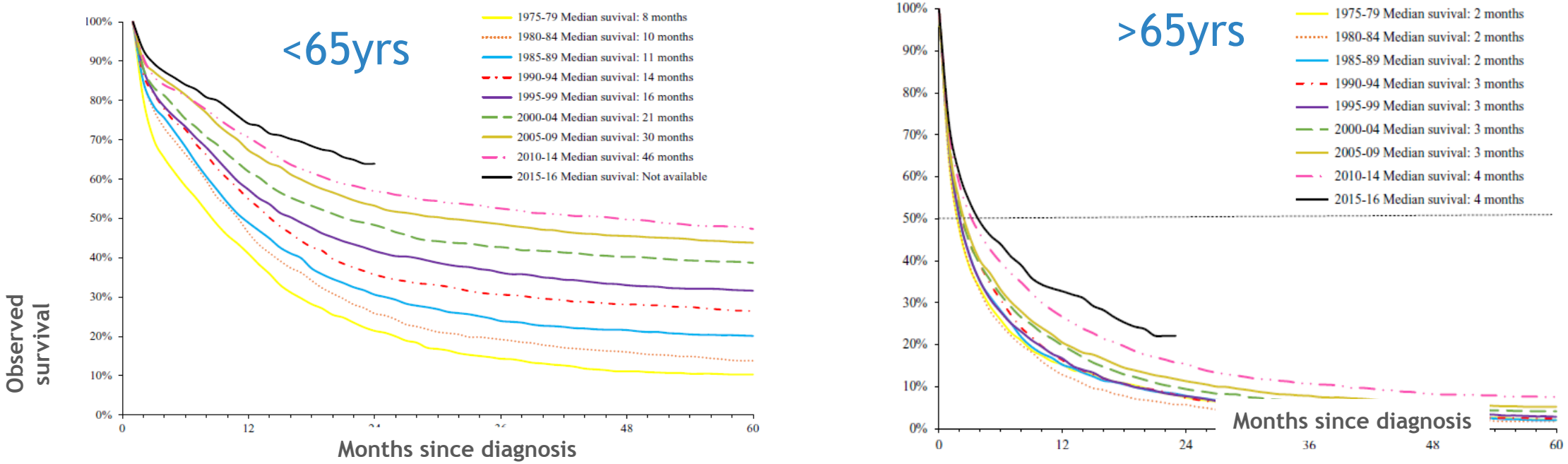
Targeted therapies for AML: flt-3 and beyond

F. Ferrara

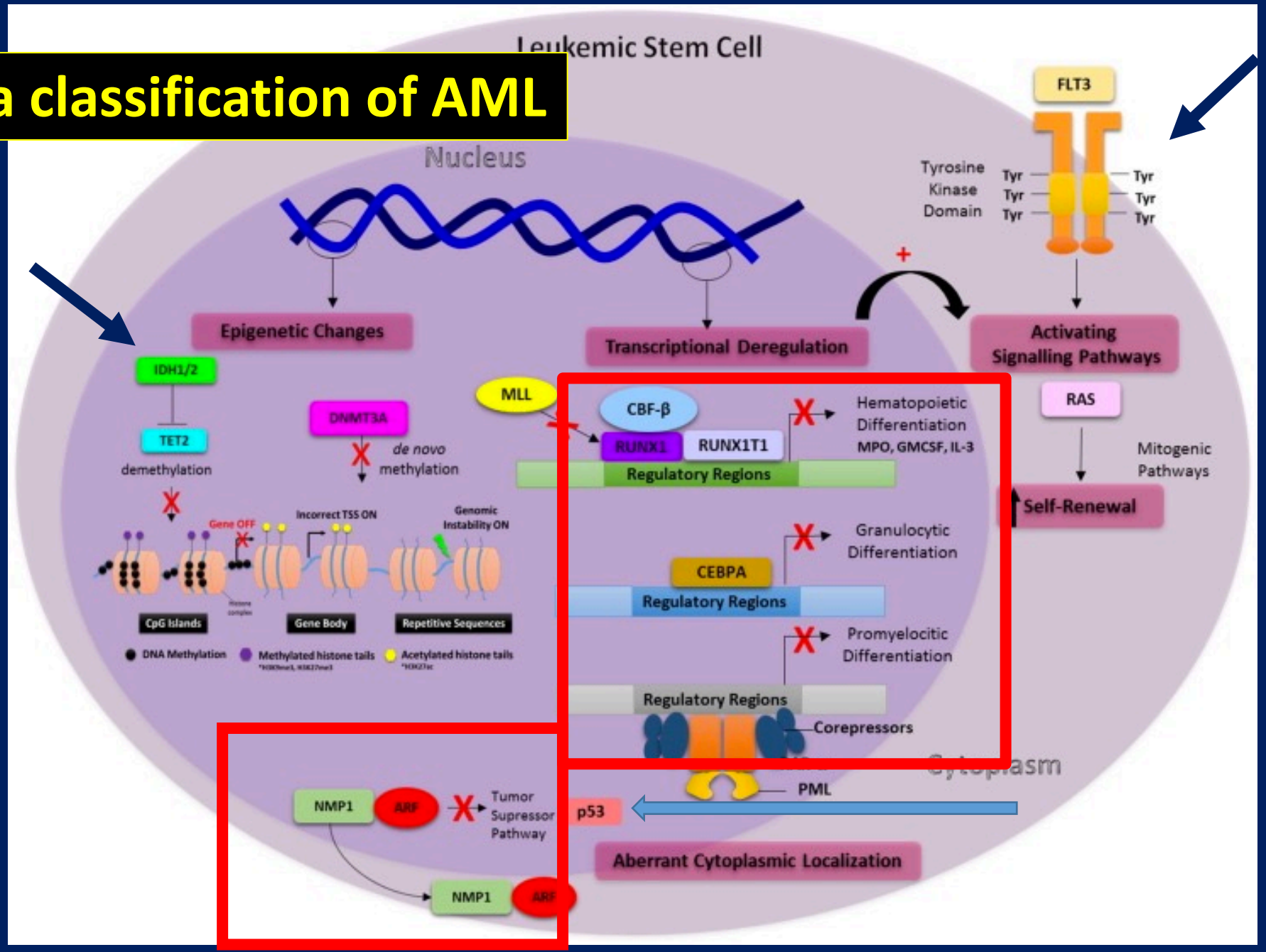
OS evolution over years in AML



- Refinement of supportive care ➡ lower ID
- More older patients treated and better selection of them
- Lower TRM
- Increased allo-transplant rate up to 70-75 yrs.
- Risk adpated treatment (ELN risk, MRD)

Shallis RM et al, Blood Rev, 2019

Ferrara classification of AML



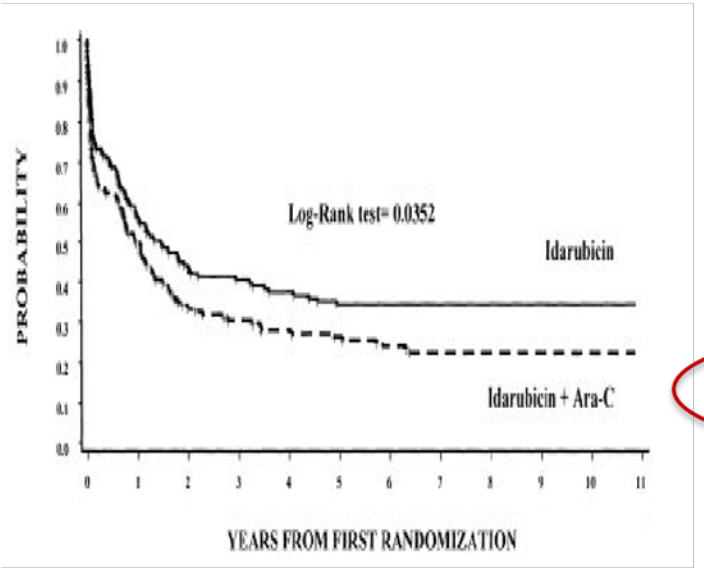
Curable AML: Chemosensitive, GO

Less curable AML: Partially chemosensitive, need specific inhibitor

Incurable AML: Chemorefractory, Need for something else, What ?

Ferrara F, unpublished

Acute promyelocytic leukemia



1957 First description

Responses with anthracycline chemo — 1973

1977 Specific chromosome lesion identified

Response to ATRA (Vit. A derivative) — 1987

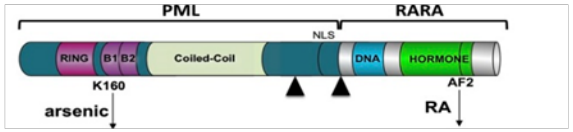
1990 Altered genes identified

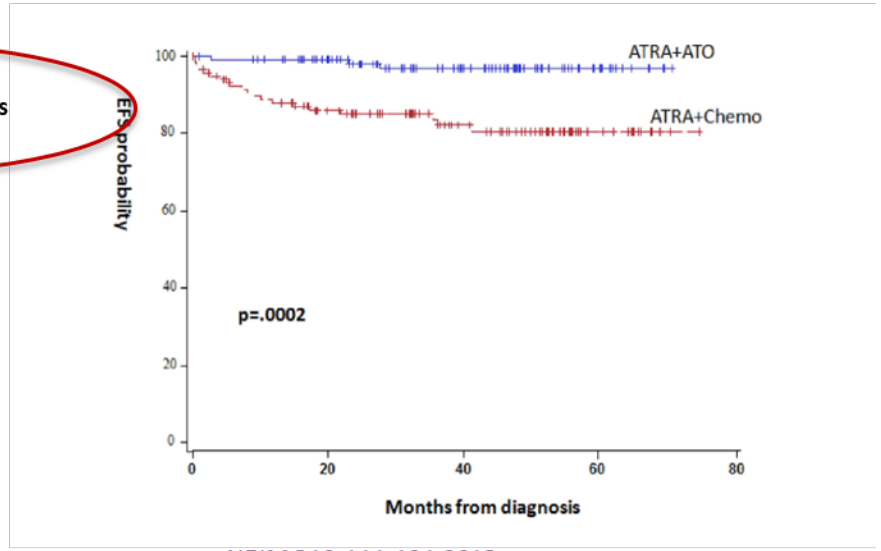
High cure rates with ATRA + Chemo — 1993

1996 Response to Arsenic Trioxide (ATO)

Improved ATRA + Chemo combination — 2004-6

2006-12 Chemo-free (ATO + ATRA) results

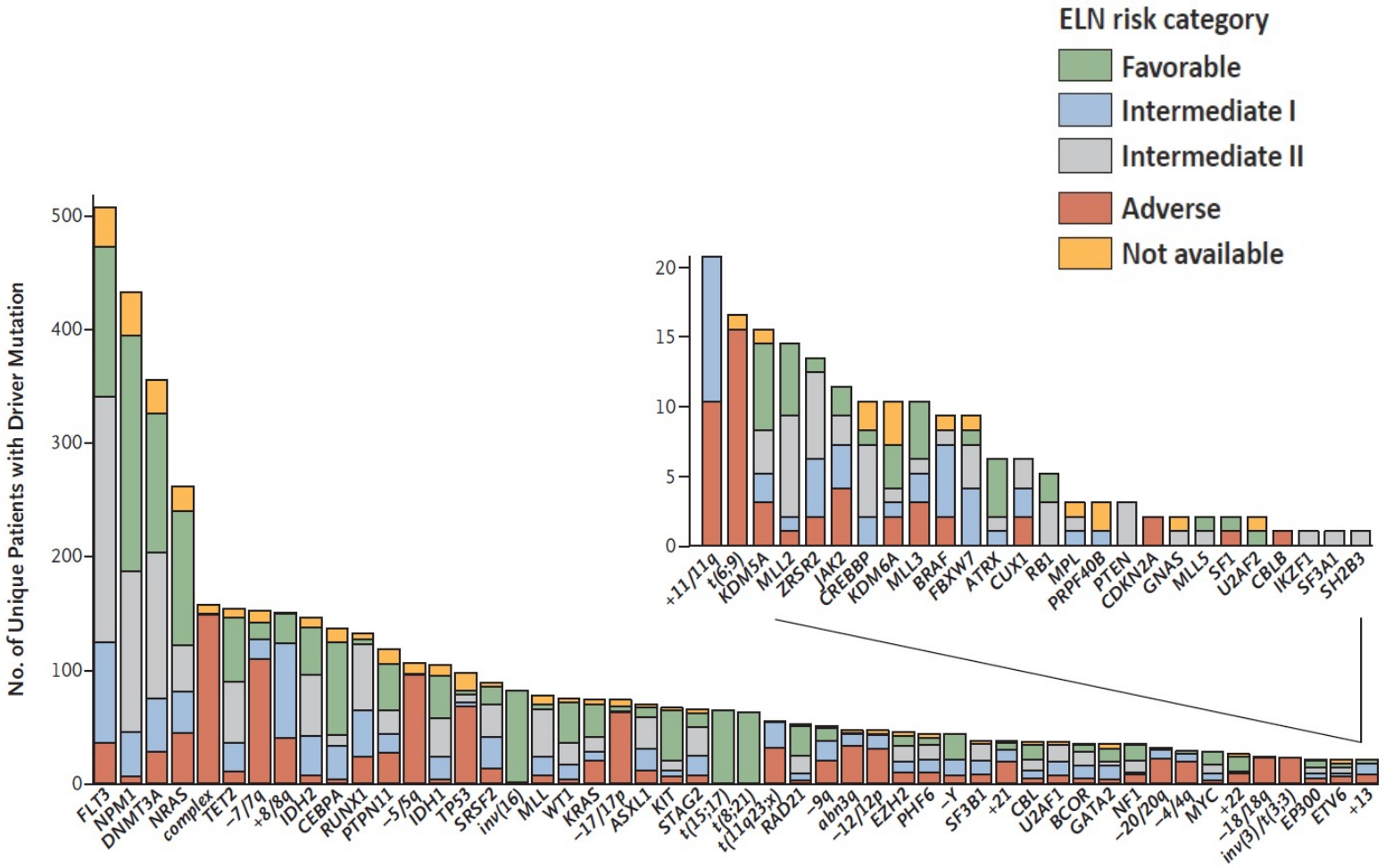




- Unique to APL (disease hallmark)
- Strongly correlated with pathogenesis
- Targeted by specific therapies
- Ideal marker for residual disease monitoring

NEJM 319:111-121,2013

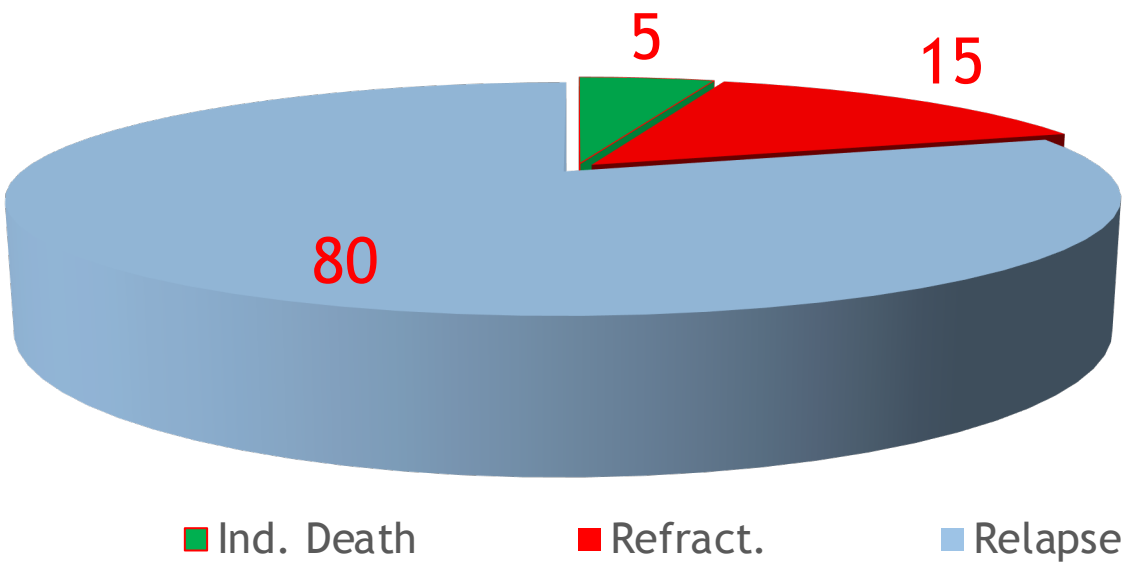
The Genomic Landscape of AML

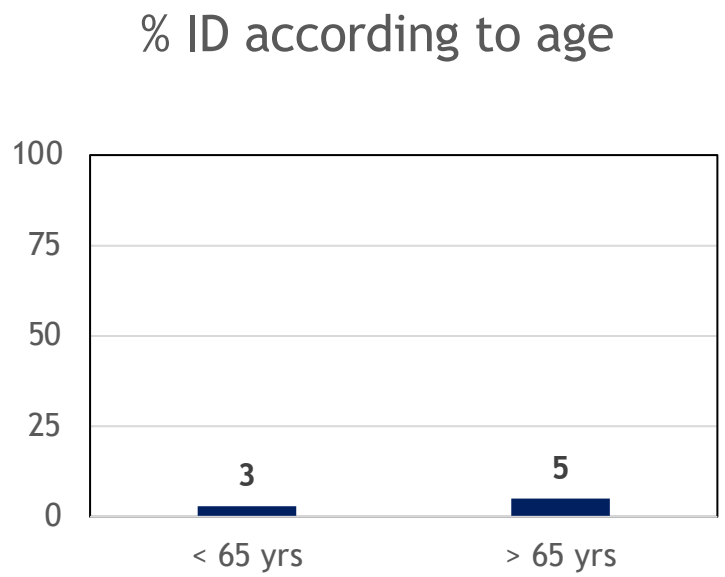


- Cytogenetic analyses and sequencing of 111 myeloid cancer genes in AML patients (N = 1540)
- Identified 5234 driver mutations involving 76 loci
- 7 loci mutated in > 10% of patients; 12 loci in 5% to 10% of patients; 58 loci in < 5% of patients

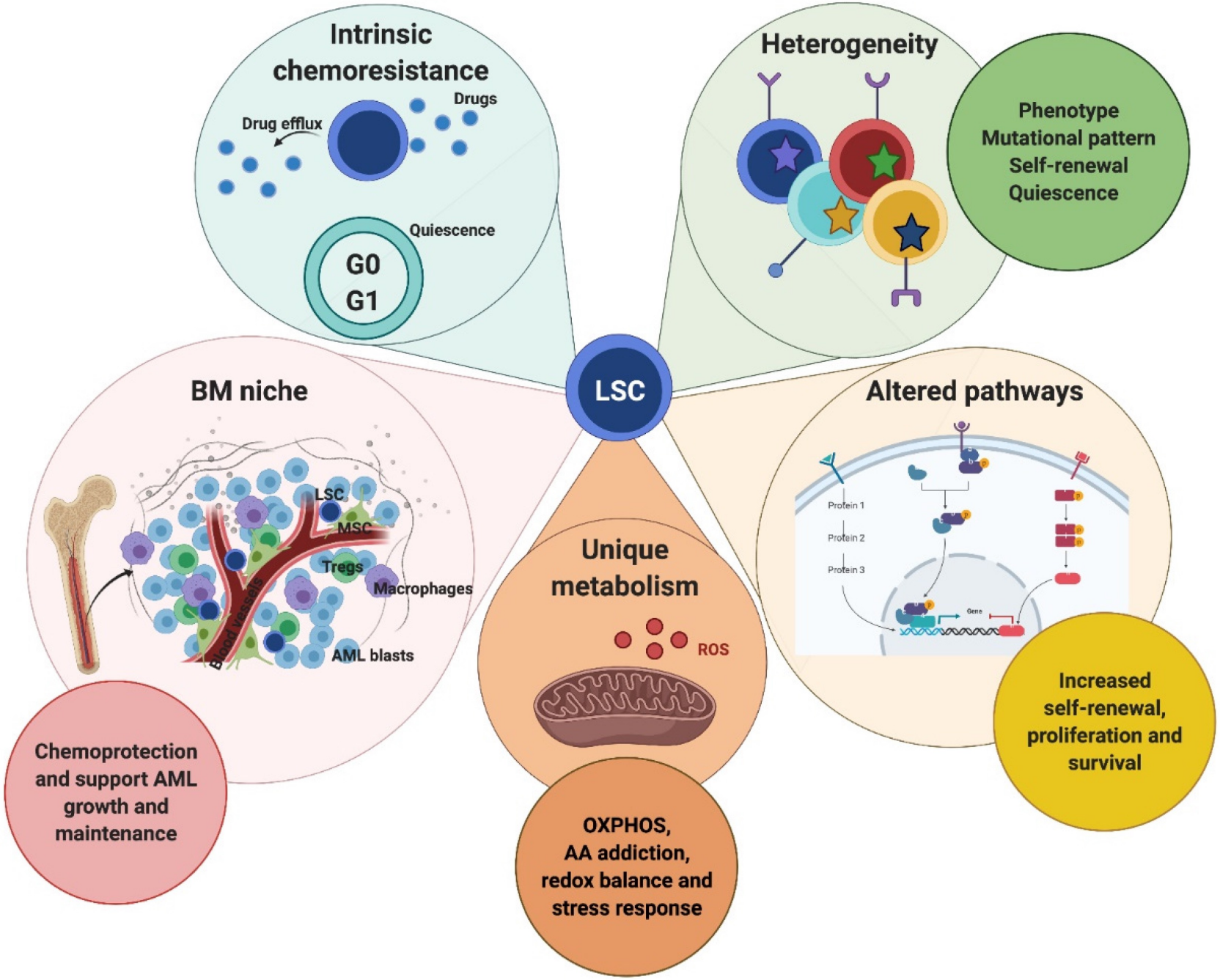
Papaemmanuil E, et al. N Eng J Med. 2016;374:2209-2221.

