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by Dominik Selleslag, Stefan Suciu, Giovanna Meloni, Petra Muus, Constantijn J.M. Halkes, Adriano Venditti, Safaa M. Ramadan, Hans Pruijt, Liv Meert, Marco Vignetti, Jean-Pierre Marie, Sébastian Wittnebel, Theo de Witte, Sergio Amadori, Roelof Willemze, and Frédéric Baron

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Low dose clofarabine in combination with a standard remission induction in patients 18-60 years with previously untreated intermediate and bad risk acute myeloid leukemia or high risk myelodysplastic syndrome: combined Phase I/II results of the EORTC/GIMEMA AML-14A Trial

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Authors: *Dominik Selleslag[1], Stefan Suciu[2], Giovanna Meloni[3], Petra Muus[4], Constantijn J.M. Halkes[5], Adriano Venditti[6], Safaa M Ramadan[2,7], Hans Pruijt[8], Liv Meert[2], Marco Vignetti[9], Jean-Pierre Marie[10], Sébastian Wittnebel[11], Theo de Witte[12], Sergio Amadori[6], Roelof Willemze[5]*, and Frédéric Baron[13]**

**RW and FB contributed equally and are co-senior authors.*

[1]Dept of Hematology AZ St-Jan Brugge-Oostende, Belgium; [2]EORTC Headquarters, Brussels, Belgium; [3]Hematology, Sapienza University, Rome, Italy; [4]Dept. of Hematology, Radboud University, Medical Center, Nijmegen, The Netherlands; [5]Dept of Hematology, Leiden University Medical Center, Leiden, The Netherlands; [6]Dept of Hematology and of Biomedicine and Prevention, Tor Vergata University, Rome, Italy; [7]Dept of Hematology, Istituto Europeo di Oncologia, Milan, Italy; [8]Jeroen Bosch Medical Center, Den Bosch, The Netherlands; [9]Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA), Rome, Italy; [10]Dept of Hematology, Hôpital Saint-Antoine, APHP, Paris, France; [11]Dept of Hematology, Institut Jules Bordet, ULB, Brussels, Belgium; [12]Dept of Tumorimmunology, Radboud University, Medical Center, Nijmegen, The Netherlands; [13]Dept of Hematology, University of Liège, Liège, Belgium

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Address for correspondence:

Frédéric Baron MD, PhD; University of Liège, Dpt of Hematology, CHU Sart-Tilman 4000 Liège Belgium.

Tel +32 - 4 - 366 72 01; Fax +32 - 4 - 366 88 55; E-mail: f.baron@ulg.ac.be

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The prognosis of younger patients with intermediate/high risk acute myelogenous leukemia (AML) or high-risk myelodysplastic syndromes (MDS) remains unsatisfactory[1-4].

Clofarabine is a purine nucleoside analog that is highly active as a single agent in AML[5]. Further, synergy between clofarabine and Ara-C has been demonstrated in vitro[6] and in AML patients[6-8]. We have recently reported the results of the randomized phase I part of the EORTC/GIMEMA-AML-14A trial and identified clofarabine at 10 mg/m^2/day on days 2, 4, 6, 8 and 10 as the maximum tolerated dose (given either in a 1-h infusion or as push injection) in combination with Ara-C and idarubicin[9]. We decided to administer clofarabine on these 5 days because we hypothesized that the synergy between clofarabine and Ara-C would be more effective when clofarabine was present in the leukemic cells during the entire period of Ara-C administration. Further, we hypothesized that push injections of clofarabine might result in higher clofarabine peak levels than a 1-h infusion schedule, leading to a better interaction with Ara-C and more pronounced anti-leukemic effects. We herein report the final results of the combined phase I and II parts of the trial.

EORTC/GIMEMA-AML-14A is an open label randomized 2-arm multicenter trial with a sequential phase I-II design (ClinicalTrial.gov: NCT00838240). The protocol was approved by the EORTC Protocol Review Committee and by the Ethical Committee of each participating center. The main objective of the phase II part of the trial was to explore the anti-leukemic activity of the aforementioned phase I selected dosage schedules of clofarabine given either as a 1-hour i.v. infusion (Arm A) or as a push injection (Arm B) over 10 minutes. The primary endpoint was the complete remission (CR)/CR with incomplete blood counts recovery (CRi) rate after 1 or 2 induction cycles. The aim was to determine whether, in each treatment group, the true CR/CRi rate was > 65% or not. Thus, for each of the arms A and B, the regimen was considered as active and feasible if ≥ 23/30 (76.7%) patients achieved a CR/CRi (see supplemental data for detailed study design and methods of statistical analyses).

