Treatment of Acute Myeloid Leukemia: Managing the AML Patient When Transplant is NOT an Option

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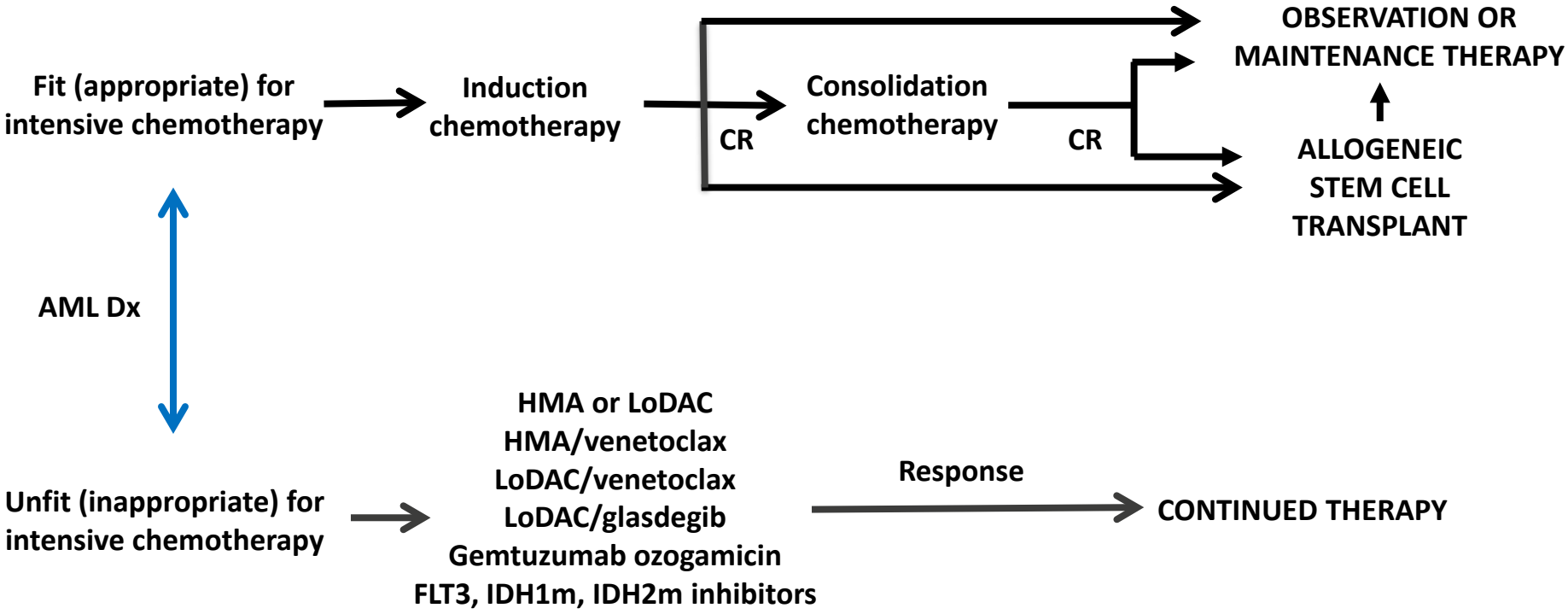
Disclosures of Potential Conflicts of Interest (09/01/2021 to 11/12/2023)

- Speaker Bureau: AbbVie, BMS, Incyte, Jazz, Novartis, Servier
- Consultant: AbbVie, Astellas, BMS, Daiichi Sankyo, Glycomimetics, Incyte, Jazz, Kura Oncology, Novartis, Pfizer, Servier, Stemline, Sumitomo Pharma
- Contracted Research: AbbVie, ALX Oncology, Amgen, Aptose, Ascentage, Daiichi Sankyo, Forma, Gilead, Glycomimetics, Immunogen, Jazz, Kura Oncology, MacroGenics, Novartis, PTC, Sumitomo Pharma
- Other: BMS (Chair, AML Registry Steering Committee), AbbVie (Chair, IRC for VIALE A and VIALE C), Glycomimetics (Scientific Steering Committee)

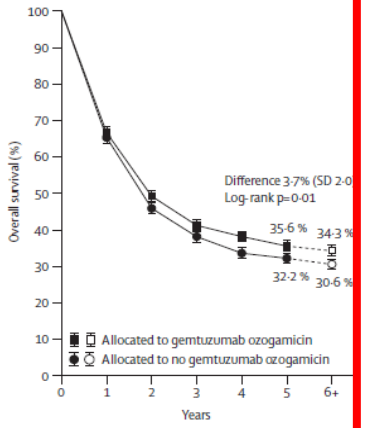
The Current AML Treatment Algorithm



Addition of GO to Induction Chemotherapy for AML

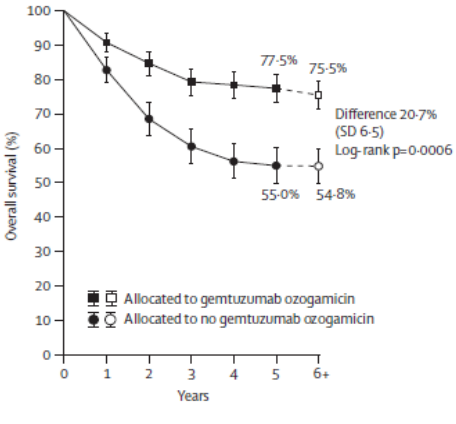
A Meta-Analysis of Data from 3325 Individual Patients

All



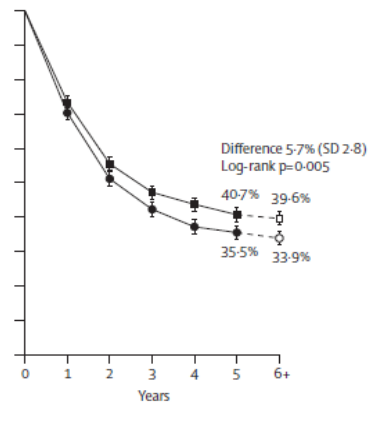
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	26·7 % SD 0·8	3·5 % SD 0·8
No gemtuzumab ozogamicin	29·5 % SD 0·9	5·2 % SD 1·0

Favorable



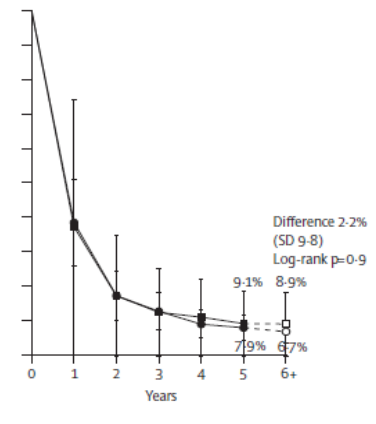
Annual event rates	Years 1–5	Years 6+
Gemtuzumab ozogamicin	5·8% SD 1·1	2·3% SD 1·3
No gemtuzumab ozogamicin	14·1% SD 1·9	0·0% SD 0·0

Intermediate



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

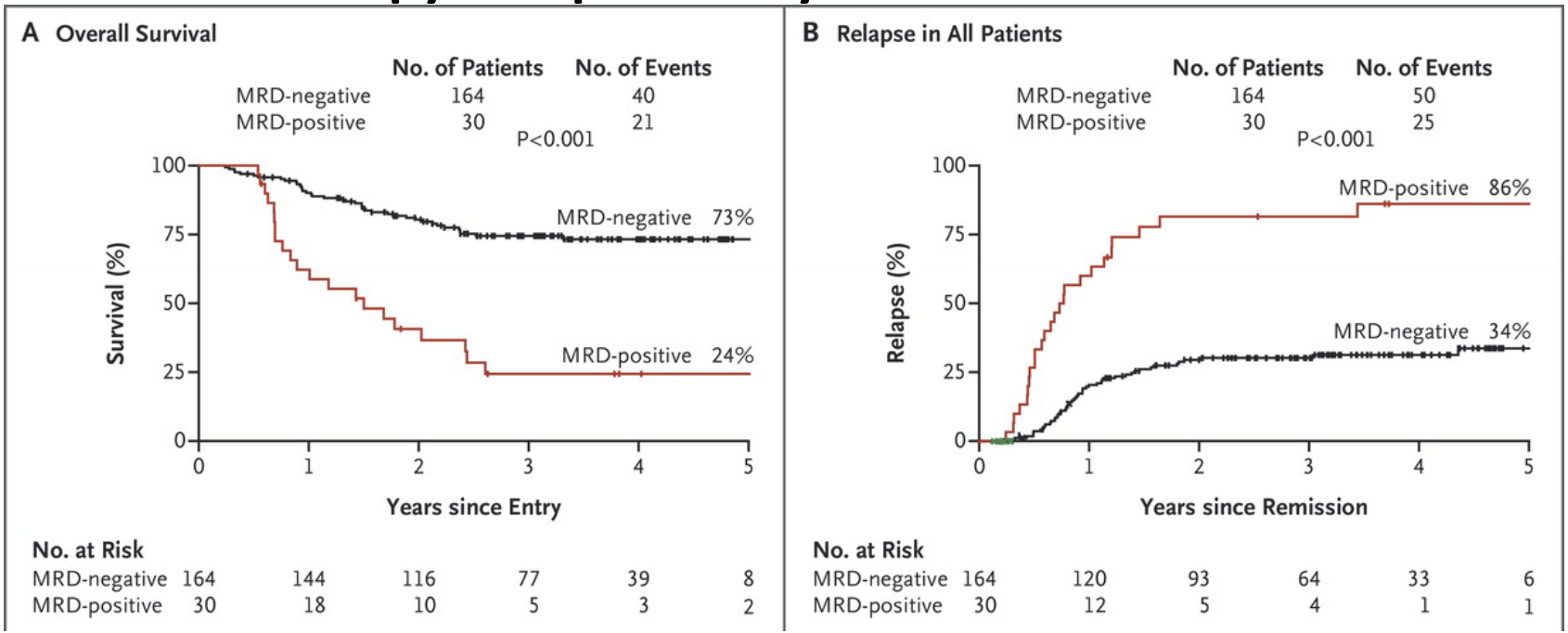
Poor Risk



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 RK, et al. ***Lancet Oncol*** **2014; 15: 686-96.**

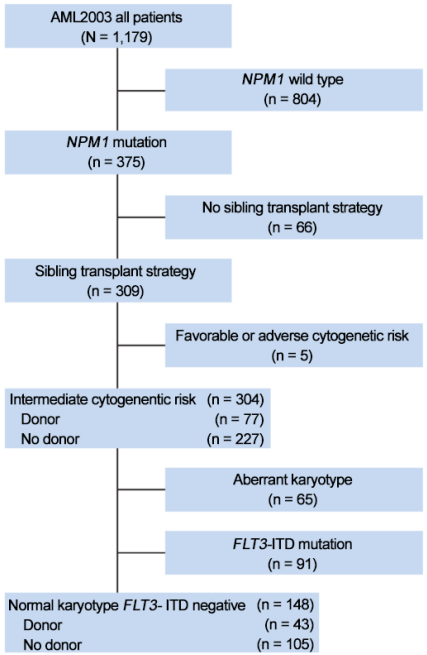
MRD Based on PCR for Mutant *NPM1* After Second Cycle of Chemotherapy Independently Predicts Clinical Outcomes

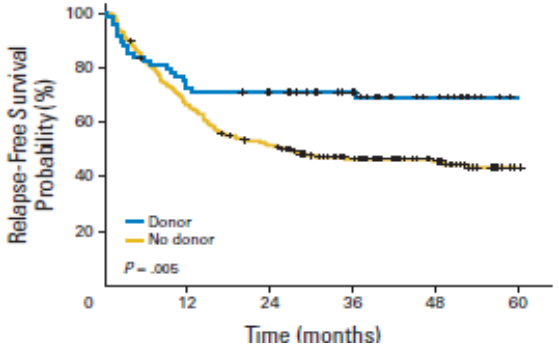


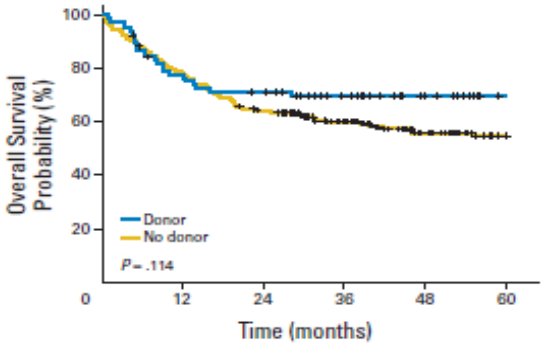
MRD = minimal residual disease; PCR = polymerase chain reaction.

