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10-day decitabine versus 3+7 chemotherapy followed by allografting in older patients with acute myeloid leukaemia: an open-label, randomised, controlled, phase 3 trial

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Summary

Background Many older patients with acute myeloid leukaemia die or cannot undergo allogeneic haematopoietic stem-cell transplantation (HSCT) due to toxicity caused by intensive chemotherapy. We hypothesised that replacing intensive chemotherapy with decitabine monotherapy could improve outcomes.

Methods This open-label, randomised, controlled, phase 3 trial was conducted at 54 hospitals in nine European countries. Patients aged 60 years and older who were newly diagnosed with acute myeloid leukaemia and had not yet been treated were enrolled if they had an Eastern Cooperative Oncology Group performance status of 2 or less and were eligible for intensive chemotherapy. Patients were randomly assigned (1:1) to receive decitabine or standard chemotherapy (known as 3+7). For the decitabine group, decitabine (20 mg/m²) was administered for the first 10 days in the first 28-day cycle, followed by 28-day cycles consisting of 5 days or 10 days of decitabine. For the 3+7 group, daunorubicin (60 mg/m²) was administered over the first 3 days and cytarabine (200 mg/m²) over the first 7 days, followed by 1–3 additional chemotherapy cycles. Allogeneic HSCT was strongly encouraged. Overall survival in the intention-to-treat population was the primary endpoint. Safety was assessed in all patients who received the allocated treatment. This trial is registered at ClinicalTrials.gov, NCT02172872, and is closed to new participants.

Findings Between Dec 1, 2014, and Aug 20, 2019, 606 patients were randomly assigned to the decitabine (n=303) or 3+7 (n=303) group. Following an interim analysis which showed futility, the IDMC recommended on May 22, 2019, that the study continued as planned considering the risks and benefits for the patients participating in the study. The cutoff date for the final analysis presented here was June 30, 2021. At a median follow-up of 4·0 years (IQR 2·9–4·8), 4-year overall survival was 26% (95% CI 21–32) in the decitabine group versus 30% (24–35) in the 3+7 group (hazard ratio for death 1·04 [95% CI 0·86–1·26]; p=0·68). Rates of on-protocol allogeneic HSCT were similar between groups (122 [40%] of 303 patients for decitabine and 118 [39%] of 303 patients for 3+7). Rates of grade 3–5 adverse events were 254 (84%) of 302 patients in the decitabine group and 279 (94%) of 298 patients in the 3+7 group. The rates of grade 3–5 infections (41% [125 of 302] *vs* 53% [158 of 298]), oral mucositis (2% [seven of 302] *vs* 10% [31 of 298]) and diarrhoea (1% [three of 302] *vs* 8% [24 of 298]) were lower in the decitabine group than in the 3+7 group. Treatment-related deaths were reported for 12% (35 of 302) of patients in the decitabine group and 14% (41 of 298) in the 3+7 group.

Interpretation 10-day decitabine did not improve overall survival but showed a better safety profile compared with 3+7 chemotherapy in older patients with acute myeloid leukaemia eligible for intensive chemotherapy. Decitabine could be considered a better-tolerated and sufficiently efficacious alternative to 3+7 induction in fit older patients with acute myeloid leukaemia without favourable genetics.

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Introduction

For older patients (ie, those aged 60 years and older) with acute myeloid leukaemia, major survival improvement has been achieved over the last two decades by the introduction of reduced-toxicity conditioning followed by allogeneic haematopoietic stem-cell transplantation (HSCT).[1] Host-intrinsic factors preventing patients from reaching this curative treatment include a reduced performance status, comorbid conditions, and other age-related functional limitations.[2] Leukaemia-intrinsic factors include adverse genetics and secondary acute myeloid leukaemia. All these factors are more prevalent with increasing patient age, and

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Research in context

Evidence before this study

The chance that acute myeloid leukaemia in older individuals, even those who are considered to have favourable risk based on genetics, can be cured without allogeneic haematopoietic stem-cell transplantation (HSCT) is low. Indeed, the question can be asked whether favourable-risk acute myeloid leukaemia does exist in older patients. This notion is supported by the publications of Büchner and colleagues, Appelbaum and colleagues, and Ostronoff and colleagues. DNA-hypomethylating agents (HMAs) provide a well-established first-line treatment foundation for older patients with acute myeloid leukaemia due to their favourable toxicity profile and activity. However, HMA's potential in patients with acute myeloid leukaemia who are fit for more intensive treatment, including the curative approach of allogeneic HSCT, is unclear. We did a PubMed search from database inception on Feb 9, 2023, with no language restrictions, with the terms "AML", "clinical trial", "transplantation" and "decitabine" or "azacitidine", which did not identify any randomised clinical trial comparing an HMA with intensive chemotherapy in this setting.

Added value of this study

We report results from the first open-label, randomised, controlled, phase 3 trial comparing HMA monotherapy to intensive chemotherapy in fit patients aged 60 years and older with acute myeloid leukaemia. With a median follow-up of 4 years, the de-escalation strategy of the experimental group with 10-day decitabine monotherapy, as compared with 3+7, yielded similar overall survival, transplantation rates, and survival from transplantation. Decitabine monotherapy showed reduced toxicity (particularly febrile neutropenia, sepsis, and oral mucositis) and a more favourable health economics profile than 3+7, supporting a role for reduced-toxicity acute myeloid leukaemia treatment in this patient group.

Implications of all the available evidence

Given the favourable toxicity profile of the HMA compared with 3+7, this treatment option appears to be suitable as a bridging strategy, leading patients with acute myeloid leukaemia to the curative approach of allogeneic HSCT in an appropriate timeframe. This finding includes patients older than 70 years or those with adverse genetics. These results support future clinical trials combining an HMA with a Bcl-2 inhibitor in this setting.

often prevent the administration of anthracycline or cytarabine-based standard remission induction chemotherapy (known as the 3+7 regimen). However, for older patients receiving 3+7, whether this regimen is the optimal treatment before allogeneic HSCT or not has been questioned, as only up to a third of older patients with acute myeloid leukaemia who were fit to receive intensive chemotherapy within large clinical trials reached HSCT.[3–5] Therefore, effective and yet better-tolerated treatment strategies to increase the allogeneic HSCT rate in older patients with acute myeloid leukaemia are urgently needed.

