What is the best induction treatment?
HMA+VEN

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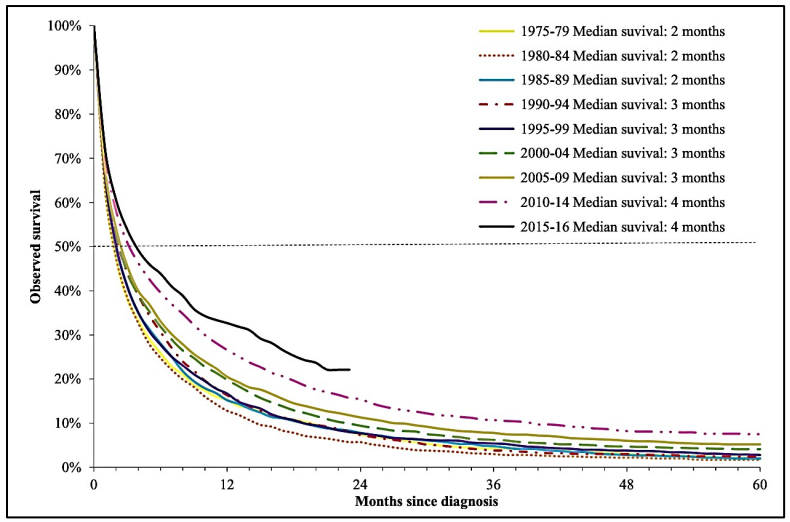
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						x	
BMS						x	
Incyte						x	
JAZZ-Pharma					x		

Historical «uncertainties» using IC

- While progress has been made particularly in younger patients through intensive chemotherapy (IC) and stem cell transplantation (HSCT), the majority of AML patients (> 60 years of age) have historically been considered to be ineligible for intensive therapies because of **comorbidities, more aggressive leukemia biology,** and **reduced tolerance to intensive therapy**. [1]
- Approximately 80% of patients aged ≥ 65 years are predicted to have induction mortality rates of ≥ 30% with intensive chemotherapy. [3]
- Only **2,4%** of patients aged ≥ 60 years are **disease-free at 10 years** after diagnosis (not transplanted setting). [2]
- The ideal IC aims to balance between **efficacy** and therapy-induced **morbidity** and **mortality** without selection bias and still needs to be defined.[1]

Median OS in pts > 65yo [4]



As a matter of fact…

Majority of patients with newly diagnosed AML who are age > 60 years receive lower-intensity therapies.[5]

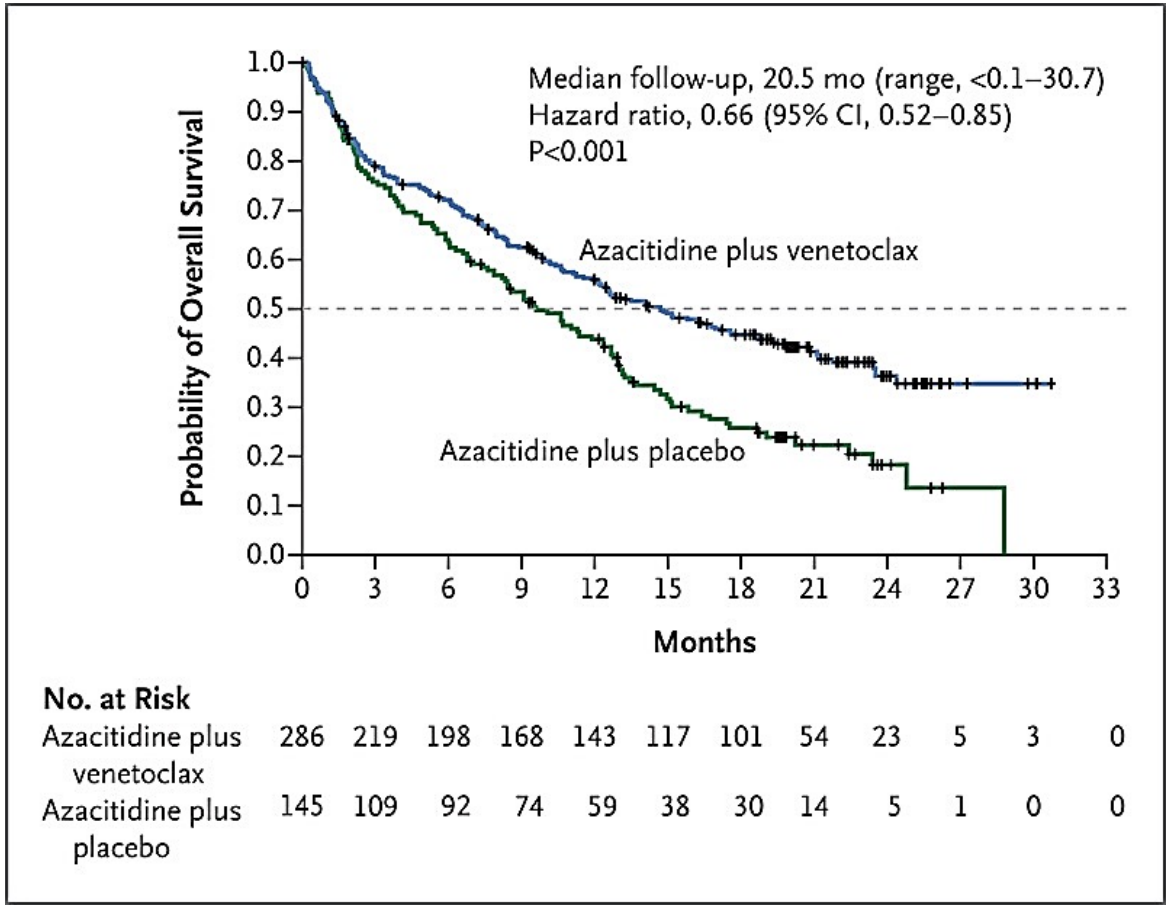
1. Niederweiser D, Annals of hematology, 2023; 2. Vasu S. et al., blood advances, 2018; 3. Kantarjian et al., Cancer, 2006; 4. Shallis RM, Blood Rev 2019; 5, Medeiros et al., Curr Med Res Opin 2019

Azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

		OS							1-y survival			
		Median		Difference		HR	95% CI	*P*				
	No. of patients	Months	95% CI	Months	95% CI				%	95% CI	Difference	95% CI
Preselected for BSC only	89											
Azacitidine	44	5.8	3.6-9.7	2.1	–1.0-5.2	0.60	0.38-0.95	.0288	30.3	17.5-44.2	11.7	–6.3-29.8
BSC	45	3.7	2.8-5.7						18.6	8.7-31.4		
Preselected for LDAC	312											
Azacitidine	154	11.2	8.8-13.4	4.8	1.7-7.9	0.90	0.70-1.16	.4270	48.5	40.3-56.2	14.5	3.5-25.5
LDAC	158	6.4	4.8-9.1						34.0	26.6-41.6		
Preselected for IC	87											
Azacitidine	43	13.3	7.2-19.9	1.1	–5.4-7.6	0.85	0.52-1.38	.5032	55.8	39.8-69.1	4.9	–16.2-26.0
IC	44	12.2	7.5-15.1						50.9	35.2-64.6		

Dombret et al., Blood, 2015

VIALE-A: OUTCOME AND SURVIVAL ANALYSIS



Complete remission plus complete remission with partial hematologic recovery was achieved in 64.7% (95% CI, 58.8 to 70.2) of the patients in the azacitidine–venetoclax group and in 22.8% (95% CI, 16.2 to 30.5) of those in the control group (P<0.001)

The 30-day mortality rate was 6%.

Transfusion independence conversion
(conversion from dependent to independent)

VEN+AZA	AZA
49%	27%
(76/155)	(22/81)

RBC and PLATELET

Patients were dependent on RBC and/or platelet transfusions at baseline

Transfusion independence maintenance
(independent from baseline to post-baseline period)

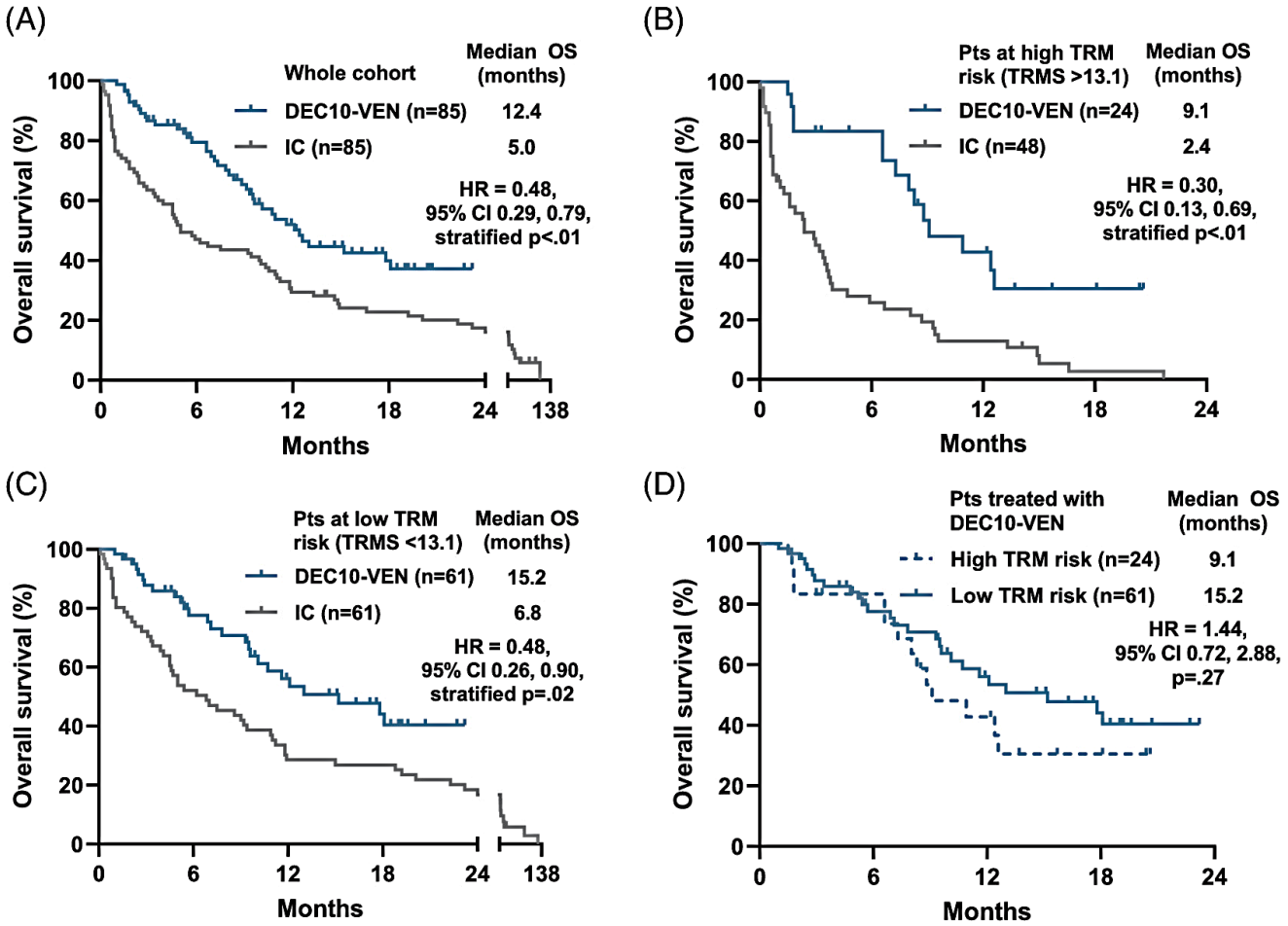
VEN+AZA	AZA
69%	42%
(90/131)	(27/64)

