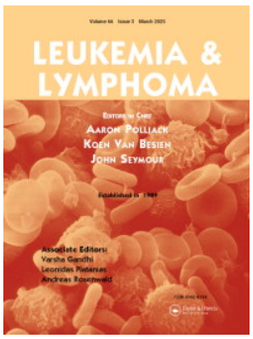

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ORIGINAL ARTICLE

Azacitidine and venetoclax with or without pevonedistat in patients with newly diagnosed acute myeloid leukemia

Nicholas J. Short[a], Agnieszka Wierzbowska[b], Thomas Cluzeau[c], Kamel Laribi[d], Christian Recher[e], Jaroslaw Czyz[f,g], Bogdan Ochrem[h], Lionel Ades[i], Maria Pilar Gallego-Hernanz[j], Mael Heiblig[k], Ernesta Audisio[l], Ewa Zarzycka[m], Shuli Li[n], Nicholas Ferenc[n], Tammie Yeh[n], Douglas V. Faller[n*], Farhad Sedarati[n] and Cristina Papayannidis[o]

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ABSTRACT

This phase 2 study investigated pevonedistat + azacitidine + venetoclax ($n = 83$) versus azacitidine + venetoclax ($n = 81$) in patients with newly diagnosed acute myeloid leukemia (AML) ineligible for intensive chemotherapy. The study was stopped early following negative results from PANTHER, which evaluated pevonedistat in higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia or low-blast AML. Outcomes were analyzed up to the datacut. For pevonedistat + azacitidine + venetoclax versus azacitidine + venetoclax, the median follow-up was 8.44 versus 7.95 months; the complete remission (CR) rate was 45% versus 49%; composite CR (CCR; CR+CR with incomplete blood count recovery) was 77% versus 72%. There were no differences in event-free survival (primary endpoint; hazard ratio [HR]: 0.99; 95% confidence interval [CI]: 0.61–1.60; $p = 0.477$) or overall survival (HR: 1.42; 95% CI: 0.82–2.49; $p = 0.896$). In exploratory analyses in *IDH*-mutated AML, CCR rates were higher with pevonedistat + azacitidine + venetoclax versus azacitidine + venetoclax. Safety was similar between treatment arms. Efficacy/safety with azacitidine + venetoclax was consistent with the phase 3 VIALE-A study.
Trial registration: NCT04266795

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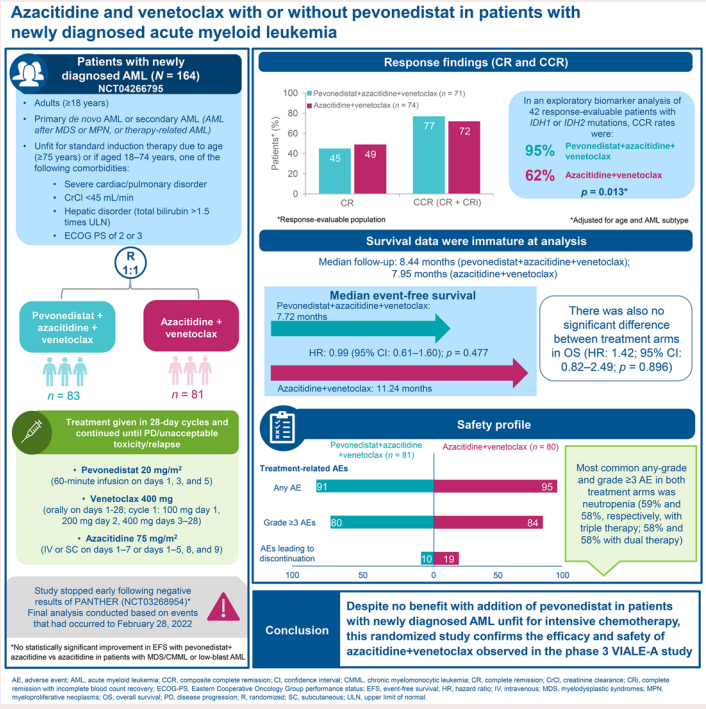
GRAPHICAL ABSTRACT



Introduction

Intensive chemotherapy is a standard treatment for patients with acute myeloid leukemia (AML) providing the greatest chance of achieving complete remission (CR) and long-term survival [1]; however, more than 50% of patients are ineligible due to advanced age and/or existing co-morbidities [2]. For many years, hypomethylating agents (HMAs), such as azacitidine [3] or decitabine [4], were the standard of care for patients who are ineligible for intensive chemotherapy; however, the long-term outcomes with HMAs remain poor [1,5]. Improvements in survival have been achieved by combining HMAs with the BCL-2 inhibitor venetoclax [6–8]. In phase 3 randomized study (VIALE-A), venetoclax and azacitidine significantly improved overall survival (OS) compared with azacitidine alone (median 14.7 vs 9.6 months; hazard ratio [HR]: 0.66, $p < 0.001$) in older patients with AML [8]. Venetoclax in combination with either azacitidine, decitabine, or low-dose cytarabine is approved for the treatment of patients with newly diagnosed AML who are aged ≥75 years or who have existing co-morbidities and are therefore ineligible for intensive induction chemotherapy, and these combinations are now standard of care in this population [9]. However, despite these advances, there remains an unmet need for novel approaches to improve patient outcomes without increasing toxicity.

