

Azacitidine–Venetoclax or Induction Chemotherapy for Acute Myeloid Leukemia

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ABSTRACT

BACKGROUND

Induction chemotherapy has long been a key component of curative therapy for fit patients with acute myeloid leukemia (AML), despite its frequently severe side effects and substantial health care utilization. For patients who are ineligible for induction chemotherapy, hypomethylating therapy plus venetoclax is the standard treatment owing to its efficacy and side-effect profile.

METHODS

In this multicenter, phase 2 trial, we randomly assigned, in a 1:1 ratio, previously untreated adults with AML who were eligible for induction chemotherapy to receive either azacitidine plus venetoclax or induction chemotherapy. Patients with core binding factor fusions, mutations in the gene encoding FMS-like tyrosine kinase 3 (*FLT3*), or mutations in the gene encoding nucleophosmin-1 (*NPM1*; unless the patient was ≥ 60 years of age) were excluded. The primary end point was event-free survival.

RESULTS

A total of 172 patients underwent randomization, with 86 patients assigned to each group. The median age of the patients was 64 years. A total of 72% of the patients had adverse-risk disease according to the European LeukemiaNet 2022 classification. At a median follow-up of 21.9 months, the median event-free survival was 14.5 months (95% confidence interval [CI], 10.4 to 24.4) in the azacitidine–venetoclax group, as compared with 6.2 months (95% CI, 4.1 to 10.1) in the induction chemotherapy group, corresponding to a hazard ratio for event or death of 0.57 (95% CI, 0.39 to 0.84; $P=0.002$ by the stratified log-rank test). Infection of grade 3 or higher occurred in 28% of the patients (95% CI, 19 to 39) receiving azacitidine–venetoclax and in 41% of those (95% CI, 30 to 52) receiving induction chemotherapy; hemorrhage of grade 3 or higher occurred in 2% (95% CI, 0.3 to 8) and 12% (95% CI, 6 to 20), respectively.

CONCLUSIONS

In this phase 2, randomized trial, azacitidine–venetoclax therapy led to significantly longer event-free survival than induction chemotherapy among induction-eligible patients with AML. (Funded by AbbVie and others; PARADIGM ClinicalTrials.gov number, NCT04801797.)

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FOR DECADES, THE STANDARD UP-FRONT treatment for functionally fit patients with acute myeloid leukemia (AML) has been intensive induction chemotherapy incorporating cytarabine and anthracyclines.^{1,3} Despite therapeutic advances in certain subsets of patients,^{4,7} induction chemotherapy yields suboptimal long-term outcomes for most patients^{6,8,9} and is associated with severe bone marrow suppression, prolonged hospitalization, infectious and bleeding complications, and other substantial toxic effects.¹⁰⁻¹⁴ For patients in remission after therapy, hematopoietic-cell transplantation is frequently recommended to lower the risk of relapse.

Among patients 75 years or older or patients who were otherwise ineligible to receive induction chemotherapy, the VIALE-A trial established the superiority of combination treatment with azacitidine plus venetoclax, as compared with azacitidine monotherapy, with a median overall survival of 14.7 months and a composite complete remission in 66% of the patients in the azacitidine–venetoclax group.¹⁵ Azacitidine–venetoclax therapy was associated with fewer and less-severe side effects than are usual with induction chemotherapy, with low early mortality. Combinations with a hypomethylating agent and venetoclax are now standard up-front therapies for patients who are ineligible for induction chemotherapy.

Outcomes with azacitidine–venetoclax compare favorably with outcomes with induction chemotherapy among older patients treated in clinical trials,^{6,8,9} and a single-group study recently suggested promise in younger patients with nonfavorable-risk disease.¹⁶ Retrospective studies have also suggested that the combination of a hypomethylating agent plus venetoclax yields encouraging outcomes as compared with induction chemotherapy, with an improved side-effect profile.¹⁷⁻¹⁹ Here, we report results from the PARADIGM trial, a randomized, phase 2 clinical trial designed to assess whether azacitidine–venetoclax would be superior to induction chemotherapy in patients with AML who were eligible to receive induction chemotherapy.

METHODS

TRIAL DESIGN, RANDOMIZATION, TREATMENT, AND OVERSIGHT

We conducted this investigator-initiated, open-label, multicenter, randomized, phase 2 clinical

trial at nine academic centers in the United States. AbbVie and Genentech provided venetoclax at no cost, as well as financial support for research staff. According to a trial agreement, the companies received confidential reports on enrollment, as well as manuscript drafts for prepublication review. The companies had no further role in the trial. The trial was designed by the first three and last two authors, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. Data were gathered and analyzed by investigators and their research staff. The first draft was written by the first author and subsequently revised in collaboration with coauthors. No one who is not an author contributed to the writing of the manuscript. The first three authors and last two authors made the decision to submit the manuscript for publication.

Patients were randomly assigned in a 1:1 ratio to receive either azacitidine–venetoclax or induction chemotherapy. Patients in the azacitidine–venetoclax group received repeating 28-day cycles of azacitidine (75 mg per square meter of body-surface area, administered intravenously on days 1 through 7) and venetoclax (400 mg orally on days 1 through 28); adjustments to dose, cycle length, and duration of venetoclax therapy were allowed in accordance with the prescription label and as appropriate for cytopenias, other toxic effects, and concurrent use of CYP3A inhibitors. Bone marrow biopsies were performed at the end of each cycle (between day 21 and day 31) to assess for response (see below). The trial treatment could be discontinued at any time in patients with progressive or persisting disease that prompted a change to alternative treatment. According to the protocol, all the patients could continue receiving treatment if they were deriving benefit according to the clinician's assessment.

