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Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

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ABSTRACT

BACKGROUND

Older patients with acute myeloid leukemia (AML) have a dismal prognosis, even after treatment with a hypomethylating agent. Azacitidine added to venetoclax had promising efficacy in a previous phase 1b study.

METHODS

We randomly assigned previously untreated patients with confirmed AML who were ineligible for standard induction therapy because of coexisting conditions, because they were 75 years of age or older, or both to azacitidine plus either venetoclax or placebo. All patients received a standard dose of azacitidine (75 mg per square meter of body-surface area subcutaneously or intravenously on days 1 through 7 every 28-day cycle); venetoclax (target dose, 400 mg) or matching placebo was administered orally, once daily, in 28-day cycles. The primary end point was overall survival.

RESULTS

The intention-to-treat population included 431 patients (286 in the azacitidine–venetoclax group and 145 in the azacitidine–placebo [control] group). The median age was 76 years in both groups (range, 49 to 91). At a median follow-up of 20.5 months, the median overall survival was 14.7 months in the azacitidine–venetoclax group and 9.6 months in the control group (hazard ratio for death, 0.66; 95% confidence interval, 0.52 to 0.85; P<0.001). The incidence of complete remission was higher with azacitidine–venetoclax than with the control regimen (36.7% vs. 17.9%; P<0.001), as was the composite complete remission (complete remission or complete remission with incomplete hematologic recovery) (66.4% vs. 28.3%; P<0.001). Key adverse events included nausea of any grade (in 44% of the patients in the azacitidine–venetoclax group and 35% of those in the control group) and grade 3 or higher thrombocytopenia (in 45% and 38%, respectively), neutropenia (in 42% and 28%), and febrile neutropenia (in 42% and 19%). Infections of any grade occurred in 85% of the patients in the azacitidine–venetoclax group and 67% of those in the control group, and serious adverse events occurred in 83% and 73%, respectively.

CONCLUSIONS

In previously untreated patients who were ineligible for intensive chemotherapy, overall survival was longer and the incidence of remission was higher among patients who received azacitidine plus venetoclax than among those who received azacitidine alone. The incidence of febrile neutropenia was higher in the venetoclax–azacitidine group than in the control group. (Funded by AbbVie and Genentech; VIALE-A ClinicalTrials.gov number, NCT02993523.)

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A Quick Take is available at NEJM.org

Acute myeloid leukemia (AML) is primarily a disease of older adults, with a median age of 68 years at diagnosis.[1,2] Standard curative treatment for AML consists of intensive induction chemotherapy followed by consolidation chemotherapy, allogeneic stem-cell transplantation, or both.[3,4] However, because of advanced age, coexisting conditions, and a high incidence of unfavorable genomic features, older patients are frequently ineligible for or have disease that is refractory to standard chemotherapy. Instead, such patients often receive less intensive regimens, including hypomethylating agents (azacitidine or decitabine) and low-dose cytarabine.[5] Among untreated patients with AML who are at least 65 years of age, azacitidine monotherapy has been associated with an incidence of remission of 30% or less and survival of less than 1 year.[6]

B-cell lymphoma 2 (BCL2) family proteins play an important role in the intrinsic mitochondrial apoptotic response.[7,8] Increased expression of BCL2 family proteins in AML blasts has been reported, and a majority of AML stem cells express aberrantly high levels of BCL2 and are dependent on BCL2 for survival.[9-11] Furthermore, high expression of BCL2 has been associated with an inferior response to chemotherapy and poor survival among patients with AML.[10,12,13] Venetoclax, a selective small-molecule BCL2 inhibitor, has been shown in preclinical studies to induce apoptosis in malignant cells that are dependent on BCL2 for survival. Single-agent venetoclax has had modest activity in AML.[14,15] Through downregulation of myeloid-cell leukemia 1 (MCL1) and induced expression of the prodeath proteins NOXA and PUMA, azacitidine may synergistically inhibit the prosurvival proteins MCL1 and BCL-XL, thereby increasing the dependence of leukemia cells on BCL2. Azacitidine and venetoclax have been shown to induce cell death in AML-derived cell lines in preclinical studies.[16,17]

A previous phase 1b study of the combination of azacitidine and venetoclax showed promising efficacy, with a combined incidence of complete remission and complete remission with incomplete hematologic recovery of 71% and a median duration of response of 21.2 months in previously untreated patients with AML who were ineligible for chemotherapy.[18] At a median follow-up of 14.9 months, the median overall survival was 16.9 months.[19]

This confirmatory trial (VIALE-A) was designed to evaluate the efficacy and safety of the azacitidine–venetoclax combination regimen as compared with a control regimen of azacitidine and placebo in previously untreated patients with AML who were ineligible for intensive induction therapy.

