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Prognostic Factors in Patients with Acute Myeloid Leukemia Treated with the Combination of Venetoclax Plus Azacitidine (VEN+AZA)

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Abstract

Objectives: To analyze the efficacy, safety, prognostic factors, factors affecting treatment continuation, suitable treatment candidates, and optimal administration schedule in patients with Acute Myeloid Leukemia (AML) treated with Venetoclax Plus Azacitidine (VEN+AZA).

Methods: We performed a retrospective analysis of the data of 39 patients with untreated or relapsed/refractory AML.

Results: The median duration of follow-up was 6 months, and the median number of treatment cycles was 2. The Composite Complete Remission (CRc) achievement rate (complete remission + complete remission with incomplete hematological recovery) was 61.5%. The treatment discontinuation rate was 76.9%, the median Overall Survival (OS) was 7.7 months, and Event-Free Survival (EFS) was 4.8 months. In subgroup analyses, significant differences in the OS were observed between subgroups stratified according to the cytogenetic risk, CRc achievement rate, and Charlson Comorbidity Index (CCI) (≤ 7 *vs.* >7). A significant difference in the EFS was also observed between subgroups stratified according to the cytogenetic risk and CRc achievement rate. The response rate tended to be lower in the adverse cytogenetic risk subgroup. Patients who received VEN for 21 days or less in the first treatment cycle tended to have a better OS.

Conclusion: A lower OS and EFS were associated with a higher treatment discontinuation rate, lower number of treatment cycles, and lower CRc achievement rate than those observed in the VIALE-A trial. We considered that treatment continuation was important to improve the prognosis. We also concluded that it is important to select candidates suitable for VEN+AZA treatment and to modify the administration schedule.

Keywords: Venetoclax; Azacytidine; Real-world; Japanese; Prognostic factors

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Introduction

The VIALE-A trial reported that the response rate to Venetoclax Plus Azacitidine (VEN+AZA) treatment increased as the number of treatment cycles increased [1]. It is also reported that Measurable Residual Disease (MRD) of $<10^{-3}$ is achieved in about 21% of patients after 7 cycles of treatment [2]. Responders to the treatment had a favorable prognosis [1-4]. Treatment continuation is important to improve the prognosis. We attempted to analyze the factors that might have an impact on treatment continuation.

The prognostic factors in patients receiving VEN+AZA treatment is unknown [5,6]. We conducted this study to explore these factors.

Data on Japanese patients receiving this treatment are limited [7-14]. In addition, it has been reported that adverse events, such as Febrile Neutropenia (FN), are more frequent in Japanese patients [7-9,11,14], and the optimal administration method for VEN+AZA in Japanese patients'

needs to be investigated.

Patients and Method

Objectives

The two primary objectives of this study were to determine the treatment response rate, Event-Free Survival rate (EFS), and overall Survival Rate (OS) of treatment-naive or previously treated AML patients treated with the combination regimen of VEN+AZA. The secondary objectives were to determine patient- and disease-related predictors of the EFS and OS in these patients, and the toxicities associated with VEN+AZA treatment.

Patient eligibility

This study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of the Institutional Review Board of Saitama Cancer Center. The eligibility criteria included all patients aged 18 years old or older with treatment-naive or previously treated Acute Myeloid Leukemia (AML) who had received at least one dose of VEN+AZA between May 2021 and September 2023. Patients were excluded if death occurred before the first dose of the disease-directed therapy or if the treatment records were unavailable for retrospective analysis.

Treatment regimen

Patients received VEN from day 1 of treatment until the end of the 28-day cycle, or for a shorter duration to, adjust for toxicity and/or drug-drug interactions. AZA 75 mg/m^2 was administered in 7-day courses. Thereafter, VEN+AZA were then administered as maintenance therapy in 28-day cycles until they could no longer tolerate the treatment, disease progression was observed, or death occurred, with cycle delays allowed for adverse events or count recovery.

Data collection and entry

We retrospectively extracted the clinical data by reviewing the electronic medical records. The clinical parameters and outcomes were recorded, including the patient demographic characteristics, comorbidities, laboratory parameters, and disease characteristics of the AML. The follow-up was started from admission for the first course of VEN+AZA.

Safety analysis

Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Treatment-related adverse events were included if they occurred between the first dose and 28 days after treatment discontinuation. Quantitative toxicities were graded and recorded throughout each patient's treatment phase, excluding electrolyte aberrations. In instances where complete records were unavailable, toxicities were marked as unavailable for the phase of treatment, to reduce bias.

Cytogenetic analyses

AML was diagnosed according to the 5th edition World Health Organization criteria, with a minimum of one bone marrow biopsy demonstrating at least 20% or greater myeloblasts [15]. The cytogenetic risk was defined as recommended by the European LeukemiaNet (ELN) 2022 guidelines [16].

Response assessment

Response assessments were performed in accordance with the modified International Working Group response criteria for AML [16]. Complete Remission (CR) was defined as an Absolute Neutrophil Count (ANC) of greater than 1,000 cells/mm^3, platelet count of greater than 100,000 cells/mm^3, transfusion independence, and a bone marrow biopsy showing less than 5% blasts. CR with incomplete hematologic recovery (CRi) was defined as all the criteria for CR, except for neutropenia (ANC ≤ 1,000 cells/mm^3) or thrombocytopenia (platelets ≤ 100,000 cells/mm^3). CR with partial hematologic recovery (CRh) was defined as all the criteria for CR except for lower ANC (>500 cells/mm^3) and platelet (>50,000 cells/mm^3) count thresholds. Progressive disease was defined as outlined by the European LeukemiaNet guidelines. Composite Complete Remission (CRc) included patients who achieved CR or CRi.

The date of relapse was defined as the date of the first bone marrow test after CRc revealing disease relapse. Transfusion independence was defined as absence of the need for red cell or platelet transfusion for at least 56 days between the first and last days of treatment.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 26 (IBS Corporation, Armonk, NY, USA). Continuous variables were expressed in median values and interquartile ranges. Categorical variables were compared between groups using Fisher's exact test. Multivariate analyses were performed using logistic regression. OS was analyzed using the Kaplan-Meier method and compared between the groups by the log-rank test. Two-tailed P values <0.05 were considered as being indicative of statistical significance.

Result

Patients' characteristics

Overall, 39 patients were included in the analysis. The patient characteristics are shown in Table 1. The median patient age was 73 years (range, 40-87). *De novo* AML and secondary AML accounted for 56.4% and 43.6% of the cases, respectively. In all 46.2% of patients were classified as poor risk according to the ELN classification. Baseline transfusion dependencies for red cell and platelet transfusions were 74.4% and 66.7%, respectively.

There were 2 or more reasons for ineligibility to receive intensive therapy in 61.5% of patients. In all, VEN+AZA was administered as first-line treatment in 41.0% of patients, as second-line treatment in 33.3% of patients, and as third- or later-line treatment in 25.6% of patients. The median number of prior therapy lines was one.

Response

The treatment responses are shown in Table 2. As the best response, CR was achieved in 19 (48.7%) patients, CRi was achieved in 5 (12.8%) patients, and Partial Response (PR) was achieved in 3 (7.7%) patients. The overall response rate was 69.2%. The CRc rate was 61.5%. As the final response, CR was achieved in 8 (20.5%) patients, CRi was achieved in 3 (7.7%) patients, and PR was achieved in 1 (2.6%) patient. The overall response rate was 30.8%. The CRc rate was 28.2%.

We investigated the impact of the cytogenetic risk classification on the treatment response (Table 3). In the intermediate risk group, as the best response, CR was achieved in 42.1% of patients and CRi in 21.1% of patients. As the final response, CR was achieved in 21.1% of patients and CRi in 10.5% of patients. In the poor risk group, as the best response, CR was achieved in 50% of patients and CRi in 5.6% of patients. As the final response, CR was achieved in 16.7% of patients and CRi in 5.6% of patients.