Pevonedistat is a first-in-class small molecule inhibitor of the NEDD8-activating enzyme (NAE), which is required for ubiquitination and degradation of select proteins upstream of the proteasome [10,11]. Inhibition of NAE with pevonedistat prevents degradation of proteins involved in DNA repair, cell cycle, and cell survival pathways, leading to cell death, including in myeloid malignancies [11,12]. Pevonedistat in combination with venetoclax has shown synergistic cytotoxic effects in AML cell lines and primary clinical AML samples [12]. In a phase 1b study (NCT01814826), pevonedistat in combination with azacitidine was tolerable and clinically active in patients aged ≥60 years with untreated AML [13]. Furthermore, the triplet combination of pevonedistat, azacitidine, and venetoclax has been investigated in a phase 1/2 study (NCT03862157) in patients with secondary AML who were unfit for intensive chemotherapy in which the recommended phase 2 dose was established and encouraging efficacy was reported in this very poor risk population [14,15].

Based on these results, we conducted a randomized phase 2 study to determine the efficacy and safety of pevonedistat in combination with azacitidine and venetoclax, compared with azacitidine and venetoclax only, in patients with untreated AML ineligible for intensive chemotherapy (NCT04266795).

Methods

Patients

Eligible patients were aged ≥18 years with a morphologically confirmed diagnosis of AML based on the 2008 World Health Organization criteria and had either newly diagnosed primary *de novo* AML or secondary AML defined as AML after myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPN), or therapy-related AML following cytotoxic therapy and/or radiotherapy. Patients were also required to be unfit for standard induction therapy due to age (≥75 years) or one of the following comorbidities if aged 18–74 years: severe cardiac or pulmonary disorder; creatinine clearance <45 Ml/min; hepatic disorder with total bilirubin >1.5 times the upper limit of normal; or an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 2 or 3. Patients with a history of MPN with *BCR::ABL1* translocation or AML with *BCR::ABL1* translocation, acute promyelocytic leukemia, extramedullary AML without evidence of bone marrow involvement, or prior treatment with HMAs for AML were excluded. Full eligibility criteria are in the supplementary appendix.

Study design

Patients were randomized 1:1 to receive either pevonedistat 20 mg/m^2 *via* a 60-minute infusion on days 1, 3, and 5, plus oral venetoclax 400 mg on days 1–28, and azacitidine 75 mg/m^2 (intravenous or subcutaneous) on days 1–7 or days 1–5, 8, and 9, or azacitidine and venetoclax at the same doses and durations, without the addition of pevonedistat. Venetoclax was administered on a ramp-up schedule in cycle 1:100 mg on day 1, 200 mg on day 2, and 400 mg on days 3–28. If remission was confirmed during the study, then venetoclax dosing could be reduced to days 1–21 and subsequently increased if judged by the investigator to be well tolerated. Treatment cycles were 28 days, with a new cycle starting as permitted by peripheral blood count recovery. Patients were stratified by age (18–74 vs ≥75) and AML subtype (*de novo* vs secondary). Treatment was given until unacceptable toxicity, relapse, or progressive disease (PD).

The study was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines and appropriate regulatory requirements. Independent ethics committees or institutional review boards approved the protocol. All patients provided written informed consent.

The protocol was amended during the conduct of the study based on results of the phase 3 PANTHER study, which showed no statistically significant improvement in event-free survival (EFS) with pevonedistat plus azacitidine versus azacitidine alone in patients with higher-risk MDS/chronic myelomonocytic leukemia (CMML) or low-blast AML [16]. The study was unblinded and patients continuing treatment after the protocol was amended were required to reconsent. The study was fully accrued and closed to enrollment at the time of unblinding. Study assessments were reduced, long-term follow-up visits for EFS, response, and OS were no longer required, and the independent review committee and independent data monitoring committee assessments were removed.

The datasets, including the redacted study protocols, redacted statistical analysis plans, and individual participants' data supporting the results of the completed study will be made available after the publication of the final study results within 3 months from the initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Endpoints and assessments

The primary endpoint was EFS, defined as the time from study randomization to the date of failure to achieve CR or CR with incomplete blood count recovery (CRi), relapse from CR/CRi, or death from any cause, whichever occurred first. Patients who did not achieve CR/CRi were counted as an event on the date of randomization as per US Food and Drug Administration guidelines. The key secondary endpoint was OS. Other secondary endpoints included 30- and 60-day mortality rates, response rates, and rates of adverse events (AEs) and serious AEs (SAEs). In exploratory analyses, endpoints included screening bone marrow aspirate (BMA) samples using next-generation sequencing (NGS) for molecular markers associated with prognosis in AML and their correlation with clinical efficacy.

Response assessment was based on the revised recommendations of the International Working Group [17]. Formal disease assessments for study endpoints were based on local BMA blast percentages, and local laboratory data at screening, cycle 1, cycle 3, and every 3 cycles thereafter, or suspected relapse. Toxicity was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 [18].

Statistical analysis

The study was originally designed to have approximately 85 events to provide 80% power to detect an

HR of 0.58 (median EFS of 19 months in the pevonedistat + azacitidine + venetoclax arm vs 11 months in the azacitidine + venetoclax arm, assuming exponential distribution of EFS) using a stratified log-rank test at a one-sided 5% significance level. One interim analysis and one final analysis for statistical analyses of efficacy were initially planned; however, following the protocol amendment based on the results from the PANTHER study, only the final analysis was performed with no event size re-estimation. A stratified log-rank test was used to compare EFS between treatment arms. An unadjusted stratified Cox regression model was used to estimate the HR and two-sided 95% confidence intervals (CIs). The response-evaluable population was defined as patients who received at least one dose of the study drug, had a disease assessment at baseline and at least one post-baseline disease assessment. The safety population was defined as all patients who received at least one dose of any of the study drugs.

