FLAG-IDA-venetoclax for high-risk newly diagnosed acute myeloid leukemia: a multicenter real-world study

Acute myeloid leukemia (AML) remains challenging, especially in high-risk disease defined by European LeukemiaNet (ELN) 2022 molecular/cytogenetic criteria or by antecedent hematologic malignancy or prior chemo-/radiotherapy.[1,2] Outcomes are poor from primary resistance and frequent relapse.[3] Recent advances for fit patients combine intensive chemotherapy with pro-apoptotic agents to deepen responses and bridge to transplant.[4,5] Among them, FLAG-IDA plus venetoclax (FIV) shows promise in newly diagnosed and relapsed/refractory AML.[6] In a phase Ib/II study (*clinicaltrials gov. Identifier: NCT03214562*), FIV improved overall response rate (ORR), measurable residual disease (MRD) negativity, and transition to allogeneic hematopoietic stem cell transplantation (allo-HCT);[6,7] an American Society of Clinical Oncology (ASCO) 2024 update reported newly diagnosed (ND) ORR 99% with 89% MRD negativity, and 2-year overall survial (OS) and event-free survival (EFS) of 75% and 68%, respectively.[8] Real-world data remain limited.

In this multicenter retrospective study, we are presenting real-life experience with FIV in 32 patients with ND high-risk AML treated with intent-to-transplant. We evaluated efficacy, safety, and survival outcomes to provide insights into the clinical utility of this regimen beyond controlled trial settings, and to explore its role in challenging subgroups.

This retrospective cohort study included adult patients with ND AML and high-risk disease, treated at two tertiary medical centers between 2022 and 2024. This study was approved by the local institutional review boards/ethics committees of both participating centers. Informed consent was waived due to the retrospective nature of the study, in accordance with institutional guidelines and national regulations. All patients were considered fit for intensive chemotherapy and were treated with FIV, as described in the phase II clinical trial protocol (*clinicaltrials gov. Identifier: NCT03214562*).[6] Induction therapy consisted of fludarabine 30 mg/m² and cytarabine 1.5 g/m² on days 2-6, idarubicin 8 -mg/m² on days 4-6, and filgrastim 300 mcg daily on days 1-7 and re-introduced on day 15 till neutrophil recovery. Venetoclax was administered orally at a target dose of 400 mg daily for 7 or 14 days, depending on physician discretion and clinical status. Treatment was delivered with curative intent and transition to allo-HCT was planned when feasible.

Treatment responses were assessed per ELN 2022 criteria. MRD negativity was defined as the absence of detectable leukemic cells by an assay with a sensitivity of at least 10^{-3} for multiparameter flow cytometry (MFC) or 10^{-4} for molecular methods, in a patient in morphologic remission. Safety assessments included hematologic and non-hematologic adverse events (AE), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[9] Counts recovery were defined as absolute neutrophil count (ANC) ≥500/μL and platelet count ≥50×10⁹/L, consistent with at least CRh by ELN 2022 criteria.

Patient demographics and baseline characteristics are summarized in Table 1. The cohort included 32 adult patients with

Table 1. Patients characteristics and outcomes.

Patients characteristics and outcomes	N=32
Age, years median (range) mean age ≥60 years, N (%)	 56 (33-75) 54.3 11 (34.3)
Sex, N (%) Male Female	 19 (59.3) 13 (40.6)
ECOG Performance Status, N (%) 0 1 ≥3	 25 (78.1) 7 (21.8) 0 (0)
ELN risk group - 2022 criteria, N (%) Favorable Intermediate Adverse	 0 (0) 3 (9.3) 29 (90.6)
BM blasts % at diagnosis, median (range)	30 (1.4-82)
Extra-medullary leukemia at diagnosis, N (%)	5 (15.6)
AML type, N (%) *De novo* s-AML ts-AML t-AML	 15 (46.8) 7 (21.8) 4 (12.5) 6 (18.7)
Response, N (%) CR/CRh PR PD	 28 (87.5) 2 (6.25) 2 (6.25)
MRD negativity - post induction and CR patients only, N (%)	17 (57.1)
DoR, days, median (range)	148 (10-1,007)
30-day mortality, N (%)	0 (0)
60-day mortality, N (%)	1 (3.1)
Median OS, months	NR
Median EFS - CR patients only, months	NR

ECOG: Eastern Cooperative Oncology Group; ELN: European LeukemiaNet; BM: bone marrow; AML: acute myeloid leukemia; sAML: secondary AML; ts-AML: treated secondary AML; t-AML: treatment-related AML; CR: complete response; PR: partial response; PD: progressive disease; MRD: measurable residual disease; DoR: duration of response; OS: overall survival; EFS: event-free survival; NR: not reached.

