



***Dati a supporto del
trattamento non intensivo
nel paziente borderline***

Dott Antonino Mulè
UOC di Oncoematologia
AO Villa Sofia-Cervello
Palermo

When we first see a patient with AML, the central question is whether that patient is fit for intensive chemotherapy?



Is my patient who is otherwise fit for intensive chemotherapy potentially suitable for a less intensive option?

There's a lot of study that provides "more reassurance," especially for patients older than age 60 or of borderline fitness, that there is now a "realistic alternative. There is more work to be done regarding whether azacitidine–venetoclax is appropriate in specific subgroups, but I think that for certain situations now, the pendulum is moving more toward not delivering intensive therapy for everyone."

Andrew Wei, MBBS, PhD from ASCO POST

The Toils of Induction Chemotherapy

- Severe marrow suppression (bleeding and infections)
- Malnutrition, mucositis, typhlitis (need for TPN, etc)
- Prolonged antibiotics & potential for resistance
- Complications impacting HCT candidacy
- Increased risk of systolic dysfunction and secondary cancer
- Psychosocial Implications (e.g. depression, anxiety, isolation)
- Healthcare costs (long hospitalizations, bed utilization, ICU care)



Statnews.com



Fiwek et al. Medicina 2022



Ammannagari N et al. BMJ Case Rep 2013

Azacitidine and Venetoclax

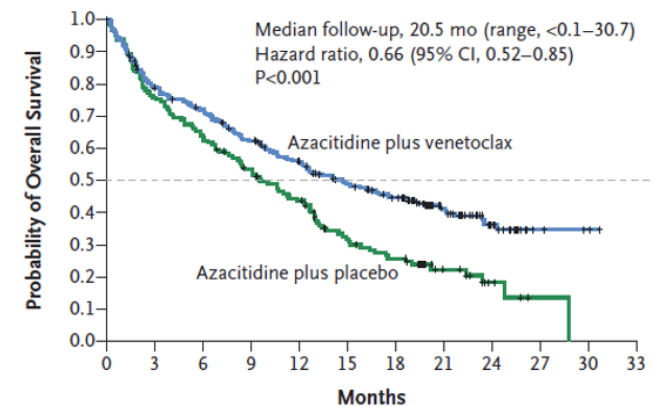
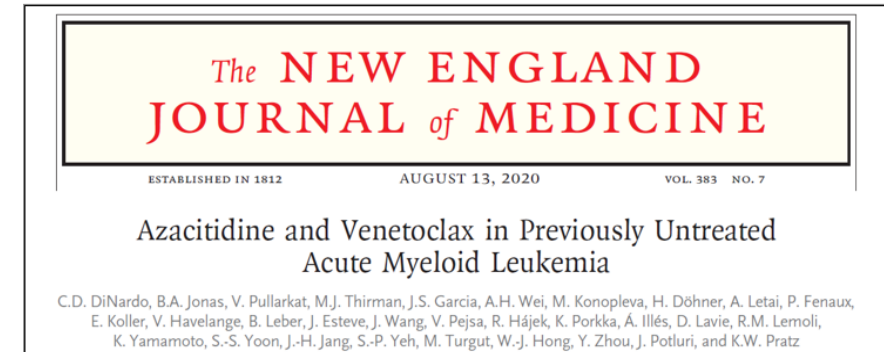
- For the IC-ineligible, VIALE-A established the superiority of azacitidine and venetoclax (Aza-Ven) to azacitidine.
- Aza-Ven was well-tolerated, with low early mortality, and could be administered and managed in clinic.
- Some retrospective studies suggested improved clinical outcomes with HMA-ven vs IC, but no prospective studies have demonstrated a therapeutic advantage.

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

Cherry EM, et al. *Blood Adv*, 2021.

Shimony S, et al. *Leukemia*, 2024.

Matthews AH, et al. *Blood Adv*, 2022.



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33
Azacitidine plus venetoclax	286	219	198	168	143	117	101	54	23	5	3	0
Azacitidine plus placebo	145	109	92	74	59	38	30	14	5	1	0	0

American Society of Hematology 2021

Real World Survival Outcomes of CPX-351 Versus Venetoclax and Azacitidine for Initial Therapy in Adult Acute Myeloid Leukemia

Andrew H. Matthews, MD¹; Alexander E. Perl, MD¹; Selina M. Luger, MD¹; Martin P. Carroll, MD¹; Daria V. Babushok MD, PhD¹; Noelle V. Frey, MD¹; Saar I. Gill, MD, PhD¹; Elizabeth O. Hexner, MD¹; Mary Ellen Martin MD¹; Shannon R. McCurdy, MD¹; David L. Porter, MD¹; Edward A. Stadtmauer MD¹; Alison W. Loren, MD¹; Vikram Paralkar, MD¹; Ivan P. Maillard, MD, PhD¹; Wei-Ting Hwang PhD²; David Margolis, MD²; Keith W. Pratz, MD¹

December 13, 2021

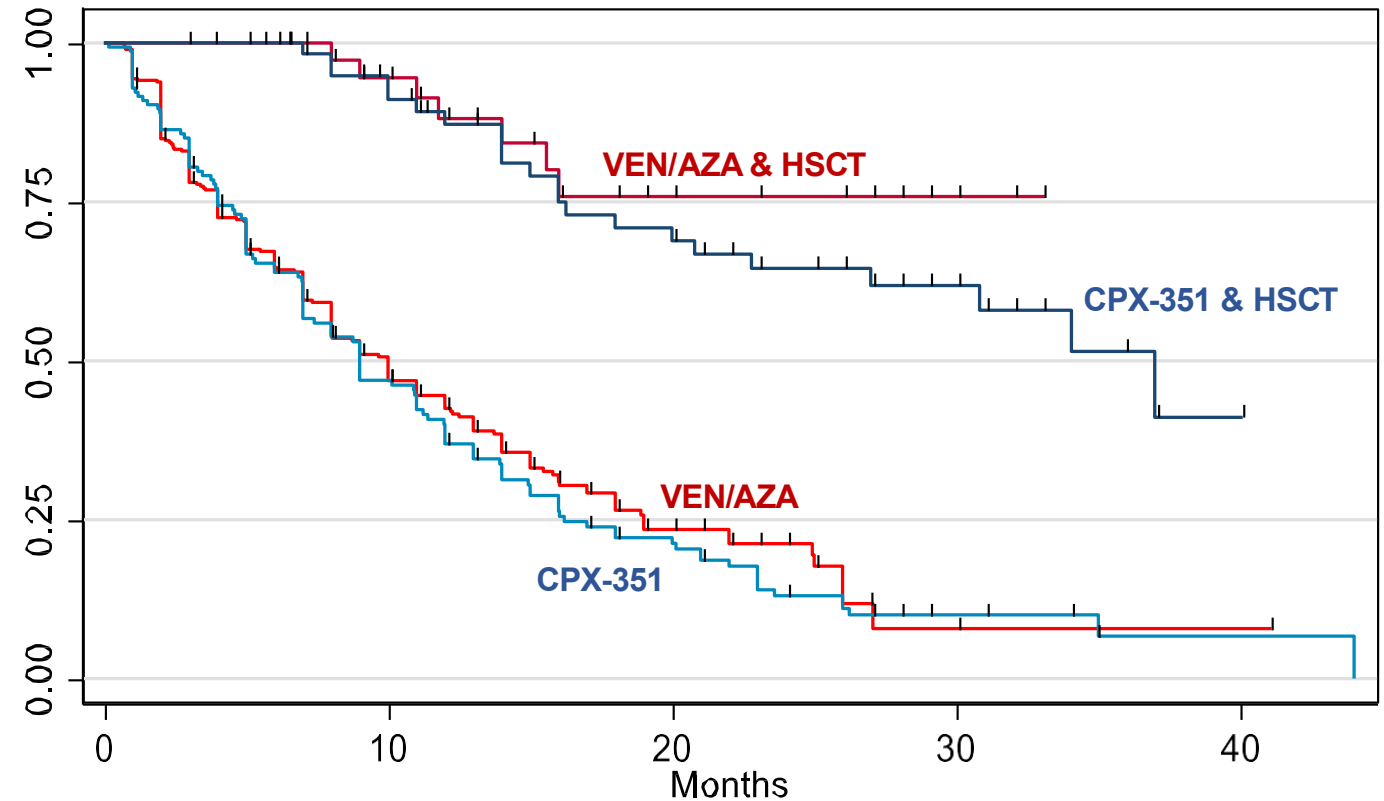
1. Division of Hematology-Oncology, Perelman Center for Advanced Medicine, University of Pennsylvania, Philadelphia, PA.

2. Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, Philadelphia, PA.

Transplant Is Critical for Survival Regardless of Initial Treatment

Retrospective analysis of real world use of CPX-351 and Venetoclax/AZA as initial treatment with AML

	Ven/Aza N=439	CPX-351 N=217	p-value
Age	75 (36-88)	67 (21-82)	<0.001
Gender			0.056
Female	191 (44%)	112 (52%)	
Male	248 (56%)	105 (48%)	
Practice Type			<0.001
Academic	149 (34%)	103 (47%)	
Community	290 (66%)	114 (53%)	
Type			<0.001
De Novo	226 (51%)	63 (29%)	
History of MDS/MPN	150 (34%)	104 (48%)	
Therapy-Related	63 (14%)	50 (23%)	
ELN Risk Group			0.84
Favorable	34 (8%)	15 (7%)	
Intermediate	117 (27%)	64 (29%)	
Adverse	172 (39%)	92 (42%)	



	Ven / Aza	CPX-351
Number (%)	44 (10%)	61 (28%)
Median Time to Transplant (range)	186 days (87 - 578)	171 days (34 - 903)
Median OS w/ HSCT	NR	37 mos
Median OS w/o HSCT	10 mos	9 mos

- Matthews AH, et al. *Blood Adv.* 2022;6(13):3997-4005.

Early Mortality Similar but Febrile Neutropenia, Infections and Average Inpatient Length of Stay was Higher for CPX-351

Flatiron & UPHS	CPX-351 n = 217	Venetoclax & Azacitidine n = 439	p-value
Median Cycles (range)	2 (1-5)	4 (1-28)	n/a
30 Day Mortality % (95% CI)	5% (2%-8%)	5% (3%-7%)	0.51
60 Day Mortality % (95% CI)	10% (6%-14%)	13% (10%-16%)	0.10
Diagnosis of Infection¹ % (95% CI)	51% (42%-61%)	20% (15%-25%)	<0.00005

UPHS Only	CPX-351 n = 52	Venetoclax & Azacitidine n = 59	p-value
Febrile Neutropenia % (95% CI)	90% (82%-98%)	54% (42%-67%)	<0.00005
Culture Positive Infection % (95% CI)	67% (55%-80%)	36% (23-48%)	0.0004
Mean Days of Inpatient Stays² (95% CI)	41 (37-45)	15 (10-20)	<0.00005

- Matthews AH, et al. *Blood Adv.* 2022;6(13):3997-4005.

