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**Letter to the Editor**

# Intensive induction therapy with FLAG-idarubicin-venetoclax for fit older high-risk patients with acute myeloid leukemia

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**Running title:** FLAG-Ida-ven for older high-risk AML patients

## Author Contribution Statement

Study concept: Avraham Frisch

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Data acquisition: Avraham Frisch, Neta Glaubach

Data analysis and interpretation: Avraham Frisch, Neta Glaubach, Israel Henig

Manuscript preparation: Baher Krayem

Manuscript review and critical input: Tsila Zuckerman, Israel Henig, Dana Yehudai-Ofir

Study supervision: Avraham Frisch

## Declaration of Interests

The authors declare no competing interests.

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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To the Editor,

Low-intensity chemotherapy combined with venetoclax (LIC-VEN) has become the standard of care for older unfit patients with acute myeloid leukemia (AML). Recently, the treatment with LIC-VEN was proposed as an acceptable alternative to intensive chemotherapy also for fit older patients[1,2], achieving similar efficacy but with less toxicity. However, high treatment failure rates with LIC+VEN were reported in AML with an adverse-risk karyotype, in AML preceded by myeloproliferative disease or evolving after hypomethylating agent failure[3-5]. More recently, *RAS* and *TP53* mutations were identified as adverse prognostic factors for remission induction and survival in patients with AML treated with LIC-VEN[6].

The treatment with fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF), and idarubicin combined with venetoclax (FLAG-Ida-ven) has gained popularity in recent years for both newly diagnosed (N/D) and relapsed/refractory (R/R) AML. In the seminal phase Ib/II study by DiNardo et al., composite complete remission rates exceeded 60% for all subgroups[7]. Moreover, most patients transitioned to an allogeneic stem cell transplantation (alloSCT) at first remission (CR1), with a 3-year overall survival for N/D and R/R cohorts of 66% and 32%, respectively[8]. Yet, these cohorts predominantly included younger patients; only 15% of patients were older than 60 years. Subsequent studies confirmed the regimen's capacity to induce high remission rates, but consistently among younger adults[9,10], thus not representing the majority of patients with AML who are diagnosed at a median age of 70 years.

The aim of this study was to evaluate the real-world experience of using FLAG-Ida-ven in consecutive patients aged 65 years or older with N/D and R/R AML, all treated with intent-to-transplant at the earliest feasible time point in a single tertiary-care center in Israel.

All the procedures involved in this study were in accordance with the ethical standards of the Institutional Review Board of the Rambam Health Care Campus (Approval # RMB-0211-25) and with the 1964 Helsinki Declaration and its later amendments.

Since 06/2021, FLAG-Ida-ven became the standard regimen for fit, high-risk patients with AML at the Rambam Health Care Campus (Haifa, Israel). During the four-year period between 6/2021 and 5/2025, 110 patients were treated with this regimen. All patients received fludarabine at a dose of 30 mg/m$^2$ for 5 days, and 14 days of 100 mg venetoclax. Cytarabine was administered at a dose of 1 g/m$^2$ for 5 days, given over 4 hours. The cumulative dose of idarubicin was 12-24 mg/m$^2$, divided into 2-3 days, and was decided for each patient based on fitness, prior therapies and cardiac status. All patients received prophylaxis with trimethoprim/sulfamethoxazole, quinolones, aciclovir, voriconazole, and began G-CSF support (5 µg/kg) on day 15, given until leucocyte recovery or treatment failure. As a lesson from the UK NRCI AML19 trial, where double induction courses with FLAG-Ida led to prolonged cytopenia and infectious complications[11], only a single cycle of FLAG-Ida-ven was prescribed with the intention to proceed to alloSCT as soon as possible. When a further therapy was needed as a bridge to alloSCT, a course of cytarabine at a medium intensity (1-1.5 g/m$^2$ for 6 doses) was given. Data collected included patient demographics, prior therapies and the genetic risk group. Hematologic and non-hematologic toxicities and 30- and 60-day mortality were recorded. For efficacy, complete remission (CR) and rates of complete remission with incomplete count recovery (CRi) were assessed, as well as the rates of morphological leukemia-free state (MLFS) and composite complete remission (CRc= CR+CRi+MLFS) at bone marrow evaluation post-treatment. All patients were examined for minimal residual disease (MRD) by flow cytometry at a sensitivity threshold of $10^{-3}$. Patients were evaluated for overall survival (OS), and those who achieved remission were separately evaluated for progression-free survival (PFS).

