Use of a Validated AML Composite Score Measuring Fitness and Cytogenetic Risk to Assess Outcomes in 1L AML Patients Receiving Venetoclax Plus Azacitidine in VIALE-A

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OBJECTIVE

To assess the benefit of venetoclax + azacitidine vs placebo + azacitidine in patients with differential fitness and disease biology across a spectrum of acute myeloid leukemia composite model scores

CONCLUSIONS

Based on AML composite model score, most patients (92%) enrolled in VIALE-A were considered likely to have decreased benefit from intensive chemotherapy (Groups B or C), and nearly a quarter of the enrolled patients were considered to be in the frailest group (Group C)

Patients treated with venetoclax + azacitidine had higher composite complete remission rates and prolonged duration of remission and overall survival compared with those who received placebo + azacitidine across all AML composite model groups

Patients who were considered to be the frailest under the AML composite model (Group C), for whom the recommended treatment per guidelines is clinical trial enrollment and/or palliative care, had longer median overall survival despite slightly higher rates of early mortality with venetoclax + azacitidine vs placebo + azacitidine

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BACKGROUND

- Approximately half of adults with acute myeloid leukemia (AML) are unable to receive standard intensive chemotherapy (IC) due to older age or comorbidities[1]
- The phase 3, double-blind VIALE-A trial (NCT02993523) evaluated the efficacy of venetoclax (Ven), an oral BCL-2 inhibitor, combined with azacitidine (Aza) in older patients who were unfit for IC based on modified Ferrara criteria[2]
  - This study demonstrated that Ven+Aza led to an increased median overall survival (OS) compared with placebo (Pbo) + Aza (14.7 vs 9.6 mo)[3]
- There is currently no defined standard method for ascertaining fitness for IC
  - The Ferrara criteria is one of several scoring methods focused on age and patient comorbidities,[2,4] but disease characteristics and cytogenetic risk should also be considered
- The AML composite model (AML-CM) is a validated system based on patient comorbidities and cytogenetic/molecular disease characteristics used to determine fitness for transplant and potentially for other intensive regimens[5]
- The goal of this analysis was to assess the benefit of Ven+Aza vs Pbo+Aza in patients with differential fitness and disease biology using AML-CM score

STUDY DESIGN & METHODS

AML-CM Score[5] Groupings

Group A
Score 1-4
Patients could potentially benefit from IC

Group B
Score 5-9
Patients have decreased benefit from IC

Group C
Score ≥10
Patients could potentially benefit from a clinical trial or palliative care

- Scoring methodology is detailed in the **Supplemental Materials**

VIALE-A Study Design and Analysis Population

Eligibility
- Newly diagnosed AML
- Ineligible for IC defined as
  - ≥75 years old
  - 18-74 with at least 1 of the following:
    - CHF requiring treatment or ejection fraction ≤50%
    - Chronic stable angina
    - DLCO ≤65% or FEV1 ≤65%
    - ECOG PS 2 or 3

2:1 Randomization (N=433)

Ven+Aza (N=286)
Ven 400 mg once daily Days 1-28
Aza 75 mg/m² SC/IV Days 1-7

Pbo+Aza (N=145)
Pbo once daily Days 1-28
Aza 75 mg/m² SC/IV Days 1-7

AML-CM Scoring (n=380)

Post Hoc Analysis Population

Ven+Aza (N=253)[a]
Group A: n=22 (9%)
Group B: n=172 (68%)
Group C: n=59 (23%)

Pbo+Aza (N=127)[b]
Group A: n=10 (8%)
Group B: n=92 (72%)
Group C: n=25 (20%)

- **Data cutoff for post hoc analysis**: December 1, 2021
- 51 patients could not be categorized due to missing data; missing data included ELN risk, obesity, hepatic comorbidities, and albumin level
- Some patients with missing data were included in the analysis if that data would not have impacted AML-CM group assignment

[a]Four patients did not receive treatment. [b]One patient did not receive treatment.
AML, acute myeloid leukemia; AML-CM, AML composite model; Aza, azacitidine; CHF, congestive heart failure; DLCO, diffusing capacity for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; FEV1, forced expiratory volume in the first second; IC, intensive chemotherapy; IV, intravenous; Pbo, placebo; SC, subcutaneous; Ven, venetoclax.

