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Venetoclax and azacitidine in untreated patients with therapy-related acute myeloid leukemia, antecedent myelodysplastic syndromes or chronic myelomonocytic leukemia

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Dear Editor,

Secondary acute myeloid leukemia (sAML), a subset of AML, may arise from antecedent hematologic disorders (antecedent myelodysplastic syndrome or chronic myelomonocytic leukemia [A-MDS/CMML]) or complication of prior cytotoxic chemotherapy or radiation therapy (therapy-related AML [tAML]) [1]. It comprises about 25% to 35% of AML cases, occurring more frequently with age [2]. Rising incidence of sAML is potentially related to increased survival from prior malignancies, greater use of chemotherapy, and improved reporting of myeloid malignancies [2]. sAML is frequently associated with adverse genetics, including *TP53* mutations, which are associated with poor outcomes in myeloid malignancies [2, 3]. Compared with primary AML, sAML is associated with unfavorable outcomes regardless of age, posing unique clinical challenges [4, 5].

Venetoclax is a first-in-class, potent, orally bioavailable, BH3-mimetic compound, highly selective for BCL2 [6]. Venetoclax in combination with the hypomethylating agent azacitidine is approved by the US FDA and European Medicines Agency, and considered a new standard of care for treatment of newly diagnosed older (≥75 years) AML patients or those unfit for intensive therapies [7, 8]. This combination has resulted in favorable responses in treatment-naïve sAML patients unfit for intensive chemotherapy [9] with efficacy superior to azacitidine monotherapy [9–11]. The objective of this pooled analysis was to evaluate outcomes (efficacy and safety) of venetoclax combined with azacitidine in patients with sAML (tAML and A-MDS/CMML).

This post hoc pooled analysis assessed patients enrolled in the randomized phase III VIALE-A (NCT02993523) [10] and M15-358 phase Ib (NCT02203773) trials [12]. The analysis comprised treatment-naïve AML patients with comorbidities and/or age ≥75 years ineligible for intensive chemotherapy, including patients with sAML (per 2017 European LeukemiaNet [ELN] classification) [13]. Only tAML patients (i.e. those who received prior cytotoxic therapies) were included in this analysis, while neo-AML (i.e. those with prior neoplasia who did not receive cytotoxic therapy) patients were excluded. Patients were also excluded if they received a venetoclax dose other than 400 mg, had a history of myeloproliferative neoplasm including myelofibrosis, essential thrombocytopenia, polycythemia vera, chronic myeloid leukemia with or without *BCR-ABL1* rearrangement, favorable-risk cytogenetics, or had prior exposure to hypomethylating agents [10]. The cutoff dates were December 1, 2021 (VIALE-A-LTFU), and July 19, 2019 (phase Ib study), respectively.

Patients received venetoclax (400 mg orally [Days 1–28]) + azacitidine (75 mg/m^2; days 1–7 of the 28-day cycle) OR azacitidine (75 mg/m^2 on days 1–7 of the 28-day cycle) + placebo (referred to as azacitidine monotherapy). Key outcomes were complete remission + complete remission with incomplete count recovery (CR+CRi), complete remission with partial recovery hematologic recovery (CRh), duration of response (DOR), OS, and safety [11]. OS was defined as the number of days from the date of randomization to the date of death for any reason. Duration of CR was defined as the number of days from the date of first CR per the modified International Working Group criteria for AML to the earliest evidence of confirmed morphologic relapse, confirmed progressive disease, or death due to disease progression. A similar approach was taken for both CR+CRi and CR+CRh.

A total of 125 patients with sAML (40 tAML, 85 A-MDS/CMML) as per the 2017 ELN classification [13] were assessed in this pooled analysis. In patients with tAML ($n = 40$), 31 patients received venetoclax + azacitidine and 9 patients received azacitidine monotherapy. In patients with A-MDS/CMML ($n = 85$), 59 patients received venetoclax plus azacitidine and 26 patients received azacitidine monotherapy (Supplementary Table 1). The median age was 76 years, with 59/90 (65.6%) male patients in the venetoclax + azacitidine treatment group and 20/35 (57.1%) male patients in the azacitidine monotherapy group. Baseline characteristics were comparable between treatment groups (Supplementary Table 2).