RBC and PLATELET

Patients were independent of both RBC and platelet transfusions at baseline

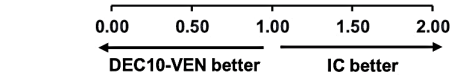
Di Nardo et al., NEJM, 2020

DEC10-VEN vs IC (retrospective)



(E)

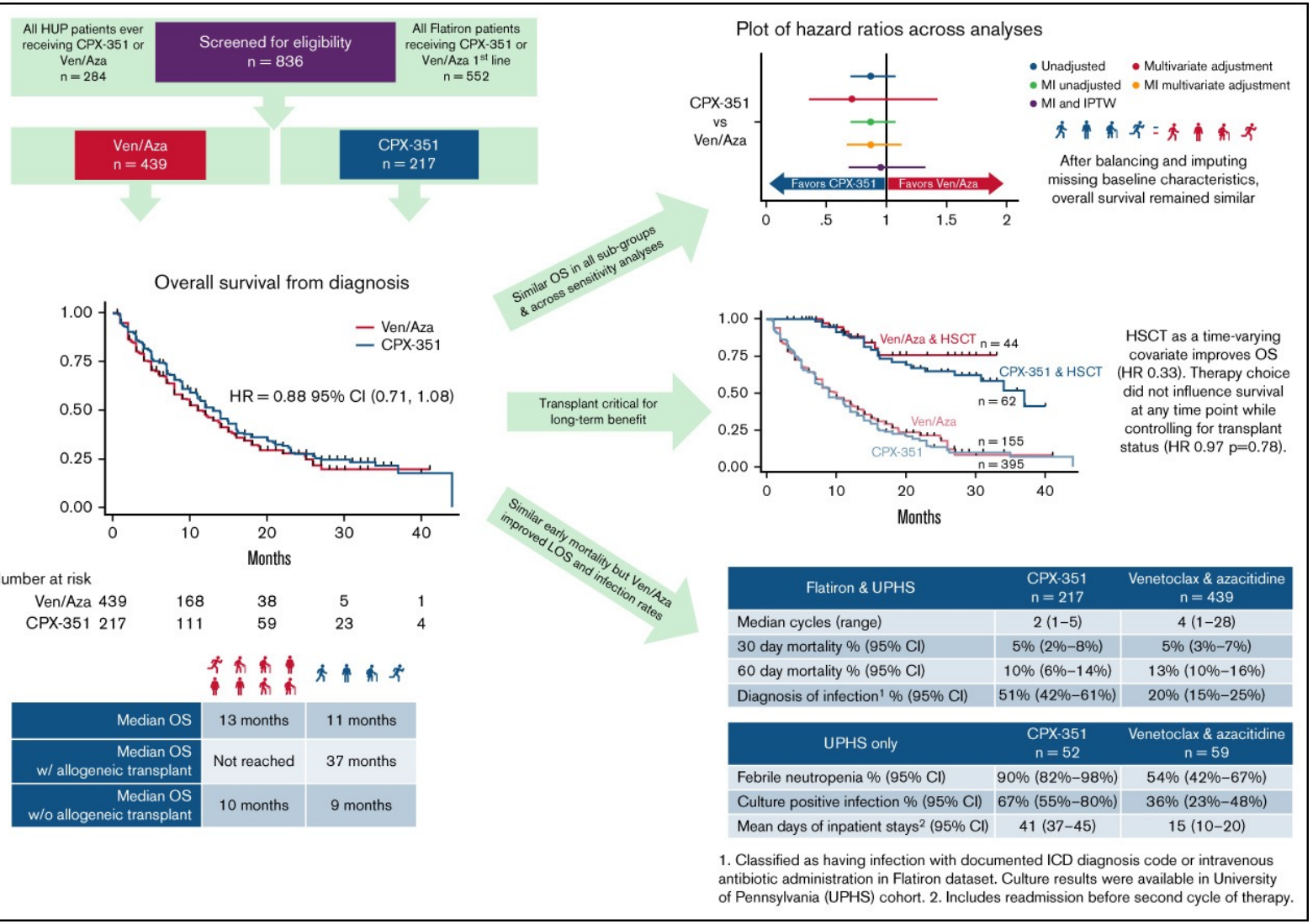
Subgroups	No. of patients	Median overall survival DEC10-VEN (n=85)	Median overall survival IC (n=405)	Hazard ratio for death (95% confidence interval)
Age		months		
61-70 yrs	322	10.9	9.9	0.91 (0.57, 1.46)
71-80 yrs	148	18.1	4.7	0.44 (0.30, 0.65)
ECOG PS				
0	77	NR	16.2	0.91 (0.42, 1.96)
1	282	13.0	9.2	0.64 (0.42, 1.00)
2	95	9.2	4.6	0.61 (0.38, 0.98)
BM blasts				
Up to 30%	132	10.7	11.2	1.05 (0.62, 1.79)
>30%	358	13.0	8.1	0.55 (0.39, 0.77)
AML				
De novo	333	NR	10.7	0.46 (0.32, 0.66)
With AHD	69	7.8	6.7	1.11 (0.59, 2.09)
Therapy-related	97	6.9	5.9	0.93 (0.50, 1.72)
Cytogenetics				
Intermediate	294	NR	12.4	0.47 (0.31, 0.70)
Adverse	195	8.0	4.7	0.75 (0.52, 1.09)
Complex	126	7.3	4.5	0.74 (0.42, 1.31)
Mutations				
NPM1	62	NR	11.3	0.39 (0.19, 0.80)
IDH1/2	52	NR	10.1	0.12 (0.06, 0.25)
FLT3-ITD/TKD	87	NR	10.3	0.21 (0.10, 0.43)
RAS	52	12.1	14.8	1.17 (0.58, 2.36)



