Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a Phase 1b study

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ABSTRACT

This analysis represents the longest-term follow-up for patients with acute myeloid leukemia (AML) treated with 400 mg of venetoclax plus azacitidine or decitabine. Adults with newly diagnosed AML ineligible for intensive chemotherapy were enrolled in an open-label, non-randomized, multicenter phase 1b trial of venetoclax with azacitidine (AZA; 75 mg/m^2; days 1–7) or decitabine (DEC; 20 mg/m^2; days 1–5). Endpoints included safety, response rates (complete remission [CR], CR with incomplete blood count recovery [CRi]), response duration and overall survival (OS). The median follow-up time was 29 and 40 months for patients treated with venetoclax plus AZA and DEC combinations, respectively. Key Grade ≥3 AEs (AZA and DEC) were febrile neutropenia (39% and 65%), anemia (30% and 26%), thrombocytopenia (25% and 23%), and neutropenia (20% and 10%). The CR/CRi rate was 71% for venetoclax plus AZA and 74% for venetoclax plus DEC. The median duration of CR/CRi was 21.9 months and 15.0 months, and the median OS was 16.4 months and 16.2 months, for venetoclax plus AZA and DEC, respectively. These results support venetoclax plus hypomethylating agents as highly effective frontline AML therapies for patients unfit for intensive chemotherapy.

1. INTRODUCTION

Older patients with acute myeloid leukemia (AML) respond poorly to intensive induction chemotherapy due to higher risk disease factors (adverse cytogenetic and molecular features, higher rates of secondary AML) and patient-related factors (end organ compromise, reduced performance status), compared to younger AML patients.[1-3] Traditional attempts to deintensify therapy, including monotherapy with gemtuzumab ozogamicin, low-dose cytarabine, azacitidine or decitabine, result in decreased toxicity but yield complete remission (CR) plus CR with incomplete blood count recovery (CRi) rates of less than 30%, and overall survival (OS) less than one year.[1,4,5]

Chemoresistance and leukemia survival are mediated by B-cell leukemia/lymphoma-2 (BCL-2) family members, including BCL-2 itself, which sequesters pro-apoptotic proteins.[6,7] Venetoclax was identified as a potent and selective small-molecule BCL-2 inhibitor that could be combined with other anti-leukemia agents,[8,9] and that has subsequently demonstrated synergistic activity in combination with hypomethylating agents in preclinical models of AML.[10] Recent data propose that the leukemia stem cell (LSC) population is targeted by venetoclax with azacitidine, due to its specific disruption of amino acid-fueled oxidative phosphorylation, on which the LSC population is uniquely reliant.[11,12] The clinical experience of escalating doses of venetoclax combined with either azacitidine or decitabine in newly diagnosed older patients with AML who were ineligible for standard induction chemotherapy demonstrated high rates of durable responses.[13,14] These venetoclax plus hypomethylating agent (HMA) combination regimens demonstrated a 67% CR/CRi response rate, with a median overall survival of 17.5

months across all three tested doses of venetoclax (400, 800, and 1200 mg per day) with 15.1 months of median follow-up.[13]

Venetoclax (at the 400 mg dose) in combination with azacitidine or decitabine received approval by the US Food and Drug Administration (FDA)[15] for the treatment of newly diagnosed adult AML patients 75 or older, or with comorbidities that preclude use of standard induction chemotherapy. The present study is a long-term follow-up of safety and efficacy outcomes in patients who received the label-recommended 400 mg dose of venetoclax plus an HMA. With a median follow-up time of 29 and 40 months for azacitidine and decitabine, respectively, we report response rates, overall survival, outcomes in patient subpopulations of interest, and important clinical information pertaining to the use of this regimen.

2. METHODS

2.1 Patients

Patients aged ≥60 years with previously untreated AML (as defined by the World Health Organization [WHO][17]) considered ineligible for intensive chemotherapy by objective medical criteria and the investigators' assessment were enrolled. Key exclusion criteria included prior therapy for AML (except hydroxyurea), prior receipt of a hypomethylating agent (HMA) for an antecedent hematologic disorder, favorable risk cytogenetics (per NCCN 2014 guidelines[18]), and/or known active central nervous system involvement from AML. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3, adequate renal and hepatic function, and a white blood cell (WBC) count of ≤25 x 10^9/L; the use of leukapheresis or hydroxyurea prior to treatment initiation was permitted. A complete list of eligibility criteria is contained in the **Supplemental Appendix**. This trial was approved by the internal review board at all participating institutions. Written informed consent was obtained from all study participants. The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki.

