

Azacitidine and Venetoclax versus Induction Chemotherapy for Untreated Acute Myeloid Leukemia (AML)

Fathi AT, Perl AE, H, Fell GG, et al.

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- **Venclexta® (venetoclax) is not FDA-approved in combination with azacitidine for AML in fit patients eligible for induction chemotherapy.**
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- This reprint summary concerns information not contained within the approved product labeling for Venclexta, and therefore may contain information for which the safety and effectiveness has not yet been established. Individual treatment decisions should be made, based upon the prescribing physician's determination of the benefits and risk.
- **Venclexta is approved:**
 - for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
 - in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
- **Contraindications**
 - Concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase in patients with CLL/SLL is contraindicated.
- **Warnings and Precautions**
 - Tumor lysis syndrome, Neutropenia, Infections, Immunization, Embryo-Fetal Toxicity, Treatment of patients with multiple myeloma with Venclexta in combination with bortezomib plus dexamethasone is not recommended outside of clinical trials.
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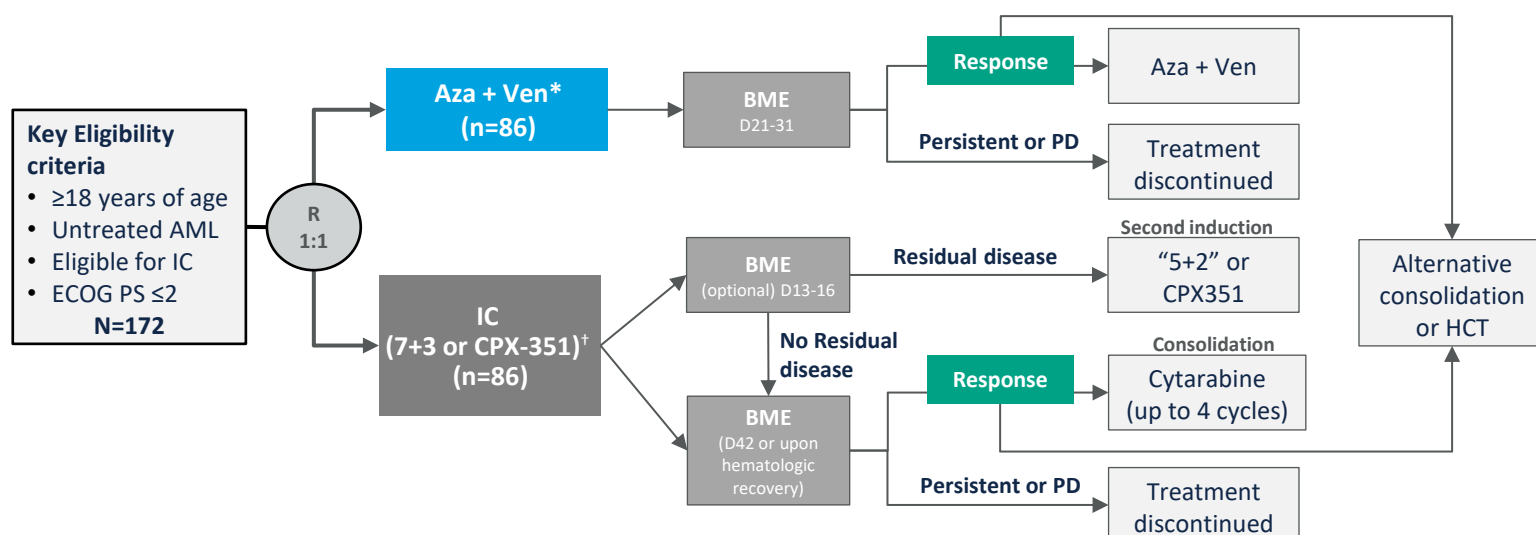
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STUDY DESIGN AND METHODS



PARADIGM is a Phase 2, randomized, open-label, multi-center, investigator-initiated study designed to assess the efficacy and safety of Aza-Ven vs induction chemotherapy (IC) in untreated, IC-eligible AML patients.



