A Randomized, Double-blind, Placebo-controlled Study of Venetoclax with Azacitidine vs Azacitidine in Treatment-naïve Patients with Acute Myeloid Leukemia Ineligible for Intensive Therapy: VIALE-A

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HEMA NEWS

Presented on: EHA 25 Virtual Congress, June 11-14, 2020

VIALE-A Study Design

(NCT02993523)

Eligibility

Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least one of the co-morbidities:
    - CHF requiring treatment or Ejection Fraction ≤50%
    - Chronic stable angina
    - DLCO ≤ 65% or FEV1 ≤ 65%
    - ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable risk cytogenetics per NCCN
- Active CNS involvement

Treatment

Randomization 2:1
N=433*

Venetoclax + Azacitidine (N=286)
Venetoclax 400 mg PO, daily, days 1-28 +
Azacitidine 75 mg/m² SC /IV days 1-7

Placebo + Azacitidine (N=145)
Placebo daily, days 1-28
+ Azacitidine 75 mg/m² SC /IV days 1-7

Randomization Stratification Factors Age (<75 vs. ≥75 years); Cytogenetic Risk (intermediate, Poor); Region

Venetoclax dosing ramp-up
Cycle 1 ramp-up Day 1: 100 mg, Day 2: 200 mg, Day 3 – 28: 400 mg
Cycle 2 → Day 1-28: 400 mg

Endpoints

Primary

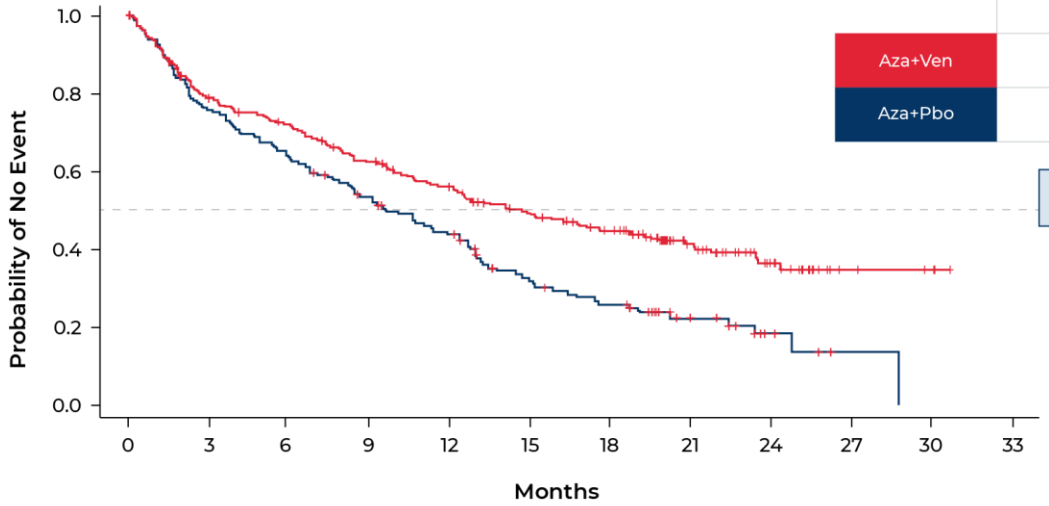
- Overall survival

Secondary

- CR+CRi rate
- CR+CRh rate
- CR+CRi and CR+CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR+CRi rates and OS in molecular subgroups
- Event-free survival

* 2 patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. 6 patients who did not receive treatment were excluded from the safety analysis set.
AML: Acute myeloid leukemia; CHF: Congestive heart failure; CNS: Central nervous system; CR: Complete remission; CRi: CR+ incomplete marrow remission; CRh: CR+ incomplete hematologic recovery; DCLO: diffusion lung capacity for carbon monoxide; ECOG: Eastern Cooperative Oncology Group; FEV1 : Forced expiratory volume; HMA: Hypomethylating agent; NCCN: National Comprehensive Cancer Network

Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall surival, months (95% CI)
Aza+Ven	161/286 (56)	7.6 (<0.1 – 30.7)	14.7 (11.9 – 18.7)
Aza+Pbo	109/145 (75)	4.3 (0.1 – 24.0)	9.6 (7.4 – 12.7)

Hazard ratio: 0.66 (95% CI: 0.52 – 0.85), p<0.001

Patients at Risk

Aza+Ven	286	219	198	168	143	117	101	54	23	5	3	0
Aza+Pbo	145	109	92	74	59	38	30	14	5	1	0	0

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18 <75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk). The hazard ratio between treatment arms were estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test.