The focus of this report is on the 34 patients aged 65-77 (median 70.5) years who were treated with the FLAG-Ida-ven regimen. They represent 29% of all similar patients at that age range (*n*=117) who were treated for acute leukemia during the study period. Fourteen patients were treated for newly diagnosed leukemia, of whom 12 had an adverse-risk karyotype, while 20 were treated for relapsed leukemia, 14 of whom had an adverse-risk karyotype. See Table 1 for further details.

A CR was achieved in 10 patients and CRi in 2, while additional 11 patients achieved MLFS post-treatment, with a CRc of 67.6%. Sixty-five percent of the 23 responding patients (*n*=15) achieved MRD negativity. Twenty of the 23 responding patients were subsequently transplanted. Three patients received one consolidation cycle before alloSCT, and 17 transitioned directly to alloSCT. An additional patient was transplanted while in active disease after FLAG-Ida-ven failure. The median time between Day 1 of induction and Day 1 of alloSCT conditioning was 52 days. Twelve patients were treated with reduced intensity conditioning, while 7 received non-myeloablative conditioning using the fludarabine/TBI protocol[12]. Only 2 patients received myeloablative conditioning with either FluBus4 or thiotepa-busulfan-fludarabine protocols (Table 2).

The median OS for the total cohort was 147 days, with an estimated 2-years OS of 28%. Median PFS and OS for patients who achieved CRc were 152 days and 255 days, respectively (Figure 1). Notably, 12 of the 20 transplanted patients are still alive and in CR1 (Supplementary Figure S1).

In univariate analysis, only prior venetoclax exposure was predictive for treatment failure (CRc of 30% vs. 83% with prior venetoclax vs. no prior treatment with venetoclax, *p*=0.005), while the ELN2022 risk category, *TP53* status and N/D vs. R/R AML were not. The median time to both platelet (>50000/µL) and neutrophil (>500/µL) recovery was 22 days. Lack of neutrophil recovery was seen in six patients, all not achieving CRc, whereas in 8/16 patients who failed platelet recovery, a CRc was observed. The median length of hospitalization was 26 days.

Non-hematologic toxicities were seen in over 80% of patients. Twenty-two patients experienced bloodstream infections (BSI), and 11 were hemodynamically unstable and required vasopressor support. In three patients, the hemodynamic instability was accompanied by respiratory failure, leading to mechanical ventilation. Two patients experienced grade 3-4 mucositis and two patients had a decrease in cardiac systolic function. The 30-day and 60-day mortality rates were 8.8% and 14.7%, respectively. All deaths between day 30 and day 60 occurred in non-responders.

Treatment of older patients with AML is challenging and OS is disappointing despite the introduction of LIC-VEN, as most of these patients will ultimately succumb to their leukemia[13]; thus, alloSCT remains the only curative option. However, only 10-15% of patients treated with LIC-VEN will actually undergo alloSCT[2,13] because of advanced age or significant comorbidities. Another common reason for deferring alloSCT is non-remission after LIC-VEN therapy, which occurs in a third of the patients[14]. Yet, the use of higher intensity regimens in fit older patients with acute leukemia is often rejected, as toxicity is higher, which could later preclude the alloSCT option. The current study evaluated the efficacy and safety of high-intensity treatment with FLAG-Ida-ven in fit, older patients with AML, harboring risk factors for treatment failure with LIC+VEN. This study reported a CRc of 67% for the entire cohort, with high rates of MRD negativity, allowing for high transplantation rates (46% of all patients, 87% of patients achieving CRc). Thus, in contrast to theoretic concerns, the intensity of the regimen actually facilitated transplantation in most patients and also enabled reducing the intensity of the pre-alloSCT conditioning. Two thirds of the cohort were conditioned with reduced intensity regimens, while only one patient in CR1 received myeloablative conditioning.