Centralized gene mutation and risk stratification

Bone marrow aspirates at screening were collected and analyzed for cytogenetics (karyotyping and/or fluorescence *in situ* hybridization) at Brigham Women's Hospital (BWH), Boston, MA, USA. Parallel samples were sent to Q2 Solutions for bone marrow mononuclear cell isolation and then to Broad Institute for DNA isolation. A portion of the DNA was sent to BWH for FMS-like tyrosine kinase-3 internal tandem duplication (*FLT3*-ITD) analyses as well as NGS using their Rapid Heme Panel (RHP) containing 88 genes commonly mutated in myeloid malignancies [19].

AML risk assessment was performed by a single pathologist for consistency at BWH by combining cytogenetic abnormalities, mutation data from the RHP, and *FLT3*-ITD results to stratify patients into three outcome groups, i.e. adverse, intermediate, and favorable using the European LeukemiaNet (ELN 2017) risk stratification system [20]. For nine of 139 samples lacking sufficient cytogenetic results for assessment at BWH (e.g. poor sample quality), cytogenetic results from pathology reports from the local sites were used instead.

Results

Patients

Between 19 November 2020 and 24 August 2021, 164 patients from 85 sites globally were randomized to receive pevonedistat + azacitidine + venetoclax ($n = 83$) or azacitidine + venetoclax ($n = 81$; Figure 1). At the data cutoff of 28 February 2022, treatment was ongoing for 23 patients in the pevonedistat + azacitidine + venetoclax arm and 25 patients in the azacitidine + venetoclax arm (Supplementary Table S1). Study treatment was discontinued in 60 (72%) patients in the pevonedistat + azacitidine + venetoclax arm, and 56 (69%) patients in the azacitidine + venetoclax arm; the primary reasons for discontinuation were AEs in 19 (23%) and 10 (12%) patients, and PD in 9 (11%) and 12 (15%) patients, respectively.

Baseline patient demographics and disease characteristics were balanced between treatment arms (Table 1). Overall, the median age was 75 years (range 50–86); 31 (37%) patients in the pevonedistat + azacitidine + venetoclax arm and 29 (36%) patients in the azacitidine + venetoclax arm had secondary AML. According to ELN 2017 risk stratification, 39 (47%) patients in the pevonedistat + azacitidine + venetoclax arm and 48 (59%) in the azacitidine + venetoclax arm had adverse risk.

Efficacy

One hundred and forty-five patients were evaluable for response. Of the 12 (14%) patients receiving pevonedistat + azacitidine + venetoclax and 7 (9%) patients receiving azacitidine + venetoclax who were not evaluable for response, the main reasons were absence of a fresh or archival BMA sample for baseline assessment, no post-baseline follow-up assessment or did not receive study treatment (2 vs 1 patient).

Response rates are summarized in Table 2. The CR rate was 45% with pevonedistat + azacitidine + venetoclax versus 49% with azacitidine + venetoclax (relative risk, 0.93; 95% CI: 0.65–1.31; $p = 0.590$). The composite complete remission (CCR [CR+CRi]) rate was 77% with pevonedistat + azacitidine + venetoclax versus 72% with azacitidine + venetoclax and the leukemia response rate (CR+CRi + partial remission [PR]+morphological leukemia-free state [MLFS]) was 85% in each arm. The median duration of CR/CRi was not estimable with pevonedistat + azacitidine + venetoclax versus 8.6 months with azacitidine + venetoclax (HR: 1.40; $p = 0.762$). The median time to first CR/CRi/PR was 1.0 month for both arms. Two patients receiving pevonedistat + azacitidine + venetoclax and 6 patients receiving azacitidine + venetoclax subsequently received a transplant.

A final analysis for EFS and OS was conducted based on all events at data cutoff, which was triggered by the results of the PANTHER study indicating that there was no statistically significant improvement in EFS with pevonedistat plus azacitidine versus azacitidine alone