Primary endpoint: EFS[‡]

Select secondary endpoints: CR, CRh, CRi, CCR (CR+CRh+CRi), PR, MLFS, Overall Response, OS, transition to HCT, toxicity, MRD, healthcare utilization metrics

Notes: *28-day cycles of azacitidine 75mg/m² IV D1-7 and venetoclax 400mg D1-28. [†]7+3" (cytarabine 200mg/m² IV D1-7 and idarubicin 12mg/m² [or daunorubicin 60mg/m²] D1-3) or CPX351 (IV liposomal daunorubicin-cytarabine 44-100mg/m² D1,3,5), with choice of "7+3" or CPX351 preselected by investigators before randomization. [‡]EFS was defined as the time from randomization to the first event of progressive disease, persistent disease prompting therapy change, relapse, hospice, or death.

Abbreviations: AML=acute myeloid leukemia; Aza=azacitidine; BME=bone marrow evaluation; CCR=composite complete remission; CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete count recovery; D=day; ECOG PS=Eastern Cooperative Oncology Group performance status; EFS=event-free survival; HCT=hematopoietic stem cell transplantation; IC=induction chemotherapy; MLFS=morphologic leukemia-free state; MRD=measurable residual disease; OS=overall survival; PD=progressive disease; PR=partial remission; PROs=patient-reported outcomes; R=randomized; Ven=venetoclax

EXCLUSION CRITERIA



Key exclusion criteria included patients with:

- t(15:17) translocation
- CBF alterations
- *FLT3* mutations with ≥5% VAF
- *NPM1* mutations (if <60 years of age)

Abbreviations: CBF=core binding factor; FLT3=FMS-like tyrosine kinase 3; NPM1=nucleophosmin 1; VAF=variant allele frequency

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SELECT PATIENT CHARACTERISTICS



Characteristic	Aza-Ven (n=86)	IC (n=86)
Age, median (range), y	65 (23-79)	64 (28-79)
≥65 y, n (%)	43 (50)	42 (49)
Sex, male, n (%)	55 (64)	60 (70)
ECOG, n (%)		
0	30 (35)	38 (44)
1	49 (57)	44 (51)
2	7 (8)	3 (3)
Secondary AML, n (%)		
AML-MRC	50 (58)	46 (53)
t-AML	4 (5)	1 (1)
ELN 2022 risk status, n (%)		
Favorable	13 (15)	9 (10)
Intermediate	15 (17)	11 (13)
Adverse	58 (67)	66 (77)
Mutations — no. (%)		
NPM1	11 (13)	5 (6)
IDH1	8 (9)	7 (8)
IDH2	19 (22)	9 (10)
DNMT3A	22 (26)	18 (21)
TP53	10 (12)	16 (19)
RUNX1	17 (20)	22 (26)
CEBPA	5 (6)	6 (7)
KRAS	6 (7)	5 (6)
NRAS	12 (14)	13 (15)

Notes: Data analysis cutoff: October 17, 2025. Median number of cycles was 4 for Aza-Ven and 2 for IC. Median duration of Ven administration was 28 days for cycles 1 and 2, and 21 days for cycle 3.

Abbreviations: AML=acute myeloid leukemia; Aza=azacitidine; ECOG=Eastern Cooperative Oncology Group; ELN=European Leukemia Net; IC=induction chemotherapy; MRC=MDS-related changes; t-AML, therapy-related AML; Ven=Venetoclax.

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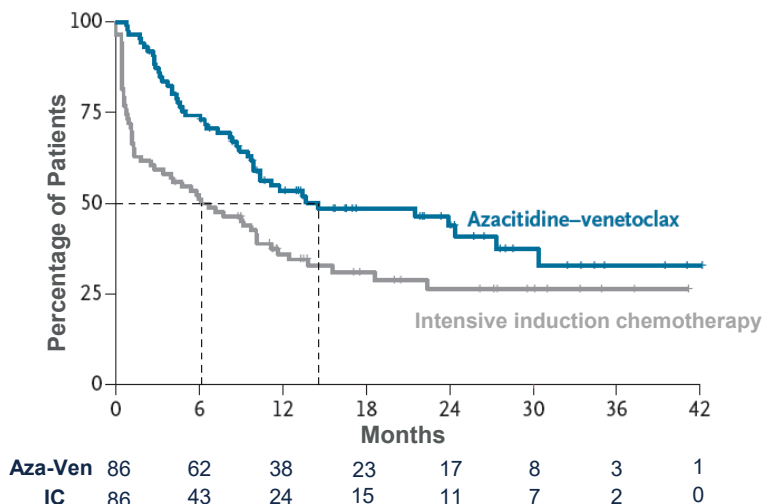
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RESULTS



