood 2015

Decitabine *vs.* '7+3'

Open-label, randomized, controlled, phase 3 trial (EORTC, GIMEMA, German MDS Study Group)



HSCT

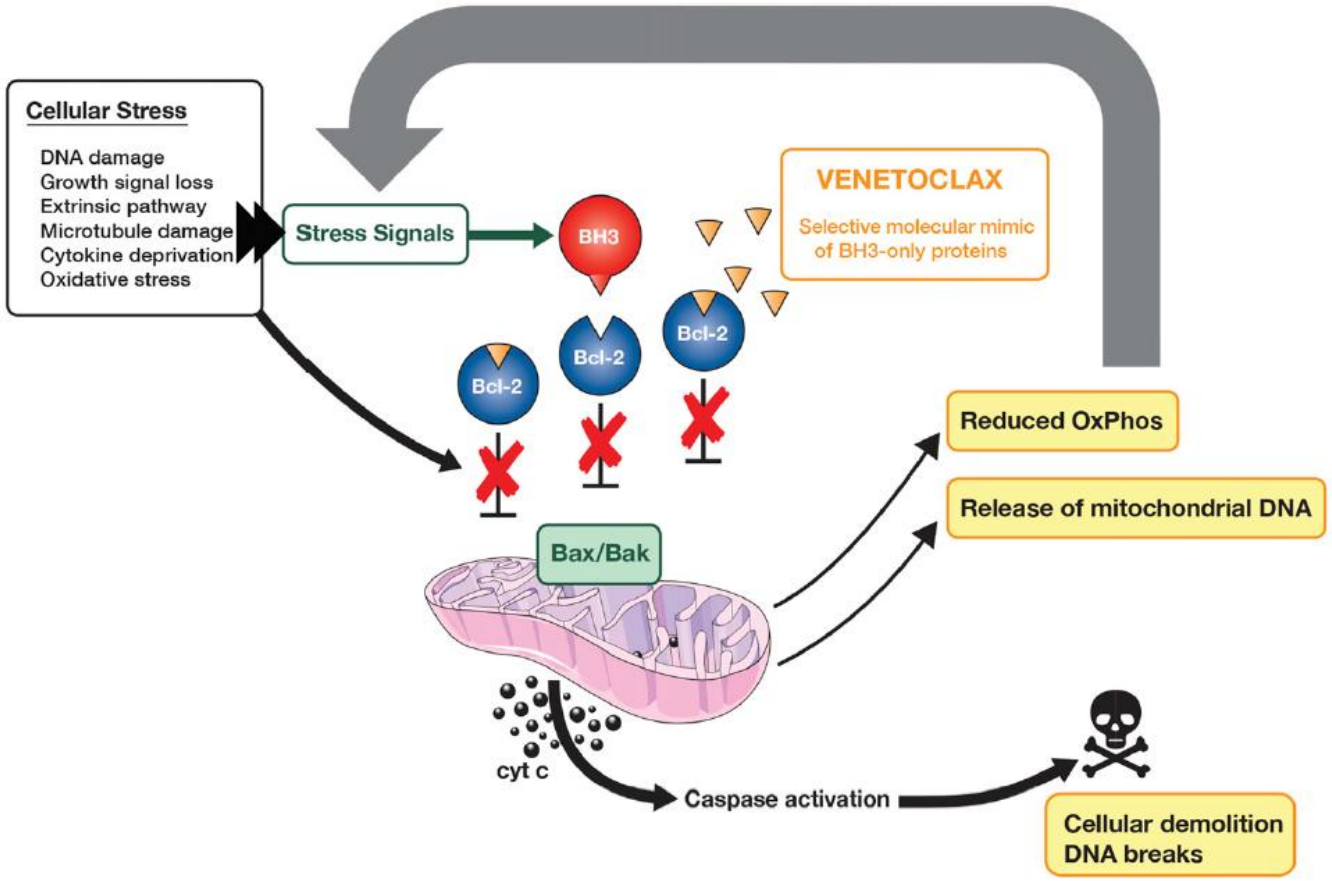
- Decitabine, 122 patients (40%)
- 7+3, 118 patients (39%)

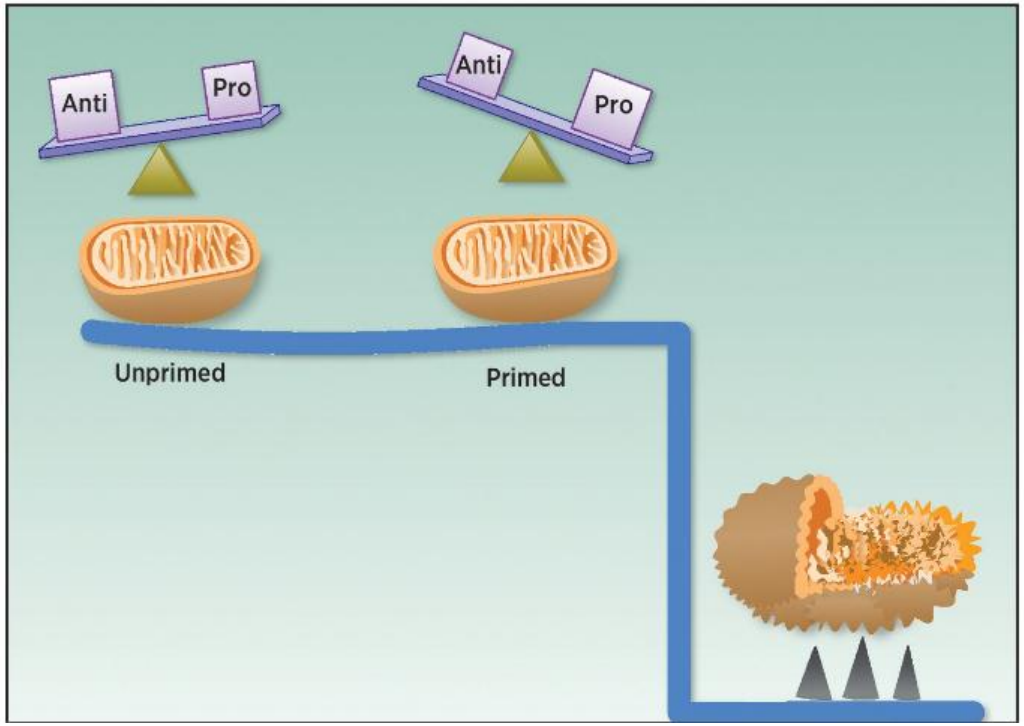
Median time to HSCT

- Decitabine, 4·2 mos. (IQR 3·0–5·3)
- 7+3, 3·5 mos. (2·9–5·0)

606 pts, >60 years, Newly-Diagnosed AML

Lübbert et al. Lancet Haematol 2023; 10: e879–89





Konepleva, Cancer Discovery 2016; Roberts AW. ASH Educational 2020; Letai, CCR 2015

VIALE A
AZA-PBO *vs.* AZA-VEN

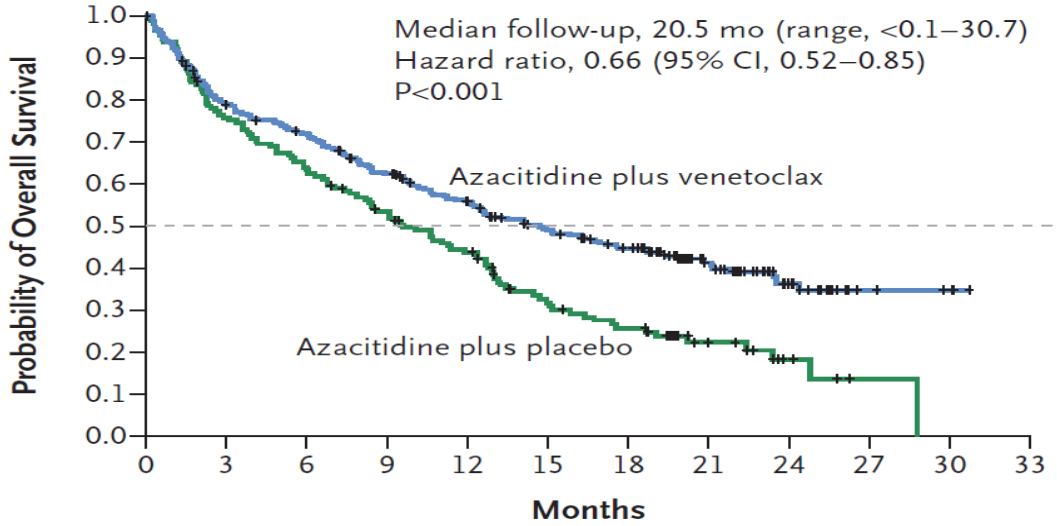
ARM A

Venetoclax: 400 mg PO, daily, days 1–28
+ Azacitidine 75 mg/m² SC/IV days 1–7

2:1 Randomization
N = 433*

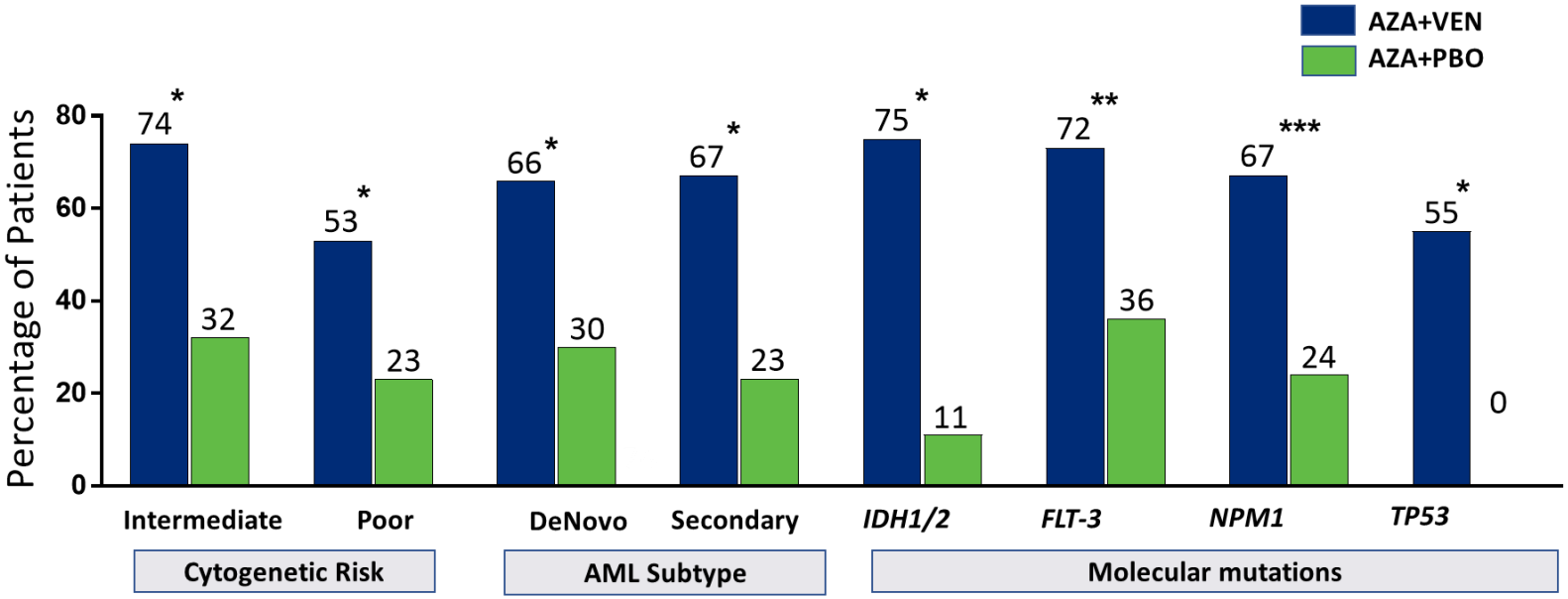
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC/IV days 1–7

