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Venetoclax with intensive induction chemotherapy in newly diagnosed adult acute myeloid leukemia: early outcomes from a real-world experience

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Running title: Venetoclax with intensive chemotherapy in adult AML

To the Editor

Over the past several decades, there has been a consistent effort to move beyond the conventional “3+7” intensive induction regimen in the treatment of acute myeloid leukemia (AML). The advent of BCL-2 inhibitors has significantly transformed the therapeutic landscape, particularly in combination with hypomethylating agents (HMAs), where this regimen has emerged as a standard of care in elderly or unfit patients. [1].

Recently, comparative studies have evaluated HMA plus venetoclax against intensive induction in younger, fit adults, demonstrating comparable efficacy [2]. Interestingly , preliminary results exploring the integration of anti-leukemic potential of BCL-2 inhibitors with curative efficacy of intensive induction chemotherapy (IC) have shown encouraging activity across all cytogenetic risk groups, with high rates of minimal residual disease (MRD) negativity and a toxicity profile similar to that of IC alone [3].

This retrospective cohort study from a tertiary care academic institute included all consecutive newly diagnosed adult patients (≥18 years) with AML deemed fit for intensive induction chemotherapy and treated between November 9, 2022 and June 15, 2025. Baseline clinical characteristics, treatment details, and outcomes were extracted from medical records and reviewed. Diagnosis and risk stratification were performed according to the European LeukemiaNet (ELN) 2022 criteria [4]. The study was approved from the Institutional Ethics Committee.

Induction chemotherapy consisted of daunorubicin 60 mg/m² intravenously for 3 days and cytarabine 100 mg/m² as a continuous IV infusion for 7 days. The administration schedule of venetoclax was 100 mg once daily from Day 1 to Day 14. Dose escalation of venetoclax was facilitated by concurrent administration of oral voriconazole 200 mg twice daily from Day 4.

Patients who failed to achieve complete remission (CR) and/or were MRD-positive on Day 28 received a second cycle of induction. Response assessment was performed via bone marrow examination either upon recovery of platelet and absolute neutrophil counts (ANC) or on Day 28, whichever occurred first. MRD evaluation was conducted by multiparametric flow cytometry.

For consolidation, patients in the adverse-risk (AR) and intermediate-risk (IR) categories received 3–4 cycles of high-dose cytarabine (HiDAC) at 9 g/m² per cycle, while favourable-risk (FR) patients received 12 g/m² per cycle.

Early mortality was defined as death occurring within 28 days of start of induction. Complete remission (CR) was defined according to the European Leukemia Net (ELN) 2022 criteria. Complete remission with incomplete hematologic recovery (CRi) was defined as meeting all criteria for CR except for persistent neutropenia (absolute neutrophil count < 1.0 × 10□/L) and/or thrombocytopenia (platelet count < 100 × 10□/L) on or after Day 28. Composite complete remission (CRc) was defined as the sum of CR and CRi. Overall CR was defined as patients achieving a CR/CRi after reinduction with a regimen of physician's choice. MRD positivity was defined as ≥ 0.1% of CD45 expressing cells with the target immunophenotype according to the ELN 2022 criteria.

Eighty consecutive adult patients with newly diagnosed, fit AML were included. Baseline characteristics are summarized in table S1. The median white blood cell (WBC) count was 28.48 × 10³/µL (range: 0.83–339.7 × 10³/µL). According to ELN 2022 risk stratification, 33.8% of patients were classified as favorable risk, 50% as intermediate risk, and 16.3% as adverse risk. Patients with CBF-AML accounted for 21.2% (17/80), while NPM1 mutations were observed in 11.2% (9/80) of patients. Additionally, bZIP CEBPA mutations were

identified in 11.2% (9/80) of the cohort. Molecular analysis failed in 4 patients. Detailed molecular profiles are shown in table S1 and figure S2.

