

## Venetoclax plus LDAC for patients with untreated AML ineligible for intensive chemotherapy: phase 3 randomized placebo-controlled trial

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Andrew Wei (Alfred hospital, Australia) Pau Montesinos (Hospital La Fe, Spain) Vladimir Ivanov (Almazov National Medical Research Center, Russian Federation) Courtney DiNardo (UT MD Anderson Cancer Center, United States) Jan Novak (University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Czech Republic) KAMEL LARIBI (CENTRE HOSPITALIER LE MANS, France) Inho Kim (Seoul National University Hospital, Korea, Republic of) Don Stevens (Norton Cancer Institute, ) Walter Fiedler (University Medical Center Hamburg-Eppendorf, Germany) Maria Pagoni (Evangelismos Hospital, Greece) Olga Samoilova (Nizhny Novgorod Regional Clinical Hospital, Russian Federation) Yu Hu (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, China) Achilles Anagnostopoulos (George Papanicolaou Hospital, Greece) Julie Bergeron (Hôpital Maisonneuve-Rosemont, Canada) Jing-Zhou Hou (University of Pittsburgh, United States) Vidhya Murthy (Heartlands Hospital, part of UHB, United Kingdom) Takahiro Yamauchi (University of Fukui, Japan) Andrew McDonald (etcare Pretoria East Hospital, Moreletapark, Pretoria, South Africa, South Africa) Brenda Chyla (etcare Pretoria East Hospital, Moreletapark, Pretoria, South Africa, South Africa) Sathej Gopalakrishnan (AbbVie, Inc., Germany) Qi Jiang (AbbVie, Inc., United States) Wellington Mendes (AbbVie, Inc., United States) John Hayslip (AbbVie, Inc., United States) Panayiotis Panayiotidis (National and Kapodistrian University of Athens, Greece)

### Abstract:

**Background:** Effective treatment options are limited for patients with acute myeloid leukemia (AML) who cannot tolerate intensive chemotherapy. **Methods:** Adults  $\geq 18$  years with newly diagnosed AML ineligible for intensive chemotherapy were enrolled in this international Phase 3 randomized, double-blind, placebo-controlled trial. Patients (N=211) were randomized 2:1 to either: venetoclax (N=143) or placebo (N=68) in 28-day cycles, plus low-dose cytarabine (LDAC) on days 1–10. The primary endpoint was overall survival (OS); secondary endpoints included response rates, transfusion independence, and event-free survival. **Results:** Median age was 76 years (range 36–93), 38% had secondary AML, and 20% had prior hypomethylating agent (HMA) treatment. The planned primary analysis showed that the venetoclax arm provided a benefit of 25% reduction in the risk-of-death over the LDAC-alone arm (hazard ratio [HR] 0.75 [95% CI 0.52–1.07],  $p=0.11$ ), although it was not statistically significant; with median OS of 7.2 months and 4.1 months, respectively. An unplanned analysis with an additional 6 months of follow up demonstrated a median OS of 8.4 months for the venetoclax arm (HR 0.70; 95% CI 0.50–0.98;  $p=0.04$ ). The CR/CRI rates were 48% and 13% for the Venetoclax plus LDAC arm and LDAC-alone arm, respectively. Key grade  $\geq 3$  adverse events (Ven vs. LDAC-alone) were febrile neutropenia (32% vs 29%), neutropenia (47% vs. 16%), and thrombocytopenia (45% vs 37%). **Conclusion:** Venetoclax plus LDAC demonstrates a clinically meaningful improvement in remission rates and OS compared to LDAC alone, in the context of a manageable safety profile. These results confirm venetoclax plus LDAC is an important frontline AML treatment option for patients unfit for intensive chemotherapy.

**Conflict of interest:** COI declared - see note

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**Agreement to Share Publication-Related Data and 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 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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Andrew H. Wei<sup>1</sup>, Pau Montesinos<sup>2</sup>, Vladimir Ivanov<sup>3</sup>, Courtney D. DiNardo<sup>4</sup>, Jan Novak<sup>5</sup>, Kamel Laribi<sup>6</sup>, Inho Kim<sup>7</sup>, Don A. Stevens<sup>8</sup>, Walter Fiedler<sup>9</sup>, Maria Pagoni<sup>10</sup>, Olga Samoilova<sup>11</sup>, Yu Hu<sup>12</sup>, Achilles Anagnostopoulos<sup>13</sup>, Julie Bergeron<sup>14</sup>, Jing-Zhou Hou<sup>15</sup>, Vidhya Murthy<sup>16</sup>, Takahiro Yamauchi<sup>17</sup>, Andrew McDonald<sup>18</sup>, Brenda Chyla<sup>19</sup>, Sathej Gopalakrishnan<sup>19</sup>, Qi Jiang<sup>19</sup>, Wellington Mendes<sup>19</sup>, John Hayslip<sup>19</sup>, Panayiotis Panayiotidis<sup>20</sup>

