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OPTI-AML: Prospective Comparison of 28 vs.14 days of Venetoclax Induction with Azacitidine in Older Adults with AML

Tracking no: BLD-2026-034611R1

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Abstract:
Azacitidine (Aza) plus venetoclax (Ven) is standard treatment for older/unfit patients with newly diagnosed (ND) acute myeloid leukemia (AML). The approved 28-day (D) Ven schedule is associated with prolonged cytopenias, causing frequent dose reductions and cycle delays. Retrospective studies show similar efficacy and reduced toxicity with abbreviated Ven dosing, but prospective data is lacking. We conducted OPTI-AML(NCT03013998), a prospective randomized phase 2 trial comparing 28D Ven (AV28) versus 14D (AV14) with Aza (75mg/m²x7D) for C1-2 in genomically agnostic ND-AML patients ≥60 years. The primary endpoint was complete remission (CR) rate achieved at any time with two cycles of therapy. Between 2023-2025, 169 patients received AV28 (n=83) or AV14 (n=86). CR across two cycles was 49.4% (AV28) versus 43% (AV14); difference of 6.4% [90%CI:-6.1% to 19.0%], not meeting non-inferiority criteria. Patients with NPM1/ IDH2 mutations had higher CR rates with AV28 (60.9% vs. 33.3%), while CR rates were equivalent (45%) for other subgroups. Composite CR rates were 80.7% (AV28) versus 68.6% (AV14) and MRD negativity was similar (77.6% vs. 76.5%). Although AV28 had more frequent treatment interruptions, count recovery after C2, grade ≥3 adverse events and early mortality were similar. In conclusion, the study did not demonstrate non-inferiority of AV14 compared with AV28 during C1-2 in an unselected ND-AML cohort. However, as the confidence interval for the difference covered 0, CR rate for AV28 was not significantly different than AV14. Certain subgroups may benefit from prolonged Ven exposure, but these findings require validation in larger studies, especially as triplet regimens evolve.

Conflict of interest: COI declared - see note

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COI notes: UB reports receiving grant support from Novartis, Sumitomo, Jazz, Incyte and Syndax, advisory and consulting fees from Takeda, Daichi-Sankyo, Sumitomo, Kura, Servier, Syndax, Genentech, AbbVie , Astellas and Geron. TL reports a Consulting or Advisory Role: Servier, Jazz Pharmaceuticals, Syndax, Daiichi Sankyo; Research funding to the institution: Bio-Path Holdings, Inc, Astellas Pharma, Celyad, Aptevo Therapeutics, Cleave Biosciences, CicloMed, Jazz Pharmaceuticals, Cardiff Oncology, Kura Oncology, Lin Biosciences. CL receives research funding from AbbVie and serves as a consultant or advisory board member for Bristol Myers Squibb, AbbVie, Rigel, Servier, Syndax, Astellas, and COTA Healthcare AAP: Research Funding from Sumitomo, Pfizer, Incyte, Servier, Stemline; Honoraria from AbbVie, Amgen, Astellas, Cycle, Geron, Jazz, Novartis, Sobi, Syndax, Refined Oncology MRB reports institutional research funding from AbbVie, Ascentage Pharma, Astellas, FORMA Therapeutics, Kite/Gilead, Kura Oncology, Sumitomo and Takeda. EMS reports receiving consuting fees from Syndax, Kura Oncology, J and J, Daiichi Sankyo, Astellas, Servier, AstraZeneca, Genentech and Abbvie. JCB reports institutional research funding from AbbVie, Newave, Kartos, and Syndax along with consulting/ownership with Eilean Therapeutics and Lomond Therapeutics. BD has a financial interest in the following companies that may have a commercial interest in the results of this research. This potential conflict of interest has been reviewed and managed by OHSU. SAB: Adela Bio, Aileron Therapeutics (inactive), Therapy Architects/ALLCRON (inactive), Cepheid (incative), Labcorp (inactive), Nemucore Medical Innovations, Novartis, RUNX1 Research Program; SAB & Stock: Aptose Biosciences, Blueprint Medicines, Enliven Therapeutics, Iterion Therapeutics, GRAIL (inactive), Recludix Pharma; Board of Directors & Stock: Amgen, Vincerx Pharma; Board of Directors: Burroughs Wellcome Fund; Joint Steering Committee: Beat AML LLS (uncompensated); Advisory Committee: Multicancer Early Detection Consortium (uncompensated), Malta North American Business Council (uncompensated); Founder: VB Therapeutics; Sponsored Research Agreement: Astra-Zeneca, DELiver Therapeutics, Immunoforge (inactive), Terns, Enliven Therapeutics (inactive), Recludix Pharma (inactive); Clinical Trial Funding: Novartis, Astra-Zeneca; Royalties from Patent 6958335 (Novartis exclusive license) and OHSU and Dana-Farber Cancer Institute (Merck exclusive license, CytoImage, Inc. exclusive license, DELiver Therapeutics non-exclusive license, Sun Pharma Advanced Research Company non-exclusive license); US Patents 4326534, 6958335, 7416873, 7592142, 10473667, 10664967, 11049247. RLL is on the SAB and a former member of the Supervisory board of Qiagen (compensation/equity), a co-founder at Ajax (equity), a board member of the Mark Foundation for Cancer Research and has been ascientific advisor to Mission Bio, Kurome, Syndax, Scorpion, Zentalis, Jubilant, Auron, Prelude, and C4 Therapeutics; for each of these entities he received equity/compensation. He has received research support from the Cure Breast Cancer Foundation (with IP rights), Calico, Zentalis and Ajax, and has consulted/provided professional services for ECOG-ACRIN, Genome Canada, Goldman Sachs and Astra Zeneca. ASM reports institutional research funding from Terns, Inc., Treadwell Therapeutics, Schrodinger Inc., and BlossomHill Therapeutics; advisory fees from BMS, Novartis, Daiichi Sankyo and Foghorn Therapeutics. JFZ reports Consultancy and/or Advisory Boards: AbbVie, Astellas, AstraZeneca, Crossbow Therapeutics, Daiichi Sankyo, Foghorn, Genentech, Genmab, Geron, Ipsen, Jazz, Johnson & Johnson, Kura Oncology, Neogenomics, Novartis, RelmadaTherapeutics, Rigel, Sellas, Servier, Shattuck Labs, Sumitomo Pharma, Syndax; Research Funding: AbbVie, Akesobio, Aptevo, Arog, Ascentage, Auron, Daiichi Sankyo, Faron, Jazz, Kura Oncology, Lin Biosciences, Loxo, Merck, Newave, Novartis, Sellas, Shattuck Labs, Stemline, Sumitomo Pharma, Zentalis. YFM has received honoraria/consulting fees from AptitudeHealth, Servier, BMS, Kura Oncology, BluePrint Medicines, Geron, OncLive and MD Education, Targeted Oncology, Curio science, and Medscape Live. YFM participated in advisory boards and received honoraria from Takeda, Foundation Medicine, Stemline Therapeutics, Blueprint Medicines, Taiho Oncology, SOBI, Rigel Pharmaceuticals, Geron, Cogent Biosciences and Abbvie. YFM received travel reimbursement from MD Education. All other authors report no relevant disclosures.

Preprint server: No;

Author contributions and disclosures: Y.H., M.J., N.H., and T.C. analyzed data. U.B., J.Z., J.B., B.D., R.L., T.L., S.H., R.S., C.L., E.T., W.S., O.O., A.P., M.B., V.D., E.S., W.B., C.V., E.C., Y.M., R.O., G.S., A.N., L.W., S.M., M.M., M.S., and L.R., helped to enroll and treat patients. U.B., J.B., A.M., Y.H., M.J., A.B., B.D., R.L., L.D., L.G., and A.Y. designed the research. U.B., Y.H., and S.H. wrote the paper. All authors reviewed the paper.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Any requests for data and supporting documents presented in this manuscript will be considered and shared to the best of our ability if possible. Data will be shared in a deidentified manner for the purposes of non-commercial research. Please contact the corresponding author for any requests.