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

Allogeneic HSCT in Younger Adults with AML with *NPM1*m without *FLT3* ITD: Donor vs. No-Donor Analysis



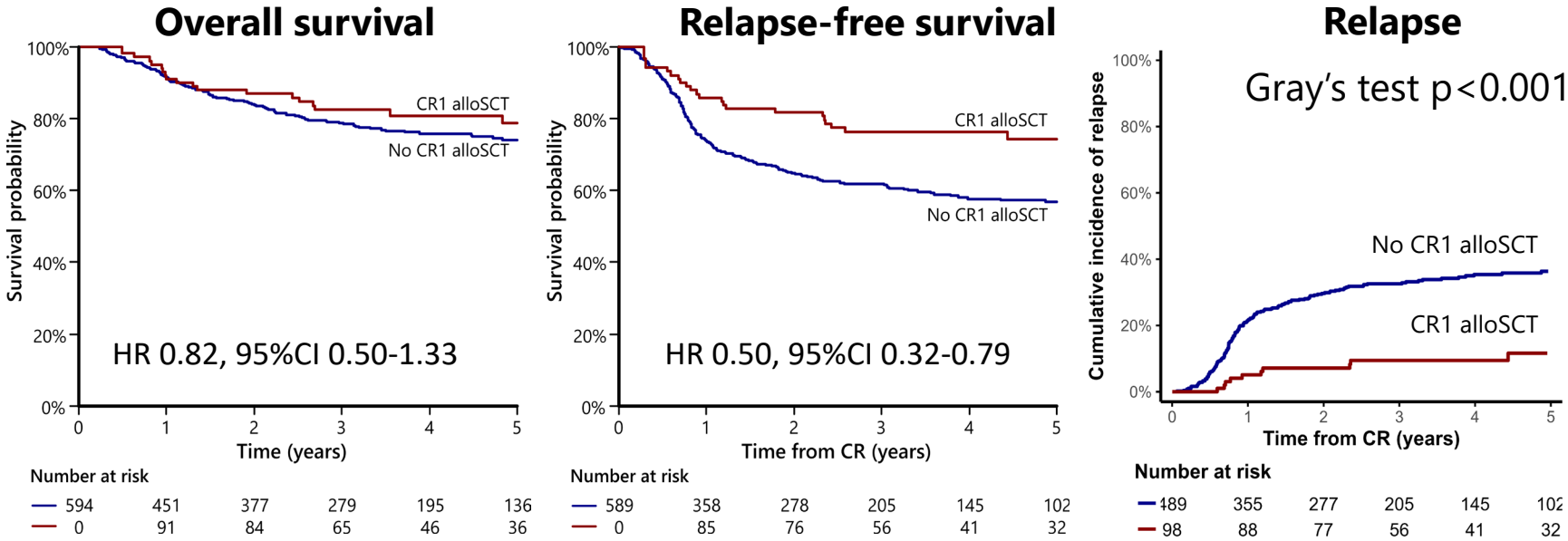




Rollig C, et al. *J Clin Oncol.* 2015; 33(5): 403-410

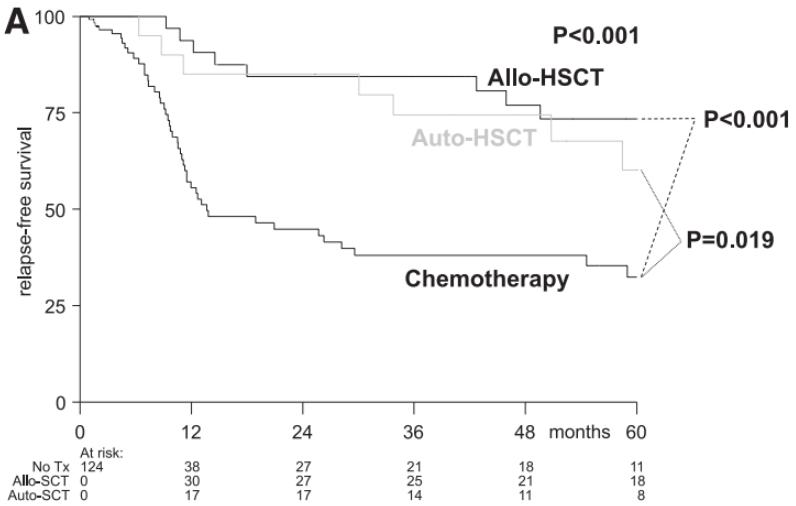
71% of donor group had allo HSCT in CR1; 9% later

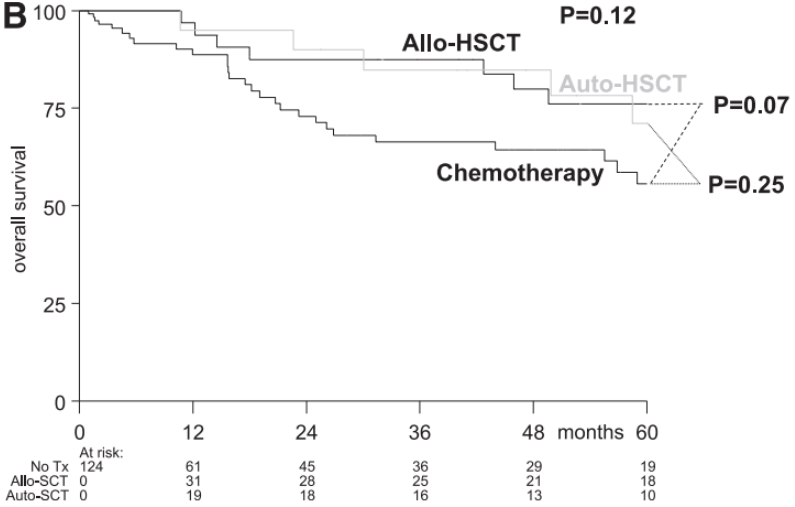
CR1-allo HSCT does not improve OS in *NPM1*^{mut} AML in PB MRD negative complete remission after induction



Othman J, et al. (UK NCRI AML 17 and AML 19). ASH 2023, San Diego CA

Allogeneic HSCT Improves Relapse-free Survival but Not Overall Survival in AML with Biallelic *CEBPA*m

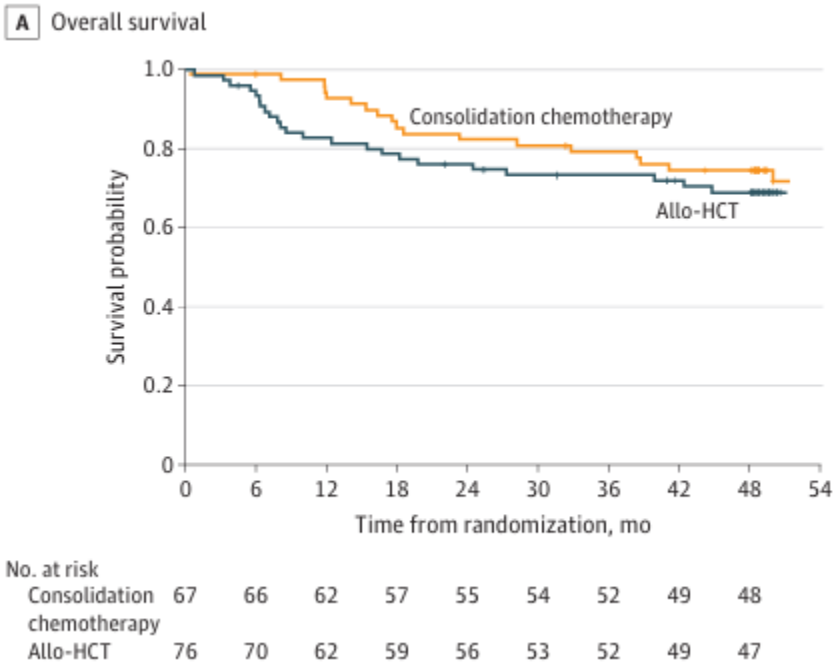


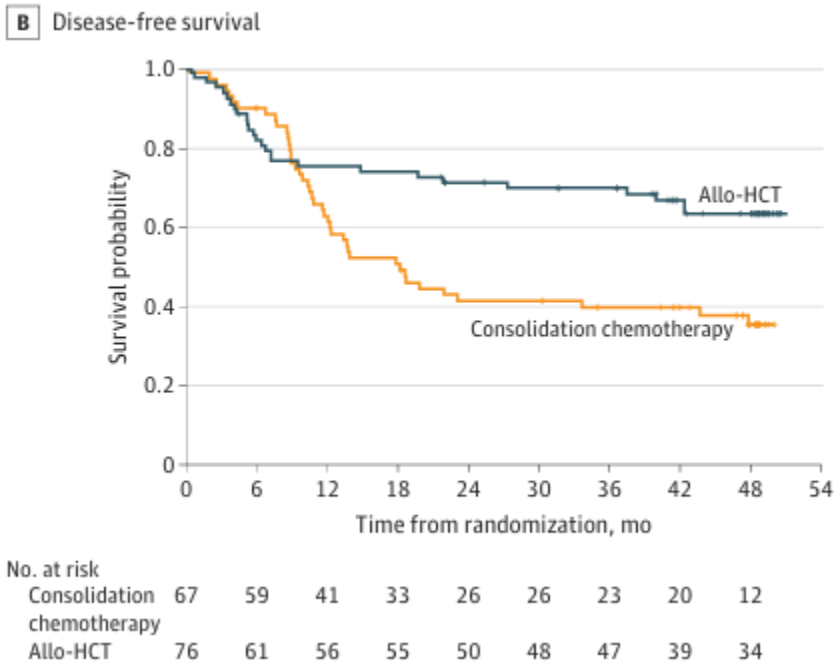


- Rate of CR2 = 83%
- 33 of 35 underwent allo HSCT in CR2
- Survival 46% at 3 years post relapse

