EHA AML SWG meeting

UNFIT AML

Stephane De Botton

ALFA
Acute Leukemia French Association

UNIVERSITÉ PARIS SUD
université PARIS-SACLAY

GUSTAVE ROUSSY

DISCLOSURES

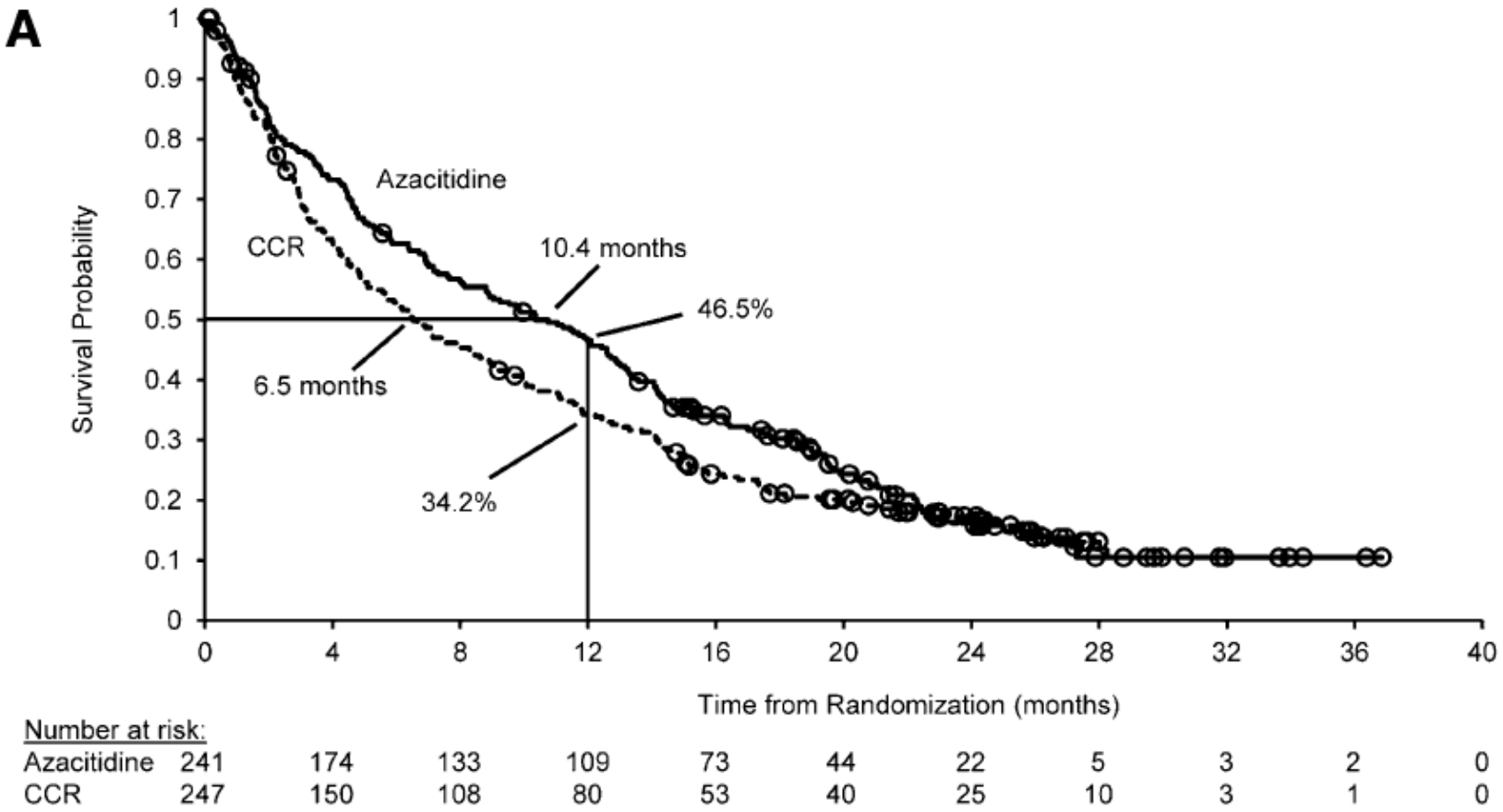
research funding from Auron and Forma, consulting fees from Bristol Myers Squibb, GlaxoSmithKline, Remix, Servier, and Syndax, and honoraria for speakers' bureaus from AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, and Servier and honoraria from Loxo and has also received travel expenses from AbbVie and Servier.

Unfit older AML patient

	CR rate	Median time to CR	Median duration of response	Median OS
HU	1%	-	-	3-4 months
LDAC	18%	3-4 months	8 months	6 months
AZA	19% (CR) 28% (CR+CRi)	3 months	10 months	10 months

Burnett AK *et al.*, Cancer 2007
Dombret H. *et al.*, Blood 2015

5-AZA



Number at risk:

Azacitidine	241	174	133	109	73	44	22	5	3	2	0
CCR	247	150	108	80	53	40	25	10	3	1	0

Dombret et al. Blood (2015) 126 (3): 291–299.

HOW to improve these results ?

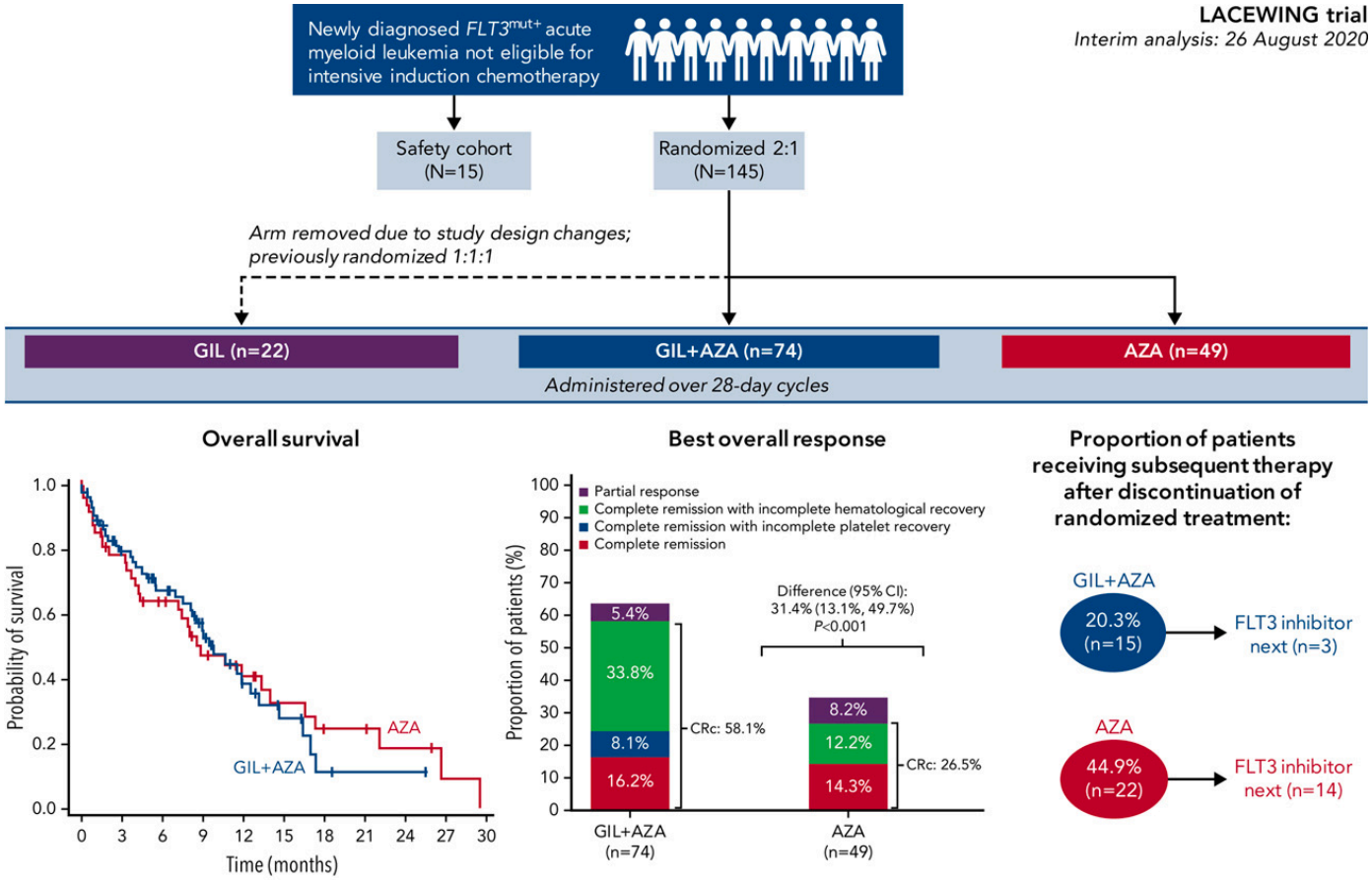
TARGETED THERAPIES

- FLT3 inhibition
- IDH1 inhibition
- IDH2 inhibition

BROAD SPECTRUM ACTION

- BCL2 inhibition

5-AZA + inhibiteur de FLT3 (Gilteritinib)



Abbreviations: AZA, azacitidine 75 mg/m^2 intravenously or subcutaneously daily on days 1–7; CI, confidence interval; CRc, composite complete remission; FLT3, FMS-like tyrosine kinase 3; GIL, gilteritinib 120 mg orally daily on days 1–28; HR, hazard ratio.

Wang E et al. Blood (2022) 140 (17): 1845–1857.

5-AZA + Enasidenib

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)	p value
Overall response*	50 (74%; 95% CI 61–84)	12 (36%; 95% CI 20–55)	0·0003
Complete remission	37 (54%; 95% CI 42–67)	4 (12%; 95% CI 3–28)	<0·0001
Complete remission or complete remission with partial haematological recovery	39 (57%)	6 (18%)	0·0002
Complete remission with incomplete blood count or platelet recovery	6 (9%)	6 (18%)	..
Partial remission	4 (6%)	2 (6%)	..
Morphological leukaemia-free state	3 (4%)	0	..
Stable disease	13 (19%)	16 (48%)	..
Disease progression	1 (1%)	1 (3%)	..
Not evaluable or missing data	4 (6%)	4 (12%)	..
Time to first response, months	1·9 (1·1–3·9)	3·6 (1·9–4·4)	..
Time to complete remission, months	5·4 (3·8–7·6)	4·4 (3·8–5·6)	..
Duration of response, months	24·1 (95% CI 10·0–NR)	9·9 (95% CI 5·5–13·6)	..
Duration of complete remission, months	NR (95% CI 7·7–NR)	12·7 (95% CI 11·7–NR)	..

Data are n (%; 95% CI), n (%), median (IQR), or median (95% CI). Data cutoff Aug 20, 2019. NR=not reached. *Overall response defined as proportion of patients with complete remission, complete remission with incomplete blood count or platelet recovery, partial remission, or morphological leukaemia-free state.

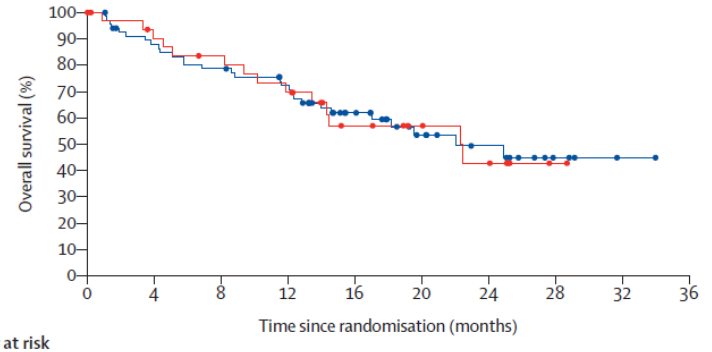
Table 2: **Haematological responses in the randomised phase 2 study portion**

DiNardo, et al. Lancet Oncol. 2021 Nov;22(11):1597-1608.

5-AZA + Enasidenib

B

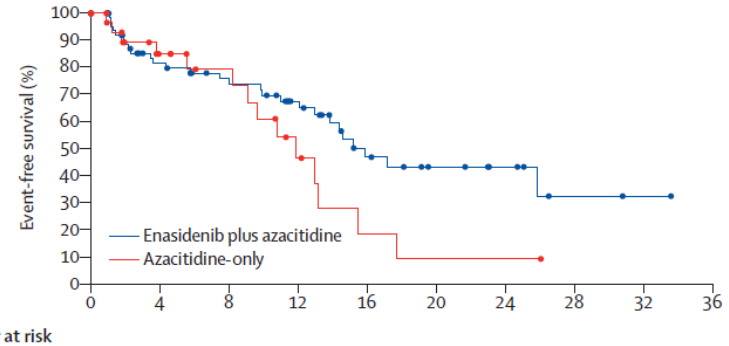
	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	29 (43%)	14 (42%)
Censored	39 (57%)	19 (58%)
Median overall survival, months	22·0 (95% CI 14·6–NR)	22·3 (95% CI 11·9–NR)
Hazard ratio	0·99 (95% CI 0·52–1·87)	
Log-rank p value	0·97	



Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	57 (3)	51 (3)	44 (6)	28 (16)	16 (25)	11 (29)	4 (35)	1 (38)	0 (39)
Azacitidine only	33 (0)	27 (3)	24 (4)	20 (4)	12 (9)	9 (12)	6 (13)	1 (18)	0 (19)	..

A

	Enasidenib plus azacitidine (n=68)	Azacitidine only (n=33)
Events	27 (40%)	14 (42%)
Censored	41 (60%)	19 (58%)
Median event-free survival, months	15·9 (95% CI 13·0–NR)	11·9 (95% CI 8·2–15·5)
Hazard ratio	0·59 (95% CI 0·30–1·13)	
Log-rank p value	0·11	



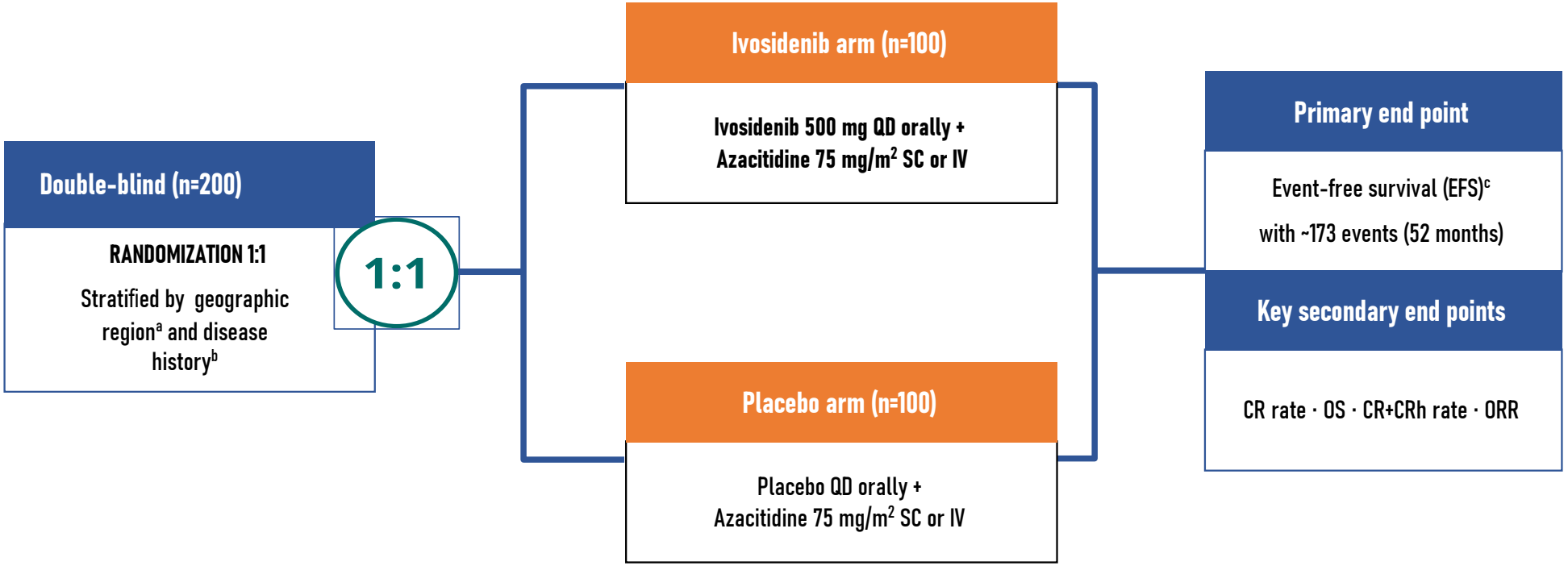
Number at risk (number censored)										
Enasidenib plus azacitidine	68 (0)	45 (12)	37 (17)	27 (23)	14 (29)	9 (33)	6 (36)	2 (39)	1 (40)	0 (41)
Azacitidine only	33 (0)	18 (11)	13 (15)	6 (17)	2 (18)	1 (18)	1 (18)	0 (19)	..	..