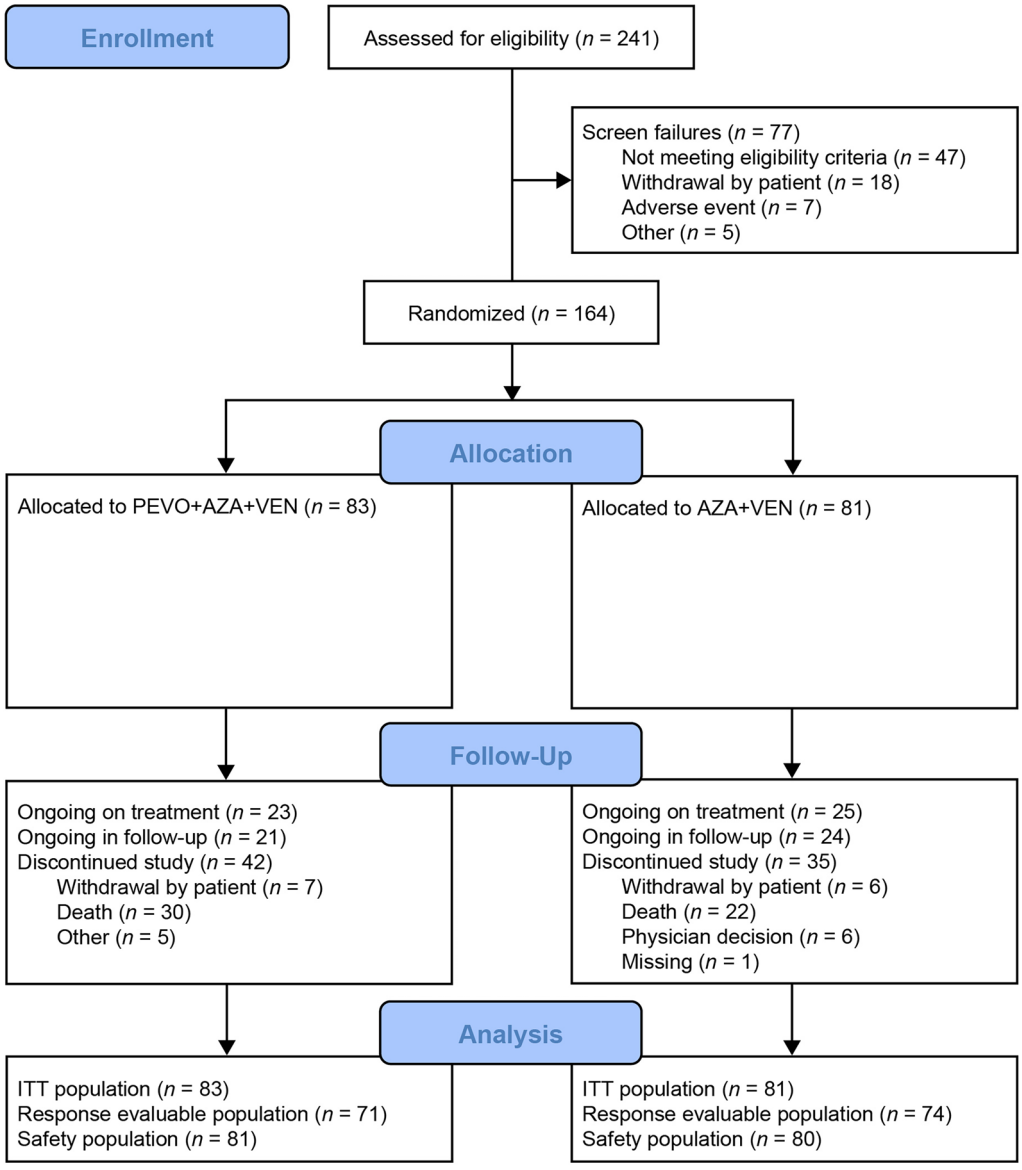


Figure 1. CONSORT diagram for the randomized phase 2 study investigating the triplet combination of pevonedistat + azacitidine + venetoclax (PEVO+AZA+VEN) compared with the current standard of care azacitidine + venetoclax (AZA+VEN). AZA+VEN: azacitidine + venetoclax; ITT: intent-to-treat; PEVO+AZA+VEN: pevonedistat + azacitidine + venetoclax.

in patients with higher-risk MDS/CMML or low-blast AML [16]. Consequently, EFS and OS data were immature at the time of analysis due to the limited number of events recorded and with median follow-up of 8.44 months for pevonedistat + azacitidine + venetoclax and 7.95 months for azacitidine + venetoclax. The study did not meet the primary endpoint of EFS with no difference observed between treatment arms (35 events with pevonedistat + azacitidine + venetoclax vs 33 events with azacitidine + venetoclax; HR: 0.99; 95% CI: 0.61–1.60; $p = 0.477$; Figure 2(A)). Analyses of EFS by stratification factors and prespecified subgroups were consistent with the overall patient population, with no differences observed between treatment arms according to age, AML subtype and blast count (Supplementary Figure 1). At the time of the final analysis, 30 patients (36%) in the pevonedistat + azacitidine + venetoclax arm and 22 patients (27%) in the azacitidine + venetoclax arm had died. There was no significant difference in OS between treatment arms (30 events with pevonedistat + azacitidine + venetoclax vs 22 events with azacitidine + venetoclax; HR: 1.42; 95% CI: 0.82–2.49; $p = 0.896$; Figure 2(B)). Despite the data being immature, it is not anticipated that a difference in favor of the triplet combination would be observed with longer follow-up as response rates were similar between treatment arms and the hazard ratio was 1.

Table 1. Patient demographics and baseline characteristics.

	Pevonedistat + azacitidine + venetoclax *n* = 83	Azacitidine + venetoclax *n* = 81	Total *N* = 164
Median age, years (range)	75 (61–85)	75 (50–86)	75 (50–86)
18–74, *n* (%)	40 (48)	40 (49)	80 (49)
≥75, *n* (%)	43 (52)	41 (51)	84 (51)
Male/female, *n* (%)	53 (64) / 30 (36)	45 (56) / 36 (44)	98 (60) / 66 (40)
Disease type, *n* (%)			
De novo	52 (63)	52 (64)	104 (63)
Secondary	31 (37)	29 (36)	60 (37)
Secondary to MDS (AML transformed from MDS)	25 (30)	23 (28)	48 (29)
Prior antineoplastic therapy	4 (5)	4 (5)	8 (5)
Missing	2 (2)	2 (2)	4 (2)
Revised WHO 2016 classification, *n* (%)			
AML with recurrent genetic abnormalities	8 (10)	2 (2)	10 (6)
AML with myelodysplasia-related changes	32 (39)	27 (33)	59 (36)
Therapy-related AML	3 (4)	2 (2)	5 (3)
AML not otherwise specified	30 (36)	37 (46)	67 (41)
Other	7 (8)	8 (10)	15 (9)
Not available	3 (4)	5 (6)	8 (5)
Evidence of extramedullary disease			
Yes	1 (1)	4 (5)	5 (3)
No	76 (92)	76 (94)	152 (93)
Unknown	6 (7)	1 (1)	7 (4)
ECOG PS, *n* (%)			
0	9 (11)	11 (14)	20 (12)
1	25 (30)	27 (33)	52 (32)
2	45 (54)	41 (51)	86 (52)
3	2 (2)	1 (1)	3 (2)
Missing	2 (2)	1 (1)	3 (2)
ELN 2017 risk stratification*, *n* (%)			
Adverse	39 (47)	48 (59)	87 (53)
Intermediate	15 (18)	18 (22)	33 (20)
Favorable	12 (14)	8 (10)	20 (12)
Missing	17 (20)	7 (9)	24 (15)
Median time from initial diagnosis, months (range)	0.7 (0.1–35.6)	0.6 (0.1–108.4)	0.6 (0.1–108.4)

*Determined at a central laboratory.
AML: acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; ELN: European LeukemiaNet; MDS: myelodysplastic syndromes; WHO: World Health Organization.

