**Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study**

## Introduction

Acute myeloid leukaemia is a heterogeneous disease with a wide range of outcomes that are determined by the genetics and age of the patient.[1](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib1) The standard induction treatment for patients with acute myeloid leukaemia is the 3+7 regimen, combining daunorubicin (50–60 mg/m2 per day for 3 days) with continuous cytarabine (100–200 mg/m2 per day for 7 days).[2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib2) However, so far, significant improvement has not been reported for a new drug used with daunorubicin and cytarabine.

Gemtuzumab ozogamicin (Mylotarg, Pfizer, New York, NY, and Ben Venue Laboratories, Bedford, OH, USA) is a humanised anti-CD33 monoclonal antibody linked to calicheamicin.[3](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib3) After internalisation and intracellular release, delivery of this highly toxic drug is targeted to CD33-expressing leukaemic cells (>80% in patients with acute myeloid leukaemia). In a phase 2 study in patients with acute myeloid leukaemia in first relapse, single-agent gemtuzumab ozogamicin at a dose of 9 mg/m2 on days 1 and 14 was associated with a 26% complete remission (CR).[4](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib4) However, haematological toxicity and frequent liver toxicity with veno-occlusive disease were reported with this initial dose and schedule.[5](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib5) To minimise toxicity, we chose a new regimen based on the repetition of a gemtuzumab ozogamicin lower dose of 3 mg/m2 (maximum dose 5 mg) on days 1, 4, and 7 (3-3-3 regimen). The rationale for lower doses was based on the responses to doses of 1–4 mg/m2 in the initial phase 1 study and a saturation of more than 80% of the CD33 sites after dosing with 4 mg/m2 or 6 mg/m2.[6](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib6) The rationale for administration of fractionated doses was based on the rapid re-expression of CD33 molecules on the cell surface after a first exposure. [[7]](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib7)and[[8]](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib8) The results of our two phase 2 studies with the 3-3-3 regimen in adult patients with relapsing acute myeloid leukaemia showed that this regimen was effective and could be used with the 3+7 chemotherapy consisting of daunorubicin doses of up to 60 mg/m2 and cytarabine doses of up 200 mg/m2 without excessive haematological and liver toxicity. [[9]](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib9)and[[10]](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib10) We assessed the addition of the 3-3-3 regimen to standard-dose 7+3 induction chemotherapy in previously untreated patients aged 50–70 years with de novo acute myeloid leukaemia.

## Methods

### Study design and patients

A randomised open-label phase 3 study was undertaken between January, 2008, and November, 2010, in 26 haematology centres in France. Previously untreated patients, aged 50–70 years, with a locally confirmed morphological diagnosis of acute myeloid leukaemia were eligible if they had normal cardiac function, assessed by use of radionucleotide scintigraphy or echography. Expression of the CD33 antigen on leukaemic blast cells was not required for study entry. Patients with previous myeloproliferative or myelodysplastic syndrome or exposure to chemotherapy or radiotherapy were not eligible. Other exclusion criteria were CNS involvement in acute myeloid leukaemia, severe uncontrolled infection, and liver (serum aminotransferase concentrations ≥2·5 upper limit of normal [ULN], serum bilirubin ≥2 ULN) or renal (serum creatinine ≥2·5 ULN) dysfunction. Immunophenotyping and cytogenetic analysis were done locally. Results for cytogenetic analysis were centrally obtained and classified according to standard International System for Human Cytogenetic Nomenclature criteria[11](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib11) as favourable, intermediate, and unfavourable subgroups ([appendix](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#sec1)). Screening for mutations in the nucleophosmin gene (NPM1), FMS-like tyrosine kinase 3 gene (FLT3) internal tandem duplication (ITD), and CCAAT/enhancer-binding protein alpha gene (CEBPA) was done centrally; favourable genotypes were defined as normal karyotype and NPM1 mutation without FLT3-ITD or a normal karyotype and CEBPA mutation, in accordance with international recommendations.[1](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib1)

The study was approved by the ethics committee of Saint-Germain en Laye, France, and by the institutional review board of the French Regulatory Agency and undertaken in accordance with the Declaration of Helsinki. All patients provided written informed consent.

### Randomisation and masking

After informed consent was obtained from a patient, the investigator faxed the required registration form to the Department of Biostatistics, Hospital Saint-Louis, Paris, France. The study statistician computer-generated the random allocation sequence by use of R software (version 2.10.1). Randomisation was undertaken centrally by use of telephone. Patients were stratified by centre and in a 1:1 allocation ratio with block sizes of four to the control and gemtuzumab ozogamicin groups. The study was open label.