Secondary endpoints included toxicity, overall survival (OS) from inclusion, OS from CR/CRi, relapse-free survival (RFS) from CR/CRi, and incidences of relapse and of death in CR/CRi.

Inclusion criteria included: age 18-60 years, primary or secondary intermediate or high-risk AML [10] or MDS with 10-19% blast cells in the bone marrow (BM), previously untreated disease, WHO Performance Status grade 0-2, and adequate organ functions. Main exclusion criteria included: good-risk AML (i.e. AML-M3, or AML with t(8;21) or inv(16)) and a white blood cell count (WBC) at diagnosis of $<100 \times 10^9$/L), blast crisis chronic myeloid leukemia or AML supervening a myeloproliferative disorder, central nervous system leukemia, evidence of severe concurrent cardiac, pulmonary, and neurological disorder, and uncontrolled infection.

Clofarabine was administered at 10 mg/m^2 on days 2, 4, 6, 8 and 10 either as a 1-hour infusion (Arm A) or as a push injection (Arm B). Ara-C was administered at 100 mg/m^2/day on days 1–10 as a continuous infusion, while idarubicin was given at 10 mg/m^2/day on days 1, 3, and 5 as a 5 minutes i.v. injection. A second identical course of induction chemotherapy was given in case of a partial response (PR). One cycle of consolidation chemotherapy consisting of Ara-C (500 mg/m^2 every 12 hours as a 2-hour i.v. infusion on days 1-6) and idarubicin (10 mg/m^2/day on days 4, 5 and 6) was administered in patients in both arms who achieved a CR/CRi. Post-consolidation treatment was left at the discretion of the local principal investigator, but it was recommended that the consolidation phase was followed by allogeneic hematopoietic cell transplantation (HCT) for patients with a HLA-identical related donor or for patients with very high-risk cytogenetics who had an HLA-compatible related or unrelated donor, or an autologous HCT in patients who were not candidate for allogeneic HCT[1].

A total of 64 patients (12 in the phase I part and 52 in the phase II part of the study) were randomized at the dosage of clofarabine of 10 mg/m^2/day (Supplemental Figure 1). Two patients had to be excluded because they did not meet the inclusion criteria. Among the remaining 62 patients, 41 had AML not otherwise specified, 11 AML with multilineage dysplasia, 5 therapy-related AML while 5 patients were diagnosed with MDS-RAEB2. Median age was 49.5 (range 20-60) years. Baseline characteristics were generally well balanced between the two arms (Table 1).

After 1 induction course, the CR/CRi rates were 26/31 patients in arm A (84%) versus 25/31 patients in arm B (80%) (Table 2). The CR/CRi rate after 1 or 2 induction courses was 84% (95% CI, 66-95%), in both arms, higher than the protocol-defined efficacy (>65%) (Table 2). Interestingly combining the results from both arms, the CR/CRi rate after 1 or 2 courses of induction was similar in patients with very high-risk cytogenetics (11/13 patients (84.6%)), and in patients with normal or high risk cytogenetics (38/46 patients (82.6%)). These results are in the same range as those observed in two recent phase II studies investigating the efficacy of higher dosages of clofarabine combined with AraC (and idarubicin) as remission induction regimen for younger AML patients[11, 12].

With a median follow-up of 1.8 (range, 1 – 5.3) years, 15/31 (48%) patients in arm A and 11/31 patients (36%) in arm B died. One-year OS from inclusion was 74% (95% CI, 55-86%) in each arm, while median survival was 2.5 (1-not reached) years in arm A, versus not yet reached in arm B (Figure 1A).

Consolidation chemotherapy was given in 26/26 patients who achieved a CR/CRi in arm A, and in 23/26 patients (88.5%) in arm B. Following consolidation chemotherapy, 12 of 26 patients in arm A received an allogeneic HCT, while, in arm B, 14 patients received an allogeneic HCT and 2 an autologous HCT. Among a total of 52 patients in CR/CRi, 1-year OS and RFS from CR/CRi were 77% (95% CI, 56-89%) and 58% (95% CI, 37-74%),

respectively, in arm A versus 73% (95% CI, 51-86%) and 65% (95% CI, 44-80%), respectively, in arm B (Figure 1B). One-year incidences of relapse and of death in CR were 23% (95% CI, 7-39%) and 19% (95% CI, 4-34%), respectively, in arm A, versus 19% (95% CI, 4-34%) and 15% (95% CI, 2-29%), respectively, in arm B (Figure 1 C-D). As expected, the incidence of relapse was higher in CR/CRi patients with very high risk cytogenetics (5/11: 45%) than in those with intermediate/high risk cytogenetics (10/38: 26%).