Schlenk RF, et al. *Blood*. 2013; 122(9) :1576-1582

Allogeneic HSCT vs Consolidation for Intermediate Risk* AML in CR1

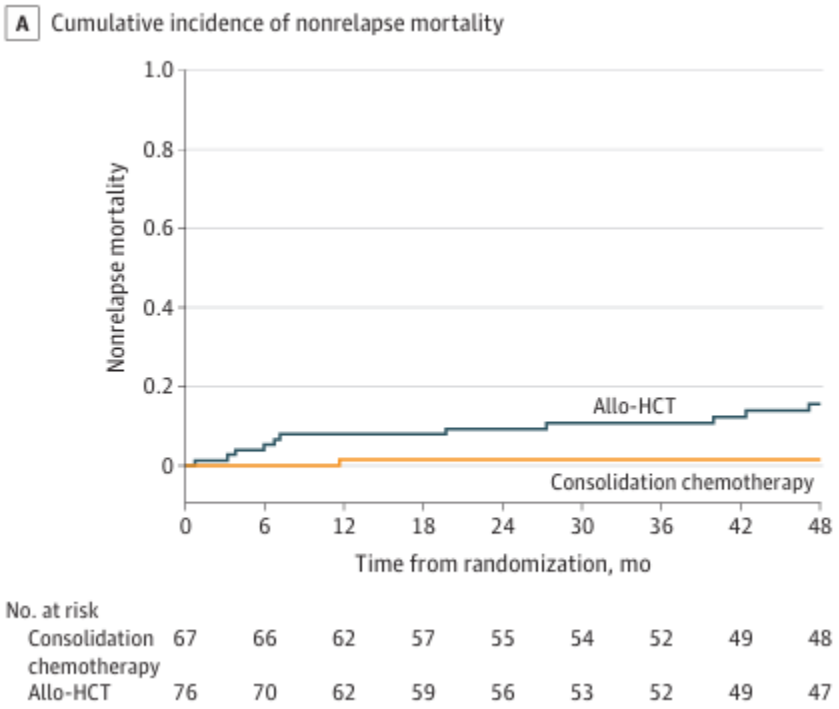


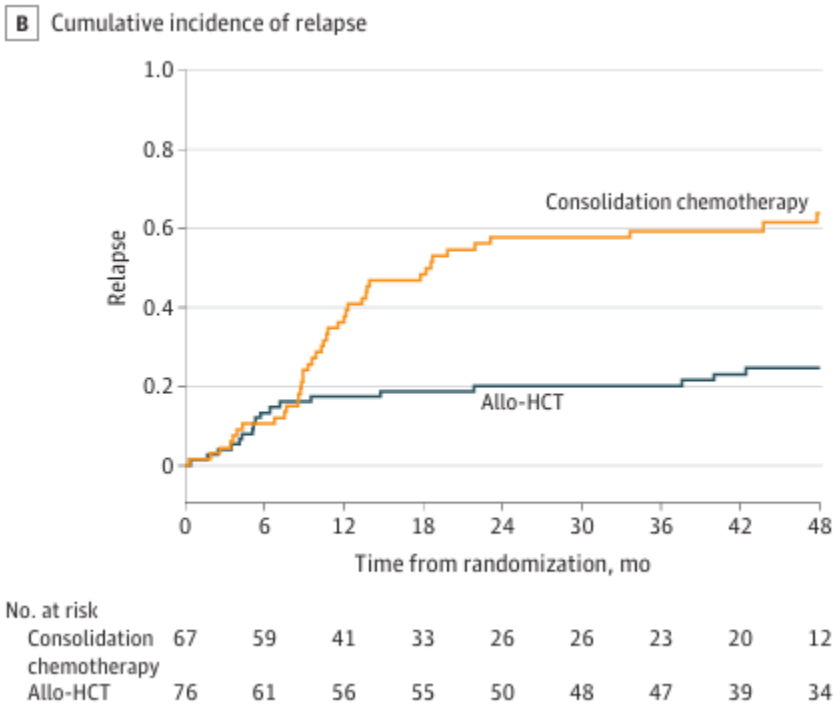


Bornhauser M, et al. *JAMA Oncol.* 2023; 9(4): 519-526.

*cytogenetically defined

Allogeneic HSCT vs Consolidation for Intermediate Risk* AML in CR1



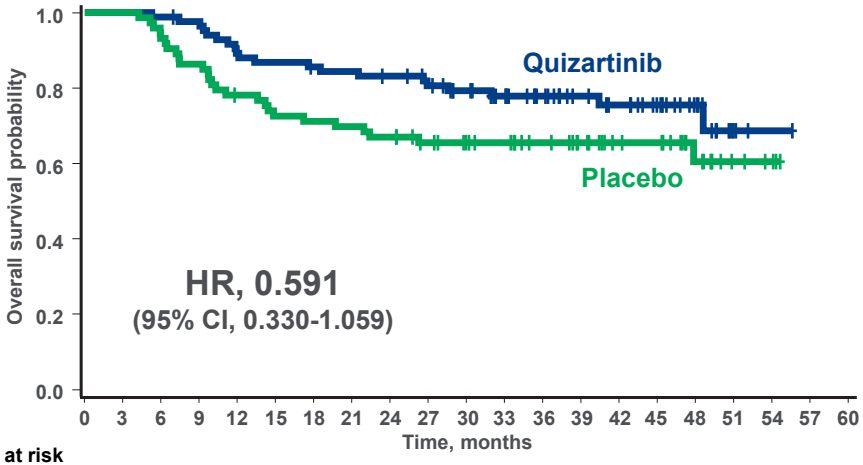


Bornhauser M, et al. *JAMA Oncol.* 2023; 9(4): 519-526.

*cytogenetically defined

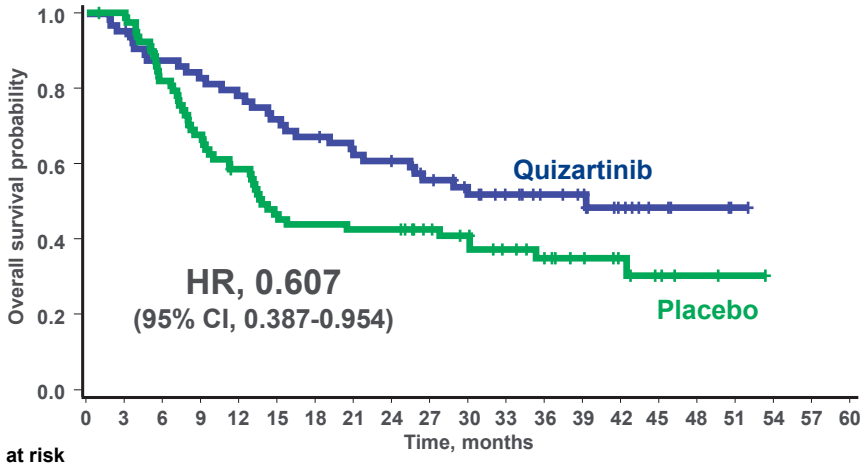
QuANTUM-First: Overall Survival in Patients Who Achieved CR

Patients With CR Who Received Allo-HCT in CR1



No. at risk																				
Quizartinib	84	84	83	81	74	72	70	69	67	63	57	50	42	34	29	22	14	3	1	0	0
Placebo	73	73	68	63	56	52	51	50	48	43	39	37	32	27	21	20	12	5	3	0	0

Patients With CR NOT Receiving Allo-HCT in CR1

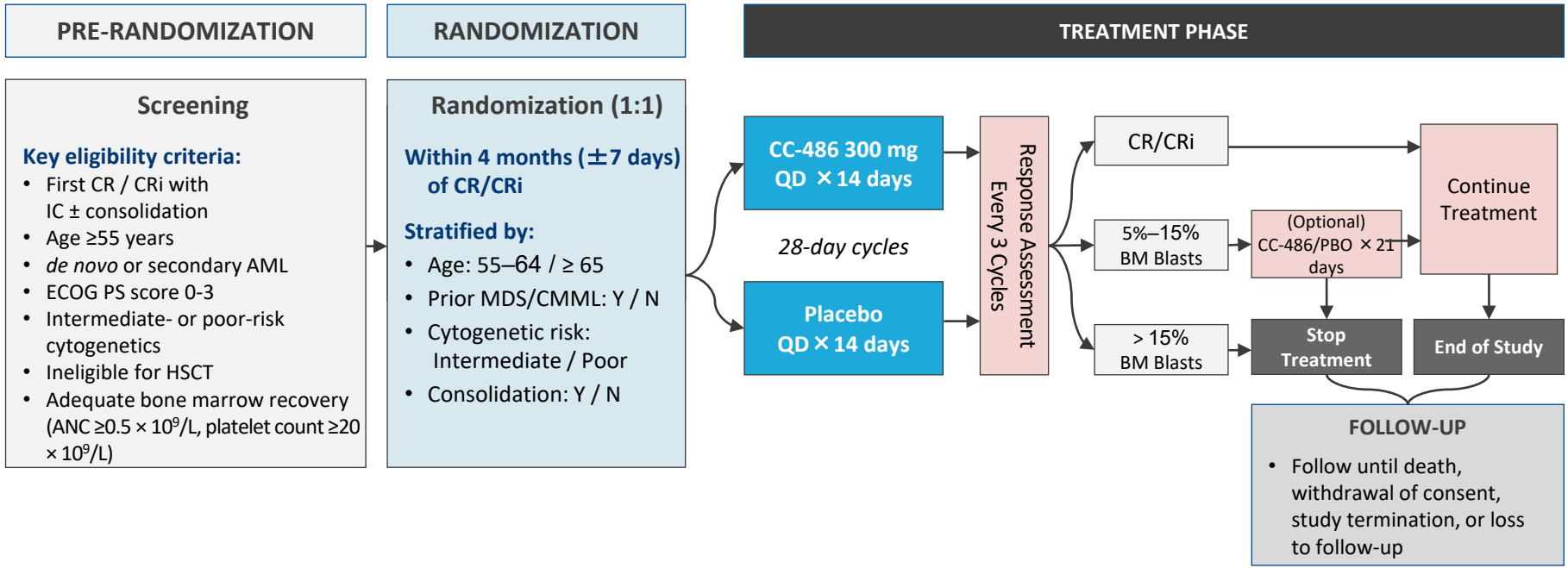


No. at risk																				
Quizartinib	63	60	54	51	48	44	41	37	35	30	25	21	17	15	9	5	3	1	0	0	0
Placebo	77	76	61	50	42	33	31	30	30	25	22	17	14	10	7	4	2	1	0	0	0

Erba HP, et al. *Lancet* 2023; 401(10388): 1571-1583

QUAZAR AML-001: Study design

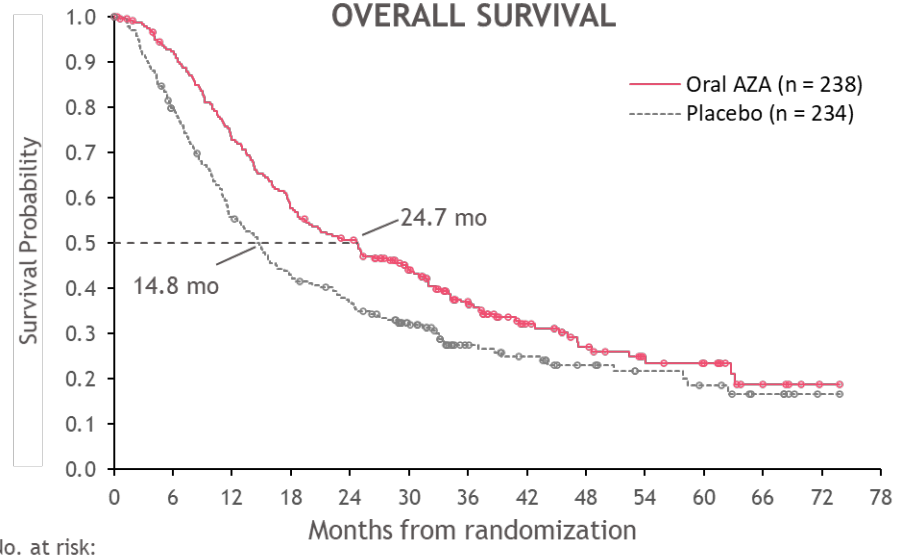
International, multicenter, placebo-controlled, double-blind, randomized, phase III study that enrolled patients from 148 sites in 23 countries (NCT01757535)

