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RESEARCH ARTICLE

Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia

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Abstract

Venetoclax-azacitidine is approved for treatment of patients with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive chemotherapy based on the interim overall survival (OS) analysis of the VIALE-A study (NCT02993523). Here, long-term follow-up is presented to address survival benefit and long-term outcomes with venetoclax-azacitidine. Patients with newly diagnosed AML who were ineligible for intensive chemotherapy were randomized 2:1 to receive venetoclax-azacitidine or placebo-azacitidine. OS was the primary endpoint; complete remission with/without blood count recovery (CR/CRi) was a key secondary endpoint. This final analysis was conducted when 100% of the predefined 360 OS events occurred. In VIALE-A, 431 patients were enrolled to venetoclax-azacitidine ($n = 286$) or placebo-azacitidine ($n = 145$). At 43.2 months median follow-up, median OS was 14.7 months (95% confidence interval [CI], 12.1–18.7) with venetoclax-azacitidine, and 9.6 months (95% CI, 7.4–12.7) with placebo-azacitidine (hazard ratio, 0.58 [95% CI, 0.47–0.72], $p < .001$); the estimated 24-month OS rate was 37.5% and 16.9%, respectively. Median OS for patients with *IDH1/2* mutations and those with measurable residual disease responses was reached in this final analysis. CR/CRi rate was similar to interim analysis. Any-grade hematologic and gastrointestinal adverse events were most common in venetoclax-azacitidine and placebo-azacitidine arms, including thrombocytopenia (47% and 42%) and neutropenia (43% and 29%). No new safety signals were identified. Long-term efficacy

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and safety confirm venetoclax-azacitidine is an improvement in standard-of-care for patients with AML who are not eligible for intensive chemotherapy because of advanced age or comorbidities.

1 | INTRODUCTION

Acute myeloid leukemia (AML) is a heterogenous neoplasm characterized by proliferation of immature myeloid cells in bone marrow and peripheral blood, leading to failure of normal hematopoiesis.[1] AML is the most common acute leukemia in adults, with a median age at diagnosis of 68 years. Estimated 5-year survival differs significantly by age and is <10% for patients older than 60 years and ~50% for younger patients.[2,3] Intensive chemotherapy remains standard-of-care for induction-eligible patients with newly diagnosed AML, often followed with allogeneic stem cell transplantation (SCT) with curative intent. However, older patients and patients with comorbidities are often inappropriate for this intensive approach, leaving an unmet need for novel AML treatments.

In 2018, the BCL-2 inhibitor, venetoclax, in combination with azacitidine was approved in many regions globally for use in patients with newly diagnosed AML aged ≥75 years or ineligible for intensive chemotherapy, based on results from a phase 1b study. The confirmatory phase 3 study, VIALE-A, met its primary endpoint of improved overall survival (OS) with venetoclax-azacitidine versus placebo-azacitidine at the primary analysis, conducted when 75% of the preplanned OS events were reached. At 20.5 months median follow-up at primary analysis, median OS was 14.7 months (95% confidence interval [CI], 11.9–18.7) for venetoclax-azacitidine versus 9.6 months (95% CI, 7.4–12.7) for placebo-azacitidine (hazard ratio [HR], 0.66 [95% CI, 0.52–0.85], $p < .001$).[4] The complete remission (CR) rate was higher with venetoclax-azacitidine versus placebo-azacitidine (36.7% vs. 17.9%; $p < .001$), as was the composite CR (CR or CR with incomplete count recovery [CR/CRi]) rate (66.4% vs. 28.3%; $p < .001$). Here, long-term efficacy and safety are reported in patients in VIALE-A at a median follow-up of 43.2 months, with the study having reached 100% of the preplanned OS events. Additionally, analyses of factors associated with durable responses and characteristics of long-term management of venetoclax-azacitidine-treated patients are reported.

2 | METHODS

2.1 | Patients and study design

Detailed procedures for the multicenter, phase 3, randomized, placebo-controlled, double-blind VIALE-A trial (NCT02993523) were previously described.[4] Patients were aged ≥18 years with previously untreated AML based on the 2016 World Health Organization criteria[5] and were considered ineligible for standard induction therapy (aged ≥75 years or with comorbid condition precluding treatment with intensive chemotherapy), with Eastern Cooperative Oncology Group performance status 0–2 for patients aged ≥75 years, or 0–3 for patients aged ≥18 to 74 years. Patients could not have received previous treatment for myelodysplastic syndrome with venetoclax, a hypomethylating agent, or chemotherapy, nor could they have favorable-risk cytogenetics per NCCN 2016 guidelines. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Council for Harmonization. The protocol was approved by regional review boards and/or ethics committees. All patients provided written informed consent.

Patients were randomized 2:1 to receive venetoclax-azacitidine or placebo-azacitidine. Venetoclax or placebo was administered orally once daily, starting with a dose ramp-up in cycle 1 (100 mg Day 1; 200 mg Day 2; 400 mg Days 3–28) and continuing at 400 mg daily for subsequent cycles. In both study arms, patients received intravenous or subcutaneous azacitidine at 75 mg/m^2 on Days 1–7 of each 28-day cycle. Venetoclax dose interruptions were allowed between cycles to allow for blood count recovery and to mitigate cytopenia; dose modifications were implemented to accommodate use of prophylactic anti-infective agents.