### Treatment

Patients were given a 3+7 induction course of intravenous daunorubicin (60 mg/m2 on days 1 to 3) and intravenous cytarabine (200 mg/m2 as continuous infusion for 7 days) without (control group) or with intravenous gemtuzumab ozogamicin (3 mg/m2 [maximum dose 5 mg] infused over 2 h on days 1, 4, and 7; gemtuzumab ozogamicin group) after premedication with methylprednisolone. The bone marrow was aspirated on day 15. If there were more than 10% persistent leukaemic blasts, a second induction course was given with intravenous daunorubicin (60 mg/m2 per day for 2 days and intravenous cytarabine (1000 mg/m2 per 12 h, infused over 2 h for 3 days) but without gemtuzumab ozogamicin, followed by daily granulocyte colony-stimulating factor (lenograstim 263 μg, intravenously) until neutrophil recovery. Clinical and haematological responses were assessed after induction therapy. Responses were classified as CR, defined as fewer than 5% blasts in a normocellular marrow and an absolute neutrophil count (ANC) of more than 1×109 per L with a platelet count of 100×109 per L or more in the peripheral blood; and CR with incomplete platelet recovery (CRp), defined as CR with residual thrombocytopenia (<100×109 platelets per L).[12](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib12) The study investigators assessed and classified disease progression in accordance with the International Working Group criteria.[12](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib12) Patients who did not respond to induction discontinued the study treatment and were given a different treatment at the discretion of their treating physician. Patients in CR or CRp were given two consolidation courses of intravenous daunorubicin (60 mg/m2 for 1 day [first course] or 2 days [second course]) in combination with intravenous cytarabine (1000 mg/m2 per 12 h, infused over 2 h on days 1–4), with or without intravenous gemtuzumab ozogamicin (3 mg/m2 on day 1) according to their initial random assignment. The protocol was amended in December, 2009, to recommend that gemtuzumab ozogamicin should not be used during consolidation in patients with a platelet count of less than 100×109 per L by day 45 after the initiation of chemotherapy. According to the protocol, patients with non-favourable acute myeloid leukaemia could be offered allogeneic stem-cell transplantation (SCT) if they had a matched related or unrelated donor. Assessment of clinical and haematological responses was repeated before the beginning of the second consolidation course and thereafter every 3 months for 2 years. Adverse events and serious adverse events were documented in accordance with the Common Terminology Criteria for [Adverse Events](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science?_ob=RedirectURL&_method=externObjLink&_locator=url&_issn=01406736&_origin=article&_zone=art_page&_plusSign=%2B&_targetURL=http%253A%252F%252Fctep.cancer.gov%252Fprotocoldevelopment%252Felectronic_applications%252Fdocs%252Fctcaev3.pdf) (version 3.0).

### Statistical analysis

The primary outcome was event-free survival (EFS), defined as the time from randomisation to the date of assessment of the response if CR or CRp had not been achieved, relapse, or death. Secondary outcomes were rates of CR with or without CRp, overall survival (OS), relapse-free survival (RFS), and safety. Outcomes were measured during treatment or at day 45 after treatment (induction or consolidation). RFS was defined as the time from achievement of CR or CRp to the date of relapse or death.

Sample size calculation showed that 140 patients per group and a total of 184 events were needed for us to detect an increase in 2 year EFS estimate from 25% in the reference group to 40% in the experimental group (hazard ratio [HR] 0·66), with a type 1 error rate of 5% and a statistical power of 80%, assuming an exponential EFS.

All patients were analysed in the group they were randomly allocated to (intention to treat), unless they withdrew consent. The censored endpoints (EFS, OS, and RFS) were analysed by failure-time data methods, at the reference date Aug 1, 2011. Right censored data were estimated by use of the Kaplan-Meier method and compared by use of the log-rank test, [[13]](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib13)and[[14]](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib14) and values for the HR with 95% CI were computed by use of Cox models after checking for proportionality of hazard functions with Grambsch and Therneau's test.[15](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib15) Treatment comparisons were then adjusted for imbalances of prognostic covariates by use of a multivariable Cox model.[16](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib16) Centre effect was assessed with frailty models. Binary data were compared by use of the Fisher's exact test and continuous distributions were compared by use of the Mann-Whitney test. EFS and RFS were also computed after censoring patients who received SCT in the first CR or CRp at the time of the transplantation. Quantitative interactions between the effect of randomisation and subsets of patients were tested with the Gail and Simon test.[17](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#bib17) In an exploratory sensitivity analysis, we incorporated the potential effect of protocol amendment by stratifying the main comparison of outcome for whether patients were included before or after the amendment. All reported p values are two-sided, with a significance level of 0·05. All analyses were done with SAS (version 9.2) and R (version 2.13.1) software.