In the induction chemotherapy group, treatment was allowed with either a “7+3” regimen (intravenous cytarabine at 200 mg per square meter on days 1 through 7 and idarubicin at 12 mg per square meter [or daunorubicin at 60 mg per square meter] on days 1, 2, and 3) or CPX-351 (a liposomal encapsulation of daunorubicin and cytarabine, at doses of 44 mg and 100 mg per square meter, respectively, administered intravenously on days 1, 3, and 5). The choice of the

7+3 regimen or CPX-351 was preselected by investigators before randomization. Bone marrow evaluation could be performed at mid-treatment (between day 13 and day 16), at which time reinduction (a “5+2” approach, with intravenous cytarabine at 200 mg per square meter on days 1 through 5 and idarubicin at 12 mg per square meter [or daunorubicin at 60 mg per square meter] on days 1 and 2, or CPX-351 on days 1 and 3, depending on the investigator’s initial choice) was allowed for residual disease. Other reinduction regimens were not allowed during the trial. Bone marrow examination was again performed in patients with hematologic recovery to assess response or by day 42 in patients without hematologic recovery. After the initial induction therapy, trial treatment was discontinued in patients with progressive or persistent disease that prompted a change by the treating physician to an alternative treatment, after which patients were followed for survival; patients with a response could continue the protocol treatment to receive up to four cycles of cytarabine consolidation therapy (see the protocol).

Patients in either group who had a response could discontinue the trial treatment and pursue alternative consolidation therapy or hematopoietic-cell transplantation. All responses were assessed according to European LeukemiaNet (ELN) recommendations.^{20,21} All patients were followed for disease progression, relapse, or death. 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.

This trial was approved by local institutional review boards at the Harvard Cancer Consortium and each trial site and was conducted according to the principles of the Declaration of Helsinki. The trial was managed as a multicenter trial by the Massachusetts General Hospital Cancer Center Protocol Office. All the patients provided written informed consent. An independent data and safety monitoring board reviewed safety data and provided recommendations.

PATIENTS

Eligible patients were at least 18 years of age with untreated AML, which had been pathologically confirmed and classified according to the World Health Organization 2016 criteria²²; each

patient had to have been deemed by the investigator as being a candidate for induction chemotherapy. Patients had to have an Eastern Cooperative Oncology Group performance-status score of no more than 2 (on a scale from 0 to 5, with higher numbers indicating greater disability), a left ventricular ejection fraction of at least 50%, liver-enzyme levels less than 3 times the upper limit of the normal range, a direct bilirubin level less than 2 times the upper limit of the normal range, and creatinine clearance of at least 30 ml per minute.

Patients with t(15;17) translocation, core binding factor fusion, or mutations in the gene encoding FMS-like tyrosine kinase 3 (*FLT3*) at a variant allele frequency of at least 5% were excluded, as were patients with mutations in the gene encoding nucleophosmin-1 (*NPM1*) and an age of less than 60 years. Molecular assessment for eligibility was performed before enrollment by local testing. Previous chemotherapy for myeloid cancer, including hypomethylating agents, except for hydroxyurea and all-*trans* retinoic acid, was an exclusion criterion, as were a white-cell count of more than 25×10^9 per liter at treatment initiation, uncontrolled infection, another cancer within the past 3 years, or central nervous system involvement. Measurable residual disease (MRD) analysis by multiparametric flow cytometry was performed centrally at Children’s Hospital Los Angeles, with the use of published methods,²³ on available samples at the time of a best bone marrow response and within 30 days before hematopoietic-cell transplantation; results were reported at 0.1% sensitivity.

END POINTS AND ASSESSMENTS

The primary end point was event-free survival, defined as the time from randomization to the first event of progressive disease, persistent disease prompting therapy change, relapse, hospice, or death, as determined by the investigator. Definitions of events were adapted from ELN 2017 recommendations.²¹ Secondary end points included complete remission, complete remission with partial hematologic recovery, complete remission with incomplete hematologic recovery, composite complete remission (i.e., a composite of complete remission, complete remission with partial hematologic recovery, or complete remission with incomplete hematologic recovery), partial remission, morphologic leukemia-free

state, overall response, transition to hematopoietic-cell transplantation, overall survival, toxic effects, MRD status, health care utilization metrics, and patient-reported outcomes (Table S12 in the Supplementary Appendix, available at NEJM.org). A post hoc analysis of event-free survival that used ELN 2022 criteria,²⁰ incorporating therapy failure (defined as an absence of a composite complete remission response with trial treatment by day 180 after randomization), relapse, and death as events, was performed.

STATISTICAL ANALYSIS

Randomization was stratified according to age (≥ 65 or < 65 years) and prerandomization selection for the induction chemotherapy regimen (7+3 regimen or CPX-351). Assuming that the true hazard ratio in the analysis of event-free survival was 0.635 with 172 patients who had undergone randomization in a 1:1 ratio, we calculated that the trial would have 85% power to detect a difference between treatments with the use of a one-sided test at a significance level of 0.10. The hazard-ratio assumption was based on an estimated 1-year event-free survival of 55% in the azacitidine–venetoclax group and 39% in the induction chemotherapy group. A futility analysis of event-free survival was performed when 50% of the patients had been enrolled. Futility was defined by a P value of more than 0.693 in a log-rank test. This trial was designed with the use of East software, version 6.5. Time-to-event end points, including event-free survival, were estimated by the Kaplan–Meier method, with the use of Greenwood’s formula for the standard error and Efron’s methods for ties (see the Supplementary Appendix).