Azanucleoside DNA-hypomethylating agents (HMAs) are cytidine analogues that epigenetically reactivate genes via DNA methyltransferase-1 inhibition, by reversal of aberrant gene silencing.[6,7] Azacitidine and decitabine have become, due to their favourable toxicity profile and anti-leukaemic activity (also in patients with adverse-risk genetics), the standard treatment foundation for patients with acute myeloid leukaemia who are not fit for induction chemotherapy.[8–10] Decitabine administered on a 10-day schedule in 28-day cycles has appeared particularly promising due to a higher complete remission rate compared with the standard 5-day schedule.[11–13] However, although repeated HMA treatment extends the median overall survival of older patients with acute myeloid leukaemia, the regimen is ultimately not curative.[7,8,14]

Allogeneic HSCT after single-agent HMA bridging is not only feasible, but HMAs could be advantageous over more intensive treatment because of their favourable toxicity profile.[15–18] Therefore, in the present study, rather than adding a third drug to the 3+7 regimen, we pursued the opposite route (ie, a de-escalation strategy), hypothesising that a single-agent regimen of extended-dose decitabine might be a better tolerated, effective treatment alternative to 3+7 induction, to safely bridge older patients with acute myeloid leukaemia patients to allogeneic HSCT.

Methods

Study design and participants

This was an international, multicentre, open-label, randomised, controlled, phase 3 trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Leukemia Group, GIMEMA, and German MDS Study Group in 54 hospitals in nine European countries (appendix 1 pp 4–5).

The EORTC Protocol Review Committee and ethics committees of all participating sites approved the protocol (appendix 2). The trial was done in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. The EORTC Independent Data Monitoring Committee (IDMC) monitored the conduct of the trial. On-site source data verification was provided by clinical research organisations (EORTC, GSO, High Research, Phidea, and TCC). All patients provided written informed consent. Here, we report the primary analysis of the trial; long-term follow-up is ongoing.

We enrolled patients aged 60 years or older (with no upper age limit), with confirmed newly diagnosed acute myeloid leukaemia (de novo or secondary). For inclusion, patients had to be eligible for induction chemotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. The patient's Sorror comorbidity index was identified before treatment start and allografting.

Patients with white blood cell counts at diagnosis of greater than 30×10^9/L could be enrolled, provided their white blood cell counts were 30×10^9/L or less after a short course of hydroxyurea cytoreduction at randomisation. Patients with acute promyelocytic leukaemia (ie, AML-M3 with t(15;17)(q22;q12); *PML::RARA* fusion gene and cytogenetic variants); blast crisis of chronic myeloid leukaemia; active CNS leukaemia; severe cardiovascular disease, which would make intensive chemotherapy impossible; active uncontrolled infection; or psychological, familial, sociological, or geographical conditions that would have hampered trial participation according to the investigators, were excluded. Patients who received previous treatment with HMAs or intensive chemotherapy within the last 3 years for myelodysplastic syndromes or myeloproliferative neoplasms were also excluded.

Randomisation and masking

Registration was done centrally at the EORTC headquarters (Brussels, Belgium) by the Department of Statistics. Eligible patients were randomly assigned (1:1) to receive decitabine or 3+7. The randomisation, based on a minimisation technique, was stratified by acute myeloid leukaemia type (de novo *vs* secondary), age (60–64 *vs* 65–69 *vs* ≥70 years), and site. The study was open label. Dedicated trialists at the different study centers enrolled participants and assigned them to trial groups.

Procedures

HLA-typing and donor search were initiated at randomisation. For the decitabine group, decitabine (20 mg/m²) was administered for the first 10 consecutive days in the first 28-day cycle. In the subsequent 28-day cycles, decitabine was administered for 5 days for those with bone marrow blasts of less than 5% and 10 days for those with bone marrow blasts of 5% or more (appendix 1 pp 21–22). For the 3+7 group, 3+7 chemotherapy consisted of daunorubicin 60 mg/m² for the first 3 days and cytarabine 200 mg/m² for the first 7 days, followed by 1–3 additional chemotherapy cycles (subsequent HMAs were not allowed). Patients in both groups with an HLA-matched donor and attaining stable disease or better after one or more treatment cycle were encouraged to have allogeneic HSCT regardless of their genetic risk profile, following reduced-toxicity conditioning. Patients from the decitabine group not receiving allogeneic HSCT could continue decitabine treatment until disease progression. Initially, the baseline acute myeloid leukaemia genetic classification by the European LeukaemiaNet (ELN) 2010 criteria[19] was used but this choice was reassessed a posteriori, switching to the ELN 2017 classification criteria when it was published.[20] Routine blood counts were done regularly as clinically indicated. Risk-based source-data verification was used.

For both groups, treatment response was evaluated by bone marrow studies after each of the first four treatment cycles, before starting allogeneic HSCT, 100 days after allogeneic HSCT, at 6 and 12 months after randomisation, and in the case of suspected relapse or progression; all using modified ELN 2017 criteria.

The international Common Terminology Criteria for Adverse Events, version 4.0, was used to define adverse events and their grades. Adverse events were continuously collected from randomisation to 30 days after the last dose of protocol treatment administration or the first day of hospital admission for HSCT, whichever occurred first. Adverse events were counted if they started or worsened in grade in the period between 1 day after randomisation and the earliest of (1) 30 days after the last administration of protocol treatment or (2) 1 day before the start of conditioning for transplantation.

Outcomes

The primary endpoint was overall survival, defined as time from randomisation to death of any cause. Secondary endpoints comprised the rate of complete remission or complete remission with incomplete haematological recovery (CRi); the rate of response achieved with the protocol treatment; the rate of overall complete remission and CRi, achieved with the protocol treatment or a salvage treatment; progression-free survival from randomisation; disease-free survival from complete remission or CRi; the safety and toxicity profiles; the proportion of allografted patients; progression-free survival from allogeneic HSCT; the incidence of progression after allogeneic HSCT; the incidence of death without progression after allogeneic HSCT; the health–economic effect of each treatment group in terms of days staying in the hospital and transfusion needs at selected sites. Health-related quality of life results[21] will be reported in a separate manuscript. Complete remission or CRi were defined as a documented complete remission or CRi before allogeneic HSCT and before the initiation of post-protocol treatments. Response was defined as a documented complete remission or CRi, partial remission, or morphological leukaemia-free state before allogeneic HSCT and before the initiation of post-protocol treatments. The overall complete remission or CRi rate was defined as documented complete remission or CRi before allogeneic HSCT (and potentially after post-protocol treatments other than allogeneic HSCT). Progression-free survival from randomisation was defined as time from randomisation to relapse, progression, or death,

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See **Online** for appendix 1 and appendix 2