Table 1: Shows the main baseline characteristics of the study population at diagnosis and prior to VEN+AZA treatment. A total of 39 patients were identified.

Characteristic	n=39
Age	
Median, years (range)	73 (40~87)
75 years, n (%)	17 (43.6)
Male, n (%)	30 (76.9)
B.S.A. median (range)	1.59 (1.25~1.89)
AML type, n (%)	
De novo	22 (56.4)
Secondary	17 (43.6)
Secondary AML type, n/N (%)	
Prior MDS or PV	9/17 (52.9)
Treatment-related AML	5/17 (29.4)
Prior MDS and treatment-related AML	3/17 (17.6)
ECOG performance status, n (%)	
0 or 1	26 (66.7)
≧ 2	13 (32.3)
Median CCI (range)	4 (0~15)
Blast count, n (%)	
<30%	14 (35.9)
≧ 30% to <50%	7 (17.9)
≧ 50%	18 (46.2)
AML with myelodysplasia-related changes, n (%)	22 (56.4)
AML with M5, n (%)	5 (10.3)
Characteristic	**n=39**
Cytogenetic risk, n (%)	
Favorable	1 (2.6)
Intermediate	19 (48.7)
Adverse	18 (46.2)
Unknown	1 (2.6)
Somatic mutation, n/N (%)	
FLT3 ITD or TKD	4/34 (11.8)
Grade 3 or 4 cytopenia at baseline, n/N (%)	
Neutropenia	21 (53.8)
Grade 3	6 (15.4)
Grade 4	15 (38.5)
Anemia	20 (51.3)
Thrombocytopenia	25 (64.1)
Transfusion dependence, at baseline, n (%)	
RBCs	29 (74.4)
Platelets	26 (66.7)
≧ 2 reasons for ineligibility to receive intensive therapy, n (%)	24 (61.5)
Prior therapy lines, n/N (%)	
0	16 (41)
1	13 (33.3)
≧ 2	10 (25.6)

Abbreviations: n: number; B.S.A: Body Surface Area; AML: Acute Myeloid Leukemia; N: Number; MDS: Myelodysplastic Syndromes; PV: Polycythemia Vera; ECOG: Eastern Cooperative Oncology Group; CCI: Charlson Comorbidity Index; M5: Acute Monocytic Leukemia; FLT 3, Fms-Like Tyrosine kinase receptor-3; ITD: Internal Tandem Duplication; TKD: Tyrosine Kinase Domain; RBCs: Red Blood Cells

Table 2: Shows the response rate, discontinuation rate, and outcome data of VEN+AZA treatment.

Response, discontinuation and outcome	n=39
Median follow up time, months (range)	6 (0.4-26.2)
Median cycles, (range)	2 (1~13)
Duration of VEN administration in the 1st cycle, days (range)	29 (1~53)
G-CSF administration, n (%)	5 (12.8)
Fluconazole administration, n (%)	37(95)
Best response, n (%)	
ORR	27 (69.2)
CR	19 (48.7)
CRi	5 (12.8)
PR	3 (7.7)
MLFS	0
RD	7 (17.9)
PD	4 (10.3)
NE	1 (2.6)
Final response, n (%)	
ORR	12 (30.8)
CR	8 (20.5)
CRi	3 (7.7)
PR	1 (2.6)
MLFS	0
RD	0
MR	6 (15.4)
PD	20 (51.3)
NE	1 (2.6)
Response, discontinuation and outcome	**n=39**
Median duration of response, months (range)	3.8 (0.4~16.8)
Early death (within 30 days)	4 (10.3)
Median time to ANC M 1 × 10^3/uL, in CR, days (range)	43.5 (32~72)
Discontinued during follow up, n (%)	30 (76.9)
Reason for discontinuation, n/N (%)	
PD	13/30 (43.3)
MR	8/30 (26.7)
Death	2/30 (6.7)
uBMT	2/30 (6.7)
Pt's request	1/30 (3.3)
Parkinson's disease	I/30 (3.3)
Cerebral hemorrhage	1/30 (3.3)
Febrile neutropenia	1/30 (3.3)
Bone marrow suppression	1/30 (3.3)
The dead during follow up, n (%)	23 (60.0)
Reason for death, n/N (%) PD	23/23 (100.0)

Abbreviations: VEN: Venetoclax; G-CSF: Granulocyte-Colony Stimulating Factor; ORR: Overall Response Rate; CR: Complete Response; CRI: CR with Incomplete Hematologic Recovery; PR: Partial Response; MLFS: Morphologic Leukemia-Free State; RD: Refractory Disease; PD: Progressive Disease; NE: Not Examined; MR: Minimal Residual; ANC: Neutrophil Count; uBMT: unrelated Bone Marrow Transplant

Table 3: Shows the treatment response by the cytogenetic risk.

Cytogenetic risk	Intermediate n=19		Adverse n=18	
Response	Best response n (%)	Final response n (%)	Best response n (%)	Final response n (%)
CR	8 (42.1)	4 (21.1)	9 (50)	3 (16.7)
CRh	0	0	0	0
CRi	4 (21.1)	2 (10.5)	1 (5.6)	1 (5.6)
MLFS	0	0	0	0
PR	2 (10.5)	1 (5.3)	1 (5.6)	0
RD	2 (10.5)	0	5 (27.8)	0
MR	0	2 (10.5)	0	3 (16.7)
PD	2 (10.5)	9 (47.4)	2 (11.1)	11 (61.1)
NE	1 (5.3)	1 (5.3)	0	0

Table 4: Shows response by the number of prior treatments.

Prior treatment lines	0 n=16		1 n=13		≧ 2 n=10	
Response	Best n (%)	Final n (%)	Best n (%)	Final n (%)	Best n (%)	Final n (%)
CR	9 (56.2)	3(18.8)	7 (53.8)	3 (23)	3 (30)	2 (20)
CRh	0	0	0	0	0	0
CRi	4 (25)	2 (12.5)	1 (7.7)	1 (7.7)	0	0
MLFS	0	0	0	0	0	0
PR	0	0	2 (15.4)	1 (7.7)	1 (10)	0
RD	1 (6.3)	0	3 (23.1)	0	3 (30)	0
MR	0	4 (25)	0	1 (7.7)	0	1 (10)
PD	1 (6.3)	6 (37.5)	0	7 (53.8)	3 (30)	7 (70)
NE	1(63)	163)	0	0	0	0

Table 5A: Shows the hematological adverse events.

	n =39	
AE, n (%)	Any grade	Grade ≧ 3
Hematological events	39 (100)	39 (100)
Thrombocytopenia	39 (100)	39 (100)
Neutropenia	37 (94.9)	36 (92.3)
Febrile neutropenia	15 (38.5)	15 (38.5)
Grade 3		14 (35.9)
Grade 4		1 (2.6)
Anemia	39 (100)	32 (82.1)
Leukopenia	37 (94.9)	37 (94.9)

Table 5B: Shows the non-hematological adverse events.

	n=39	
AE, n (%)	Any grade	Grade ≧ 3
Non-Hematological	37 (95%)	7 (17.9%)
T-Bil increased	6 (15.4)	0
AST increased	27 (69.2)	1 (2.6%)
ALT increased	27 (69.2)	1 (2.6%)
ALP increased	3 (7.7%)	0
T-chol increased	1 (2.6%)	0
Cr increased	19 (48.7%)	1 (2.6%)
CPK increased	7 (17.9%)	0
Na abnormality	30 (76.9%)	1 (2.6%)
K abnormality	13 (33.3%)	7 (17.9%)
Ca abnormality	30 (76.9%)	2 (5.1%)
Anorexia	1 (2.6%)	1 (2.6%)
COVID-19 infection	1 (2.6%)	0

Abbreviations: T-Bil: Total Bilirubin; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; T-chol: Total Cholesterol; Cr: Creatinine; CPK: Creatine Phosphokinase; Na: Sodium; K: Potassium; Ca: Calcium; COVID-19: Coronavirus Disease 2019

We then investigated how the number of prior therapy lines might impact the treatment response (Table 4). In the group with no (0) prior therapy lines, as the best response, CR was achieved in 56.2% of patients and CRi in 25% of patients. As the final response, CR was achieved in 18.8% of patients and CRi in 12.5%. In the group with one prior therapy line, as the best response, CR was achieved in 53.8% of patients and CRi in 7.7%. As the final response, CR was achieved in 23.0% of patients and CRi in 7.7% of patients. In the group with two or more prior therapies, as the best response, CR was achieved in 30.0% of cases and CRi in 0.0% of cases. As the final response, CR was achieved in 20.0% of cases and CRi in 0.0% of cases.