ARM B



No. at Risk

Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

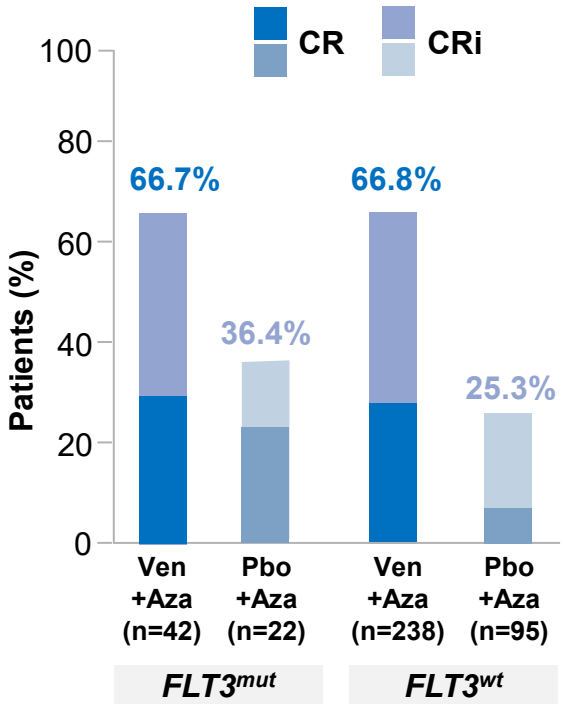


DiNardo et al, NEJM.2020

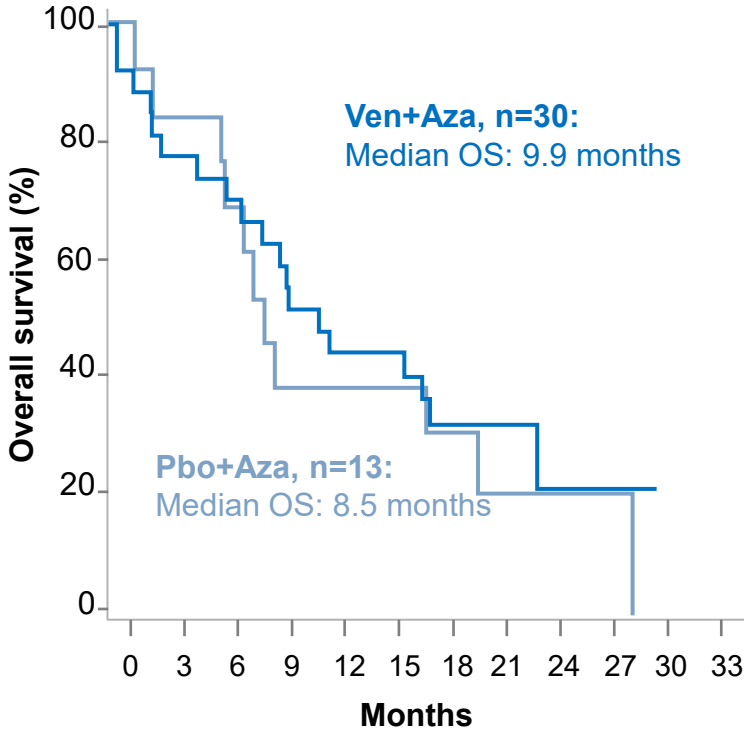
Impact of *FLT3* mutation on outcomes with doublet regimen Ven + Aza

Pooled analysis of patients with ND AML in VIALE-A and phase 1b study (N=498)

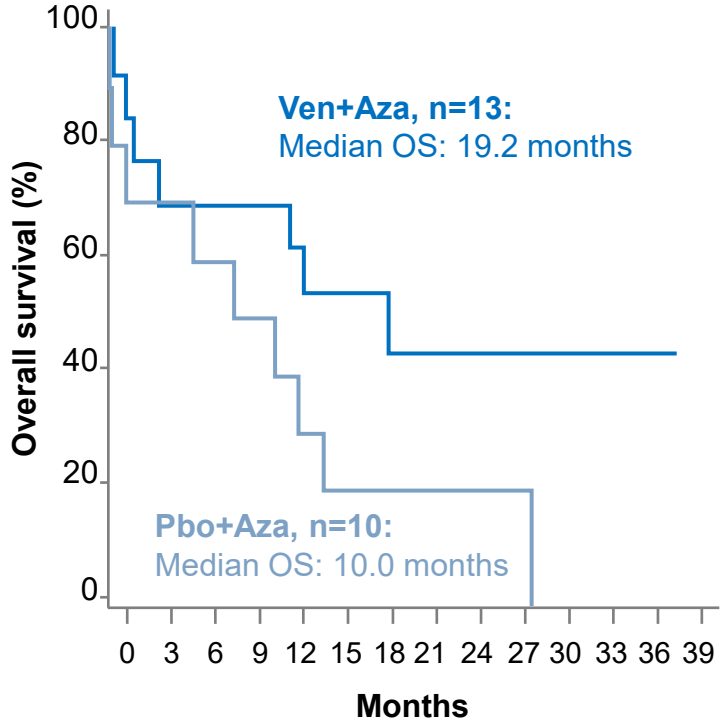
Remission rates: *FLT3*^{mut} vs *FLT3*^{wt}



OS in patients with *FLT3*-ITD



OS in patients with *FLT3*-TKD



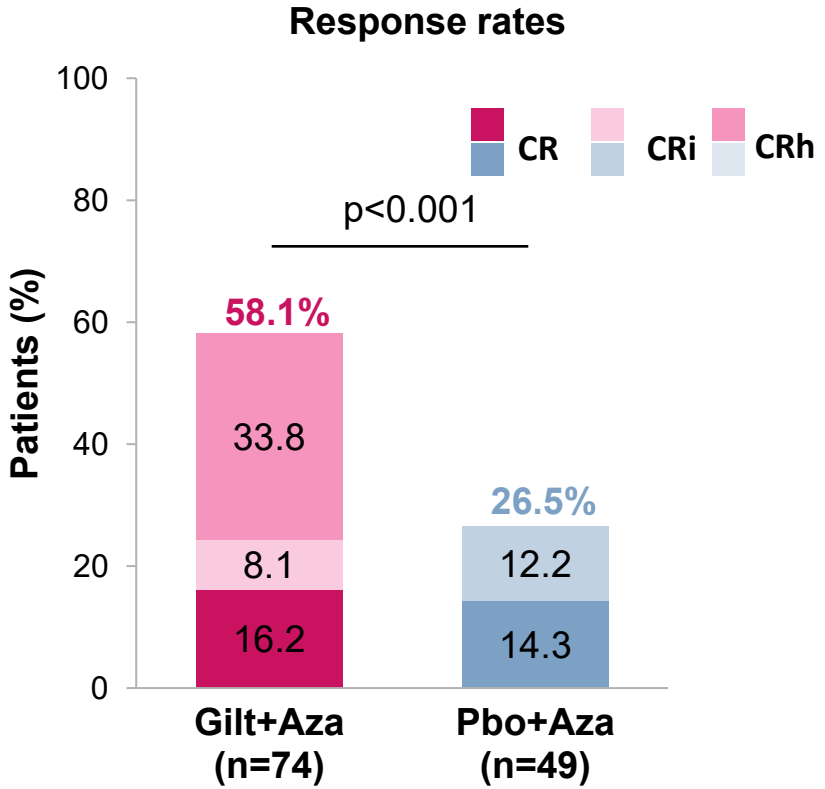
The safety and tolerability of the Ven+Aza in patients with *FLT3*^{mut} were similar to patients with *FLT3*^{wt} mutation status.

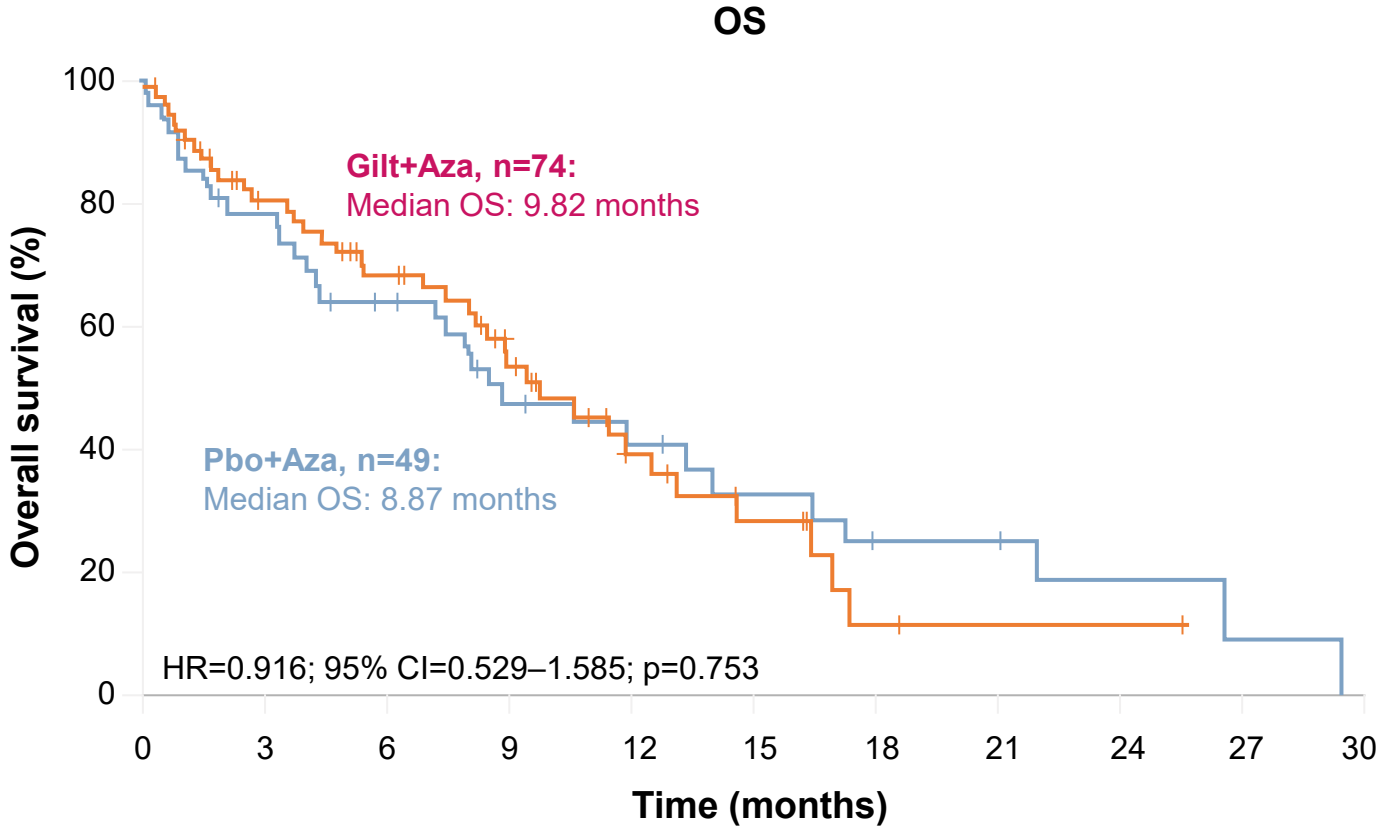
AZA, azacitidine; ITD, internal tandem duplication; mut, mutated; ND, newly diagnosed; Pbo, placebo; TKD, tyrosine kinase domain; Ven, venetoclax; wt, wild type.

Konopleva M, *et al*. *Clin Cancer Res* 2022; ePub ahead of print.