Significance for the primary end point was assessed by the stratified log-rank test following the intention-to-treat principle. The intention-to-treat population included all patients according to their randomized assignment. Multivariable analysis of event-free survival was implemented with the use of the “best subset model” selection procedure with the Akaike information criterion for a Cox model. Although the trial was designed with examination at a one-sided 0.10 level of significance, two-sided 95% confidence intervals are presented, in accordance with *Journal* policy. The confidence intervals are not adjusted

for multiplicity of testing and should not be interpreted as hypothesis tests. The safety population included all the patients who received at least one dose of their assigned therapy. Analyses were performed with the use of R software, version 4.5.1; the survival analysis was estimated with the use of the survival package (version 3.8.3), and the model selection procedure was implemented with the StepReg package (version 1.6.0). We used a validated instrument to assess patient-reported quality of life, symptom burden, and mood symptoms at baseline and at 2, 4, 12, and 24 weeks (see the Supplementary Appendix).

RESULTS

PATIENT POPULATION

Patients were enrolled from May 2021 through January 2025. A total of 366 patients were screened, and 172 underwent randomization, with 86 patients assigned to each group. Most screening failures were due to exclusionary molecular alterations or non-AML diagnoses (Fig. 1). The cutoff date for the data analysis was October 17, 2025.

The characteristics of the patients at baseline are shown in Table 1. The demographic characteristics of the patients in the trial were representative of patients with AML in the overall U.S. population (Table S13). The median age of the patients was 65 years (range, 23 to 79) in the azacitidine–venetoclax group and 64 years (range, 28 to 79) in the induction chemotherapy group. A total of 64% of the patients in the azacitidine–venetoclax group and 70% of those in the induction chemotherapy group were men. A total of 72% of the patients had adverse-risk disease according to the ELN 2022 criteria. The distribution of the demographic characteristics, risk categories, and mutations was similar in the two groups.

The median number of treatment cycles was four for azacitidine–venetoclax and two for induction chemotherapy (including cycles of intensive consolidation therapy during the trial). The median duration of venetoclax administration was 28 days for cycles 1 and 2 and 21 days for cycle 3 (Table S7). Among patients with refractory disease in the azacitidine–venetoclax group,

the median duration of treatment was 71 days (range, 25 to 98). In the induction chemotherapy group, 54% of the patients received treatment according to the 7+3 regimen and 46% received CPX-351. Four patients were randomly assigned to the induction chemotherapy group but declined participation in order to pursue alternative treatment outside the trial; one patient who had been randomly assigned to the azacitidine–venetoclax group was removed shortly after initiation owing to an eligibility violation (*NPM1* mutation). All the patients were included in the

efficacy analyses according to their randomized assignment, in accordance with the intention-to-treat principle.

PRIMARY END POINT

Overall, the median follow-up was 21.9 months (95% confidence interval [CI], 16.6 to 25.7). The median event-free survival was significantly longer in the azacitidine–venetoclax group (14.5 months; 95% CI, 10.4 to 24.4) than in the induction chemotherapy group (6.2 months; 95% CI, 4.1 to 10.1) (Fig. 2A). Event-free survival was superior in the

