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

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Venetoclax and azacitidine for IDH1/2^{mut} AML pts

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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 3 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 to azacitidine alone, and patients with *IDH2* mutations had numerically better outcomes than patients with *IDH1* mutations. Additional analysis demonstrated that cytogenetic risk by NCCN 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.

Abstract (250/250 words)

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 3 study (NCT02993523) that compared patients treated with venetoclax+azacitidine or placebo+azacitidine and a prior Phase 1b study (NCT02203773) where patients were treated with venetoclax+azacitidine. Enrolled patients were ineligible for intensive therapy due to age ≥75 years and/or co-morbidities. 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 were 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 to 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.

Conclusion:

Patients with *IDH1/2*mut who receive 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.

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) (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 co-occurring mutations (10-12).

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 US FDA (13). The safety and efficacy of both molecules are currently being evaluated in combination with azacitidine (NCT02677922) and have been demonstrated to be safe with encouraging efficacy (14-16).

Venetoclax is a potent BCL-2 inhibitor. Pre-clinical 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 (17). The results from the randomized Phase 3 study demonstrated significantly higher CRc rates (75.4% versus 10.7%) and longer median overall survival (not reached [NR] versus 6.2 months) for the venetoclax and azacitidine group as compared to azacitidine alone (18). 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.

Methods

Patients and treatment

This pooled analysis included patients from the Phase 3 study (NCT02993523, VIALE-A) and a non-randomized, single-arm Phase 1b study (NCT02203773). The full study designs and eligibility criteria have been previously reported (17,18). 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 Aza 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 (19). 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 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (20). Baseline cytogenetic risk was determined locally and evaluated using the National Comprehensive Cancer Network (NCCN) criteria (Supplemental Table ST1) (18).

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 1b 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 1b study and the Leukostrat FLT3 CDx assay and/or MyAML for the Phase 3 study. In addition, the MyAML assay was also used to detect the presence of other mutations, including *NPM1 and TP53* in both the Phase 1b and Phase 3 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 hazard ratios (HR) and 95% confidence intervals (CIs) between treatment groups were estimated using the Cox proportional-hazards model.

Results

Patient disposition and baseline characteristics

The clinical data cut-off dates were January 4, 2020, for the Phase 3 study and July 19, 2019, for the Phase 1b study. The pooled analysis included 353 patients in the venetoclax and azacitidine group (Phase 3, n=286; Phase 1b, 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 81/308 (26%) in the venetoclax and azacitidine group and 28/127 (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. *IDH*1/2 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 — 37.0) vs. 2.5 (1.0 — 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 2A**), the median time to CR or

CRi response was 1.1 (range: 0.7 ─ 8.8) vs. 3.4 (2.1 - 7.1) months, and the median DoR was 29.5 (95% CI: 16.7 ─ not estimable [NE]) vs. 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) vs. 31.3% (n=31); the median time to first response for CR or CRi was 1.3 (range: 0.8 ─ 9.9) vs. 2.9 (0.8 ─ 13.2) months**,** and the median DoR was 17.5 (95% CI: 10.6 ─ 23.5) vs. 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) vs. 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) vs. 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) vs. 11.1% (n=2) for azacitidine (**Fig 2C**) and median time to CR or CRi was 1.1 (range 0.7 ─ 8.8) vs. 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* mutated 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 Supplemental Table ST2. The remission rates of patients who achieved CR and CR with partial hematologic remission (CRh) are shown in Supplemental Table ST3.

Overall survival

In patients with *IDH1/2* mutations treated with venetoclax and azacitidine vs. azacitidine, the median OS was 24.5 months (95% CI: 15.2 ─ NE) vs. 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) vs. 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) vs. 13.0 (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 co-mutation 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 vs. without *NPM1* co-mutation (**Fig 4E)**. However, median OS was inferior in the presence of *FLT3* co-mutation vs. no *FLT3* co-mutation, 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 Supplemental Table ST4. 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 azacitidine group compared to the azacitidine group, regardless of mutation status, as was previously reported (18). 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 vs. 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 (21). 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 to 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 (13). Ivosidenib combinations are also under investigation in this population; in a Phase 1b trial of azacitidine and ivosidenib, CRc rate was 69.6% with CR rate 60% (14); a Phase 3 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 2 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 (22). 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 (23).

