

**Azacitidine and Venetoclax in AML:  
When I Use It Today, Where I am Starting to  
Use It, and Where I Believe I Will Use It.**

**Jeffrey Lancet, MD**

Chair, Department of Malignant Hematology

Moffitt Cancer Center

Tampa, FL

# Disclosures

- Consulting: Treadwell Therapeutics, Bristol Myers Squibb, Moderna, AbbVie
- Research Funding: AbbVie

---

# United States FDA Label for Venetoclax in Combination with Azacitidine, Decitabine, or Low-Dose Cytarabine in AML

- Newly diagnosed AML in adults:
  - 75 years or older
  - OR with comorbidities precluding intensive induction chemotherapy

# VIALE-A: Azacitidine ± Venetoclax in Treatment-Naive Patients With AML Ineligible For Standard Induction Therapy

Adults with previously untreated AML ineligible for standard cytarabine/anthracycline due to age ( $\geq 75$  yrs) or comorbidities, no hypomethylating agent for antecedent hematologic disorder (N = 431)

Azacitidine 75 mg /m<sup>2</sup> SC or IV QD for D1-7 + Venetoclax 400 mg PO QD (with 3 day ramp up in cycle 1) on 28-day cycles (n = 286)

Azacitidine 75 mg /m<sup>2</sup> SC or IV QD for D1-7 + Placebo PO QD on 28-day cycles (n = 145)

*Until progression, intolerance, or withdrawal*

- Primary endpoint: OS, rate of CR + CRi (outside the US)
- Other endpoints: composite CR or CRi, EFS, OS by molecular subtype, QoL, CR, transfusion independence

Comorbidities: ECOG 2-3

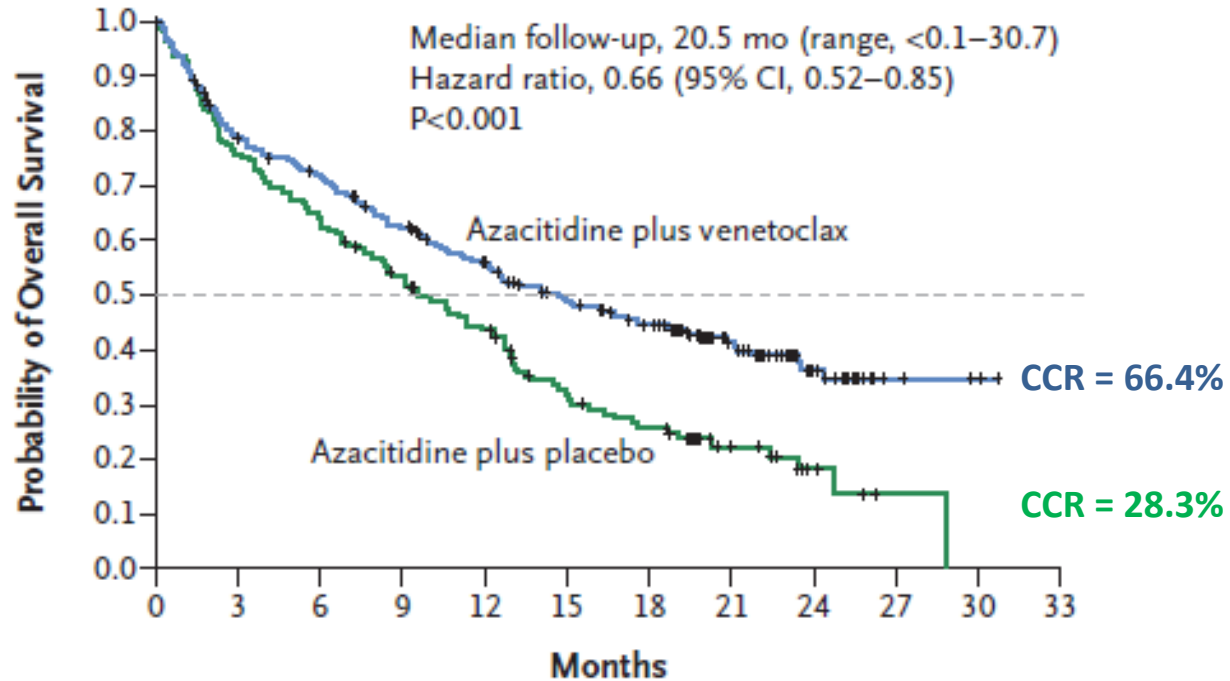
CHF requiring treatment or LVEF  $\leq 50\%$

DLCO  $\leq 65\%$  or FEV1  $\leq 65\%$

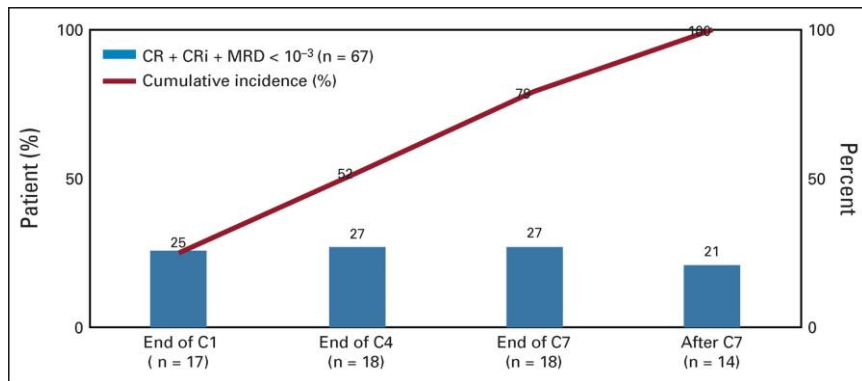
Creatinine clearance  $\geq 30$  to  $< 45$  ml/min

T.bili  $> 1.5$  to  $\leq 3.0$ x ULN

# VIALE-A: Azacitidine ± Venetoclax in Treatment-Naive Patients With AML Ineligible For Standard Induction Therapy



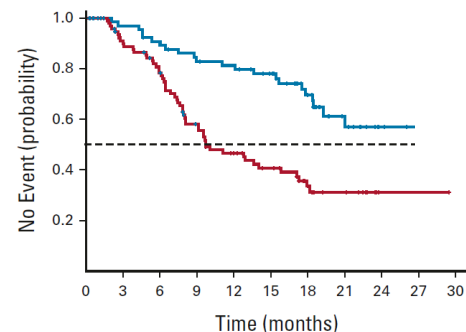
# MRD Following HMA/Venetoclax (VIALE-A)