Clinical trial registration information (if any): clinicaltrials.gov: NCT03013998

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Manuscript Title

OPTI-AML: Prospective Comparison of 28 vs 14 days of Venetoclax Induction with Azacitidine in Older Adults with AML

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Running Title

OPTI-AML: 28 vs 14D Aza-Ven in older untreated AML

Key Points

1. AV14 did not meet noninferiority in achieving CR vs. AV28 in C1-2 for ND AML pts ≥60; although CR rates were not significantly different

2. CR benefit with AV28 was driven by *NPM1/IDH2* with similar responses in other groups, supporting the need for molecularly tailored Ven dosing

Counts:

Abstract: 250
Manuscript: 3965
Figures: 2
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Abstract

Azacitidine (Aza) plus venetoclax (Ven) is standard treatment for older/unfit patients with newly diagnosed (ND) acute myeloid leukemia (AML). The approved 28-day Ven schedule is associated with prolonged cytopenias, causing frequent dose reductions and cycle delays. Retrospective studies show similar efficacy and reduced toxicity with abbreviated Ven dosing, but prospective data is lacking. We conducted OPTI-AML(NCT03013998), a prospective randomized phase 2 trial comparing 28-day Ven (AV28) versus 14-day (AV14) with Aza (75mg/m²x7D) for C1-2 in genomically agnostic ND-AML patients ≥60 years. The primary endpoint was complete remission (CR) rate achieved at any time with two cycles of therapy. Between 2023-2025, 169 patients received AV28 (n=83) or AV14 (n=86). CR across two cycles was 49.4% (AV28) versus 43% (AV14); difference of 6.4% [90%CI:-6.1% to 19.0%], not meeting non-inferiority criteria. Patients with *NPM1/ IDH2* mutations had higher CR rates with AV28 (60.9% vs. 33.3%), while CR rates were equivalent (45%) for other subgroups. Composite CR rates were 80.7% (AV28) versus 68.6% (AV14) and MRD negativity was similar (77.6% vs. 76.5%). Although AV28 had more frequent treatment interruptions, count recovery after C2, grade ≥3 adverse events and early mortality were similar. In conclusion, the study did not demonstrate non-inferiority of AV14 compared with AV28 during C1-2 in an unselected ND-AML cohort. However, as the confidence interval for the difference covered 0, CR rate for AV28 was not significantly different than AV14. Certain subgroups may benefit from prolonged Ven exposure, but these findings require validation in larger studies, especially as triplet regimens evolve.

Introduction

The addition of BCL-2 inhibitor venetoclax (Ven) to the hypomethylating agent azacitidine (Aza) led to a significant improvement in median overall survival (14.7 months vs. 9.6 months with Aza alone) in older patients with acute myeloid leukemia (AML) unfit for

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intensive chemotherapy, becoming the new standard of care in this patient population[1]. Additionally, the PARADIGM study suggests that Aza-Ven may have a role even in younger, fit AML patients with intermediate or adverse risk AML as a bridge to curative allogeneic stem cell transplant[2].

While effective, Aza-Ven is associated with considerable hematological toxicity. In VIALE-A, grade ≥3 neutropenia (42%), thrombocytopenia (45%), febrile neutropenia (42%) and infections of any grade (85%) occurred frequently in the Aza-Ven arm, commonly resulting in Ven dose reductions (53%), and cycle delays[1]. The recommended 28-day Ven schedule was adopted without formal dose-optimization studies, and subsequent real-world experience has demonstrated that delivering continuous 28-day Ven is challenging[3].

In practice, Ven duration is frequently shortened to facilitate hematologic recovery. Several retrospective and small cohort studies have evaluated abbreviated Ven durations of 7-, 14-, or 21-days to mitigate myelosuppression[4-7]. These reports suggest that shorter Ven exposure may maintain comparable remission rates with lesser transfusion requirements and infectious complications. However, these studies are limited by nonrandomized design and heterogeneity in patients and dosing strategies, resulting in substantial practice variation.

Another challenge is combining novel targeted therapies with the Aza-Ven backbone. Several early phase studies with targeted therapeutics have demonstrated prolonged cytopenias when combined with Aza-Ven, despite minimal myelosuppression as monotherapy[8-15]. As Aza-Ven is not curative for most patients, optimizing its tolerability while preserving efficacy is critical to maintaining long-term therapy and enabling effective combination strategies. Inability to do so will impact the efficacy and tolerability of ongoing phase 3 combination studies with targeted agents with the Aza-Ven backbone.

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To evaluate whether a shortened Ven duration could maintain efficacy while decreasing toxicity, we conducted the OPTI-AML trial, the first prospective randomized noninferiority study to compare the complete remission (CR) rate of a standard 28-day Ven schedule to an abbreviated 14-day schedule in combination with Aza for the first 2 cycles in newly diagnosed AML patients ≥60 years of age deemed ineligible for intensive chemotherapy.

Methods

Study Design and Participants

OPTI-AML was a multicenter randomized phase 2 study conducted within the Beat AML Master Trial (NCT03013998), across 12 academic US sites to compare the efficacy and safety of the standard 28-day Ven schedule versus a 14-day schedule in combination with Aza for the initial 2 cycles of therapy. Eligible patients were aged ≥60 years with newly diagnosed AML[16] irrespective of molecular subtype considered unfit for intensive induction chemotherapy. Patients willing or able to receive intensive chemotherapy were excluded. Unlike VIALE-A, eligibility was not restricted by predefined comorbidity criteria. The trial was approved by a central institutional review board, and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization of Good Clinical Practice guidelines.

Procedures

Patients were randomized 1:1, stratified by age (<75 vs. ≥75 years), to receive either a 28-day (AV28) or a 14-day (AV14) Aza-Ven regimen for two cycles (**Fig. 1A**). Aza was administered at 75 mg/m^2 subcutaneously or intravenously on days 1-7 of each cycle (C). Ven was administered as a dose ramp-up during C1 and dose adjusted for azole usage per label[17].

Patients remained on study for up to 2 cycles, after which they continued treatment off trial with an Aza-Ven schedule per treating physician at participating sites or locally. Response

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was evaluated according to modified ELN 2017 guidelines[18] with a bone marrow biopsy on day 21 (+4 days) of each cycle and count recovery assessed within 14 days of the biopsy. Patients who achieved <5% bone marrow blasts (marrow remission) were recommended to await recovery of absolute neutrophil count (ANC) ≥ $1.0x10^9$/L and platelets ≥ $100x10^9$/L prior to starting the next cycle but could proceed to C2 earlier at treating physician's discretion. Patients in AV28 arm continued to receive Ven for 28 days as per protocol even if the day-21 biopsy showed marrow remission. G-CSF use was allowed per institutional practices or treating physician's discretion. Patients without marrow blast clearance started the next cycle immediately after day 28. Bone marrow measurable residual disease (MRD) was assessed centrally at Hematologics Inc., by flow cytometry with a sensitivity of 0.02%[19].

Objective and Assessments

The primary endpoint was complete remission (CR) achieved at any time with two cycles of therapy. Secondary endpoints included composite complete remission (cCR; CR/CR with incomplete recovery [CRi]/CR with partial hematologic recovery [CRh]), MRD negativity, ANC recovery, progression-free survival (PFS), OS, and safety.

Statistical Analysis

The study's primary objective was to demonstrate that the CR rate following AV14 was not inferior to that following AV28 with two cycles of therapy. The planned enrollment of 166 patients (83 per arm) provided 80% power to test a 10% non-inferiority margin at a one-sided alpha of 0.05, assuming a CR rate of 36% for AV28 (per VIALE-A) and 45% for AV14. We hypothesized that AV14 would have similar efficacy to AV28, with faster count recovery, and hence may demonstrate a higher CR rate. In the VIALE-A study, the CR rate was 36.7% and 17.9% for the Aza-Ven and Aza arms respectively, and the difference favoring Aza-Ven was 18.8% with a confidence interval (CI) of 10.4%- 27.2%. The lower bound of this CI was chosen as our non-inferiority margin because it represents the smallest clinically meaningful difference

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required to establish 28-day Aza-Ven as the standard of care relative to Aza alone. Non-inferiority would be established if the upper limit of the 90% CI of the difference in CR rates (AV28 - AV14) was ≤10% (**Fig. S1**).

All randomized patients who initiated treatment were included in efficacy and safety analyses per the modified intent-to-treat analysis detailed in the protocol. Patients who received even 1-day of the assigned treatment were included but those who did not initiate therapy at all after randomization were excluded to preserve the ability to detect treatment-specific differences in this modest-sized non-inferiority study. The difference in CR rate with 90% CI was estimated with the Cochran-Mantel-Haenszel (CMH) test stratified by age. Additional statistical methods are detailed in the **Supplementary Appendix**. SAS software version 9.4 was used for statistical analysis. All p-values reported are two-sided and exploratory as not testing the primary objective of the trial.

