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Final results of a randomized multicenter phase II study of alvociclib, cytarabine, and mitoxantrone versus cytarabine and daunorubicin (7 + 3) in newly diagnosed high-risk acute myeloid leukemia (AML)

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Despite recent advances in the management of subpopulations of AML, overall outcomes remain unsatisfactory. Encouraging results were seen with alvocidib (formerly known as flavopiridol), a CDK9 inhibitor with pan-cyclin-dependent kinase (CDK) activity, followed by cytarabine and mitoxantrone (FLAM) in serial phase I-II studies in newly diagnosed AML patients [1–7]. Therefore, we conducted a randomized phase II clinical trial comparing FLAM to cytarabine and daunorubicin (7 + 3) in newly diagnosed AML patients 18–70 years of age with non-favorable risk cytogenetics [8]. We previously published results of this trial revealing no significant differences in overall survival (OS) between FLAM and 7 + 3 despite significantly higher complete remission (CR) rates with FLAM. It is imperative to analyze long-term OS on this study as a secondary endpoint. Furthermore, we hypothesized that the survival trends may change with longer follow-up. We report the final long-term OS results of this trial.

This study randomized 165 patients between FLAM (n = 109) and 7 + 3 (n = 56) with a median age of 59 years (range: 19–70 years) across 10 institutions. Overall, 41% of patients had adverse-risk features based on 2010 European Leukemia Net Guidelines [9]. The primary endpoint of this trial was the rate of CR (including CR with incomplete hematologic recovery: CRi) with FLAM and 7 + 3. FLAM led to significantly increased CR rates when compared with 7 + 3 with 1 or 2 cycles of treatment (70% vs. 47%, $p = 0.003$, and 70% vs. 57%, $p = 0.08$, respectively). Despite the improvement in CR rates with FLAM, our earlier published results did not reveal significant differences in overall survival (OS) and event-free survival (EFS) between the arms, with median follow-up 811 days (range: 1–1217 days) by reverse Kaplan-Meier methodology.

The final database lock was on November 21, 2017. The first and last patient enrolled on this study on May 25, 2011 and July 26, 2013, respectively. Median follow-up by reverse

Kaplan-Meier methodology is 1644 days (4.5 years; range: 1–2203 days). Overall, 76/109 (70%) patients died on the FLAM arm compared with 39/56 (70%) patients on the 7 + 3 arm (Table 1). Relapses were seen in 31/70 (44%) and 18/32 (56%) CR patients who received FLAM and 7 + 3 (1 or 2 cycles), respectively. Post-remission therapy was not standardized between both arms on this trial. Of the CR patients on the FLAM arm, 46% received a second cycle of FLAM consolidation, 28% received high dose cytarabine (HiDAC) consolidation, 17% underwent an allogeneic stem cell transplant (SCT) without consolidation therapy, 7% did not receive post-remission therapy due to poor performance status, and 3% either re-lapsed or received subsequent salvage chemotherapy for persistent cytogenetic abnormalities while in CR. In contrast, among the CR patients on the 7 + 3 arm, 81% received HiDAC consolidation, 9% underwent a SCT without consolidation therapy, 6% did not receive post-remission due to poor performance status and 3% refused further therapy. An allogeneic stem cell transplant (SCT) was performed in 50% of patients on both arms. Receipt of SCT was not significantly associated with OS in either arm, and there was no effect modification between treatment arm and receipt of SCT on OS using a time-varying covariate analysis approach (interaction $p = 0.32$). Fig. 1A and B display the Kaplan-Meier estimates of OS and EFS for FLAM and 7 + 3. The EFS analysis censored patients at the time of receipt of SCT or alternative therapy. Median OS was 17.5 months for FLAM and 23.1 months for 7 + 3 ($p = 0.5$). Five-year OS rates were 28% (95% confidence interval (CI): 21–39%) and 26% (95% CI: 16–43%) for FLAM and 7 + 3, respectively. Median EFS for FLAM vs. 7 + 3 = 9.7 vs. 3.4 months, respectively ($p = 0.18$). Five-year EFS rates for FLAM vs. 7 + 3 were 19% (95% CI: 10%–35%) and 26% (95% CI: 14%–48%), respectively. If we remove the censoring and follow patients for relapse or death post-SCT, the median EFS for FLAM vs. 7 + 3 = 9.8 vs. 7.7 months, respectively ($p = 0.48$). Five-year EFS rates for FLAM vs. 7 + 3 were 25% (95% CI: 18%–35%) and 16% (95% CI: 8%–30%), respectively. The majority of long-term survivors (i.e., alive 5 years after randomization) on both arms received a SCT in CR1. Two long-term survivors on the FLAM arm received only 1 cycle of consolidation in CR1 without a SCT.