Table 2. Response rates and time to response in the response-evaluable population.

n (%), unless stated otherwise	Pevonedistat + azacitidine + venetoclax *n* = 71	Azacitidine + venetoclax *n* = 74
CR	32 (45)	36 (49)
CCR (CR+CRi)	55 (77)	53 (72)
ORR (CR+CRi + PR)	59 (83)	58 (78)
CR+CRh	34 (48)	38 (51)
Leukemia response (CR+CRi + PR+MLFS)	60 (85)	63 (85)
Median duration of CR or CRi, months (95% CI)	NE (5.16–NE)	8.61 (6.44–NE)
Median time to first CR/CRi/PR, months (95% CI)	0.95 (0.89–1.22)	1.02 (0.92–1.58)

CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete blood count recovery; CRh: complete remission with partial hematologic recovery; CCR: composite complete remission; PR: partial remission, MLFS: morphological leukemia-free state; NE: not estimable; ORR: overall response rate.

Safety

At the data cutoff, patients in both treatment arms had received a median of 5 treatment cycles, both overall and for each drug (range 1–13 with each drug in the triplet combination and range 1–13 with venetoclax and 1–15 with azacitidine in the doublet combination). The safety profile for each treatment arm is summarized in Table 3. The rates of any-grade and grade ≥3 treatment-emergent AEs (TEAEs) were similar between treatment arms; the most frequent grade ≥3 TEAEs with pevonedistat + venetoclax + azacitidine versus azacitidine + venetoclax were neutropenia (58% vs 58%), thrombocytopenia (46% vs 38%), anemia (32% vs 34%), and febrile neutropenia (30% vs 38%; Supplementary Table S2). The rate of SAEs was higher in the pevonedistat + azacitidine + venetoclax arm compared with the azacitidine + venetoclax arm (77% vs 69%); the majority of SAEs were grade ≥3