Toxicity

Thirty-nine (100%) patients experienced at least one hematological toxicity of any grade (Table 5A). Grade 3 or more severe hematological toxicities that were observed included thrombocytopenia in 100%, leukopenia in 94.9%, neutropenia in 92.3%, and anemia in 82.1% of patients. FN occurred in 38.5% of the patients (Table 5A). Grade 3 or more severe non-hematological toxicities were observed in 17.9% of patients (Table 5B). There were no cases of death due to adverse events.

Table 6: Lists studies of VEN+AZA treatment in Japan.

6A)

	Design	N	Combined with	Age (yr)	Cytogenetic risk	FLT-3	Follow-up	median number of Cycles	Number of VEN treatment days in the 1st cycle
1	Phase I	ND:5 RR:1	AZA	75 (66-80)	n.a	n.a	11.4 m	n.a	28
2	Phase III	ND:24	AZA	77.5 (68-85)	Intermediate: 75% Adverse: 25%	8.7%	16.3 m	n.a	28
3	Retrospective Study	12	AZA:11 LDAC:1	74 (70-85)	n.a	n.a	7.3 m	n.a	n.a
4	Retrospective Study	ND:13	AZA	79 (72-86)	Adverse: 61.5%	n.a	VEN14: 141d VEN28: 192d	n.a	14, 28
5	Retrospective Study	ND:14 RR:27	AZA:39 LDAC:2	74 (46-89)	Favorable: 12.1% Intermediate: 41.4% Adverse: 46.3%	12.2%	240 d	2 (1-18)	18 (1-33)
G	Retrospective Study	ND:30 RR:27	AZA:48 Ara-C:9	74 (39-87)	Favorable: 2% Intermediate: 60% Adverse: 39%	ITD 18%	10.8 m	n.a	n.a
7	Retrospective Study	411 AZA	AZA	73 (66-78)	n.a	n.a	11 m	2	27 (17-30)
D	Retrospective Study	ND:16 RR:23	AZA	73 (40-87)	Favorable: 2.6% Intermediate: 48.7% Adverse: 46.2% unknown: 2.6%	11.80%	6 m	2	29 (1-53)

6B)

CR	Median OS	Median EFS	FN (%)	Correlative studies	XR
CR: 50% CRi: 33%	ND: 3.4 m RR: 15.7 m	n.a	67	Incidence of any AEs necessitating VEN discontinuation: 33%. There were no AEs necessitating VEN dose reduction.	7
CR: 45.9% CRi: 20.0%	NR	16.3 m	79.2	Effect of VEN on treatment-emergent Grade ≧ 3 neutropenia was similar in both Asian and non-Asian patients.	8
ORR: 66.7% CR: 41.6%	n.a	n.a	63.6	Most patients enrolled in the study had a high Cmin. Small BSA tended to be associated with higher venetoclax concentrations.	9
VEN14, CR:50.0%, CRc: 75.0% VEN28, CR: 40.0%, CRc: 80.0%	VEN14: NR VEN28: 254 d	VEN14: NR VEN20: 178 d	VEN14: 37.5% VEN28: 80.0%	VEN14: CRc: 75%; EFS: NR; OS: NR; FN: 37.5% VEN28: CRc: 00%; EFS:178 d; OS: 254 d; FN: 80%	10
CR: 36.5% CRi: 36.5%	287 d	n.a	58.5	Use of G-CSF and dose reduction of venetoclax may be beneficial in the Japanese population	11
CRc: 54%	os@1y: 53.3%	n.a	n.a	Patients administered anthracycline immediately before the VEN regimen showed a higher cCR rate than those that were not (79% *vs.* 45%) although this association was not statistically significant (P=0.079).	12
n.a	4.3 m	n.a	n.a	Use of G-CSF and the shortening of the VEN administration period to 21 days or less during the two cycles were significantly associated with the continuation rate of VEN+AZA for three or more cycles.	13
CR: 48.7% CRi: 12.8%	7.7 m	4.8 m	38.5	Poor EFS and OS in the adverse-risk patients. Good EFS and os in patients who achieved CR or Cri. Poor OS in patients with CCI>7	This Case

Abbreviations: N: Number; FLT-3: Fms-Like Tyrosine Kinase Receptor-3; VEN: Venetoclax; OS: Overall Survival Rate; EFS: Event-Free Survival Rate; FN: Febrile Neutropenia; ND: Newly Diagnosed; RR: Relapsed/Refractory; AZA: Azacitidine; n.a: Not Available; m: Months; CR: Complete Response; CRI: CR with Incomplete Hematologic Recovery; LDAC: Low Dose Cytarabine; ORR: Overall Response Rate; Cmin: Minimum Blood Drug Concentration; B.S.A: Body Surface Area; d: Days; CRc: Composite CR; NR: Not Reached; G-CSF: Granulocyte-Colony Stimulating Factor; Ara-C: Cytarabine; ITD: Internal Tandem Duplication

Survival

The median overall survival was 7.7 months, event-free survival was 4.8 months, and the median duration of follow-up was 6 months, as shown in Table 2 and Figure 1A, 1B.

No significant differences in either the OS or EFS were observed among the subgroups stratified by the number of prior treatments (Figure 2A, 2B).

No significant difference in either the OS or EFS was observed between the MRC and non-MRC subgroups (Figure 3A, 3B).

No significant difference in either the OS or EFS was observed between the *de novo* and secondary subgroups (Figure 4A, 4B).

Among the groups stratified by the cytogenetic risk, the OS and EFS were significantly worse in the adverse cytogenetic risk subgroup than in the intermediate cytogenetic risk subgroup (Figure 5A, 5B).

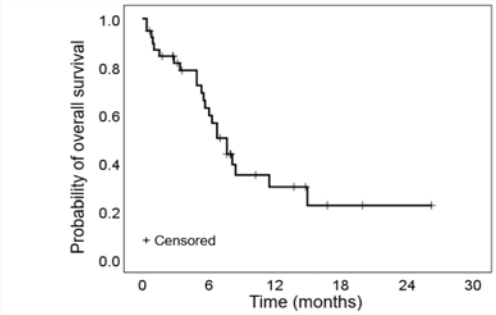
No significant difference in either the OS or EFS was observed between the Fms-Like Tyrosine kinase 3 (FLT3) mutation-positive and FLT3 mutation-negative subgroups (Figure 6A, 6B).

No significant differences in either the OS or EFS were observed among the subgroups stratified by the percentage of bone marrow blasts (Figure 7A, 7B).

No significant difference in either the OS or EFS was observed between the M5 and non-M5 subgroups (Figure 8A, 8B).

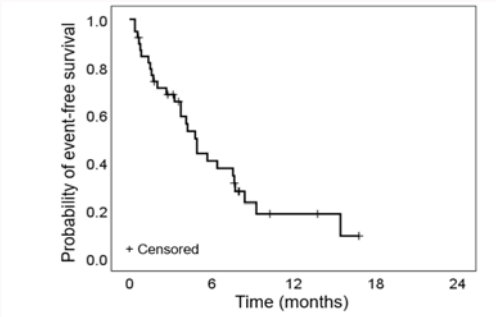
Among the subgroups stratified by the treatment response, the OS and EFS were significantly better in the CR and CRi subgroups (Figure 9A, 9B).

