

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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Background

Current available therapies for patients (pts) with acute myeloid leukemia (AML) who are ineligible for intensive therapy yield limited responses with poor survival. Venetoclax (VEN) is a selective small-molecular inhibitor of BCL-2. Clinical data from a prior phase 1b study (NCT02203773) showed that VEN and Azacitidine (AZA) combination had promising efficacy with an acceptable safety profile.

Aims

We evaluated efficacy of AZA+VEN combination regimen compared to AZA + Placebo (PBO) in treatment-naïve pts with AML ineligible for intensive therapy.

Methods

This phase 3, randomized, double-blinded, multicenter, placebo-controlled study (NCT02993523) included pts with confirmed AML who were ineligible for intensive induction therapy due to medical comorbidities and/or age > 75 years. Prior treatment with a hypomethylating agent for an antecedent hematologic disorder was excluded. Pts were randomized to 2:1 AZA+VEN or AZA+PBO. Pts on AZA+VEN received AZA 75 mg/m² subcutaneous or intravenous on days 1–7 per 28-day cycle and once daily 400 mg VEN orally on days 1–28 with a 3-day ramp up in cycle 1. Pts on AZA+PBO received AZA 75 mg/m² on days 1–7 per 28-day cycle and once daily PBO orally on days 1–28. The primary endpoint was to compare overall survival (OS). Secondary endpoints were rates of: composite complete remission [complete remission (CR) + CR with incomplete count recovery (CRi)], CR+CRi by initiation of cycle 2, CR, transfusion independence [TI; red blood cells (RBC) or platelets], CR+CRi and OS by molecular subgroups, and event-free survival (EFS). A sample size of 400 was estimated to detect a hazard ratio (HR) of 0.7 in OS with 2-sided alpha of 4% and power of 87%.

OS and EFS were analyzed by the Kaplan-Meier method and compared between arms using the log-rank test stratified by age (18 to <75 vs ≥75) and cytogenetic risk (intermediate vs poor).

Results

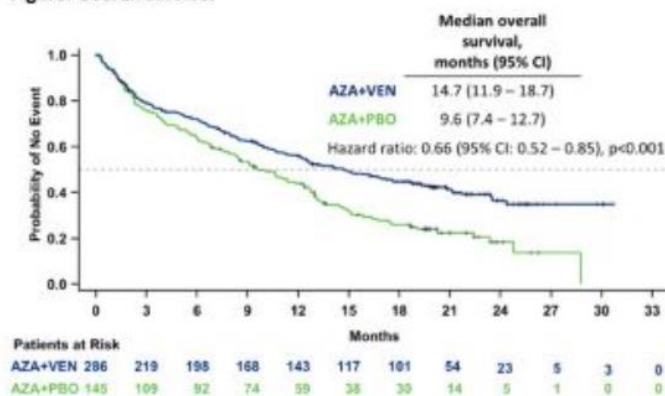
As of 04 Jan 2020, 431 patients (median age 76 years, range 49–91) were randomized to AZA+VEN (n=286) or AZA+PBO (n=145). With median follow-up of 20.5 months (mos), the median OS was 14.7 mos in AZA+VEN and 9.6 mos in AZA+PBO (HR: 0.66, 95% CI: 0.52–0.85, $p < 0.001$) respectively, representing a 34% reduction in risk of death (Figure). Pts received a median number of 7.0 (range: 1–30) and 4.5 (1–26) cycles of study drug in AZA+VEN and AZA+PBO. CR+CRi rates in AZA+VEN/AZA+PBO were 66%/28% ($p < 0.001$) respectively. Median time (95% CI) to first CR or CRi response was 1.3 (0.6–9.9)/2.8 (0.8–13.2) mos and duration of CR+CRi was 17.5/13.4 mos respectively. Response rates in pts with poor and intermediate cytogenetic risk was 53%/23% and 74%/32% respectively. Response rates in pts with DeNovo and secondary AML were 66%/30% and 67%/23% respectively. Other secondary endpoints are summarized in the Table. Grade ≥ 3 hematological adverse events (AEs) included (AZA+VEN/AZA+PBO) thrombocytopenia (45%/38%), neutropenia (42%/29%), febrile neutropenia (42%/19%), anemia (26%/20%), and leukopenia (21%/12%). All grade gastrointestinal AEs were common with nausea (44%/35%), constipation (43%/39%), diarrhea (41%/33%), and vomiting (30%/23%). Notable serious AEs (grade ≥ 3) were febrile neutropenia (30%/10%) and pneumonia (16%/22%). Laboratory tumor lysis syndrome was rare at 1% in AZA+VEN. The 30-day mortality rates were 7% (n=21)/6% (n=9) respectively.

Table: Patient responses in treatment groups

	AZA+VEN (n=286)	AZA+PBO (n=145)	p-value
CR + CRi rate, % (95% CI)	66.4 (60.6-71.9)	28.3 (21.1-36.3)	<0.001
CR+CRi by initiation of cycle 2, % (95% CI)	43.4 (37.5-49.3)	7.6 (3.8-13.2)	<0.001
CR rate, % (95% CI)	36.7 (31.1-42.6)	17.9 (12.1-25.2)	<0.001
TI, % (95% CI)			
Red blood cells	59.8 (53.9-65.5)	35.2 (27.4-43.5)	<0.001
Platelets	68.5 (62.8-73.9)	49.7 (41.3-58.1)	<0.001
CR+CRi rates in molecular subgroups, % (95% CI)			
<i>IDH1/2</i>	75.4 (62.7-85.5)	10.7 (2.3-28.2)	<0.001
<i>FLT3</i>	72.4 (52.8-87.3)	36.4 (17.2-59.3)	0.021
<i>NPM1</i>	66.7 (46.0-83.5)	23.5 (6.8-49.9)	0.012
<i>TP53</i>	55.3 (38.3-71.4)	0	<0.001
Event free survival, months (95% CI)	9.8 (8.4–11.8)	7.0 (5.6–9.5)	<0.001

AZA+VEN: Azacitidine+Venetoclax; AZA+PBO: Azacitidine+Placebo; CR: Complete remission; CRi: CR with incomplete marrow recovery; CRh: CR with partial hematologic recovery; TI: Transfusion independence (defined as ≥ 56 days with no RBC or platelet transfusion between first and last day of treatment)

Figure. Overall survival



Conclusion

Among treatment-naïve predominantly elderly pts with AML ineligible for intensive therapy, the combination regimen of AZA+VEN led to statistically significant and clinically meaningful improvement in response rates and OS as compared to AZA, with a manageable safety profile.

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Keyword(s): AML, BCL2, Clinical trial, Elderly