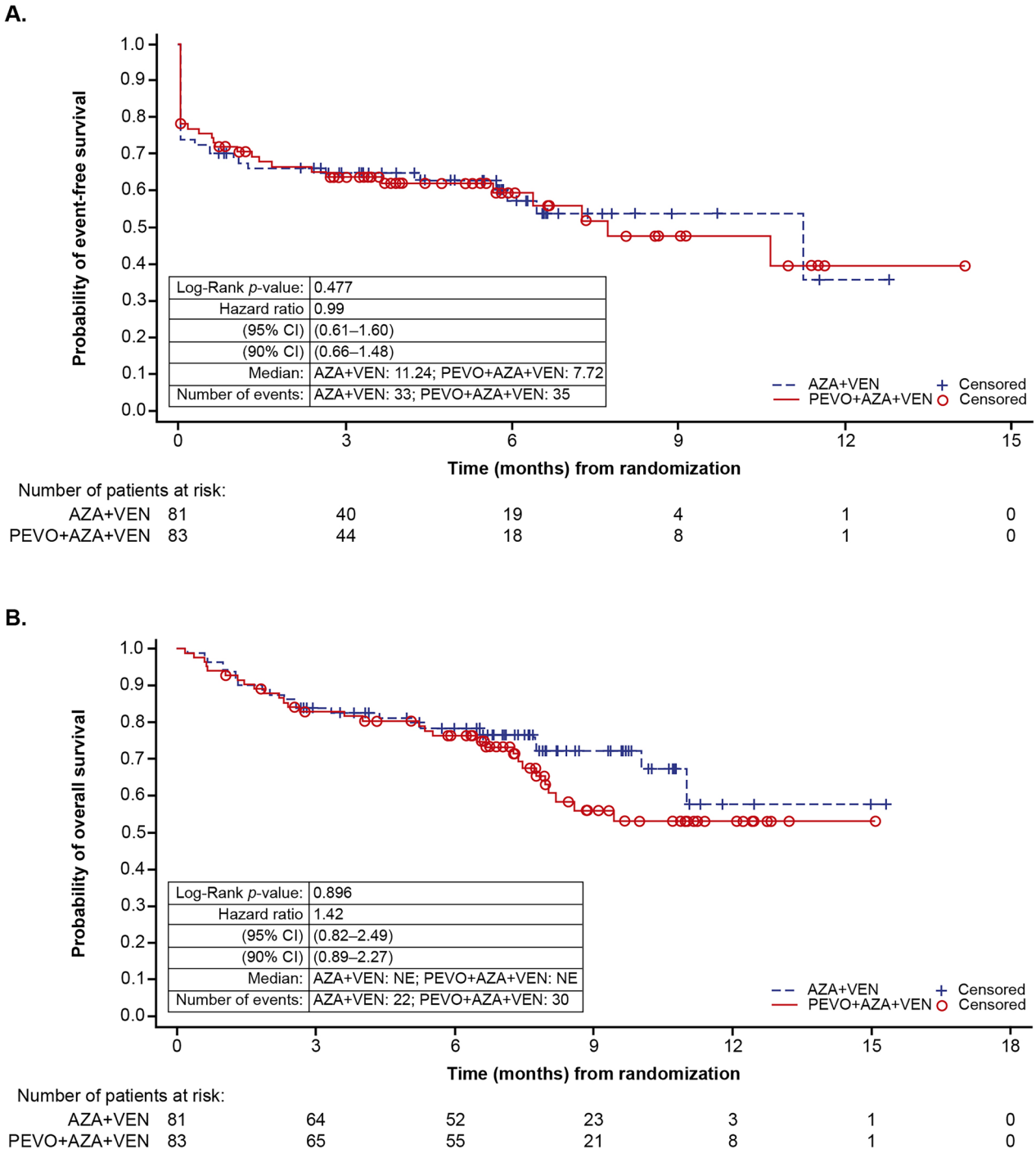


Figure 2. Investigator assessment of EFS (A) and OS (B) in the ITT population. AZA+VEN: azacitidine + venetoclax; CI: confidence interval; ITT: intent-to-treat; OS: overall survival; PEVO+AZA+VEN: pevonedistat + azacitidine + venetoclax; NE: not estimable.

(Supplementary Table S3). The rates of infectious and hematologic SAEs were similar between treatment arms (Supplementary Table S4).

A higher proportion of patients in the pevonedistat + azacitidine + venetoclax arm experienced a TEAE resulting in study drug discontinuation compared with azacitidine + venetoclax (35% vs 24%). The most common were thrombocytopenia (5% vs 3%), septic shock (5% vs 0%), neutropenia (4% vs 1%), multiple organ dysfunction syndrome (2% vs 3%), and pneumonia (1% vs 4%; Supplementary Table S5). The 30-day mortality rate was 6% with pevonedistat + azacitidine + venetoclax versus 5% with azacitidine + venetoclax and the 60-day mortality rate was 11% in both treatment arms. The rate of drug-related deaths was higher with pevonedistat + azacitidine + venetoclax compared with azacitidine + venetoclax (5% vs 3%), and included septic shock (2 events), multiorgan failure, and pneumonia

Table 3. Overall safety profile.

n (%)	Pevonedistat + azacitidine + venetoclax *n* = 81	Azacitidine + venetoclax *n* = 80	Total *N* = 161
Any TEAE	81 (100)	80 (100)	161 (100)
Any drug-related TEAE	74 (91)	76 (95)	150 (93)
Any grade ≥3 TEAE	81 (100)	79 (99)	160 (99)
Any drug-related grade ≥3 TEAE	65 (80)	67 (84)	132 (82)
Any SAE	62 (77)	55 (69)	117 (73)
Any drug-related SAE	32 (40)	28 (35)	60 (37)
TEAEs leading to discontinuation	28 (35)	19 (24)	47 (29)
Drug-related TEAEs leading to discontinuation	8 (10)	15 (19)	23 (14)
On-study deaths	18 (22)	15 (19)	33 (20)
TEAEs leading to death	17 (21)	15 (19)	32 (20)
Study drug-related TEAEs leading to death	4 (5)	2 (3)	6 (4)

SAE: serious adverse event; TEAE: treatment-emergent adverse event.

with pevonedistat + azacitidine + venetoclax and sepsis and pneumonia with azacitidine + venetoclax.

The study was designed with a ramp up dosing schedule for venetoclax dosing in cycle 1 and to permit flexible venetoclax dosing for patients achieving remission. Dose adjustments for all study drugs are summarized in Supplementary Table S6. The venetoclax dose was reduced (either dose reduction or administration reduced to 21 days from 28 days in patients with confirmed remission) for 64% of patients in both treatment arms. The median dose intensity of pevonedistat was 100%; there was no difference in median dose intensity with azacitidine and venetoclax between treatment arms (median 100% vs 100% for azacitidine and median 49% for venetoclax).

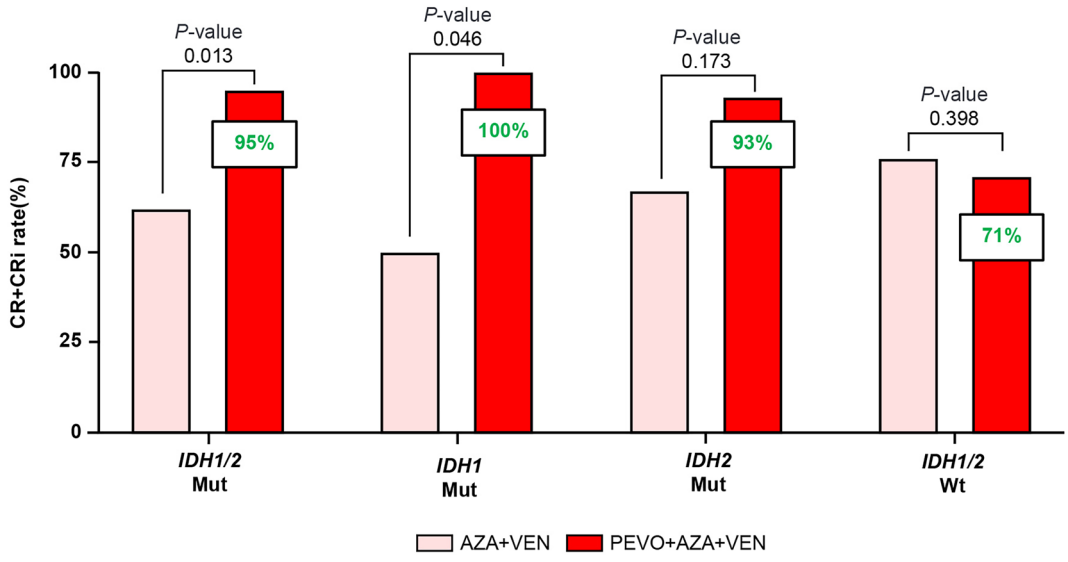
Exploratory biomarker analyses

Bone marrow aspirates were collected at screening to evaluate biomarkers that may identify those patients who could benefit most from addition of pevonedistat to azacitidine + venetoclax. Evaluation of key genes frequently found in AML was performed using an NGS panel and *FLT3*-ITD assays. In addition, ELN risk scores were centrally assigned based on these results and parallel cytogenetic assessments.