	Decitabine	3+7
Age		
Median (IQR), years	67 (65–71)	68 (64–71)
60–64 years	75/303 (25%)	76/303 (25%)
65–69 years	127/303 (42%)	124/303 (41%)
≥70 years	101/303 (33%)	103/303 (34%)
Sex		
Male	163/303 (54%)	182/303 (60%)
Female	139/303 (46%)	119/303 (39%)
Unknown	1/303 (<1%)	2/303 (1%)
ECOG performance status		
0	153/303 (51%)	157/303 (52%)
1	126/303 (42%)	121/303 (40%)
2	24/303 (8%)	25/303 (8%)
Sorror comorbidity index		
0–1	162/300 (54%)	175/299 (59%)
2	38/300 (13%)	30/299 (10%)
≥3	100/300 (33%)	94/299 (31%)
Acute myeloid leukaemia type		
De novo	214/303 (71%)	219/303 (72%)
Secondary from myelodysplastic syndrome, myeloproliferative neoplasm, or chronic myelomonocytic leukaemia	36/303 (12%)	43/303 (14%)
Therapy-related	51/303 (17%)	39/303 (13%)
Not acute myeloid leukaemia but myelodysplastic syndrome	2/303 (1%)	2/303 (1%)
Acute myeloid leukaemia with myelodysplasia-related changes	88/303 (29%)	82/301 (27%)
White blood cell count at diagnosis		
$<5\times10^9$/L	167/303 (55%)	189/303 (62%)
$5–30\times10^9$/L	82/303 (27%)	78/303 (26%)
$\geq30\times10^9$/L	54/303 (18%)	36/303 (12%)
Cytogenetics		
Normal karyotype	145/275 (53%)	126/281 (45%)
Abnormal karyotype, not monosomal	88/275 (32%)	113/281 (40%)
Monosomal karyotype	42/275 (15%)	42/281 (15%)
ELN 2017 risk group		
Favourable	68/272 (25%)	47/278 (17%)
Intermediate	123/272 (45%)	134/278 (48%)
Adverse	81/272 (30%)	97/278 (35%)

Data are n/N (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. ELN=European Leukemia Net. Ethnic and racial backgrounds of the participants were not collected in this trial.

Table 1: **Baseline characteristics**

whichever occurred first. Disease-free survival from complete remission or CRi was defined as time from complete remission or CRi, achieved in response to the protocol treatment, to relapse or death, whichever occurred first.

Statistical analysis

The study had a power of 85% to conclude superiority of decitabine with a level of statistical significance of 0·025 for a one-sided test assuming a hazard ratio (HR) of 0·75. 441 deaths were required to achieve this power and 600 patients were planned to be randomised. The design foresaw one interim analysis with a binding stopping rule for futility when 200 deaths were observed. The O'Brien-Fleming stopping boundary using Lan-DeMets β-spending function was 0·426 on the one-sided p value scale. The IDMC reviewed this interim analysis upon its completion on May 22, 2019. At that time, the accrual had almost been completed. The one-sided p value of 0·576 from the Cox model, adjusted by the two stratification factors used for randomisation (acute myeloid type and age), indicated futility of the experimental treatment. The adjusted hazard ratio was 1·02 (95% CI 0·80–1·31). However, the IDMC recommended the study to continue as planned, considering the risks and benefits for the patients participating in the study. Because the death rate was much lower than originally projected, the IDMC was consulted again with regards to timing of the final analysis. On May 19, 2021, the IDMC agreed to set the clinical cut-off date of the final analysis to June 30, 2021, irrespective of the number of deaths at that time.

Efficacy analyses were done in the intention-to-treat population, defined as all randomly assigned patients. Safety was assessed in all patients who received at least one dose of the allocated study treatment.

Main efficacy comparisons regarding overall survival and progression-free survival were done using a Cox model, adjusted by the two stratification factors used for randomisation (ie, acute myeloid leukaemia type and age); p values were derived by the Wald test. The proportional hazards assumption was checked using the approach of Lin and colleagues,[22] based on martingale residuals. The Kaplan-Meier method was used to obtain estimates of survival-type distributions. The reverse Kaplan-Meier method was used to estimate the median follow-up duration. The main comparison regarding the complete remission or CRi rate was done using a logistic regression model, adjusted by the two stratification factors used for randomisation. All reported p values are two-sided.

For exploratory purposes, we assessed the predictive importance of several factors on the treatment differences regarding overall survival. Forest plots were produced and a test for interaction between each variable and the trial group in a Cox model was done. For these subgroup analyses, the HRs were plotted along with their 99% CIs.

In the analyses of relapse from complete remission or CRi and progression from allogeneic HSCT, deaths without relapse and progression were treated as competing events. In the analyses of the incidences of death without relapse from complete remission or CRi and without progression after allogeneic HSCT, relapse and progression were treated as competing events. Overall survival and overall survival from allogeneic HSCT were censored at last contact with the patient or the clinical cut-off date, whichever came first. Remaining time-to-event endpoints were censored at the time of last disease evaluation. Additional methods for time-to-event analyses are provided in appendix 1 (p 3).

Health economics were evaluated during cycles 1–3 of protocol treatment in a subset of patients from specific sites. The total number of days in hospital, total number of visits to emergency room, total number of visits to haemato-oncologist, total number of days with growth factors use, the number of units of red blood cells transfused, and the number of units of platelets transfused were compared using the non-parametric Mann-Whitney test. The proportion of patients who required intravenous antibiotics and antifungals were compared using the exact Fisher test.

Data were collected and analysed at EORTC Headquarters, using SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT02172872.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 1, 2014, and Aug 20, 2019, 606 patients were randomly assigned to treatment groups, resulting in 303 participants in each group. An interim analysis on May 22, 2019, showed futility, however, the study continued on the basis of the IDMC's recommendation. The cutoff date for the final analysis presented here was June 30, 2021. The median age of patients was 68 years (range 60–81) and 557 (92%) had an ECOG performance status of 0 or 1 (table 1; appendix 1 p 6).

302 individuals received decitabine and 298 received 3+7 (figure 1; safety population). The median time between diagnosis and randomisation was 7 days. The median time between randomisation and treatment start was 1 day in both treatment groups. A median of three treatment cycles were administered with decitabine and two treatment cycles with 3+7, with 25% of patients in the decitabine group receiving five or more cycles (appendix 1 p 7). In total, 122 patients (40%) in the decitabine group and 118 patients (39%) in the 3+7 group received allogeneic HSCT according to the protocol. The median time to allogeneic HSCT on protocol was 4·2 months (IQR 3·0–5·3) in the decitabine group and 3·5 months (2·9–5·0) in the 3+7 group. Including post-protocol interventions, the allogeneic HSCT rate was approximately 52% in both groups (appendix 1 p 8). Among patients with a *TP53* mutation, 17 (36%) of 47 patients were transplanted in the decitabine group and 17 (35%) of 49 were transplanted in the 3+7 group. In the decitabine group, 94 (31%) patients received intensive chemotherapy post-protocol, whereas in the 3+7 group, 91 (30%) patients received HMAs post-protocol (appendix 1 p 9).