ND AML, all of whom were considered high-risk according to the 2022 ELN criteria. The median age at diagnosis was 56 years (range, 33-75), and 34% (N=11) were aged ≥60 years. The majority of patients were male (59%, N=19). AML subtypes included *de novo* AML in 47% (N=15), secondary AML in 34% (N=11), and therapy-related AML in 19% (N=6). Among the secondary AML group, eight patients had antecedent myeloproliferative neoplasms (MPN), primarily myelofibrosis or post-polycythemia vera myelofibrosis. Extramedullary involvement at diagnosis was present in 16% (N=5), all with concurrent medullary disease.

Adverse-risk cytogenetics per ELN 2022 criteria were observed in 69% (N=22), with 14 patients harboring complex karyotypes and three harboring MECOM rearrangements. Two patients had *BCR-ABL1* translocations: one with transformation from chronic-phase CML and one with *de novo* *BCR-ABL1*-positive AML. One patient received dasatinib concomitantly with FIV induction, while the other did not. Mutations associated with secondary-type AML were found in 22% (N=7), including *ASXL1* (N=4) and *RUNX1* (N=3). Mutations in *IDH1* and *IDH2* were found in one patient each. One patient had *FLT3*-internal tandem duplications at low allelic burden and a concurrent *NUP98* translocation. Although one patient harbored an *NPM1* mutation, he was categorized as adverse-risk due to preceding myelofibrosis. *TP53* mutations were present in 28% (N=9), with 78% demonstrating multi-hit alterations, consistent with ultra-high-risk disease.

The duration of venetoclax was 14 days in 81% (N=26) of patients, and 19% (N=6) received 7 days of venetoclax, in five patients as an institutional policy at one center and in one case venetoclax was interrupted due to acute respiratory failure requiring intensive care unit admission. Idarubicin was given at 8 mg/m² for 3 days in 91% (N=29), with three patients receiving reduced doses for cardiac comorbidities. Fludarabine was administered uniformly at 30 mg/m² intravenously (IV) daily on days 2-6. Cytarabine was age-adapted: 1.5 g/m² for patients <60 years, and 1 g/m² for patients ≥60 years, both on days 2-6. Granulocyte colony stimulating factor was administered routinely beginning on day 1-7, and again on day 15 till count recovery.

The median hospitalization duration during induction was 26 days (range, 20-56). The median time to ANC recovery ≥500/μL was 23 days (range, 19-42), and platelet recovery ≥50×10⁹/L occurred by day 25.5 (range, 18-47). No dose-limiting toxicities were observed.