Results

Patients and Treatment

Baseline characteristics:

From May 2023 through September 2025, 175 patients were randomized; six patients did not start study treatment due to withdrawal of consent or death. Among 169 patients who started the study treatment, 83 patients were randomized to AV28 and 86 to AV14 (**Fig. 1B**). The median age of the cohort was 73 years (range 60-90); 38.5% were 75 years or older. Baseline demographics were balanced between the two arms (**Table 1**), except for more male patients in AV14 (65.1% vs. 49.4%; p=0.04).

Molecular subgroups and risk stratification:

Mutations in *NPM1* were identified in 5.9% of patients, *FLT3* in 11.2%, *IDH1* and *IDH2* in 10.1% and 17.2%, and *NRAS* and *KRAS* in 7.7% and 4.7%, respectively. Nineteen percent of

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patients harbored a *TP53* mutation, and 30.5% had a complex karyotype (≥3 abnormalities). According to the ELN2024 genetic risk stratification[20] for patients receiving less-intensive regimens, 65.1% of our cohorts were classified as favorable risk, 16.0% as intermediate risk, and 18.9% as adverse risk. By the Beat-AML 2024 ELN-refined risk score[21], 21.4% patients were classified as favorable, 57.1% intermediate, and 21.4% adverse risk. The cytogenetic and molecular features, as well as the risk classifications, were mostly distributed evenly between the two arms (**Table 2**).

Aza-Ven dosing and G-CSF use:

In C1, 68.4% of patients received 28-day Ven in AV28 as compared to 89.2% receiving 14-day Ven in AV14. (**Table S1, Fig. S2**). Majority of patients (93.7%) received at least 14 days of Ven and 87.3% received >21 days Ven in AV28 in C1. In cycle 2, 67.1% of patients in AV28 and 75.6% in AV14 received 28 and 14 days of Ven per assignment. Seventeen percent of patients in each arm went off study prior to starting C2. Across both cycles, 53.2% of patients in AV28 completed the protocol-intended 2-cycle 28-day regimen, whereas 71.3% of patients in AV14 completed both cycles of the 14-day regimen. However, the median duration of treatment for C1-2 remained 28 and 14 days as intended for respective arms. The primary reason for treatment interruption in both arms during C1 was infection (28.0% of patients in AV28, 22.2% in AV14). Aza dosing details are outlined in **Table S2**. Granulocyte colony-stimulating factor (G-CSF) was used in 21.3% of patients in the entire cohort: 16.9% in AV28 and 25.6% in AV14 (**Table 3, Table S3**), primarily for delayed count recovery.

Efficacy

The CR rate after 2 cycles was 49.4% (41/83, 95% CI: 38.2% - 60.6%) in AV28, and 43.0% (37/86, 95% CI: 32.4% - 54.2%) in AV14. The CMH strata-adjusted difference in CR rates (AV28 - AV14) was 6.4%, with a strata-adjusted 90% CI of (-6.1% - 19.0%). Since the upper limit of this CI (19.0%) exceeded the pre-specified non-inferiority margin of 10%, we could not

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conclude that AV14 was non-inferior to AV28 with respect to the CR rate. Logistic regression models did not identify any significant prognostic factors for CR in either arm or between both arms (**Table S4)**.

Composite CR (cCR) was higher with AV28 than AV14 (80.7% vs. 68.6%), and overall response rate was 84.3% versus 77.9%, respectively. Among patients achieving cCR in cycle 1, MRD was undetectable in 63.6% and 72.7% of patients in AV28 and AV14, respectively. By the end of cycle 2, MRD negativity among responders was nearly identical between arms (77.6% in AV28 and 76.5% in AV14) (**Table 3, Table S5**).

Safety and Count Recovery

The most common treatment-emergent adverse events (TEAEs) of any grade, regardless of attribution, were hematologic, including thrombocytopenia (61.5%), neutropenia (60.4%), anemia (56.2%), and leukopenia (55%) (**Table S6**). Febrile neutropenia occurred at similar rates (24.1% in AV28; 29.1% in AV14). No significant differences in grade ≥3 AEs, serious adverse effects (SAEs) and hospitalizations were observed between the two arms (**Table 4, Table S7**). Among patients achieving cCR, the median time to ANC recovery (≥1×10^9/L) after C1 was shorter with AV14 (35 days; 95% CI: 32–36) compared with AV28 (38 days; 95% CI: 35–41); p= 0.02. In contrast, after cycle 2, median time to neutrophil recovery with AV28 was 36 days (95% CI: 35–40) vs. 43 days (95% CI: 37–50) with AV14; p=0.16 (**Table S8, Fig. S3**).The median time to platelet recovery (≥ 100x10^9/L) was comparable after cycle 1 - 22 days (95% CI: 20–24) with AV28 vs. 23 days (95% CI: 22–29) with AV14 (p=0.78) and was after cycle 2 – 35 days (95% CI: 20-24) with AV14 vs. 24 days (95% CI: 1-39) with AV28; p=0.78 (**Table S9, Fig. S4**). Median cycle length was also not significantly different between arms; 36 vs. 35 days in C1 and 42 vs 38 days in C2, for AV28 and AV14 respectively (**Table S10**).

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Survival

With a median follow-up of 12.4 months (range: 3.0-32.6), the median PFS was 11.3 months (95% CI: 9.0-13.6 months) across both arms: 13.1 months (95% CI: 8.9- 21.4) in AV28 and 9.9 months (95% CI: 7.2-13.6 months) in AV14 (p-value = 0.15) (**Fig. 2A**). The median OS was 17.1 months (95% CI: 13.1-23.2 months) for all patients. In AV28, the median OS was 21.4 months (95% CI: 13.4-not reached (NR)); in AV14, the median OS was 13.6 months (95% CI: 9.7-22.8 months) (p-value = 0.07) (**Fig. 2B**). By ELN2024 risk categorization, the median OS was not reached, 13.1 and 6.3 months in favorable, intermediate, and adverse groups, for AV28 as compared to 22.8, 11.9 and 9.1 months for AV14; respectively (**Fig. S5**). Early mortality was low and similar, with 30-day and 60-day mortality rates of 4.8% vs. 3.5%, and 7.2% vs. 8.1%, for AV28 and AV14 respectively. Among death events with a known cause, 22 (71.0%) in AV28 vs. 28 (65.1%) in AV14 were attributed to underlying AML (**Table S11**). Eleven patients received allogeneic transplant in the entire cohort with 6 on AV28 and 5 on AV14. In the multivariable model adjusting for covariates, independent predictors of worse OS included ECOG performance status (PS) 2 (HR 2.47), *KRAS* mutation (HR 3.48) and *TP53* mutation (HR 3.14). Treatment arm did not have a significant impact on OS in univariable (HR 1.53 for AV14 vs. AV28, 95% CI: 0.97–2.41) or multivariable analyses (HR 1.33, 95% CI: 0.83–2.12) (**Table 5**). To better understand the relevance of composite CR, we compared the OS in patients achieving CR vs CRi/CRh. While not significant, median OS was not reached in those with CR vs. 19.7 months in those with CRi/CRh; p=0.08 (**Figure S6**).

Subgroup Outcomes

Age

The randomization was stratified by age (<75 vs. ≥75 years). In patients ≥75 years, 35.5% vs. 70.4% received the planned complete-dose Ven, and the CR rate was 51.5% vs.

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37.5% in AV28 and AV14, respectively. The median OS was not reached in AV28 and was 13.4 months in the AV14 arm (**Table S12, Fig. S7**).

Molecular subgroups

For patients with *NPM1* or *IDH2* mutations, CR rate was higher in the AV28 arm (60.9% vs. 33.3%) (**Table 3**), and so was the cCR rate (87.0% vs. 73.3%) (**Table S13**). The MRD negativity rate by C2 among patients achieving cCR was 100% in both arms. The 1-year OS was 78% in AV28 and 73% in AV14 in this molecular subgroup (**Fig. S8**). In patients who did not carry these mutations, the CR rate (45%) was equivalent in both arms. Patients with *TP53* mutations had similar CR rate (53.9% vs. 57.9%) and median OS (6.3 vs. 9.1 months) between AV28 vs. AV14. (**Fig. S9**).