The overall median follow-up was 4·0 years (IQR 2·9–4·8) at the time of analysis. A total of 423 patients died: 218 in the decitabine group and 205 in the 3+7 group. The 4-year overall survival rate was 26% (95% CI 21–32) in the decitabine group and 30% (24–35) in the 3+7 group. The median overall survival from randomisation was 15 months (95% CI 13–18) in the decitabine group and 18 months (95% CI 14–22) in the 3+7 group. The HR for death for decitabine versus 3+7 was 1·04 (95% CI 0·86–1·26, p=0·68; figure 2). The exploratory subgroup analysis found that, according to age, the estimated HR for death for decitabine versus 3+7 was 1·34 (99% CI 0·79–2·28) for patients aged 60–64 years, 1·14 (0·77–1·69) for those aged 65–69 years, and 0·84 (0·55–1·26) for those 70 years and older (trend test for interaction: p=0·058). According to ELN 2017, the estimated HR was 1·56 (0·78–3·10) for patients with favourable risk, 1·18 (0·80–1·75) for those with intermediate risk, and 0·90 (0·59–1·37) for those with adverse risk (test for interaction p=0·18). According to *NPM1* mutation status,

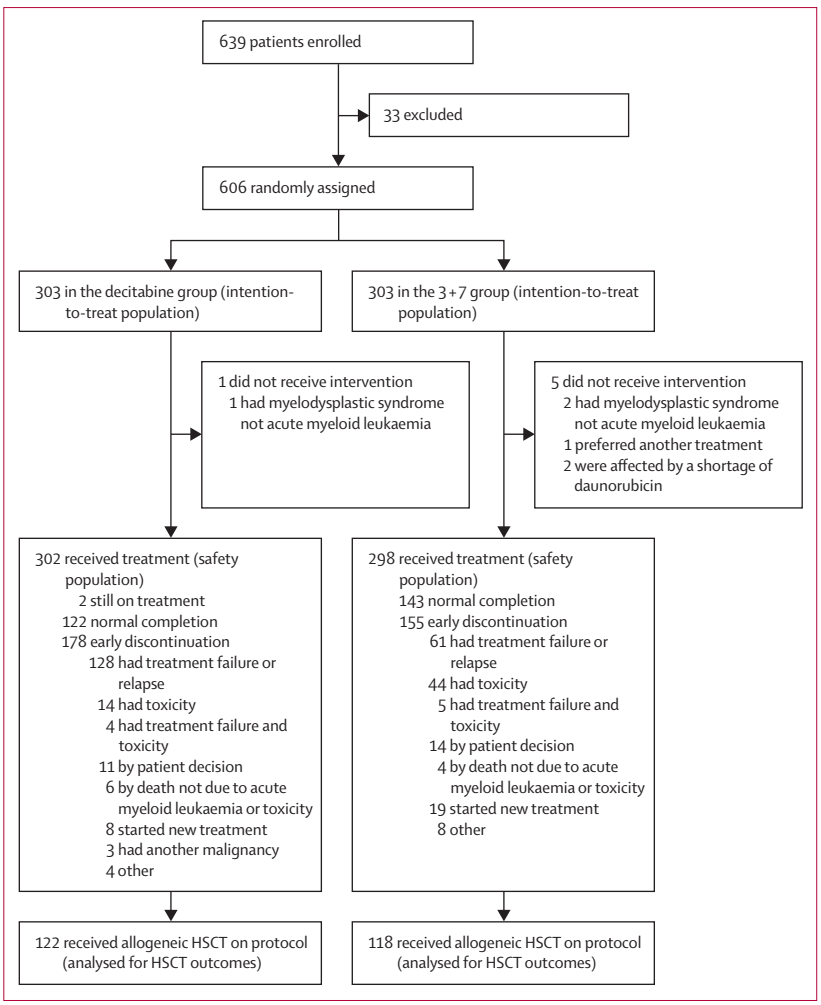

Figure 1: **Trial profile**
For all 423 patients who died, the exact date of death was available. Among 183 patients still alive, the last follow-up visit took place within 90 days before the clinical cut-off date for 174 patients. The intention-to-treat population was used for the analyses of overall survival, progression-free survival, and response. The safety population was used for the analyses of adverse events and treatment exposure. The allogeneic HSCT population was used for the analyses of efficacy after allogeneic HSCT and toxicity of allogeneic HSCT. HSCT=haematopoietic stem cell transplantation.

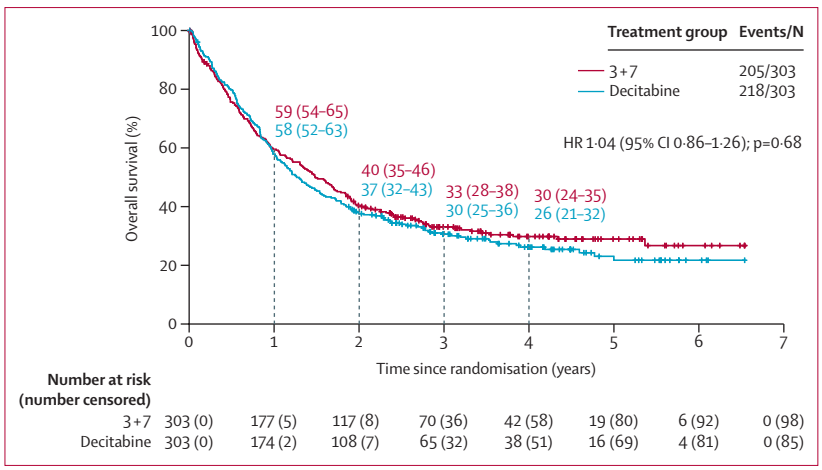

Figure 2: **Overall survival in the intention to treat population**
The estimate of the HR and the p value are based on a Cox model adjusted for the stratification factors used at randomisation (ie, age and acute myeloid leukaemia type). There was no indication of non-proportional hazards. Overall survival estimates (95% CI) at 1, 2, 3, and 4 years from randomisation are displayed. HR=hazard ratio.

the HR was 2·00 (0·96–4·17) for patients with mutated *NPM1* and 1·02 (0·77–1·34) for those with wildtype *NPM1* (test for interaction: p=0·026); the HR was 0·77 (0·43–1·38) for patients with a monosomal karyotype and 1·14 (0·85–1·53) for those without monosomal karyotype (figure 3, appendix 1 p 23–26). There was no strong difference in the treatment effect between patients with mutated and wild-type *TP53* (figure 3, appendix 1 p 27).

