RESEARCH LETTER

blood neoplasia

TO THE EDITOR:

Ten-day decitabine vs "3+7" in patients with AML aged ≥60 years: long-term results of the randomized phase 3 EORTC trial AML21

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In older patients with acute myeloid leukemia (AML), cure by hematopoietic stem cell transplantation (HSCT) is often not achieved after standard intensive chemotherapy (IC) because of intercurrent infections or other sequelae of IC. Extended, that is, 10-day decitabine (DEC [5-aza-2′-deoxycytidine]), treatment is effective and well tolerated in older patients with AML,[1,2] providing a rational alternative to IC as bridging to HSCT, particularly in patients with adverse genetics. Embarking on this de-escalation approach, we conducted a randomized trial (DEC vs standard 3 + 7 induction) in older patients with AML fit for IC, with the goal of effectively leading them to HSCT.

As previously reported, similar overall survival (OS) was attained after a median follow-up of 4 years,[3] whereas the rates of nonhematologic adverse events were lower in the DEC group, as was attrition in health-related quality of life.[4] Here, we present the long-term follow-up of this trial, providing critical insights into the durability of responses and post-HSCT outcomes in this population.

This open-label, randomized, controlled, phase 3 trial was conducted at 54 hospitals in 9 European countries. Patients were aged ≥60 years, had newly diagnosed AML, had an Eastern Cooperative Oncology Group performance status of 0 to 2, and were eligible for IC. Patients were randomized (1:1) to receive DEC or 3 + 7 IC and were stratified by age and AML type. DEC (20 mg/m^2) was

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This article is a continuation of a previous report.[1]

Case-level data are not publicly available due to the risk of reidentification. Individual participant data will not be shared. Original data are available from the corresponding author, Michael Lübbert (michael.luebbert@uniklinik-freiburg.de) on request.

The full-text version of this article contains a data supplement.

administered for the first 10 days in the first 28-day cycle, followed by 28-day cycles of 5 or 10 days of DEC according to remission status. Patients in the 3 + 7 group received daunorubicin (60 mg/m^2 on days 1-3) and cytarabine (200 mg/m^2 on days 1-7), followed by 1 to 3 additional chemotherapy cycles. In both groups, HSCT, after reduced-toxicity conditioning, was strongly encouraged. In the intention-to-treat population, OS from randomization was the primary end point; secondary end points included progression-free survival (PFS) and disease-free survival (DFS) (supplemental Methods), as well as HSCT rates and outcomes after HSCT (cumulative incidence of progression and death without progression). The primary analysis of OS and PFS used a Cox model adjusted for the stratification factors at randomization. OS, PFS, and DFS probabilities were estimated using the Kaplan-Meier estimator, and progression and death without progression probabilities were estimated using the Aalen-Johansen estimator, treating the other event as a competing event. OS was censored at the last visit, and the remaining end points at the last disease evaluation. Safety was assessed in all patients who received the allocated treatment. This trial was registered at www.clinicaltrials.gov as NCT02172872.

All individuals described in this letter provided written informed consent for research participation. The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization.

Between 1 December 2014 and 20 August 2019, 606 patients were randomized to the DEC (n = 303) or 3 + 7 (n = 303) group (CONSORT diagram, supplemental Figure 1). The median patient age was 68 years, 57% were males, 13% had secondary AML, 15% had leukocyte counts ≥30 × 10^9/L, 15% had a monosomal karyotype, and 19%, 17%, and 63% had favorable, intermediate, and adverse risk, respectively, according to European LeukemiaNet 2022 criteria[5] (Table 1). The cutoff date for the present analysis was 30 June 2023 and median follow-up was 5.8 years.

A total of 452 deaths were reported: 230 in the DEC group and 222 in the 3+7 group. The 6-year OS rate was 23.7% (95% confidence interval [CI], 18.9-28.7) in the DEC group and 25.5% (95% CI, 20.5-30.8) in the 3+7 group (Figure 1A). The estimated hazard ratio (HR) was 1.02 (95% CI, 0.84-1.22). The estimated HR was 1.29 (99% CI, 0.77-2.15) for patients aged 60 to 64 years, 1.12 (99% CI, 0.77-1.65) for patients aged 65 to 69 years, and 0.82 (99% CI, 0.55-1.21) for patients aged 70 years or older (*P*-value for trend = .056).

