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Burnett, A. K., Russell, N. H., Hills, R. K., Knapper, S., Freeman, S., Huntly, B., Clark, R. E., Thomas, I. F., Kjeldsen, L., McMullin, M. F., Drummond, M., Kell, J., & Spearing, R. (2020). Defining the Optimal Total Number of Chemotherapy Courses in Younger Patients With Acute Myeloid Leukemia: A Comparison of Three Versus Four Courses. Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology, JCO2001170. https://doi.org/10.1200/JCO.20.01170

Published in:
Journal of Clinical Oncology: official journal of the American Society of Clinical Oncology

Document Version:
Publisher’s PDF, also known as Version of record

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

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Defining the Optimal Total Number of Chemotherapy Courses in Younger Patients With Acute Myeloid Leukemia: A Comparison of Three Versus Four Courses

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abstract

PURPOSE The optimum number of treatment courses for younger patients with acute myeloid leukemia (AML) is uncertain. The United Kingdom National Cancer Research Institute AML17 trial randomly assigned patients who were not high risk to a total of three versus four courses.

PATIENTS AND METHODS Patients received two induction courses based on daunorubicin and cytarabine (Ara-C), usually with gemtuzumab ozogamicin. Following remission, 1,017 patients were randomly assigned to a third course, MACE (amsacrine, etoposide, and Ara-C), plus a fourth course of MidAc (mitoxantrone and Ara-C) and following an amendment to one or two courses of high-dose Ara-C. Primary end points were cumulative incidence of relapse (CIR), relapse-free survival (RFS), and overall survival (OS). Outcomes were correlated with patient characteristics, mutations, cytogenetics, induction treatments, and measurable residual disease (MRD) postinduction.

RESULTS In logrank analyses, CIR and RFS at 5 years were improved in recipients of four courses (50% vs 58%; hazard ratio [HR] 0.81 [0.69-0.97], P = .02 and 43% vs 36%; HR 0.83 [0.71-0.98], P = .03, respectively). While OS was not significantly better (63% vs 57%; HR 0.84 [0.69-1.03], P = .09), the noninferiority of three courses to four courses was not established. The impact on relapse was only significant when the fourth course was Ara-C. In exploratory analyses, although MRD impacted survival, a fourth course had no effect in either MRD-positive or MRD-negative patients. A fourth course was beneficial in patients who lacked a mutation of FLT3 or NPM1, had 3 mutations in other genes, or had a presenting WBC of < 10 × 10^9 L^-1.

CONCLUSION Although a fourth course of high-dose Ara-C reduced CIR and improved RFS, it did not result in a significant OS benefit. Subsets including those with favorable cytogenetics, those lacking a mutation of FLT3 or NPM1, or those with < 3 other mutations may derive survival benefit.

J Clin Oncol 00. © 2020 by American Society of Clinical Oncology

INTRODUCTION

A number of different induction schedules and combinations given to patients with acute myeloid leukemia (AML) will achieve morphological marrow blast clearance in 75%-85% of younger patients, arbitrarily defined as < 60 years of age. More intensive combinations often only require a single induction course. In remission, the risk of relapse is based on several factors including presenting WBC count, age, secondary disease, morphological response of the bone marrow if not in remission, cytogenetics, and mutation analysis. More recently, estimates of minimal residual disease (MRD) assessed after the first or second induction course have also been shown to be important for relapse risk, although further data are required to establish when the MRD status is predictive of what the optimal treatment should be. From the combined prognostic information, patients will be regarded as at high, intermediate, or low risk of relapse. Usually, the issue requiring clarification is whether a stem cell transplant should be recommended. Prospective studies have now demonstrated that for patients who have FLT3 mutation type 1 inhibitors, midostaurin10 but not lestaurtinib11 will reduce relapse risk and improve survival. Other recently approved drugs may deliver further reductions in relapse for particular subgroups.

High-dose cytarabine (Ara-C) has been an established standard of care for consolidation following the
CONTEXT

Key Objective
After two courses of induction treatment, patients who were in remission and not high risk were randomly assigned to one or two more courses of treatment.

Knowledge Generated
Patients given two courses of high-dose cytarabine (ie, a total of four courses) had a reduced cumulative incidence of relapse and an improved relapse-free survival but did not result in a significant benefit in overall survival.

The trial did not establish that three courses of chemotherapy were noninferior to the standard of care of four courses. Although measurable residual disease (MRD) predicted the risk of relapse, overall administration of a fourth course had no survival benefit on either MRD-positive or MRD-negative patients.

Relevance
This study contributes information to the question of how much chemotherapy is required for younger patients with acute myeloid leukemia.