## Flow cytometry based MRD in CR/CR<sub>i</sub> patients

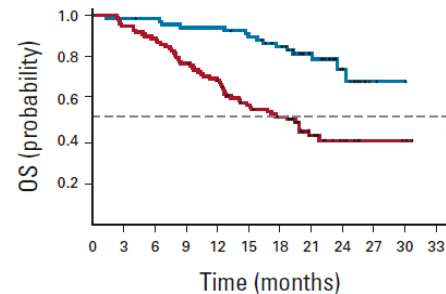
MRD < 10<sup>-3</sup> = 41%

MRD ≥ 10<sup>-3</sup> = 59%



No. at risk:

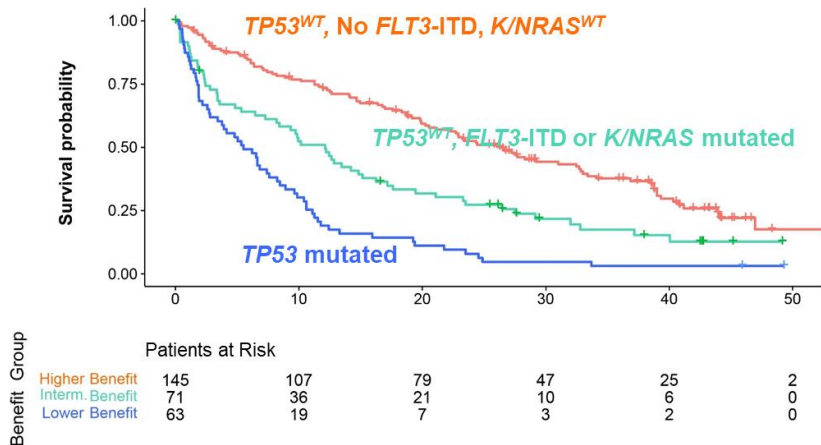
CR + CRi + MRD < 10 <sup>-3</sup>	67	63	58	52	50	44	30	14	3	1	0
CR + CRi + MRD ≥ 10 <sup>-3</sup>	97	80	67	46	34	27	14	9	1	1	0



No. at risk:

CR + CRi + MRD < 10 <sup>-3</sup>	67	66	65	62	62	58	52	30	13	2	1	0
CR + CRi + MRD ≥ 10 <sup>-3</sup>	97	92	86	74	64	49	42	21	10	3	2	0

# 4-Gene Classifier for OS with Aza + Ven

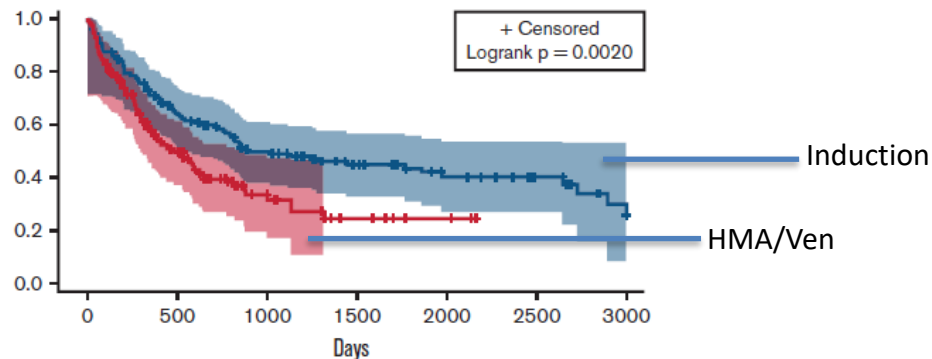


Ven + Aza (N = 279)	n	Events	Median OS, months (95% CI)
Higher Benefit	145	96	<b>26.51</b> (20.24, 32.69)
Intermediate Benefit	71	57	<b>12.12</b> (7.26 – 15.15)
Lower Benefit	63	61	<b>5.52</b> (2.79 – 7.59)

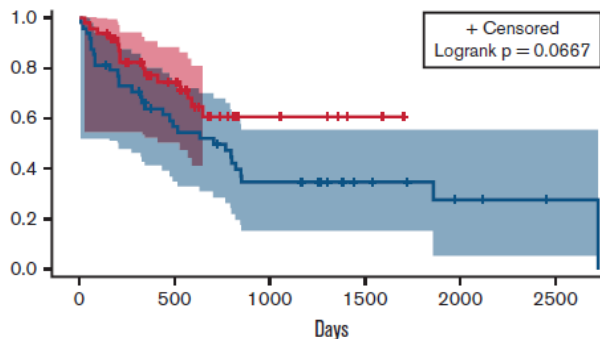
# What about HMA + Venetoclax in Younger or Fitter Patients?

Variable	Ven/aza	IC	<i>P</i> (ven/aza vs IC)
<b>Response</b>			
CR	89 (62.2)	96 (64.4)	
CRi	13 (9.1)	4 (2.7)	
MLFS	8 (5.6)	5 (3.4)	
Overall response (CR + CRi + MLFS)	110/143 (76.9)	105/149 (70.5)	.2109
<b>Death</b>			
Within 30 d of treatment	7 (4.9)	8 (5.4)	.8545

OS (all patients)



OS (propensity-matched patients)



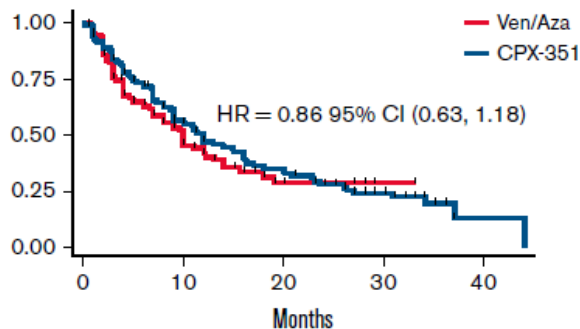
**Favoring HMA/Ven**

RUNX1  
Splicing mutation  
Prior Rx  
Age > 65  
ELN Adverse



# CPX-351 vs HMA-Venetoclax – Real World Experience

Restricted to CPX-351 trial-eligible patients



Number at risk						
		0	10	20	30	40
Ven/Aza	129	46	7	1	0	
CPX-351	137	67	39	17	1	