<sup>1</sup>The Alfred Hospital and Monash University, Melbourne, VIC, Australia; <sup>2</sup>Hospital Universitario y Politecnico La Fe, Valencia, Spain and CIBERONIC, Instituto Carlos III, Madrid, Spain; <sup>3</sup>Almazov National Medical Research Center, Saint Petersburg, Russia; <sup>4</sup>Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>5</sup>Department of Internal Medicine and Hematology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine, Charles University, Prague, Czech Republic; <sup>6</sup>Centre Hospitalier Le Mans, Le Mans, France; <sup>7</sup>Seoul National University Hospital, Seoul, South Korea; <sup>8</sup>Norton Cancer Institute, Louisville, Kentucky, USA; <sup>9</sup>Hubertus Wald University Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; <sup>10</sup>Evangelismos General Hospital, Athens Greece; <sup>11</sup>Nizhny Novgorod Regional Clinical Hospital, Russia; <sup>12</sup>Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; <sup>13</sup>George Papanicolaou General Hospital, Thessaloniki, Greece; <sup>14</sup>CIUSSSEMTL, Installation Maisonneuve-Rosemont, Montreal, Quebec, Canada; <sup>15</sup>University of Pittsburgh Medical Center (UPMC) Cancer Center, Pittsburgh, PA, USA; <sup>16</sup>Heartlands Hospital, Birmingham, United Kingdom; <sup>17</sup>University of Fukui Hospital, Fukui, Japan; <sup>18</sup>Netcare Pretoria East Hospital, Moreletapark, Pretoria, South Africa; <sup>19</sup>AbbVie Inc., North Chicago, IL, USA; <sup>20</sup>National and Kapodistrian University of Athens Medical School, Laiko General Hospital, Athens, Greece

## CORRESPONDING AUTHOR:

**Andrew H. Wei, MBBS, PhD**

Department of Haematology

The Alfred Hospital and Monash University

Commercial Road, Melbourne VIC 3004 Australia

Telephone: +61 (0)3 9076 3451

Fax: +61 (0)3 9076 2298

E-mail: [a.wei@alfred.org.au](mailto:a.wei@alfred.org.au)

## KEY POINTS

- Venetoclax+LDAC improves response rate, transfusion independence, and patient reported outcomes versus LDAC alone in older patients with AML
- The median overall survival for patients receiving venetoclax+LDAC was 8.4 months, compared to 4.1 months with LDAC alone

## ABSTRACT

**Background:** Effective treatment options are limited for patients with acute myeloid leukemia (AML) who cannot tolerate intensive chemotherapy.

**Methods:** Adults  $\geq 18$  years with newly diagnosed AML ineligible for intensive chemotherapy were enrolled in this international Phase 3 randomized, double-blind, placebo-controlled trial. Patients (N=211) were randomized 2:1 to either: venetoclax (N=143) or placebo (N=68) in 28-day cycles, plus low-dose cytarabine (LDAC) on days 1–10. The primary endpoint was overall survival (OS); secondary endpoints included response rates, transfusion independence, and event-free survival.

**Results:** Median age was 76 years (range 36–93), 38% had secondary AML, and 20% had prior hypomethylating agent (HMA) treatment. The planned primary analysis showed that the venetoclax arm provided a benefit of 25% reduction in the risk-of-death over the LDAC-alone arm (hazard ratio [HR] 0.75 [95% CI 0.52–1.07],  $p=0.11$ ), although it was not statistically significant; with median OS of 7.2 months and 4.1 months, respectively. An unplanned analysis with an additional 6 months of follow up demonstrated a median OS of 8.4 months for the venetoclax arm (HR 0.70; 95% CI 0.50–0.98;  $p=0.04$ ). The CR/CRi rates were 48% and 13% for the Venetoclax plus LDAC arm and LDAC-alone arm, respectively. Key grade  $\geq 3$  adverse events (Ven vs. LDAC-alone) were febrile neutropenia (32% vs 29%), neutropenia (47% vs. 16%), and thrombocytopenia (45% vs 37%).

**Conclusion:** Venetoclax plus LDAC demonstrates a clinically meaningful improvement in remission rates and OS compared to LDAC alone, in the context of a manageable safety profile. These results confirm venetoclax plus LDAC is an important frontline AML treatment option for patients unfit for intensive chemotherapy.

## INTRODUCTION

Older adults and patients with significant comorbidities are often ineligible for intensive chemotherapy. The median age at diagnosis for acute myeloid leukemia (AML) is over 68 years, thus a large portion of patients diagnosed with AML have limited effective treatment options.<sup>1,2</sup> Less intense frontline treatments, such as hypomethylating agents (azacitidine or decitabine), are often utilized and provide complete remission (CR) plus CR with incomplete blood count recovery (CRi) rates of less than 30%.<sup>3-5</sup> Response rates to low-dose cytarabine (LDAC) as frontline therapy in older patients with AML is similarly poor (11%–19% CR/CRi), with median survival times  $\leq 6$  months.<sup>5-7</sup> These results highlight the lack of highly effective, well-tolerated treatment options for older adults with AML, particularly those who are ineligible to receive intensive chemotherapy.

B-cell leukemia/lymphoma-2 (BCL2) family members, including BCL2, BCL-X<sub>L</sub>, and MCL1, mediate cancer cell survival by sequestering proapoptotic proteins, and BCL2 activity promotes chemoresistance and enhances survival of leukemic progenitor and blast cells.<sup>8,9</sup> Venetoclax is a potent and selective small-molecule BCL2 inhibitor that has been studied in several hematologic malignancies as both monotherapy and in combination with other agents.<sup>10-16</sup> Resistance to venetoclax may be mediated by other pro-survival proteins, such as MCL1 and BCL-X<sub>L</sub>, that sequester endogenous BH3-only proteins released by venetoclax upon BCL2 binding. Cytotoxic drugs, including cytarabine, synergize with venetoclax by enhancing BH3-only activity and/or suppressing MCL1 to promote apoptosis in pre-clinical models of AML.<sup>17-19</sup> Translating these pre-clinical observations, a Phase 2 study of venetoclax combined with LDAC in AML resulted in a CR/CRi rate of 54%, with a median overall survival (OS) of approximately 10 months,<sup>16</sup> comparing favorably with historical response rates and survival outcomes previously reported for LDAC monotherapy in AML. Notably, responses were achieved rapidly and with low early

mortality, suggesting the addition of venetoclax to LDAC may represent a useful clinical advance for older patients currently receiving LDAC alone.

