

# Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study

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**PURPOSE** Effective treatment options are limited for patients with acute myeloid leukemia (AML) who cannot tolerate intensive chemotherapy. An international phase Ib/II study evaluated the safety and preliminary efficacy of venetoclax, a selective B-cell leukemia/lymphoma-2 inhibitor, together with low-dose cytarabine (LDAC) in older adults with AML.

**PATIENTS AND METHODS** Adults 60 years or older with previously untreated AML ineligible for intensive chemotherapy were enrolled. Prior treatment of myelodysplastic syndrome, including hypomethylating agents (HMA), was permitted. Eighty-two patients were treated at the recommended phase II dose: venetoclax 600 mg per day orally in 28-day cycles, with LDAC (20 mg/m<sup>2</sup> per day) administered subcutaneously on days 1 to 10. Key end points were tolerability, safety, response rates, duration of response (DOR), and overall survival (OS).

**RESULTS** Median age was 74 years (range, 63 to 90 years), 49% had secondary AML, 29% had prior HMA treatment, and 32% had poor-risk cytogenetic features. Common grade 3 or greater adverse events were febrile neutropenia (42%), thrombocytopenia (38%), and WBC count decreased (34%). Early (30-day) mortality was 6%. Fifty-four percent achieved complete remission (CR)/CR with incomplete blood count recovery (median time to first response, 1.4 months). The median OS was 10.1 months (95% CI, 5.7 to 14.2), and median DOR was 8.1 months (95% CI, 5.3 to 14.9 months). Among patients without prior HMA exposure, CR/CR with incomplete blood count recovery was achieved in 62%, median DOR was 14.8 months (95% CI, 5.5 months to not reached), and median OS was 13.5 months (95% CI, 7.0 to 18.4 months).

**CONCLUSION** Venetoclax plus LDAC has a manageable safety profile, producing rapid and durable remissions in older adults with AML ineligible for intensive chemotherapy. High remission rate and low early mortality combined with rapid and durable remission make venetoclax and LDAC an attractive and novel treatment for older adults not suitable for intensive chemotherapy.

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## INTRODUCTION

The median age at diagnosis of acute myeloid leukemia (AML) is 68 years. Older adults are often ineligible for intensive chemotherapy and thus have limited effective treatment options.<sup>1,2</sup> Less-intensive approaches to treatment, such as low-dose cytarabine (LDAC), are associated with poor response rates (11% to 19%) and median survival times (< 6 months).<sup>3-5</sup> Similarly, initial treatment with azacitidine, decitabine, or gemtuzumab ozogamicin result in complete remission (CR) plus CR with incomplete blood count recovery (CRI) rates of less than 30%.<sup>5-7</sup> In part because of limited expectation of success, many older

patients do not receive leukemia therapy.<sup>8</sup> These factors underscore the high unmet need for more-effective and less-toxic treatment options for older adults with AML, particularly those who are ineligible for intensive chemotherapy.

B-cell leukemia/lymphoma-2 (BCL-2) family members, including BCL-2, BCL-X<sub>L</sub>, and MCL1, promote cell survival by binding and sequestering pro-apoptotic proteins in cancer cells. BCL-2 has been shown to mediate chemoresistance and enhance survival of leukemic blast and progenitor cells.<sup>9,10</sup> Venetoclax, a selective, potent, orally bioavailable small-molecule BCL-2 inhibitor, has been studied alone and in

## ASSOCIATED CONTENT

### Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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combination with other agents in several hematologic malignancies.<sup>11-16</sup> A phase II study reported an overall response rate (ORR) of 19% with venetoclax monotherapy in heavily pretreated patients with AML.<sup>17</sup> Resistance to venetoclax monotherapy may be mediated by other pro-survival proteins, such as MCL1, that sequester endogenous BCL-2 homology domain 3-only proteins (eg, Bim) released by venetoclax on BCL-2 binding. Several drugs—including anthracyclines, hypomethylating agents (HMAs), and cytarabine—have demonstrated the ability to down-regulate MCL1 expression and act synergistically with venetoclax against AML cells in preclinical studies.<sup>18-20</sup> As proof of concept, a 61% CR/CRi rate was reported for venetoclax combined with HMAs (ie, azacitidine or decitabine) in treatment-naïve older adults with AML,<sup>21</sup> exceeding previously reported response rates for HMAs alone.<sup>5,7</sup> Here, a phase Ib/II study was conducted to determine the safety and preliminary efficacy of venetoclax in combination with LDAC in previously untreated adults with AML who were ineligible for intensive chemotherapy.