The toxicity profile of the two tested remission-induction chemotherapy regimens was acceptable and comparable in the two arms (Table 2), confirming data observed in the phase I of our study[9]. Median time to neutrophils $\geq 0.5x10^9$/L and $\geq 1.0\ x10^9$/L were 28 (range, 22-96) and 31 (range, 22-99+) days, respectively, in arm A, versus 27 (range, 20-50) and 29 (range, 21-50) days, respectively, in arm B (Table 2). Further, median time to platelet levels $\geq 20x10^9$/L or $\geq 100x10^9$/L were 28 (range, 24-83) and 31.5 (range, 24-99+) days, respectively, in arm A, versus 27 (range, 23-44) and 31 (range, 24-51) days, respectively, in arm B. Besides hematologic recovery, the grade > 2 toxicities observed in the AML-14A patients were in the same range as currently observed after standard remission-induction chemotherapy, with the possible exception of a higher incidence of grade > 2 hyperbilirubinemia that was observed in 18% of the AML-14A patients.

We finally compared the outcomes of the AML14A patients to those of a subgroup of 201 patients from the standard arm of the previous EORTC/GIMEMA-AML-12 study (combining standard dose Ara-C, daunorubicin and etoposide, see supplemental data)[1] who met the same inclusion criteria as current patients, and were treated in the centers that contributed patients to the current AML14A study. As shown in the Supplemental table 1, patient characteristics were comparable in the 2 groups. However, since these analyses were not planned beforehand in the protocol they should be seen as indicative. The rate of CR/CRi after 1 or 1-2 cycles of induction chemotherapy were 82.3% and 83.9%, respectively, in

current AML14A patients versus 66.7% and 72.6%, respectively in the cohort of AML12 patients (Supplemental Table 2). A higher proportion of patients included in the AML-14A (50%) than in AML-12 (30%) were offered an allogeneic HCT, probably reflecting at least in part the higher CR/CRi rate achieved in AML-14A patients. One-year OS and RFS rates were 74.1% (95% CI, 61.3-83.3%) and 61.5% (95% CI, 47.0-73.2%), respectively, in current AML14 patients, and 58.0% (95% CI, 50.9-64.5%) and 54.1% (95% CI, 45.7-61.8%), respectively, in AML12 patients. Finally, among patients who reached a CR, the 1-year cumulative incidences of relapse and of death in CR were 23.3% and 17.3%, respectively, in AML-14A, as compared with 37.7% and 9.6%, respectively, in AML-12.

In conclusion, the two tested clofarabine containing regimens yielded an impressive CR/CRi rate and encouraging 1-year OS/RFS rates among patients with intermediate/high-risk AML or high-risk MDS. These results are worth confirming in a large phase III study.

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CONFLICTS OF INTEREST

DS has received speaker honoraria from Genzyme/Sanofi. FB has received speaker honoraria and travel grants from Genzyme/Sanofi. RW has been member of the Scientific Advisory

Board of Genzyme/Sanofi concerning clofarabine. The other authors have nothing to disclose with respect to clofarabine.

AUTHOR CONTRIBUTIONS

Conception and design: Dominik Selleslag, Stefan Suciu, Petra Muus, Roel Willemze, Sergio Amadori, Theo de Witte, Jean-Pierre Marie.

Provision of study materials or patients: Dominik Selleslag, Giovanna Meloni, Petra Muus, Constantijn J.M. Halkes, Adriano Venditti, Hans Pruijt, Jean-Pierre Marie, Sébastian Wittnebel, Theo de Witte, Sergio Amadori, and Roelof Willemze

Collection and assembly of data: Dominik Selleslag, Stefan Suciu, Giovanna Meloni, Petra Muus, Constantijn J.M. Halkes, Adriano Venditti, Safaa M Ramadan, Hans Pruijt, Liv Meert, Marco Vignetti, Jean-Pierre Marie, Sébastian Wittnebel, Theo de Witte, Sergio Amadori, Roelof Willemze, and Frédéric Baron

Data analysis and interpretation: Dominik Selleslag, Stefan Suciu, Liv Meert, Safaa Mahmoud Ramadan, Frédéric Baron

Manuscript writing: All authors

Final approval of manuscript: All authors

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Table 1. Baseline patients' characteristics.