2.2 | Endpoints and assessments

The primary endpoint was OS, calculated as the number of days from randomization to death from any cause. Key secondary endpoints were rates of CR, CR/CRi, and CR with/without partial hematologic recovery (CR/CRh); OS and CR/CRi in prespecified (*IDH1/2* or *FLT3* mutations) subgroups; measurable residual disease (MRD) response rate (<10^{-3} by flow cytometry) in patients who achieved CR/CRi; post-baseline transfusion independence rate; and patient-reported quality-of-life measures. MRD and disease assessments were performed at the end of cycle 1 and every 3 cycles, thereafter. Disease assessments were based on modified International Working Group criteria and European LeukemiaNet (ELN) criteria[6,7] A recovery period of up to 2 weeks after bone marrow evaluation was permitted to allow for improved blood counts for response assessments. Non-CR/CRi responders were defined as patients who did not achieve CR or CRi, including those with morphologic leukemia-free state or partial remission. Assessment of quality-of-life was based on patient questionnaires for Patient-Reported Outcomes Measurement Information System (PROMIS) Cancer Fatigue SF 7a and European Organization for Research and Treatment of Cancer (EORTC) Core Quality-of-Life (QLQ)-C30. Exploratory and post-hoc analyses included investigation of factors associated with durable responses and characteristics of long-term management of venetoclax in patients with AML.

Safety analyses included all patients who received ≥1 dose of azacitidine or venetoclax. Adverse events (AEs) were graded based on National Cancer Institute Common Terminology Criteria for AEs, version 4.03.[8]

2.3 | Statistical analysis

Clinical data cutoff for this final analysis was December 1, 2021. OS was assessed on reaching 100% ($n = 360$) of the target number of OS events, which provided 86.7% power to detect a statistically significant difference in OS between the 2 treatment arms at α of 0.04. OS distribution was estimated using Kaplan–Meier methodology. HRs between treatment groups were estimated using Cox proportional-hazards model stratified according to age and cytogenetic risk. The composite response rate between treatment groups was compared using the Cochran–Mantel–Haenszel test. All *p* values reported are nominal *p* values.

3 | RESULTS

3.1 | Patients

In total, 433 patients were randomized, and 431 were included in the intent-to-treat population ($n = 286$ venetoclax-azacitidine; $n = 145$ placebo-azacitidine; Figure S1).[4] Baseline characteristics previously described[4] are presented by response subgroup (Table S1). The median follow-up was 43.2 months (range, <0.1–53.4), and 21 patients remained on treatment ($n = 21$ venetoclax-azacitidine; $n = 0$ placebo-azacitidine; Figure S1). Three patients received SCT following treatment, with none reported since the last analysis.[4]

3.2 | Updated efficacy analysis

Median OS remained 14.7 months versus 9.6 months for patients treated with venetoclax-azacitidine versus placebo-azacitidine, respectively (HR, 0.58 [95% CI, 0.47–0.72]; $p < .001$ [stratified log-rank test]; Figure 1A), with improved HR over the 75% OS interim analysis (HR, 0.66 [95% CI, 0.52–0.85]).[4] Estimated 24-month OS rates were 37.5% (95% CI, 31.8–43.3) with venetoclax-azacitidine versus 16.9% (95% CI, 11.2–23.5) with placebo-azacitidine. Prespecified subgroup analyses included OS in patients with *IDH1/2* or *FLT3* mutations. Median OS for patients with *FLT3* mutations was not significantly different between the venetoclax-azacitidine and placebo-azacitidine arms at the previous analysis[4] or the current analysis. In those with *IDH1/2* mutations, median OS was reached at 19.9 months (95% CI, 12.2–27.7) with venetoclax-azacitidine ($n = 61$) vs. 6.2 months (95% CI, 2.3–12.7) with placebo-azacitidine ($n = 28$; HR, 0.31 [95% CI, 0.19–0.52]; $p < .001$ [unstratified log-rank test]; Figure 1B). Among patients with *IDH1* mutations, median OS was 10.2 months (95% CI, 2.3–25.1) and 2.2 months (95% CI, 1.1–5.6) in the venetoclax-azacitidine arm ($n = 23$) and placebo-azacitidine arm ($n = 11$), respectively (HR, 0.28 [95% CI, 0.12–0.66]; $p = .002$; Figure S2A). In patients with *IDH2* mutation, median OS was 27.5 months (95% CI, 16.4–36.9) and 13.0 months (95% CI, 3.8–14.9) in the venetoclax-azacitidine arm ($n = 40$) and placebo-azacitidine arm ($n = 18$), respectively (HR, 0.30 [95% CI, 0.16–0.57]; $p < .001$; Figure S2B).