Ven dose

Dosing completion of the protocol-directed Ven course was associated with higher CR rates, with 56.1% and 49.1% of patients achieving CR in the AV28 and AV14 arms, respectively. In contrast, incomplete Ven delivery was associated with lower CR rates in both arms (38.9% in AV28 and 34.8% in AV14). The median OS in patients who received complete Ven dose in C1 was not reached in AV28 and was 14.5 months in AV14 (**Table S14, Fig. S10**).

Discussion

OPTI-AML is the first prospective randomized study conducted to systematically compare AV28 vs. AV14 for the first 2 cycles of AML therapy in induction-ineligible patients ≥60 years old, to assess the impact of abbreviated Ven schedules in the real world (7-,14-, and 21-days), especially in the induction phase of therapy in ND-AML patients, in response to the prolonged and cumulative myelosuppression[1,3] of Aza-Ven. The shorter 14-day Ven dosing did not meet criteria for noninferiority compared with the standard 28-day schedule as the upper

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bound of the 90% CI for the difference in CR rates (-6.1% to 19.0%) exceeded the prespecified margin of 10%. The observed difference in CR rates (49.4% with AV28 vs. 43.0% with AV14) was not statistically significant as the CI for the difference covered 0. Nevertheless, these findings do not support routine substitution of a 14-day schedule for the standard 28-day regimen in an unselected older AML population for cycles 1-2.

Our study population was clinically and genomically representative of the older AML patients, except for lower *NPM1*-mutated patients (5.9% vs. 17.6% in VIALE-A[1]) and slightly lower *FLT3-ITD/TKD* patients (10.0% vs 16.2% in VIALE-A[1]) due to enrollment on competing triplet trials[14,22]. Although excluded from VIALE-A, a small proportion (4.9%) of core binding factor AML patients whose advanced age (median 78y, range 71-81) and comorbidities made them exceptionally high risk for receiving standard of care high dose cytarabine and gemtuzumab ozogamicin were included in this study. The distribution of high, intermediate, and lower benefit risk groups per ELN2024 was 65%, 16%, and 19% in OPTI-AML compared to 52%, 25%, and 23% respectively in VIALE-A. The increased proportion of the higher-benefit group in our study was not due to higher numbers of the known Ven-sensitive mutations such as *NPM1/IDH* which constituted 27% of the entire cohort. When comparing molecular distribution in AV28 vs AV14, acknowledging small numbers, there were imbalances in the *IDH2* (7 more pts in AV28) and *TP53* mutated patients (6 more pts in AV14). In line with prior studies[5,23,24], patients with *NPM1* or *IDH2* mutations had higher CR rates with AV28 (60.9% vs. 33.3%), whereas patients without these mutations had identical CR rates (45%) between arms. Although the study was underpowered for this subgroup analysis, this is a critical observation since non *NPM1/IDH2* mutated AML constitutes a large majority of AML cases (60-70%) where AV14 may be equally effective[7,23,24]. Overall, the CR rates in our study are higher than those observed in VIALE-A, due to differences in study cohort as OPTI-AML included younger patients (38.5% vs.

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61% aged ≥75 years), core-binding factor AML and did not require RBC transfusion independence for CR as in VIALE-A[1].

Our study also highlights the difficulty of comparing alternative Ven regimens in a randomized setting. This was due to the frequent dose holds on the AV28 arm as early as C1, likely due to the presumption of 28-day Ven being more toxic though our study suggests otherwise. While the majority (93.7%) of patients in the AV28 arm received at least 14 consecutive days of Ven in C1, interruptions beyond this point were common. This pattern may reflect physician practice of holding Ven during hospitalizations after patients had received at least 14 days, influenced by retrospective data suggesting comparable efficacy with shorter durations and concern for prolonged myelosuppression from Ven in the setting of active infections. Across both cycles, the variability of Ven dosing in the 2 cycles for both the AV28 and AV14 protocol-intended regimens underscored the gap between protocol-defined and real-world treatment delivery as well as overall morbidity in this patient population for this standard of care AML therapy, even when cared for in academic settings.

Inability to complete protocol-directed Ven duration in either arm negatively impacted CR. Half of the patients who received the full intended Ven course achieved a CR in both arms, compared to ~1/3 in those with Ven interruptions. While this may reflect underlying patient frailty or clinical instability necessitating dose holds and contributing to poorer outcomes, our study demonstrates that reducing Ven exposure at this early timepoint in the disease did not significantly impact recovery. We did not see significant differences in cycle length, ANC and platelet count recovery in the two arms except for faster ANC recovery after C1 in AV14, but this was not sustained after C2 for either ANC or platelets. Contrary to our expectations, count recovery after C2 was longer with AV14. However, this is congruent with the observation that AV28 resulted in higher CR rates (33.3% vs 24.4%) whereas AV14 had more frequent CRh (26.7% vs 18.1%) after C2. Importantly, we did not see meaningful differences in serious

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adverse events between the two arms for both hematologic and non-hematologic events including hospitalizations, suggesting that there may be competing factors between optimal disease control and therapy induced cytopenias that impact patient outcomes in the early phase of AML therapy. Rates of febrile neutropenia observed in our study were also lower at 24-28% as compared to 42% observed in VIALE-A which may be due to shorter follow-up on study, widespread adoption of antimicrobial prophylaxis and G-CSF use. Of note, use of G-CSF did not seem to impact CR rates or OS.. Overall G-CSF use in both arms, even after achievement of a cCR was less than 25% despite data showing safe use in 50% of the VIALE-A and C participants, suggesting that G-CSF may be underutilized in this setting despite studies suggesting effective use for count recovery and therapy contiunuation[25,26].

With a relatively short median follow-up of 12.4 months, the OS was 17.1 months for all patients, comparable to the OS from VIALE-A[27]. Median OS was 21.4 months in AV28 and 13.6 months in AV14 (p=0.07). Early mortality was not different between treatment arms, with majority of patients in both arms dying of relapsed disease or infectious complications. As previously reported[5], ELN2024 favorable risk group had a median OS of 22.8 months with AV14 vs. not reached with AV28 (p=0.32) with no appreciable differences for intermediate/ low benefit groups (**Fig. S5**). However, treatment arm was not independently associated with OS after adjustment for baseline characteristics. Instead, independent predictors of OS were primarily patient and disease characteristics, including ECOG performance status and adverse-risk mutations such as *KRAS* and *TP53*. *TP53* mutations were more frequent in AV14 (19 vs 13 in AV28); which may have contributed to the apparent OS difference favoring AV28.

Our study highlights that optimal Aza-Ven dosing remains an open question that needs to be optimized for molecularly defined subsets of AML especially in the context of Aza-Ven potentially becoming used as a front-line regimen younger induction eligible adverse-risk AML patients as suggested by recent data[2]. Our study was not powered to evaluate genomic subsets

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of AML, which limited these analyses. Our study also did not dictate the dose and duration of Ven after the first 2 cycles but focused on the question of optimizing Ven dosing during the treatment induction as most patients achieve a response by the end of 2 cycles[1]. We were committed to the pragmatic nature of this study and strong patient preference to continue this well-established standard of care[1] with oncologists in their communities, while balancing the practicalities of the size, duration and economics of a study that would generate meaningful data for the AML community[28]. The primary limitation was the assumption that AV14 might yield higher CR rates due to improved count recovery while maintaining efficacy; however, this optimistic premise likely underestimated the required sample size (only 83 patients per arm) to prove non-inferiority. Contrary to our assumption, a 6% difference in CR rates favoring AV28 was observed, leading to reduced statistical power as suggested by the wide CI which undermined our ability to demonstrate non-inferiority. It also limited genomic subgroup analyses where different Ven dosing schedules could have a clinically significant impact.