Combined cohort (n = 656)

	CPX-351 (n = 217)	ven/aza (n = 439)	P
Median cycles (range)	2 (1-5)	4 (1-28)	Not applicable
30-day mortality, % (95% CI)	5% (2%-8%)	5% (3%-7%)	.51
60-day mortality, % (95% CI)	10% (6%-14%)	13% (10%-16%)	.10
Diagnosis of infection,* % (95% CI)	51% (42%-61%)	20% (15%-25%)	<.00005

# Prospective Studies Comparing Induction Chemotherapy vs HMA-VEN

Study	Phase	Type	Therapy	Key inclusion	Key exclusion
NCT04801797	II	Randomized	<ul style="list-style-type: none"> <li>• IC</li> <li>• AZA-VEN</li> </ul>	<ul style="list-style-type: none"> <li>• Age 18+</li> <li>• ECOG <math>\leq 2</math></li> </ul>	<ul style="list-style-type: none"> <li>• <i>FLT3</i></li> <li>• Age &lt;60 with <i>NPM1</i> mutated</li> <li>• Favorable risk</li> </ul>
NCT03573024	II	Single arm	<ul style="list-style-type: none"> <li>• AZA-VEN</li> </ul>	<ul style="list-style-type: none"> <li>• Age 18–59</li> <li>• ECOG <math>\leq 2</math></li> <li>• Adverse risk</li> </ul>	<ul style="list-style-type: none"> <li>• Willing to receive IC</li> </ul>
NCT05554393 (MyeloMATCH)	II	Randomized	<ul style="list-style-type: none"> <li>• 7+3</li> <li>• 7+3 + VEN</li> <li>• AZA-VEN</li> </ul>	<ul style="list-style-type: none"> <li>• Age 18–59</li> <li>• ECOG 0–3</li> </ul>	<ul style="list-style-type: none"> <li>• Favorable and adverse risk by ELN 2017 criteria</li> <li>• <i>FLT3-ITD/TKD</i></li> <li>• Secondary or therapy-related AML</li> </ul>
NCT05554406 (MyeloMATCH)	II	Randomized	<ul style="list-style-type: none"> <li>• CPX-351</li> <li>• 7+3</li> <li>• AZA-VEN</li> <li>• 7+3+ VEN</li> <li>• CPX-351 + VEN</li> </ul>	<ul style="list-style-type: none"> <li>• Age 18–59</li> <li>• ECOG 0–3</li> <li>• Adverse risk per ELN 2017 criteria</li> </ul>	<ul style="list-style-type: none"> <li>• Favorable or intermediate risk</li> <li>• <i>FLT3-ITD/TKD</i></li> </ul>

# What about HMA-VEN for Remission Induction Prior to Allogeneic Transplant?

Study	Type	Participating sites	Number of patients	12-month NRM (%)	12-month CIR	12-month RFS (%)	12-month OS (%)	Relapse (%) / median LFS (month)	OS (months)
Pasvolsky et al <sup>35</sup>	Retrospective	Multicenter	24	19.1		58	63		
Winters et al <sup>36</sup>	Retrospective	Single center	29			66.1	74.5		
Pollyea et al <sup>37,38</sup>	Retrospective	Single center	21	11		80			NR
Kennedy et al <sup>39,40</sup>	Retrospective	Multicenter	88	17	18		73		
Nizamuddin et al <sup>41</sup>	Retrospective	Single center	36					39/11.2	25.4
Rautenberg et al <sup>42</sup>	Retrospective	Single center	26			67	81		NR

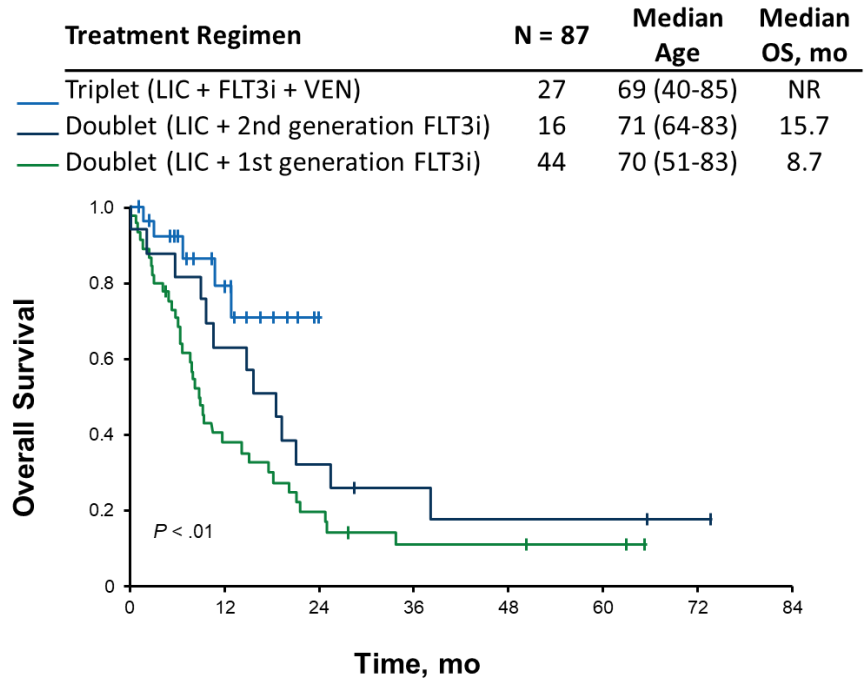
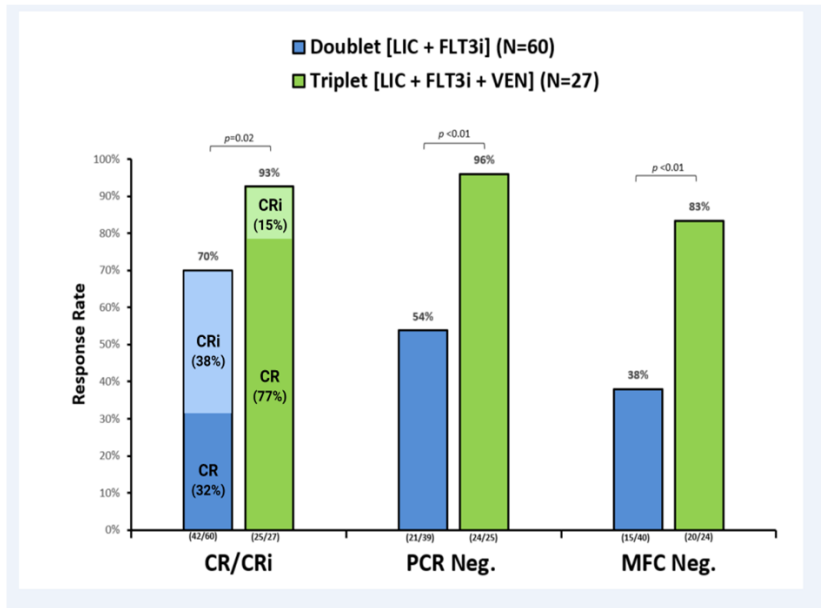
---