CR/CRi rates and OS with Gilt + Aza vs Aza in *FLT3*^{mut} AML

LACEWING: Randomized, phase 3 trial in patients ineligible for intensive chemotherapy





AEs rates (any grade and Gr≥3) were similar in both arms

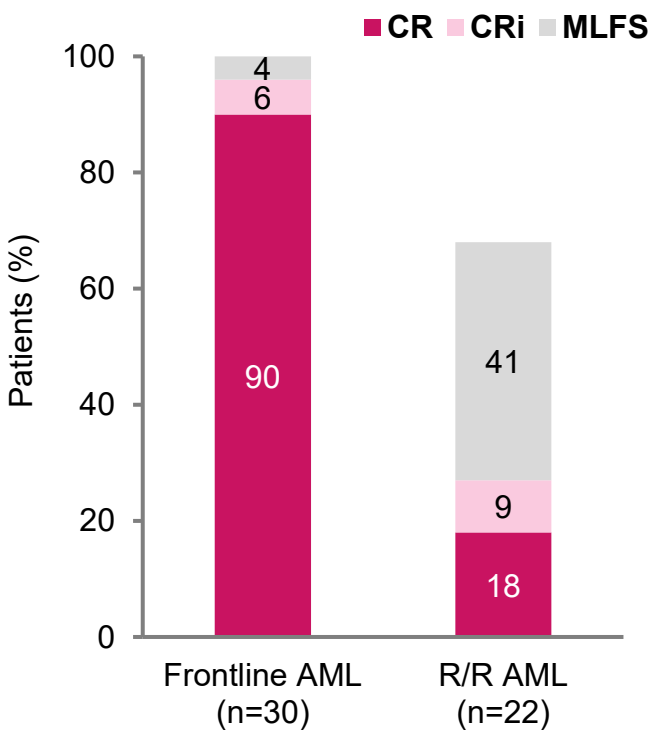
No new safety signals were reported

- Aza, azacitidine; Gilt, gilteritinib; mut, mutation.
- Wang ES, *et al.* Blood 2022

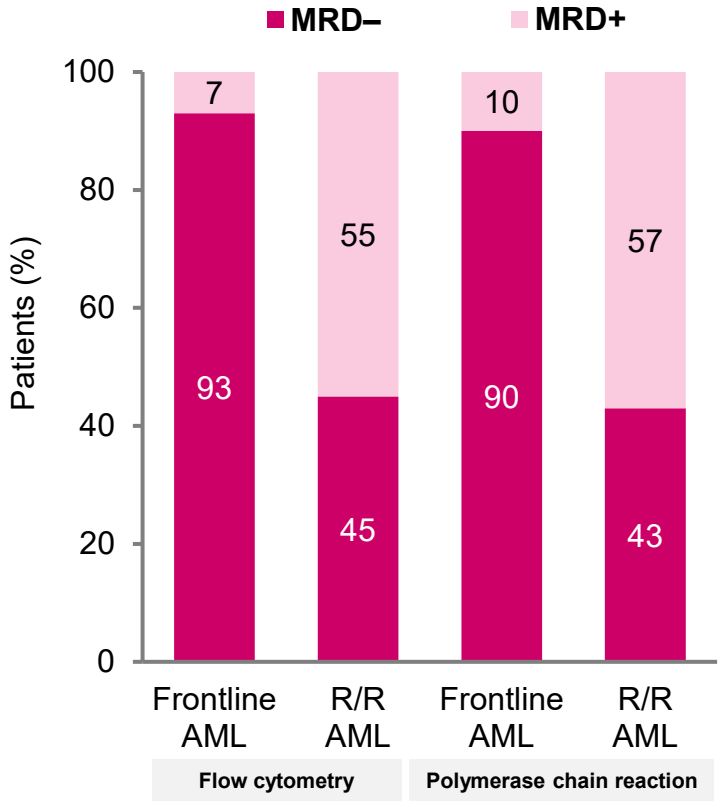
Ven+Aza+Gilt in IC-ineligible *FLT3*^{mut} AML

Phase 1/2 study in untreated IC-ineligible patients with *FLT3*^{mut} AML (N=52)

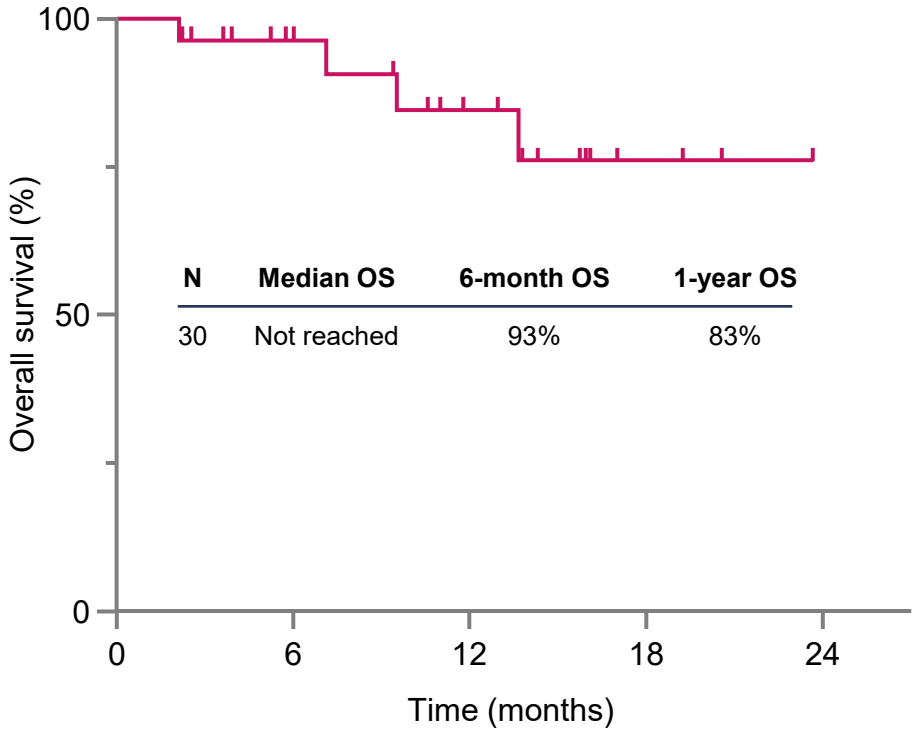
Response



Best minimal residual disease response

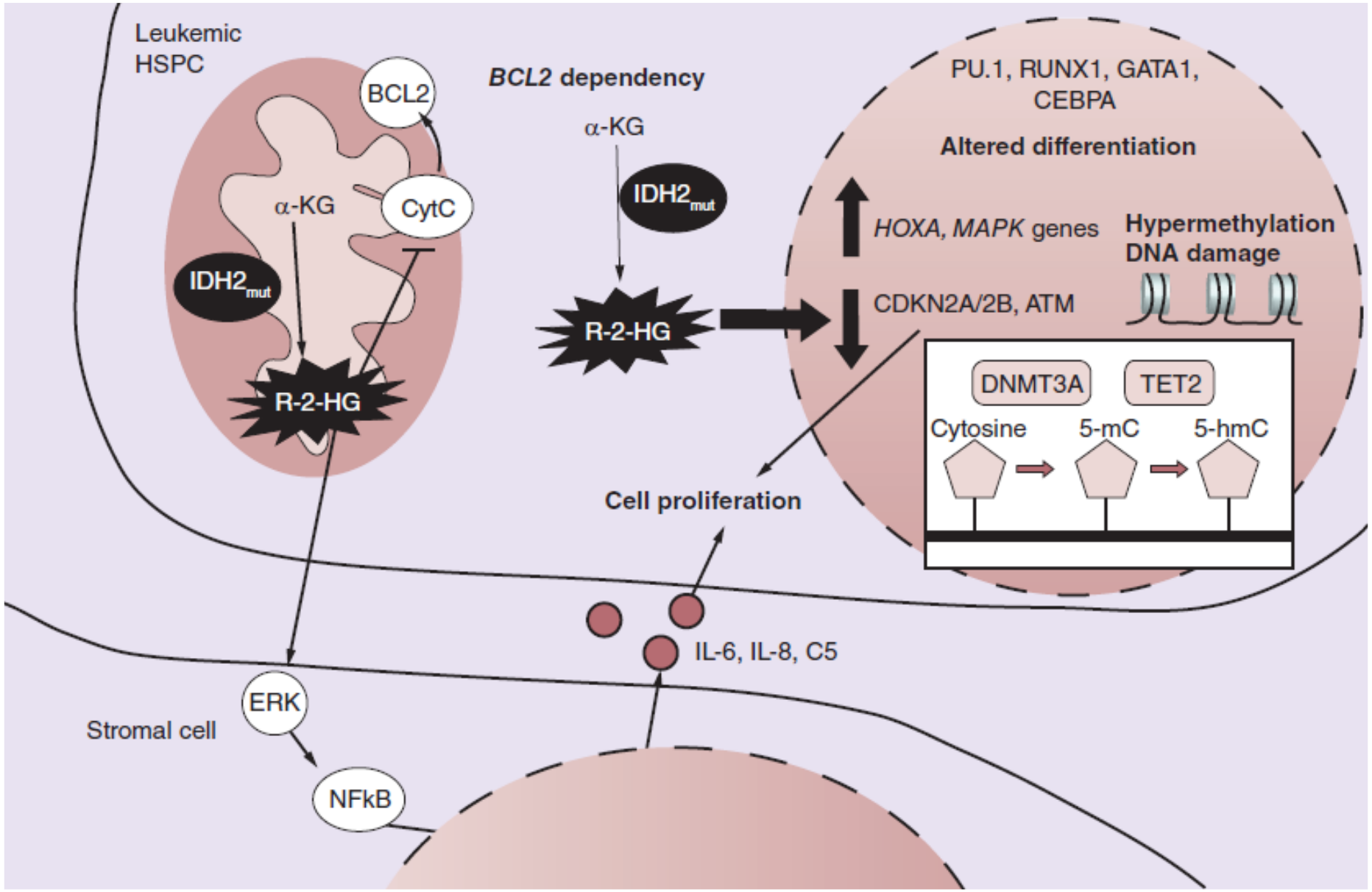


Overall survival (ND)



Most common Grade ≥3 hematologic adverse events (>10% of patients) were infections, febrile neutropenia, sepsis, GI bleeding, and hypotension. Myelosuppression was common but manageable with mitigation strategies

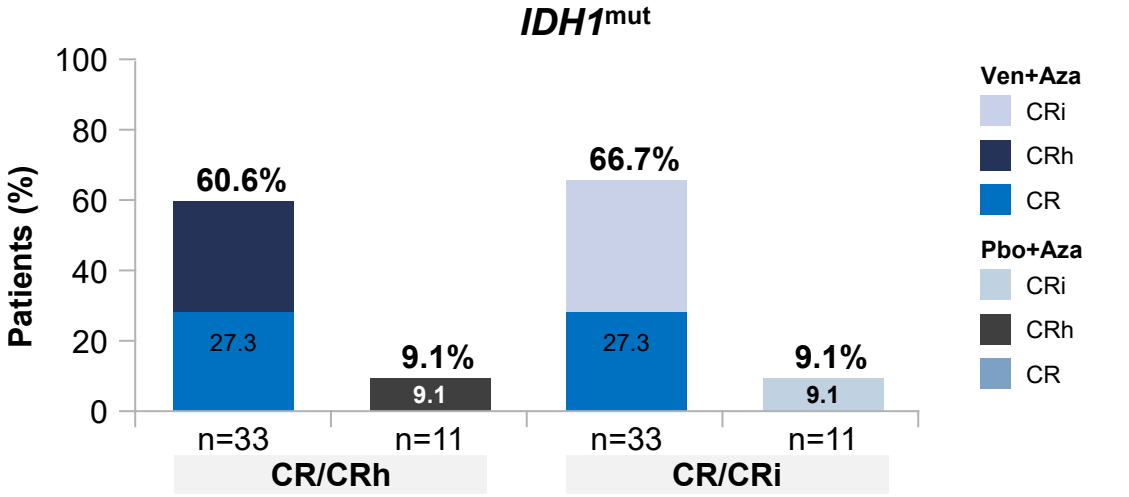
Adapted from Short N, *et al*. *JCO* 2024 May 1;42(13):1499-1508

