haematologica
Journal of the Ferrata Storti Foundation

# Cusatuzumab combined with venetoclax with or without azacitidine in unfit patients with newly diagnosed acute myeloid leukemia: phase Ib ELEVATE study

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*Received: March 20, 2026.*
*Accepted: August 25, 2026.*

*Citation: Gail J. Roboz, Thomas Pabst, Ahmed Aribi, Joseph M. Brandwein, Hartmut Döhner, Walter Fiedler, Carsten Riether, Domenica Gandini, Michelle Geddes, Jing-Zhou Hou, Karen Yee, Anna Hultberg, Eric Huselton, Julie Jacobs, Piotr Zabrocki, Ewa Lech-Marańda, Marieke Louwers, Kerri Nottage, Uwe Platzbecker, Raajit Rampal, Masha Salman, Priya Shah, Kayla Wilson, Monic Stuart, Marion Subklewe, Anne Sumbul, Eunice S. Wang, Agnieszka Wierzbowska, Bin Yao, Ravi Patel, Adam George, Nazmul Islam, Clay Smith, Michael Boyiadzis and Gautam Borthakur. Cusatuzumab combined with venetoclax with or without azacitidine in unfit patients with newly diagnosed acute myeloid leukemia: phase Ib ELEVATE study. Haematologica. 2026 Sept 3. doi: 10.3324/haematol.2026.300917 [Epub ahead of print]*

# Cusatuzumab combined with venetoclax with or without azacitidine in unfit patients with newly diagnosed acute myeloid leukemia: phase Ib ELEVATE study

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Running head (max 50 characters): **Cusatuzumab in AML**

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## Data sharing statement

The raw datasets supporting the conclusions in this article are not readily available, however, they can be requested by qualified researchers who engage in rigorous independent scientific research. The sharing of any data will be based upon the review and approval of a research proposal and statistical analysis plan, and the execution of a data sharing agreement between the researcher and the Company. Data requests can be submitted at any time and the data will be accessible for 12 months. Requests to access the datasets should be directed to info@oncoverity.com

ClinicalTrials.gov identifier: NCT04150887


## Acknowledgments

The authors would like to thank all patients and staff who participated in this study. Medical writing support, under the direction of the authors, was provided by Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, with funding from argenx, in accordance with Good Publication Practice (GPP3) guidelines.

## Funding

The trial was funded by Janssen, Pharmaceutical Companies of Johnson & Johnson Innovative Medicine, and OncoVerity in collaboration with argenx.

## Contributions

GR, TP, HD, AW, DG, AH, JJ, PZ, ML,MS, AS, KN, MS contributed to conceptualization. GR, TP, AA, JB, HD, WF, CR, MG, JH, KY, EH, EL, UP, RR, KW, MS, EW, AW, GB contributed patients to the study. GR, MS, BY, RP, AG, NI, CS, MB analyzed the data. GR, MB prepared the initial manuscript. All authors contributed to the preparation of the manuscript and approved the final manuscript.

## Disclosures

Gail J. Roboz, MD: **Consulting or Advisory Role:** AbbVie, Amgen, AstraZeneca, Astellas, Bristol Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, Genoptix GlaxoSmithKline, Geron, Gilead, Glycomimetics, Janssen, Jasper Pharmaceuticals, Jazz Pharmaceuticals, Kyowa Kirin, Molecular Partners, Morphosys, Neogenomics, Novartis, Oncoprecision, Oncoverity, Pfizer, Rigel, Roche, Servier, Syndax, Telix **Research Funding:** AbbVie (Inst), Astex Pharmaceuticals (Inst), Celgene (Inst), CTI (Inst), Karyopharm Therapeutics (Inst), Moffitt (Inst), Novartis (Inst), Pfizer (Inst), Cellectis (Inst), Janssen (Inst). **Travel, Accommodations, Expenses:** Janssen, Novartis, AbbVie, Jazz Pharmaceuticals, Roche/Genentech, Bristol Myers Squibb/Celgene, Servier

Thomas Pabst, MD: no conflict of interest

Ahmed Aribi, MD: Consulting or Advisory Role: Seagen, Seagen

Joseph M. Brandwein, MD: Advisory role with honoraria: AbbVie, Amgen, Astellas, Bristol Myers Squibb, Daiichi Sankyo, Jazz, Pfizer, Servier, Takeda

Hartmut Döhner, Consultancy: AbbVie, CHARM Therapeutics, Servier, Syndax; clinical research funding to institution: AbbVie, Astellas, Bristol Myers Squibb, Jazz Pharmaceuticals, Servier, Syndax; travel, accommodation: Servier

Walter Fiedler, MD: Advisory role: Amgen, ARIAD/Incyte, Novartis, Pfizer; Celgene, Morphosys, Abbvie, Jazz Pharmaceuticals, Stemline, Clinigene, Servier; Royalties: Amgen;

Received support for meeting attendance from Amgen, Gilead, Jazz Pharmaceuticals, Daiichi Sankyo, Servier

Carsten Riether, PhD: Inventor on various patents targeting CD70 in AML

Domenica Gandini, MD, PhD: argenx employee who may have shares and stock options in the company

Michelle Geddes, MD, FRCPC: speaker honoraria from BMS, and has participated in an advisory board for Jazz, Abbvie, Avir, Astellas, BMS, and Novartis.

Jing-Zhou Hou, MD, PhD: Investigator on an AbbVie-funded trial

Karen Yee, MD: no conflict of interest

Anna Hultberg, PhD: argenx employee who may have shares and stock options in the company

Eric Huselton, MD: no conflict of interest

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Ewa Lech-Marańda, MD, PhD: no conflict of interest

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Uwe Platzbecker, MD: has acted as a consultant or advisor to AbbVie, Takeda, Celgene/BMS, Curis, Jazz Pharmaceuticals, Novartis, and Servier; has received clinical

research support to his institution from Astellas, Celgene, Cellectis, Daiichi-Sankyo, FortySeven/Gilead, Novartis, and Rafael Pharmaceuticals; and has received royalties from UpToDate.

Raajit Rampal, MD, PhD:  has received consulting fees from Beyond Spring, Celgene, Constellation, Jazz, Partner Therapeutics, and Stemline and contracted research fees from Constellation and Stemline.

Masha Salman, PhD: employee of Johnson & Johnson who may have shares and stock options in the company

Priya Shah, MBBS: employee of Johnson & Johnson who may have shares and stock options in the company

Monic Stuart, MD, MPH: consultant for argenx

Marion Subklewe, MD: reports receiving research support from Amgen, BMS/Celgene, Gilead/Kite, Janssen, Miltenyi Biotec, Molecular Partners, Novartis, Roche, Seagen, Takeda; participating in speakers' bureaus for AstraZeneca, BMS, Gilead/Kite, GSK, Janssen, Novartis, Pfizer, Roche, Springer Healthcare; serving in a consultancy role or on an advisory board for AbbVie, Amgen, Autolus, AvenCell, BMS, CanCell Therapeutics, Genmab US, Gilead, Ichnos Sciences, Incyte Biosciences, Interius BioTherapeutics, Janssen, Miltenyi Biomedicine, Molecular Partners, Nektar Therapeutics, Novartis, Orbital Therapeutics, Pfizer, Roche, Sanofi, Scare, Takeda; and receiving travel support from Gilead, Pfizer, and Roche.

Anne Sumbul, MSc: previous argenx employee who may have shares and stock options in the company

Eunice S. Wang, MD:  Consulting or Advisory Role: AbbVie, Cullinan, Novartis, Kura Oncology, Daiichi Sankyo/, Menarini, Rigel, Johnson & Johnson/Janssen, Servier, . Speakers' Bureau:  Astellas PharmaTakedaOther Relationship: UpToDate

Agnieszka Wierzbowska, MD, PhD: research grants: Jazz Pharmaceuticals; honoraria: AbbVie, Astellas, BMS/Celgene, Gilead/Kite, Janssen, Novartis, Pfizer, Servier; advisory boards: AbbVie, Astellas, BerGenBio, BMS/Celgene, Gilead/Kite, Janssen, Novartis, Pfizer, Servier.

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Gautam Borthakur, MD: reports research support and honoraria from Astex, Aptevo, Bio Ascend, Bristol Myers Squibb Company, Epigentix, Molecular Partners, Nkarta, Novartis, Pacylex, and Treadwell Therapeutics; and personal/consulting fees from AbbVie, PPD Development, and Lava Therapeutics outside the submitted work. Naval Daver reports grants/research funding from AbbVie, Amgen, Astellas Pharma, Bristol Myers Squibb Company, Daiichi Sankyo Company, FATE Therapeutics, Pfizer Inc., Gilead Sciences Inc., Servier Pharmaceuticals LLC, Genentech USA Inc., ImmunoGen, Trillium, Hanmi, Trovagene, Novimmune, Glycomimetics, and Kite Pharma Inc.; and personal/consulting fees from Daiichi Sankyo Company, Bristol Myers Squibb Company, Pfizer Inc., Gilead Sciences Inc., Servier Pharmaceuticals LLC, Genentech, Astellas Pharma, AbbVie, Trillium, Arog Pharmaceuticals, Amgen, Novartis, Jazz Pharmaceuticals, Celgene, Syndax, Shattuck Labs, Agios Pharmaceuticals, Kite Pharma Inc., and Stemline/Menarini outside the submitted work

## Abstract (227/250 words)

Cusatuzumab is a monoclonal antibody that binds with high affinity to CD70, a cell surface protein overexpressed on CD34+ acute myeloid leukemia (AML) progenitors and leukemia stem cells. This phase Ib study assessed the safety, tolerability and efficacy of adding cusatuzumab to standard-of-care azacitidine and venetoclax (CVA) or a cusatuzumab and venetoclax (CV) doublet regimen in patients newly diagnosed with AML who were ineligible for intensive chemotherapy. Cusatuzumab 20 mg/kg was administered intravenously on days 3 and 17 of 28-day cycles combined with standard dosing of venetoclax ± azacitidine. Overall, 44 patients were treated with CVA. Common hematologic treatment-emergent adverse events (TEAEs) were neutropenia (77.3%), thrombocytopenia (77.3%) and anemia (45.5%); non-hematologic TEAEs included nausea (45.5%), diarrhea (43.2%), constipation (40.9%), fatigue (36.4%) and vomiting (31.8%). Grade ≥3 infectious complications included febrile neutropenia (38.6%), sepsis (36.4%) and pneumonia (9.1%). The overall composite response rate (complete remission [CR] + CR with partial hematologic recovery [CRh] + CR with incomplete hematologic recovery [CRi]) was 77.3% (CR, 47.7%; CRh, 20.5%; CRi, 9.1%). Among CR/CRi responders, 53% achieved negative measurable residual disease by multiparameter flow cytometry. Median overall survival was 12.0 months (95% confidence interval: 8.7-NE) months. Sixteen patients were treated with CV and had similar safety but less favorable responses and survival than those treated with CVA. These results support further development of CVA for the treatment of AML (clinicaltrials.gov identifier: NCT04150887).