PFS was also comparable between the treatment groups (HR, 1.06; 95% CI, 0.89-1.27; *P* = .52; Figure 1B): 18.3% (95% CI, 13.9-23.2) in the DEC group and 20.6% (95% CI, 15.9-25.8) in the 3+7 group at 6 years from randomization. DFS from complete remission with complete or incomplete hematologic recovery at 6 years was 23.2% (95% CI, 16.4-30.8) in the DEC group and 27.5% (95% CI, 20.8-34.6) in the 3+7 group.

Rates of on-protocol allogeneic HSCT were similar between groups: 122 of 303 patients (40%) in the DEC group and 118 of 303 patients (39%) in the 3+7 group. At the time of HSCT, 23% and 9% of patients with an evaluable response were not in CR/CRi after DEC and 3+7, respectively (supplemental Table 1). However, OS at 6 years from HSCT was nearly identical in both groups: 41.6% (95% CI, 32.6-50.4) in the DEC group and 41.2% (95% CI, 32.0-50.2) in the 3+7 group (Figure 1C). Specifically, in the DEC group, among those in CR/CRi at the time of transplant (n = 92), the 6-year OS from HSCT was 41.9% (95% CI, 31.3-52.1), and among those not in CR/CRi at the time of transplant (n = 28), it was 42.9% (95% CI, 24.6-60.0) (Figure 1D). In the 2 randomized groups, both time to progression (Figure 1E) and time to death without progression from HSCT (Figure 1F) were similar.

DNA hypomethylating agents (HMA) were initially developed, at age-appropriate doses and schedules, for older and medically nonfit patients with AML or myelodysplastic syndrome. Given their

Table 1. Characteristics of patients at baseline

	Decitabine (N = 303)	3 + 7 (N = 303)
Age, y, n (%)		
Median (range)	67 (60-80)	68 (60-81)
60-64	75 (25)	76 (25)
65-69	127 (42)	124 (41)
≥70	101 (33)	103 (34)
Sex, n (%) (N = 603)		
Male	163 (54)	182 (60)
Female	139 (46)	119 (40)
ECOG performance status, n (%)		
0	153 (50)	157 (52)
1	126 (42)	121 (40)
2	24 (8)	25 (8)
Sorror comorbidity index, n (%) (N = 599)		
0-1	162 (54)	175 (59)
2	38 (13)	30 (10)
≥3	100 (33)	94 (31)
AML type, n (%)		
De novo	214 (71)	219 (72)
Secondary from MDS, MPN, or CMML	36 (12)	43 (14)
Therapy-related	51 (17)	39 (13)
Not AML (MDS)	2 (1)	2 (1)
WBC at diagnosis, 10^9/L, n (%)		
<5	167 (55)	189 (62)
≥5 and <30	82 (27)	78 (26)
≥30	54 (18)	36 (12)
Cytogenetics, n (%) (N = 556)		
Normal karyotype	145 (53)	126 (45)
Abnormal karyotype, MK$^-$	88 (32)	113 (40)
MK+	42 (15)	42 (15)
ELN 2022 risk group, n (%) (N = 526)		
Favorable	63 (25)	38 (14)
Intermediate	45 (18)	46 (17)
Adverse	149 (58)	185 (69)

CMML, chronic myelomonocytic leukemia; ECOG, Eastern Cooperative Oncology Group; MDS, myelodysplastic syndrome; MK, monosomal karyotype; MPN, myeloproliferative neoplasm; WBC, white blood cells.