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 co-mutation of *IDH1/2* with *FLT3* resulted in inferior OS, while the presence of a co-mutation 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 (24). 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 co-occurrence 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 (17,18). 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 3 and a Phase 1b 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 1b 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 warrants 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 co-occurring mutations.

The present 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*.

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.

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)

Abbreviation: AML, Acute myeloid leukemia; 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.

403 Table 2. Treatment-emergent adverse events

Adverse event[a], n (%)	Venetoclax + Azacitidine		Azacitidine	
	IDH 1/2 mutated **n = 81**	**Overall Population n = 353**	***IDH 1/2 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)
Hematological 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)

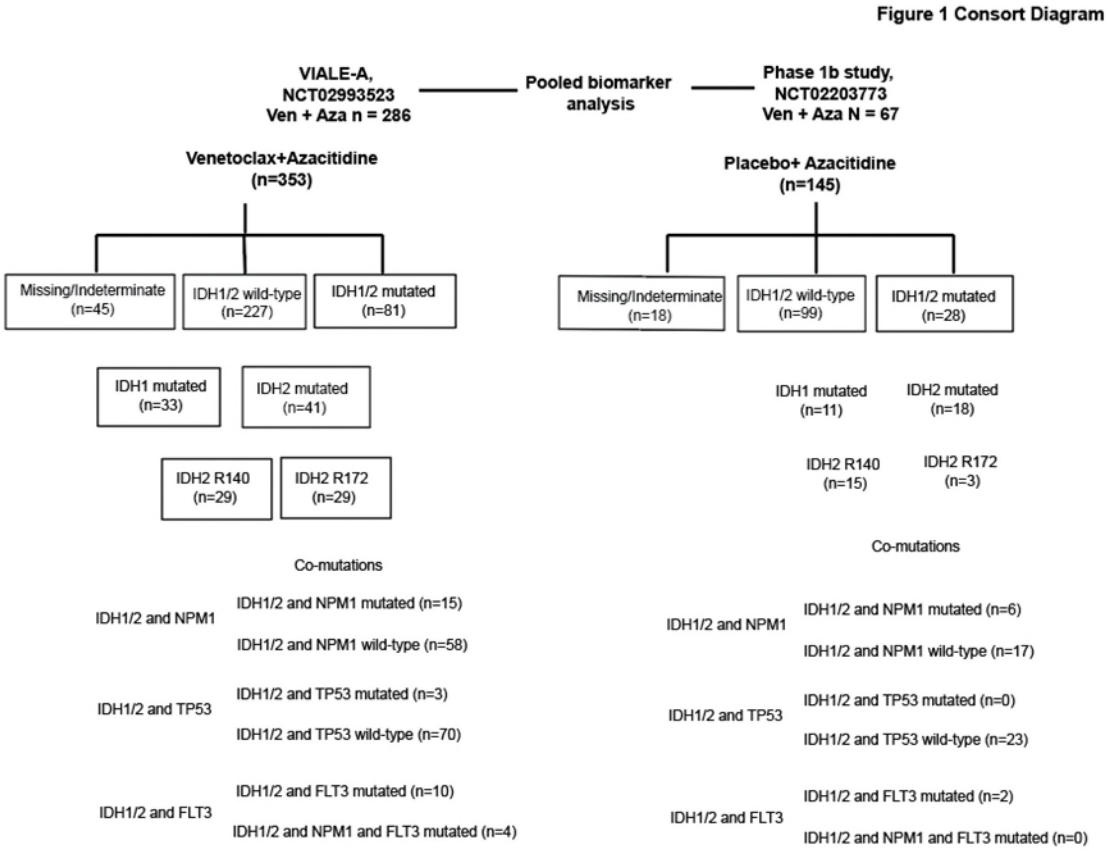
404 Abbreviation: AE, adverse event.

