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CORRESPONDENCE

The impact of post-remission granulocyte colony-stimulating factor use in the phase 3 studies of venetoclax combination treatments in patients with newly diagnosed acute myeloid leukemia

To the Editor:

Based on results from the randomized, placebo-controlled phase 3 VIALE-A (NCT02993523) and VIALE-C (NCT03069352) trials,[1–4] venetoclax in combination with hypomethylating agents or low-dose cytarabine (LDAC) has become standard of care in patients with newly diagnosed acute myeloid leukemia (AML) who are ineligible for intensive chemotherapy. Cytopenias are common adverse events with venetoclax and are primarily managed with protocol-mandated dose modifications, including dose interruptions and cycle delays.[2,5] Neutropenia and febrile neutropenia may be mitigated with granulocyte-colony stimulating factor (G-CSF)[4,6]; however, limited evidence exists on G-CSF use and impact on safety and efficacy in patients receiving low-intensity therapies. The present analysis assessed outcomes by G-CSF use post-remission (i.e., following blast clearance) among patients with newly diagnosed, intensive-chemotherapy–ineligible AML who received venetoclax-azacitidine or venetoclax-LDAC in the VIALE-A and VIALE-C trials, respectively.

VIALE-A and VIALE-C study designs have been previously described.[1,3] Both trials enrolled patients aged ≥18 years with newly diagnosed AML who were ineligible for induction chemotherapy (aged ≥75 years or with comorbid conditions precluding intensive chemotherapy treatment). In VIALE-A, patients received venetoclax-azacitidine or placebo-azacitidine; in VIALE-C, patients received venetoclax-LDAC or placebo-LDAC. Both trial protocols allowed G-CSF use with administration for cytopenia management as per institutional practice. In this exploratory post hoc analysis, patients treated with venetoclax combinations who had achieved a best response of complete remission (CR)/CR with incomplete hematologic recovery (CRi) were assessed for outcomes by G-CSF use, including overall survival (OS), duration of CR/CRi (DOR), and safety. G-CSF use was analyzed from the time of remission achievement (post-remission), defined as blast clearance (<5% bone marrow blasts) for this analysis. Clinical data cutoff was December 1, 2021 for VIALE-A and February 15, 2021 for VIALE-C.[2,3] The analysis populations included patients who achieved best response of CR/CRi, unless otherwise specified.[1,3] Data presentation is descriptive in nature, and formal statistical comparisons were not performed due to the post hoc nature of this analysis. Additional details are in the Data S1.

Approximately half of patients treated with venetoclax combinations in VIALE-A and VIALE-C received G-CSF post-remission. In VIALE-A, 50% (95/191) of CR/CRi responders in the venetoclax-azacitidine arm and 26% (11/42) in the placebo-azacitidine arm received G-CSF post-remission (Tables S1 and S2). In VIALE-C, 46% (32/69) of CR/CRi responders in the venetoclax-LDAC arm and 22% (2/9) in the placebo-LDAC arm received G-CSF post-remission (Tables S3 and S4). In both trials, baseline characteristics, including baseline grade ≥3 neutropenia, were generally similar between patients who received G-CSF and those who did not (Tables S5 and S6). In VIALE-A, the median time to first G-CSF use after remission was 36 days (range, 2–483) in the venetoclax-azacitidine arm, and 45/95 patients (47%) received G-CSF in ≥50% of treatment cycles; similar results were observed in the placebo arm (Table S2). Patients received concomitant G-CSF for a median of five treatment cycles in both arms (Table S2). Time to G-CSF use and treatment cycles for VIALE-C are in Table S3.

In the venetoclax-azacitidine arm of VIALE-A, 89% of CR/CRi responders who received G-CSF and 83% of those who did not had ≥1 occurrence of grade 4 neutropenia (defined as a laboratory value of ANC <500/μL) after remission (Table S7). The median time to neutrophil count recovery (absolute neutrophil count ≥500/μL) from onset of grade 4 neutropenia was similar in the venetoclax arm regardless of G-CSF use (14 days [IQR, 8–22] in patients who received G-CSF; 14 days [IQR, 8.5–30.5] in those who did not). Similarly, most patients in the placebo-azacitidine arm (73% of those who received G-CSF; 55% of those who did not) had ≥1 occurrence of grade 4 neutropenia after remission. The median time to neutrophil count recovery from first post-remission grade 4 neutropenia was shorter with G-CSF use (12 days [IQR, 10.5–21.5] in patients who received G-CSF; 21 days [IQR, 13–39] in those who did not). Nadir and median neutrophil counts per treatment cycle among patients

who achieved CR/CRi and received G-CSF in the venetoclax-azacitidine arm of the VIALE-A trial generally increased with each cycle (Figure S1). Similar trends were observed in VIALE-C (Table S8 and Figure S2).