DiNardo, et al. Lancet Oncol. 2021 Nov;22(11):1597-1608.

5-AZA + Ivosidenib

AZA + Ivosidenib

Phase III randomized trial



Montesinos P. *et al.*, N Engl J Med 2022.

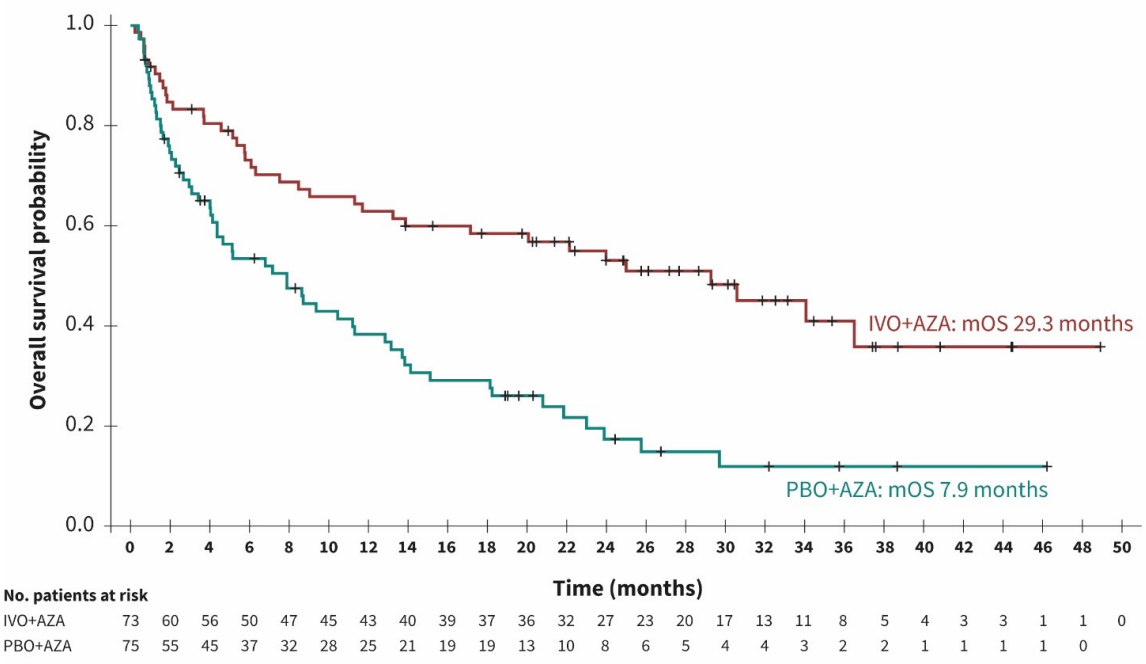
IDH1-mutant AML

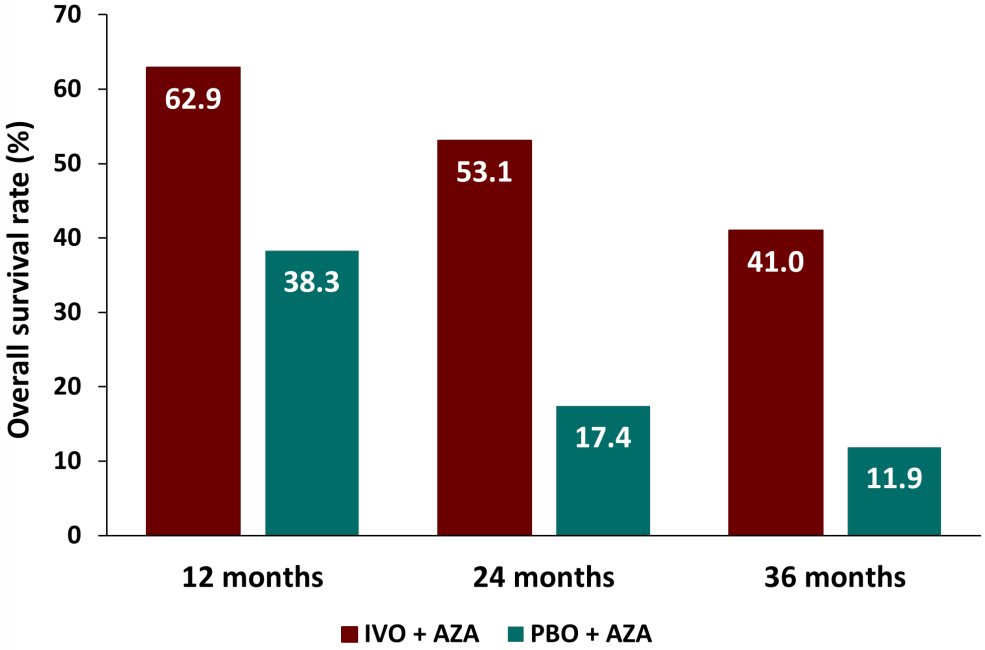
AZA + Ivosidenib *Phase III randomized trial*

Response rates	IVO+AZA (n=72)	PBO+AZA (n=74)
CR rate, n (%) [95% CI]	34 (47.2) [35.3, 59.3]	11 (14.9) [7.7, 25.0]
Odds ratio (95% CI); 1-sided *P* value	4.8 (2.2, 10.5); *P*<0.0001	
Median duration of CR (95% CI), months	NE (13.0, NE)	11.2 (3.2, NE)
Median time to CR (range), months	4.3 (1.7–9.2)	3.8 (1.9–8.5)
CR+CRh rate, n (%) [95% CI]	38 (52.8) [40.7, 64.7]	13 (17.6) [9.7, 28.2]
Odds ratio (95% CI); 1-sided *P* value	5.0 (2.3, 10.8); *P*<0.0001	
Median duration of CR+CRh (95% CI), months	NE (13.0, NE)	9.2 (5.8, NE)
Median time to CR+CRh (range), months	4.0 (1.7–8.6)	3.9 (1.9–7.2)
ORR, n (%) [95% CI]	45 (62.5) [50.3, 73.6]	14 (18.9) [10.7, 29.7]
Odds ratio (95% CI); 1-sided *P* value	7.2 (3.3, 15.4); *P*<0.0001	
Median duration of response (95% CI), months	22.1 (13.0, NE)	9.2 (6.6, 14.1)
Median time to first response (range), months	2.1 (1.7–7.5)	3.7 (1.9–9.4)

Montesinos P. *et al.*, N Engl J Med 2022.

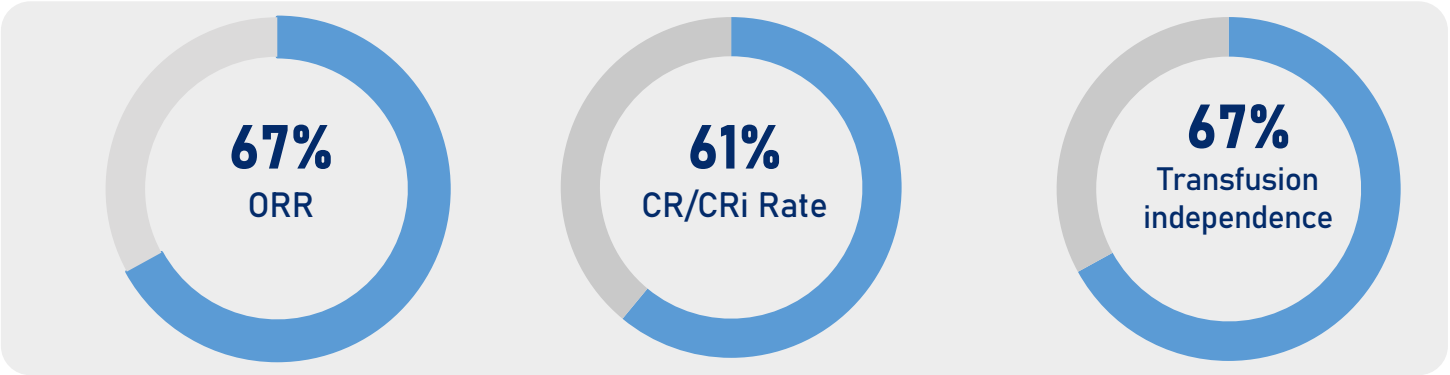
5-AZA + Ivosidenib





Montesinos P. *et al.*, N Engl J Med 2022.
De Botton S. *et al.*, ASCO 2023.

5-AZA + Tamibarotene in newly diagnosed unfit AML patients RARα +



1.2 months
Time to response

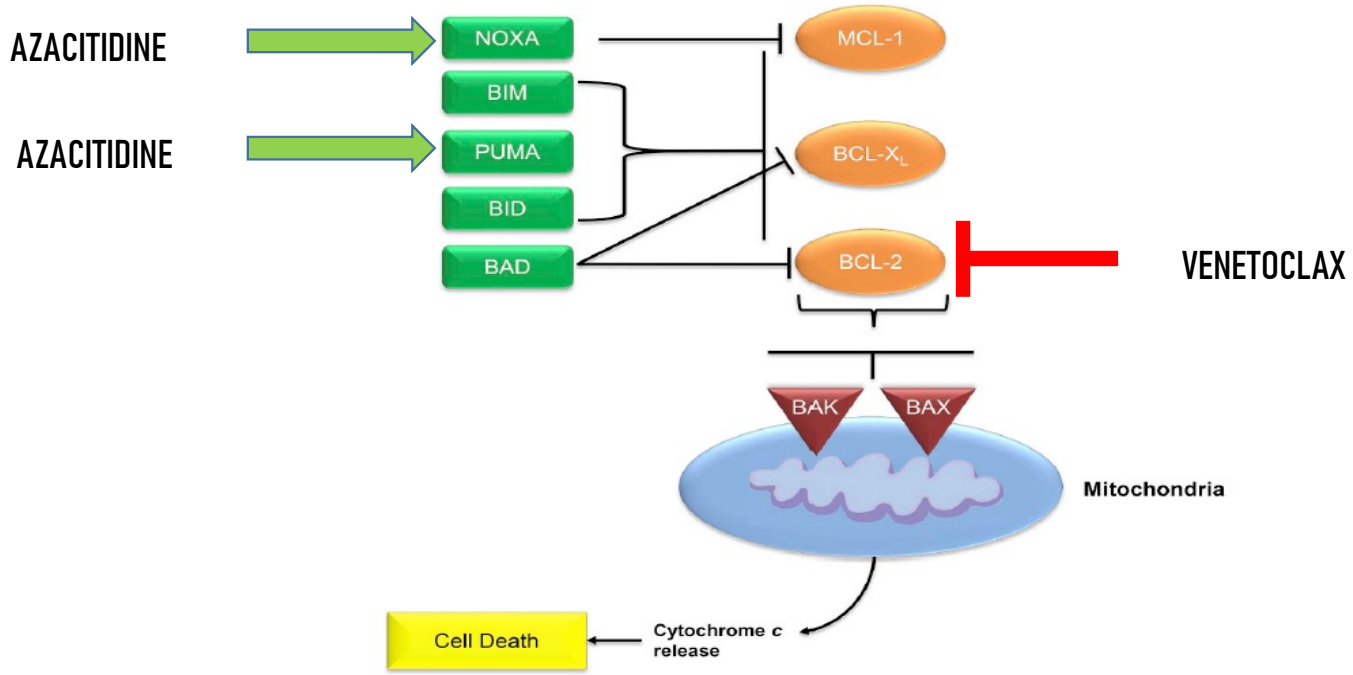
10.8 months
Duration of response

18 months
Overall survival for complete responders

(de Botton, Blood Advances 2022)

AML without Targeted therapies

AZA + Venetoclax

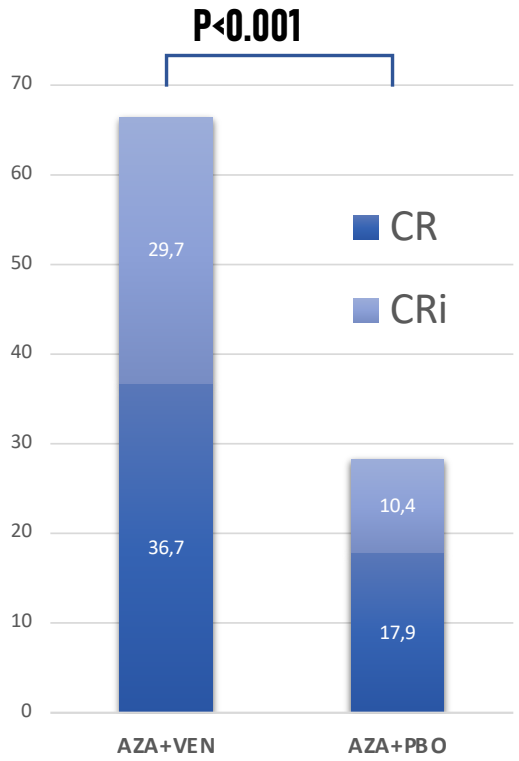


Jin S. *et al.*, Clin Cancer Res 2020

VEN + 5-AZA

AZA + Venetoclax

Phase III randomized, placebo-controlled trial



	AZA+VEN	AZA+PBO
Median time to CR/CRi	1.0 month	2.6 months
Median duration of response	17.5 months	13.4 months
RBC transfusion independance	59.8%	35.2%
Platelet-transfusion independance	68.5%	49.7%

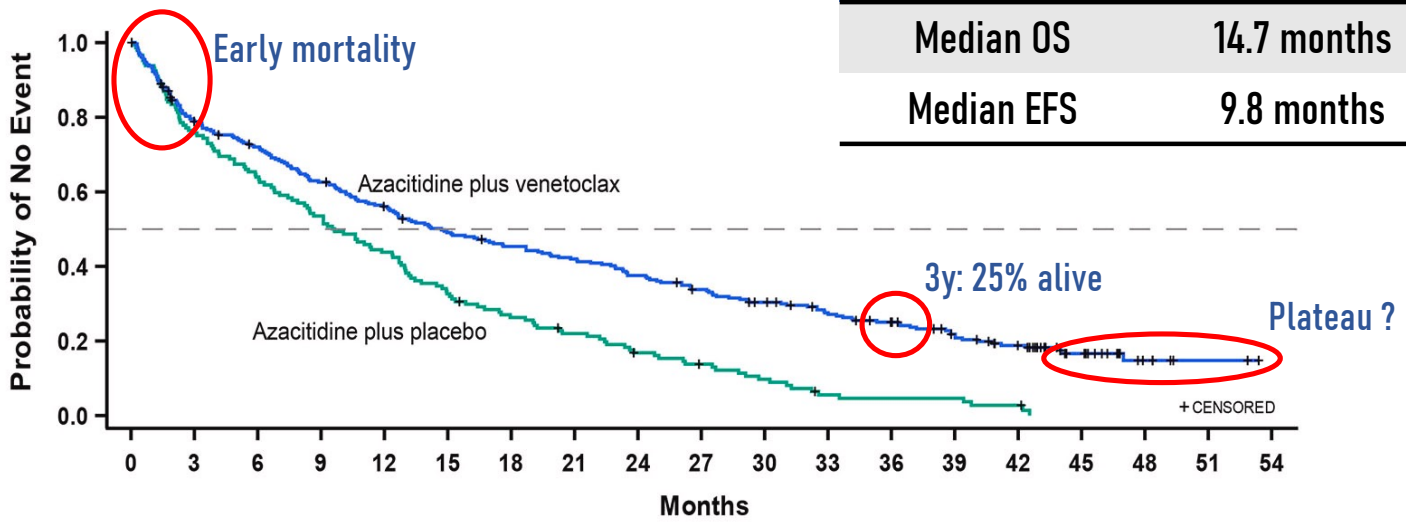
DiNardo CD *et al.*, N Engl J Med 2020.