2.2 Study design

The dose-escalation[14] and expansion[13] cohorts in this study were previously described and analyzed elsewhere. The study was an open-label, non-randomized, multicenter phase 1b study that enrolled patients between November 2014 and June 2017. Data cutoff in this analysis was July 19, 2019. Reponses were evaluated in accordance with the International Working Group criteria for AML.[16] Efficacy endpoints

included: complete remission (CR), CR with incomplete blood count recovery (CRi), partial remission (PR), overall survival (OS), and duration of response (DOR). Exploratory endpoints included the number of patients that achieved independence from red blood cell (RBC) or platelet transfusion, as well as the number of patients who achieved minimal residual disease (MRD). Safety of the combinations was also analyzed.

2.3 Treatment

Dose escalation was as previously described; details are in the **Supplemental Appendix**.[13,14] All patients were hospitalized for tumor lysis syndrome (TLS) prophylaxis prior to initiation of cycle 1 and for the entirety of the venetoclax ramp-up, until at least 24 hours after the target venetoclax dose was reached. Prophylaxis for TLS included a uric acid reducing agent and oral and/or intravenous hydration. All patients received supportive care measures per institutional guidelines including prophylactic anti-infective agents, blood product transfusions, and growth factor support. Triazole anti-fungals were excluded in the dose escalation and early expansion portions and were permitted with appropriate venetoclax dose modifications[13,19] for patients enrolled in the latter expansion cohort (**Supplemental Table ST2**).

2.4 Safety assessments

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.[20] Treatment-emergent AEs were defined as those that occurred between the first dose of study drug until 30 days after the last dose of the study drug. Laboratory and clinical TLS were identified as previously defined.[21] Per protocol, for patients with ongoing cytopenia(s) after morphologic clearance of leukemia, subsequent cycles of venetoclax and HMA could be delayed until

ANC reached ≥500/μL or for up to 14 days to allow for blood count recovery. When venetoclax was delayed, both venetoclax and HMA were resumed on the same day of the new cycle. For recurrent cytopenia, in subsequent cycles, in addition to the delay between treatment cycles, stepwise dose modifications starting with reduced duration of venetoclax to 21 days of each 28 day cycle and azacitidine dose modifications guided by the bone marrow cellularity and duration of cytopenia were implemented.[22]

2.5 Efficacy assessments

Bone marrow aspirate and biopsy were performed at the end of Cycle 1, Cycle 4, and end of every 3 Cycles thereafter. Responses were assessed per International Working Group response criteria for AML[16] and included complete remission (CR), CR with incomplete blood count recovery (CRi), and partial remission (PR), morphologic leukemia-free state (MLFS) and resistant disease (RD). For patients who required a delay in the next cycle of study treatment for blood count recovery after a bone marrow evaluation, hematology values for up to 2 weeks from the bone marrow-evaluation could be used to determine the response. Overall survival (OS) was defined as the number of days from date of first dose of the study drug to date of death; living patients were censored at the last known date alive. Duration of response (DOR) for patients who achieved a CR or CRi was also evaluated. For patients in remission and started post-study treatment, including stem cell transplant, DOR was censored at the start of new treatment.

2.6 Other assessments and statistical analyses

Information on statistical analyses, assessment of cytogenetics, baseline mutations, minimal residual disease, and transfusion independence can be found in the Supplemental Appendix.

3. RESULTS

3.1 Patient enrollment and disposition

Across the entire study, 115 patients were treated at the 400 mg dose of venetoclax; 84 patients received venetoclax plus azacitidine for a median duration was 6.4 months (range: 0.1–38), and 31 were treated with venetoclax plus decitabine for a median duration of 5.7 months (range: 0.5–42). The primary reasons for discontinuation of venetoclax (azacitidine and decitabine combination, respectively) were: progressive disease per protocol (32% and 39%), adverse event not related to disease progression (20% and 10%), adverse event related to progression (4% and 3%), withdrawal of consent (2% and 3%), and all other (31% and 35%; including those who had allogeneic stem cell transplant). Of note, 17/84 (20%) and 4/31 (13%) patients, respectively, went on to receive allogeneic stem cell transplant.

Efficacy information for patients treated with 800 mg or 1200 mg of venetoclax is provided in the tables for completeness (**Table 3**; **Supplementary Table ST3**); demographics and other information on these patients has been previously presented.[13,14]

3.2 Patient Demographics and Clinical Characteristics

Baseline patient demographics and clinical characteristics are shown in **Table 1**, separated by venetoclax and HMA combination. For patients treated with azacitidine and decitabine combinations, respectively: the median age was 75 and 72, poor cytogenetic risk features were present in 39% and 48%, and 25% and 29% had secondary AML. Baseline transfusion dependence for red blood cells (61% and 74%) and platelets (32% and 16%) was common. Baseline grade 3 or 4 neutropenia was present in 67% and 74% of patients

treated with the azacitidine and decitabine combination, respectively. Rates of somatic mutations were similar across both treatment groups; across all patients with mutational data (n=109), *TP53* was mutated in 23% (25/109), *FLT3* was mutated in 15% (16/109), *IDH1* in 15% (16/109), *IDH2* in 13% (14/109), and *NPM1* in 18% (20/109) of patients.