# Where I Believe I Will Use It.

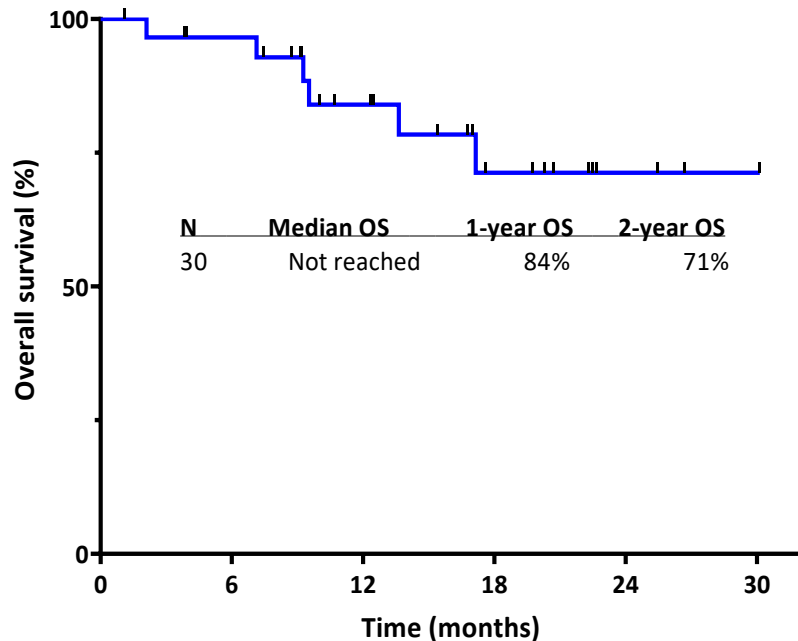
- Triplets
- Sequencing
- Time-limited therapy

# Frontline Lower Intensity FLT3i “Doublet” vs “Triplet” with the Addition of Venetoclax: Retrospective Pooled Analysis

LIC = lower intensity chemotherapy



# Aza + Ven + Gilteritinib in Newly Diagnosed FLT3-Mutated AML



**CRc 100% in the frontline setting**

90% CR, 6% CRi, 4% MLFS

**87% MRD negative by flow**

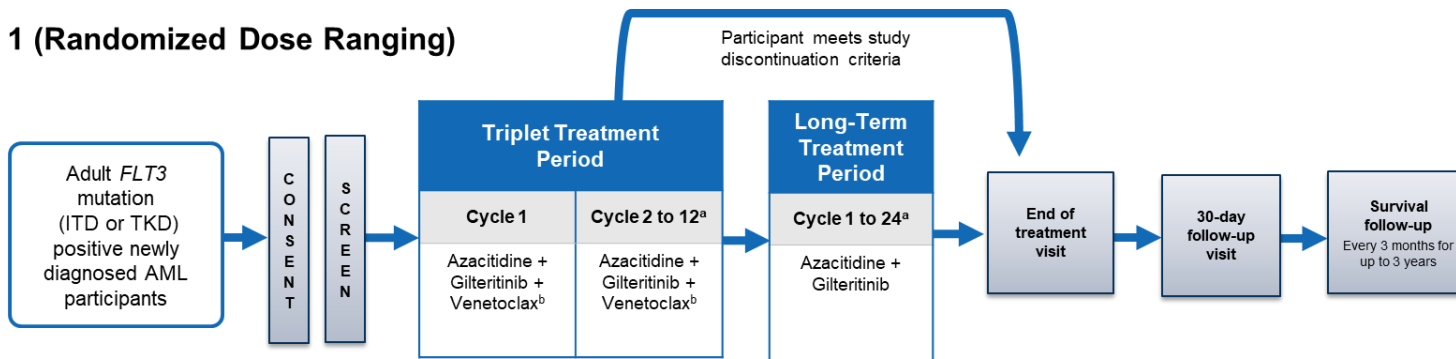
40% (n=12) proceeded to alloSCT in CR1

No 30 or 60 day mortality, 1 death in CR

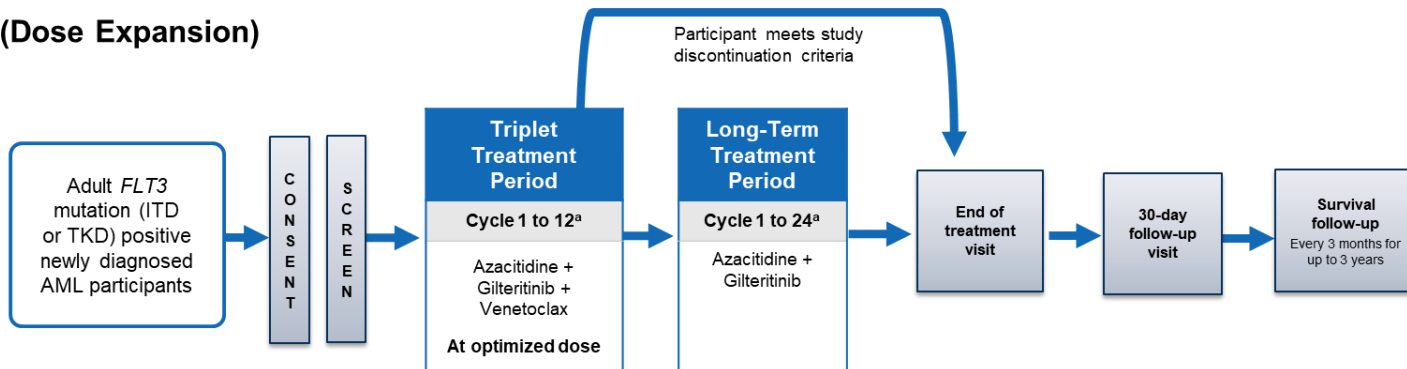
4 relapses to date (13% relapse rate)