Therefore, this study compared the safety and efficacy of treatment with venetoclax co-administered with LDAC to placebo plus LDAC in previously untreated patients with AML, either  $\geq 75$  years old or with comorbidities precluding intensive chemotherapy.

## METHODS

### *Study Design*

This randomized, double-blind, placebo controlled, phase 3 study (NCT03069352) enrolled patients between May 2017 and November 2018. The study was conducted globally across 76 sites, including in North and South America, Europe, Asia, Africa and Australia (complete list of countries in Supplemental Information). Data cutoff for this initial analysis was February 15, 2019; cutoff for additional follow-up time was August 15, 2019. The primary objective was to evaluate whether venetoclax, when co-administered with LDAC, improved the overall survival (OS) of patients compared to those treated with placebo plus LDAC. Secondary objectives were to compare the following measures between treatment arms: complete remission (CR) rate; CR + CR with partial hematologic recovery (CRh) rate; CR + CR with incomplete hematologic recovery (CRi) rate; proportion of patients with CR/CRi and CR/CRh by the initiation of therapy cycle 2; rate of transfusion independence (TI); event-free survival (EFS); minimal residual disease (MRD) response rate; response rates and OS in the subsets of patients with mutations in *NPM1*, *IDH1/2*, *FLT3* and *TP53* ; fatigue, global health status and quality of life, based on patient reported outcomes. A detailed list of objectives is outlined in the **Supplemental Appendix**.

### *Patients*

Patients aged  $\geq 18$  years with previously untreated AML (as defined by the World Health Organization [WHO]<sup>20</sup>) and ineligible for intensive chemotherapy were enrolled. Patients were considered ineligible for intensive induction chemotherapy if they were  $\geq 75$  years of age or  $\geq 18$  to 74 years of age and fulfilled at least one criterion associated with lack of fitness for intensive induction chemotherapy, including: an Eastern Cooperative Oncology Group (ECOG) Performance status of 2–3, cardiac history of congestive heart failure requiring treatment or Ejection Fraction  $\leq 50\%$  or chronic stable angina, DLCO

≤65% or FEV1 ≤65%, creatinine clearance ≥30 mL/min to <45 mL/min, had moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × ULN, or had any other comorbidity that was physician-judged to be incompatible with conventional intensive chemotherapy. The **Supplemental Appendix** contains a complete list of eligibility criteria. Patients with secondary AML with or without prior treatment with HMAs for myelodysplastic syndrome (MDS) were included; those with secondary AML from underlying myeloproliferative neoplasms were not. Exclusion criteria included prior therapy for AML (except hydroxyurea prior to and during the first cycle of study treatment), and any previous exposure to cytarabine for any indication. 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.

### ***Patient Randomization***

Patients were randomized 2:1 via interactive response technology to receive either venetoclax plus LDAC, or placebo plus LDAC. Randomization was stratified by AML status (secondary vs. de novo), age (18–<75 vs. ≥75), and region [US, Europe (EU), China, Japan, Rest of the world (ROW)].

### ***Treatment***

Patients were hospitalized for tumor lysis syndrome (TLS) evaluation and prophylaxis during the venetoclax ramp-up period (4 days) in treatment cycle 1, until 24 hours after the target venetoclax dose was reached. Prophylaxis for TLS included a uric acid reducing agent and oral or intravenous hydration. Venetoclax was administered orally, once daily, with food. Venetoclax dosing began at 100 mg on day one and increased stepwise over 4 days to reach the target dose of 600 mg (100 mg, 200 mg, 400 mg, 600 mg); dosing was continued at 600 mg per day from day 4 through day 28. In all subsequent 28-day cycles, venetoclax was commenced at the target dose. For patients randomized to the placebo arm, placebo (identical appearance tablet) was administered in the same fashion as venetoclax. For patients



in both arms, LDAC (20 mg/m<sup>2</sup>) was administered by subcutaneous injection once daily, on days 1–10 in all cycles. Patients could continue receiving treatment until progression or until study-treatment discontinuation criteria were met (**Supplemental Appendix**). Patients remained on study for OS assessment and follow-up, even if they initiated additional lines of treatment. Since venetoclax is a CYP3A and P-glycoprotein (P-gp) substrate, protocol recommended dose modifications for patients receiving these inhibitors were applied: venetoclax dose was reduced to 50% if co-administered with moderate CYP3A inhibitors or P-gp inhibitors, and reduced to 50 mg if co-administered with any strong CYP3A inhibitors.<sup>21</sup> If a patient was on multiple inhibitors, venetoclax dose adjustment was based on the strongest inhibitor.

## **Study Assessments**

### *Safety*

Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.<sup>22</sup> Treatment-emergent AEs, including clinical TLS, were defined as those that occurred between the first dose of study drug until 30 days after the last dose of study drug. Laboratory TLS was defined as previously reported by Howard *et al.*<sup>23</sup>

### *Efficacy*

Response assessments were performed after cycle 1 (patients with resistant disease after cycle 1 had repeat assessments after cycles 2 or 3 to assess initial CR/CRi response), and every three cycles thereafter (starting at the end of cycle 4 and continuing until disease progression) until two consecutive samples confirmed stable achievement of CR or CRi. Assessments were also performed if there was suspected relapse, and/or at the final study visit. Criteria for evaluation of disease assessment are outlined in the **Supplemental Appendix**. Clinical responses were defined according to modified

International Working Group response criteria for AML (Supplemental Appendix Methodology).<sup>24</sup> Progressive disease was defined per European LeukemiaNet (ELN) recommendations.<sup>25</sup> Treatment failure was defined as failure to achieve MLFS or higher response (CR, CRi, PR) after at least 6 cycles of treatment. Event-free survival (EFS) was defined as the number of days from randomization to disease progression, confirmed relapse, treatment failure, or death.