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 (HUP) cohort. 2 Includes readmission before second cycle of therapy. P-values by Fisher's exact test

Full Length Article
Allogeneic – Adult

Outcomes Are Similar After Allogeneic Hematopoietic Stem Cell Transplant for Newly Diagnosed Acute Myeloid Leukemia Patients who Received Venetoclax + Azacitidine Versus Intensive Chemotherapy

Amanda C. Winters^{1,*}, Grace Bosma², Diana Abbott², Mohd Minhajuddin³, Craig Jordan³, Daniel A. Pollyea³, Jonathan A. Gutman³

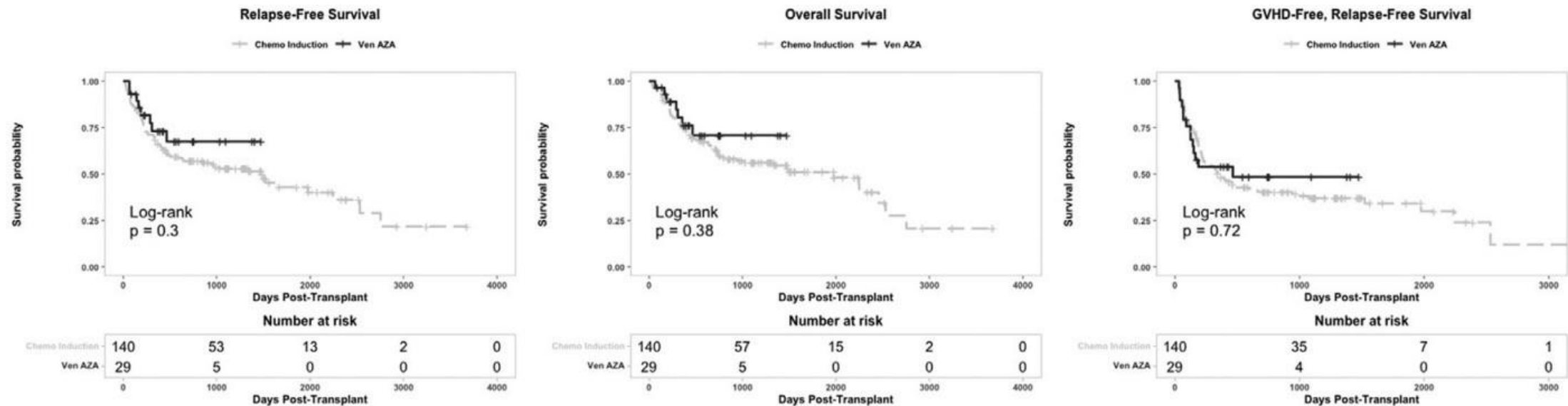


Figure 1. Post-transplantation survival outcomes do not differ among patients receiving IC versus ven/aza for remission induction. (a) RFS, (b) OS, and (c) GVHD-free relapse-free survival are measured from date of SCT for the IC cohort patients (*gray dashed lines*) and for ven/aza cohort patients (*black solid lines*). *P* values are nonsignificant and are indicated on the respective charts.

Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia

Evan M. Cherry,^{1,*} Diana Abbott,^{2,*} Maria Amaya,¹ Christine McMahon,¹ Marc Schwartz,¹ Julie Rosser,³ Audrey Sato,³ Jeffrey Schowinsky,³ Anagha Inguva,¹ Mohd Minhajuddin,¹ Shanshan Pei,¹ Brett Stevens,¹ Amanda Winters,¹ Craig T. Jordan,¹ Clayton Smith,¹ Jonathan A. Gutman,¹ and Daniel A. Pollyea¹

¹Division of Hematology, Department of Medicine; ²Center for Innovative Design and Analysis, Department of Biostatistics and Informatics; and ³Department of Pathology, University of Colorado, Aurora, CO

Table 1. Baseline characteristics of patients who received ven/aza or IC

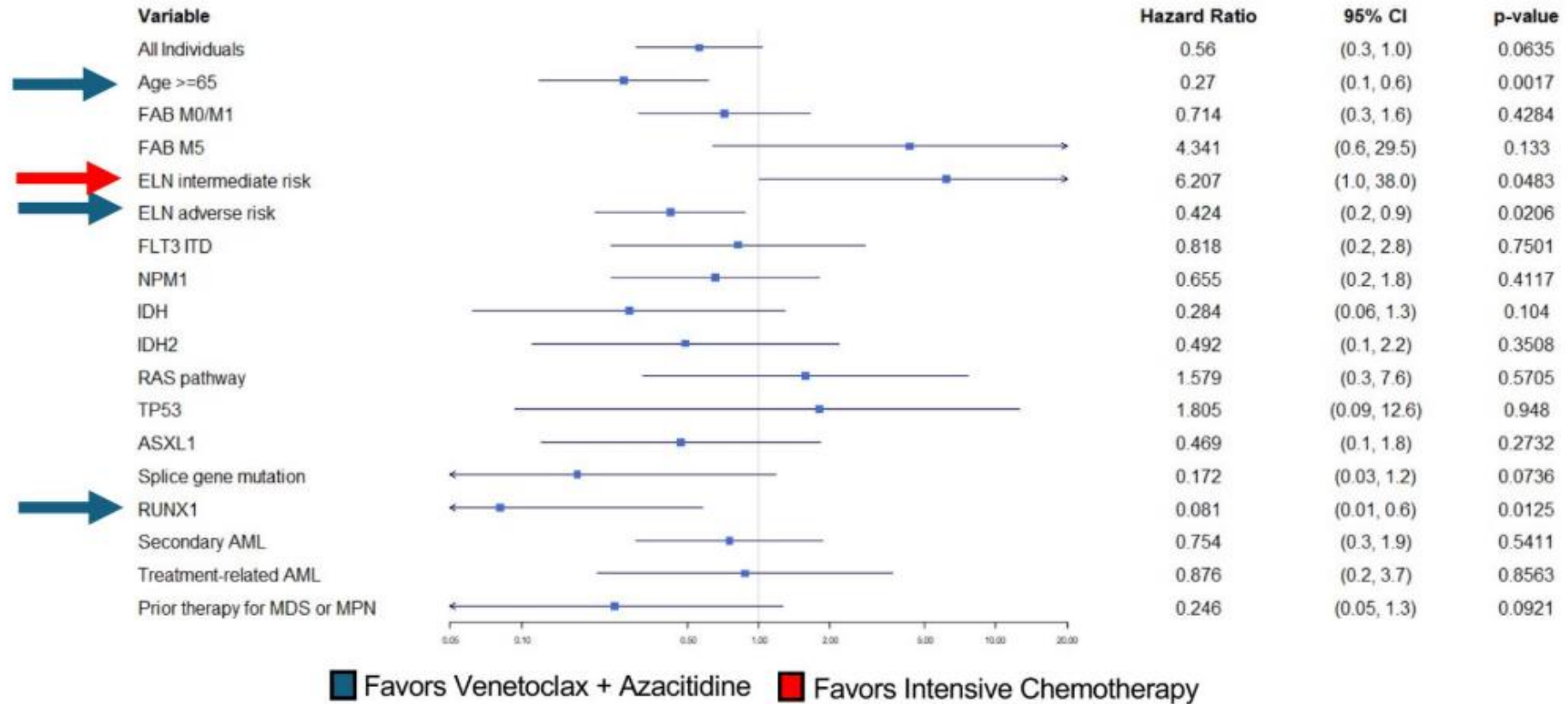
Variable	Ven/aza (n = 143)	IC (n = 149)	<i>P</i> (IC vs ven/aza)
Sex			.1168*
Male	72 (50.4)	78 (52.3)	
Female	71 (49.6)	71 (47.7)	
Median age (range), y	69.5 (22-91)	52.7 (19-81)	<.0001†‡
Median bone marrow blast (range), %	50.3 (10-96.5)	55.7 (10.5-95.5)	.0639‡
FAB M0/M1	87 (60.8)	63 (42.3)	.0015*†
FAB M5	14 (9.8)	19 (12.7)	.4243*
<i>KMT2A</i> rearranged	7 (4.9)	13 (8.8)	.1954*
ELN risk group			<.0001*†
Adverse	93 (65.0)	60 (40.3)	
Favorable	24 (16.8)	23 (15.4)	
Intermediate	24 (16.8)	24 (16.1)	
Unable to assess	2 (1.4)	42 (28.2)	

Table 2. Response rates and early deaths for patients who received ven/aza or IC

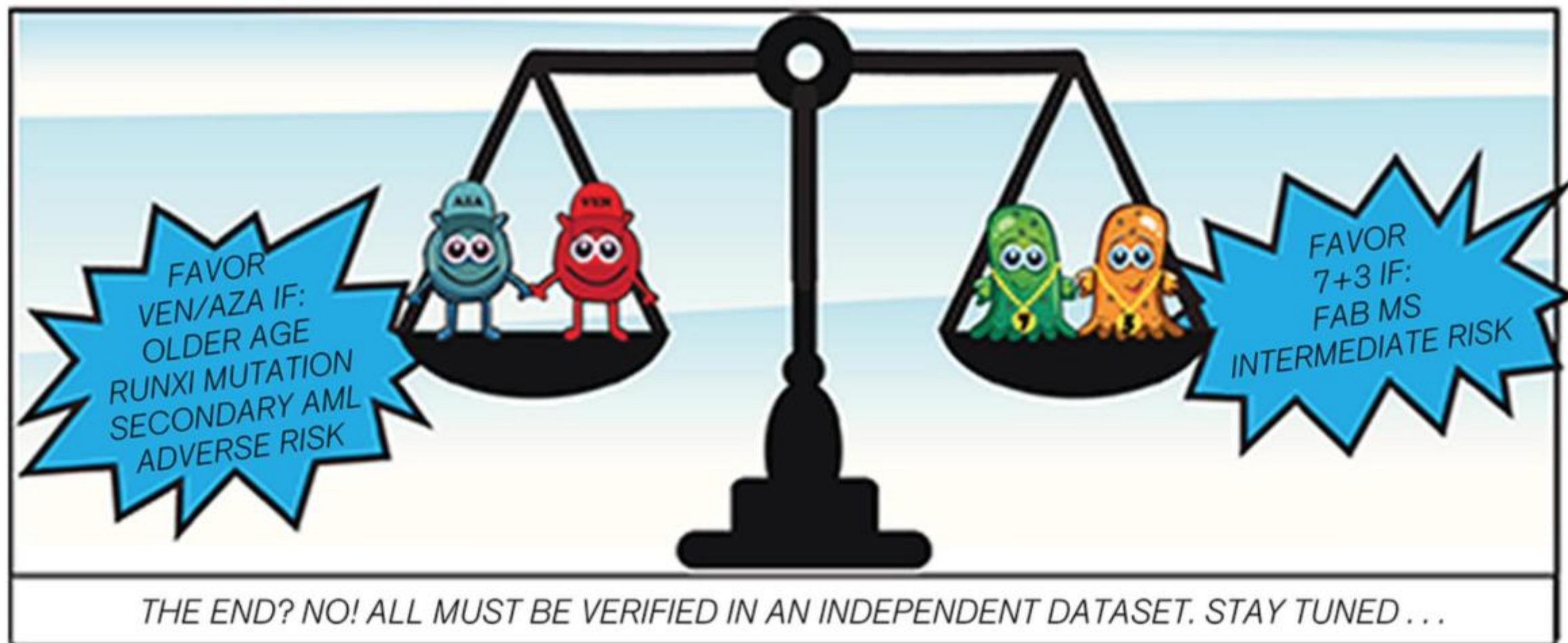
Variable	Ven/aza	IC	<i>P</i> (ven/aza vs IC)
Response			
CR	89 (62.2)	96 (64.4)	
CRi	13 (9.1)	4 (2.7)	
MLFS	8 (5.6)	5 (3.4)	
Overall response (CR + CRi + MLFS)	110/143 (76.9)	105/149 (70.5)	.2109
Death			
Within 30 d of treatment	7 (4.9)	8 (5.4)	.8545