No significant difference in either the OS or EFS was observed between the subgroups classified according the Performance Status (PS) score (PS 0-1 and PS ≥ 2). However, the PS 0 to 1 subgroup



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox-proportional HR(95%CI)
All Cases (N=39)	23	62.7(46.4, 79.0)	29.8(12.4, 47.2)	7.7(5.9, 9.4)	-	-

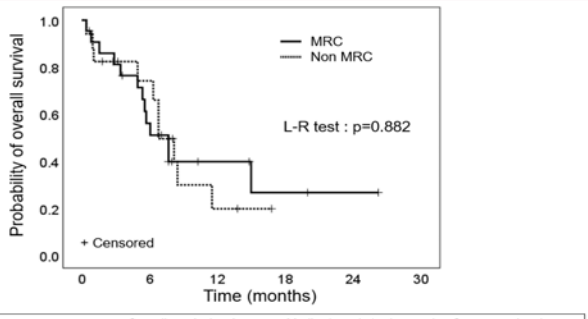
1A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
All Cases (N=39)	28	40.5(24.0, 57.0)	18.5(3.8, 33.2)	4.8(3.7, 5.9)	-	-

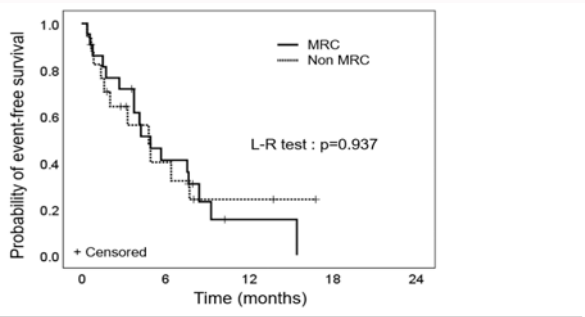
1B) EFS.

Figure 1: All cases.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
MRC (N=22)	13	56.0(34.4, 77.6)	39.6(17.6, 61.6)	7.7(5.0, 10.3)	0.882	Cont.
Non MRC (N=17)	10	74.1(51.8, 96.4)	19.8(0, 43.7)	6.8(4.9, 8.7)		1.06(0.47, 2.44)

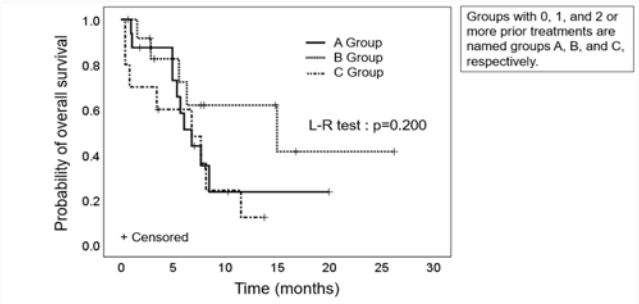
3A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
MRC (N=22)	17	41.0(19.4, 62.6)	15.4(0, 33.6)	4.9(2.7, 7.1)	0.937	Cont.
Non MRC (N=17)	11	40.1(14.2, 66.0)	24.1(1.0, 47.2)	4.8(2.1, 7.5)		0.97(0.45, 2.08)

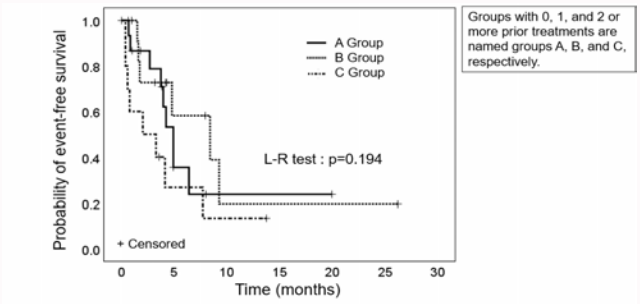
3B) EFS.

Figure 3: MRC and non-MRC subgroups.



	Events	Survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
A Group (N=16)	10	58.3(32.6, 84.0)	23.3(0, 48.8)	6.8(4.8, 8.7)	0.200	Cont.
B Group (N=13)	5	72.2(45.2, 99.2)	61.9(32.1, 91.7)	15.0(0, 31.1)		0.49(0.17, 1.48)
C Group (N=10)	8	60.0(29.6, 90.4)	12.0(0, 34.0)	6.8(1.1, 12.5)		1.35(0.53, 3.45)

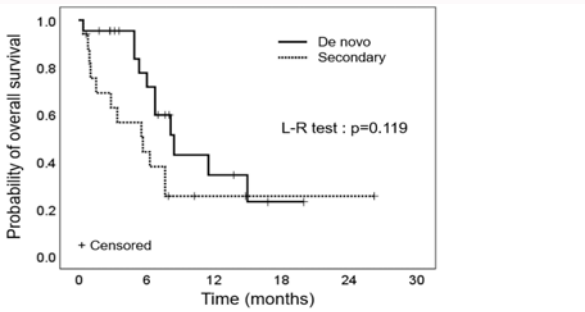
2A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
A Group (N=16)	9	35.5(8.1, 62.9)	23.6(0, 49.9)	4.9(4.0, 5.9)	0.194	Cont.
B Group (N=13)	6	58.2(25.1, 91.3)	19.4(0, 55.9)	8.4(1.3, 15.5)		0.71(0.25, 2.02)
C Group (N=10)	8	40.0(9.6, 70.4)	13.3(0, 36.8)	2.0(0, 5.9)		1.79(0.69, 4.70)

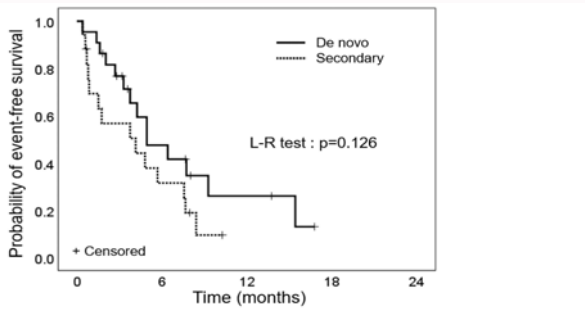
2B) EFS.

Figure 2: By number of prior treatment lines.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
De novo (N=22)	11	77.6(58.0, 97.2)	34.1(8.4, 59.8)	8.5(5.9, 11.0)	0.119	Cont.
Secondary (N=17)	12	43.9(19.6, 68.2)	25.1(3.7, 46.5)	5.7(1.3, 10.1)		1.89(0.83, 4.31)

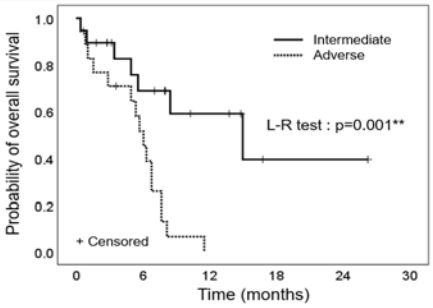
4A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
De novo (N=22)	14	47.5(24.4, 70.6)	26.0(3.5, 48.5)	4.9(2.1, 7.7)	0.126	Cont.
Secondary (N=17)	14	31.5(8.8, 54.2)	9.5(0, 25.8)	4.1(0, 8.8)		1.79(0.84, 3.83)

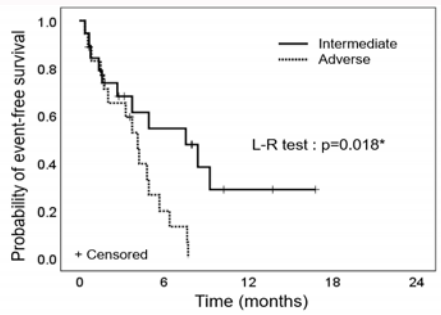
4B) EFS.