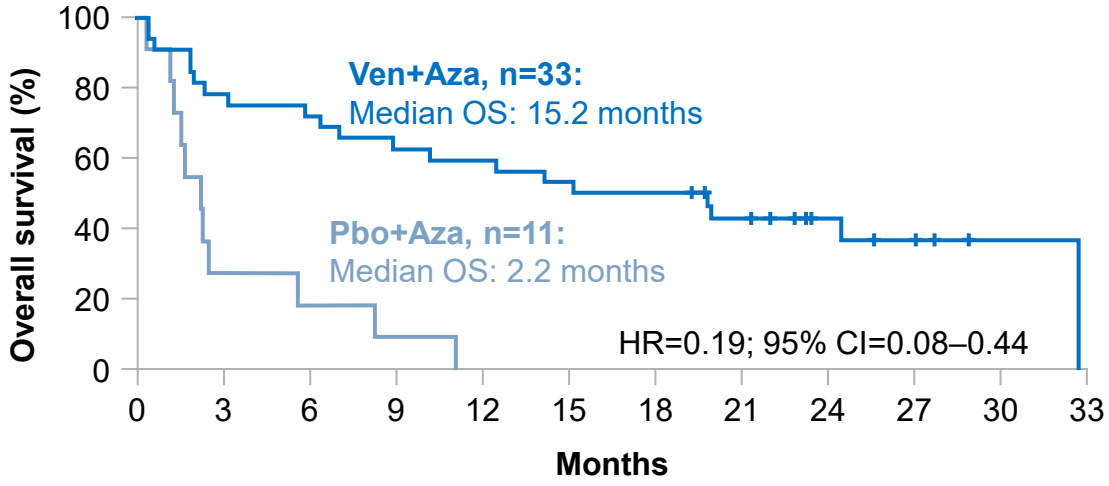


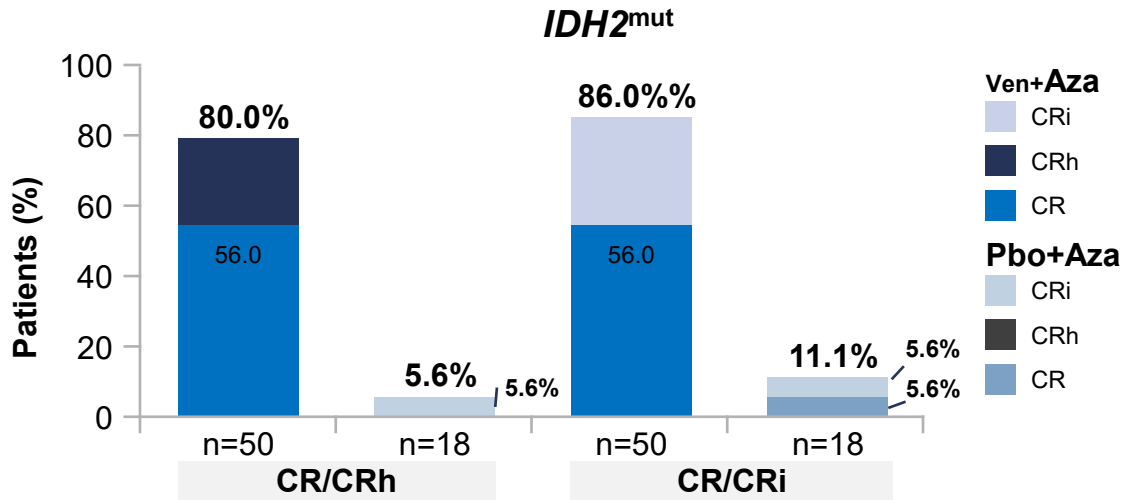
Montalban-Bravo, Fron Onco 2018

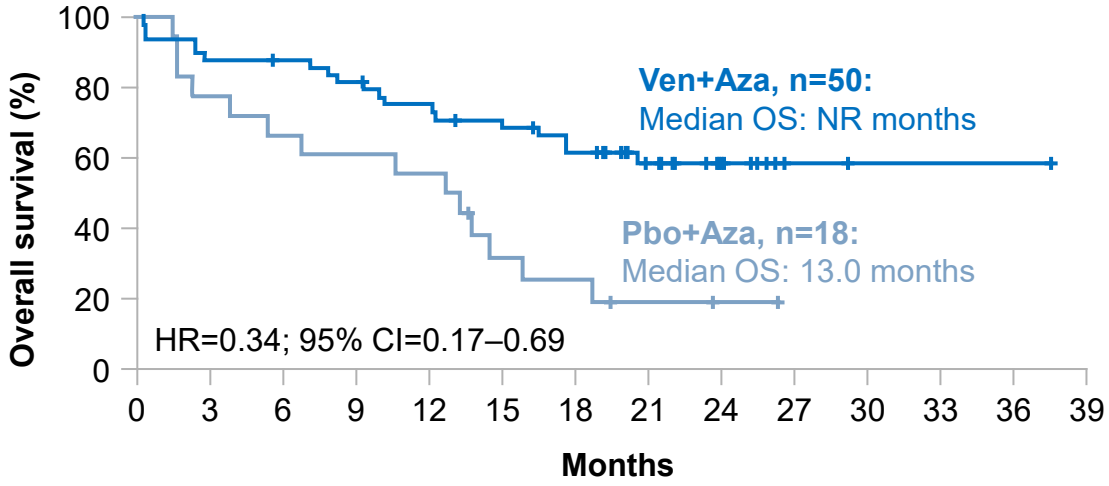
Response rates and OS of patients with doublet regimen Ven + Aza

Pooled analysis of ND AML with IDH1^{mut} or IDH2^{mut} in VIALE-A and phase 1b study (N=498)









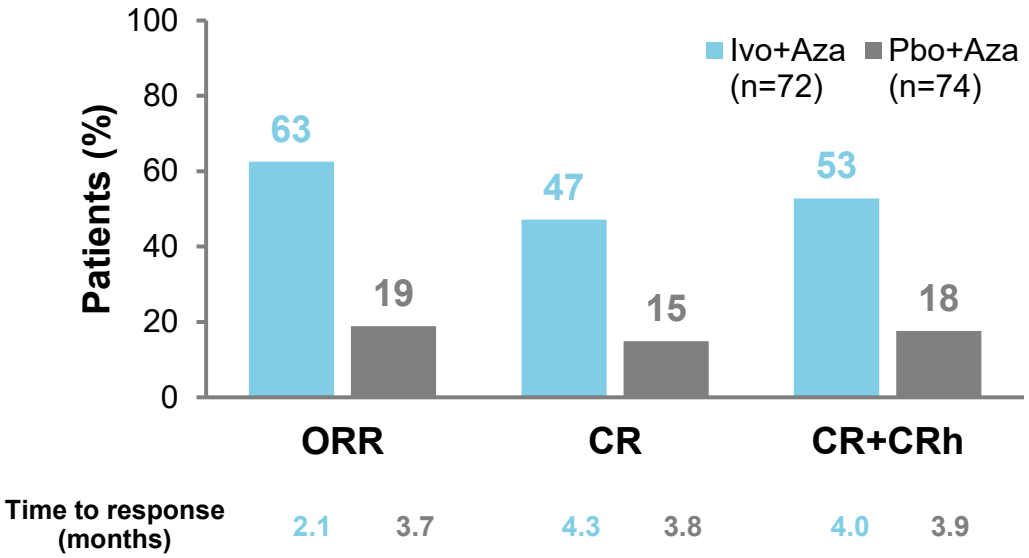
Aza, azacitidine; CRh, CR with partial hematologic recovery; ND, newly diagnosed; Pbo, placebo; Ven, venetoclax.

Pollyea DA, *et al. Clin Cancer Res* 2022; ePub ahead of print.

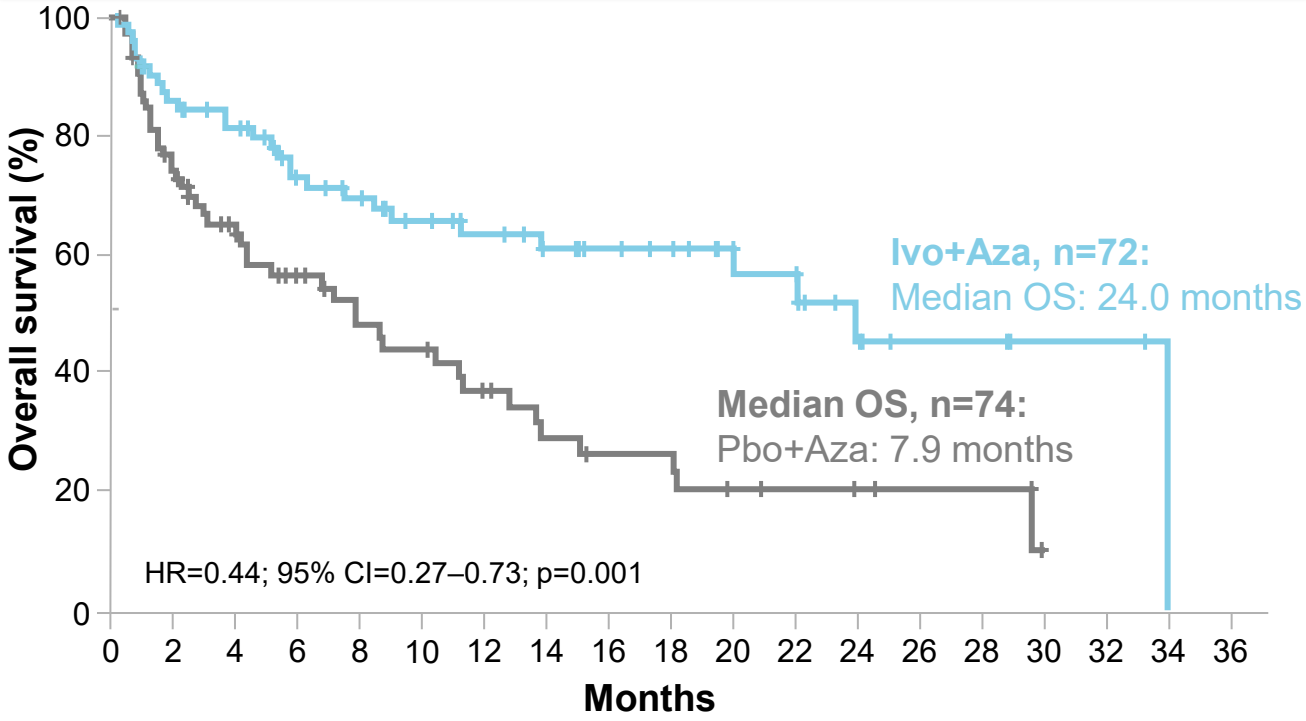
AGILE: Overall Survival and Safety Summary

Randomized Phase 3 trial evaluating ivosidenib + aza in newly diagnosed IDH1^{mut} AML

Response



AGILE (Ivo + Aza): OS (secondary endpoint)[1]



- **Most common Grade ≥3 hematologic AEs:** anemia, febrile neutropenia, neutropenia, and thrombocytopenia
- **Most common Grade ≥3 non-hematologic AE:** pneumonia

- Grade ≥3 differentiation syndrome and QT interval prolongation of ECG occurred in both arms
- Discontinuation due to AEs: Ivo+Aza 19 (27%) and Pbo+Aza 19 (26%)

Median follow-up: 15.1 months. AE, adverse event; AML, acute myeloid leukemia; Aza, azacitidine; CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; Ivo, ivosidenib; mut, mutated; OS, overall survival; Pbo, placebo.