Failure in AML (%)



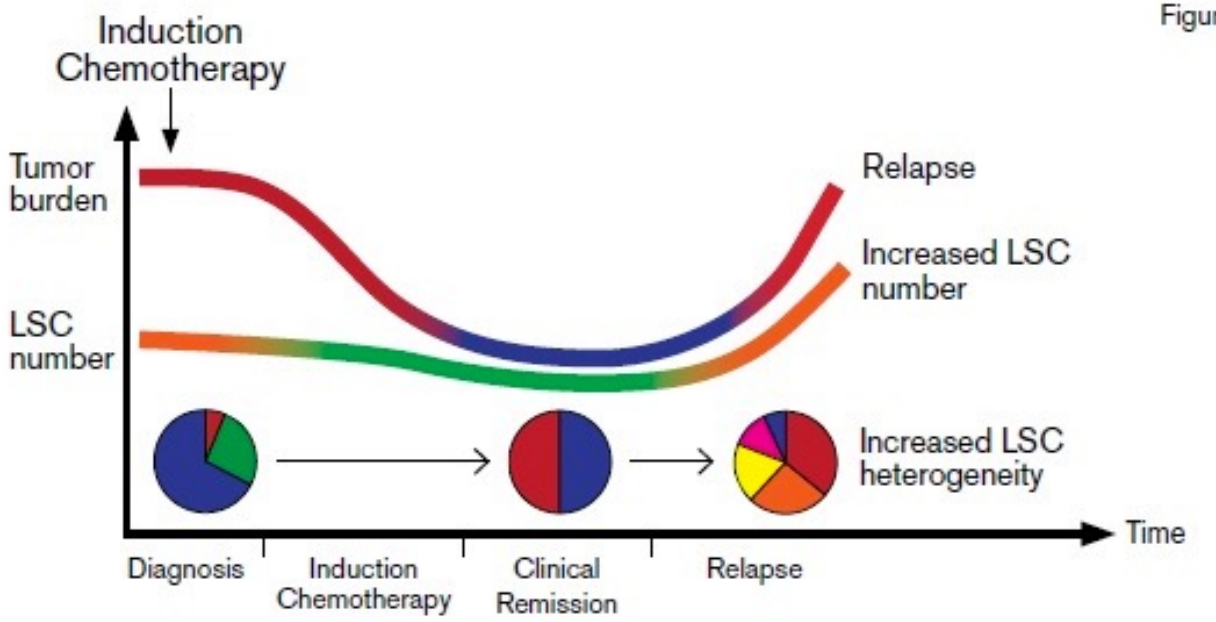


Speaker's experience



Michelozzi IM et al. Cancers 2021, 13(11), 2816

Figure

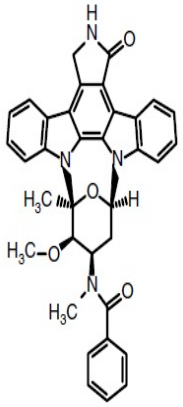


The impact of induction chemotherapy on acute myeloid leukemia (AML) that ultimately relapses. With treatment, there can be an initial decrease in the quantity and diversity of leukemia stem cells (LSCs), but at the time of relapse, the quantity and diversity of LSCs is greater than at the time of initial diagnosis, supporting the hypothesis that induction chemotherapy results in the iatrogenic worsening of AML. (Figure adapted with permission, courtesy of Shanshan Pei, PhD.)

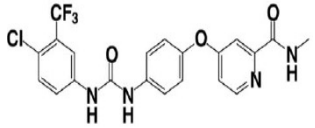
can be slain. In light of these reports, we must consider the reality that very often, when treating AML with intensive chemotherapy, we are not simply passive users of a therapy that doesn't work very well, but instead, *we are responsible for making this disease worse*. Call relapsed AML after induction what it is: iatrogenic AML (Figure).

(Cont. on page 13)

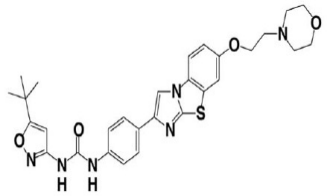
FLT3 Inhibitors



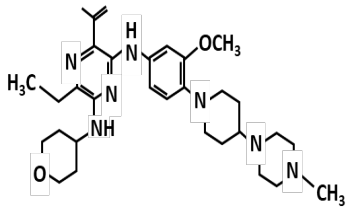
Midostaurin



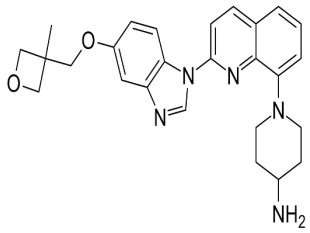
Sorafenib



Quizartinib



Gilteritinib



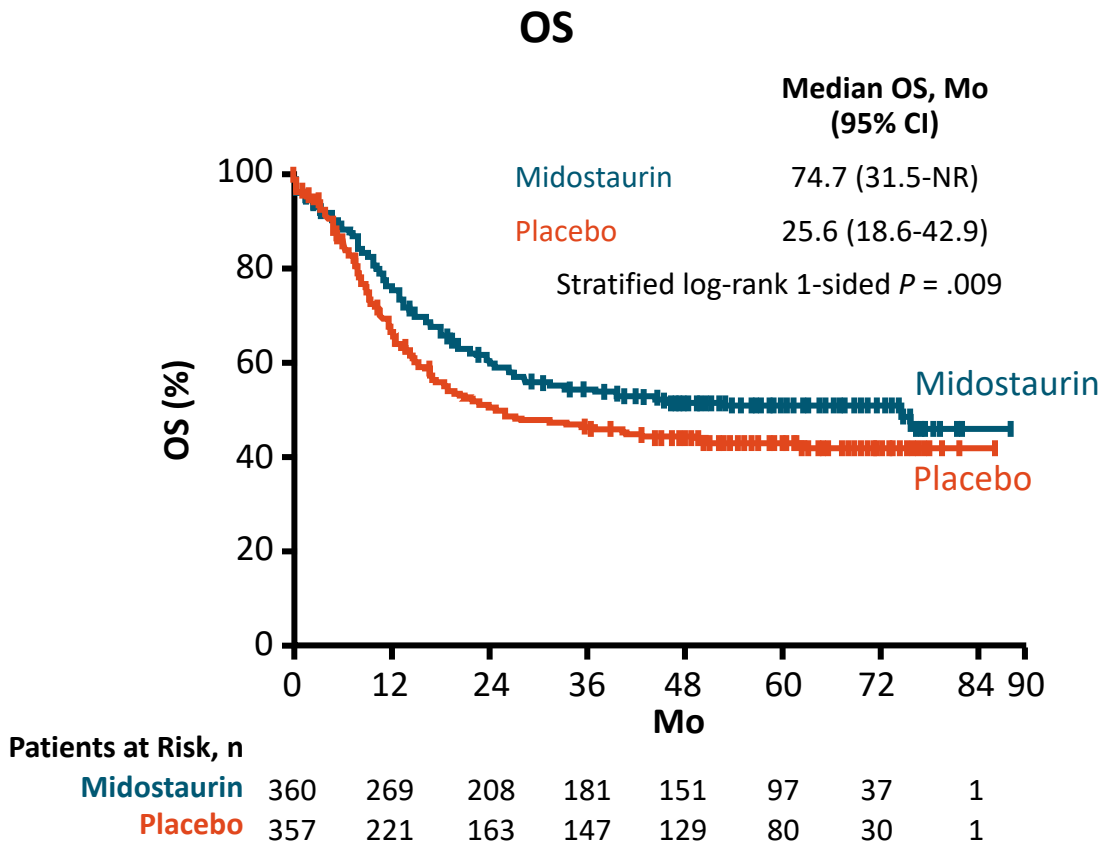
Crenolanib

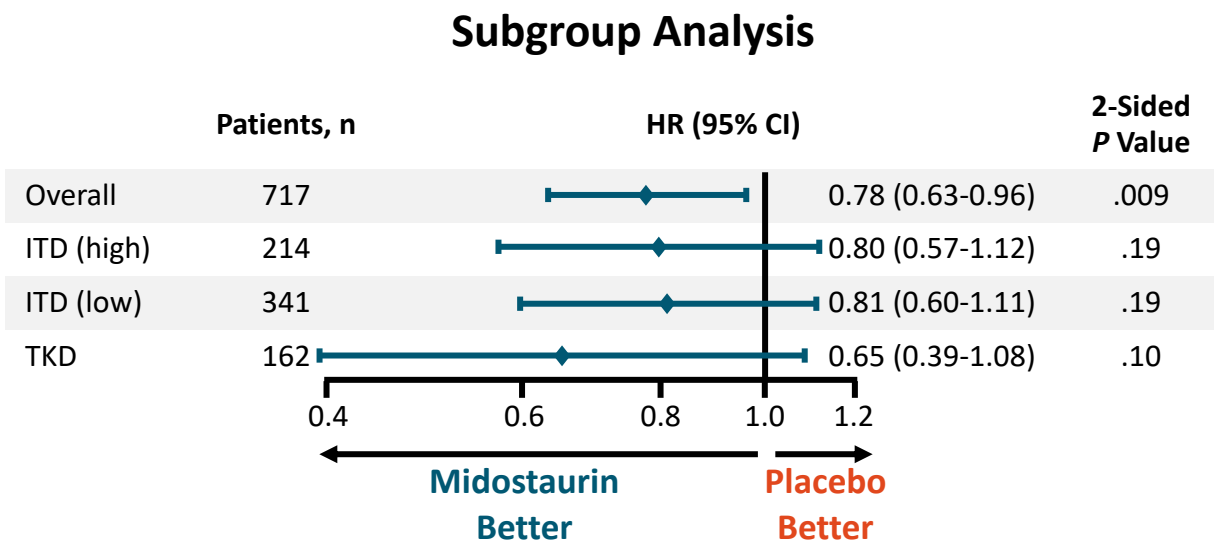
First Generation

Second Generation

Levis. Blood. 2017;129:3404. Zarrinkar. Blood. 2009;114:2984.

RATIFY: Overall Survival

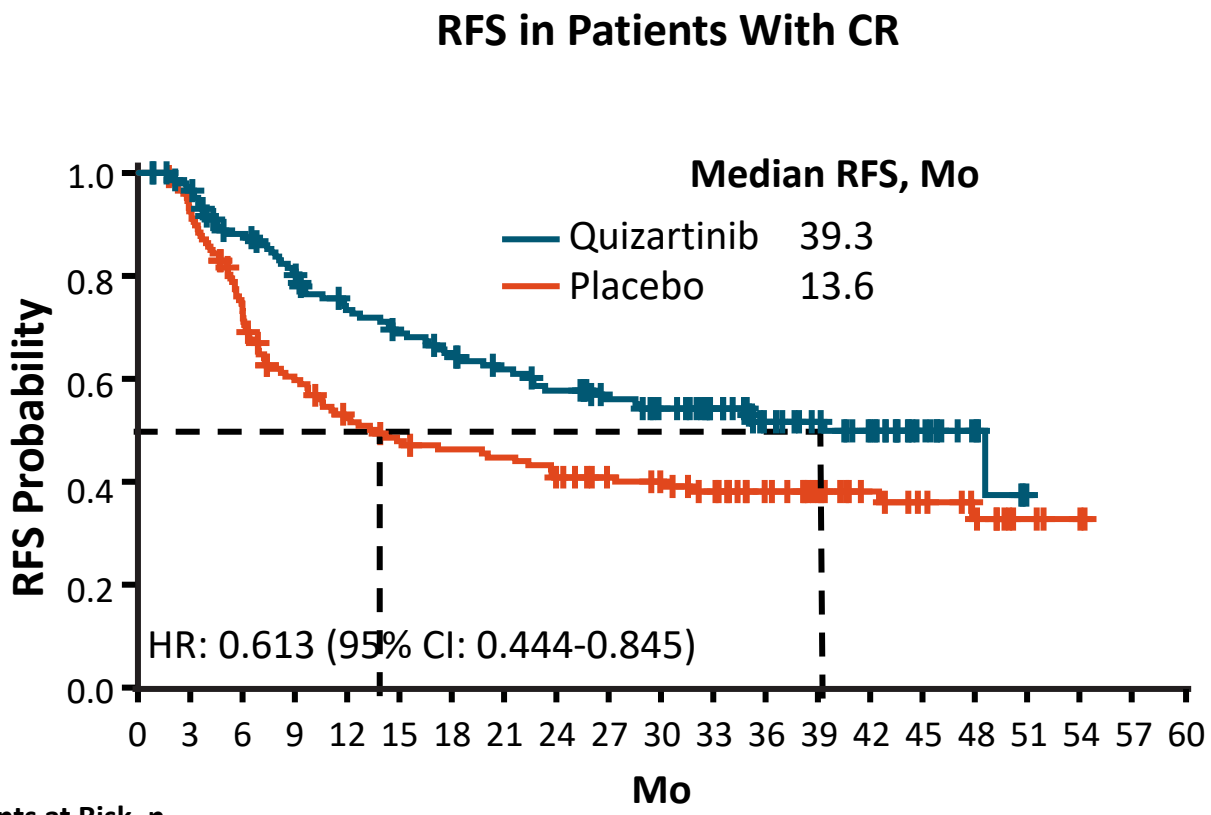


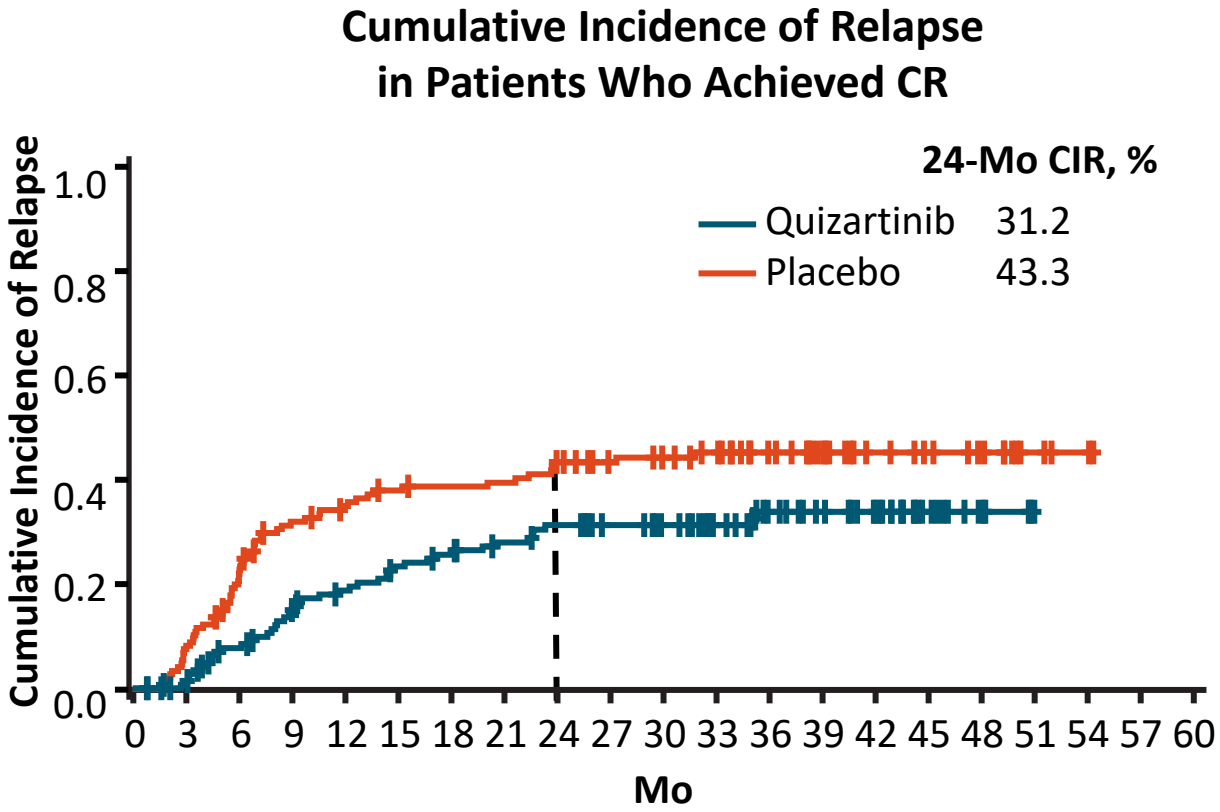


- **OS was significantly longer with midostaurin vs placebo group (HR: 0.78; *P* = .009)**
- 24.3% reduced risk of death in midostaurin arm
- At 4 yr, 63.7% were alive in midostaurin arm vs 55.7% in placebo arm

Stone. NEJM. 2017;377:454.