RESULTS

Patient Baseline Characteristics

- Patients with higher AML-CM scores generally had poor prognostic disease characteristics, adverse ELN risk, decreased pulmonary function, and other comorbidities
- Of those evaluated in the Ven+Aza group, *TP53* mutations were detected in 0/11 patients (0%) in Group A, 30/119 patients (25%) in Group B, and 8/34 patients (24%) in Group C
  - In the Pbo+Aza group, *TP53* mutations were detected in 0/7 (0%), 11/59 (19%), and 1/18 (6%) in Groups A, B, and C, respectively
- Scan the QR code to access **Supplemental Materials** for a complete list of baseline characteristics

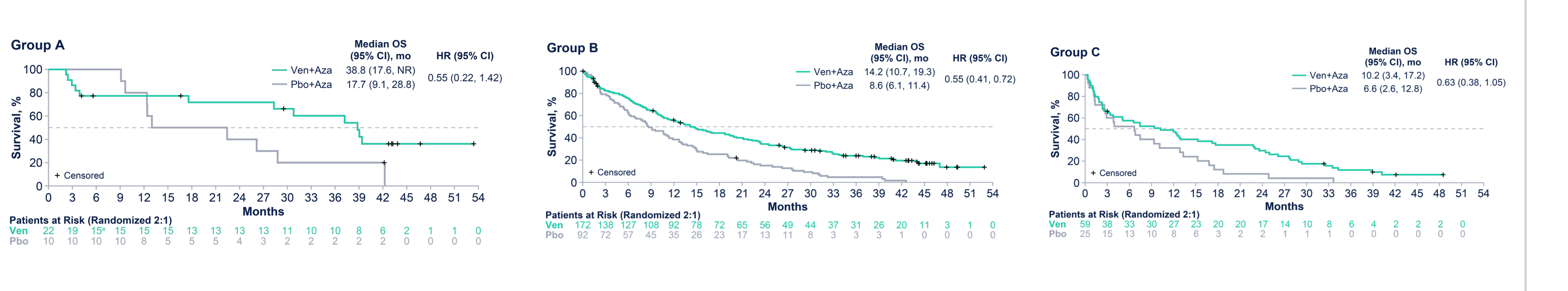
	Group A		Group B		Group C	
	Ven+Aza (n=22)	Pbo+Aza (n=10)	Ven+Aza (n=172)	Pbo+Aza (n=92)	Ven+Aza (n=59)	Pbo+Aza (n=25)
Median follow up (range), mo	42.7 (0.7-53.4)	42.1 (0.7-42.2)	43.3 (0.0-52.9)	NE (0.2-42.5)	42.0 (0.4-48.4)	NE (NE-NE)
Median age (range), y	75 (66-84)	73 (65-79)	77 (49-91)	76.5 (60-90)	74 (65-90)	75 (62-87)
ECOG PS, n (%)						
0-1	13 (59)	5 (50)	92 (53)	54 (59)	36 (61)	14 (56)
2-3	9 (41)	5 (50)	80 (47)	38 (41)	23 (39)	11 (44)
Reasons for ineligibility for IC, n (%)						
≥75 years of age	13 (59)	5 (50)	109 (63)	56 (61)	29 (49)	11 (44)
18-74 years of age with	9 (41)	5 (50)	63 (37)	36 (39)	30 (51)	14 (56)
ECOG PS 2-3	8 (36)	5 (50)	54 (31)	28 (30)	17 (29)	8 (32)
CHF requiring treatment	0	0	1 (1)	1 (1)	0	2 (8)
Ejection fraction ≤50%	0	0	3 (2)	2 (2)	2 (3)	0
Chronic stable angina	0	0	3 (2)	1 (1)	2 (3)	0
DLCO ≤65%	0	0	6 (3)	4 (4)	3 (5)	8 (32)
FEV1 ≤65%	0	0	1 (1)	3 (3)	9 (15)	4 (16)
Creatinine clearance ≥30 to <45 mL/min	0	0	4 (2)	4 (4)	6 (10)	1 (4)
Hepatic impairment with total bilirubin >1.5 to ≤3× ULN	0	0	0	0	3 (5)	0
Other	2 (9)	1 (10)	7 (4)	1 (1)	3 (5)	4 (16)
ELN[a] risk group, n (%)						
Favorable	12 (63)	4 (57)	19 (13)	13 (16)	3 (6)	2 (9)
Intermediate	6 (32)	2 (29)	41 (28)	16 (20)	5 (10)	1 (4)
Adverse	1 (5)	1 (14)	86 (59)	52 (64)	43 (84)	20 (87)