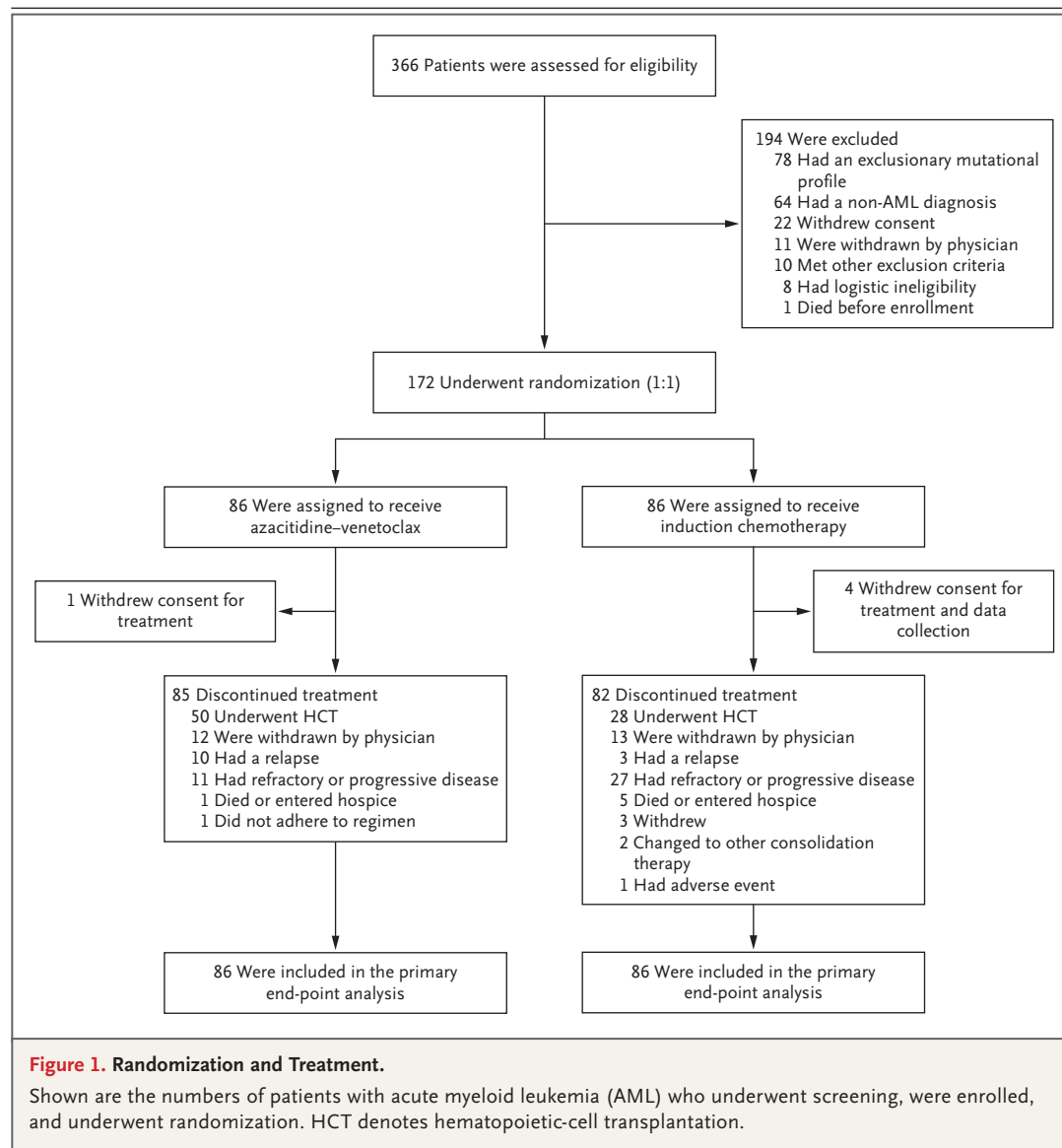


Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Azacitidine– Venetoclax (N=86)	Induction Chemotherapy (N=86)	Total (N=172)
Age			
Median (range) — yr	65 (23–79)	64 (28–79)	64 (23–79)
Distribution — no. (%)			
≤64 yr	43 (50)	44 (51)	87 (51)
≥65 yr	43 (50)	42 (49)	85 (49)
Sex — no. (%)			
Male	55 (64)	60 (70)	115 (67)
Female	31 (36)	26 (30)	57 (33)
Race or ethnic group — no. (%)†			
White	65 (76)	69 (80)	134 (78)
Black	5 (6)	5 (6)	10 (6)
Hispanic	6 (7)	7 (8)	13 (8)
Asian	10 (12)	5 (6)	15 (9)
ECOG performance-status score — no. (%)‡			
0	30 (35)	38 (44)	68 (40)
1	49 (57)	44 (51)	93 (54)
2	7 (8)	3 (3)	10 (6)
Unknown	0	1 (1)	1 (1)
Secondary AML — no. (%)			
AML with myelodysplasia-related changes	50 (58)	46 (53)	96 (56)
Therapy-related AML	4 (5)	1 (1)	5 (3)
ELN 2022 risk status — no. (%)			
Favorable	13 (15)	9 (10)	22 (13)
Intermediate	15 (17)	11 (13)	26 (15)
Adverse	58 (67)	66 (77)	124 (72)
Mutations — no. (%)			
<i>NPM1</i>	11 (13)	5 (6)	16 (9)
<i>IDH1</i>	8 (9)	7 (8)	15 (9)
<i>IDH2</i>	19 (22)	9 (10)	28 (16)
<i>DNMT3A</i>	22 (26)	18 (21)	40 (23)
<i>TP53</i>	10 (12)	16 (19)	26 (15)
<i>RUNX1</i>	17 (20)	22 (26)	39 (23)
<i>CEBPA</i>	5 (6)	6 (7)	11 (6)
<i>KRAS</i>	6 (7)	5 (6)	11 (6)
<i>NRAS</i>	12 (14)	13 (15)	25 (15)

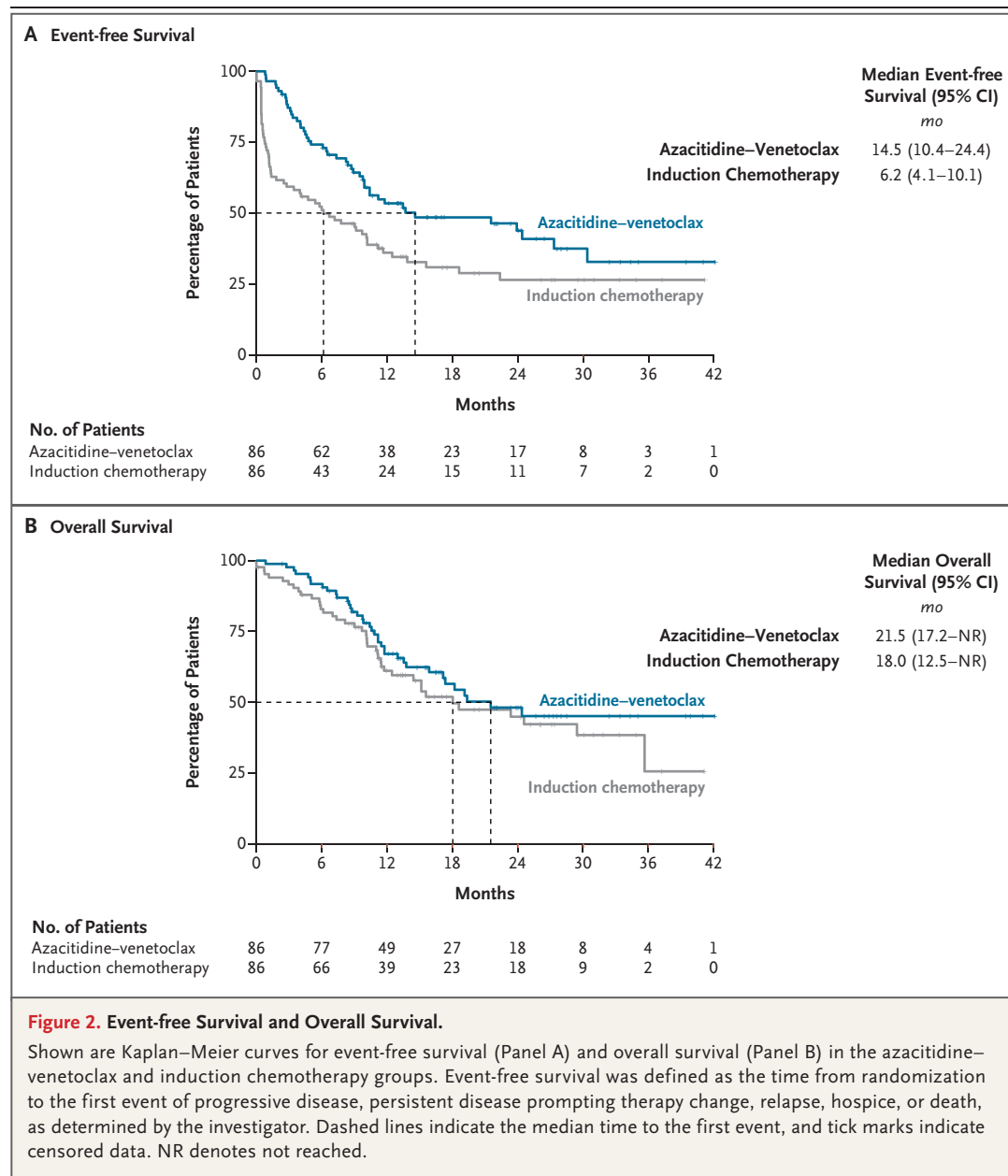
* Percentages may not total 100 because of rounding. AML denotes acute myeloid leukemia, and ELN European LeukemiaNet.

