Impact of Venetoclax and Azacitidine in Treatment-Naïve Patients with Acute Myeloid Leukemia and *IDH1/2* Mutations

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ABSTRACT

Purpose: To evaluate efficacy and safety of venetoclax + azacitidine among treatment-naïve patients with *IDH1/2*-mutant (mut) acute myeloid leukemia (AML).

Patients and Methods: Data were pooled from patients enrolled in a phase III study (NCT02993523) that compared patients treated with venetoclax + azacitidine or placebo + azacitidine and a prior phase Ib study (NCT02203773) where patients were treated with venetoclax + azacitidine. Enrolled patients were ineligible for intensive therapy due to age ≥75 years and/or comorbidities. Patients on venetoclax + azacitidine received venetoclax 400 mg orally (days 1–28) and azacitidine (75 mg/m^2; days 1–7/28-day cycle).

Results: In the biomarker-evaluable population, *IDH1/2*mut was detected in 81 (26%) and 28 (22%) patients in the venetoclax + azacitidine and azacitidine groups. Composite complete remission [CRc, complete remission (CR)+CR with incomplete hematologic recovery (CRi)] rates (venetoclax + azacitidine/azacitidine) among patients with *IDH1/2*mut were 79%/11%, median duration of remission (mDoR) was 29.5/9.5 months, and median overall survival (mOS) was 24.5/6.2 months. CRc rates among patients with *IDH1/2* wild-type (WT) were 63%/31%, mDoR 17.5/10.3 months, and mOS 12.3/10.1 months. In patients with *IDH1*mut, CRc rates (venetoclax + azacitidine/azacitidine) were 66.7%/9.1% and mOS 15.2/2.2 months. In patients with *IDH2*mut, CRc rates were 86.0%/11.1% and mOS not reached (NR)/13.0 months. Patients with *IDH1/2* WT AML treated with venetoclax + azacitidine with poor-risk cytogenetics had inferior outcomes compared with patients with *IDH1/2*mut, who had superior outcomes regardless of cytogenetic risk (mOS, *IDH1/2*mut: intermediate-risk, 24.5 months; poor-risk, NR; *IDH1/2* WT: intermediate, 19.2 and poor, 7.4 months). There were no unexpected toxicities in the venetoclax + azacitidine group.

Conclusions: Patients with *IDH1/2*mut who received venetoclax + azacitidine had high response rates, durable remissions, and significant OS; cytogenetic risk did not mitigate the favorable outcomes seen from this regimen for *IDH1/2*mut.

See related commentary by Perl and Vyas, p. 2719

Introduction

Acute myeloid leukemia (AML) is a biologically and clinically heterogeneous malignancy (1, 2) in which outcomes to therapy may vary by commonly occurring cytogenetic and molecular features (3). Recurrent mutations in isocitrate dehydrogenase (*IDH*) enzymes have been identified to occur in approximately 20% of patients with AML, with 7%–14% and 8%–19% of patients possessing the *IDH1*- and *IDH2*-mutant subtypes, respectively (4). The *IDH* enzymes catalyze the conversion of isocitrate to α-ketoglutarate, a critical intermediate in cellular metabolism. Mutations in *IDH1/2* produce high levels of the oncometabolite 2-hydroxyglutarate (2-HG; ref. 5). Elevated 2HG levels can lead to multiple downstream effects related to inhibition of α-ketoglutarate-mediated reactions, resulting in a hypermethylated phenotype, impaired cellular differentiation, and ultimately the promotion of tumorigenesis (1, 6–8). For *IDH1*, the heterozygous mutations are predominantly located at codon 132 (*IDH1*^{R132}), and for *IDH2*, *IDH2*^{R140} are the more common alterations than *IDH2*^{R172} (9, 10). The prognostic impact of *IDH1*^{R132}, *IDH2*^{R140}, and *IDH2*^{R172} mutations have not been fully elucidated and likely depend on the presence or absence of other prognostic cooccurring mutations (6, 10, 11).

For treatment-naïve patients with AML and *IDH1/2* mutations who are ineligible for induction chemotherapy, there is no standard therapy. Ivosidenib and enasidenib are oral small-molecule inhibitors that are approved for the targeted inhibition of mutant *IDH1* and *IDH2* in relapsed/refractory AML, respectively. For treatment-naïve and chemotherapy-ineligible *IDH1*-mutated AML patients, ivosidenib as monotherapy is also approved by FDA (12). The safety and efficacy of both molecules are currently being evaluated in combination with

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Translational Relevance

Approximately 20% of patients with acute myeloid leukemia (AML) have isocitrate dehydrogenase (*IDH*) mutations that result in tumorigenesis due to alterations in cellular metabolism. The preliminary analysis of the ongoing randomized phase III trial (NCT02993523) reported that patients treated with venetoclax and azacitidine had higher remission rates and more prolonged overall survival (OS) than patients treated with placebo and azacitidine. We further evaluated the efficacy and safety of the combination and reported that the remission rates and OS among patients with *IDH1/2* mutations were superior as compared with azacitidine alone, and patients with *IDH2* mutations had numerically better outcomes than patients with *IDH1* mutations. Additional analysis demonstrated that cytogenetic risk by National Comprehensive Cancer Network was not prognostic of OS in patients with *IDH1/2* mutations when treated with the combination, whereas among *IDH1/2* wild-type, cytogenetic risk was prognostic of OS. These findings warrant validation in future analyses.

azacitidine (NCT02677922) and have been demonstrated to be safe with encouraging efficacy (13–15).

