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POSTER ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Outcomes in Chemotherapy-Ineligible Elderly Patients with Newly Diagnosed Acute Myeloid Leukemia Treated with Venetoclax Plus Azacitidine: A Pooled Analysis

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Introduction:
Elderly patients (aged ≥75 years), with newly diagnosed acute myeloid leukemia (ND AML) frequently are ineligible to receive intensive chemotherapy (IC) and therefore have limited treatment options. The BCL-2 inhibitor venetoclax (Ven) in combination with azacitidine (Aza) was approved for the treatment of patients with ND AML who are ineligible for IC due to age or comorbidities based on the phase 3 VIALE-A trial. Treatment with Ven+Aza demonstrated rapid and durable remissions, with improved median overall survival (OS) versus placebo (Pbo)+Aza (14.7 vs 9.6 mo; hazard ratio [HR] 0.64) in patients enrolled in the VIALE-A trial (median age, 76 years). Although a subgroup analysis showed improvement in patients aged ≥75 years (HR 0.54; DiNardo C, et al. *N Engl J Med.* 2020;383:617), detailed analyses are lacking to further understand the impact of advanced patient age on the safety and efficacy of Ven+Aza. Here, we evaluate the outcomes of Ven+Aza across elderly age cohorts in patients with ND AML pooled from the open-label, single-arm, Phase 1b M14-358 trial of Ven plus hypomethylating agents in patients with ND AML who were ≥65 years old and IC-ineligible (NCT02203773) and the Phase 3 VIALE-A trial of Ven+Aza versus Pbo+Aza in patients with ND AML who were IC-ineligible (NCT02993523).

Methods:
This analysis included IC-ineligible patients aged ≥75 years with ND AML pooled from the Ven+Aza arm of the M14-358 trial (NCT02203773) and the Ven+Aza and Pbo+Aza arms of the VIALE-A trial (NCT02993523). In both studies, patients received Ven daily (400 mg) with 75 mg/m ^{2} subcutaneous (SC) or intravenous (IV) Aza on Days 1-7 of 28-day cycles). In VIALE-A, patients were randomized 2:1 to Ven+Aza or Pbo+Aza and received Ven (400 mg) or Pbo daily with Aza at the same schedule. For this post hoc analysis, patients were stratified by age (75-79 years, 80-84 years, and ≥85 years) to evaluate efficacy and safety, including complete remission (CR)/CR with incomplete hematologic recovery (CRi) rate, minimal residual disease (MRD) response ($<10^{-3}$) rate, OS, and Grade ≥3 treatment-emergent adverse events (TEAEs).

Results:
A total of 216 patients treated with Ven+Aza and 87 patients treated with Pbo+Aza were included, with n=120 and n=54 aged 75-79 years, n=75 and n=27 aged 80-84 years, and n=21 and n=6 aged ≥85 years (**Table 1**). Baseline disease characteristics

were largely similar across age cohorts, including ECOG performance status and poor cytogenetic risk (**Table 1**). Baseline grade 3/4 neutropenia was more prevalent in patients aged ≥85 years.

Across the 75-79, 80-84, and ≥85 age cohorts, the CR/CRi rate was higher with Ven+Aza (67%, 68%, and 81%) vs Pbo+Aza (19%, 22%, and 17%) (**Table 1**). Ven+Aza also elicited a higher rate of MRD response ($<10^{-3}$;30%, 29%, and 29%) vs Pbo+Aza (13%, 11%, and 17%). Median OS (95% CI) was 14.1 mo (10.2-24.9) for those aged 75-79 years, 12.2 mo (8.0-21.8) for those aged 80-84 years, and 16.2 mo (9.3-20.5) for those aged ≥85 years in the Ven+Aza arm; in the Pbo+Aza arm, median OS (95% CI) was 8.5 mo (6.8-10.7), 10.1 mo (2.3-14.5), and 2.6 mo (0.2-not reached), respectively. In the Ven+Aza arm, median Ven dosing per cycle was 21 days across all age cohorts, with a median time from Day 1 of a cycle until Day 1 of the next cycle (including dose holds), of 31, 35, and 31 days for the 75-79, 80-84, and ≥85 age cohorts, respectively.

Rates of Grade ≥3 non-hematologic TEAEs were similar between age cohorts (**Table 2**). Consistent with the known safety profile of Ven+Aza, the most frequently reported hematologic TEAEs for the 75-79, 80-84, and ≥85 age cohorts included anemia (30%, 26%, and 48%), febrile neutropenia (43%, 38%, and 52%), neutropenia (34%, 37%, and 29%), and thrombocytopenia (36%, 48%, and 43%).

Conclusions:

Ven+Aza led to higher rates of remission, including higher rates of MRD response, and longer median OS vs Pbo+Aza, while maintaining consistent safety data across all older patient cohorts (Table 1). Findings were consistent with data from the overall population in VIALE-A (median age of 76 years), emphasizing the benefit of Ven+Aza in the older population. Although the post hoc nature of the analysis and limited sample sizes require careful interpretation of differences between cohorts, these findings confirm Ven+Aza provides benefit across elderly patient cohorts with ND AML who are ineligible for IC.