405 [a]Includes all patients who received at least one dose of study treatment.

406

Figure Legends

Figure 1



Study design and molecular classification

*Two patients had both *IDH1/2* mutations. ** One patient had both *IDH1/2* mutations.

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

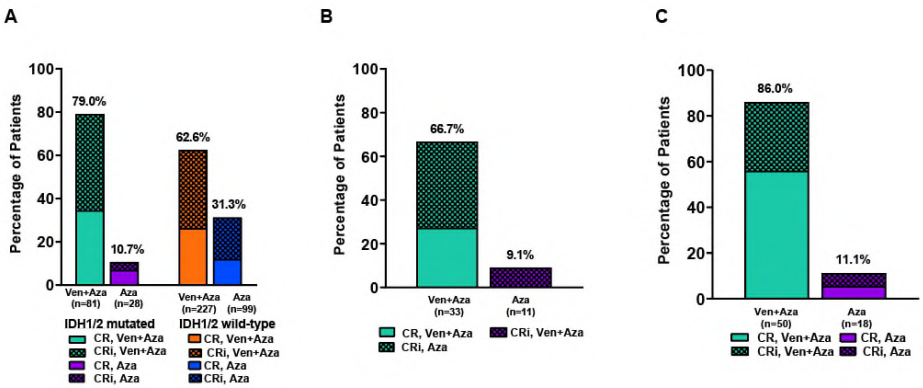


Figure 3

Kaplan-Meier curves for overall survival A) patients with *IDH1/2* mutated treated with venetoclax and azacitidine versus azacitidine groups; B) patients with *IDH1* mutated by treatment groups; C) patients with *IDH2* mutated by treatment groups; D) patients with *IDH1/2* wild-type by treatment groups

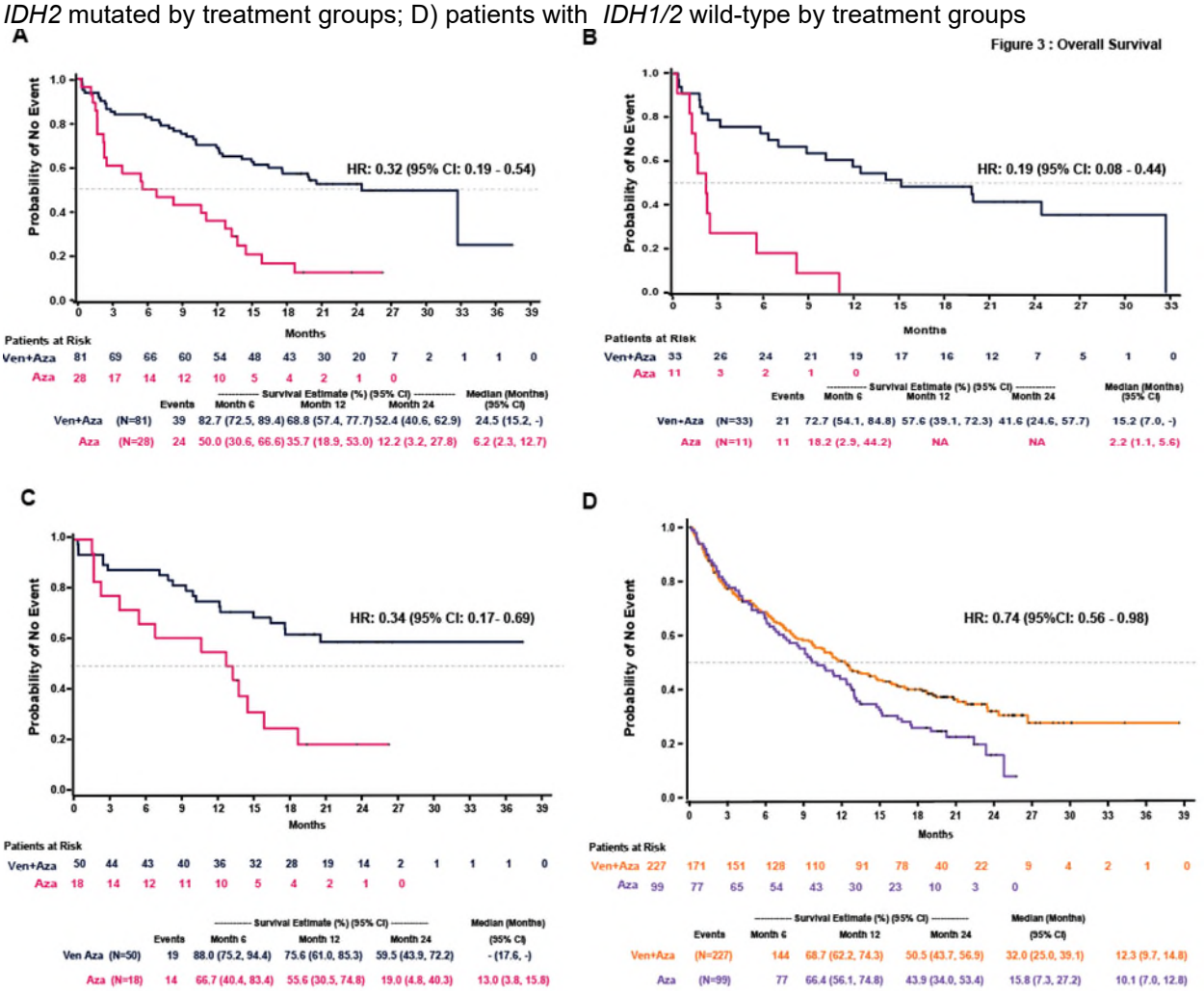
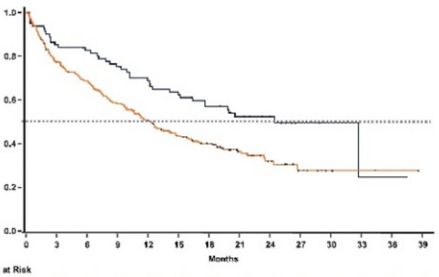