In conclusion, our study did not demonstrate that the shorter AV14 schedule was non-inferior to AV28 during Aza-Ven induction therapy for 2 cycles in an unselected population of ND-AML patients. However, our findings highlight important biological heterogeneity in responses. The apparent advantage of prolonged Ven exposure was largely confined to favorable molecular subsets, particularly *NPM1* and *IDH2*-mutated AML, whereas patients without these mutations had comparable outcomes with 28 or 14-day schedules. We, therefore, encourage further prospective studies to determine the optimal dosing regimen of Aza-Ven in different genomic subsets. As novel Aza-Ven triplet combinations continue to be investigated for molecular subsets in large, randomized Phase 3 studies, our findings urge for careful evaluation of the overall efficacy of abbreviating Ven duration in induction and continuation phases, which may be necessary to mitigate hematologic and various other toxicities. For example, in *NPM1*-mutated AML—particularly in the context of menin inhibitor-based triplets—reducing Ven

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duration to 14 days may risk compromising efficacy, especially in the induction phase, given the higher CR rates observed with AV28 in this subgroup. In contrast, in *FLT3/ RAS* mutated AML where CR rates were comparable between AV14 and AV28, a shorter Ven schedule may be a reasonable strategy to mitigate overlapping toxicities and facilitate safe incorporation of additional targeted agents.

Our study also highlights the challenges of retrospective series and expert opinion in making clinical decisions about the duration of venetoclax dosing in the real-world setting and demonstrates the utility of prospective, adequately powered pragmatic studies to answer these critical questions. The unknown impact of Ven dosing variation post C2 and the sparse use of G-CSF to help count recovery and prevent infectious complications warrant further study to make Aza-Ven therapy as effective and safe as possible for our older AML patients.

Acknowledgments

The study was sponsored by Blood Cancer United. Funding for the BAML-16-001-S12/Opti-AML sub-study was made possible by the Harry T. Mangurian, Jr. Foundation, Neil and Emily Kishter, Judy and Charlie Lynch and many other generous donors.

Authorship

Contribution: Y.H., M.J., N.H., and T.C. analyzed data. U.B., J.Z., J.B., B.D., R.L., T.L., S.H., R.S., C.L., E.T., W.S., O.O., A.P., M.B., V.D., E.S., W.B., C.V., E.C., Y.M., R.O., G.S., A.N., L.W., S.M., M.M., M.S., and L.R., helped to enroll and treat patients. U.B., J.B., A.M., Y.H., M.J., A.B., B.D., R.L., L.D., L.G., and A.Y. designed the research. U.B., Y.H., and S.H. wrote the paper. All authors reviewed the paper.

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Conflict of Interest Statements

UB reports receiving grant support from Novartis, Sumitomo, Jazz, Incyte and Syndax, advisory and consulting fees from Takeda, Daichi-Sankyo, Sumitomo, Kura, Servier, Syndax, Genentech, AbbVie , Astellas and Geron.

TL reports a Consulting or Advisory Role: Servier, Jazz Pharmaceuticals, Syndax, Daiichi Sankyo; Research funding to the institution: Bio-Path Holdings, Inc, Astellas Pharma, Celyad,

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Aptevo Therapeutics, Cleave Biosciences, CicloMed, Jazz Pharmaceuticals, Cardiff Oncology, Kura Oncology, Lin Biosciences.

CL receives research funding from AbbVie and serves as a consultant or advisory board member for Bristol Myers Squibb, AbbVie, Rigel, Servier, Syndax, Astellas, and COTA Healthcare

AAP: Research Funding from Sumitomo, Pfizer, Incyte, Servier, Stemline; Honoraria from AbbVie, Amgen, Astellas, Cycle, Geron, Jazz, Novartis, Sobi, Syndax, Refined Oncology

MRB reports institutional research funding from AbbVie, Ascentage Pharma, Astellas, FORMA Therapeutics, Kite/Gilead, Kura Oncology, Sumitomo and Takeda.

EMS reports receiving consuting fees from Syndax, Kura Oncology, J and J, Daiichi Sankyo, Astellas, Servier, AstraZeneca, Genentech and Abbvie.

JCB reports institutional research funding from AbbVie, Newave, Kartos, and Syndax along with consulting/ownership with Eilean Therapeutics and Lomond Therapeutics.

BD has a financial interest in the following companies that may have a commercial interest in the results of this research. This potential conflict of interest has been reviewed and managed by OHSU. SAB: Adela Bio, Aileron Therapeutics (inactive), Therapy Architects/ALLCRON (inactive), Cepheid (incative), Labcorp (inactive), Nemucore Medical Innovations, Novartis, RUNX1 Research Program; SAB & Stock: Aptose Biosciences, Blueprint Medicines, Enliven Therapeutics, Iterion Therapeutics, GRAIL (inactive), Recludix Pharma; Board of Directors & Stock: Amgen, Vincerx Pharma; Board of Directors: Burroughs Wellcome Fund; Joint Steering Committee: Beat AML LLS (uncompensated); Advisory Committee: Multicancer Early Detection Consortium (uncompensated), Malta North American Business Council (uncompensated); Founder: VB Therapeutics; Sponsored Research Agreement: Astra-Zeneca, DELiver Therapeutics, Immunoforge (inactive), Terns, Enliven Therapeutics (inactive), Recludix Pharma (inactive); Clinical Trial Funding: Novartis, Astra-Zeneca; Royalties from Patent 6958335 (Novartis exclusive license) and OHSU and Dana-Farber Cancer Institute (Merck exclusive license, CytoImage, Inc. exclusive license, DELiver Therapeutics non-exclusive license, Sun Pharma Advanced Research Company non-exclusive license); US Patents 4326534, 6958335, 7416873, 7592142, 10473667, 10664967, 11049247.

RLL is on the SAB and a former member of the Supervisory board of Qiagen (compensation/equity), a co-founder at Ajax (equity), a board member of the Mark Foundation for Cancer Research and has been ascientific advisor to Mission Bio, Kurome, Syndax, Scorpion, Zentalis, Jubilant, Auron, Prelude, and C4 Therapeutics; for each of these entities he received equity/compensation. He has received research support from the Cure Breast Cancer Foundation (with IP rights), Calico, Zentalis and Ajax, and has consulted/provided professional services for ECOG-ACRIN, Genome Canada, Goldman Sachs and Astra Zeneca.

ASM reports institutional research funding from Terns, Inc., Treadwell Therapeutics, Schrodinger Inc., and BlossomHill Therapeutics; advisory fees from BMS, Novartis, Daiichi Sankyo and Foghorn Therapeutics.

JFZ reports Consultancy and/or Advisory Boards: AbbVie, Astellas, AstraZeneca, Crossbow Therapeutics, Daiichi Sankyo, Foghorn, Genentech, Genmab, Geron, Ipsen, Jazz, Johnson & Johnson, Kura Oncology, Neogenomics, Novartis, RelmadaTherapeutics, Rigel, Sellas, Servier, Shattuck Labs, Sumitomo Pharma, Syndax; Research Funding: AbbVie, Akesobio, Aptevo,

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Arog, Ascentage, Auron, Daiichi Sankyo, Faron, Jazz, Kura Oncology, Lin Biosciences, Loxo, Merck, Newave, Novartis, Sellas, Shattuck Labs, Stemline, Sumitomo Pharma, Zentalis.

YFM has received honoraria/consulting fees from AptitudeHealth, Servier, BMS, Kura Oncology, BluePrint Medicines, Geron, OncLive and MD Education, Targeted Oncology, Curio science, and Medscape Live. YFM participated in advisory boards and received honoraria from Takeda, Foundation Medicine, Stemline Therapeutics, Blueprint Medicines, Taiho Oncology, SOBI, Rigel Pharmaceuticals, Geron, Cogent Biosciences and Abbvie. YFM received travel reimbursement from MD Education.

All other authors report no relevant disclosures.

Presented in abstract form at the 31st European Hematology Association Congress, Stockholm, Sweden, 11 to 14 June 2026.

Data Sharing Statement:

Any requests for data and supporting documents presented in this article will be considered and shared to the best of our ability if possible. Data will be shared in a deidentified manner for the purposes of noncommercial research. Please contact the corresponding author for any requests.

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Figure Legends

Figure 1. Study Schema and Consort Diagram

(A) Study schema. Patients aged ≥60 years with newly diagnosed AML unfit for intensive chemotherapy were randomized 1:1, stratified by age (60–74 vs. ≥75 years), to receive azacitidine (75 mg/m² x 7 days) with venetoclax administered either for 28 days (AV28) or 14 days (AV14) during cycles 1 and 2. Bone marrow assessments were performed at the end of each cycle for response assessment. After completion of two cycles, patients came off study to continue therapy per physician discretion. **(B) Consort Diagram.** A total of 175 patients were randomized, of whom 169 initiated study treatment (AV28, n=83; AV14, n=86). 68 (AV28) and 71 (AV14) patients completed 2 cycles of therapy on the trial. Reasons for early treatment discontinuation are provided for each arm.