The study is registered with EudraCT, number 2007-002933-36.

### Role of the funding source

Wyeth (Pfizer) kindly provided the study drug. This trial was an investigator-initiated trial by the Acute Leukemia French Association (ALFA). The sponsorship was assumed by the Hospital of Versailles, France. The Research Clinical Unit of the Hospital of Versailles gathered the data with the help of the central ALFA coordination office. The Biostatistics Department of the Saint-Louis Hospital, Paris (Assistance Publique-Hôpitaux de Paris) did the statistical analysis. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

## Results

280 patients were randomly assigned between January, 2008, and November, 2010, and two were excluded because they withdrew consent ([figure 1](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig1)). Some imbalances were noted between the groups—namely, slightly higher median age and more men in the gemtuzumab ozogamicin group than in the control group ([table 1](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl1)). The results of the cytogenetics analysis were available for 249 patients; the analysis did not work on tumour samples from 21 patients and was not done for eight patients. 275 patients were screened for mutations in FLT3, 274 in NPM1, and 247 in CEBPA genes; 48 of 143 patients with a normal karyotype were classified as being in the favourable genotype subset ([table 1](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl1); [appendix](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#sec1)). The median actual follow-up was 14·8 months (IQR 9·3–23·8) overall, and 20·0 (14·5–30·5) months in survivors.

Overall, complete remission was achieved in 202 patients (73%) and CRp in 15 patients (5%; [table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2)). No significant differences were noted in the response to induction therapy between the groups despite patients in the gemtuzumab ozogamicin group having a lower rate of resistant disease and higher rate of CRp. The number of induction deaths in the control and gemtuzumab ozogamicin groups did not significantly differ (p=0·41). 104 (75%) of 139 patients had CR or CRp in the control group and 113 (81%) of 139 in the gemtuzumab ozogamicin group (p=0·25).

[Table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2) shows the primary and secondary outcomes. By the reference date, 15 patients died during induction therapy, 46 had resistant disease after induction therapy, 110 relapsed, and ten died in first CR or CRp ([table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2)). At 2 years, EFS was lower in the control group than in the gemtuzumab ozogamicin group ([table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2); [figure 2A](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig2)). Overall, 131 patients have died ([table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2)). At 2 years, OS was also lower in the control group ([table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2); [figure 2B](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig2)). In patients who achieved CR or CRp, the estimated 2 year RFS was much higher in the gemtuzumab ozogamicin group ([table 2](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2); [figure 2C](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig2)). Differences remained significant after patients who received SCT in CR or CRp were censored at the date of transplantation for EFS (HR 0·61, 95% CI 0·45–0·83; log-rank p=0·002) and RFS (0·56, 0·38–0·83; log-rank p=0·003). In the gemtuzumab ozogamicin group, RFS was not different for patients in CRp and CR ([appendix](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#sec1)). Estimates of treatment effect were not greatly affected when the analysis was stratified for the period of inclusion in relation to protocol amendment (data not shown).