# VICEROY: Phase 2 Multicenter Frontline Optimization Trial of Azacitidine, Venetoclax, and Gilteritinib (N = 80~100)

## Phase 1 (Randomized Dose Ranging)



## Phase 2 (Dose Expansion)



# Survival Comparison: AZA/VEN/Magrolimab vs HMA/VEN – TP53-Mutated Arm

Comparator datasets from Phase 1b/2 AZA+VEN and Dac10+VEN F/L studies from MDACC (N = 150)\*

Comparison of baseline characteristics among TP53m patients only

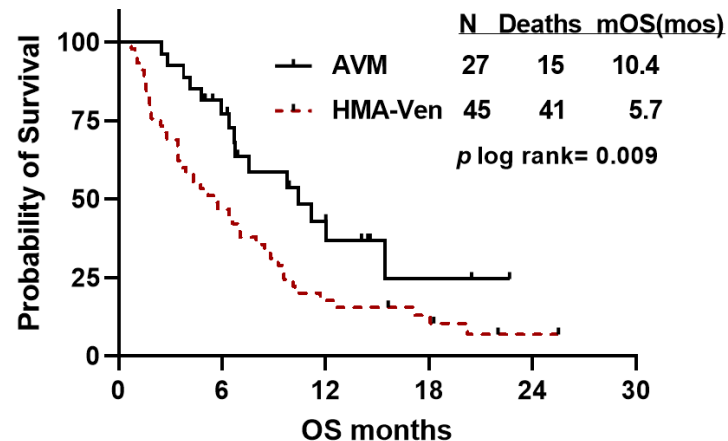
Parameters	A-V-M (N = 27)	HMA-Ven (N = 45)
Age, years	66 [58 to 84]	74 [61 to 86]
t-AML	12 (44)	17 (38)
CTG- HR	22 (82)	43 (96)
CTG-CK	21 (78)	41 (91)
ASXL1	2 (7)	2 (4)
RUNX1	2 (7)	2 (4)

MV Cox regression analysis

Variable	HR	95% Confidence interval
Age	0.9865	0.9522 to 1.025
t-AML[Y]	1.213	0.6974 to 2.074
CTG HR[Y]	1.202	0.4719 to 3.700
Rx arm [AVM]	0.4091	0.1781 to 0.8811

Adjusted HR for AVM arm  
for death = 0.41,  
95% CI = 0.18-0.88

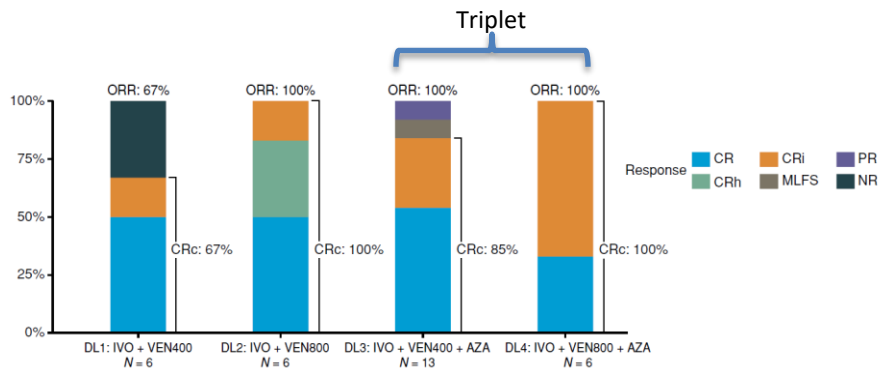
Comparison of overall survival (unmatched groups)