In the tAML group, CR was achieved by 32% of patients (10/31) who received venetoclax + azacitidine compared to 11% of patients (1/9) who received azacitidine monotherapy. Moreover, CR+CRi was reached by 61% of patients (19/31) who received venetoclax + azacitidine compared to 11% of patients (1/9) who received azacitidine monotherapy. In the A-MDS/CMML subgroup, CR was 36% (21/59) following venetoclax + azacitidine compared to 12% (3/26) following azacitidine monotherapy. Furthermore, in the A-MDS/CMML subgroup, CR+CRi was 66% (39/59) following venetoclax + azacitidine compared with 31% (8/26) following azacitidine monotherapy (Table 1). Median DOR for total sAML who achieved response at any timepoint was 21.0 months (95% CI, 15.7–25.5) for patients treated with venetoclax + azacitidine ($n = 90$) and 5.8 months (95% CI 1.0—15.6) in patients who received azacitidine monotherapy ($n = 35$). Specifically, median DOR for tAML was 25.5 months (95% confidence interval [CI] 17.8 to not evaluable) for patients treated with venetoclax + azacitidine ($n = 31$) and 8.5 months (95% CI non estimable [NE]–NE) in patients who received azacitidine monotherapy ($n = 9$); median DOR was 17.3 months

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Table 1. Response rates and duration of response in patients treated with venetoclax + azacitidine or azacitidine alone.

Response parameter	Venetoclax + azacitidine			Azacitidine		
	All secondary AML ($N = 90$)	tAML ($n = 31$)	A-MDS/CMML ($n = 59$)	All secondary AML ($N = 35$)	tAML ($n = 9$)	A-MDS/CMML ($n = 26$)
CR + CRi, *n* (%) (95% CI)	58 (64.4) (53.7–74.3)	19 (61.3) (42.2–78.2)	39 (66.1) (52.6–77.9)	9 (25.7) (12.5–43.3)	1 (11.0) (0.3–48.2)	8 (30.8) (14.3–51.8)
CR, *n* (%)	31 (34.4)	10 (32.3)	21 (35.6)	4 (11.4)	1 (11.1)	3 (11.5)
CRi, *n* (%)	27 (30.0)	9 (29.0)	18 (30.5)	5 (14.3)	0	5 (19.2)
Median duration of CR/CRi, months (95% CI)	21.0 (15.7–25.5)	25.5 (17.8–NE)	17.3 (9.6–25.1)	5.8 (1.0–15.6)	8.5 (NE)	5.8 (1.0–NE)

A-MDS/CMML antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia, *CR* complete remission, *CRi* complete remission with incomplete count recovery, *tAML* therapy-related acute myeloid leukemia.

(95% CI 9.6–25.1) following venetoclax + azacitidine compared with 5.8 months (1.0–NE) following azacitidine alone in patients with A-MDS/CMML (Table 1). In sAML patients who received venetoclax + azacitidine ($n = 90$), median OS was 15.9 months (95% CI 10.4–24.4, adjusted hazard ratio [HR] = 0.622) compared with 10.6 months (95% CI 4.9–13.2) following azacitidine monotherapy (Fig. 1i). In tAML patients, median OS was 16.4 months (95% CI 4.1–27.7, HR = 0.679) versus 11.3 months (95% CI 0.6–17.5) following venetoclax + azacitidine versus azacitidine monotherapy (Fig. 1ii). In A-MDS/CMML patients, median OS was 14.2 months (95% CI 10.4–24.5, HR = 0.660) versus 10.1 months (95% CI 4.7–14.5) following venetoclax + azacitidine vs azacitidine monotherapy (Fig. 1iii).

Response rates (CR+CRi) in patients who received the venetoclax + azacitidine combination in intermediate and poor cytogenetic risk subgroups were 75% (95% CI, 61.1–86.0) and 51.4% (95% CI, 34.4–86.0) respectively, compared with 31.3% and 21.1%, respectively, in patients treated with azacitidine monotherapy. Response rates (CR/CRi) were numerically higher for patients harboring *FLT3* (77.8%), *IDH1/2* (76.2%), and *TP53* mutations (53.8%) following combination venetoclax + azacitidine, compared with azacitidine alone (Supplementary Table 3).

In patients with tAML treated with venetoclax + azacitidine, OS was numerically favorable (adjusted HR, 0.263 [95% CI 0.058–1.198]) for patients with intermediate cytogenetic risk and patients with complex (≥3) karyotypes (poor cytogenetic risk) (adjusted HR, 0.386 [95% CI 0.103–1.451]) (Supplementary Fig. 1i). In patients with A-MDS/CMML, OS among patients harboring poor cytogenetic risk was favorable (adjusted HR, 0.551 [95% CI, 0.259–1.171]), including complex ≥3 karyotypes (adjusted HR, 0.579 [95% CI, 0.232–1.441]), in both the molecular mutations *FLT3* (adjusted HR, 0.168 [95% CI, 0.027–1.044]) and *IDH1/2* (adjusted HR, 0.160 [95% CI, 0032–0.810]), and in patients aged ≥75 years (adjusted HR, 0.562 [95% CI, 0.317–0.997]) receiving venetoclax + azacitidine; *TP53* mutations were not estimable (Supplementary Fig. 1ii). Interpretation of the data may be limited due to the small sample sizes of the subgroups.