Figure 4

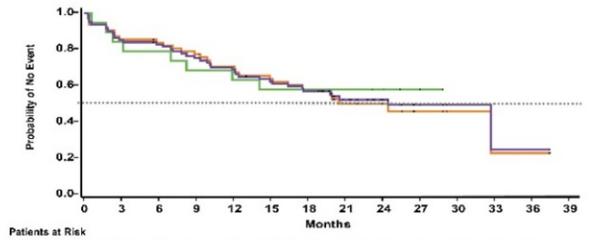
Kaplan-Meier curves for overall survival A) patients with *IDH1/2* mutated and *IDH1/2* wild-type and treated with venetoclax and azacitidine; B) patients with *IDH1/2* mutated treated with venetoclax and azacitidine and stratified by National Comprehensive Cancer Network (NCCN) risk categories for acute myeloid leukemia; B) patients with *IDH1/2* wild-type treated with venetoclax and azacitidine and stratified by NCCN cytogenetic risk categories; C) Venn-diagrams showing co-mutations of *NPM1*, *FLT3,* and *TP3* with *IDH1/2* in patients treated with venetoclax and azacitidine; D) patients with *IDH1/2* and *NPM1* mutant or wild-type in the venetoclax and azacitidine group; E) patients with *IDH1/2* and *FLT3* mutant or wild-type in the venetoclax and azacitidine group

A



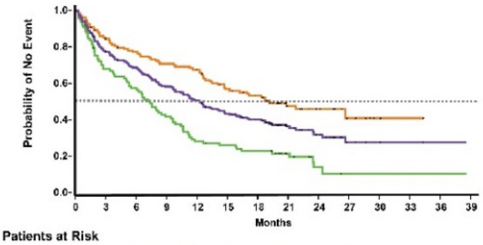
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
Ven+Aza IDH1/2mutated (N=81)	39	82.7 (72.5, 89.4)	68.8 (57.4, 77.7)	52.4 (40.6, 62.9)	24.5 (15.2, -)
Ven+Aza IDH1/2wildtype (N=227)	144	68.7 (62.2, 74.3)	50.5 (43.7, 56.9)	32.0 (25.0, 39.1)	12.3 (9.7, 14.8)