No statistically significant correlations were identified between ELN risk score (adverse, intermediate, and favorable) and any of the response criteria. We next focused on 11 commonly mutated genes with prognostic and/or therapeutic importance in AML (i.e. *ASXL1*, *CEBPA*, *DNMT3A*, *FLT3*, *IDH1*, *IDH2*, *NPM1*, *RUNX1*, *SRSF2*, *TET2*, *TP53*) and looked for any associations with clinical response. Interestingly, we found a statistically significant association between treatment arm and the CCR rate (i.e. CR+CRi) in patients with an *IDH1* or *IDH2* mutation (Figure 3). In total, there were 42 response-evaluable patients with an *IDH1* or *IDH2* mutation, with 21 in the pevonedistat + azacitidine + venetoclax arm ($n = 7$ *IDH1*, $n = 15$ *IDH2*) and 21 in the azacitidine + venetoclax arm ($n = 6$ *IDH1*, $n = 15$ *IDH2*). The CCR rate for the pevonedistat + azacitidine + venetoclax arm was 95% (20/21), versus 62% (13/21) in the azacitidine + venetoclax arm ($p = 0.013$ adjusted for age and AML subtype based on pre-specified randomization stratification factors). Furthermore, in patients who had wildtype *IDH1* and *IDH2*, the CCR rate was 71% (29/41) for the pevonedistat + azacitidine + venetoclax arm and 76% (35/46) for the azacitidine + venetoclax arm ($p = 0.398$), demonstrating the CCR rate of 95% was only observed in the *IDH1* or *IDH2* mutant population. The addition of pevonedistat to azacitidine + venetoclax was also associated with significant improvements in the overall response rate (CR + CRi + PR; $p = 0.020$) and leukemia response (CR + CRi + PR + MLFS); $p = 0.035$). No significant correlations between mutation status and response were observed for any of the other genes evaluated (Supplementary Table S7).

Discussion

The approval of azacitidine + venetoclax as a frontline treatment option for AML has significantly improved the outcomes of older adults with AML and of those who are unfit for intensive chemotherapy [8]. Despite this progress, approximately one-third of patients do not respond and will ultimately relapse, and so the outcomes of this population are suboptimal [8, 21]. Many phase 2 single-arm studies using novel HMAs plus venetoclax-based triplet regimens are ongoing, some of which have resulted in promising early data and are now being explored in larger, randomized phase 3 studies [22, 23]. As many patients with AML may not be suitable candidates for intensive chemotherapy, the development of new, tolerable and effective regimens for this older and less fit population of patients with AML is a major research priority.



	IDH1/2 mutant		*IDH1* mutant		*IDH2* mutant		wildtype *IDH1/2*	
	Total (*n*)	CR/CRi (*n*,%)	Total (*n*)	CR/CRi (*n*,%)	Total (*n*)	CR/CRi (*n*,%)	Total (*n*)	CR/CRi (*n*,%)
AZA+VEN	21	13 (62)	6	3 (50)	15	10 (67)	46	35 (76)
PEVO+AZA+VEN	21	20 (**95**)	7	7 (**100**)	15	14 (**93**)	41	29 (**71**)

Figure 3. CCR rate in patients with an *IDH1* or *IDH2* mutation. Note: Analysis based on pre-specified randomization stratification factors (i.e. age/AML subtype). AZA+VEN: azacitidine + venetoclax; CCR: composite complete remission; CR: complete remission; CRi: complete remission with incomplete blood count recovery; Mut: mutant; PEVO+AZA+VEN: pevonedistat + azacitidine + venetoclax; Wt: wildtype.

In this randomized study, we observed no differences in response rates or EFS with the addition of pevonedistat to the standard of care azacitidine + venetoclax backbone. While it is challenging to compare across studies, our study appeared to be more enriched with patients with higher-risk disease, including 37% with secondary AML (vs approximately 25% in VIALE-A) and 54% with an ECOG PS of 2–3 (vs approximately 45% in VIALE-A) [8]. Despite these differences, the response rates and EFS observed in our study appear similar to those from VIALE-A. This is an important confirmatory finding that highlights that these clinical endpoints remain appropriate benchmarks for future registrational studies in this older AML population.

Our study also implemented routine dose reduction of venetoclax after achievement of remission to 21 days in consolidation cycles—which was done in nearly two-thirds of patients in both arms—a practice that may result in less myelosuppression and which is more aligned with clinical practice at many centers and with some expert recommendations [24]. The similarity of the clinical outcomes in our study and those from VIALE-A suggests that this dosing strategy could be implemented in future studies of HMA and venetoclax-based regimens. Moreover, despite the higher-risk patient population involved in this study, the data reflect the progress that has been made in daily clinical practice with regard to routine use of azacitidine + venetoclax combinations and management of toxicity through dose modifications.