1. Montesinos P, et al. *N Engl J Med.* 2022;386(16):1519–1531.

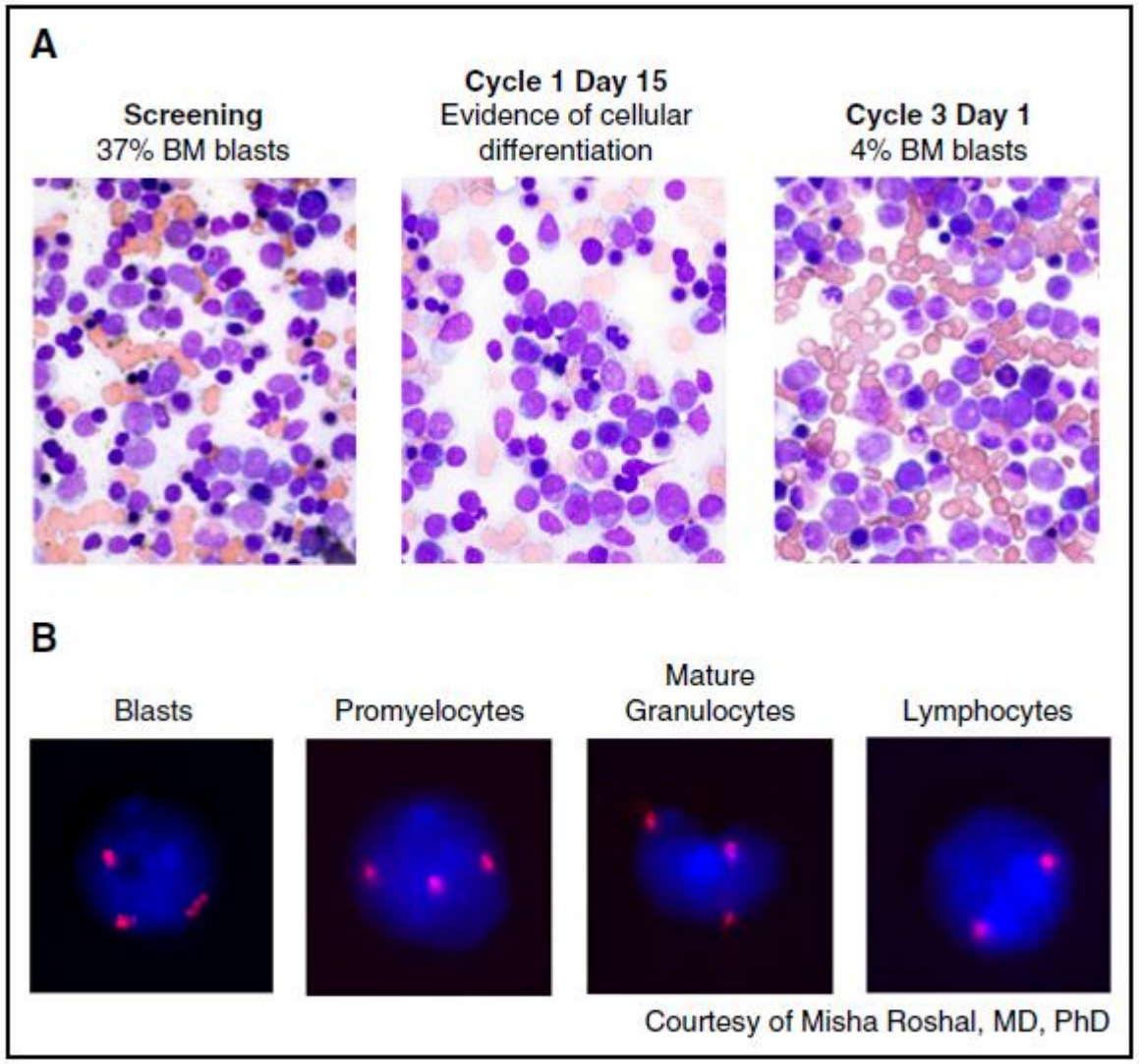


Figure. Differentiation Syndrome Review Committee Amended Protocol for Isocitrate Dehydrogenase Differentiation Syndrome (IDH-DS) Diagnosis and Management

Suspicion of IDH-DS
New onset or worsening of characteristic symptoms of unexplained etiology, including fever, rapid weight gain or edema, repiratory symptoms with or without infiltrates, pleural or pericardial effusions, hypotension, and acute renal failure[a]

→ Initiate treatment with dexamethasone, 10 mg twice daily, as indicated
- Empiric therapy for other possible causes (eg, anti-infective agents)
- Hydroxyurea for management of co-occurring leukocytosis
- Hyperuricemia agents for co-occurring tumor lysis syndrome

→ Hospitalization indicated in setting of rapidly progressing symptoms (especially respiratory symptoms), development of hypoxia, renal failure, rising WBC count, or DIC
- Stop/interrupt enasidenib treatment[b]

→ Improvement of IDH-DS signs/symptoms → Continue dexamethasone until significant improvement or resolution of signs/symptoms, then taper per institutional guidelines

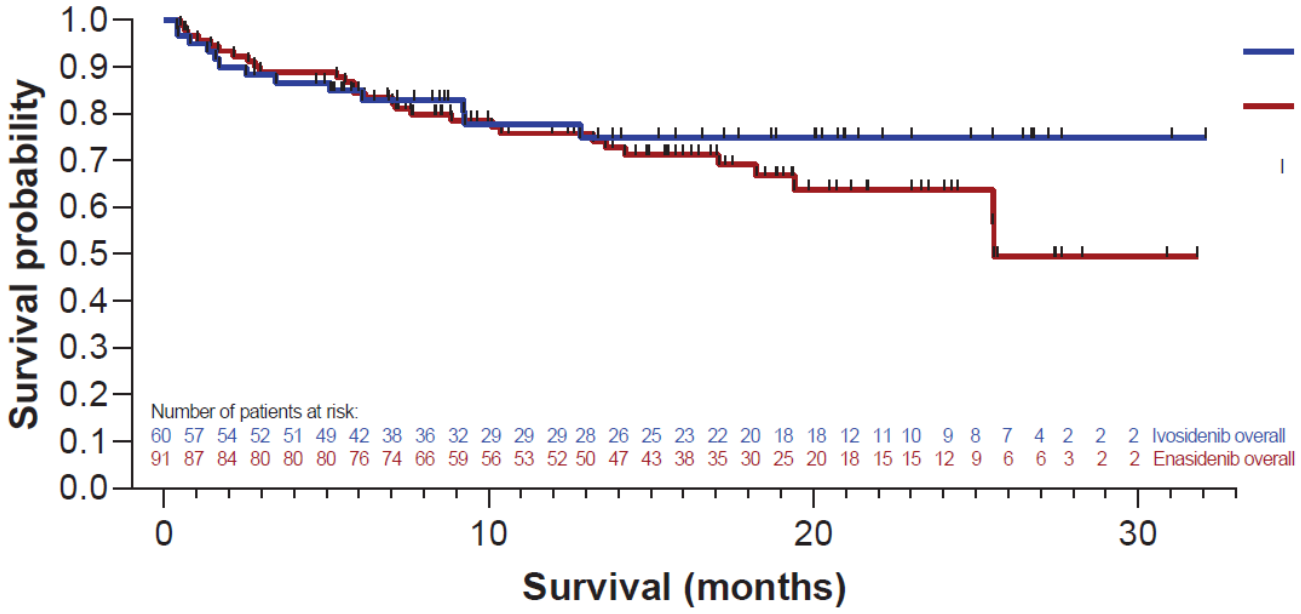
Stein, Blood 2017; Fathi, JAMA Onco 2018

Can we Optimize intensive induction outcome

Adding IVO/ENA to intensive induction

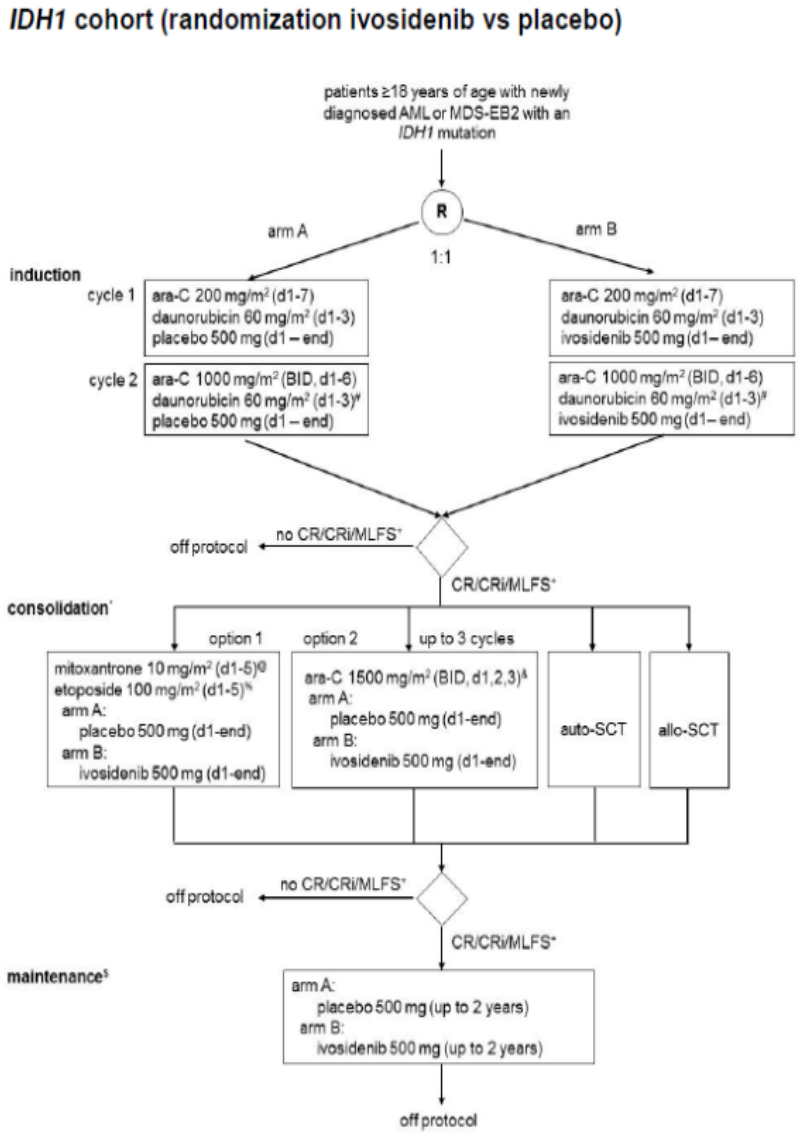
.

7+3+IVO or ENA (Phase 1)[1]



Response category	Ivosidenib 500 mg + chemotherapy, n (%)			Enasidenib 100 mg + chemotherapy, n (%)		
	All, N = 60	De novo AML, n = 42	Secondary AML, n = 18	All, N = 91*	De novo AML, n = 56	Secondary AML, n = 35
CR/CRi/CRp	46 (77)	37 (88)	9 (50)	67 (74)	45 (80)	22 (63)
CR	41 (68)	32 (76)	9 (50)	50 (55)	36 (64)	14 (40)

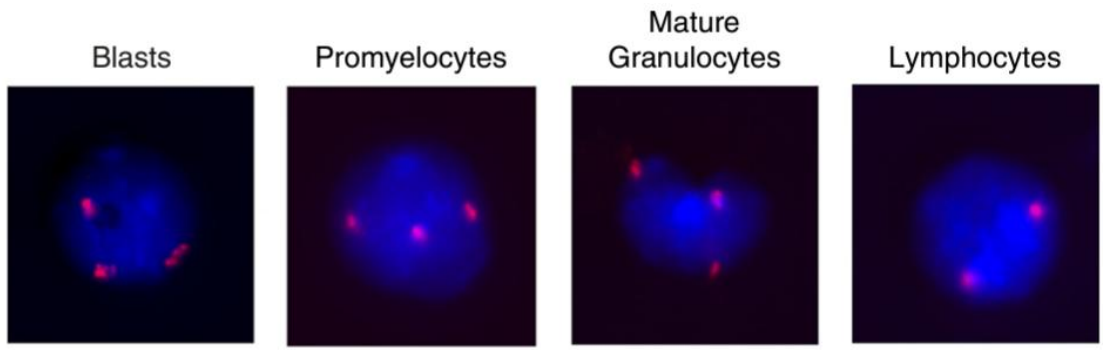
HOVON 150 (phase 3)[2]