Methods

Patients

Key eligibility criteria included an age of 18 years or older and a confirmed diagnosis of previously untreated AML according to World Health Organization criteria. Patients were considered to be ineligible for standard induction therapy if they were 75 years of age or older or if they had at least one of the following coexisting conditions precluding intensive chemotherapy: a history of congestive heart failure for which treatment was warranted or an ejection fraction of 50% or less or chronic stable angina, a diffusing capacity of the lung for carbon monoxide of 65% or less or a forced expiratory volume in 1 second of 65% or less, and an Eastern Cooperative Oncology Group performance-status score of 2 or 3 (on a 5-point scale, with higher numbers indicating greater disability). Previous receipt of any hypomethylating agent, venetoclax, or chemotherapy for myelodysplastic syndrome was exclusionary. Patients with a favorable cytogenetic risk according to the AML National Comprehensive Cancer Network (NCCN) guidelines were also excluded. Molecular mutations were assessed at a central laboratory. Full eligibility criteria are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Trial Design and Regimens

This phase 3, multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of azacitidine plus venetoclax, as compared with azacitidine plus placebo (the control regimen). Eligible patients were assigned, in a 2:1 ratio, either to the azacitidine–venetoclax group or to the control group. All the patients were hospitalized on or before day 1 of cycle 1 and for at least 24 hours after receiving the final dose of venetoclax in order to receive prophylaxis against the tumor lysis syndrome and for monitoring. All the patients received an agent to reduce the level of

uric acid as well as oral hydration, intravenous hydration, or both, and all the patients underwent scheduled laboratory assessments.

Venetoclax was administered orally, once daily, with food. For mitigation of the tumor lysis syndrome during cycle 1, the dose of venetoclax was 100 mg on day 1 and 200 mg on day 2; on day 3, the target dose of 400 mg was reached and continued until day 28. In all subsequent 28-day cycles, the dose of venetoclax was initiated at 400 mg daily. Patients in the control group received an oral venetoclax placebo according to the same schedule. Patients in both groups received azacitidine at a dose of 75 mg per square meter of body-surface area, subcutaneously or intravenously, on days 1 through 7 every 28-day cycle. To mitigate cytopenia and related clinical consequences, venetoclax was interrupted between cycles for recovery of blood counts after clearance of leukemia from the bone marrow, and dose modifications related to prophylactic antiinfective agents for venetoclax dose equivalency were implemented. The criteria for dose modifications are summarized in Tables S1 and S2 in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary trial end point was overall survival. The secondary end points were composite complete remission (complete remission or complete remission with incomplete hematologic recovery), complete remission with or without partial hematologic recovery, complete remission by the initiation of cycle 2, red-cell and platelet transfusion independence, composite complete remission and overall survival in molecular and cytogenetic subgroups, event-free survival, measurable residual disease by flow cytometry, and quality of life according to patient-reported outcomes.

Overall survival was defined as the number of days from randomization to the date of death; event-free survival was defined as the number of days from randomization to disease progression, treatment failure (failure to achieve complete remission or <5% bone marrow blasts after at least six cycles of treatment), confirmed relapse, or death. Data for each patient were censored at the date of the last visit or the date on which the patient was last known to be alive. Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a complete remission or a complete remission with incomplete hematologic recovery. Disease assessments were performed with the use of the modified International Working Group response criteria for AML.[20]

Complete remission was defined as an absolute neutrophil count of more than 1000 cells per cubic millimeter, a platelet count of more than 100,000 per cubic millimeter, red-cell transfusion independence, and bone marrow with less than 5% blasts. Complete remission with incomplete hematologic recovery was defined as all the criteria for complete remission, except for neutropenia (absolute neutrophil count, ≤1000 per cubic millimeter) or thrombocytopenia (platelet count, ≤100,000 per cubic millimeter). Complete remission with partial hematologic recovery was defined as all the criteria for complete remission, except that both the neutrophil and platelet counts were lower than the threshold designated for complete recovery (for neutropenia >500 per cubic millimeter and a platelet count of more than >50,000 per cubic millimeter). Progressive disease was defined according to the recommendations of the European LeukemiaNet.[3] Cytogenetic risk was evaluated by the investigators according to the NCCN guidelines for AML, version 2.2016. Transfusion independence was defined as the absence of a red-cell or platelet transfusion for at least 56 days between the first and last day of treatment. In patients who had composite complete remission, measurable residual disease was assessed by flow cytometry, with negativity defined according to European LeukemiaNet guidelines as less than 1000 aberrant blasts.[21] Quality of life was assessed with the use of the Patient-Reported Outcomes Measurement Information System Fatigue SF7a patient questionnaire and the Core Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer C30.