In the venetoclax-azacitidine arm of VIALE-A, grade ≥3 neutropenia occurred in 34% (32/95) of patients receiving G-CSF versus 28% (27/96) not receiving G-CSF (median duration, 16.0 vs. 15.5 days post-remission; Tables S9 and S10). Grade ≥3 febrile neutropenia

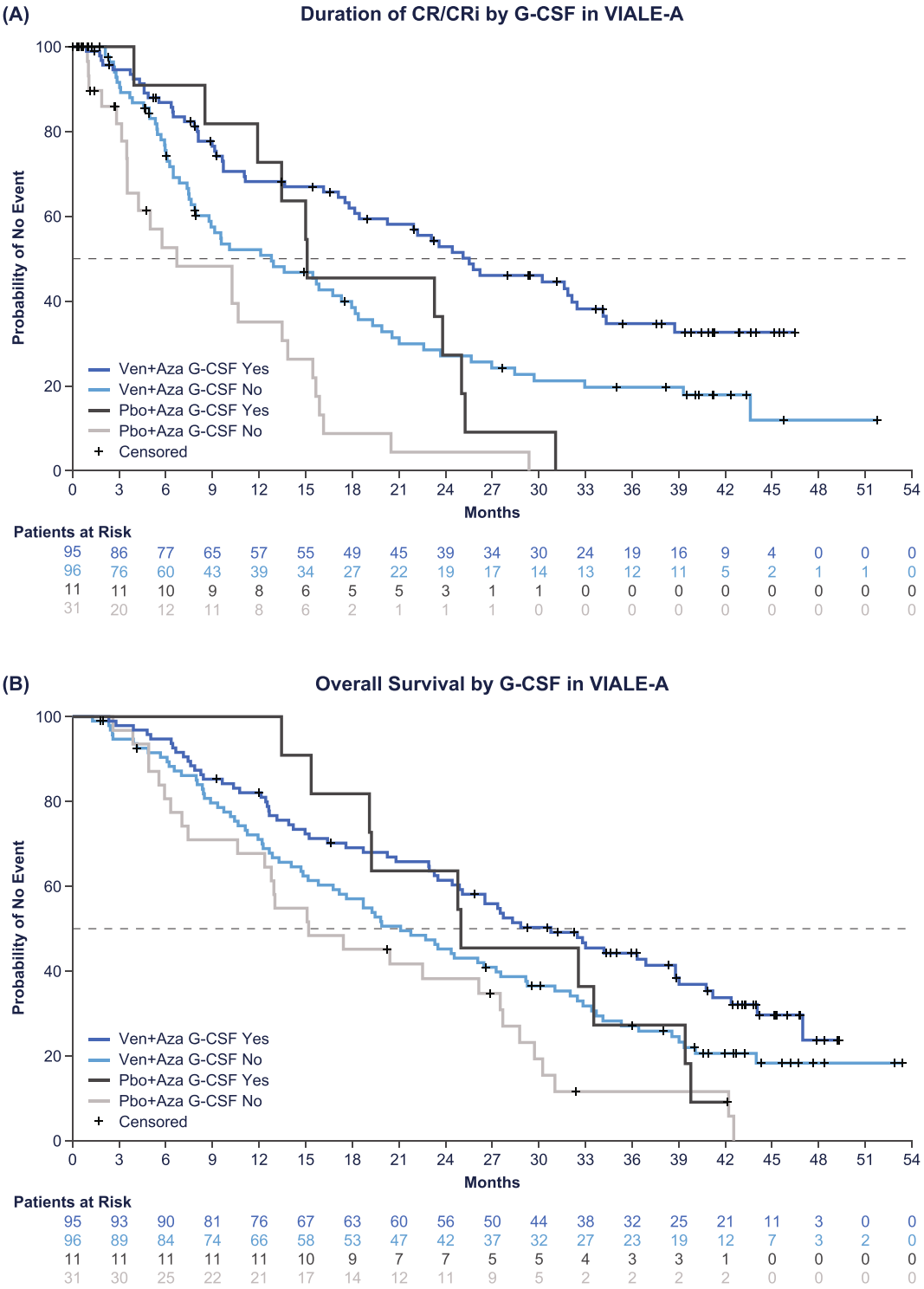

FIGURE 1 Duration of CR/CRi (A) and overall survival (B) by G-CSF use post-remission in patients achieving CR/CRi in VIALE-A. Aza, azacitidine; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; G-CSF, granulocyte-colony stimulating factor; Pbo, placebo; Ven, venetoclax.

occurred in 44% (42/95) of patients receiving G-CSF versus 21% (20/96) of patients not receiving G-CSF (median duration, 8.5 vs. 9.5 days). Grade ≥3 infections occurred in 62 patients (65%) who received G-CSF and 47 patients (49%) who did not. Selected grade ≥3 treatment-emergent adverse events and durations among CR/CRi responders are summarized in Tables S9 and S10 for VIALE-A and Tables S11 and S12 for VIALE-C. A clear impact of G-CSF use on incidence or duration of febrile neutropenia was not observed, which may be confounded by more frequent G-CSF use in patients experiencing neutropenia.