Venetoclax is a potent BCL-2 inhibitor. Preclinical investigations of venetoclax showed that cells with *IDH1/2* mutations were especially susceptible to venetoclax therapy (7). *IDH* mutations predicted higher rates of response to BCL-2 inhibition through the production of 2-HG and inhibition of cytochrome c oxidase (COX) activity making AML cells dependent on BCL-2 for survival, as COX inhibition increases activation of the BAX/BAK complex leading to apoptosis upon BCL-2 inhibition (7).

In a previous phase 1b study, treatment with venetoclax and a hypomethylating agent (azacitidine or decitabine) resulted in a favorable composite complete remission [CRc, defined by complete remission (CR) plus CR with incomplete hematologic recovery (CRi)]. CR rate was 71% in treatment-naive ineligible patients with AML and *IDH1/2* mutation (16). The results from the randomized phase III study demonstrated significantly higher CRc rates (75.4% vs. 10.7%) and longer median overall survival [not reached (NR) vs. 6.2 months] for the venetoclax and azacitidine group as compared with azacitidine alone (17). Herein, we further detail the efficacy and safety of venetoclax and azacitidine among treatment-naïve patients with AML and co-morbidities, and/or age ≥ 75 years, ineligible for intensive treatment and harboring *IDH1/2* mutations. We also explore the prognostic impact of cytogenetic risk and molecular genetics on treatment.

Patients and Methods

Patients and treatment

This pooled analysis included patients from the phase III study (NCT02993523, VIALE-A) and a non-randomized, single-arm phase Ib study (NCT02203773). The full study designs and eligibility criteria have been previously reported (16, 17). Patients assessed in this pooled analysis were scheduled to receive either 400-mg venetoclax by mouth daily on days 1–28 and 75 mg/m^2 azacitidine intravenously or subcutaneously on days 1–7 every 28-day cycle, or azacitidine monotherapy. Individuals enrolled in both trials had a confirmed diagnosis of AML by the World Health Organization criteria and must have been ineligible for standard induction chemotherapy due to age ≥75 years or the presence of co-morbidities.

Both studies were approved by the local ethics committees and were conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Assessment of outcomes

Response assessments were performed at screening, end of cycle 1, and every three cycles thereafter and were evaluated per modified International Working Group (IWG) response criteria for AML (18). Duration of CRc was defined as the number of days from the date of first response (CR or CRi) per the modified IWG criteria for AML to the earliest evidence of confirmed morphologic relapse, confirmed disease progression, or death due to disease progression. OS was defined as the time from randomization to the date of death from any cause. Adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (19). Baseline cytogenetic risk was determined locally and evaluated using the National Comprehensive Cancer Network (NCCN) criteria (Supplementary Table S1; ref. 17).

Assessment of molecular data

DNA was isolated from bone marrow aspirates collected from patients prior to the first dose of the study drug and analyzed centrally. Different assays were used to detect *IDH1* and *IDH2* mutations across the two studies. The phase Ib study utilized the MyAML panel (Invivoscribe), while patient samples from the Phase 3 study were analyzed using the MyAML panel and/or a RealTime *IDH1* or *IDH2* assays (Abbott). Concordance between the RealTime *IDH1* or *IDH2* assays and MyAML assays for *IDH*1/2 mutation was evaluated using positive percent agreement and negative percent agreement instead of sensitivity and specificity as both assays have the potential for false-negative tests. The limit of detection was 2% and 2.5% for the CDx assay and MyAML assay, respectively. Patients with missing specimens or inconclusive results were excluded from the analysis. *FLT3* mutations were evaluated by the MyAML assay for the phase Ib study and the Leukostrat FLT3 CDx assay and/or MyAML for the phase III study. In addition, the MyAML assay was also used to detect the presence of other mutations, including *NPM1 and TP53* in both the phase Ib and phase III studies.

Statistical analysis

Demographics were summarized by descriptive statistics. Remission rates were summarized in counts and proportions. OS and DoR were evaluated by the Kaplan–Meier methodology. The HRs and 95% confidence intervals (CI) between treatment groups were estimated using the Cox proportional-hazards model.

Data sharing statement

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following the review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and 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://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

Results

Patient disposition and baseline characteristics

The clinical data cut-off dates were January 4, 2020, for the phase III study and July 19, 2019, for the phase Ib study. The pooled analysis included 353 patients in the venetoclax and azacitidine group (phase III, $n = 286$; phase Ib, $n = 67$) and 145 patients in the azacitidine group.

The biomarker evaluable population included 308/353 (87%) venetoclax and azacitidine patients and 127/145 (88%) azacitidine patients. *IDH1/2* mutations were detected in 81 of 308 (26%) in the venetoclax and azacitidine group and 28 of 127 (22%) in the azacitidine group. Two patients in the venetoclax and azacitidine group and one patient in the azacitidine group had both *IDH1* and *IDH2* mutations, respectively. An overview of the study design and the molecular categorization of patients is shown in **Fig. 1**.

Baseline characteristics of patients with *IDH1/2* mutations are shown in **Table 1**. Compared with *IDH1/2*-mutated patients, *IDH1/2* WT had a higher incidence of poor-risk cytogenetics [venetoclax and azacitidine group (*IDH1/2* mutated vs. *IDH1/2* WT): 23.5% vs. 42.7%; azacitidine group: 32.1% vs. 42.4%], and a higher incidence of blast percentage <30 [venetoclax and azacitidine group (*IDH1/2* mutated vs. *IDH*1/2 WT): 17.3% vs. 36.1%; azacitidine group: 21.4% vs. 30.3%].