## PATIENTS AND METHODS

### Patients

Patients age 60 years or older with previously untreated AML and ineligible for intensive chemotherapy were enrolled (Data Supplement). Patients with secondary AML or prior treatment with HMAs for myelodysplastic syndrome (MDS) were permitted. Exclusion criteria included prior therapy for AML or any previous use of cytarabine for any indication (more details in the Treatment section). Local ethics committee approval was obtained, and patients provided written informed consent. The study was conducted in accordance with the International Conference on Harmonization, Good Clinical Practice guidelines, and the Declaration of Helsinki.

### Study Design

This open-label, multicenter, multinational phase Ib/II study ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02287233) enrolled patients between January 2015 and May 2017. Data cutoff for efficacy in this analysis was November 8, 2017; cutoff for safety was January 30, 2018. Primary objectives in the dose-escalation phase were to assess safety, pharmacokinetics (PK), maximum tolerated dose, and recommended phase II dose of venetoclax combined with LDAC. In dose expansion, the primary objectives were to obtain preliminary estimates of efficacy: ORR, including CR, CRi, and partial remission (PR); duration of response (DOR); and safety of the combination at the recommended phase II dose.<sup>22</sup> Exploratory objectives were to identify biomarkers of efficacy and resistance.

### Treatment

Patients were hospitalized and tumor lysis syndrome (TLS) prophylaxis was initiated at least 24 hours before the first dose of venetoclax and continued during a ramp-up period

until the target venetoclax dose was reached. Venetoclax was administered orally, once daily, after food. Venetoclax dosing began at 50 or 100 mg and increased over 4 to 5 days to the target venetoclax dose; dosing was continued through day 28 of each cycle. In subsequent 28-day cycles, venetoclax was commenced at the target dose. LDAC (20 mg/m<sup>2</sup>) was administered by subcutaneous injection once daily, on days 1 to 10. At the completion of a 28-day cycle, if bone marrow blasts were less than 5%, venetoclax dosing was interrupted if needed to promote recovery of neutrophils and platelets. Patients could start the next cycle of therapy when the neutrophil count recovered to least  $0.5 \times 10^9/L$  and the platelet count to at least  $25 \times 10^9/L$ . Once morphologic evidence of leukemia was cleared, granulocyte colony stimulating factor was permitted at investigator's discretion. Patients could continue receiving treatment until disease progression or until discontinuation criteria were met (Data Supplement).

Because venetoclax is a Cytochrome P450 (CYP3A) substrate, patients receiving CYP3A inhibitors (CYP3A4i) had their venetoclax dose reduced by approximately 50% for moderate CYP3A inhibitors and approximately 75% to 90% for strong inhibitors.<sup>23</sup> If a patient was on multiple inhibitors, venetoclax dose adjustment was based on the strongest CYP3A4i.

### Study Assessments

**Safety.** Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.<sup>24</sup> Dose-limiting toxicities (DLTs) were determined during cycle 1 of the dose-escalation phase and defined as grade 4 toxicity, excluding AEs commonly caused by AML (eg, neutropenia, fever). Hematologic DLT was defined as failure of platelet recovery to  $25 \times 10^9/L$  or greater and neutrophils to  $0.5 \times 10^9/L$  or greater within 14 days of the last dose of venetoclax in the absence of residual AML. Clinical and laboratory TLS were considered as previously defined.<sup>25</sup>