DEC10-VEN compared to intensive che-motherapy offered comparable rates of CR but lower 30-day mortality(0% vs 33%, p=N/A) and lower 60-day mortality (17% vs 44%, p=0,03).

Maiti et al., American Journal of Hematology, 2020

Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia



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

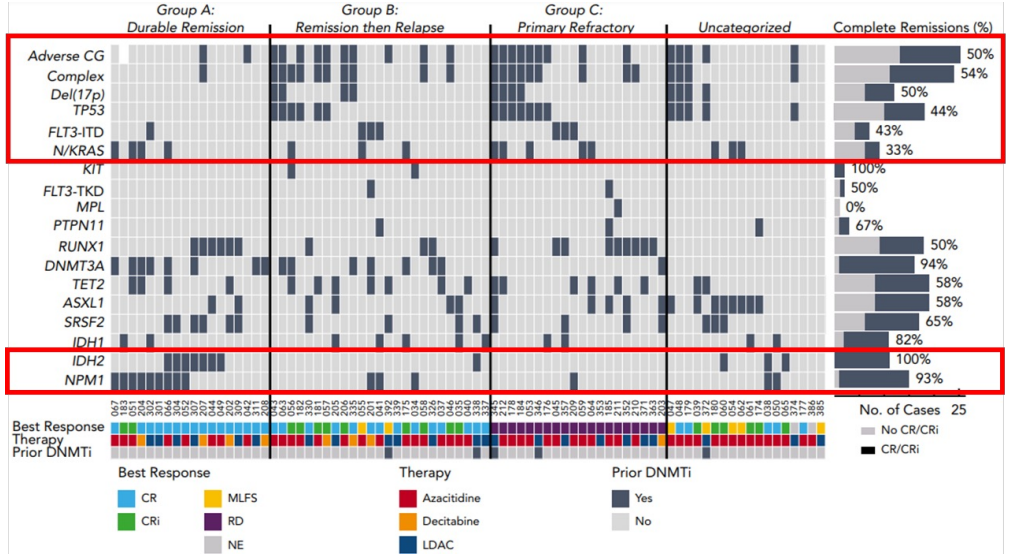
UPHS only	CPX-351 n = 52	Venetoclax & azacitidine n = 59
Febrile neutropenia % (95% CI)	90% (82%–98%)	54% (42%–67%)
Culture positive infection % (95% CI)	67% (55%–80%)	36% (23%–48%)
Mean days of inpatient stays[2] (95% CI)	41 (37–45)	15 (10–20)

1. Classified as having infection with documented ICD diagnosis code or intravenous antibiotic administration in Flatiron dataset. Culture results were available in University of Pennsylvania (UPHS) cohort. 2. Includes readmission before second cycle of therapy.

- First-line treatment with CPX-351 or the combination of venetoclax and azacitidine resulted in similar overall survival.
- Early mortality was also similar; infection, neutropenic fever, and inpatient length of stay were higher with CPX-351.