	Treatment arm		
	1-hour infusion (Arm A, n=31)	**Push injection (Arm B, n=31)**	**Total (n=62)**
Gender, # of patients (%)			
Male	16 (51.6)	11 (35.5)	27 (43.5)
Female	15 (48.4)	20 (64.5)	35 (56.5)
Age, years			
Median	46.0	50.0	49.5
Range	20.0 - 60.0	22.0 - 60.0	20.0 - 60.0
Presence of poor prognosis features[a] at randomization, # of patients (%)	6 (19.4)	5 (16.1)	11 (17.7)
WHO performance status, # of patients (%)			
0	23 (74.2)	23 (74.2)	46 (74.2)
1	7 (22.6)	7 (22.6)	14 (22.6)
2	1 (3.2)	1 (3.2)	2 (3.2)
WHO classification, # of patients (%)			
AML with multilineage dysplasia	5 (16.1)	6 (19.4)	11 (17.7)
AML therapy related	2 (6.5)	3 (9.7)	5 (8.1)
AML not otherwise specified	23 (74.2)	18 (58.1)	41 (66.1)
MDS RAEB II	1 (3.2)	4 (12.9)	5 (8.1)
Type of disease, # of patients (%)			
De novo AML or MDS	29 (93.5)	28 (90.3)	57 (91.9)
Secondary AML or MDS	2 (6.5)	3 (9.7)	5 (8.1)
WBC at diagnosis, # of patients (%)			
$< 100 \times 10^9$/L	27 (87.1)	30 (96.8)	57 (91.9)
$\geq 100 \times 10^9$/L	4 (12.9)	1 (3.2)	5 (8.1)
Cytogenetics[b], # of patients (%)			
Normal	19 (61.3)	13 (41.5)	32 (51.6)
With FLT3-ITD and unmutated/unk NPM1	3 (9.7)	3 (9.7)	6 (9.7)
Without FLT3-ITD and with mutated NPMI	6 (19.4)	5 (16.1)	11 (17.7)
With FLT3-ITD and with mutated NPMI	3 (9.7)	1 (3.2)	4 (6.5)
Other or unknown molecular markers	7 (22.6)	4 (12.9)	11 (17.7)
Good risk	0	0	0
High risk	3 (9.7)	10 (32.3)	13 (21)
Very high risk	8 (25.8)	5 (16.1)	13 (21.0)
Unknown/ failure / missing	1[c] (3.2)	3 (9.7)	4 (6.5)
Bone marrow blasts (%)			
Median	70	57	60.5
Range	19-97	12-99	12-99

[a]defined as WBC at diagnosis $\geq 100 \times 10^9$/L or very high-risk cytogenetics or FLT3-ITD positivity;
[b]Cytogenetics: good risk includes inv(16) or t(8;21) ; very bad risk includes complex abnormalitis (>3 abnormalities), monosomies 5, 7 and 5q-, 7q-, 3q, t(6;9), t(9;22), 11q23, t(9;11) ; bad risk includes all other chromosomal abnormalities; [c] 47,XY,dup(1)(q1?1q4?2),+8[7] / 46,XY,-17,+mar2[4] / 46,XY,-17,+mar1[3].

Table 2. Disease response (primary endpoint) and adverse events.