In the decitabine group, 145 (48%, 95% CI 42–54) of 303 patients reached complete remission or CRi with decitabine, whereas in the 3+7 group, 186 (61%, 56–67) of 303 patients reached complete remission or CRi (appendix 1 p 8). In the adjusted analysis the odds ratio was 0·57 (0·42–0·80). In the subgroup analysis by age, the estimated complete remission or CRi rate was 48% (36 of 75) for patients in the decitabine group versus 76% (58 of 76) in the 3+7 group for patients aged 60–64 years; 45% (57 of 127) for those in the decitabine group versus 56% (69 of 124) for those in the 3+7 group for patients aged 65–69 years; and 51% (52 of 101) for those in the decitabine group versus 57% (59 of 103) for those in the 3+7 group for patients aged 70 years or older (appendix 1 p 10). In the ELN 2017 favourable-risk group, the complete remission or CRi rate was 56% (38 of 68) with decitabine versus 85% (40 of 47) with 3+7; in intermediate-risk group the rate was 43% (53 of 123) with decitabine versus 66% (89 of 134) with 3+7, but it was similar in ELN 2017 adverse-risk patients (44% [36 of 81] with decitabine *vs* 43% [42 of 97] with 3+7). The percentage of patients with a response (complete remission, CRi, morphological leukaemia-free state, or partial remission) was 57% (95% CI 51–63%) in the decitabine group and 67% (62–73%) in the 3+7 group. After a post-protocol treatment, 38 additional patients in the decitabine group and 17 patients in the 3+7 group reached complete remission or CRi. Therefore, overall, 183 (60%, 95% CI 55–66) of 303 patients in the decitabine group and 203 (67%, 61–72) of 303 patients in the 3+7 group reached complete remission or CRi (adjusted OR 0·75, 95% CI 0·54–1·05; appendix 1 pp 8, 10).

In the intention-to-treat population, a total of 447 patients progressed, relapsed, or died: 230 in the decitabine group and 217 in the 3+7 group. At 4 years from randomisation, the progression-free survival rate was 22% (95% CI 18–28) in the decitabine group and 24% (19–30) in the 3+7 group; the HR was 1·10 (95% CI 0·91–1·32, p=0·33; appendix 1 p 28). In patients who reached complete remission or CRi, the 4-year disease free survival rate was 28% (95% CI 20–36) in the decitabine group and 32% (25–39) in the 3+7 group (appendix 1 p 29). The 4-year cumulative incidence of relapse was 52% (43–61) in the decitabine group and 43% (35–50) in the 3+7 group (appendix 1 p 30), whereas the 4-year incidence of death without relapse was 20% (14–28) for the decitabine group and 26% (19–32) for the 3+7 group (appendix 1 p 31).

At the start of conditioning, 92 (75%) of 122 patients in the decitabine group and 107 (91%) of 118 patients in the 3+7 group had a documented complete remission or CRi. The overall survival rate at 4 years from allogeneic HSCT within the protocol was 45% (95% CI 35–55) in the decitabine group and 47% (37–56) in the 3+7 group (appendix 1 p 32). In the decitabine group, overall survival was similar between patients with and without documented complete remission or CRi at the start of conditioning (appendix 1 p 33). The 4-year progression-free survival rates from allogeneic HSCT were similar in the treatment groups: 45% (95% CI 35–55) in the decitabine group versus 44% (34–54) in the 3+7 group (appendix 1 p 34). Similarity was also found for the 4-year incidence of relapse or progression from allogeneic HSCT (24%, 16–32 in the decitabine group *vs* 22%, 15–31 in the 3+7 group; appendix 1 p 35), and the 4-year incidence of death without relapse and progression (31%, 22–40 in the decitabine group *vs* 33%, 25–42 in the 3+7 group; appendix 1 p 36).

During protocol treatment, the incidence of grade 3–5 adverse events was lower in the decitabine group (84% [254 of 302] of those who started the protocol treatment) than in the 3+7 group (94% [279 of 298] of those who stared the protocol treatment). The largest differences were observed in the System Organ Classes: blood and lymphatic disorders, infections, and gastrointestinal disorders (table 2; appendix 1 pp 12, 37). The rates of grade 3–5 infections (41% [125 of 302] *vs* 53% [158 of 298]), oral mucositis (2% [seven of 302] *vs* 10% [31 of 298]) and diarrhoea (1% [three of 302] *vs* 8% [24 of 298]) were lower in the decitabine group than in the 3+7 group. The estimated 30-day mortality rates were 3·6% (95% CI 2·0–6·5) for the decitabine group and 6·3% (95% CI 4·1–9·7) for the 3+7 group. The estimated 60-day mortality rates were 8·0% (95% CI 5·4–11·6) for the decitabine group and 10·7% (95% CI 7·7–14·7) for the 3+7 group. The number of patients for