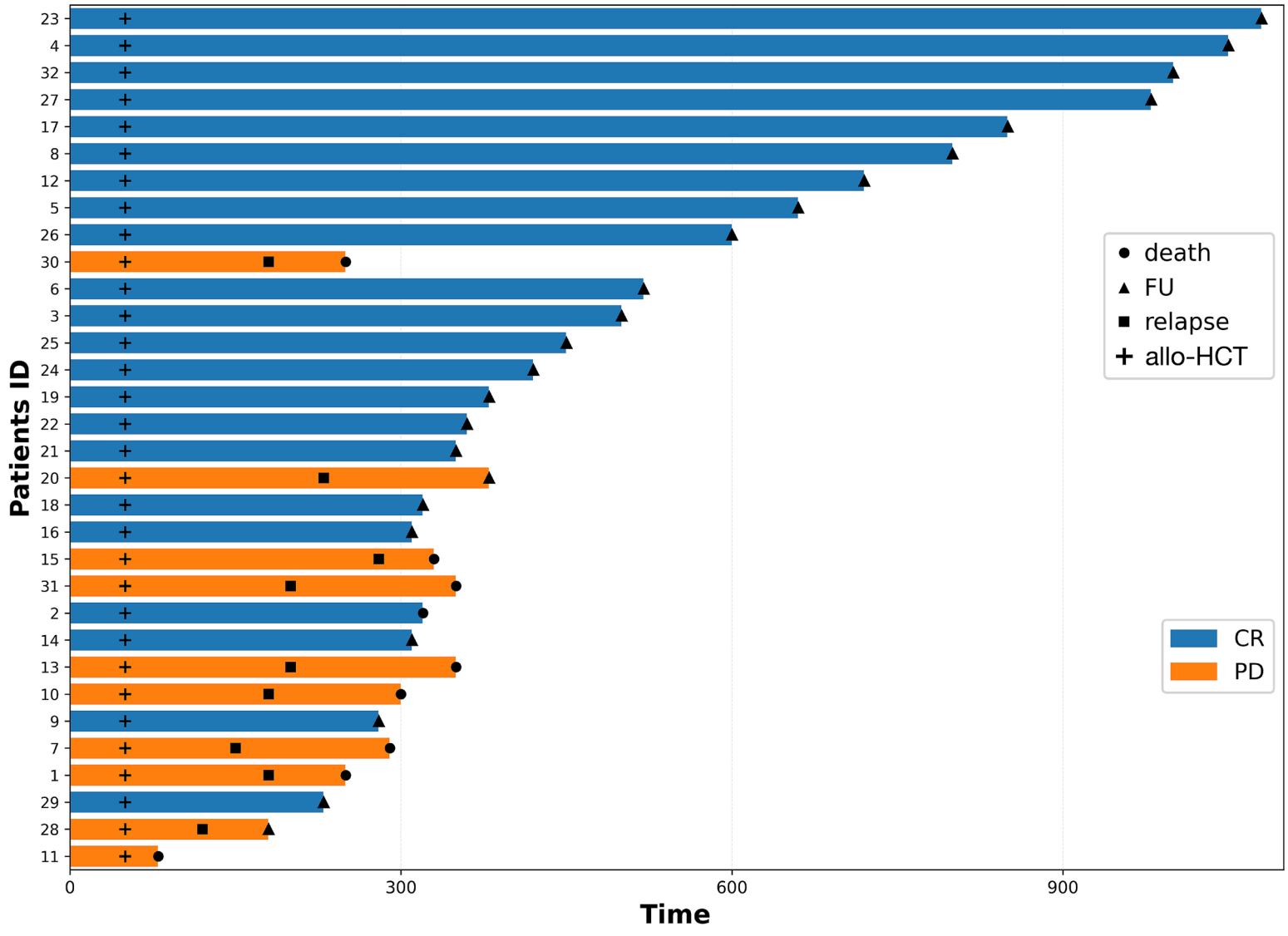


Figure 1. Swimmer plot depicting treatment timelines and outcomes for individual study participants. Each horizontal bar represents 1 patient. Bar color indicates best response, and symbols denote key clinical events, as shown in the figure legend. CR: complete response; allo-HCT: allogeneic stem cell transplantation; PD: progressive disease; FU: follow-up.

Febrile neutropenia occurred in all patient. Pneumonia was diagnosed in 34% (N=11), including five cases of invasive pulmonary aspergillosis, all in patients receiving voriconazole prophylaxis. Bronchoalveolar lavage (BAL) was performed in all cases: four were proven and one was classified as probable by clinical and radiologic criteria. Viral reactivations were observed in 22% (N=7) of patients, including HHV-6 (N=4), adenovirus (N=1), Varicella-zoster virus (N=1) and Herpes simplex virus (HSV, N=1), all managed without mortality. Mucositis was observed in 38% (N=12) of patients, with all cases being grade 1-2. No grade ≥4 mucositis, gastrointestinal bleeding, or intracranial hemorrhages occurred. The 30-day mortality rate was 0%, and the 60-day mortality was 3% (N=1, due to transplant-related toxicity). Overall safety profile supports the tolerability of FIV in the transplant-eligible high-risk AML population.