# Triplets with IDH Inhibitors: Early Promise

## Response Rates

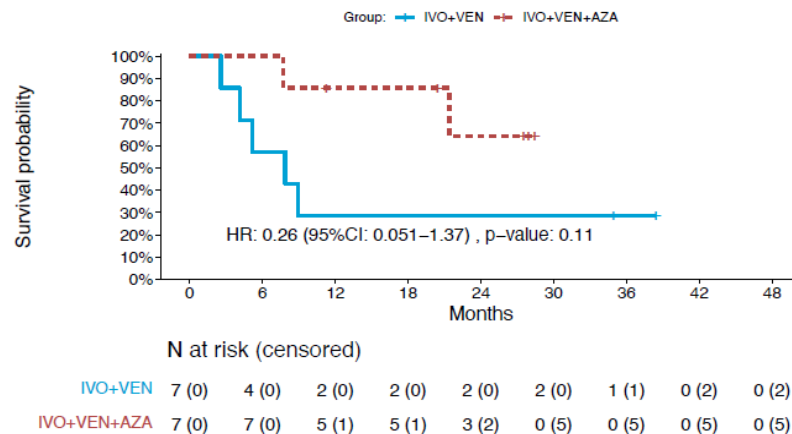


## Newly Diagnosed AML - MRD Rates

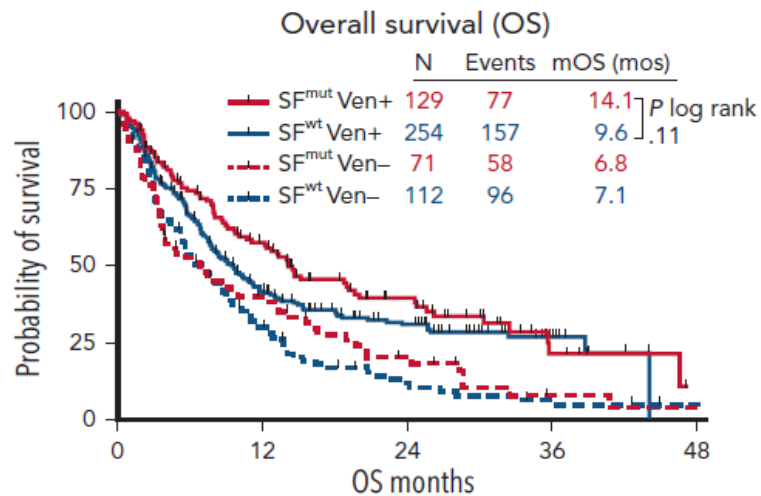
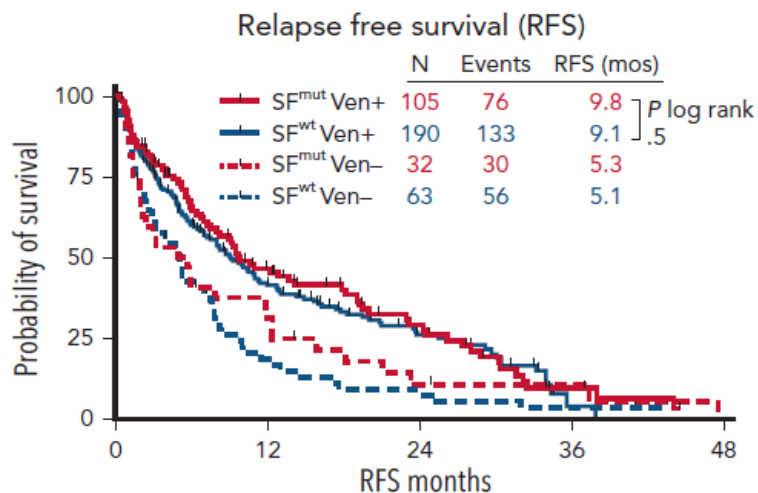
Ivo + Ven = 25%

Ivo + Ven + HMA = 83%

## OS in AML with Signaling Mutations

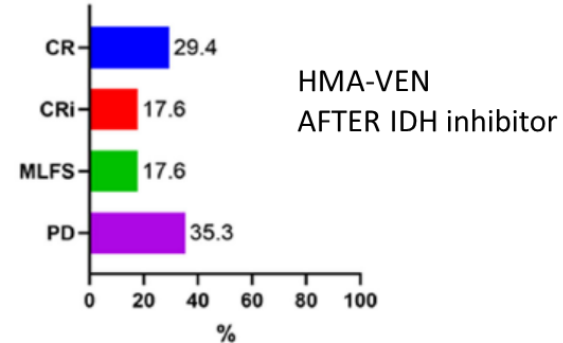
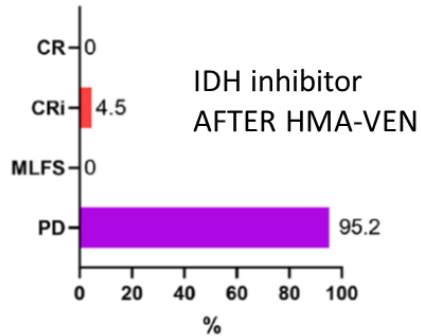


# HMA/Ven Maintains Beneficial Effect in AML with Secondary Type Mutations

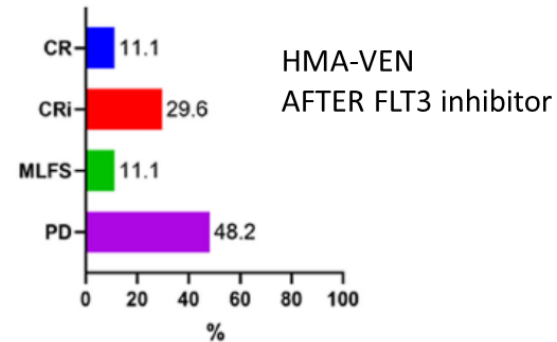
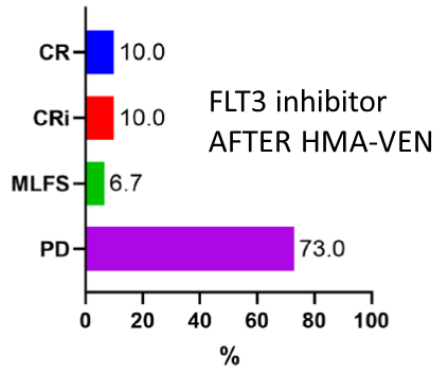