Among CR/CRi responders treated with venetoclax-azacitidine in VIALE-A, the median DOR was 25.5 months (95% CI, 18.1–32.4) for those receiving G-CSF and 12.8 months (95% CI, 7.9–18.0) for those not receiving G-CSF (Figure 1A, Table S13). In the placebo-azacitidine arm, the median DOR was 15.1 months (95% CI, 8.5–25.0) for patients receiving G-CSF and 6.7 months (95% CI, 3.5–13.5) for those not receiving G-CSF. The median OS was 30.8 months (95% CI, 24.4–38.8) for CR/CRi responders in the venetoclax-azacitidine arm receiving G-CSF versus 21.1 months (95% CI, 15.8–27.3) for those not receiving G-CSF (Figure 1B, Table S13). In the placebo-azacitidine arm, the median OS was 25.0 months (95% CI, 15.4–39.4) for CR/CRi responders receiving G-CSF versus 15.2 months (95% CI, 10.6–27.5) for those not receiving G-CSF. Similar outcomes were observed in VIALE-C (Figure S3, Table S14).

In both trials, patients who received venetoclax and achieved MRD response ($<10^{-3}$) appeared more likely to receive G-CSF. In VIALE-A, among CR/CRi responders in the venetoclax-azacitidine arm who received G-CSF, 51% (41/80) achieved an MRD response, whereas 49% (39/80) did not. Among patients who did not receive G-CSF, 33% (28/85) achieved an MRD response, whereas 67% (57/85) did not (Table S15). This may partially explain the numerically higher OS and DOR observed in patients who received G-CSF. The median OS among patients with MRD response in the venetoclax-azacitidine arm was 38.8 months (95% CI, 28.8-not estimable) for patients who received G-CSF and 29.3 months (95% CI, 21.1–40.1) for those who did not. Among patients who did not achieve MRD response, the median OS was 22.9 months (95% CI, 12.7–36.3) for patients who received G-CSF and 15.2 months (95% CI, 11.2–21.8) for those who did not. The placebo-azacitidine arm showed similar trends. VIALE-C results are in Table S16.

In the venetoclax-azacitidine arm of VIALE-A, the median venetoclax dosing duration was 21 days (IQR, 21–28) per cycle among all CR/CRi responders, irrespective of G-CSF use (Table S17, Figure S4). Among all CR/CRi responders, the median duration of end-of-cycle dose holds (defined as reduced venetoclax duration per cycle plus delay of next cycle) was 12 days (IQR, 7–18) versus 14 (IQR, 7–21) days in patients with versus without G-CSF use, respectively (Table S17, Figure S4). The median time from day 1 of one cycle to day 1 of the next cycle was 32 days (IQR, 28–38) for those receiving G-CSF and 35 days (IQR, 28–42) for those who did not. The median duration of end-of-cycle dose holds in CR/CRi responders was 10 days (IQR, 7–15) in those who frequently received G-CSF (≥50% of cycles) versus 13 days (IQR, 7–20) in those who received G-CSF in <50% of cycles. The median time from the start of one cycle to the start of the next cycle was 30 days (IQR, 28–36) in responders with frequent G-CSF use versus 33 days (IQR, 28–38) in patients receiving G-CSF in <50% of cycles. Shorter delays between treatment cycles were also observed in long-term CR/CRi responders who received ≥6 cycles of venetoclax-azacitidine (Table S17). VIALE-C results are in Figure S4 and Table S18.

In this exploratory analysis of the VIALE-A and VIALE-C trials, post-remission G-CSF use was not associated with new safety signals and had no negative impact on DOR or OS among venetoclax-treated patients. Delays between treatment cycles were shorter in patients who received post-remission G-CSF. While G-CSF itself is unlikely to provide direct anti-leukemic benefits, the ability to maintain treatment cycles with shorter delays may translate into benefit for patients. Limitations of this analysis include small patient numbers and administration of G-CSF as per institutional practice rather than protocol-mandated, potentially leading to heterogeneous G-CSF use. Although VIALE-A and VIALE-C studies were not designed to evaluate the impact of G-CSF on cytopenia management, this post hoc analysis supports the use of G-CSF in addition to recommended dose modifications for management of cytopenias in patients with intensive-chemotherapy–ineligible AML who receive venetoclax-based therapy.

AUTHOR CONTRIBUTIONS

Conception and design: KP. Provision of study materials or patients: CD, KP, PP, XW, VV, AI, IK, VI, CR. Collection and assembly of data: All authors. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY 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, 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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