Remission rates

Among patients with *IDH1/2* mutation (venetoclax and azacitidine vs. azacitidine), the median number of treatment cycles administered was 8.0 (range: 1.0 Ð 37.0) versus 2.5 (1.0 Ð 18.0). Patients with *IDH1/2* mutations and treated with venetoclax and azacitidine had higher CRc rates than patients with *IDH1/2* mutations and treated with azacitidine [79.0% ($n = 64$) vs. 10.7% ($n = 3$); **Fig. 2**A], the median time to CR or CRi response was 1.1 (range: 0.7–8.8) versus 3.4 (2.1 - 7.1) months, and the median DoR was 29.5 [95% CI, 16.7–not estimable (NE)] versus 9.5 (3.5–NE) months. In the *IDH1/2* WT (venetoclax and azacitidine group vs. azacitidine group), the CRc rates were 62.6% ($n = 142$) versus 31.3% ($n = 31$); the median time to first response for CR or CRi was 1.3 (range: 0.8–9.9) versus 2.9 (0.8–13.2) months, and the median DoR was 17.5 (95% CI, 10.6–23.5) versus 10.3 (5.0–13.8) months.

In patients with *IDH1*, the CRc rate (venetoclax and azacitidine group vs. azacitidine group) was 66.7% ($n = 22$) versus 9.1% ($n = 1$; **Fig. 2B**) and the median time to first response for CR or CRi was 1.2 (range: 0.8–8.1) versus 3.4 (3.4–3.4) months. The median DoR in the *IDH1*-mutated venetoclax and azacitidine group was 21.9 (95% CI: 7.8–NE) months. In patients with *IDH2* mutations, the CRc rate for venetoclax and azacitidine was 86% ($n = 43$) versus 11.1% ($n = 2$) for azacitidine (**Fig. 2C**) and median time to CR or CRi was 1.1 (range 0.7–8.8) versus
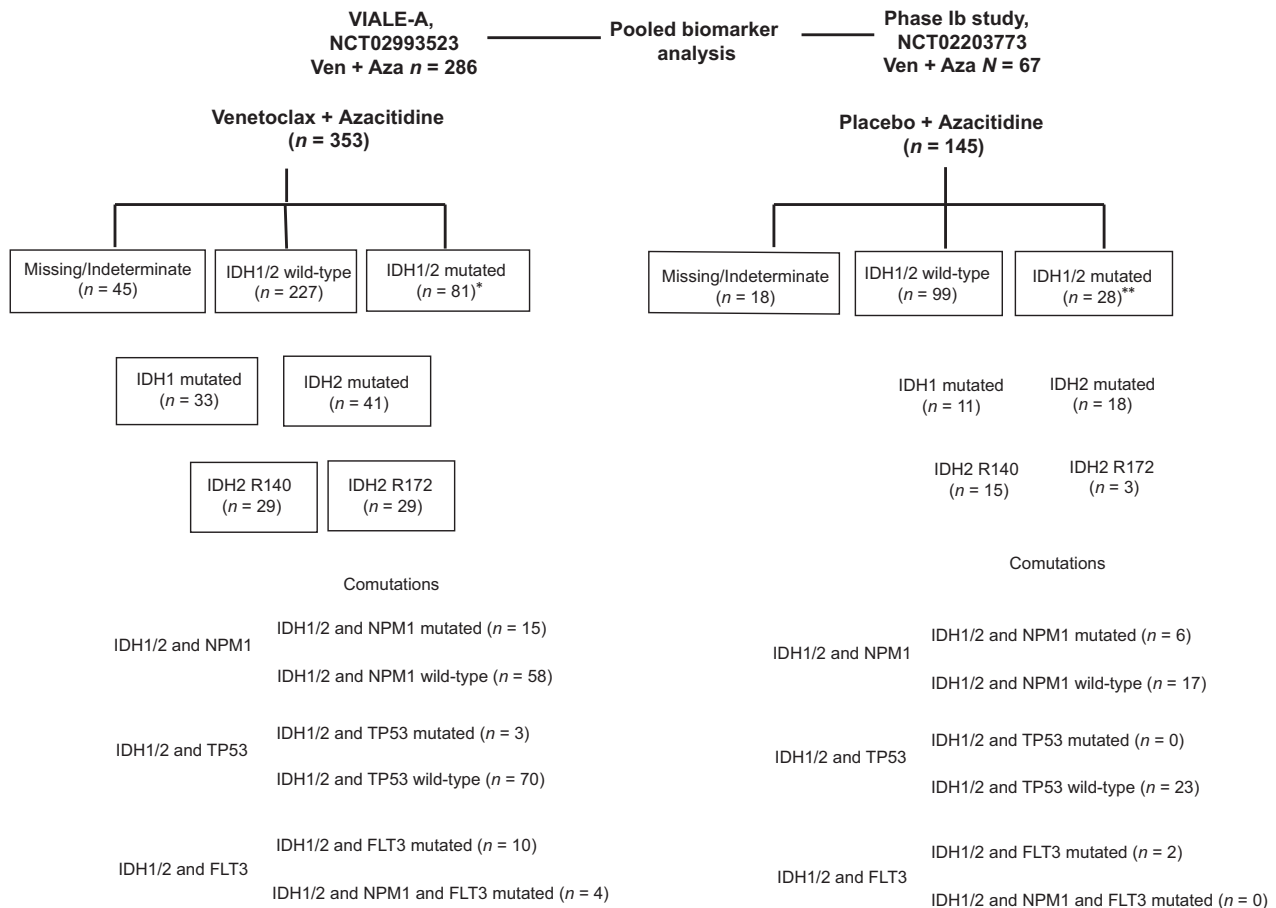
Figure 1.
Study design and molecular classification. *Two patients had both *IDH1/2* mutations. **One patient had both *IDH1/2* mutations. Ven, venetoclax; Aza, azacitidine.