In additional subgroups analyzed, most treated with venetoclax-azacitidine had continued OS benefit over those in the placebo-azacitidine arm (Figure 2). In an exploratory multivariate analysis of OS in the venetoclax-azacitidine arm, OS did not significantly vary by baseline age (18–75 vs. ≥75 years), sex, ECOG performance status (<2 vs. ≥2), or AML status (de novo vs. secondary; Table S2). Patients with poor cytogenetic risk score at baseline, however, had significantly poorer OS relative to intermediate-risk patients (adjusted HR, 0.575 [95% CI, 0.44–0.76], $p < .001$). Median OS by MRD response was reached at this long-term follow-up. In the venetoclax-azacitidine arm, attainment of MRD response (MRD $<10^{-3}$) was associated with longer median OS (34.2 months [95% CI, 27.7–44.0]) vs. no MRD response (18.7 months [95% CI, 12.9–23.5]; Figure 1C).

CRs were observed in 111/286 patients (38.8% [95% CI, 33.1–44.7]) vs. 26/145 patients (17.9% [95% CI, 12.1–25.2]; $p < .001$) with venetoclax-azacitidine and placebo-azacitidine, respectively (Table S3). CR/CRi rates were 66.8% (191/286 [95% CI, 61.0–72.2]) vs. 29.0% (42/145 [95% CI, 21.7–37.1]; $p < .001$), with similar rates for CR/CRh (Table S3). Median time to first CR/CRi was 1.3 months (range, 0.6–19.7) for venetoclax-azacitidine and 2.8 months (range, 0.8–26.8) for placebo-azacitidine, consistent with the previous analysis.[4] Subgroup analyses for CR/CRi are presented in Figure S3. Median duration of response (DOR) for CR was 22.1 months (95% CI, 16.7–27.0) for venetoclax-azacitidine, and 13.4 months (95% CI, 10.3–15.1) for placebo-azacitidine (Figure S4A); median DOR for CR/CRi was 18.2 months (95% CI, 13.6–23.1) and 10.7 months (95% CI, 5.0–15.1), respectively (Figure S4B). Consistent with the interim analysis, rates of transfusion independence were significantly higher in the venetoclax-azacitidine arm (Table S4).[4] Median durations of transfusion independence were similar in both arms. Event-free survival was significantly longer in the venetoclax-azacitidine arm (median 9.9 [95% CI, 8.4–11.8] vs. 7.4 months [95% CI, 5.6–9.5]; HR, 0.58 [95% CI, 0.470–0.726]; $p < 0.001$; Figure S5), also consistent with previous analysis.[4]

Of those with CR/CRi responses and evaluable MRD, 69/165 patients (42%) in the venetoclax arm (Table S5) and 11/35 patients (31%) in the control arm (Table S6) attained MRD responses per ELN guidelines at any point during the study. Of the 69 patients who had CR/CRi and MRD responses at any time in the venetoclax-azacitidine arm, 17 (25%), had poor-risk cytogenetics and 18 (26%) had secondary AML (Table S5). Of the 11 patients who had CR/CRi and MRD responses at any time in the placebo-azacitidine arm, 2 (18%) had poor-risk cytogenetics and 2 (18%) had secondary AML (Table S6). In both arms, CR/CRi and MRD responses were achieved independent of somatic mutations. In the venetoclax-azacitidine arm, 33% (21/64) of patients who achieved CR/CRi with an MRD response had *IDH1/2* mutations, 33% (15/45) had *NPM1* mutations, 19% (10/52) had *FLT3* mutations, and 13% (6/45) had *TP53* mutations (Table S5). In the