**Efficacy.** Bone marrow assessments were performed at screening, after cycles 1 and 3, and then every three cycles until two consecutive samples confirmed CR. Additional bone marrow studies were performed if there was clinical suspicion of recurrence and at final visit. Clinical responses were defined according to International Working Group response criteria for AML (Data Supplement).<sup>22</sup>

**PK and exploratory biomarkers.** Pharmacokinetic assessment is described in the Data Supplement. Biomarkers that may be predictive of venetoclax activity and response were assessed during the trial (Data Supplement). Clinical outcome was correlated with the WHO 2008 classification<sup>26</sup> and cytogenetic and molecular markers, including the chromatin-spliceosome, *TP53*-aneuploidy, and *IDH* R172 mutation subgroups, as recently proposed.<sup>27</sup> Karyotypic abnormalities were classified using site-reported results, and centrally reported next-generation sequencing data were used to supplement molecular mutation results.

## Statistical Analyses

All baseline summary statistics and analyses were based on patient characteristics obtained before initiation of venetoclax or LDAC. The safety population included patients who received at least one dose of venetoclax; the DLT-evaluable population included patients who received at least 80% of planned cycle 1 doses during dose-escalation phase. Further details of statistical analyses are contained in the Data Supplement. For the phase II portion, it was initially planned to enroll 25 patients at the recommended phase II dose to enable a 95% CI for estimation of ORR with margin of error not exceeding plus or minus 25%. The study was later amended to enroll an additional 28 patients to provide further precision regarding the observed response rate estimates, and another 21 patients were enrolled to evaluate patients allowed to receive concomitant strong CYP3Ai if indicated.

## RESULTS

All patients enrolled at least 6 months before this analysis. At the time of analysis, the median treatment duration was 4.2 months (range, 0.2 to 29 months), and the median number of cycles of therapy was five. The median number of cycles of LDAC delivered to patients who achieved CR was seven (range, two to 30), and five (range, one to 16) for patients achieving CRi. Seven patients (9%) remained in the study therapy at time of analysis.

### Patient Demographics and Clinical Characteristics

Eighty-two patients were enrolled to a 600 mg venetoclax cohort and received at least one dose of venetoclax. Baseline demographics and clinical characteristics for the 600 mg venetoclax cohort are shown in Table 1. The median age was 74 years (range, 63 to 90 years). Forty-nine percent of patients had secondary AML, and 50% had concomitant CYP3A inhibitor use. Baseline mutations in *TP53*, *FLT3*, *IDH1/2*, and *NPM1* were detected in 14%, 23%, 25%, and 13% of patients, respectively.

### DLT and Maximum Tolerated Dose

No DLTs were observed in the 600 mg venetoclax cohort during the dose-escalation phase of the study. Of the six patients in the 600 mg dose escalation cohort who proceeded to subsequent cycles, only one patient required dose interruption between cycles 1 and 2, because of thrombocytopenia without residual morphologic AML. At the 800 mg dose level ( $n = 10$ ), most patients who proceeded to subsequent cycles needed dose interruption between cycles 1 and 2 to permit count recovery, and one patient experienced a hematologic dose-limiting toxicity (grade 4 thrombocytopenia lasting more than 42 days without evidence of residual leukemia in a patient with AML secondary to myeloproliferative neoplasm). Therefore, the recommended phase II dose was determined to be venetoclax 600 mg when combined with LDAC.

## Safety Profile

A summary of treatment-emergent AEs for the venetoclax 600 mg cohort is shown in Table 2; further breakdown is available in the Data Supplement. Consistent with expectations for AML, the common grade 3 or 4 AEs, irrespective of cause, were frequently hematologic and included febrile neutropenia (42%), thrombocytopenia (38%), neutropenia (27%), and anemia (27%). The most common non-hematologic AEs of any grade or cause were nausea (70%), diarrhea (49%), hypokalemia (48%), and fatigue (43%). Serious AEs other than AML progression, occurring in at least 5% of patients, were anemia (31%), febrile neutropenia (27%), pneumonia (10%), and sepsis (7%).