VEN + 5-AZA

AZA + **Venetoclax**

Phase III randomized, placebo-controlled trial

Overall Survival Median FU 43 months



	AZA+VEN	AZA+PBO	P
Median OS	14.7 months	9.6 months	<0.001
Median EFS	9.8 months	7.0 months	<0.001

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

DiNardo CD *et al.*, N Engl J Med 2020.
Pratz K.H. *et al.*, ASH 2022.

The VEN + AZA synergy in real-life

AZA + Venetoclax *Phase III randomized, placebo-controlled trial*

- Median OS <13 months in real-life setting

ND AML 1st line Aza-Ven	Country	N	Median OS	Median EFS
Mayo Clinic	Real life (USA)	44	**11.0 months**	
REVIVE	Real life (Israel)	127	**9.6 months**	
AVALON	Real life (Italy)	43	**12.7 months**	5.8 months
University of Pennsylvania	Real life (USA)	439	**11.0 months**	

- Toxicity remains problematic
  - Febrile neutropenia grade III/IV: 42%
  - Postremission grade IV cytopenia >7days: 87%

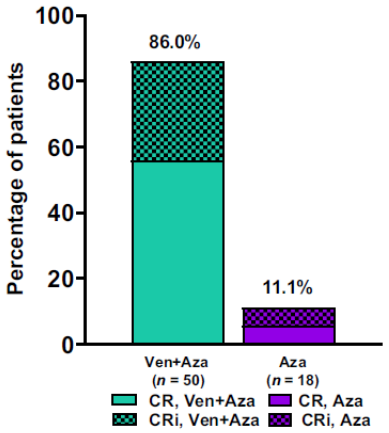
Morsia E. et al, Am J Hematol 2020. Wolach O. et al. ASH 2021. Todisco E. et al. Cancer 2022. Matthews AH. et al. Blood Adv 2022.
DiNardo CD *et al.*, N Engl J Med 2020. Pratz K.H. *et al.*, ASH 2022.

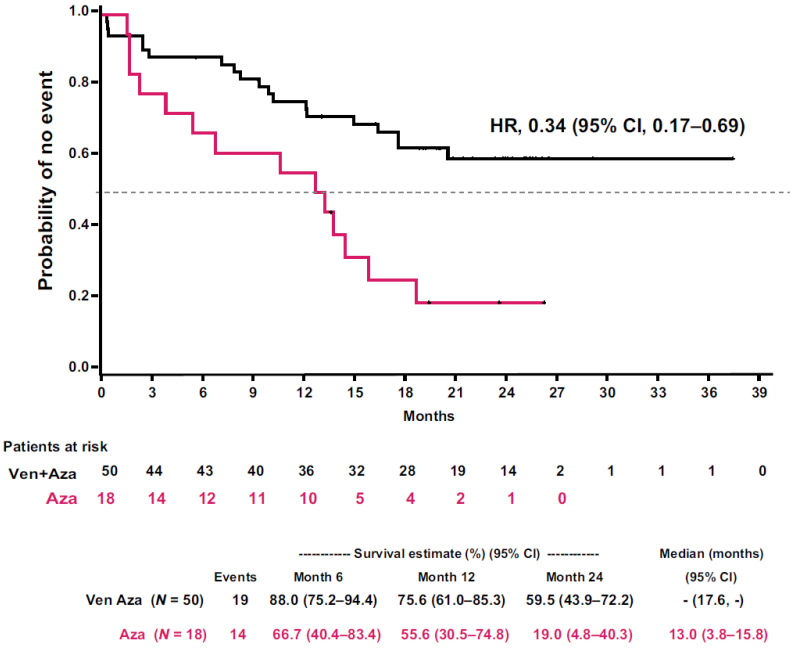
VEN + 5-AZA (vs AZA alone) ?

AZA + Venetoclax

Phase III randomized, placebo-controlled trial

- >75y +++
- Performans status <2
- Non defavorable cytogenetic
- *NPM1*-mut
- *IDH2*-mut +++





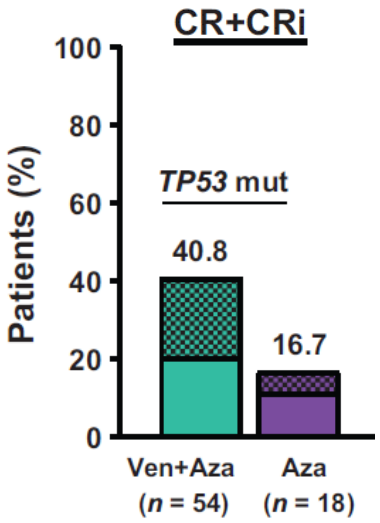
	Events	Survival estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (months) (95% CI)
Ven Aza (*N* = 50)	19	88.0 (75.2–94.4)	75.6 (61.0–85.3)	59.5 (43.9–72.2)	- (17.6, -)
Aza (*N* = 18)	14	66.7 (40.4–83.4)	55.6 (30.5–74.8)	19.0 (4.8–40.3)	13.0 (3.8–15.8)

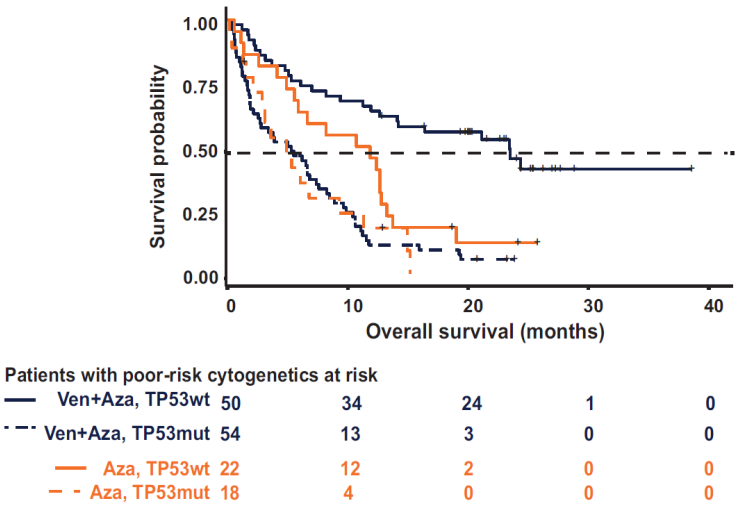
DiNardo CD *et al.*, N Engl J Med 2020.
Polleya DA *et al.*, Clin Cancer Res 2022.

VEN + 5-AZA

AZA + Venetoclax

- *TP53* mutation/délétion *+++*





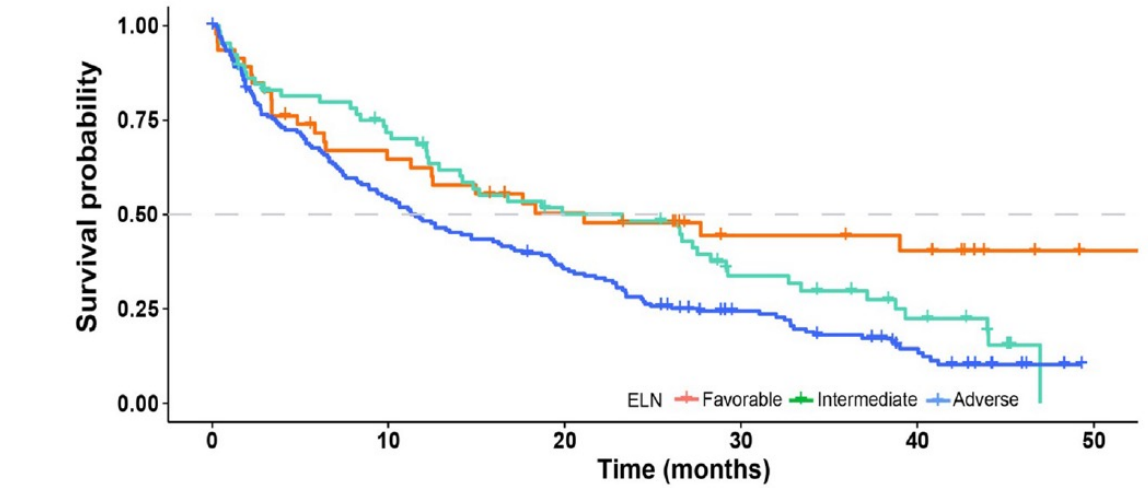
	Median OS, months (95% CI)
Ven+Aza *TP53* wt	23.43 (11.93–NR)
Ven+Aza *TP53* mut	5.17 (2.17–6.83)
Aza *TP53* wt	11.29 (4.9–12.78)
Aza *TP53* mut	4.90 (2.14–9.30)

DiNardo CD *et al.*, Blood 2020
Pollyea D *et al.*, Clin Cancer Res 2022

ELN-2022 classification is not predictive

AZA + Venetoclax

Figure 2: Overall survival among patients treated with VEN+AZA

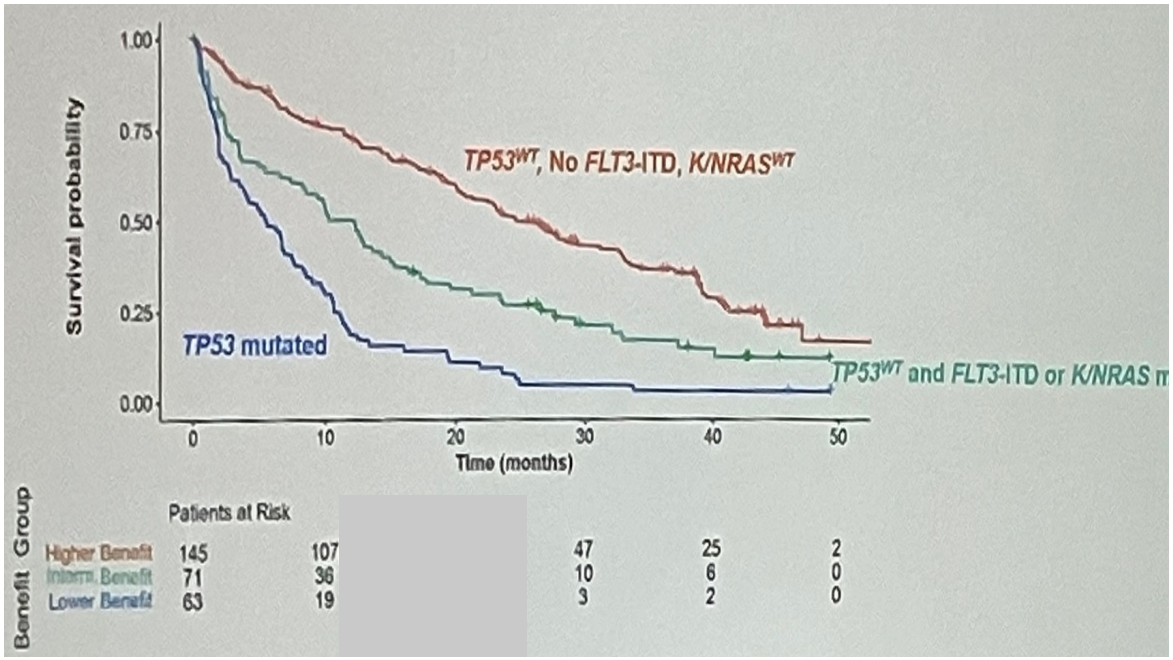


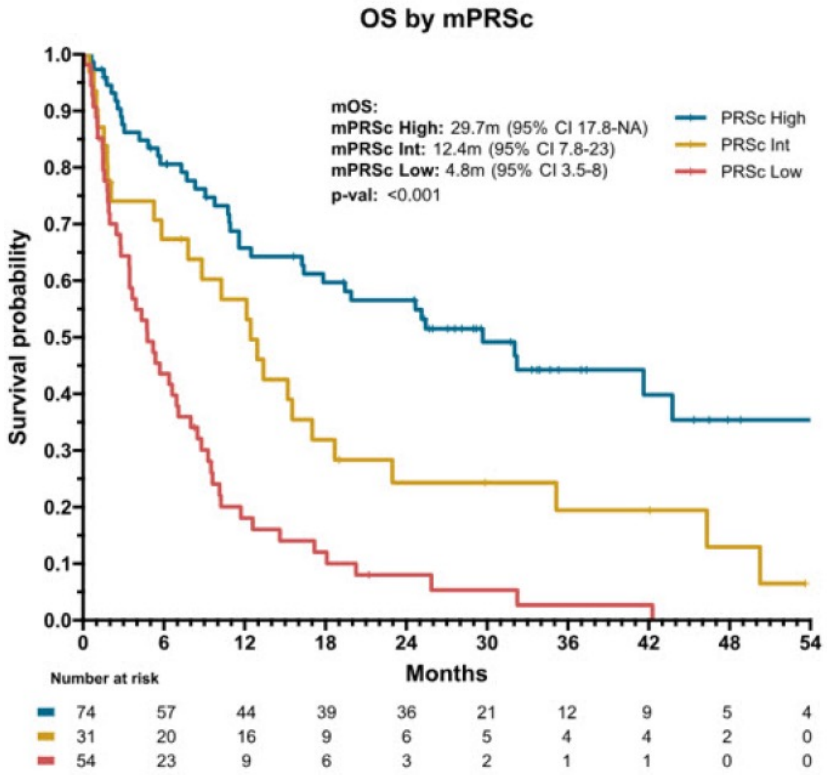
	No. at risk:					
ELN Favorable	46	28	20	12	10	2
Intermediate	65	44	29	17	9	0
Adverse	168	90	58	31	14	0

Döhner H *et al.*, ASH 2022.

mPRS is predictive of survival

AZA + Venetoclax

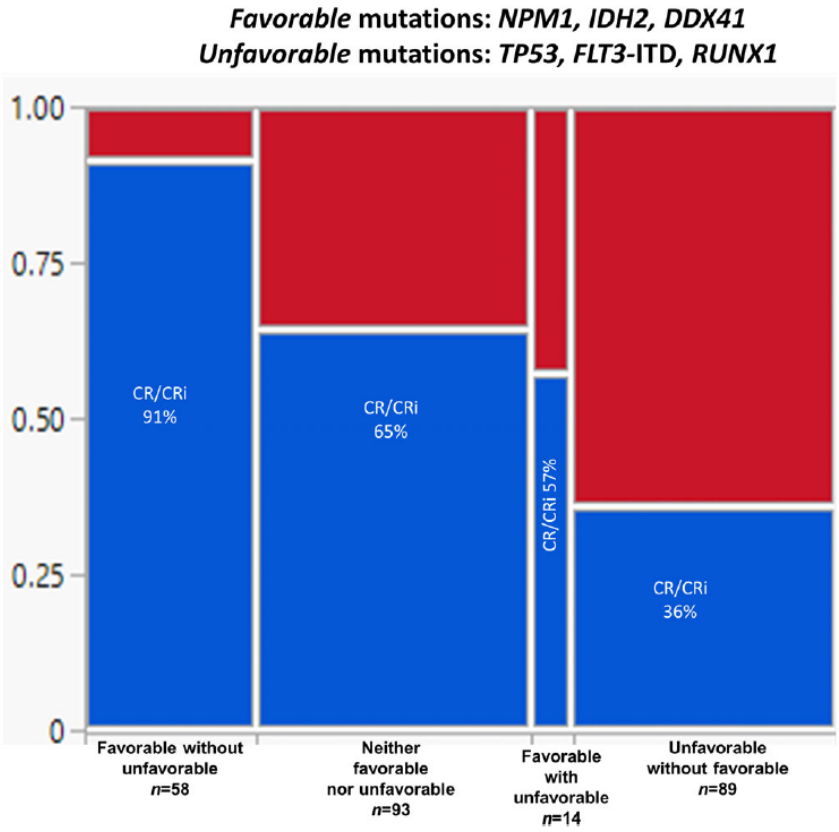




Döhner H. *et al.*, ASH 2022.
Bataller A. *et al.*, Blood Adv 2023.