Subset analyses on this study revealed that younger patients (< 50 years) had significantly improved CR rates with FLAM versus 1 cycle of 7 + 3 (CR rates = 96% vs. 57%, respectively) when compared with older patients (≥ 50 years: CR rates = 61% vs. 43%, respectively) when testing for heterogeneity of treatment effect ($p = 0.04$). Therefore, we analyzed long-term OS and EFS of FLAM versus 7 + 3 in those < 50 years and ≥ 50 years. As expected, patients < 50 years had improved OS when compared with those ≥ 50 years on both arms (Median OS = 46.9 months versus 15.9 months, respectively). In patients < 50 years, median OS was not reached with FLAM versus 34.9 months with 7 + 3 (Fig. 1C). Long-term OS appeared to be better in patients < 50 years who were randomized to FLAM with 5-year OS = 56% (95% CI: 40–78%) versus 36% (95% CI: 18–72%) with 7 + 3, compared with those ≥ 50 years (19% versus 22%, respectively), but the interaction was not statistically significant ($p = 0.15$).

OS analyses need to be interpreted cautiously in this clinical trial given the 2:1 randomization (FLAM: $n = 109$ versus 7 + 3: $n = 56$), heterogeneity in the post-remission therapies between both arms, and the lack of power to detect an OS difference between both regimens. The FLAM regimen was initially studied as 1 induction cycle followed by a

subsequent consolidation course identical to induction in those who achieve CR. However, those randomized to FLAM had the option of either FLAM or HiDAC consolidation at the time of CR, whereas those randomized to 7 + 3 received varying cycles of HiDAC consolidation, which confounds the OS analyses. Future randomized trials should stipulate the post-remission therapy and number of courses for both arms explicitly. Additionally, when compared to contemporary randomized phase II-III clinical trials, those on the 7 + 3 arm appeared to have better than expected outcomes. In the randomized phase III study of 7 + 3 with high dose (90 mg/m²) compared with standard dose (45 mg/m²) daunorubicin conducted by the Eastern Cooperative Oncology Group (ECOG) in newly diagnosed AML patients, median OS was 23.7 months in patients on the high dose daunorubicin arm [10]. However, 15.6% of patients on the ECOG study had favorable-risk cytogenetics and the upper age limit was 60 years. In contrast, our study excluded favorable-risk cytogenetics and the upper age limit was 70 years. Patients ≥ 60 years have worse outcomes compared with their younger counterparts [11–13]. In the present study, 44% and 55% of patients were ≥ 60 years on the FLAM and 7 + 3 arms, respectively, thus making direct comparisons challenging for similarly designed randomized phase II-III clinical trials in AML in younger or older patient populations.

Despite the lack of improvement in OS when compared with 7 + 3, these findings corroborate alvocidib's activity in AML and support further development. Retrospective mitochondrial profiling revealed that NOXA, a BH3 pro-apoptotic protein that antagonizes myeloid leukemia cell-1 (MCL-1), priming in the bone marrow was significantly higher in patients achieving CR compared with non-responders (45% versus 5%, respectively) treated with FLAM [14]. A high NOXA priming score reflects dependence of leukemic cells on MCL-1 for survival. Further investigation of alvocidib (FLAM) is being performed in a biomarker-driven phase II clinical trial in newly diagnosed and re-lapsed/refractory AML patients with high NOXA (≥ 40%) priming scores ([NCT02520011](#)). Additionally, a phase I study of alvocidib followed by 7 + 3 in newly diagnosed AML with non-favorable cytogenetics is currently enrolling patients ([NCT03298984](#)).

Since inception of this trial, Gemtuzumab Ozogamicin (GO) was FDA-approved in combination with 7 + 3 for newly diagnosed CD33⁺ AML. This approval was based on findings from the ALFA-0701 randomized phase 3 trial of 7 + 3 (daunorubicin 60 mg/m²) with or without GO on days 1, 4 and 7 in newly diagnosed AML patients between 50 and 70 years of age. EFS, but not CR, was improved with the addition of GO. Subset analyses suggest that the benefit of GO was largely seen in the non-adverse risk patient population [15]. 7 + 3 + GO would be an appropriate comparison arm for further studies of alvocidib in AML, though it is noteworthy that ALFA-0701 used lower doses of daunorubicin and did not include patients < 50 years.

In summary, our final analysis reveals that FLAM leads to higher CR rates compared with 1 or 2 cycles of 7 + 3 induction in newly diagnosed AML patients 18–70 years with non-favorable cytogenetics but no significant difference was seen in OS or EFS. Subset analyses suggest that younger patients are more likely to achieve CR on FLAM compared with 7 + 3. Ongoing trials of alvocidib will provide further direction for its role in the current treatment armamentarium for AML.

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Fig. 1. Kaplan-Meier estimates by treatment arm.

(A): OS for the entire cohort.

(B): EFS for the entire cohort.

(C): OS in patients < 50 years.

Table 1

Causes of Death.

Survival Outcomes	FLAM (n = 109)	7 + 3 (n = 56)
Causes of Death	47 (62%)	31 (79%)
Leukemia	9 (12%)	1 (3%)
Infection	8 (11%)	5 (13%)
Post-SCT complications	3 (4%)	0
Hemorrhage/Coagulopathy	2 (3%)	1 (3%)
TLS	1 (1%)	1 (3%)
Multi-organ Failure	1 (1%)	0
Stroke	5 (7%)	0
Unknown Causes # of Deaths (%)	76 (70%)	39 (70%)