† Race and ethnic group were reported by the patient.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. One patient in the induction chemotherapy group had an ECOG score of less than 3 and was thus eligible for the trial, but the exact ECOG score was not captured and therefore is not available.

azacitidine–venetoclax group (hazard ratio for event or death, 0.57; 95% CI, 0.39 to 0.84; $P=0.002$ by a stratified log-rank test) (Table S1). Event-free survival at 1 year was 53% in the azacitidine–venetoclax group and 36% in the induction chemotherapy group. When we estimated the Cox multivariable model, incorporating demographic, disease-risk, and mutational candidate variables (see the Supplemental Methods section in the

Supplementary Appendix), adverse risk according to the ELN 2022 criteria appeared to be associated with shorter event-free survival and transplantation appeared to be associated with longer event-free survival. Treatment in the azacitidine–venetoclax group appeared to remain associated with longer event-free survival than treatment in the induction chemotherapy group (hazard ratio, 0.59; 95% CI, 0.40 to 0.87) (Table S2 and Fig. S3).



A post hoc analysis of event-free survival according to ELN 2022 criteria²⁰ was also performed (hazard ratio for event or death, 0.62; 95% CI, 0.42 to 0.91) (Fig. S5). Additional post hoc subgroup analyses are provided in Figure S9.

SECONDARY END POINTS

Details of disease responses and transition to hematopoietic-cell transplantation are provided in Figures 3A, 3B, and 3C and Table S3. An overall response was observed in 88% of the patients (95% CI, 80 to 94) in the azacitidine–venetoclax group and in 62% of those (95% CI, 50 to 72) in the induction chemotherapy group. A total of 78% of the patients (95% CI, 68 to 86) in the azacitidine–venetoclax group and 53% of those (95% CI, 42 to 64) in the induction chemotherapy group had a composite complete remission response, with a complete remission seen in 56% (95% CI, 45 to 66) and 49% (95% CI, 38 to 60), respectively. The incidence of hematopoietic-cell transplantation was 60% (95% CI, 53 to 68) in the azacitidine–venetoclax group and 40% (95% CI, 32 to 47) in the induction chemotherapy group. The median times to a first response, best response, and hematopoietic-cell transplantation appeared to be similar in the two groups (Table S11). The median overall survival was 21.5 months (95% CI, 17.2 to not reached) in the azacitidine–venetoclax group and 18.0 months (95% CI, 12.5 to not reached) in the induction chemotherapy group (Fig. 2B). Graphical presentation of event-free and overall survival in each trial group, according to whether patients received hematopoietic-cell transplantation or not, is shown in Figure S8.

Among patients in the induction chemotherapy group who had a relapse or refractory disease after trial treatment, 68% received combination therapy with a hypomethylating agent and venetoclax as subsequent treatment outside the trial. In the azacitidine–venetoclax group, 47% of the patients who had a relapse or refractory disease received induction chemotherapy reinstitution subsequently (Table S6).

MRD-negative status among patients with available samples, assessed at a specificity of 0.1%, was observed at the time of composite complete remission in 71% of the patients (95% CI, 59 to 82) in the azacitidine–venetoclax group

and in 74% of those (95% CI, 57 to 87) in the induction chemotherapy group. MRD-negative status within 30 days before hematopoietic-cell transplantation was seen in 91% (95% CI, 79 to 98) and 82% (95% CI, 60 to 95) of the patients with available samples in the azacitidine–venetoclax and induction chemotherapy groups, respectively (Fig. 3D and 3E).