The response rates were 76.9% for ven/aza and 70.5% for IC. The median overall survival (OS) was 884 days for IC compared with 483 days for ven/aza

Venetoclax + Azacitidine Versus 7+3: Factors that Predict Survival (Propensity Cohort)

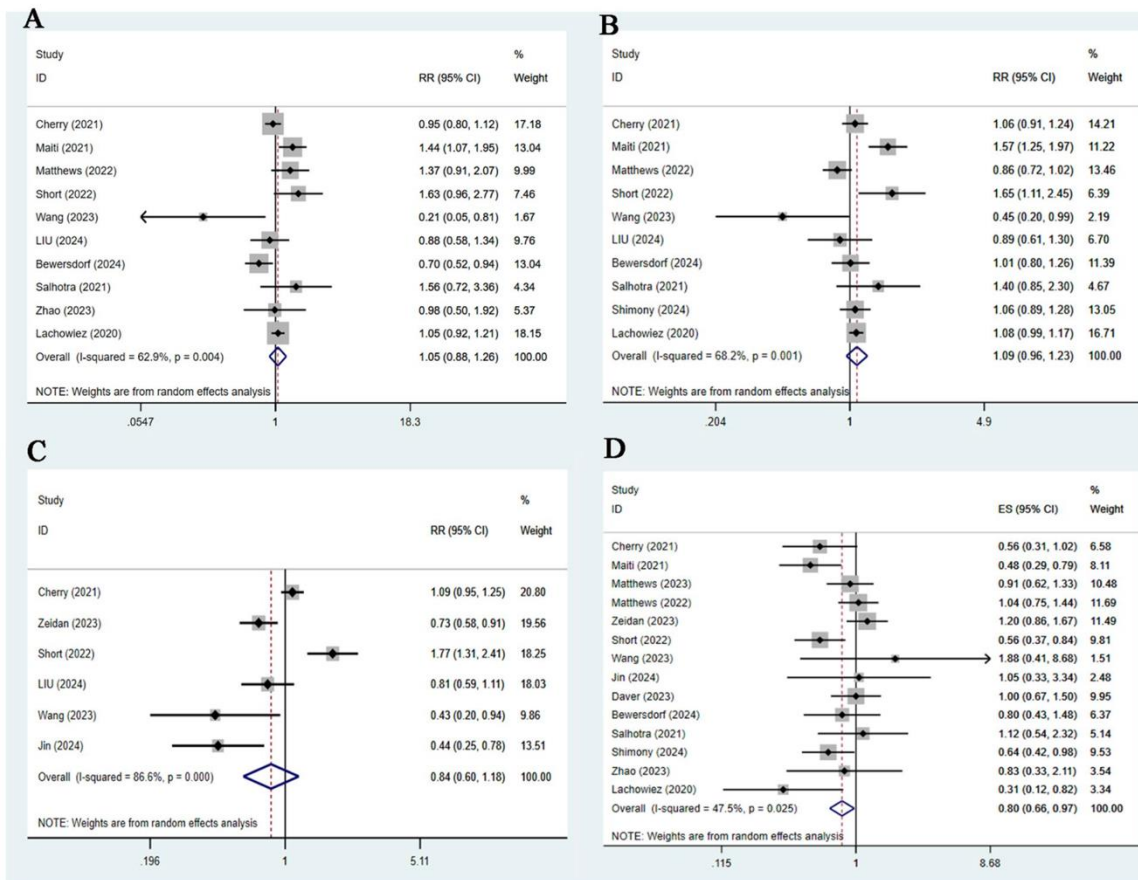


Cherry EM et al. *Blood Adv.* 2021;5(24):5565-5573.



Venetoclax and hypomethylating agents versus induction chemotherapy for newly diagnosed acute myeloid leukemia patients: a systematic review and meta-analysis

Yun Liu^{1,2†}, Ying Zhang^{3†}, Jinhong Gao^{1,4}, Lijuan Wang², Fang Xie¹, Chengtao Zhang¹, Peimin Mao^{3*} and Jinsong Yan^{1*}

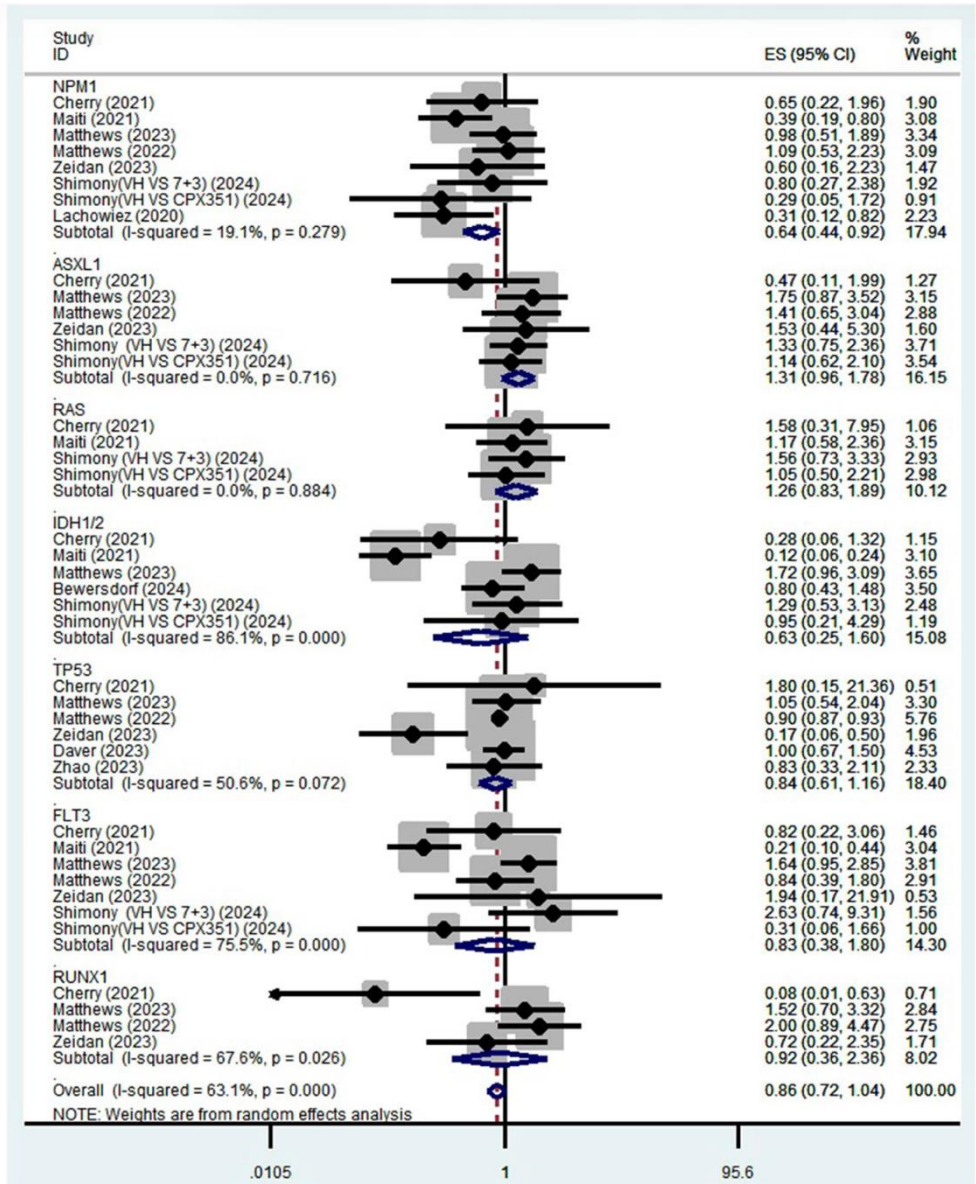


This meta-analysis synthesizes data from 15 retrospective cohort studies (n= 3809) comparing VEN-HMAs with IC in ND-AML

VEN-HMAs significantly improve OS compared to IC (HR =0.80, 95% CI 0.66–0.97) while maintaining comparable CR, CR/CRi, ORR and 30-day mortality.

OS benefits were similar in other subgroup analyses based on cytogenetic risk, age, and AML type.

OS subgroup analysis regarding mutations.



Mutations in NPM1 AML have been reported to be highly sensitive to VEN-based treatment regimens and our findings confirmed with this.

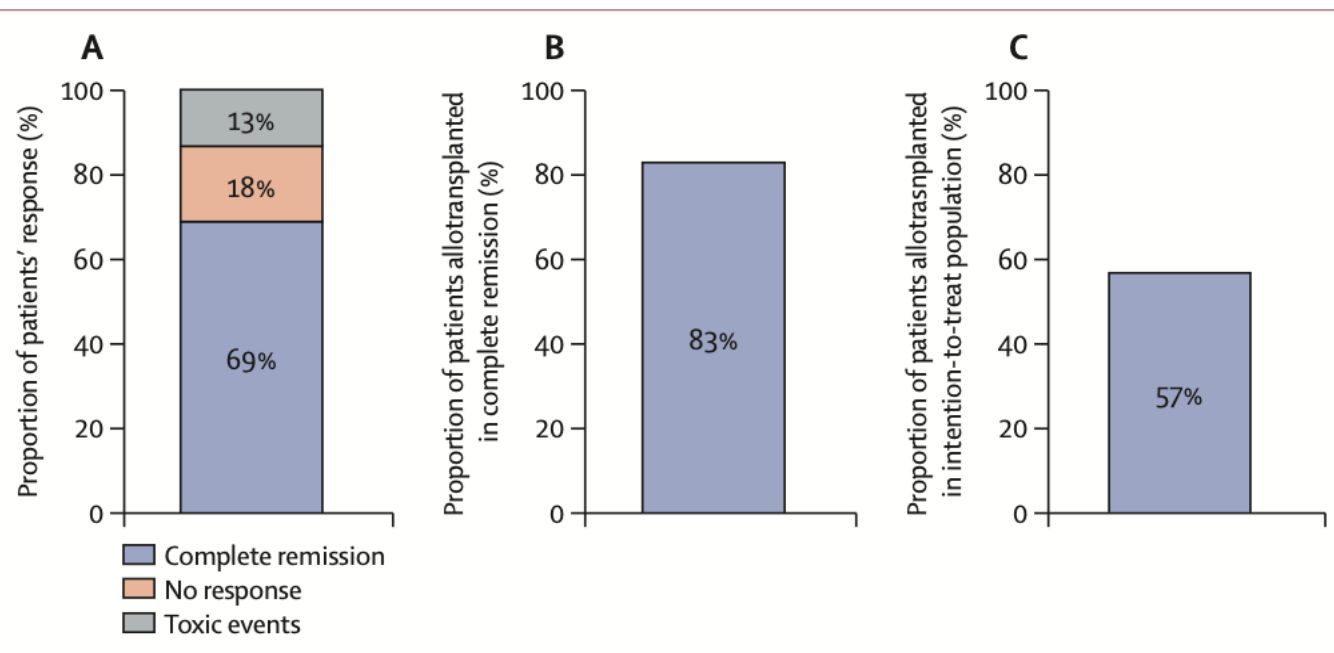
As the beneficial impact of NPM1 decreases with increasing age in patients treated with IC, based on our findings, we suggest VEN-HMAs as the optimal treatment for patients with this molecular subgroup, especially for elderly patients.