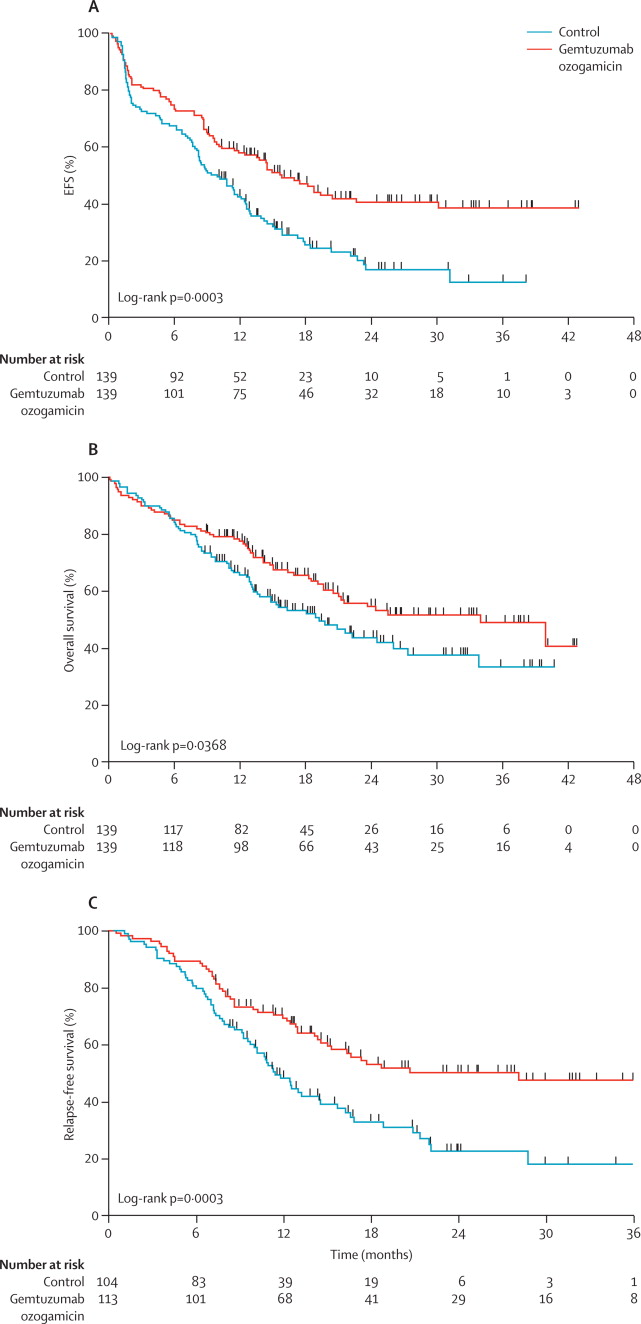
Table 2. Outcomes

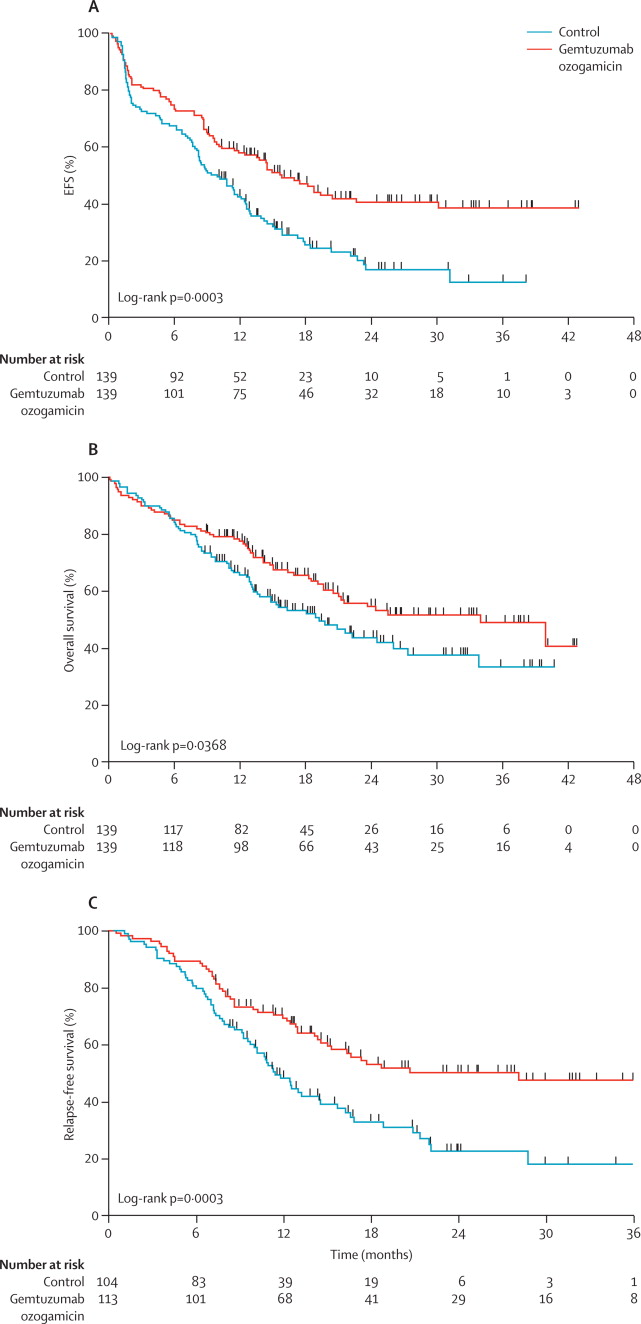
|  |  |  | | | **Control group** | **Gemtuzumab ozogamicin group** | | | **Point estimate (95% CI)** | | **p value** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| All patients | | | | | 139 | 139 | | |  | |  | |
| CR + CRp | | | | | 104 (75%) | 113 (81%) | | | 1·46[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2fn1) (0·82–2·59) | | 0·25 | |
|  | Induction courses | | | | | | | | | | | |
|  |  | 1 | | | 104 (75%) | 113 (81%) | | |  | |  | |
|  |  | 2 | | | 35 (25%) | 25 (18%) | | |  | |  | |
|  | Death before induction | | | | 1 (<1%) | 0 | | |  | |  | |
|  | Death during induction | | | | 5 (4%) | 9 (6%) | | |  | |  | |
|  | Resistant disease (no CR or CRp) | | | | 29 (21%) | 17 (12%) | | |  | |  | |
|  | CR | | | | 100 (72%) | 102 (73%) | | |  | |  | |
|  | CRp | | | | 4 (3%) | 11 (8%) | | |  | |  | |
| Event-free survival | | | | |  |  | | | 0·58[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2fn2) (0·43–0·78) | | 0·0003 | |
|  | Death before or during induction | | | | 6 (4%) | 9 (6%) | | |  | |  | |
|  | Resistant disease (no CR or CRp) | | | | 29 (21%) | 17 (12%) | | |  | |  | |
|  | Relapse | | | | 61 (44%) | 49 (35%) | | |  | |  | |
|  | Death in CR or CRp | | | | 8 (6%) | 2 (1%) | | |  | |  | |
|  | Time (months; median, range) | | | | 9·7 (8·0–11·9) | 15·6 (11·7–22·4) | | |  | |  | |
|  | Estimated rate at 2 years (95% CI) | | | | 17·1% (10·8–27·1) | 40·8% (32·8–50·8) | | |  | |  | |
| Overall survival | | | | |  |  | | | 0·69[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2fn2) (0·49–0·98) | | 0·0368 | |
|  | Death | | | | 72 (52%) | 59 (42%) | | |  | |  | |
|  | Time (months; median, range) | | | | 19·2 (13·8–26·0) | 34·0 (20·5–NR) | | |  | |  | |
| Estimated rate at 2 years (95% CI) | | | | 41·9% (33·1–53·1) | | | 53·2% (44·6–63·5) |  | |  | |
| Patients in CR or CRp | | | | | | | 104 (75%) | 113 (81%) | |  | |  |
| Relapse-free survival | | | | | | |  |  | | 0·52[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl2fn2) (0·36–0·75) | | 0·0003 |
|  | | | Relapse | | | | 61 (44%) | 49 (35%) | |  | |  |
|  | | | Death before relapse | | | | 8 (6%) | 2 (1%) | |  | |  |
|  | | | Time (months; median, range) | | | | 11·4 (9.9–14.5) | 28·1 (15·0–NR) | |  | |  |
|  | | | Estimated rate at 2 years (95% CI) | | | | 22·7% (14·5–35·7) | 50·3% (41·0–61·6) | |  | |  |