### *Pharmacokinetics*

Blood samples were collected for pharmacokinetic (PK) analysis in cycles 1, 2, 4, and 8. Details on PK sample timepoints are found in the **Supplemental Appendix**.

### *Other assessments*

Assessment of cytogenetic risk followed the NCCN guidelines for AML, version 2.2016. Fatigue and global health status/quality of life were assessed via the PROMIS Fatigue SF7a and EORTC QLQ-C30 patient outcomes scale, respectively.

### *Statistical analyses*

The planned sample size was 210 patients, randomized 2:1, required to observe 133 events at the time of analysis. The study was designed to detect a 45.5% reduction in mortality with 90% power and a significance level with two-sided alpha of 0.05. An interim analysis was planned when 75% of death events occurred. The O'Brien-Fleming boundary was used to control the type-I error rate at 0.05 (two-sided). Information on endpoint analyses is detailed in the **Supplemental Appendix**.

## RESULTS

Overall, 211 patients were enrolled and 210 were treated; 68 patients were randomized to the placebo (placebo plus LDAC) arm, and 143 were randomized to the venetoclax (venetoclax plus LDAC) arm (1 of these patients never received treatment). The CONSORT diagram in **Supplemental Figure S1** shows the flow of patients through the trial. In the venetoclax arm (as of February 15, 2019), the median treatment duration was 3.9 months (range: 0–17) and the median number of cycles delivered was 4. In the placebo arm, the median treatment duration was 1.7 months (range: 0.1–14) and the median number of treatment cycles delivered was 2. The median time on study (observation time for event-free patients) was 12 months for both arms. Post-study therapy was received by 33/143 (23%) patients in the venetoclax plus LDAC arm and by 30/68 (44%) of those in the placebo arm. No patients went on to receive stem cell transplant post-study treatment. The primary reasons for discontinuation of study drug (venetoclax + LDAC vs placebo + LDAC) were: treatment failure (12% vs 19%), progressive disease (11% vs 16%), death (12% for both), withdrawal of consent (6% vs 10%), adverse events not related to disease progression (9% for both), adverse events related to disease progression (4% for both), physician decision (5% vs 12%), morphologic relapse (13% vs 4%), and other (4% vs 3%).

### ***Patient Demographics and Clinical Characteristics***

Baseline demographics are shown in **Table 1**, separated by treatment arm. Across all patients: the median age was 76 years, 32% had poor cytogenetic risk, 38% had secondary AML, 20% had prior HMA exposure, and baseline mutations in *TP53*, *FLT3*, *IDH1/2*, and *NPM1* were detected in 19%, 18%, 20%, and 15% of patients (in whom data were available), respectively. The majority of baseline characteristics had similar frequencies across the randomized arms, except the rates of secondary AML (41% vs. 34%) and poor cytogenetic risk (33% vs. 29%), which were more frequent in the venetoclax-containing arm.

## ***Safety Profile***

Two-hundred and ten patients (142 venetoclax arm and 68 placebo arm) were evaluated for safety. The median dose intensity across all patients, accounting for dose reductions due to planned drug-drug interactions, was 96.7%. Overall, a total of 141 patients (99%) in the venetoclax arm and 67 patients (99%) in the placebo arm experienced at least one adverse event. A summary of treatment emergent adverse events is shown in **Table 2**. Consistent with expectations and prior studies in AML, the most frequently reported Grade 3 or higher AEs, irrespective of cause, were hematologic in nature and included (Venetoclax + LDAC vs Placebo + LDAC) febrile neutropenia (32% vs 29%), neutropenia (46% vs 16%), thrombocytopenia (45% vs 37%), and anemia (25% vs 22%). The most common non-hematologic AEs of any grade (Venetoclax + LDAC vs Placebo + LDAC) were nausea (42% vs 31%), hypokalemia (28% vs 22%), diarrhea (28% vs 16%), and constipation (18% vs 31%). Serious AEs (any grade) were reported in 66% and 62% of patients in the venetoclax and placebo arms, respectively. Serious AEs common to patients with AML included febrile neutropenia (16% vs 18%), pneumonia (13% vs 10%) and sepsis (6% in both arms). There were no other serious AEs observed in  $\geq 10\%$  of patients in either arm. Although there was a higher percentage of Grade 3+ bleeding AEs in patients receiving venetoclax + LDAC (15 patients; 11%) compared to placebo + LDAC arm (5 patients; 7%), the incidence of fatal bleeding events was similar in both arms (1.4% for venetoclax + LDAC and 1.5% for placebo + LDAC). There were 8 patients (6%) with TLS reported in the study, all in the venetoclax arm. Of these 8 cases, two were reported as serious AEs related to TLS; both patients received TLS prophylaxis as per protocol.

Overall, a similar percentage of patients in both arms had AEs leading to death (33 patients [23%] and 14 patients [21%], respectively). The 30-day mortality rates were 13% (n=18) and 16% (n=11) in the venetoclax and placebo arms, respectively.

Thirty-six (25%) of patients treated with venetoclax plus LDAC and 16 (24%) patients treated with placebo plus LDAC had AEs leading to treatment discontinuation. Sixty-three percent and 53% of patients in the venetoclax and placebo arms, respectively, had dose interruptions due to AEs; dose reductions due to AEs occurred in 9% and 6% of patients, respectively. The most common adverse events ( $\geq 5\%$  of patients) leading to dose interruption or reduction were (venetoclax + LDAC vs placebo + LDAC): neutropenia (18% vs 7%), thrombocytopenia (15% vs 9%), febrile neutropenia (6% vs 7%), and pneumonia (6% vs 7%).

Venetoclax exposures during preplanned dose modifications for coadministration with CYP3A or P-gp inhibitors were generally comparable to the exposures of patients when not receiving these inhibitors (**Supplemental Figure S1**).