Our review showed similar survival benefits in the ASXL1, RAS, IDH1/2, TP53, FLT3, and RUNX1 mutation cohorts.

Venetoclax plus decitabine as a bridge to allogeneic haematopoietic stem-cell transplantation in older patients with acute myeloid leukaemia (VEN-DEC GITMO): final report of a multicentre, single-arm, phase 2 trial



Domenico Russo, Nicola Polverelli, Simona Bernardi, Stella Santarone, Mirko Farina, Erika Borlenghi, Francesco Onida, Luca Castagna, Stefania Bramanti, Angelo Michele Carella, Roberto Sorasio, Massimo Martino, Caterina Alati, Attilio Olivieri, Germana Beltrami, Antonio Curti, Calogero Vetro, Salvatore Leotta, Valentina Mancini, Elisabetta Terruzzi, Massimo Bernardi, Piero Galieni, Pellegrino Musto, Raffaella Cerretti, Luisa Giaccone, Cristina Skert, Vera Radici, Marika Vezzoli, Stefano Calza, Alessandro Leoni, Luca Garuffo, Cristian Bonvicini, Simone Pellizzeri, Michele Malagola, Fabio Ciceri



»Venetoclax plus decitabine can significantly enhance the feasibility of allogeneic HSCT in older patients with acute myeloid leukaemia who are deemed fit for transplantation at the time of diagnosis.»

Patients enrolled (n=93)	
Age, years	68.5 (60.3–74.7)
Sex	
Male	50 (54%)
Female	43 (46%)
Race	
White	93 (100%)
Eastern Cooperative Oncology Group score	
0	54 (58%)
1	32 (34%)
2	7 (8%)
Hematopoietic Stem Cell Transplantation Specific-Comorbidity Index	
Low (0)	43 (46%)
Intermediate (1–2)	33 (35%)
High (≥3)	17 (18%)
Italian Lymphoma Foundation score	
Unfit	23 (25%)
Fit	70 (75%)
Patients with comorbidities	50 (54%)
Haemoglobin count, g/dL	8.7 (8.2–9.7)
White blood cell count, × 10 ⁶ /L	3.4 (1.8–23.9)
Platelet count, × 10 ⁹ /L	53.0 (28.0–115.0)
Bone marrow blasts	40.0% (25.0–70.0)
Circulating blasts	8.0% (2.0–31.0)
Karyotype	
Normal	48 (52%)
Abnormal	41 (44%)
Complex	18 (19%)
Unavailable	4 (4%)
Molecular biology (RT-qPCR, nested-PCR, or HPLC)	
NPM1A	10 (11%)
FLT3-ITD	19 (20%)
FLT3-TKD (n=84)	1 (1%)
WT1 (n=64)	28 (44%)

VEN+HMA vs IC? Results of First Randomized Non-Inferiority Trial

Context of Research: Multicenter, Open-label, Randomized, Phase 2b Trial

- To evaluate the noninferiority of venetoclax plus decitabine (VEN-DEC) vs intensive chemotherapy (IC) as induction therapy in untreated young fit acute myeloid leukemia (AML) patients, with a 5% margin and 2.5% one-sided type I error.

Patients, Methods, and Main Findings



188 Patients

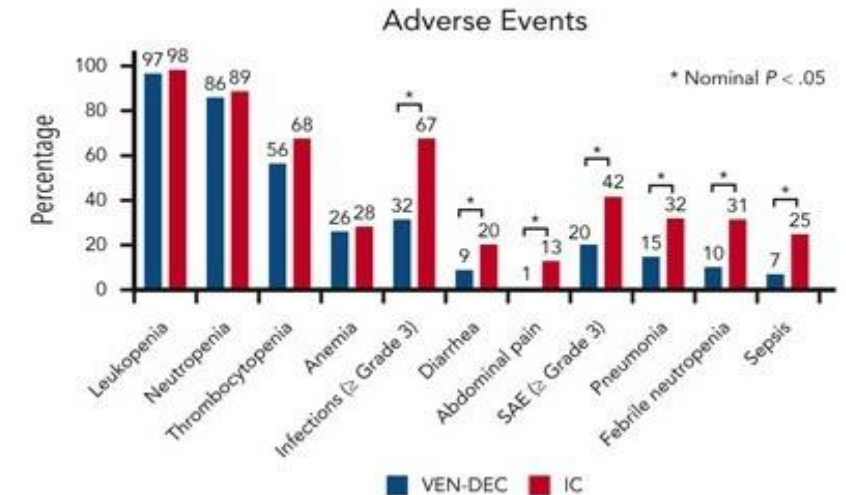
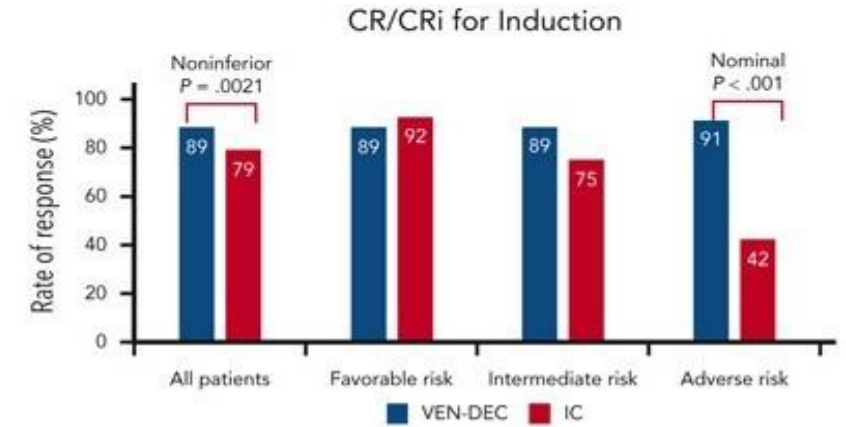
- Untreated AML
- 18-59 years old
- No extramedullary disease
- No prior Venetoclax /HMA use

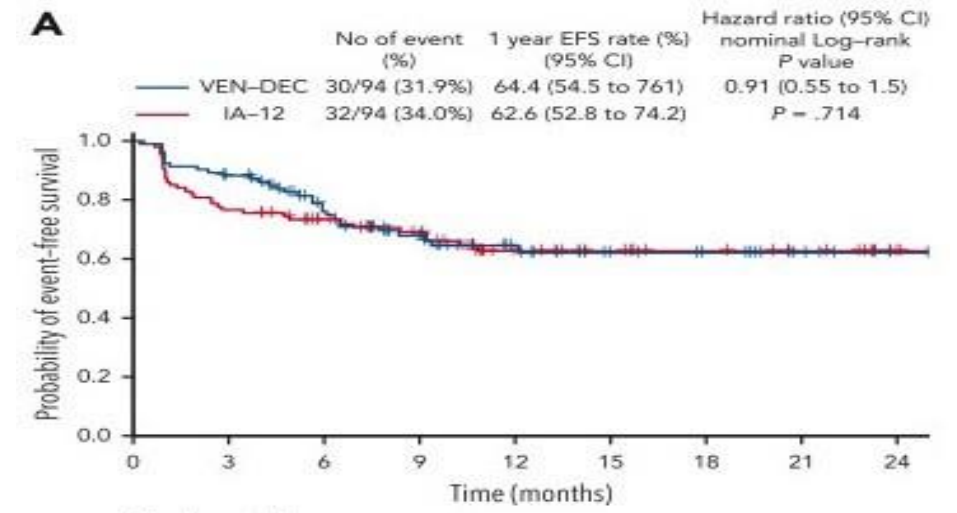
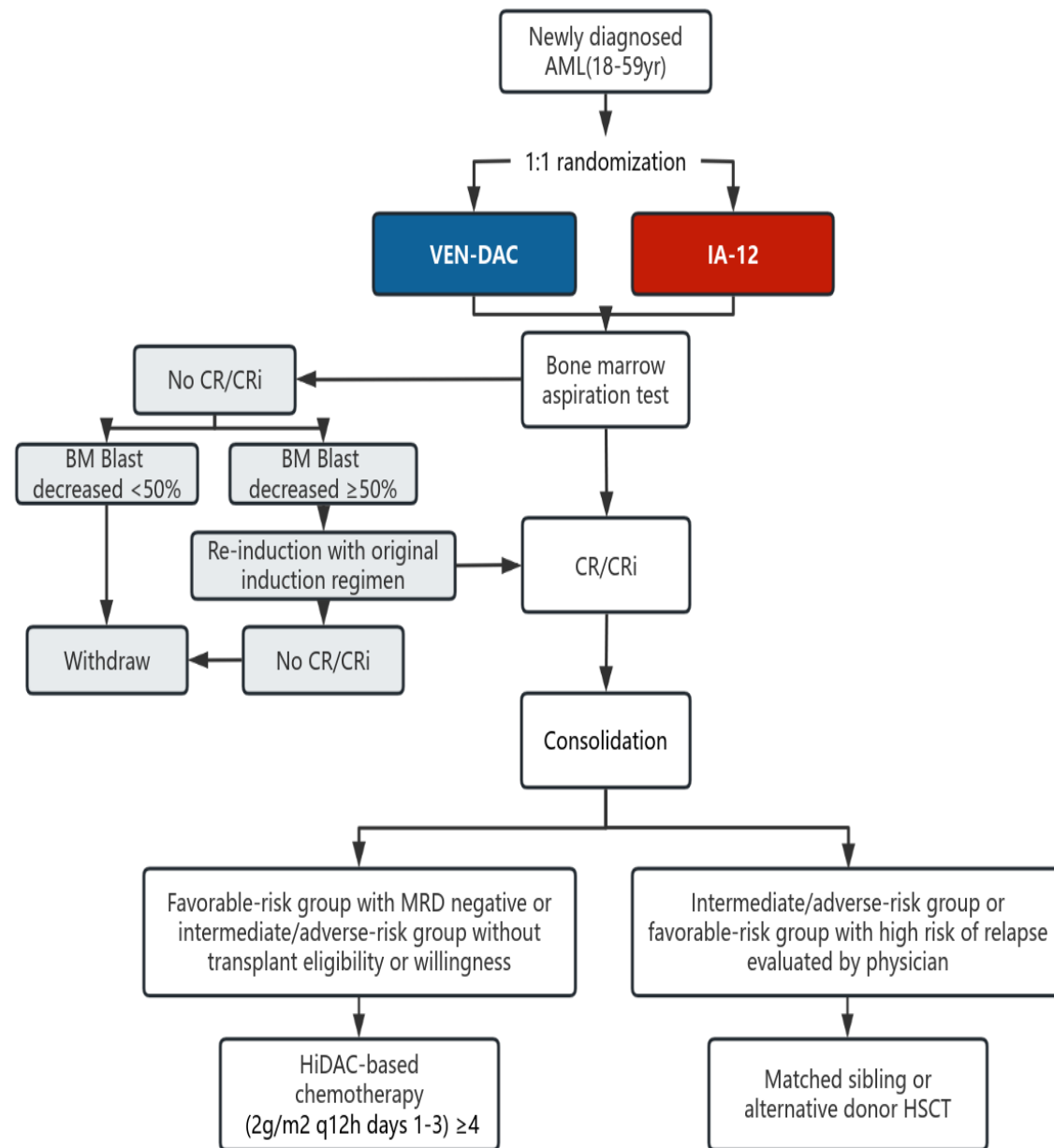
Induction/Reinduction