Forty-five (55%) patients had venetoclax dose interruptions due to AEs, most commonly between subsequent 28-day cycles (due to delayed neutrophil and platelet recovery in eight and 10 patients, respectively). Dose reductions were necessary in six patients (7%), the majority due to thrombocytopenia. Reduced duration of venetoclax administration to 21 and 14 days occurred in 25 patients (30%) and 14 patients (17%), respectively. Laboratory-defined TLS was reported in two patients (elevations of potassium and phosphorus in one patient and elevations of uric acid and phosphorus in the other), although both were able to complete the venetoclax ramp-up to the intended dose. No clinical TLS was reported. The 30-day mortality rate was 6% ( $n = 5$ ).

## Efficacy

In phase I and II, a total of 82 patients were enrolled to the venetoclax 600 mg dose level. The CR/CRi rate was 54% (95% CI, 42% to 65%); CR was achieved in 26% of patients, and CRi in 28% (Fig 1). Median time to first CR/CRi was 1.4 months (range, 0.8 to 14.9 months). Patients with de novo AML and intermediate-risk cytogenetic features and without prior HMA exposure had the highest rates of CR/CRi: 71%, 63%, and 62%, respectively (Fig 1). A complete breakdown of responses by baseline patient features is shown in the Data Supplement. Among patients achieving CR/CRi after venetoclax plus LDAC, the median duration of remission was 8.1 months (95% CI, 5.3 to 14.9 months; Fig 2A). The median OS for all patients was 10.1 months (95% CI, 5.7 to 14.2 months; Fig 2B). Observed survival for the study population was better for patients achieving CR, CRi, or both (Fig 2C). The 12-month estimated survival rate for those who achieved CR, CRi, CR/CRi, or no response was 100%, 49%, 73%, and 5%, respectively (Fig 2C, arrows). Patients without prior HMA exposure had a longer median OS (13.5 months; 95% CI, 7.0 to 18.4 months) than patients with AML previously exposed to prior HMA (4.1 months; 95% CI, 2.9 to 10.1 months; Fig 2D).

Most patients who achieved remission became transfusion independent. Among patients treated with venetoclax in combination with LDAC, 46% (38 of 82) achieved independence from both RBC and platelet transfusion.

**TABLE 1.** Patient Demographics and Clinical Characteristics

| Characteristic                  | Venetoclax 600 mg + LDAC (n = 82) |
|---------------------------------|-----------------------------------|
| Age, years, median (range)      | 74 (63-90)                        |
| ≥ 65                            | 80 (98)                           |
| ≥ 75                            | 40 (49)                           |
| Male                            | 53 (65)                           |
| AML type                        |                                   |
| De novo                         | 42 (51)                           |
| Secondary                       | 40 (49)                           |
| ECOG performance status         |                                   |
| 0                               | 12 (15)                           |
| 1                               | 46 (56)                           |
| 2                               | 23 (28)                           |
| 3                               | 1 (1)                             |
| Bone marrow blast count         |                                   |
| < 30%                           | 27 (33)                           |
| ≥ 30% to < 50%                  | 18 (22)                           |
| ≥ 50%                           | 36 (44)                           |
| Antecedent hematologic disorder | 40 (49)                           |
| Prior HMA treatment             | 24 (29)                           |
| Cytogenetic risk category       |                                   |
| Intermediate                    | 49 (60)                           |
| Poor                            | 26 (32)                           |
| No mitosis                      | 7 (8)                             |
| Somatic mutations*              |                                   |
| <i>TP53</i>                     | 10 (14)                           |
| <i>FLT3</i>                     | 16 (23)                           |
| <i>IDH1/2</i>                   | 18 (25)                           |
| <i>NPM1</i>                     | 9 (13)                            |
| CYP3A inhibitor use             | 41 (50)                           |

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: AML, acute myeloid leukemia; CYP3A, Cytochrome P450; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agent; LDAC, low-dose cytarabine.

\*Mutation data missing for 11 patients; percentage calculated based on the number of patients with data (n = 71).