All patients who received at least one dose of either azacitidine or venetoclax were included in the safety analysis. Treatment-related adverse events were defined as those that occurred from the first dose until 30 days after the discontinuation of treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[22]

Patients continued to receive treatment until they had disease progression or unacceptable

toxic effects, until they withdrew consent, or until they met any protocol-defined criteria. Except for patients who withdrew consent, all patients who discontinued a trial regimen were followed for survival.

TRIAL OVERSIGHT

AbbVie and Genentech, the sponsors, provided financial support for the trial and participated in the design, trial conduct, analysis, and interpretation of the data. All the authors had full access to the data, signed confidentiality agreements with the sponsors regarding the data, and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol, available at NEJM.org. The first draft of the manuscript was written by the first author and a medical writer employed by AbbVie, with input from all the authors. All the authors critically reviewed and provided feedback on all subsequent versions of the manuscript. The trial was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. The protocol and related documents were approved by the applicable regional review boards, ethics committees, or both, and all the patients provided written informed consent. An independent data and safety monitoring committee reviewed unblinded safety data and provided recommendations for continuation or termination of the trial.

STATISTICAL ANALYSIS

The clinical data cutoff date was January 4, 2020. The intention-to-treat population included all 431 patients who underwent randomization. For the primary end point of overall survival, we estimated that 360 deaths among 400 patients would provide 86.7% power to detect a hazard ratio of 0.70 with the use of a log-rank test at a two-sided significance level of 0.04.

In March 2020, the trial was declared to be successful (i.e., the trial showed efficacy of azacitidine plus venetoclax as compared with the control) at the recommendation of the independent data and safety monitoring committee, which reviewed the prespecified interim efficacy analysis of overall survival after 75% of the target number of deaths had occurred. Efficacy analyses were performed in the intention-to-treat population. The distribution of overall survival was estimated for each treatment group with the use of the Kaplan–Meier method and compared with the use of the log-rank test stratified according to age and cytogenetic risk. The hazard ratio between the treatment groups was estimated with the Cox proportional-hazards model with the same stratification factors. Composite complete remission was compared between the treatment groups with the use of the Cochran–Mantel–Haenszel test with the same stratification factors.

RESULTS

PATIENTS

From February 6, 2017, through May 31, 2019, a total of 579 patients underwent screening, 433 underwent randomization, and 431 were included in the intention-to-treat population from 134 sites across 27 countries (Fig. 1 and Table S3). With 2:1 randomization, 286 patients were assigned to azacitidine plus venetoclax and 145 were assigned to azacitidine plus placebo. In both groups, the median age was 76 years, and 60% of the patients were male. Secondary AML was reported in 25% of the patients in the azacitidine–venetoclax group and in 24% of the patients in the control group, and poor cytogenetic risk was reported in 36% and 39%, respectively. Nearly half the patients (141 [49%] in the azacitidine–venetoclax group and 65 [45%] in the control group) had at least two reasons for ineligibility for intensive therapies. Key baseline and clinical characteristics are summarized in Table 1.

The most common reason for trial discontinuation during the follow-up for survival was death (in 161 patients [56%] in the azacitidine–venetoclax group and 109 patients [75%] in the control group) (Table S4). Death was related to disease progression in 27% of the patients in the azacitidine–venetoclax group (78 patients) and in 44% of the patients in the control group (64 patients).

EFFICACY

Primary End Point

The median duration of follow-up was 20.5 months (range, <0.1 to 30.7). At the time of the analysis, 77 of the patients in the azacitidine–venetoclax group (27%) and 18 of the patients in

the control group (12%) were receiving treatment (Fig. 2). The median overall survival was 14.7 months (95% confidence interval [CI], 11.9 to 18.7) in the azacitidine–venetoclax group and 9.6 months (95% CI, 7.4 to 12.7) in the control group (hazard ratio for death, 0.66; 95% CI, 0.52 to 0.85; P<0.001).

Secondary End Points

Composite complete remission was achieved in 66.4% (95% CI, 60.6 to 71.9) of the patients in the azacitidine–venetoclax group and 28.3% (95% CI, 21.1 to 36.3) of the patients in the control group (P<0.001); composite complete remission before the initiation of cycle 2 was achieved in 43.4% (95% CI, 37.5 to 49.3) and in 7.6% (95% CI, 3.8 to 13.2), respectively (P<0.001). The median time to first response (either complete remission or complete remission with incomplete hematologic recovery) was 1.3 months (range, 0.6 to 9.9) and 2.8 months (range, 0.8 to 13.2), respectively. The median duration of composite complete remission was 17.5 months (95% CI, 13.6 to not reached [NR]) in the azacitidine–venetoclax group and 13.4 months (95% CI, 5.8 to 15.5) in the control group. Complete remission was achieved in 36.7% and 17.9% of the patients, respectively (P<0.001), and the duration of complete remission was 17.5 months (95% CI, 15.3 to NR) and 13.3 months (95% CI, 8.5 to 17.6).