PATIENTS AND METHODS

The AML17 Trial
The United Kingdom MRC AML17 trial (ISRCTN5675535) tested a number of interventions for induction, which have already been reported.11,16-18 Briefly, patients of age from 18 years usually up to 60 years were initially randomly assigned to receive ADE (Ara-C, daunorubicin, and etoposide) or DA (daunorubicin and Ara-C) for the first two courses combined with gemtuzumab ozogamicin as a single dose of 3 mg/m² or 6 mg/m² in course 1, in which neither the addition of etoposide nor dosing of gemtuzumab ozogamicin at 6 mg/m² improved the result.18 In a subsequent amendment, induction treatment was DA treatment where the daunorubicin dose in course 1 was either 60 mg/m² or 90 mg/m². In this comparison, no overall difference was found,4 but it later emerged that patients with a FLT3 mutation benefited from the dose of 90 mg/m².19 Patients with high-risk myelodysplastic syndrome (defined as >10% marrow blasts), with de novo or secondary AML, with any WHO performance score could be included, but the blast transformation of chronic myeloid leukemia and acute promyelocytic leukemia was excluded. After the first course of induction treatment, patients were designated as high-, intermediate-, or low-risk based on our validated weighted risk score,5,6 which is based on the presenting WBC count, age, cytogenetics, and secondary disease and is presented in detail in the Protocol (online only).

Intermediate-risk patients with a FLT3 mutation could enter a random assignment of the addition of FLT3 inhibitor, lestaurtinib, or not, while other intermediate-risk patients without the FLT3 mutation could be randomly assigned to the addition of the mammalian target of Rapamicin inhibitor, everolimus, or not. The results of both interventions have previously been reported with neither addition showing overall benefit.11,17 After the two induction courses, all intermediate- and good-risk patients, whether receiving lestaurtinib or everolimus or not, were eligible to be randomly assigned to have one or two consolidation courses following the confirmation of remission (ie, three or four courses of treatment in total). This random assignment helped in recruiting patients from April 2009 to December 2014. Initially, until June 2010, the consolidation treatment random assignment for the third and fourth courses was between MACE (amsacrine, Ara-C, and etoposide) and MACE plus MidAc (mitoxantrone and Ara-C) (n = 120). In light of the results of the previous MRC AML15 trial, which
compared MACE/MidAc with two courses of Ara-C, a subsequent protocol amendment changed the random assignment to one versus two courses of high-dose Ara-C (3 g/m² twice a day days 1, 3, and 5) (n = 897). Random assignment took place after count recovery following the second induction course. The aim of the three versus four random assignment was to define if a fourth treatment course was necessary and whether the treatments involved were relevant. The trial flow diagram and details of drugs used are shown in Fig 1.

**Correlative Studies**

Cytogenetic analyses were undertaken locally in laboratories that participate in the national quality assurance scheme, centrally reviewed, and classified according to our established criteria. Mutation analysis of the FLT3 and NPM1 status was performed in a single reference lab. Although not integral to therapeutic decisions in the trial, samples for MRD, which were not disclosed to investigators, were collected after each induction course and undertaken by flow cytometry in one of the two reference labs by methods previously described and whole genome sequencing (Sanger sequencing) as described elsewhere of additional 82 genes was undertaken on 443 stored samples from participants in this random assignment at the Sanger Centre (Cambridge, United Kingdom). The FLT3 mutation status was provided during the trial to enable entry to the lestaurtinib random assignment.

Patients were randomly assigned in 110 centers in the United Kingdom, five in Denmark, and five in New Zealand. The trial was sponsored by Cardiff University and approved by the All Wales Research Ethics Committee on behalf of all UK investigators, by the Danish Medicines Agency for sites in Denmark, and by the New Zealand Medicines and Medical Devices Safety Agency for sites in New Zealand.

Written consent was obtained for each random assignment and for the storage of diagnostic samples. The trial was conducted in accordance with the Declaration of Helsinki.

**Statistical Considerations and End Points**

The primary outcome measure for this random assignment was overall survival (OS) at 5 years. It was anticipated that about 55% of patients who entered the whole AML17 trial would be available for the consolidation chemotherapy random assignment. The trial was anticipated to detect, with 90% power, a difference in survival from 55% to 65%, equivalent to a hazard ratio (HR) of 0.71; a critical number of 370 events was required to evaluate this difference. The primary question was whether three courses were non-inferior to four courses, at a one-sided significance of 0.025; consequently, effect sizes are reported with 95% two-sided CIs throughout. Noninferiority would be concluded if the lower 95% CI bound was above 0.71. Toxicity (hematologic recovery times and nonhematologic toxicity) was scored using the National Cancer Institute Common Toxicity Criteria, Version 3, and resource use data (blood product support, days on antibiotics, and hospitalization) were collected. All end points were defined according to the revised International Working Group criteria, where OS and relapse-free survival (RFS) were measured from the point of random assignment.

The analyses are by intention to treat. Categorical end points (eg, OS) were compared using Mantel-Haenszel tests, giving Peto odds ratios (ORs) and CIs. Continuous/scale variables were analyzed by nonparametric (Wilcoxon rank-sum) tests. Time-to-event outcomes were analyzed using the logrank test, with Kaplan-Meier survival curves. Analyses adjusted for random assignment parameters are performed using the Cox regression and given in parallel to the assumption-free logrank approach. ORs/HRs < 1 indicate benefit for the extra course of chemotherapy. All survival percentages are at 5 years unless otherwise stated. The median follow-up at the time of final analysis was 55.1 months (range, 1.2-99.4 months).