Early mortality occurred in 12 patients, and disease response could not be evaluated in these individuals. All deaths were attributed to fulminant sepsis, with 25% of cases showing culture positivity for multidrug-resistant organisms; all patients had febrile neutropenia. The composite CR rate (CR + CRi) was 70% (56/80), with an overall CR rate of 75% (60/80). Stratification by risk groups showed CR rates of 88.9%, 67.5%, and 38.5% for favorable, intermediate, and adverse risk groups, respectively (Table 1). The median time to platelet recovery (defined as platelets ≥ 100 × 10^3/μL) was 26 days (range, 16–78 days), and the median time to ANC recovery (defined as ANC ≥ 1× 10^3/μL) was 25 days (range, 15–93 days). The median length of hospital stay during induction was 30 days (range, 7-60 days). Five patients received less than 14 days of venetoclax owing to early mortality. The median duration of drug intake was 14 days (range, 3–14 days). Among the 56 patients achieving CR, the MRD-negative rate was 92.8% (52/56).

Of the 4 patients in CR who were MRD-positive, 2 received reinduction therapy (one with FLAG-Ven, the other with 7+3+Ven) and subsequently converted to MRD-negative status. Among the 12 patients who did not achieve CR after the first cycle, 8 received a second induction regimen, including FLAG-Ida (3 patients), 7+3+Midostaurin (1 patient), 7+3+Ven (2 patients), and Azacitidine-Venetoclax plus Sorafenib (1 patient). Four of these patients achieved CR after reinduction. At the time of data cut-off, none of the patients in CR were transplanted.

At a median follow-up of 11 months (range 0.1–31.6), the median overall survival (OS) was 21.3 months (95% CI: 12.2–NR). OS differed significantly across risk groups (Table 2). The median event-free survival (EFS) was 10.9 months (range 7.7–14.4), with significant differences between all risk groups (Figure 1).

At the data cut-off of June 15, 2025, 16 (26.7%) of the 60 patients who achieved CR relapsed. The median relapse-free survival (RFS) was not reached (NR) in the favorable-risk group (13.2 months-NR), 12.7 months (range 9.7–NR) in the intermediate-risk group, and 8.5 months (range 7.8–NR) in the adverse-risk group. The overall cohort's median RFS was NR (10.1 months-NR).

Among the 24 patients with FLT3-ITD mutations, 16 (66.7%) achieved CR following the first induction cycle and 4 had early induction mortality. Due to financial constraints, none among these patients received FLT3 inhibitors. Four patients who did not achieve CR initially received reinduction therapy, with two achieving remissions. The median OS and EFS for this cohort were 14.2 months and 9.5 months, respectively. (Figure S1).

Our findings in this study demonstrate robust and deeper responses across all risk groups. Historically, CR rates with standard intensive induction therapy have ranged from 60% to 70%. Our results compare favorably with both regional and international studies [5,6]. Venetoclax demonstrated impressive activity across all risk categories, with particularly remarkable efficacy in the favorable-risk subset. All evaluable patients in this group not only achieved CR after a single induction cycle but also achieved measurable residual disease (MRD) negativity.

Recent evidence has established MRD as a powerful surrogate for long-term outcomes in AML. Moreover, achieving MRD negativity prior to allogeneic transplant is increasingly recognized as a key predictor of durable remission and survival [7]. Consistent with prior studies, our cohort showed a high rate of MRD negativity, which is encouraging [5,8]. In contrast, conventional chemotherapy has been associated with significantly lower rates of MRD clearance [9].

Our study also provides insights into the efficacy of venetoclax combined with cytotoxic chemotherapy in patients with FLT3-mutated AML—a subset commonly encountered in

clinical practice. Historically, CR rates in this group with standard intensive induction have ranged from 55% to 60% [10]. Early trials of venetoclax with hypomethylating agents (HMAs) showed suboptimal responses in FLT3-mutated AML [11]. However, our findings suggest that combining venetoclax with intensive chemotherapy may overcome inherent resistance mechanisms in this subgroup. This is in line with a recently published study that also reported high response rates with this regimen [12].

The optimal dose and schedule of venetoclax in combination with intensive chemotherapy remain subjects of ongoing investigation. In our study, we did not observe a significant incidence of tumor lysis syndrome despite starting venetoclax from Day 1. An ongoing clinical trial is currently comparing the efficacy of 8-day versus 14-day venetoclax schedules which may help establish the optimal duration and dosing strategy [13].