Similarly, 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); this end point was reached before the beginning of cycle 2 in 39.9% (95% CI, 34.1 to 45.8) and 5.5% (95% CI, 2.4 to 10.6), respectively (P<0.001). The median time to first response was 1.0 month (range, 0.6 to 14.3) and 2.6 months (range, 0.8 to 13.2), and the duration of response was 17.8 months (95% CI, 15.3 to NR) and 13.9 months (95% CI, 10.4 to 15.7), respectively. The incidence of postbaseline transfusion independence was higher among patients in the azacitidine–venetoclax group than among those in the control group. Red-cell transfusion independence occurred in 59.8% (95% CI, 53.9 to 65.5) of the patients in the azacitidine–venetoclax group and in 35.2% (95% CI, 27.4 to 43.5) of those in the control group (P<0.001), and platelet transfusion independence occurred in 68.5% (95% CI, 62.8 to 73.9) and 49.7% (95% CI, 41.3 to 58.1) (P<0.001), respectively.

In the analysis of the molecular subgroups, the combination of azacitidine plus venetoclax was associated with a significantly higher inci-

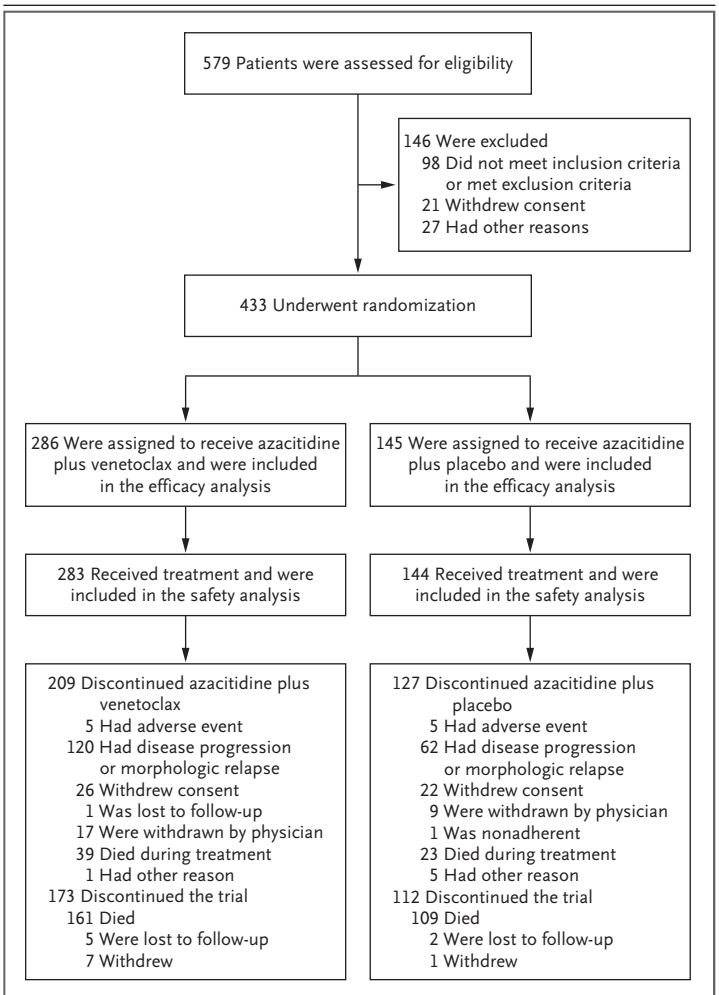


Figure 1. Randomization and Treatment.

Two of the 433 patients who underwent randomization were not stratified according to cytogenetic risk. They were excluded from the efficacy analysis but included in the safety analysis. Six patients who did not receive treatment were excluded from the safety analysis. Two patients who were assigned to receive azacitidine plus venetoclax and 1 patient who was assigned to receive azacitidine plus placebo did not receive any treatment because of worsening of preexisting medical illness. Patients who discontinued azacitidine or venetoclax were followed for survival, but patients who discontinued the trial were no longer observed for survival follow-up. Two patients in the azacitidine–venetoclax group and 1 patient in the azacitidine–placebo group underwent transplantation after discontinuing azacitidine–venetoclax or azacitidine–placebo.