In addition to overall analyses, exploratory analyses were performed stratified by the random assignment stratification parameters and other important variables, including correlations with MRD, with suitable tests for interaction. Because of the well-known dangers of subgroup analysis, these were interpreted cautiously.

**RESULTS**

**Patient Characteristics**

Between April 2009 and December 2014, a total of 1,709 patients, on recovery from induction course 2, were eligible for this random assignment of whom 1,017 (60%) were randomly assigned. The reasons for not being randomly assigned were only listed as patient or clinician preference. The interval between diagnosis and random assignment was 2.6 months (range, 1.4-5.2 months). Patients not entering the random assignment were generally similar but were less likely to be de novo AML, to have worse cytogenetics, and to have received DA60 in induction (Protocol); however, the OS at 5 years of those eligible who reached the median time of random assignment but did not enter the random assignment was 60%, which was the same for those who were randomly assigned (60%; P = .4). The characteristics and treatments of the randomly assigned patients are shown in Table 1. There were no differences between those randomly assigned with respect to age, sex, performance score, presenting WBC count, cytogenetic risk group, NPM1 status, induction treatments, and risk score or number given stem cell transplant overall or in CR1. There was a modest difference in 479 patients whose MRD status was known after course 1 or in 365 randomly assigned patients whose MRD status was known after course 2, with fewer patients allocated to three courses to be MRD-negative. As previously stated, the MRD status of patients was not made available to investigators. There was no difference in the frequency of mutations or in the
**FIG 1.** Protocol flow diagram. *Following closure of the CEP-701 randomly assigned, patients were guided by risk score to either poor risk or nonpoor risk options. **Following closure of the mTOR inhibition random assignment, patients in this group received DA 50mg alone. ***Following closure of the D Clofarabine arm, patients were recommended to receive FLAG-Ida (which was also the case if renal criteria were not met). 1Following closure of the high-dose daunorubicin arm, patients were allocated DA60. ADE, Ara-C, daunorubicin, and etoposide; APL, acute promyelocytic leukemia; CBF, core binding factor; DA, daunorubicin and Ara-C; FLAG-Ida, fludarabine, Ara-C, granulocyte colony-stimulating factor, and idarubicin; GO, gemtuzumab ozogamicin; MACE, amsacrine, etoposide, and Ara-C; MidAc, mitoxantrone and Ara-C; mTor, mammalian target of Rapamycin.
TABLE 1. Patient Characteristics

| Characteristic          | 3 Courses (n = 510) | 4 Courses (n = 507) |
|-------------------------|---------------------|---------------------|
| Treatment               |                     |                     |
| MACE/MidAc              | 58 (11%)            | 62 (12%)            |
| Ara-C                   | 452 (89%)           | 445 (88%)           |
| Age                     |                     |                     |
| 16-29                   | 68 (13%)            | 66 (13%)            |
| 30-39                   | 70 (14%)            | 71 (14%)            |
| 40-49                   | 150 (29%)           | 148 (29%)           |
| 50-59                   | 162 (32%)           | 164 (32%)           |
| 60+                     | 60 (12%)            | 58 (11%)            |
| Median                  | 47                  | 48                  |
| Range                   | 16-70               | 16-72               |
| Sex                     |                     |                     |
| Female                  | 274 (54%)           | 282 (56%)           |
| Male                    | 236 (46%)           | 225 (44%)           |
| Diagnosis               |                     |                     |
| De novo                 | 488 (96%)           | 486 (96%)           |
| Secondary               | 6 (1%)              | 8 (2%)              |
| MDS                     | 16 (3%)             | 13 (3%)             |
| WHO PS                  |                     |                     |
| 0                       | 364 (71%)           | 365 (72%)           |
| 1                       | 124 (24%)           | 124 (24%)           |
| 2                       | 12 (2%)             | 12 (2%)             |
| 3                       | 10 (2%)             | 5 (1%)              |
| 4                       | 0                   | 1 (<0.5%)           |
| WBC                     |                     |                     |
| 0-9.9                   | 258 (51%)           | 247 (49%)           |
| 10-49.9                 | 192 (38%)           | 180 (36%)           |
| 50-99.9                 | 43 (8%)             | 52 (10%)            |
| 100+                    | 17 (3%)             | 28 (6%)             |
| Median                  | 9.4                 | 10.4                |
| Range                   | 0.6-306.0           | 0.6-395.0           |
| Cytogenetics            |                     |                     |
| Favorable               | 119 (24%)           | 115 (24%)           |
| Intermediate            | 369 (75%)           | 371 (76%)           |
| Adverse                 | 1 (<0.5%)           | 1 (<0.5%)           |
| Unknown                 | 21                  | 20                  |
| FLT3 TKD                |                     |                     |
| WT                      | 397 (83%)           | 399 (83%)           |
| Mutant                  | 79 (17%)            | 83 (17%)            |
| Unknown                 | 34                  | 25                  |
| NPM1c                   |                     |                     |
| WT                      | 289 (62%)           | 288 (60%)           |
| Mutant                  | 178 (38%)           | 190 (40%)           |
| Unknown                 | 43                  | 29                  |