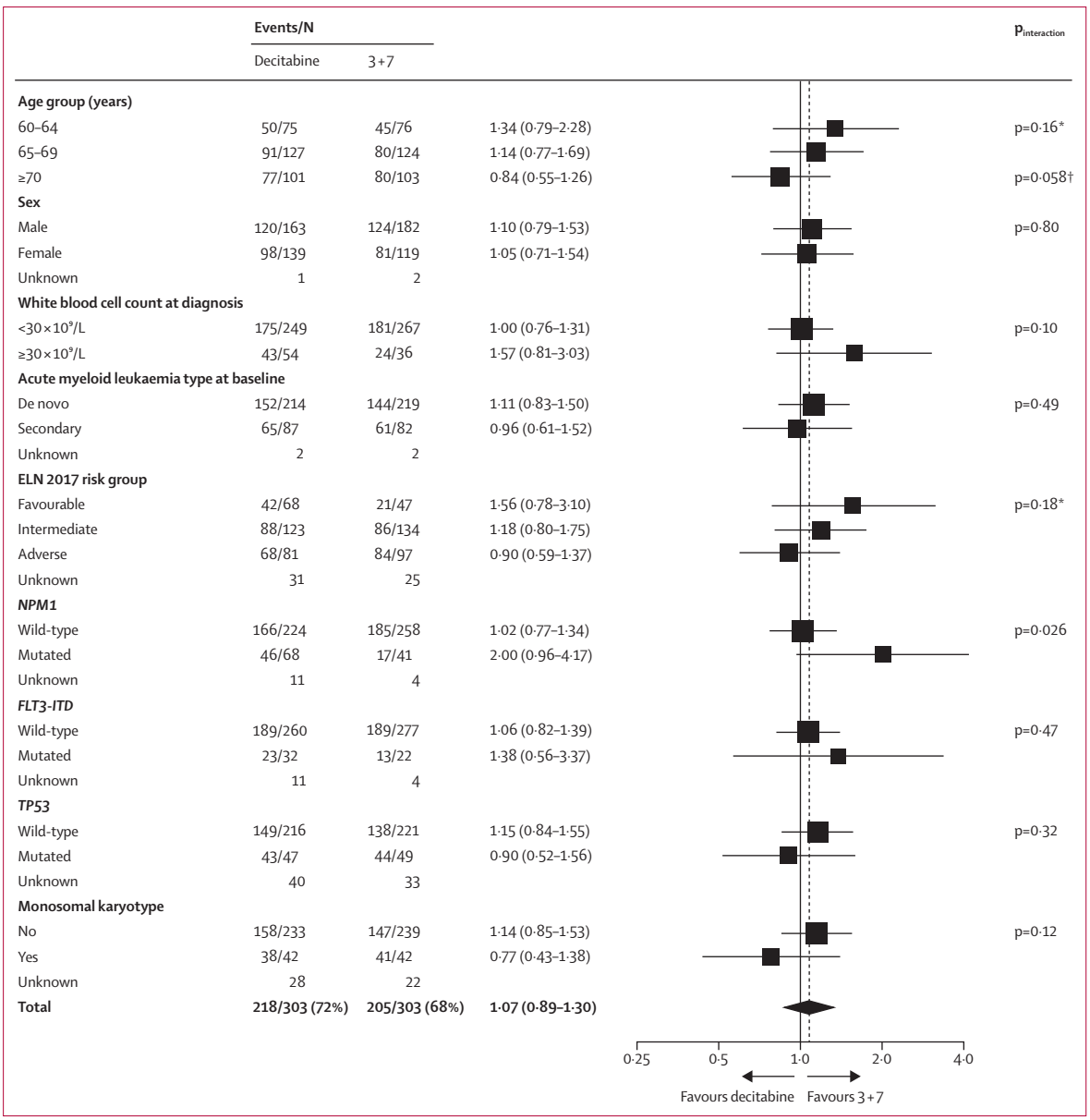

Figure 3: **Overall survival according to subgroup**
An unstratified univariate Cox model was used to estimate the HR for death in the decitabine group as compared with the 3+7 group among all patients. The diamond indicates a 95% CI and the dashed line the estimated HR from this model. For each covariate, a separate unstratified Cox model was used including the covariate, the treatment group, and the interaction term. Error bars indicate 99% CIs and squares are hazard ratios. All p values are to 1 degree of freedom unless otherwise specified by footnotes. ELN=European Leukemia Net. HR=hazard ratio. *2 degrees of freedom. †Trend test.

whom death was attributed by the investigators to toxicity of the protocol treatment only was 35 (12%) of 302 patients in the decitabine group and 41 (14%) of 298 patients in the 3+7 group. The toxic deaths in the decitabine group included 15 (43%) patients who died due to an infection, 13 (37%) patients who died due to graft versus host disease (GVHD), six (17%) patients who died due to both GVHD and infection, and one (3%) patient with another cause of death. The toxic deaths in the 3+7 group included 29 (71%) patients who died due to an infection, three (7%) patients who died due to GVHD, four (10%) patients who died due to both GVHD and infection, and five (12%) patients with another cause of death.

Health economics were evaluated in a subset of 173 patients: 89 in the decitabine group and 84 in the 3+7 group. Hospital stays were shorter for those in the decitabine group than those in the 3+7 group (mean 40 days, SD 24 *vs* 52 days, 24; p=0·0072). Intravenous antibiotics were needed for 81% (95% CI 71–88) of patients from the decitabine group and 98% (92–100) of

patients from the 3+7 group (p=0·0004). Patients in the decitabine group had reduced numbers of red blood cell transfused units compared with the 3+7 group (mean 12, SD 6 for the decitabine group *vs* 15, 7 for the 3+7 group), and of number of platelet units (18, 31 for the decitabine group *vs* 31, 45 for the 3+7 group; appendix 1 p 20).

Discussion

In this trial we tested a de-escalation strategy (toxicity-reduced *vs* standard, intensive first-line treatment) in fit patients with acute myeloid leukaemia aged 60 years and older. Both overall survival and transplantation rate were similar in the two treatment groups, with reduced toxicity and more favourable health–economic parameters (ie, duration of hospital stay, requirements for transfusions, and antibiotics use) in patients treated with decitabine monotherapy when compared with intensive chemotherapy. Although the study was not designed to provide conclusive evidence in subgroups of patients, some characteristics appeared to be predictive of overall survival: patients aged 60–64 years and those with favourable genetics, in particular an *NPM1* mutation, appeared to benefit more from 3+7 than from decitabine.

In contrast, patients with adverse genetics appeared to benefit more from decitabine than from 3+7—eg, those with a monosomal karyotype appeared to have higher response rates and longer overall survival when receiving decitabine. Patients aged 70 years and older appeared to have longer overall survival with decitabine compared with 3+7; this might guide, particularly in non-favourable-risk patients, the treatment decision against more aggressive therapy, particularly when allogeneic HSCT is the goal.

The 10-day decitabine schedule was chosen due to its effectiveness and favourable safety profile in patients unfit for induction, as first described by Blum and colleagues[11] and Ritchie and colleagues.[12] The complete remission or CRi rates attained in the present trial are better than those initially reported, and confirm the complete remission and CRi rates obtained in a recent prospective study.[23] Still, 10-day decitabine represents a lower-intensity treatment with an expected lower complete remission rate than 3+7, which might affect the allogeneic HSCT rate if only patients in complete remission or CRi were to proceed to allografting. However, the view that complete remission or CRi is not an absolute requirement for successful allografting is more and more accepted.[24,25] Indeed, 25% of patients in the decitabine group and 9% in the 3+7 group were not in complete remission or CRi at the time of transplantation. Despite this imbalance, the 4-year overall survival rate from allogeneic HSCT (done for around 40% of all patients in both groups) appeared similar between the treatment groups. Here, the differences in treatment-related mortality, which is lower with decitabine compared with 3+7, might have high clinical relevance. On a mechanistic level, a graft-versus-leukaemia effect could be speculated to be more active when previous HMA was administered, for example in the case of de-repression of immunogenic molecules (eg, for cancer testis antigens or repetitive elements).[26–29]

Our study was designed as a superiority trial. Although the estimated treatment effect in terms of the HR was close to 1, the results do not provide conclusive evidence of non-inferiority of decitabine as compared with 3+7. However, the large sample size enabled an accurate estimation of the treatment effect. Absence of superiority of decitabine as compared with 3+7 was already concluded at the time of the interim analysis (May 22, 2019). However, the accrual was close to completion at the time, and the IDMC recommended to continue the trial as originally planned. Therefore, the interim analysis results had no effect on the further conduct of this trial.