3.3 Safety

All patients experienced at least one adverse event (AE), with 82 patients (98%) in the azacitidine-treated group and 31 patients (100%) in the decitabine-treated group experiencing an AE of Grade 3 or higher. A summary of treatment emergent adverse events is shown in **Table 2**. Consistent with prior studies in AML, the most frequently reported Grade 3 or higher AEs were hematologic and included (azacitidine group and decitabine group, respectively) febrile neutropenia (39% and 65%), anemia (30% and 26%), thrombocytopenia (25% and 23%), and neutropenia (20% and 10%). The most common non-hematologic AEs of any grade (azacitidine group and decitabine group, respectively) were nausea (64% vs. 65%), diarrhea (61% vs. 45%), and constipation (50% vs. 52%), most being Grade 1 or 2. Serious AEs were reported in 77% of patients treated with venetoclax plus azacitidine and 81% of patients treated with venetoclax plus decitabine. Serious AEs included (azacitidine group and decitabine group) febrile neutropenia (31% and 42%), pneumonia (26% and 29%), and sepsis (4% and 7%) expected in AML patients There were no AEs related to TLS. The 30-day mortality rates were 2% (n=2) and 7% (n=2) in the azacitidine and decitabine groups, respectively.

Twenty-one (25%) patients treated with the azacitidine combination and 8 (26%) patients treated with the decitabine combination had AEs leading to venetoclax discontinuation. Sixty-eight percent and 65%

of patients in the azacitidine and decitabine groups, respectively, had venetoclax dose interruptions due to AEs. Many such interruptions were to allow for hematologic recovery per protocol; venetoclax dose reductions due to AEs occurred in 1% and 7% of azacitidine and decitabine-treated patients, respectively. Venetoclax duration was reduced to 21 days during a treatment cycle in 62% (52/84) of patients in the azacitidine and 87% (27/31) of patients in the decitabine treated groups. Due to the limited number of patients who received 21 day and 28 day dosing, the differences in the outcome could not be evaluated.[23]

At baseline, 69% (79/115) of all patients had grade ≥3 neutropenia, and 49% (n=56) of patients received anti-bacterial prophylaxis, 37% (n=43) received antifungal prophylaxis, and 18% (n=21) received antiviral prophylaxis during the first 30 days of venetoclax treatment. Concomitant intermittent GCSF use was reported in 44% (51/115) of all patients, regardless of treatment regimen. Grade ≥3 AEs related to infections or infestations were experienced by 52% and 51% of all patients treated with venetoclax plus azacitidine or decitabine, respectively. The most common infections were pneumonia (34%), urinary tract infection (16%), upper respiratory tract infection (10%), and bacteremia (10%). Forty two percent of patients (48/115; 36 with azacitidine and 12 with decitabine) had infections that occurred in within 30 days of treatment initiation. Across all therapy cycles, 76% (63/83; 44 with azacitidine and 19 with decitabine) of patients who achieved a response of CR or CRi had an infection. Of those that could be determined, there were 7 patients with fungal infections and 17 with bacterial infections in the azacitidine arm, and 1 patient with fungal infection and 7 with bacterial infections in the decitabine arm; no patients

had viral infections. Grade ≥3 AEs classified as Infections and Infestations occurred less frequently in patients achieving a best response of CR/CRi than in patients who did not achieve CR/CRi.

3.4 Efficacy

The median duration of follow up was 29 months (range: 0.4–42) in the venetoclax plus azacitidine group, and the median OS was 16.4 months (95% CI 11.3–24.5). Median duration of follow up was 40 months (range: 0.7–43) in the venetoclax plus decitabine group, with a median OS of 16.2 months (95% CI 9.1–27.8) (**Figure 1A**).

The rate of CR/CRi was 71% (95% CI 61–81) in the venetoclax plus azacitidine-treated group, with 44% (n=37) of patients achieving CR. Similarly, 74% of patients in the decitabine-treated group achieved CR/CRi, with 55% (n=17) having achieved CR (**Table 3**). Forty-six percent (95% CI 36–58) and 32% (95% CI 17–51) of patients, respectively, achieved CR/CRi prior to initiation of cycle 2 therapy. While most patients experienced a CR/CRi within the first 2 therapy cycles, many patients achieved early MLFS and continued to deepen their response over time. Specifically, 13% (n=11) of patients in the azacitidine arm and 23% (n=7) in the decitabine arm achieved MLFS prior to the start of cycle 2. Of those patients, 7/11 in the azacitidine arm and 5/7 in the decitabine arm went on to achieve CR/CRi in subsequent cycles after achieving MLFS prior to cycle 2. The median time to first response for patients that, at some point, achieved CR/CRi was 1.2 months (Range 0.7–7.7) with azacitidine and 1.9 months (Range 0.9–5.4) with decitabine, while the median time to best response was 1.4 and 3.6 months, respectively.