Mayo clinic stratification predictive of response

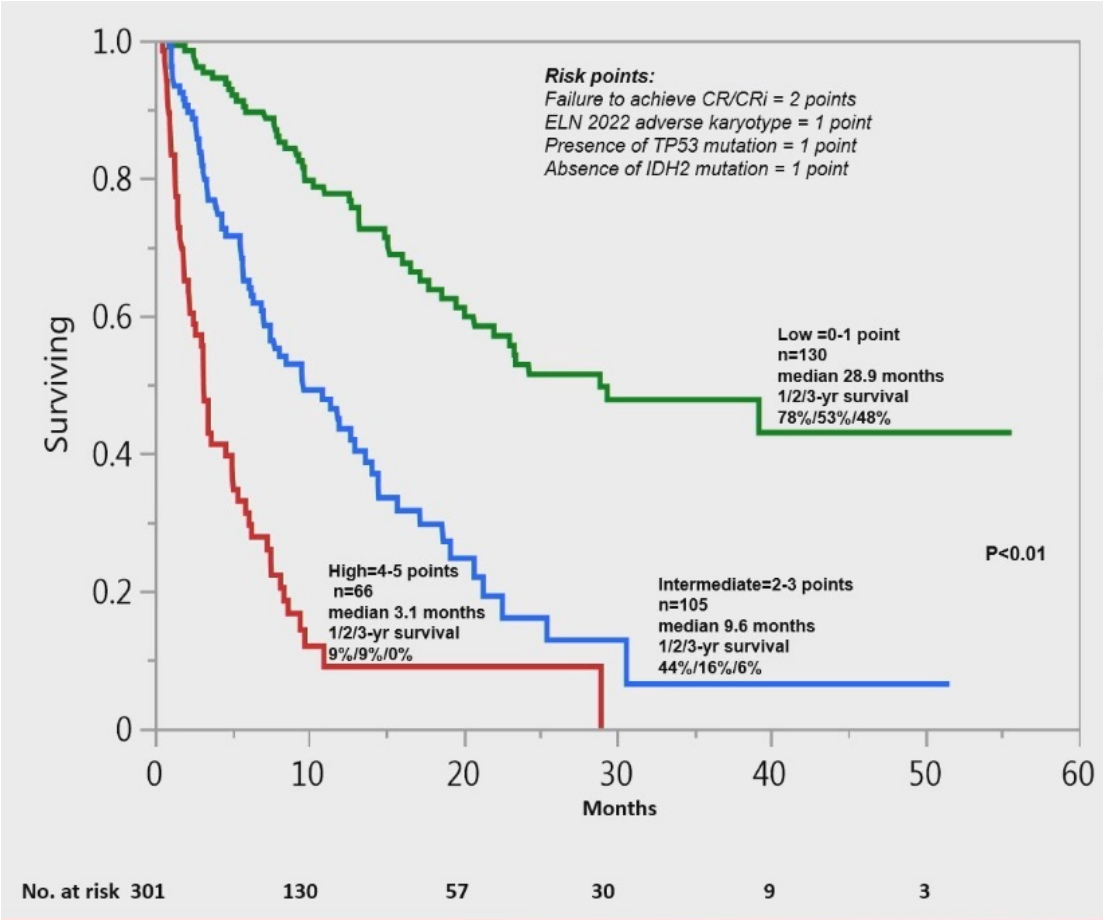
AZA + Venetoclax



Gangat N. *et al.*, Am J Hematol 2023.

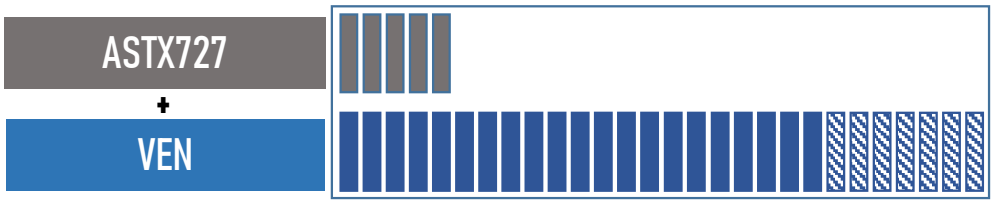
Mayo clinic stratification predictive of survival

AZA + Venetoclax



Gangat N. *et al.*, Am J Hematol 2023.

Toward a full oral/ambulatory treatment ?

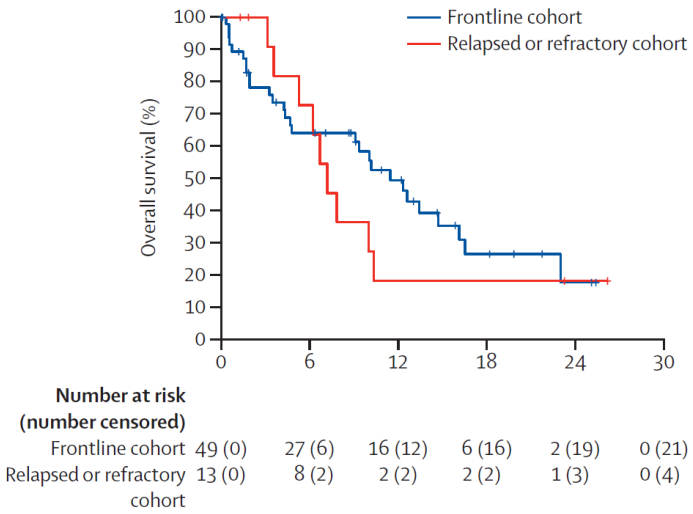


Phase II
ND (N=49) and R/R (N=13) AML

	Frontline treatment cohort (n=49)
Age, years	80 (76–82)
Eastern Cooperative Oncology Group performance status	
0	3 (6%)
1	23 (47%)
2	22 (45%)
Cytogenetics	
Normal	17 (35%)
-17/17p-	4 (8%)
Complex	12 (24%)
Mutations	
NPM1	7 (14%)
FLT3-ITD	3 (6%)
IDH1/IDH2	3 (6%)
TP53	8 (16%)
European LeukemiaNet 2022 risk	
Adverse	39 (80%)
Previous untreated myelodysplastic syndrome or myeloproliferative neoplasm	11 (22%)

	Frontline treatment cohort (n=47)
Overall response rate†	30 (64%; 49–77)
Complete remission	16 (34%; 21–49)
Complete remission with incomplete blood count recovery	11 (23%; 12–38)
Partial remission	0 (0%; 0–8)
Morphologic leukaemia-free state	3 (6%; 1–18)
Cycles given	3 (1–7)
Cycles to first response	1 (1–1)
Cycles to best response	1 (1–1)
4-week mortality	5 (11%; 4–23)
8-week mortality	8 (17%; 8–31)

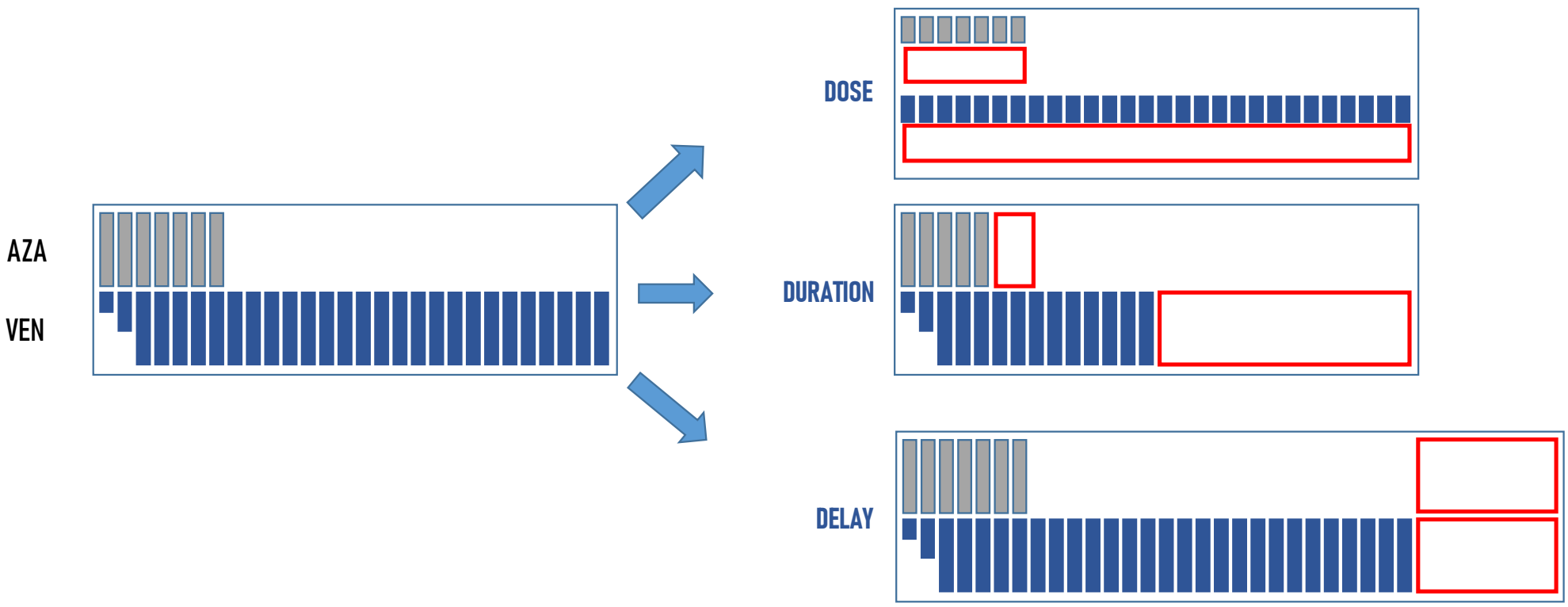
Febrile neutropenia: 18%



Median OS: 11.5 months (IC95: 9.1.-16.6)
Median DOR: 13.2 months

Bazinet A. *et al.*, Lancet Haematol 2024.

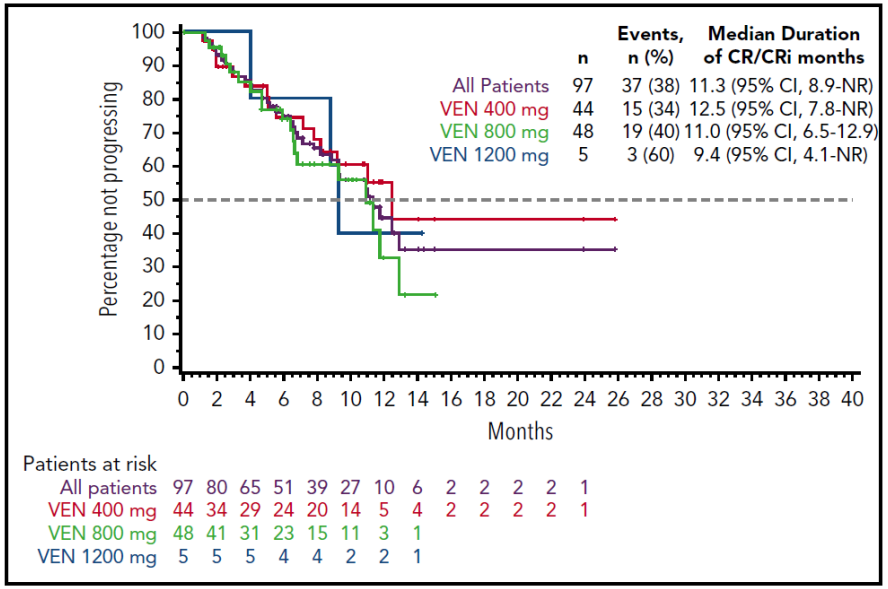
VEN + AZA scheme optimization



VEN + AZA scheme optimization

➢ ***Dose ?***

Cohort	N	Composite Response Rate, (CR+CRi) n (%)	Overall Response Rate (CR+CRi+PR) n (%)	Median Duration of CR+CRi (95% CI)	Median OS (95% CI)
All patients	145	97 (67)	99 (68)	11.3 (8.9-NR)	17.5 (12.3-NR)
VEN 400 mg + HMA	60	44 (73)	44 (73)	12.5 (7.8-NR)	NR (11.0-NR)
VEN 800 mg + HMA	74	48 (65)	50 (68)	11.0 (6.5-12.9)	17.5 (10.3-NR)



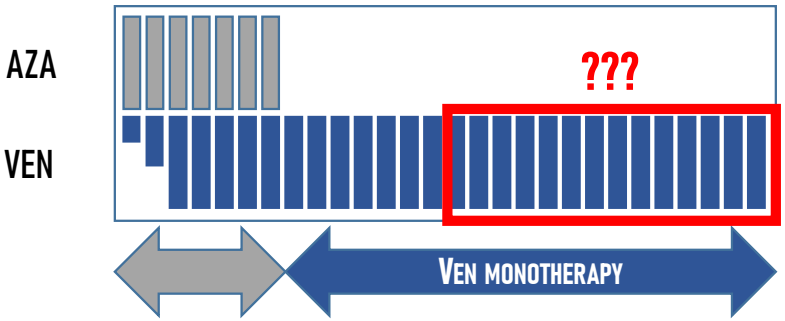
Background for AZA-VEN optimization:

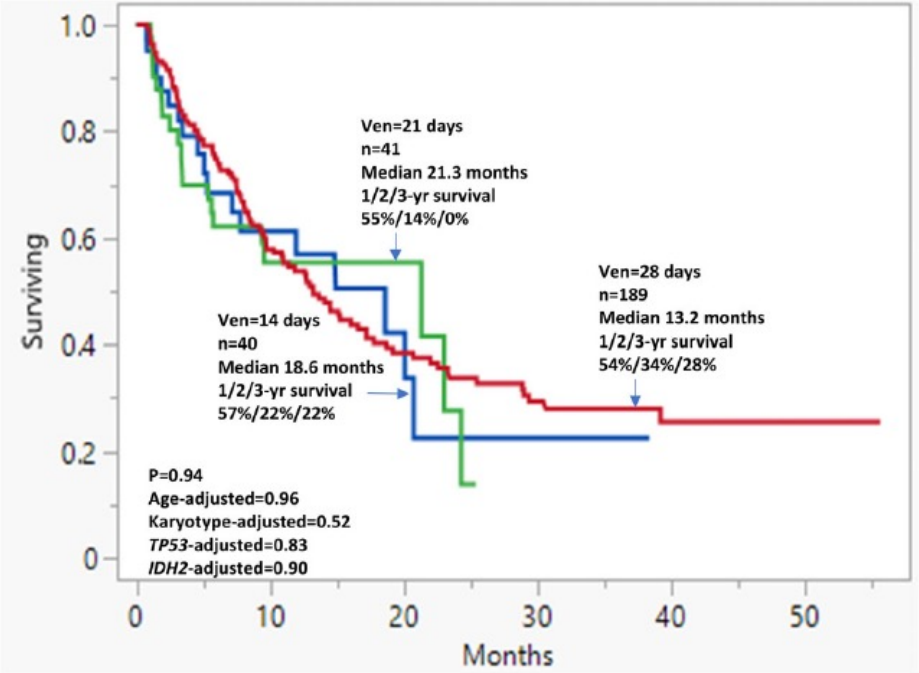
- **Limited efficacy of VEN monotherapy** in de novo or R/R AML
- Efficacy of AZA-VEN combination is based on **synergistic effect**

DiNardo C.D. *et al.*, Blood 2019.