[a]ELN risk groups are based on 2017 criteria
Aza, azacitidine; CHF, congestive heart failure; DLCO, diffusing capacity for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; FEV1, forced expiratory volume in the first second; IC, intensive chemotherapy; Pbo, placebo; Ven, venetoclax; ULN, upper limit of normal.

Efficacy

- The 12-month OS rates were:
  - **Ven+Aza**: 77% (Group A), 56% (Group B), and 47% (Group C)
  - **Pbo+Aza**: 80% (Group A), 38% (Group B), and 32% (Group C)

Overall Survival

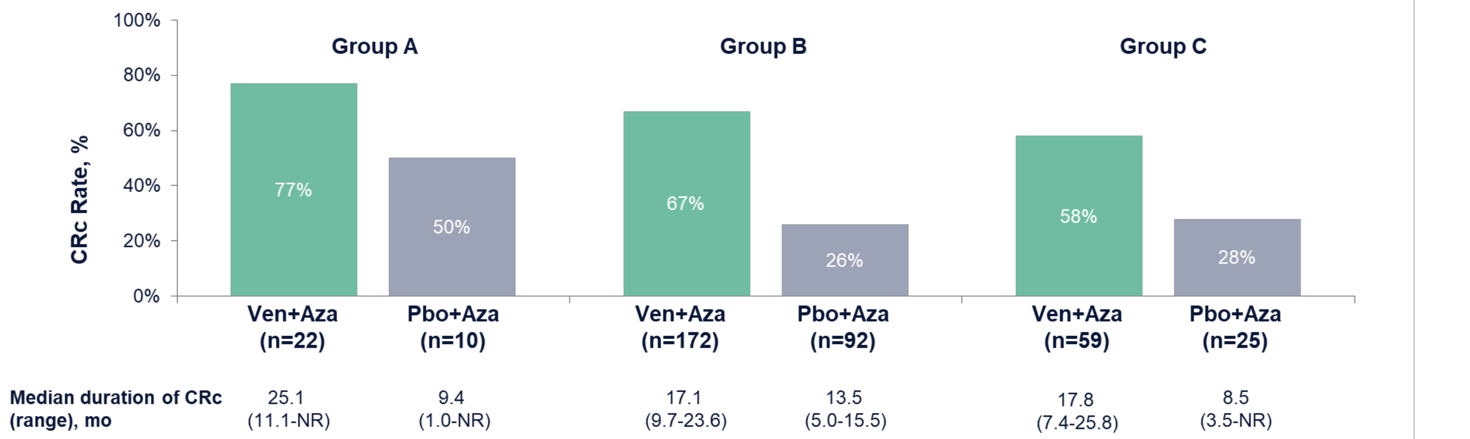


[a]4 deaths occurring within 6 months in the Ven+Aza arm were due to AEs.
Aza, azacitidine; HR, hazard ratio; OS, overall survival; Pbo, placebo; Ven, venetoclax.