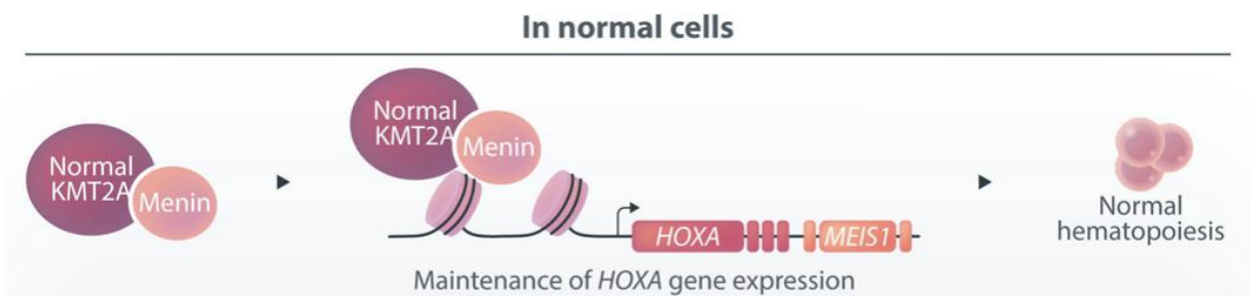


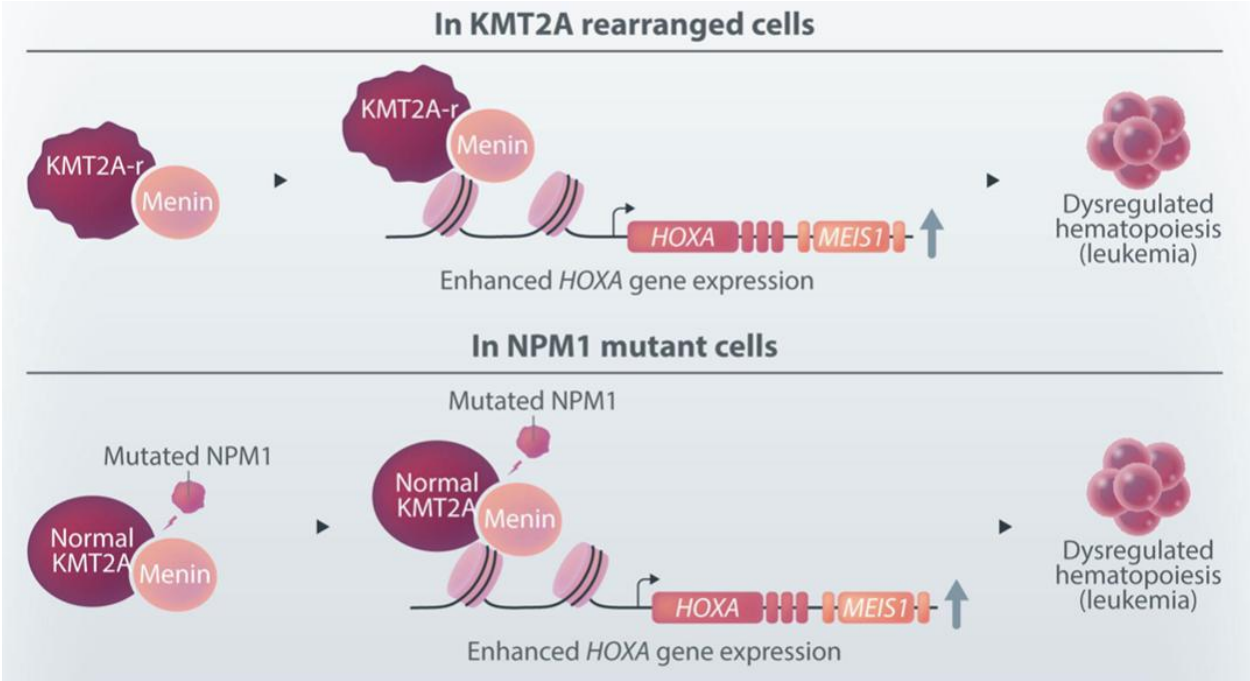
Stein et al. Blood. 2021;137(13):1792-1803; 2.. https://hovon.nl/nl/trials/ho150 accessed 08/11/2025

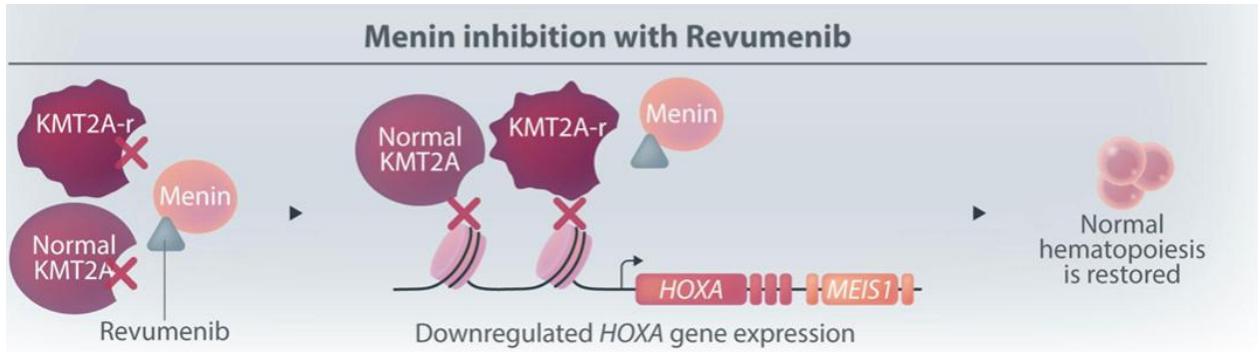
Menin inhibitors –
An emerging therapeutic class

Differentiating Agent
ATRA/ATO
IDH Inhibitors
FLT3 Inhibitors
Menin Inhibitors
Other differentiating agents



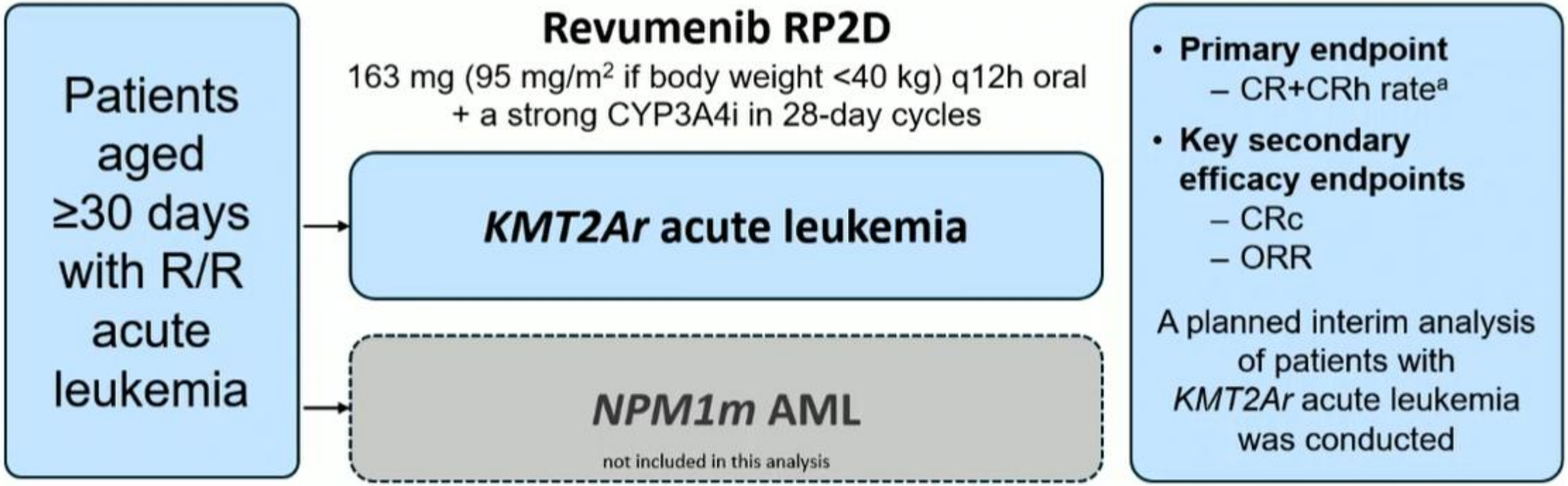






Adapted from Issa et al. Blood 2024; Stein et al. Blood, 2017; 130 (6): 722-731; Salman & Stein. Haematologica 2024

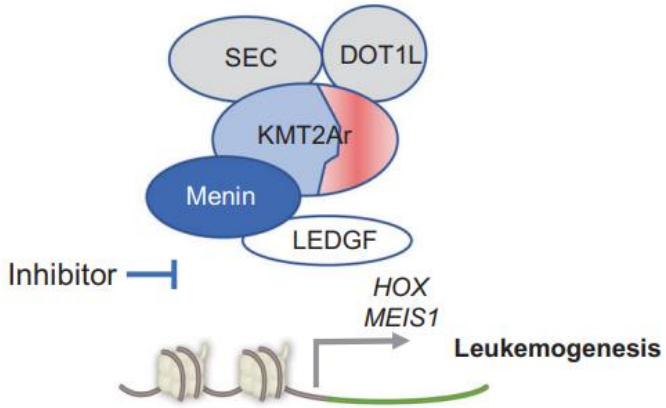
AUGMENT-101
Phase 2 study

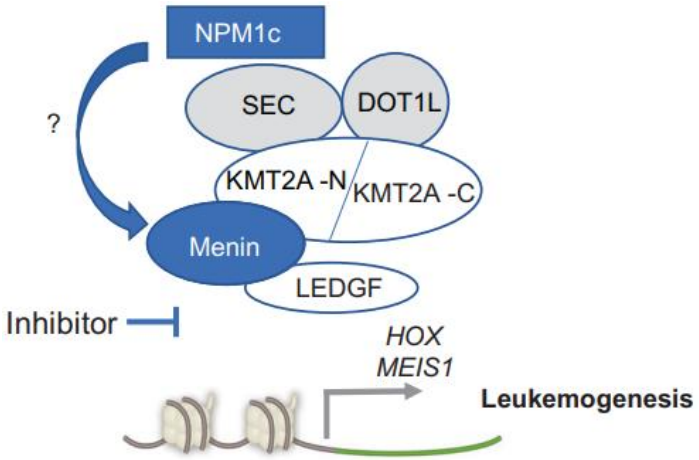


[a]CR+CRh rate >10% in adult evaluable population considered lower efficacy bound.