Figure 4: *De novo* and secondary subgroups.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
Intermediate (N=19)	7	68.8(45.7, 91.9)	59.0(32.3, 85.7)	15.0(3.0, 26.9)	0.001**	Cont.
Adverse (N=18)	16	51.5(27.2, 75.8)	6.4(0, 18.6)	6.1(4.9, 7.3)		4.31(1.63, 11.39)

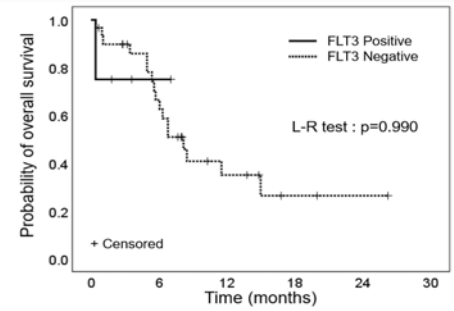
5A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
Intermediate (N=19)	11	54.4(30.5, 78.3)	28.6(3.5, 53.7)	7.6(2.6, 12.5)	0.018*	Cont.
Adverse (N=18)	16	19.8(0, 39.6)	0	4.1(3.0, 5.3)		2.65(1.14, 6.15)

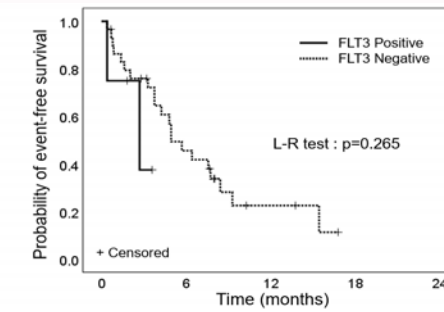
5B) EFS.

Figure 5: Subgroups stratified by the cytogenetic risk.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
FLT3 Positive (N=4)	1	75.0(32.5, 100)	-	-	0.990	Cont.
FLT3 Negative(N=30)	17	66.3(48.3, 84.3)	34.8(14.8, 54.8)	8.2(5.8, 10.5)		0.99(0.13, 7.63)

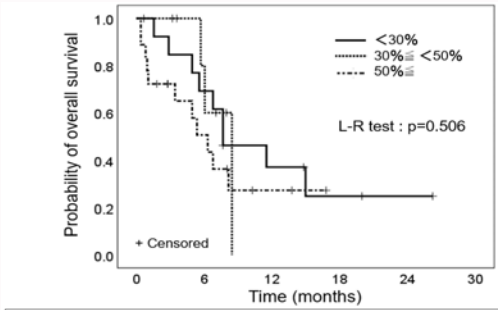
6A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
FLT3 Positive (N=4)	2	37.5(0, 93.6)	-	2.7(0, 6.1)	0.265	Cont.
FLT3 Negative(N=30)	21	45.6(26.8, 64.4)	22.5(5.1, 39.9)	4.9(2.9, 6.9)		0.43(0.09, 2.01)

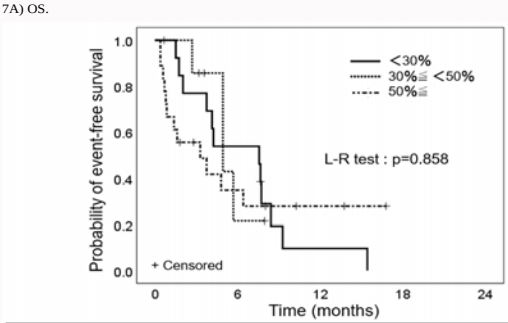
6B) EFS.

Figure 6: FLT3-positive and FLT3-negative subgroups.



		Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
<30%	(N=14)	9	69.2(44.1, 94.3)	36.9(9.9, 63.9)	7.7(2.5, 12.9)	0.506	Cont.
30%≦ <50%	(N=7)	3	80.0(44.9, 100)	-	8.5(-)		0.93(0.25, 3.51)
50%≦	(N=18)	11	50.6(25.5, 75.7)	27.1(3.0, 51.2)	6.3(3.9, 8.7)		1.58(0.65, 3.87)

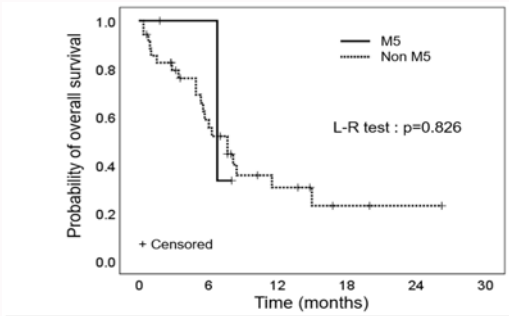
7A) OS.



		Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
<30%	(N=14)	12	53.8(26.8, 80.8)	9.6(0, 27.2)	7.6(3.4, 11.7)	0.858	Cont.
30%≦ <50%	(N=7)	4	21.4(0, 58.2)	-	4.9(2.6, 7.2)		0.83(0.26, 2.62)
50%≦	(N=18)	12	34.7(11.2, 58.2)	27.8(5.5, 50.1)	3.3(0, 7.0)		1.14(0.51, 2.54)

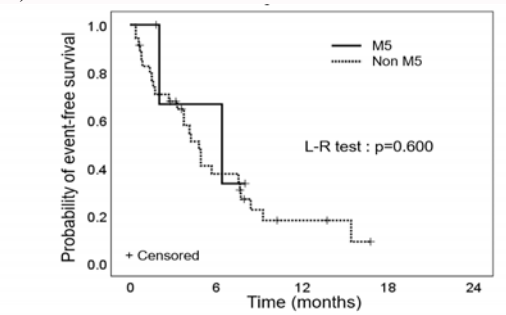
7B) EFS.

Figure 7: Subgroups stratified by the percentage of bone marrow blasts.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
M5 (N=4)	2	100(-)	-	6.8(-)	0.826	Cont.
Non M5 (N=35)	21	58.7(41.3, 76.1)	30.5(12.5, 48.5)	7.7(5.0, 10.3)		1.18(0.27, 5.12)

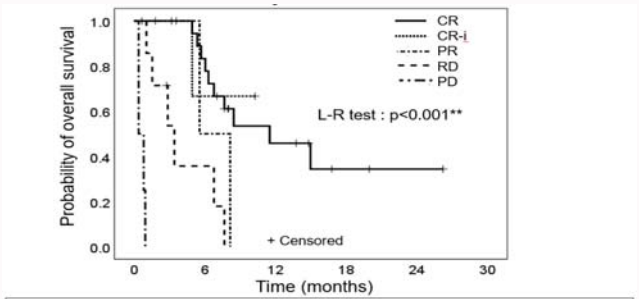
8A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
M5 (N=4)	2	66.7(13.4, 100)	-	6.4(0, 13.4)	0.600	Cont.
Non M5 (N=35)	26	37.4(20.3, 54.5)	17.9(3.2, 32.6)	4.8(3.6, 6.0)		1.47(0.35, 6.23)

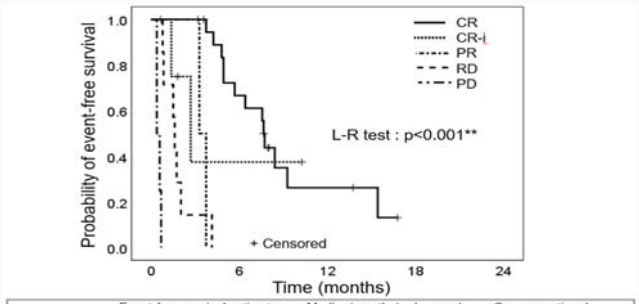
8B) EFS.