# Sequencing of HMA-Ven with Other Targeted Therapies

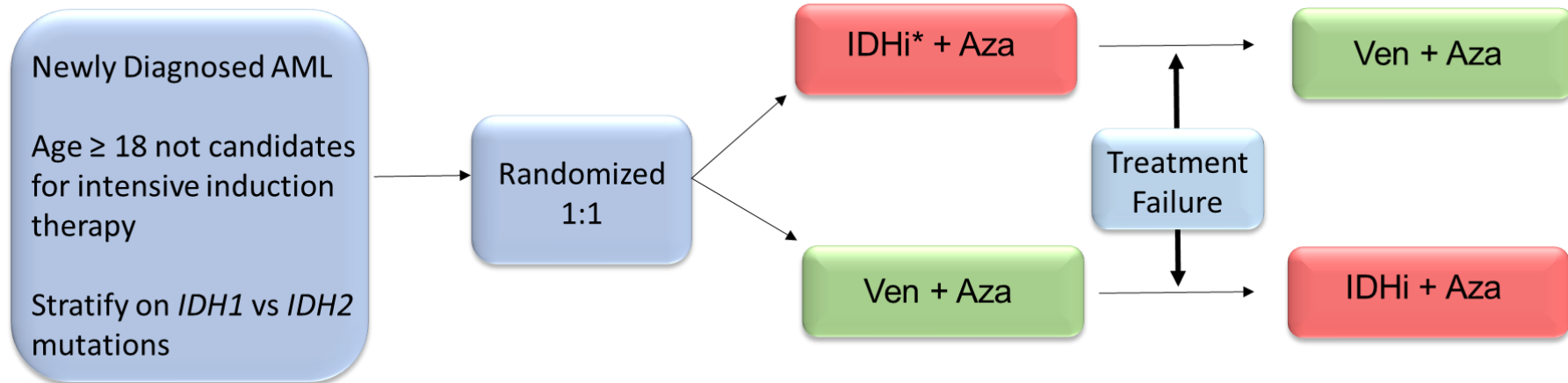
IDH mutant



FLT3 mutant

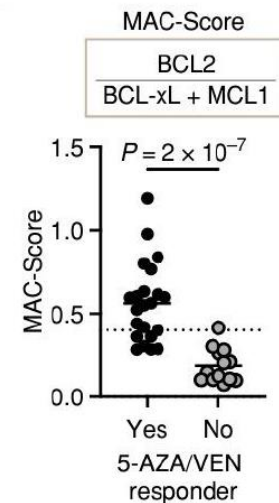
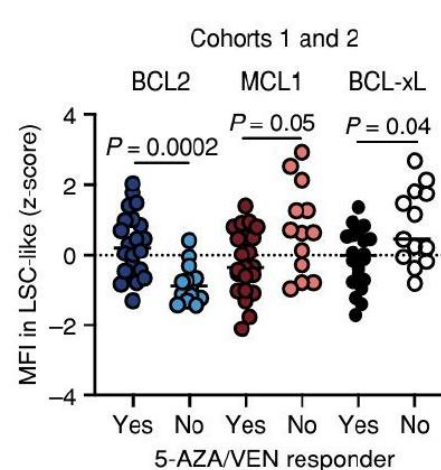
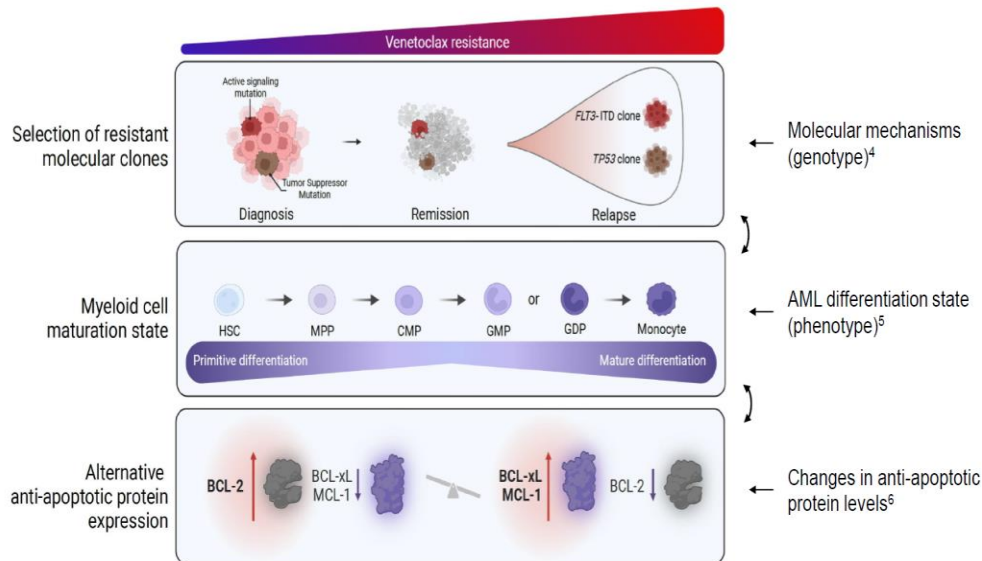


# Choosing the Best Initial Therapy: I-DATA Study



Primary Objective: Overall treatment failure rate at 24 months

# What About Aza/Ven Resistance?



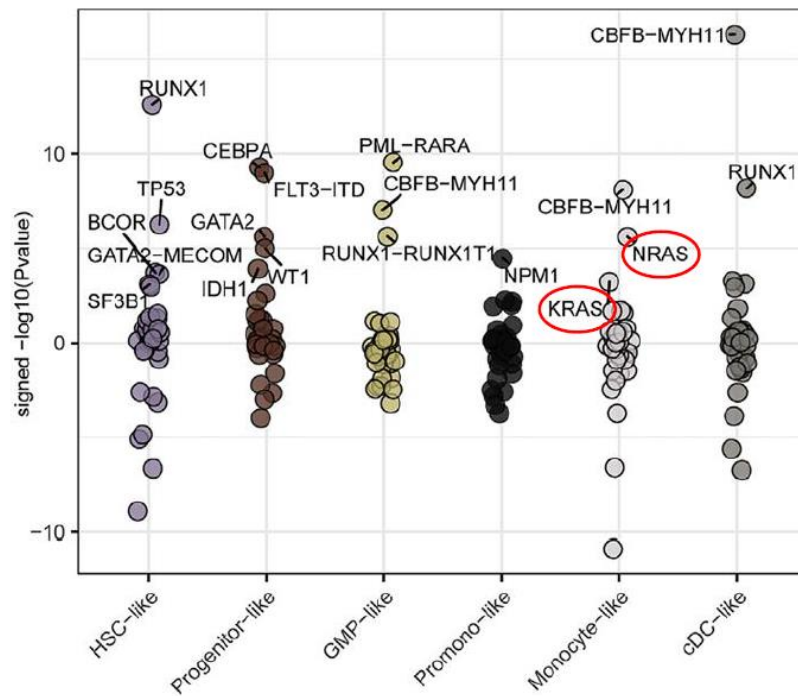
Waclacwizek, et al. Cancer Discovery 2023