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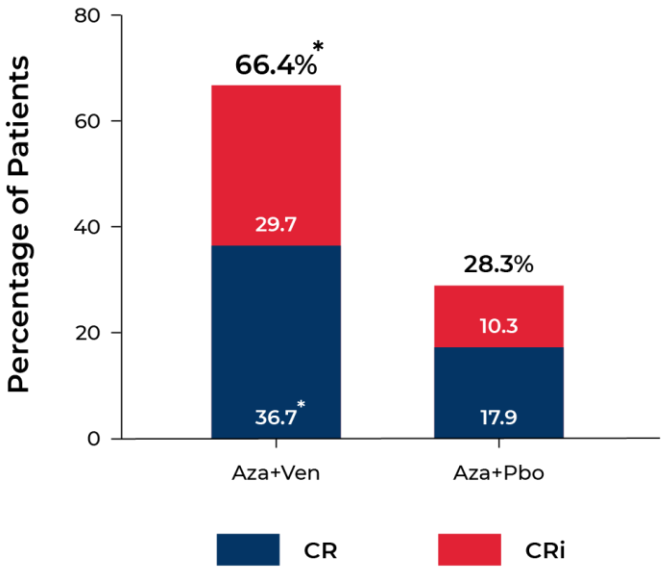
Composite Response Rate (CR+CRi)



	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR+CRi by initiation of Cycle 2, n (%)
Aza+Ven (n=286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza+Pbo (n=145)	4.5 (1.0 – 26.0)	2.8 (0.8 – 13.2)	11 (7.6)

*CR+CRi rate, CR rate, and CR+CRi by initiation of cycle 2 are statistically significant with p<0.001 by CMH test

Aza: Azacitidine; Pbo: Placebo; Ven: Venetoclax; CR: Complete remission; CRi: CR with incomplete-count recovery; CR was defined as absolute neutrophil count >10^3/µl, platelets >10^5/µl, red cell transfusion independence (TI), and bone marrow with <5% blasts; CRi was defined as all criteria for CR, except for neutropenia ≤10^3/µl or thrombocytopenia ≤10^5/µl.
CR + CRi rate was compared using Cochran-Mantel-Haenszel (CMH) test stratified by age (18 - < 75, ≥ 75) and cytogenetic risk (intermediate, poor).

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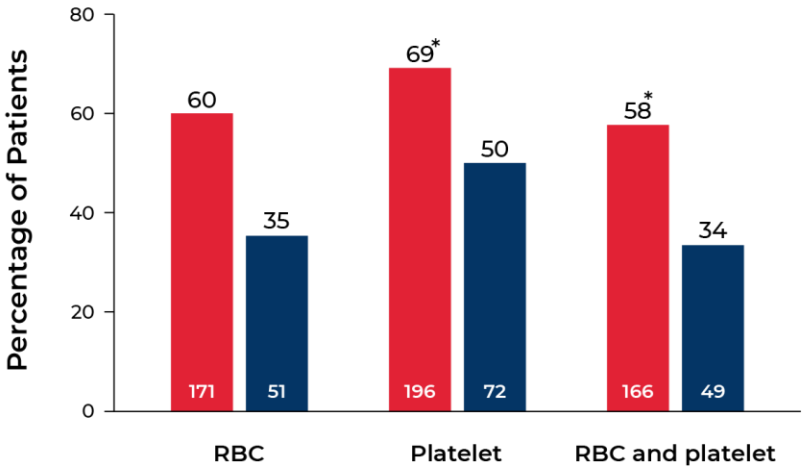
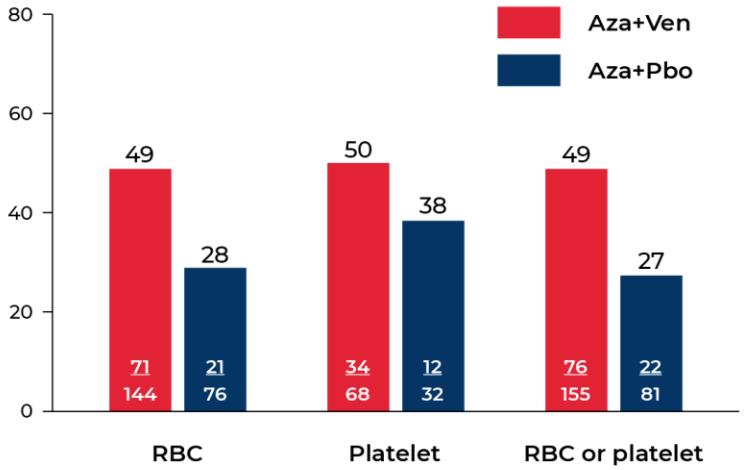
Patients with ≥8 Weeks of Transfusion-free Interval



Transfusion independence



Conversion rate of transfusion independence

*p<0.001 by CMH test

The post-baseline transfusion independence is defined as a period of ≥56 days with no RBC or platelet transfusion during the evaluation period;

Post-baseline transfusion evaluation period is from the first dose to the last dose of study drug +30 days;

Conversion rate of transfusion independence is the proportion of patients being post-baseline transfusion independent from baseline dependence.

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Summary of Treatment-emergent Adverse Events

Adverse events^, n (%)	Aza+Ven		Aza+Pbo	
	All grade* n=283	Grade 3/4** n=276	All grade* n =144	Grade 3/4** n =136
All AEs	**283 (100)**	**279 (99)**	**144 (100)**	**139 (97)**
Hematologic AEs	**236 (83)**	**233 (82)**	**100 (69)**	**98 (68)**
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (29)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Non-hematologic AEs	**47 (17)**	**46 (17)**	**44 (31)**	**44 (31)**
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalemia	81 (29)	30 (11)	41 (29)	15 (10)
Peripheral edema	69 (24)	1 (0)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	0	25 (17)	0

AE, adverse event, ^Includes all patients who received at least one dose of either of the treatment *Adverse events shown were reported in ≥20% of patients in either treatment arms; ** Grade 3 or 4 AEs ≥10% occurrence.