Primary Endpoint: EFS

EFS	Aza-Ven (n=86)	IC (n=86)
Events, n	46	59
Median (95% CI), mo	14.5 (10.4-24.4)	6.2 (4.1-10.1)
HR (95% CI)	0.57 (0.39-0.84)	
Stratified P value	0.002	
1-year EFS, %	53	36
A post-hoc analysis of EFS per ELN 2022		
Median, mo	11.8	4.03
HR (95% CI)	0.62 (0.42-0.91)	



Notes: The median follow-up for all patients was 21.9 months (95%CI: 16.6-25.7)

Abbreviations: Aza=azacitidine; CI=confidence interval; EFS=event-free survival; ELN=European Leukemia Net; HR=hazard ratio; IC=induction chemotherapy; mo=months.

Secondary Endpoints

	Aza-Ven (n=86)	IC (n=86)
Response rates		
Overall Response*, n (%) [95% CI]	76 (88.4) [79.7-94.3]	53 (61.6) [50.5-71.9]
CCR [†] , n (%) [95% CI]	67 (77.9) [67.7-86.1]	46 (53.5) [42.4-64.3]
CR + CRh, n (%) [95% CI]	55 (64) [52.9-74]	43 (50) [39-61]
CR, n % [95% CI]	48 (55.8) [44.7-66.5]	42 (48.8) [37.9-59.9]
Best response		
CRh, n (%)	7 (8.1)	1 (1.2)
CRi, n (%)	12 (14)	3 (3.5)
PR, n (%)	2 (2.3)	3 (3.5)
MLFS, n (%)	7 (8.1)	4 (4.7)
HCT rate, % (95% CI)	60 (53-68)	40 (32-47)
Median OS (95% C), mo	21.5 (17.2-NR)	18 (12.5-NR)
MRD-negativity		
At time of CCR ^{†‡} , % (95% CI)	71 (59-82)	74 (57-87)
Within 30 days before HCT [§] , % (95% CI)	91 (79-98)	82 (60-95)
Healthcare utilization		
Median duration of hospitalization (during first 30 days), days (IQR)	10 (8)	30 (5)
Median inpatient days (during first 6 months), days (IQR)	35 (38)	57 (31)
ICU admission, %	0	9.8

Notes: *Overall response includes CR+CRi+PR+MLFS. [†] CCR includes CR+CRh+CRi. [‡] n=63 for Aza-Ven; n=38 for IC of patients evaluable for MRD at CCR. [§] n=45 for Aza-Ven; n=22 for IC of patients evaluable for MRD before HCT.

Abbreviations: Aza=azacitidine; CCR=composite complete remission; CI=confidence interval; CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; FACT-Leukemia=Functional Assessment of Cancer Therapy-Leukemia; HCT=hematopoietic stem cell transplantation; IC=induction chemotherapy; ICU=intensive care unit; MLFS=morphologic leukemia-free state; mo=months; MRD=measurable residual disease; NR=not reached; ORR=overall response rate; OS=overall survival; PR=partial remission; Ven=venetoclax.