QuANTUM-First: Relapse-Free Survival





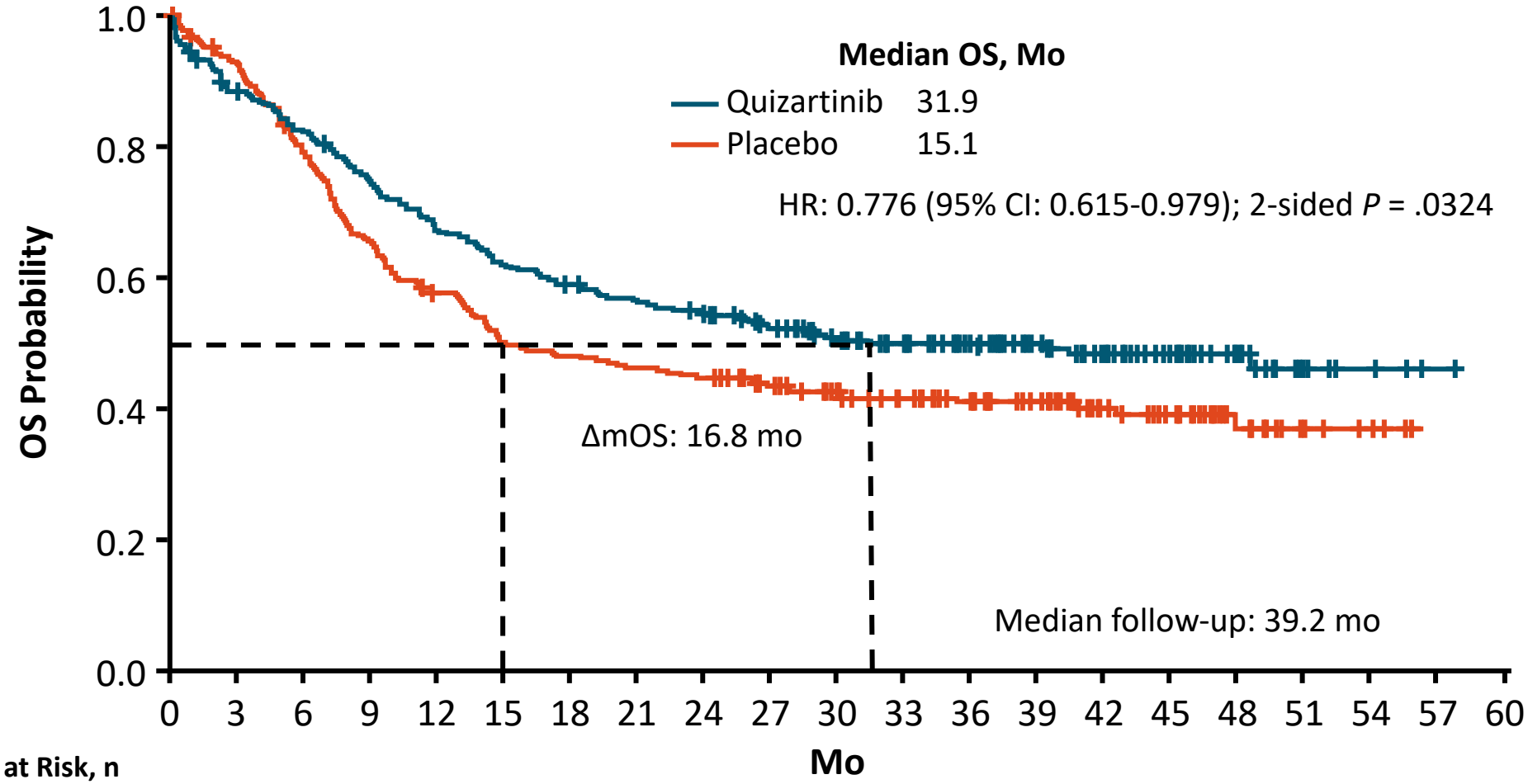
Patients at Risk, n

Quizartinib	147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
Placebo	150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

147	140	123	111	97	90	84	77	71	63	57	48	36	31	24	13	6	0	0	0	0
150	136	103	82	70	63	60	58	52	47	44	39	31	24	18	14	10	4	2	0	0

Erba. EHA 2022. Abstr S100.

QuANTUM-First: OS (Primary Endpoint)

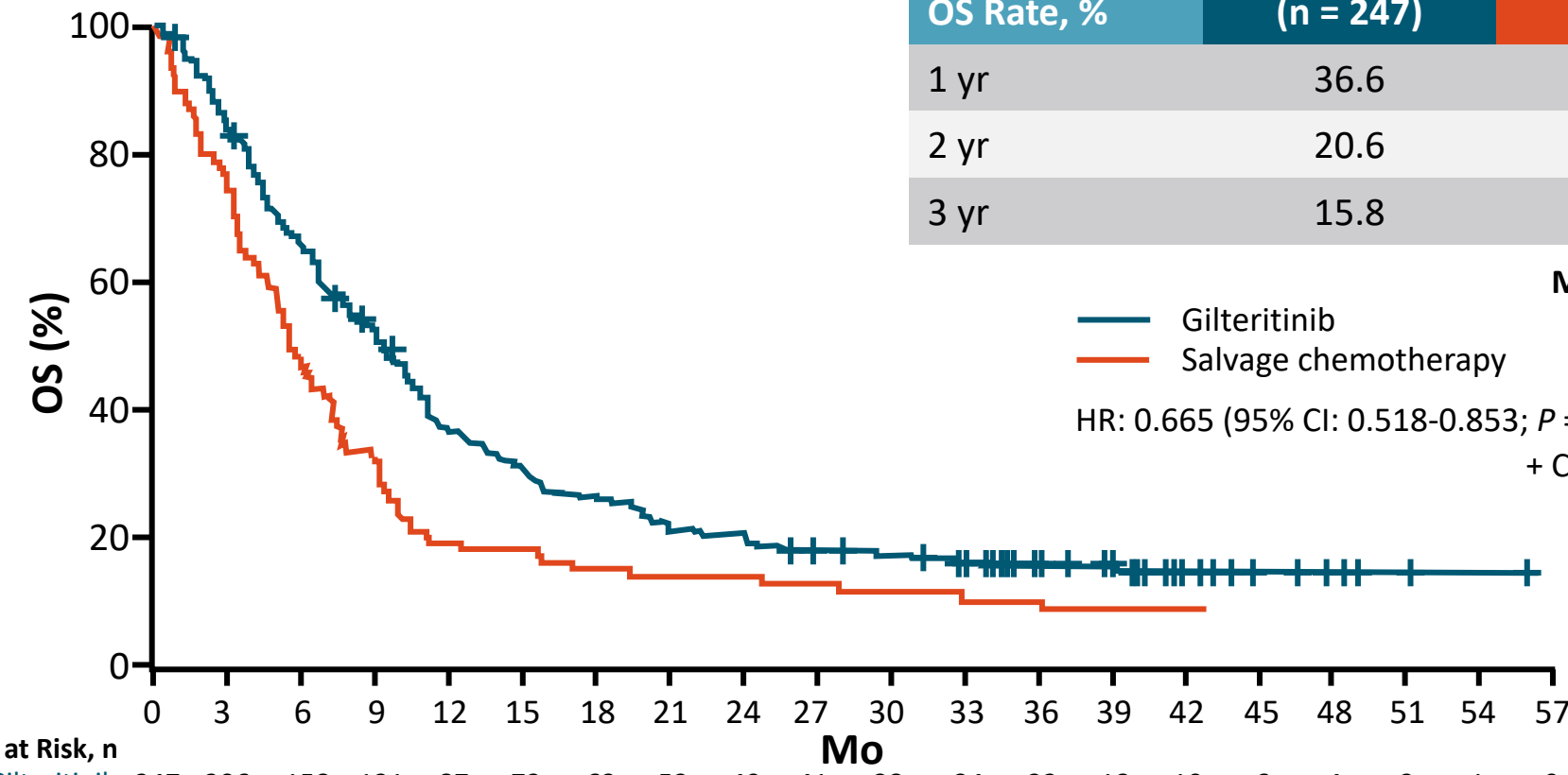


Patients at Risk, n																				
Quizartinib	268	233	216	195	176	162	153	145	139	126	110	96	83	68	53	36	24	8	4	1	0
Placebo	271	249	211	175	151	131	126	121	117	103	97	81	70	56	39	31	17	8	5	0	0

Erba. EHA 2022. Abstr S100.

ADMIRAL: Gilteritinib Prolongs OS in m*FLT3* R/R AML

OS Rate, %	Gilteritinib (n = 247)	Salvage CT (n = 124)
1 yr	36.6	19.2
2 yr	20.6	14.2
3 yr	15.8	10.4

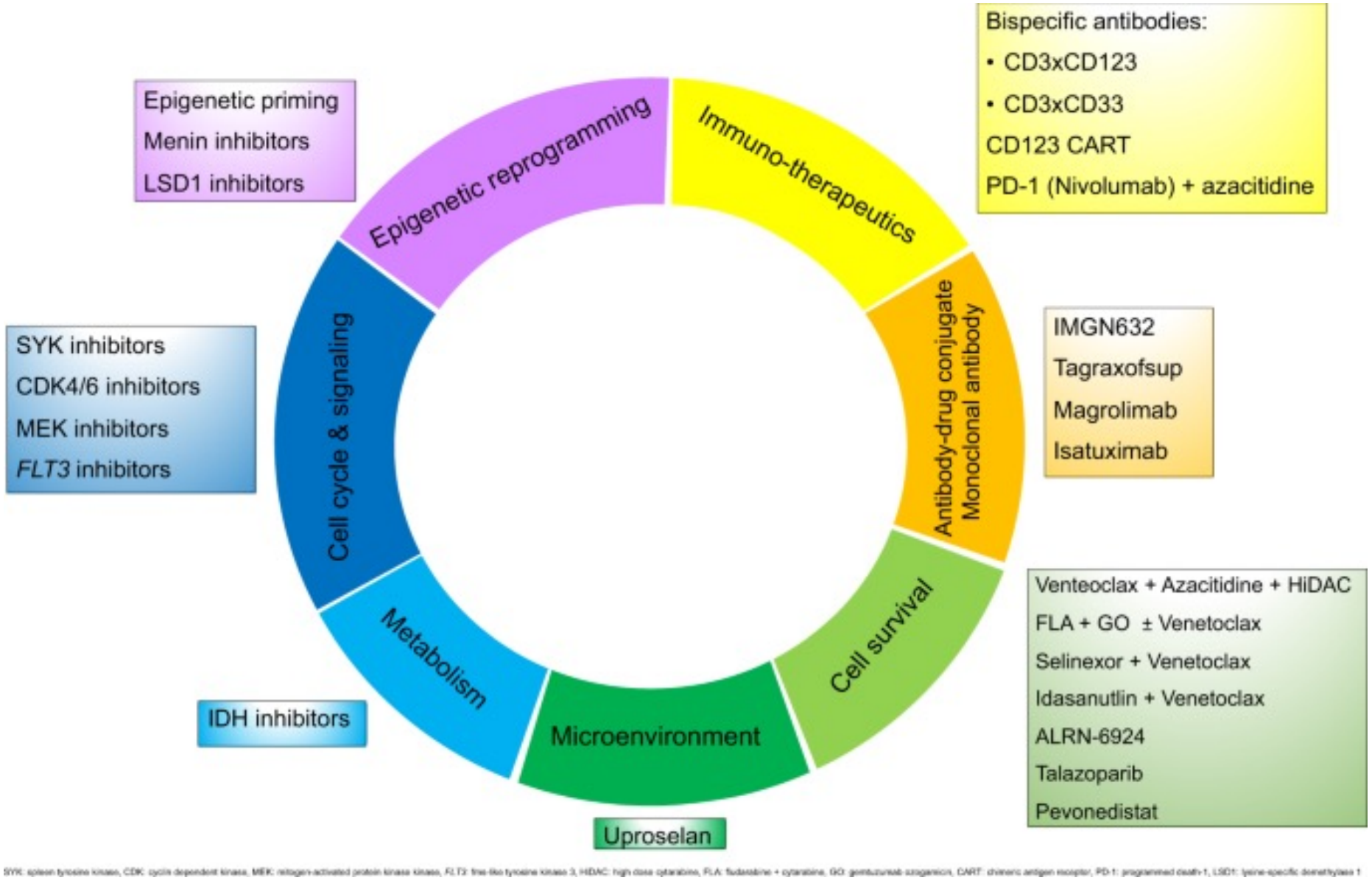


Perl. Blood 2022;139:3366.

FLT3 inhibition – future perspectives

	Frontline + 3+7	Frontline unfit	Post-transplant	R/R
FLT3i	Quizartinib Crenolanib Gilteritinib	Time for triplets? Gilteritinib + VEN + HMA Quizartinib + VEN + HMA	Gilteritinib – MORPHO study Quizartinib Crenolanib	Novel FLT3i (MKIA-088-001-Nerviano) Triplets vs doublets: TKI+AZA +/- VEN

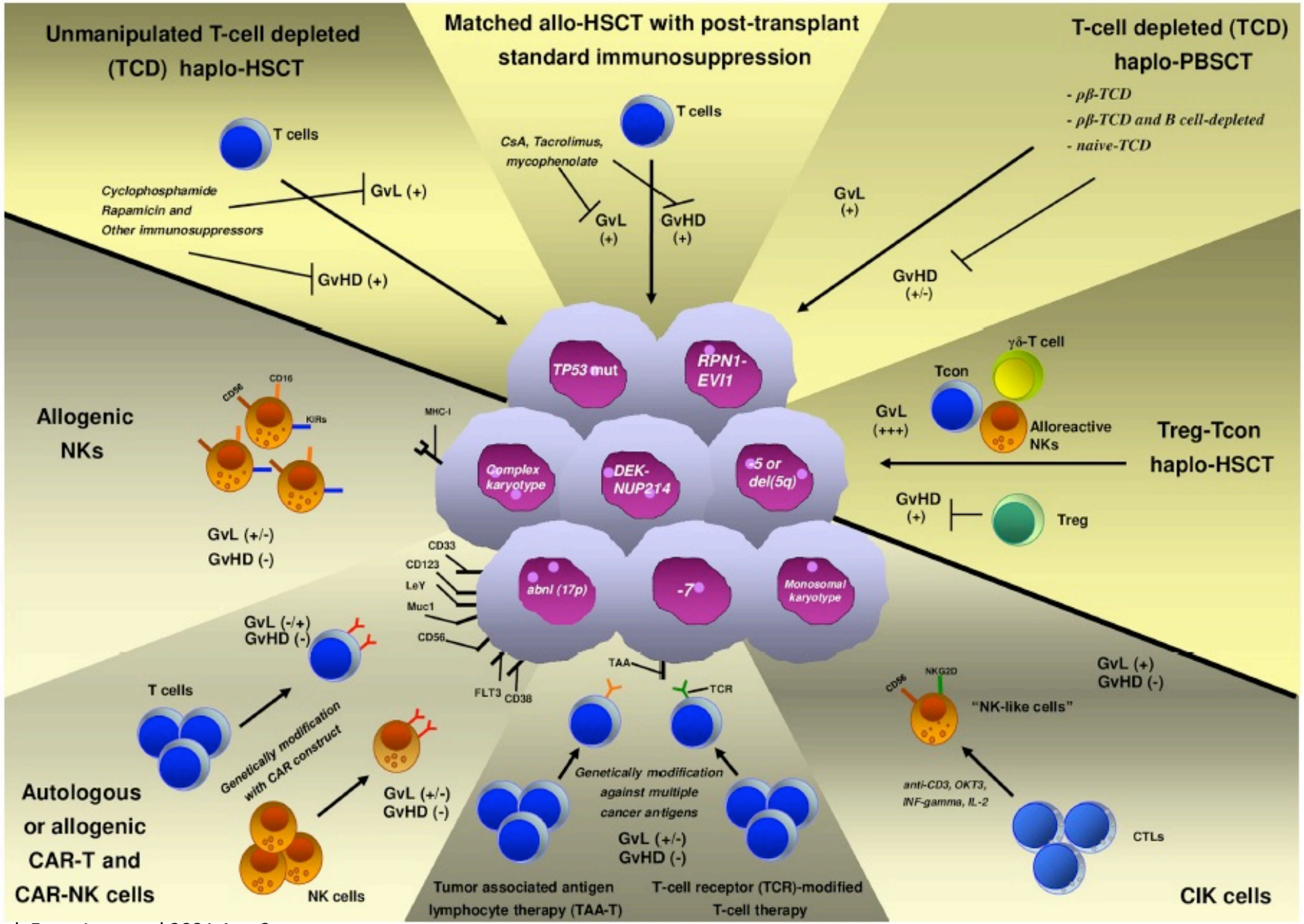
Quizartining and crenolanib are NOT APPROVED by EMA for use in AML
Gilteritinib in association to AZA and Venetoclax is NOT APPROVED by EMA for use in AML



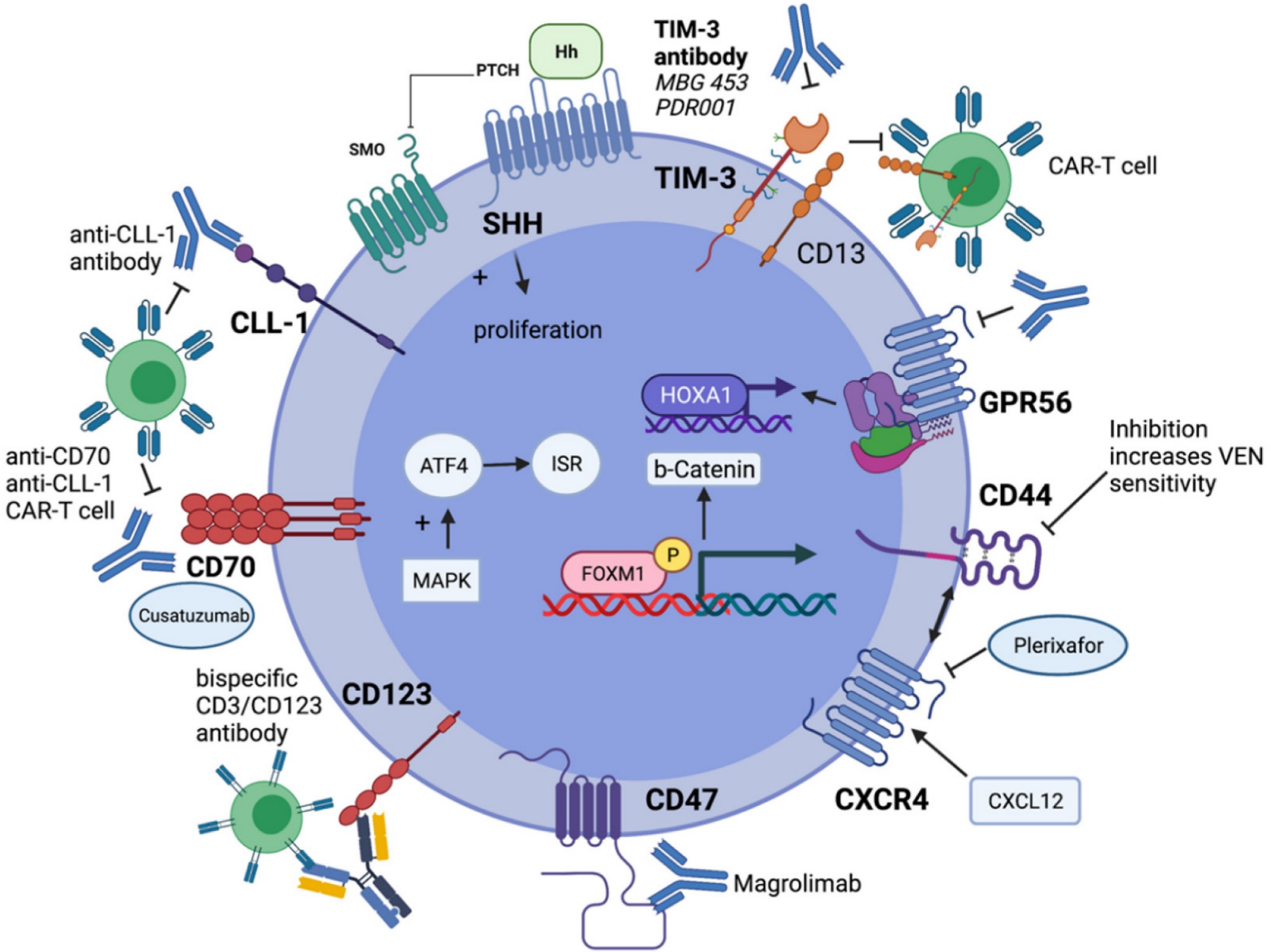
Zarnegar-Lumley S. et al. 2022 Aug;36(8):1951-1960

Nivolumab, IMGN632, Tagraxofsup, Magrolimab, Isatuximab, ALRN-6924, Talazoparib, Pevonedistat, Uproselan are NOT APPROVED by EMA for use in AML