Data are number or number (%), unless otherwise indicated. CR=complete remission. CRp=complete remission with incomplete platelet recovery. NR=not reached.

\* Odds ratio.

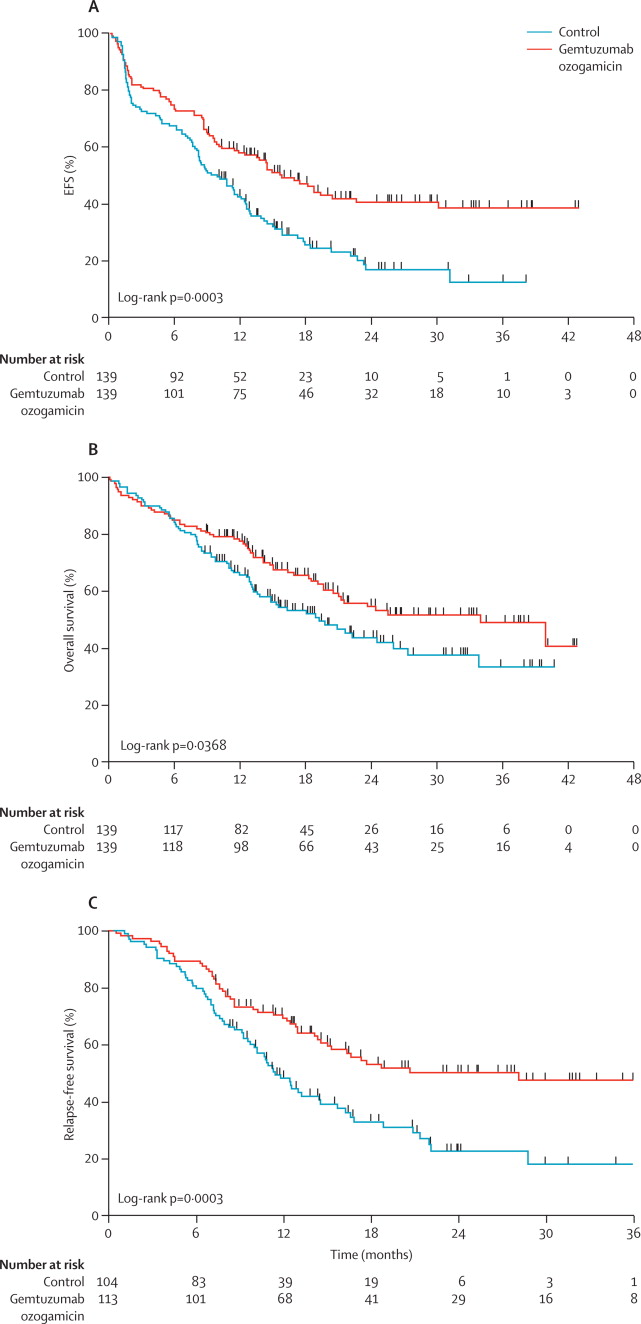
† Hazard ratio.





