Overall survival with intensive chemotherapy versus non-intensive chemotherapy in patients with newly diagnosed acute myeloid leukemia from the Connect® Myeloid Disease Registry ineligible for randomized clinical trials

Poster Number AML-251

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Introduction

- Patients with acute myeloid leukemia (AML) enrolled in randomized clinical trials (RCTs) often do not reflect the population in clinical practice due to restrictive eligibility criteria[1]
- Ferrara et al. have proposed criteria to define patients unfit to receive intensive chemotherapy (IC) or non-IC for AML[2]
- AML trials of non-IC typically enroll a narrow subset of patients
  - The phase 3, multicenter, randomized, double-blind, placebo-controlled VIALE-A trial evaluated the efficacy and safety of non-IC (azacitidine + venetoclax versus azacitidine + placebo) in previously untreated patients with confirmed AML who were ineligible for standard chemotherapy[3]
  - However, many patients, including those with abnormal liver and kidney function, a prior malignancy, human immunodeficiency virus (HIV) infection, and high ECOG scores, were ineligible for the trial[3]
- The characteristics and outcomes of patients who are ineligible for these trials remain largely unknown

Objective

- To evaluate patient outcomes of IC vs venetoclax-based regimens based on enrollment eligibility for the VIALE-A trial from patients with AML in the Connect® Myeloid Disease Registry (NCT01688011)

Methods

Connect® Myeloid Disease Registry

- The Connect® Myeloid Disease Registry is a large, non-interventional, ongoing, prospective cohort study of newly diagnosed AML patients more representative of the general United States (US) AML population[4,5]
  - Enrollment began in December 2013

Patient stratification

- Patients were stratified into 3 groups based on the non-IC phase 3 VIALE-A trial eligibility criteria (**Figure 1**):

1. "Eligible" patients **met all** VIALE-A inclusion criteria including a projected life expectancy of ≥ 12 weeks; ECOG score 0-2 (≥ 75 y of age) or 0-3 (18-74 y of age); adequate renal function (creatinine clearance ≥ 30 mL/min); and adequate liver function (AST ≤ 3.0 × upper limit of normal [ULN], ALT ≤ 3.0 × ULN, bilirubin ≤ 1.5 × ULN [≤ 3.0 × ULN for < 75 y of age])

2. "Unfit" patients who would have been ineligible for VIALE-A due to **any of the following**: abnormal liver/kidney function, age 18-74 y with ECOG score ≥ 4 or age ≥ 75 y with ECOG score ≥ 3, prior malignancy ≤ 1 year of informed consent signing date, comorbidities score ≥ 2 by adult comorbidity evaluation (ACE)-27, hepatic grade ≥ 1, acquired immunodeficiency syndrome (AIDS) grade ≥ 1

3. "Fit" patients who would have been ineligible for a venetoclax-based regimen in VIALE-A because they would have qualified for IC (**defined as meeting all the following**: ≤ 74 y of age, ECOG score ≤ 1, no apparent cardiovascular/renal comorbidities, and did not meet any criteria in #2)

Analysis and statistical methods

- Demographics and patient characteristics at baseline were summarized by eligibility group
- Comparison of overall survival (OS) between 3 eligibility groups was performed using the Kaplan-Meier (KM) method and pairwise comparisons were performed using a Cox model with factors for age, European LeukemiaNet (ELN) risk, ECOG score, frailty score, and comorbidity index
- Induction regimens were categorized as
  - Venetoclax-based
  - IC (any regimens containing 7+3 [cytarabine and daunorubicin], MEC [mitoxantrone, etoposide, and cytarabine], CLAG [granulocyte colony-stimulating factor, cladribine, and cytarabine], or FLAG [fludarabine, cytarabine, and filgrastim])

Results

Patients characteristics

- Of 734 patients with AML enrolled in the Registry until December 2021, the median age was 71 years (range, 55-97), 60.9% of patients were male, and most of the patients were White (84.3%) (**Table 1**)

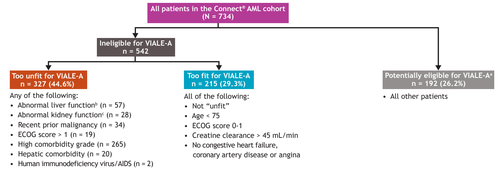
Table 1. Demographics and patient characteristics at baseline