- VEN-DEC:
Venetoclax (target 400 mg/d) × 28d
Decitabine (20 mg/m²/d) × 5d
- IC:
Idarubicin (12 mg/m²/d) × 3d
Cytarabine (100 mg/m²/d) × 7d

Efficacy and safety assessment

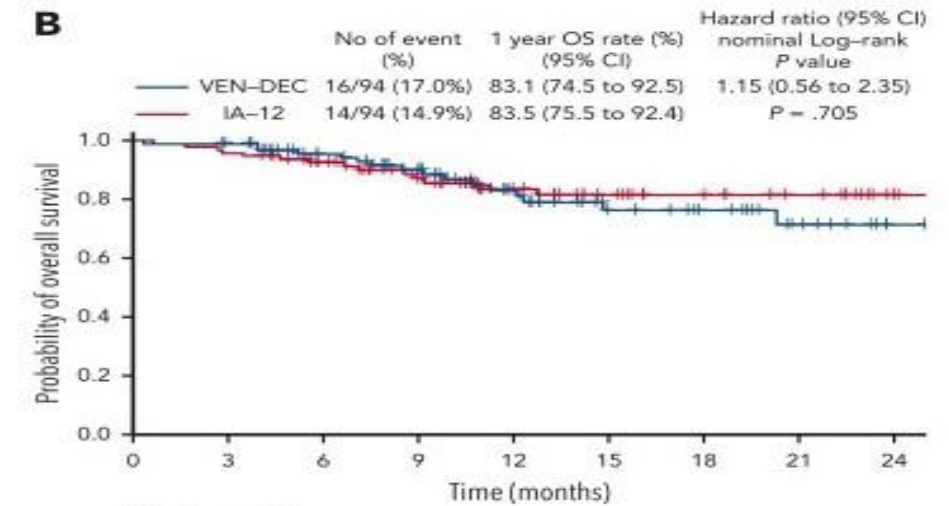
- Primary endpoint:
CR/CRi for Induction
- Secondary endpoints:
Safety, Survival, MRD negativity





Number at risk

	0	3	6	9	12	15	18	21	24
VEN-DEC	94	80	58	43	28	18	15	9	4
IA-12	94	72	58	47	29	20	15	11	4



Number at risk

	0	3	6	9	12	15	18	21	24
VEN-DEC	94	90	74	60	41	26	21	13	4
IA-12	94	90	75	59	41	29	21	15	5



American Society of Hematology

Helping hematologists conquer blood diseases worldwide

Results from PARADIGM - A phase 2 randomized multi-center study comparing azacitidine and venetoclax to conventional induction chemotherapy for newly diagnosed fit adults with AML

Amir T. Fathi¹, Alexander E. Perl², Geoffrey G. Fell³, Brian A. Jonas⁴, Brittany K. Ragon⁵, Alice S. Mims⁶, Uma Borate⁶, Gabriel N. Mannis⁷, Karen Quillen⁸, Maximilian Stahl^{3,9}, Paul Koller¹⁰, Andrew S. Artz¹⁰, Monzr M. Al Malki¹⁰, Guido Marcucci¹⁰, Mary Linton B. Peters⁸, Timothy A Graubert¹, Peter Westervelt¹, Philip C. Amrein¹, Hanno R. Hock¹, Andrew M. Brunner¹, Gabriela Hobbs¹, Rupa Narayan¹, Michelle H. Lee¹, Brandon J. Aubrey¹, Alyssa L. Watson¹, Richard Hao¹, Shilton Dhaver¹, Michael R. Grunwald⁵, Yi-Bin Chen¹, Andrew H. Matthews², Brent L. Wood¹¹, Chris S. Hourigan¹², Donna S. Neuberg³, Areej El-Jawahri¹, Ibrahim Aldoss¹⁰

1. Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA. 2. Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA. 3. Dana Farber Cancer Institute, Harvard Medical School, Boston, MA. 4. University of California Davis School of Medicine, Sacramento, CA. 5. Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC. 6. The Ohio State University Comprehensive Cancer Center, Columbus, OH. 7. Stanford Cancer Institute, Stanford University, Stanford, CA. 8. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA. 9. Yale University School of Medicine, New Haven, CT. 10. City of Hope National Medical Center, Duarte, CA. 11. Children's Hospital of Los Angeles, Los Angeles, CA. 12. Fralin Biomedical Research Institute, Virginia Tech FBRI Cancer Research Center, Washington, DC.

PARADIGM: Background

- Intensive induction chemotherapy with cytarabine and an anthracycline (7+3) has been the standard of care for fit patients with AML, yet clinical challenges persist, including significant toxicity and plateaued efficacy¹
- For patients not eligible for intensive chemotherapy, the BCL2 inhibitor venetoclax plus azacitidine is the standard of care based on survival benefits demonstrated in the phase III VIALE-A trial²
- Retrospective data suggest azacitidine + venetoclax may possess superior efficacy vs intensive chemotherapy in fit populations, but this hypothesis had not been validated in a prospective, randomized setting^{3,4}
- The randomized phase II PARADIGM trial was designed to prospectively compare azacitidine + venetoclax with conventional intensive chemotherapy (7+3 or CPX-351) in fit patients with newly diagnosed AML⁵

• 1. Okoniewski. Am Soc Clin Oncol Educ Book. 2025;45:e473646. 2. DiNardo. NEJM. 2020;383:617.
3. Cherry. Blood Adv. 2021;5:5565. 4. Matthews. Blood Adv. 2022;6:3997-4005.
5. Fathi. ASH 2025. Abstr 6.

PARADIGM: Study Design

- Randomized, multicenter phase II trial

- Stratified by age (≥ 65 vs < 65 yr) and prerandomization selection to 7+3 or CPX-351

Patients aged ≥ 18 yr with untreated AML eligible for intensive chemotherapy; no $t(15;17)$, $PML-RARA$, CBF alteration, $FLT3$ ITD/TKD ($\geq 5\%$ VAF), $NPM1$ mutations (if age < 60 yr), $BCR::ABL1$ fusion, or mixed phenotype (N = 172)

Aza/Ven
Azacitidine +
venetoclax
(n = 86)

BM biopsy
D21-31

Aza/Ven
Cycle 2+

Conventional IC
7+3 or CPX-351
(n = 86)

If residual
disease

Second induction
(5+2 or CPX-351)

BM biopsy
D13-16

If ablation

**Assess count recovery,
then consolidation with
cytarabine or CPX-351**

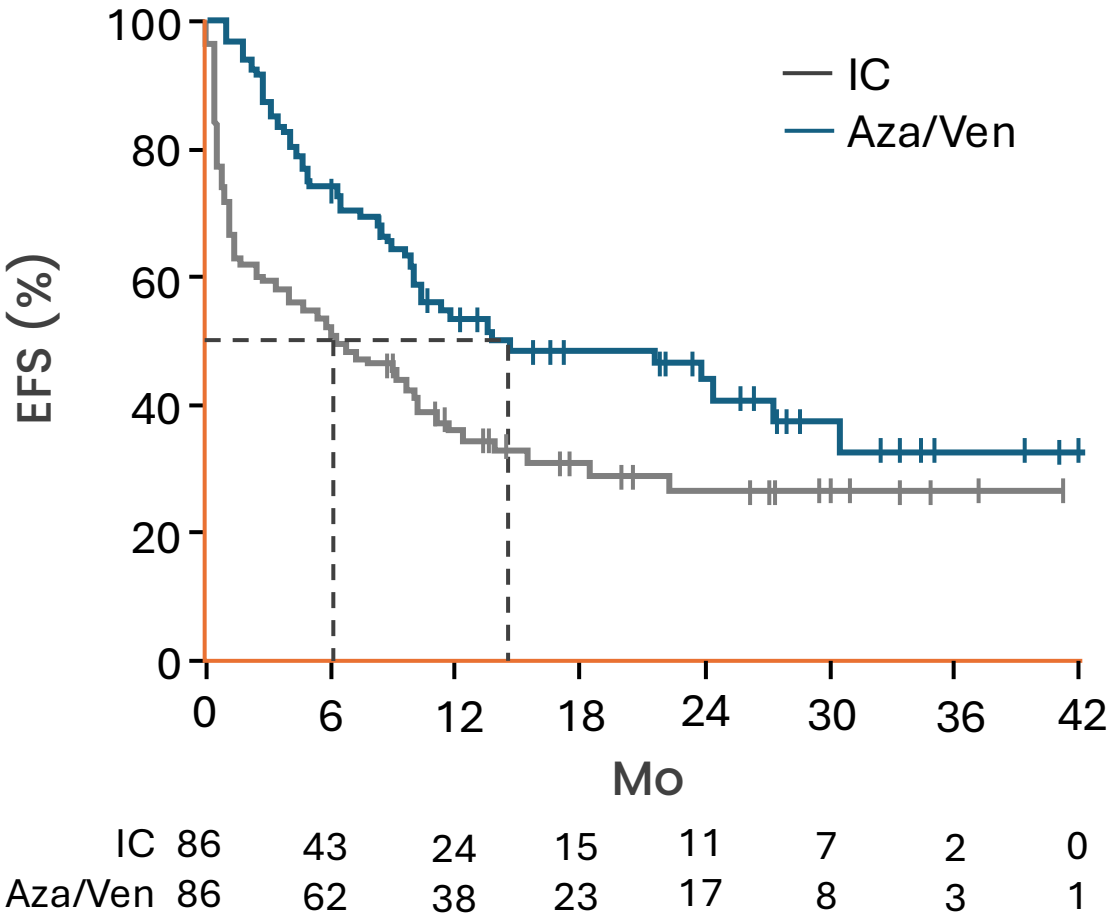
HSCT
allowed
at any
time
following
disease
response

- Primary endpoint:** EFS
- Secondary endpoints:** response, OS, toxicity, MRD, hospitalization metrics, QoL