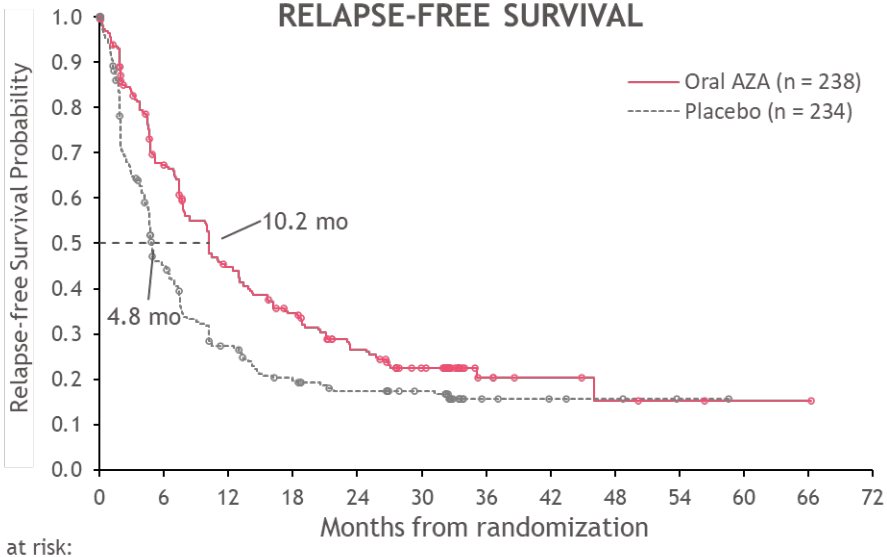


Wei A et al. *N Engl J Med* 2020; 383: 2526-37. Wei A et al. *Blood* 2019;134(Supplement2):LBA-3.

QUAZAR: Overall and Relapse-free Survival

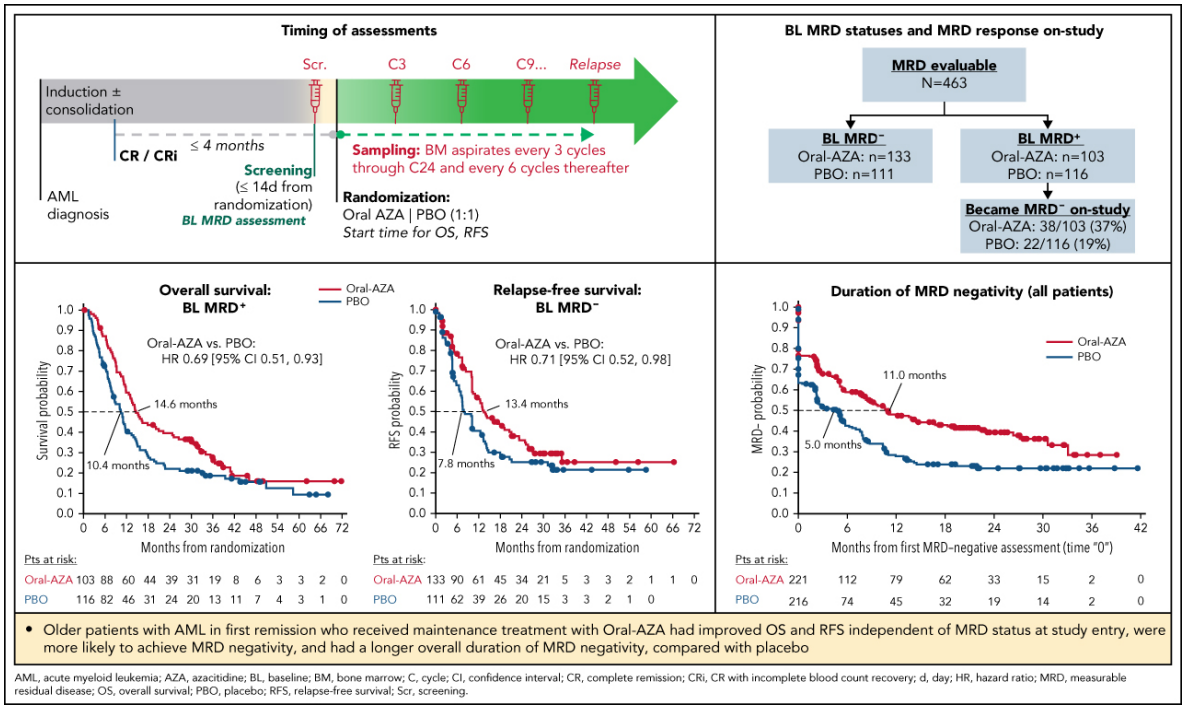
Oral AZA 300 mg QD was associated with significantly improved overall survival (OS) (*P* = 0.0009) and relapse-free survival (RFS) (*P* = 0.0001) vs. PBO





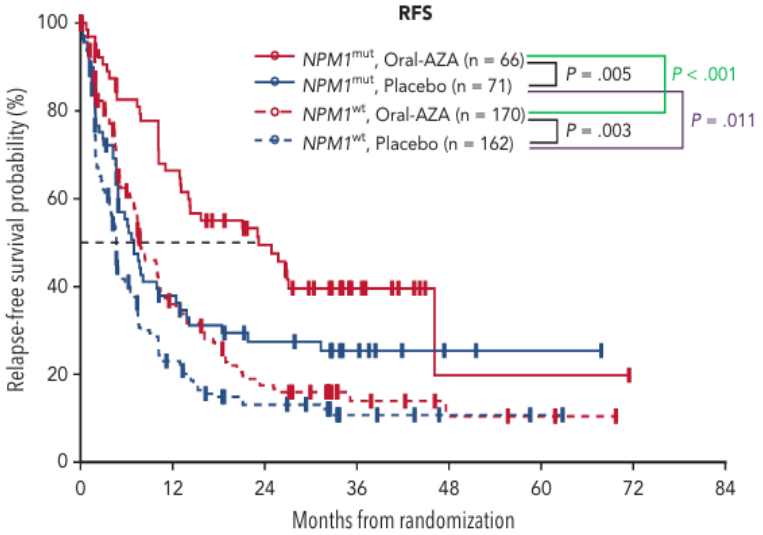
Wei A et al. *N Engl J Med* 2020; 383: 2526-37. Wei A et al. *Blood* 2019;134(Supplement2):LBA-3.

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



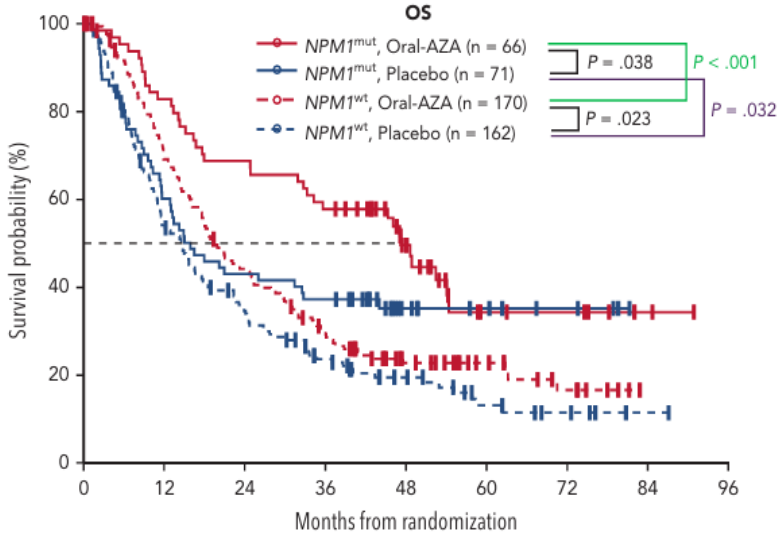
Roboz GJ, et al. *Blood* 2022; 139(14): 2145.

Prognostic Impact of NPM1 Mutation in Patients with AML in CR1 Treated with Oral Azacitidine Maintenance Therapy



Median RFS, months

NPM1^{mut}, Oral-AZA	**23.2**	*NPM1*^{wt}, Oral-AZA	**7.7**
NPM1^{mut}, Placebo	**6.9**	*NPM1*^{wt}, Placebo	**4.6**



Median OS, months

NPM1^{mut}, Oral-AZA	**47.2**	*NPM1*^{wt}, Oral-AZA	**19.6**
NPM1^{mut}, Placebo	**15.9**	*NPM1*^{wt}, Placebo	**14.6**

Dohner H, et al. *Blood* 2022; 140(15): 1674.

VIALE-A Study Design

Eligibility

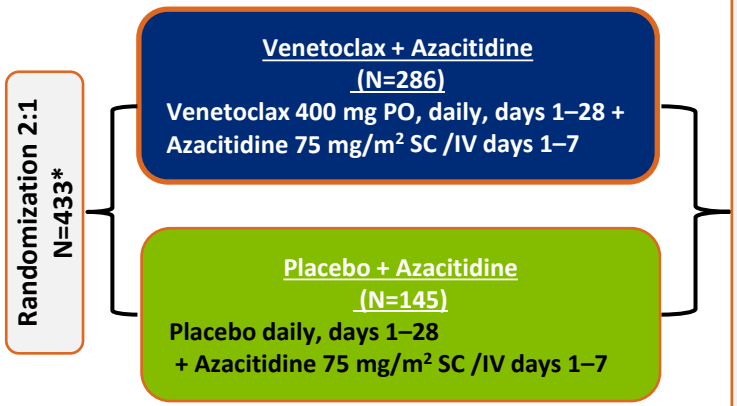
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - – CHF requiring treatment or Ejection Fraction ≤50%
    - – Chronic stable angina
    - – DLCO ≤ 65% or FEV1 ≤ 65%
    - – ECOG 2 or 3

Exclusion

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

Treatment



Endpoints

Primary

- Overall survival

Secondary

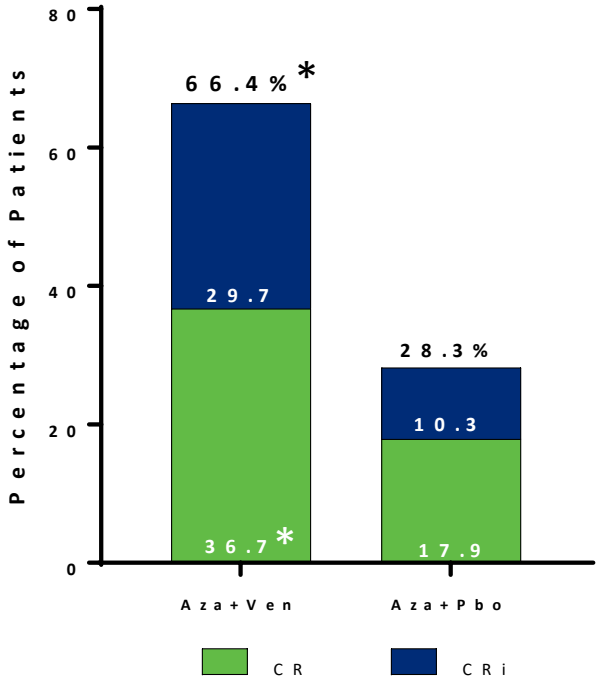
- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