Figure 2. Survival Outcomes

(A) Progression-free survival (PFS). Median PFS was 13.1 months (95% CI: 8.9-21.4) in the AV28 arm and was 9.9 months (95% CI: 7.2–13.6) in the AV14 arm (p=0.15). A stratified-by-age log-rank test was used to calculate the p-value. **(B) Overall survival (OS).** With a median follow-up of 12.4 months (range: 3.0-32.6) for the entire cohort, 44 and 32 death events occurred in AV14 and AV28, respectively. Median OS was 21.4 months (95% CI: 13.4–NR) in the AV28 arm and was 13.6 months (95% CI: 9.7–22.8) in the AV14 arm (p=0.07). A stratified-by-age log-rank test was used to calculate the p-value. Tick marks indicate censored observations. By month 3, 16 death events occurred on AV14 arm, 5 due to sepsis, 5 due to AML disease, 2 bleeding, 1 infection, 1 respiratory failure, 1 cardiac complication, and 1 unknown.

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Tables

Table 1. Baseline Characteristics

Table 1: Baseline Characteristics	Overall (N=169)	AV28 (N=83)	AV14 (N=86)
Age at consent, years, Median (range)	73 (60-90)	72 (60-88)	73 (60-90)
Age ≥ 75 years, no. (%)	65 (38.5)	33 (39.8)	32 (37.2)
Gender, no. (%)			
Female	72 (42.6)	42 (50.6)	30 (34.9)
Male	97 (57.4)	41 (49.4)	56 (65.1)
Race, no. (%)			
Caucasian	147 (89.1)	71 (88.8)	76 (89.4)
African American	13 (7.9)	6 (7.5)	7 (8.2)
Other	5 (3.0)	3 (3.8)	2 (2.4)
Unknown	4	3	1
Ethnicity, no. (%)			
Not Hispanic or Latino	162 (98.8)	80 (98.8)	82 (98.8)
Hispanic or Latino	2 (1.2)	1 (1.2)	1 (1.2)
Unknown	5	2	3
ECOG Performance Status at Screening, no. (%)			
0	51 (30.9)	27 (33.3)	24 (28.6)
1	80 (48.5)	40 (49.4)	40 (47.6)
2	34 (20.6)	14 (17.3)	20 (23.8)
Unknown	4	2	2
Bone Marrow Blasts, %, Median (range)*	40 (0-98)	41 (1-98)	37.5 (0-93)
Unknown	6	2	4
White Blood Cell Count, 10^9/L, Median (Range)	2.6 (0.3-23.6)	2.9 (0.7-23.6)	2.5 (0.3-22.7)

*Based on baseline bone marrow aspirate samples only. Eligibility on study considered additional factors such as AML defining abnormalities, additional blast equivalents, and bone marrow biopsy samples.

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Table 2. Molecular Characteristics

Table 2: Molecular Characteristics			
Mutations, n (%)	**Overall (N=169)**	**AV28 (N=83)**	**AV14 (N=86)**
NPM1	10 (5.9)	6 (7.2)	4 (4.7)
IDH2	29 (17.2)	18 (21.7)	11 (12.8)
IDH1	17 (10.1)	7 (8.4)	10 (11.6)
NRAS	13 (7.7)	5 (6.0)	8 (9.3)
KRAS	8 (4.7)	4 (4.8)	4 (4.7)
FLT3	19 (11.2)	9 (10.8)	10 (11.6)
FLT3-ITD	10 (5.9)	3 (3.6)	7 (8.1)
FLT3-TKD	7 (4.1)	4 (4.8)	3 (3.5)
TP53	32 (18.9)	13 (15.7)	19 (22.1)
Cytogenetics, n (%)	**Overall (N=168)***	**AV28 (N=82)**	**AV14 (N=86)**
Core Binding Factor	8 (4.9)	1 (1.3)	7 (8.2)
unknown	4	3	1
Complex Karyotype	50 (30.5)	22 (27.9)	28 (32.9)
unknown	4	3	1
ELN Risk Classification, n (%)	**Overall**	**AV28**	**AV14**
ELN 2022	**(N=168)**&	**(N=82)**	**(N=86)**
Favorable	21 (12.5)	10 (12.2)	11 (12.8)
Intermediate	15 (8.9)	6 (7.3)	9 (10.5)
Adverse	132 (78.6)	66 (80.5)	66 (76.7)
ELN 2024	**(N=169)**	**(N=83)**	**(N=86)**
Favorable	110 (65.1)	58 (70.0)	52 (60.5)
Intermediate	27 (16.0)	12 (14.5)	15 (17.4)
Adverse	32 (18.9)	13 (15.7)	19 (22.1)
Beat-AML 2024 ELN-refined#	**(N=168)**&	**(N=82)**	**(N=86)**
Favorable	36 (21.4)	16 (19.5)	20 (23.3)
Intermediate	96 (57.1)	51 (62.2)	45 (52.3)
Adverse	36 (21.4)	15 (18.3)	21 (24.4)

*one patient did not have cytogenetic data; &ELN 2022 requires both mutation and cyto data; #Refined from ELN 2022 where 2022 “Favorable” and “Intermediate” were grouped into new “Favorable”, and 2022 “Adverse” was split into new “Intermediate” and “Adverse” by mutation status of *IDH2*, *KRAS*, *MLL2*, and *TP53*.

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562 **Table 3. Clinical Outcomes**

Table 3: Clinical Outcomes	Overall (N=169)	AV28 (N=83)	AV14 (N=86)
Best Response Across 2 Cycles, n (%)			
CR	78 (46.2)	41 (49.4)	37 (43.0)
CRh	26 (15.4)	12 (14.5)	14 (16.3)
CRi	22 (13.0)	14 (16.9)	8 (9.3)
MLFS	11 (6.5)	3 (3.6)	8 (9.3)
PR	4 (2.4)	2 (2.4)	2 (2.3)
Stable Disease	19 (11.2)	6 (7.2)	13 (15.1)
Not Assessed	9 (5.3)	5 (6.0)	4 (4.7)
Composite Complete Remission Across 2 Cycles (CR, CRi, CRh), n (%)	126 (74.6)	67 (80.7)	59 (68.6)
Overall Response Rate Across 2 Cycles (CR, CRi, CRh, MLFS), n (%)	137 (81.1)	70 (84.3)	67 (77.9)
MRD Negative Rate in cCR, n (%)			
Cycle 1	**(n=88)**	**(n=44)**	**(n=44)**
	60 (68.2)	28 (63.6)	32 (72.7)
Cycle 2	**(n=100)**	**(n=49)**	**(n=51)**
	77 (77.0)	38 (77.6)	39 (76.5)
CR per Mutation Group, n/n (%)			
NPM1	6/10 (60.0)	5/6 (83.3)	1/4 (25.0)
IDH2	14/29 (48.3)	10/18 (55.6)	4/11 (36.4)
IDH1	11/17 (64.7)	5/7 (71.4)	6/10 (60.0)
FLT3	13/19 (68.4)	7/9 (77.8)	6/10 (60.0)
FLT3-ITD	6/10 (60.0)	3/3 (100.0)	3/7 (42.9)
FLT3-TKD	5/7 (71.4)	2/4 (50.0)	3/3 (100.0)
TP53	18/32 (56.3)	7/13 (53.9)	11/19 (57.9)
Non *TP53*	56/137 (40.8)	30/70 (42.9)	26/67 (38.8)
TP53 or Complex Karyotype	24/53 (45.3)	10/24 (41.7)	14/29 (48.3)
NPM1/*IDH2*	19/38 (50.0)	14/23 (60.9)	5/15 (33.3)
Non *NPM1*/*IDH2*	59/131 (45.0)	27/60 (45.0)	32/71 (45.1)
Off Treatment Reason, n (%)			
Completion of Protocol Defined Therapy*	139 (82.3)	68 (81.9)	71 (82.6)
Other	12 (7.1)	5 (6.0)	7 (8.1)
Adverse events	6 (3.6)	5 (6.0)	1 (1.2)
Death	5 (3.0)	1 (1.2)	4 (4.7)
Recurrence after a response	3 (1.8)	2 (2.4)	1 (1.2)
Disease progression	3 (1.8)	1 (1.2)	2 (2.3)
Withdrew consent	1 (0.6)	1 (1.2)	0 (0)
Use of GCSF, n (%)			

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No	133 (78.7)	69 (83.1)	64 (74.4)
Yes	36 (21.3)	14 (16.9)	22 (25.6)

*Completion of protocol defined therapy requires two full cycles of Aza/Ven treatment. Patients could continue Aza/Ven treatment per physician's discretion afterwards.