B



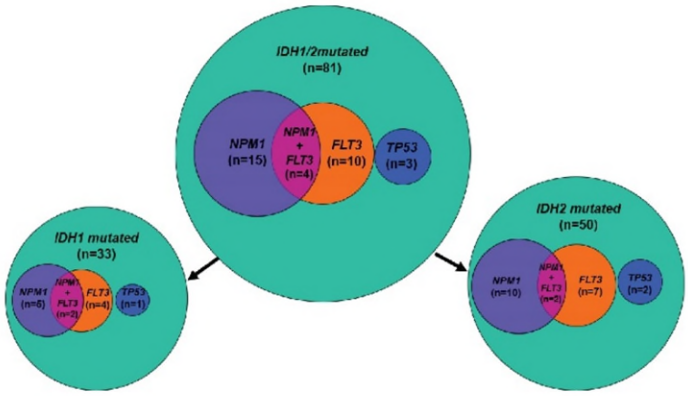
	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
Intermediate (N=62)	31	83.8 (72.0, 91.0)	70.5 (57.4, 80.3)	50.1% (36.3%, 62.3%)	24.5 (15.2, -)
Poor (N=19)	8	78.9 (53.2, 91.5)	63.2 (37.9, 80.4)	57.9% (33.2%, 76.3%)	- (7.0, -)
All Patients (N=81)	39	82.7 (72.5, 89.4)	68.8 (57.4, 77.7)	52.4% (40.6%, 62.9%)	24.5 (15.2, -)

C

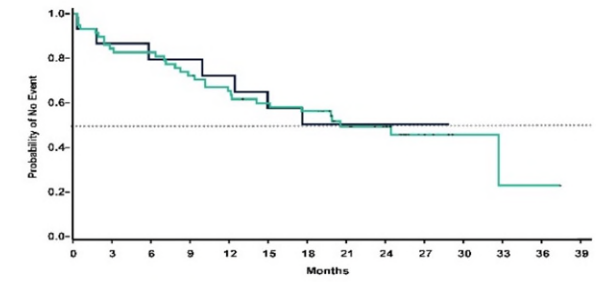


	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
Intermediate (N=130)	65	77.2 (68.9, 83.6)	67.6 (58.6, 75.0)	46.0% (36.4%, 55.2%)	19.2 (14.7, -)
Poor (N=97)	79	57.4 (47.0, 66.6)	28.2 (19.8, 37.4)	14.0% (6.6%, 24.1%)	7.4 (5.3, 9.6)
All Patients (N=227)	144	68.7 (62.2, 74.3)	50.5 (43.7, 56.9)	32.0% (25.0%, 39.1%)	12.3 (9.7, 14.8)

D

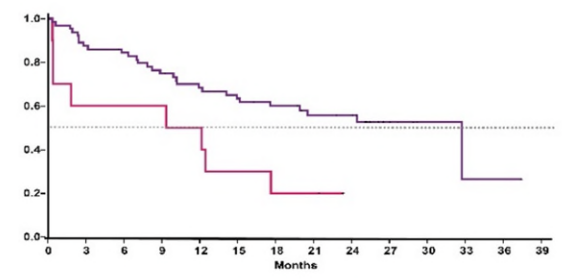


E



	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
IDH1/2 mutated + NPM1 mutated (N=15)	7	79.4 (48.8, 92.9)	72.2 (41.7, 88.6)	50.6 (23.3, 72.7)	- (5.8, -)
IDH1/2 mutated+ NPM1 wild-type (N=58)	30	82.8 (70.3, 90.3)	65.3 (51.6, 76.1)	49.5 (35.5, 62.0)	20.5 (12.1, -)