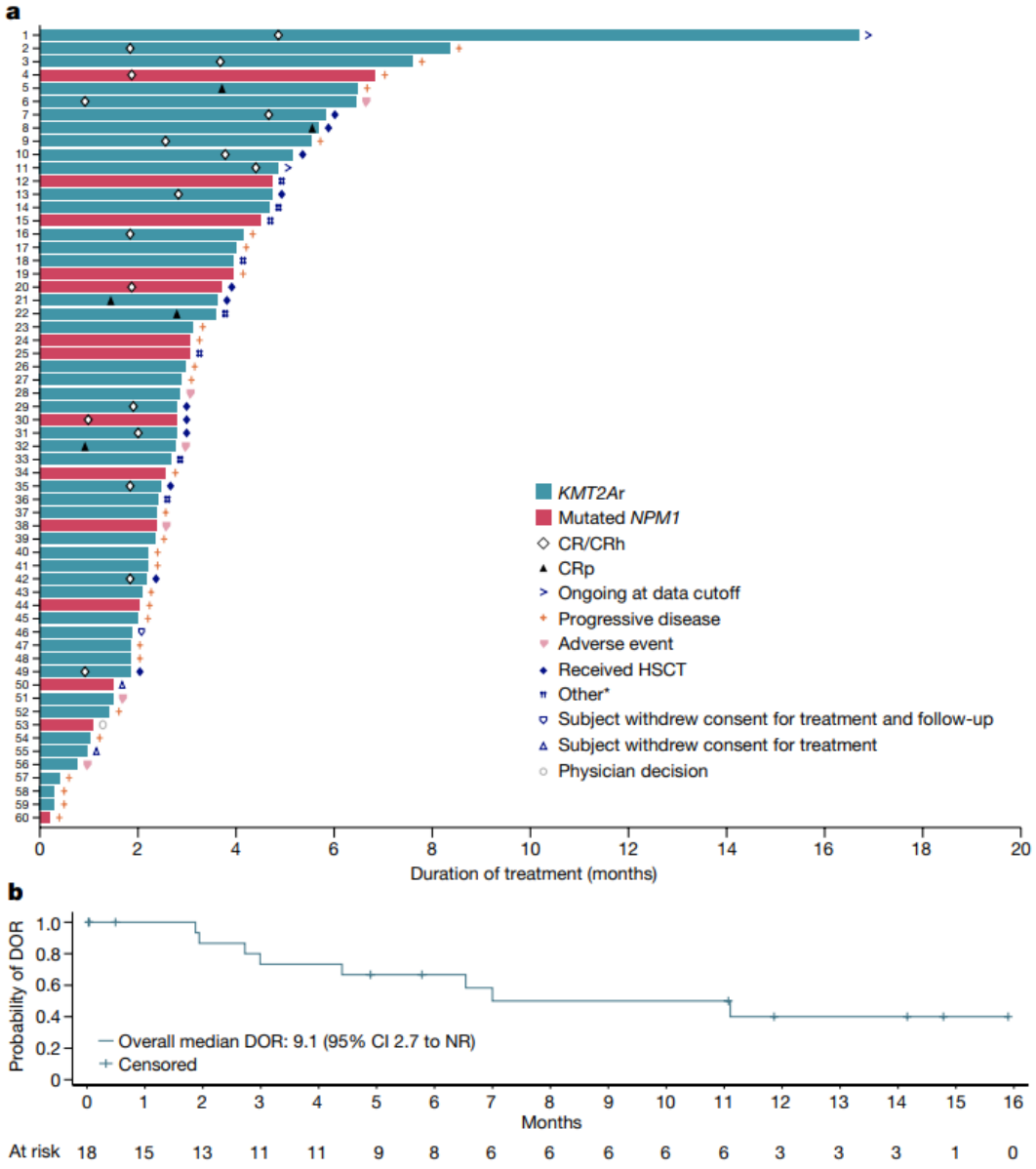
Issa et al. EHA 2024; S131

AUGMENT-101
Phase 2 study



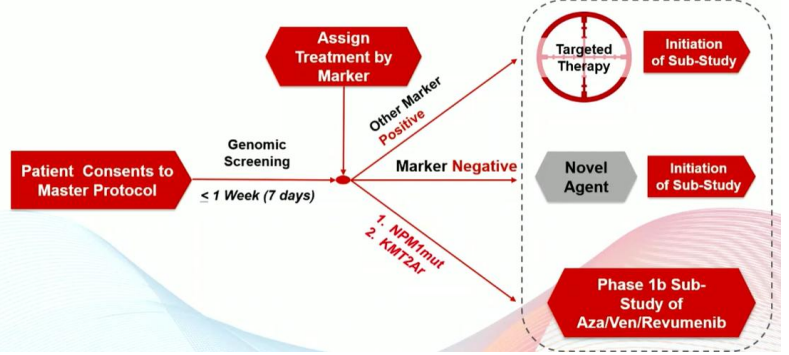


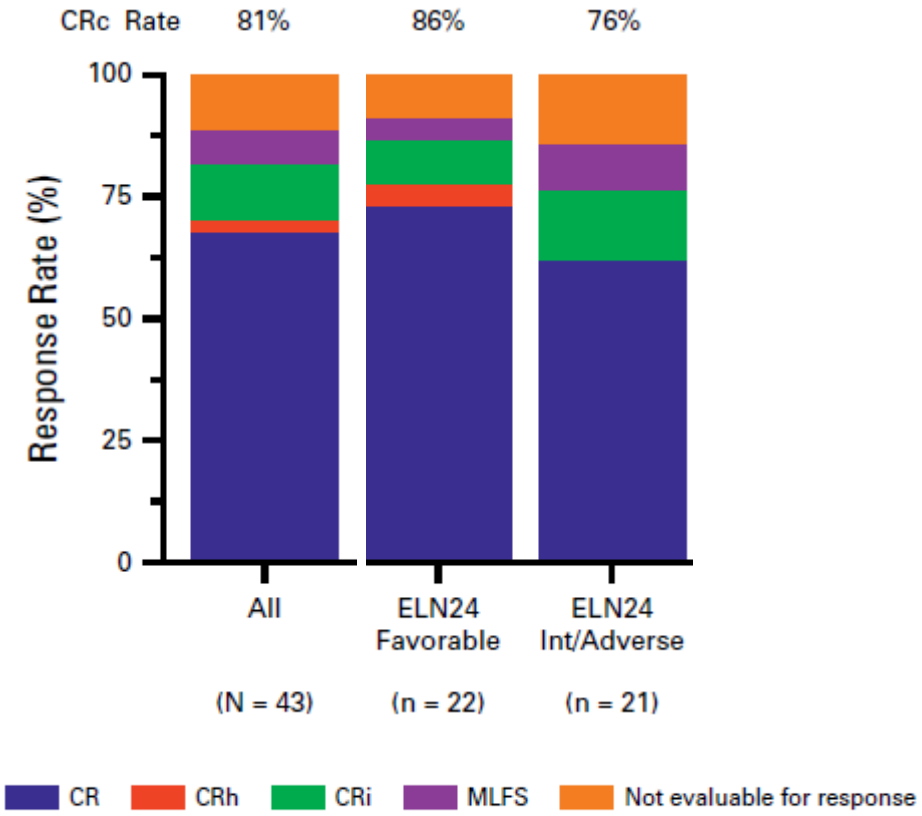
Revumenib (SNDX-5613)

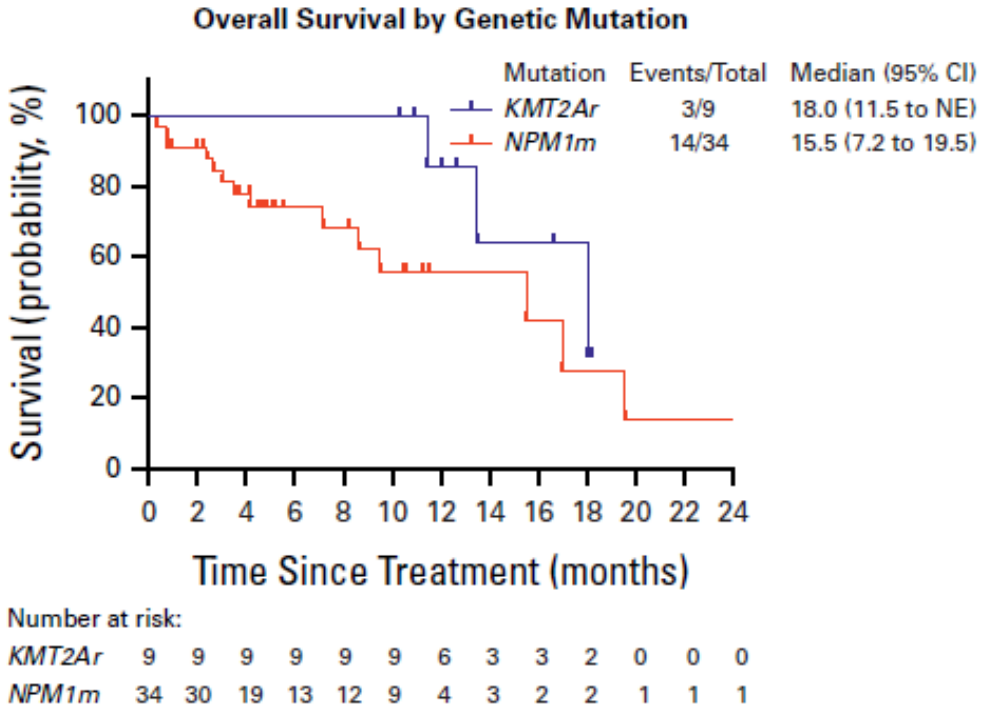


Issa et al. Leukemia (2021) 35:2482–2495; Issa et al. Nature Medicine (2023)

Menin inhibitor triplets,
AZA-Ven+revumenib (BEAT AML sub-study)







DS in 19% (8 pt), 2> G3

QTc prolongation in 44% (19 pt), 5> G3

Zeidner et al. JCO 2025;2606-2615:(23)43;

Ven+Aza±Magro in IC-ineligible *pts.*

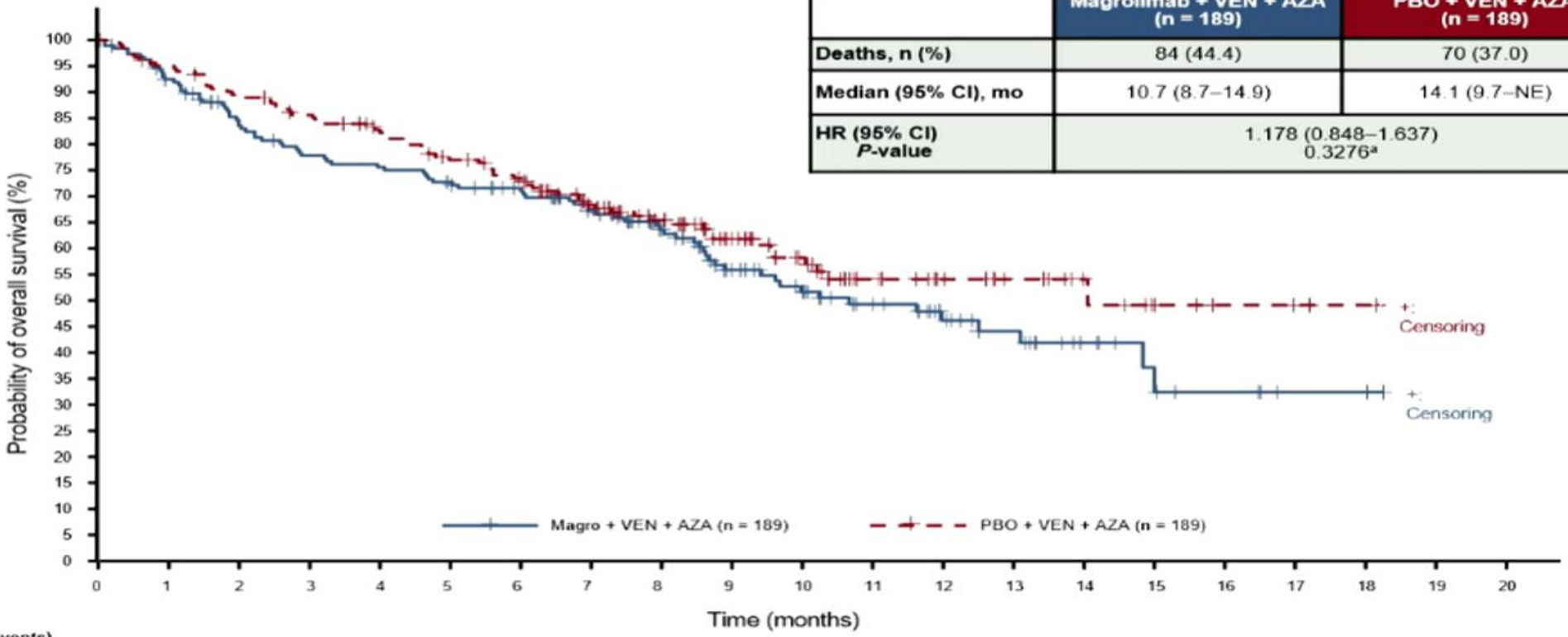
Key eligibility criteria
- Untreated AML
- Ineligible for IC[a]
- ECOG PS 0–2 (≥ 75 years) or 0–3 (< 75 years)

R 1:1

- Magrolimab + venetoclax + azacitidine[b]
- Placebo + venetoclax + azacitidine[c]

Overall Survival at Final Analysis: ENHANCE-3

	Magrolimab + VEN + AZA (n = 189)	PBO + VEN + AZA (n = 189)
Deaths, n (%)	84 (44.4)	70 (37.0)
Median (95% CI), mo	10.7 (8.7–14.9)	14.1 (9.7–NE)
HR (95% CI) *P*-value	1.178 (0.848–1.637) 0.3276[a]	



N at risk (events)