Table 1. Baseline characteristics of patients.

	Venetoclax + Azacitidine		Azacitidine	
	IDH1/2 mutated $n = 81^a$	IDH1/2 wild-type $n = 227$	IDH 1/2 mutated $n = 28^b$	IDH 1/2 wild-type $n = 99$
Median age, years (min, max)	76 (64, 90)	76 (49, 91)	77.5 (62, 90)	76 (60, 87)
<65, n (%)	1 (1.2)	8 (3.5)	1 (3.6)	3 (3.0)
65–<75	27 (33.3)	77 (33.9)	10 (35.7)	32 (32.3)
≥75 years	53 (65.4)	142 (62.6)	17 (60.7)	64 (64.6)
Sex, n (%)				
Female	34 (42.0)	92 (40.5)	11 (39.3)	40 (40.4)
Male	47 (58.0)	135 (59.5)	17 (60.7)	59 (59.6)
AML type, n (%)				
De novo	60 (74.1)	164 (72.2)	24 (85.7)	69 (69.7)
Secondary	21 (25.9)	63 (27.8)	4 (14.3)	30 (30.3)
AML with myelodysplasia-related changes, n (%)	19 (23.5)	83 (36.6)	7 (25.0)	41 (41.4)
ECOG performance status, n (%)				
0–1	46 (56.8)	133 (58.6)	19 (67.9)	60 (60.6)
2–3	35 (43.2)	94 (41.4)	9 (32.1)	39 (39.4)
Cytogenetic risk category, n (%)				
Intermediate	62 (76.5)	130 (57.3)	19 (67.9)	57 (57.6)
Poor	19 (23.5)	97 (42.7)	9 (32.1)	42 (42.4)
Bone marrow blast count, n (%)				
<30%	14 (17.3)	82 (36.1)	6 (21.4)	30 (30.3)
≥30–<50%	20 (24.7)	51 (22.5)	5 (17.9)	24 (24.2)
≥50%	47 (58.0)	94 (41.4)	17 (60.7)	45 (45.5)

Abbreviations: AML-MRC, AML with myelodysplasia-related changes; ECOG, Eastern Cooperative Oncology Group.
[a]Two patients had both *IDH1* and *IDH2* mutations.
[b]One patient had both *IDH1* and *IDH2* mutations.

4.6 (2.1–7.1) months. The median DoR in the venetoclax and azacitidine group was not reached (95% CI, 16.7–NE), while the median DoR was 9.5 (3.5–NE) months for azacitidine. The estimated 12-month median DoR for patients with *IDH2* mutation who received venetoclax and azacitidine was 71.1% (95% CI, 53.8%–82.9%).

The outcomes in patients harboring $IDH2^{R140}$ and $IDH2^{R172}$ mutations were similar and are shown in Supplementary Table S2.

The remission rates of patients who achieved CR and CR with partial hematologic remission (CRh) are shown in Supplementary Table S3.

Overall survival

In patients with *IDH1/2* mutations treated with venetoclax and azacitidine versus azacitidine, the median OS was 24.5 months (95%
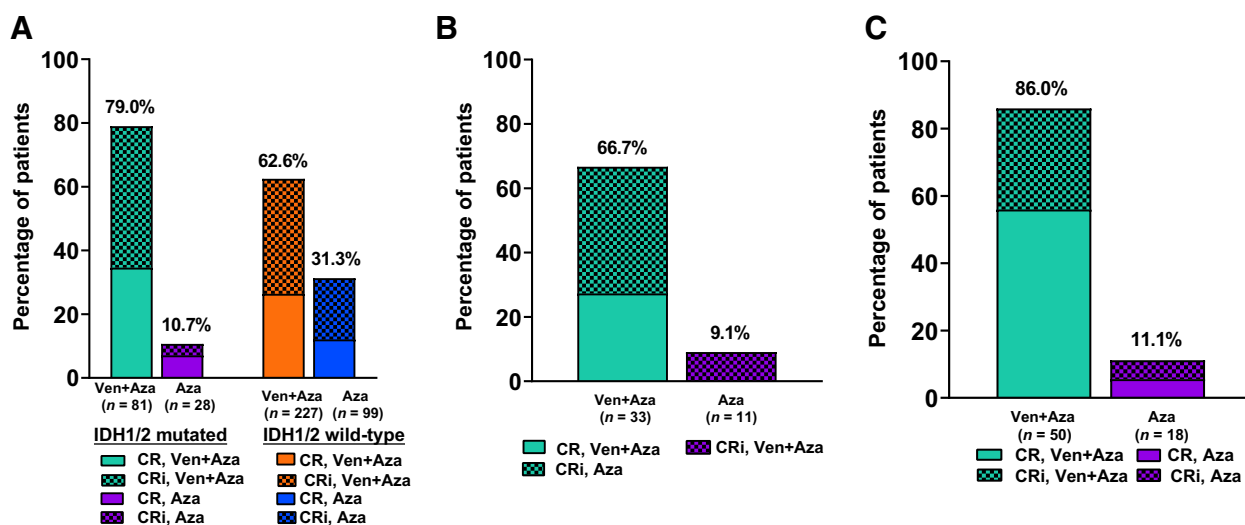