The duration of CR/CRi response was 21.9 months (95% CI 15.1–30.2) for those treated with venetoclax plus azacitidine, and 15.0 months (95% CI 7.2–30.0) for patients who received the decitabine combination

(**Figure 1B**). For patients in remission and who received another treatment after study drug completion, including stem cell transplant, DOR was censored at the start of new therapy.

Response rates and duration of response for patients with baseline somatic mutations in *TP53*, *IDH1/2*, *FLT3*, and NPM1 and other key baseline prognostic factors among those treated with venetoclax plus azacitidine are shown in **Table 3**. Patients with intermediate (vs. poor) prognosis cytogenetic risk, *de novo* (vs. secondary) AML, and *NPM*1, *IDH1 or IDH2* mutant AML trended toward higher rates of CR+CRi and longer DOR. Those who had *de novo* AML (treated with 400 mg venetoclax plus azacitidine) had 76% CR/CRi rate, and a DOR of 17.9 months (95% CI 10.6–29.5), compared to 57% CR/CRi rate for those with secondary AML (median DOR not reached). Though the median DOR was not reached, the 12 patients with secondary AML that achieved CR/CRi had an estimated 24-month no event rate of 62% (95% CI 21–86). Patients with intermediate cytogenetic risk had a median duration of response of 26.5 months, compared to 7.8 months for those with poor risk. Those with *IDH1* or *IDH2* mutations had a median DOR of 29.5 months, while those with *TP53* mutation had a median DOR of 6.5 months. Those with *FLT3* and *NPM1* mutations had not yet reached their median DOR. Interestingly, older patients (≥75 years) had a longer median DOR (29.5 months) than younger patients (15.9 months).

Of those patients that had a best response of CR or CRi, minimal residual disease (10^{-3} cutoff; <0.1% leukemic cells) was achieved by 48% (29/60) of patients treated with venetoclax plus azacitidine, and by 39% (9/23) of patients treated with venetoclax plus decitabine.

Posttreatment rates of independence from both red blood cell and platelet transfusion (definition in Supplemental Appendix) were above 60% for patients treated with either venetoclax plus HMA

combination (**Supplemental Table ST1**). Patients treated with venetoclax plus azacitidine had a median of 148 days (range: 58–1,134) of RBC transfusion independence, while those treated with the decitabine combination had a median of 259 days (range: 63–1,178) of RBC independence. Duration of platelet transfusion independence for those treated with azacitadine or decitabine combinations was similar, at 169 days (range: 57–1,139) and 127 days (range: 57–1,181), respectively.

A total of 21 patients received stem cell transplant at investigator discretion (17 in azacitidine arm and 4 in decitabine arm). Fifteen (71%) remained alive at 12 months posttransplant, and 7 additional patients that have reached 24 months follow-up posttransplant remain alive (not all have enough follow-up time to get an accurate percentage).

4. DISCUSSION

Older patients with AML are often managed with supportive care after diagnosis. Treatment is regarded as unappealing, as intensive approaches are associated with high rates of treatment related mortality, significant periods of hospitalization, reduced quality of life; and alternative lower intensity treatments often providing only limited response rates and modest survival benefits.[24] Prior analysis of this phase 1b trial data demonstrated that treating patients with 400 mg venetoclax, combined with azacitidine or decitabine, resulted in a CR/CRi rate of 73%, with a median OS that had not been reached at the time of prior analysis (median follow up of 15 months).[13] The initial phase 1b results were confirmed in the phase 3 VIALE-A study that reported a CR/CRi rate of 66.4% with azacitidine–venetoclax (compared to 28.3% with the control regimen; P<0.001) at a median follow up of 20.5 months.[25] This extended follow up study provides long term outcomes of both efficacy and safety in patients treated with either of the hypomethylating agents, azacitidine and decitabine, at the approved label dose in the overall population and in selected biomarker subgroups.

The current analysis focuses on patients that received the label-recommended dose[15] of venetoclax (400 mg) plus either azacitidine or decitabine, analyzing safety and efficacy in all patients, with a median follow-up time of 29 and 40 months, respectively. With this longer follow-up time, patients had a CR/CRi rate of over 70%, with a median OS of over 16 months. For those treated with venetoclax plus azacitidine, 46% achieved CR/CRi by the start of therapy cycle 2, with 20% of all achieving CR by that time; the median duration of response for these patients was nearly two years (21.6 months).