VEN + AZA scheme optimization

➢ *Duration reduction*





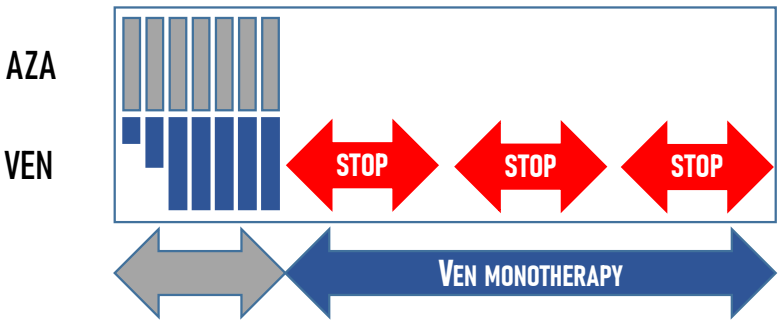
Background for AZA-VEN optimization:

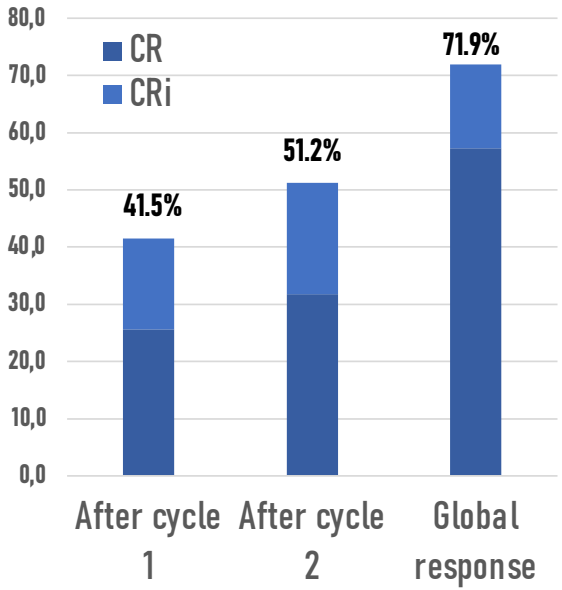
- **Limited efficacy of VEN monotherapy** in de novo or R/R AML
- Efficacy of AZA-VEN combination is based on **synergistic effect**
- **No impact on survival of VEN exposure reduction to 21 days/28**

Aiba M. *et al.*, Ann Hematol 2023.
Karrar O. *et al.*, Am J Hematol 2024.

VEN + AZA scheme optimization

➢ *Duration reduction*





Median **OS: 11.3 months** (IC95: 6.7-13.8)

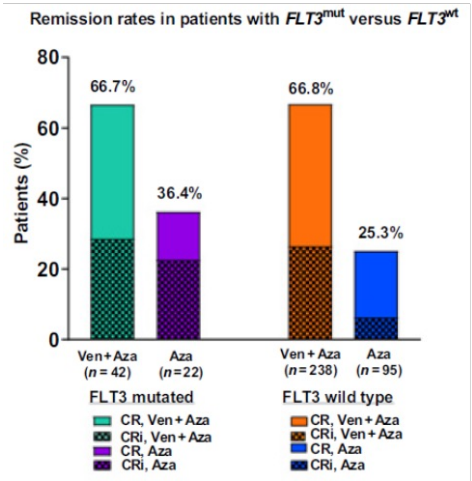
Median **EFS: 7.3 months** (IC95: 4.9-9.2)

Willekens C. *et al.*, ASH 2023.

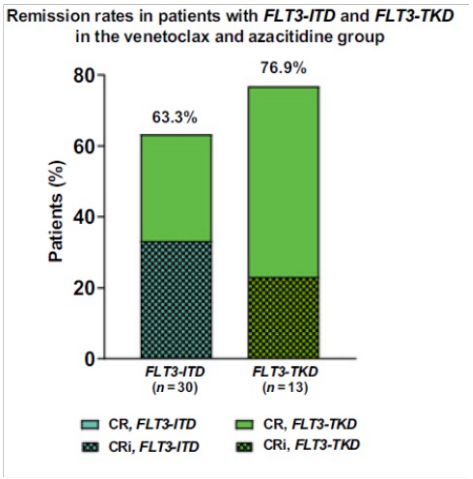
Improve results by adding a third drug (triplet combination) ?

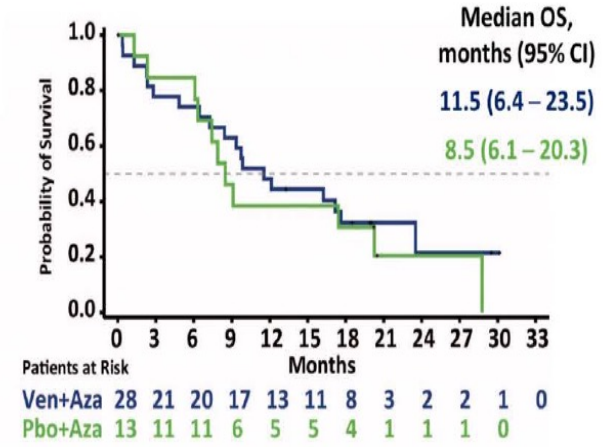
5-AZA + VENETOCLAX FLT3 population

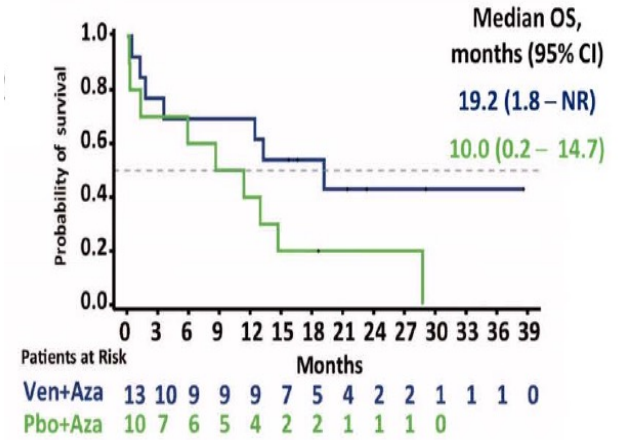
FLT3mut vs FLT3wt



FLT3-ITD vs FLT3-TKD



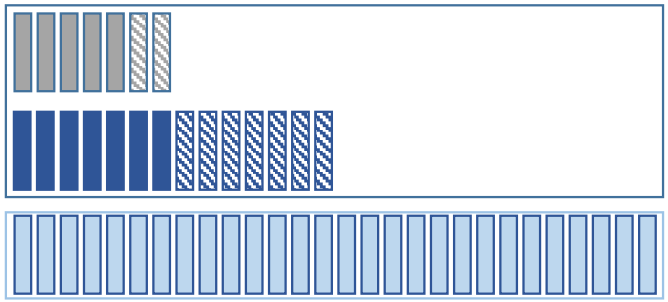




Konopleva M, Clin Cancer Res 2022

adding a third drug (triplet combination) FLT3

AZA
+
VEN
+
GILTERITINIB

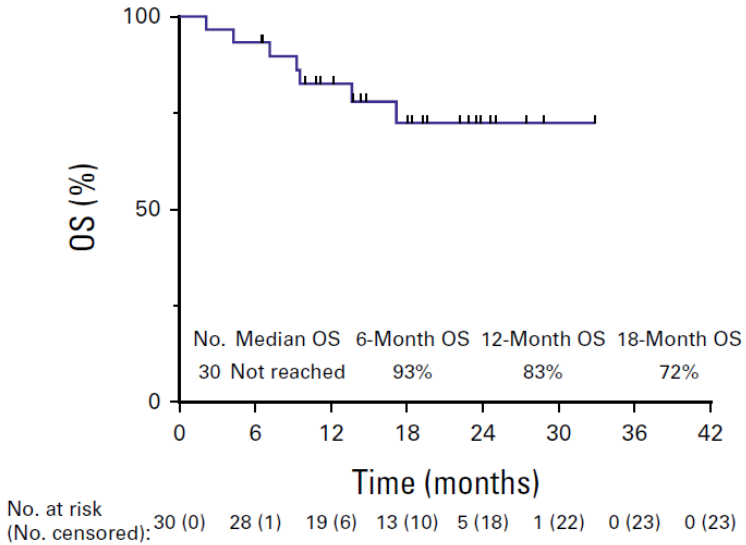


RP2D: 80mg/d

Phase I/II
ND and R/R AML with FLT3mut

→ ND-AML (N=30)
Median Age: 71y
FLT3-ITD: 73%
NPM1: 43%

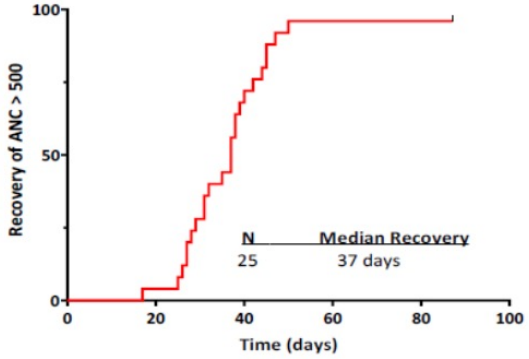
Hematologic Response	Frontline Cohort (n = 30)
mCRc (CR/CRi/MLFS), No. (%)	30 (100)
CR	27 (90)
CRi	2 (6)
MRD Response[c]	**Frontline Cohort (n = 30)**
MRD by flow cytometry (after cycle 1), No. (%)	
Negative	9/16 (56)
Positive	7/16 (44)
MRD by flow cytometry (best response), No. (%)	
Negative	25/27 (93)
Positive	2/27 (7)
MRD by PCR for *FLT3* (after cycle 1), No. (%)	
Negative	11/30 (37)
Positive	19/30 (63)
MRD by PCR for *FLT3* (best response), No. (%)	
Negative	27/30 (90)
Positive	3/30 (10)



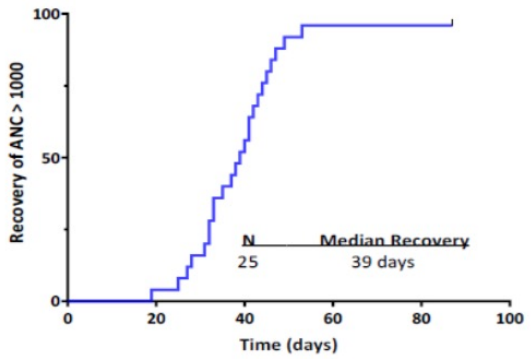
Short N.J. *et al.*, J Clin Oncol 2024.

adding a third drug (triplet combination) FLT3

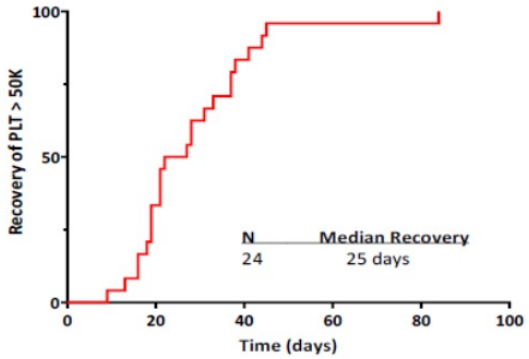
ANC >500*



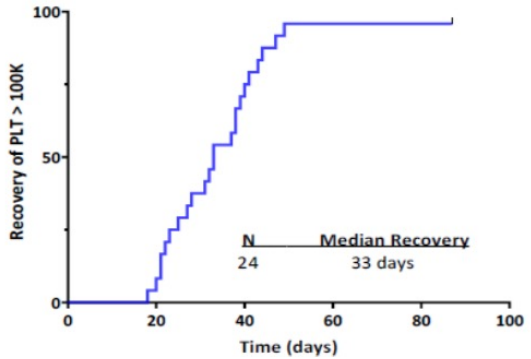
ANC >1000*



Platelets >50K



Platelets >100K

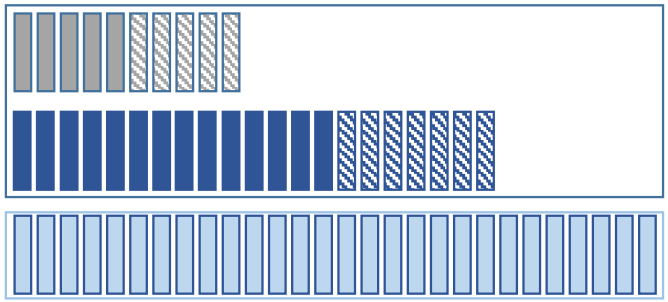


Short et al. ASH 2022 Abstract #831

adding a third drug (triplet combination) FLT3-ITD

DEC
+
VEN
+
QUIZARTINIB

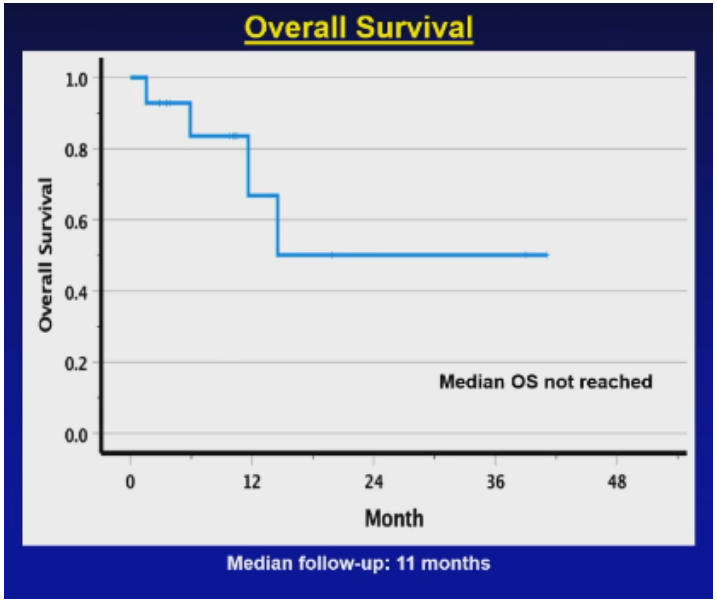
RP2D: 30mg/d



Phase I/II
ND and R/R AML with FLT3-ITD
→ ND-AML (N=14)
Median Age: 70y
FLT3-ITD: 100%
NPM1: 21%

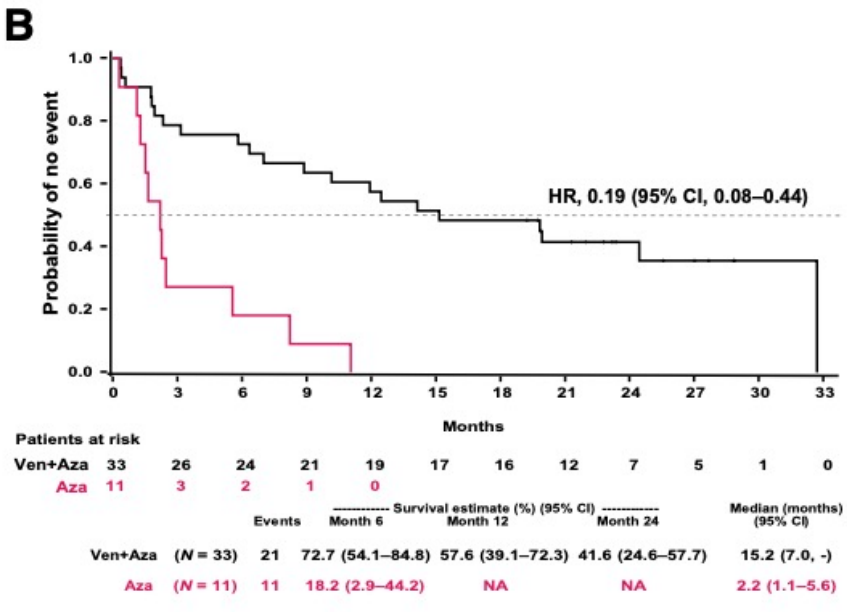
Response*, N (%)	All Patients (N=14)
CRc	**14 (100)**
CR	11 (79)
CRi	3 (21)
MLFS	0 (0)
Day 14 BM blasts ≤5%¥	**14 (100)**

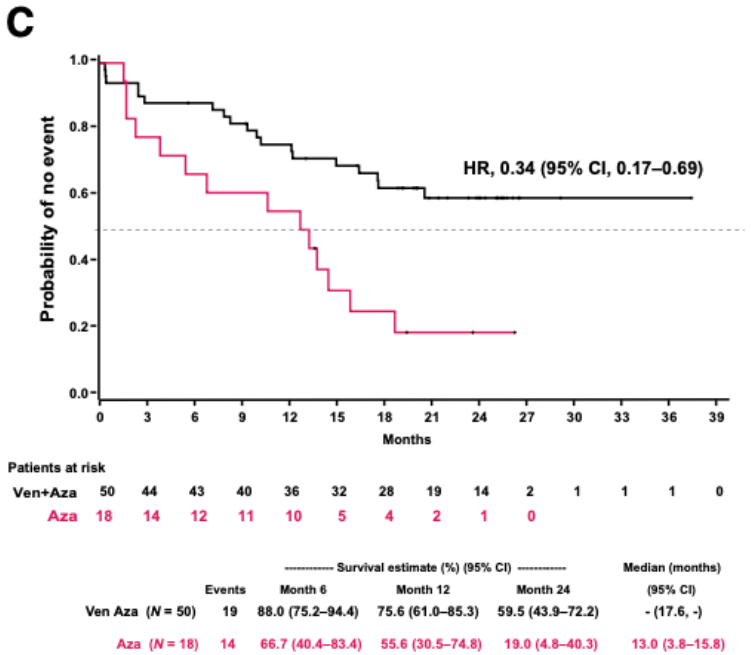
Response*, N (%)	All Patients (N=14)
Best MRD, anytime	
Flow Cytometry (-)	9/12 (75)
FLT3 PCR (-)	12/14 (86)
30-day mortality	0 (0)
60-day mortality	**1 (7)**
Bridge to ASCT	**4 (19)**



Yilmaz M. *et al.*, ASH 2023.