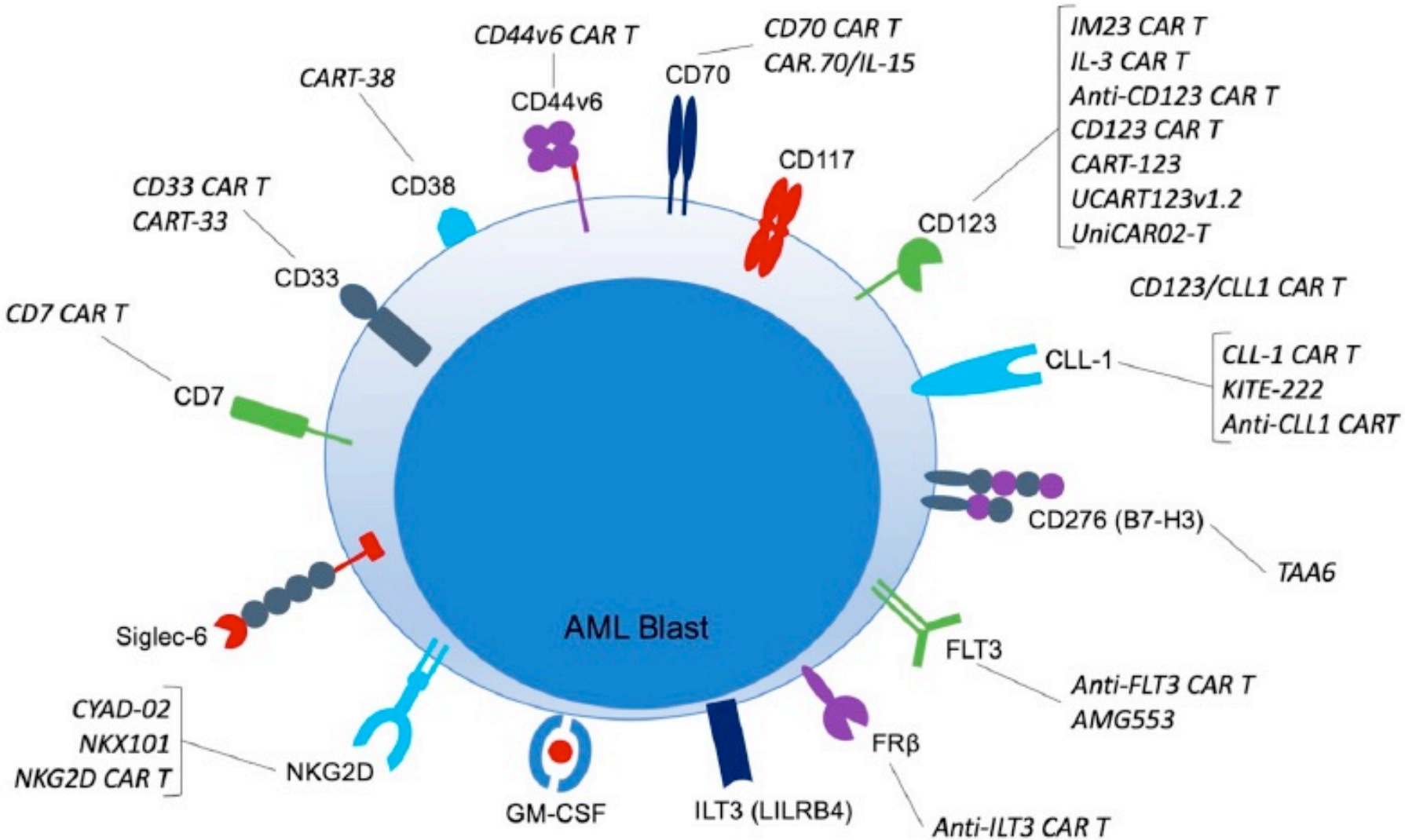
Venetoclax in association to HiDAC, selinexor, idasanutlin or FLA+GO is NOT APPROVED by EMA for use in AML



Limongello R et al. Front Immunol 2021 Aug 3



Fleischmann M et al. Cancers 2021, 13, 5722

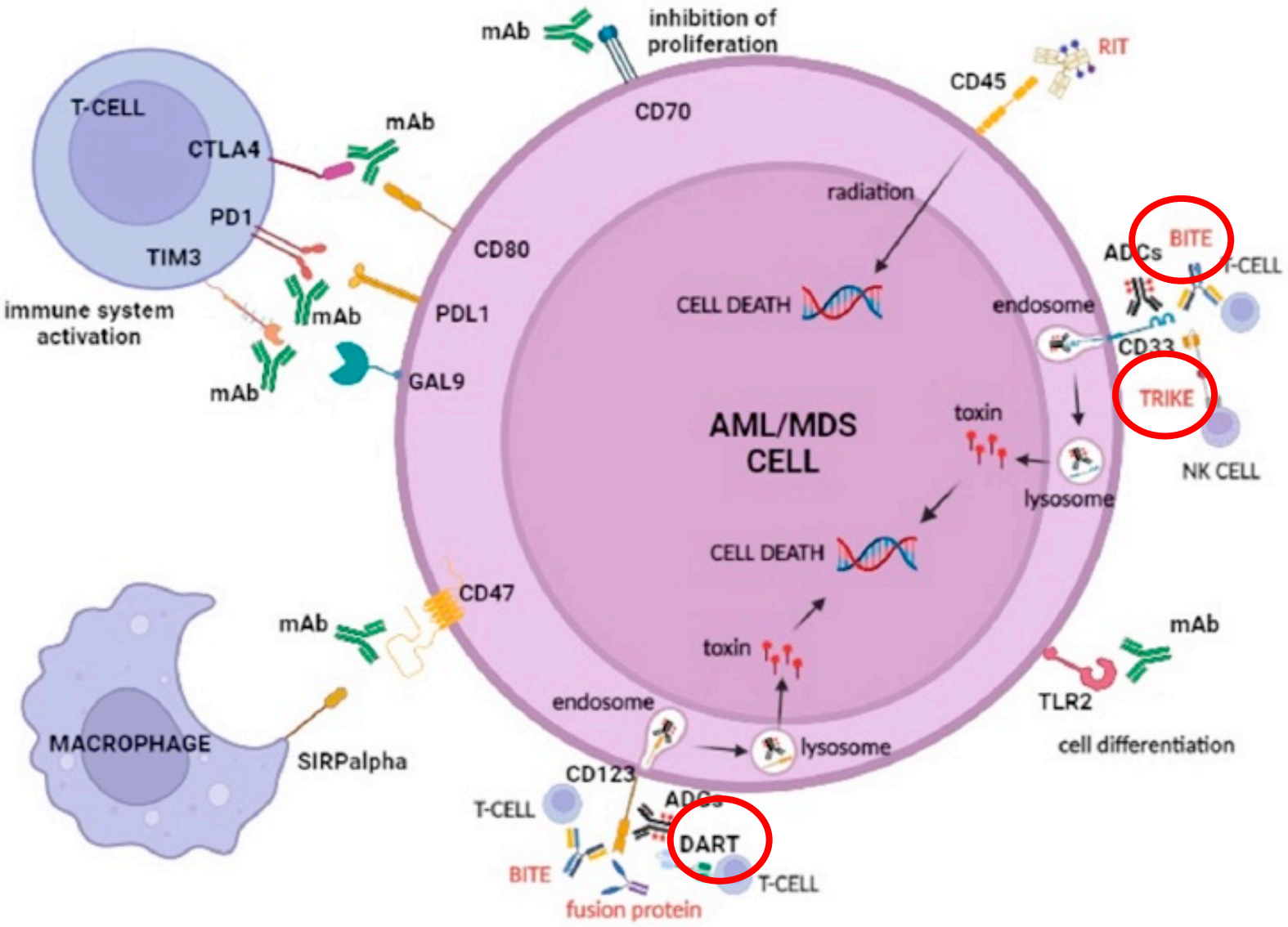


Marvin-Peek J et al. Cancers 2022, 14, 497

Table 1. Ongoing CAR therapy trials in AML.

Target Antigen	Name of Drug	CAR Cell Type	Phase	https://clinicaltrials.gov/ (accessed on 21 December 2021) ID	Age (years)	Country
CD7	CD7 CAR-T	T	I/II	NCT04762485	12 to 65	China
CD7	CD7 CAR-T	T	I/II	NCT04033302	Up to 75	China
CD19	CAR-T CD19	T	II/III	NCT04257175	18 and up	Israel
CD33	CD33 CAR-T	T	I/II	NCT04835519	1 to 70	China
CD33	CD33CART	T	I/II	NCT03971799	1 to 35	USA
CD33	CART-33	T	I	NCT02799680	50 and up	China
CD33	PRGN-3006	T	I	NCT03927261	18 and up	USA
CD33/CLL1	Dual CD33-CLL1 CAR-T	T	I	NCT05016063	18 to 70	China
CD38	CART-38	T	I/II	NCT04351022	6 to 65	China
CD44v6	CD44v6 CAR-T	T	I/II	NCT04097301	1 to 75	Italy
CD70	CD70 CAR-T	T	I	NCT04662294	All	China
CD70	CAR.70/IL-15	NK	I/II	NCT05092451	18 and up	USA
CD123	IM23 CAR-T	T	I	NCT03585517	3 to 80	China
CD123	IL-3 CAR-T	T	I	NCT04599543	All	China
CD123	Anti-CD123 CAR-T	T	I	NCT04014881	18 to 70	China
CD123	CD123-CAR-T	T	I	NCT04318678	Up to 21	USA
CD123	CART-123	T	I/II	NCT03556982	14 to 75	China
CD123	CD123 CAR-T	T	I/II	NCT04272125	3 to 75	China
CD123	CD123 CAR-T	T	I/II	NCT04265963	2 to 75	China
CD123	UCART123v1.2	T	I	NCT03190278	18 to 65	USA
CD123	UniCAR02-T	T	I	NCT04230265	18 and up	Germany
CD123	CD123-CAR-CD28-CD3z-EGFRt	T	I	NCT02159495	12 and up	USA
CD123	CART123	T	I	NCT04678336	1 to 29	USA
CD123	CART123	T	I	NCT03766126	18 and up	USA
CD123/CLL-1	CD123/CLL1 CAR-T	T	II/III	NCT03631576	Up to 70	China
CD276	TAA6	T	I	NCT04692948	18 to 70	China
CLL-1	CLL-1 CAR-T	T	I	NCT04219163	Up to 75	USA
CLL-1	KITE-222	T	I	NCT04789408	18 and up	USA
CLL1	Anti-CLL1 CART	T	I/II	NCT04884984	6 to 65	China
CLL1	Anti-CLL1 CART	T	I	NCT04923919	2 to 75	China
FLT3	Anti-FLT3 CAR-T	T	I/II	NCT05023707	16 to 65	China
FLT3	AMG553	T	I	NCT03904069	12 and up	USA
FLT3	TAA05	T		NCT05017883	18 to 70	China
ILT3	Anti-ILT3 CAR-T	T	I	NCT04803929	18 to 70	China
NKG2D	CYAD-02	NK	I	NCT04167696	18 and up	USA
NKG2D	NKX101	NK	I	NCT04623944	18 and up	USA
NKG2D	NKG2D CAR-T	NK	I	NCT04658004	3 to 70	China

Marvin-Peek J et al. Cancers 2022, 14, 497

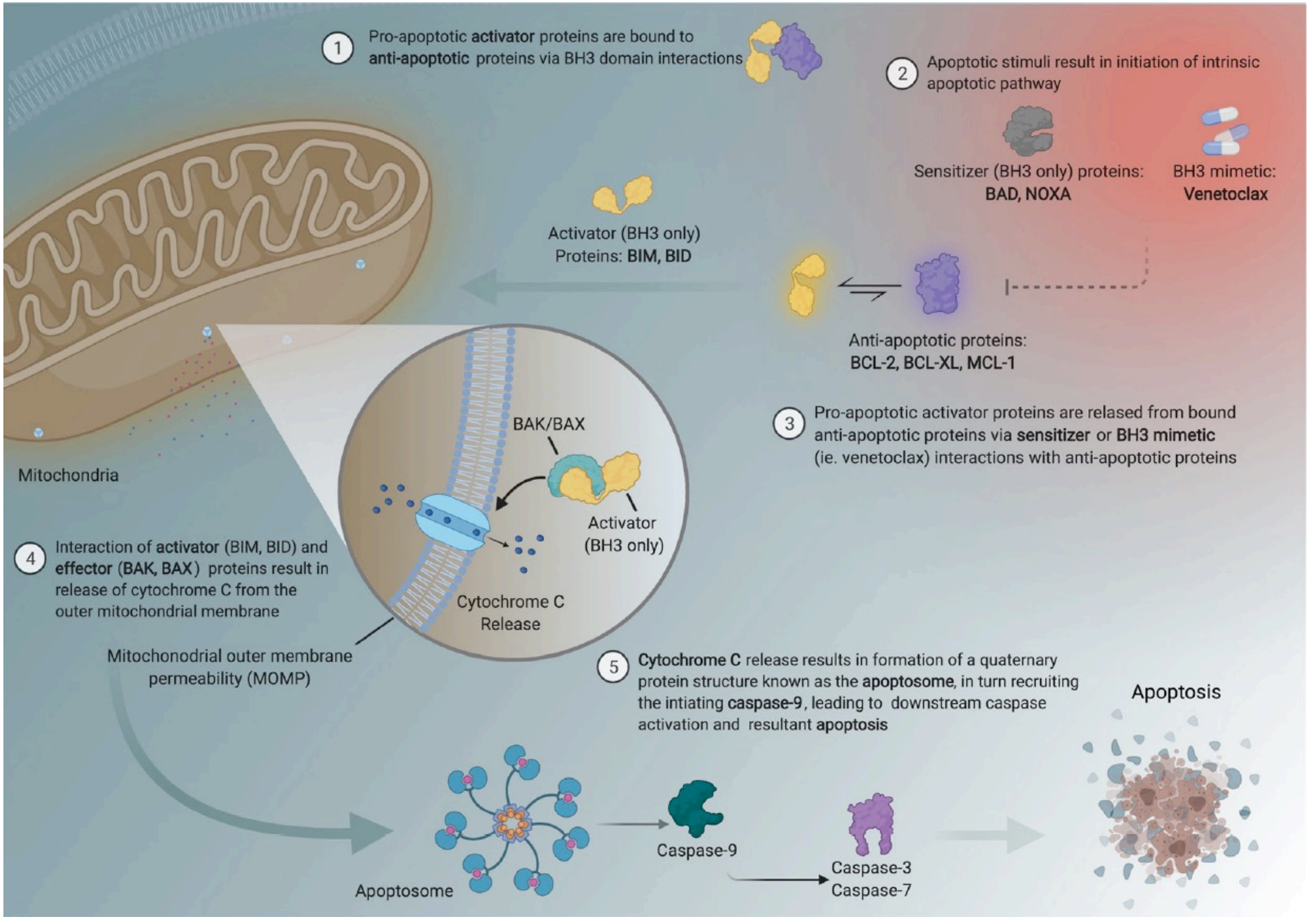


Gallazzi et al, Int J Mol Sci, 2022

Table 1. Clinical trials with innovative mAbs in AML.

NCT Code	Trial	Target	Study Population	Efficacy Results	Ref.
NCT03248479	Ongoing phase Ib, magrolimab + AZA	CD47	untreated AML unfit for induction chemotherapy.	ORR 69%: 50% CR or CRi, 13% PR and 31% SD	[18]
NCT02678338	Phase I, magrolimab	CD47	R/R AML	N/A	[19]
NCT04755244	Ongoing phase I/II, evorpacept + venetoclax + AZA	CD47	R/R AML ineligible for standard induction chemotherapy	N/A	N/A
NCT01822509	Phase I/Ib, ipilimumab	CTLA-4	R/R AML after allogeneic HSCT	Durable response (>1 year): 4/22	[20]
NCT02397720	Ongoing phase II, nivolumab + AZA	PD-1	R/R AML	ORR: 33% mOS: 10.6 months	[21]
NCT02530463	Ongoing phase II, ipilimumab + nivolumab + AZA vs. nivolumab + AZA vs. AZA	PD-1	R/R AML	Ipilimumab + nivolumab + AZA arm: mOS 7.6 months; Nivolumab + AZA arm: mOS 5.9 months; AZA control arm: mOS 4.4 months	[22]
NCT03066648	Phase Ib, sabatolimab +/− PDR001 + HMA	TIM-3	AML	ND AML unsuitable for induction chemotherapy: ORR 41.2%, CR 8%, CRi 3%, PR 3%	[23]
NCT02785900	Phase III, vadastuximab talirine + AZA/decitabine vs. placebo	CD33	Older ND AML	Terminated (due to poor safety)	[24,25]
NCT02575963	Phase II, 225 Ac-lintuzumab	CD33	AML	69% remission	[26]
NCT02520427	Ongoing phase I, AMG330	CD33	R/R AML	CR/CRi 11.4%	[27]
NCT03647800	Phase IB, APVO436	CD123	R/R AML	N/A	[28]
NCT02730312	Ongoing phase I, vibecotamab	CD123	R/R AML	CR/CRi: 23%	[29]
NCT03386513	Ongoing phase I/II, IMGN632	CD123	R/R AML	CR: 1/12, CRi: 3/12	[30]
NCT03113643	Ongoing phase I, tagraxofusp + AZA vs. AZA/venetoclax	CD123	AML	N/A	[31]
NCT02152956	Ongoing phase I/II, flotetuzumab	CD123	R/R AML	ORR 13.6%, CR 11.7%	[32]
NCT00008177	Phase I, iomab-B + FLU + 2 Gy TBI	CD45	Over 50 years AML	N/A	[33]
NCT02665065	Ongoing phase III, iomab-B + FLU + low-dose TBI	CD45	R/R AML	N/A	[33]
NCT01300572	Phase I, 90Y-BC8 + FLU/TBI	CD45	AML ineligible for allogeneic HSCT	OS at 1.8 years: 53%	[34]
NCT03030612	Phase I/II, cusatuzumab monotherapy followed by cusatuzumab + AZA	CD70	Untreated older AML	CR/CRi: 83%	[35]

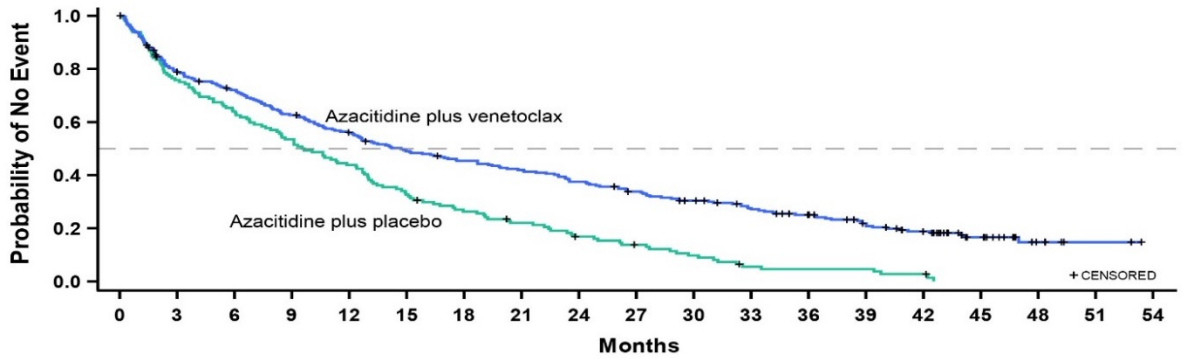
Gallazzi et al, Int J Mol Sci, 2022



Lachowiez C A et al. Ther Adv Hematol 2022, Vol. 13: 1–15

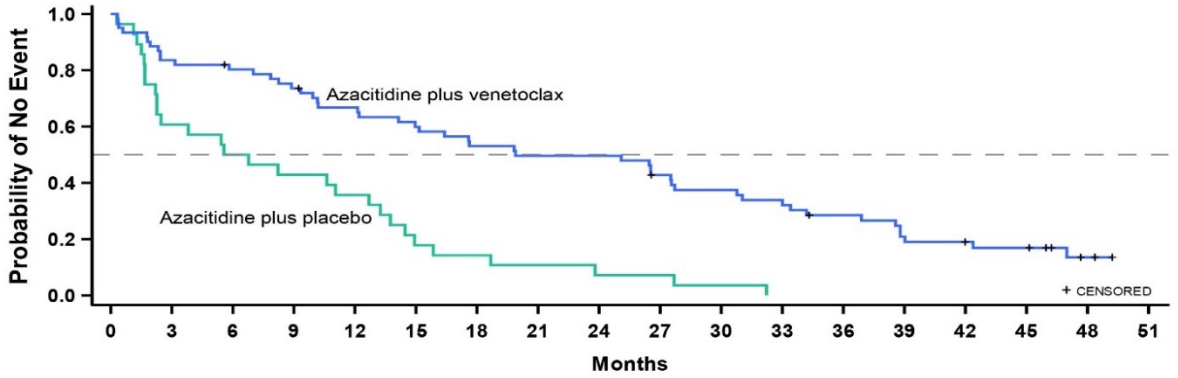
219 Long-Term Follow-up of the Phase 3 Viale-A Clinical Trial of Venetoclax Plus Azacitidine for Patients with Untreated Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy

Figure 1. Overall Survival



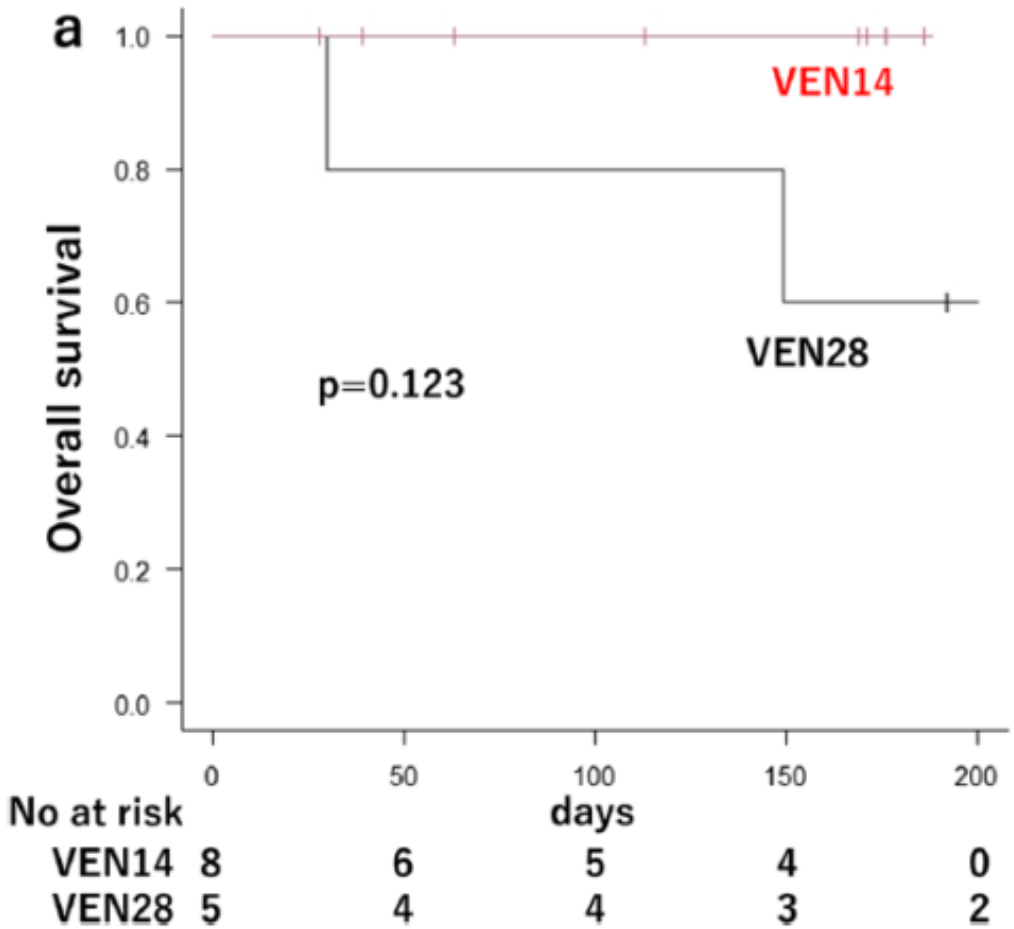
Patients at Risk																		
Azacitidine plus placebo	145	109	92	77	63	47	37	30	22	17	12	6	5	5	3	0		
Azacitidine plus venetoclax	286	220	199	173	153	133	122	113	101	89	78	67	57	45	34	18	6	2	0

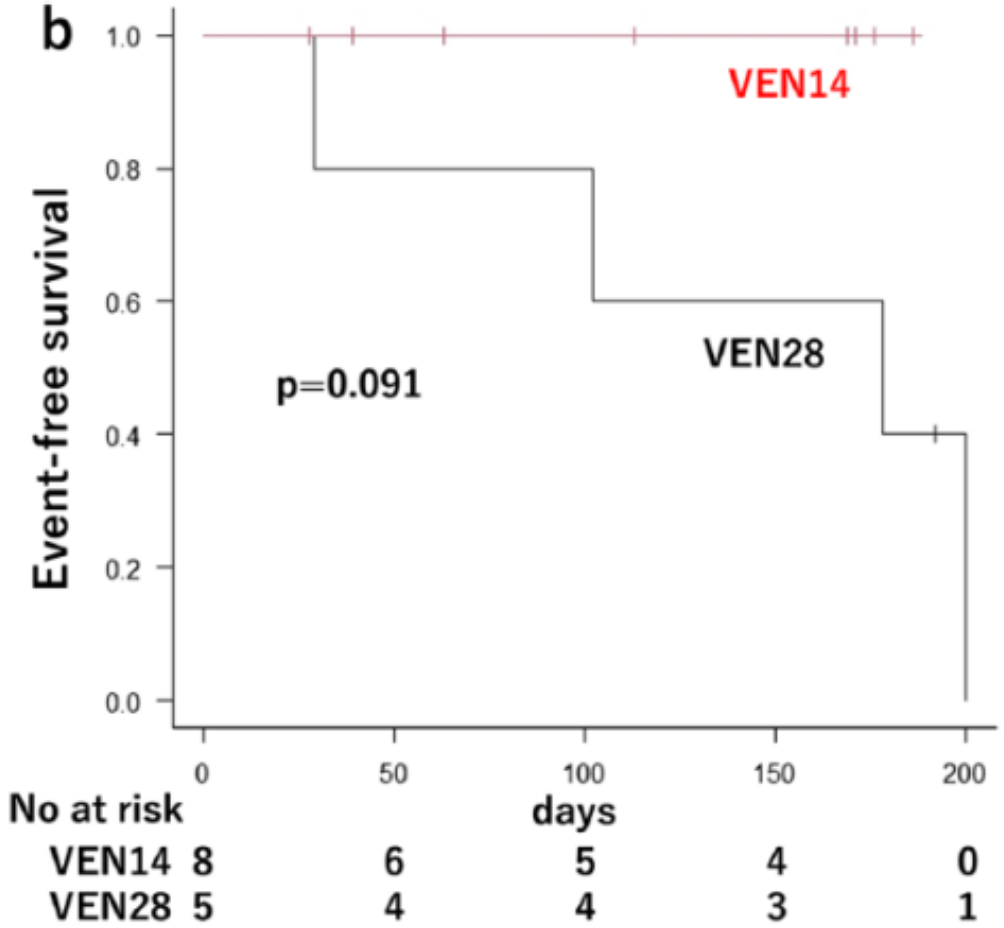
Figure 2. Median OS reached for patients with IDH1/2 mutations treated with azacitidine plus venetoclax



Patients at Risk																	
Azacitidine plus placebo	28	17	14	12	10	5	4	3	2	2	1	0					
Azacitidine plus venetoclax	61	51	48	44	39	35	31	29	29	24	21	19	15	11	9	8	3	0

Pratz et al. ASH 2022, OP





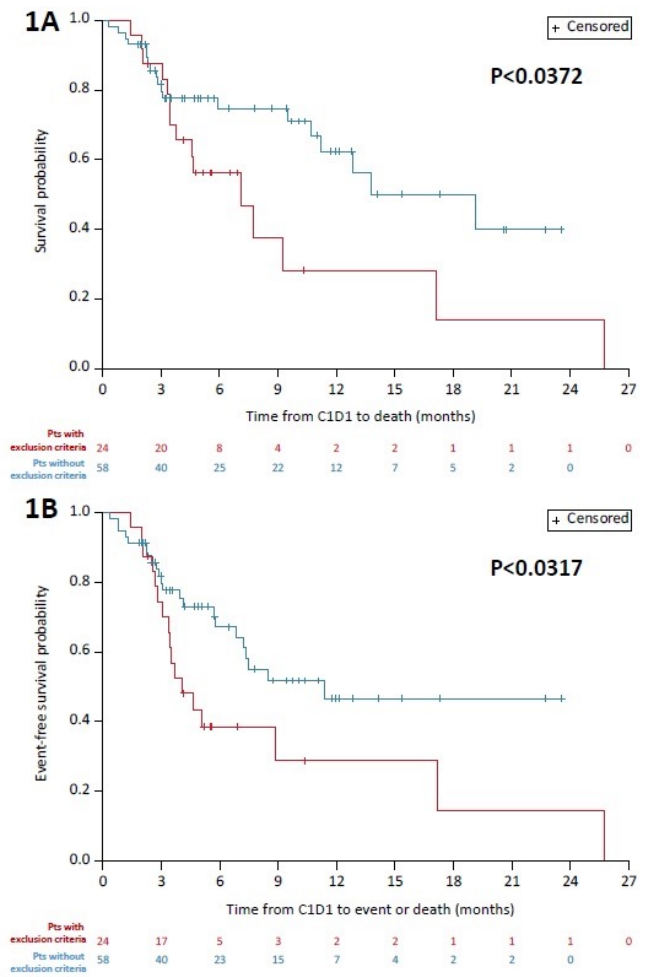
Aiba et al, Ann Hemat, 2023

222 Reduced Venetoclax Exposition to Seven Days of Azacitidine Is Efficient in Treatment-Naïve Patients with Acute Myeloid Leukemia

Table 1: Characteristics of the patients

Age	
Median (range) – year	75.2 (50.5 – 89)
≥75 year – N (%)	46 (56.1%)
ECOG performance status score – N (%)	
0 - 1	52 (63%)
2 - 4	30 (37%)
Exclusion criteria's to VIALE-A protocol – N (%)	24/82 (29.3%)
Active solid/lymphoid neoplasia at AML diagnosis	11 (45.8%)
Altered ECOG Performans Status (≥3 if ≥75 years; ≥4 if <75 years)	6 (25.0%)
Chronic renal failure (creatinine clearance <30ml/min)	4 (16.7%)
Prior myeloproliferative neoplasm	3 (12.5%)
AML type – N (%)	
De novo	36 (44%)
Secondary	46 (56%)
Secondary AML – N (% from secondary AML)	
Therapy-related AML	26 (56%)
History of MDS or CMML	17 (37%)
History of MPN	3 (7%)
AML with MRC (WHO 2016) – N (%)	24 (29%)
WBC at diagnosis – median, G/L (range)	4.8 (0.3 – 168.3)
Baseline cytopenia at C1 D1 grade ≥3	
Anemia – N (%)	10 (12%)
Neutropenia – N (%)	41 (50%)
Thrombocytopenia – N (%)	34 (41%)
Cytogenetic risk NCCN 2016 – N (%)	
Favorable	1 (1.2%)
Intermediate	49 (59.8%)
Normal karyotype	33 (40.2%)
Poor	27 (32.9%)
Complex (≥3 abnormalities)	17 (22.1%)
NA	5 (6.1%)
Gene mutations (VAF ≥1%) – N (%)	
TP53	17/80 (21.3%)
NPM1	12/82 (14.6%)
FLT3-ITD	11/82 (13.4%)
IDH2	9/80 (11.3%)
IDH1	7/80 (8.8%)
ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1 or *ZRSR2*	37/77 (48.0%)
ELN-2022 risk classification – N (%)	
Favorable	11/82 (13.4%)
Intermediate	14/82 (17.1%)
Adverse	57/82 (69.5%)

Figure 1: OS (1A) and EFS (1B) according to VIALE-A protocol exclusion criteria.



Willekens et al. ASH 2022, OP

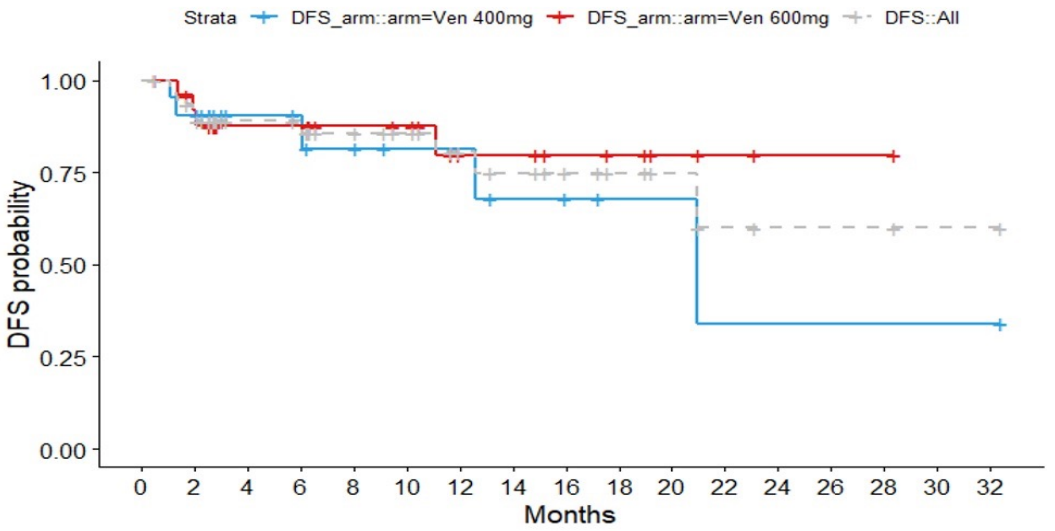
710 Gimema AML1718 Part 1: Planned Interim Analysis of a Safety Run-in and Phase 2 Open-Label Study of Venetoclax, Fludarabine, Idarubicin and Cytarabine (V-FLAI) in the Induction Therapy of Non Low-Risk Acute Myeloid Leukemia

Table 1: Response assesment after induction

		Arm		
Characteristic	Overall, N = 57	Ven 400mg, N = 28	Ven 600mg, N = 29	p-value[1]
CR	38 (70%)[2]	15 (58%)	23 (82%)[2]	0.19
CRp	7 (13%)	6 (23%)	1 (3.6%)	
CRi	2 (3.7%)	1 (3.8%)	1 (3.6%)	
PR	3 (5.6%)	2 (7.7%)	1 (3.6%)	
SD	4 (7.4%)	2 (7.7%)	2 (7.1%)	
CRR	**48 (84%)[2]**	**22 (79%)**	**26 (90%)[2]**	**0.30**

[1]Fisher's exact test
[2]1 patient obtained PR after 1st induction and CR after 2nd V-FLAI

VEN: venetoclax; CR: complete response; CRp: complete response without full platelet recovery; CRi: complete response without platelet and neutrophils recovery; PR: partial response; SD: stable disease; CCR: cumulative complete remission.



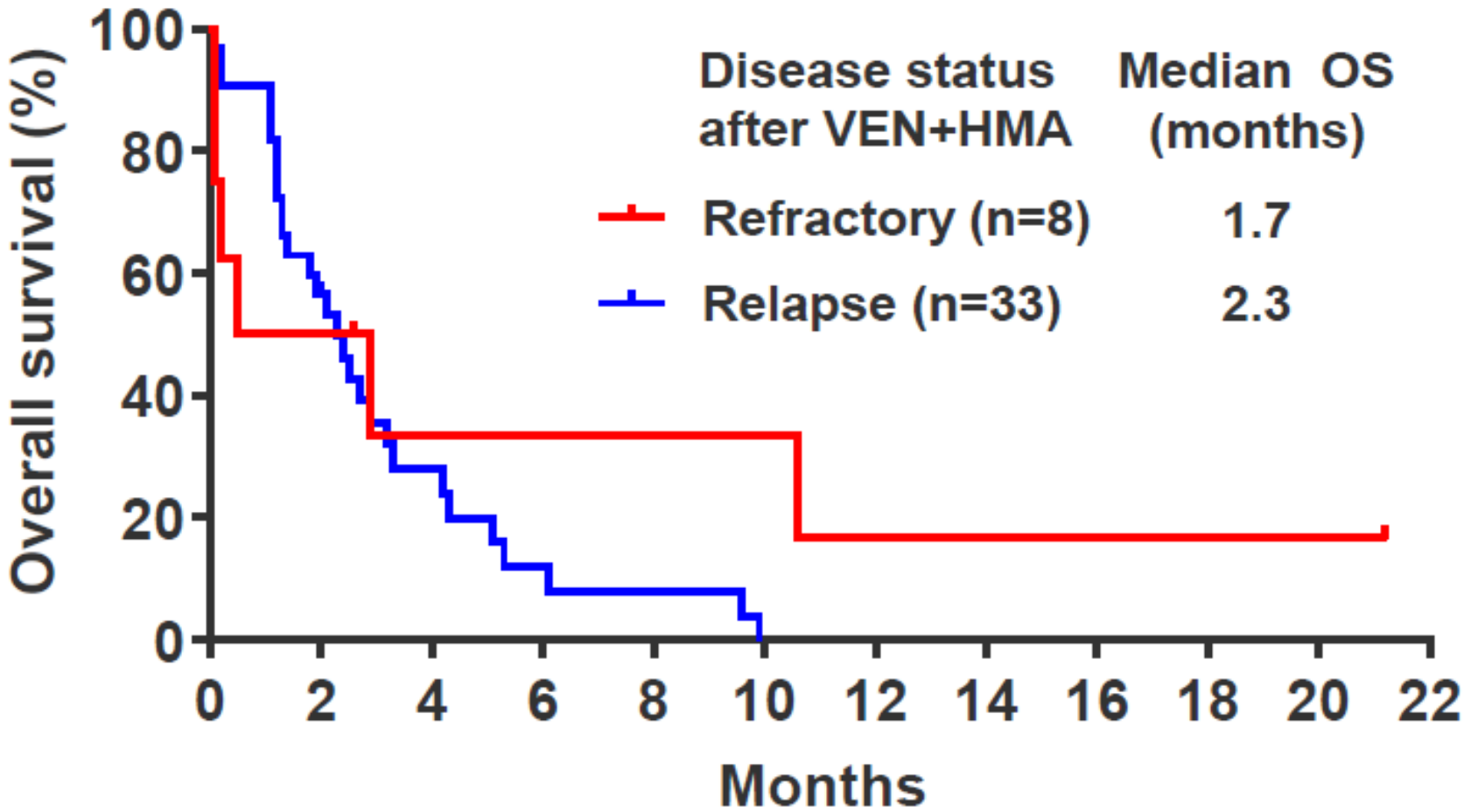
Marconi et al, ASH 2022

The successful combination of grapefruit juice and venetoclax in an unfit acute myeloid leukemia patient with adverse risk: A case report

Zhangbiao Long†, Min Ruan†, Wei Wu, Qingshu Zeng, Qingsheng Li* and Zhengqi Huang*

Department of Hematology, The First Affiliated Hospital of Anhui Medical University, Hefei, China

Front Oncol, 2022



Maiti et al, Haematologica, 2020

Venetoclax plus hypomethylating agents or low-dose cytarabine in acute myeloid leukemia: all that glitters is gold?

Felicetto Ferrara[1]

Table 2 Pros and cons for Ven/HMA and ICT for older AML-fit patients.

	Pros	Cons
Ven/HMA	Possible outpatient management	Undefined duration of therapy
	Low early mortality rate	Complex antifungal prophylaxis
	High response rate in either intermediate or unfavorable ELN risk categories	Uncertainty on response evaluation
		Poor outcome at progression/relapse
ICT	Short-term therapy	Low response rate in poor-risk patients
	Fast bridge to allo-SCT	Prolonged hospitalization
		Potentially high early mortality rate
		Toxicity restricting eligibility to allo-SCT

Ferrara F, BCJ, 2020

MRD in Venetoclax-Based Treatment for AML: Does it Really Matter?