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

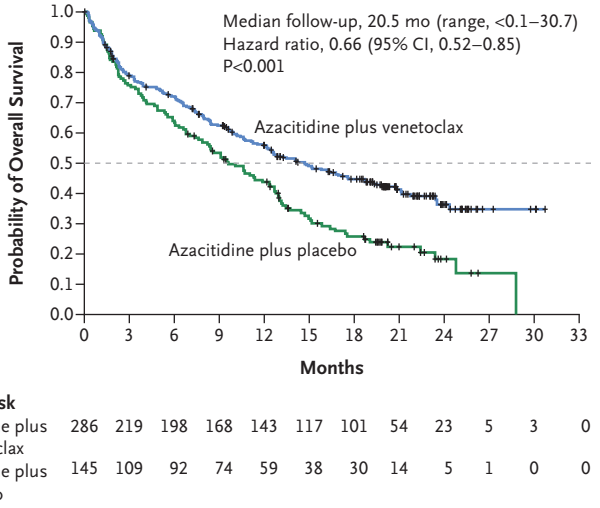
Characteristic	Azacitidine–Venetoclax Group (N=286)	Azacitidine–Placebo Group (N=145)
Age		
Median (range) — yr	76 (49–91)	76 (60–90)
≥75 yr — no. (%)	174 (61)	87 (60)
Male sex — no. (%)	172 (60)	87 (60)
AML type — no (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML — no./total no. (%)		
History of myelodysplastic syndrome or CMML	46/72 (64)	26/35 (74)
Therapy-related AML	26/72 (36)	9/35 (26)
ECOG performance-status score — no. (%)†		
0–1	157 (55)	81 (56)
2–3	129 (45)	64 (44)
Bone marrow blast count — no. (%)		
<30%‡	85 (30)	41 (28)
≥30 to <50%	61 (21)	33 (23)
≥50%	140 (49)	71 (49)
AML with myelodysplasia-related changes — no. (%)	92 (32)	49 (34)
Cytogenetic risk category — no. (%)§		
Intermediate	182 (64)	89 (61)
Normal karyotype — no.	128	62
Trisomy 8; +8 alone — no.	13	10
Poor	104 (36)	56 (39)
7 or 7q deletion — no.	20	11
5 or 5q deletion — no.	46	22
Complex, ≥3 clonal abnormalities — no.	75	36
Somatic mutations — no./total no. (%)		
IDH1 or *IDH2*	61/245 (25)	28/127 (22)
FLT3 ITD or TKD	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)
Baseline cytopenia grade ≥3¶		
Anemia — no. (%)	88 (31)	52 (36)
Neutropenia — no./total no. (%)	206/286 (72)	90/144 (62)
Thrombocytopenia — no. (%)	145 (51)	73(50)
Baseline transfusion dependence — no. (%)‖		
Red cells	144 (50)	76 (52)
Platelets	68 (24)	32 (22)
≥2 Reasons for ineligibility to receive intensive therapy — no. (%)	141 (49)	65 (45)

* AML denotes acute myeloid leukemia, CMML chronic myelomonocytic leukemia, HMA hypomethylating agent, ITD internal tandem duplications, and TKD tyrosine kinase domain.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability.
‡ These bone marrow blast counts were between 20 and 29%.
§ Only cytogenetic risks of interest are shown.
¶ Cytopenia was graded according to the Common Terminology Criteria for Adverse Events.
‖ Baseline transfusion dependence was transfusion within 8 weeks before the first dose of azacitidine–venetoclax or azacitidine–placebo or randomization.

dence of composite complete remission than the control regimen. In patients with *IDH1* or *IDH2* mutations, the incidence of composite remission was 75.4% (95% CI, 62.7 to 85.5) in the azacitidine–venetoclax group and 10.7% (95% CI, 2.3 to 28.2) in the control group (P<0.001); in those with *FLT3* mutations, the incidence was 72.4% (95% CI, 52.8 to 87.3) and 36.4% (95% CI, 17.2 to 59.3), respectively (P=0.02); in those with *NPM1*, 66.7% (95% CI, 46.0 to 83.5) and 23.5% (95% CI, 6.8 to 49.9), respectively (P=0.012); and in those with *TP53*, 55.3% (95% CI, 38.3 to 71.4) and 0%, respectively (P<0.001). Responses according to key prognostic features at baseline are shown in Figure S1. In patients with composite complete remission, measurable residual disease negativity occurred in 23.4% (95% CI, 18.6 to 28.8) of the patients who received azacitidine plus venetoclax and in 7.6% (95% CI, 3.8 to 13.2) of those in the control group.