Forty-eight percent (39 of 82) achieved RBC transfusion independence, and 60% (49 of 82) achieved platelet transfusion independence. Among the patients who were dependent on transfusions before enrollment, 43% (23 of 53) of those dependent on RBC transfusions and 65% (15 of 23) of those dependent on platelet transfusions became transfusion independent while in the study. The time required for platelet ( $\geq 50 \times 10^9/L$ ) and neutrophil ( $\geq 0.5 \times 10^9/L$ ) recovery was assessed among patients who achieved CR/CRi (Data Supplement). The median time to platelet recovery was 28 days, with 90% or more reaching this threshold by day 53. The median time to absolute neutrophil count recovery was 32 days, with 90% recovered by day 64.

## PK

Venetoclax and cytarabine PK parameters are shown in the Data Supplement. PK concentration-time profiles of venetoclax and cytarabine are shown in the Data Supplement. These studies showed no impact on drug exposures of combining venetoclax with cytarabine, thus indicating an absence of substantial PK interaction.

## Key AML Genetic Mutations and Clinical Response

There are several key genetic mutations that have been identified in driving the progression, prognosis, and outcome in AML, including mutations in *TP53*, *FLT3*, *IDH1/2*, and *NPM1*; a genomic classification system for AML has been recently developed, largely around these molecular drivers (among others).<sup>27,28</sup> Patients with somatic mutations in *NPM1* or *IDH1/2* had higher than average CR/CRi rates (89% and 72%, respectively), whereas those with *TP53* or *FLT3* mutations had lower CR/CRi rates (30% and 44%, respectively; Data Supplement).

## DISCUSSION

Optimizing treatment selection for older adults with AML remains challenging. Higher incidence of treatment-related complications is expected from intensive chemotherapy because poor performance status and comorbidities are more prevalent in the elderly.<sup>29</sup> Poor outcomes with intensive chemotherapy are also typical for older patients with poor-risk cytogenetics, monosomal karyotype, secondary AML, or MDS after failure of prior HMA therapy.<sup>30-32</sup> For patients older than 65 years receiving intensive chemotherapy, reported remission rates range between 45% and 57% and median OS between 5 and 12 months.<sup>33,34</sup> For patients between 60 and 75 years of age and previously treated with an HMA, CR/CRi rates are only 28% for intensive 7 plus 3 chemotherapy and 37% for patients receiving liposomal daunorubicin and cytarabine (CPX-351).<sup>35</sup> Accordingly, many physicians and patients elect a low-intensity approach to therapy or no active treatment at all.<sup>36</sup>

Low-intensity therapies, such as LDAC monotherapy, have historically been administered with palliative intent, with CR/CRi rates of 11% to 19% and median OS of approximately 5.5 months.<sup>4,31</sup> Therefore, the observed CR/CRi rate of 54% and 10.1-month median survival for patients treated with venetoclax plus LDAC seems favorable. Among patients older than 75 years, the rate of CR/CRi remained 60%, with median OS of 14.9 months. Importantly, the higher clinical response rate was achieved without an increase in early mortality: the 30-day mortality rate was 6% in the first month after LDAC plus venetoclax treatment, compared with 8% to 13% with LDAC alone from literature reports.<sup>4,31</sup> This raises the possibility of also evaluating venetoclax combined with low-intensity therapy in younger and/or more fit patients with AML, with the goal of sparing patients the greater toxicity generally observed with intensive chemotherapy.