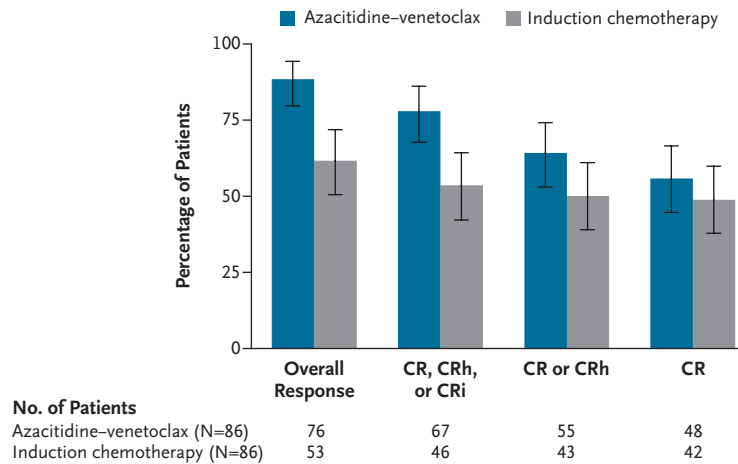
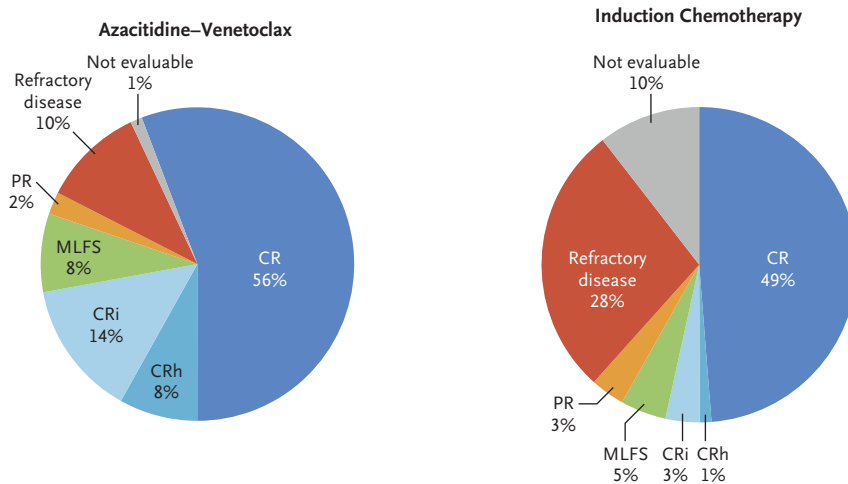
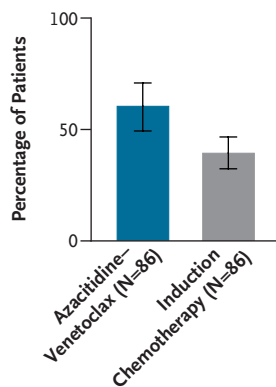
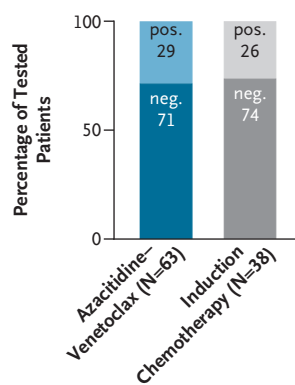
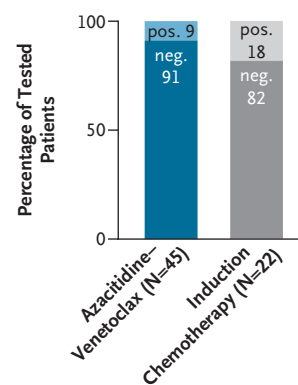
Table S5 shows patient-reported outcomes at 2 weeks. Figure S1 shows patient-reported outcomes longitudinally.

SAFETY

The safety population included 86 patients in the azacitidine–venetoclax group and 82 patients in the induction chemotherapy group. Grade 3 or higher adverse events that occurred in at least 10% of the patients in either group are listed in Table 2. These adverse events were primarily hematologic, and the incidence was similar in the two groups. The incidence of individual infectious and bleeding adverse events of grade 3 or higher is also shown in Table 2. Infectious adverse events of grade 3 or higher occurred in

Figure 3 (facing page). Treatment Response, Transition to HCT, and Measurable Residual Disease Status.

Shown are bar plots summarizing the overall percentages of patients with a response after treatment (Panel A), pie charts summarizing the best response to therapy in each treatment group (Panel B), and bar plots indicating successful transition of patients in first response to HCT (Panel C) in the azacitidine–venetoclax group (52 patients [60%]) and the induction chemotherapy group (34 patients [40%]). Overall response included complete remission (CR), complete remission with partial hematologic recovery (CRh), complete remission with incomplete hematologic recovery (CRi), partial remission (PR), and morphologic leukemia-free state (MLFS). Composite complete remission included CR, CRh, and CRi. The confidence intervals (I bars) in Panels A and C are not adjusted for multiplicity and may not be used in place of a hypothesis test. If no post-treatment bone marrow evaluation was available, then patients were considered not to have had a response and were included in the denominator for response assessment. Data on measurable residual disease (MRD) status (positive or negative) are provided on the basis of patients with available samples at the time of the best morphologic bone marrow response (CR, CRh, and CRi) (Panel D) and within 4 weeks before HCT among patients who underwent transplantation after trial treatment (Panel E).