(continued in next column)

TABLE 1. Patient Characteristics (continued)

| Characteristic          | 3 Courses (n = 510) | 4 Courses (n = 507) |
|-------------------------|---------------------|---------------------|
| FLT3 TKD                |                     |                     |
| WT                      | 422 (89%)           | 443 (92%)           |
| Mutant                  | 51 (11%)            | 37 (8%)             |
| Unknown                 | 37                  | 27                  |
| Induction chemotherapy ADE (nonrandomized) | 18 (4%) | 16 (3%) |
| ADE                     | 42 (8%)             | 45 (9%)             |
| ADE+GO3                 | 33 (6%)             | 31 (6%)             |
| ADE+GO6                 | 35 (7%)             | 33 (7%)             |
| DA+GO3                  | 35 (7%)             | 34 (7%)             |
| DA+GO6                  | 34 (7%)             | 35 (7%)             |
| DA 90 mg                | 94 (18%)            | 96 (19%)            |
| DA 60 mg                | 91 (18%)            | 90 (18%)            |
| DA 60 mg (nonrandomized)| 128 (25%)           | 127 (25%)           |
| Lestaurtinib random assignment | 68 (13%) | 68 (13%) |
| Lestaurtinib            | 45                  | 45                  |
| No lestaurtinib         | 23                  | 23                  |
| Everolimus random assignment | 114 (22%) | 113 (22%) |
| Everolimus              | 76                  | 77                  |
| No everolimus           | 38                  | 36                  |
| Post Course 1 Risk Score |                     |                     |
| Good risk               | 130 (26%)           | 136 (27%)           |
| Standard risk           | 377 (74%)           | 369 (73%)           |
| Unknown                 | 3                   | 2                   |
| MRD status post course 1|                     |                     |
| CR, MRD-negative        | 95 (40%)            | 117 (48%)           |
| CR, MRD-positive        | 128 (54%)           | 116 (48%)           |
| No CR                   | 12 (5%)             | 11 (5%)             |
| Unknown                 | 275                 | 263                 |
| MRD status post C2      |                     |                     |
| MRD-negative            | 113 (64%)           | 139 (74%)           |
| MRD-positive            | 64 (36%)            | 49 (26%)            |
| Not known               | 333                 | 319                 |
| Transplanted            | 191 (37%)           | 164 (32%)           |
| Any allograft           | 153 (30%)           | 142 (28%)           |
| Any transplant in CR1   | 37 (7%)             | 42 (8%)             |
| Allograft in CR1        | 29 (6%)             | 39 (8%)             |

Abbreviations: ADE, Ara-C, daunorubicin, and etoposide; CR, complete remission; DA, daunorubicin and Ara-C; GO, gemtuzumab ozogamicin; ITD, internal tandem duplication; MACE, amsacrine, Ara-C, and etoposide; MDS, myelodysplastic syndrome; MidAc, mitoxantrone and Ara-C; MRD, measurable residual disease; PS, performance score; TKD, tyrosine kinase domain; WT, wild type.

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Although there appears to be a significant difference in favor of four courses (63% vs 56%) with respect to survival (Fig 4A). Considering the question of whether three courses were noninferior to four courses, the CI in both unadjusted and adjusted analyses crosses the threshold of 0.71, meaning that there is no evidence to conclude noninferiority at this threshold. In spite of the reduced CIR, there was no detectable survival difference in patients treated in the MACE/MidAc arm (Fig 4B), but there were nonsignificant differences in favor of four courses in patients treated in the Ara-C arms in both risk groups (Figs 4C-4E). If the 79 patients who received a transplant in CR1 were censored at transplant, the survival rates are 63% for three courses and 72% for four courses. The overall outcomes are summarized in the Protocol.

**Exploratory Subgroup Analyses**

The outcome was not affected by any of the patients’ characteristics or induction treatments (Protocol), although those presenting with a low WBC < 10.0 × 10⁹/L had a significant benefit from four courses. MRD information was obtained after course 1 in 456 patients and in 365 patients after course 2. The OS at 5 years in patients who were MRD-negative after the first or second induction courses (n = 464) at 73% was better than that in the MRD-positive patients (n = 357) at 50%. In patients who were assessed after course 1 of induction, the OS was not significantly different between the treatment arms, irrespective of the MRD status (Figs 5A-5B).

In patients with MRD information after course 2, the OS was 69% if MRD-negative and 37% if MRD-positive, but again there was no significant difference in either groups if allocated to three or four courses (Figs 5C-5D).

Although there appears to be a significant advantage of four courses in patients who received daunorubicin 90 mg/m² in induction (Protocol), the test for heterogeneity was not significant, suggesting that any apparent heterogeneity was not conclusive.