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

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

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: Composite Response Rate (CR+CRi)



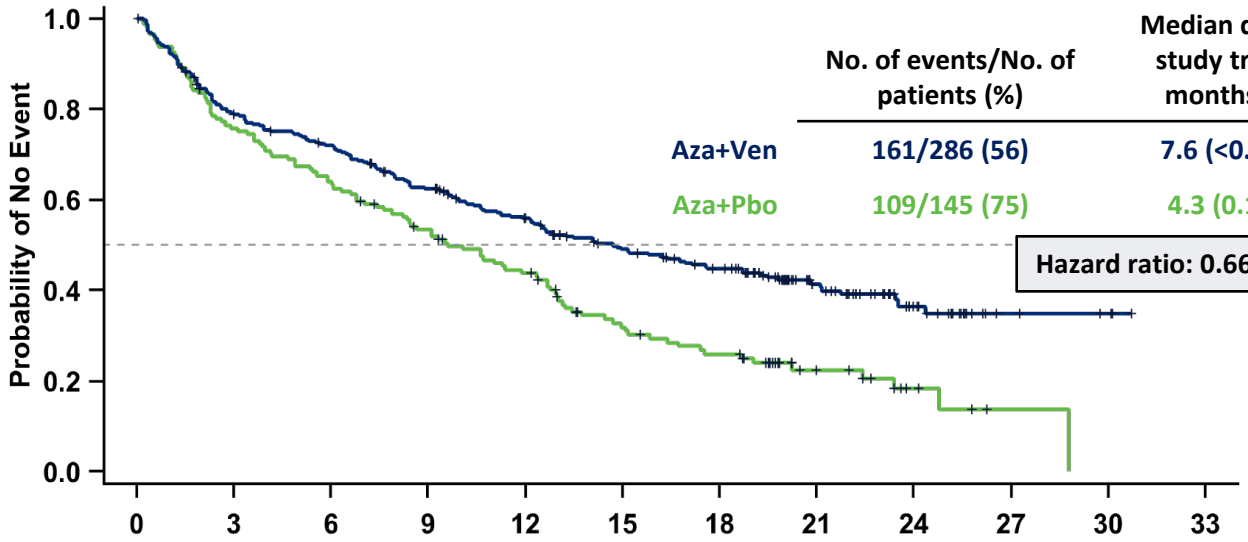
	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; CR: Complete remission; CRi: CR with incomplete-count recovery; CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/µL or thrombocytopenia ≤10^5/µL.
CR + CRi rate was compared using Cochran-Mantel-Haenszel (CMH) test stratified by age (18 – < 75, ≥ 75) and cytogenetic risk (intermediate, poor).

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

VIALE A: Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

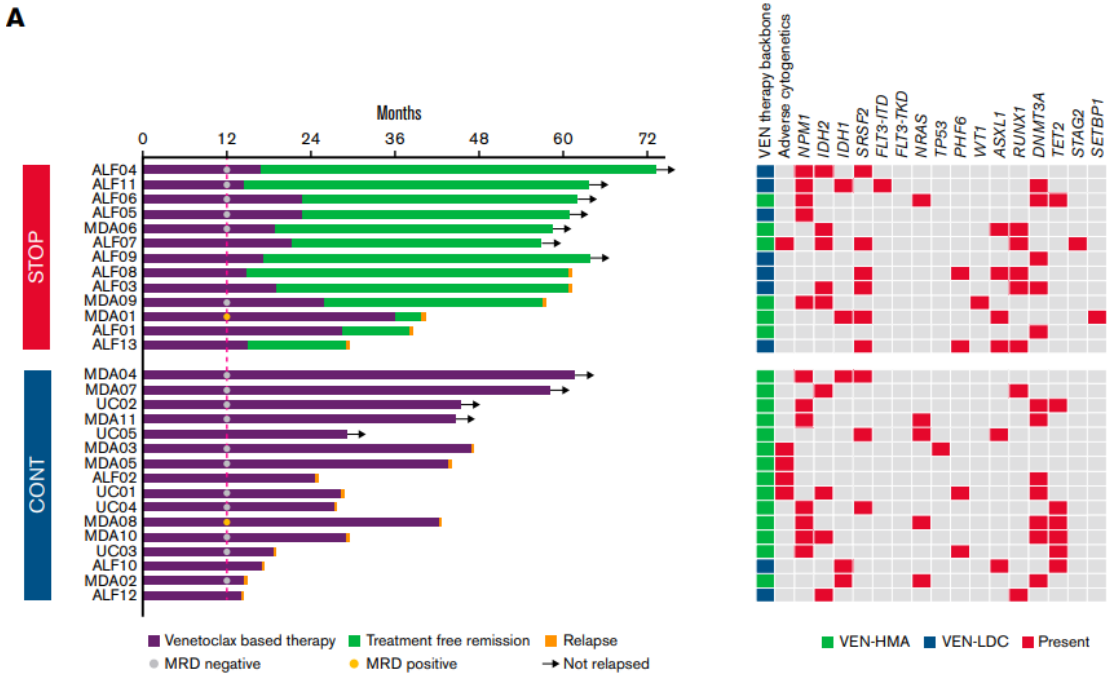
Patients at Risk

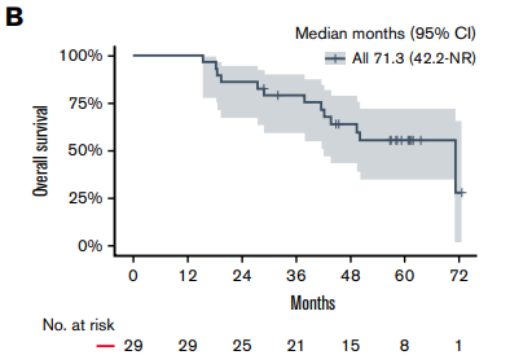
Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

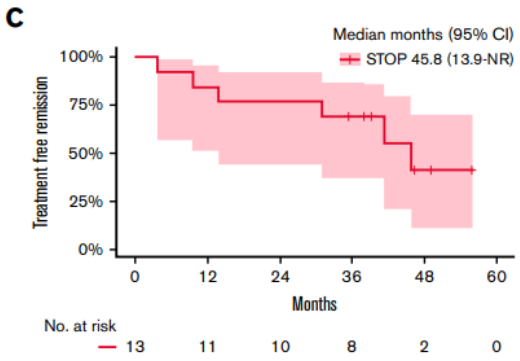
Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo C, et al. *N Engl J Med* 2020; 383(7): 617-629.

Treatment-Free Remission for AML Patients in CR following > 12 months VEN/AZA or VEN/LoDAC







Chua CC, et al. *Blood Adv.* 2022; 6(13): 3879

STOP-VEN Study design

Objective:

- To study the outcome of patients who stopped AZA and/or VEN while in remission.

Key inclusion/exclusion criteria:

- Adult AML patients treated with ≥1 VEN-AZA cycle
- in response (CR, CRi or MLFS)
- VEN and/or AZA cessation >3 months
- Patients who stopped VEN for progression or lack of response or allogeneic stem cell transplantation were not included in the study.

Garciaz S, et al. (FILO) ASH 2023. San Diego CA

Patient characteristics at AML diagnosis

	ND (n=62)
Male gender, n (%)	33 (53.2)
Age, Median (range)	75 (26-89)
WHO 2016 classification	
De Novo, n (%)	34 (54.8)
MRC-AML, n (%)	23 (37)
Therapy-related AML, n (%)	5 (8)
Prior AZA exposure, n (%)	6 (9.7)
WBC, Median (range)	2.7 (0.6-200)
ANC, Median (range)	0.7 (0-31.6)
Platelets, Median (range)	52 (9-296)
Cytogenetics	
Favorable, n (%)	3 (4.8)
Intermediate, n (%)	47 (75.8)
Poor-risk, n (%)	12 (19.4)
Main mutations	
NPM1 (n=61), n (%)	11 (18)
IDH (n=61), n (%)	20 (32.7)
FLT3-ITD (n=60), n (%)	4 (6.6)
TP53 (n=54), n (%)	4 (7.4)

Reasons for VEN-AZA discontinuation:

- hematological toxicities = 36 (58%),
- patient preference = 8 (13%)
- extra-hematological toxicities = 5 (8%)
- poor general status = 3 (5%)

Response to VEN-AZA:

ORR= 57 (92%)

CR= 44 (79%)

CRi = 13 (21%).

MLFS = 5 (8%).

CR MRDneg 21/25 (78%)

11 molecular MRD (NPM1)

10 flow cytometry MRD

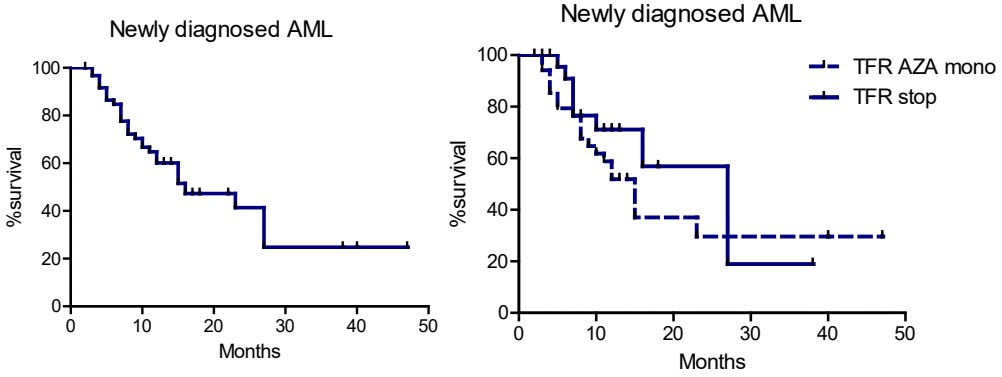
Garciaz S, et al. (FILO) ASH 2023. San Diego CA

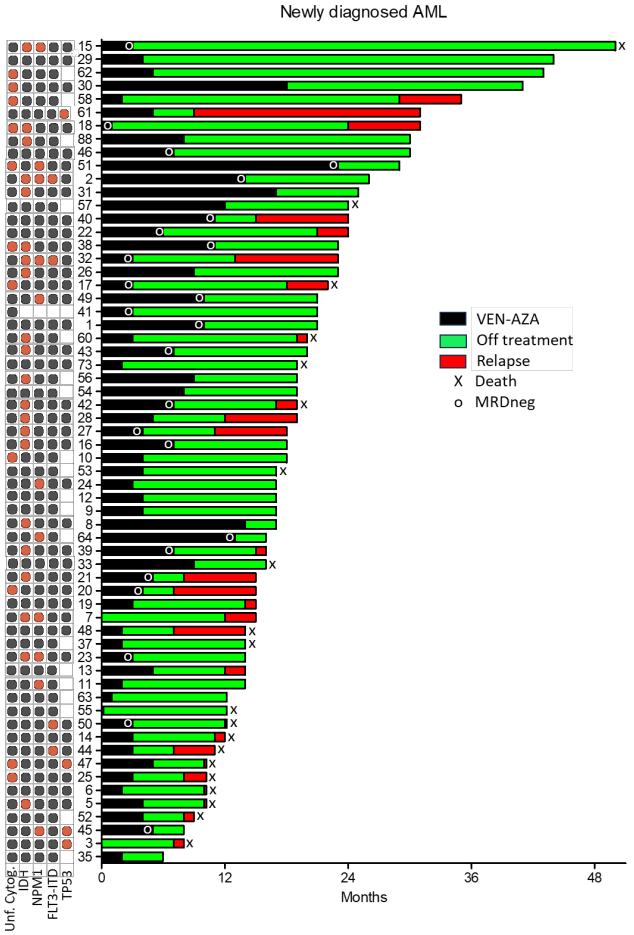
Correction of cytopenias

- 23/39 documented cases (59%)