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566 **Table 4. Treatment Emergent Adverse Events (Grade 3+)**

Table 4: Treatment Emergent Adverse Events (Grade 3+)	AV28 (n=83)	AV14 (n=86)	Overall (n=169)
Hematologic Adverse Events			
Neutropenia	51 (61.4)	47 (54.7)	98 (58)
Leukopenia	43 (51.8)	47 (54.7)	90 (53.3)
Thrombocytopenia	42 (50.6)	47 (54.7)	89 (52.7)
Anemia	36 (43.4)	42 (48.8)	78 (46.2)
Lymphopenia	20 (24.1)	24 (27.9)	44 (26)
Febrile neutropenia	19 (22.9)	24 (27.9)	43 (25.4)
Non-Hematologic Adverse Events			
Pneumonia	6 (7.2)	13 (15.1)	19 (11.2)
Hypoxia	4 (4.8)	9 (10.5)	13 (7.7)
Hypokalaemia	7 (8.4)	2 (2.3)	9 (5.3)
Hypotension	4 (4.8)	4 (4.7)	8 (4.7)
Hypoalbuminemia	3 (3.6)	3 (3.5)	6 (3.6)
Dyspnea	1 (1.2)	4 (4.7)	5 (3)
Fatigue	3 (3.6)	2 (2.3)	5 (3)
Muscular weakness	2 (2.4)	3 (3.5)	5 (3)
Pulmonary oedema	3 (3.6)	2 (2.3)	5 (3)
Diarrhea	3 (3.6)	1 (1.2)	4 (2.4)
Hypophosphatemia	2 (2.4)	2 (2.3)	4 (2.4)
Aspartate aminotransferase increased	2 (2.4)	1 (1.2)	3 (1.8)
Blood bilirubin increased	1 (1.2)	2 (2.3)	3 (1.8)
Hypomagnesemia	1 (1.2)	2 (2.3)	3 (1.8)
Hyponatremia	1 (1.2)	2 (2.3)	3 (1.8)
Arthralgia	0 (0)	2 (2.3)	2 (1.2)
Constipation	1 (1.2)	1 (1.2)	2 (1.2)
Epistaxis	2 (2.4)	0 (0)	2 (1.2)
Fall	0 (0)	2 (2.3)	2 (1.2)
Hypocalcemia	2 (2.4)	0 (0)	2 (1.2)
Peripheral edema	0 (0)	2 (2.3)	2 (1.2)
Pain in extremity	1 (1.2)	1 (1.2)	2 (1.2)
Alanine aminotransferase increased	1 (1.2)	0 (0)	1 (0.6)
Blood creatinine increased	1 (1.2)	0 (0)	1 (0.6)
Decreased appetite	0 (0)	1 (1.2)	1 (0.6)
Dizziness	0 (0)	1 (1.2)	1 (0.6)
Headache	0 (0)	1 (1.2)	1 (0.6)
International normalized ratio increased	0 (0)	1 (1.2)	1 (0.6)
Nausea	0 (0)	1 (1.2)	1 (0.6)
Stomatitis	1 (1.2)	0 (0)	1 (0.6)

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Table 5. Univariable and Multivariable Cox Proportional Hazards Regression Models for Overall Survival

Table 5: Univariable/Multivariable Regression Models for Overall Survival	Univariable models		Multivariable model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Arm, AV14 vs. AV28	1.53 (0.97-2.41)	0.07	1.33 (0.83-2.12)	0.23
Age, 5-years older	1.23 (1.01-1.49)	0.04	----	----
Sex, M vs. F	1.30 (0.82-2.06)	0.27	----	----
Race, White vs. non-white	0.60 (0.30-1.21)	0.16	----	----
ECOG PS, vs. 0				
1	1.71 (0.96-3.04)	0.07	1.49 (0.82-2.68)	0.19
2	2.40 (1.26-4.59)	0.0081	2.47 (1.27-4.81)	0.0078
Hemoglobin, 10-unit increase	0.78 (0.66-0.93)	0.0066	----	----
WBC, 1-unit increase	1.03 (0.99-1.08)	0.12	----	----
Platelet, 50-unit increase	0.74 (0.59-0.93)	0.0086	----	----
ANC, 1-unit increase	0.95 (0.87-1.05)	0.31	----	----
Complex karyotype	2.30 (1.44-3.66)	0.0005	----	----
CBF	1.39 (0.60-3.21)	0.44	----	----
NPM1	0.97 (0.42-2.25)	0.94	----	----
IDH1	0.78 (0.34-1.79)	0.56	----	----
IDH2	0.38 (0.17-0.82)	0.01	----	----
FLT3-ITD	1.71 (0.82-3.57)	0.15	----	----
NRAS	1.33 (0.61-2.91)	0.47	----	----
KRAS	2.53 (1.00-6.41)	0.05	3.48 (1.31-9.25)	0.01
TP53	2.54 (1.53-4.23)	0.003	3.14 (1.80-5.47)	<.0001
ELN 2022, vs. Adverse				
Favorable	0.83 (0.44-1.59)	0.58	----	----
Intermediate	0.53 (0.21-1.33)	0.18		
ELN 2024, vs. Adverse				
Favorable	0.34 (0.20-0.58)	<.0001	----	----
Intermediate	0.65 (0.34-1.25)	0.2		
Beat-AML 2024 ELN-refined, vs. Adverse				
Favorable	0.34 (0.18-0.66)	0.0012	----	----
Intermediate	0.37 (0.22-0.62)	0.0002		
Usage of G-CSF, vs. No	0.96 (0.55-1.66)	0.87	----	----

ECOG PS-Eastern Cooperative Oncology Group Performance Status, WBC- white blood cell, ANC-absolute neutrophil count, CBF-core-binding factor, ELN-European LeukemiaNet, G-CSF-granulocyte colony-stimulating factor. P-values were generated from the stratified Cox proportional hazards models.

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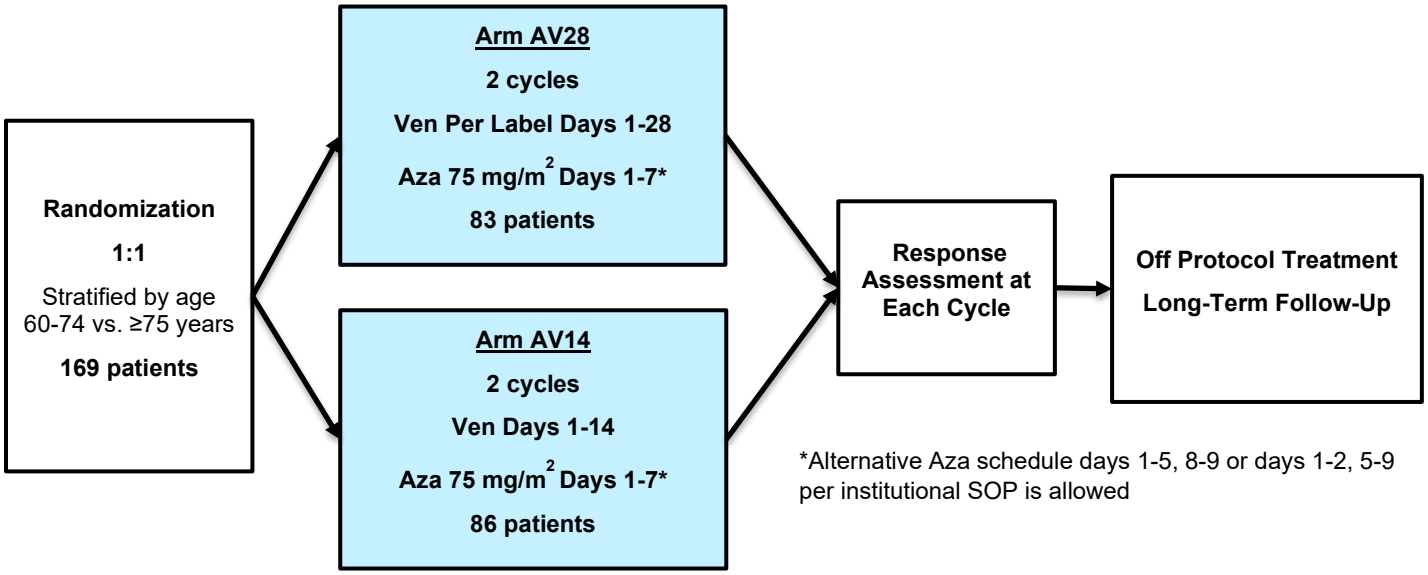
Figure 1. Study Schema and Consort Diagram