Figure 2.
A, Remission rates in patients with *IDH1/2* mutations and *IDH1/2* wild-type by treatment groups. **B,** Remission rates in patients with *IDH1* mutations in the venetoclax and azacitidine group. **C,** Remission rates in patients with *IDH2* mutations in the venetoclax and azacitidine group.
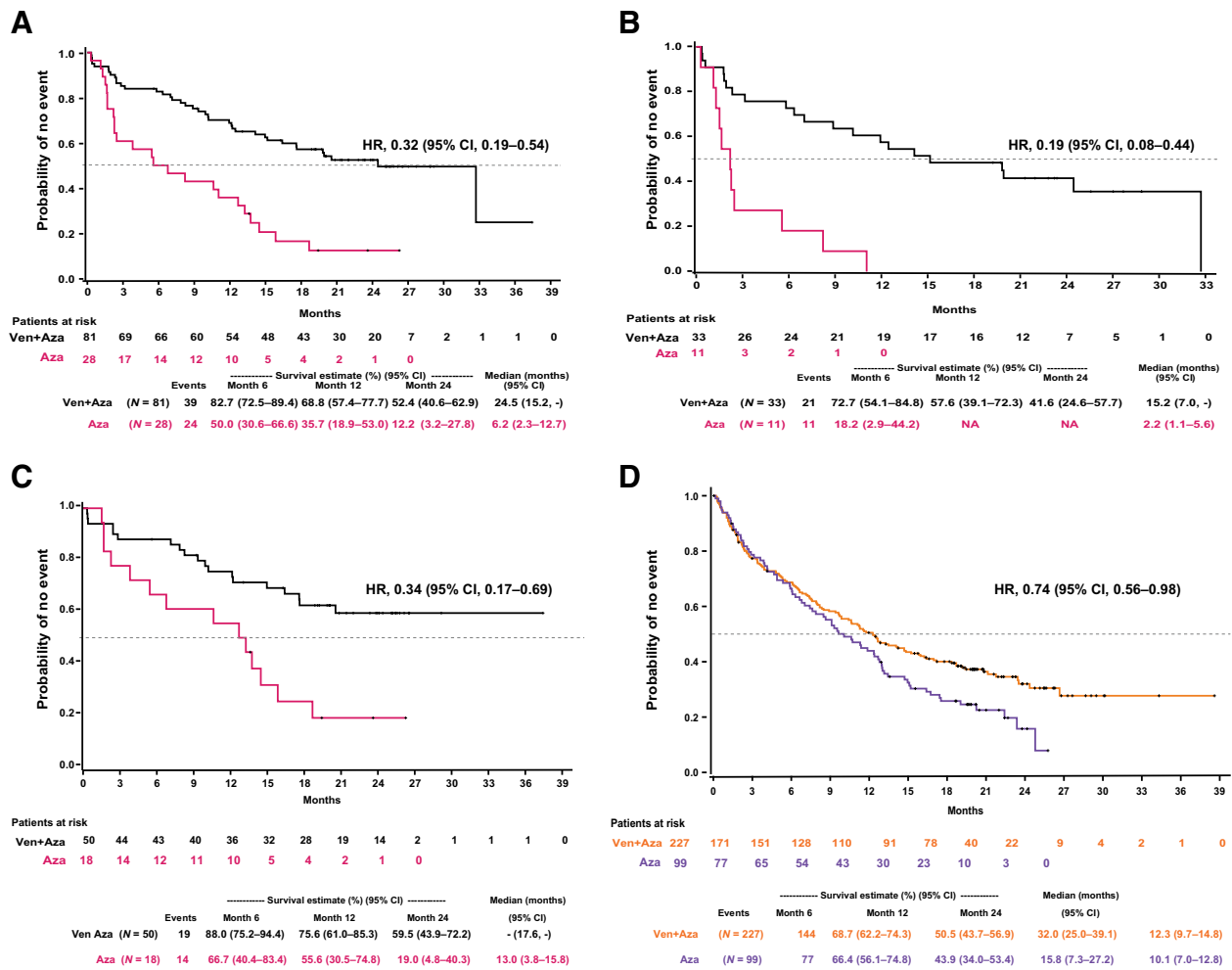
Figure 3.
Kaplan–Meier curves for OS (**A**) patients with *IDH1/2* mutation treated with venetoclax (Ven) and azacitidine (Aza) versus azacitidine groups, patients with *IDH1* mutation by treatment groups (**B**); patients with *IDH2* mutated by treatment groups (**C**); and patients with *IDH1/2* wild-type by treatment groups (**D**).