## Introduction

Acute myeloid leukemia (AML) is an aggressive, biologically heterogeneous hematopoietic stem cell neoplasm that has poor outcomes in elderly patients.[1] Based on the randomized VIALE-A study, the BCL-2 inhibitor venetoclax (VEN) combined with azacitidine (AZA) became one of the approved standard of care alongside decitabine or low-dose cytarabine for patients with AML who are ≥75 years old or who have comorbidities precluding treatment with intensive chemotherapy.[2] In VIALE-A, complete remission (CR) was higher with AZA + VEN than with AZA + placebo (36.7% *vs.* 17.9%, respectively; *P*<0.001), as was CR or CR with incomplete hematologic recovery (CRi) (66.4% *vs.* 28.3%, respectively; *P*<0.001).[2] The median overall survival (OS) was also significantly longer with VEN + AZA (14.7 *vs.* 9.6 months; hazard ratio, 0.66; 95% confidence interval [CI]: 0.52-0.85).[3] However, despite these improvements, the majority of patients newly diagnosed with AML who are ineligible for transplant still relapse after VEN + AZA, including those who attain initial CR, and long-term survival remains limited.[4,5] Furthermore, patients who relapse after VEN-based low-intensity induction have dismal outcomes, regardless of salvage therapy.[6]

A key driver of AML relapse following VEN-based therapies is the proliferation of residual leukemia stem cells (LSC).[7] LSCs exhibit molecular and metabolic plasticity and become progressively resistant to BCL-2 inhibition by VEN.[8] Cusatuzumab (ARGX-110, referred to as CUSA from here on) is a monoclonal antibody that binds with high affinity to human cell surface receptor CD70. CD70 expression is low to absent on healthy tissues but overexpressed in several hematologic malignancies and solid tumors. CD34+ AML cells (progenitors and

LSCs) express both CD70 and its receptor, CD27. In AML, cell-autonomous CD70/CD27 signaling propagates the disease.[9] CUSA blocks CD70/CD27 signaling, leading to inhibition of LSC proliferation and a reduction in leukemic blasts. CUSA also exerts direct Fc-mediated effector functions, such as enhanced antibody-dependent cellular cytotoxicity.[9-11]

A phase I/II dose-escalation study showed the feasibility of combining CUSA 1-20 mg/kg every 2 weeks with AZA in patients with AML who were ineligible for intensive chemotherapy.[12,13] In the subsequent dose-optimization CULMINATE clinical study assessing CUSA 10 mg/kg or 20 mg/kg combined with AZA 75 mg/m$^2$ in 28-day cycles, an overall response rate (ORR; defined as CR + CR with partial hematological recovery [CRh] + CRi]) of 40% and an acceptable safety profile resulted in CUSA 20 mg/kg being selected as the optimal dose for further clinical studies.[14]

Preclinical data have shown synergy between CUSA and VEN in eliminating LSCs, the major cause of relapse in patients with AML.[15,16] Furthermore, both AZA and VEN have been shown to up-regulate CD70 expression, the target for CUSA, on AML LSCs.[13] The significant unmet need for improved outcomes in AML, the acceptable toxicity of CUSA observed so far and the strong preclinical rationale for a synergistic combination regimen prompted this multicenter, multicohort, phase Ib study of CUSA + VEN ± AZA in patients newly diagnosed with AML who were ineligible for intensive chemotherapy.

## Methods

### Study design

ELEVATE was an open-label, multicohort, multicenter, international, phase Ib study (clinicaltrials.gov identifier: NCT04150887) evaluating CUSA + VEN + AZA (CVA cohort) or CUSA + VEN (CV cohort) in patients newly diagnosed with AML who were ineligible for intensive chemotherapy. Patients who had been previously treated with a hypomethylating agent for antecedent myelodysplastic syndrome and those deemed unlikely to tolerate a triplet regimen based on comorbidities were assigned to receive CV. Following a 28-day (maximum) screening phase, CUSA 20 mg/kg was administered intravenously on days 3 and 17, with VEN 400 mg orally once daily after a three-day ramp-up period to prevent tumor lysis syndrome during cycle 1. In the CVA cohort, subcutaneous or intravenous AZA 75 mg/m$^2$ was administered on days 1-7 of every 28-day cycle in addition to CV. To mitigate infusion-related reactions, acetaminophen, an antihistamine, and corticosteroids were administered before CUSA administration. The treatment schema is summarized in *Online Supplementary Figure S1*, and dose modifications related to cytopenias and/or other adverse events (AEs) are described in the *Online Supplementary Information*. Patients were treated until disease progression, relapse, unacceptable toxicity, withdrawal due to investigator discretion or withdrawal of consent. All consenting patients were followed for survival. Patients received supportive care, including transfusions, growth factor support and antimicrobial agents according to institutional standards. The study was approved by local institutional review boards and conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki of 1975 as revised in 2013. Patients provided written informed consent.

## Participants

Eligible adult patients had previously untreated, histologically confirmed *de novo* or secondary AML and were ineligible for intensive chemotherapy due to age ≥75 years old or age 18-74 years old with at least one significant medical comorbidity (*Online Supplementary Table S1*). Full eligibility criteria are listed in the *Online Supplementary Information*.

## Endpoints and assessments

The primary objective was to assess the safety and tolerability of CUSA + VEN ± AZA, including assessment of treatment-emergent AEs (TEAEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Secondary objectives included pharmacokinetics (PK), immunogenicity, response (ORR, [CR + CRh + CRi], CR, CRh, and CRi, using European LeukemiaNet [ELN] 2017 criteria[17] and morphologic leukemia-free state [MLFS]), time to and duration of response, and time to transfusion independence (TI) (*Online Supplementary Table S2*).

Measurable residual disease (MRD) was assessed centrally by Covance Inc. by multiparameter flow cytometry; negativity was defined as <1 blast in 1,000 leukocytes (MRD $10^{-3}$) (*Online Supplementary Information*). Blood samples were analyzed to determine drug concentrations and presence of anti-CUSA antibodies. Event free survival (EFS) and overall survival (OS) were exploratory analyses. EFS was defined for all patients in the trial measured from treatment day 1 to the date of treatment failure, disease progression, hematologic relapse from CR/CRh/CRi or death from any cause, whichever occurred first; treatment failure was defined as not

achieving either CR, CRh or CRi by 24 weeks and was considered an event on day 1. OS was defined as time from first study treatment dose to death.

### Statistical analyses

All enrolled patient data were included for safety and efficacy analyses. No formal hypothesis testing or comparisons between cohorts were planned. Safety data were summarized descriptively. Response rates were summarized using the number and percentage of patients plus two-sided 95% Clopper-Pearson CIs. The Kaplan-Meier method was used for time-to-event endpoints. PK parameters were derived using descriptive statistics and population PK modeling. The data cutoff was November 9, 2021. EFS and OS analyses were ad hoc. In addition to an OS analysis cut-off in 2021, an OS analysis for the CVA arm was conducted with a cut-off date of 26 February 2025, to identify long-term responders (defined as individuals who survived beyond 2 years following treatment). Statistical analyses were performed using SAS version 9.4 and R.

## Results

The study enrolled 60 patients and was conducted at 19 centers: Poland (9), Canada (14), United States (21), Germany (10) and Switzerland (6).

### CVA cohort: patient characteristics

The CVA cohort included 44 patients enrolled from January 14, 2020 to November 9, 2021. The first three patients enrolled in the United States received 10 mg/kg CUSA intravenously on days 3 and 17 in cycle 1, per regulatory request. No safety concerns were noted by the drug review committee, and the dose was increased to

20 mg/kg from cycle 2 onwards (*Online Supplementary Figure S1*). The median age was 75.0 (range, 32-89) years, 81.8% of patients had an Eastern Cooperative Oncology Group performance score of 1 or 2 and the majority (n=27, 61.4%) had adverse genetic risk per ELN 2017 criteria: *RUNX1*, *TP53*, *FLT3* and *ASXL1* mutations were present in 11 (25.0%), eight (18.2%), six (13.6%) and six (13.6%) patients, respectively. Secondary AML was reported in 16 patients (36.4%). Demographics and baseline disease characteristics are summarized in Table 1. Three patients (6.8%) used prior systemic therapy (hydroxycarbamide for polycythemia vera: n=1; ruxolitinib for myelofibrosis: n=2). Hydroxycarbamide was used for 15 patients (34.1%) for control of leukocytosis prior to starting protocol therapy. Thirty-four patients (77.3%) discontinued study treatment due to progressive or relapsed disease (n=14, 31.8%), TEAEs (n=6, 13.6%), allogeneic hematopoietic cell transplantation (n=6, 13.6%) or death (n=2, 4.5%) (Figure 1).

**CVA cohort: safety and tolerability**

The median duration on study treatment was 6.4 (range, 0.1-15.1) months, and the median number of treatment cycles was four (range, 1.0-14.0). The median relative dose intensity (dose intensity/planned dose intensity*100) of CUSA, VEN and AZA was 100%, 41.9% and 99.7%, respectively. Dose intensity for VEN took into account both dose and duration of treatment including cycle delays, leading to a lower intensity than CUSA and AZA. As expected, based on clinical practice guidelines, the median number of days of VEN administration per cycle decreased after the first cycle, as shown in *Online Supplementary Figure S2*. By cycle 5, the median duration of VEN dosing was 14 days. Dose reductions of AZA were uncommon: six patients had reduced AZA administration, from seven to five days, and three patients had a

dose reduction of AZA to 50% (37.5 mg/m$^2$) for five days. Most patients (n=38, 95%) had cycle delays (median 14.0 [range, 1.0-127.0] days), and hematologic AEs were the most common reason. Thirty-four patients (87%) who achieved remission had a cycle delay due to cytopenia. Delays occurred in 31 patients (70%) due to neutropenia, seven patients (16%) due to neutropenia with thrombocytopenia and four patients (9%) due to thrombocytopenia. Granulocyte colony stimulating factor was used for 30 patients (68.2%).

All patients reported TEAEs (Table 2); 97.7% (n=43) reported grade ≥3 TEAEs. CUSA-related TEAEs of any grade were reported in 33 patients (75%) (Table 2). Twelve patients (27.3%) reported CUSA-related serious AEs. Four patients (9.1%) developed grade 1-2 infusion-related reactions, which included chills, nausea and hypoxia. One patient developed an infusion-related reaction of grade 4 hypoxia, which led to discontinuation of study treatment.

TEAEs are reported in Table 3. The most common hematologic TEAEs were neutropenia, thrombocytopenia and anemia, and most were grade ≥3 (n=42, 95.5%). Common non-hematologic TEAEs included nausea, diarrhea, constipation, fatigue, vomiting, dyspnea and abdominal pain, which were generally grades 1-2. Pneumonia was reported in 6 CVA patients (13.6%), with grade ≥3 in 4 patients (9.1%).

Eight TEAEs leading to treatment discontinuation were reported in six patients (13.6%), including two cases (4.5%) of sepsis and one case (2.3%) each of pneumonia, cerebrovascular accident, intracranial hemorrhage, right hemisphere deficit syndrome, thrombocytopenia and hypoxia.

Treatment-emergent infections of all grades were reported in 59.1% of patients, including most commonly sepsis and pneumonia. Sepsis (definitions detailed in Table 3), occurred in 36.4% of patients. COVID-19 infection was reported in 11.4% of patients; 4.5% were grade ≥3. There was one grade 5 event of pneumonia in a patient with active leukemia not responsive to protocol treatment. No events of laboratory or clinical tumor lysis syndrome were reported.

The rates of 30- and 60-day mortality were 4.5% and 6.8%, respectively. The most common causes of death were related to progressive disease or TEAEs and are presented in *Online Supplementary Table S3*.

**CVA cohort: efficacy**

The investigator-assessed ORR was 77.3% (CR, 47.7%; CRh, 20.5%; CRi, 9.1%), and the composite CR rate was 56.8% (CR, 47.7%; CRi, 9.1%) (Table 4). In an exploratory subgroup analysis, the ORRs in patients with favorable, intermediate and poor ELN 2017 genetic risk were 87.5% (95% CI: 52.9-97.8), 88.9% (95% CI: 56.5-98.0) and 70.4% (95% CI: 51.5-84.1), respectively. The median time to first response (CR, CRh or CRi) was 5.5 (range, 2.4-25.0) weeks; the median duration of response was 29.1 (95% CI: 22.1-45.3) weeks. Based on an *ad hoc* analysis on a separate data cutoff (September 30, 2021), early responses were not limited to patients with a favorable ELN risk status and 27 patients (61%) responded within a mean of 3.4 weeks from baseline at the first disease evaluation (*Online Supplementary Figure S3*).

MRD negativity, assessed centrally by Covance Inc. by multiparameter flow cytometry, was achieved in five (23.8%) of the patients who reached CR and 18

(52.9%) of those who reached CR or CRi. The median time to achieve MRD negativity in these patients was 12 (range, 3.1-34.4) weeks.

In total, 62.5% achieved red blood cell (RBC) TI, 60.0% achieved platelet TI and 57.1% achieved both RBC TI and platelet TI during treatment. The median time to achieve RBC TI, platelet TI and both RBC and platelet TI was 4.6, 2.1 and 4.5 weeks, respectively. The median duration of RBC TI, platelet TI and both RBC and platelet TI was 46.4, 32.6 and 28.1 weeks, respectively.

*Ad hoc* analyses of EFS and OS were conducted. The median EFS was 7.4 (95% CI: 5.75-10.02) months. The median OS was 12.0 (95% CI: 8.7-NE) months at a median follow-up of 43.1 weeks (Figure 2). Although no statistically significant difference in OS was observed between MRD-negative or MRD-positive patients in the CVA cohort (hazard ratio, 0.45; 95% CI: 0.15-1.40; *P*=0.2), the point estimate favored MRD negativity; this finding should be considered exploratory and hypothesis-generating. 32% of the responding patients (11/34) lived for ≥2 years after treatment and median OS was 57.9 months (95% CI: 49.5-NA) in these patients (*Supplementary Figure S4*).