The median time to first response with this regimen in patients with CR/CRi was only 1.2 months with azacitidine and 1.9 months with decitabine. Historically, median times to first response with azacitidine or decitabine monotherapy are 3.5 and 4.3 months, respectively.[1,5] The reported response rate of azacitidine and decitabine monotherapy in newly diagnosed AML patients who are at least 65 years old ranges between 10 and 50 percent CR/CRi,[1,5,26-28] with median OS between 6 and 12 months.[29,30] Here, the addition of venetoclax to the backbone therapy provided over 16 months of OS regardless of HMA combination, with nearly 3 out of every 4 patients achieved CR or CRi. Other frontline AML therapies recently approved by the US Food and Drug Administration include glasdegib plus LDAC (CR/CRi 27% and median OS of about 6 months),[31] liposomal cytarabine and daunorubicin for secondary AML (CR/CRi 48% and median OS of 9.5 months).[32]

Importantly, the benefits of venetoclax-based therapy come in the context of a manageable safety profile.[1,5] As is expected from patients with AML, most key adverse events were hematologic in nature, and patients treated with venetoclax plus either HMA had rates of grade 3 (or higher) cytopenia that were similar to previously-reported venetoclax-based low intensity therapies in older patients with AML.[33] In addition, a low early mortality (2% and 7% for AZA and DEC, respectively) was also observed for patients treated with venetoclax.

It is important to note that most patients that were determined to have CRi, but not CR, were due to lack of ANC recovery, and that the majority of patients receiving these combinations became transfusion independent. A majority of patients (70%) received concomitant anti-microbial prophylaxis within the first 30 days of treatment, and 42% of all patients had documented infections during that period. Notably, of

the 83 patients that achieved CR or CRi, 76% of them had an infectious AE during the course of the study, suggesting that infection-related AEs did not preclude beneficial outcomes with venetoclax.

Response rates differ in patients with intermediate versus poor-risk cytogenetics in the context of LDAC, azacitidine, or decitabine monotherapy show moderate difference in response rates between patients with intermediate- and poor-risk cytogenetics (between 3–13%).[25,34] In this study, rates of CR/CRi were similar for patients with intermediate- and poor-risk cytogenetics, 76% and 67% respectively, when treated with venetoclax plus azacitidine. Among patients with *TP53* mutation, poor cytogenetic risk, or secondary AML, the CR/CRi rate with venetoclax plus azacitidine was lower than the study rate overall (ie, <71%); yet while rates of response were relatively high regardless of risk features, these known risk factors appear to play a more prominent role in predicting duration of response. The key genetic mutations (*TP53*, *FLT3*, *IDH1/2*, and *NPM1*) that have been identified in driving outcomes in patients with AML, as well as cytogenetic risk groups, showed variability in DOR. Among patients treated with venetoclax plus azacitidine, those with somatic mutations in *NPM1* or *IDH1/2* had longer than average median duration of response (not yet reached and 29.5 months, respectively), while those with *TP53* mutations had shorter median DOR (6.5 months). Similarly, patients with intermediate cytogenetic risk had a median DOR of 26.5 months, compared to 7.8 months in those with poor risk features; a result confounded as all patients (100%; 25/25) with baseline *TP53* mutations were also categorized as having poor risk cytogenetics. DOR for cytogenetic risk groups, as well as *de novo* and secondary AML are shown in **Supplemental Figures S1 and S2**. Given the success of stem cell transplant demonstrated in this study, these findings may also suggest that allogeneic SCT may be important, particularly for high risk patients who become transplant eligible after venetoclax treatment. The ongoing randomized VIALE-A study, further assessing the efficacy

of venetoclax plus azacitadine in patients with AML, should provide more information as to the effectiveness of this combination in all patient subgroups.

In conclusion, the combination of 400 mg venetoclax with HMAs (azacitidine or decitabine) demonstrated high rates of complete remission with long-term OS benefit in newly diagnosed older patients with AML. Patients had rapid induction of remission, and experience continued durable responses and transfusion independence, with a favorable safety profile. These data suggest that the addition of 400 mg of venetoclax to azacitidine or decitabine monotherapy is a clinically effective treatment option for patients not suitable for intensive chemotherapy.

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Data Availability Statement

This 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 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-andinformation-sharing-with-qualified-researchers.html.