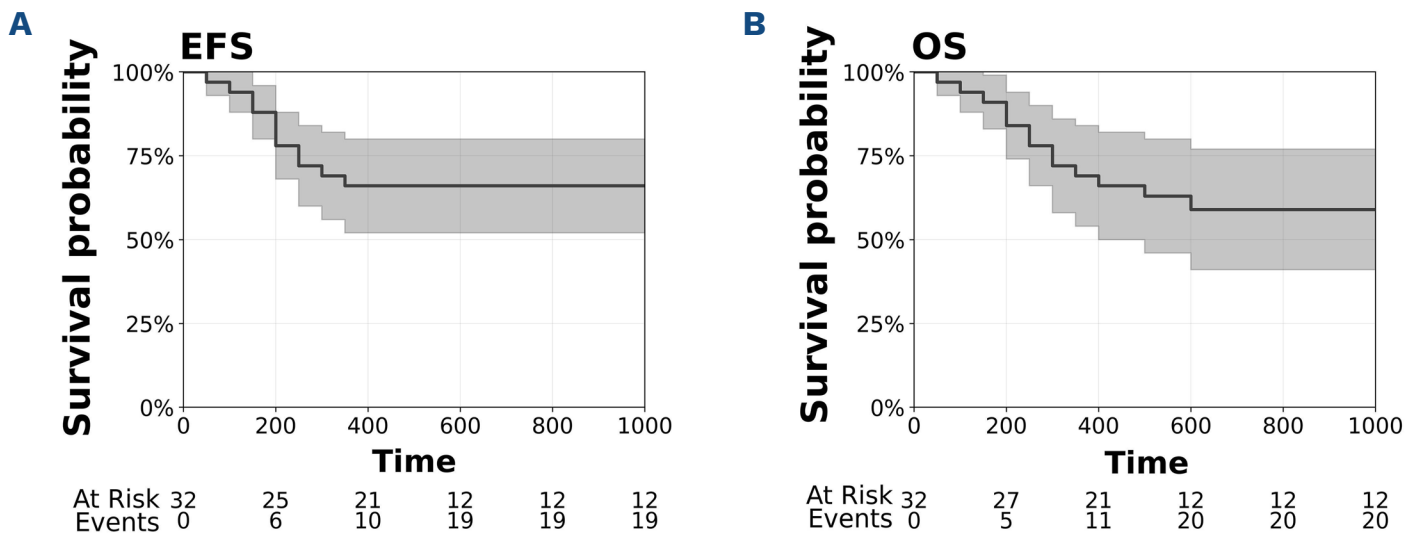


Figure 2. Survival outcomes among study participants. (A, B) Event-free survival (EFS) and overall survival (OS) for the entire cohort. (C, D) EFS and OS by European LeukemiaNet 2022 cytogenetic risk group (0 = intermediate risk, 1 = adverse risk). (E, F) EFS and OS by acute myeloid leukemia (AML) type (0 = *de novo* AML, 1 = secondary or therapy-related AML). Survival between subgroups in panels (C-F) were not statistically significant.

Response rate was defined as complete response (CR) and and CR with partial hematologic recovery (CRh) rate (CR/CRh), and was 87.5% (N=28), 6.25% (N=2) had partial remission (PR), and 6.25% (N=2) did not respond to the treatment. Counts recovery was observed in all patients achieving CR/CRh, with a median time of 23 days (range, 19-42) and 25.5 days (range, 18-47) to ANC and platelet recovery as defined above, respectively. Among the 28 complete responders, 24 underwent MRD assessment via MFC. Of these, 58% (N=14) achieved MRD negativity post induction. MRD testing via NGS was available for six patients, with 50% (N=3) achieving MRD negativity by this method. MRD negativity was associated with improved OS and EFS at the time of analysis, although the cohort size precluded formal statistical modeling (Table 1). All non-complete-responders (N=4) had clinically *de novo* AML. Two had inv(3), one had a complex karyotype with *TP53* mutation, and one exhibited a secondary-type mutation profile. Subgroup analyses revealed CR/CRh in all eight post-MPN AML patients, with 62% (N=5) MRD negativity rate. Among *TP53*-mutated patients (N=9), 89% (N=8) achieved CR/CRh, and 55% (N=5) were MRD-negative post induction. Among those with adverse-risk cytogenetics (N=23), CR/CRh was achieved in 87% (N=20). Elderly patients (age ≥60 years, N=11), demonstrated good tolerance with high CR/CRh rate (91%, N=10), suggesting FIV is feasible in selected older fit patients. Of 32 patients, 97% (N=31) proceeded to allo-HCT, reflecting both high response rates and transplant eligibility. Seventy four percent of patients (N=23) remained in remission at last follow-up. The median time from FIV initiation to allo-HCT was 54 days (range, 38-76). Notably, 71% (N=22) underwent transplant within 60 days, often without interim consolidation. Of the four non-responders, two underwent allo-HCT using a sequential protocol, reflecting an institutional policy that patients previously exposed to venetoclax were not offered additional venetoclax-based salvage. A third patient with inv(3) received azacitidine-venetoclax combined with lenalidomide, achieved remission, and subsequently underwent allo-HCT.