**TABLE 2.** Summary of Treatment-Emergent AEs

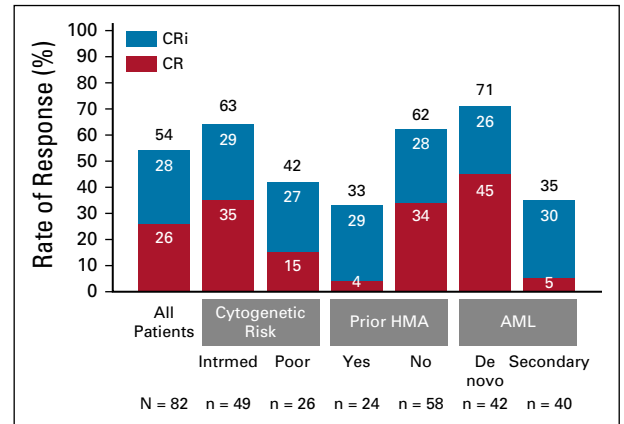
| AE                         | Venetoclax 600 mg + LDAC (n = 82) |
|----------------------------|-----------------------------------|
| Any AE                     | 82 (100)                          |
| AE with grade $\geq$ 3     |                                   |
| Febrile neutropenia        | 34 (42)                           |
| Thrombocytopenia           | 31 (38)                           |
| WBC count decreased        | 28 (34)                           |
| Anemia                     | 22 (27)                           |
| Neutropenia                | 22 (27)                           |
| Platelet count decreased   | 20 (24)                           |
| Lymphocyte count decreased | 15 (18)                           |
| Neutrophil count decreased | 14 (17)                           |
| Hypophosphatemia           | 13 (16)                           |
| Hypokalemia                | 12 (15)                           |
| Hypertension               | 9 (11)                            |
| Pneumonia                  | 9 (11)                            |
| Sepsis                     | 9 (11)                            |
| Serious AE                 |                                   |
| Anemia                     | 25 (31)                           |
| Febrile neutropenia        | 22 (27)                           |
| Pneumonia                  | 8 (10)                            |
| AML progression            | 7 (9)                             |
| Sepsis                     | 6 (7)                             |

NOTE. Data are presented as No. (%). Adverse events (AEs) were listed if they were reported for at least 10% of patients with grade 3 or higher or at least 5% of patients with serious AEs.

Abbreviation: AML, acute myeloid leukemia.

The outcomes achieved with venetoclax plus LDAC also compare favorably with those obtained during recent studies of HMA monotherapy in older patients with AML: decitabine resulted in CR/CRi of 25.6% and median OS of 7.7 months in older adults with newly diagnosed AML<sup>5</sup>; azacitidine achieved CR/CRi of 27.8% and median OS of 10.4 months in another phase III study, which included patients either eligible or ineligible for intensive chemotherapy.<sup>7</sup> Importantly, both historical studies excluded patients who had received prior HMA for MDS, whereas in the current study, 29% of patients had previously received an HMA. For HMA-naïve participants in the current study, the CR/CRi rate was 62%, with a median duration of response 14.8 months and median OS of 13.5 months.

Historical rates of CR/CRi for patients treated with LDAC, azacitidine, or decitabine monotherapy are between 11% and 26%,<sup>5,37</sup> with moderate difference in CR rates observed between patients with intermediate-risk versus poor-risk cytogenetics (reported differences between 3% and 13%).<sup>38,39</sup> In the current study, rates of CR/CRi were 63% and 42% for patients with intermediate-risk and poor-risk cytogenetics, respectively. Among patients with mutant