Four courses were significantly beneficial in patients without an FLT3 internal tandem duplication or tyrosine kinase domain or NPM1 mutation or in 92 of the 433 patients with < 3 mutations as detected using Sanger sequencing (Fig 6). The benefit appeared greatest in patients with FLT3/NPM1 wild type, although there was no significant interaction. For the purpose of assessing the prognostic value of the mutations detected using Sanger sequencing, only mutations that occurred in more than 20 of the 433 patients were considered, but no correlations were observed (Protocol).
FIG 3. Cumulative incidence of relapse. AML, acute myeloid leukemia; HR, hazard ratio; MidAc, mitoxantrone and Ara-C.
**FIG 4.** Overall survival. AML, acute myeloid leukemia; HR, hazard ratio; MidAc, mitoxantrone and Ara-C.
FIG 5. Effect of measurable residual disease (MRD). MRD, measurable residual disease; HR, hazard ratio.

DISCUSSION

The recent approvals of new drugs for AML may move the treatment algorithm in the relevant subgroups. However, it is yet to be established for some of these new drugs whether combination with standard chemotherapy may be their optimal use.\textsuperscript{25} It therefore remains important to define the optimal total treatment with chemotherapy that is required. There has been extensive effort to establish the best agents and doses for induction, but less attention to the dose and number of courses of postinduction treatment. Recruiting sufficiently large numbers to reliably answer questions at this stage of treatment is a logistical challenge. Definitive studies 25 years ago established high-dose Ara-C as the standard of care for up to four courses at a dose level of 3 g/m\textsuperscript{2}. The MRC AML15 trial (ISRCTN17161961) established that our previous standard of care (MACE plus MidAc) was superior to high-dose Ara-C in adverse-risk patients.\textsuperscript{15} There was little survival difference between 3 g/m\textsuperscript{2} and 1.5 g/m\textsuperscript{2} Ara-C dose levels. The addition of a fifth course was tested in the MRC AML12 and 15 trials\textsuperscript{14,15} with no evidence of benefit for a fifth course. A number of collaborative group trials have assessed the number of courses without providing a universally accepted conclusion.\textsuperscript{25-27}

In this trial, random assignment took place after the completion of two induction courses and 1,709 (53\%) of the original trial entrants were eligible. In the intent-to-treat analysis of the 1,017 patients randomly assigned, it emerged that the addition of the fourth course significantly reduced the CIR and significantly improved the RFS, but neither of which reached statistical significance. Although the numbers become too small for conventional (CIR and RFS) of the original trial entrants were eligible. In the intent-to-treat analysis of the 1,017 patients randomly assigned, it emerged that the addition of the fourth course significantly reduced the CIR and significantly improved the RFS, but neither of which reached statistical significance. Although the numbers become too small for conventional statistical significance. Although the numbers become too small for conventional statistical significance. Although the numbers become too small for conventional statistical significance.
there is a strong trend for benefit in the recipients of Ara-C, but not for the recipients of MACE/MidAC.

Among the several subgroups examined where a significant difference was observed in conjunction with a test for heterogeneity, which reached significance, were patients who lacked a FLT3 or NPM1 mutation, patients with one or two mutations compared with >2, and patients with presenting WBCs of <10 × 10^9/L. Patients who were MRD-negative (at a level of 1 in 10^4) after course 1 or 2 had a significantly better survival than those who were positive at either time point, but the addition of a fourth course was not beneficial in either group. In general, patients with more favorable characteristics appear to benefit from a fourth course, but only when high dose Ara-C consolidation is used, whereas those with intermediate-risk characteristics do not, although these were only trends for benefit.

There was a price to pay for the fourth course with respect to days in hospital, days on antibiotics, and blood product.
support although there were no excessive deaths in remission. However, as a consequence of the greater number of relapses, more salvage transplants were required in patients receiving just three courses (Table 1). It could be speculated that the most useful interaction will eventually be the initial discrimination based on the MRD status after the first or second induction course, where there may be little benefit in a fourth course for those who are MRD-positive, but benefit for those who are negative, or vice versa.

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CLINICAL TRIAL INFORMATION

ISRCTN55675555 (AML17)

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.01170.

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ACKNOWLEDGMENT

We would like to thank Cancer Research UK for research support and the Cardiff University Haematology Clinical Trials Unit staff for supervision of the trial and the staff of the Sanger Centre, Cambridge, for undertaking sequencing under contract with the sponsor.
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Authors' Disclosures of Potential Conflicts of Interest

Defining the Optimal Total Number of Chemotherapy Courses in Younger Patients With Acute Myeloid Leukemia: A Comparison of Three Versus Four Courses

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.
APPENDIX

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FIG A1. Patients’ score derived from multiplying each relevant characteristic by the value derived from the Cox model: 0.01325*age (in years) + 0.16994*sex (1 = male, 0 = female) + 0.22131*diagnosis (1 = de novo, 2 secondary) + 0.65082*cytogenetics (1 = favorable, 2 = intermediate, 3 adverse) + 0.19529*status post C1 (1 = complete remission, 2 = partial remission, 3 = no response) + 0.00169* WBC (x109/l). Distribution of patients in MRC AML 10,12 trials by index: Taking into account the apparent bimodality of the curve, patients with an index of 2 or below were deemed good risk, and the data were arbitrarily divided at the 75th centile between standard and poor risk. Survival index from complete remission in AML10,12 according to the risk groups was validated on data from MRC AML15 Trial.5
FIG A2. Relapse-free survival (RFS). CR, complete remission.
### AML13: Consolidation Randomisation
#### Relapse-Free Survival