CI, 15.2–NE) versus 6.2 months (95% CI, 2.3–12.7); HR: 0.32 (95% CI, 0.19–0.54; **Fig. 3A**). In patients with *IDH1* mutations, the median OS in the venetoclax and azacitidine vs. azacitidine group was 15.2 months (95% CI, 7.0–NE) versus 2.2 months (95% CI, 1.1, 5.6), HR: 0.19 (0.08–0.44), respectively (**Fig. 3B**). The median OS in patients with *IDH2* mutations (venetoclax and azacitidine vs. azacitidine) was NR (95% CI, 17.6–NE) versus 13.0 months (95% CI: 3.8, 15.8) months (HR, 0.34; 95% CI, 0.17–0.69), respectively (**Fig. 3C**). In patients with *IDH1/2* WT, the median OS was 12.3 months (95% CI, 9.7–14.8) in patients treated with venetoclax and azacitidine and 10.1 (7.0–12.8) months, HR: 0.74 (95% CI, 0.56–0.98) in patients treated with azacitidine (**Fig. 3D**).

Among patients treated with venetoclax and azacitidine, those with *IDH1/2* mutations have longer OS than *IDH1/2* WT (**Fig. 4A**). Further analysis revealed that NCCN cytogenetic risk is prognostic in patients with *IDH1/2* WT but does not impact OS in patients with *IDH1/2* mutation. In *IDH1/2* mutated, patients with intermediate and poor-risk had comparable OS (intermediate-risk, 24.5 months; poor-risk, NR; estimated 12-month median OS for intermediate-risk, 70.5%; poor-risk, 63.2%; **Fig. 4B**). Whereas in *IDH1/2* WT, the median OS was inferior among patients with poor cytogenetic risk (7.4 months) than those with intermediate-risk (19.2 months; **Fig. 4C**). These

findings show that venetoclax and azacitidine provide similar OS benefits to patients with intermediate cytogenetic risk regardless of *IDH1/2* mutation, while in patients with poor cytogenetic risk, IDH 1/2 mutation is associated with differential outcomes.

In the *IDH1/2*-mutated cohort treated with venetoclax and azacitidine, only a small subset of patients exhibited a comutation with *NPM1* ($n = 19/81$, 23%) or *FLT3* ($n = 14/81$, 17%; **Fig. 4D**). Among patients with *IDH1/2* mutated AML, the median OS was similar in patients with versus without *NPM1* comutation (**Fig. 4E**). However, median OS was inferior in the presence of *FLT3* comutation versus no *FLT3* comutation, as shown in **Fig. 4F**. The median OS of patients who had *IDH1/2* with a co-mutation in *NPM1* or *FLT3* and treated with azacitidine are shown in Supplementary Table S4. Three patients treated with venetoclax and azacitidine had *IDH1/2* and *TP53* co-mutation, and the 12-month estimate of OS was 33.3% (95% CI, 0.9%–77.4%).

Safety

All patients in the safety population experienced at least one adverse event, regardless of the treatment group (**Table 2**). Higher rates of grade ≥3 hematologic AEs were observed in the venetoclax and
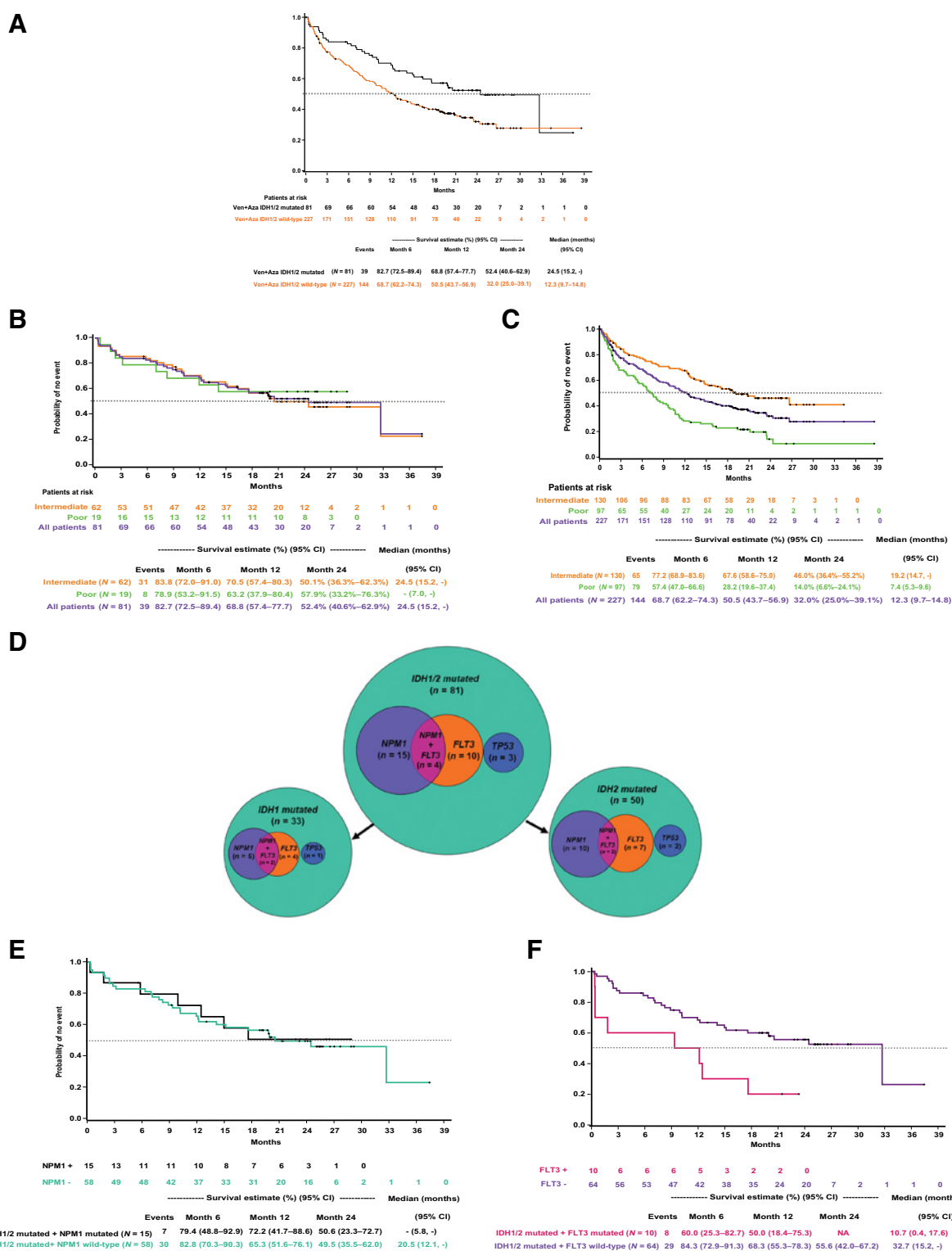
Figure 4.
Kaplan–Meier curves for overall survival (**A**) patients with *IDH1/2* mutated and *IDH1/2* wild-type and treated with venetoclax and azacitidine; patients with *IDH1/2* mutation treated with venetoclax and azacitidine and stratified by NCCN risk categories for AML (**B**); patients with *IDH1/2* wild-type treated with venetoclax and azacitidine and stratified by NCCN cytogenetic risk categories (**B**); Venn diagrams showing co-mutations of *NPM1*, *FLT3*, and *TP3* with *IDH1/2* in patients treated with venetoclax and azacitidine (**C**); patients with *IDH1/2* and *NPM1*-mutant or wild-type in the venetoclax and azacitidine group (**D**); patients with *IDH1/2*- and *FLT3*-mutant or wild-type in the venetoclax and azacitidine group (**E**).