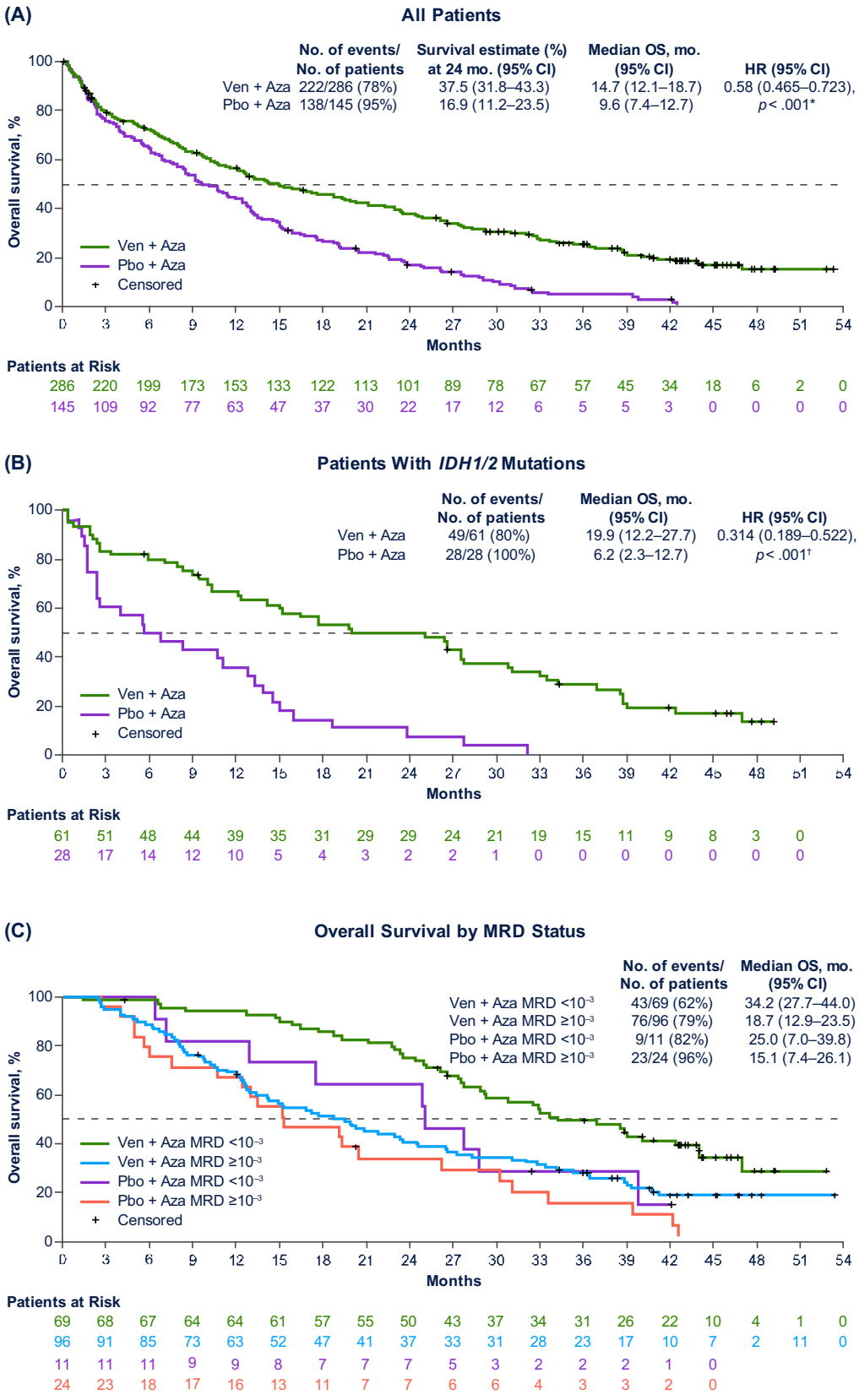


FIGURE 1 Overall survival in patients treated with venetoclax-azacitidine or placebo-azacitidine at median follow-up of 43.2 months. (A) All patients. (B) Patient subgroups by *IDH1/2* mutation status. (C) Patient subgroups by measurable residual disease (MRD) $<10^{-3}$ or $\geq 10^{-3}$. *Stratified log-rank nominal *p* value. †Unstratified log-rank nominal *p* value. Aza, azacitidine; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; Pbo, placebo; Ven, venetoclax.