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FIGURE LEGEND

Figure 1. (A) Overall Survival and (B) Duration of Response

Abbreviations: Aza, azacytidine; Dec, decitabine; DOR, duration of response; OS, overall survival; Ven, venetoclax

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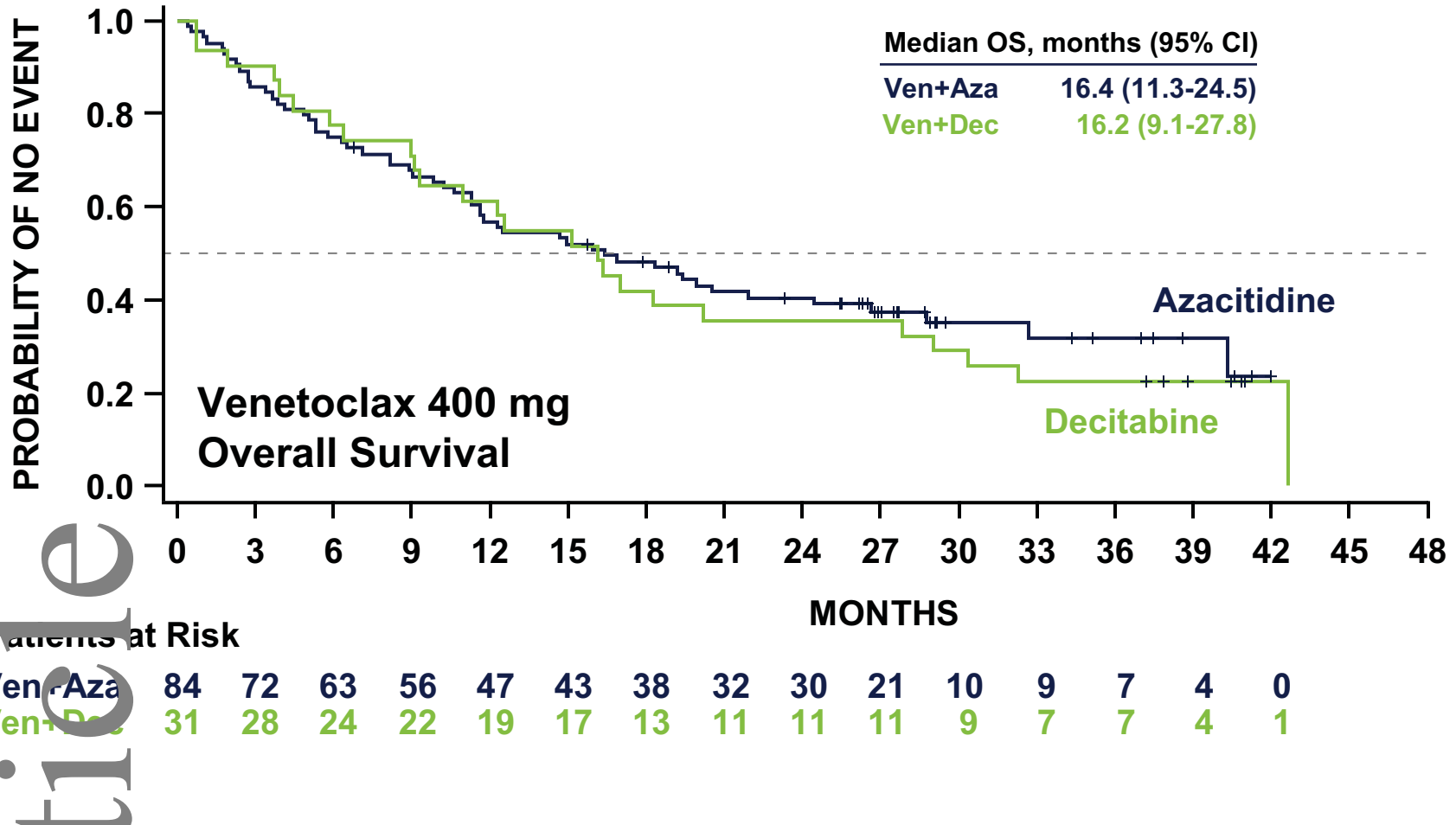