A Treatment Response**B Response According to Treatment Type****C Hematopoietic-Cell Transplantation****D MRD Status at Best Response****E MRD Status before HCT**

28% of the patients (95% CI, 19 to 39) who received azacitidine–venetoclax and in 41% of those (95% CI, 30 to 52) who received induction chemotherapy; hemorrhagic adverse events of grade 3 or higher occurred in 2% (95% CI, 0.3 to 8) and 12% (95% CI, 6 to 20), respectively (Fig. S4). Some patients had multiple reported adverse events of grade 3 or higher. Three episodes of grade 3 tumor lysis syndrome were reported with azacitidine–venetoclax. At 30 days and 60 days, no patient in the azacitidine–venetoclax group had died; in the induction chemotherapy group, 30-day mortality was 3% and 60-day mortality was 5%. Additional data on adverse events of grade 3 or higher are provided in Table S4.

HEALTH CARE UTILIZATION

During the first 30 days after randomization, the mean number of inpatient days was 12.5 (95% CI, 11.0 to 13.9) in the azacitidine–venetoclax group and 27.3 (95% CI, 25.8 to 28.7) in the induction chemotherapy group. No patient in the azacitidine–venetoclax group was admitted to the intensive care unit (ICU), and 10% of the patients in the induction chemotherapy group were admitted to the ICU (Fig. S2). During the first 6 months, the mean number of inpatient days was 39.3 (95% CI, 33.8 to 44.8) in the azacitidine–venetoclax group and 58.5 (95% CI, 52.8 to 64.2) in the induction chemotherapy group.

DISCUSSION

This multicenter, randomized, phase 2 trial showed that among patients who were eligible for induction chemotherapy, treatment with azacitidine–venetoclax led to longer event-free survival than induction chemotherapy. Treatment with azacitidine–venetoclax allowed the transition of patients, the majority of whom had adverse-risk disease, to hematopoietic-cell transplantation.

Our data show the superiority of azacitidine–venetoclax to induction chemotherapy as upfront treatment for patients who are eligible for induction chemotherapy. Multiple retrospective studies have investigated the potential benefits of combination therapy with a hypomethylating agent plus venetoclax as compared with induction chemotherapy,^{17–19} but few prospective trials

of hypomethylating agent–based regimens in these patients have been published. A phase 3 trial²⁴ compared 10-day decitabine monotherapy with induction chemotherapy in older patients who were eligible for induction chemotherapy. Although the incidence of remission was lower with decitabine than with induction chemotherapy, the incidence of hematopoietic-cell transplantation and overall survival were similar in the two groups. Other researchers have recently published single-group data regarding azacitidine–venetoclax in younger patients with nonfavorable-risk disease, reporting a high incidence of remission and subsequent hematopoietic-cell transplantation.¹⁶ A recent Chinese randomized trial showed that a combination of decitabine plus venetoclax was noninferior to induction chemotherapy.²⁵ The percentage of patients with a composite complete remission response was higher with decitabine–venetoclax than with induction chemotherapy, but event-free survival and overall survival were similar in the two groups. It is worth noting that cytarabine consolidation was incorporated into both groups, and core binding factor and *FLT3* alterations were not exclusion criteria, factors that contributed to a population that predominantly had favorable- or intermediate-risk AML.

In comparison, our trial sought to assess the superiority of azacitidine–venetoclax over induction chemotherapy and differed in composition from previous trials. The majority of the patients in our trial had adverse-risk AML, and although approximately half the patients were younger than 65 years of age, this was a comparatively older patient population. These trends were largely driven by eligibility criteria, which excluded patients with core binding factor and *FLT3* alterations and younger patients with *NPM1* mutations. The exclusions were necessary to avoid the random assignment of such patients to treatments lacking approved therapies, including gemtuzumab ozogamicin or *FLT3* inhibitors.^{4,5,7,26} We are not suggesting that the combination of a hypomethylating agent plus venetoclax may not hold promise in these mutational subgroups, but dedicated studies that incorporate relevant targeted therapies are warranted. The currently recommended treatment for fit patients with *FLT3* mutation is induction chemotherapy, as supported by data from phase 3 trials.^{5,7} This guidance