We did not include venetoclax during consolidation primarily due to concerns regarding delayed hematologic recovery when venetoclax is combined with high dose cytarabine, as noted in the CAVEAT trial [14].

All induction-related deaths, and a few during consolidation, in our cohort were attributed to uncontrolled sepsis. This finding is consistent with other studies from the region and underscores the high burden of multidrug-resistant organisms and the healthcare delivery challenges faced in low- and middle-income countries (LMICs) [6,15].

Our study has limitations, including its retrospective design, short follow-up duration, and lack of access to targeted agents and bone marrow transplant for most patients. Furthermore, some patients who died during induction could not be evaluated for disease response, which could have impacted the results.

In conclusion, venetoclax combined with intensive chemotherapy appears to be a promising therapeutic option for fit adult patients with AML. The high rate of CR and MRD negativity

observed in this study supports its further evaluation in larger, prospective, randomized trials. The results of this study may help refine the treatment strategies for AML, especially in patients with high-risk disease or those with FLT3 mutations.

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Table 1: Treatment outcomes and survival outcomes

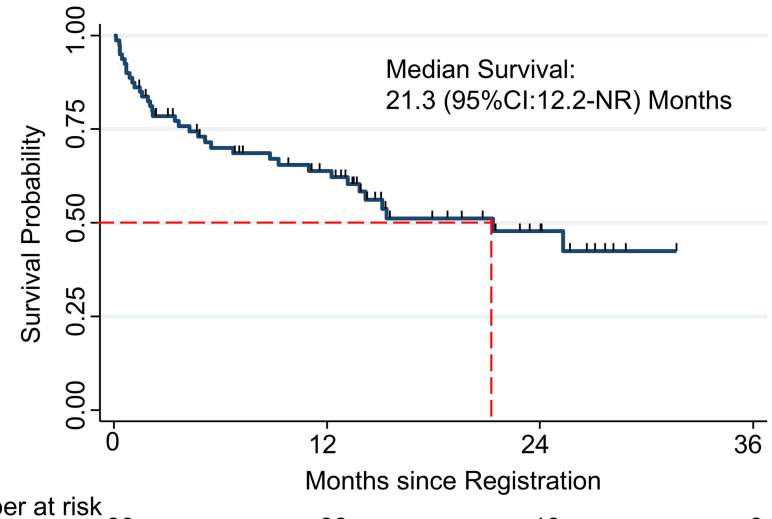
Treatment outcomes					
	Overall [N=80]	**FR* [N=27]**	**IR* [N=40]**	**AR* [N=13]**	**p-value**
CR after 1st Induction					
CR	41(51.2%)	18(66.7 %)	19(47.5%)	4(30.8%)	0.026
CRi	15(18.7%)	6(22.2 %)	8(20%)	1(7.7%)	
cCR (CR+CRi)	56(70.0 %)	24(88.9%)	27(67.5%)	5(38.5%)	
Survival outcomes [N=80]					
Median Overall Survival in months (95%CI)	21.3 (12.2–NR)	25.3 (15.4-NR)	15.1 (8.8-NR)	5.1 (1.4-NR)	0.043 (log-rank)
1 Year OS	62.8% (50.6%-72.2%)	74.5% (51.8%-87.6%)	65.3% (47.9%-78.2%)	30.4% (8.4%-56.5%)	
2 Year OS	46.8% (33.3%-59.2%)	66.6% (40.7%-83.2%)	42.3% (24.5%-59.0%)	30.4% (8.4%-56.5%)	
Median EFS in months (95%CI)	10.9 (7.7-14.4)	NR (9.1-NR)	9.8 (3.6-14.0)	1.0 (0.7-9.5)	<0.001 (log-rank)
1 Year EFS	46.6% (34.9%-57.5%)	70.2% (47.5-84.5)	41.3% (25.7%-56.3%)	16.7% (2.7%-41.3%)	
2 Year EFS	36.5% (24.3%-48.8%)	61.4% (35.2%-79.7%)	28.9% (14.3%-45.3%)	16.7% (2.7%-41.3%)	

* = Prognostic stratification according to European Leukemia Net 2022 risk category

Data are point estimate (95% CI) [n], median (IQR), or n (%). NR=not reached.