	All N = 734	Eligible n = 192 (26.2%)	Fit n = 215 (29.3%)	Unfit n = 327 (44.6%)
Age, years	n = 732	n = 192	n = 213	n = 327
Mean (standard deviation)	70.6 (8.2)	75.5 (7.8)	66.2 (5.2)	70.7 (8.4)
Median (range)	71.0 (55-97)	76.0 (56-97)	67.0 (55-74)	71.0 (55-92)
Sex, n (%)	n = 732	n = 192	n = 213	n = 327
Male	447 (61.1)	109 (56.8)	125 (58.7)	213 (65.1)
Race, n (%)	n = 734	n = 192	n = 215	n = 327
White	619 (84.3)	164 (85.4)	174 (80.9)	281 (85.9)
Black	45 (6.1)	10 (5.2)	16 (7.4)	19 (5.8)
Pacific Islander/American Indian/Alaskan Native	5 (0.7)	0	2 (0.9)	3 (0.9)
Asian	4 (0.5)	1 (0.5)	3 (1.4)	0
Other	2 (0.3)	0	1 (0.5)	1 (0.3)
Not specified	60 (8.2)	17 (8.9)	20 (9.3)	23 (7.0)
Ethnicity, n (%)	n = 734	n = 192	n = 215	n = 327
Hispanic/Latino	50 (6.8)	16 (8.3)	14 (6.5)	20 (6.1)
Non-Hispanic/Latino	625 (85.1)	161 (83.9)	185 (86.0)	279 (85.3)
Not specified	59 (8.0)	15 (7.8)	16 (7.4)	28 (8.6)
Site classification, n (%)	n = 732	n = 191	n = 215	n = 326
Community	426 (58.2)	123 (64.4)	109 (50.7)	194 (59.5)
Academic	292 (39.9)	63 (33.0)	104 (48.4)	125 (38.3)
Government	14 (1.9)	5 (2.6)	2 (0.9)	7 (2.1)
ECOG, n (%)	n = 616	n = 165	n = 162	n = 289
0	130 (21.1)	24 (14.5)	51 (31.5)	55 (19.0)
1	320 (51.9)	65 (39.4)	111 (68.5)	144 (49.8)
2	121 (19.6)	67 (40.6)	0	54 (18.7)
3	39 (6.3)	9 (5.5)	0	30 (10.4)
≥4	6 (1.0)	0	0	6 (2.1)
ECOG Group, n (%)	n = 616	n = 165	n = 162	n = 289
0/1	450 (73.1)	89 (53.9)	162 (100.0)	199 (68.9)
≥2	166 (26.9)	76 (46.1)	0	90 (31.1)
Transplant Intent, n (%)	n = 734	n = 192	n = 215	n = 327
Yes	250 (34.1)	40 (20.8)	114 (53.0)	96 (29.4)
No	484 (65.9)	152 (79.2)	101 (47.0)	231 (70.6)

Percentages shown are for patients with non-missing data for these variables.

- Only 26.2% of patients (n = 192) were eligible for a non-IC RCT, 44.6% (n = 327) were ineligible due to unfitness, and 29.3% (n = 215) were ineligible due to qualifying for IC (fit)
  - Reasons for unfitness included high overall comorbidity (36.1%), abnormal liver function (7.8%), recent prior malignancy (4.6%), abnormal kidney function (3.8%), hepatic comorbidity (2.7%), ECOG score > 1 (2.6%), and HIV/AIDS (0.3%) (**Figure 1**)

Figure 1. Patient groups based on the VIALE-A trial eligibility criteria



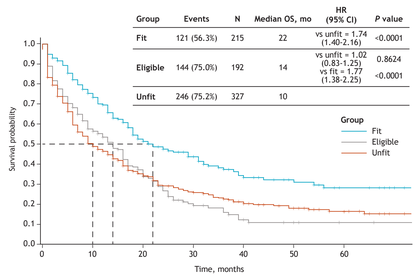
[a]Very few (27/192; 14%) patients in this group received venetoclax-based therapy.
[b]AST and/or ALT ≥ 100 U/L, bilirubin > 2 mg/dL.
[c]Creatine clearance < 30 mL/min.

- In the **eligible** group, 39.4% and 40.6% of patients had ECOG scores of 1 and 2, respectively; whereas in the **unfit** and **fit** groups, the most frequently reported ECOG score was 1 (**unfit** group, 49.8%; **fit** group, 68.5%)
- Patients in the **fit** group intended to undergo transplant more often (53.0%) compared with patients in the **unfit** (29.4%) or **eligible** (20.8%) groups

Analysis of overall survival

- Analysis of OS between patient groups using the KM method demonstrated that the OS among patients in the **fit** group (median OS = 22 months; 95% CI, 18.0-31.0) was significantly better than patients in both the **unfit** (median OS = 10 months; 95% CI, 8.0-14.0; $P < 0.001$) and **eligible** groups (median OS = 14 months; 95% CI, 10.0-16.0; $P < 0.001$)
  - No statistically significant differences in OS were observed between patients in the **eligible** and **unfit** groups (**Figure 2**)

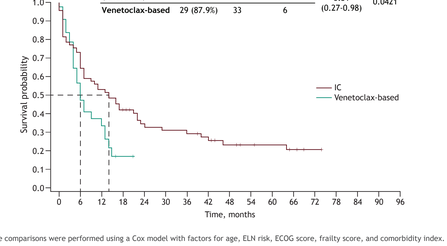
Figure 2. Overall survival for the *eligible*, *fit*, and *unfit* groups