Treatment-free remission

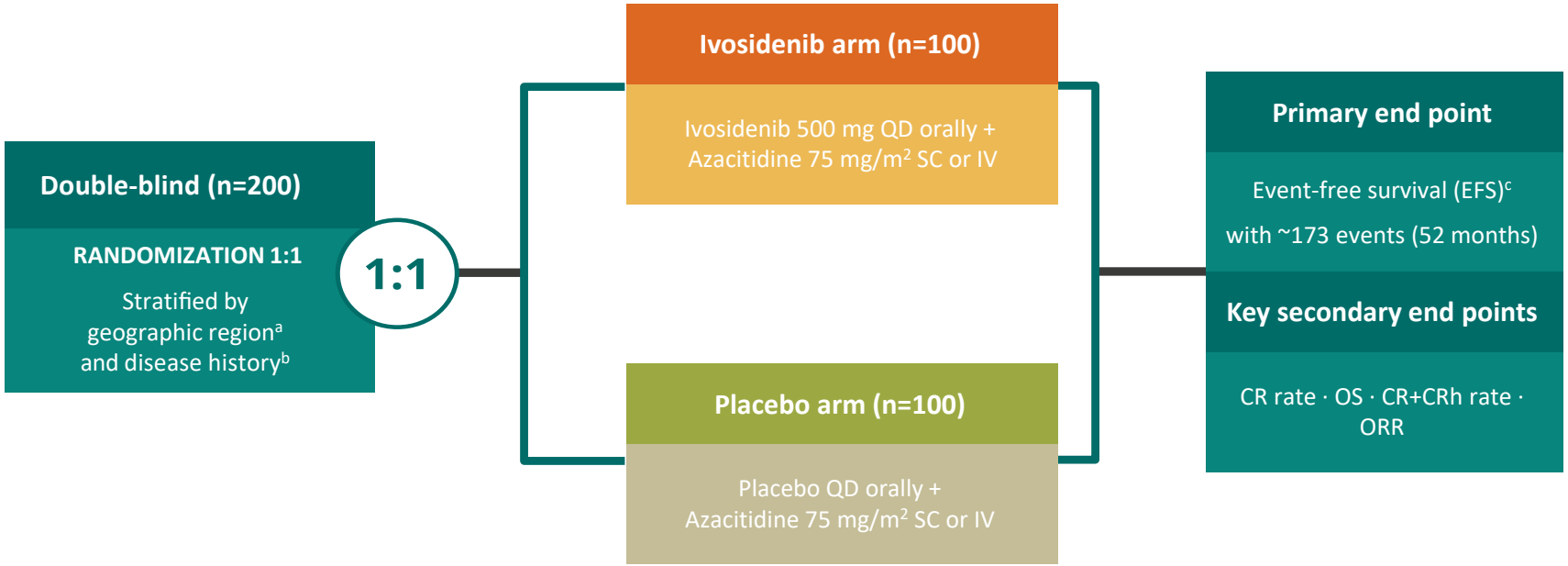
- 16 months
- 45 patients (72.5%) had a time without treatment longer than time with treatment or with disease recurrence





Garciaz S, et al. (FILO) ASH 2023. San Diego CA

AGILE: study design and end points



- As of the data cutoff date (18March2021), 146 patients have been randomized (IVO+AZA, n=72; PBO+AZA, n=74).
- As of 12May2021, the IDMC recommended to halt enrollment based on a noted difference in clinical importance between the treatment groups, not related to safety.
- A total of 148 patients were enrolled at 155 active sites in 20 countries.

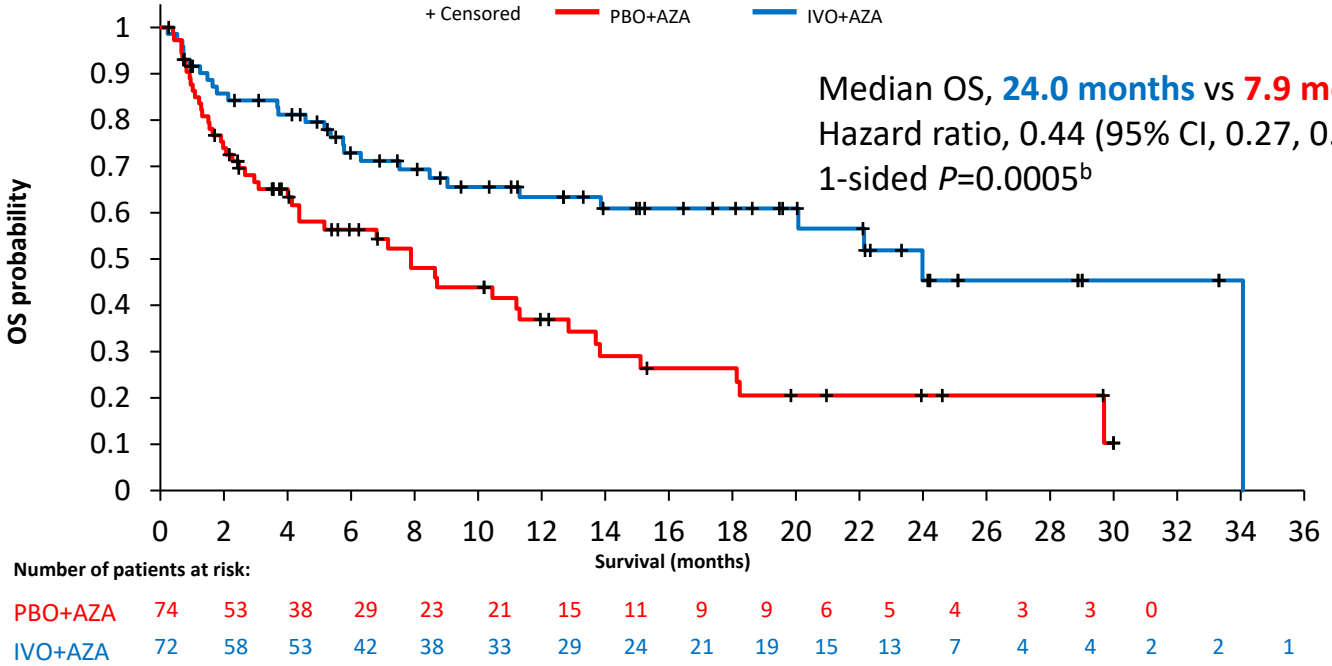
Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: Baseline demographic and disease characteristics

Characteristic	IVO+AZA (n=72)	PBO+AZA (n=74)
Median (range) age, years	76 (58–84)	75.5 (45–94)
Sex, n (%)		
Male/Female	42 (58.3)/30 (41.7)	38 (51.4)/36 (48.6)
ECOG PS score, n (%)		
0/1/2	14 (19.4)/32 (44.4)/26 (36.1)	10 (13.5)/40 (54.1)/24 (32.4)
Disease history (per investigator), n (%)		
De novo AML	54 (75.0)	53 (71.6)
Secondary AML[a]	18 (25.0)	21 (28.4)
Median (range) m*IDH1* VAF in BMA, % (range)[b]	36.7 (3.1–50.5)	35.5 (3.0–48.6)
Cytogenetic risk, n (%)[c]		
Favorable/intermediate/poor	3 (4.2); 48 (66.7); 16 (22.2)	7 (9.5); 44 (59.5); 20 (27.0)
Median (range) bone marrow blasts, %	54 (20–95)	48.0 (17–100)

Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: IVO+AZA significantly improves OS compared with PBO/AZA



OS benefit was consistent across subgroups: de novo status, region, age, baseline ECOG PS score, sex, race, baseline cytogenetic risk status, WHO classification of AML, baseline white blood cell count, baseline BM blast percentage.

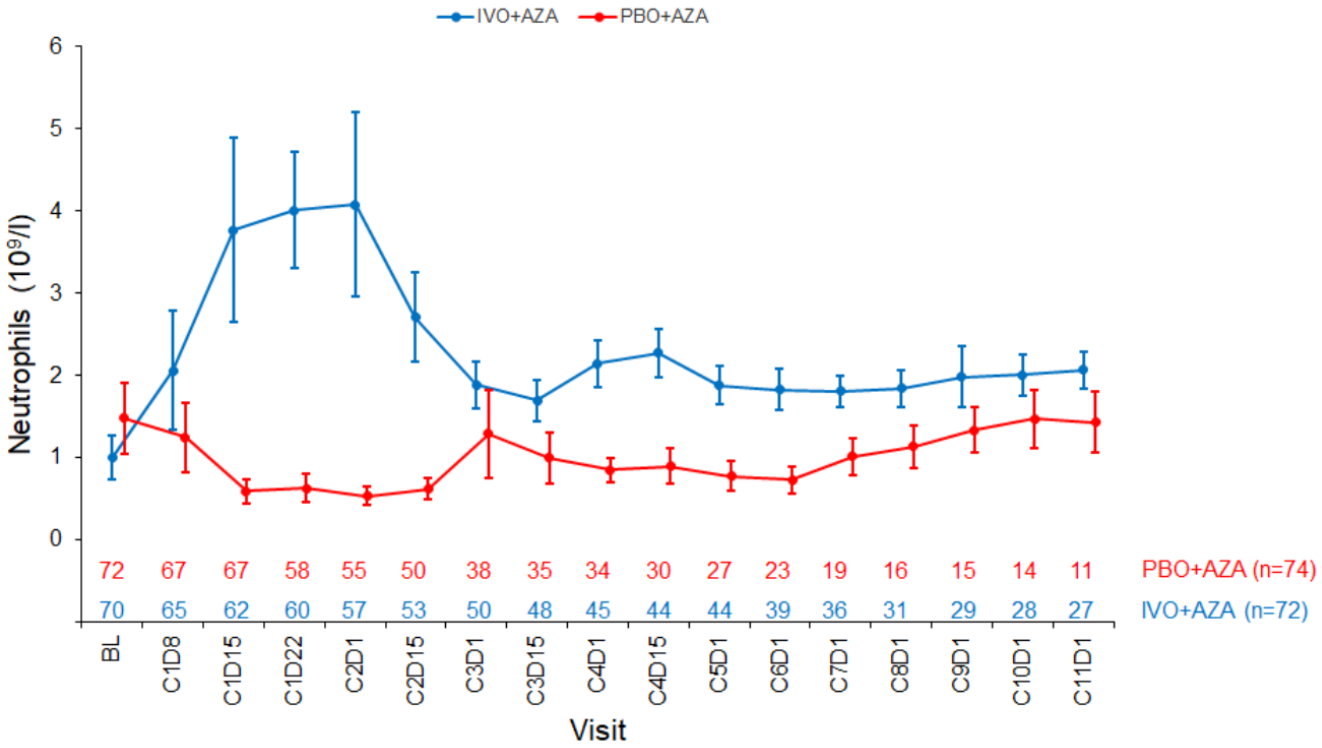
Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: Response Rate, Response Duration, and Time to Response