The ELN 2024 classification[18] has been suggested as an alternative prognostic stratification system for patients with AML treated with lower-intensity regimens. An exploratory analysis of this study, limited by small patient numbers in each prognostic group, suggested no differences in OS using ELN 2024 (*Online Supplementary Figure S5*).

**CVA cohort: PK and immunogenicity evaluation**

The median time to maximum serum concentrations of CUSA was 5.21 hours. The mean maximum serum concentration was 386 μg/mL, and the mean area under the curve value was 61,631 μg·h/mL. The mean apparent terminal elimination half-life was 229.9 hours in the CVA cohort. Forty-two samples were available for testing for anti-CUSA antibodies and two patients (4.8%) developed non-neutralizing anti-drug antibodies (ADA). Peak titers were 1:10 and 1:20; one patient developed ADA after the first cycle and one after cycle 2.

**CV cohort: participant characteristics**

Sixteen patients were enrolled in the CV cohort and were included in this analysis. Baseline characteristics are summarized in *Online Supplementary Table S4*. Over half (56.3%) had an ECOG PS of 2, and five (31.3%) had prior AZA treatment for myelodysplastic syndrome. Compared with the CVA arm, patients in the CV cohort were older (75% were aged >75 years old) and had more co-morbidities (69% had cardiac, renal or lung comorbidities), with inferior ECOG performance status (56% had ECOG PS 2); 31% had prior HMA. As of November 9, 2021, all 16 patients in the CV cohort had discontinued treatment (Figure 1).

**CV cohort: safety and tolerability**

The median (range) duration of treatment was 2.0 (0.3-8.0) months, and a median (range) of 2.5 (1.0-8.0) cycles were delivered. The median relative dose intensity of CUSA and VEN was 100% and 82.9%, respectively, and the median days of VEN administration per cycle decreased from cycle 1 to cycle 8 (*Online Supplementary*

*Figure S6*). Cycle delays were reported for seven patients (58.3%), for which AEs were the most common reason (n=5, 41.7%).

Grade ≥3 TEAEs occurred in 15 patients (93.8%). CUSA-related TEAEs of any grade occurred in 12 patients (75.0%) (*Online Supplementary Table S5*), the most common of which were thrombocytopenia, chills and febrile neutropenia (*Online Supplementary Table S6*). CUSA-related serious AEs occurred in five patients (31.3%). Four patients in the CV arm reported pneumonia, all grade ≥3. There were 3 grade 5 sepsis events, two of which occurred in patients with active leukemia who were not responding to protocol treatment.

**CV cohort: efficacy**

Investigator-assessed ORR rate was 25.0%, and the composite CR rate was 25% (n=4; CR, 12.5% [n=2]; CRh, 0%; CRi, 12.5%[n=2]) (*Online Supplementary Table 7*). Median time to first response (CR, CRh or CRi) was 9.1 (range, 3.3-11.4) weeks and median duration of response was 14.4 (range 2.4-NE) weeks. MRD negativity was achieved in 1/4 (25.0%) patients who reached CR or CRi. In total, 15.4% achieved RBC TI, 28.6% achieved platelet TI and 15.4% achieved both RBC TI and platelet TI during treatment. Ad hoc analyses identified protocol-defined failure events in all 16 patients, with median EFS of 0.03 (95% CI: 0.03-0.03) months. Median OS to be 3.4 (95% CI: 1.3-7.6) months at a median follow-up of 14.8 weeks (*Online Supplementary Table S7).*

Subgroup analyses by ELN genetic risk could not be performed in the CV cohort due to small sample size.

### CV cohort: PK and immunogenicity evaluation

PK data for the CV cohort can be found in *Online Supplementary Table S8*. Overall, 14 patients had samples available for testing for anti-CUSA antibodies. Six patients (42.9%) developed non-neutralizing ADA, with peak titers1:5 (n=3), 1:10 (n=2) and 1:40 (n=1). Five positive results developed after the first cycle, and one developed after cycle 2. There was a slight trend for mean serum concentration-time profiles of CUSA to be marginally lower in anti-CUSA antibody–positive *versus* –negative patients, although comparison is limited due to the small sample size.

## Discussion

This phase Ib study assessed the combination of CUSA with or without VEN and AZA for the treatment of patients newly diagnosed with AML who were ineligible for intensive chemotherapy due to advanced age, poor performance status or medical comorbidities. The study results support previous data suggesting favorable safety and efficacy of CUSA in this patient population.[12,14] The CULMINATE study evaluated the combination of CUSA and AZA in adults with newly diagnosed AML who were ineligible for intensive chemotherapy; the CR rate in patients receiving CUSA 20 mg/kg was 27% (14 of 52), with median OS 9.9 (range, 5.5-16.2) months.[14] RBC, platelet, and both RBC and platelet TI were achieved in 42%, 52%, and 37% of patients, respectively.[14] In the current study, CUSA combined with VEN and AZA resulted in improved responses, OS and TI rates compared with CUSA and AZA in CULMINATE and compared with the CV cohort in the present study. As with prior studies, CUSA-related infusion-related reactions were usually mild or moderate in intensity and were generally managed successfully with supportive care.[12] The PK

data for CUSA 20 mg/kg were consistent with previous clinical investigations, demonstrating approximate dose proportionality and a terminal half-life of 8-11 days.[10,14] Limitations of this study include the relatively small sample size and non-randomized design, which may restrict generalizability of results.

The most common TEAEs were hematologic toxicities and infections, as expected for patients with AML undergoing treatment with AZA and VEN. Hematologic AEs were managed through delays in treatment cycles and reductions in VEN dosing days and rarely led to premature study discontinuation; treatment-related mortality was low. While cross-study comparisons should be interpreted with caution, the myelosuppression observed in ELEVATE was similar to that reported for VEN-AZA combined with magrolimab immunotherapy in the ENHANCE-3 study, in which common grade ≥3 hematologic TEAEs (≥15%) were reported as neutropenia (62%), anemia (43%), thrombocytopenia (36%) and febrile neutropenia (33%).[19] Despite ELEVATE having been conducted during the height of the COVID-19 pandemic, only one death was attributed to COVID-19. Overall, the safety events observed with CUSA-VEN-AZA were comparable to those reported in other VEN-AZA studies of the same AML population. For example in ELEVATE, all-grade pneumonia was reported in 6 patients (13.6%, with 4 [9.1%] grade ≥3) in the CVA cohort and in 4 patients (25.0%, all grade ≥3) in the CV cohort. Pneumonia TEAEs were reported in 26% of patients (23% grade ≥3) on the VEN-AZA arms of the VIALE-A study, 15% of patients (10% grade ≥3) of the ENHANCE-3 study of VEN-AZA combined with magrolimab immunotherapy and in the CUSA 20mg/m$^2$-AZA arm of the phase 2 study 25% all grade (12% grade ≥3).[5,14,19]

Although VEN + AZA is the worldwide standard of care for older patients with AML or those unable to undergo intensive induction,[20] OS is limited, and cure is almost non-existent. In the registrational VIALE-A study, 27% of deaths were attributed to progressive disease, highlighting the need for novel combinations.[2] Many three drug regimens combining hypomethylating agents with VEN and novel agents are under investigation to improve outcomes in this patient population.[21,22] ELEVATE was rationally designed based on preclinical data suggesting a synergistic mechanism of action between CUSA and VEN: by increasing CD70 expression on AML LSCs, VEN exposure may sensitize LSCs to CUSA-mediated cytolytic activity, potentially enhancing eradication of LSC populations resistant to BCL-2 inhibition by VEN.[13,15] The efficacy results from the CVA triplet in ELEVATE are encouraging with ORR 77.3% and 53% MRD negativity. The regimen was effective across all risk groups, with CR/CRi 70.4% in adverse risk patients. 32% of responding patients lived beyond 2 years after treatment and importantly, 13.6% of the patients were able to proceed with allogeneic hematopoietic stem cell transplantation. Based on the promising safety and efficacy results a phase II, randomized, open-label, multicenter, multinational trial evaluating the efficacy and safety of VEN + AZA + CUSA compared with VEN + AZA in patients with newly diagnosed AML who are ineligible for intensive chemotherapy is in progress (NCT06384261).

## References


1. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.

2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.

3. U.S. Food & Drug Administration. FDA approves venetoclax in combination for AML in adults. https://www.fda.gov/drugs/fda-approves-venetoclax-combination-aml-adults Accessed November 14, 2025.

4. Othman J, Lam HPJ, Leong S, et al. Real-world outcomes of newly diagnosed AML treated with venetoclax and azacitidine or low-dose cytarabine in the UK NHS. Blood Neoplasia. 2024;1(3):100017.

5. Pratz KW, Jonas BA, Pullarkat V, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024;99(4):615-624.

6. Maiti A, Rausch CR, Cortes JE, et al. Outcomes of relapsed or refractory acute myeloid leukemia after frontline hypomethylating agent and venetoclax regimens. Haematologica. 2021;106(3):894-898.

7. Stelmach P, Trumpp A. Leukemic stem cells and therapy resistance in acute myeloid leukemia. Haematologica. 2023;108(2):353-366.

8. Nachmias B, Aumann S, Haran A, Schimmer AD. Venetoclax resistance in acute myeloid leukaemia—clinical and biological insights. Br J Haematol. 2024;204(4):1146-1158.

9. Riether C, Schürch CM, Bührer ED, et al. CD70/CD27 signaling promotes blast stemness and is a viable therapeutic target in acute myeloid leukemia. J Exp Med. 2017;214(2):359-380.

10. Aftimos P, Rolfo C, Rottey S, et al. Phase I dose-escalation study of the anti-CD70 antibody ARGX-110 in advanced malignancies. Clin Cancer Res. 2017;23(21):6411-6420.

11. Silence K, Dreier T, Moshir M, et al. ARGX-110, a highly potent antibody targeting CD70, eliminates tumors via both enhanced ADCC and immune checkpoint blockade. MAbs. 2014;6(2):523-532.

12. Pabst T, Vey N, Adès L, et al. Results from a phase I/II trial of cusatuzumab combined with azacitidine in patients with newly diagnosed acute myeloid leukemia who are ineligible for intensive chemotherapy. Haematologica. 2023;108(7):1793-1802.

13. Riether C, Pabst T, Höpner S, et al. Targeting CD70 with cusatuzumab eliminates acute myeloid leukemia stem cells in patients treated with hypomethylating agents. Nat Med. 2020;26(9):1459-1467.

14. Pabst T, Papayannidis C, Demirkan F, et al. Cusatuzumab plus azacitidine in newly diagnosed acute myeloid leukaemia ineligible for intensive chemotherapy (CULMINATE): part one of a randomised, phase 2, dose optimisation study. Lancet Haematol. 2023;10(11):e902-e912.

15. Riether C, Chiorazzo T, Johnson AJ, et al. The combination of the BCL-2 antagonist venetoclax with the CD70-targeting antibody cusatuzumab synergistically eliminates primary human leukemia stem cells. Blood. 2019;134(Supplement_1):3918.

16. Pollyea DA, Stevens BM, Jones CL, et al. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med. 2018;24(12):1859-1866.

17. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.

18. Döhner H, DiNardo CD, Appelbaum FR, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024;144(21):2169-2173.

19. Daver N, Vyas P, Huls G, et al. The ENHANCE-3 study: venetoclax and azacitidine plus magrolimab or placebo for untreated AML unfit for intensive therapy. Blood. 2025;146(5):601-611.

20. Forsberg M, Konopleva M. Therapy for acute myeloid leukemia in older and unfit adults. Haematologica. 2024;109(12):3832-3834.

21. Short NJ, Daver N, Dinardo CD, et al. Azacitidine, venetoclax, and gilteritinib in newly diagnosed and relapsed or refractory *FLT3*-mutated AML. J Clin Oncol. 2024;42(13):1499-1508.

22. Venugopal S, Takahashi K, Daver N, et al. Efficacy and safety of enasidenib and azacitidine combination in patients with IDH2 mutated acute myeloid leukemia and not eligible for intensive chemotherapy. Blood Cancer J. 2022;12(1):10.