While there were no differences in response rates or EFS in the primary analysis or in the prespecified stratification factors, a *post hoc* analysis suggested possible benefit with the pevonedistat + azacitidine + venetoclax regimen in patients harboring an *IDH1* or *IDH2* mutation. *IDH*-mutated AML has a lower apoptotic threshold than *IDH* wildtype AML and is relatively sensitive to venetoclax-based regimens [25,26]. In preclinical studies, pevonedistat upregulated NOXA, leading to downstream neutralization of myeloid cell leukemia 1 (MCL-1), a well-established mechanism of resistance to BCL-2 inhibitors such as venetoclax [12]. Furthermore, in a phase 2 study of pevonedistat + azacitidine involving older patients with previously untreated TP53-mutated AML, no patients achieved CR/CRi, although treatment did result in upregulation of the NOXA protein [27]. In a phase 1/2 study of azacitidine, venetoclax, and pevonedistat in patients with newly diagnosed secondary AML, the CR/CRi rate was 66%, and in an exploratory analysis, early upregulation of NOXA expression was observed [15]. It is possible that the combined pro-apoptotic pressure from both

venetoclax and pevonedistat through inhibition of both anti-apoptotic BCL-2 and MCL-1 may explain the particularly high CCR rate (95%) observed in patients with *IDH1*- or *IDH2*-mutated AML. Unfortunately, evaluation of apoptotic protein expression levels by flow cytometry in this study was uninterpretable due to poor assay quality. Due to the early termination of the study, robust EFS and OS data are not available to determine whether the high CCR rates also translated to better long-term outcomes. Nevertheless, these findings are hypothesis-generating and could be further evaluated in other studies of pevonedistat or other agents that directly or indirectly inhibit MCL-1.

A major limitation to this study is the early termination and short follow-up. The median follow-up of the study was only was 8.44 months with pevonedistat + azacitidine + venetoclax and 7.95 months with azacitidine + venetoclax, which is shorter than the median EFS for the azacitidine + venetoclax arm in VIALE-A [8]. However, given the negative findings of the randomized PANTHER study, which evaluated pevonedistat in newly diagnosed higher-risk MDS/CMML or low-blast AML, in combination with the lack of difference in response rate or EFS in the interim analysis of the present study, the sponsor elected to close the study and limit long-term EFS and survival follow-up. Given the limited follow-up, we cannot rule out a longer-term difference between the two arms. However, such a difference seems unlikely, particularly considering the observation that in the VIALE-A study, differences in EFS and OS were observed within the first few months following randomization.

In conclusion, although the addition of pevonedistat to azacitidine + venetoclax failed to significantly improve response rates or EFS in patients with newly diagnosed AML who were unfit for intensive chemotherapy, this randomized study confirms the efficacy and safety of the azacitidine + venetoclax standard-of-care first described in VIALE-A, with potential benefit of adding pevonedistat in *IDH*-mutated AML.

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Author contributions

N.S., N.F., D.V.F., and F.S. designed the research. A.W., T.C., C.R., J.C., B.O., L.A., M.H., E.A., N.F., D.V.F., F.S., and C.P. performed the research. A.W., T.C., K.L, C.R., J.C., B.O., L.A., M.H., E.Z., and C.P. provided study materials for enrolled patients. A.W., T.C., T.Y., and C.P. collected and assembled data. N.S., C.R., N.F., T.Y., D.V.F., F.S., and C.P. analyzed and interpreted the data. N.S., T.Y., D.V.F., and C.P. wrote the manuscript. All authors reviewed and revised the manuscript and provided their final approval of the version to be published.

Disclosure statement

N.S. has received consulting fees from Pfizer Inc., GSK, NKARTA, and Sanofi; grants or funding from Takeda Oncology, Astellas Pharma Inc., Xencor, Stemline Therapeutics, and NextCure; and other potential financial relationships with Adaptive Biotechnologies, Novartis, Amgen, Takeda Oncology, Pfizer Inc., Astellas Pharma Inc., Sanofi, and BeiGene. A.W. has been on an advisory board or committee for Abbvie, Astellas, and Servier; has received honoraria from Abbvie, Astellas, Celgene/BMS, Jazz Pharmaceuticals/Swixx Biopharma, Novartis, Pfizer, and Servier; and has also received grants/funding from Jazz Pharmaceuticals/Swixx Biopharma. T.C. reports positions on an advisory council or committee for BMS/Celgene, Abbvie, Jazz Pharma, Novartis, Agios, Servier, and BluePrint; has received honoraria from Novartis, Astellas, Celgene/BMS, Jazz Pharma, Servier, Incyte; and also reports non-financial conflicts with Pfizer, Celgene/BMS, Novartis, Abbvie, Servier, and Gilead. K.L. is or has been on the board of directors for Beigene, Novartis, Takeda, and AstraZeneca; has received honoraria from Abbvie, Beigene, BMS, Janssen, and Takeda; and received grants or funding from Novartis, Abbvie, Beigene, and Amgen. C.R. reports being on an advisory council or committee for and receiving honoraria from Abbvie, Amgen, Astellas, BMS, Boehringer Ingelheim, Jazz Pharmaceuticals, and Servier; has received consulting fees from Abbvie, BMS, Jazz Pharmaceuticals, and Servier; and has also received grants or funding from Abbvie, Amgen, Astellas, BMS, Iqvia, and Jazz Pharmaceuticals. L.A. reports receiving consulting fees from Takeda, BMS, Novartis, and Jazz Pharmaceuticals. N.F., and F.S., are employees of Takeda. T.Y., and S.L., are employees of and report ownership of stocks/shares for Takeda. D.V.F. is or has been an employee of Oryzon Genomics; holds stocks and shares for Oryzon Genomics and Viracta Therapeutics; has been on an advisory council or committee for Viracta Therapeutics; and has received consulting fees from Skyhawk Therapeutics, Molecular Partners, and Viracta Therapeutics. J.C., B.O., M.P.G.H., M.H., E.Z., and C.P. have no potential conflicts of interest.

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