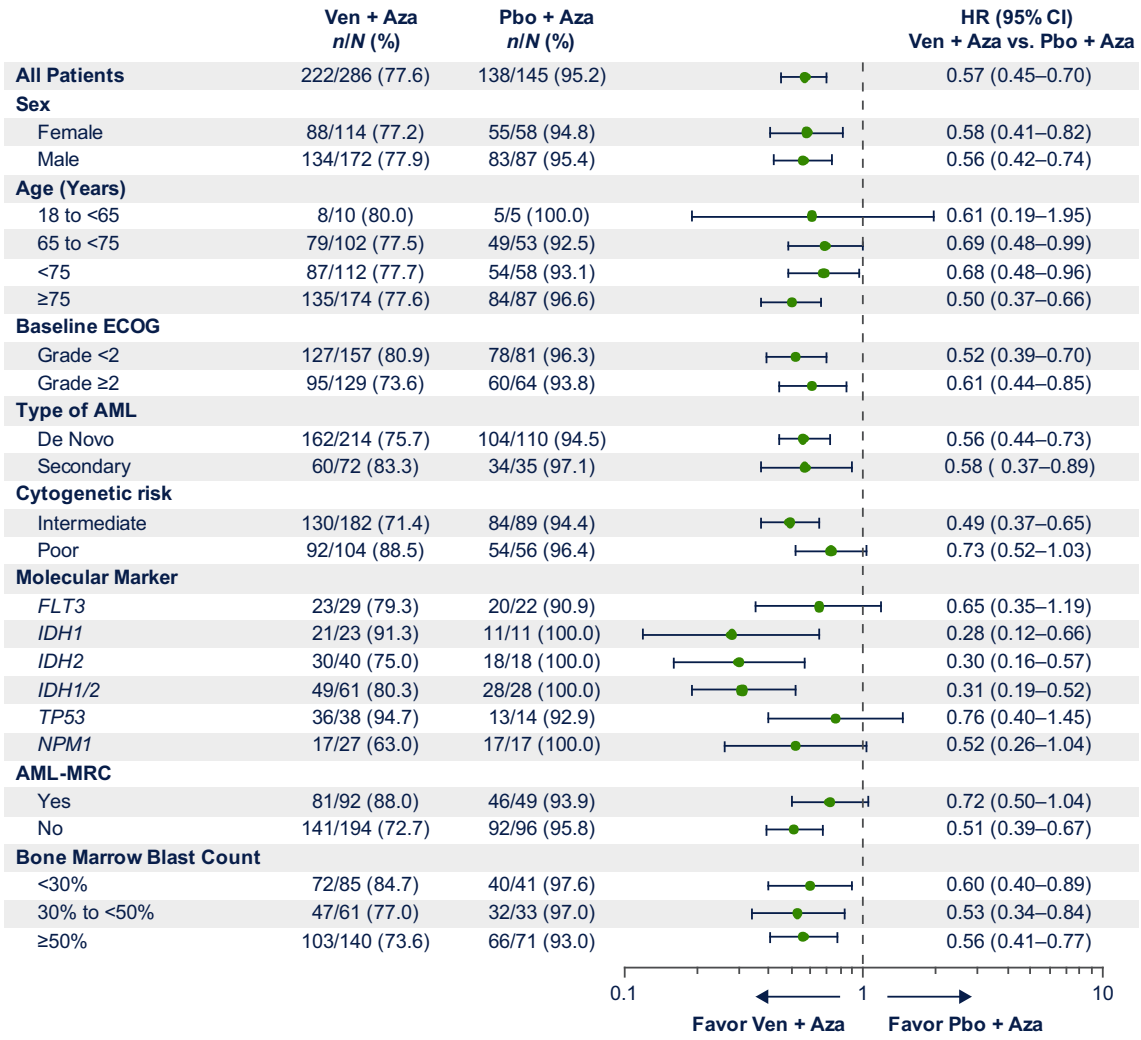


FIGURE 2 Subgroup analysis of overall survival. AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; Aza, azacitidine; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval; HR, hazard ratio; Pbo, placebo; Ven, venetoclax.

placebo-azacitidine arm, 10% (1/10) of those who achieved CR/CRi with an MRD response had *IDH1/2* mutations, 25% (2/8) had *NPM1* mutations, 36% (4/11) had *FLT3* mutations, and 0% (0/8) had *TP53* mutations (Table S6). Outcomes for patients in VIALE-A who achieved CR/CRi with an MRD response have been described in detail previously.[9]

In an exploratory analysis of long-term survival, 98/191 patients (51%) with CR/CRi in the venetoclax-azacitidine arm survived ≥2 years, and 55/191 (29%) survived ≥3 years. In the placebo-azacitidine arm, 18/42 patients (43%) and 5/42 patients (12%) with CR/CRi survived ≥2 and ≥3 years, respectively. In the venetoclax-azacitidine arm, 38% (35/93) of responders who lived <2 years and 20% (20/98) of those who lived ≥2 years had poor-risk cytogenetics. In the control arm, 33% (8/24) and 28% (5/18) of patients with CR/CRi who survived <2 and ≥2 years, respectively, had poor-risk cytogenetics (Table S1). Of responders who survived ≥2 years in the venetoclax-azacitidine and placebo-azacitidine arms, 35% (29/82) and 7% (1/14) had *IDH1/2* mutations, 11% (7/65) and 23% (3/13) had *FLT3* mutations, 20% (10/50) and 18% (2/11) had *NPM1* mutations, and 8% (4/50) and 0% (0/11) had *TP53* mutations, respectively.

Of those who achieved CR/CRi, 100/191 patients (52%) and 31/42 patients (74%) in the venetoclax-azacitidine and placebo-azacitidine arms, respectively, subsequently had progressive disease (PD) or morphologic relapse (MR); 42/100 (42%) and 15/31 (48%) received a subsequent therapy (Table S7). Median time from PD/MR to initiation of subsequent treatment was 28 days (range, 2–201) in the venetoclax-azacitidine arm and 46 days (range, 5–473) in the placebo-azacitidine arm. Two patients in the venetoclax-azacitidine arm and 3 patients in the placebo-azacitidine arm received subsequent venetoclax. Among all patients in the venetoclax-azacitidine arm, irrespective of initial response to venetoclax, median OS from PD or confirmed MR or resistant disease was 6.8 months (95% CI, 5.4–8.9), and median OS from initiation of subsequent therapy was 6.2 months (95% CI, 3.9–8.5; Figure S6).

3.3 | Updated safety analysis

Safety analysis included 283 patients in the venetoclax-azacitidine arm and 144 patients in the placebo-azacitidine arm. No new safety

signals were identified at 43.2 months median follow-up (Table 1) compared with the earlier analysis.[4] Overall rates of treatment-emergent AEs (TEAEs) were similar between treatment arms, with higher rates of hematologic TEAEs in the venetoclax-azacitidine versus placebo-azacitidine arms, including grade ≥3 thrombocytopenia (46% vs. 40%), neutropenia (43% vs. 29%), and febrile neutropenia (43% vs. 19%; Table 1). With longer follow-up, 242 patients (86%) in the venetoclax-azacitidine arm and 111 (77%) patients in the control arm had serious TEAEs (Table S8). TEAEs led to treatment discontinuation in 85/283 (30%) and 32/144 (22%) patients in the venetoclax-azacitidine and placebo-azacitidine arms, respectively (Table S9). Overall, 360 patients died in the study from any reason, including 222/286 in the venetoclax-azacitidine arm and 138/145 in the placebo-azacitidine arm. TEAEs led to death in 71/283 patients (25%) in the venetoclax-azacitidine arm and 31/144 patients (22%) in the placebo-azacitidine arm (Table S10). Six patients died while in CR/CRi, including 4 from infections (severe sepsis, septic shock, pneumonia, and sepsis; all 4 had grade 3/4 neutropenia) and 2 from other reasons (worsening of general condition and cardiovascular event); all were in the venetoclax-azacitidine arm. Of those who died from infections, venetoclax treatment duration was reduced to 21 days in 2 patients in CR and the other 2 in CRi remained at 28 days.