Table 2. Treatment-emergent adverse events.

| Adverse event[a], n (%) | Venetoclax + Azacitidine | | Azacitidine | |
	IDH1/2 mutated $n = 81$	Overall population $n = 353$	IDH1/2 mutated $n = 28$	Overall population $n = 145$
AE of any grade	81 (100)	349 (98.9)	28 (100)	143 (98.6)
AE grade ≥3	79 (97.5)	343 (97.2)	26 (92.9)	138 (95.2)
Hematologic AE	67 (82.7)	280 (79.3)	19 (67.9)	97 (66.9)
Anemia	24 (29.6)	94 (26.6)	7 (25.0)	29 (20.0)
Febrile neutropenia	34 (42.0)	143 (40.5)	7 (25.0)	27 (18.6)
Neutropenia	28 (34.6)	131 (37.1)	7 (25.0)	41 (28.3)
Thrombocytopenia	37 (45.7)	141 (39.9)	10 (35.7)	55 (37.9)
Infections	48 (59.3)	215 (60.9)	15 (53.6)	73 (50.3)
Pneumonia	22 (27.2)	80 (22.7)	9 (32.1)	36 (24.8)
Serious AEs	66 (81.5)	288 (81.6)	23 (82.1)	105 (72.4)
Febrile neutropenia	24 (29.6)	102 (28.9)	4 (14.3)	15 (10.3)
Pneumonia	17 (21.0)	66 (18.7)	8 (28.6)	32 (22.1)
Anemia	6 (7.4)	15 (4.2)	1 (3.6)	6 (4.1)
Sepsis	5 (6.2)	17 (4.8)	4 (14.3)	12 (8.3)
Neutropenia	4 (4.9)	13 (3.7)	1 (3.6)	3 (2.1)
Atrial fibrillation	3 (3.7)	13 (3.7)	0	2 (1.4)

Abbreviation: AE, adverse event.
[a]Includes all patients who received at least one dose of study treatment.

azacitidine group compared to the azacitidine group, regardless of mutation status, as was previously reported (17). In the overall population of the pooled analysis, 79.3% of patients in the venetoclax and azacitidine group experienced grade ≥3 hematologic AEs compared with 66.9% of patients in the azacitidine group. In the venetoclax and azacitidine group, grade ≥3 pneumonia was reported in 27.2% of patients with *IDH1/2* mutations versus 22.7% in the overall population of the pooled analysis.

Serious AEs occurred in 81.5% of *IDH1/2* mutant in the venetoclax and azacitidine group and 82.1% in the azacitidine group. In both the venetoclax and azacitidine and azacitidine groups, febrile neutropenia (29.6% vs.14.3%) and pneumonia (21.0% vs. 28.6%) were the most common serious AEs among patients with *IDH1/2* mutant AML. No incidences of tumor lysis syndrome were reported among patients with *IDH1/2* mutations in either treatment group.

Among patients with *IDH1/2* mutations, 6 of 81 (7.4%) in the venetoclax and azacitidine group and 3 of 28 (10.7%) in the azacitidine group received concomitant hydroxyurea therapy.

Discussion

For older patients with AML who are ineligible for intensive chemotherapy, treatment with venetoclax and azacitidine is now recommended as the new standard of care by the NCCN clinical practice guidelines for AML regardless of mutation status (20). Among all patients with *IDH1/2*-mutated AML, treatment with venetoclax and azacitidine led to a higher remission rate (68%) and a 68% reduction in the risk of death compared with treatment with azacitidine alone.