This is in contrast to the reported outcome of patients allo-transplanted after induction with LIC-VEN, 20-30% of whom were conditioned with myeloablative regimens[13].

High remission rates with FLAG-Ida-ven were obtained in all subgroups, including patients with *TP53*-mutated acute leukemia. The only exception was patients who failed prior treatment with LIC+VEN, and were salvaged with FLAG-Ida-ven. This is in line with prior reports on the poor prognosis of LIC-VEN failure[15].

The hematologic toxicity of the FLAG-Ida-ven regimen was manageable, with a rapid recovery of both neutrophils and platelets at median of 22 days. However, one of the 8 patients who achieved CRc and yet did not recover the platelet count until transplantation experienced spontaneous intracranial bleeding after discharge, and was successfully treated conservatively. In comparison, the NRCI AML19 trial reported significantly longer median time to platelet and neutrophil recovery of 29 and 30 days, respectively[11]. Indeed, we set a lower limit for recovery than that of the NRCI trial, as no bleeding or sepsis events were evident beyond that limit.

Infectious complications were observed in the majority of patients, leading half to hemodynamic instability, which was most often short-lived. Similar BSI incidence was reported with other intensive regimens[2], including FLAG-Ida-ven when given to younger patients[9]. Early mortality rates in this reported cohort were in line with the incidence in other intensively and non-intensively treated cohorts, mostly composed of younger patients[2,9,11,13].

Study limitations are related to its single-center, single-arm design and broad variability in idarubicin doses used. Yet, this reflects the real-world practice, where patients differ in their fitness.

This report of 34 consecutive patients in a single center suggests that in fit, older patients with high-risk acute leukemia, intensive chemotherapy with a single cycle of FLAG-Ida-ven can lead to a deep remission and effective, prompt bridging to transplantation, potentially improving survival compared to lower-intensity regimens. These results warrant evaluation in a larger randomized controlled setting.

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**Table 1: Patient characteristics**

| | **Newly diagnosed cohort** *n* = 14 | **Relapse/refractory cohort** *n* = 20 |
|---|---|---|
| Age range (median), years | 65-76 (70) | 65-77 (71) |
| **Disease** | | |
| AML | 11 | 16 |
| ALL | 0 | 1 |
| Ambiguous lineage leukemia | 3 | 3 |
| **Leukemia ontogeny** | | |
| Therapy-related | 5 | 4 |
| Prior MDS | 4 | 5 |
| Prior MPN | 5 | 3 |
| De novo leukemia | 3 | 9 |
| **ELN 2022 risk group** | | |
| Favorable | 1 | 2 |
| Intermediate | 1 | 3 |
| Adverse | 12 | 15 |
| Prior alloSCT | 2 | 1 |
| Prior HMA treatment | 2 | 9 |
| Prior venetoclax treatment | 0 | 10 |
| Prior anthracycline treatment | 0 | 10 |
| Idarubicin dose | | |
| 24 mg/m$^2$ | 9 | 9 |
| 16 mg/m$^2$ | 4 | 6 |
| 12 mg/m$^2$ | 1 | 5 |
| Median days of platelets <50K/µL | 24.5 | 19 |
| Median days of ANC <500/µL | 22 | 22 |
| Median days in hospital | 24.5 | 31 |
| **Response to treatment** | | |
| CR+CRi | 7 | 5 |
| MLFS | 4 | 7 |
| Refractory | 2 | 6 |
| Death before evaluation | 1 | 2 |
| MRD-negativity | 8 | 7 |
| Proceeded to alloSCT | 12 | 9 |
| Median days until alloSCT | 53 | 42 |

MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasms; HMA: hypomethylating agent; ANC: absolute neutrophil count; CR+CRi: complete remission + complete remission with incomplete count recovery; MLFS: morphological leukemia-free state

**Table 2: Transplantation modality**

| | **Newly diagnosed cohort** *n* = 12 | **Relapse/refractory cohort** *n* = 9 |
|---|---|---|
| Gender male/female | 10/2 | 8/1 |
| **ELN 2022 risk group** | | |
| Favorable | 1 | 2 |
| Intermediate | 0 | 2 |
| Adverse | 11 | 5 |
| **Type of donor** | | |
| Matched related | 2 | 1 |
| Matched unrelated | 5 | 6 |
| Haploidentical/mismatched | 5 | 2 |
| **Conditioning regimen** | | |
| Myeloablative | 1 | 1 |
| Reduced intensity | 6 | 6 |
| Non-myeloablative | 5 | 2 |
| **GVHD prophylaxis** | | |
| CNI+MTX | 1 | 1 |
| CNI+MTX+ATG | 1 | 3 |
| CNI+MMF | 1 | 0 |
| CNI+MMF+ATG | 5 | 4 |
| PTCY+CNI+MMF | 4 | 1 |

CNI+MTX: calcineurin inhibitor + methotrexate; CNI+MTX+ATG: calcineurin inhibitor + methotrexate + anti-thymocyte globulin; CNI+MMF: calcineurin inhibitor + mycophenolate mofetil; CNI+MMF+ATG: calcineurin inhibitor + mycophenolate mofetil + anti-thymocyte globulin; PTCY+CNI+MMF: post-transplant cyclophosphamide + calcineurin inhibitor + mycophenolate mofetil