### **Efficacy**

At the preplanned primary analysis, the median follow-up time was 12.0 months in both the venetoclax (range: 0.1–17.6) and placebo (range: 0.2–17.0) arms. At the time of the preplanned analysis, 40% (57/143) and 31% (21/68) of patients remained alive in the venetoclax and placebo arms, respectively. The median OS for patients treated with venetoclax plus LDAC was 7.2 months (95% CI 5.6–10.1), compared to 4.1 months (95% CI 3.1–8.8) for those treated with placebo plus LDAC, with a hazard ratio between the two treatment arms (venetoclax vs. placebo) of 0.75 (95% CI 0.52–1.07);  $p=0.11$  (**Figure 1A**). To determine the independent effect of venetoclax on overall survival, and to identify baseline prognostic factors that may have influenced OS, a *post hoc* stepwise multivariate Cox proportional hazard model was used. This analysis identified AML status (*de novo* vs. secondary), cytogenetic risk (intermediate vs. poor), ECOG performance status ( $<2$  vs.  $\geq 2$ ), and age ( $<75$  vs.  $\geq 75$  years) as significantly correlated with OS (**Table 3**), and demonstrated that, when controlling for baseline prognostic factors, the adjusted hazard ratio (venetoclax vs. placebo) for the venetoclax arm was 0.67 (95% CI 0.47–0.96);

p=0.03. Additionally, at the time of the preplanned OS analysis, there was greater censoring of patients on the venetoclax-containing arm, as more patients had not yet reached the median OS by the study cutoff date (15 Feb 2019) for the primary analysis. With an additional 6 months of follow up, the majority of patients had passed the median survival time in both arms, demonstrating a median OS of 8.4 months (95% CI 5.9–10.1) for patients treated with venetoclax plus LDAC, compared to 4.1 months (95% CI 3.1–8.1) for placebo plus LDAC (**Figure 1B**). The hazard ratio between the two treatment arms (venetoclax vs. placebo) after this additional follow-up was 0.70 (95% CI 0.50–0.99) with a nominal p-value of 0.04.

CR/CRi was achieved in 48% (95% CI 39–56) of patients in the venetoclax arm, compared to 13% (95% CI 6–24) in the placebo arm, with CR achieved in 27% and 7% of patients, respectively. Responses were also achieved more rapidly with addition of venetoclax, with CR/CRi prior to initiation of cycle 2 observed in 34% (95% CI 27–43), compared to only 3% (95% CI 0–10) of patients achieving this response in the placebo arm (**Table 4**). Concordantly, higher rates of remission in the venetoclax-treated arm were accompanied by a longer median event-free survival of 4.7 months (95% CI 3.7–6.4) versus 2.0 months (95% CI 1.6–3.1) in the placebo arm (hazard ratio 0.58; 95% CI 0.42–0.82) (**Table 4**). Rates of transfusion independence were also significantly higher for patients treated with venetoclax plus LDAC, with 37% (95% CI 29–46) of patients achieving red blood cell and platelet transfusion independence, compared to 16% (95% CI 8–27) for those treated with LDAC alone. Upon confirmation of morphologic CR or CRi, 6% (8/143) of those in the venetoclax arm and 1% (1/68) of those in the placebo arm had a flow cytometry MRD level of <0.1%.

Response rates and overall survival times were also determined for subsets of patients with baseline intermediate and poor cytogenetic risk, somatic mutations in *TP53*, *IDH1/2*, *FLT3*, and *NPM1*, as well as those with key baseline prognostic factors. Response rates for these subgroups are shown in

**Supplemental Table ST1.** Across all patient subgroups, those treated with venetoclax plus LDAC had increased rates of remission (CR, CRi, CRh) compared to those treated with placebo plus LDAC. Similarly, patient survival showed a trend toward longer median OS in those treated with venetoclax compared to placebo across most patient subgroups, except those with mutant *FLT3* (**Supplemental Table ST2**). *FLT3* mutations were detected in 29 patients; 9 patients in the placebo arm and 20 in the venetoclax arm (1 patient was randomized but never treated). Among the *FLT3* mutation positive (*FLT3*+) patients in placebo arm; 3 had coexisting *NPM1* mutations, and all 3 (100%) such patients achieved CR/CRi; 1 of the remaining 6 (17%) *FLT3* patients without *NPM1* mutation achieved CRi. Among the 20 *FLT3* patients in the venetoclax arm; 6 had coexisting *NPM1* mutations (n=1, not treated), and all 5 (100%) who received therapy achieved CR/CRi; 4 of the remaining 14 (29%) *FLT3* patients without *NPM1* mutation achieved CR/CRi with a median OS of 2.2 months. In contrast, the median OS for patients with coexisting *FLT3* and *NPM1* mutations was 10.2 months in the placebo arm, and not yet reached in the venetoclax arm.

Patients in the placebo + LDAC arm showed only marginally improved fatigue by cycle 5 (mean change from baseline: -0.3), with further improvements over time that were sustained by cycle 9 (mean change from baseline: -3.5) (**Supplemental Table ST3**). In contrast, fatigue scores changed rapidly in the venetoclax + LDAC arm, with improvements already evident by cycle 3 (mean change from baseline: -2.9) and a trend for greater improvements in fatigue scores (p=0.13) compared to the LDAC alone arm that were sustained by cycle 9 (mean change from baseline: -5.1). Similar improvements were recorded in Global Health Status and Quality of Life (p=0.09) scores compared to the placebo arm (**Supplemental Table ST3**).