Figure 1: Kaplan Meier curves depicting overall survival and event-free survival. 1a. Overall survival in the entire cohort of 80 patients, 1b. Event-free survival of the entire cohort of 80 patients, 1c. Overall survival by ELN 2022 risk stratification, 1d. Event-free survival by ELN 2022 risk stratification. FR favourable risk, IR intermediate risk, AR adverse risk, aHR adjusted hazard ratio

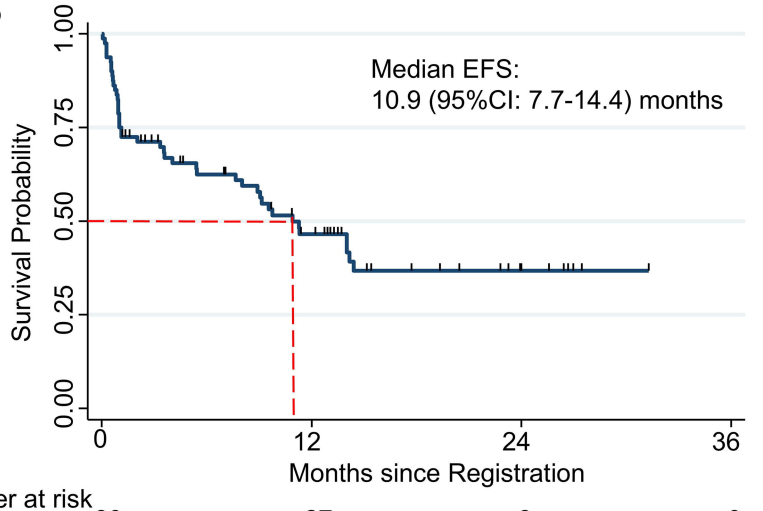
1a



Number at risk

	80	38	10	0

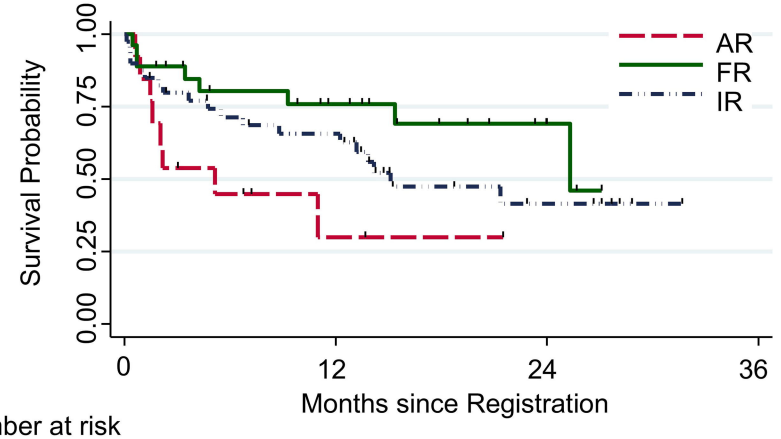
1b



Number at risk

	80	27	6	0

1c

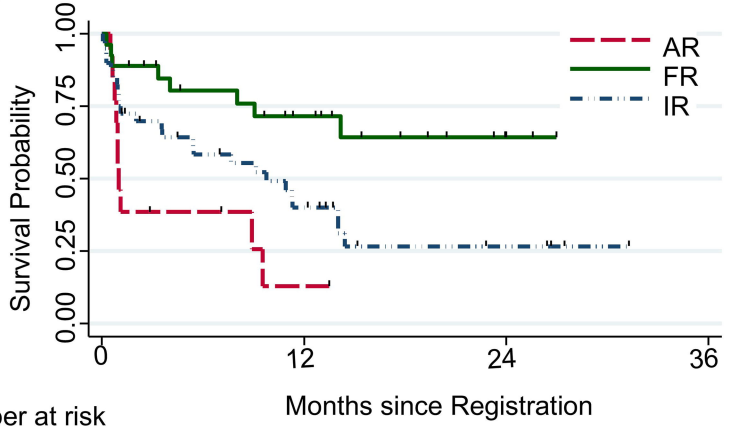


Number at risk

AR	13	2	0	0
FR	27	14	4	0
IR	40	22	6	0

Logrank p-value= 0.043
aHR(95%CI):
IR vs FR: 1.68 (0.73-3.87), p-value: 0.225
AR vs FR: 3.21 (1.18-8.78), p-value: 0.023