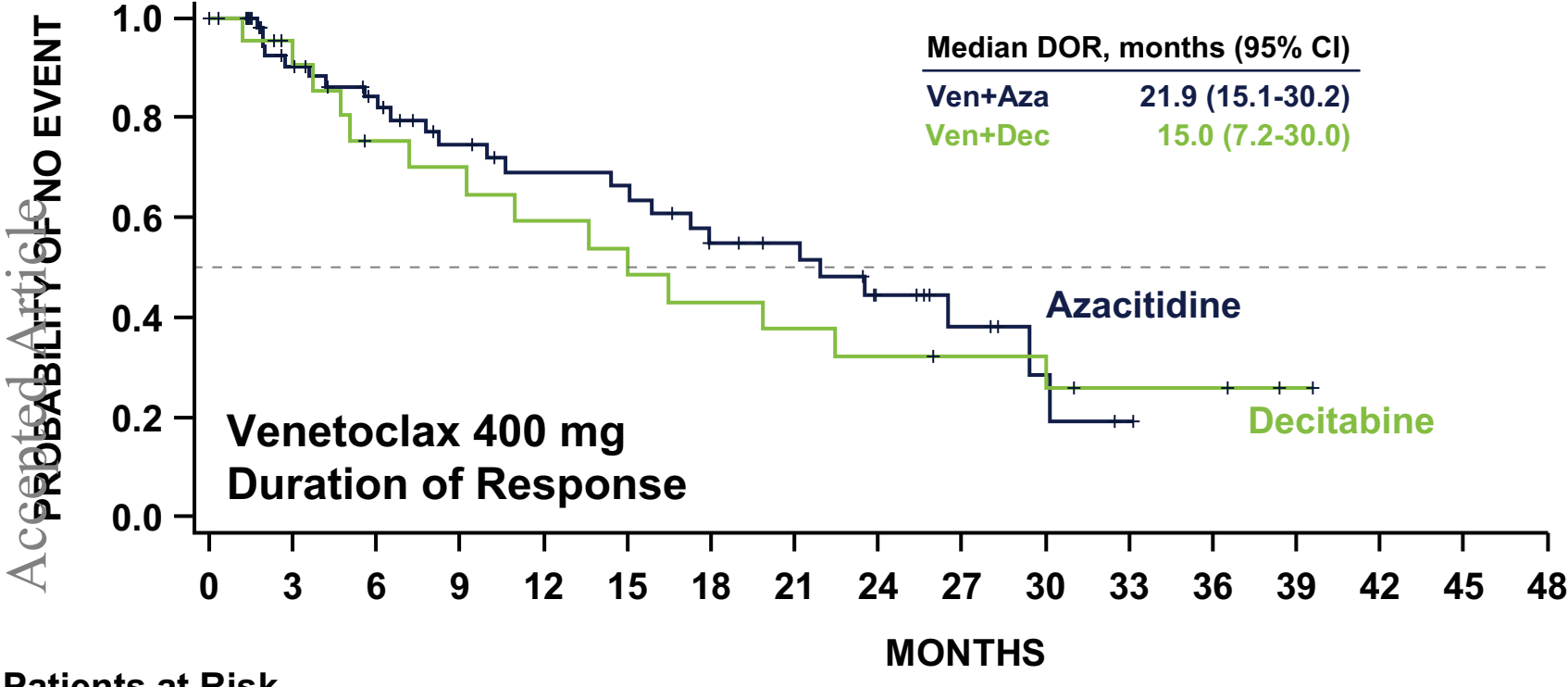

Patients at Risk

Ven+Aza	60	46	38	29	25	24	18	16	10	6	3	1	0	0	0
Ven+Dec	23	18	14	13	11	9	8	7	6	5	5	3	3	1	0

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Venetoclax + Azacitidine n = 84	Venetoclax + Decitabine n = 31
Age		
Median (range) years	75 (61 – 90)	72 (65 – 86)
≥75 years, n (%)	42 (50)	8 (26)
Male, n (%)	51 (61)	15 (48)
AML type, n (%)		
De novo	63 (75)	22 (71)
Secondary	21 (25)	9 (29)
ECOG performance status, n (%)		
0	14 (17)	7 (23)
1	44 (52)	20 (64)
2	24 (29)	4 (13)
3	2 (2)	0
Bone marrow blast count, n (%)		
20-30%	24 (29)	7 (23)
≥30 – <50%	29 (34)	14 (45)
≥50%	31 (37)	10 (32)
Antecedent hematologic disorder, n (%)	17 (20)	5 (16)
Baseline neutropenia, n (%)		
Grade 3	17 (20)	4 (13)
Grade 4	39 (46)	19 (61)
Cytogenetic risk category, n (%)		
Intermediate	50 (60)	16 (52)
Poor	33 (39)	15 (48)
No mitosis	1 (1)	0
Somatic mutations*, n (%)		
TP53	17 (21)	8 (28)
FLT3	12 (15)	4 (14)
IDH1	13 (16)	3 (10)
IDH2	9 (11)	5 (17)
NPM1	14 (18)	6 (21)
Transfusion dependent at baseline†, n (%)		
Red blood cells	51 (61)	23 (74)
Platelets	27 (32)	5 (16)

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group

* Missing samples or unevaluable samples for 4 and 2 patients in the azacitidine and decitabine groups, respectively. Cytogenetic risks: TP53, poor (n=25); FLT3, poor (n=3), intermediate (n=13); IDH1, poor (n=4), intermediate (n=12); IDH2, poor (n=1), intermediate (n=13); NPM1, poor (n=1), intermediate (n=19). FLT3: In the Aza arm, n=6 FLT3-ITD; n=3 FLT3-TKD; n=1 FLT3-other and n=2 FLT3-ITD and FLT3 other mutations; In the Dec arm, n=2 FLT3-ITD; n=2 FLT3-TKD.