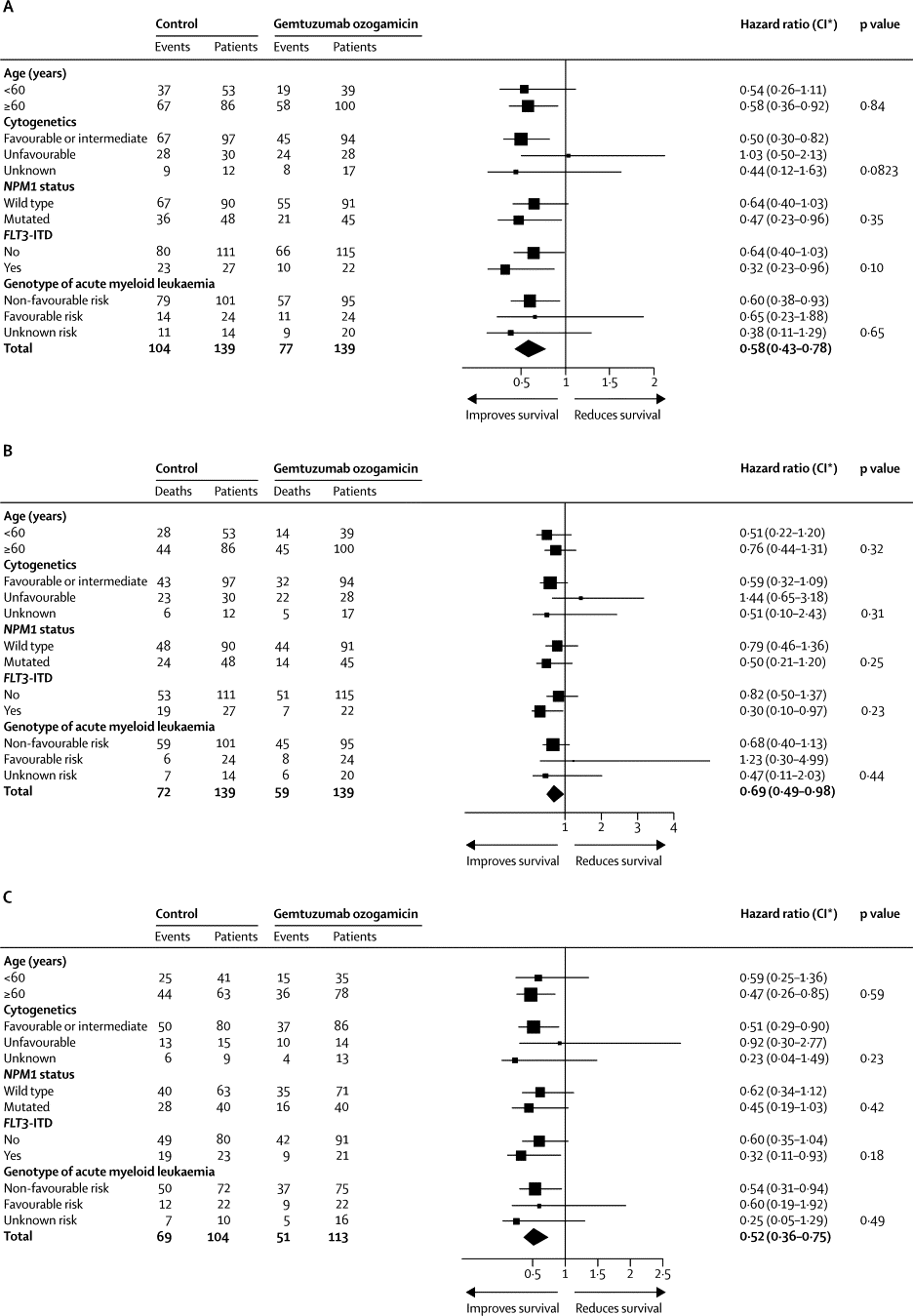
**Control**

**Control**



**Control**

Exploratory analyses, subsets analyses, and adjustments for prognostic factors were also done. No centre effects were noted on EFS (p=0·91), OS (p=0·21), or RFS (p=0·92). With the maximum gemtuzumab ozogamicin dose (5 mg), no interaction was noted between treatment and the patient's body-surface irrespective of the endpoint (EFS, p=0·93; OS, p=0·71; RFS, p=0·27). Interactions between the effect of randomisation and the following baseline subsets were studied: age (cutoff at 60 years), cytogenetics, NPM1 mutation, and FLT3-ITD status ([figure 3](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig3); [appendix](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#sec1)). No main heterogeneity was noted in the benefit in EFS with gemtuzumab ozogamicin for any of the patients' characteristics ([figure 3A](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig3)). Treatment-by-covariate interactions were noted in the survival benefit for cytogenetics and FLT3-ITD status, as selected by the Gail and Simon test ([figure 3B](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#fig3)). Therefore, besides treatment group, cytogenetics and genotype were the only factors of prognostic importance. Notably, age (HR 1·01, 95% CI 0·98–1·04; p=0·41), white blood cell count (1·07, 0·80–1·43; p=0·66), and CD33 expression on blast cells (0·78, 0·50–1·21; p=0·26) were not associated with EFS; similar results were noted for OS and RFS (data not shown). After adjustment for these factors, randomisation to the gemtuzumab ozogamicin group remained significantly associated with longer EFS (0·61, 95% CI 0·45–0·82; p=0·001) and longer RFS (0·54, 0·37–0·78; p=0·001), but not with OS (0·66, 0·41–1·04; p=0·07).

[](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#gr3)Figure 3. Forest plot of the subsets of patients and pooled data for (A) event-free survival, (B) overall survival, and (C) relapse-free survival\*99% CI are given for the subset analyses and 95% CI for the overall results. p values obtained with the Gail and Simon interaction tests are also reported.

Duration of treatment-induced neutropenia was significantly longer in the intervention than in the control group after the first and second consolidation courses, whereas the duration of treatment-induced thrombocytopenia was significantly longer after all three chemotherapy courses ([table 3](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3)). Persistent grade 3 and 4 thrombocytopenia, defined as the non-recovery of a platelet count above 50×109 per L at day 45 after the start of a previous chemotherapy course, was reported in four (3%) patients in the control group and 22 (16%) in the gemtuzumab ozogamicin group (p<0·0001; [table 3](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3)). After each course, the median number of platelet transfusion episodes was significantly higher in the gemtuzumab ozogamicin group ([table 3](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3)).

Table 3. Haematological toxicity

|  |  | | **Control group (n=139)** | | **Gemtuzumab ozogamicin group (n=139)** | | | **Point difference (95% CI)** | **p value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Duration of treatment-induced cytopenias (days)**[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) | | | | | | | | | |
| Neutropenia (<0·5×109 cells per L) | | | | | | | | | |
|  | After induction | | 22 (18–27) | | 22 (20–26) | | | −0·4[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−2·6 to −1·8) | 0·68[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After first consolidation | | 10 (8–15) | | 13 (10–18) | | | −2·9[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−5·4 to −0·6) | 0·0017[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After second consolidation | | 13 (10–16) | | 15 (12–20) | | | −3·7[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−6·2 to −1·4) | 0·0021[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