IDH-mutated AML frontline
Venetoclax+ 5-AZA



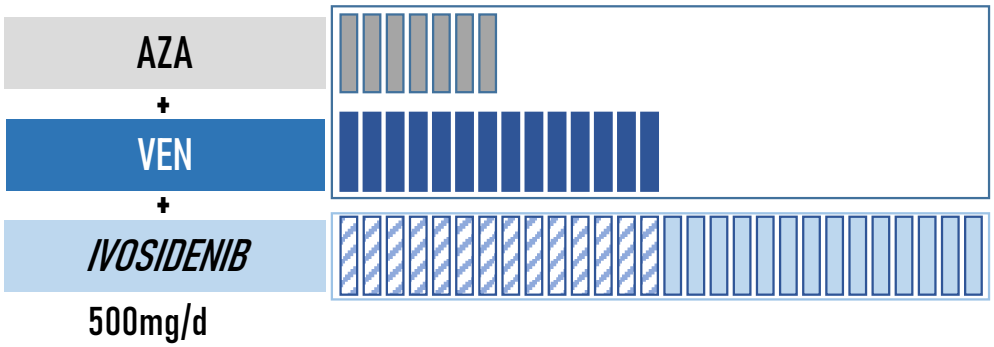


Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and *IDH1/2* Mutations

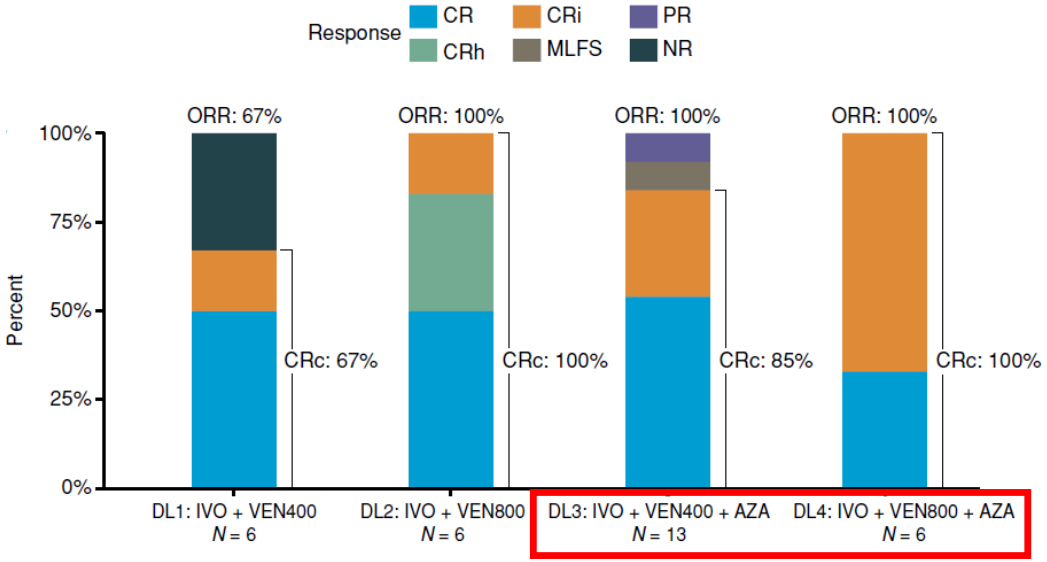
Daniel A. Pollyea[1], Courtney D. DiNardo[2], Martha L. Arellano[3], Arnaud Pigneux[4], Walter Fiedler[5], Marina Konopleva[2], David A. Rizzieri[6], B. Douglas Smith[7], Atsushi Shinagawa[8], Roberto M. Lemoli[9,10], Monique Dail[11], Yinghui Duan[12], Brenda Chyla[12], Jalaja Potluri[12], Catherine L. Miller[12], and Hagop M. Kantarjian[2]

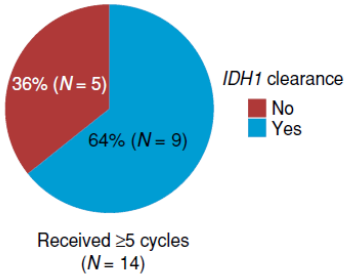
doi: 10.1158/1078-0432.CCR-21-3467

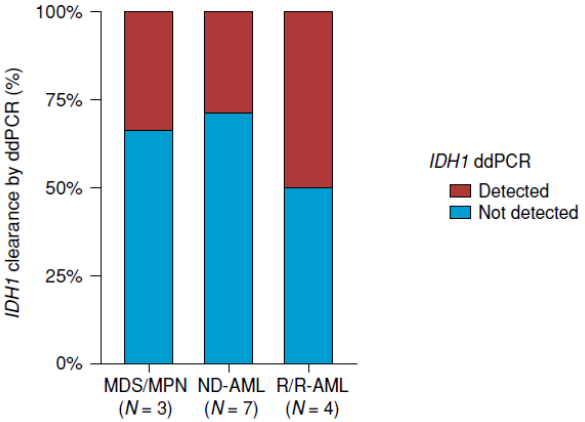
adding a third drug (triplet combination) IDH1



Phase Ib
ND and R/R AML with IDH1mut
IVO+VEN (N=12) and IVO+VEN+AZA (N=19)







Lachowiez C.A. *et al.*, Blood Cancer Discov 2023.

adding a third drug (triplet combination) IDH2

A PHASE II STUDY OF ENASIDENIB WITH VENETOCLAX +/- AZACITIDINE I N IDH2-MUTATED MYELOID MALIGNANCIES

Venugopal S et al, *Blood Cancer Journal* volume 12, Article number: 10 (2022)

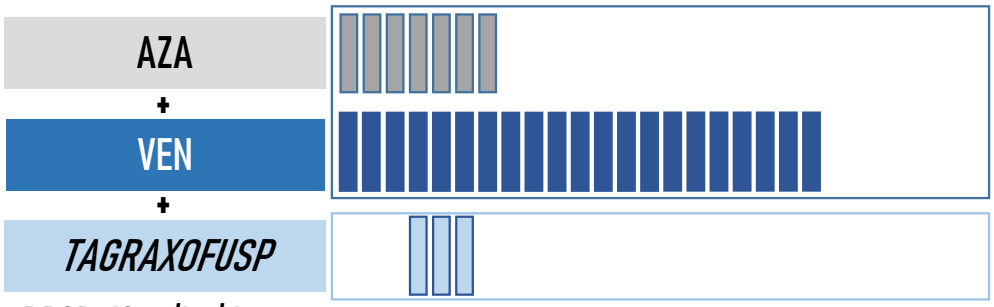
Table 2. Outcomes in newly diagnosed and relapsed/refractory patients with *IDH2* mutant acute myeloid leukemia.

Response	Newly diagnosed $n = 7$	Relapsed/ refractory $n = 19$
CRc	7 (100)	11 (58)
CR	5 (72)	5 (26)
CRi	2 (28)	6 (32)
MRD negativity by FCM	7/7 (100)	2/9 (22)
Not evaluable	0	1 (5)
No response	0	7 (37)
Median number of cycles given (range)	3 (1–8)	4 (1–17)
Median time to best response, months (range)	1.6 (1.0–4.2)	1.8 (0.8–5.4)

CRc -composite complete remission rate = CR + CRi, *CR*- complete remission, *CRi* -CR with incomplete hematologic recovery, *MRD*- measurable residual disease, *FCM*- flowcytometry

All results expressed as No. (%) or median [Minimum–maximum], unless specified.

adding a third drug (triplet combination) no target (CD 123 pos)

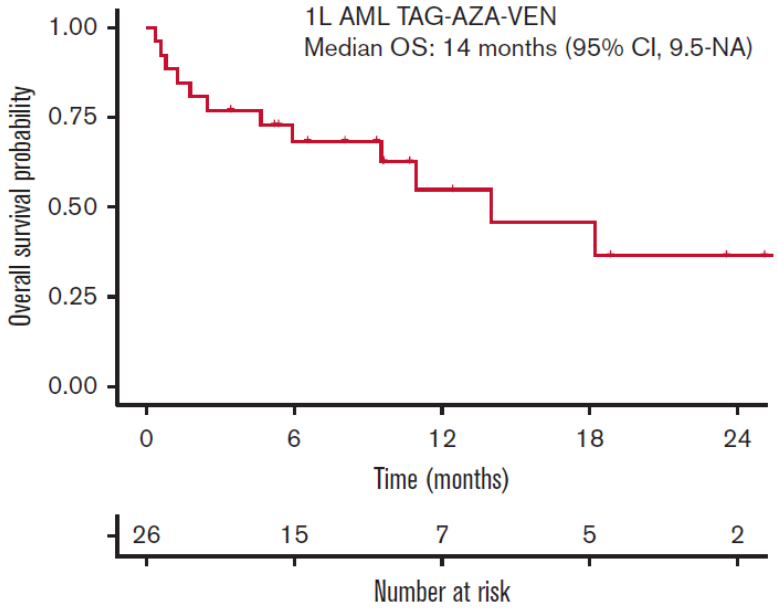


RP2D: 12µg/kg/d

Phase Ib
ND AML (N=26)
TP53: 50%

CR/CRi: 58%
Phenotypic negative MRD in response: 71%
TP53mut: 6/13 (46%)

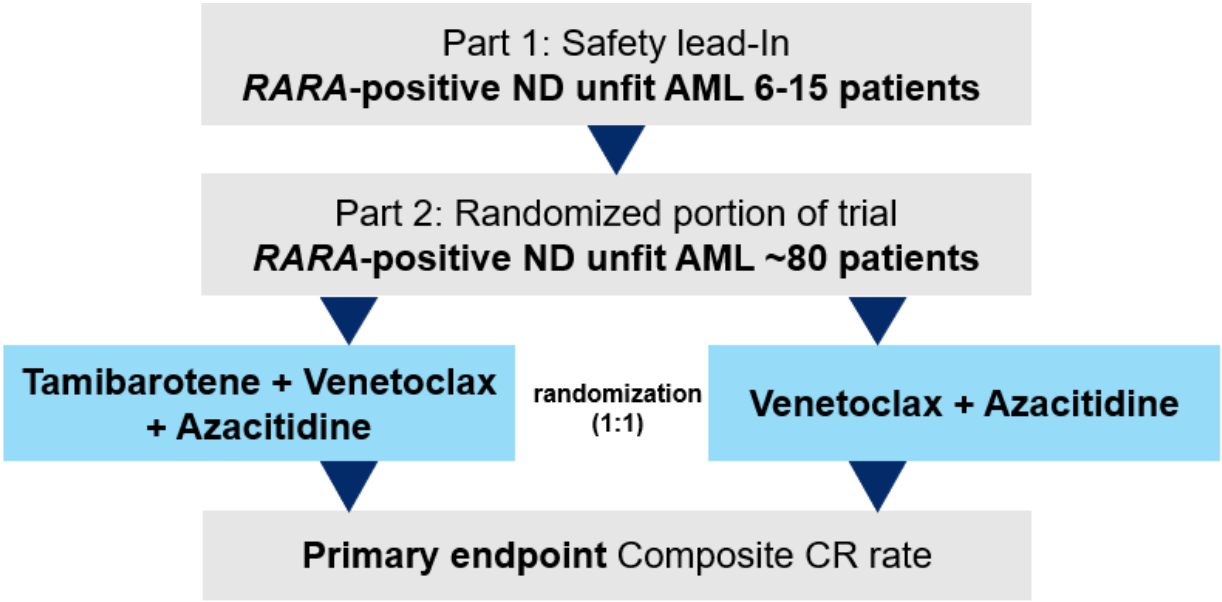
30d mortality: 10%
Capillary leak syndrome: 5/26



Lane A.A. *et al.*, Blood Adv 2023.