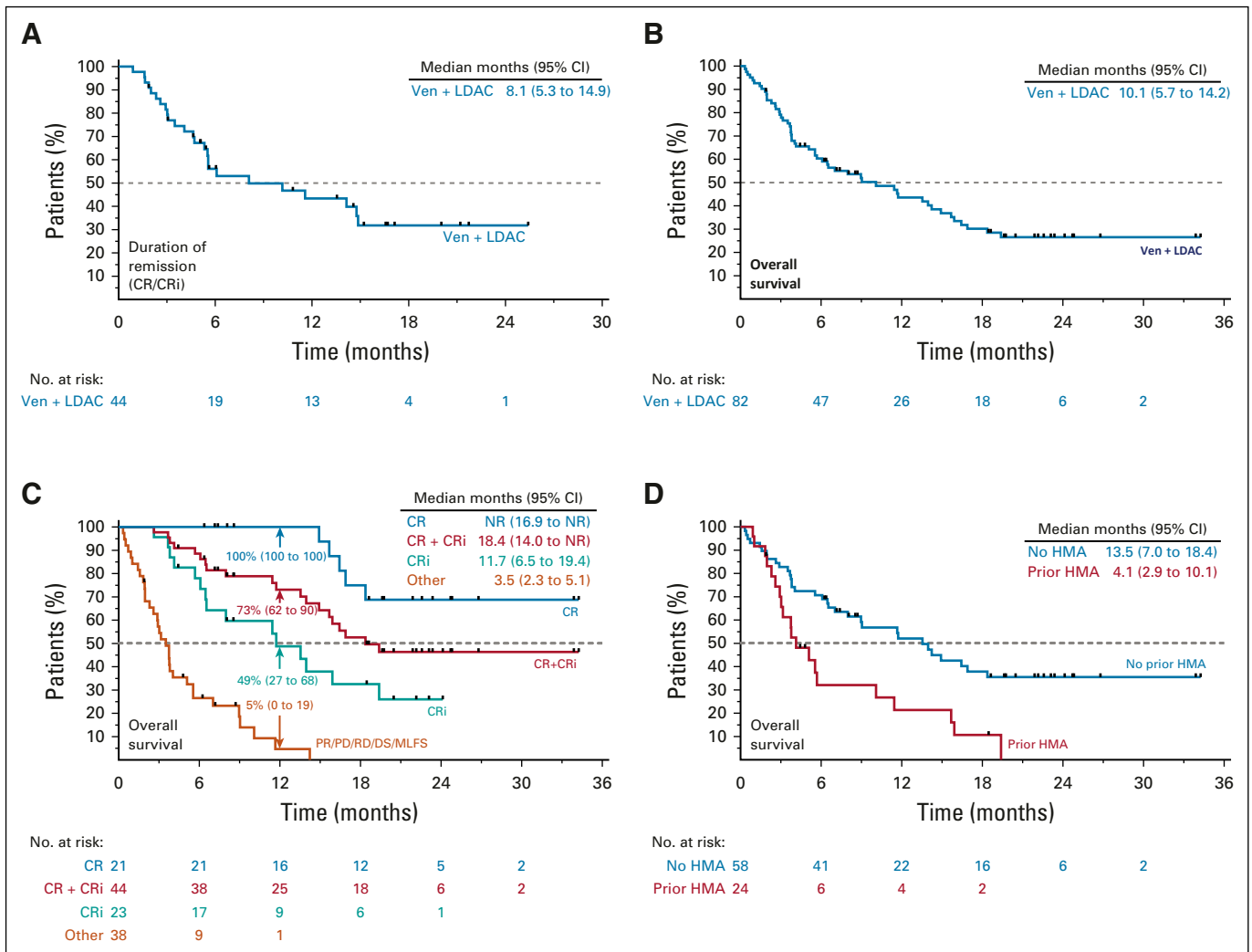


**FIG 1.** Complete remission (CR)/CR with incomplete blood count recovery (CRi) rates by patient subgroups. The graph shows the rates of CR and CRi in all patients, as well as key patient subgroups sorted by baseline characteristics. The numbers in the bars represent the percentage of patients with a given response, and the black number at the top of each bar is the total CR/CRi percentage in a given subgroup. Partial remissions are not shown, because only one patient had a partial remission. AML, acute myeloid leukemia; HMA, hypomethylating agent; intrmed, intermediate.

*NPM1*, the CR/CRi rate was 89% (eight of nine), which included two patients with coexisting *FLT3* and *IDH1/2* mutations and three additional patients with either mutant *FLT3* or *IDH1/2*; all eight patients remain alive at more than 1 year. Although larger validation studies are needed, these preliminary observations suggest that such patients may be especially responsive to venetoclax plus LDAC therapy.