At a median follow-up of 11.3 months, median OS and EFS were not reached. Estimated 6- and 12-month OS rates were 85% and 66%, respectively, and 12-month EFS was 63% (Table 1; Figure 1).

In the *TP53*-mutated subgroup (N=9), five patients relapsed and subsequently died of disease progression. One patient died of transplant-related complications. Three patients remained alive and relapse-free at 12 months. The median OS in this group was 7.95 months (median follow-up 8.3 months). All five relapses occurred within 5 months post allo-HCT. One patient had primary induction failure but eventually underwent sequential myeloablative transplant without achieving remission, experiencing early post-transplant relapse. Two patients with monoallelic *TP53* mutations remain alive at last follow-up, whereas only one of seven patients with biallelic mutations survived. Notably, even patients achieving MRD negativity in this subgroup did not experience long-term survival. Among patients with post-MPN AML, 75% (N=6) were alive and relapse-free at 12 months. These patients had no early deaths or significant transplant-related complications.

Survival did not differ significantly between patients aged ≥60 *versus* <60 years, or between *de novo* and secondary AML, suggesting that FIV followed by allo-HCT may attenuate the impact of traditional high-risk features. However, longer follow-up is required to confirm these trends (Figure 2).

Our real-world analysis of FIV in newly diagnosed high-risk AML provides meaningful insight into the application of this regimen in clinical practice. While previous studies, including phase I/II trials and retrospective series, have demonstrated encouraging outcomes with FIV, our study represents one of the largest reports to date, focused exclusively on high-risk AML, as defined by ELN 2022 criteria.

A distinguishing characteristic of our cohort is the relatively older median age (56 years), with over one-third aged ≥60 years. This is notably older than populations typically enrolled in clinical trials of intensive chemotherapy, where younger and more selectively fit patients often predominate. Despite this, our findings suggest that FIV is both feasible and effective in older, fit individuals, supporting its applicability beyond trial settings and underscoring the importance of individualized fitness assessments for intensive therapy.

Two subgroups warrant particular attention. First, all eight patients with post-MPN AML achieved CR/CRh and proceeded to allo-HCT, with 75% remaining relapse-free at 12 months. Historically, this rare subgroup has been underrepresented in clinical trials and exhibited poor responsiveness to standard chemotherapy, with median survival often under 6 months.[10] To our knowledge, this represents one of the largest reported series of patients with post-MPN AML treated with a chemotherapy-venetoclax combination.

Second, patients with *TP53* mutations achieved a high CR/CRh rate (89%), with over half attaining MRD negativity. While these outcomes are encouraging, long-term survival remains poor, with a median OS of 7.95 months. These data reinforce the ongoing challenge of *TP53*-altered AML, where deep remissions do not necessarily translate into durable survival.

In summary, our real-world data support FIV as an effective and tolerable induction for high-risk AML. The consistent efficacy across age groups and AML subtypes, along with high remission and MRD-negative rates, reinforce its frontline potential. FIV enables timely transition to allo-HCT, but further follow-up is needed to confirm long-term benefit and identify predictors of sustained remission in adverse-risk subgroups.

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Contributions

TZ, AF and BN oversaw the work. BK and SA, AF, DY, IH, HK, NG, AH and SA performed data collection. BK and AF drafted the manuscript. BN and SA edited the manuscript. BK and SA performed statistical analysis. All authors reviewed the manuscript.

Data-sharing statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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