Efficacy *(continued)*

- The median time to first composite complete remission (CRc [CR + CRi]) was
  - **Ven+Aza**: 1.2 mo (Group A), 1.3 mo (Group B), and 1.1 mo (Group C)
  - **Pbo+Aza**: 4.2 mo (Group A), 3.0 mo (Group B), and 2.6 mo (Group C)

CRc Rates and Duration by AML-CM Group

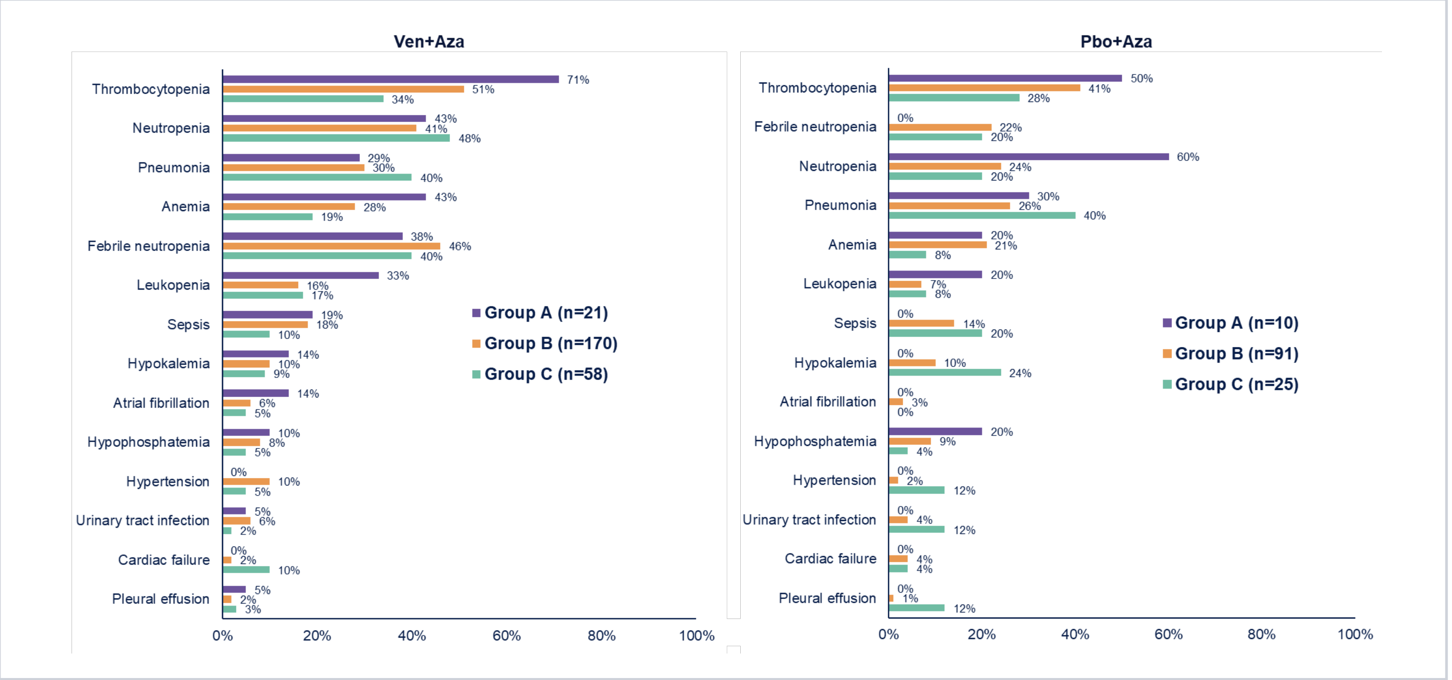


AML-CM, acute myeloid leukemia composite model; Aza, azacitidine; CR, complete remission; CRc, composite complete remission; CRi, complete remission with incomplete count recovery; NR, not reported; Pbo, placebo; Ven, venetoclax.

Safety

- 22 patients died within 30 days of the first dose of Ven+Aza or Pbo+Aza, with 1 death from disease progression and 21 deaths from adverse events
  - 4 patients died from cardiac complications, 3 from infections, 3 from respiratory distress/failure, 3 from multiple organ failure, 3 from AML, 2 from hemorrhage/bleeding, 1 from brain edema, 1 from celiac artery occlusion, and 1 from worsening of general condition
  - Scan the QR code to access the **Supplemental Materials** for a complete list of deaths within 30 days of the first dose by AML-CM group

Grade ≥3 TEAEs Occurring in >10% of Patients in any AML-CM Group



AML-CM, acute myeloid leukemia composite model; Aza, azacitidine; Grp, Group; Pbo, placebo; TEAE, treatment-emergent adverse event; Ven, venetoclax.