PARADIGM: Baseline Characteristics

Characteristic	All Patients (N = 172)	Aza/Ven (n = 86)	IC (n = 86)
Median age, yr (range)	64 (23-79)	65 (23-79)	64 (28-79)
Age ≤65 yr, n (%)	87 (50.6)	43 (50.0)	44 (51.2)
Male, n (%)	115 (66.9)	55 (64.0)	60 (69.98)
Race, n (%)			
▪ White	134 (77.9)	65 (75.6)	69 (80.2)
▪ Black	10 (5.8)	5 (5.8)	5 (5.8)
▪ Hispanic	13 (7.6)	6 (7.0)	7 (8.1)
▪ Asian	15 (8.7)	10 (11.6)	5 (5.8)
ECOG PS, n (%)			
▪ 0/1	161 (93.6)	79 (91.9)	82 (95.4)
▪ 2	10 (5.8)	7 (8.1)	3 (3.5)
ELN 2022 risk, n (%)			
▪ Favorable	22 (12.8)	13 (15.1)	9 (10.5)
▪ Intermediate	26 (15.1)	15 (17.4)	11 (12.8)
▪ Adverse	124 (72.1)	58 (67.4)	66 (76.7)
Mutations, n (%)			
▪ <i>NPM1</i>	16 (9.3)	11 (12.8)	5 (5.8)
▪ <i>IDH1</i>	15 (8.7)	8 (9.3)	7 (8.1)
▪ <i>IDH2</i>	28 (16.3)	19 (22.1)	9 (10.5)
▪ <i>TP53</i>	25 (14.5)	9 (10.5)	16 (18.6)
▪ <i>RUNX1</i>	32 (18.6)	14 (16.3)	18 (20.9)
▪ <i>KRAS/NRAS</i>	32 (18.6)	17 (19.8)	15 (17.5)

PARADIGM: EFS



	Aza/Ven (n = 86)	IC (n = 86)	HR (P Value)
Median EFS, mo	14.6	6.15	0.57 (.0022)
1-yr EFS, %	53.4	36.0	

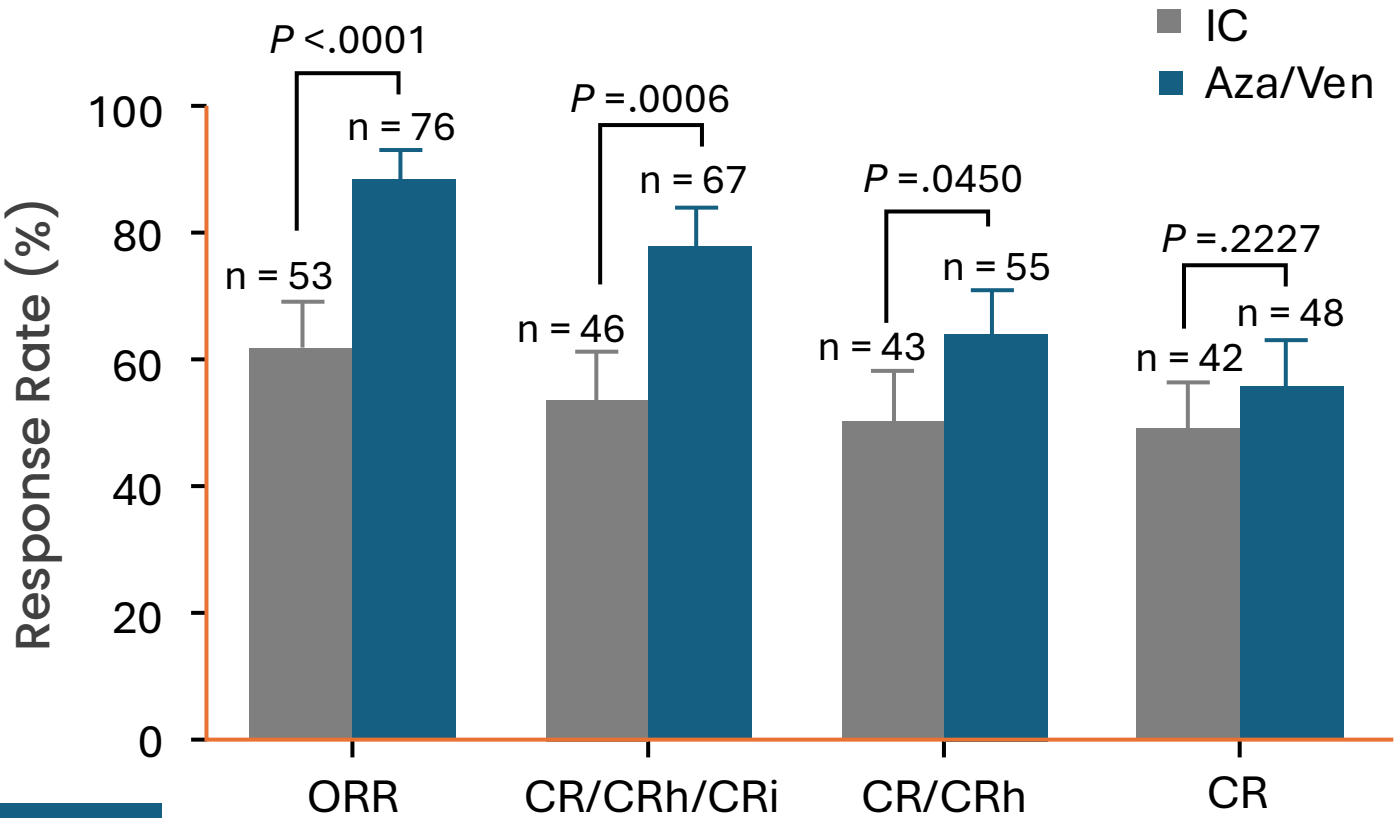
- In a multivariate analysis, the adjusted HR for EFS with aza/ven vs IC remained significant (HR: 0.66; $P = .0231$)

Median follow-up of 21.9 mo.

PARADIGM: Response

Parameter	Aza/Ven (n = 86)	IC (n = 86)
Best response, %		
• CR	55.8	48.8
• CRh	8.1	1.2
• CRi	14.0	3.5
• MLFS	8.1	4.7
• PR	2.3	3.5
• Refractory	10.5	27.9
• Not evaluable	1.2	10.5

Outcome	Aza/Ven (n = 86)	IC (n = 86)	P Value
Proceeding to HSCT, n	52*	34	.009
Median OS, mo	21.5	18.6	.1873



• Fathi. ASH 2025. Abstr 6. Reproduced with permission.

PARADIGM: PROs and Healthcare Utilization

Wk 2 PRO Score (95% CI)	Aza/Ven (n = 86)	IC (n = 86)	P Value
FACT-Leukemia (QoL)	126.1 (121.9-130.3)	115.4 (110.7-120.2)	.001
HADS (Anxiety)	4.3 (3.6-5.0)	4.6 (3.8-5.4)	.565
HADS (Depression)	4.8 (4.0-5.6)	6.9 (6.0-7.9)	.0007
ESAS (Symptom burden)	22.2 (18.7-26.6)	28.6 (24.6-32.6)	.0186

Healthcare Utilization Parameter	Aza/Ven (n = 86)	IC (n = 86)	P Value
Index hospitalization length of stay, days	14.8	35.9	< .001
Hospital days in first 6 mo, days	41.0	58.5	< .001
ICU admission in first 30 days, %	0	9.6	.003

PARADIGM: Safety

Grade ≥3 AEs in ≥10% of Patients, n (%)	Aza/Ven (n = 86)			IC (n = 86)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Febrile neutropenia	46 (53.5)	3 (3.5)	0	51 (62.2)	1 (1.2)	0
Platelet count decreased	8 (9.3)	38 (44.2)	0	3 (3.7)	47 (57.3)	0
Anemia	34 (39.5)	1 (1.2)	0	35 (40.7)	3 (3.5)	0
Neutrophil count decreased	1 (1.2)	48 (55.8)	0	1 (1.2)	39 (47.6)	0
WBC decreased	2 (2.3)	24 (27.9)	0	0	20 (24.4)	0
Lymphocyte count decreased	11 (12.8)	6 (7.0)	0	9 (11.0)	8 (9.8)	0
Lung infection	12 (14.0)	0	0	11 (15.6)	2 (2.4)	2 (2.4)
Sepsis	5 (5.8)	1 (1.2)	0	10 (12.2)	2 (2.4)	0
Anorexia	4 (4.7)	0	0	12 (14.6)	0	0
Hypoxia	4 (4.7)	0	0	7 (8.5)	2 (2.4)	0

Compared with IC, aza/ven was associated with significantly lower rates of grade ≥3 infection (15.1% vs 20.8%; OR: 0.53; $P = .04$) and bleeding (1.3% vs 6.3%; OR: 0.16; $P = .01$) and a trend toward lower 60-day mortality rate (0% vs 4.7%; $P = .0802$)

PARADIGM: Investigator's Conclusions

- Randomized phase II PARADIGM trial met its primary endpoint, demonstrating that azacitidine + venetoclax significantly improves EFS vs IC in fit, newly diagnosed adults with AML
- Azacitidine + venetoclax induced deeper and more frequent responses than IC (ORR: 88% vs 62%) and allowed a significantly higher proportion of patients to successfully bridge to allogeneic HSCT
- The investigative regimen challenged the historical toxicity burden of induction therapy, showing lower early mortality (0% vs 4.7%), reduced healthcare utilization (shorter hospital stays/ICU use), and superior PROs/QoL
- The investigators suggested that these findings support the use of azacitidine + venetoclax in fit patients with newly diagnosed intermediate-risk or adverse-risk *FLT3*-wild type AML

What effect, if any, do you expect the plenary presentation of the PARADIGM trial (azacitidine and venetoclax versus conventional induction chemotherapy for fit patients with newly diagnosed AML) will have on current clinical management?