Response Category	Ivosidenib + Azacitidine (N = 72)	Placebo + Azacitidine (N = 74)
Complete remission		
Percentage of patients (95% CI)	47 (35–59)	15 (8–25)
Odds ratio vs. placebo (95% CI); P value	4.8 (2.2–10.5); two-sided P<0.001	
Median duration of complete remission (95% CI) — mo	NE (13.0–NE)	11.2 (3.2–NE)
Median time to complete remission (range) — mo	4.3 (1.7–9.2)	3.8 (1.9–8.5)
Complete remission or complete remission with partial hematologic recovery		
No. of patients	38	13
Percentage of patients (95% CI)	53 (41–65)	18 (10–28)
Odds ratio vs. placebo (95% CI); P value	5.0 (2.3–10.8); two-sided P<0.001	
Median duration of complete remission or complete remission with partial hematologic recovery (95% CI) — mo	NE (13.0–NE)	9.2 (5.8–NE)
Median time to complete remission or complete remission with partial hematologic recovery (range) — mo	4.0 (1.7–8.6)	3.9 (1.9–7.2)

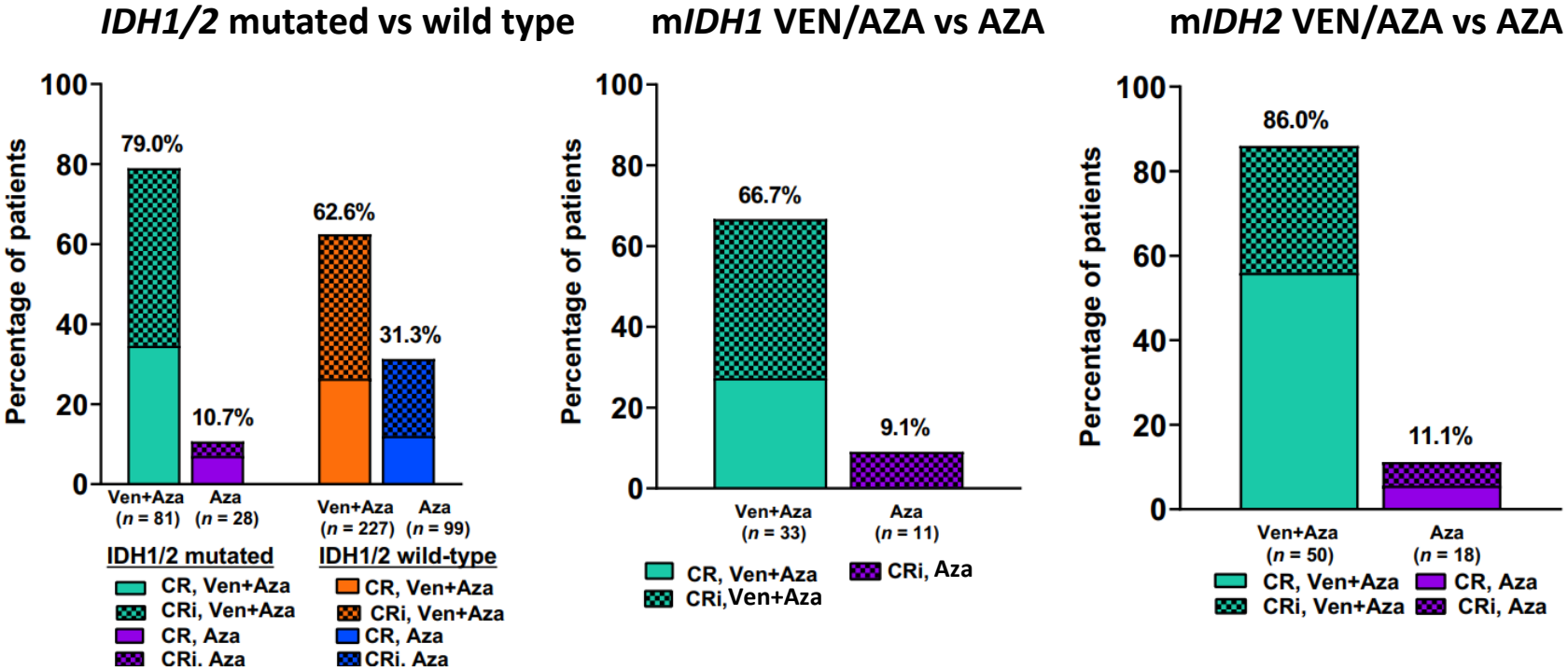
Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

AGILE: Neutrophil Recovery from Baseline



Montesinos P, et al. *N Engl J Med* 2022; 386: 1519-1531

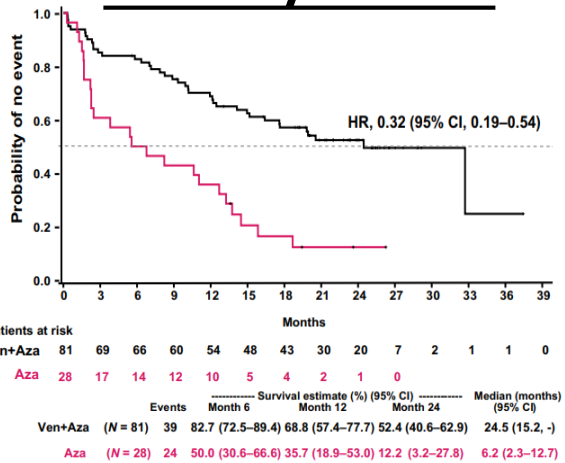
VEN/AZA in IC-Ineligible m*IDH* AML: Response Rates



Pollyea DA, et al. *Clin Cancer Res.* 2022; 28(13): 2753-2761

VEN/AZA in IC-Ineligible m*IDH* AML: Overall Survival

m*IDH1*/m*IDH2*

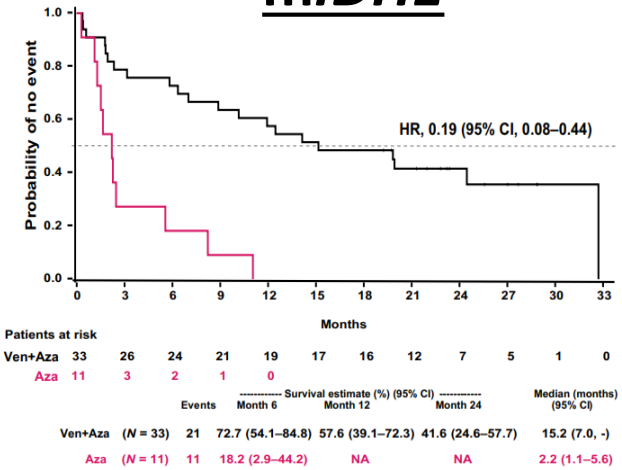


		Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven+Aza	(*N* = 81)	39	82.7 (72.5–89.4)	68.8 (57.4–77.7)	52.4 (40.6–62.9)	24.5 (15.2, -)
Aza	(*N* = 28)	24	50.0 (30.6–66.6)	35.7 (18.9–53.0)	12.2 (3.2–27.8)	6.2 (2.3–12.7)

Median OS

Ven+Aza	24.5 months
Aza	6.2 months

m*IDH1*

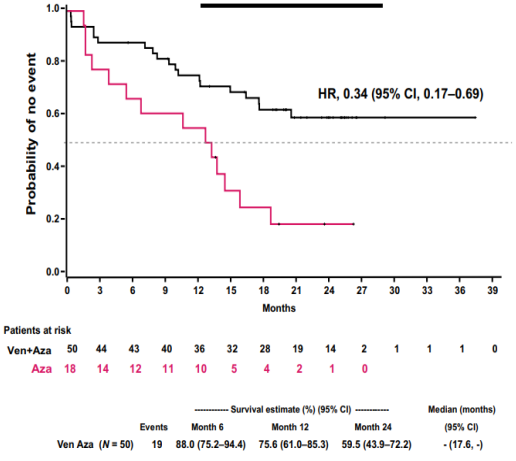


		Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven+Aza	(*N* = 33)	21	72.7 (54.1–84.8)	57.6 (39.1–72.3)	41.6 (24.6–57.7)	15.2 (7.0, -)
Aza	(*N* = 11)	11	18.2 (2.9–44.2)	NA	NA	2.2 (1.1–5.6)

Median OS

Ven+Aza	15.2 months
Aza	2.2 months

m*IDH2*



		Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven Aza	(*N* = 50)	19	88.0 (75.2–94.4)	75.6 (61.0–85.3)	59.5 (43.9–72.2)	- (17.6, -)
Aza	(*N* = 18)	14	66.7 (40.4–83.4)	55.6 (30.5–74.8)	19.0 (4.8–40.3)	13.0 (3.8–15.8)

Median OS

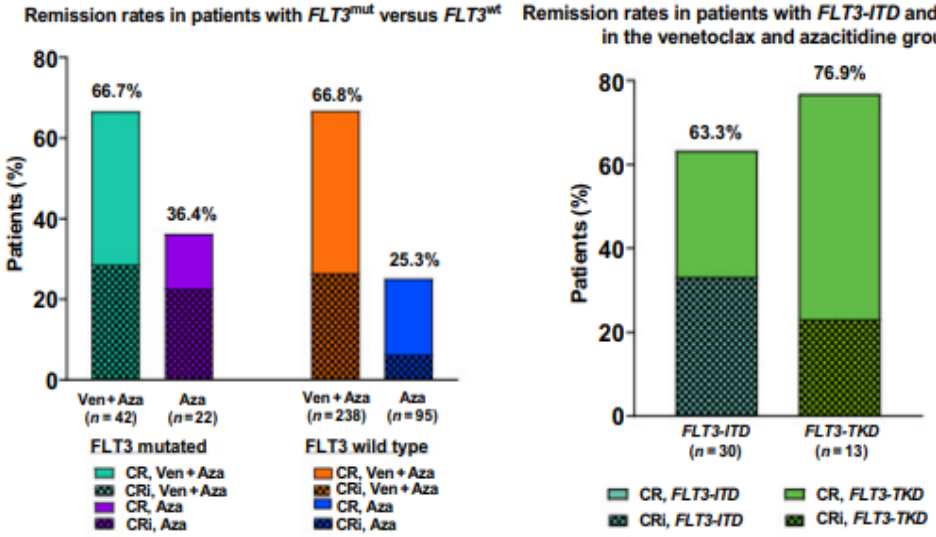
Ven+Aza	Not Reached
Aza	13.0 months

Pollyea DA, et al. *Clin Cancer Res.* 2022; 28(13): 2753-2761

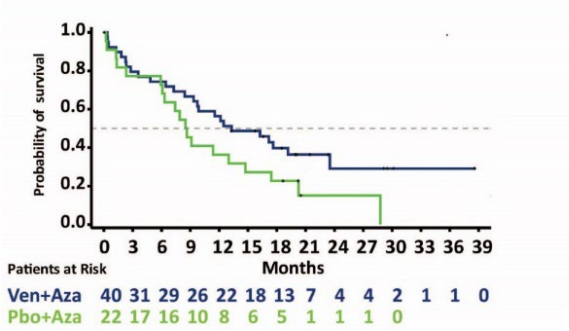
VEN/AZA vs IVO/AZA in IC-Ineligible m*IDH1* AML

	VEN/AZA	IVO/AZA
Mutation agnostic	Yes	No
Response Rate	CR/CRi 67%	CR/CRh 53%
Time to response	1 month	4 month
Median overall survival	15 months	24 months
Options in second line	IVO (if m*IDH1* present)	VEN/HMA
Toxicity	Myelosuppression, Tumor lysis syndrome	Differentiation syndrome, QT prolongation
Ease of administration	Dose modifications for cytopenias	