Quality-of-life assessments indicated no differences in fatigue score between arms ($p = .65$; Table S11). Compared with those in the placebo-azacitidine arm, patients in the venetoclax-azacitidine arm experienced a trend toward longer time to deterioration in global health score based on the EORTC QLQ-C30 questionnaire (Table S12).

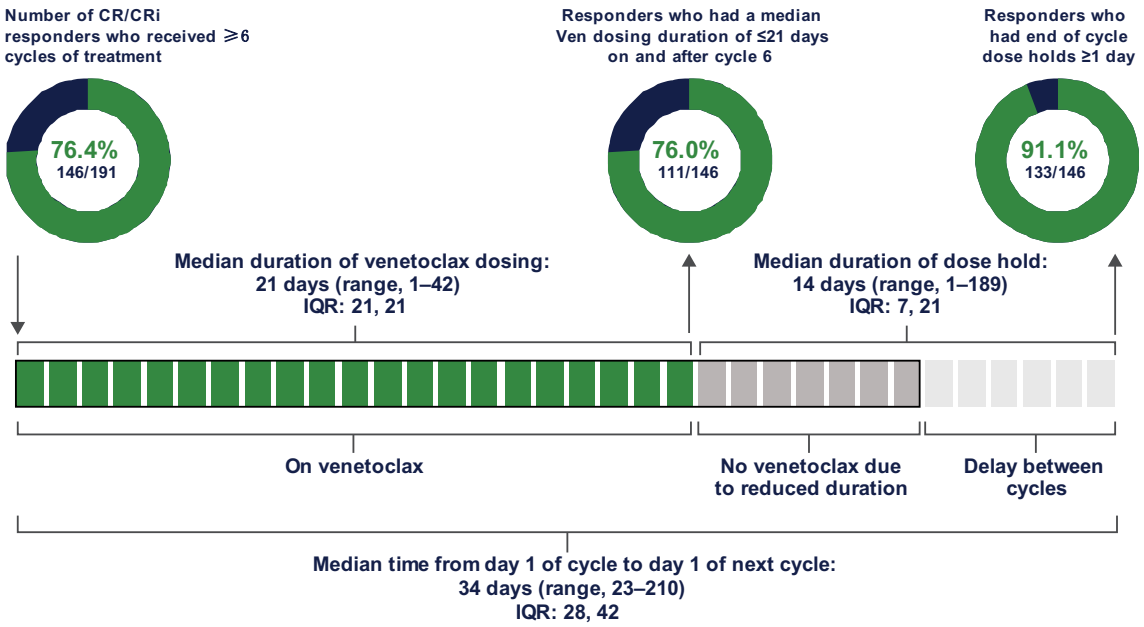
3.4 | Exploratory analysis of long-term treatment in the venetoclax-azacitidine arm

Among patients in the venetoclax-azacitidine arm who achieved CR/CRi as best response (191/282 [68%]), median number of treatment cycles was 13 (range, 1–46), with 146/191 (76%) receiving ≥6 cycles (Figure 3). Median total treatment cycle duration in these patients, defined as the start of a cycle until the start of the next cycle (including dose holds), was 34 days (range, 23–210), and median venetoclax dosing duration was 21 days (range, 1–42) per cycle. Beginning on or after cycle 6, 101/146 (69%) CR/CRi responders had a median dosing duration between 15 and 21 days, and 10/146 (7%) had a median dosing duration <15 days.

Of these responders who received ≥6 cycles of therapy in the venetoclax-azacitidine arm, 115/146 (79%) had ≥1 event of grade ≥3

TABLE 1 Treatment-emergent adverse events of any grade in ≥20% or at grade ≥3 in ≥5% of patients in either arm.

	Venetoclax-azacitidine ($N = 283$)		Placebo-azacitidine ($N = 144$)	
Adverse event, no. (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
All adverse events	283 (100)	279 (99)	144 (100)	139 (97)
Hematologic adverse events	240 (85)	236 (83)	101 (70)	99 (69)
Thrombocytopenia	134 (47)	130 (46)	60 (42)	57 (40)
Febrile neutropenia	121 (43)	121 (43)	27 (19)	27 (19)
Neutropenia	121 (43)	121 (43)	42 (29)	41 (29)
Anemia	87 (31)	80 (28)	33 (23)	32 (22)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Non-hematologic adverse events				
Diarrhea	128 (45)	13 (5)	49 (34)	4 (3)
Nausea	126 (45)	5 (2)	53 (37)	1 (1)
Constipation	124 (44)	4 (1)	57 (40)	2 (1)
Hypokalemia	84 (30)	33 (12)	43 (30)	16 (11)
Vomiting	85 (30)	6 (2)	34 (24)	1 (1)
Decreased appetite	79 (28)	14 (5)	27 (19)	3 (2)
Pyrexia	75 (27)	6 (2)	33 (23)	2 (1)
Peripheral edema	70 (25)	1 (<1)	27 (19)	0
Fatigue	62 (22)	10 (4)	25 (17)	2 (1)
Hypophosphatemia	36 (13)	22 (8)	17 (12)	11 (8)
Hypertension	30 (11)	21 (7)	12 (8)	6 (4)
Infections	245 (87)	189 (67)	101 (70)	78 (54)
Pneumonia	74 (26)	66 (23)	43 (30)	40 (28)
Urinary tract infection	32 (11)	15 (5)	10 (7)	8 (6)
Sepsis	22 (8)	21 (7)	13 (9)	13 (9)
Lung infection	21 (7)	15 (5)	4 (3)	3 (2)