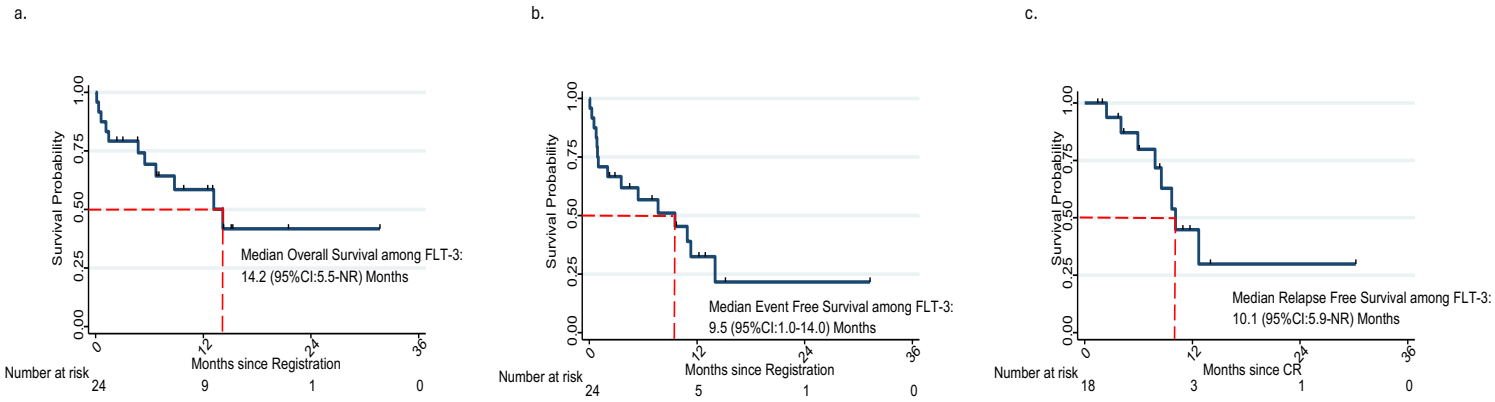
1d



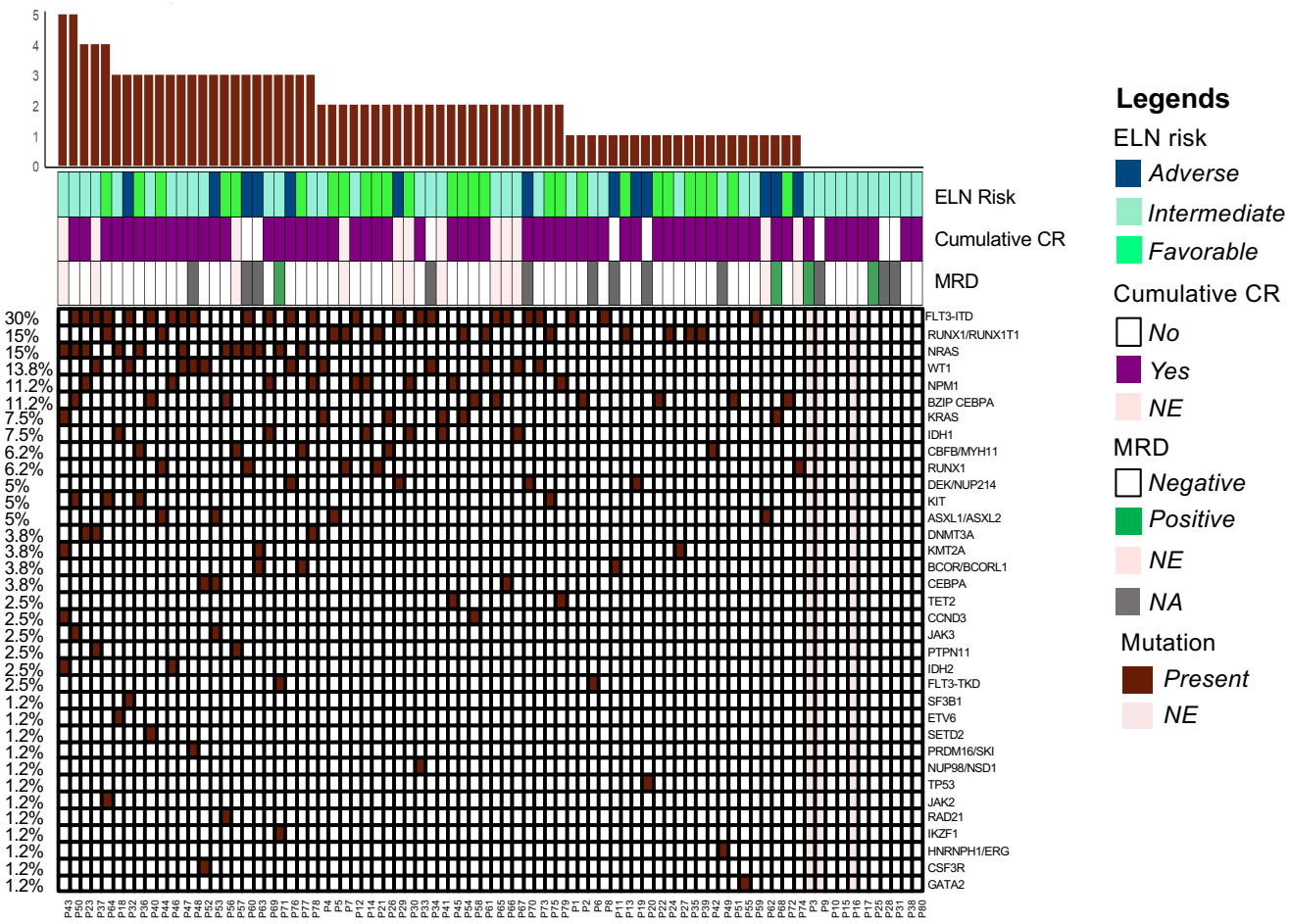
Number at risk

AR	13	1	0	0
FR	27	13	4	0
IR	40	13	2	0

Logrank p-value= <0.001
aHR(95%CI):
IR vs FR: 2.73 (1.22-6.11), p-value:0.015
AR vs FR: 5.53 (2.11-14.5), p-value: 0.001



Supplementary figure 1: Kaplan Meier curve depicting a) overall survival, b) event-free survival and, c) relapse-free survival in the FLT3-ITD mutated cohort



Supplementary figure 2: Heat map depicting molecular abnormalities by next-generation sequencing. NE Not evaluated, NA Not applicable.

Supplementary table 1: Baseline characteristics

variables		Patients (n=80)
Age in Years [Median (Range)]		33.5 (17-68)
Sex		
	Male	37 (53.8%)
	Female	43 (46.3%)
Symptom Duration in Months [Median (Range)]		1 (0.2-6.0)
Bone marrow blasts percentage [Median (Range)]		74 (10-100)
ELN 2022 Risk stratification		
	Favorable risk (FR)	27 (33.8%)
	Intermediate Risk (IR)	40 (50.0%)
	Adverse Risk (AR)	13 (16.3%)
Selected Molecular alteration		
RUNX1/RUNX1T1		12
CBFB/MYH11		5
NPM1		9
bZIP CEBPA		9
CEBPA		3
FLT3		26
KIT		4
ASXL1/2		4
RUNX1		5
IDH1		6
IDH2		2
BCOR / BCORL1		3
WT1		11
GATA2		1
DNMT3A		3
KMT2A		3
HNRNPH1-ERG		1

CSF3R	1
NRAS / KRAS	18
TP53	1
SF3B1	1
TET2	2
DEK-NUP214	3
IKZF1	1
PTPN1	2
RAD21	1
ETV6	1
SETD2	1
PRDM16/SKI	1
NUP98/NSD1	1
CCND3	2
JAK2	1
JAK3	2