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Table 1. Baseline Characteristics and Efficacy by Age Cohort

	75-79 Years		80-84 Years		≥85 Years	
Baseline Characteristics	**Ven+Aza (n=120)**	**Pbo+Aza (n=54)**	**Ven+Aza (n=75)**	**Pbo+Aza (n=27)**	**Ven+Aza (n=21)**	**Pbo+Aza (n=6)**
Median age (range), mo	77 (75-79)	77 (75-79)	81 (80-84)	81 (80-84)	86 (85-91)	86 (85-90)
ECOG PS, n (%)						
0-1	85 (71)	39 (72)	61 (81)	23 (85)	15 (71)	3 (50)
2-3	35 (29)	15 (28)	14 (19)	4 (15)	6 (29)	3 (50)
CTCAE grade of neutropenia, n (%)						
1-2	15 (13)	11 (20)	8 (11)	5 (19)	2 (10)	1 (17)
3-4	84 (70)	33 (61)	55 (73)	18 (67)	19 (90)	5 (83)
Cytogenetics, n (%)						
Intermediate	77 (67)[a]	31 (57)	47 (66)[a]	19 (70)	14 (70)[a]	3 (50)
Poor	38 (33)[a]	23 (43)	24 (34)[a]	8 (30)	6 (30)[a]	3 (50)
Bone marrow blast count, n (%)						
<30%	38 (32)	16 (30)	20 (27)	8 (30)	5 (24)	0
30 to <50%	26 (22)	13 (24)	23 (31)	4 (15)	6 (29)	4 (67)
≥50%	56 (47)	25 (46)	32 (43)	15 (56)	10 (48)	2(33)
Type of AML, n (%)						
Primary/de novo	82 (68)	38 (70)	55 (73)	19 (70)	18 (86)	5 (83)
Secondary	38 (32)	16 (30)	20 (27)	8 (30)	3 (14)	1 (17)
AML with Myelodysplasia related changes, n (%)	41 (34)	21 (39)	23 (31)	9 (33)	8 (38)	2 (33)
Efficacy						
CR/CRi, n (%)	80 (67)	10 (19)	51 (68)	6 (22)	17 (81)	1 (17)
Median time to best response of CR/CRi (range), mo	1.4 (0.8-38.7)	3.0 (0.8-6.3)	2.0 (0.9-46.2)	2.3 (1.0-12.2)	1.1 (0.7-10.9)	5.3 (5.3-5.3)
Best MRD response, n/n (%)						
Response ($<10^{-3}$)	36 (30)	7 (13)	22 (29)	3 (11)	6 (29)	1 (17)
Positive ($\geq 10^{-3}$)	58 (48)	33 (61)	42 (56)	20 (74)	14 (67)	4 (67)
Not evaluable	26 (22)	14 (26)	11 (15)	4 (15)	1 (5)	1 (17)
Median OS (95% CI), mo	14.1 (10.2-24.9)	8.5 (6.8-10.7)	12.2 (8.0- 21.8)	10.1 (2.3-14.5)	16.2 (9.3-20.5)	2.6 (0.2-NR)

[a]Cytogenetics data were missing from some patients (n=5, age 75-79; n=4, age 80-84; n=1, age ≥85); percentages exclude missing patients.

Table 2. Most Common[a] Grade ≥3 Treatment-Emergent Adverse Events by Age Cohort

	75-79 Years		80-84 Years		≥85 Years	
Adverse Event, n (%)	**Ven+Aza (n=119)**	**Pbo+Aza (n=54)**	**Ven+Aza (n=73)**	**Pbo+Aza (n=26)**	**Ven+Aza (n=21)**	**Pbo+Aza (n=5)**
All adverse events	117 (98)	52 (96)	72 (99)	25 (96)	21 (100)	4 (80)
Hematologic adverse events						
Anemia	36 (30)	10 (19)	19 (26)	4 (15)	10 (48)	1 (20)
Febrile neutropenia	51 (43)	9 (17)	28 (38)	4 (15)	11 (52)	0
Leukopenia	18 (15)	2 (4)	9 (12)	3 (12)	2 (10)	0
Neutropenia	41 (34)	14 (26)	27 (37)	7 (27)	6 (29)	1 (20)
Neutrophil count decreased[b]	11 (9)	0	9 (12)	1 (4)	0	0
Platelet count decreased[b]	12 (10)	0	9 (12)	1 (4)	2 (10)	0
Thrombocytopenia	43 (36)	17 (31)	35 (48)	12 (46)	9 (43)	2 (40)
White blood cell count decreased[b]	13 (11)	1 (2)	5 (7)	0	3 (14)	0
Nonhematologic adverse events						
Atrial fibrillation	9 (8)	1 (2)	4 (5)	2 (8)	1 (5)	0
Fatigue	6 (5)	0	5 (7)	1 (4)	2 (10)	0
Hypertension	12 (10)	1 (2)	6 (8)	2 (8)	1 (5)	0
Hypokalemia	17 (14)	6 (11)	3 (4)	3 (12)	2 (10)	2 (40)
Hypophosphatemia	12 (10)	6 (11)	7 (10)	2 (8)	4 (19)	1 (20)
Infections						
Pneumonia	29 (24)	14 (26)	26 (36)	7 (27)	7 (33)	0
Sepsis	9 (8)	5 (9)	1 (1)	3 (12)	3 (14)	0
Urinary tract infection	7 (6)	4 (7)	2 (3)	0	3 (14)	0

[a]Treatment Emergent Adverse Events presented include those that occurred in ≥5% of patients in the combined age cohorts of the Ven+Aza arm or Ven+Pbo arm.
[b]Terms "neutrophil count decreased", "platelet count decreased", and "white blood cell count decreased" are reported separately from "neutropenia", "thrombocytopenia" and "leukopenia" because they fall under the Investigations System Organ Class within MedDRA.

Figure 1

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