# Tables

**Table 1.** Demographics and baseline disease characteristics in the CVA cohort.

| **Characteristics** | | **CVA (N=44** |
|---|---|---|
| Age, years | Median (range) | 75.0 (32.0-89.0) |
| | ≥75 years, n (%) | 25 (56.8) |
| Sex, n (%) | Male | 25 (56.8) |
| | Female | 19 (43.2) |
| Race, n (%) | White | 38 (86.4) |
| | Black | 2 (4.5) |
| | Asian | 1 (2.3) |
| | Not reported or unknown | 3 (6.8) |
| Geographic region, n (%) | North America | 29 (65.9) |
| | Europe | 15 (34.1) |
| Type of AML, n (%) | *De novo* | 28 (63.6) |
| | Secondary | 16 (36.4) |
| ECOG PS, n (%) | 0 | 8 (18.2) |
| | 1 | 18 (40.9) |
| | 2 | 18 (40.9) |
| 2017 ELN risk category, n (%) | Favorable | 8 (18.2) |
| | Intermediate | 9 (20.5) |
| | Adverse | 27 (61.4) |
| Cytogenetic abnormalities, n (%) | Complex | 12 (27.3) |
| | Del 5q | 9 (20.5) |
| | Monosomy 7 | 6 (13.6) |
| Somatic mutations, n (%) | *IDH1/IDH2* | 11 (25.0) |
| | *RUNX1* | 11 (25.0) |
| | *NPM1* | 8 (18.2) |
| | *TP53* | 8 (18.2) |
| | *FLT-3 ITD or TKD* | 6 (13.6) |
| | *ASXL1* | 6 (13.6) |
| | *CEBPA* | 4 (9.1) |
| Baseline bone marrow blast count aspiration (%) | N | 42 |
| | Median (range) | 49 (13-97) |
| Baseline peripheral blast count (%), median (range) | | 17.5 (0-88) |
| Baseline transfusion dependence, n (%) | RBCs or platelets | 28 (63.6) |
| | RBCs | 24 (54.5) |
| | Platelets | 15 (34.1) |

AML: acute myeloid leukemia; CVA: cusatuzumab + venetoclax + azacitidine; ECOG PS: Eastern Cooperative Oncology Group performance status; ELN: European LeukemiaNet; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; RBC: red blood cell.

**Table 2.** Overall summary of TEAEs: all treated patients in the CVA cohort.

| **n (%)** | | **CVA N=44** |
|---|---|---|
| Patients with ⩾1 TEAE | All | 44 (100) |
| | CUSA-related TEAE | 33 (75.0) |
| | Grade ≥3 TEAE | 43 (97.7) |
| Treatment-emergent SAE | All | 34 (77.3) |
| | CUSA-related SAE | 12 (27.3) |
| | Grade ≥3 SAE | 33 (75.0) |
| TEAEs leading to discontinuation of any study drug | | 6 (13.6) |
| Grade 5 TEAEs | | 6 (13.6) |

AE: adverse event; CUSA: cusatuzumab; CVA: cusatuzumab + venetoclax + azacitidine; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

**Table 3.** All grades and grade ⩾3 TEAEs following treatment with CVA reported in ⩾20% of all treated patients in the CVA cohort.

| TEAE, n (%) | | CVA (N=44) | |
|---|---|---|---|
| | | All grades | Grade ≥3 |
| Hematologic TEAEs | Neutropenia | 34 (77.3) | 34 (77.3) |
| | Thrombocytopenia | 34 (77.3) | 33 (75.0) |
| | Anemia | 20 (45.5) | 19 (43.2) |
| | Febrile neutropenia | 17 (38.6) | 17 (38.6) |
| | Leukopenia | 14 (31.8) | 14 (31.8) |
| Infections | Sepsis[a] | 16 (36.4) | 16 (36.4) |
| Non-hematologic TEAEs | Nausea | 20 (45.5) | 1 (2.3) |
| | Hypokalemia | 20 (45.5) | 5 (11.4) |
| | Diarrhea | 19 (43.2) | 1 (2.3) |
| | Constipation | 18 (40.9) | 1 (2.3) |
| | Fatigue | 16 (36.4) | 3 (6.8) |
| | Vomiting | 14 (31.8) | 0 |
| | Decreased appetite | 14 (31.8) | 1 (2.3) |
| | Dyspnea | 13 (29.5) | 0 |
| | Abdominal pain | 12 (27.3) | 1 (2.3) |
| | Hypocalcemia | 12 (27.3) | 2 (4.5) |
| | Hypophosphatemia | 12 (27.3) | 0 |
| | Dizziness | 12 (27.3) | 1 (2.3) |
| | Insomnia | 11 (25.0) | 0 |
| | Peripheral edema | 10 (22.7) | 1 (2.3) |
| | Pyrexia | 10 (22.7) | 0 |
| | Blood creatinine increased | 10 (22.7) | 0 |

CVA: cusatuzumab + venetoclax + azacitidine; TEAE: treatment-emergent adverse event. [a]Sepsis was reported as abdominal sepsis, bacteremia, bacterial sepsis, *Enterobacter* bacteremia, intestinal sepsis, *Klebsiella* bacteremia, *Pseudomonas* bacteremia, pulmonary sepsis, *Salmonella* bacteremia, sepsis, septic shock, *Staphylococcal* bacteremia.

**Table 4.** Best response to CVA according to investigator in all treated patients.

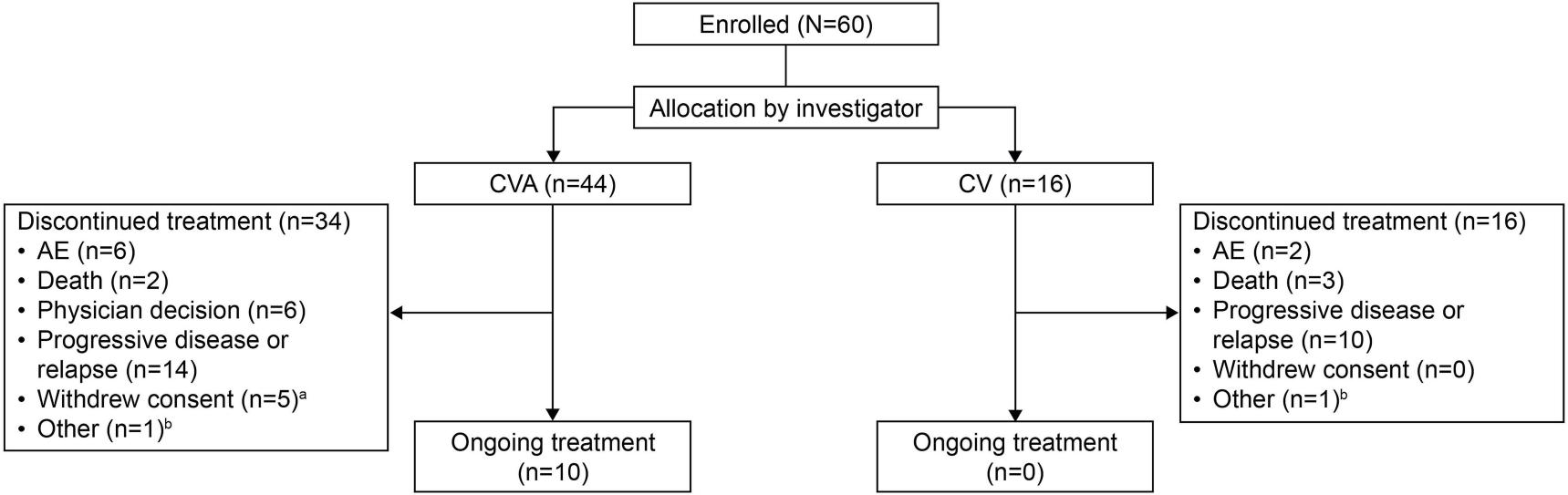
| **Response** | **CVA N=44** |
|---|---|
| ORR (CR + CRh + CRi), n (% [95% CI]) | 34 (77.3 [63.0–87.2]) |
| CR, n (% [95% CI]) | 21 (47.7 [33.8, 62.1]) |
| CRi, n (% [95% CI]) | 4 (9.1 [3.6, 21.2]) |
| CRh, n (% [95% CI]) | 9 (20.5 [11.2, 34.5]) |
| MLFS, n (%) | 5 (11.4) |
| Combined CR (CR + CRh + CRi) + MLFS, % | 88.7 |
| Not evaluable,[a] n (%) | 2 (4.5) |
| MRD negativity in responders after initial response of CR/CRi, n (%)[b] | 18 (52.9) |

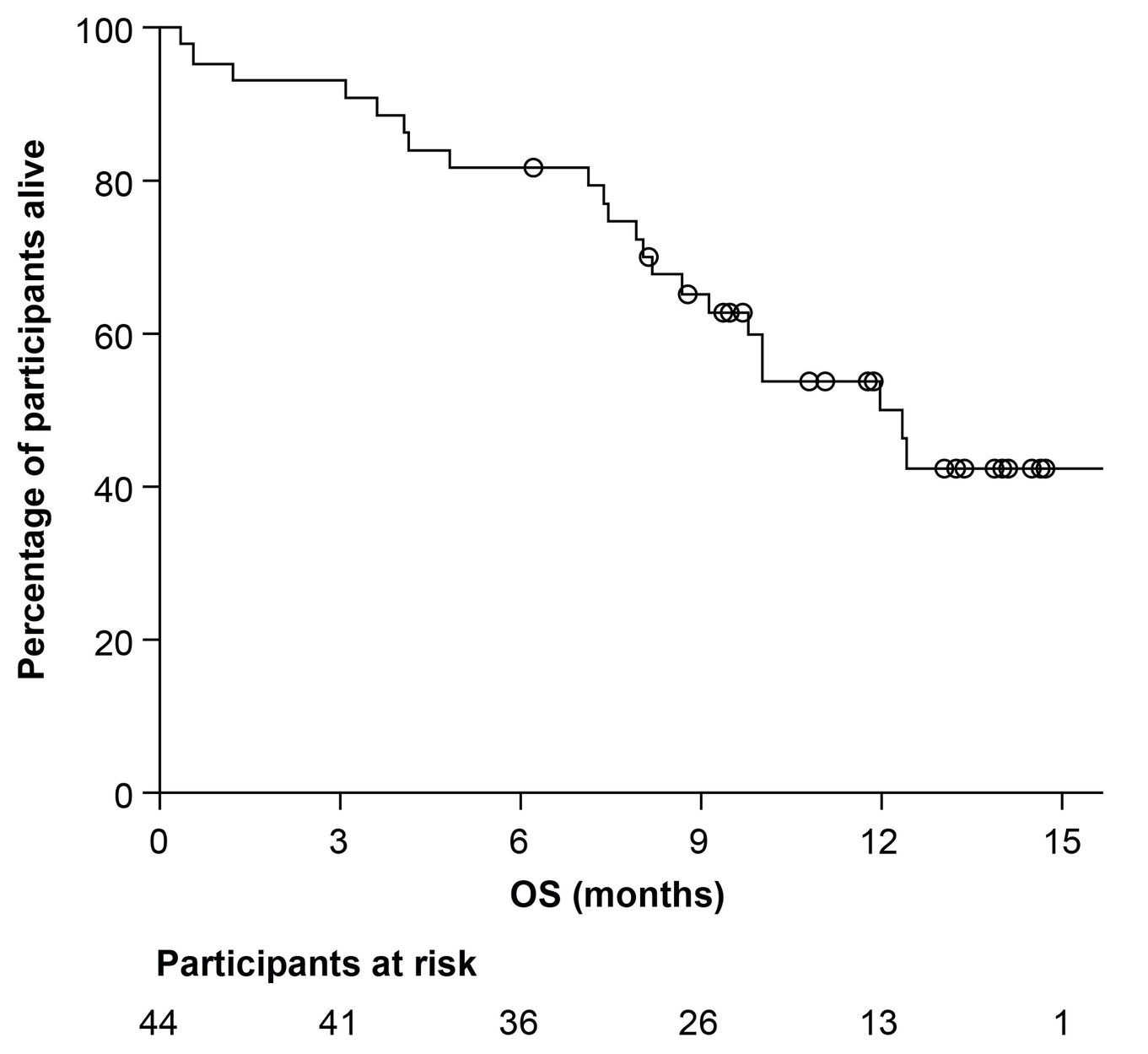
CI: confidence interval; CR: complete remission; CRh: complete remission with partial hematologic recovery; CRi: complete remission with incomplete hematologic recovery; CVA: cusatuzumab + venetoclax + azacitidine; MLFS: morphologic leukemia-free state; MRD: measurable residual disease; ORR: overall response rate. [a]Two patients who did not have a post-baseline disease evaluation. [b]Among 34 responders (those with best response of CR/CRi per investigator assessment)

## Figure legends

**Figure 1. Patient disposition.** AE: adverse event; CV: cusatuzumab + venetoclax; CVA: cusatuzumab + venetoclax + azacitidine. [a]Reasons for patient withdrawal of consent included commuting difficulties, refusal to continue with study procedures, opted for palliative end-of-life care and refusal to continue due to long treatment interruptions due to therapy-induced myelosuppression. [b]Included lack of benefit/efficacy.