A. Study Schema



B. Consort Diagram

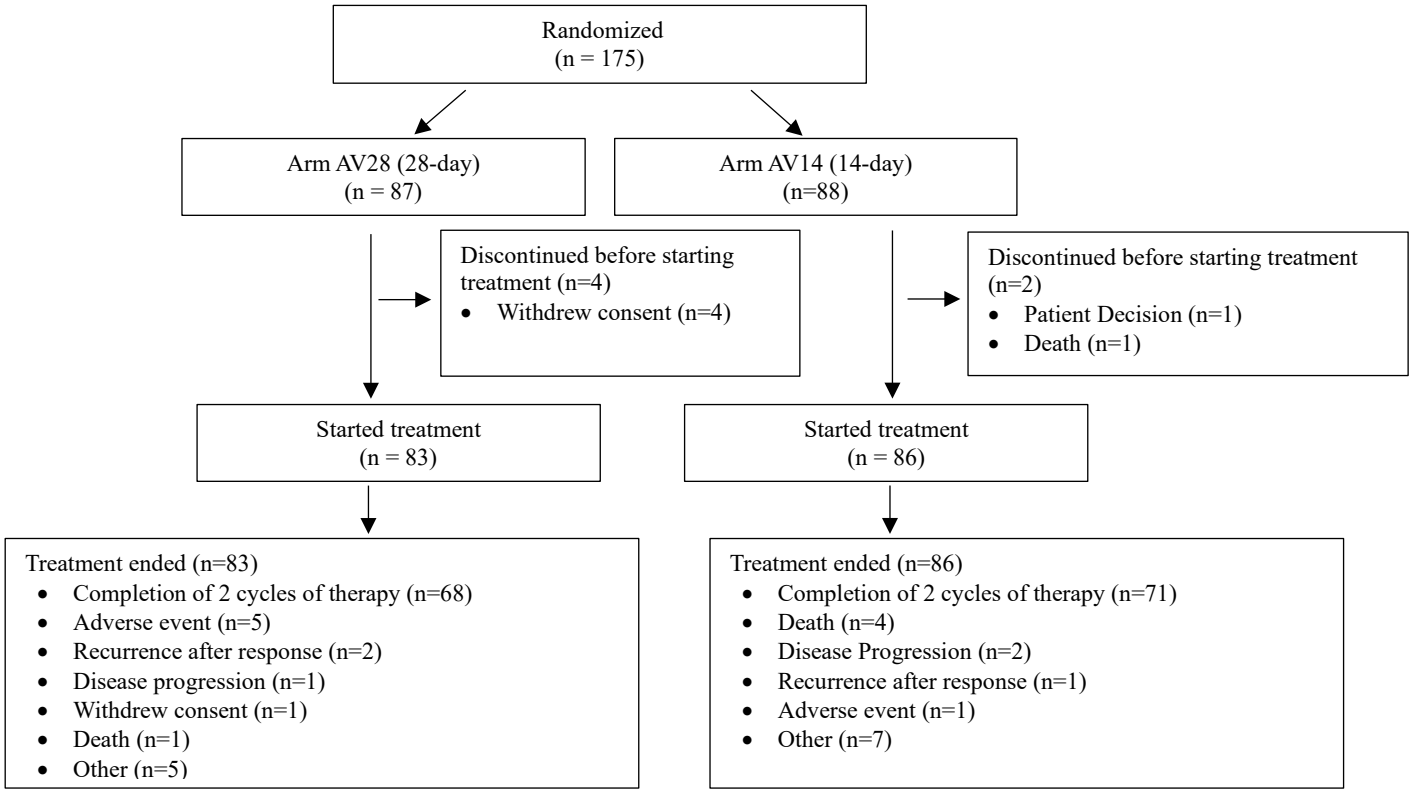


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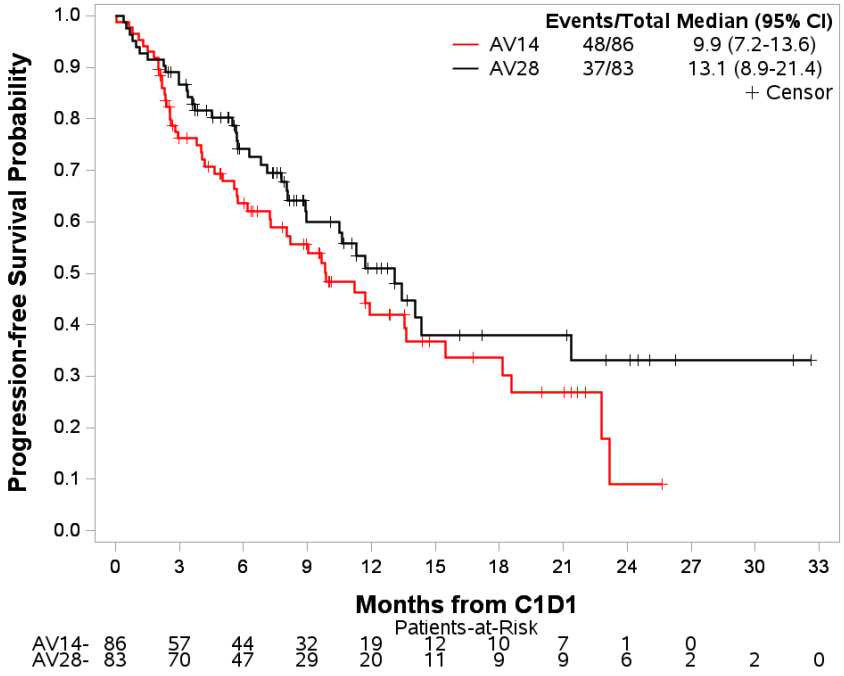
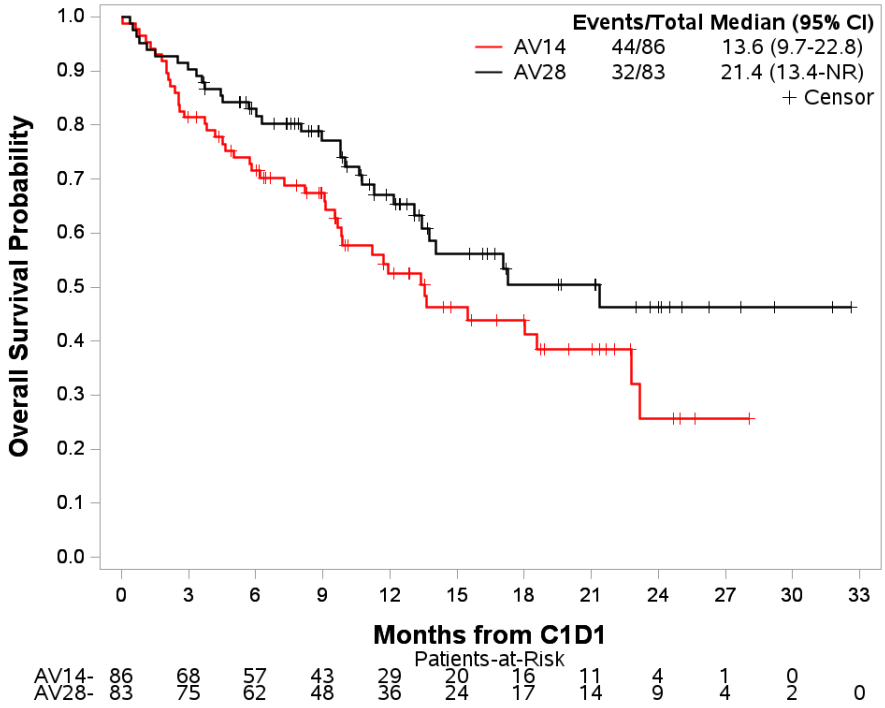
Figure 2. Survival Outcomes

A. Progression-free Survival



B. Overall Survival



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