| Thrombocytopenia (<50×109 cells per L) | | | | | | | | | |
|  | After induction | | 21 (18–25) | | 25 (20–30) | | | −3·3[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−5·8 to −0·8) | 0·0006[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After first consolidation | | 9 (6–13) | | 17 (11–27) | | | −9·5[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−16·4 to −2·8) | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After second consolidation | | 13 (9–20) | | 24 (15–35) | | | −9·5[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−13·5 to −5·4) | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
| **Transfusion episodes**[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) | | | | | | | | | |
| Red blood cells | | | | | | | | | |
|  | After induction | | 8 (6–12) | | 8 (6–10) | | | 0·5[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−0·6 to 1·6) | 0·52[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After first consolidation | | 4 (3–6) | | 4 (3–6) | | | −1·0[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−1·6 to −0·3) | 0·0009[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After second consolidation | | 4 (2–6) | | 4 (2–6) | | | 0[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−0·8 to 0·8) | 0·99[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
| Platelets | | | | | | | | | |
|  | After induction | | 7 (5–9) | | 12 (9–17) | | | −5·8[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−7·6 to −4·0) | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After first consolidation | | 2 (1–3) | | 6 (4–10) | | | −5·0[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−6·3 to −3·7) | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | After second consolidation | | 3 (2–4) | | 7 (5–10) | | | −4·1[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−5·2 to −3·0) | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
| **Persistent thrombocytopenia (<50×109 cells per L)** | | | | | | | | | |
| By day 45 after induction | | | 0/139 | | 4/139 (3%) | | | 0[‡](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn3) (0 to 0·9) | 0·12[§](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn4) |
| By day 45 after first consolidation | | | 2/98 (2%) | | 9/99 (9%) | | | 0·2[‡](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn3) (0·1 to 0·9) | 0·0582[§](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn4) |
| By day 45 after second consolidation | | | 2/90 (2%) | | 9/85 (11%) | | | 0·2[‡](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn3) (0·1 to 0·8) | 0·0289[§](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn4) |
| Platelets | | | | | | | | | |
|  | | After induction | | 7 (5–9) | | 12 (9–17) | −5·8[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−7·6 to −4·0) | | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | | After first consolidation | | 2 (1–3) | | 6 (4–10) | −5·0[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−6·3 to −3·7) | | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
|  | | After second consolidation | | 3 (2–4) | | 7 (5–10) | −4·1[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn1) (−5·2 to −3·0) | | <0·0001[†](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn2) |
| **Persistent thrombocytopenia (<50×109 cells per L)** | | | | | | | | | |
| By day 45 after induction | | | | 0/139 | | 4/139 (3%) | 0[‡](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn3) (0 to 0·9) | | 0·12[§](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn4) |
| By day 45 after first consolidation | | | | 2/98 (2%) | | 9/99 (9%) | 0·2[‡](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn3) (0·1 to 0·9) | | 0·0582[§](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn4) |
| By day 45 after second consolidation | | | | 2/90 (2%) | | 9/85 (11%) | 0·2[‡](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn3) (0·1 to 0·8) | | 0·0289[§](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl3fn4) |