Group	Events	N	Median OS, mo	HR (95% CI)	*P* value
Fit	121 (56.3%)	215	22	vs unfit = 1.74 (1.40-2.16)	<0.0001
Eligible	144 (75.0%)	192	14	vs unfit = 1.02 (0.83-1.25) vs fit = 1.77 (1.38-2.25)	0.8624 <0.0001
Unfit	246 (75.2%)	327	10		

- Among patients in the **unfit** group, those receiving IC had more than double the OS compared with patients receiving a venetoclax-based regimen (median OS, 14 vs 6 months, respectively; HR, 0.51 [95% CI, 0.27-0.98]; $P = 0.042$; **Figure 3**)
- **Unfit** patients who received IC tended to be younger (mean age, 65.7 years) than those who received venetoclax-based therapy (mean age, 74.1 years)
- A higher proportion of patients in the **unfit** group who received IC were treated at academic centers (47%, 36/76) compared with those who received venetoclax-based therapies (15%, 5/33)
- No statistically significant differences in baseline ELN risk score were observed between patients in the **unfit** group who received IC compared with those who received venetoclax-based therapies

Figure 3. Overall survival among patients in the *unfit* group who would be ineligible for an RCT

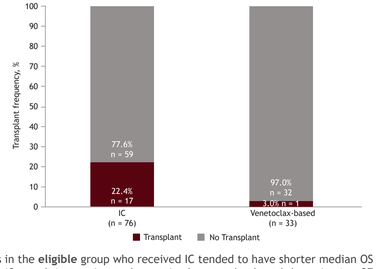


Group	Events	N	Median OS, mo	HR (95% CI)	*P* value
IC (reference)	52 (68.4%)	76	14	0.51 (0.27-0.98)	0.0421
Venetoclax-based	29 (87.9%)	33	6		

Pairwise comparisons were performed using a Cox model with factors for age, ELN risk, ECOG score, frailty score, and comorbidity index.

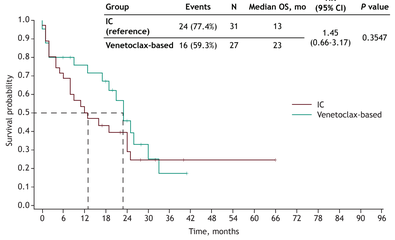
- Patients in the **unfit** group who received IC underwent hematopoietic stem cell transplantation (HSCT) more frequently than those who received venetoclax-based therapies (**Figure 4**)

Figure 4. HSCT frequency among patients in the *unfit* group



- Patients in the **eligible** group who received IC tended to have shorter median OS (n = 31; 13 months) vs patients who received venetoclax-based therapies (n = 27; 23 months; hazard ratio (HR), 1.45 [95% CI, 0.66-3.17]; $P = 0.3547$; **Figure 5**)

Figure 5. Overall survival among patients in the *eligible* group



Group	Events	N	Median OS, mo	HR (95% CI)	*P* value
IC (reference)	24 (77.4%)	31	13	1.45 (0.66-3.17)	0.3547
Venetoclax-based	16 (59.3%)	27	23		

Pairwise comparisons were performed using a Cox model with factors for age, ELN risk, ECOG score, frailty score, and comorbidity index.

- There were not enough patients in the **fit** group to make inferences

Strengths and limitations

- As the Registry is still enrolling, factors associated with therapy or diagnosis may change as more patients enroll
- Because the Registry began prior to the approval of venetoclax, relatively few patients in the Registry have received treatment with venetoclax-based regimens
- As there were no scheduled clinic visits, evaluation intervals may have varied between patients. This could impact the assessment of outcome measures and limit comparisons of observational data with clinical trial results
- Despite this, the Registry provides the opportunity to observe real-world patterns of treatment and diagnosis and the changes that occur over time as treatment options and diagnostic testing guidelines evolve
- Furthermore, the Registry has the ability to query sites for more information on questionable data

Conclusions

- Almost 75% of patients with newly diagnosed AML in the Connect® Myeloid Disease Registry would have been ineligible for the VIALE-A trial either because they were too **fit** or did not meet the Ferrara criteria
- For the small subset of patients in the Connect® Myeloid Disease Registry who were **eligible** for VIALE-A and received a venetoclax-based therapy, the OS was comparable to that achieved with IC, which supports the results from 2 previously presented analyses[6,7]
- The patients who were ineligible for VIALE-A because they were **unfit** and did not meet the Ferrara criteria but still received IC (n = 76) had an OS benefit compared to those who received venetoclax-based therapy suggesting that the Ferrara criteria may not be able to identify selected patients who would benefit from IC compared with a venetoclax-based therapy
- Selected Ferrara-**unfit** patients were able to undergo IC and proceed to transplant, with improved OS

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