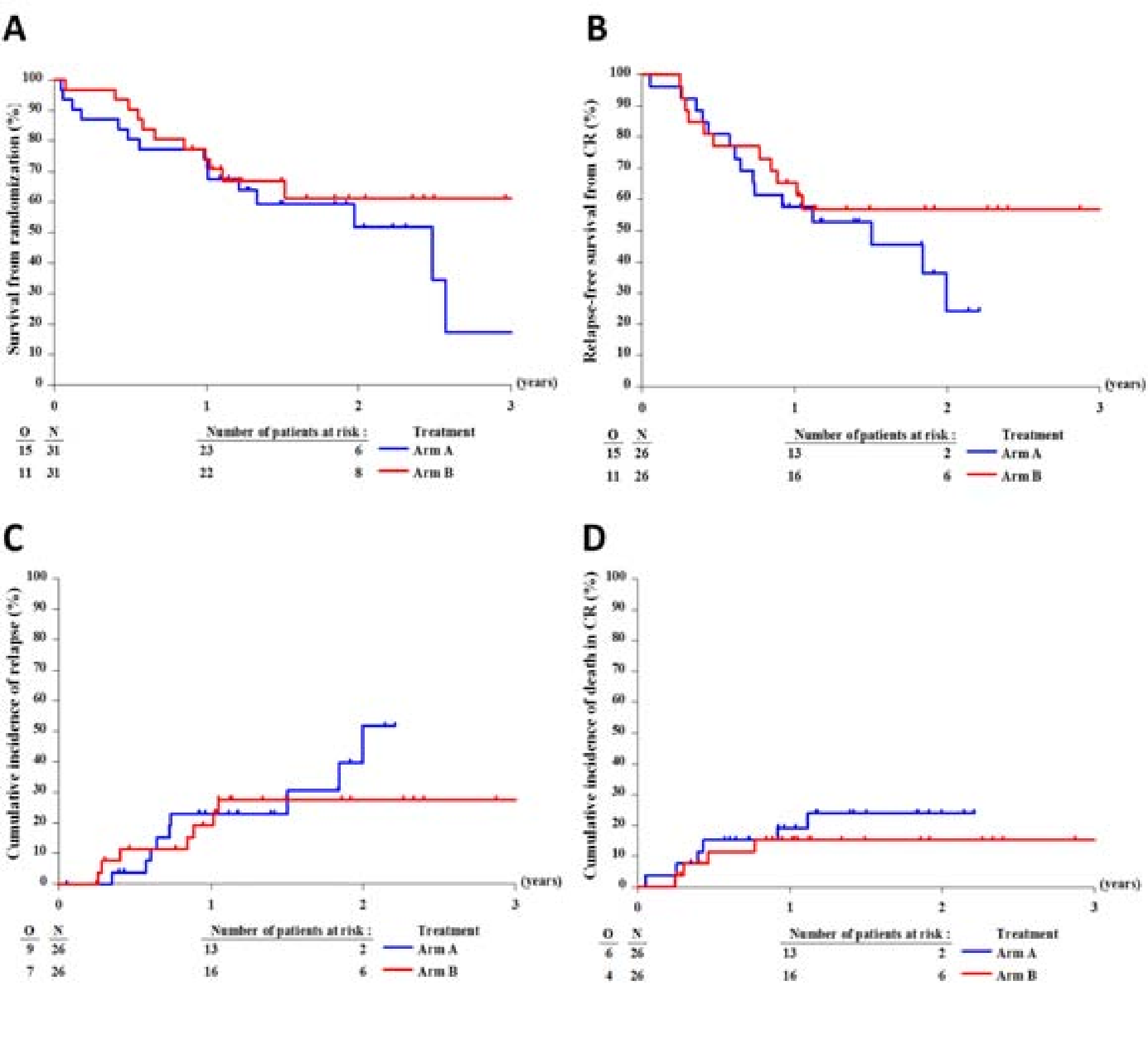
	Treatment arm		
	1-hour infusion (Arm A, n=31)	**Push injection (Arm B, n=31)**	**Total (n=62)**
Response[a] to induction #1, # of patients (%)			
CR	23 (74.2)	24 (77.4)	47 (75.8)
CRi	3 (9.7)	1 (3.2)	4 (6.5)
PR	1 (3.2)	1 (3.2)	2 (3.2)
Failure due to resistant disease	0 (0.0)	4 (12.9)	4 (6.5)
Failure due to complication from aplasia	2 (6.5)	1 (3.2)	3 (4.8)
Hypoplasia	1 (3.2)	0 (0.0)	1 (1.6)
Not assessable	1 (3.2)	0 (0.0)	1 (1.6)
Response to inductions #1 / 2, # of patients (%)			
CR	23 (74.2)	25 (80.6)	48 (77.4)
CRi	3 (9.7)	1 (3.2)	4 (6.5)
PR	1 (3.2)	0 (0.0)	1 (1.6)
Failure due to resistant disease	0 (0.0)	4 (12.9)	4 (6.5)
Failure due to complication from aplasia	2 (6.5)	1 (3.2)	3 (4.8)
Hypoplasia	1 (3.2)	0 (0.0)	1 (1.6)
Not assessable	1 (3.2)	0 (0.0)	1 (1.6)
Most frequent (>5% in at least one arm) grade III-IV[b] biochemical abnormalities, # of patients (%)			
Bilirubin	4 (12.9)	6 (19.4)	10 (16.1)
ALT	4 (12.9)	4 (12.9)	8 (12.9)
Alkaline phosphatase	0	2 (6.5)	2 (3.2)
Most frequent (>5% in at least one arm) grade III-IV[b] adverse events, # of patients (%)			
Febrile neutropenia	23 (74.2)	13 (41.9)	36 (58.1)
Documented infection	13 (42.0)	22 (70.9)	35 (56.5)
Anorexia	6 (19.4)	10 (32.3)	16 (25.8)
Diarrhea	7 (22.6)	6 (19.4)	13 (21.0)
Dyspnea	3 (9.7)	1 (3.2)	4 (6.5)
Fatigue	1 (3.2)	2 (6.5)	3 (4.8)
Rash	3 (9.7)	1 (3.2)	4 (6.5)
Nausea	2 (6.5)	1 (3.2)	3 (4.8)
Hemorrhage	3 (9.7)	0	3 (4.8)
Deshydratation	0	2 (6.5)	2 (3.2)
Documented grade II-IV fungal infection, # of patients (%)	4 (12.9)	9 (29.0)	13 (21.0)
Causes of death			
Acute myeloid leukemia	4 (12.9)	4 (12.9)	8 (12.9)
Toxicity	4 (12.9)	1 (3.2)	5 (8.1)
Transplant-related mortality	7 (22.6)	5 (16.1)	12 (19.4)
Other	0	1 (3.2)	1 (1.6)