Dinardo, et al. Blood 2020

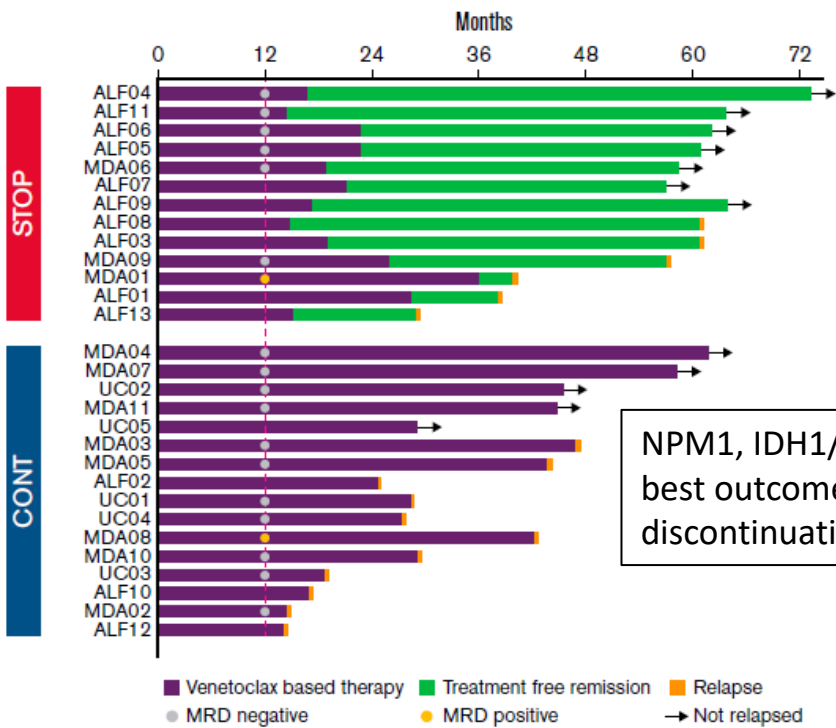
Pei, et al. Cancer Discovery 2020

# Monocytic AML Related to Ven Resistance

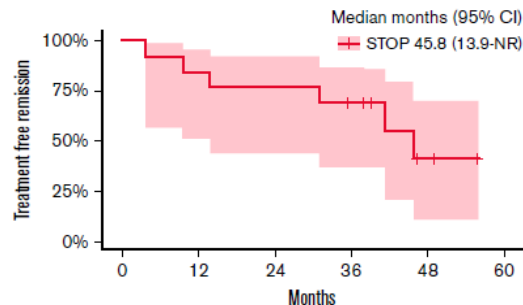
Baseline Variables	Univariate OR	P-value	Multivariate OR	P-value
Age	0.98 (0.95-1.02)	0.40		
Antecedent Hematologic Dz	0.57 (0.12-2.77)	0.48		
Complex Cytogenetics	2.67 (0.86-8.24)	0.09		
ELN Risk Group	4.08 (0.50-33.64)	0.07		
RAS Pathway	6.42 (1.81-22.71)	0.004	2.27 (0.20-25.52)	0.51
TP53	1.48 (0.28-7.77)	0.64		
NPM1	0.162 (0.02-1.30)	0.09	0.49 (0.034-7.0)	0.60
FLT3	0.66 (0.14-3.27)	0.61		
FAB M0/M1	0.13 (0.04-0.43)	0.0008		
FAB M5	18.30 (4.70-71.13)	<0.0001	33.48 (2.66-421.9)	0.0066



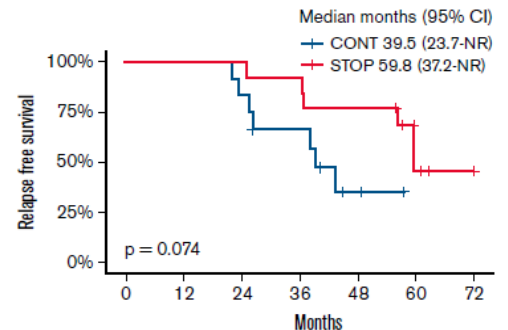
# Can HMA-VEN Be Discontinued?



NPM1, IDH1/2 mutants best outcomes after discontinuation

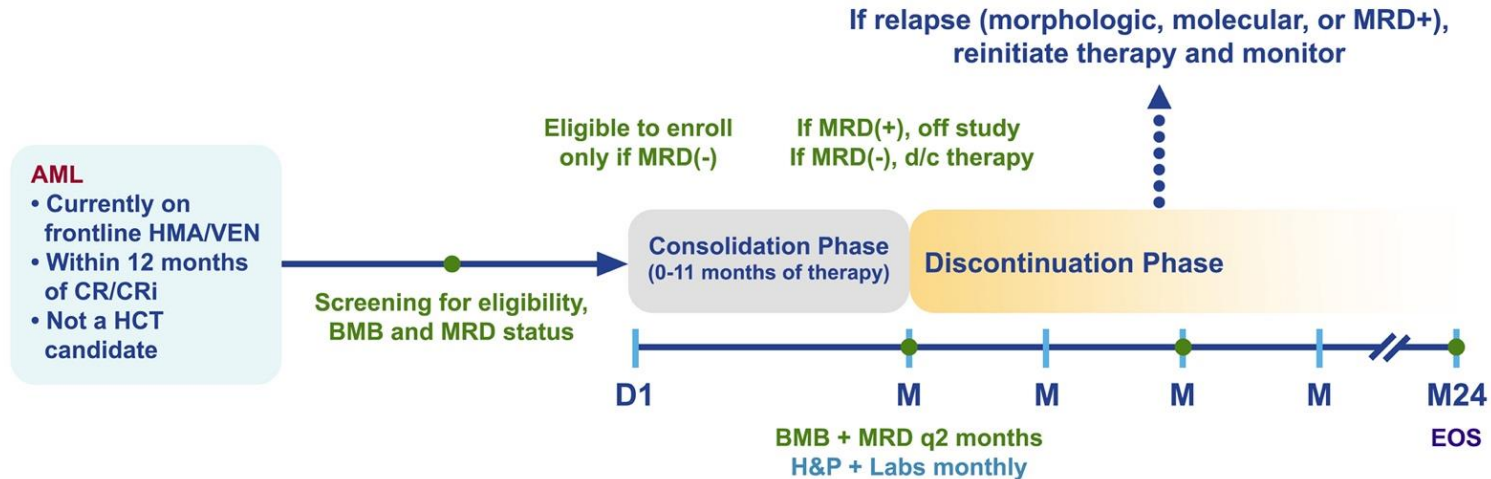


No. at risk  
— 13 11 10 8 2 0



No. at risk  
— 12 12 10 7 2 0 0  
— 13 13 13 12 10 4 0

# Prospective HMA-VEN Discontinuation Trial



Primary Endpoint: Rates of CR/CRI at 18 months from time of discontinuation of HMA/VEN

Secondary Endpoints: 1) OS in MRD-negative patients who continue HMA/VEN, 2) Duration of TFMR, 3) Response rates to re-treatment following relapse



---

# Summary

- HMA-Venetoclax combination is an effective standard-of-care for older, less fit adults
- Equivalence to induction chemotherapy in younger, more fit patients appears likely, but evidence is not yet supported by a randomized trial
- Triplet combinations that include targeted agents (IDH, FLT3 inhibitors) appear promising
  - HMA-Ven sequencing with IDH inhibitors needs further study
- Risk-adapted discontinuation strategies under development

# THANK YOU

Jeffrey.Lancet@moffitt.org