Massimo Bernardi[1], Felicetto Ferrara[2], Matteo Giovanni Carrabba[1], Sara Mastaglio[1], Francesca Lorentino[1], Luca Vago[1,3] and Fabio Ciceri[1,3]*

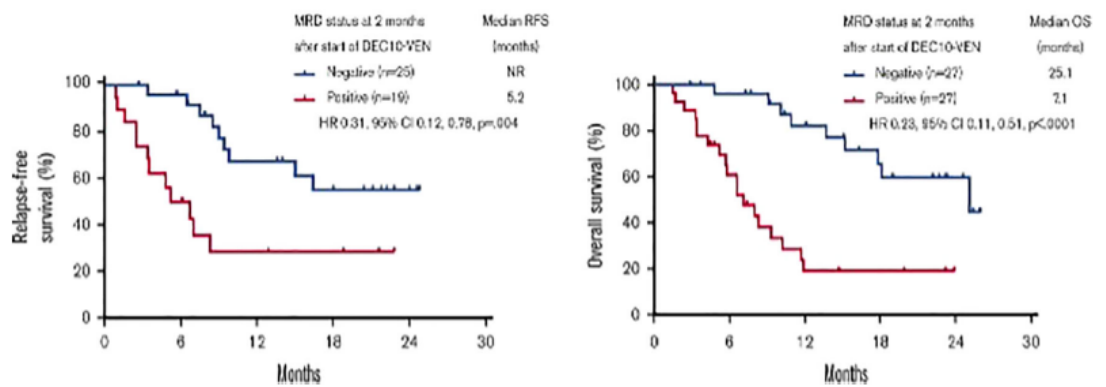


FIGURE 2 | Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia (10). Figure from Maiti A, et al. Blood Adv 2021 (10). HR, hazard ratio; NR, not reached.

Front Oncol, , 2022

Practical Take-homes on VEN + AZA Therapy in AML

- VEN/AZA remains optimal approach for newly diagnosed AML not suitable for intensive therapy, irrespective of cytogenetic or molecular features at this time
  - Generally well tolerated, with 30-day mortality of 6% to 7%
  - Prolonged neutropenia compared with AZA alone
  - Early bone marrow assessment (EOC1) with VEN interruption and shortened VEN duration for count recovery is recommended
- Responses are quick, with a median time to response of 1 mo
  - Therapy is indefinite
  - Flow MRD negative status predicts for improved DoR and OS

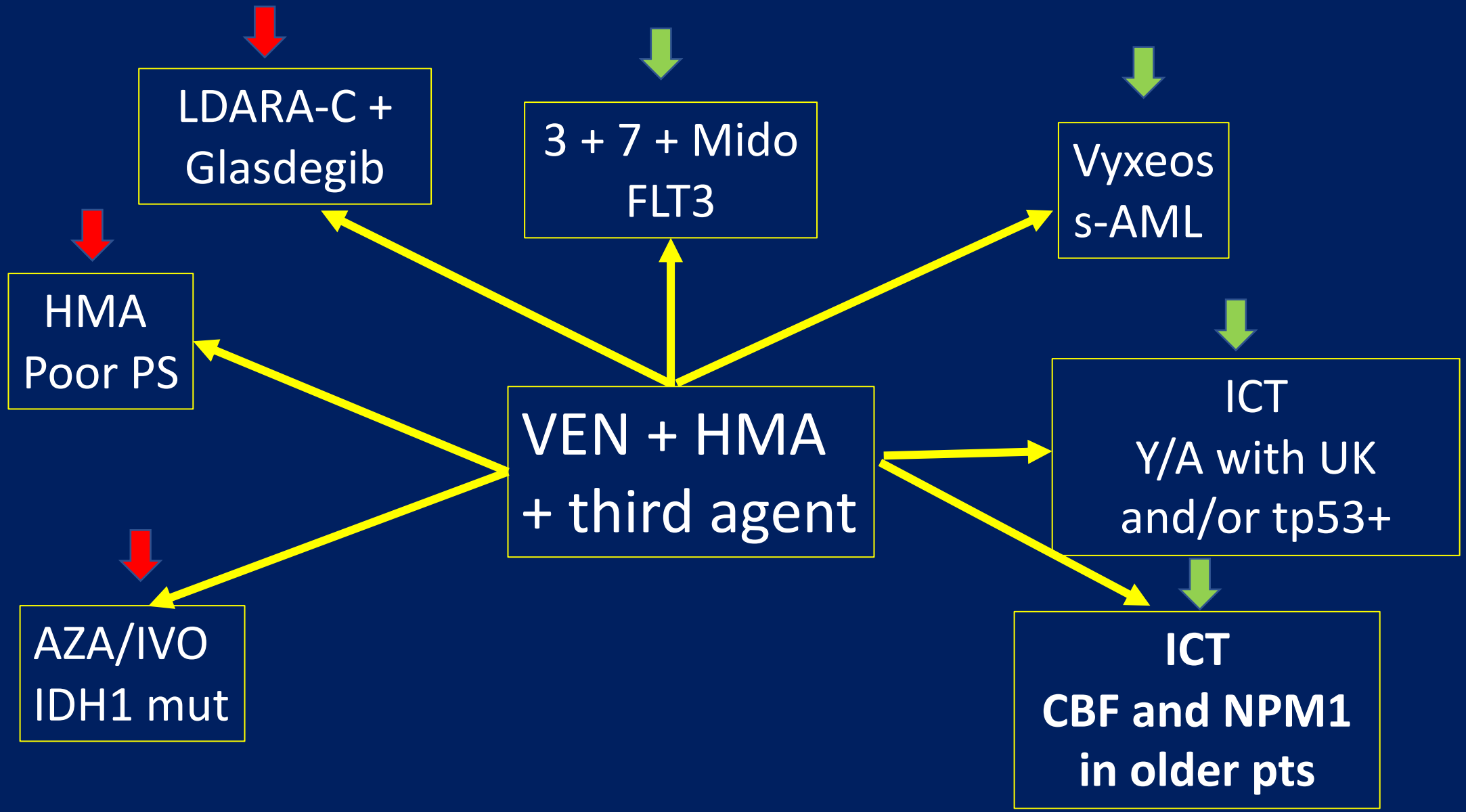
Pratz. JCO. 2022;40:855. Pratz. ASH 2020. Abstr 1944.

How to further improve therapeutic results of VEN/HMA combination ?

Add additional tergeted therapies to VEN/HMA backbone, (eg. Triplets)

- **HMA/VEN + FLT3 inhibitor**
- **HMA/VEN + MoAbs (GO; sabatolimab, magrolimab, BITES)**
- **HMA/VEN + any other investigational targeted therapy**

Ongoing competition



Speaker suggestion

AGILE: Study Design

IVO+AZA Combination Therapy in 1L IC-Ineligible AML Patients with an IDH1 mutation

A Global, Phase 3 Trial

20 Countries

Double-blind (n=200)

RANDOMIZATION 1:1

Stratified by geographic region & de novo status*

1:1

- Geographic regions: US/Canada; Western Europe, Israel & Australia; Japan; and ROW
- De novo status – De novo v/s secondary

Ivosidenib Arm (n=100)

Ivosidenib 500 mg PO QD, days 1-28 + Azacitidine 75 mg/m^2 SC or IV, days 1-7

Placebo Arm (n=100)

Placebo PO QD, days 1-28 + Azacitidine 75 mg/m^2 SC or IV, days 1-7

1°

Primary Endpoint

Event Free Survival (EFS)

with ~173 events (52 months)

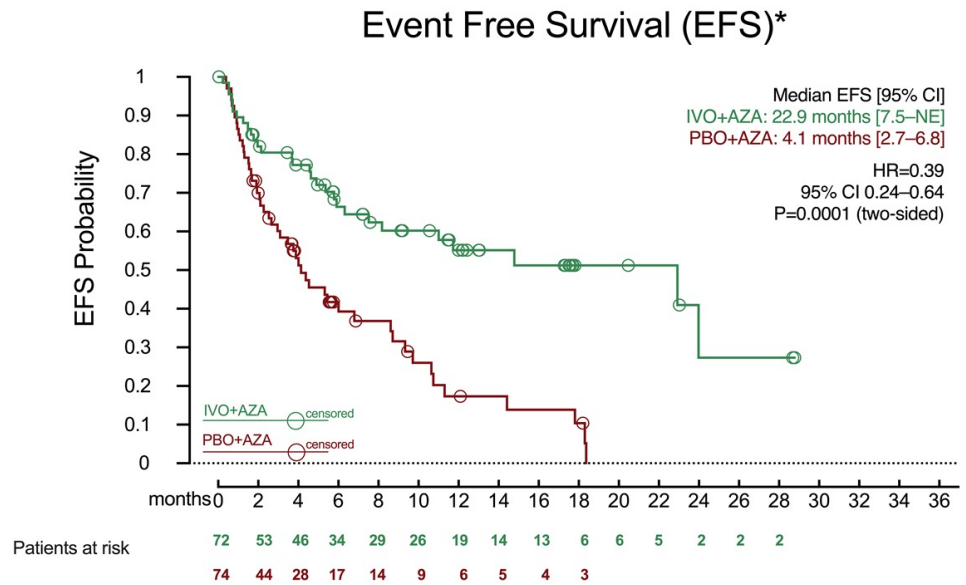
2°

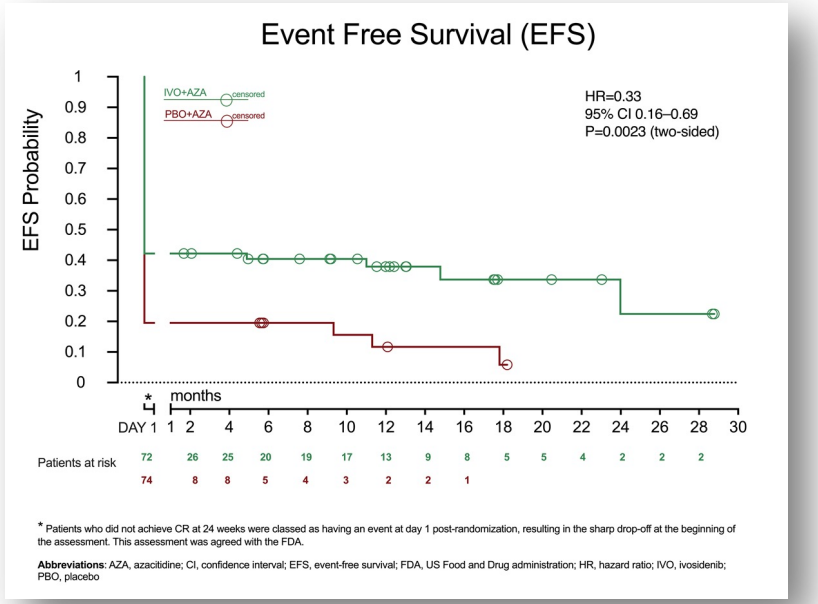
Secondary Endpoint

OS ·
Clinical Response
(CR, CR+CRh, ORR)

Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, Heuser M, Calado RT, Schuh AC, Yeh SP, Daigle SR. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. New England Journal of Medicine. 2022 Apr 21;386(16):1519-31.

Primary Endpoint: Event Free Survival



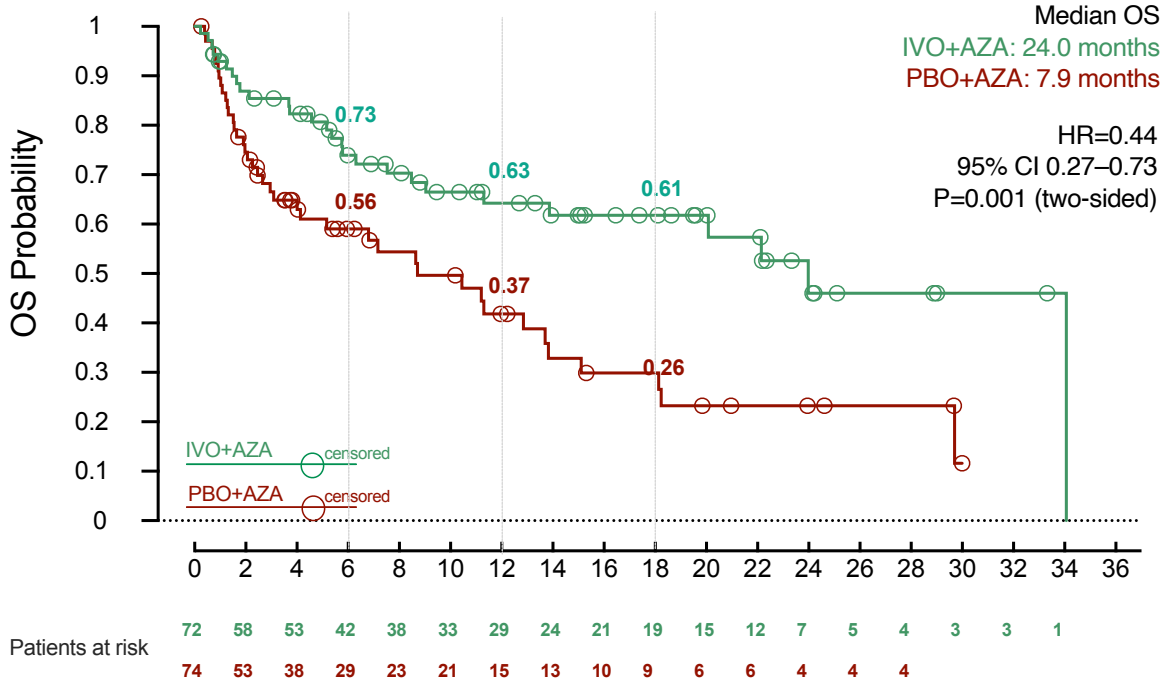


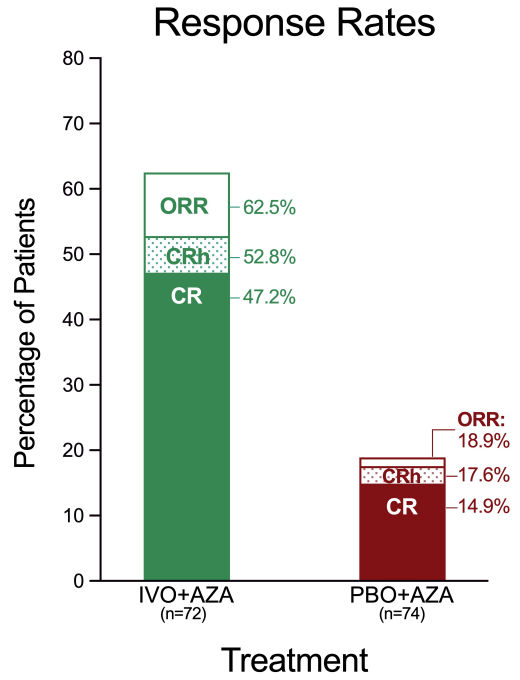
*Exploratory analysis of EFS: The day of the event is the earliest date of treatment failure / relapse / death. Treatment failure was defined as absence of CR, CRi or MLFS by week 24

Abbreviations: AZA, azacitidine; CI, confidence interval; EFS, event-free survival; CR(i), complete response (with incomplete hematologic recovery); EFS, event-free survival; HR, hazard ratio; IVO, ivosidenib; MLFS morphologic leukemia-free state; NE, not estimable; PBO, placebo

Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, Heuser M, Calado RT, Schuh AC, Yeh SP, Daigle SR. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. New England Journal of Medicine. 2022 Apr 21;386(16):1519-31.

Secondary Endpoints: Overall Survival & Response Rates



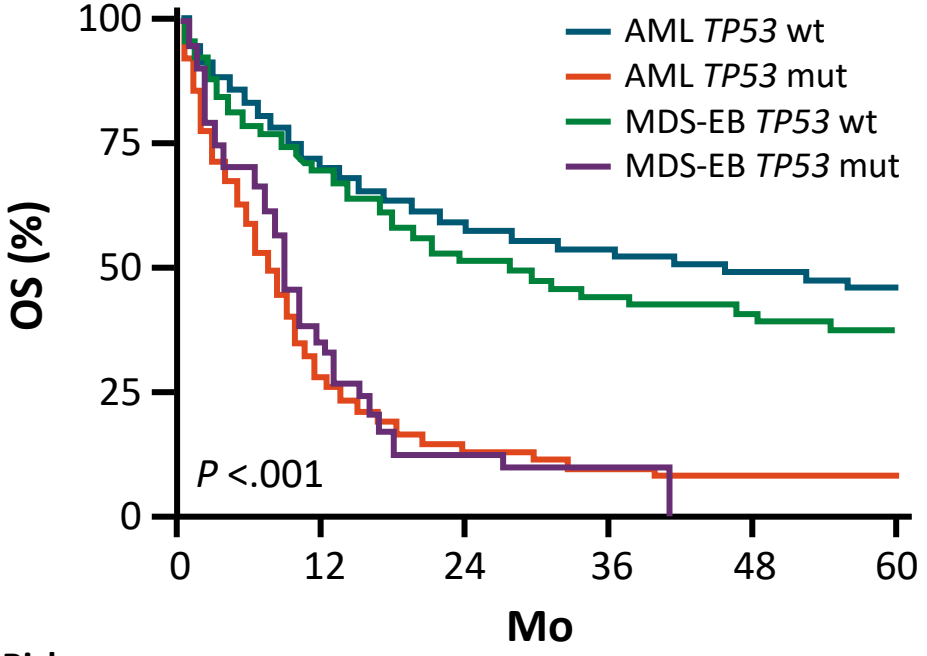


Abbreviations: ORR Overall Response rate; CR Complete response; CRh complete response with partial hematologic recovery; IVO Ivosidenib; PBO placebo; AZA Azacitidine; CI Confidence interval

Montesinos P, Recher C, Vives S, Zarzycka E, Wang J, Bertani G, Heuser M, Calado RT, Schuh AC, Yeh SP, Daigle SR. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. New England Journal of Medicine. 2022 Apr 21;386(16):1519-31.

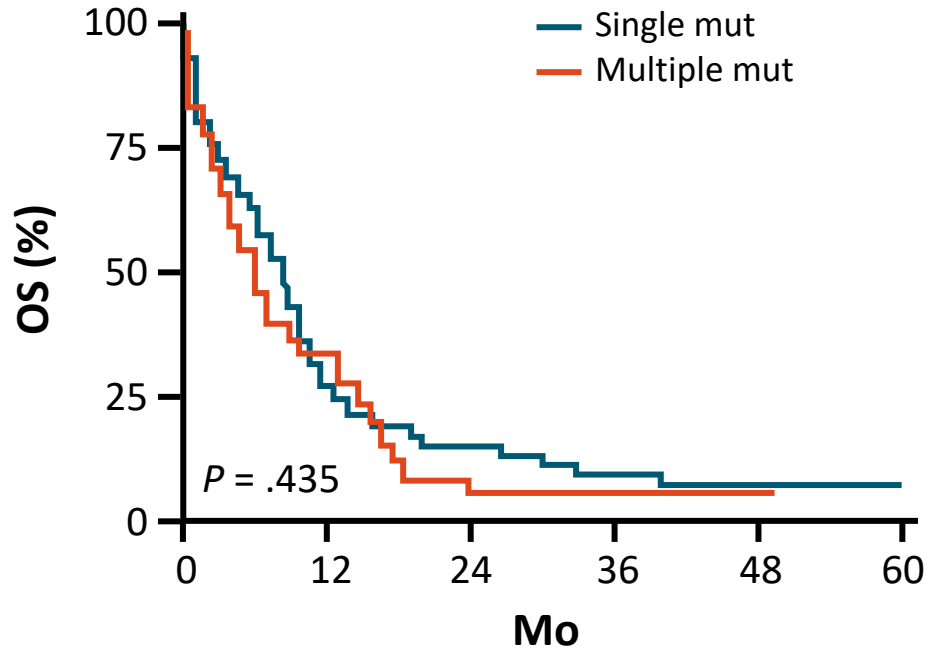
Mutated *TP53* in AML and MDS With Excess Blasts

- Accumulating evidence, both clinical and molecular: AML and MDS with mutated *TP53* represent a distinct molecular disease entity