**Stratified analysis**

|                      | Events/Patients | Statistics | OR & 95% CI          |
|----------------------|-----------------|------------|----------------------|
|                      | 4 courses       | 3 courses  | (O−E) Var.           | (4 courses : 3 courses) |
| **By comparison:**   |                 |            |                      |                         |
| MACE/MidAc           | 33/62           | 36/57      | −3.1                 | 17.2                    |
| ara-C                | 237/438         | 269/447    | −22.9                | 126.2                   |
| **Subtotal:**        | 270/500         | 305/504    | −26.0                | 143.3                   |
|                      |                 |            |                      | 0.83 (0.71, 0.98)        |

Test for heterogeneity between subgroups: $\chi^2 = 0.0; P = 1.0; NS$

**By cytogenetics:**

|                      | Events/Patients | Statistics | OR & 95% CI          |
|----------------------|-----------------|------------|----------------------|
|                      | 4 courses       | 3 courses  | (O−E) Var.           | (4 courses : 3 courses) |
| Favorable            | 39/113          | 55/118     | −9.0                 | 23.4                    |
| Intermediate         | 222/368         | 233/365    | −10.5                | 113.5                   |
| **Subtotal:**        | 261/481         | 288/483    | −19.4                | 136.9                   |
|                      |                 |            |                      | 0.87 (0.73, 1.03)        |

Test for heterogeneity between subgroups: $\chi^2 = 1.6; P = 2; NS$

**By MRD post course 1:**

|                      | Events/Patients | Statistics | OR & 95% CI          |
|----------------------|-----------------|------------|----------------------|
|                      | 4 courses       | 3 courses  | (O−E) Var.           | (4 courses : 3 courses) |
| MRD −ve              | 47/117          | 45/94      | −5.2                 | 22.5                    |
| MRD +ve              | 77/115          | 85/128     | −4.4                 | 40.4                    |
| Not in CR            | 7/9             | 4/11       | 3.4                  | 2.3                     |
| **Subtotal:**        | 131/241         | 134/233    | −6.1                 | 65.2                    |
|                      |                 |            |                      | 0.91 (0.71, 1.16)        |

Test for heterogeneity between subgroups: $\chi^2 = 3.6; P = .04$

Test for trend between subgroups: $\chi^2 = 2.4; P = .1; NS$

**By MRD post course 2:**

|                      | Events/Patients | Statistics | OR & 95% CI          |
|----------------------|-----------------|------------|----------------------|
|                      | 4 courses       | 3 courses  | (O−E) Var.           | (4 courses : 3 courses) |
| MRD −ve              | 65/138          | 60/111     | −5.9                 | 30.6                    |
| MRD +ve              | 38/49           | 46/64      | 1.0                  | 20.7                    |
| **Subtotal:**        | 103/187         | 106/175    | −4.9                 | 51.3                    |
|                      |                 |            |                      | 0.91 (0.69, 1.19)        |

Test for heterogeneity between subgroups: $\chi^2 = 0.7; P = .4; NS$

**Unsatified**

|                      | Events/Patients | Statistics | OR & 95% CI          |
|----------------------|-----------------|------------|----------------------|
|                      | 270/500         | 305/504    | −26.0                | 143.3                   |
|                      |                 |            |                      | 0.83 (0.71, 0.98)        |

**Effect $2P = 0.03$**

**FIG A3.** Stratified analysis of relapse-free survival. CR, complete remission; MRD, measurable residual disease.
AML17: Consolidation Randomisation
Overall Survival
Stratified analysis

|                          | Events/Patients | Statistics | OR & 95% CI |
|--------------------------|-----------------|------------|-------------|
|                          | 4 courses       | 3 courses  | (O−E) Var.  | (4 courses : 3 courses) |
| By comparison:           |                 |            |             |                         |
| MACE/MidAc               |                 |            |             |                         |
| ara−C                    |                 |            |             |                         |
| Subtotal:                |                 |            |             |                         |
| By age:                  |                 |            |             |                         |
| Age 15−29                | 25/62           | 25/58      | 0.3         | 12.4                    | 1.02 (0.59, 1.78) |
| Age 30−39                | 147/444         | 177/452    | −17.1       | 80.9                    | 0.81 (0.65, 1.01) |
| Age 40−49                | 42/148          | 58/150     | −10.3       | 24.9                    | 0.94 (0.65, 1.38) |
| Age 50−59                | 68/164          | 73/162     | −2.1        | 35.1                    | 0.94 (0.68, 1.31) |
| Age 60−69                | 25/58           | 28/60      | −1.1        | 13.2                    | 0.92 (0.54, 1.58) |
| Subtotal:                | 172/506         | 202/510    | −16.8       | 93.3                    | 0.84 (0.68, 1.02) |
| Test for heterogeneity between subgroups: $\chi^2 = 0.6; P = .4$; NS |
| By sex:                  |                 |            |             |                         |
| Female                   |                 |            |             |                         |
| Male                     |                 |            |             |                         |
| Subtotal:                |                 |            |             |                         |
| By WBC:                  |                 |            |             |                         |
| WBC 0−9.9                |                 |            |             |                         |
| WBC 10−49.9              |                 |            |             |                         |
| WBC 50−99.9              |                 |            |             |                         |
| WBC 100+                 |                 |            |             |                         |
| Subtotal:                |                 |            |             |                         |
| By WHO performance status:|                 |            |             |                         |
| Performance Status 0     |                 |            |             |                         |
| Performance Status 1     |                 |            |             |                         |
| Performance Status 2     |                 |            |             |                         |
| Performance Status 3+     |                 |            |             |                         |
| Subtotal:                |                 |            |             |                         |
| By diagnosis:            |                 |            |             |                         |
| de Novo                  |                 |            |             |                         |
| Secondary                |                 |            |             |                         |
| High risk myelodysplastic syndrome |         |            |             |                         |
| Subtotal:                |                 |            |             |                         |
| By cytogenetics:         |                 |            |             |                         |
| Favorable                |                 |            |             |                         |
| Intermediate             |                 |            |             |                         |
| Subtotal:                |                 |            |             |                         |
| Unstratified             |                 |            |             |                         |
|                          |                 |            |             |                         |
| Test for heterogeneity between subgroups: $\chi^2 = 0.4; P = .5$; NS |