The median overall survival among patients with de novo AML (i.e., in those with no history of myelodysplastic syndrome, myeloproliferative disorder, or exposure to potentially leukemogenic agents) was 14.1 months (95% CI, 10.7 to 19.3) in the azacitidine–venetoclax group and 9.6 months (95% CI, 6.8 to 13.0) in the control group (hazard ratio, 0.67; 95% CI, 0.51 to 0.90), and the median overall survival among patients with secondary AML was 16.4 months (95% CI, 9.7 to 24.4) and 10.6 months (4.9 to 13.2), respectively (hazard ratio, 0.56; 95% CI, 0.35 to 0.91). Among patients with an intermediate cytogenetic risk, the median overall survival was 20.8 months (95% CI, 16.4 to NR) in the azacitidine–venetoclax group and 12.4 months (95% CI, 9.1 to 15.8) in the control group (hazard ratio for death, 0.57; 95% CI, 0.41 to 0.79), whereas in those with a poor cytogenetic risk, the median overall survival was 7.6 months (95% CI, 5.3 to 9.9) and 6.0 months (95% CI, 3.6 to 10.7), respectively (hazard ratio, 0.78; 95% CI, 0.54 to 1.1).

The median event-free survival was 9.8 months (95% CI, 8.4 to 11.8) in the azacitidine–venetoclax group and 7.0 months (95% CI, 5.6 to 9.5) in the control group (hazard ratio for death, 0.63; 95% CI, 0.50 to 0.80; P<0.001) (Fig. S2). In patients with composite complete remission who had measurable residual disease of less than 1 residual blast per 1000 leukocytes, overall survival at 24 months was 73.6% in the azacitidine–venetoclax group and 63.6% in the control group.



No. at Risk

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

Figure 2. Overall Survival.

The distributions were estimated for each treatment group with the use of the Kaplan–Meier method and were compared with the log-rank test stratified according to age (18 to <75 years or ≥75 years) and cytogenetic risk (intermediate risk or poor risk). The hazard ratio for death was estimated with the use of the Cox proportional-hazards model with the same stratification factors used in the log-rank test. The data included are subject to a cutoff date of January 4, 2020. The dashed line indicates 50% overall survival probability, and the tick marks indicate censored data.

The results of a subgroup analysis with respect to overall survival are shown in Figure 3. In patients with *IDH1* or *IDH2* mutations at baseline, overall survival at 12 months was 66.8% among those in the azacitidine–venetoclax group, as compared with 35.7% among those in the control group (hazard ratio for death, 0.35; 95% CI, 0.20 to 0.60; P<0.001).

SAFETY

Overall, 427 patients were included in the safety analysis (283 in the azacitidine–venetoclax group and 144 in the control group). Patients in the azacitidine–venetoclax group received a median of 7.0 treatment cycles (range, 1.0 to 30.0), as compared with 4.5 treatment cycles (range, 1.0 to 26.0) in the control group. All patients had at least one adverse event; 235 patients in the azacitidine–venetoclax group (83%) and 105 of those in the control group (73%) had a serious

Subgroup	Azacitidine plus Venetoclax	Azacitidine plus Placebo	Hazard Ratio for Death (95% CI)
	no. of events/total no. (%)		
All patients	161/286 (56.3)	109/145 (75.2)	0.64 (0.50–0.82)
Sex			
Male	61/114 (53.5)	41/58 (70.7)	0.68 (0.46–1.02)
Female	100/172 (58.1)	68/87 (78.2)	0.62 (0.46–0.85)
Age			
<75 yr	66/112 (58.9)	36/58 (62.1)	0.89 (0.59–1.33)
≥75 yr	95/174 (54.6)	73/87 (83.9)	0.54 (0.39–0.73)
Geographic region			
United States	27/50 (54.0)	21/24 (87.5)	0.47 (0.26–0.83)
Europe	70/116 (60.3)	46/59 (78.0)	0.67 (0.46–0.97)
China	9/24 (37.5)	5/13 (38.5)	1.05 (0.35–3.13)
Japan	10/24 (41.7)	9/13 (69.2)	0.52 (0.20–1.33)
Rest of world	45/72 (62.5)	28/36 (77.8)	0.73 (0.45–1.17)
Baseline ECOG score			
Grade <2	89/157 (56.7)	65/81 (80.2)	0.61 (0.44–0.84)
Grade ≥2	72/129 (55.8)	44/64 (68.8)	0.70 (0.48–1.03)
Type of AML			
De novo	120/214 (56.1)	80/110 (72.7)	0.67 (0.51–0.90)
Secondary	41/72 (56.9)	29/35 (82.9)	0.56 (0.35–0.91)
Cytogenetic risk			
Intermediate	84/182 (46.2)	62/89 (69.7)	0.57 (0.41–0.79)
Poor	77/104 (74.0)	47/56 (83.9)	0.78 (0.54–1.12)
Molecular marker			
FLT3	19/29 (65.5)	19/22 (86.4)	0.66 (0.35–1.26)
IDH1	15/23 (65.2)	11/11 (100.0)	0.28 (0.12–0.65)
IDH2	15/40 (37.5)	14/18 (77.8)	0.34 (0.16–0.71)
IDH1 or *IDH2*	29/61 (47.5)	24/28 (85.7)	0.34 (0.20–0.60)
TP53	34/38 (89.5)	13/14 (92.9)	0.76 (0.40–1.45)
NPM1	16/27 (59.3)	14/17 (82.4)	0.73 (0.36–1.51)
AML with myelodysplasia-related changes			
Yes	56/92 (60.9)	38/49 (77.6)	0.73 (0.48–1.11)
No	105/194 (54.1)	71/96 (74.0)	0.62 (0.46–0.83)
Bone marrow blast count			
<30%	46/85 (54.1)	28/41 (68.3)	0.72 (0.45–1.15)
30 to <50%	36/61 (59.0)	26/33 (78.8)	0.57 (0.34–0.95)
≥50%	79/140 (56.4)	55/71 (77.5)	0.63 (0.45–0.89)