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SAFETY



Grade ≥3 TEAEs in ≥10% of Patients*

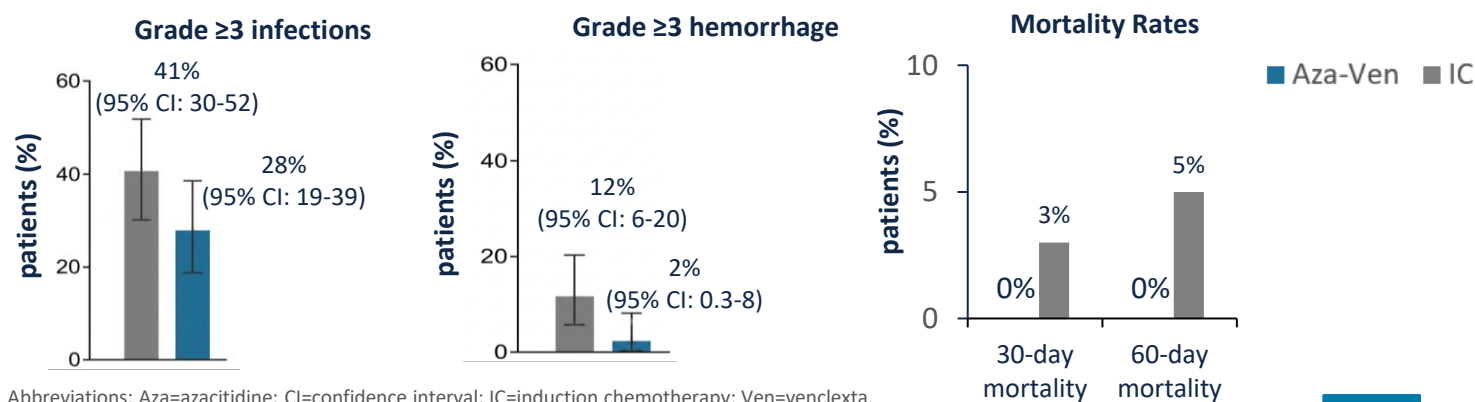
Toxicities	Aza-Ven (N=86)				IC (N=82)			
	Grade 3	Grade 4	Grade 5	Grade ≥3	Grade 3	Grade 4	Grade 5	Grade ≥3
Febrile neutropenia	46 (53)	3 (4)	0 (0)	49 (57)	51 (62)	1 (1)	0 (0)	52 (63)
Platelet count decreased	8 (9)	38 (44)	0 (0)	46 (53)	3 (4)	47 (57)	0 (0)	50 (61)
Anemia	34 (40)	1 (1)	0 (0)	35 (41)	35 (43)	3 (4)	0 (0)	38 (46)
Neutrophil count decreased	1 (1)	48 (56)	0 (0)	49 (57)	1 (1)	39 (48)	0 (0)	40 (49)
White blood cell decreased	2 (2)	24 (28)	0 (0)	26 (30)	0 (0)	20 (24)	0 (0)	20 (24)
Lymphocyte count decreased	11 (13)	6 (7)	0 (0)	17 (20)	9 (11)	8 (10)	0 (0)	17 (21)
Lung infection	12 (14)	0 (0)	0 (0)	12 (14)	11 (13)	2 (2)	2 (2)	15 (18)
Sepsis	5 (6)	1 (1)	0 (0)	6 (7)	10 (12)	2 (2)	0 (0)	12 (15)
Anorexia	4 (5)	0 (0)	0 (0)	4 (5)	12 (15)	0 (0)	0 (0)	12 (15)
Hypoxia	4 (5)	0 (0)	0 (0)	4 (5)	7 (9)	2 (2)	0 (0)	9 (11)

Notes: *Adverse events were assessed throughout the course of trial treatment in both groups and for an additional 30 days after the conclusion of trial treatment. Some patients had multiple reported grade 3 or higher adverse events.

Abbreviations: Aza=azacitidine; IC=induction chemotherapy; TEAEs=treatment-emergent adverse events; Ven=venetoclax.

Additional Safety Results

- Three episodes of **Grade 3 tumor lysis syndrome** were reported with Aza-Ven.



LIMITATIONS



Study limitation that can introduce bias include the following:

- No blinded central review of events was performed, and assessments were made in real time by treating clinicians.
- The trial was conducted at 9 academic centers with varying management approaches and patient populations.

Trial was designed with examination at a one-sided 0.10 level of significance. Two-sided 95% confidence intervals are presented in accordance with the journal policy.

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