Our study has certain limitations. Importantly, allografting was an essential part of the treatment strategy in the decitabine group. The results of this study are therefore only generalisable to countries where access to allografting is similar to that in Europe. Also, the addition of the Bcl2 inhibitor venetoclax to the 10-day decitabine regimen[30] probably would have increased response rate and prolonged overall survival; however, at the time of protocol development, the powerful in vivo synergism of HMAs with venetoclax could not be anticipated. The 4-year survival rate was approximately 28%, showing improvement of the management of this disease with time as compared with 14% in the EORTC and GIMEMA trial AML17.[3] However, the rate implies that the majority of patients are still not cured. Of note, this trial excluded patients with a white blood cell count more than 30×10^9, in whom a short course of hydroxyurea was unable to control the initial hyperleukocytosis. This decision was driven by the concern that these patients might not achieve sufficient disease control by HMA monotherapy, as decitabine is not a fast-acting drug. Therefore, the results of this trial might not be generalisable to all patients with a high white blood cell count. The study was open label, which involves a risk of investigator bias. However, the primary study endpoint was overall survival, which can be objectively measured. The use of a *FLT3* inhibitor, such as midostaurin, was not allowed for *FLT3-ITD* mutated patients; as midostaurin was only approved in 2017 for this indication by the EMA, participating centres either did not have access, or if they did have access they did not include patients deemed to receive *FLT3* inhibitors during the course of the study. Therefore, ultimately only six patients received midostaurin.

Finally, the unsatisfactory outcome for patients with adverse genetics continues to be a major concern. Therefore, dual treatments combining an HMA with venetoclax are currently extended to triplets, integrating drugs that have shown activity in individuals with adverse genetics and acute myeloid leukaemia, such as those containing anti-CD47 antibodies or all-trans retinoic

	Decitabine (n=302)					3+7 (n=298)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade ≥3	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade ≥3
Patients' worst grade	44 (14%)	105 (35%)	122 (40%)	27 (9%)	254 (84%)	12 (4%)	120 (40%)	131 (44%)	28 (9%)	279 (94%)
Blood and lymphatic system disorders	7 (2%)	154 (51%)	3 (1%)	1 (<1%)	158 (52%)	2 (1%)	181 (61%)	13 (4%)	1 (<1%)	195 (65%)
Anaemia	9 (3%)	66 (22%)	2 (1%)	0	68 (23%)	6 (2%)	68 (23%)	6 (2%)	0	74 (25%)
Febrile neutropaenia	0	112 (37%)	0	0	112 (37%)	0	165 (55%)	5 (2%)	0	170 (57%)
Gastrointestinal disorders	137 (45%)	23 (8%)	2 (1%)	1 (<1%)	26 (89%)	159 (53%)	71 (24%)	6 (2%)	0	77 (26%)
Diarrhoea	60 (20%)	3 (1%)	0	0	3 (1%)	142 (48%)	24 (8%)	0	0	24 (8%)
Enterocolitis	0	1 (<1%)	0	0	1 (<1%)	2 (1%)	8 (3%)	0	0	8 (3%)
Oral mucositis	30 (10%)	7 (2%)	0	0	7 (2%)	69 (23%)	28 (9%)	3 (1%)	0	31 (10%)
Nausea	53 (18%)	2 (1%)	0	0	2 (1%)	94 (32%)	10 (3%)	0	0	10 (3%)
Small intestinal mucositis	3 (1%)	1 (<1%)	0	0	1 (<1%)	9 (3%)	5 (2%)	1 (<1%)	0	6 (2%)
General disorders and administration site conditions	111 (37%)	8 (3%)	0	6 (2%)	14 (5%)	122 (41%)	15 (5%)	3 (1%)	11 (4%)	29 (10%)
Fever	51 (17%)	4 (1%)	0	0	4 (1%)	71 (24%)	6 (2%)	0	0	6 (2%)
Multi-organ failure	0	0	0	5 (2%)	5 (2%)	0	0	1 (<1%)	10 (3%)	11 (4%)
Infections and infestations	58 (19%)	78 (26%)	30 (10%)	17 (6%)	125 (41%)	53 (18%)	89 (30%)	49 (16%)	20 (7%)	158 (53%)
Catheter-related infection	8 (3%)	8 (3%)	1 (<1%)	0	9 (3%)	15 (5%)	28 (9%)	0	0	28 (9%)
Enterocolitis infection	1 (<1%)	2 (1%)	0	0	2 (1%)	3 (1%)	7 (2%)	1 (<1%)	0	8 (3%)
Lung infection	15 (5%)	41 (14%)	8 (3%)	10 (3%)	59 (20%)	17 (6%)	51 (17%)	6 (2%)	7 (2%)	64 (22%)
Sepsis	0	1 (<1%)	22 (7%)	4 (1%)	27 (9%)	0	0	33 (11%)	11 (4%)	44 (15%)
Tooth infection	3 (1%)	7 (2%)	0	0	7 (2%)	2 (1%)	1 (<1%)	0	0	1 (<1%)
Urinary tract infection	8 (3%)	9 (3%)	0	0	9 (3%)	8 (3%)	7 (2%)	0	0	7 (2%)
Investigations	72 (24%)	18 (6%)	102 (34%)	0	120 (40%)	61 (21%)	19 (6%)	99 (33%)	0	118 (40%)
GGT increased	16 (5%)	4 (1%)	3 (1%)	0	7 (2%)	16 (5%)	6 (2%)	0	0	6 (2%)
Neutrophil count decreased	1 (<1%)	8 (3%)	50 (17%)	0	58 (19%)	1 (<1%)	3 (1%)	35 (12%)	0	38 (13%)
Platelet count decreased	2 (1%)	6 (2%)	65 (22%)	0	71 (24%)	0	8 (3%)	86 (29%)	0	94 (32%)
White blood cell count decreased	0	4 (1%)	4 (1%)	0	8 (3%)	0	0	9 (3%)	0	9 (3%)
Metabolism and nutrition disorders	43 (14%)	26 (9%)	3 (1%)	0	29 (10%)	39 (13%)	44 (15%)	2 (1%)	2 (1%)	48 (16%)
Anorexia	15 (5%)	8 (3%)	0	0	8 (3%)	18 (6%)	21 (7%)	0	0	21 (7%)
Hypokalaemia	23 (8%)	15 (5%)	2 (1%)	0	17 (6%)	28 (9%)	16 (5%)	2 (1%)	0	18 (6%)
Hyponatraemia	4 (1%)	4 (1%)	0	0	4 (1%)	6 (2%)	11 (4%)	0	0	11 (4%)
Nervous system disorders	46 (15%)	12 (4%)	1 (<1%)	2 (1%)	15 (5%)	47 (16%)	11 (4%)	1 (<1%)	4 (1%)	16 (5%)
Syncope	0	8 (3%)	0	0	8 (3%)	0	9 (3%)	0	0	9 (3%)
Renal and urinary disorders	16 (5%)	1 (<1%)	1 (<1%)	0	2 (1%)	22 (7%)	6 (2%)	2 (1%)	2 (1%)	10 (3%)
Acute kidney injury	5 (2%)	0	1 (<1%)	0	1 (<1%)	6 (2%)	3 (1%)	2 (1%)	2 (1%)	7 (2%)
Respiratory, thoracic and mediastinal disorders	82 (27%)	15 (5%)	6 (2%)	5 (2%)	26 (9%)	60 (20%)	25 (8%)	5 (2%)	7 (2%)	37 (12%)
Dyspnea	35 (12%)	0	2 (1%)	0	2 (1%)	12 (4%)	12 (4%)	0	0	12 (4%)
Respiratory failure	0	0	3 (1%)	5 (2%)	8 (3%)	0	0	2 (1%)	1 (<1%)	3 (1%)
Skin and subcutaneous tissue disorders	54 (18%)	7 (2%)	0	0	7 (2%)	100 (34%)	18 (6%)	0	0	18 (6%)
Maculo-papular rash	24 (8%)	4 (1%)	0	0	4 (1%)	65 (22%)	12 (4%)	0	0	12 (4%)
Vascular disorders	42 (14%)	13 (4%)	3 (1%)	0	16 (5%)	51 (17%)	9 (3%)	0	0	9 (3%)
Hypertension	13 (4%)	6 (2%)	0	0	6 (2%)	7 (2%)	8 (3%)	0	0	8 (3%)