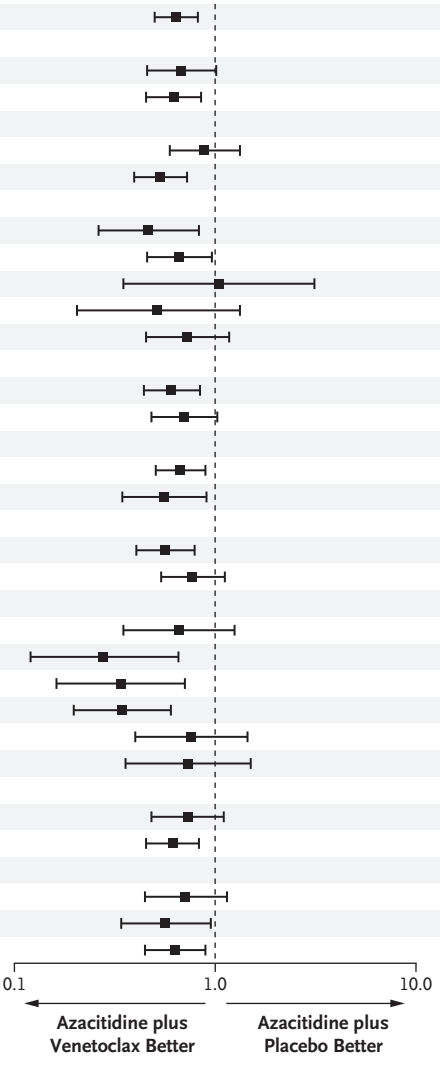


Figure 3. Subgroup Analysis of Overall Survival.

The hazard ratio for death was estimated with the unstratified Cox proportional-hazards model. Data included are subject to a cutoff date of January 4, 2020. The dashed vertical line represents a hazard ratio of 1.0. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating greater disability. *TP53* and *NPM1* data are from the central laboratory and were determined with the use of the MyAML assay. *IDH1* or *IDH2* and *FLT3* data were determined with the use of the CDx assay.

adverse event. Common adverse events are summarized in Table 2. The most frequently reported hematologic adverse events of grade 3 or higher in the azacitidine–venetoclax and control groups included thrombocytopenia (in 45% and 38%, respectively), neutropenia (in 42% and 28%), febrile neutropenia (in 42% and 19%), anemia (in 26% and 20%), and leukopenia (in 21% and 12%). Gastrointestinal adverse events of any grade were common and predominantly included nausea (in 44% of the patients in the azacitidine–venetoclax group and 35% of those

Table 2. Adverse Events.*

Event	Azacitidine–Venetoclax Group (N=283)		Azacitidine–Placebo Group (N=144)	
	All Grades†	≥Grade 3‡	All Grades†	≥Grade 3‡
	number of patients (percent)			
All adverse events	283 (100)	279 (99)	144 (100)	139 (97)
Hematologic adverse events	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Nonhematologic adverse events				
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (28)	15 (10)
Peripheral edema	69 (24)	1 (<1)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	12 (4)	25 (17)	1 (1)
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious adverse events§	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

* The safety population included all patients who received at least one dose of azacitidine–venetoclax or azacitidine–placebo.
† Adverse events reported in at least 20% of patients in either treatment group are listed.
‡ Adverse events of grade 3 or higher that were reported in at least 10% of patients in either treatment group are listed.
§ Serious adverse events that were reported in at least 5% of patients in either treatment group are listed.

in the control group), constipation (in 43% and 39%, respectively), diarrhea (in 41% and 33%), and vomiting (in 30% and 23%). Notable serious adverse events (grade ≥3) were febrile neutropenia (in 30% of the patients in the azacitidine–venetoclax group and 10% of those in the control group) and pneumonia (in 16% and 22%). Tumor lysis syndrome was reported during the ramp-up period (on days 1 through 3 when the dose of venetoclax was increased) in 3 patients (1%) in the azacitidine–venetoclax group and in none of the patients in the control group; all 3 patients had transient biochemical changes that resolved with uricosuric agents and calcium supplements without interruption of azacitidine–venetoclax or azacitidine–placebo.