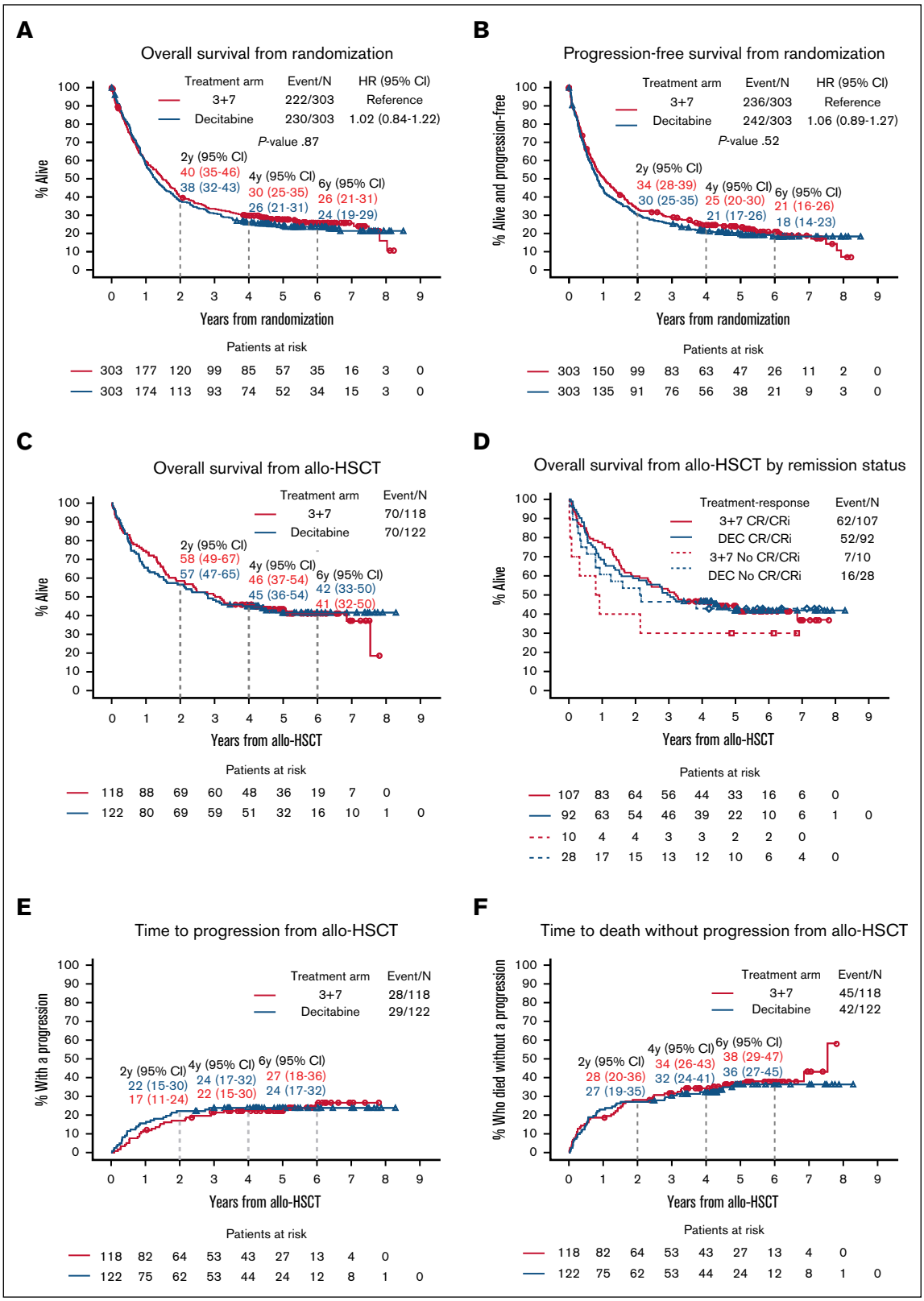

Figure 1. Survival endpoints. Similar outcomes in both treatment groups from randomization (A-B) and from time of allografting (C-F). The marks on the plot indicate censoring of individual patients. HR estimates and *P* values are based on a Cox model adjusted for the stratification factors used at randomization (age and AML type). Allo-HSCT, allogeneic HSCT; N, number of patients.