Data are median (IQR) or n/N (%), unless otherwise indicated. CR=complete remission. CRp=complete remission with incomplete platelet recovery.

\* Mean difference.

† p values calculated with two-sided Wilcoxon test.

‡ Relative risk.

§ p values calculated with two-sided Fisher's exact test.

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More grade 3 and 4 haemorrhages were reported in the gemtuzumab ozogamicin group, though the difference was not significant ([table 4](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl4)). The incidences of cardiac events, infectious events, transfers to intensive care unit, and deaths from toxic effects did not differ significantly between the two groups ([table 4](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl4)). Grade 3 and 4 liver toxicity was reported mainly in the context of sepsis in both groups. Two of three patients who developed veno-occlusive disease in the gemtuzumab ozogamicin group died, one after the induction course and the other after the first consolidation course. Generally, grade 3 and 4 adverse haematological and non-haematological adverse events were increased with gemtuzumab ozogamicin, contributing to a smaller percentage of patients in CR and CRp having the two planned consolidation courses.

Table 4. Non-haematological toxicity

|  |  | **Control group (n=139)** | **Gemtuzumab ozogamicin group (n=139)** | **Relative risk (95% CI)** | **p value** |
| --- | --- | --- | --- | --- | --- |
| Induction death | | 5/139 (4%) | 9/139 (6%) | 0·56 (0·20–1·54) | 0·41 |
| Transfer to intensive-care unit | | 17/139 (12%) | 20/139 (14%) | 0·85 (0·47–1·54) | 0·72 |
| Treatment-related death during CR or CRp | | 8/104[\*](http://www.sciencedirect.com.iclibezp1.cc.ic.ac.uk/science/article/pii/S0140673612604851#tbl4fn1) (8%) | 2/113 (2%) | 4·35 (1·07–17·84) | 0·051 |
| Grade 3 and 4 adverse events | | | | | |
|  | Haemorrhage | 4/139 (3%) | 12/139 (9%) | 0·33 (0·12–0·95) | 0·068 |
|  | Cardiac | 9/139 (6%) | 11/139 (8%) | 0·82 (0·36–1·87) | 0·82 |
|  | Liver | 9/139 (6%) | 18/139 (13%) | 0·50 (0·24–1·05) | 0·10 |
|  | Skin or mucosa | 25/139 (18%) | 32/139 (23%) | 0·11 (0·03–0·42) | 0·37 |
|  | Gastrointestinal | 14/139 (10%) | 22/139 (16%) | 0·64 (0·34–1·18) | 0·21 |
|  | Pulmonary | 16/139 (12%) | 16/139 (12%) | 1·00 (0·53–1·90) | 1·00 |
| Grade 3 and 4 infections | | | | | |
|  | During induction | 50/131 (38%) | 59/129 (46%) | 0·83 (0·62–1·11) | 0·26 |
|  | During first consolidation | 38/95 (40%) | 48/97 (49%) | 0·80 (0·59–1·11) | 0·19 |
|  | During second consolidation | 38/82 (46%) | 38/81 (47%) | 0·99 (0·71–1·37) |  |