In patients treated with venetoclax + azacitidine ($n = 90$), 58 patients (64.4%) achieved CR+CRi as best response, with a median time from the start of one cycle to the next cycle of 30 days (range 26–126). (Supplementary Fig. 2; Table 1; Supplementary Table 4). Of those 58 patients, 46 (79.3%) received ≥ 6 cycles of treatment with a median duration of 21 days per cycle (range 1–42). Thirty-five of these 46 responders (76.1%) had a median venetoclax dosing duration of ≤ 21 days during and after cycle 6. Furthermore, 2 patients from the tAML and A-MDS/CMML subgroups underwent allogenic stem cell transplantation.

Any grade ≥ 3 adverse events occurred in 87/90 (96.7%) sAML patients treated with venetoclax + azacitidine, and in all 35 (100%) sAML patients treated with azacitidine monotherapy. The most common grade ≥ 3 adverse events that occurred in both the venetoclax + azacitidine and azacitidine monotherapy groups included febrile neutropenia (40% and 11.4%, respectively), thrombocytopenia (37.8% and 57.1%, respectively), neutropenia (36.7% and 31.4%, respectively), pneumonia (28.9% and 34.3%, respectively), and anemia (24.4% and 14.3%, respectively). Serious adverse events occurred in 73/90 (81.1%) sAML patients treated with venetoclax + azacitidine and in 25/35 (71.4%) sAML patients treated with azacitidine monotherapy (Supplementary Table 5).

The phase III VIALE-A confirmatory trial demonstrated improvement in CR+CRi and higher median OS with venetoclax + azacitidine in an elderly AML population ineligible for intensive chemotherapy compared with placebo + azacitidine [10]; benefits were sustained in long-term follow-up [14]. Herein, higher response rates and improved median OS were observed following combination treatment with venetoclax + azacitidine compared with azacitidine monotherapy in patients with treatment-naïve sAML. Most long-term responding patients (CR/CRi) receiving ≥ 6 cycles of therapy were treated with a 21-day venetoclax duration per treatment cycle. Further, higher response rates and improved OS were observed among patients with intermediate-risk cytogenetics; not in *TP53*-mutated patients. Compared to other studies of venetoclax in sAML and tAML, outcomes and data may vary depending on differing study methodologies and patient selection. The safety profiles for patients in the tAML and A-MDS/CMML subgroups following venetoclax + azacitidine were similar to the overall study population of VIALE-A, with no additional toxicities identified compared with the overall population. A limitation of this analysis is the interpretation of the data, specifically due to the small sample size in the subgroups. Many patients with sAML receive HMA therapy for their antecedent hematologic disorder, and this high-risk population was not represented in this study. Additionally, as the definition and classification of sAML have evolved with the updated ELN 2022 guidelines, continued analyses are important to properly distinguish correct classifications [15]. However, these findings may prove clinically relevant because sAML is associated with poor outcomes and inferior response rates. This analysis demonstrated a clear OS and DOR benefit in elderly, treatment-naïve AML patients who received venetoclax + azacitidine compared with azacitidine monotherapy. In conclusion, given the high efficacy and manageable toxicity profile observed following venetoclax + azacitidine treatment, this combination is an important treatment option to consider in patients with tAML and A-MDS/CMML who are ineligible for intensive chemotherapy.