Dr Erba

More oncologists will adopt ven/HMA for ELN 2022 adverse-risk disease



Dr Fathi

HMA and venetoclax is acceptable in younger, fit patients with intermediate- or adverse-risk, FLT3-WT AML



Dr Lin

Many will adopt this, especially for intermediate/high-risk AML proceeding to transplant. This will impact ongoing/planned clinical trials and potentially adjust control arms away from 7 + 3



Dr Perl

Much less 7 + 3 will be given for ELN 2022 adverse-risk AML and perhaps generally in patients who plan to proceed to transplant in CR1



Dr Stein

More physicians will use aza/ven for patients with adverse risk around the age of 60-65 and above



Dr Cortes

I expect some use in general practice but not full adoption. It may allow for more patients treated in the community



Dr DiNardo

In the US, I think it will lead to a substantial increase in the number of patients “induced” with HMA + ven, often in their local community practice



Dr Wang

May lead to clinicians offering fit patients with adverse-risk AML induction with HMA/ven instead of SOC 7 + 3

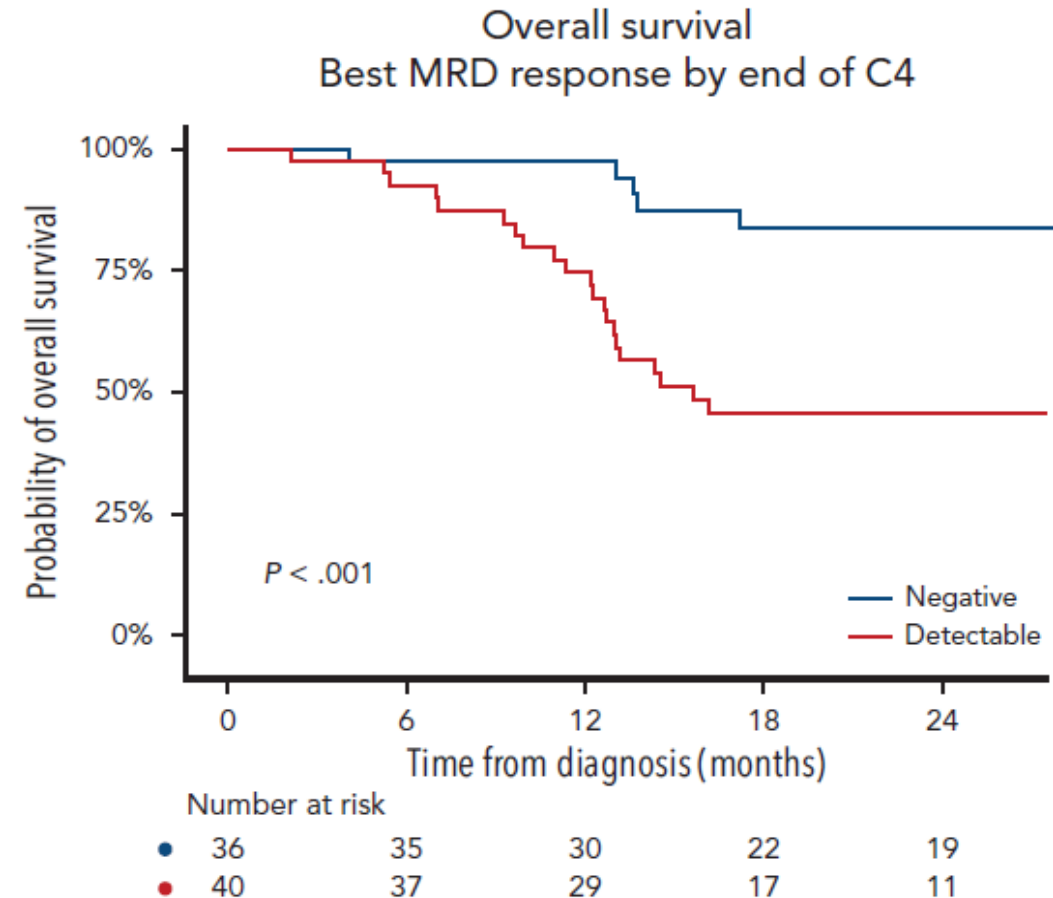
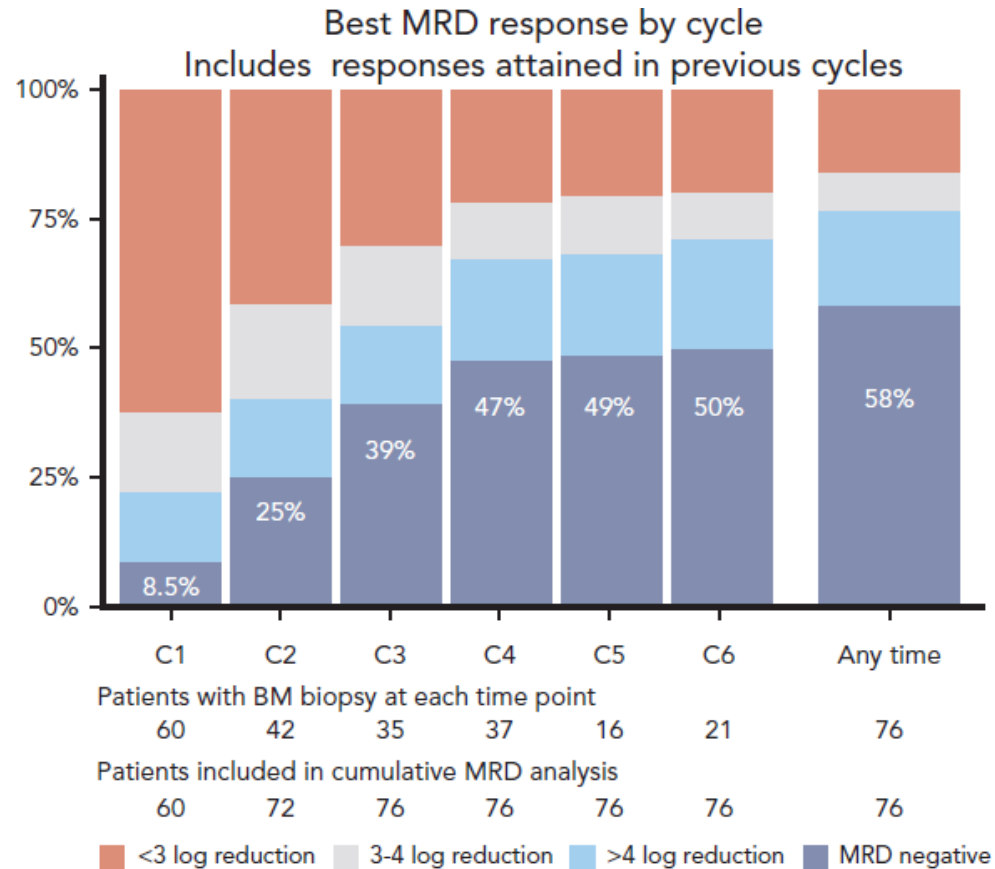
NPM1-mutated AML

- Represents one of the most venetoclax-sensitive genotypes, with venetoclax + azacitidine (ven/aza) achieving high composite complete remission (CRc) rates, durable remissions, and favorable MRD clearance in this molecular subgroup.
- In the VIALE-A trial, patients with *NPM1* mutations treated with ven/aza achieved a CRc rate of 66.7%(95% CI, 46.0–83.5) compared to 23.5% with azacitidine alone (P=0.012).
- NPM1 molecular MRD monitoring is strongly prognostic in patients receiving venetoclax-based low-intensity therapy.
- Primary and adaptive resistance was most commonly characterized by acquisition or enrichment of clones activating signaling pathways such as *FLT3* or *RAS*, or biallelically perturbing *TP53*.

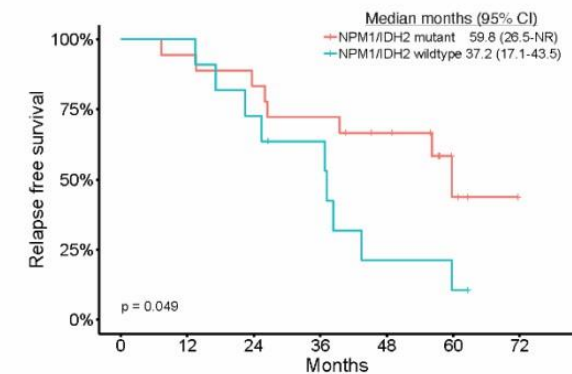
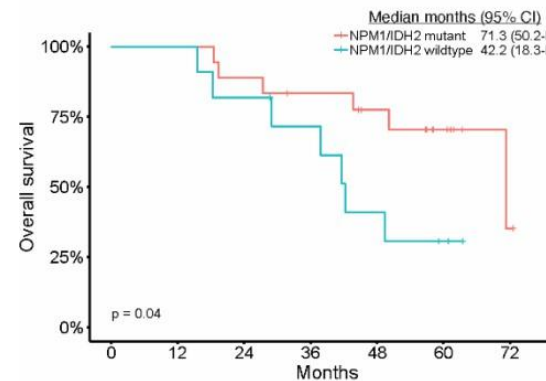
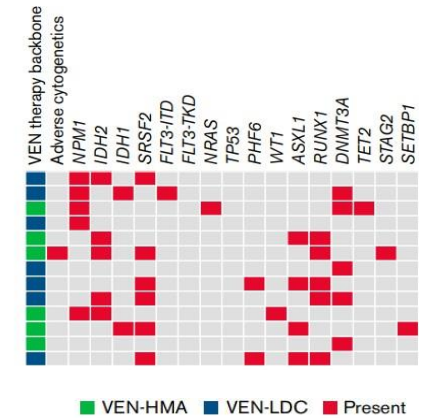
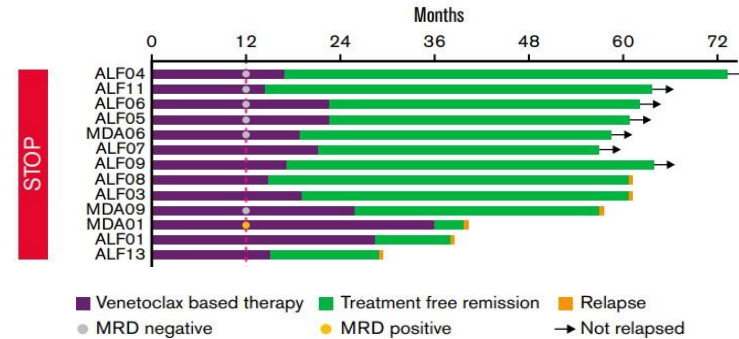
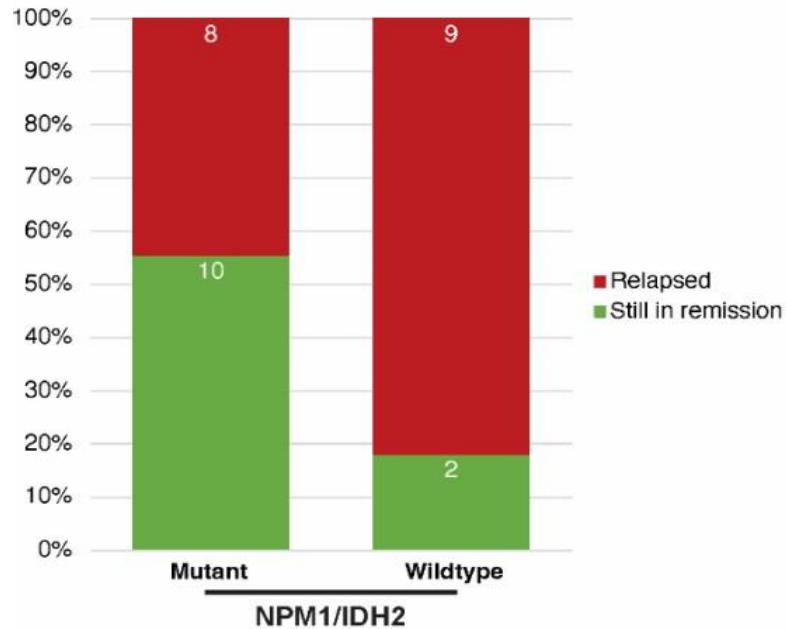
Lancet. 2023. DiNardo CD, Erba HP, Freeman SD, Wei AH.