Impact of *FLT3* Mutation on Outcome after Venetoclax and Azacitidine for Patients with Treatment-Naïve Acute Myeloid Leukemia



VEN/AZA v PBO/AZA

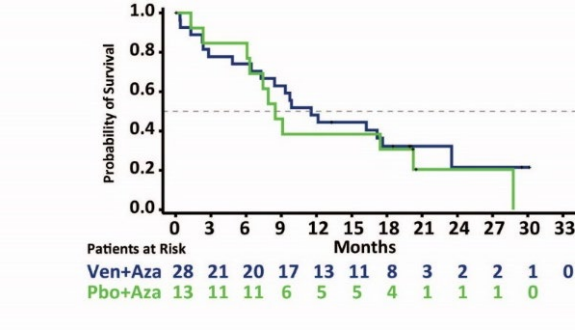


FLT3mut

Median OS, months (95% CI)

13.3 (8.4 – 23.5)

8.6 (5.9 – 14.7)



FLT3-ITD

Median OS, months (95% CI)

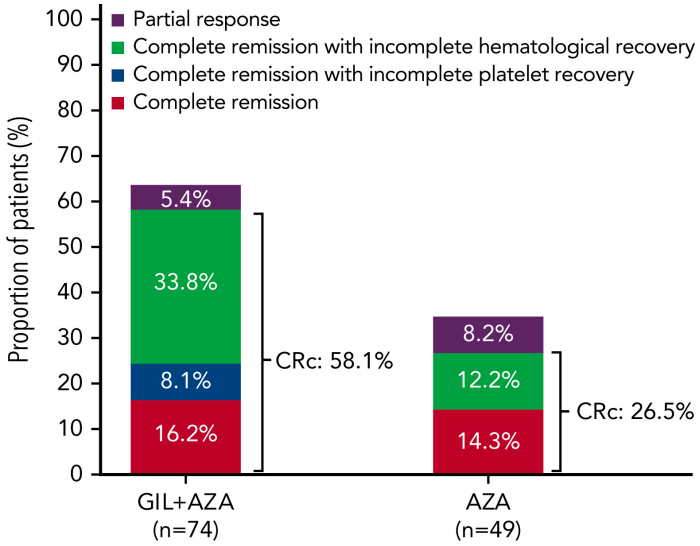
11.5 (6.4 – 23.5)

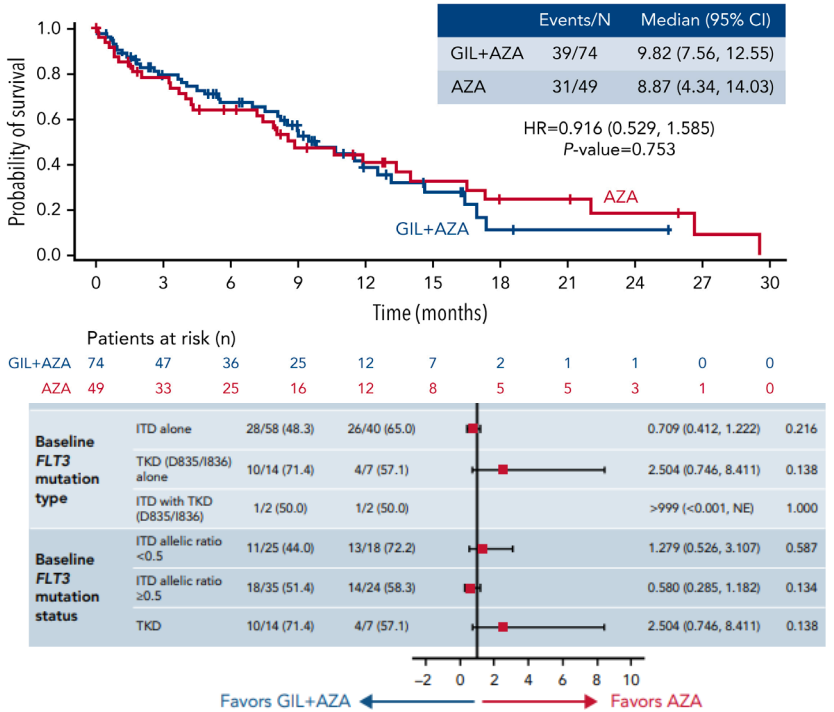
8.5 (6.1 – 20.3)

Konopleva M, et al. *Clin Cancer Res.* 2022; 28: 2744-2752

Konopleva M, et al. ASH 2020.

Phase 3 Trial of Gilteritinib plus Azacitidine versus Azacitidine for Newly Diagnosed *FLT3*m+ AML Ineligible for Intensive Chemotherapy: LACEWING



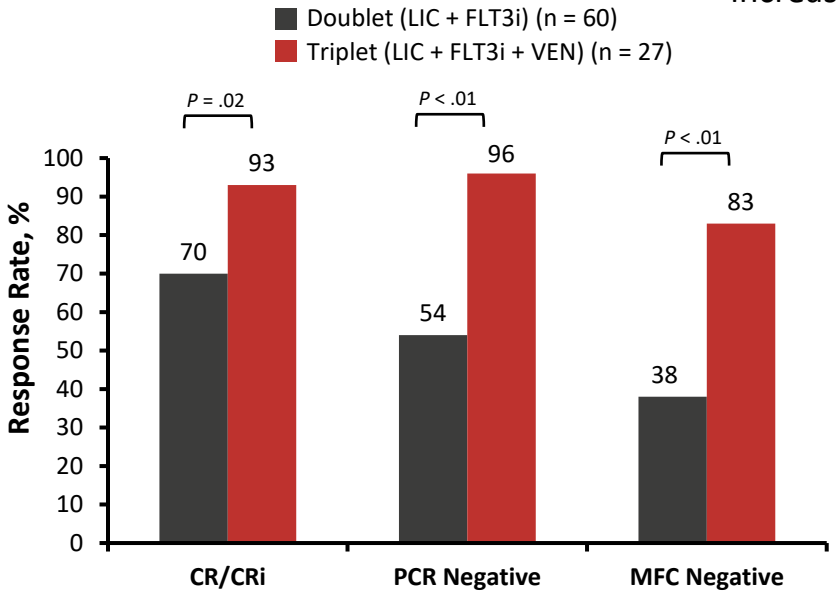


Wang ES, et al. *Blood* 2022; 140(17): 1845-1857.

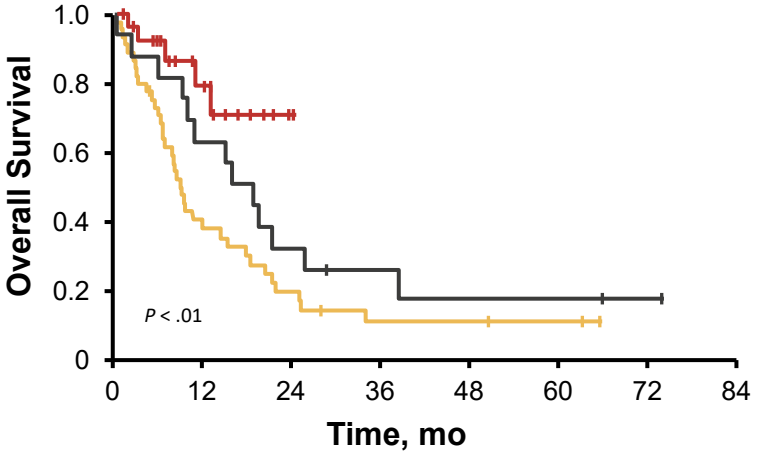
Retrospective Assessment Suggests That Triplets May Be Highly Active in *FLT3*-Mutated AML

First- and second-generation FLT3i-based doublets and triplets in older, IC-ineligible adults with ND *FLT3*-mutated AML (N = 87)

- **Doublets** (FLT3i + low-intensity chemo) CRc: 70%; OS 9-16 months
- **HMA + venetoclax + FLT3i combination** significantly improved CR/CRi rates, CR rates, *FLT3*-PCR and MFC MRD rates, as well as OS, without increasing 60-day mortality (7% vs 10%)



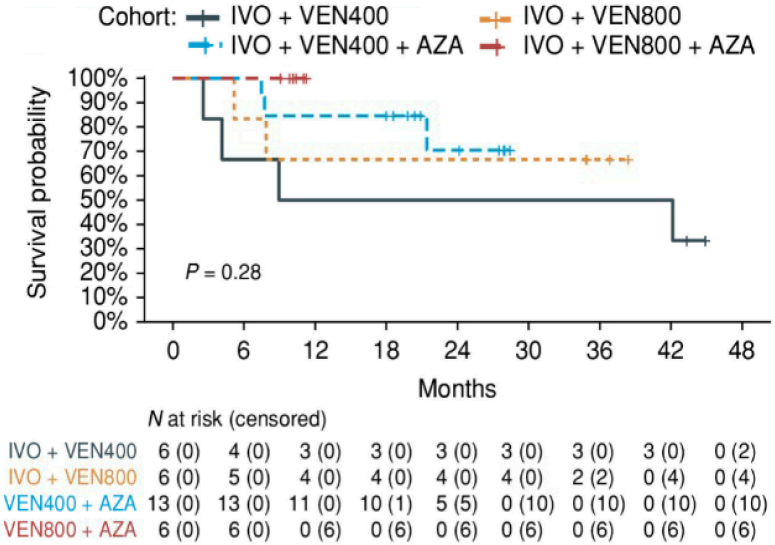
Treatment Regimen	N = 87	Median Age, y	Median OS, mo
Triplet (LIC + FLT3i + VEN)	27	69 (40-85)	NR
Doublet (LIC + 2nd-generation FLT3i)	16	71 (64-83)	15.7
Doublet (LIC + 1st-generation FLT3i)	44	70 (51-83)	8.7



Yilmaz M et al. *Blood Cancer J*. 2022; 12: 77.

Triplet Therapy in IDH Mutated AML

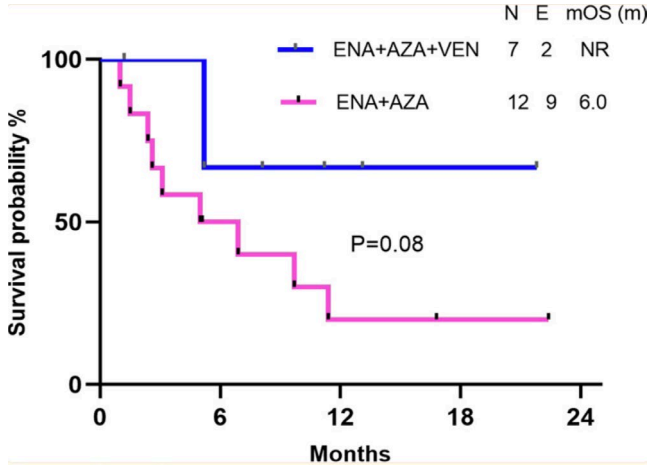
IVO + VEN ± Azacitidine



CRc of IVO + VEN + Aza 90% vs. 83% for IVO + VEN in overall cohort (both ND and R/R)

Lachowiez et al. Blood Cancer Discovery. 2022

ENA + AZA ± VEN



CRc of 61% in patients with R/R AML (n=18) with CRc of 86% with ENA + Aza + VEN (n=7)

Venugopal et al. Blood. 2022

The Current AML Treatment Algorithm