Table 2. Grade 3 or Higher Adverse Events.*

Event	Azacitidine–Venetoclax (N=86)				Induction Chemotherapy (N=82)			
	Grade 3	Grade 4	Grade 5	Grade ≥3	Grade 3	Grade 4	Grade 5	Grade ≥3
	number of patients with event (percent)							
Grade ≥3 adverse events occurring in ≥10% of patients								
Febrile neutropenia	46 (53)	3 (3)	0	49 (57)	51 (62)	1 (1)	0	52 (63)
Platelet count decreased	8 (9)	38 (44)	0	46 (53)	3 (4)	47 (57)	0	50 (61)
Anemia	34 (40)	1 (1)	0	35 (41)	35 (43)	3 (4)	0	38 (46)
Neutrophil count decreased	1 (1)	48 (56)	0	49 (57)	1 (1)	39 (48)	0	40 (49)
White-cell count decreased	2 (2)	24 (28)	0	26 (30)	0	20 (24)	0	20 (24)
Lymphocyte count decreased	11 (13)	6 (7)	0	17 (20)	9 (11)	8 (10)	0	17 (21)
Lung infection	12 (14)	0	0	12 (14)	11 (13)	2 (2)	2 (2)	15 (18)
Sepsis	5 (6)	1 (1)	0	6 (7)	10 (12)	2 (2)	0	12 (15)
Anorexia	4 (5)	0	0	4 (5)	12 (15)	0	0	12 (15)
Hypoxemia	4 (5)	0	0	4 (5)	7 (9)	2 (2)	0	9 (11)
All grade ≥3 infectious adverse events								
Lung infection	12 (14)	0	0	12 (14)	11 (13)	2 (2)	2 (2)	15 (18)
Sepsis	5 (6)	1 (1)	0	6 (7)	10 (12)	2 (2)	0	12 (15)
Typhlitis or neutropenic enterocolitis	0	0	0	0	4 (5)	0	1 (1)	5 (6)
Catheter-related infection	2 (2)	0	0	2 (2)	5 (6)	0	0	5 (6)
Skin infection	2 (2)	0	0	2 (2)	5 (6)	0	0	5 (6)
Enterocolitis	0	0	0	0	5 (6)	0	0	5 (6)
Infection or infestation	1 (1)	0	0	1 (1)	4 (5)	0	0	4 (5)
Fungemia	0	0	0	0	3 (4)	0	0	3 (4)
Fever	0	0	0	0	2 (2)	0	0	2 (2)
Urinary tract infection	4 (5)	0	0	4 (5)	2 (2)	0	0	2 (2)
Bacteremia	0	0	0	0	1 (1)	0	0	1 (1)
Conjunctivitis	0	0	0	0	1 (1)	0	0	1 (1)
Pharyngitis	0	0	0	0	1 (1)	0	0	1 (1)
Wound infection	0	0	0	0	1 (1)	0	0	1 (1)
Anorectal infection	1 (1)	0	0	1 (1)	0	0	0	0
Lymph-gland infection	2 (2)	0	0	2 (2)	0	0	0	0
Sinusitis	1 (1)	0	0	1 (1)	0	0	0	0
Tooth infection	1 (1)	0	0	1 (1)	0	0	0	0
Upper respiratory tract infection	1 (1)	0	0	1 (1)	0	0	0	0
All grade ≥3 bleeding adverse events								
Hematoma	0	0	0	0	3 (4)	0	0	3 (4)
Lower GI hemorrhage	0	0	0	0	2 (2)	0	0	2 (2)
Epistaxis	1 (1)	0	0	1 (1)	2 (2)	0	0	2 (2)
Oral hemorrhage	0	0	0	0	1 (1)	0	0	1 (1)
Upper GI hemorrhage	1 (1)	0	0	1 (1)	1 (1)	0	0	1 (1)
Intracranial hemorrhage	0	0	0	0	1 (1)	0	0	1 (1)
Menorrhagia	1 (1)	0	0	1 (1)	0	0	0	0

* 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. GI denotes gastrointestinal.

also applies to those with favorable-risk disease, particularly AML with core binding factor fusion, who have heightened responsiveness to intensive therapies. We also cannot know the applicability of our results to patients with previous exposure to hypomethylating agents, since they were ineligible.

Other end points were explored. No apparent between-group difference in overall survival was seen; the trial was not designed to enable formal assessment of this end point. Decreasing the incidence of prolonged hospitalizations is beneficial to patients and can enhance hospital capacity and availability of staffing and resources. Finally, given our enrolled patient population, we believe that our data are applicable to patients who are eligible to pursue hematopoietic-cell transplantation, and we do not see a benefit with the use of indefinite treatment with a hypomethylating agent plus venetoclax, which is often used in older populations. In our trial, outcomes were very poor without subsequent hematopoietic-cell transplantation, which highlights the importance of this consolidative approach after up-front treatment. Supportive measures, such as growth factors, can further optimize safety in patients receiving a hypomethylating agent plus venetoclax.

Our trial compared a low-intensity therapy with a high-intensity therapy for AML. We derived our definitions of events from the ELN 2017 recommendations,²¹ which defined event-free survival as the time from trial entry to the occurrence of primary refractory disease, relapse, or death. However, the definition of “primary refractory” is derived from trials of induction chemotherapy and is not readily applicable to low-intensity treatment. A persisting but decreasing leukemia burden after two cycles of azacitidine–venetoclax is not necessarily a therapeutic failure, since remission may follow.²⁷ We therefore adjusted the event definition to include persistent disease that prompted a change in therapy, so that the failure of therapy was captured in both groups. A similar definition was used by another recent trial comparing a low-intensity therapy with a high-intensity therapy.²⁵ Other approaches may be reasonable. The ELN 2022 definition of event-free survival,²⁰ which was published after the launch of our trial, defined “treatment failure”

as not having a composite complete remission response by a landmark date — after two cycles of intensive therapy or 180 days of nonintensive therapy. We analyzed event-free survival post hoc using this definition, applying a single criterion of 180 days to both trial groups. The beneficial effect of azacitidine–venetoclax according to this post hoc definition of event-free survival appeared to be similar to that seen with the definition used for the primary end point.

The proportions of patients with MRD-negative status, as assessed by multiparametric flow cytometry, at the time of composite complete remission and before transplantation were similar in the two groups. It is worth noting that most patients had adverse-risk AML, a population in whom the predictive importance of MRD is not well characterized. Additional analyses focusing on MRD status, including those based on DNA sequencing, are underway. Studies using such sensitive measures will be essential for understanding depth of response and the predictive and prognostic relevance of MRD status²⁸⁻³⁰ in patients receiving a hypomethylating agent plus venetoclax.

We acknowledge certain limitations of the trial. A blinded central review of events was not performed, with these assessments being made in real time by treating clinician investigators — an approach that can introduce bias. This trial was conducted at academic centers, which can also introduce bias owing to varying management approaches and patient populations.

This phase 2 trial showed that among patients who were eligible for induction chemotherapy, treatment with azacitidine–venetoclax led to longer event-free survival than induction chemotherapy. A high proportion of patients in the azacitidine–venetoclax group proceeded to hematopoietic-cell transplantation. These data support the use of azacitidine–venetoclax in fit patients who are eligible for transplantation and have nonfavorable-risk, *FLT3*-nonmutated AML.

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