![FIG A4. Stratified analysis of overall survival.](image-url)
### AML17: Consolidation Randomisation

#### Overall Survival

|                  | Events/Patients | Statistics | OR & 95% CI |
|------------------|-----------------|------------|-------------|
|                  | 4 courses       | 3 courses  | (O−E) Var.  |
|                  |                 |            |             |
| ADE alone (not rand) | 7/16            | 8/18       | −0.2 3.7    |
| ADE Alone        | 18/45           | 18/42      | −0.7 9.0    |
| ADE + GO 3mg     | 9/31            | 14/33      | −2.5 5.7    |
| ADE + GO 6mg     | 13/33           | 19/35      | −2.9 8.0    |
| DA + GO 3mg      | 17/34           | 16/35      | 1.2 8.2     |
| DA + GO 6mg      | 14/35           | 18/34      | −2.6 7.7    |
| DA (60mg) − protocol 7 | 33/95           | 27/94      | 3.4 15.0    |
| DA (90mg) − protocol 7 | 25/90           | 38/91      | −8.0 15.7   |
| DA 60mg − not rand. | 36/126          | 43/128     | −2.9 19.4   |
|                  | **Subtotal:**   | **201/510**| **−15.3 92.3**|
|                  |                 |            |             |
| Test for heterogeneity between subgroups: $\chi^2 = 6.0; P = .6; NS$
| By course 1 status: |                 |            |             |
| Confirmed CR MRD− | 28/117          | 27/95      | −3.5 13.4   |
| Confirmed CR MRD + | 50/116          | 60/128     | −3.2 27.2   |
| Not in remission  | 6/11            | 4/12       | 2.1 2.3     |
|                  | **Subtotal:**   | **91/235** | **−4.7 43.0**|
| Test for trend between subgroups: $\chi^2 = 1.5; P = .2; NS$
| By course 2 status: |                 |            |             |
| MRD −ve          | 38/139          | 37/113     | −4.5 18.4   |
| MRD +ve          | 28/49           | 36/64      | 0.3 15.6    |
|                  | **Subtotal:**   | **73/177** | **−4.1 34.0**|
| Test for heterogeneity between subgroups: $\chi^2 = 0.6; P = .4; NS$

#### Test for stratification

|                  | Effect | 2P | 2P  |
|------------------|--------|----|----|
| Unstratified     | 0.84   | 0.68 | 1.02 |