The percentages of patients who discontinued azacitidine–venetoclax or azacitidine–placebo ow-

ing to adverse events were similar in the two groups (24% in the azacitidine–venetoclax group and 20% in the control group). The interruption of azacitidine–venetoclax or azacitidine–placebo between cycles owing to adverse events occurred in 72% of the patients in the azacitidine–venetoclax group and 57% of the patients in the control group, and reduction in the dose of azacitidine–venetoclax or azacitidine–placebo owing to adverse events occurred in 3% and 4% of the patients, respectively; these dose interruptions and reductions were primarily because of neutropenia (in 19% and 10%), febrile neutropenia (in 20% and 4%), and thrombocytopenia (in 10% and 4%). Dose interruptions, including delays between treatment cycles and reductions in the duration of treatment from 28 to 21 days per cycle for count recovery after leukemia clearance from bone marrow, occurred in 53% of the patients in the azacitidine–venetoclax group and 28% of the patients in the control group; at least two interruptions for count recovery occurred in 15% and 2% of the patients, respectively. Mortality at 30 days was similar in the two groups (7% [21 patients] in the azacitidine–venetoclax group and 6% [9 patients] in the control group). No differences were observed between the two treatment groups with respect to quality-of-life measures.

DISCUSSION

In this phase 3 trial involving patients with AML who had not received treatment previously and who were either elderly or otherwise ineligible to receive intensive chemotherapy, combination treatment with azacitidine plus venetoclax was superior to azacitidine alone. The median overall survival among patients who were randomly assigned to azacitidine plus venetoclax was 14.7 months, as compared with 9.6 months with azacitidine alone (hazard ratio for death, 0.66; P<0.001).

The incidence of composite complete remission was 66.4% among the patients who received azacitidine plus venetoclax; this incidence was more than twice as high as that among those who received azacitidine alone. This higher incidence of remission resulted in significant increases in the incidence of transfusion independence.[6,23-25] Responses were both rapid and durable. Nearly half (43%) of the patients who received azacitidine plus venetoclax had a first response (either complete remission or complete remission with incomplete hematologic recovery) before the initiation of cycle 2 and a median duration of remission of 17.5 months. The incidence of composite complete remission was notably improved across all AML genomic risk groups, including patients with adverse cytogenetic risk, secondary AML, and high-risk molecular mutations. These improvements in responses also translated into an increased overall survival in many of the evaluated subgroups, most notably among patients with either de novo or secondary AML, intermediate cytogenetic risk, and *IDH1* or *IDH2* mutations.

Interpretation of these findings should be tempered by the fact that the number of patients in each of these subgroups was not large. Ongoing and future analyses are needed to more comprehensively evaluate the efficacy of azacitidine plus venetoclax according to detailed genomic characteristics and to suggest potential agents or mechanisms to further increase the durations of response in the higher-risk subgroups, such as those involving patients with poor cytogenetic risk, the presence of *TP53* mutations, or both. Limitations to the generalizability of the results of this trial include the exclusion of patients with core-binding factor AML and patients who had previously received a hypomethylating agent.

The safety profile of azacitidine plus venetoclax was consistent with the known side-effect profiles of both agents, and adverse events were consistent with expectations for an older AML population; no differences between the two treatment groups with respect to quality-of-life measures were seen. The most common adverse events in both groups were gastrointestinal and hematologic, with a higher frequency of neutropenia and febrile neutropenia in the azacitidine–venetoclax group; these findings are consistent with those in previous studies.[26] We observed a higher incidence of dose interruptions (but not discontinuations of treatment or reductions in doses) to allow for hematologic recovery in patients with a response in the azacitidine–venetoclax group than in the control group. Early bone marrow assessments to determine response, most importantly after the completion of cycle 1, promote the appropriate application of interrup-

tions in venetoclax between treatment cycles to augment hematologic recovery. The majority of patients who received azacitidine–venetoclax (53%) had modifications to the duration of venetoclax, and 32% also received granulocyte colony-stimulating factor during remission. In addition, good supportive care such as the incorporation of prophylactic antimicrobial agents (i.e., antibiotic, antiviral, and antifungal therapy) is recommended for patients who are receiving azacitidine plus venetoclax.[27,28]

The prognosis in older patients with AML who are ineligible to receive intensive chemotherapy has been dismal. The combination of azacitidine plus venetoclax in this challenging patient population in this trial was an effective treatment regimen that led to significant improvements in the incidence of composite complete remission and overall survival. Unlike monitoring of patients who receive azacitidine alone, ongoing attentiveness to the monitoring and management of myelosuppression is key for patient safety with this combination therapy.

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APPENDIX

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