activity also in patients with adverse genetics, HMA-based treatment has become an important option for bridging to HSCT in fit older patients with AML as an alternative to standard 3+7. The de-escalation approach chosen thus features an asymmetrical design, with patients in the 3+7 induction arm receiving total cytarabine and daunorubicin doses of 1400 mg/m^2 and 180 mg/m^2, respectively, compared to a total decitabine dose of 200 mg/m^2. The AML21 trial constitutes the first prospective, randomized, phase 3 trial in fit patients with AML comparing an HMA-based de-escalation treatment approach to standard intensive induction. With longer follow-up, the results of the primary analysis of the AML21 trial were confirmed and extended: 10-day DEC resulted in survival comparable to that with 3+7 (HR, 1.02; with the 6-year OS rate ~25% in each group), with a more favorable safety profile.[1,4]

Regarding OS by European LeukemiaNet 2022 risk, decitabine, compared to 3+7, appeared to be more beneficial in patients with adverse risk than in those with favorable risk, with the intermediate group in the middle (trend not statistically significant). The CR/CRi rate was somewhat lower with decitabine than with 3+7 in the favorable- and intermediate-risk groups but similar in the adverse-risk group (F. E. M. in 't Hout, M. Kicinski, A. O. de Graaf, S Chantepie, W. J. F. M. Van der Velden, R. Noppeney, L. Griškevičius, A. Neubauer, M. Crysandt, R. Vrhovac, M. Luppi, S. Fuhrmann, E. Audisio, A. Candoni, O. Legrand, R. Foà, G. Gaidano, D. van Lammeren-Venema, E. F. M. Posthuma, M. Hoogendoorn, S. Antunes, K. Verhoeft, M. Stevens-Kroef, F. Efficace, E. Ammatuna, Q. Levesque, R. Wäsch, H. Becker, S. van Dorp, U. Dührsen, F. Baron, S. Suciu, S. Amadori, A. Venditti, P. W. Wijermans, M. Lübbert, G. Huls and J. H. Jansen, unpublished results, March 2026).

Both the HSCT rate (~40%) and survival from HSCT were very encouraging; patients in the DEC group who were not in CR/CRi at the time of HSCT (supplemental Table 1) had the same long-term survival as patients in CR/CRi (~40%), confirming that attainment of CR/CRi is not an absolute prerequisite for successful HSCT.[6] Our 2-year OS rate from HSCT is closely aligned with the 67% rate reported in a recently published phase 2 study of generally high-risk patients with AML who reached CR.[7] The occurrence of late events after HSCT in the 3+7 arm but not in the decitabine arm warrants longer follow-up.

Of 154 patients treated at Gruppo Italiano Malattie Ematologiche dell'Adulto centers, 130 (84%) were subjected to minimal residual disease (MRD) analysis by flow cytometry. The key finding of this study was that the 10-day DEC schedule was able to induce a substantial proportion of MRD-negative responses, close to 30% using the 0.1% multiparameter flow cytometry threshold. However, in this reduced-toxicity arm, allografting appeared necessary to avoid relapse regardless of MRD status.[8]

More recent studies have prospectively pursued bridging of patients with AML to HSCT after induction with 5-day DEC combined with venetoclax. The Gruppo Italiano Trapianto di Midollo Osseo also achieved a transplant rate of 57% (53/93 patients, all in CR) in patients with AML and a median age of 65 years.[9] Very recently, Lu et al have conducted a randomized phase 2 de-escalation trial in patients with AML aged 18 to 59 years, demonstrating overall similar outcome in patients receiving the experimental treatment of 5-day decitabine in combination with venetoclax compared to standard induction,[10] with a transplant rate of 44%. The PARADIGM study by Fathi et al, taking a similar approach, showed improved event-free survival with azacitidine/venetoclax compared to standard induction.[11]

In conclusion, this first randomized phase 3 trial in fit patients with AML comparing HMA-based treatment to intensive induction, supports the concept that less intensive induction may be an alternative to standard induction in subgroups of AML, particularly when bridging to timely allografting is the goal.

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