Figure 8: M5 and non-M5 subgroups.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
CR (N=19)	10	83.3(66.1, 100)	45.8(20.9, 70.7)	115(4.7, 18.3)	0.000**	Cont.
CR-i (N=5)	1	66.7(13.4, 100)	-	-		0.91(0.11, 7.36)
PR (N=3)	2	50.0(0, 100)	0	5.6(-)		2.84(0.60, 13.51)
RD (N=7)	6	35.7(0, 74.5)	0	3.4(1.4, 5.5)		6.48(2.11, 19.88)
PD (N=4)	4	0	0	0.4(-)		-

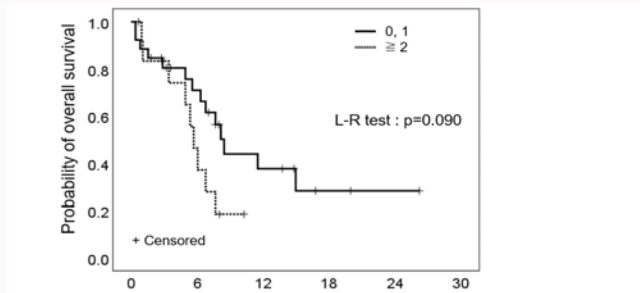
9A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
CR (N=19)	13	66.7(44.9, 88.5)	26.3(3.0, 49.6)	7.7(7.3, 8.0)	0.000**	Cont.
CR-i (N=5)	2	37.5(0, 93.6)	0	2.7(0.7, 4.7)		1.63(0.36, 7.46)
PR (N=3)	2	0	0	3.3(-)		8.03(1.29, 50.07)
RD (N=7)	7	0	0	1.6(1.4, 1.9)		24.17(5.81, 100.62)
PD (N=4)	4	0	0	0.4(-)		-

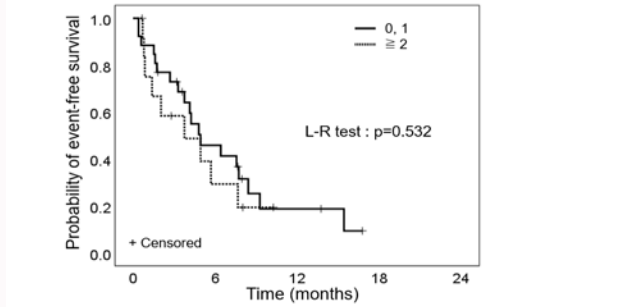
9B) EFS.

Figure 9: Subgroups stratified by the best response.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
0, 1 (N=26)	14	70.9(52.4, 89.3)	37.6(15.5, 59.7)	8.5(7.1, 9.9)	0.090	Cont.
≧ 2 (N=13)	9	46.3(16.9, 75.7)	-	5.7(4.6, 6.8)		2.10(0.87, 5.06)

10A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
0, 1 (N=26)	19	45.7(25.3, 66.1)	18.8(1.0, 36.6)	4.9(2.4, 7.5)	0.532	Cont.
≧ 2 (N=13)	9	29.2(2.0, 56.4)	-	3.8(0, 8.1)		1.29(0.58, 2.88)

10B) EFS.

Figure 10: Subgroups stratified by the performance status.

showed a trend towards improvement of the OS (Figure 10A, 10B).

Comparison of the groups stratified by the Charlson Comorbidity Index (CCI) (≤ 7 *vs.* >7) showed that the OS was significantly better in the CCI ≤ 7 subgroup, while no significant difference in the EFS was observed between the two groups (Figure 11A, 11B).

No significant difference in the either OS or EFS was observed between the subgroups treated and not treated with Granulocyte Colony Stimulating Factor (G-CSF) (Figure 12A, 12B).

No significant difference in either the OS or EFS was observed between the subgroups with and without resistance to AZA (Figure 13A, 13B).

No significant difference in either the OS or EFS was observed between the subgroups previously treated and not treated with an anthracycline (Figure 14A, 14B).

No significant differences in either the OS or EFS were observed among the subgroups stratified by the duration of VEN treatment (1-21 days, 22-28 days, 29-53 days) (Figure 15A, 15B). A favorable trend was observed in the subgroup treated for 1 to 21 days.

No significant difference in either the OS or EFS was observed between the subgroups with and without FN (Figure 16A, 16B).

Discussion

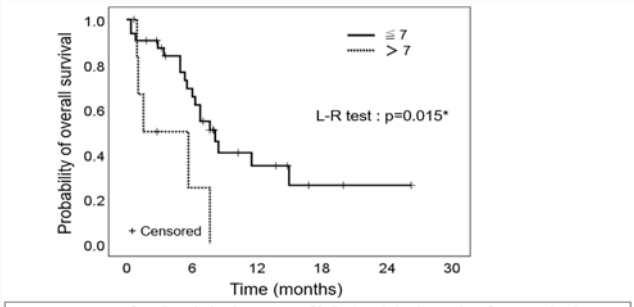
It has been reported [12] that a favorable OS is obtained with VEN+AZA treatment in both previously untreated and relapsed/refractory cases of AML who show CR+CRi in real-world clinical practice. The results obtained in the present study were consistent with this previous report (Figure 9A). In addition, the OS was better in patients with negative MRD than in those with positive MRD [6]. Similarly, in the VIALE-A trial also, the OS was better in patients with MRD<10^{-3} than in those with MRD>10^{-3} [2]. It has been suggested that achievement of a deep response is associated with an improved prognosis.

In the VIALE-A trial, the median duration of follow-up was 20.5 months, and the median number of cycles was 7. The CRc achievement rate was 66.4%. The median OS was 14.7 months, and the median EFS was 9.8 months. The median OS in patients who responded to the treatment was 24.4 months, demonstrating treatment benefit [3].

Of all the patients who responded to the treatment, a response was achieved by the 2nd cycle in 75% of cases, by the 4th cycle in 93% of cases, and after 8 cycles in 3% of cases [1]. It has also been reported that MRD<10^{-3} is achieved after the 7th cycle in 21% of patients [2]. These findings suggest that the response rate increases with continued treatment, and that a deep response can be expected.

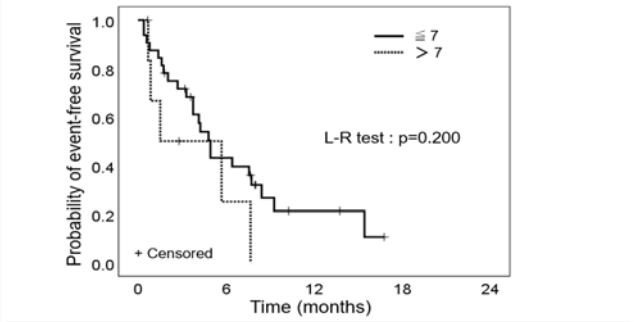
A meta-analysis of untreated AML patients treated with VEN+AZA or VEN plus decitabine (DEC) in real-world clinical practice reported a median OS of 9.37 months, which was worse than that reported from the VIALE-A trial [17]. The high treatment discontinuation rate (≥ 50%) was considered as the cause of the eventual decrease in the OS (in the VIALE-A trial, the rate of discontinuation due to adverse events was 24%) [17]. We consider it important to continue the study in actual clinical practice.

In this study, the median duration of follow-up was 6 months and the median number of cycles was 2. The discontinuation rate was



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
≦ 7 (N=32)	18	69.2(52.3, 86.1)	34.8(15.0, 54.6)	8.2(6.2, 10.1)	0.015*	Cont.
> 7 (N=7)	5	25.0(0, 65.0)	-	1.5(0, 6.0)		3.37(1.19, 9.60)

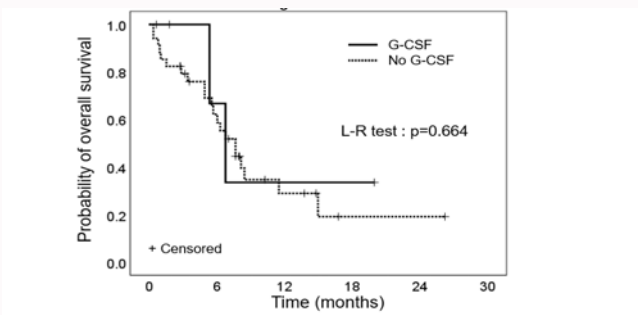
11A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
≦ 7 (N=32)	23	43.1(25.1, 61.1)	21.3(4.6, 38.0)	4.9(3.9, 5.9)	0.200	Cont.
> 7 (N=7)	5	25.0(0, 65.0)	-	1.5(0, 6.2)		1.89(0.70, 5.09)

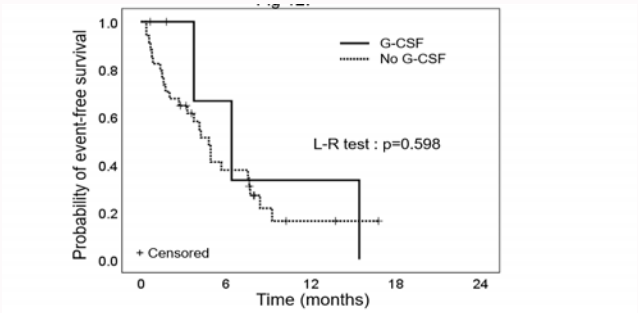
11B) EFS.