a) Evaluation of response was scheduled around day 31 after the start of the induction course. CR was defined as less than 5% marrow blasts and recovery of normal hematopoiesis with a neutrophil count $\geq 1 \times 10^9$/L and a platelet count $\geq 100 \times 10^9$/L in addition to disappearance of all clinical, laboratory, or radiological evidence of disease. The term incomplete CR (CRi) was used to define patients who met all CR criteria, but had neutrophil counts between 0.5 and 1.0 $\times 10^9$/L and/or platelet counts between 50 and 100 $\times 10^9$/L. Finally, partial remission (PR) was defined as 5-25% blast cells in the bone marrow and a reduction of at least 50% of blasts in the bone marrow, irrespective of count recovery.

b) Adverse events were graded with CTCAE version 3.0 scoring system (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

FIGURE LEGENDS

Figure 1. Overall Survival (A), Disease-free survival from CR (B), cumulative incidence of relapse from CR (C) and cumulative incidence of death in CR (D) in the 2 arms.


A
Survival from randomization (%)
100
90
80
70
60
50
40
30
20
10
0
(years)
0
1
2
3
O N
15 31
11 31
Number of patients at risk :
23 6
22 8
Treatment
Arm A
Arm B
B
Relapse-free survival from CR (%)
100
90
80
70
60
50
40
30
20
10
0
(years)
0
1
2
3
O N
15 26
11 26
Number of patients at risk :
13 2
16 6
Treatment
Arm A
Arm B
C
Cumulative incidence of relapse (%)
100
90
80
70
60
50
40
30
20
10
0
(years)
0
1
2
3
O N
9 26
7 26
Number of patients at risk :
13 2
16 6
Treatment
Arm A
Arm B
D
Cumulative incidence of death in CR (%)
100
90
80
70
60
50
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30
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3
O N
6 26
4 26
Number of patients at risk :
13 2
16 6
Treatment
Arm A
Arm B

Supplemental material and methods

Study design

The combined phase I and II part of the trial, exploring the efficacy of clofarabine of 10 mg/m^2/day, was performed in 8 centers. After the maximum tolerated dose was reached in the phase I of the trial, additional patients were randomized in the phase II part of the trial using a 1-sample Fleming design. The statistical considerations were the following: P0 was 65%; P1 was 85%; beta error was 0.05 (actual one 0.07) and alpha error was 0.15 (actual one 0.12). Thus, for each of the arms A and B, the regimen was considered as active and feasible if ≥ 23/30 (76.7%) patients achieved a CR/CRi. A total of 30 patients were required in each arm (24 patients in addition to the 6 from the phase 1 of the trial using the same dosage of clofarabine).