## DISCUSSION

To evaluate venetoclax in combination with LDAC, a multinational, randomized, placebo-controlled Phase III study involving 25 countries was conducted, allocating patients in a 2:1 ratio to arms treated with either venetoclax or placebo, plus LDAC. A 25% reduction in the risk of death was observed with the addition of venetoclax, showing that venetoclax plus LDAC was associated with a clinically meaningful improvement in median OS (7.2 vs. 4.1 months). Despite this finding, the primary endpoint was not met (HR, 0.75 [95% CI 0.52–1.07];  $p = 0.11$ ) at the time of planned analysis. It was observed that several imbalances in baseline characteristics (secondary AML, prior hematologic disorder-related secondary AML, and poor cytogenetic risk) between the randomized arms, as well as increased administrative censoring in the venetoclax arm before the median OS time, may have impacted the analyses. To evaluate the impact of the imbalances in baseline characteristics, a *post hoc* multivariate Cox proportional hazard analysis was performed; this analysis indicated that venetoclax added significant clinical benefit for OS over placebo when controlling for those baseline prognostic factors (AML type, cytogenetic risk, ECOG performance status and age). Regarding the high number of administratively censored patients, trial enrollment was ongoing as recent as 3.4 months prior to the pre-planned OS analysis and administrative censoring of patients still alive at time of analysis occurred more frequently in the venetoclax plus LDAC arm than in the placebo plus LDAC arm (17 [12%] patients vs 4 [6%] patients within the first 6 months). However, a longer-term analysis with an additional six months of patient follow-up, now with the majority of the patients censored in both arms beyond the median OS time, demonstrated a clinically meaningful increase in median OS in the venetoclax arm, with a hazard ratio of 0.70 (95% CI 0.50–0.99) and a nominal  $p$ -value of 0.04. Concordant with these findings, all secondary endpoints were robustly in favor of the venetoclax-based combination as well, including higher rates of response, earlier remissions, increased transfusion independence and longer event-free



survival. Achievement and prolongation of remission are key determinants of quality of life for patients with AML. In line with this, the higher rates of response and transfusion independence, as well as increased median overall survival in the venetoclax-containing arm correlated with strong improvements in patient-reported outcomes, such as fatigue and quality of life.

Venetoclax plus LDAC was well tolerated and manageable, with treatment exposure longer for patients in the venetoclax arm; median 4 cycles (compared to 2 cycles in the placebo plus LDAC arm). Although the venetoclax treatment arm showed modest increases in hematologic AEs, the rate of AEs leading to treatment discontinuation (24% vs. 25%) and the rate of serious AEs such as pneumonia (13% vs. 10%) or sepsis (6% in each arm) was nearly identical between venetoclax plus LDAC versus placebo plus LDAC, respectively. Although there was a numerically higher rate of Grade  $\geq 3$  bleeding events in the venetoclax arm (11% vs. 7%), the incidence of fatal bleeding events was similar in the venetoclax and placebo arms (1.4% and 1.5%, respectively). The safety profile of the combination of venetoclax plus LDAC is a reassuring factor for the treatment of elderly or unfit AML patients, as it is known that this patient population has limited effective treatment options; with the increased risk of treatment-related toxicity associated with intensive chemotherapy a deterring factor for those considering this option.<sup>25</sup>

Because concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure, the study protocol prospectively recommended venetoclax dose modifications when co-administered with these inhibitors. Pharmacokinetic analyses showed that recommended venetoclax dose adjustments while receiving concomitant moderate or strong CYP3A inhibitors, resulted in venetoclax exposures comparable to the exposures when patients were not receiving these inhibitors, supporting the dose-modification scheme used in this study.

This study enrolled a challenging AML population, with nearly 60% being  $\geq 75$  years and a high proportion of patients with secondary disease (38%), prior HMA treatment (20%), poor cytogenetic risk

(32%) and *TP53* mutation (15%), which are known factors associated with a dismal prognosis in AML. Although the rate of patients that achieved an MRD value <0.1% appears lower in the current study (6% [8/143]), compared to the prior phase 1b/2 study of venetoclax plus LDAC (21% [17/82] of all patients),<sup>26</sup> the MRD assessments from the Phase 2 and 3 studies cannot be directly compared; in the present study bone marrow MRD assessment was not required after confirmation of complete remission (contrary to the phase 2 study). For this reason, the Phase 2 study was likely more proficient in capturing the deeper responses achieved over time in patients with CR/CRi. In our recent phase 1b/2 study combining venetoclax with low-dose cytarabine in 82 treatment naïve older patients with AML, CR/CRi responses (54%) were achieved with a short median time to first response (1.4 months).<sup>16</sup> Among the CR/CRi population, the median duration of remission was 8.1 months and the median OS for all patients was 10.1 months. Interestingly, a survival plateau beyond 18 months was observed, with approximately 25% of patients demonstrating extended and ongoing long-term survival. Survival outcome was particularly promising for patient sub-groups with *NPM1* (median OS not reached) and *IDH1/2* mutant (median OS 19.4 months) AML.

In the current study, induction of disease remission was notable in the venetoclax arm, with a CR/CRi rate of 48% (including 27% CR), compared to only 13% in the placebo arm. Glasdegib plus LDAC, also available for frontline AML treatment, recently showed a CR/CRi rate of 27%.<sup>27</sup> Venetoclax plus LDAC also performed well in patients with mutant *IDH*; studies have demonstrated a CR/CRh rate of 42% for those treated with ivosidenib for *IDH1* mutant AML, while those with *IDH1/2* mutations treated with venetoclax plus LDAC resulted in 57% CR/CRi.<sup>28</sup> In addition, the rate of CR observed in this study is in line with previously reported rates for venetoclax combined with azacitidine (37%).<sup>16,29</sup>

In this study, LDAC plus placebo was associated with CR/CRi rates of 16% and 10% for patients with intermediate- and poor-risk karyotype, respectively, which is on par with historical response rates in the

literature.<sup>30,31</sup> In comparison, patients treated with LDAC plus venetoclax had CR/CRi rates of 56% and 28% for intermediate- and poor-risk, respectively.