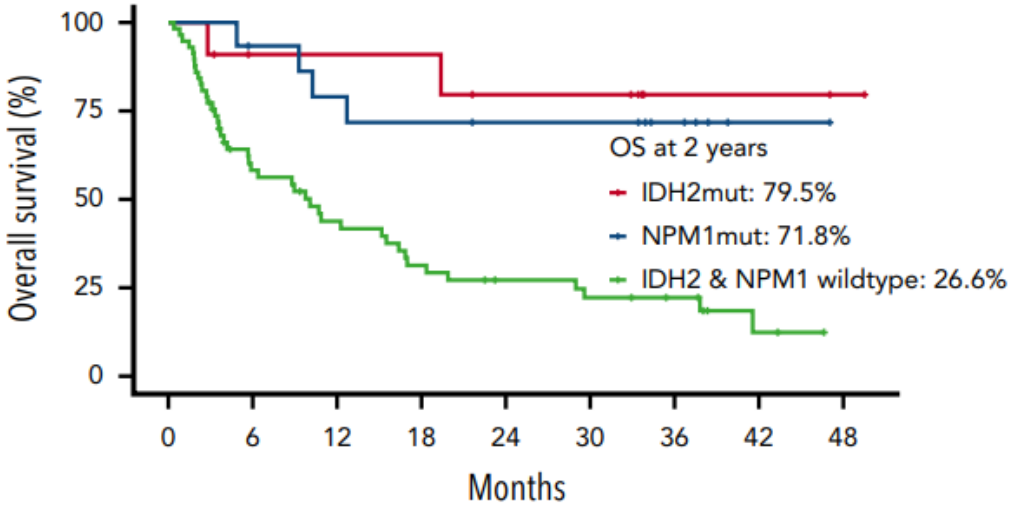
Matthews et al., Blood Adv, 2022

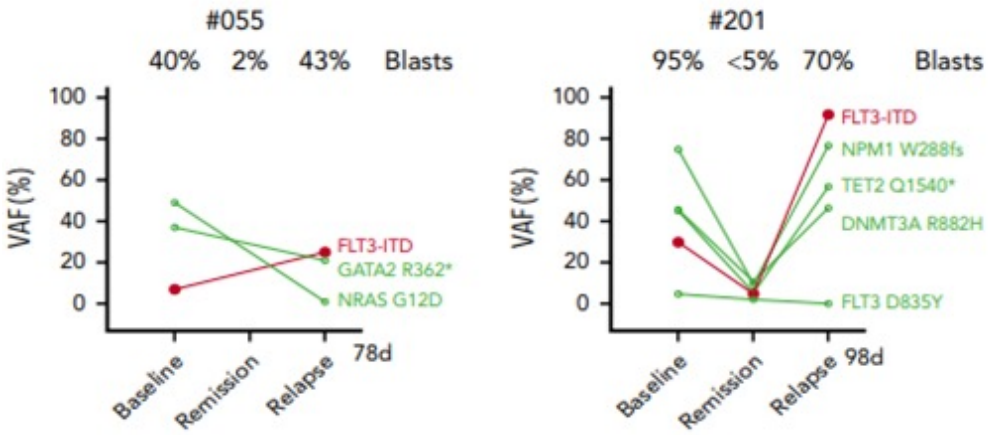
Molecular pattern in older patients treated with venetoclax combinations