The protocol was approved by the EORTC Protocol Review Committee and by the Ethical Committee of each participating center. Patients were prospectively randomized at the EORTC Headquarters after signed written informed consent was obtained according to ICH/GCP and national/local regulations. Randomization was stratified by institution and by presence of any of the following poor prognostic features known at the time of inclusion: white blood cells (WBC) at diagnosis >=100 x 10^9/L, very high-risk cytogenetics (defined as either monosomies 5, 7, or 5q-, 7q-, abn(3), t(6;9), t(9;22), or complex abnormalities (>3 abnormalities)), or FLT3-ITD positivity.

Comparison with a historical matched cohort of patients

The rate of CR/CRi after 1 or 2 cycles of induction chemotherapy as well as OS and Relapse-free survival (RFS) in the current study were compared with a cohort of comparable patients from the standard arm of the previous EORTC/GIMEMA study (AML-12)[1]. They met the same inclusion criteria as current AML-14A patients, and were from the centers that contributed patients to the current study. These analyses were not

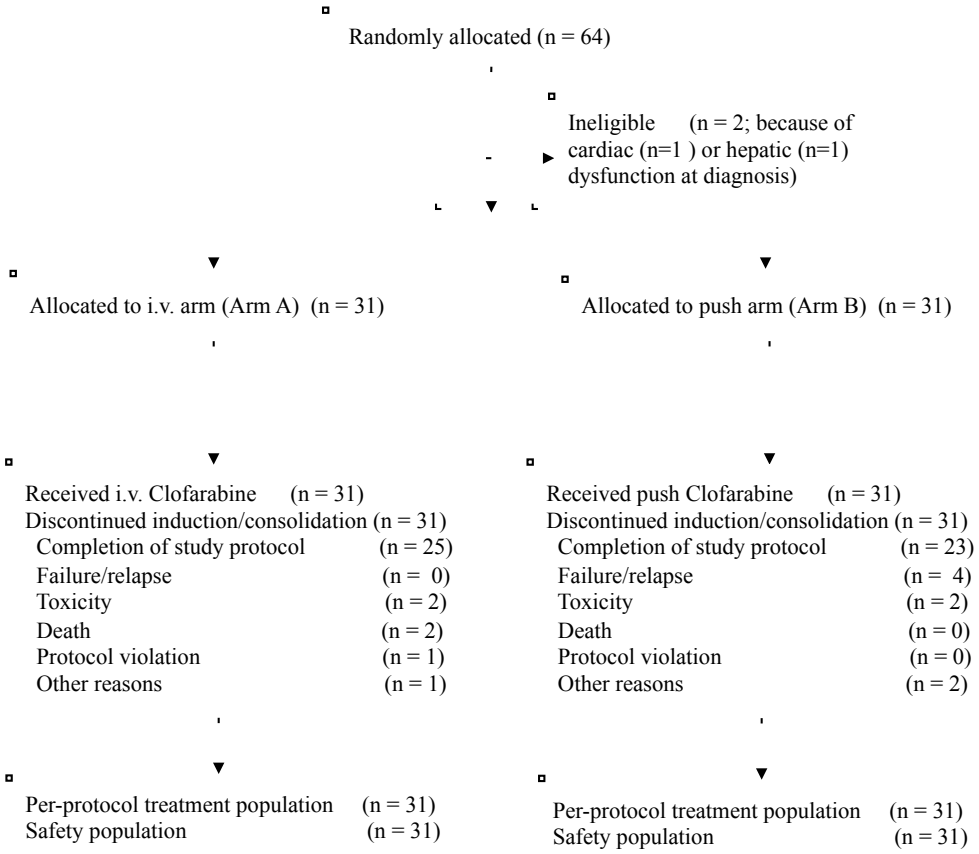
planned beforehand in the protocol. The standard arm of the AML-12 trial consisted of remission induction including Ara-C (100 mg/m^2 per day as continuous i.v. infusion for 10 days) plus daunorubicin (50 mg/m^2 per day as a 5-minute push injection on days 1, 3, and 5) plus etoposide (50 mg/m^2 per day by 1-hour i.v. infusion on days 1 through 5). Post-remission consolidation therapy consisted of intermediate-dose Ara-C (500 mg/m^2 every 12 hours as a 2-hour i.v. infusion on days 1 through 6) plus daunorubicin (50 mg/m^2 per day as a 5-minute push injection on days 4 through 6). Recommended post-consolidation treatment was as in the current protocol.