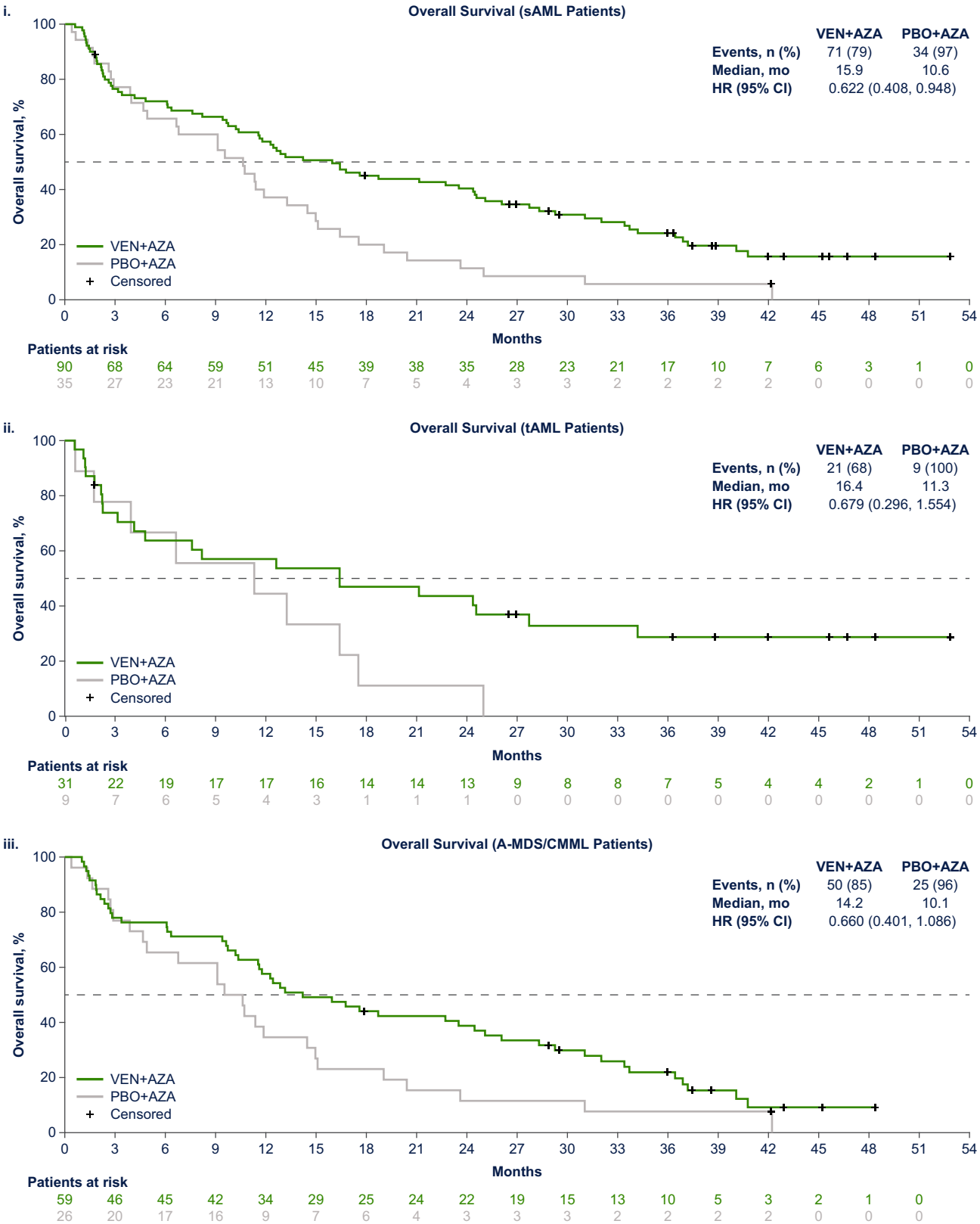

Fig. 1 Overall survival in patients treated with venetoclax + azacitidine or azacitidine monotherapy. i. All sAML patients; ii. therapy-related AML; and iii. antecedent MDS/CMML. A-MDS/CMML antecedent myelodysplastic syndrome/chronic myelomonocytic leukemia, AML acute myeloid leukemia, AZA azacitidine, PBO placebo, sAML secondary acute myeloid leukemia, tAML therapy-related acute myeloid leukemia, Ven venetoclax.

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DATA AVAILABILITY

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, clinical study reports, or analysis plans), 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, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States 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://vivli.org/ourmember/abbvie/, then select "Home".

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AUTHOR CONTRIBUTIONS

Conception and design: all authors (VP, KWP, HD, CR, MJT, CDD, PF, ACS, AHW, AP, J-HJ, GJ, YM, DS, MLA, CL, JAR, JP, JS, MK). Provision of study materials or patients: all authors (VP, KWP, HD, CR, MJT, CDD, PF, ACS, AHW, AP, J-HJ, GJ, YM, DS, MLA, CL, JAR, JP, JS, MK). Collection and assembly of data: all authors (VP, KWP, HD, CR, MJT, CDD, PF, ACS, AHW, AP, J-HJ, GJ, YM, DS, MLA, CL, JAR, JP, JS, MK). Data analysis and interpretation: all authors (VP, KWP, HD, CR, MJT, CDD, PF, ACS, AHW, AP, J-HJ, GJ, YM, DS, MLA, CL, JAR, JP, JS, MK). Manuscript writing: all authors (VP, KWP, HD, CR, MJT, CDD, PF, ACS, AHW, AP, J-HJ, GJ, YM, DS, MLA, CL, JAR, JP, JS, MK). Final approval of manuscript: all authors (VP, KWP, HD, CR, MJT, CDD, PF, ACS, AHW, AP, J-HJ, GJ, YM, DS, MLA, CL, JAR, JP, JS, MK).

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COMPETING INTERESTS

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ADDITIONAL INFORMATION

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