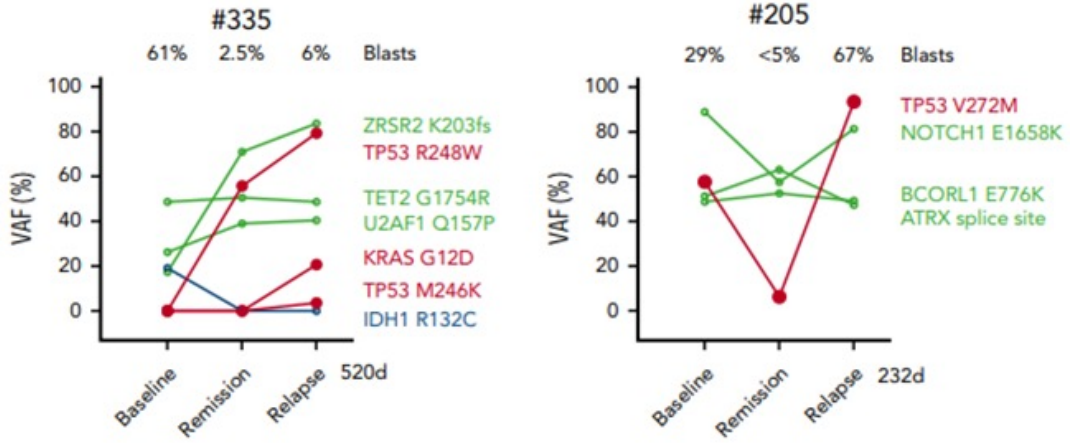


R/R

Durable remission

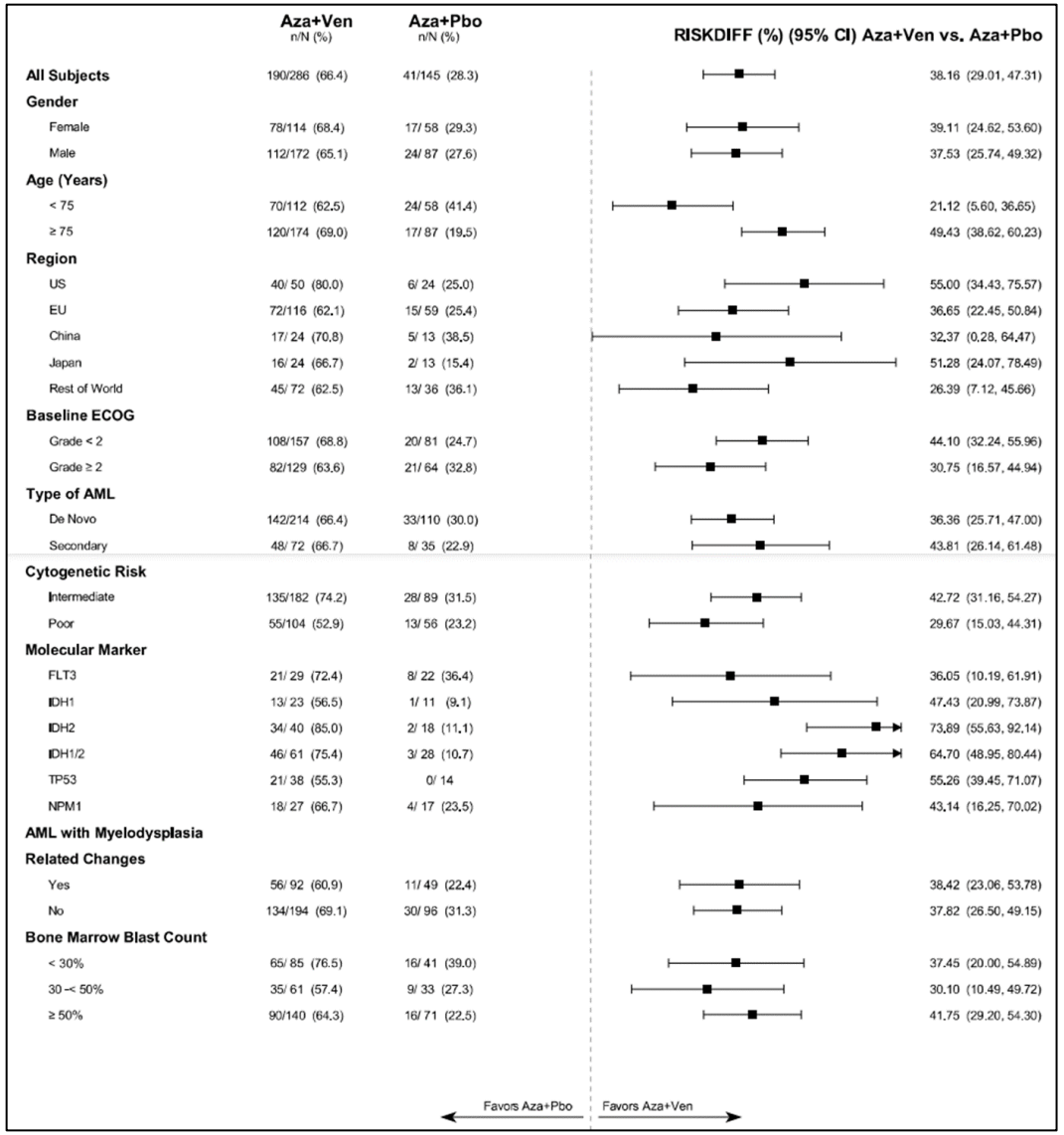


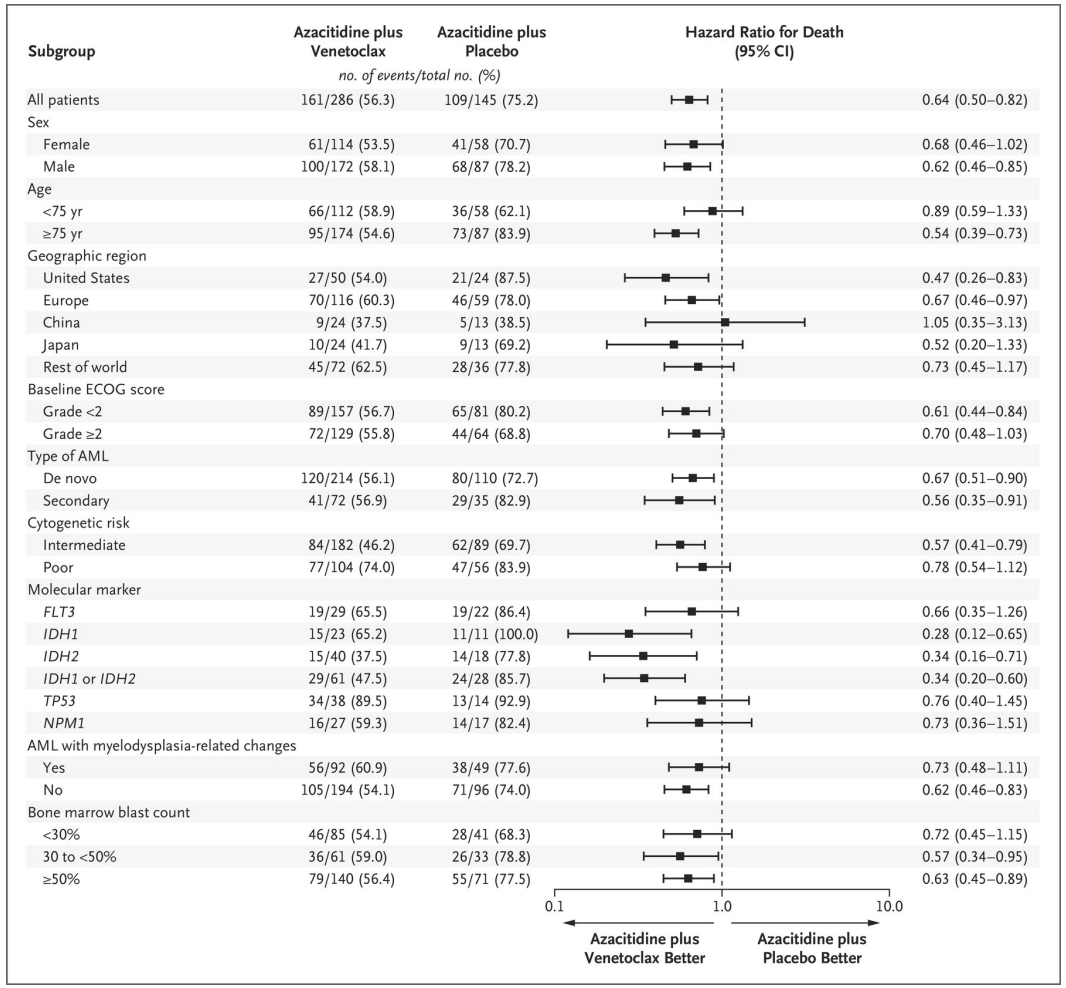




Di Nardo et al., Blood. 2020;135(11):791-803

VIALE-A: Subgroup Analysis of Overall Survival





Di Nardo et al., NEJM, 2020

Should high risk AML >60 yo receive HSCT?