**FIG A5.** Analysis stratified by prior treatment and MRD status. CR, complete remission; MRD, measurable residual disease.
FIG A6. Sanger sequencing.
FIG A7. Analysis stratified by Sanger sequencing.
| Characteristic | Randomly Assigned (n = 1017) | Not Randomly Assigned (n = 692) | P |
|---------------|-------------------------------|-------------------------------|---|
| Treatment*    |                               |                               | .08 |
| MACE/MidAc    | 120 (12%)                     | 63 (9%)                       |   |
| Ara-C         | 897 (88%)                     | 629 (91%)                     |   |
| Age           |                               |                               | .2 |
| 16-29         | 134 (13%)                     | 100 (14%)                     |   |
| 30-39         | 141 (14%)                     | 104 (15%)                     |   |
| 40-49         | 298 (29%)                     | 154 (22%)                     |   |
| 50-59         | 326 (32%)                     | 207 (30%)                     |   |
| 60 +          | 118 (12%)                     | 127 (18%)                     |   |
| Median Range  |                               |                               |   |
| Sex           |                               |                               | > .95 |
| Female        | 556 (55%)                     | 378 (55%)                     |   |
| Male          | 461 (45%)                     | 314 (45%)                     |   |
| Diagnosis     |                               |                               | < .001 |
| De novo       | 974 (96%)                     | 618 (89%)                     |   |
| Secondary     | 14 (1%)                       | 33 (5%)                       |   |
| MDS           | 29 (3%)                       | 41 (6%)                       |   |
| WHO PS        |                               |                               | .9 |
| 0             | 729 (72%)                     | 480 (69%)                     |   |
| 1             | 248 (24%)                     | 193 (28%)                     |   |
| 2             | 24 (2%)                       | 12 (2%)                       |   |
| 3             | 15 (1%)                       | 7 (1%)                        |   |
| 4             | 1 (< 0.5%)                    | 0                             |   |
| WBC           |                               |                               | .7 |
| 0-9.9         | 505 (50%)                     | 381 (55%)                     |   |
| 10-49.9       | 372 (37%)                     | 204 (29%)                     |   |
| 50-99.9       | 95 (9%)                       | 62 (9%)                       |   |
| 100 +         | 45 (4%)                       | 45 (7%)                       |   |
| Median Range  |                               |                               |   |
| Cytogenetics  |                               |                               | < .0001 |
| Favourable    | 234 (24%)                     | 94 (15%)                      |   |
| Intermediate  | 740 (76%)                     | 498 (80%)                     |   |
| Adverse       | 2 (< 0.5%)                    | 27 (4%)                       |   |
| Unknown       | 41                             | 73                             |   |
| FLT3 ITD      |                               |                               | .01 |
| WT            | 796 (83%)                     | 485 (78%)                     |   |
| Mutant        | 162 (17%)                     | 137 (22%)                     |   |
| Unknown       | 59                             | 70                             |   |
| NPM1c         |                               |                               | .5 |
| WT            | 577 (61%)                     | 388 (63%)                     |   |
| Mutant        | 368 (39%)                     | 229 (37%)                     |   |
| Unknown       | 72                             | 75                             |   |

(continued on following page)
### TABLE A1. Patient Characteristics of Those Eligible by Entry to Random Assignment (n = 1017) or Not (n = 692)\(^\text{back}\) (continued)

| Characteristic | Randomly Assigned (n = 1017) | Not Randomly Assigned (n = 692) | \(P\) |
|----------------|------------------------------|---------------------------------|------|
| FLT3 TKD       |                              |                                 |      |
| WT             | 865 (91%)                    | 575 (93%)                       | .2   |
| Mutant         | 88 (9%)                      | 45 (7%)                         |      |
| Unknown        | 64                           | 72                              |      |
| Induction chemotherapy |                   |                                 | .006 |
| ADE (not randomly assigned) | 34 (3%)              | 22 (3%)                         |      |
| ADE            | 87 (9%)                      | 39 (6%)                         |      |
| ADE + GO3      | 64 (6%)                      | 48 (7%)                         |      |
| ADE + GO6      | 68 (7%)                      | 31 (4%)                         |      |
| DA + GO3       | 69 (7%)                      | 39 (6%)                         |      |
| DA + GO6       | 69 (7%)                      | 43 (6%)                         |      |
| DA 90 mg       | 190 (19%)                    | 111 (16%)                       |      |
| DA 60 mg       | 181 (18%)                    | 128 (19%)                       |      |
| DA 60 mg (not randomly assigned) | 255 (25%)         | 231 (33%)                       |      |

Abbreviations: ADE, Ara-C, daunorubicin, and etoposide; DA, daunorubicin and Ara-C; MACE, amsacrine, Ara-C, and etoposide; ITD, internal tandem duplication; MDS, myelodysplastic syndrome; TKD, tyrosine kinase domain; WT, wild type.

\(^\text{a}\)Treatment is imputed for those not entering the random assignment based on entry to trial (what would have been the option at that stage).

### TABLE A2. Clinical Outcomes by Treatment Armback

| End Point                        | 3 Courses, % | 4 Courses, % | Unadjusted HR and CI | \(P\) | Adjusted HR and CI | Adjusted \(P\) |
|----------------------------------|--------------|--------------|-----------------------|------|--------------------|---------------|
| 5-year cumulative incidence of relapse | 58           | 50           | 0.81 (0.69 to 0.97)   | .02  | 0.82 (0.69 to 0.97) | .02           |
| 5-year cumulative incidence of death in CR | 6            | 6            | 1.04 (0.62 to 1.75)   | .9   | 1.03 (0.61 to 1.73) | .9            |
| 5-year RFS                       | 36           | 43           | 0.83 (0.71 to 0.98)   | .03  | 0.84 (0.71 to 0.99) | .03           |
| 5-year OS                        | 57           | 63           | 0.84 (0.69 to 1.03)   | .09  | 0.84 (0.69 to 1.03) | .10           |
| 5-year survival postrelapse      | 31           | 34           | 0.93 (0.74 to 1.16)   | .5   | 0.92 (0.74 to 1.15) | .5            |
| 5-year OS censored at SCT        | 63           | 72           | 0.85 (0.66 to 1.10)   | .2   | 0.86 (0.66 to 1.12) | .3            |

Abbreviations: CR, complete remission; OS, overall survival; RFS, relapse-free survival; SCT, stem-cell transplantation.