In conclusion, the combination of venetoclax plus LDAC demonstrated a well-tolerated and manageable safety profile, together with clinically meaningful benefits in overall survival, rates of remission, event free survival, transfusion requirements and patient-reported outcomes, compared to LDAC alone, in previously untreated patients with AML who were ineligible for intensive chemotherapy. The rapid induction of remission and favorable benefit-risk profile suggest that the addition of venetoclax to LDAC may provide an important treatment option for patients not suitable for intensive chemotherapy.

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

Characteristic	Placebo + LDAC n = 68	Venetoclax + LDAC n = 143
Age		
Median (range) years	76 (41 – 88)	76 (36 – 93)
≥75 years, n (%)	40 (59)	82 (57)
Male, n (%)	39 (57)	78 (55)
AML type, n (%)		
De novo	45 (66)	85 (59)
Secondary	23 (34)	58 (41)
Type of Secondary AML, n/N (%)		
Therapy-related AML	4/23 (17)	6/58 (10)
Prior Hematologic Disorder	19/23 (83)	52/58 (90)
ECOG performance status, n (%)		
0	11 (16)	22 (15)
1	23 (34)	52 (36)
2	25 (37)	63 (44)
3	9 (13)	6 (4)
Bone marrow blast count, n (%)		
<30%	18 (27)	42 (29)
≥30 – <50%	22 (32)	36 (25)
≥50%	28 (41)	65 (46)
Antecedent hematologic disorder, n (%)	17 (25)	47 (33)
Prior HMA treatment, n (%)	14 (21)	28 (20)
Cytogenetic risk category, n (%)		
Favorable	3 (4)	1 (1)
Intermediate	43 (63)	90 (63)
Poor	20 (29)	47 (33)
No mitosis / missing	2 (3)	5 (3)
Somatic mutations*, n (%)		
<i>TP53</i>	9 (17)	22 (20)
<i>FLT3</i>	9 (17)	20 (18)
<i>IDH1/2</i>	12 (23)	21 (19)
<i>NPM1</i>	7 (14)	18 (16)
Transfusion dependent at baseline†, n (%)		
Red blood cells	53 (78)	104 (73)
Platelets	24 (35)	53 (37)

AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; HMA, hypomethylating agent

\* Mutation data missing for 16 and 31 patients in the placebo and venetoclax arms, respectively; percentage calculated based on the number of patients with data

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

**Table 2. Summary of Treatment Emergent AEs by frequency across all patients**

Adverse event, n (%)	Placebo + LDAC n = 68	Venetoclax + LDAC n = 142
<b>Hematologic AEs (Grade ≥3)*</b>		
Thrombocytopenia	25 (37)	64 (45)
Neutropenia	11 (16)	66 (46)
Febrile neutropenia	20 (29)	45 (32)
Anemia	15 (22)	36 (25)
<b>Non-hematologic AEs (Any Grade)*</b>		
Nausea	21 (31)	60 (42)
Hypokalemia	15 (22)	40 (28)
Diarrhea	11 (16)	40 (28)
Constipation	21 (31)	26 (18)
Vomiting	9 (13)	36 (25)
Pneumonia	11 (16)	29 (20)
Oedema peripheral	14 (21)	19 (13)
<b>Selected key AML serious AEs</b>		
Febrile neutropenia	12 (18)	23 (16)
Pneumonia	7 (10)	18 (13)
Sepsis	4 (6)	8 (6)
Thrombocytopenia	2 (3)	7 (5)
Anemia	0	4 (3)
Neutropenia	0	4 (3)

AML, acute myeloid leukemia; AE, adverse event

\*Adverse events shown were reported in ≥20% of patients in either treatment arm

## FIGURES 1A and 1B

**Figure 1. Overall survival.** Kaplan-Meier plots showing the overall survival rate of all patients over time, separated by treatment arm; patients at risk at each time point is shown below the graph. Tick marks indicate censored data. (A) Plot showing preplanned OS analysis; (B) Plot showing OS analysis with 6 months additional follow-up time. *Abbreviations: Ven, venetoclax; Pbo, placebo; LDAC, low dose cytarabine; CI, confidence interval.*

**Table 3. Multivariable Cox Regression of Preplanned OS Analysis**

<b>Covariates</b>	<b>Hazard Ratio (95% CI)</b>	<b>p value</b>
<b>Treatment arm (Ven vs. Placebo)</b>	<b>0.67 (0.47–0.96)</b>	<b>0.03</b>
Age (<75 vs. ≥75)	0.56 (0.37–0.84)	0.005
AML status ( <i>de novo</i> vs. secondary)	0.59 (0.41–0.85)	0.004
ECOG performance status (<2 vs. ≥2)	0.48 (0.33–0.70)	<0.001
Cytogenetic risk (intermediate vs. poor)	0.57 (0.40–0.82)	0.003

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival

**Table 4. Summary of response rates and efficacy endpoints**

Endpoint	Placebo + LDAC n = 68	Venetoclax + LDAC n = 143	p value
<b>Remission Rates, % (95% CI)</b>			
CR	7% (2–16)	27% (20–35)	<0.001
CR/CRi	13% (6–24)	48% (39–56)	<0.001
By initiation of cycle 2	3% (0–10)	34% (27–43)	<0.001
CR/CRh	15% (7–25)	47% (39–55)	<0.001
By initiation of cycle 2	4% (1–12)	31% (23–39)	<0.001
<b>Other Endpoints</b>			
Event-free survival, median (95% CI) months	2.0 (1.6–3.1)	4.7 (3.7–6.4)*	0.002
Transfusion independence, % (95% CI)			
Red Blood Cells	18% (10–29)	41% (32–49)	0.001
Platelets	32% (22–45)	48% (39–56)	0.040
Both	16% (8–27)	37% (29–46)	0.002