**Figure 2. Kaplan-Meier curve of OS in the CVA cohort at median follow-up of 43.1 weeks.** CVA: cusatuzumab + venetoclax + azacitidine; OS: overall survival.


Enrolled (N=60)
Allocation by investigator
CVA (n=44)
CV (n=16)
Discontinued treatment (n=34)
• AE (n=6)
• Death (n=2)
• Physician decision (n=6)
• Progressive disease or relapse (n=14)
• Withdrew consent (n=5)[a]
• Other (n=1)[b]
Ongoing treatment (n=10)
Ongoing treatment (n=0)
Discontinued treatment (n=16)
• AE (n=2)
• Death (n=3)
• Progressive disease or relapse (n=10)
• Withdrew consent (n=0)
• Other (n=1)[b]


Percentage of participants alive
100
80
60
40
20
0
0
3
6
9
12
15
OS (months)
Participants at risk
44
41
36
26
13
1

# Supplementary files

## Cusatuzumab combined with venetoclax with or without azacitidine in unfit patients with newly diagnosed acute myeloid leukemia: phase Ib ELEVATE study

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**Supplementary Table S1.** Key eligibility criteria in ELEVATE.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Diagnosis of AML according to WHO 2016 criteria[1] | Patients with APL |
| *De novo* or secondary AML | Leukemic involvement in the CNS |
| Previously untreated[a] | Use of immune suppressive agents for the 4 weeks before the first administration of CUSA[b] |
| Ineligible for intensive chemotherapy based on the following criteria:<br>a) ≥75 years of age, or<br>b) 18-74 years of age with ⩾1 of the following comorbidities:<br>• Severe cardiac morbidity[c]<br>• Severe pulmonary comorbidity[d]<br>• Moderate hepatic impairment[e]<br>• CrCl 30 mL/min/1.73 $m^2$ to <45 mL/min/1.73 $m^2$[f]<br>• Comorbidity that, in the investigator's opinion, makes the patient unsuitable for intensive chemotherapy[g] | Eligible for an allogeneic hematopoietic stem cell transplantation at study entry |
| ECOG PS score of 0, 1 or 2 | |
| Adequate liver and renal function[h] | |

AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; CNS: central nervous system; CrCl: creatinine clearance; CUSA, cusatuzumab; ECOG PS: Eastern Cooperative Oncology Group performance status; WHO: World Health Organization. [a]Except: emergency leukapheresis, hydroxyurea and/or one dose of 1-2 g/$m^2$ cytarabine prior to study entry to control hyperleukocytosis. Must be discontinued ≥24 hours prior to start of study drug. [b]Patients may only be included if free of systemic corticosteroids for a minimum of 5 days before the first administration of cusatuzumab with the exception of corticosteroids at physiologic replacement doses. [c]Defined as congestive heart failure or ejection fraction

≤50%. [d]Defined as documented pulmonary disease with lung-diffusing capacity for carbon monoxide ≤65% of expected or forced expiratory volume in 1 second ≤65% of expected. [e]Defined according to National Cancer Institute organ dysfunction classification criteria (total bilirubin ≥1.5 up to 3 × upper limit of normal [ULN]). [f]By Modification of Diet in Renal Disease formula. [g]Must be documented and approved by the sponsor before enrollment. [h]Aspartate transferase and alanine transferase <3 × ULN; total bilirubin ≤1.5 × ULN, unless the bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin; CrCl ≥30 mL/min/1.73 $m^2$ (by Modification of Diet in Renal Disease formula).

**Supplementary Table S2.** Key secondary endpoint criteria.

| Response | Definition |
|---|---|
| CR[2,3] [a] | Bone marrow blasts <5%; absence of circulating blasts[b] and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × $10^9$/L (1,000/μL); platelet count ≥100 × $10^9$/L (100,000/μL) |
| CRi[2,3] | All CR criteria except for residual neutropenia (<1.0 × $10^9$/L [1,000/μL]) or thrombocytopenia (<100 × $10^9$/L [100,000/μL]) |
| CRh | All CR criteria except for residual neutropenia (ANC >0.5 × 109/L [500/μL]) and thrombocytopenia (platelets >50 × $10^9$/L [50,000/μL]) |
| MLFS[2,3] | Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required |
| ORR | Composite of CR, CRi and CRh |
| Time to response | Time from first dose to achieving the first response of CR, CRh, or CRi |
| Duration of response | Time from achieving the first response of CR, CRh, or CRi to hematologic relapse or death of any cause |
| TI | A period of ≥56 consecutive days with no transfusion between first dose of study drug and the last dose of study drug + 30 days |

ANC: absolute neutrophil count; CBC: complete blood count; CR: complete remission; CRi: CR with incomplete hematologic recovery; CRh: CR with partial hematologic recovery; G-CSF: granulocyte colony-stimulating factor; MLFS: morphologic leukemia-free state; ORR: overall response rate; TI: transfusion independence.

[a]In subjects with bone marrow remission who require G-CSF for support of neutropenia, the CBC used for response assessment should be at least 5 days after the last dose of G-CSF. Hematology values within 14 days from the bone marrow sample can be used to determine response. Recovery of both neutrophils and platelets needs to be documented on the same CBC. [b]Unless a low level of circulating blasts can be attributed to a recent G-CSF administration.

**Supplementary Table S3.** Summary of deaths in all treated participants.

| **n (%)** | | **CVA N=44** | **CV N=16** |
|---|---|---|---|
| Deaths | All deaths | 22 (50.0) | 15 (93.8) |
| | AE | 6 (13.6) | 5 (31.3) |
| | Progressive disease | 8 (18.2) | 4 (25.0) |
| | Other[a,b] | 8 (18.2) | 6 (37.5) |
| Deaths ≤30 days after first dose of study treatment | All reasons | 2 (4.5) | 0 |
| | AE | 1 (2.3) | 0 |
| | Other[b] | 1 (2.3) | 0 |
| Deaths ≤60 days after first dose of study treatment | All reasons | 3 (6.8) | 5 (31.3) |
| | AE | 2 (4.5) | 2 (12.5) |
| | Progressive disease | 0 | 3 (18.8) |
| | Other[b] | 1 (2.3) | 0 |
| Deaths ≤30 days after last dose of study treatment | All reasons | 7 (15.9) | 8 (50.0) |
| | AE | 6 (13.6) | 5 (31.3) |
| | Progressive disease | 0 | 3 (18.8) |
| | Other[b] | 1 (2.3) | 0 |
| Deaths ≤60 days after last dose of study treatment | All reasons | 10 (22.7) | 9 (56.3) |
| | AE | 6 (13.6) | 5 (31.3) |
| | Progressive disease | 0 | 3 (18.8) |
| | Other[b] | 4 (9.1) | 1 (6.3) |

AE: adverse event; CV: cusatuzumab + venetoclax; CVA: cusatuzumab + venetoclax + azacitidine. [a]CVA cohort “other” includes one death due to COVID-19, one death due to pneumonia, one death due to post-transplant complications, one elected medical assistance in dying and four due to an unknown cause. CV cohort “other” includes one death due to multiorgan failure, one had no information and four were due to an unknown cause. [b]CVA cohort “other” includes one participant who had fatal pneumonia that started after the start of subsequent therapy but was considered related to study medications.

**Supplementary Table S4.** Demographics and baseline characteristics of the CV cohort.

| **Characteristics** | | | **CV N=16** |
|---|---|---|---|
| Age, years | Median (range) | | 78.0 (72-87) |
| | ≥75 years, n (%) | | 13 (81.3) |
| Sex, n (%) | Male | | 8 (50.0) |
| | Female | | 8 (50.0) |
| Race, n (%) | White | | 14 (87.5) |
| | Black | | 0 |
| | Asian | | 2 (12.5) |
| | Not reported or unknown | | 0 |
| Type of AML, n (%) | *De novo* | | 8 (50.0) |
| | Secondary | All | 8 (50.0) |
| | | History of MDS | 6 (75.0) |
| | | History of MPN | 2 (25.0) |
| | | Therapy-related | 0 |
| | | Unknown | 0 |
| ECOG PS, n (%) | 0 | | 2 (12.5) |
| | 1 | | 5 (31.3) |
| | 2 | | 9 (56.3) |
| 2017 ELN risk category[3], n (%) | Favorable | | 2 (12.5) |
| | Intermediate | | 4 (25.0) |
| | Adverse | | 10 (62.5) |
| Cytogenetic abnormalities, n (%) | Complex | | 2 (12.5) |
| | Del 5q | | 1 (6.3) |
| | Monosomy 7 | | 2 (12.5) |
| Somatic mutations, n (%) | *IDH1/IDH2* | | 7 (43.8) |
| | *RUNX1* | | 6 (37.5) |
| | *NPM1* | | 4 (25.0) |
| | *TP53* | | 1 (6.3) |
| | *FLT-3 ITD or TKD* | | 6 (37.5) |
| | *ASXL1* | | 3 (18.8) |
| | *CEBPA* | | 1 (6.3) |
| Prior AZA use for MDS, n (%) | Yes | | 5 (31.3) |
| Baseline bone marrow blast count aspiration (%) | N | | 15 |
| | Median (range) | | 47.6 (18.0-90.0) |
| Baseline peripheral blast count (%) | Median (range) | | 32 (0-86.0) |
| Baseline transfusion dependence, n (%) | RBCs or platelets | | 13 (81.3) |
| | RBCs | | 13 (81.3) |
| | Platelets | | 7 (43.8) |

AML: acute myeloid leukemia; AZA: azacitidine; CV: cusatuzumab + venetoclax; ECOG PS: Eastern Cooperative Oncology Group performance status; ELN: European

LeukemiaNet; MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; RBC: red blood cell.

**Supplementary Table S5.** Overall summary of TEAEs: all treated participants in the CV cohort.

| **n (%)** | | **CV N=16** |
|---|---|---|
| **Participants with ≥1** | TEAE | 16 (100) |
| | CUSA-related AE | 12 (75.0) |
| | Grade ≥3 AE | 15 (93.8) |
| **Treatment-emergent SAEs** | Any | 13 (81.3) |
| | CUSA-related SAE | 5 (31.3) |
| | Grade ≥3 SAE | 12 (75.0) |
| **TEAEs leading to discontinuation of any study drug** | | 2 (12.5) |
| **Grade 5 TEAEs** | | 5 (31.3) |

AE: adverse event; CUSA: cusatuzumab; CV: cusatuzumab + venetoclax; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

**Supplementary Table S6.** All grades and grade ≥3 TEAEs following treatment with CV reported in ≥10% of all treated participants in the CV cohort.