	Ven + Aza (*N* = 282)
Patients who achieved CR/CRi as best response, no. (%)	191 (68)
Median no. of cycles (range)	13 (1–46)
Responders who had ≥6 cycles, no./No. (%)	146/191 (76)

FIGURE 3 Treatment duration and dosing schedule among patients who achieved complete remission with or without blood count recovery (CR/CRi). Aza, azacitidine; IQR, interquartile range; Ven, venetoclax.

neutropenia. The median duration of delays between cycles in these patients ranged from 8 to 19 days. At cycle 6, median duration of any-grade neutropenia among responders in the venetoclax-azacitidine arm ($n = 59$) was 29 days, and median duration remained similar across cycles thereafter. Median neutrophil counts for patients with available data generally trended upwards with each cycle (Figure S7). Eighty-one patients (55%) had ≥1 event of grade ≥3 thrombocytopenia, 101 (69%) experienced a grade ≥3 infection, and 16 (11%) experienced a grade ≥3 hemorrhage event.

4 | DISCUSSION

Long-term follow-up of the VIALE-A trial continues to demonstrate a favorable risk–benefit profile for venetoclax-azacitidine in patients with untreated AML who are ineligible for intensive chemotherapy due to older age or comorbid conditions. Following approximately 2 years of additional median follow-up, at a median of 43.2 months, longer median OS (14.7 vs. 9.6 months), reduced risk of death (HR, 0.58, $p < .001$), and higher CR/CRi rates (67% vs. 29%) were seen in the venetoclax-azacitidine arm compared with placebo-azacitidine, consistent with the interim analysis of this study.[4] In addition, longer follow-up resulted in increased median DOR for CR/CRi (18.2 vs. 17.5 months) in the venetoclax-azacitidine arm and decreased median DOR for CR/CRi (10.7 vs. 13.4 months) in the placebo-azacitidine arm versus interim analysis.[4] These findings indicate sustained benefit of venetoclax-azacitidine with additional follow-up in the current analysis.

Analysis of baseline characteristics associated with response, MRD outcomes, and survival indicated that venetoclax-azacitidine provides continued benefit over azacitidine across patient subpopulations. A higher proportion of patients with poor-risk cytogenetics (25% vs. 18%), *IDH1/2* (33% vs. 10%), *NPM1* (33% vs. 25%), or *TP53* (13% vs. 0%) mutations achieved MRD responses in the venetoclax-azacitidine versus placebo-azacitidine arms, respectively. Attainment of MRD response in the venetoclax arm was associated with longer survival compared with persistently MRD-positive patients with CR/CRi (median OS of 34 vs. 19 months), supporting previous evidence indicating that MRD response is associated with better outcomes, even with non-cytotoxic therapy.[9–11] In a previous analysis, patients achieving MRD response after one treatment cycle and patients reporting MRD response thereafter demonstrated similarly high OS rates (88% vs. 96% at 12 months and 82% vs. 86% at 18 months, respectively), with no further advantage provided by earlier MRD responses.[9] Long-term survival (≥2 years) was observed with venetoclax-azacitidine in patients with *IDH1/2* mutations, *NPM1* mutations, MRD response regardless of underlying genomics, and in poor cytogenetic risk groups (Table S1, Figure 1), indicating that

venetoclax-azacitidine is beneficial in subgroups of patients with poorer outcomes to conventional therapies.[12] Both patients with *IDH1* and *IDH2* mutations experienced improved OS when treated with venetoclax-azacitidine compared with azacitidine (HR, 0.28 and 0.30, respectively; Figure S2). *IDH2* mutation was associated with longer OS than *IDH1* in both treatment arms, which aligns with a previously reported analysis.[13] Detailed analyses of outcomes based on the presence of key mutations or MRD response in patients treated with venetoclax-azacitidine have been recently published[9,13–15] and are supported by these long-term findings.

Poor-risk cytogenetics and *TP53* mutations are particularly associated with poor outcomes to conventional therapies.[12,16] A previous combined analysis of VIALE-A and a phase 1b study evaluating venetoclax-azacitidine indicated that *TP53* mutations are a primary driver of inferior OS outcomes in patients with poor-risk cytogenetics treated with venetoclax-azacitidine. In the current analysis, few patients with *TP53* mutations (irrespective of cytogenetic risk) survived for ≥2 years (8%; $n = 4$), indicating better therapies are still needed for this resistant genomic subgroup. Additional data are required to further understand the impact of venetoclax-azacitidine across the spectrum of mutational and cytogenetic subgroups, which will be the subject of future analyses.