Blood. 2024. Othman J, Tiong IS, O'Nions J, et al.

VEN/HMA As Initial Treatment of Adults with *NPM1*m AML



Treatment Free Remission May Be Possible for *NPM1*- and *IDH2*-Mutated AML Patients in MRD Negative CR After Venetoclax-Based Less Intensive Therapy



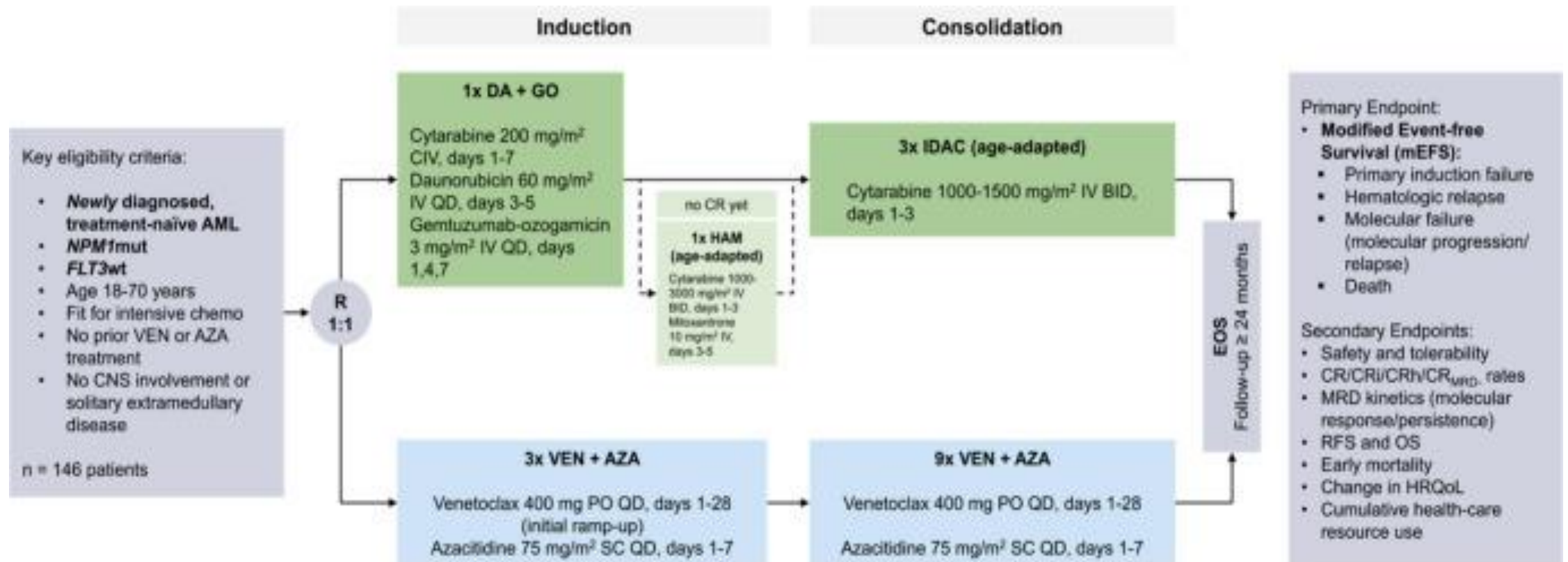
- Of the 7 subjects remaining in a treatment free remission (TFR), 6 had *NPM1* or *IDH2* mutations.
- At least five of these six had achieved an MRD negative CR by 12 months VEN/AZA or VEN/ARA-C
- One subject with both *NPM1* and *IDH2* mutation in an MRD negative CR by 12 months VEN/AZA or VEN/ARA-C, relapsed after 3-year TFR

Post-Remission Strategies in NPM1-Mutated Acute Myeloid Leukemia.

Post-Remission Strategy	Patient Indications	Advantages	Limitations/Risks	Supporting Evidence
Active Observation	MRD-negative patients without additional genetic risks	Avoids treatment toxicity; maintains good quality of life	Risk of relapse if MRD monitoring is inadequate	Retrospective study by Chua et al. [7], prospective study by DiNardo et al. [14]
Maintenance with Venetoclax	Patients in molecular remission without persistent MRD	Potential prolongation of remission duration	Lack of randomized trial evidence; empirical approach	Retrospective data from SEER, CIBMTR registries [10]; NCCN guidelines [20]
Allogeneic Transplant	MRD-positive patients or those with high-risk mutations	Potentially definitive treatment via graft-versus-leukemia effect	Transplant-related toxicity and mortality	NILG and Fraccaroli et al. studies [21]; EBMT guidelines [22]

VINCENT: A randomized-controlled trial evaluating venetoclax plus azacitidine versus intensive chemotherapy in patients with newly diagnosed, *NPM1*-mutated AML

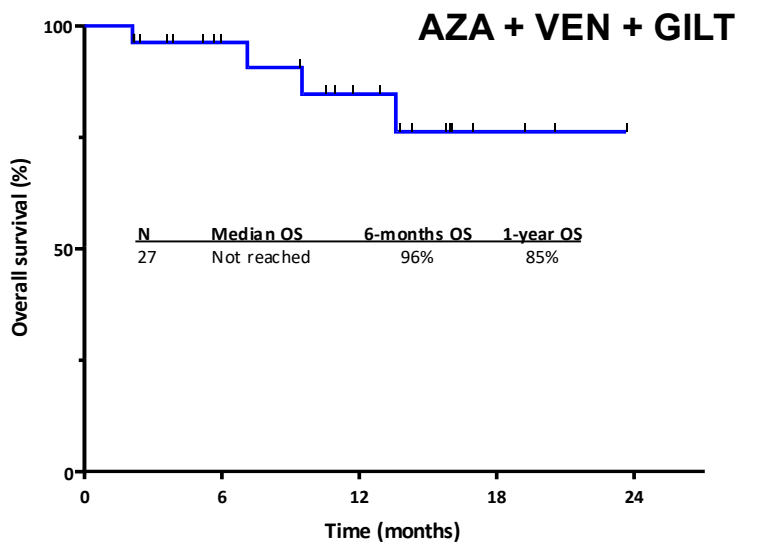
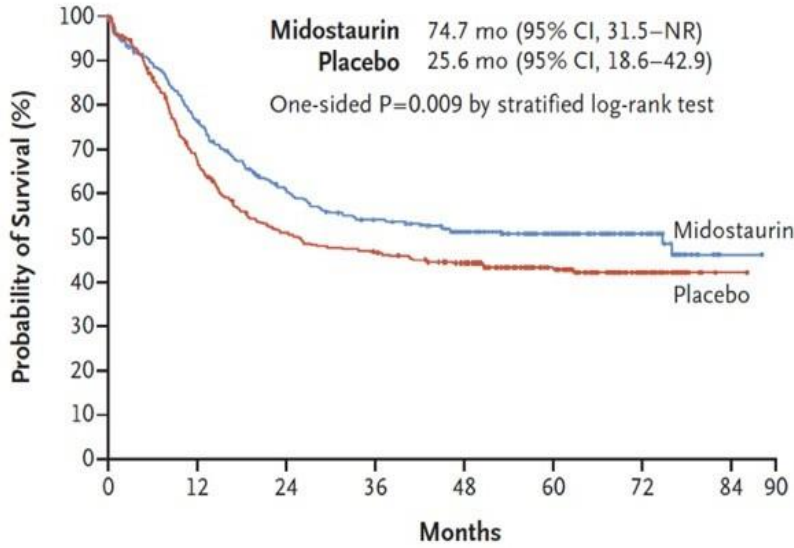
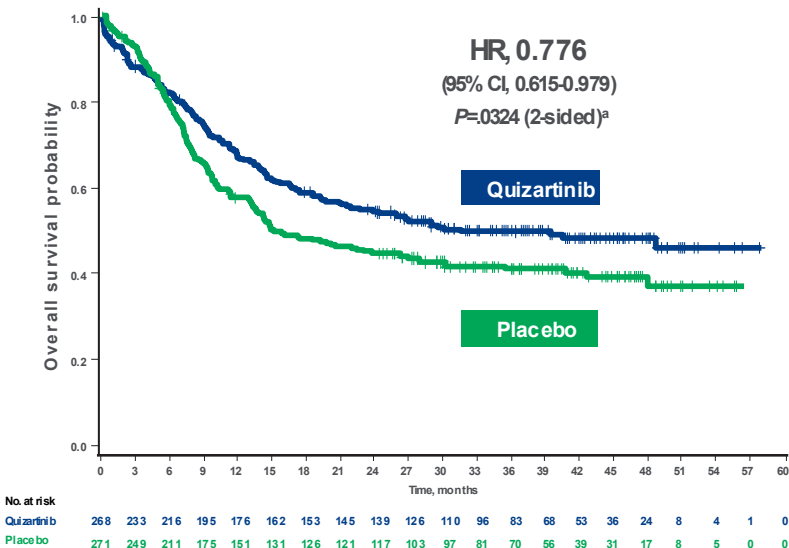
Lydia Kretschmer¹ · Leo Ruhnke¹ · Christoph Schliemann² · Lars Fransecky³ · Björn Steffen⁴ · Martin Kaufmann⁵ · Andreas Burchert⁶ · Christoph Schmid⁷ · Maher Hanoun⁸ · Tim Sauer⁹ · Klaus H. Metzeler¹⁰ · Kerstin Schäfer-Eckart¹¹ · Mathias Hänel¹² · Martina Crysandt¹³ · Paul Jäger¹⁴ · Stefan W. Krause¹⁵ · Christine Dierks¹⁶ · Stefan Klein¹⁷ · Nadia Maguire¹⁸ · Lukas P. Frenzel¹⁹ · Veit L. Bücklein²⁰ · Wolfgang Blau²¹ · Ulrich Kaiser²² · Kai Wegehenkel²³ · Alexander Höllein²⁴ · Ruth Seggewiss-Bernhardt^{25,26} · Wenke Markgraf¹ · Frank Fiebig¹ · Anna Harig¹ · Katharina Schmidt-Brücken¹ · Christian Thiede^{1,27} · Jan Moritz Middeke¹ · Richard Dillon²⁸ · Claudia D. Baldus³ · Hubert Serve⁴ · Karsten Spiekermann²⁰ · Wolfgang Hiddemann²⁰ · Richard F. Schlenk⁹ · Carsten Müller-Tidow⁹ · Martin Bornhäuser¹ · Christoph Röllig¹



Could triplet therapies (i.e. HMA+VEN+FLT3i) be effective option even for younger/fitter pts?

QUIZZICAL: Randomized Ph II HMA+VEN+Quiz vs IC+QUIZ for FLT3-ITD AML(50-75 yr)

UK-MRC and US sites
PIs: Craddock and Daver



Conclusions

- ▶ HMA/Ven achieves remissions at rates comparable to conventional chemotherapy.
- ▶ Prospective and Real-World data suggest comparable outcomes to induction with conventional therapy
- ▶ Future randomized studies will be needed to determine best frontline therapy
- ▶ Best frontline therapy will likely be dependent on molecular drivers