| **TEAE, n (%)** | | **CV N=16** | |
|---|---|---|---|
| | | **All grades** | **Grade ≥3** |
| Hematologic TEAEs | Neutropenia | 8 (50.0) | 8 (50.0) |
| | Thrombocytopenia | 10 (62.5) | 10 (62.5) |
| | Anemia | 5 (31.3) | 4 (25.0) |
| | Febrile neutropenia | 5 (31.3) | 5 (31.3) |
| | Leukopenia | 2 (12.5) | 2 (12.5) |
| | Lymphopenia | 2 (12.5) | 2 (12.5) |
| Infections | Sepsis[a] | 4 (25.0) | 4 (25.0) |
| | Pneumonia[b] | 4 (25.0) | 4 (25.0) |
| | *Clostridioides difficile* colitis | 4 (25.0) | 3 (18.8) |
| Non-hematologic TEAEs | Nausea | 6 (37.5) | 0 |
| | Hypokalemia | 10 (62.5) | 4 (25.0) |
| | Diarrhea | 4 (25.0) | 0 |
| | Constipation | 5 (31.3) | 0 |
| | Fatigue | 3 (18.8) | 0 |
| | Vomiting | 0 | 0 |
| | Decreased appetite | 3 (18.8) | 0 |
| | Dyspnea | 3 (18.8) | 1 (6.3) |
| | Abdominal pain | 3 (18.8) | 0 |
| | Hypocalcemia | 5 (31.3) | 4 (25.0) |
| | Hypophosphatemia | 4 (25.0) | 1 (6.3) |
| | Peripheral edema | 4 (25.0) | 0 |
| | Pyrexia | 5 (31.3) | 0 |
| | Stomatitis | 2 (12.5) | 0 |
| | Chills | 5 (31.3) | 1 (6.3) |
| | Hypomagnesemia | 4 (25.0) | 0 |
| | Arthralgia | 2 (12.5) | 0 |
| | Pruritus | 5 (31.3) | 0 |
| | Pain in extremity | 2 (12.5) | 0 |
| | Hypotension | 4 (25.0) | 1 (6.3) |
| | Hypoxia | 2 (12.5) | 1 (6.3) |
| | Asthenia | 2 (12.5) | 0 |
| | Hyperphosphatemia | 3 (18.8) | 0 |
| | Hematoma | 2 (12.5) | 0 |
| | Non-cardiac chest pain | 2 (12.5) | 0 |
| | Musculoskeletal chest pain | 2 (12.5) | 0 |
| | AST increase | 3 (18.8) | 2 (12.5) |
| | GGT increase | 3 (18.8) | 1 (6.3) |
| | Pleural effusion | 2 (12.5) | 0 |
| | ALT increase | 2 (12.5) | 1 (6.3) |
| | Delirium | 2 (12.5) | 1 (6.3) |

| | | | |
|---|---|---|---|
| | Epistaxis | 2 (12.5) | 0 |
| | Hyperkalemia | 2 (12.5) | 0 |
| | Blood fibrinogen decrease | 2 (12.5) | 1 (6.3) |
| | Acute kidney injury | 2 (12.5) | 2 (12.5) |

ALT: alanine transferase; AST: aspartate transferase; CV: cusatuzumab + venetoclax; GGT: gamma-glutamyl transferase; TEAE: treatment-emergent adverse event. [a]Sepsis was reported as abdominal sepsis, bacteremia, bacterial sepsis, Enterobacter bacteremia, intestinal sepsis, Klebsiella bacteremia, Pseudomonas bacteremia, pulmonary sepsis, Salmonella bacteremia, sepsis, septic shock, Staphylococcal bacteremia. [b]Pneumonia was reported as *Pneumocystis jirovecii* pneumonia, pneumonia, pneumonia bacterial, pneumonia fungal.

**Supplementary Table S7.** Secondary and *ad hoc* efficacy outcomes in the CV cohort.

| | | **CV N=16** |
|---|---|---|
| ORR (CR + CRh + CRi), n (% [95% CI]) | | 4 (25 [10.2-49.5]) |
| Response | CR, n (% [95% CI]) | 2 (12.5 [3.5-36.0]) |
| | CRi, n (% [95% CI]) | 2 (12.5 [3.5-36.0]) |
| | CRh, n (% [95% CI]) | 0 (0 [NE-NE]) |
| | MLFS, n (%) | 2 (12.5) |
| | Combined CR (CR + CRh + CRi) + MLFS, % | 37.5 |
| | Not evaluable, n (%) | 0 |
| MRD negativity after initial response of CR/CRi, n (%) | | 1 (25.0) |
| Median time to first response (CR, CRh or CRi) (range), weeks | | 9.1 (3.3-11.4) |
| Median duration of response (range), weeks | | 14.4 (2.4-NE) |
| Median EFS (95% CI), months | | 0.03 (0.03-0.03) |
| Median OS (95% CI),[a] months | | 3.4 (1.3-7.6) |
| RBC TI, %[b] | | 15.4 |
| Platelet TI, %[c] | | 28.6 |
| RBC TI and platelet TI, %[b] | | 15.4 |

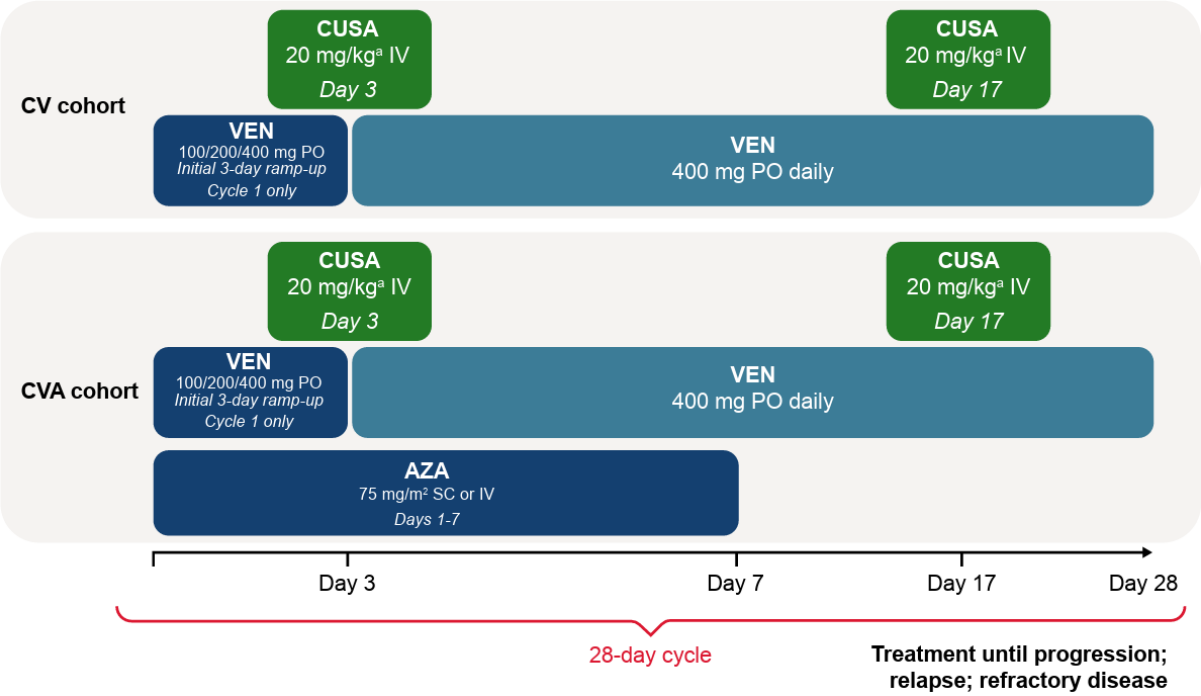
CI: confidence interval; CR: complete remission; CRh: complete remission with partial hematologic recovery; CRi: complete remission with incomplete hematologic recovery; CV: cusatuzumab + venetoclax; MLFS: morphologic leukemia-free state; MRD: measurable residual disease; NE: not evaluable; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; RBC: red blood cell; TI: transfusion independence. [a]Median follow-up: 14.8 weeks. [b]Denominator N=13. [c]Denominator, N=7.

**Supplementary Table S8.** Serum concentrations of CUSA in the CV cohort.

| | **CV N=16** |
|---|---|
| Median (range) time to $C_{max}$, hours | 4.95 (4.67-31.02) |
| Mean (SD) $C_{max}$, µg/mL | 381 (73.5) |
| Mean (SD) AUC, µg·h/mL | 60801 (13460) |
| Mean (SD) $t_{1/2}$, hours | 205.1 (41.0) |

AUC: area under the curve; $C_{max}$: maximum concentration; CUSA: cusatuzumab; CV: cusatuzumab + venetoclax; $t_{1/2}$: terminal elimination half-life.

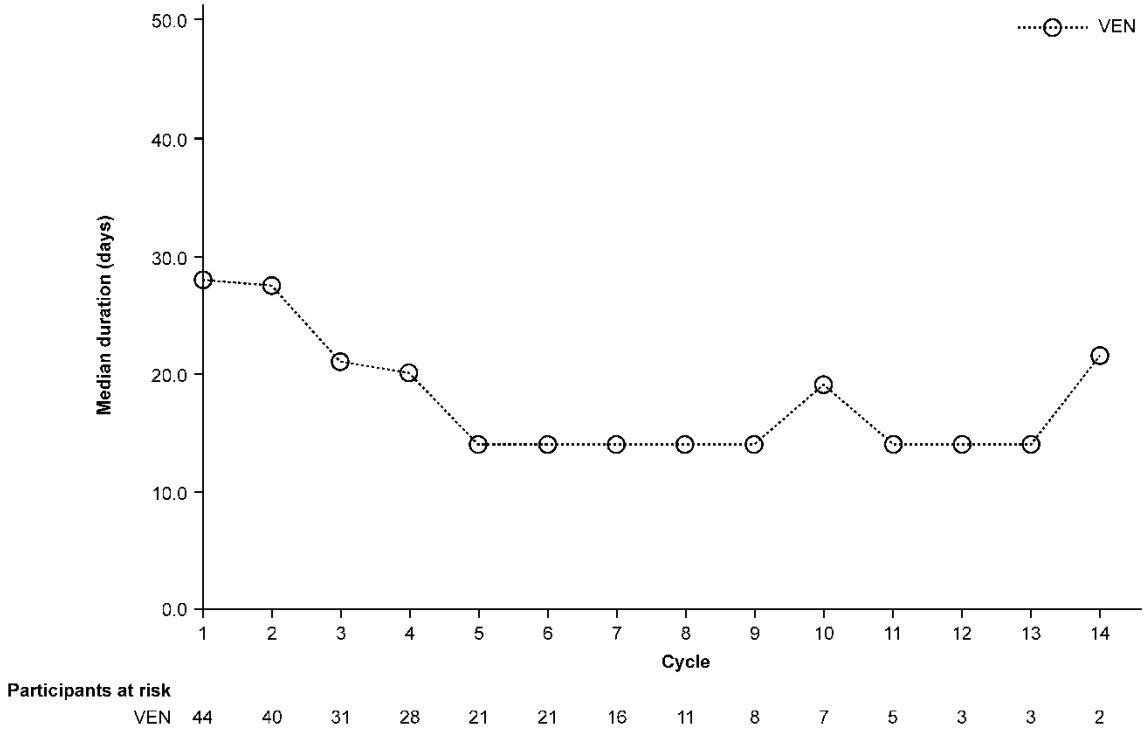
**Supplementary Figure S1.** Study design.




AZA: azacitidine; CV: cusatuzumab + venetoclax; CVA: cusatuzumab + venetoclax + azacitidine; CUSA: cusatuzumab; IV: intravenous; PO: oral administration; SC: subcutaneous; VEN: venetoclax. [a]The first three participants enrolled in the United States received 10 mg/kg CUSA IV on days 3 and 17 in cycle 1. No safety concerns at this dose were noted by the data review committee, and therefore the dose was increased to 20 mg/kg from cycle 2 onwards. One participant increased the dose to 20 mg/kg from cycle 3, and the other two participants discontinued study treatment prior to increasing the dose (one due to death and the other due to decision to undergo allogeneic stem cell transplant).