No new safety signals were identified for venetoclax-azacitidine or placebo-azacitidine compared with interim analysis, and the safety profile was consistent with known toxicities for both agents.[4] With longer follow-up and longer duration of treatment, grade ≥3 TEAEs at any time on study were slightly higher (Table 1) than earlier analysis.[4] Hematologic TEAEs were common in both arms, with thrombocytopenia, neutropenia, and febrile neutropenia being the most frequently observed grade ≥3 TEAEs. There were 4 deaths in remission due to infectious complications in the venetoclax-azacitidine arm in patients with high-grade neutropenia, with 2 having no reduction in venetoclax duration. Previous analysis suggests granulocyte colony-stimulating factor used per institutional practice following blast clearance can reduce duration of neutropenia without negatively impacting remission duration or OS with venetoclax-azacitidine.[17]

The VIALE-A study protocol recommended dose schedule modifications following achievement of CR/CRi to manage hematologic AEs.[4,18] These modifications could include a delay in the initiation of next cycle, reduction in the number of venetoclax dosing days per cycle, or a combination of both scenarios (Figure 3). In this analysis, most patients who achieved CR/CRi received ≥6 cycles (median 13 cycles) of treatment and had venetoclax duration modifications to allow for hematologic recovery. Although almost half of the patients in the venetoclax-azacitidine arm experienced grade ≥3 neutropenia, both nadir and median absolute neutrophil count levels generally increased by cycle over the course of treatment, suggesting a trend toward improved blood counts in later cycles. Most patients in remission who remained on ≥6 cycles of treatment had a median venetoclax dosing duration of 21 days or shorter per cycle; these findings highlight the importance of recommended dose modifications to manage cytopenias while on venetoclax-azacitidine therapy. Notably, a previous post-hoc analysis of VIALE-A indicated that venetoclax dosing modifications did not adversely affect survival outcomes.[18] Bone marrow assessments of response at end of cycle 1 and in early cycles of venetoclax-azacitidine therapy could inform response status and allow for implementation of effective management of persistent cytopenias by venetoclax dose schedule modifications.[18]

In summary, long-term VIALE-A data demonstrate that venetoclax-azacitidine continues to show significant improvement in OS compared to azacitidine and maintain remission in older patients and patients who are otherwise ineligible for intensive chemotherapy. The study also identified shared characteristics among long-term responders and provides guidance on key aspects of managing AML patients receiving this regimen. Venetoclax-azacitidine helps address the need for effective therapy in these patients who otherwise have few treatment options.

AUTHOR CONTRIBUTIONS

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DATA AVAILABILITY STATEMENT

AbbVie and Genentech are committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after global approval and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://vivli.org/ourmember/abbvie/ then select "Home".

PATIENT CONSENT

All patients provided written informed consent for this trial.

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REFERENCES

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136-1152.
2. SEER data base: cancer stat facts: leukemia – acute myeloid leukemia (AML). Accessed January 25, 2023. https://seer.cancer.gov/statfacts/html/amyl.html
3. Sasaki K, Ravandi F, Kadia TM, et al. De novo acute myeloid leukemia: a population-based study of outcome in the United States based on the Surveillance, Epidemiology, and End Results (SEER) database, 1980 to 2017. *Cancer*. 2021;127(12):2049-2061.
4. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
5. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
6. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol*. 2003;21(24):4642-4649.
7. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
8. *Common Terminology Criteria for Adverse Events (CTCAE)*, v4.03. National Cancer Institute; 2010.
9. Pratz KW, Jonas BA, Pullarkat V, et al. Measurable residual disease response and prognosis in treatment-naive acute myeloid leukemia with venetoclax and azacitidine. *J Clin Oncol*. 2022;40(8):855-865.
10. Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. *JAMA Oncol*. 2020;6(12):1890-1899.
11. Ivey A, Hills RK, Simpson MA, et al. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med*. 2016;374(5):422-433.
12. Döhner H, Dolnik A, Tang L, et al. Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care. *Leukemia*. 2018;32(12):2546-2557.
13. Pollyea DA, Pratz KW, Wei AH, et al. Outcomes in patients with poor-risk cytogenetics with or without TP53 mutations treated with venetoclax and azacitidine. *Clin Cancer Res*. 2022;28(24):5272-5279.
14. Konopleva M, Thirman MJ, Pratz KW, et al. Impact of FLT3 mutation on outcomes after venetoclax and azacitidine for patients with treatment-naive acute myeloid leukemia. *Clin Cancer Res*. 2022;28(13):2744-2752.
15. Pollyea DA, DiNardo CD, Arellano ML, et al. Impact of venetoclax and azacitidine in treatment-naive patients with acute myeloid leukemia and IDH1/2 mutations. *Clin Cancer Res*. 2022;28(13):2753-2761.
16. Rücker FG, Schlenk RF, Bullinger L, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. *Blood*. 2012;119(9):2114-2121.
17. DiNardo C, Pratz K, Panayiotidis P, et al. P510: the impact of post-remission granulocyte colony-stimulating factor use in the phase 3 studies of VENETOCLAX combination treatments in patients with newly diagnosed acute myeloid leukemia. *HemaSphere*. 2022;6:409-410.
18. Pratz KW, DiNardo CD, Selleslag D, et al. Postremission cytopenia management in patients with acute myeloid leukemia treated with venetoclax and azacitidine in VIALE-A. *Am J Hematol*. 2022;97(11):E416-E419.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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