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# Long-term follow-up of VIALE-C in patients with untreated AML ineligible for intensive chemotherapy

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**Abstract:**

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

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**Agreement to Share Publication-Related Data and Data Sharing Statement**: 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 (e.g., 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. These 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 after approval in the US and Europe and after acceptance of this manuscript for publication. 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.

**Clinical trial registration information (if any)**: NCT03069352, https://beta.clinicaltrials.gov/

# Long-term follow-up of VIALE-C in patients with untreated AML ineligible for intensive chemotherapy

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Venetoclax (VEN) in combination with low dose cytarabine (LDAC) is FDA-approved for the treatment of unfit patients with newly diagnosed AML ineligible for intensive chemotherapy, based on a response rate of 54% (complete remission with or without blood count recovery [CR/CRi]) in the original phase Ib/II study.[1] The VIALE-C phase 3 study (NCT03069352), compared VEN vs placebo (PBO) in combination with LDAC in 210 patients with untreated AML ineligible for intensive chemotherapy.[2,3] The primary overall survival (OS) endpoint was event-driven and did not show a significant benefit in favor of VEN + LDAC after a median follow-up time of 12 months.[2] This initial analysis was associated with substantial early censoring of patients with <6 months follow-up. In a subsequent post hoc analysis with median follow-up 17.5 months (range 0.1 – 23.5), median OS was significantly longer in patients receiving VEN + LDAC (8.4 vs. 4.1 months; HR = 0.70, 95% CI 0.50, 0.99; *P* = 0.04). Rates of CR/CRi were higher for patients receiving VEN + LDAC (48.3%), compared to PBO + LDAC (13.2%). In the present study, a final analysis with 2-years additional follow-up was undertaken to determine if the survival benefit of VEN +LDAC was sustained. In addition, clinical and molecular correlates of survival among patients receiving VEN + LDAC were assessed. These analyses demonstrated that survival outcome was influenced by prior exposure to hypomethylating agents, clinical response, cytogenetic risk and molecular genotype, with best outcomes observed for patients with *NPM1* mutation. This longer-term final analysis confirmed the survival improvement of VEN + LDAC in patients unfit for intensive chemotherapy.

At last follow-up on 15 February 2021 (median follow-up 34.7 months; range 0.1 – 41.3), 83.9% (n = 120; Ven + LDAC) and 89.7% (n = 61; PBO + LDAC) of patients had died with 7% of patients (n =10) still receiving Ven + LDAC. No patient was receiving LDAC + PBO at this follow-up. Two patients on Ven + LDAC were lost to follow-up, and five withdrew consent (VEN + LDAC 3 [2.1%] and PBO + LDAC 2 [2.9%]). With an additional 2 years of follow-up from the

last analysis,[3] improvement in median OS with VEN + LDAC vs PBO + LDAC was unchanged (8.4 vs 4.1 months) (Fig. 1A, Supplementary Table 1). Two-year OS was 21.5% for patients in the VEN + LDAC arm and 12.4% for patients receiving PBO + LDAC (number needed to treat = 11). No new adverse event signal was noted (Supplementary Table 2). We next investigated correlates of outcome in the VEN + LDAC treated arm.