In this analysis, patients with *IDH1/2*-mutated AML were confirmed to benefit from the combination of venetoclax and azacitidine, with an overall CRc rate of 79% and OS of 24.5 months. Specifically, among the *IDH1*-mutated subgroup ($n = 33$) receiving the combination, the CRc rate was 67%, and the CR rate was 27%, with a median OS of 15 months. This compares favorably to the outcomes with ivosidenib monotherapy for newly diagnosed AML, with CRc 42% and OS of 12.6 months (12). Ivosidenib combinations are also under investigation in this population; in a phase Ib trial of azacitidine and

ivosidenib, CRc rate was 69.6% with CR rate 60% (13); a phase III placebo-controlled study of azacitidine ± ivosidenib is ongoing for patients with *IDH1* mutations. Patients with *IDH2*-mutated AML appear to derive particular benefit with venetoclax and azacitidine, with a CRc rate of 86%, a CR rate of 56%, and a median OS that was not reached. Results from an ongoing randomized phase II study of the targeted *IDH2* inhibitor enasidenib in combination with azacitidine (vs. azacitidine alone) reported promising efficacy as well, with the combination leading to improved responses including 63% CRc rate and 54% CR, although OS benefit with the azacitidine and enasidenib combination (vs. azacitidine alone) was not confirmed (21). Future studies may explore alternate combinations using venetoclax, with or without azacitidine, and a targeted *IDH1/2* inhibitor to maximize efficacy and minimize the toxicity of treating patients with *IDH1/2*-mutated AML. Currently, an early clinical trial evaluating ivosidenib with venetoclax with or without azacitidine (NCT03471260) among treatment-naïve patients reported that the combination therapy with or without azacitidine had an acceptable safety profile and efficacy (22).

In an additional analysis, we found that in the presence of *IDH1/2* mutations, the NCCN cytogenetic classification system of intermediate and poor-risk cytogenetics was not prognostic of OS. However, in the absence of an *IDH1/2* mutation, this classification system remained relevant and predictive of OS; intermediate-risk had superior outcomes while the patients with poor-risk had inferior outcomes. Further evaluation may describe the underlying biology of these findings.

The presence of a comutation of *IDH1/2* with *FLT3* resulted in inferior OS, while the presence of a comutation with *NPM1* did not impact survival. *FLT3-ITD* mutations have been reported to confer rapid escape from venetoclax as a single agent and associate with earlier relapse and outgrowth of *FLT3*-mutant clones in HMA or LDAC and venetoclax combination, likely through upregulation of alternative BCL-2 family proteins like MCL-1, not targeted by venetoclax (23). In such patients, the addition of *FLT3* inhibitor to HMA and venetoclax can be exploited. Further research is also warranted to understand whether additional prognostic factors, such as the cooccurrence of a *TP53* mutation, may impact the efficacy of venetoclax and azacitidine.

The safety and tolerability of venetoclax and azacitidine among patients were similar irrespective of *IDH1/2* mutation status. The toxicities were predominantly hematological and consistent with the safety data of the overall study population (16, 17). No significant increase in neutropenia-related AEs was identified, and no events of IDH differentiation syndrome were reported. All toxicities were effectively managed by the standard of care.

There were a few limitations of the study. First, data were pooled from a phase III and a phase Ib trial to increase the number of patients with *IDH*1/2 mutations for this analysis; however, due to the 2:1 randomization of VIALE-A and single-arm design of the phase Ib trial, the number of patients in the azacitidine group was limited and interpretation of key findings between the two treatments were not possible. In addition, patients included in this study may not truly represent all *IDH*1/2-mutated patients in real-world clinical practice; hence, the descriptive results of treatment effects in the groups warrant caution and validation in future studies. Likewise, the small sample sizes in the molecular subgroups further limited detailed comparisons between the *IDH*-mutant isoforms and various cooccurring mutations.

The current data demonstrate the efficacy of venetoclax and azacitidine in patients with *IDH1/2*-mutated AML that warrant further investigation, including extending this treatment to younger "fit" patients with *IDH*1/2 mutations, and/or evaluating time-limited therapy for responding patients with this genomic profile who achieve measurable residual disease negativity. Future analyses can also establish the role and potential benefit of sequencing or combining additional effective *IDH*1/2-directed therapies such as targeted inhibitors of *IDH1/2*.

Authors' Disclosures

Authors' Contributions

D.A. Pollyea: Supervision, writing–review and editing. **C.D. DiNardo:** Supervision, writing–review and editing. **M.L. Arellano:** Supervision, writing–review and editing. **A. Pigneux:** Supervision, writing–review and editing. **W. Fiedler:** Supervision, writing–review and editing. **M. Konopleva:** Supervision, writing–review and editing. **D.A. Rizzieri:** Supervision, writing–review and editing. **B.D. Smith:** Supervision, writing–review and editing. **A. Shinagawa:** Supervision, writing–review and editing. **R.M. Lemoli:** Supervision, writing–review and editing. **M. Dail:** Supervision, writing–review and editing. **Y. Duan:** Data curation, supervision, methodology, writing–review and editing. **B. Chyla:** Data curation, methodology, writing–review and editing. **J. Potluri:** Conceptualization, data curation, supervision, methodology, writing–review and editing. **C.L. Miller:** Conceptualization, supervision, methodology, writing–review and editing. **H.M. Kantarjian:** Supervision, writing–review and editing.

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