

One-Year Survival with Standard 3+7 Versus FLAG/FLAG-IDA Induction in Newly Diagnosed Acute Myeloid Leukemia: A Real-World Propensity Score–Matched Cohort Study

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1. INTRODUCTION

- **The Clinical Debate**
 - 3+7 (daunorubicin/idarubicin + cytarabine) has been the frontline standard for intensive induction since the 1970s.
- Fludarabine, Cytarabine, and G-CSF (FLAG-based) regimens (± idarubicin) offer theoretical advantages through fludarabine/G-CSF priming of leukemic blasts, enhancing cytarabine cytotoxicity.
- Evidence from randomized trials like NCRI AML19 supports improved outcomes but was conducted in selected younger populations without adverse genetics.
- This leaves the performance of these regimens in unselected real-world practice, including secondary AML, undefined.

2. STUDY OBJECTIVES

- (A) To compare survival (primary: 1-year mortality) and early outcomes (ICU admission, toxicity, early mortality) between standard 3+7 and FLAG/FLAG-IDA frontline induction.
- (B) To compare outcomes stratified by disease origin: de novo vs. secondary/therapy-related AML.

3. METHODS

- This study emulated a target trial using the TriNetX Global Collaborative Network (204M+ patients, 180 sites).
- Eligible adults with newly diagnosed AML (excluding APL) received either 3+7 or FLAG/FLAG-IDA.
- 1:1 nearest-neighbor propensity score matching balanced demographics, comorbidities, and six baseline laboratory strata (Hb, albumin, WBC, platelets, creatinine, LDH) measured within 1 day of index, ensuring complete covariate balance (all SMDs < 0.1).

4. PSM VISUAL GUIDE

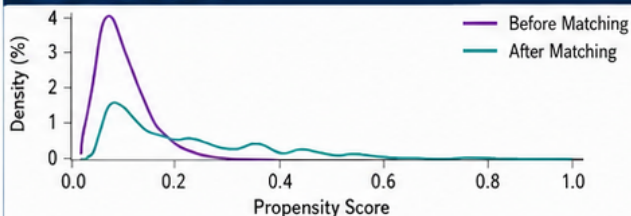


Figure 2: Propensity Score Density Before and After Matching

KEY STATISTICAL CALLOUT BOX

**3+7 INDUCTION YIELDS 26%
HAZARD REDUCTION IN
1-YEAR MORTALITY OVERALL
(HR 0.74, p=0.0002)**

2. PRIMARY RESULTS TEXT

- Analysis of the robust matched cohort of 877 pairs.
- 1-year mortality was significantly lower with 3+7: 31.0% (272/877) vs. 39.1% (343/877).
- Cox analysis shows a highly significant hazard reduction (HR 0.74; 95% CI, 0.63–0.87; log-rank p = 0.0002).
- This benefit persisted at 2 years: 41.4% mortality (3+7) vs. 45.4% (FLAG/FLAG-IDA) (HR 0.84; p = 0.015).

3. PRIMARY SURVIVAL VISUAL GUIDE

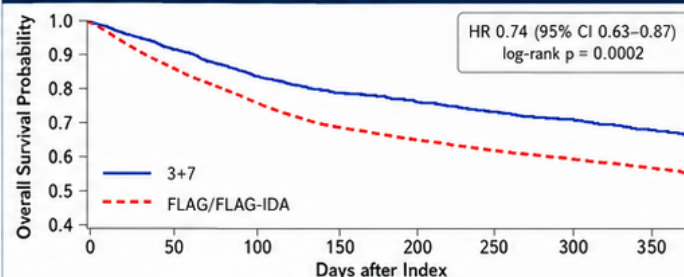


Figure 3: Kaplan-Meier Overall Survival Curve

4. EARLY TOXICITY & SAFETY

- There were no significant differences in short-term safety.
- Early mortality:
 - 30-day (7.0% vs. 7.9%; p = 0.404)
 - 60-day (11.8% vs. 13.9%; p = 0.187)
- Acute toxicity rates:
 - 60-day ICU admission (15.9% vs. 14.3%; p = 0.396)
 - 60-day sepsis/septic shock incidence (49.2% vs. 48.2%; p = 0.743)

DISEASE ORIGIN SUBGROUP RESULTS (THE KEY INSIGHT)

- Analysis of 413 matched pairs with De Novo AML
 - Standard 3+7 is significantly superior:
1-year mortality 33.9% vs. 45.0% with FLAG/FLAG-IDA (HR 0.67; 95% CI, 0.54–0.83; p = 0.0003)
- In contrast, 506 matched pairs with Secondary / Therapy-Related AML
 - Outcomes are equivalent:
1-year mortality 32.8% vs. 33.4% (HR 0.98; 95% CI, 0.79–1.22; p = 0.881)

5. SUBGROUP VISUAL GUIDE

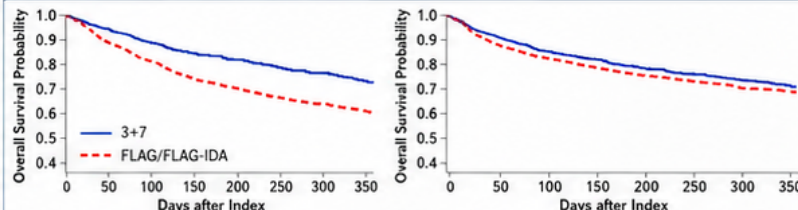


Figure 5A: OS De Novo AML

Figure 5B: OS Secondary/t-AML

6. HSCT & TRANSPLANTATION

- Confounding by indication. While overall 1-year transplantation rates favored FLAG/FLAG-IDA (19.7% vs. 16.4%; p = 0.011), this difference is confined to secondary/therapy-related AML (27.3% vs. 22.7%; p = 0.040) and completely absent in de novo AML (9.2% vs. 8.5%; p = 0.368).
- High transplantation in FLAG recipients is due to its use in patients whose disease biology necessitates HSCT.

7. SEPSIS BURDEN & HOSPITALIZATION

- FLAG/FLAG-IDA had fewer mean 60-day sepsis episodes (2.85 vs. 4.18 with 3+7; p = 0.0001) and shorter median 60-day stays (33 vs. 36 days; p = 0.0001).
- This paradoxical finding (identical overall sepsis rates but fewer recurrent episodes with FLAG) suggests different immune patterns: 3+7 causes prolonged neutropenia leading to recurrent bacterial/fungal infections, while fludarabine/G-CSF or increase T-cell suppression or receive different prophylaxis.

8. CLINICAL CONCLUSIONS

For adults with newly diagnosed AML:

- (1) Standard 3+7 was associated with superior 1-year and 2-year survival overall.
- (2) The survival advantage was confined to de novo AML; outcomes were equivalent in secondary/therapy-related AML.
- (3) FLAG/FLAG-IDA was associated with fewer recurrent sepsis episodes and shorter hospitalization.
- (4) The higher HSCT rate with FLAG/FLAG-IDA likely reflects selective use in secondary disease rather than a direct treatment effect.