Patients at Risk, n

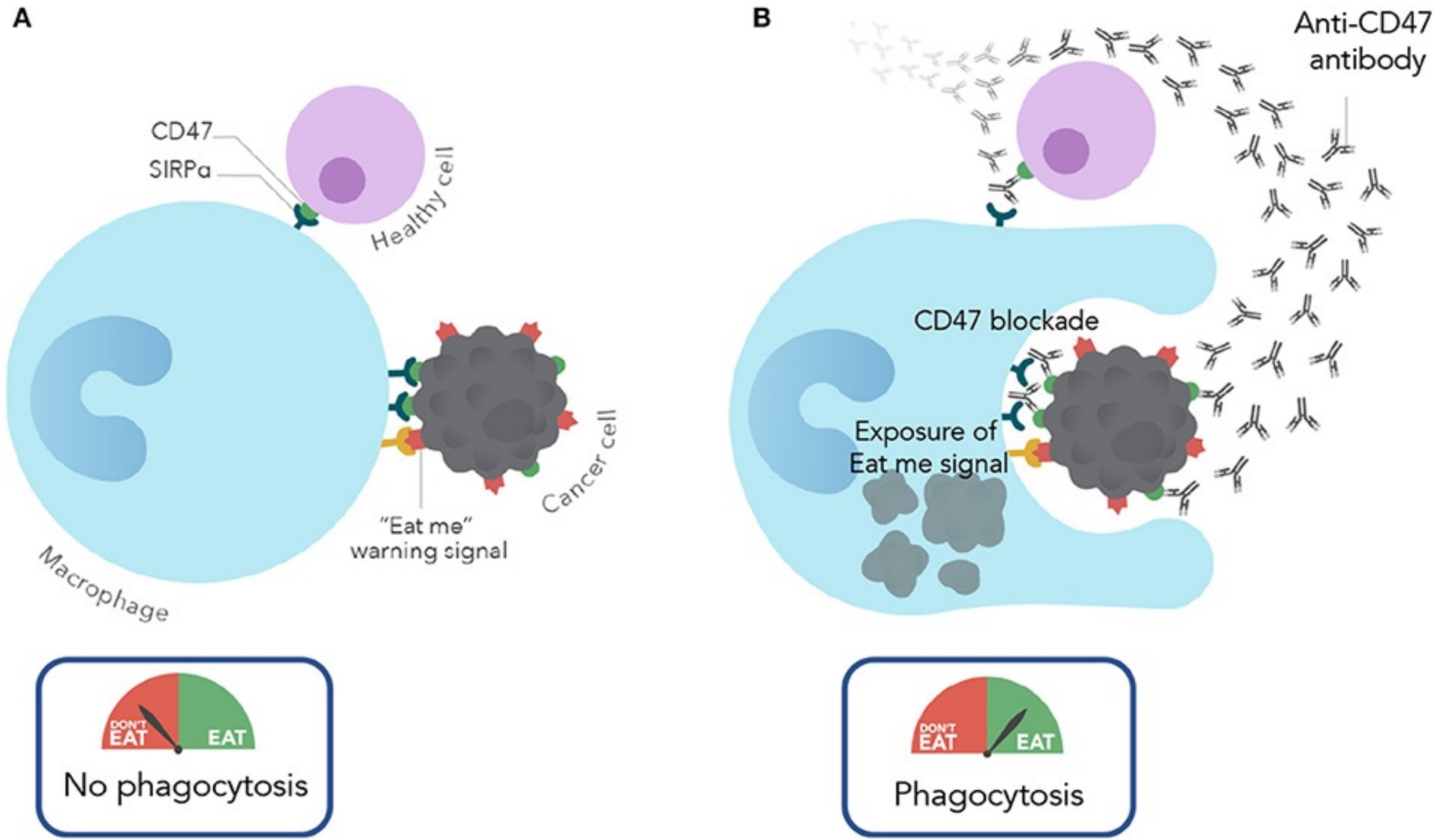
AML *TP53* wt	1805	1255	1014	807	572	397
AML *TP53* mut	186	50	23	14	9	5
MDS-EB *TP53* wt	165	114	81	62	45	35
MDS-EB *TP53* mut	44	15	5	1	0	0



Patients at Risk, n

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

Grob. Blood. 2022;139:2347.


A
CD47
SIRPα
Healthy cell
Cancer cell
"Eat me"
warning signal
Macrophage
DON'T EAT
EAT
No phagocytosis
B
Anti-CD47
antibody
CD47 blockade
Exposure of
Eat me signal
DON'T EAT
EAT
Phagocytosis

Outcomes for Newly Diagnosed *TP53*-Mutated AML

Agent/Regimen	Study Phase	Patients With *TP53* Mutation, n	Response, %	CR Rate, %	mOS, Mo
AZA or decitabine	II; retrospective	22	CR/CRi: 22-38	13-22	2.1-7.3
VEN + AZA or 5-day decitabine	Ib/II, III	36, 54	CR/CRi: 47, 41	NR, 20	4.9-7.2
VEN + 10-day decitabine	II; post hoc	26	ORR: 77	48	5.4
Magrolimab + AZA	Ib	72	CR/CRi: 49	33	10.8
Magrolimab + VEN + AZA	Ib/II	14	ORR: 86	64	NR
Eprenetapopt + AZA	Ib/II	18	ORR: 33	17	10.4
Sabatolimab + HMA	Ib	5	CR/CRi: 40	20	DoR: 6.4
SGN-CD33A ± HMA	I/II	7	CR/CRi: 86	NR	NA
Nivolumab + intensive chemotherapy	Post hoc	4	ORR: 50	NA	NA
Intensive chemotherapy	Retrospective	Various	ORR: 47-55	45-55	6.8-8.8
Low-intensity chemotherapy	Retrospective	Various	ORR: 14-50	36	6.7-9.0

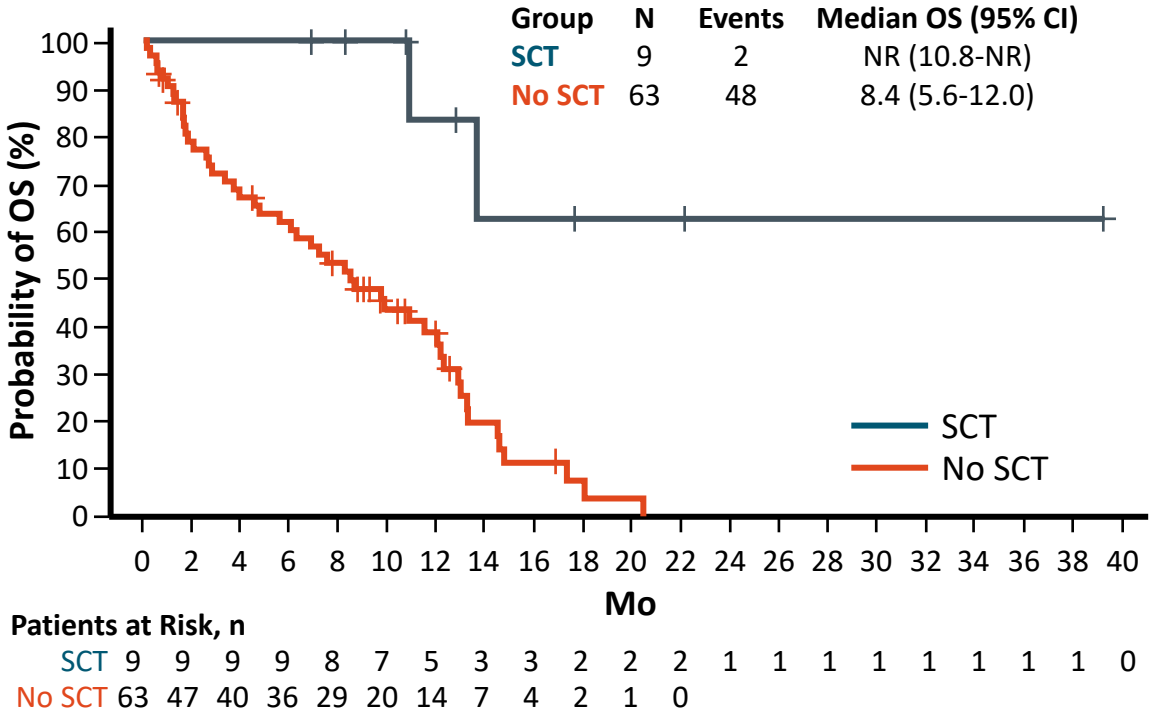
Daver. Cancer Discov. 2022;12:2516.

Magrolimab in Combination With AZA Demonstrated Encouraging Response Rates in *TP53*^{mut} AML

Efficacy Endpoints (Intention-to-Treat Analysis)

Outcome	*TP53*^{mut} (n = 72)
ORR, n (%) ▪ CR ▪ CRi/CRh ▪ PR ▪ MLFS	45 (48.6) 24 (33.3) 6 (8.3) 4 (5.6) 1 (1.4)
Median DoR, mo	8.7
Median DCR, mo	7.7
Median TOR, mo	2.0
Median TCR, mo	3.0
CCyR, n/N (%)	10/31 (32.3)
MRD negativity in CR, n/N (%)	12/24 (50)
Median PFS, mo	7.3
Median OS, mo	10.8

Overall Survival With and Without SCT



- CR was achieved by 33.3% of patients, with one half of patients with CR being MRD negative
- 30 (41.7%) patients achieved CR/CRi
- 29.7% and 45.8% of baseline transfusion-dependent patients converted to RBC and platelet transfusion independence

Daver. EHA 2022. Abstr S132.

Phase Ib Trial of Azacitidine, Venetoclax, and Magrolimab in AML: Efficacy

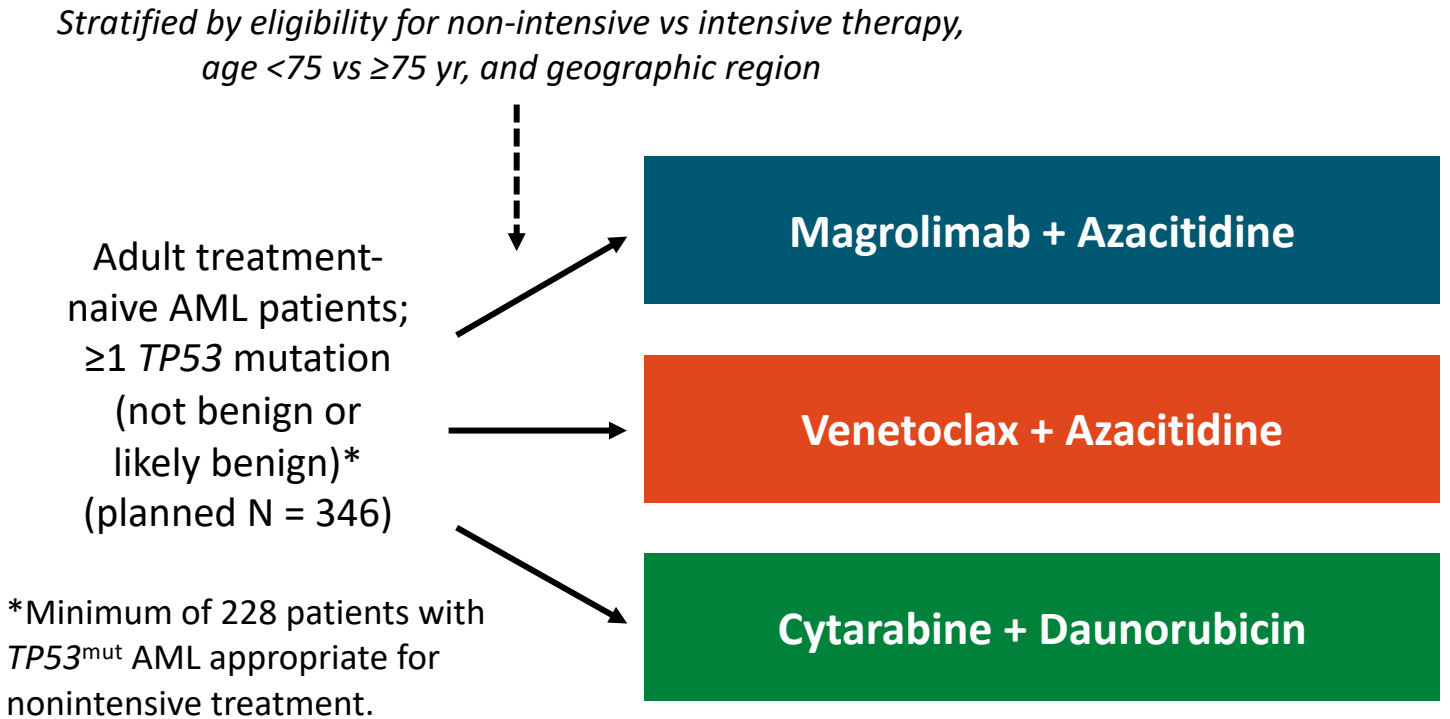
Outcome	ND Cohort (n = 25)		R/R Cohort (n = 23)	
	TP53^{mut} (n = 14)	*TP53*^{wt} (n = 11)	VEN Naive (n = 8)	Prior VEN (n = 15)
ORR, n (%)	12 (86)	11 (100)	6 (75)	3 (20)
▪ CR/CRi	**9 (64)**	10 (91)	5 (63)	3 (20)
▪ CR	**9 (64)**	7 (64)	3 (38)	0
▪ CRi	0	3 (27)	2 (25)	3 (20)
▪ MLFS/PR	3 (21)	1 (9)	1 (13)	0
MRD neg,* n/N (%)	**5/9 (55)**	4/9 (45)	2/6 (33)	0
CCyR, n/N (%)	4/9 (44)	5/6 (83)	3/5 (60)	1/2 (50)
No response	2 (14)	0	2 (25)	12 (80)
Time to first response, mo	0.7 (0.6-1.9)	0.7 (0.7-1.5)	0.7 (0.6-4.1)	2.2 (1.8-2.6)
Time to best response, mo	1.5 (0.7-3.2)	1.1 (0.7-2.9)	1.5 (1.0-4.1)	2.0 (1.2-3.9)
Time to ANC >500, days	28 (20-41)			
Time to plts >50,000, days	24 (18-41)			
8-wk mortality, n (%)	0	0	1 (13)	3 (20)

*By flow cytometry.

Daver. ASH 2021. Abstr 371.

ENHANCE-2 Trial: Magrolimab + Azacitidine vs Physician's Discretion in Frontline *TP53*-Mutated AML

- Randomized, open-label phase III study of magrolimab + azacitidine

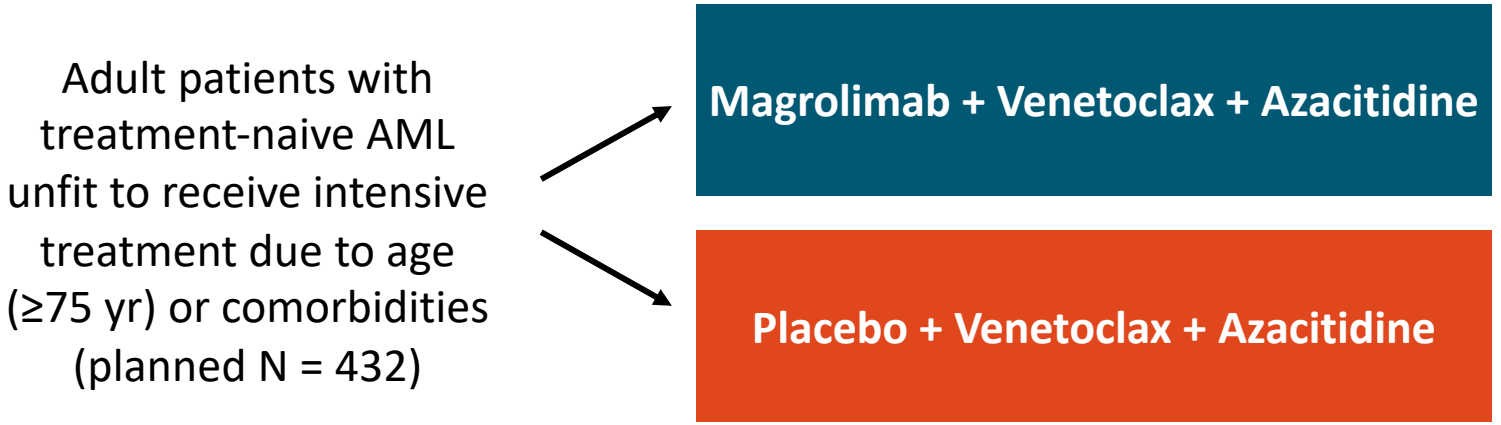


- Primary endpoint: OS in patients appropriate for nonintensive treatment
- Key secondary endpoints (in all patients): OS, EFS, transfusion independence, CR, CR MRD-

Daver. EHA 2022. Abstr P551. NCT04778397.

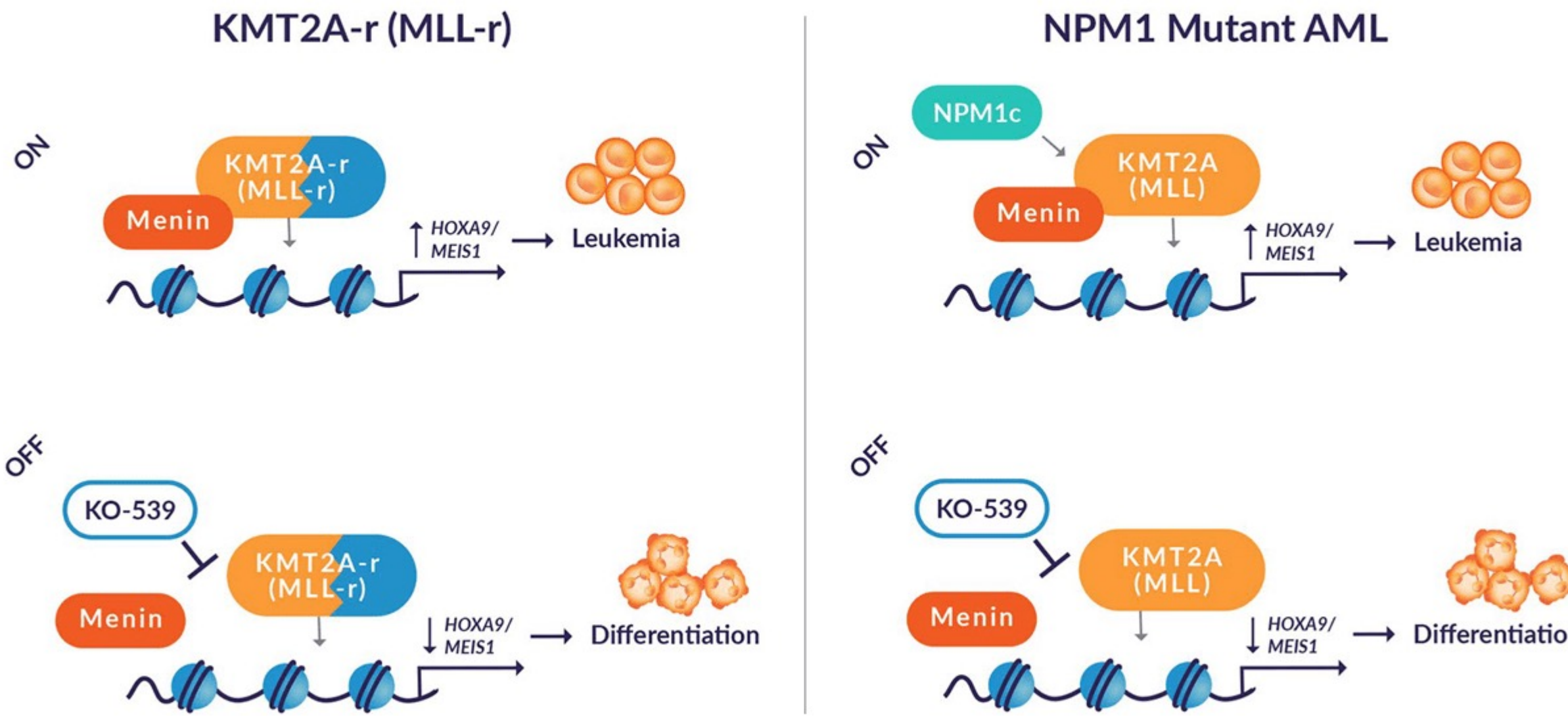
ENHANCE-3 Trial: Firstline Magrolimab + VEN + AZA vs VEN + AZA in Patients Ineligible for Intensive Treatment

- Randomized, double-blind, placebo-controlled phase III study



- Primary endpoints: CR, OS
- Key secondary endpoints: CR MRD-, CR + CRh, duration of CR, duration of CR + CRh, transfusion independence, EFS, QoL/PRO

Daver. EHA 2022. Abstr P550. NCT05079230.