HSCT seems to be the only «curative» option

BUT

- frequency of comorbidities increases with age
- biological reserve declines
- socioeconomic support is often tenuous

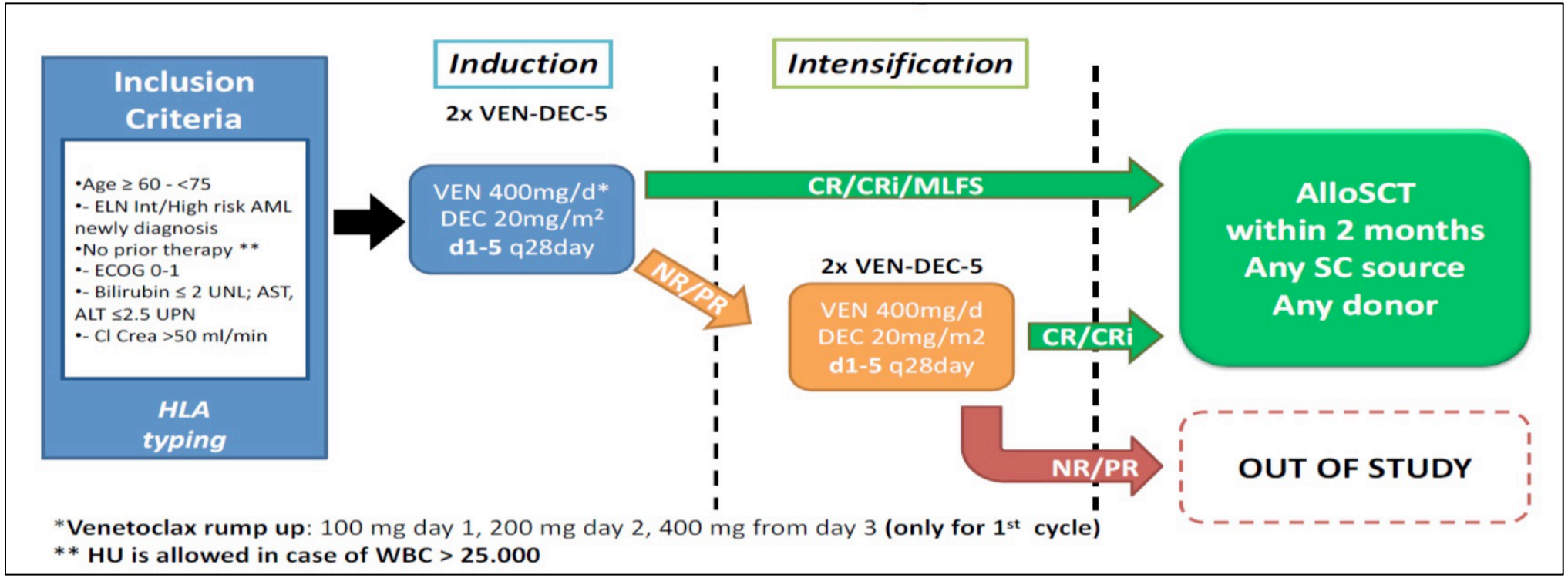
HMA/VEN as bridge to transplant strategy

Study	Sample size	cCR	12-mo NRM	%12-mo RFS	12-mo OS
Sandhu et al., 2020*	32	-------	18,8 %	43,8 %	62,5 %
Salhotra et al., 2021	51	68,6%	100 day NRM 12%	67% in case of HSCT 33% in case of no HSCT	58% (88% in case of HSCT)
Apel et al., 2021					Not reched median after
Pollyea et al., 2022*	- 21 HSCT - 31 potentially eligible	-------	CI of TRM %	CIR 12%	- Median surival not reached - Median survival 17 mo
Winters et al., 2022*	- 140 IC - 29 AZA/VEN	------	----------	- IC 66,1% - AZA/VEN 73,2 %	- IC 74,1 % - AZA/VEN 76,3 %
Pasvolsky et al., 2022*	24	------	19%	58	63%
Short et al., 2022*	- 44 IC - 29 LIT - 54 LIT+VEN	-------	- 27% (2y-NRM) - 17% - 16%	- 54% - 41% - 60%	- 58% - 41% - 72%

* post-HSCT analysis only

Retrospective studies

PHASE II STUDY ON VENETOCLAX PLUS DECITABINE FOR ELDERLY (≥60 <75YEARS) PATIENTS WITH NEWLY DIAGNOSED HIGH-INTERMEDIATE RISK AML ELEGIBLE FOR ALLO-SCT : MIDTERM UPDATE OF VEN-DEC GITMO STUDY



At data cut-off, 41/94 (43.6%) patients have been successfully undergone allo-SCT and 12 patients are awaiting for transplant.

Russo D. et al., EHA 2023

Venetoclax and Azacitidine for Non-Elderly Adult Patients With Acute Myeloid Leukemia

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03573024

Recruitment Status : Recruiting
First Posted : June 28, 2018
Last Update Posted : March 17, 2023

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Sponsor:
University of Colorado, Denver

Collaborator:
AbbVie

Information provided by (Responsible Party):
University of Colorado, Denver

Venetoclax + Azacitidine vs. Induction Chemotherapy in AML

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04801797

Recruitment Status : Recruiting
First Posted : March 17, 2021
Last Update Posted : November 17, 2022

See **Contacts and Locations**

View this study on Beta.ClinicalTrials.gov

Sponsor:
Massachusetts General Hospital

Collaborator:
AbbVie

Information provided by (Responsible Party):
Amir Fathi, Massachusetts General Hospital