CR, complete response; CRi, CR with incomplete blood count recovery; CRh, CR with partial hematologic recovery; CI, confidence interval

CR: bone marrow with <5% blasts; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count  $\geq 10^3/\mu\text{L}$ , platelets  $\geq 10^5/\mu\text{L}$  and red cell transfusion independence

CRi: all of the criteria for CR except for absolute neutrophil count  $< 10^3/\mu\text{L}$  or platelets  $< 10^5/\mu\text{L}$   $\pm$  red cell transfusion independence

CRh: bone marrow with <5% blasts; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count  $> 0.5 \times 10^3/\mu\text{L}$  and platelets  $\geq 0.5 \times 10^5/\mu\text{L}$

\* Hazard ratio = 0.58 (95% CI 0.42–0.82)

## 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 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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## AUTHOR CONTRIBUTIONS

**Conception and design:**

**Provision, collection and assembly of data:** All authors contributed to data collection.

**Data analysis and interpretation:** All authors had access to the data and participated in data collection and interpretation (of note: AHW, CDD, JB, PP, WM and JH). Analysis was initially done by BC, SG, and QJ; all authors contributed thereafter.

**Manuscript writing:** All authors contributed to revision of the manuscript.

**Final approval of manuscript:** All authors.

## AUTHOR DISCLOSURES AND CONFLICTS OF INTEREST

**DISCLOSURES:** AbbVie sponsored the study (NCT03069352), contributed to its design, collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the abstract. All authors had access to relevant data. Venetoclax (ABT-199/GDC-0199) is being developed in collaboration between AbbVie and Genentech.

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FIGURE 1A

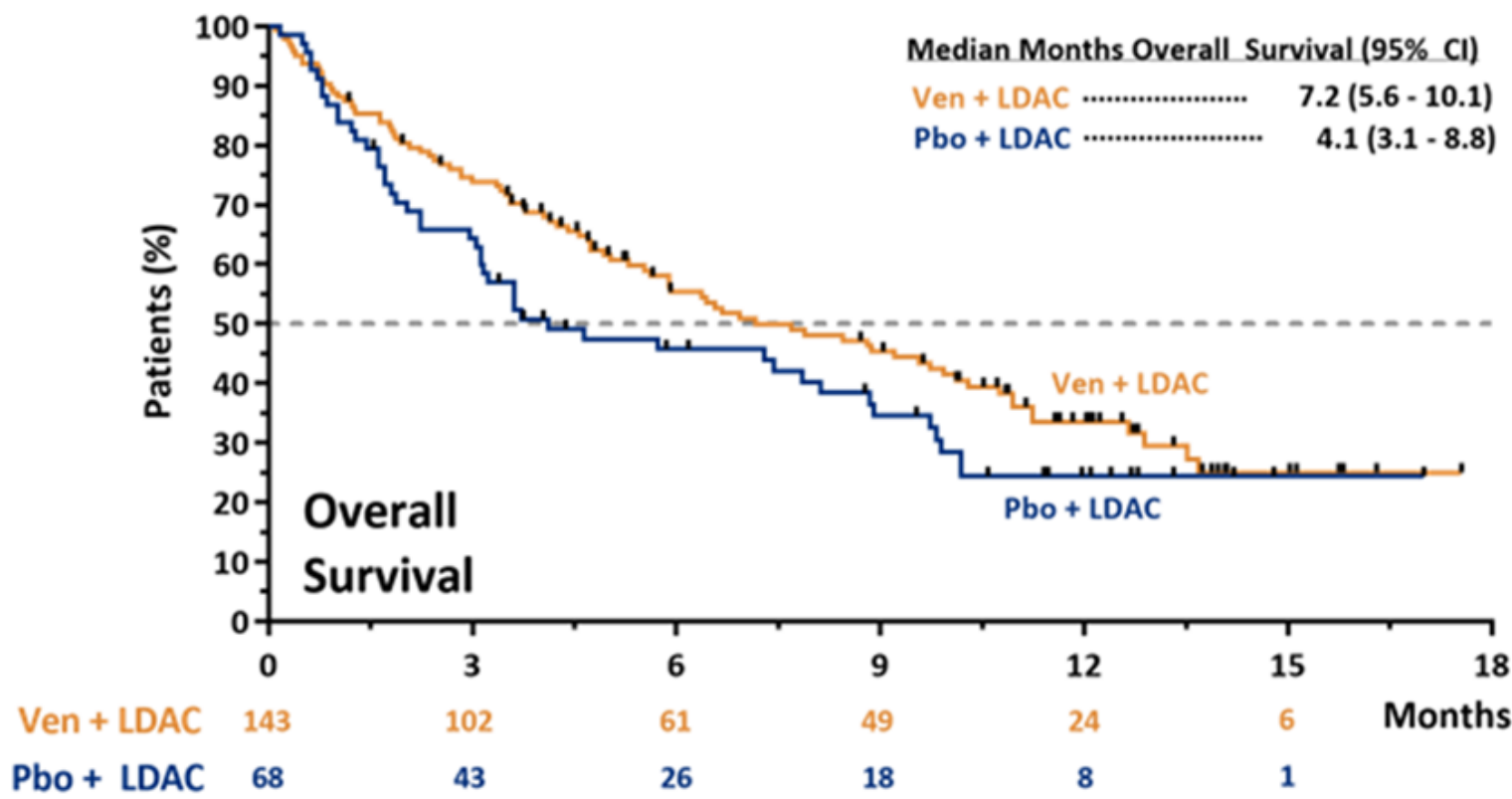


FIGURE 1B

