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TO THE EDITOR:

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 (ClinicalTrials.gov Identifier: NCT03069352), compared VEN vs placebo (PBO) in combination with LDAC in 211 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 of 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; $P = .04$). Rates of CR/CRi were higher for patients receiving VEN + LDAC (48.3%), compared with 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 the last follow-up on 15 February 2021 (median follow-up of 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. A total of 2 patients on VEN + LDAC were lost to follow-up, and 5 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) (Figure 1A, supplemental Table 1, available on the *Blood* website). 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 (supplemental Table 2). We then investigated the 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 2 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 (Figure 1B). In contrast to the VIALE-A study, patients enrolled in the VIALE-C trial included 20% patients with a history of HMA treatment. Patients who did not receive prior HMA treatment had a longer OS (8.9 months [95% CI, 6.6-10.9]) than those who received prior HMA therapy (5.6 months [95% CI, 3.4-9.6]) (Figure 1C). Among the 29% of patients achieving CR, median OS was 24.3 months (95% CI, 20.1-28.3) (Figure 1D). Of the 48% patients achieving CR/CRi, median OS was 20.7 months (95% CI, 12.7-24.5), compared with 3.4 months (95% CI, 2.1-4.1) for those not achieving remission (Figure 1D). OS for patients with de novo AML was 9.2 months (95% CI, 7.2-12.7), compared with 5.6 months (95% CI, 3.4-9.8) in patients with secondary AML (Figure 1E). Patients categorized according to NCCN classification as intermediate risk had a longer OS of 11.2

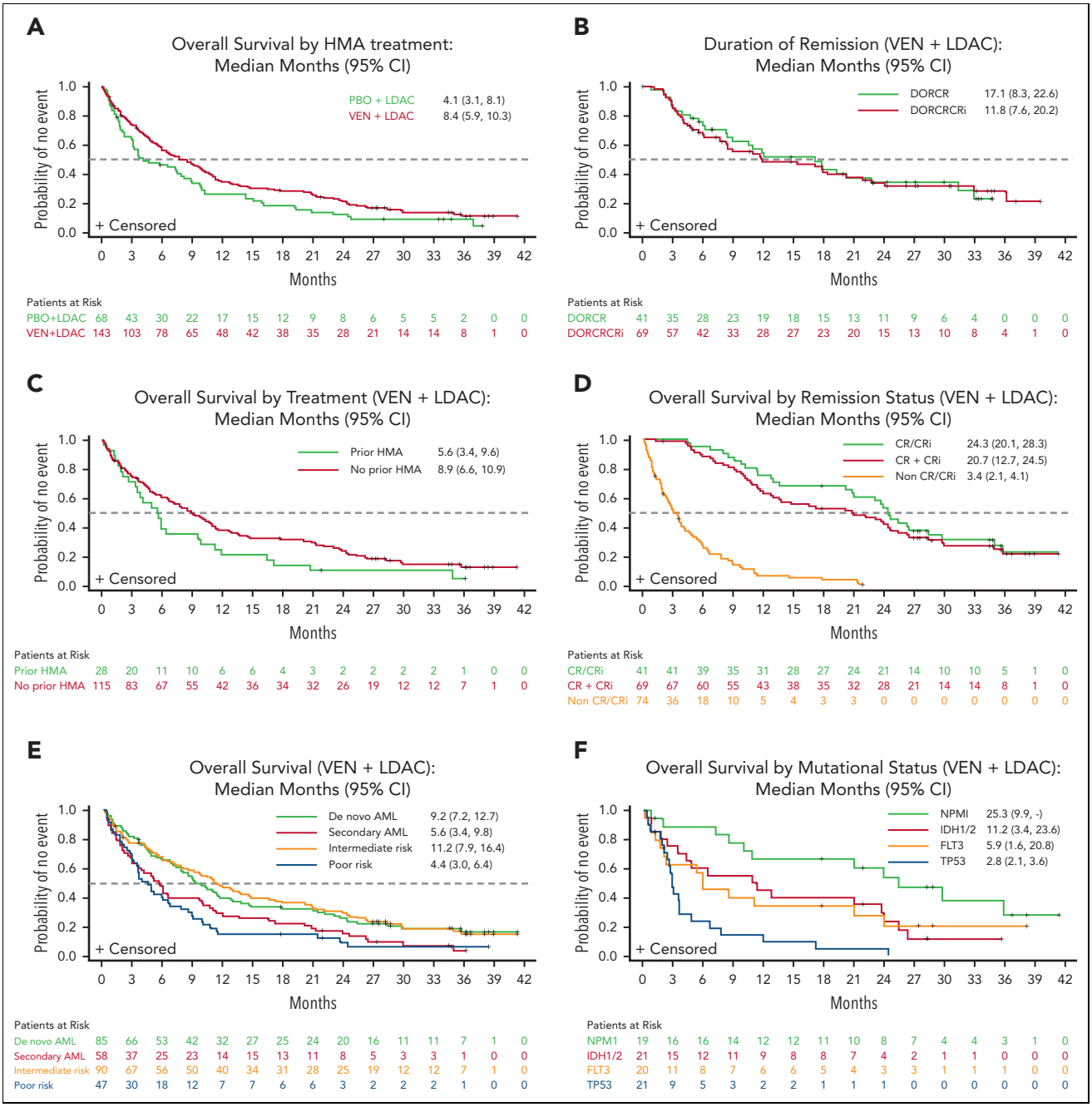

Figure 1. Survival outcomes and response in patients treated with VEN compared with PBO. (A) Kaplan-Meier OS curves of all patients. Number of patients at risk for each time is shown below and separated by treatment arms. (B) Kaplan-Meier duration of response curves in patients treated with VEN + LDAC. Number of patients at risk for each time is shown below and separated by response. (C) Kaplan-Meier OS 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 OS 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 OS 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 OS 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.

months (95% CI, 7.9-16.4) compared with 4.4 months (95% CI, 3.0-6.4) in patients at poor risk (Figure 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-not reached), 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 (Figure 1F). These outcomes should be interpreted with caution, because of the limited size of these subgroups.

Although a mOS difference was apparent between patients with *NPM1* or *IDH1/2* mutations at baseline, this may be attributed to co-occurrence of other poor prognostic factors in the IDH1/2 mutated cohort. Patients with *IDH1/2* mutations

were represented in secondary AML (38%), poor cytogenetic risk per NCCN 2016 classification (24%), and received prior treatment with HMA (19%) more frequently when compared with patients with *NPM1* mutation (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 mOS 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.

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Footnotes

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The online version of this article contains a data supplement.

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