Data are n (%). Adverse events are displayed if their grade 3 or higher incidence was at least 2% in one group. System organ class totals are displayed if there is at least one adverse event belonging to the class that satisfies this criterion. The incidence of all adverse events is available in the appendix 1 (p 12).

Table 2: **Adverse events**

acid.[18] Our clinical trial, which suggested that good outcomes could be achieved with a single-agent HMA therapy, provides a strong rationale for, and therefore should boost, the further development of novel treatment strategies using HMAs as a foundation for the treatment of fit patients with acute myeloid leukaemia, and randomised trials comparing HMA and venetoclax to intensive chemotherapy are underway in older patients with acute myeloid leukaemia and younger patients with adverse genetics.

The clinical benefit of reduced toxicity, and improved quality of life obtained with decitabine[21] compared with 3+7 appears to be particularly relevant in a setting where the treatment must be considered non-curative for two-thirds of the patients (given the <33% rate of 4-year overall survival). The concept of time toxicity,[31] (ie, burdening of the patients [and health-care systems] with length of hospital stay, outpatient visits, and more) encompasses the parameters captured in this trial and should be routinely applied to future acute myeloid leukaemia trials in this patient population.

In conclusion, the difference in overall survival between 10-day decitabine and 3+7 was not statistically significant in the overall study population, despite a substantially lower complete remission or CRi rate achieved during the protocol treatment in the decitabine group. The rate of allografting was similar between the treatment groups. The subgroup analyses suggested that the comparison between the two treatment groups might be affected by the age of patients and genetics, in particular the presence of the *NPM1* mutation, with better outcomes for 3+7 in younger patients and those with favourable cytogenetics, and better outcomes for decitabine in older patients and those with adverse cytogenetics, in particular a monosomal karyotype. Overall, 10-day decitabine could be considered a better-tolerated and sufficiently efficacious alternative to 3+7 induction in fit older patients with acute myeloid leukaemia without favourable genetics.

Contributors

MLü, PWW, GH, FB and SA were involved in study design, patient accrual, data collection, data analysis, data interpretation, manuscript writing, and manuscript review. MK did the statistical analysis and was involved in manuscript writing and review. SS participated in study design, manuscript writing and review, and statistical analysis. MK and SS accessed and verified the data. SC, WJFMV, RN, LG, AN, MC, RV, MLu, SF, EAm, AC, OL, RF, GG, DLV, EFMP, MH, EAu, JPV, RW, HB, NB, UD, and AV participated in patient accrual, data collection, data analysis, data interpretation, and manuscript review. MS-K reviewed and interpreted cytogenetic data. JHJ was involved in study design, generation and interpretation of molecular analyses, data collection, data analysis, data interpretation, and manuscript review. AOdG generated and interpreted the molecular analyses. AG participated in the data analysis and interpretation and manuscript writing and review. FE was involved in data analysis, data interpretation, and manuscript writing and review. All authors had full access to the data in the study and had final responsibility to submit the manuscript for publication.

Declaration of interests

MLü received research support to his institution from Janssen and European Organisation for Research and Treatment of Cancer (EORTC); is on the advisory boards for AbbVie, Astex, Janssen-Cilag, Otsuka, and Syros; and is currently working in an ongoing trial with a study drug provided by Cheplapharm. MK received research funding from Merck, Bristol Myers Squibb (BMS), Pierre Fabre, Janssen, and Immunocore. SF received personal funding by BMS and Celgene. AG received a grant for study conduct, and drug supply for Dacogen from Janssen Pharma Educational. JHJ received support for molecular analysis from Janssen and EORTC. FE received personal funding from AbbVie, Incyte, Janssen, Novartis, and Syros. RW received consulting fees from Amgen, BMS, Celgene, Janssen, Kite, Gilead, Novartis, Pfizer, and Sanofi; payment from AbbVie, Amgen, BMS, Celgene, Janssen, Kite, Gilead, Pfizer, and Sanofi; and support for attending meetings or travel from Janssen. HB is secretary of EORTC Leukemia Group; received research funding by the German Jose Carreras Leukemia Foundation and German Research Foundation; and honoraria from AbbVie, BMS, Celgene, Merck, Novartis, and Servier. UD received personal honoraria for participation in a data safety monitoring board from Avencell Europe and data safety monitoring board for an acute myeloid leukaemia CAR-T cell trial from Avencell Europe. FB received payments to his institution from Incyte Biosciences, Takeda, ExCellThera, and MaaT Pharma. SS received funding to his institution from Janssen Pharmaceuticals. All other authors declare no competing interests.

Data sharing

EORTC supports developing greater knowledge to improve diagnostics, treatments, survival, and quality of life. Data requestors are invited to submit a research proposal, according to the EORTC data sharing policy by using the online form at https://www.eortc.org/data-sharing/.

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