Figure 11: Subgroups stratified by the CCI.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
G-CSF (N=5)	2	66.7(13.4, 100)	33.3(0, 86.6)	6.8(4.5, 9.0)	0.664	Cont.
Non G-CSF (N=34)	21	62.1(45.0, 79.2)	28.7(10.3, 47.1)	7.7(5.4, 9.9)		1.38(0.32, 5.91)

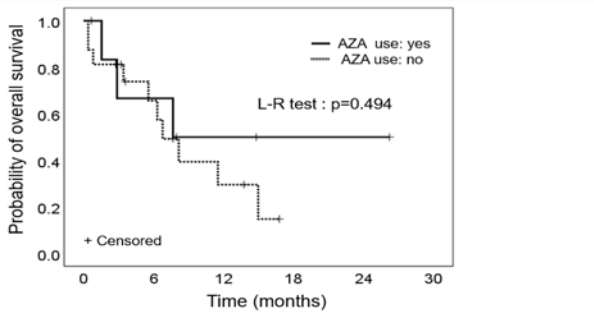
12A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
G-CSF (N=5)	3	66.7(13.4, 100)	33.3(0, 86.6)	6.4(2.2, 10.7)	0.598	Cont.
Non G-CSF (N=34)	25	37.6(20.5, 54.7)	16.1(1.0, 31.2)	4.8(3.6, 6.0)		1.39(0.41, 4.71)

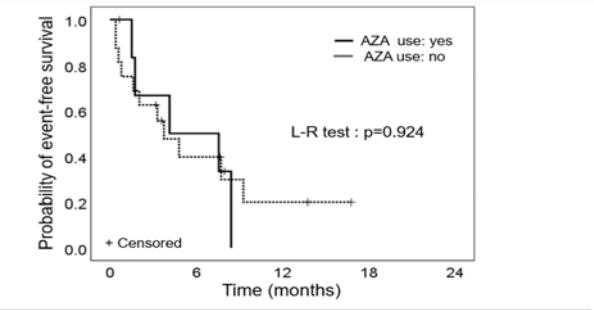
12B) EFS.

Figure 12: Subgroups treated and not treated with G-CSF.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
None (N=16)	10	65.7(40.8, 90.6)	29.5(2.8, 56.2)	6.8(4.0, 9.5)	0.494	Cont.
Can be (N= 7)	3	66.7(29.1, 100)	50.0(10.0, 90.0)	7.7(-, -)		0.64(0.18, 2.33)

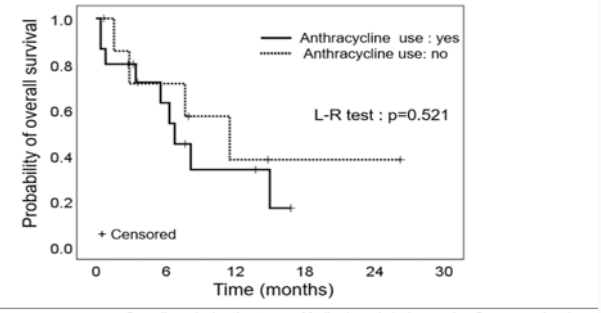
13A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
None (N=16)	11	39.7(14.0, 65.4)	19.8(0, 43.1)	3.8(1.3, 6.2)	0.924	Cont.
Can be (N= 7)	5	50.0(10., 90.0)	-	4.1(0, 11.1)		1.05(0.36, 3.10)

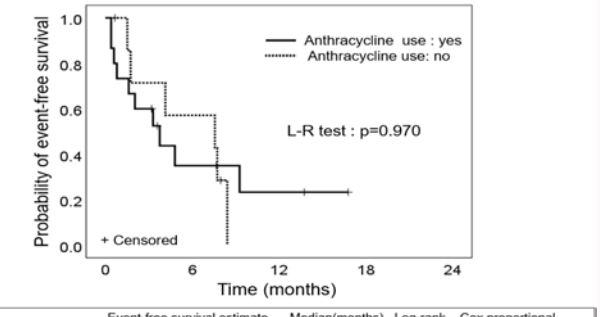
13B) EFS.

Figure 13: Subgroups with and without resistance to AZA.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
None (N=8)	4	71.4(37.9, 100)	38.1(0, 77.1)	11.5(3.6, 19.4)	0.521	Cont.
can be (N=15)	9	63.0(36.5, 89.5)	33.8(5.2, 62.4)	6.8(4.9, 8.7)		1.47(0.45, 4.81)

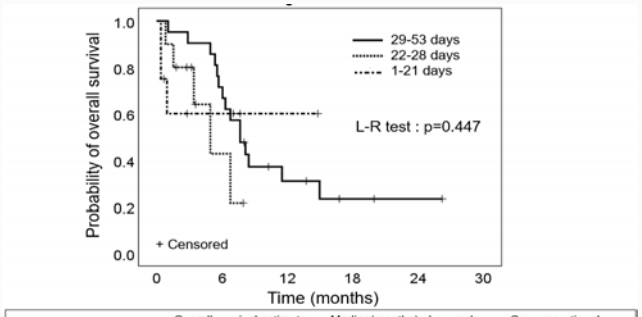
14A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
None (N= 8)	6	57.1(20.4, 93.8)	-	7.6(0, 16.3)	0.970	Cont.
Can be (N=15)	10	35.0(8.7, 61.3)	23.3(0, 48.8)	3.8(1.0, 6.5)		0.98(0.35, 2.78)

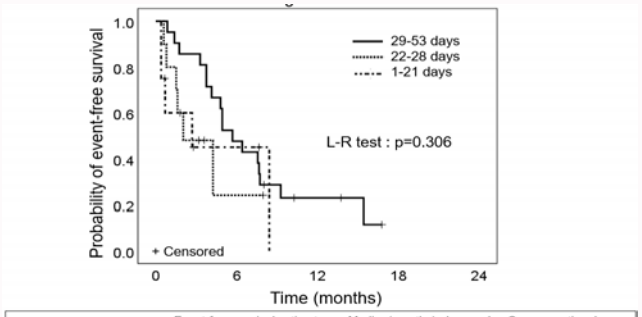
14B) EFS.