Clinical response rates were similar to the previously published 6-month follow-up (supplemental table 1), with 28.7% and 19.6% achieving CR and CRi, respectively. At two years, clinical response was sustained in 34.3% and 31.6% of patients initially achieving CR or CR/CRi, respectively, in the VEN + LDAC arm, indicating a similar duration of response for both response categories (Fig. 1B). In contrast to the VIALE-A study, patients enrolled in the VIALE-C trial included 20% with a prior history of HMA treatment. Patients not receiving prior HMA treatment had a longer OS than those who received prior HMA therapy, 8.9 months (95% CI 6.6, 10.9) vs 5.6 months (95% CI 3.4, 9.6), respectively (Fig. 1C). Among the 29% of patients achieving CR, median OS was 24.3 months (95% CI 20.1, 28.3)(Fig. 1D). Of the 48% patients achieving CR/CRi, median OS was 20.7 months (95% CI 12.7, 24.5), compared to 3.4 months (95% CI 2.1, 4.1) for those not achieving remission (Fig. 1D). OS for patients with *de novo* AML was 9.2 months (95% CI 7.2, 12.7), compared to 5.6 months (95%CI 3.4, 9.8) in patients with secondary AML (Fig. 1E). Patients categorized according to NCCN classification as intermediate risk had a longer OS, 11.2 months (95% CI 7.9, 16.4) compared to 4.4 months (95%CI 3.0,6.4) in poor risk patients (Fig. 1E). We further analyzed OS according to the presence of somatic mutations in patients treated with VEN + LDAC. Median OS was 25.3 (95% CI 9.9, -), 11.2 (95% CI 3.4, 23.6), 5.9 (95% CI 1.6, 20.8) and 2.8 (95% CI 2.1, 3.6) months in patients with *NPM1*, *IDH1/2*, *FLT3* and *TP53* mutations, respectively (Fig. 1F). These outcomes should be interpreted with caution, due to the limited size of these sub-groups.

The mOS difference between patients with a NPM1 and IDH1/2 baseline mutations can be attributed to other prognostic factors such as secondary AML, poor cytogenetic risk and prior HMA treatment. Patients with IDH1/2 mutation presented secondary AML (38%), poor cytogenetic risk per NCCN 2016 classification (24%) and received prior treatment with HMA (19%) more frequently when compared to NPM1 patients (16%, 16% and 5%, respectively) (Supplemental table 3).

In conclusion, among patients with newly diagnosed AML ineligible for intensive chemotherapy, longer-term follow-up confirmed that patients receiving VEN + LDAC had longer median OS than patients receiving PBO + LDAC. CR/CRi responses in the VEN + LDAC were durable, with 31.6% remaining in remission for >2 years. Notably, for patients with *NPM1* mutation treated with VEN + LDAC, OS at 24 months was ~50%. In contrast, outcomes for patients with *TP53* mutation remained poor. This 2-year follow-up analysis confirms long-term benefit for patients treated with VEN + LDAC, with no new safety findings.

**Data sharing statement**

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 (e.g., 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.

These 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 after acceptance of this manuscript for publication. 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: AbbVie, Inc. Provision, collection, and assembly of data: all authors contributed to data collection. Data analysis and interpretation done by A.H.W., Q.J., Y.S., B.C., and W.M.; all authors contributed thereafter. Manuscript writing, critical revision, and final approval: all authors.

## Conflict of interest

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 manuscript.

All authors had access to relevant data. No honoraria or payments were made for authorship. Venetoclax (ABT-199/GDC-0199) is being developed in collaboration between AbbVie and Genentech.

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**Figure Legend**

**Figure 1. Survival outcomes and response in patients treated with venetoclax compared to placebo.** A) Kaplan-Meier overall survival curves of all patients. Number of patients at risk for each time is shown below and separated by treatment arms. B) Kaplan-Meier duration of response curves in patients treated with VEN + LDAC. Number of patients at risk for each time is shown below and separated by response. C) Kaplan-Meier overall survival by prior HMA treatment curves in patients treated with VEN + LDAC. Number of patients at risk for each time is shown below and separated by prior HMA treatment. D) Kaplan-Meier overall survival by remission status curves in patients treated with VEN + LDAC. Number of patients at risk for each time is shown below and separated by response. E) Kaplan-Meier overall survival by AML type curves in patients treated with VEN + LDAC. Number of patients at risk for each time is shown below and separated by AML type. F) Kaplan-Meier overall survival by mutational status curves in patients treated with VEN + LDAC. Number of patients at risk for each time is shown below and separated by mutational status. AML, acute myeloid leukemia; CR, complete remission; CRi, complete remission with incomplete blood count recovery; DOR, duration of remission; HMA, hypomethylating agent; LDAC, low dose cytarabine; PBO, placebo; VEN, venetoclax

Figure 1