Venetoclax + Decitabine vs. "7+3" Induction Chemotherapy in Young AML

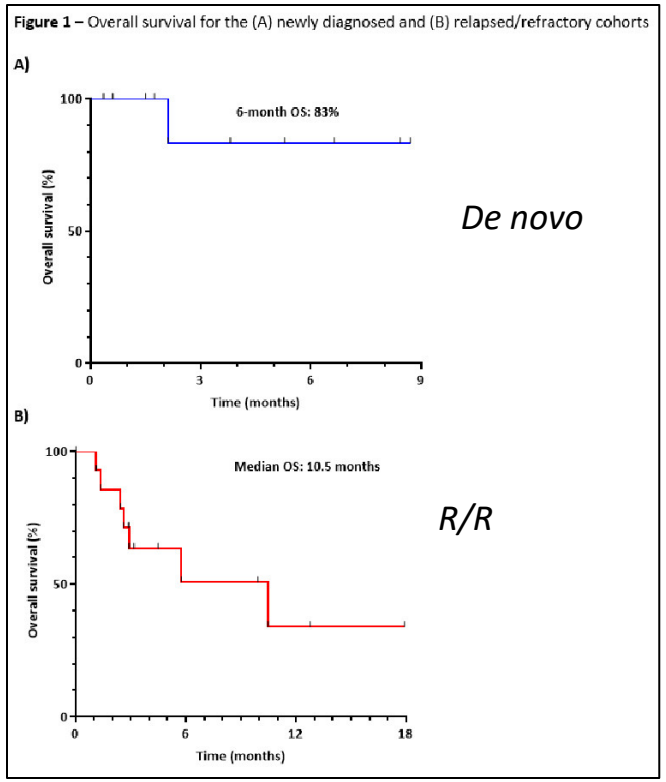
The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
Chen Suning

Information provided by (Responsible Party):
Chen Suning, The First Affiliated Hospital of Soochow University

Addition of a third agent?

AZA/VEN/GILT (Phase 1b/2)



De novo

R/R

Short et al., Blood, Volume 138, Supplement 1, 23 November 2021, Page 696

IVO/VEN ± AZA (Phase 1b/2)

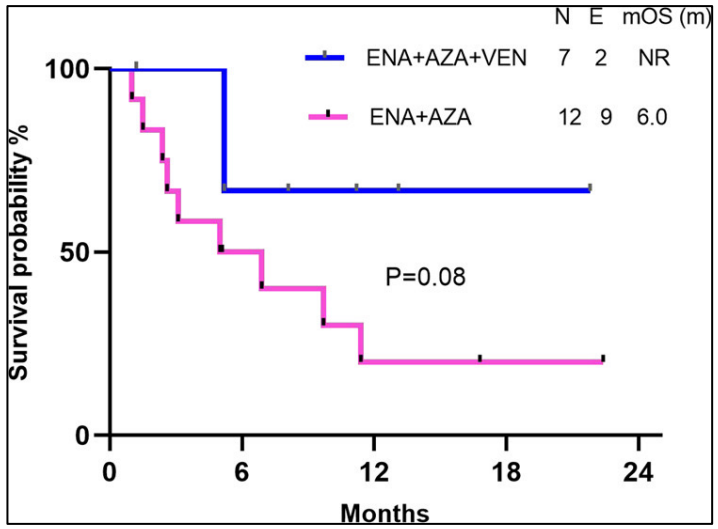
	All (N=25)	DL #1 (N=6)	DL #2 (N=6)	DL #3 (N=13)
ORR	23	4	6	13
CRc	21	4	6	11
CR	13	3	3	7
CRh	2	-	2	-
CRi	6	1	1	4
MLFS	1	-	-	1
PR	1	-	-	1
NR	2	2	-	-
EFS	NR (9.4-NR)	9.6 (2.8-NE)	9.4 (7-NE)	NR
OS	NR	9.7 (4.5-NE)	NR (8.5-NE)	NR

DL1: IVO/VEN 400
DL2: IVO/VEN 800
DL3: IVO/VEN 400 + AZA

ORR 92%

Lachowiez et al., J Clin Oncol 39, 2021 (suppl 15; abstr 7012)

AZA/VEN/ENA (Phase 2)



ORR 100% in ND

Venogupal et al., Blood Cancer J. 2022

CLAD and LDAC plus VEN alternating with AZA in older patients with de novo AML

Response, % (unless otherwise stated)	Total (N = 60)
Best response	
CR	80
CRi	13
NR	5
Died	1.7
ORR (CR + CRi + PR)	93
CRc rate (CR + CRi)	93
Patients requiring re-induction cycle (n = 57)	7
MRD at response assessment (n = 51)	
Negative	84
Positive	16
Median number of treatment cycles (IQR)	3.0 (2.0–5.0)
Responders receiving allo-HSCT (n = 56)	34
Mortality rate at 4 weeks	1.7
Mortality rate at 8 weeks	6.7

Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete response; CRc, composite complete response; CRi, complete response with incomplete hematologic recovery; MRD, measurable residual disease; NR, no response; ORR, overall response rate; PR, partial response; IQR, interquartile range.

- The most frequent Grade 3 or 4 nonhematologic adverse events (AEs) was febrile neutropenia (55%), pneumonia (23%), and allergic reaction (3%).
- Grade 4 tumor lysis occurred only in one patient.
- Median time to absolute neutrophil count (ANC) recovery of >500 and >1,000 was 25 and 27 days, respectively, and median time to platelet recovery of >50,000 and >100,000 was 21 and 24 days, respectively.

Reville et al., ASH 2021

Conclusions

- HMA/VEN possible option in fit AML >60y

- Pitfalls:
    1. Standardization of treatment (ancillary therapy; number of cycles…)
    2. Lack of prospective randomized trials
    3. HSCT approach

- Addition of a third agent could increase remission rate and, hopefully, survival