Figure 14: Subgroups that had and had not previously received anthracyclines.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
1-21 days (N=8)	3	60.0(24.3, 95.7)	-	-	0.447	Cont.
22-28 days(N=10)	5	42.7(1.5, 83.9)	-	4.9(2.0, 7.9)		1.75(0.41, 7.53)
29-53 days(N=21)	15	71.4(52.0, 90.8)	30.9(10.1, 51.7)	7.7(5.7, 9.7)		0.88(0.25, 3.10)

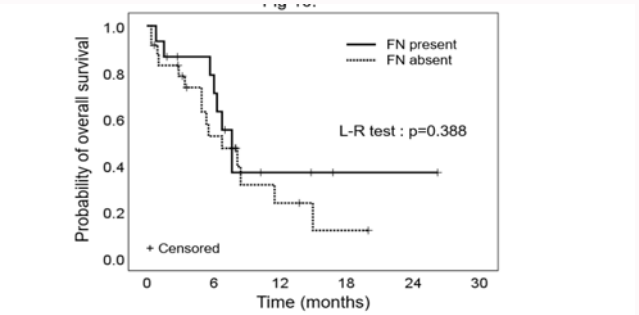
15A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
1-21 days (N=8)	5	45.0(8.2, 81.8)	-	2.7(0, 7.6)	0.306	Cont.
22-28 days(N=10)	6	24.0(0, 60.8)	-	2.0(0, 4.4)		1.10(0.33, 3.69)
29-53 days(N=21)	17	47.6(26.2, 69.0)	22.9(4.5, 41.3)	5.7(3.9, 7.5)		0.57(0.21, 1.58)

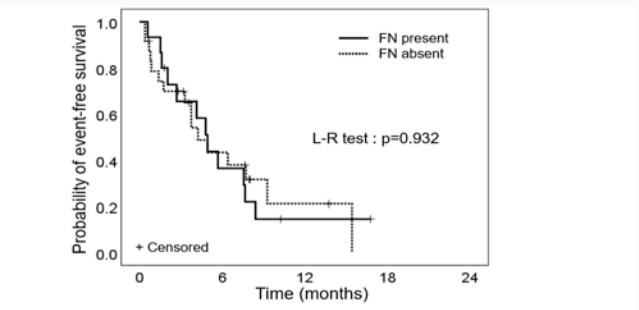
15B) EFS.

Figure 15: Subgroups stratified by the duration of VEN treatment during the 1st cycle.



	Events	Overall survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
FN absence (N=24)	15	52.5(30.7, 74.3)	23.6(1.8, 45.4)	6.8(3.4, 10.1)	0.388	Cont.
FN presence(N=15)	8	78.8(57.2, 100)	36.8(9.4, 64.2)	7.7(6.3, 9.0)		0.69(0.29, 1.63)

16A) OS.



	Events	Event-free survival estimate (%)(95%CI) Month 6	Month 12	Median(months) (95%CI)	Log-rank P-value	Cox proportional HR(95%CI)
FN absence (N=24)	16	43.2(21.4, 65.0)	21.0(0, 43.0)	4.2(2.6, 5.9)	0.932	Cont.
FN presence(N=15)	12	36.4(11.1, 61.7)	14.5(0, 33.1)	4.9(3.5, 6.3)		1.03(0.49, 2.19)

16B) EFS.

Figure 16: No significant difference in either the OS or EFS was observed between the subgroups with and without FN.

76.9%. CRc was achieved in 61.5% of patients (Table 2). The overall median OS was 7.7 months, and the median EFS was 4.8 months (Figure 1A, 1B). The higher discontinuation rate, fewer dosing cycles, and lower CRc achievement rate were considered as being the reasons for the lower OS and EFS in this as compared with the VIALE-A study.

In the subgroup analyses in this study, significant differences in the OS and EFS were observed in the subgroups stratified by the cytogenetic risk (Figure 5A, 5B) and CRc achievement rate (Figure 9A, 9B). In relation to the OS, a significant difference was also observed in the subgroup with CCI ≤ 7 (Figure 11A). No significant differences in the OS or EFS were observed in relation to any of the other factors (Figures 3, 4, 6-8, 10, 12-16A, 16B, 11B).

In the comparison of the CRc achievement rate between the subgroups stratified by the cytogenetic risk, the CRc achievement rate using the best response was low in the adverse cytogenetic risk subgroup (63.2% and 55.6% in the intermediate and adverse cytogenetic risk groups, respectively). Also, when analyzed using the final response, the CRc achievement rate was low in the adverse cytogenetic risk subgroup (31.6% and 22.3% in the intermediate and adverse cytogenetic risk groups, respectively) (Table 3). These results suggest that the patients classified as having an adverse cytogenetic risk are less likely to respond to treatment. It has been reported that VEN+AZA treatment improves the OS in patients with an adverse cytogenetic risk in whom MRD negativity is achieved [2,6]. These findings suggest that obtaining an MRD-negative response is necessary to improve the prognosis in the adverse cytogenetic risk subgroup. This necessitates the development of strategies to help patients continue treatment.

No significant difference in the OS was observed between the subgroups stratified by the PS; however, the PS 0 to 1 showed a trend towards a better OS (Figure 10A).

A worse OS was observed in the subgroup with CCI ≤ 7 (Figure 11A). Therefore, it is considered that selection of patients by the PS and CCI would be useful.

There was no significant difference in the OS depending on the number of prior treatments (Figure 2A). The response rate by the number of prior treatments is shown in Table 4. In the subgroup that received ≥ 2 prior treatments, the rate of CRc as the best response was low, being 30% (81.2% and 61.5% in the subgroups that received 0 or 1 prior treatment, respectively). These findings suggest that VEN+AZA treatment is more likely to evoke a deeper response when given at an earlier stage of treatment.

B-Cell Lymphoma-2 (BCL-2) expression has been reported to be induced by anthracycline administration in a leukemia cell line [18]. In addition, one previous study reported a trend toward a better OS in patients previously treated with anthracyclines [12]. In the present study, however, no such trend was observed (Figure 14A). The reason for this discrepancy remains unknown. It is also known that FLT3 inhibitors increase the susceptibility to VEN [19]. In the present report, however, there were no cases that received VEN+AZA treatment after FLT3 inhibitor treatment, and we could not verify the effect of FLT3 treatment on the response to VEN.

There are several reports of VEN+AZA treatment from Western countries, but few from Japan [7-13]. It has been reported that Asians tend to have higher blood levels of VEN [20], and similar results have been reported in Japanese patients [9]. Therefore, we consider it necessary to analyze the VEN levels in Japanese subjects. The reports from Japan are shown in Table 6. The incidence of FN tends to be high in Japanese patients [7-9,11,14]. Although the number of such reports identified was limited to 3, the median number of treatment cycles was as low as 2. It was considered that patients were unable to continue the treatment due to adverse events. A multivariate analysis showed that in order to enable at least 3 cycles to be administered, VEN should be administered for 21 days or less by the 2nd cycle, along with the administration of G-CSF [13]. In a report comparing the duration of VEN treatment (14 days *vs.* 28 days) during the 1st cycle, the EFS and OS tended to be better in the 14-day VEN group. In addition, the incidence of FN was lower in this group, with a treatment-related mortality rate of 0 [10]. These findings suggest that shortening the duration of VEN treatment and use of G-CSF may improve the prognosis of the patients.

In this study, the median duration of VEN treatment during the 1st cycle was 29 days. Although the difference was not significant, the OS tended to be better in patients who received VEN for 21 days or less (Figure 15A). No significant difference in the OS was observed between the subgroups that were and were not administered G-CSF (Figure 12A). The reason for this remains unknown, but it could be related to the limited number of patients (5 patients) who received G-CSF. Taken together, it is considered necessary, specifically in Japanese patients, to shorten the duration of VEN treatment and modify the administration method of G-CSF.

The Adverse Events (AEs) encountered in the patients are shown in Table 6a, 6b. Grade 3 or more severe hematological toxicities were observed in 100% of the patients, with grade 3 or more severe non-hematological toxicities observed in 17.9% of the patients. Caution is needed against the development of hematological toxicities. Since there were no cases of treatment-related death, the treatment was considered as being reasonably safe.

There were limitations to this study, including the short duration of follow-up, small sample size, and no attempts to detect MRD.

Key Message

1. VEN+AZA treatment was associated with a poorer prognosis in patients who had adverse cytogenetic risk, did not achieve CRc, and had a CCI of >7. However, continuation of VEN+AZA treatment is expected to increase the response rate and to elicit a deep response. Treatment continuation is especially important for the adverse cytogenetic risk subgroup.

2. For treatment continuation, shortening the duration of VEN treatment and concomitant use of G-CSF have been suggested to be effective.

3. PS and CCI may be useful factors for selecting patients for this treatment. It would be desirable to establish an optimal administration method, an optimal patient subgroup, and the prognostic factors in Japanese patients with AML receiving VEN+AZA treatment.

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