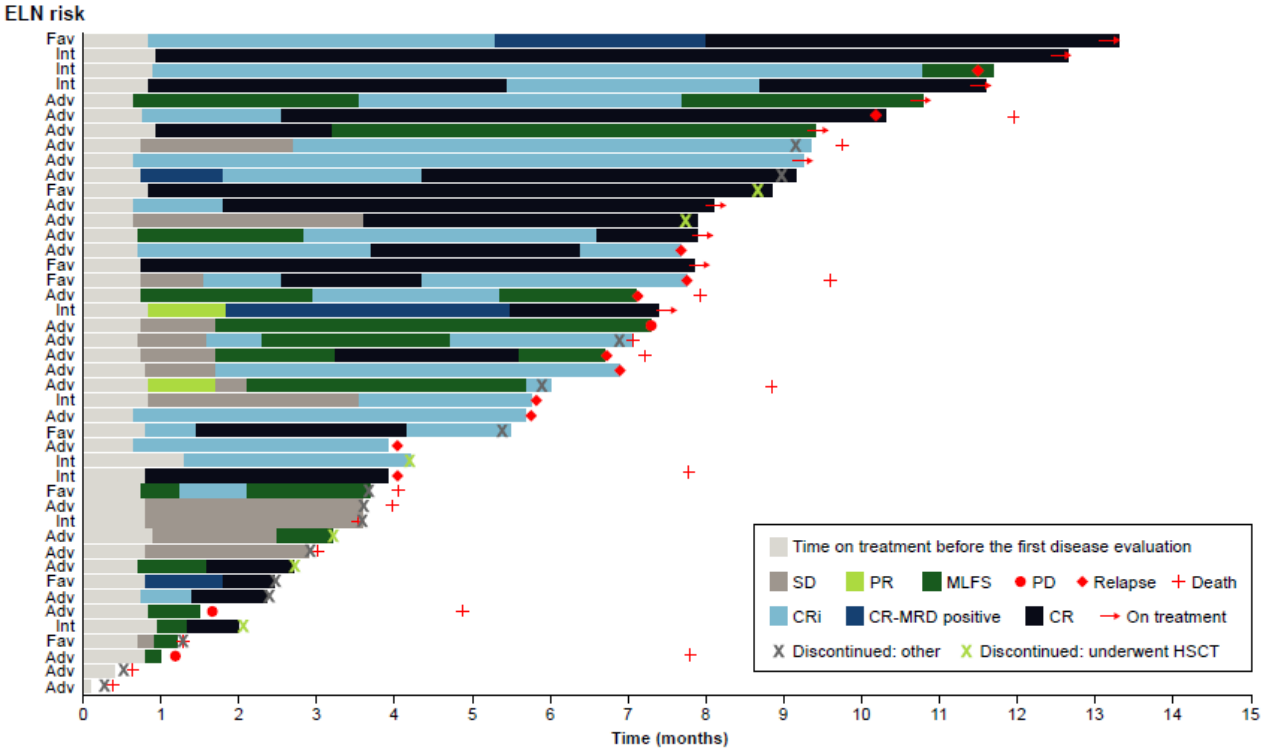
Participants received supportive care measures including transfusions, antimicrobial agents and growth-factor support per institutional standards. Note that for participants receiving concomitant cytochrome P450 3A and P-glycoprotein inhibitors, the VEN ramp-up period may have been from day -1 to day 5. Cohorts evaluating CUSA + AZA and CUSA + cytarabine and daunorubicin were planned but not initiated and therefore have been omitted from the study design.

**Supplementary Figure S2.** Median duration of VEN cycle in the CVA cohort.



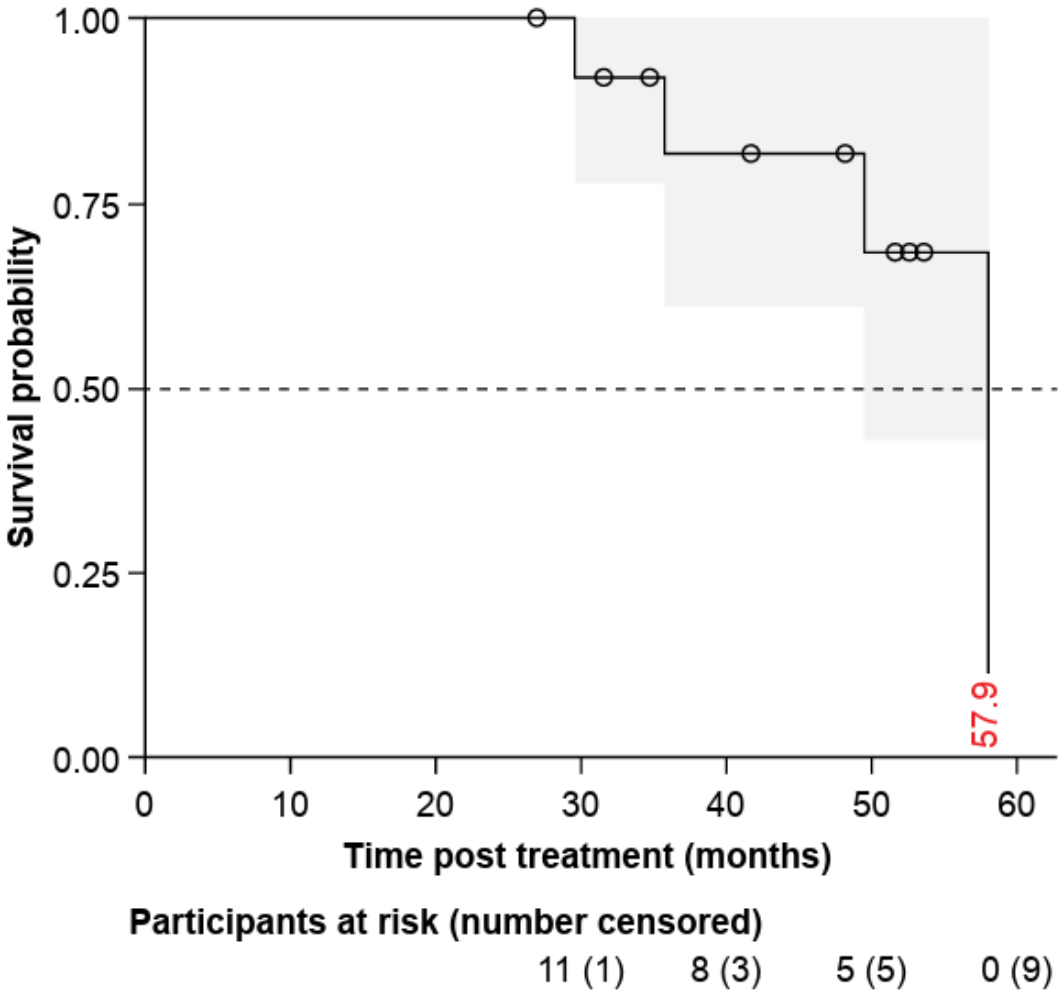

CVA: cusatuzumab + venetoclax + azacitidine; VEN: venetoclax.

**Supplementary Figure S3.** Responses and time on treatment in the CVA cohort based on the data cutoff of September 30, 2021.



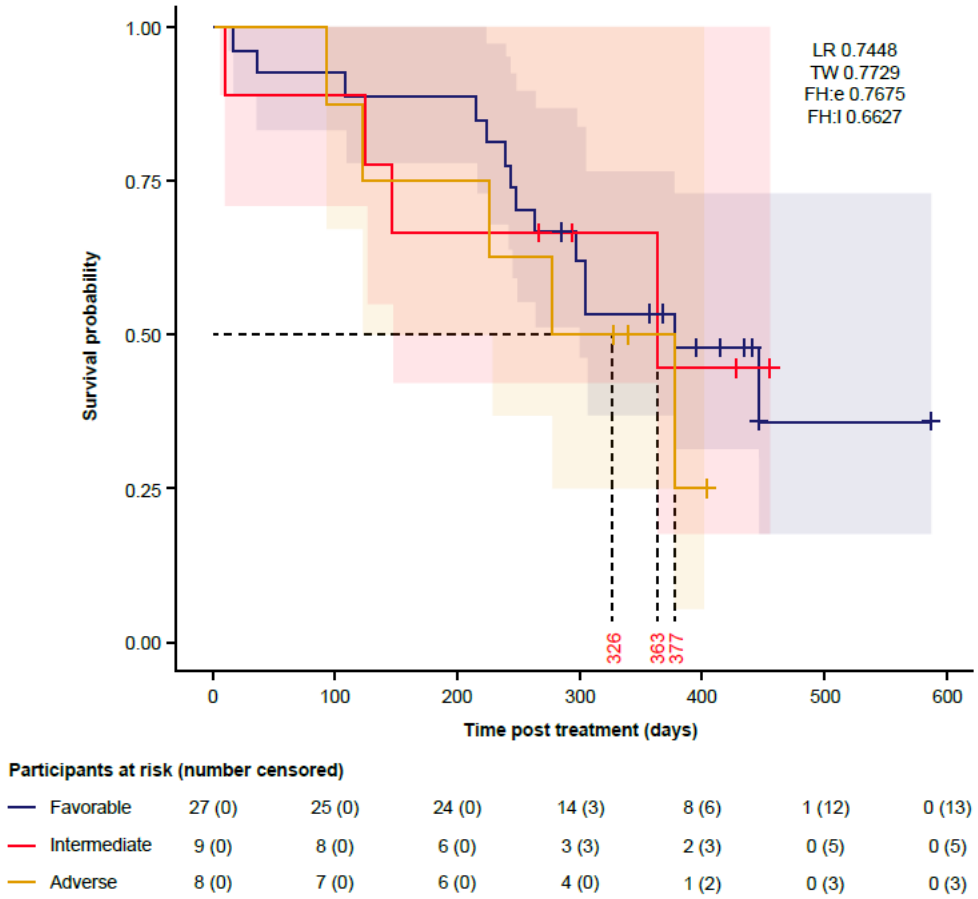

Adv: adverse; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; CVA: cusatuzumab + venetoclax + azacitidine; ELN: European LeukemiaNet; Fav: favorable; HSCT: hematopoietic stem cell transplant; Int: Intermediate; MLFS: morphologic leukemia-free state; MRD: measurable residual disease; PD: progressive disease; PR: partial response; SD: stable disease.

**Supplementary Figure S4.** Kaplan-Meier curve of OS in the CVA cohort assessing long-term responders



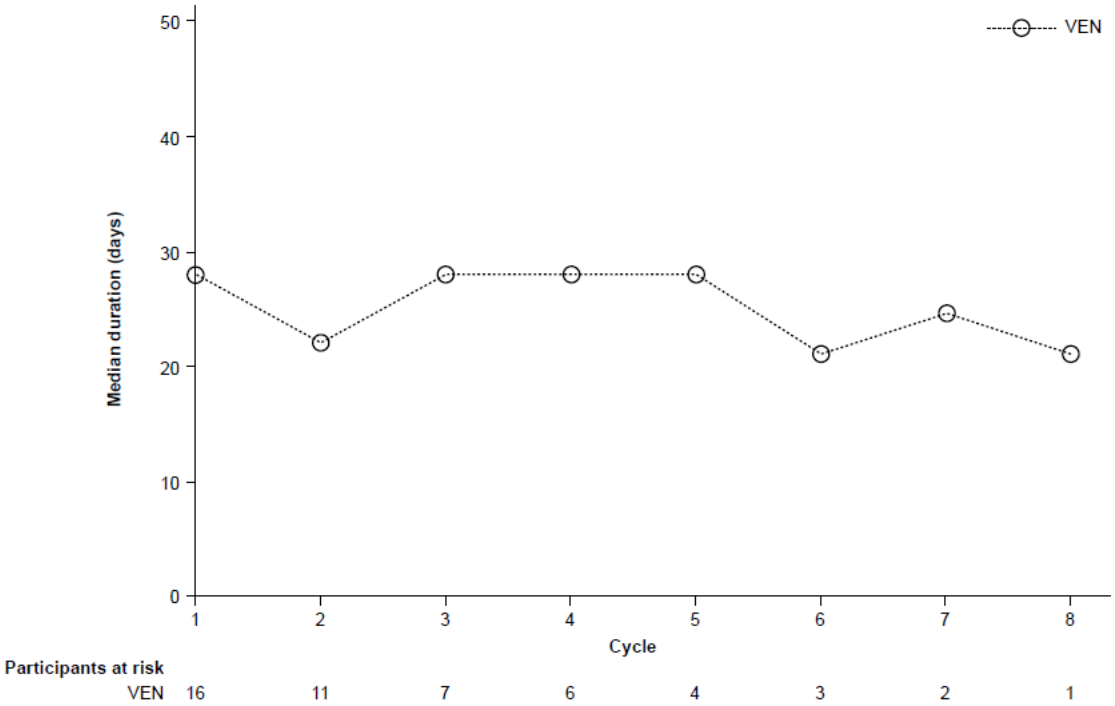

Kaplan-Meier (KM) analyses were performed for long-term responders (defined as individuals who survived beyond two years following treatment), to evaluate OS with a censoring date set as February 26, 2025. The corresponding 95% confidence intervals and median time-to-event were reported. Given the limited sample size, the findings from this subset should be interpreted with caution. Moreover, the KM estimation of the corresponding survival probabilities is likely overestimated due to immortal time (selection) bias among the selected patients.