SELECT-AML-1 study design

- Newly diagnosed adult AML patients with *RARA* gene overexpression, ineligible for standard intensive induction therapy based on age, performance status or comorbidities, WBC <25K at study drug initiation



Part 3: Trial includes a cohort in which the triplet will be evaluated as a salvage strategy for patients in venetoclax+azacitidine control arm who experience progressive disease, relapse, or treatment failure

Kambhampati, ASH 2022

SELECT-AML-1 study

Best Overall Response	N=6 n (%)
CR/CRi*	5 (83)
CR	2 (33)
CRi	3 (50)
PD	1 (17)

CR = complete response; CRi = CR with incomplete hematologic recovery; PD = progressive disease
* 4/5 patients with CR/CRi had high MES predictive of venetoclax resistance

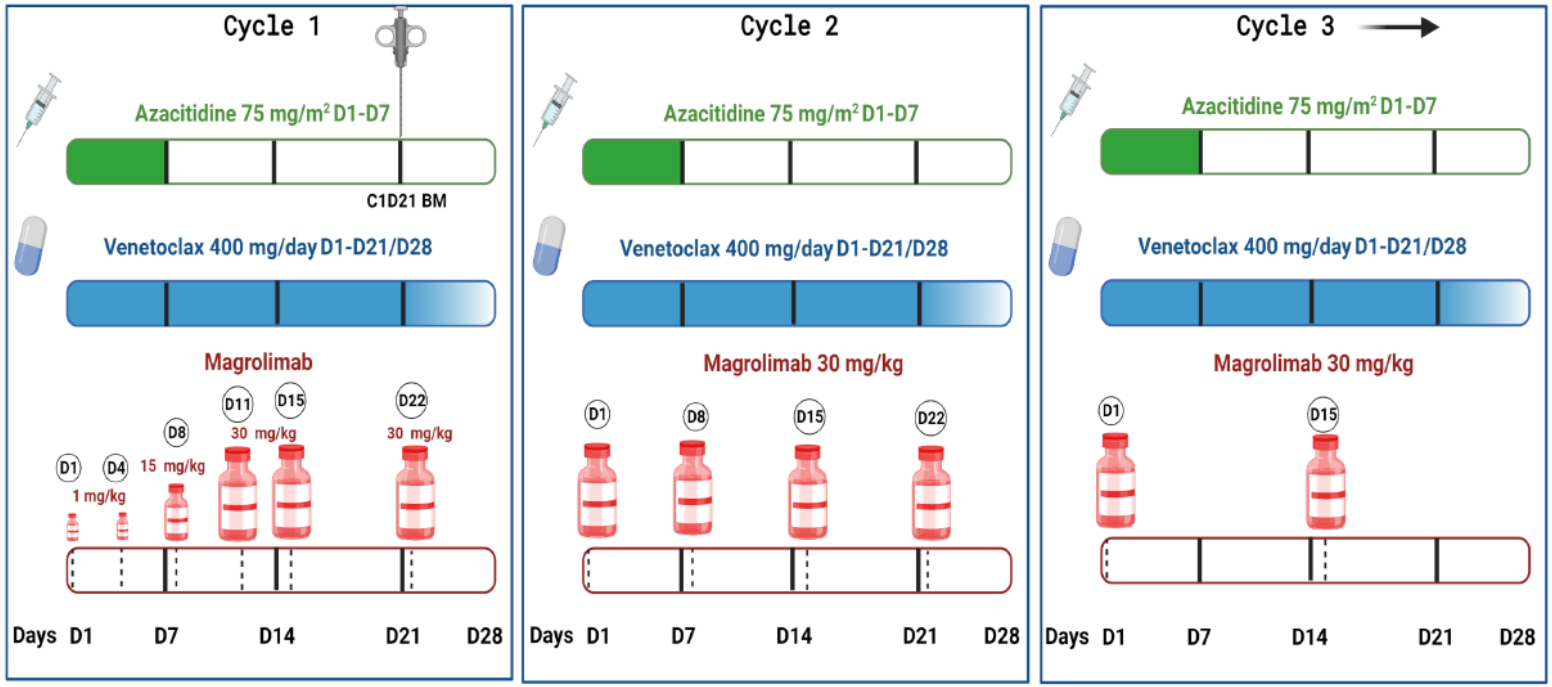
Median Time to CR/CRi: 33 days (range 25–88 days); median 1 cycle (range 1-2 cycles)

Median Duration of Treatment: 76.5 days (range 20 - 104 days)

Median Duration of Follow-Up: 107 days (range 56 – 314 days)

Kambhampati, ASH 2022

DAVER et al 61 (ASH) - Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML



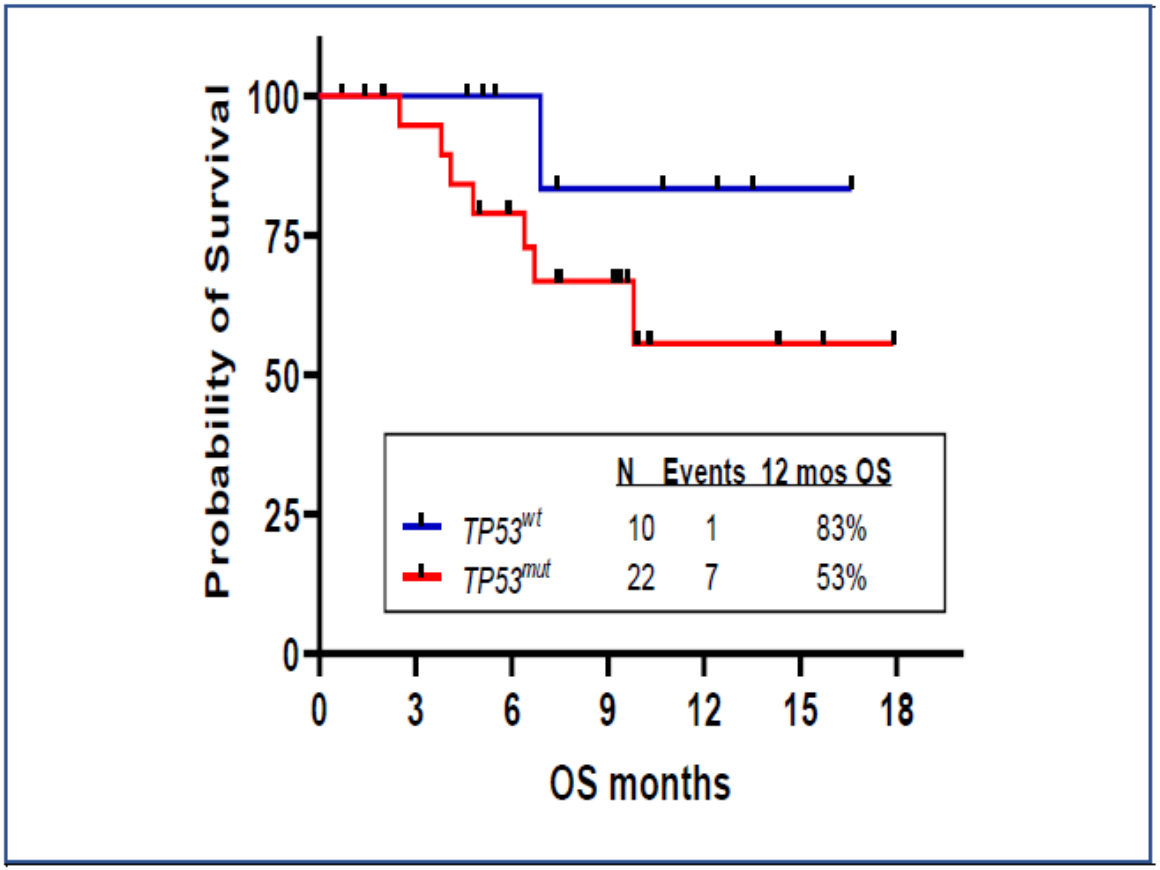
- Magrolimab given on D1, 4, 8, 11 as a dose ramp up and then weekly in C1 and C2, then every 2 weeks
- Venetoclax stopped if cycle 1 day 21 marrow showed marrow ablation / insufficiency or <5% blasts
- VEN duration could be reduced in subsequent cycles for myelosuppression

DAVER et al 61 (ASH) - Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

Parameters		Full Front line	De novo		Secondary AML	
		N=43	*TP53*^{mut} (N=22)	*TP53*^{WT} (N=11)	*TP53*^{mut} (N=5)	*TP53*^{WT} (N=5)
			N (%), Median [range]			
Overall response	CR	21 (49)	10 (46)	6 (55)	2 (40)	3 (60)
	CRi	10 (23)	4 (18)	4 (36)	1 (20)	1 (20)
	CR + CRi	31 (72)	14 (64)	10 (91)	3 (60)	4 (80)
	MLFS	4 (9)	1 (5)	1 (9)	2 (40)	0 (0)
MRD-ve best responses[#]	FCM-CR/CRi	16/28 (67)[#]	8/14 (64)	6/10 (60)	0 (0)	2/4 (50)
Cytogenetic responses*	CCyR	11/21 (52)*	5/10 (50)	4/6 (67)	2/5 (40)	
Time to response (days)	First response	23 [19-105]	24 [20-81]	20 [20-29]	20 [19-105]	27 [20-73]
	Best response	51 [20-130]	49 [20-130]	33 [20-63]	48 [20-105]	62 [20-88]
Counts recovery (days)	ANC ≥ 500/cu mm	36 [16-88]	36 [16- 88]	34 [26-62]	34 [31-36]	39 [23-59]
	Platelet ≥ 100 x 10^9/L	32 [0-74]	31 [15-55]	33 [19-74]	28 [22-49]	33 [0-46]
Cycles on therapy		3 [1-17]	3 [2-6]	3 [1-17]	1 [1-3]	2 [1-3]

DAVER et al 61 (ASH) - Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed (ND) Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML

Overall Survival (De Novo patients, n=33)



A new drug class in *KMT2A*

Menin inhibitor

REVUMENIB

Response

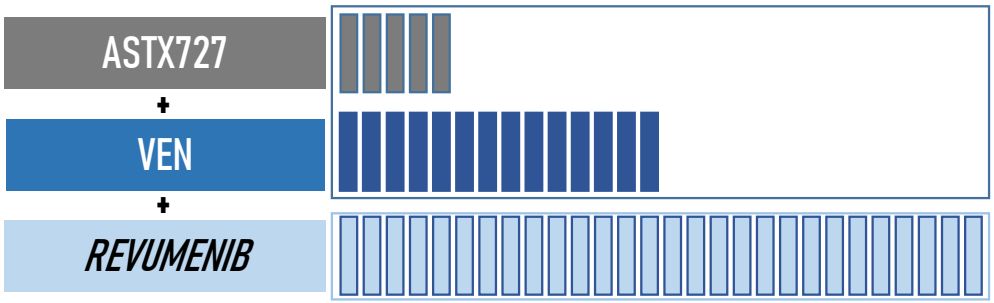
Parameter	Efficacy population (n=57)
ORR, n (%)	**36 (63)**
CR+CRh rate, n (%)	13 (23)
95% CI	12.7–35.8
P value, 1-sided	0.0036
CRc	25 (44)
95% CI	30.7–57.6
Negative MRD status[a]	
CR+CRh	7/10 (70)
CRc	15/22 (68)

Parameter	Efficacy population (n=57)
Best response, n (%)	
CR	10 (18)
CRh	3 (5)
CRi	1 (1.8)
CRp	11 (19)
MLFS	10 (18)
PR	1 (1.8)
PD	4 (7)
No response	14 (25)
Other[b]	3 (5)

Data cutoff: July 24, 2023. [a]MRD done locally; not all patients had MRD status reported. [b]Includes patients without postbaseline disease assessment.

Aldoss I. *et al.*, ASH 2023.

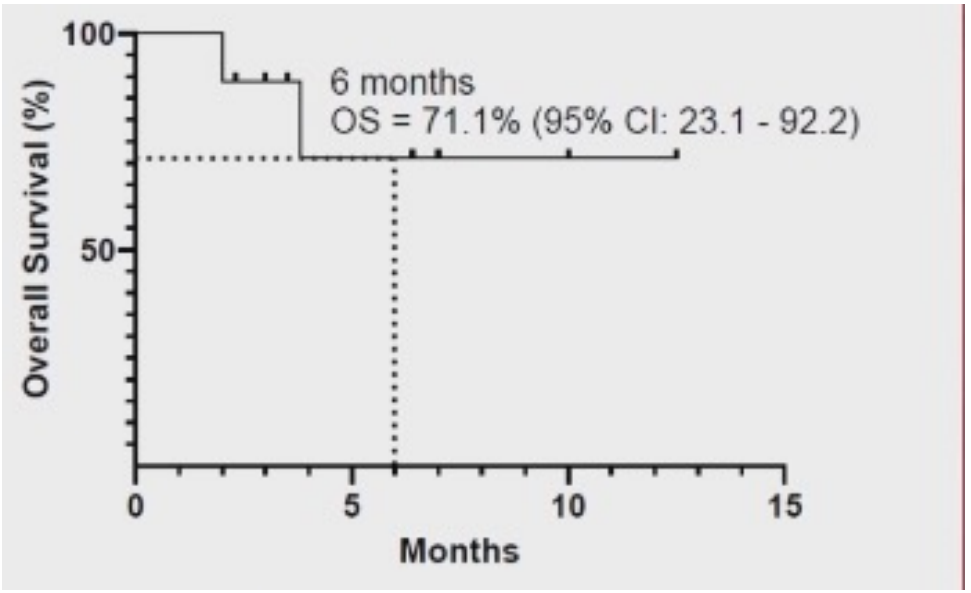
Full oral triplet combination



Phase I/II
R/R AML KMT2Ar or NPM1mut or NUP98r (N=9)
Median age 30y

CR/CRi: 44%
Phenotypic negative MRD: 67%

Median follow-up of 6.4 months (range 0.4 to 12.3) (N=9)



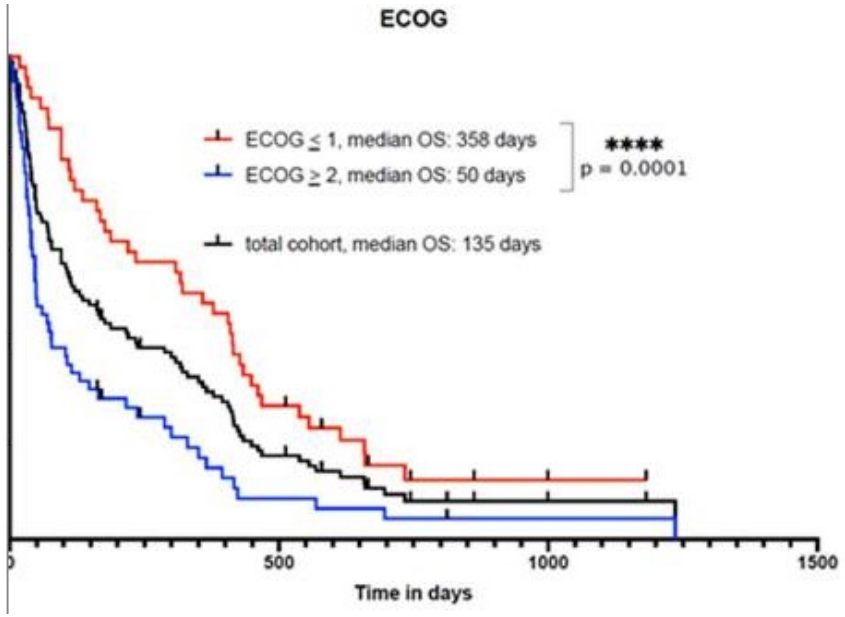
Issa G.C. *et al.*, ASH 2023.

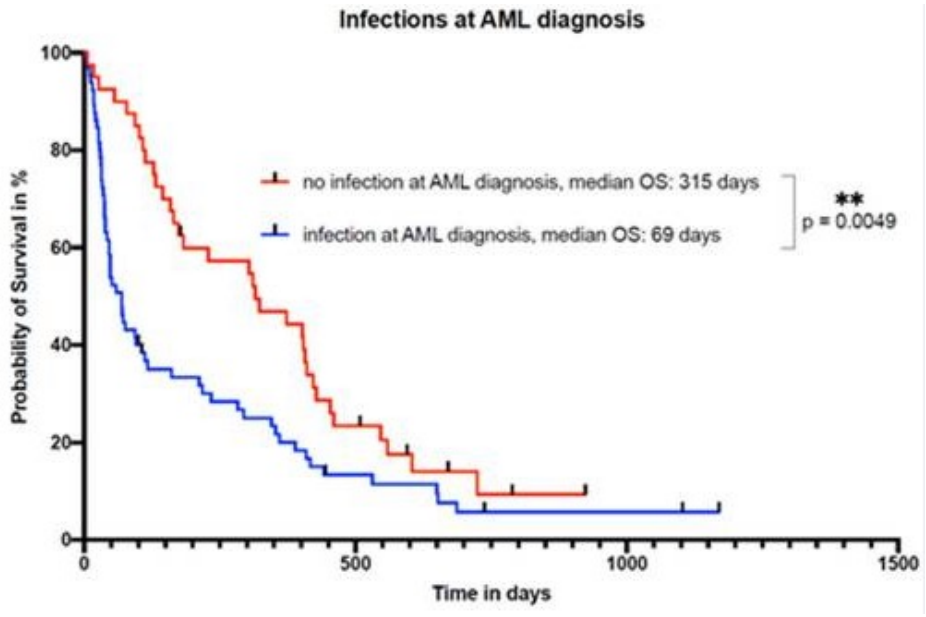
Unfit older AML patient

NOT for all situations

Unfit older AML patient

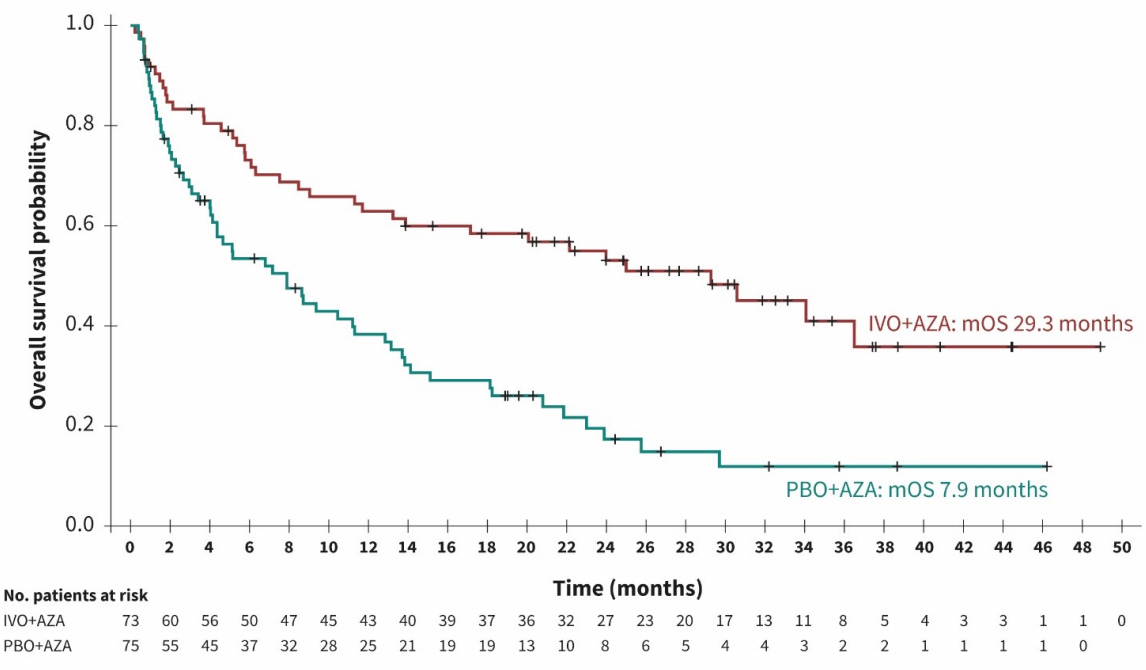
In a palliative AML treatment population (n = 118; median age of 75 years) **HMA or LDAC**
high ECOG score and presence of infection at diagnosis resulted in inferior outcomes