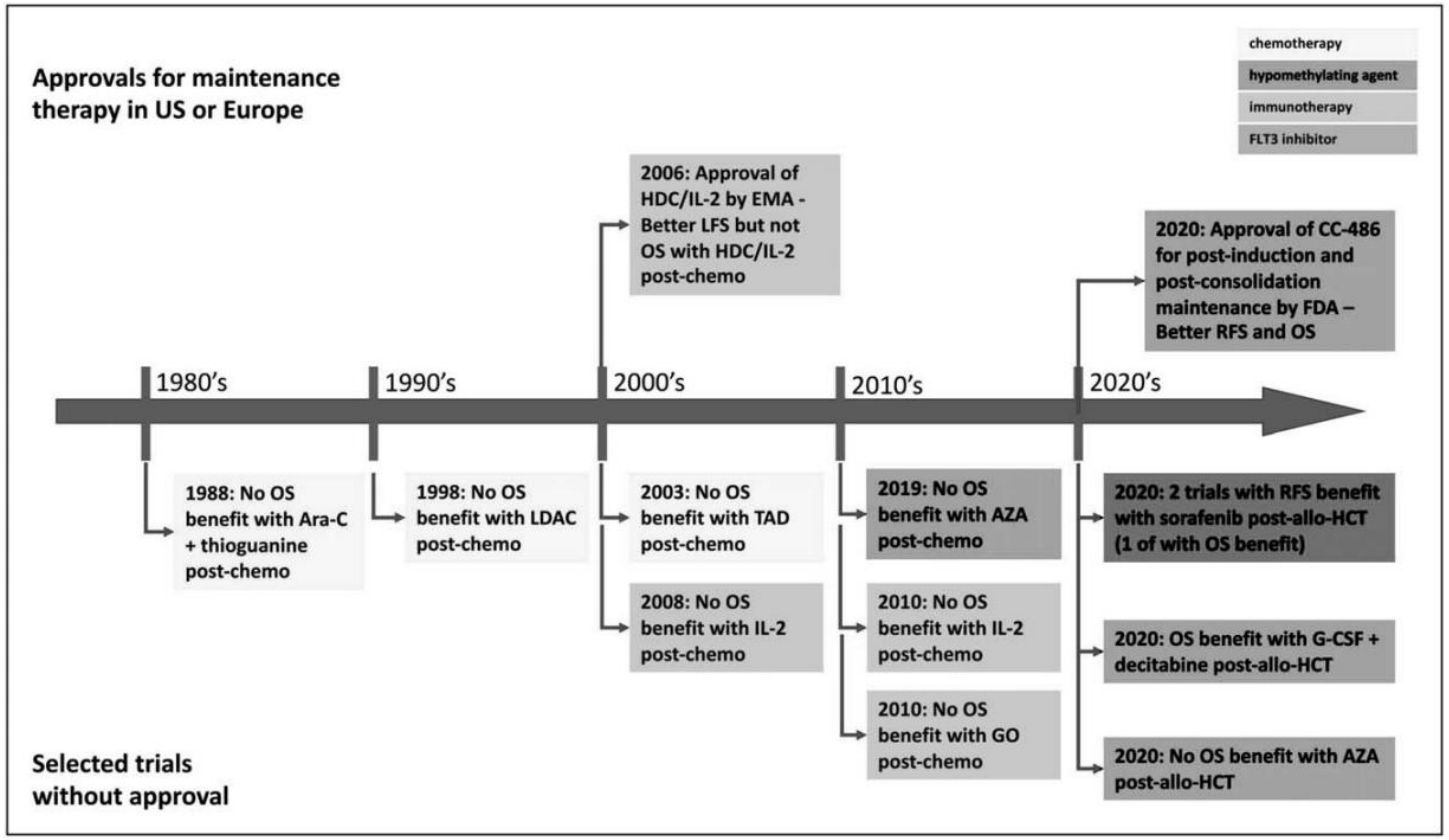
Magro + VEN + AZA	189 (0)	173 (13)	152 (27)	138 (40)	135 (43)	129 (49)	120 (51)	107 (56)	84 (61)	61 (72)	50 (75)	38 (78)	30 (79)	20 (81)	13 (82)	8 (83)	5 (84)	2 (84)	2 (84)	0 (84)
PBO + VEN + AZA	189 (0)	174 (9)	163 (19)	154 (26)	146 (30)	134 (40)	125 (47)	104 (54)	84 (59)	63 (63)	46 (66)	29 (69)	22 (69)	16 (69)	12 (69)	8 (70)	3 (70)	3 (70)	1 (70)	0 (70)

Daver N, *et al. Blood 2025* .601-611:(5)146

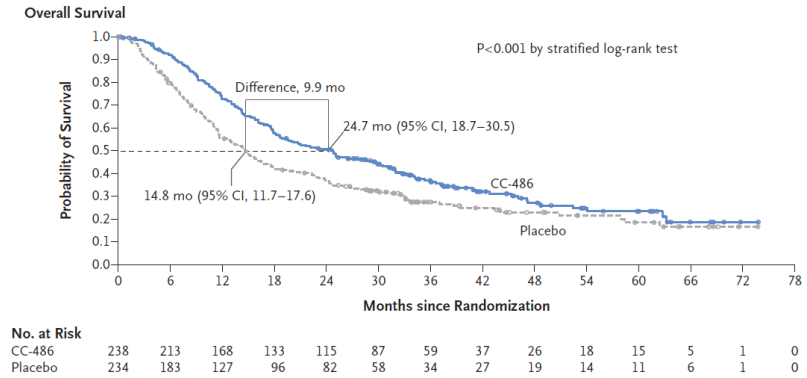
Venetoclax is used in combination with either Azacitidine or low-dose cytarabine in Japan.
Please refer to the Venclexta package insert for further details.

Improving patient outcome – maintenance is back…

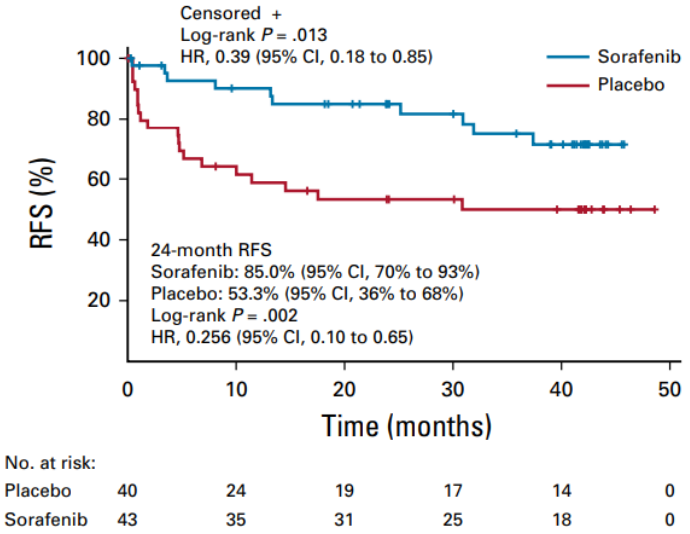
The long road for effective maintnance[1]



Oral AZA (non-SCT)[2]

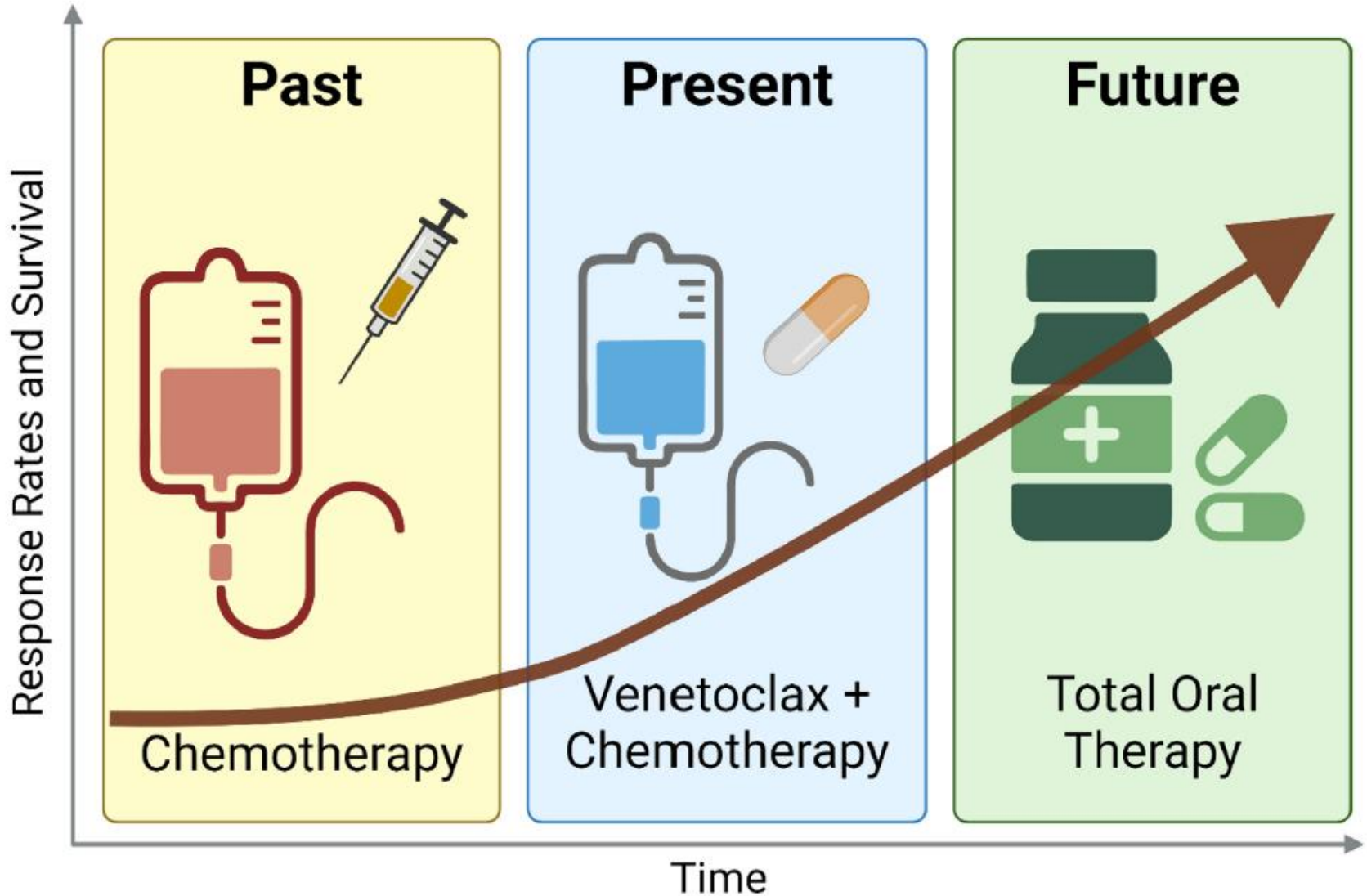


Post allo SCT (FLT3-ITD)[3]

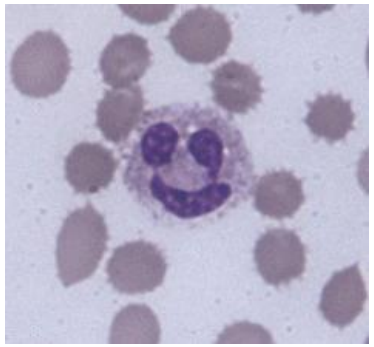


1. Bewesdorf et a. Curr Opinion Oncology 2021 Nov 1;33(6):658-669;

2. Wei et al. N Engl J Med 2020;383:2526-37 3. Burchert et al. JCO 2020 Sep 10;38(26):2993-3002



Wei-Ying Jen, et al. BJH 2024;205:30-47



owolach@gmail.com

Post-remission approach

AML risk group‡	AML risk assessment criteria at diagnosis	MRD after cycle 2	Risk of relapse following consolidation approach		Prognostic scores for NRM that indicate alloHSCT as preferred consolidation		
			Chemotherapy or autoHSCT (%)	AlloHSCT (%)	EBMT score[52]	HCT-CI score[53]	NRM risk (%)
Good	–t(8;21) or *AML1-ETO*, WBC <20 –inv16/t(16;16) or *CBFB-MYH11* –CEBPA-biallelic mutant-positive –FLT3-ITD-negative/NMP1-positive	Positive or negative	35-40	15-20	NA (≤1)	NA (<1)	10-15
Intermediate	–CN –X –Y, WBC <100, CRe –t(8;21) or *AML1-ETO* plus WBC >20 or mutant KIT	Negative	50-55	20-25	≤2	≤2	<20-25
Poor	–CN –X –Y, WBC <100, CRe –t(8;21) or *AML1-ETO*, WBC >20 and/or mutant KIT –CN –X –Y, WBC <100, no CRe –CN –X –Y, WBC >100 –CA, but non-CBF, MK-negative, no abn3q26	Positive Positive Negative Negative	70-80	30-40	≤3-4	≤3-4	<30
Very poor	–CN –X –Y, WBC >100 –CA, but non-CBF, MK-negative, no abn3q26, EVI1-negative –MK-positive –abn3q26 –Non-CBF, EVI1-positive –Non-CBF with mutant p53, or –mutant RUNX1, or mutant ASXL1 –or biallelic FLT3-ITD with –FLT3-ITD:FLT3 WT ratio of >0.6	Positive Positive Positive or negative	>90	40-50	≤5	≤5	<40

Cornelissen & Blaise. Blood 2016