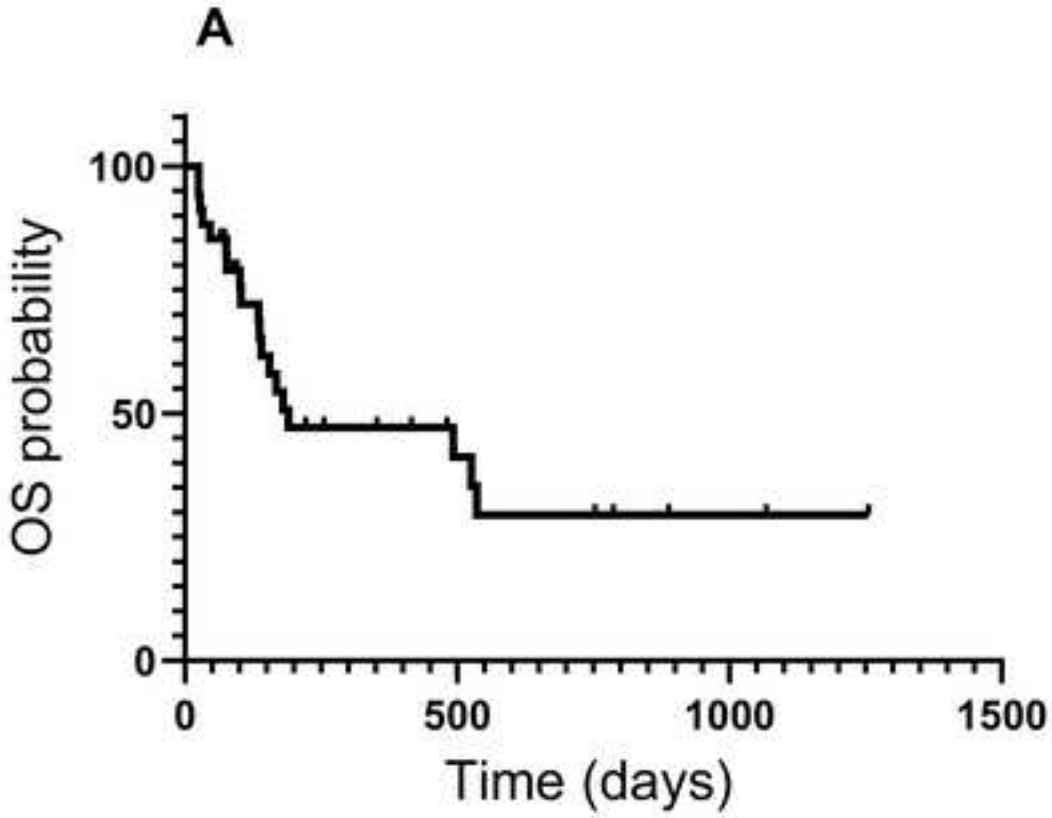
**Figure legends**

**Figure 1. Survival outcomes: Results of Kaplan-Meier analysis**

(A) Overall survival of the entire cohort

(B) Progression-free survival for patients who achieved CRc

**Figure 1**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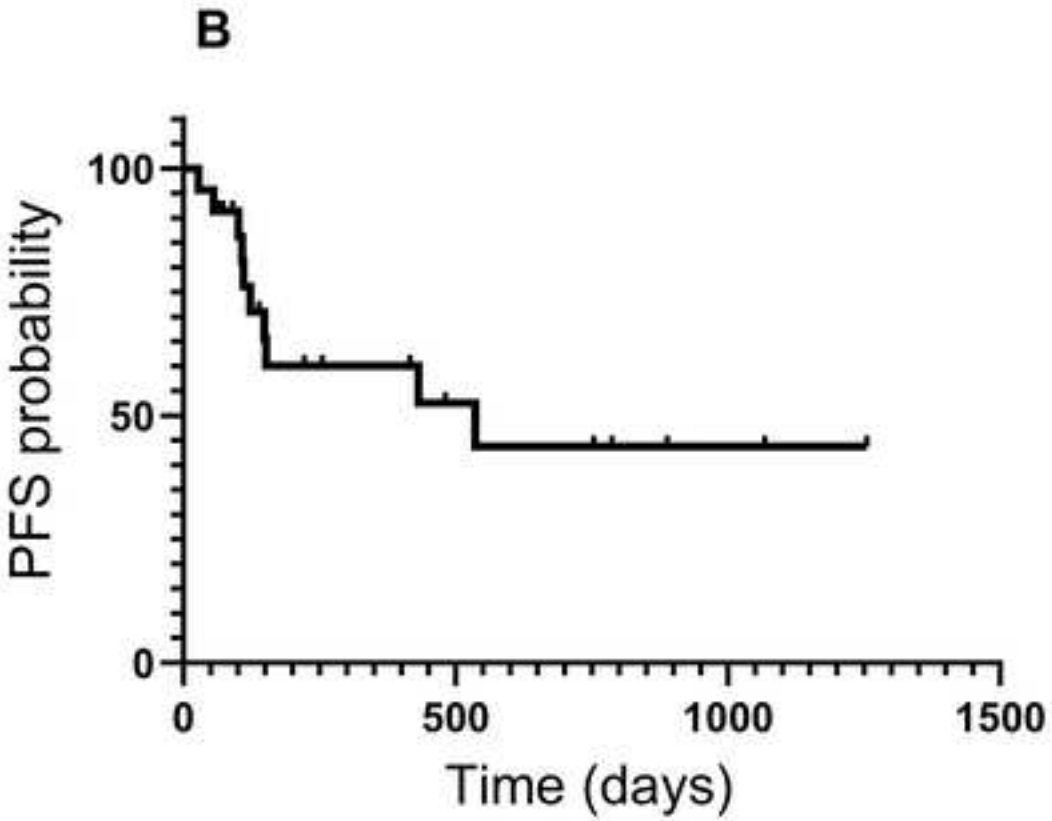
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**Figure S1: Overall (A) and progression-free survival (B) in patients who underwent allogeneic stem cell transplantation following induction with FLAG-Ida-ven**