† Had transfusion within 8 weeks prior to first dose of study drug

Table 2. Summary of Treatment Emergent AEs

Adverse event, n (%)	Venetoclax + Azacitidine n = 84	Venetoclax + Decitabine n = 31
Any Grade*		
Nausea	54 (64)	20 (65)
Diarrhea	51 (61)	14 (45)
Constipation	42 (50)	16 (52)
Edema peripheral	34 (41)	10 (32)
Febrile neutropenia	33 (39)	20 (65)
Vomiting	32 (38)	12 (39)
Fatigue	30 (36)	14 (45)
Hypokalemia	29 (35)	11 (36)
WBC decreased	28 (33)	14 (45)
Pneumonia	27 (32)	12 (39)
Pyrexia	25 (30)	10 (32)
Dizziness	22 (26)	12 (39)
Decreased appetite	25 (30)	10 (32)
Neutrophil count decreased	23 (27)	9 (29)
Headache	21 (25)	10 (32)
Grade ≥3†		
Febrile neutropenia	33 (39)	20 (65)
Anemia	25 (30)	8 (26)
Thrombocytopenia	21 (25)	7 (23)
Pneumonia	27 (32)	10 (32)
Neutropenia	17 (20)	3 (10)
Selected serious AEs		
Febrile neutropenia	26 (31)	13 (42)
Pneumonia	22 (26)	9 (29)
Sepsis	3 (4)	2 (7)

AML, acute myeloid leukemia; AE, adverse event

* AEs listed occurred in ≥25% of patients in both treatment groups

† AEs listed occurred in ≥20% of patients in both treatment groups; excludes laboratory investigations

Table 3. Summary of Rate and Duration of Response

All patients	N	CR n (%)	CR/CRi n (%)	DOR mos. (95% CI)
400 mg venetoclax				
Venetoclax + Azacitidine	84	37 (44)	60 (71)	21.9 (15.1–30.2)
Response by cycle 2 start*	84	17 (20)	39 (46)	–
Venetoclax + Decitabine	31	17 (55)	23 (74)	15.0 (7.2–30.0)
Response by cycle 2 start†	31	1 (3)	10 (32)	–
800 mg venetoclax				
Venetoclax + Azacitidine	37	15 (41)	22 (59)	16.1 (10.9–31.0)
Response by cycle 2 start	37	10 (27)	15 (41)	–
Venetoclax + Decitabine	37	17 (46)	27 (73)	9.2 (6.7–NR)
Response by cycle 2 start	37	8 (22)	20 (54)	–
1200 mg venetoclax				
Venetoclax + Azacitidine	6	1 (17)	2 (33)	5.8 (2.3–9.4)
Response by cycle 2 start	6	0	0	–
Venetoclax + Decitabine	5	3 (60)	3 (60)	NR (6.3–NR)
Response by cycle 2 start	5	1 (20)	2 (40)	–
400 mg venetoclax – Venetoclax + Azacitidine Patient Subgroups				
Cytogenetic risk				
Intermediate	50	26 (52)	38 (76)	26.5 (17.9–NR)
Poor	33	11 (33)	22 (67)	7.8 (2.0–17.3)
AML type				
De novo	63	31 (49)	48 (76)	17.9 (10.6–29.5)
Secondary	21	6 (29)	12 (57)	NR (1.9–NR)
Age				
60 – <75 years	42	19 (45)	33 (79)	15.9 (6.0–23.5)
≥75 years	42	18 (43)	27 (64)	29.5 (15.1–NR)
Mutation subgroup				
TP53	17	5 (29)	9 (53)	6.5 (1.9–17.3)
FLT3	12	6 (50)	7 (58)	NR (2.8–NR)
IDH1/2	22	10 (46)	19 (86)	29.5 (17.9–NR)
NPM1	14	8 (57)	11 (79)	NR (15.1–NR)

AML, acute myeloid leukemia; CR, complete response; CRi, CR with incomplete blood count recovery; HMA, hypomethylating agent; NR, not yet reached; CI, confidence interval; DOR, duration of response

CR: bone marrow with <5% blasts; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count ≥10^3/μL, platelets ≥10^5/μL and red cell transfusion independence

CRi: all of the criteria for CR except for absolute neutrophil count <10^3/μL or platelets <10^5/μL ± red cell transfusion independence

DOR: calculated only for those patients who achieved a best response of CR or CRi

* 11 (13%) patients had MLFS before start of cycle 2

† 7 (23%) patients had MLFS before start of cycle 2