**Supplementary Figure S5.** ELEVATE ELN 2024 OS.




ELN: European LeukemiaNet; FH:e: Fleming–Harrington early-weight; FH:I: Fleming–Harrington late-weight; LR: log-rank; OS: overall survival; TW: Tarone-Ware. No significant differences in OS were found among the three ELN 2024 risks. *DDX41*, which is one of the critical features in refined ELN 2024,[4] is missing in the analytical dataset and thus was not used in calculating the stratum. Missing values in the respective features (i.e., *TP53*, *FLT3ITD*, *NRAS*, *KRAS*, *NPM1*, *IDH1*, *IDH2*) were imputed by modes for three participants. In cases where none of these seven features was positive or exhibited mutations, the participant was categorized as favorable. The equality of survival curves was tested by LR, TW and Flaming-Harrington approaches. Median survival curves were highlighted by vertical "red" lines.

**Supplementary Figure S6.** Median duration of VEN cycle in the CV cohort.




CV: cusatuzumab + venetoclax; VEN: venetoclax.

# Supplementary information

## Inclusion and exclusion criteria

*Inclusion criteria*

1. Diagnosis of acute myeloid leukemia (AML) according to World Health Organization 2016 criteria[1]. Participants with acute promyelocytic leukemia (APL) are not eligible
2. Must be ineligible for intensive chemotherapy based on the following criteria:
    - ≥75 years of age or
    - ≥18 to 74 years of age with at least one of the following comorbidities:
        - Severe cardiac comorbidity, defined as congestive heart failure or ejection fraction ≤50%
        - Severe pulmonary comorbidity, defined as documented pulmonary disease with lung diffusing capacity for carbon monoxide ≤65% of expected or forced expiratory volume in 1 second ≤65% of expected or dyspnea at rest requiring oxygen
        - Moderate hepatic impairment, defined according to National Cancer Institute organ dysfunction classification criteria (total bilirubin ≥1.5 up to 3 × upper limit of normal [ULN])
        - Creatinine clearance ≥30 mL/min/1.73 $m^2$ to <45 mL/min/1.73 $m^2$ (by Modification of Diet in Renal Disease formula)
        - Comorbidity that, in the investigator's opinion, makes the participant unsuitable for intensive chemotherapy, which must be documented and approved by the sponsor before enrollment

3. *De novo* or secondary AML

4. Previously untreated AML (except: emergency leukapheresis, hydroxyurea and/or one dose of 1-2 g/$m^2$ cytarabine prior to study entry to control hyperleukocytosis; these treatments should not be given until after the screening bone marrow assessment and must be discontinued ≥24 hours prior to starting the study drug). Empiric all-trans retinoic acid treatment for presumed APL is permitted, but APL

must be ruled out and all-trans retinoic acid must be discontinued ≥24 hours prior to starting the study drug

5. ECOG PS of 0, 1 or 2

6. Adequate liver and renal function, defined as follows:

- Aspartate aminotransferase and alanine aminotransferase <3 × ULN; for participants with leukemic infiltration of the liver (documented by biopsy or imaging), aspartate aminotransferase and alanine aminotransferase <5 × ULN is permitted
- Total bilirubin ≤1.5 × ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin. Participants who are <75 years of age may have bilirubin ≤3 × ULN
- Creatinine clearance ≥30 mL/min/1.73 $m^2$ (by Modification of Diet in Renal Disease formula)

7. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin) or urine pregnancy test at screening

8. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies

    - Women of childbearing potential (defined as: fertile, following menarche and until becoming postmenopausal, unless permanently sterile):
        - Must be practicing a highly effective method of birth control (failure rate of <1% per year when used consistently and correctly) while receiving study treatment and for 3 months after the last dose of study drug
        - Must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during treatment and for 3 months after the last dose of study drug
        - Must not be breastfeeding and not planning to become pregnant during treatment and for 3 months after the last dose of study drug
        - Women of childbearing potential receiving venetoclax (VEN) must agree to use a barrier method of birth control (e.g., diaphragm or cervical cap) with spermicidal foam/gel/film/cream/suppository

during treatment and for 3 months after the last dose of study treatment

- Men who are sexually active with women of childbearing potential and have not had a vasectomy must:
    - Agree to use a barrier method of birth control (e.g., either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap [diaphragm or cervical/vault caps] with spermicidal foam/gel/film/cream/suppository) during treatment and for 3 months after the last dose of study treatment
    - Agree to not donate sperm during treatment and for 3 months after the last dose of study drug
    - Not plan to father a child during treatment or within 3 months after the last dose of study drug

9. Must sign an informed consent form indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study

*Exclusion criteria*

1. Leukemic involvement of the central nervous system

2. Use of immune suppressive agents for the 4 weeks before the first administration of cusatuzumab (CUSA). Participants may only be included if free of systemic corticosteroids for a minimum of 5 days before the first administration of CUSA, with the exception of corticosteroids at physiologic replacement doses

3. Any prior treatment for AML (except for that mentioned in inclusion criterion 4)

4. Eligible for an allogeneic hematopoietic stem cell transplantation at study entry

5. Received a live, attenuated vaccine within 4 weeks prior to initiation of study drug

6. Active malignancies (i.e., progressing or requiring treatment change in the past 24 months) other than the disease being treated under study. The only allowed exceptions are:

- Non-melanoma skin cancer treated within the past 24 months that is considered completely cured

- Adequately treated breast lobular carcinoma *in situ* and breast ductal carcinoma *in situ*
- Adequately treated cervical carcinoma *in situ* without evidence of disease
- History of localized breast cancer and receiving antihormonal agents, or history of localized prostate cancer (N0M0) and receiving androgen deprivation therapy
- Malignancy that is considered cured with minimal risk of recurrence

7. Any active systemic infection

8. A history of being HIV antibody positive or tests positive for HIV if tested at screening

9. Active hepatitis B or C infection or other clinically active liver disease

- Seropositive for hepatitis B: defined by a positive test for hepatitis B surface antigen. Participants with resolved infection (i.e., participants who are hepatitis B surface antigen negative with antibodies to total hepatitis B core antigen with or without the presence of hepatitis B surface antibody) must be screened using real-time polymerase chain reaction (RT-PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are RT-PCR positive will be excluded. Participants with serologic findings suggestive of HBV vaccination (hepatitis B surface antibody positivity as the only serologic marker) AND a known history of prior HBV vaccination do not need to be tested for HBV DNA by RT-PCR
- Known hepatitis C infection or positive serologic testing for hepatitis C (anti–hepatitis C virus antibody)

10. New York Heart Association class 3 or 4 heart failure or ongoing unstable angina

11. Known allergies, hypersensitivity or intolerance to CUSA, VEN, azacitidine (AZA) or their excipients (e.g., mannitol, an excipient of AZA)

12. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g., it would compromise their well-being) or physical limitations that could prevent, limit or confound the protocol-specified assessments

13. Major surgery (e.g., requiring general anesthesia) within 4 weeks prior to the initiation of study treatment

14. CVA cohort: prior treatment with a hypomethylating agent for antecedent myelodysplastic syndrome

15. White blood cell count >25 × $10^9$/L (hydroxyurea is permitted to meet this criterion)

16. Received strong and moderate cytochrome P450 3A inducers or inhibitors within 7 days prior to the initiation of study drug

17. Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within 3 days prior to the initiation of study treatment

18. Inability or difficulty swallowing capsules/tablets, malabsorption syndrome or any disease or medical condition significantly affecting gastrointestinal function

19. Prior treatment with VEN or prior hematopoietic stem cell transplantation for myelodysplastic syndrome

**Dose Modifications of Venetoclax, Azacitadine and Cusatuzmab in Participants with Myelosuppression**

*Venetoclax, Azacitidine, and Cusatuzumab Dose Management Guidelines Until Marrow Remission is Achieved (<5% blasts)*

| Bone marrow blasts (%) | ANC (cells/μL) | Platelet count (cells/μL ) | Action |
|---|---|---|---|
| <5% | ≥1,000 | ≥100,000 | **CR with normocellular marrow.** Continue to next cycle without interruption; administer VEN at the same dose for 28 days. **CR with hypocellular marrow (~<10%).** Per investigator's discretion, option to delay next cycle (all study medications) by 14 days and monitor blood counts or continue to next cycle without interruption. If next cycle is delayed, repeat marrow assessment on day 42 (up to -2d); begin next cycle if ANC ≥500/μL and platelets ≥50,000/μL. |
| <5% | <1,000 | <100,000 | Delay next cycle (all study medications) up to 14 days.[a,b] The aim is to confirm a CR before the next cycle whenever possible. • If ANC ≥1,000/μL and platelets ≥100,000/μL by day 42, resume VEN at the same dose for 28 days; • If ANC ≥500/μL and platelets ≥50,000/μL by day 42, resume VEN at the same dose for 21 days of the 28-day cycle; • If no count recovery (i.e., ANC <500/μL or platelets <50,000/μL) by day 42, repeat marrow assessment on day 42, and contact sponsor medical monitor to determine if treatment should continue or be delayed. |
| >5% | Any | Any | Continue to next cycle without interruption; administer VEN at the same dose for 28 days. |

ANC: absolute neutrophil count; CR: complete remission; VEN: venetoclax.

a. G-CSF may be administered per institutional guidelines when in marrow remission for support of neutropenia. Sponsor recommendations is to give G-CSF until ANC is ≥1,000/□L, then repeat CBC ≥5 days after last dose of G-CSF for determination of response.

b. Transfuse blood products, administer prophylactic and/or treatment anti-infectives as clinically indicated.

A bone marrow aspiration and biopsy will be performed at the end of Cycle 1 (Days 21-28). Assessments should be resulted prior to the administration of Cycle 2. If remission is not achieved after Cycle 1, treatment should be administered as advised below and a marrow assessment should be repeated at the end of Cycle 2 (Days 21-28). The guidance below should again be followed based on marrow results. Prior to achieving marrow remission, doses of azacitidine and cusatuzumab should be withheld concurrently with venetoclax as discussed in the table above. If no marrow remission is achieved after Cycle 2, discuss with Sponsor Medical Monitor whether or not the subject should continue with study treatments. Note: If marrow remission is achieved before Cycle 1 Day 28, venetoclax may be interrupted according to the dose modification guidance until ANC ≥500/□L and platelets ≥50,000/μL.

*VEN dosing guidelines for myelosuppression management after remission achieved*

| Occurrence | Action to be taken |
|---|---|
| First | 400 mg daily; administer for 21 days for each subsequent 28-day cycle |
| Second | 400 mg daily; administer for 14 days for each subsequent 28-day cycle |
| Third | 400 mg daily; administer for 10 days for each subsequent 28-day cycle |
| Fourth | Further reductions are to be discussed with the sponsor |

The duration of venetoclax must be modified according to the guidelines in Table above for any of these toxicities lasting ≥7 days in subjects who have achieved remission: □ Grade 4 neutropenia. G-CSF may be administered when in marrow remission for support of neutropenia. □ Grade 3 thrombocytopenia with significant bleeding or Grade 4

thrombocytopenia: Transfuse blood products and administer prophylactic and/or treatment anti-infectives as clinically indicated.

After achieving marrow remission, hematologic toxicities should first be managed by reducing the duration of treatment with venetoclax as per the table above If hematologic toxicities persist despite venetoclax reductions, doses of azacitidine may be reduced or held as described in the table below, and at the investigator's discretion.

*Azacitidine dose reductions with VEN dosing*

| Occurrence | Action to be taken |
|---|---|
| First | Administer at 100% recommended dose × 5 days |
| Second | Reduce recommended dose to 50% × 5 days |
| Third | Reduce recommended dose to 33% × 5 days |

*Recommended dose modifications for concomitant cytochrome P450 3A or P-glycoprotein inhibitors*

| Co-administered drug | VEN dose modification during initiation and ramp-up phase | VEN dose modification during steady daily dose (after ramp-up phase) |
|---|---|---|
| **Posaconazole** | Day 1: 10 mg<br>Day 2: 20 mg<br>Day 3: 50 mg<br>Day 4: 70 mg | Reduce dose to 70 mg |
| **Other strong CYP3A inhibitor** | Day 1: 10 mg<br>Day 2: 20 mg<br>Day 3: 50 mg<br>Day 4: 100 mg | Reduce dose to 100 mg |
| **Moderate CYP3A inhibitor** | Reduce dose by ≥50% | |
| **P-gp inhibitor** | | |

CYP3A: cytochrome P450 3A; P-gp: P-glycoprotein; VEN: venetoclax.

## Supplementary material references

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

2. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.

3. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.

4. Döhner H, DiNardo CD, Appelbaum FR, et al. Genetic risk classification for adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024;144(21):2169-2173.