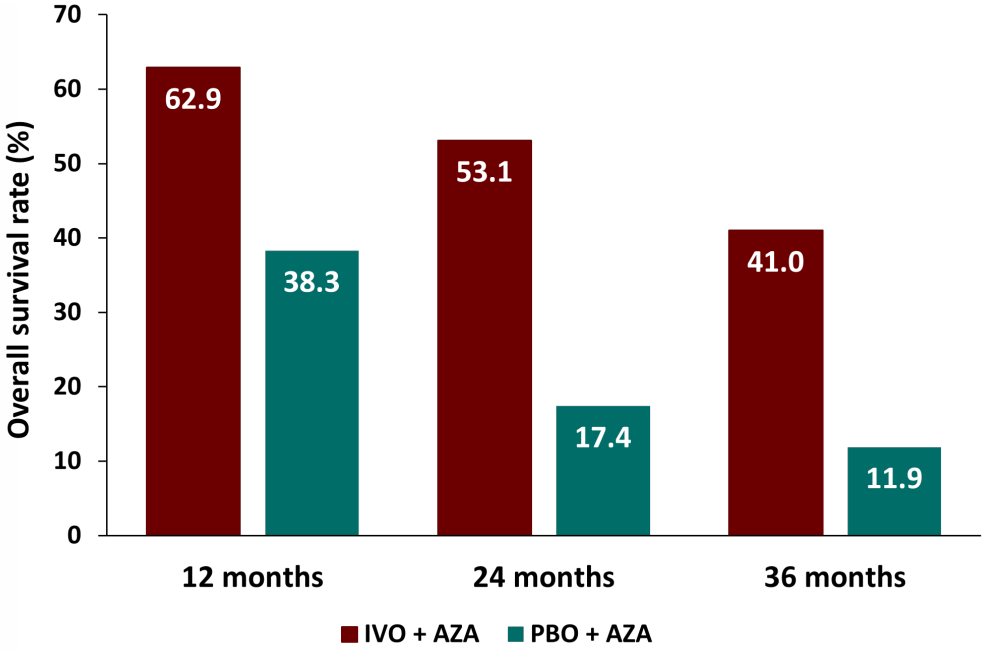




Tober R, et al. J Cancer Res Clin Oncol. 2023; 149(4):1569–1583.

5-AZA + Ivosidenib
Can we do better in the population ?





Montesinos P. *et al.*, N Engl J Med 2022.
De Botton S. *et al.*, ASCO 2023.

Combo or sequential ?

FIGURE AND TABLES

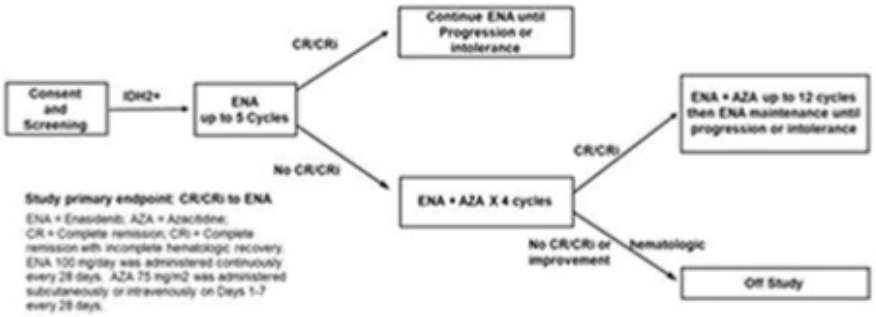


Figure 1. Schematic of the study design showing the flow and transfer of patients from Phase 2 to Phase 1b portion of the study.

Phase 2 (n= 60)	Phase 1b (n=17)
enasidenib 100 mg/d	Enasidenib + 5-AZA
CR 37%	CR 18 %
CRi 10 %	CRi 24 %
ORR 50 %	ORR 47 %
Duration of response : NR	OS = 8.9 months
OS : 24.4 months	

44 pts with IDH2 R140 (55%) and 16 with IDH2 R172 mutation (25%) (p=0.04)

Eytan M. Stein et al ; A Completed Phase 2/1b Sub-Study of the Beat AML Master Trial, Blood, 2020,

Combo or sequential ?

Previous IDH inhibitor therapy in 50 %

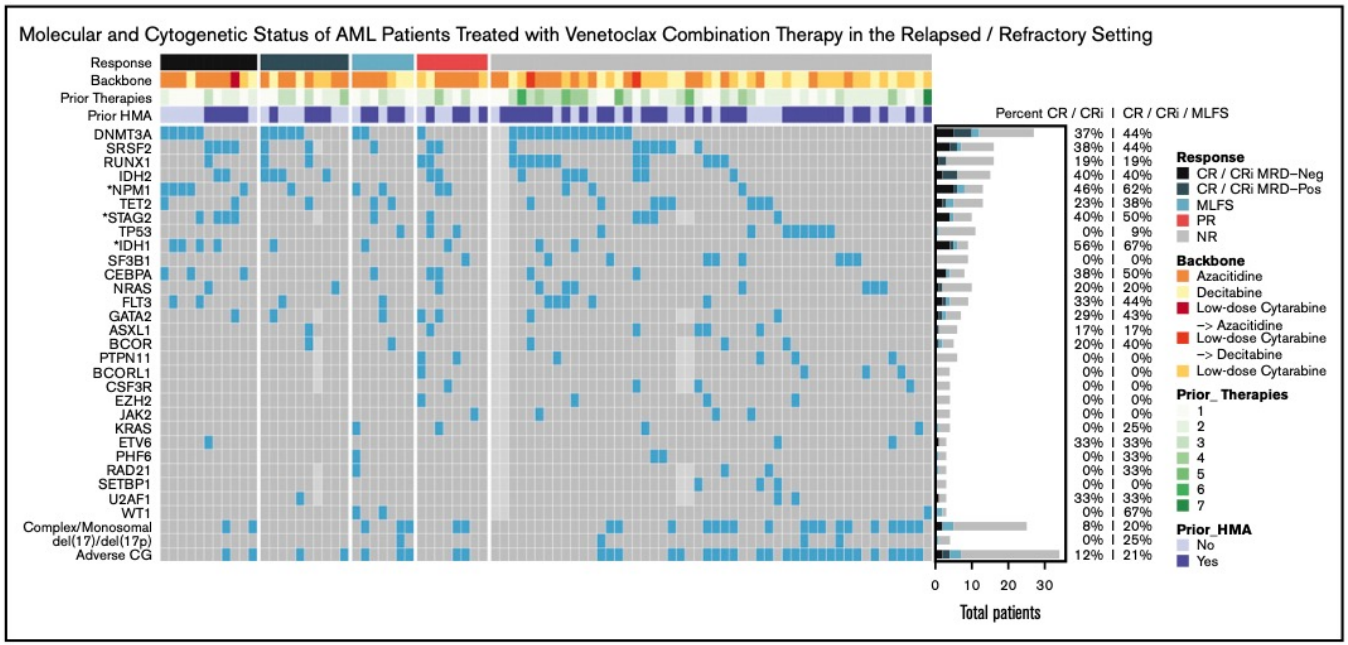


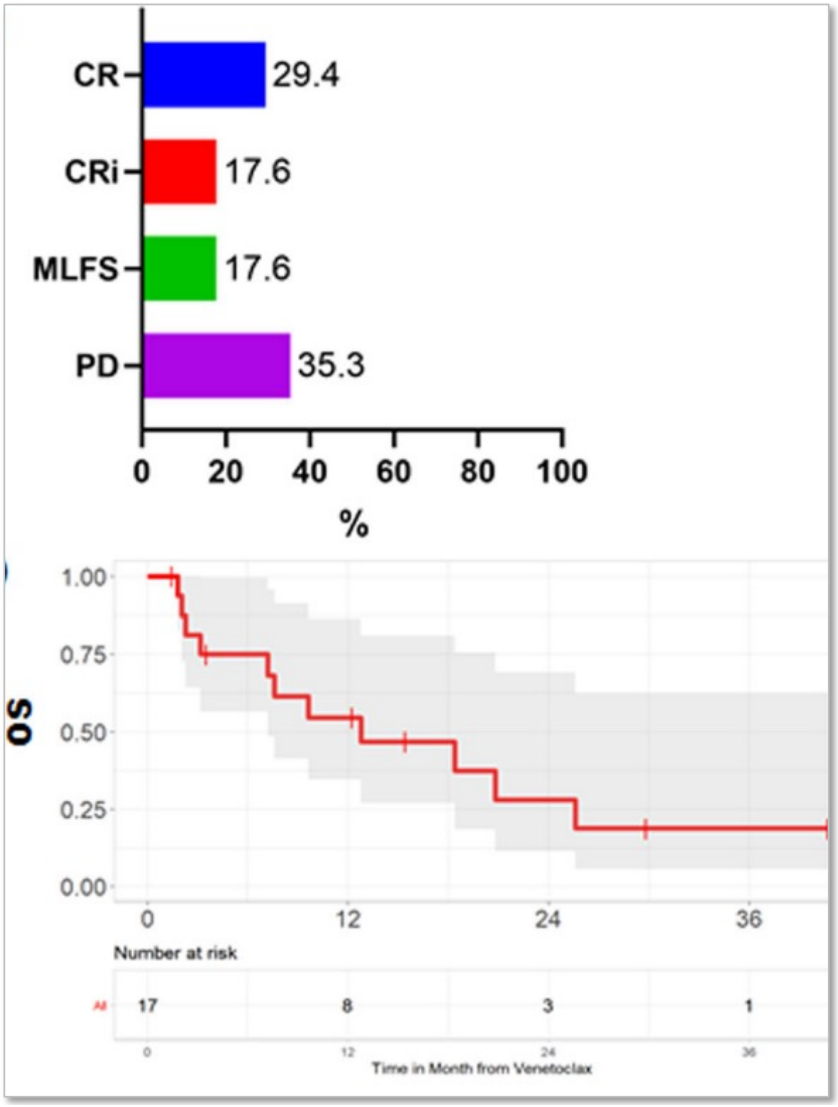
Figure 3. Molecular predictors of response. Oncoprint showing mutational and cytogenetic characteristics at diagnosis for 86 patients treated in the RR setting. Light gray boxes represent missing data. Patients are grouped by best response, annotated with colored bars above the grid. The type of backbone used in combination with venetoclax, the number of previous lines of therapy, and previous exposure to HMA are also annotated at the top. The filled bar plot on the right shows the number of patients with each mutation who achieved CR, CRi, and MLFS, with percentages to the right. Asterisks indicate genes with $P < .05$ for either percent CR/CRi MRD negative, CR/CRi, or ORR.

IDH1 (n=9)
CR/CRi = 56 %
ORR = 67 %

IDH2 (n=15)
CR/Cri = 56 %
ORR = 67 %

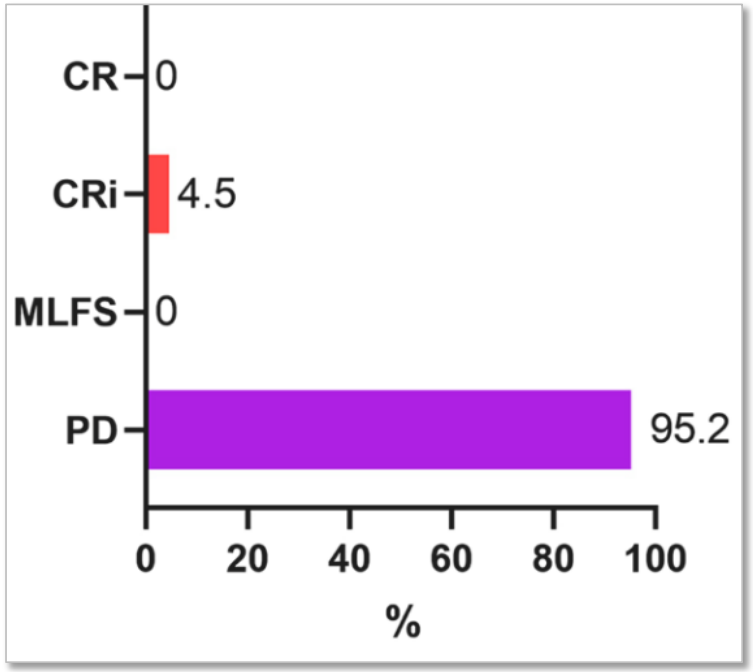
Stahl et al 2021 Mar 9;5(5):1552-1564. doi: 10.1182/bloodadvances.2020003734.

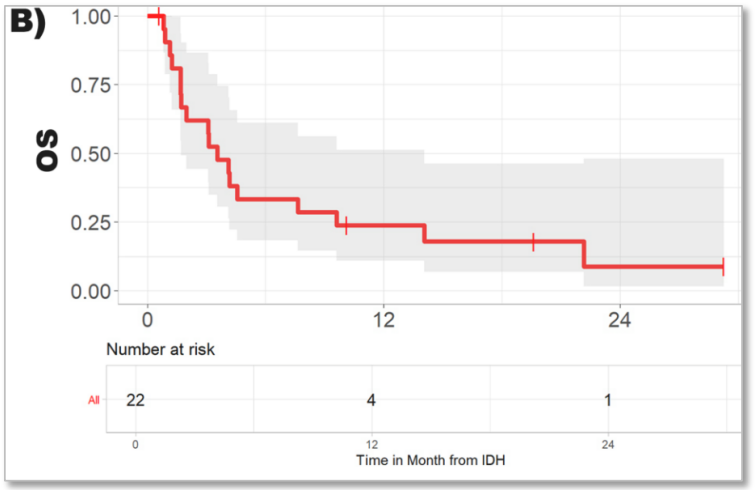
AZA-VEN after targeted therapies



Bewersdorf Leukemia Lymphoma 2022

Targeted therapies post 5-AZA + VEN





Bewersdorf Leukemia Research 2022