F



	Events	Survival Estimate (%) (95% CI) Month 6	Month 12	Month 24	Median (Months) (95% CI)
IDH1/2 mutated + FLT3 mutated (N=10)	8	60.0 (25.3, 82.7)	50.0 (18.4, 75.3)	NA	10.7 (0.4, 17.6)
IDH1/2 mutated + FLT3 wild-type (N=64)	29	84.3 (72.9, 91.3)	68.3 (55.3, 78.3)	55.6 (42.0, 67.2)	32.7 (15.2, -)

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

Supplemental Appendix

Supplemental Table ST1. National Comprehensive Cancer Network Risk Categorization: Guidelines for Acute Myeloid Leukemia Version 2.2016

Risk category	Cytogenetics
Favorable risk[a]	Core binding factor: inv (16) or t(16;16) or t(8;21) t(15;17)
Intermediate risk	Normal cytogenetics +8 alone t(9;11) Other non-defined
Poor risk	Complex (≥ 3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11 q23 non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)

[a]Patients with favorable risk were excluded from both studies included in this pooled analysis

Supplemental Table ST2. Response Rates and Overall survival in $IDH2^{R140}$ and $IDH2^{R172}$

	Venetoclax + Azacitidine		Azacitidine	
	***IDH2*^{R140} n = 36**	***IDH2*^{R172} n = 14**	***IDH2*^{R140} n = 15**	***IDH2*^{R172} n = 3**
CR+CRi, n(%)	30 (83.3)	13 (92.9)	1 (6.7)	1 (33.3)
DoR for CR+CRi months, median (95% CI)	NR (11.1 – NE)	17.1 (7.5 – NE)	15.5 (NE – NE)	3.5 (NE – NE)
CR+CRh, n(%)	27 (75.0)	13 (92.9)	1 (6.7)	0
DoR for CR+CRh months, median (95% CI)	NR (17.8 – NE)	17.3 (7.5 – NE)	15.5 (NE – NE)	–
Median overall survival, months (95% CI)	NR (15.0 – NE)	NR (12.2 – NE)	12.7 (1.7 – 15.8)	13.7 (10.6 – NE)

Abbreviations: CR, complete remission; CRi, CR + incomplete hematologic recovery; CRh, CR + partial hematologic recovery; DoR, duration of remission; NE, not evaluable; NR, not reached

Supplemental Table ST3. CR+CRh rates in patients treated with venetoclax and azacitidine or azacitidine

	Venetoclax + Azacitidine				**Azacitidine**			
	***IDH1/2* mutated n = 81**	**IDH1 mutated n = 33**	***IDH2* mutated n = 50**	***IDH1/2* wild-type n = 227**	***IDH1/2* mutated n = 28**	***IDH1* mutated n = 11**	***IDH2* mutated n = 18**	***IDH1/2* wild-type n = 99**
CR, n(%)	36 (44.4)	9 (27.3)	28 (56.0)	82 (36.1)	1 (3.6)	0	1 (5.6)	19 (19.2)
CR+CRh, n(%)	59 (72.8)	20 (60.6)	40 (80.0)	137 (60.4)	2 (7.1)	1 (9.1)	1 (5.6)	24 (24.2)

Abbreviations: CR, complete remission; CRh, CR+ partial hematological recovery
CR was defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRh is defined as all the criteria for CR, except for neutropenia >0.5 X10^3/µL, and platelets >0.5 x 10^5 /µL.

Supplemental Table ST4. Overall survival in patients with *IDH1/2* with *NPM1* or *FLT3* treated with azacitidine

	Azacitidine	
	***IDH 1/ 2* & *NPM1* mutated (n=6)**	***IDH 1/ 2* & *FLT3* mutated (n=2)**
No. of events (deaths) - n (%)	4 (66.7%)	2 (100%)
Median OS (95% CI)	14.9 (1.7 ─ NE)	0.8 (0.3 ─ NE)

Abbreviations: NE, not evaluable; OS, Overall survival