KMT2A-r (MLL-r)
ON
KMT2A-r (MLL-r)
Menin
HOXA9/ MEIS1
Leukemia
OFF
KO-539
KMT2A-r (MLL-r)
Menin
HOXA9/ MEIS1
Differentiation
NPM1 Mutant AML
ON
NPM1c
KMT2A (MLL)
Menin
HOXA9/ MEIS1
Leukemia
OFF
KO-539
KMT2A (MLL)
Menin
HOXA9/ MEIS1
Differentiation

AUGMENT-101: Baseline Characteristics

Characteristic	Safety Population (N = 68*)
Median age, yr (range)	42.5 (0.8-79)
▪ Adult (n = 60)	50.5
▪ Pediatric (n = 8)	2.5
Female, n (%)	42 (62)
Leukemia type, n (%)	
▪ AML	56 (82)
▪ ALL	11 (16)
▪ MPAL	1 (2)
Median prior therapies, n (range)	4 (1-12)
▪ Stem cell transplant, n (%)	31 (46)
▪ Venetoclax, n (%)	41 (60)

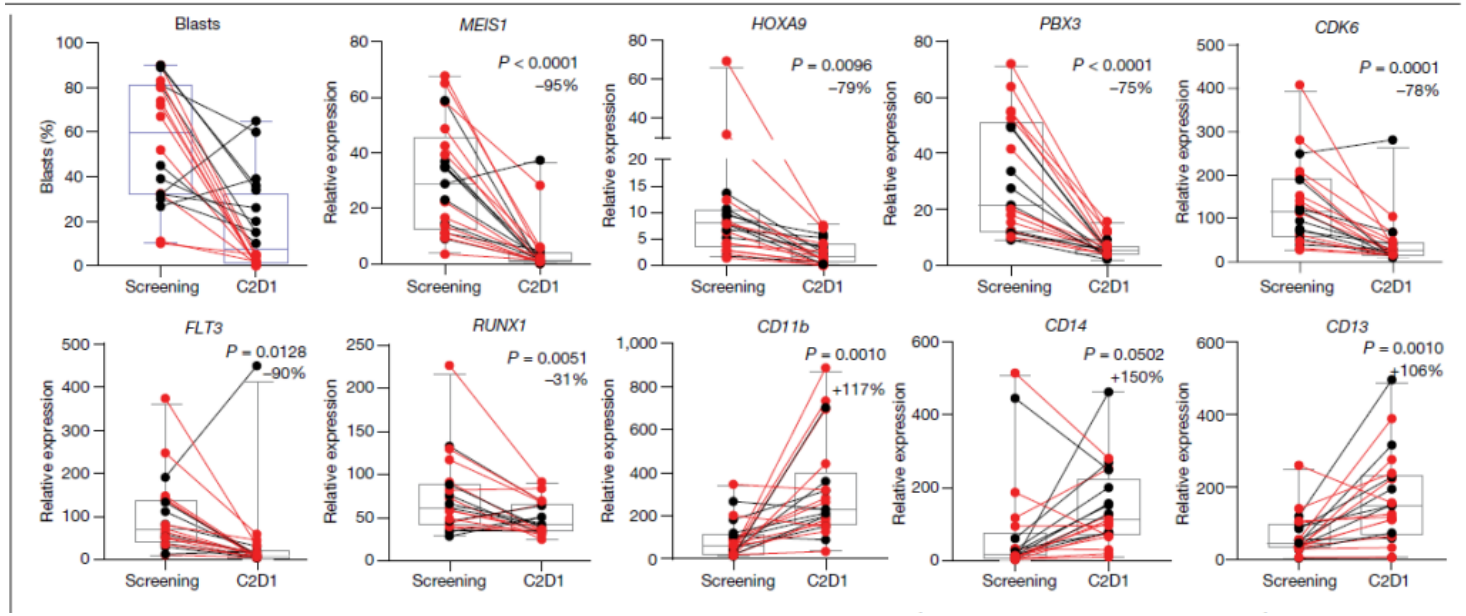
Characteristic	Safety Population (N = 68*)
KMT2Ar, n (%)	46 (68)
▪ t(9;11)	10 (15)
▪ t(11;19)	9 (13)
▪ t(4;11)	6 (9)
▪ t(6;11)	3 (4)
▪ t(11;17)	2 (3)
▪ Other	16 (24)
mNPM1, n (%)	14 (21)
KMT2a and *NPM1* WT, n (%)	8 (12)
Co-occurring mutations, n (%)†	
▪ *FLT3*	14 (25)
▪ *RAS*	12 (29)
▪ *TP53*	4 (10)

*Safety population included patients who received ≥1 dose of revumenib.
†In patients for whom co-occurring mutation data were available.

Issa. ASH 2022. Abstr 63.

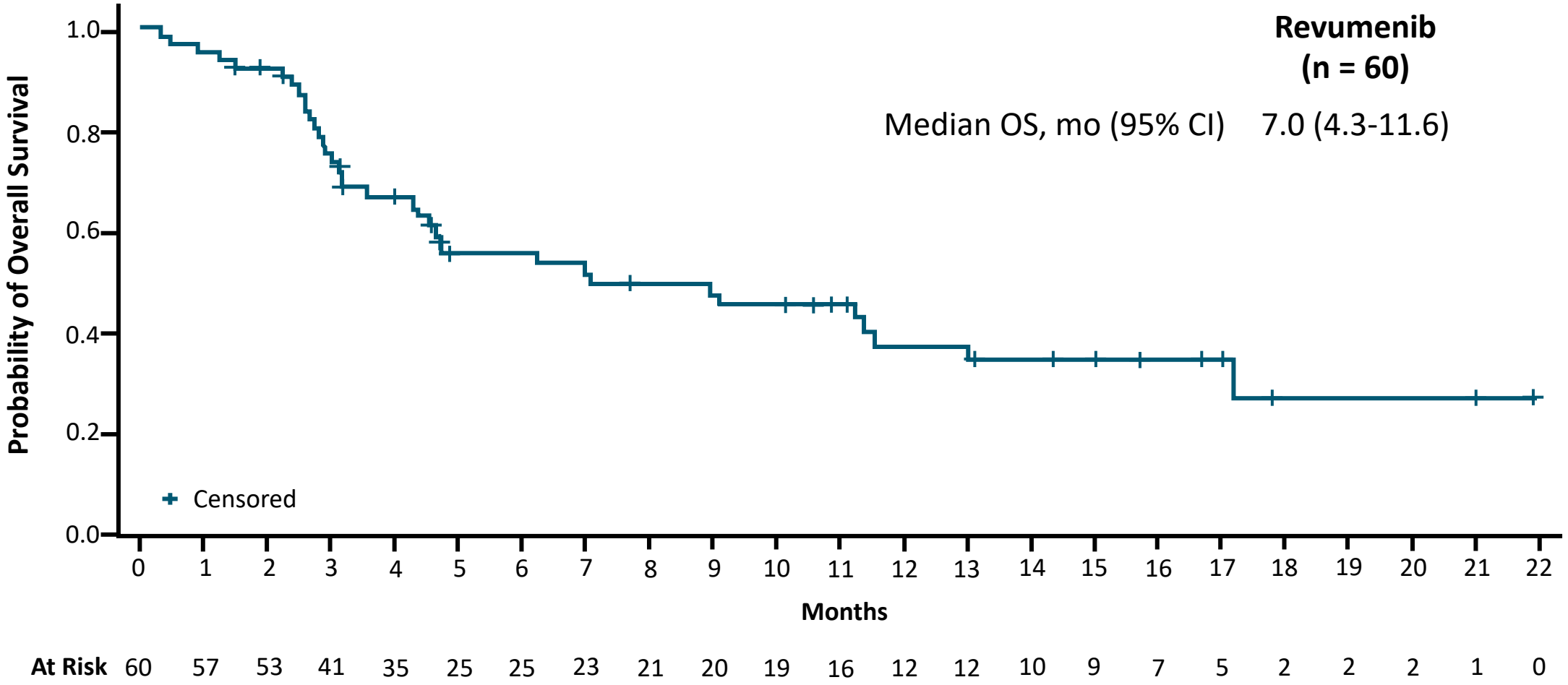
Article

The menin inhibitor revumenib in *KMT2A*-rearranged or *NPM1*-mutant leukaemia



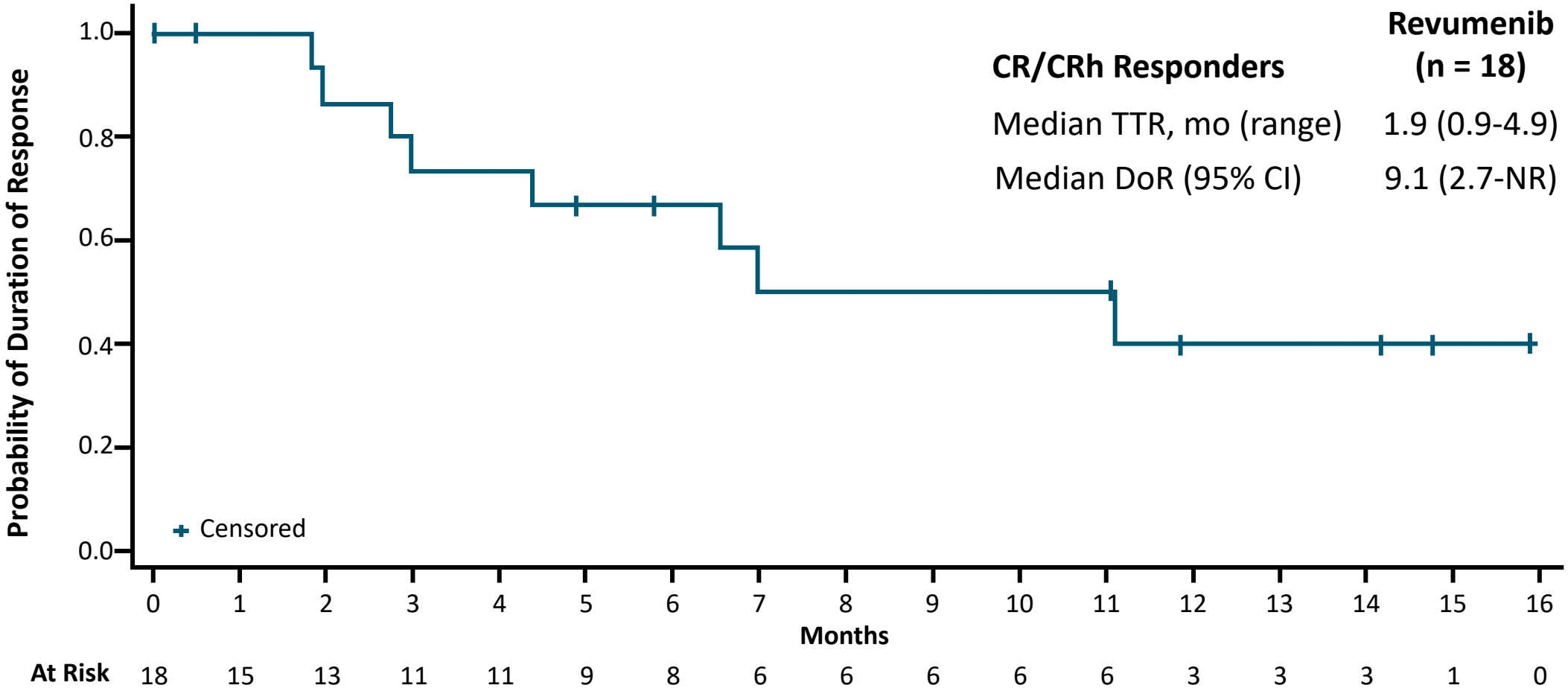
Issa et al, Nature, 2023

AUGMENT-101: OS



Issa. ASH 2022. Abstr 63. Reproduced with permission.

AUGMENT-101: DoR



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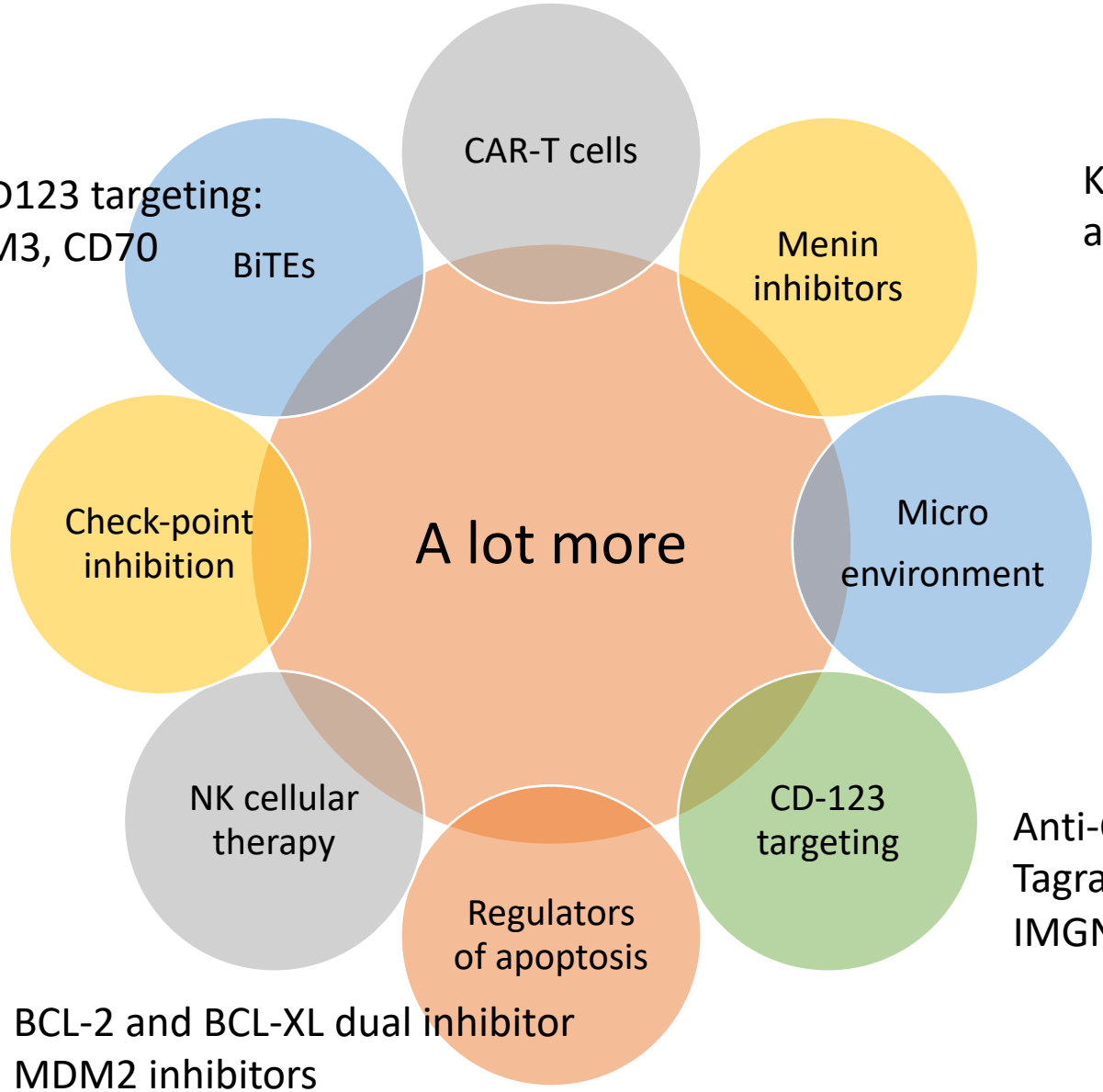
The future in AML is bright



Beyond CD33/CD123 targeting:
CLL1, IL1RAP, TIM3, CD70

KO-530 phase I: *NPM1*^{mut} and *KMT2A* rearranged AML

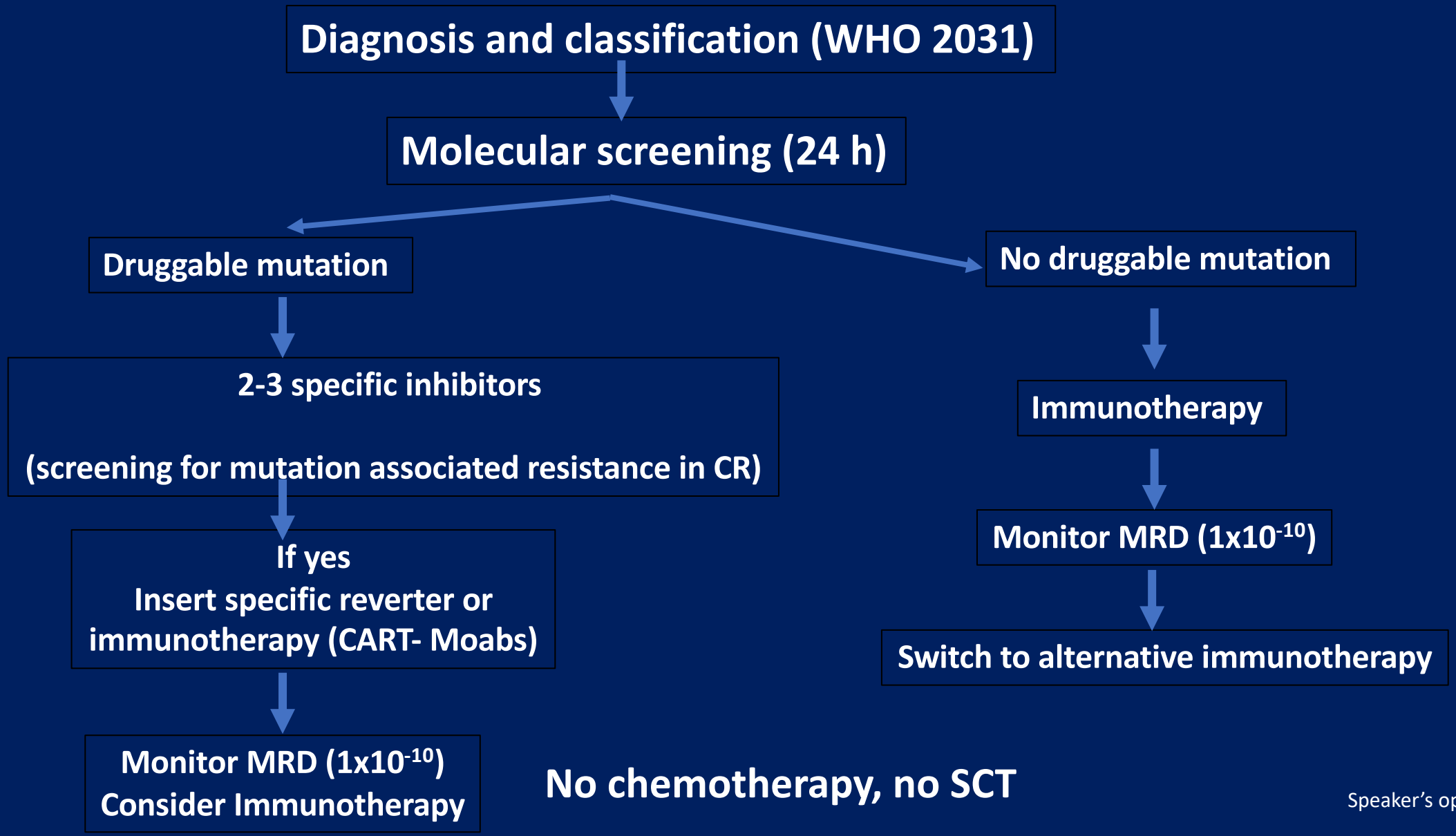
E-selectin antagonist:
Uproleselan (GMI-1271)

Anti-CD123 Ab drug-conjugate:
Tagraxofusp
IMGN-636

BCL-2 and BCL-XL dual inhibitor
MDM2 inhibitors

Speaker's opinion
Tagraxofsup and Uproselan are NOT APPROVED by EMA for use in AML

Therapeutic algorithm of AML in 2032



No chemotherapy, no SCT

Speaker's opinion

E’ IL 2035…

- Ormai guidiamo solo auto elettriche
- Il Napoli ha vinto 8 scudetti consecutivi e 3 champions
- Nella sala di attesa dell’Ematologia i pazienti vengono accolti da ALEXA…
- Non più chemioterapia e trapianto allogenico per AML
- L’Italia avrà un governo serio ? Tutti gli italiani pagheranno le tasse?