Stastistical analyses

Time to hematologic recovery from the start of the first induction course was assessed in patients who achieved a CR/CRi. The duration of OS was calculated from the date of randomization until death. RFS was calculated as the time from CR/CRi until the first relapse or death. The Kaplan-Meier method was used to estimate time-to-event outcomes. One-year OS and RFS rates and medians were presented with 95% confidence intervals (CI) based on the Brookmeyer and Crowley method[2]. Cumulative incidences of relapse or of death in CR/CRi were estimated from the date of CR/CRi achievement until either relapse or death without relapse by using competing risk methods[2]. Comparison of CR/CRi rate in current AML-14A patients and in comparable historical AML-12 patients was carried out with Fisher's exact test. SAS 9.3 software (SAS Institute Inc. Cary, NC) was used for the statistical analyses.

Supplemental Results

Supplemental figure 1. Disposition of patients in each arm of AML-14A study.



Supplemental Table 1. Baseline patients and historic controls (patients treated in the standard arm of the EORTC/GIMEMA AML-12 study) characteristics.

	Study	
	AML-14A (n=62)	**AML-12 (n=201)**
Gender, # of patients (%)		
Male	27 (43.5)	100 (49.8)
Female	35 (56.5)	101 (50.2)
Age, # of patients (%)		
15-45 years	26 (41.9)	91 (45.3)
46-60 years	36 (58.1)	110 (54.7)
WHO performance status, # of patients (%)		
0	46 (74.2)	125 (62.2)
1	14 (22.6)	67 (33.3)
2+	2 (3.2)	9 (4.5)
Type of disease, # of patients (%)		
De novo AML or MDS	57 (91.9)	194 (96.5)
Secondary AML or MDS	5 (8.1)	7 (3.5)
WBC at diagnosis, # of patients (%)		
< 100 $x10^9$/L	57 (91.9)	174 (86.5)
≥ 100 $x10^9$/L	5 (8.1)	27 (13.4)
Cytogenetics[a], # of patients (%)		
Good risk with ≥ 100$x10^9$ WBC/L at diagnosis	0 (0)	4 (2)
Normal (or –Y) without FLT3-ITD	22 (35.5)	83 (41.3)
High / very high risk or FLT3-ITD	36 (58)	90 (44.8)
Unknown/ failure / missing	4[c] (6.5)	24 (11.9)
Bone marrow blasts (%)		
Median	60.5	63.0
Range	12-99	2-96

[a]Cytogenetics: good risk includes inv(16) or t(8;21) ; very bad risk includes complex abnormalitis (>3 abnormalities), monosomies 5, 7 and 5q-, 7q-, 3q, t(6;9), t(9;22), 11q23, t(9;11) ; bad risk includes all other chromosomal abnormalities.

Supplemental table 2. Comparison results from the AML14A study with a matched group of patients treated in the standard arm of the EORTC/GIMEMA AML-12 study [1].

	Study		***P****
	AML-14A	**AML-12**	
# of patients	62	201	
Response to induction #1, # of patients (%)			
CR / CRi	51 (82.3)	134 (66.7)	0.025
CR / CRi / PR	53 (85.5)	153 (76.1)	
Resistant disease, hypoplasia, death	9 (14.5)	48 (23.9)	
Response to inductions #1 / #2, # of patients (%)			
CR / CRi	52 (83.9)	146 (72.6)	0.092
PR, resistant disease, hypoplasia, death	10 (16.1)	55 (27.4)	
Allogeneic transplantation in CR1, # of patients [%]**	26 [50.0]	43 [29.5]	
One-year outcomes, % (95% CI)			
Overall survival rate	74.1 (61.3 - 83.3)	58.0 (50.9 - 64.5)	
Relapse-free survival rate**	61.5 (47.0 - 73.2)	54.1 (45.7 - 61.8)	
Relapse incidence**	23.3 (11.7 – 34.8)	37.7 (29.8 – 45.5)	
Death in CR incidence**	17.3 (7.0 – 27.6)	9.6 (4.8 – 14.4)	

*: Using the Fisher's exact test

**: Computed in patients who reached CR after induction

References

1. Willemze R, Suciu S, Meloni G, et al. High-Dose Cytarabine in Induction Treatment Improves the Outcome of Adult Patients Younger Than Age 46 Years With Acute Myeloid Leukemia: Results of the EORTC-GIMEMA AML-12 Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2014;32(3):219-228.
2. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. . John Wiley, 2002.