Responses to venetoclax monotherapy have been previously reported in patients with *IDH1* or *IDH2* mutations.<sup>40</sup> In the current study, venetoclax plus LDAC resulted in a CR/CRi rate of 72% (13 of 18) and median OS of 19.4 months among patients with *IDH1/2*-mutant AML. Therefore, venetoclax plus LDAC may also represent a useful treatment strategy for patients with treatment-naïve *IDH1/2*-mutant AML who are ineligible for intensive chemotherapy; further integration of *IDH1/2* inhibitors into this regimen for patients with persistent *IDH*-positive disease may be an objective for future clinical trials. Among patients with *TP53* mutation or poor cytogenetic risk, the CR/CRi rate with LDAC and venetoclax was 30% (three of 10) or 42% (11 of 26), respectively, indicating that these historically identified features of poor prognosis remain relevant for this combination.

Venetoclax plus LDAC was associated with rapid achievement of CR/CRi, with median time to first response of 1.4 months, compared with 3.1 months for LDAC alone<sup>4</sup> and 3.5 to 4.1 months with HMA therapies.<sup>37</sup> However, clinical vigilance and robust supportive care measures are necessary until blast clearance and hematologic recovery are achieved. At the onset of this trial, antifungal prophylaxis with azole antifungals (CYP3A inhibitors) was prohibited because of the potential of increasing venetoclax exposure.<sup>41</sup> However, separate pharmacokinetic studies reported that



**FIG 2.** Overall survival and duration of response. Kaplan-Meier curves showing (A) duration of remission for patients who had complete remission (CR)/CR with incomplete blood count recovery (CRi); (B) overall survival of all patients; (C) overall survival broken down by the patients' best response; (D) overall survival by prior hypomethylating agent (HMA) exposure. NOTE: Numbers in parentheses are 95% CIs. DS, discontinued prior to assessment; LDAC, low-dose cytarabine; MLFS, morphologic leukemia-free state; NA, not available; NR, not reached; PD, progressive disease; PR, partial remission; RD, resistant disease; Ven, venetoclax.

venetoclax can be administered, with appropriate dose reductions, to patients with AML using concomitant moderate or strong CYP3A inhibitors (such as the anti-fungal azoles voriconazole or posaconazole).<sup>23</sup> Consequently, a cohort was added to prospectively evaluate the impact of allowing CYP3A inhibitors when medically required. As such, 50% of the patients enrolled and treated had concomitant CYP3A inhibitor use; no increase in adverse events related to potential CYP3A inhibitor interaction was observed.

Because patients with prior HMA exposure were included in the current study, it is difficult to directly compare efficacy between the current study and historical results. Clinical trials of low-intensity therapies have historically excluded patients who received prior treatment with HMAs, and such patients have an especially poor prognosis. In the current study, nearly

one-third (29%) of patients had prior HMA exposure. The CR/CRi rate for those patients with prior HMA exposure was 33%, comparable to rates reported for intensive chemotherapy or CPX-351 for patients experiencing disease progression after prior HMA therapy for antecedent conditions. Among patients without prior HMA treatment, the CR/CRi rate for venetoclax plus LDAC was 62%, which is similar to the reported CR/CRi rate of 67% in a recently published study that combined venetoclax with HMAs for patients with AML.<sup>21</sup> As such, both venetoclax studies, in combination with LDAC or HMAs, support a role for venetoclax as an integral component of standard therapy, especially in older adults with AML. International randomized studies are currently underway for venetoclax or placebo combined with either LDAC (ClinicalTrials.gov identifier: NCT03069352) or azacitidine (ClinicalTrials.gov identifier: NCT02993523).

In conclusion, the combination of venetoclax and LDAC is tolerable and associated with high rates of remission in patients with previously untreated AML who are ineligible for intensive chemotherapy. The high remission rate, low

early mortality, rapid induction of remission, and durable length of remission make the combination with venetoclax an attractive and novel treatment option for older adults not suitable for intensive chemotherapy.

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## PRIOR PRESENTATION

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AbbVie is committed to responsible data-sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

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-and-information-sharing-with-qualified-researchers.html>.

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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients With Acute Myeloid Leukemia: Results From a Phase Ib/II Study**

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