ARTICLE

Gemtuzumab ozogamicin for *de novo* acute myeloid leukemia: final efficacy and safety updates from the open-label, phase III ALFA-0701 trial

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ABSTRACT

The randomized, phase III ALFA-0701 trial showed that a reduced and fractionated dose of gemtuzumab ozogamicin added to standard front-line chemotherapy significantly improves event-free survival (EFS) in adults with *de novo* acute myeloid leukemia (AML). Here we report an independent review of EFS, final overall survival (OS), and additional safety results from ALFA-0701. Patients (n=271) aged 50-70 years with *de novo* AML were randomized to receive conventional front-line induction chemotherapy (3+7 daunorubicin+cytarabine) with/without gemtuzumab ozogamicin 3 mg/m^2 on days 1, 4, and 7 during induction. Patients in remission following induction therapy received 2 courses of consolidation therapy (daunorubicin+cytarabine) with/without gemtuzumab ozogamicin (3 mg/m^2/day on day 1) according to their initial randomization. The primary end point was investigator-assessed EFS. Secondary end points included OS and safety. A blinded independent review confirmed the investigator-assessed EFS results [August 1, 2011; hazard ratio (HR) 0.66; 95% Confidence Interval (CI): 0.49-0.89; 2-sided *P*=0.006], corresponding to a 34% reduction in risk of events in the gemtuzumab ozogamicin *versus* control arm. Final OS at April 30, 2013 favored gemtuzumab ozogamicin but was not significant. No differences in early death rate were observed between arms. The main toxicity associated with gemtuzumab ozogamicin was prolonged thrombocytopenia. Veno-occlusive disease (including after transplant) was observed in 6 patients in the gemtuzumab ozogamicin arm and 2 in the control arm. In conclusion, gemtuzumab ozogamicin added to standard intensive chemotherapy has a favorable benefit/risk ratio. These results expand front-line treatment options for adult patients with previously untreated AML. (Trial registered at *clinicaltrials.gov;identifier: 00927498.*)

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous disease, with classification based on morphological, cytogenetic, molecular, and immunophenotypic characteristics,[1] which, along with patients' characteristics, such as age and Eastern Cooperative Oncology Group Performance Status (ECOG PS), influence treatment recommendations and outcomes.[2] Gemtuzumab ozogamicin (GO) is an antibody-drug conjugate composed of the CD33-directed monoclonal antibody that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin.[3] Efficacy with single-agent GO (9 mg/m^2 for each of 2 doses administered 14 days apart) was initially established in patients with CD33-positive AML in first recurrence based on clinically meaningful response rates observed in 3 phase II studies in patients with AML in first relapse. However, liver toxicity and a long duration of cytopenia were observed.[4] Additional *in vitro* study results, showing that CD33-expressing leukemic cells rapidly re-express CD33 molecules on their cell surface after treatment with an anti-CD33 antibody,[5] led the Acute Leukemia French Association (ALFA) to investigate the use of a fractionated dosing regimen of GO that might enhance the internalization process while improving safety compared with higher unfractionated dosing.[6]

The randomized, phase III ALFA-0701 study compared the efficacy and safety of the standard 3+7 daunorubicin (DNR; days 1-3) and cytarabine (AraC; days 1-7) induction regimen (D+A), with or without fractionated dosing of GO (3 mg/m^2 on days 1, 4, and 7), in patients aged 50-70 years with treatment-naive AML.[6] Patients in remission following induction therapy received 2 courses of consolidation therapy consisting of D+A with or without GO (3 mg/m^2/day on day 1) according to their initial randomization. The initial results as of the cut-off date of August 1, 2011, reported for the ALFA-0701 trial by Castaigne *et al.* in 2012 showed that the study met its primary end point, with a significant improvement in investigator-assessed event-free survival (EFS) without an increase in the risk of death from toxicities when GO was added to the standard chemotherapy.[6] Following publication of the initial results, the Centre Hospitalier de Versailles, in collaboration with Pfizer, performed a retrospective collection of additional data to provide a more complete assessment of the safety profile of GO, and to conduct a retrospective, independent, blinded review of EFS. This report presents the final overall survival (OS) results from the ALFA-0701 study based on a longer follow-up date (cut-off date, April 30, 2013), the results of the independent review of EFS, as well as additional safety results focused on adverse events (AEs) of special interest considered the most important for understanding the safety profile of GO.

Methods

Details of this randomized, open-label, multicenter, phase III ALFA-0701 study have been previously described.[6]

Patients and treatment

A total of 280 patients were randomized 1:1 to receive conventional 3+7 D+A induction chemotherapy, with DNR 60 mg/m^2/d on days 1 to 3 and AraC 200 mg/m^2/d on days 1 to 7 without (control arm) or with GO (GO arm) 3 mg/m^2/d on days 1, 4, and 7; the total dose of GO per infusion was not to exceed one 5 mg vial.

A second induction course, with DNR and AraC, was given if leukemic blasts persisted at day 15 bone marrow aspirate (BMA). Patients with a complete remission (CR) or CR with incomplete platelet recovery (CRp) after induction treatment received 2 courses of consolidation, including DNR and AraC with or without GO 3 mg/m^2/d on day 1 according to their randomization, provided the platelet count was ≥50x10^9/L on the planned day 1 of the consolidation course.

Patients who experienced CR could be considered for allogeneic transplant according to ECOG PS, age, if a donor had or had not been found, and cytogenetic and molecular risk categories. An interval of two months between the last dose of GO and transplantation was recommended.

The study was approved by the Saint-Germain en Laye ethics committee in France and the institutional review board of the French Regulatory Agency. All procedures were conducted in compliance with the Declaration of Helsinki. Written informed consent was provided by all patients (EuduraCT n.: 2007-002933-36).

Efficacy analyses

This report presents: 1) final results of the secondary end point of OS, defined as the time from date of randomization to date of death from any cause at the cut-off date of April 30, 2013; 2) results of a blinded and independent review of the EFS end point, defined as the time from randomization to relapse, death from any cause, or failure to achieve CR or CRp, performed by hematology experts to study the reproducibility of this clinically important end point in AML trials; 3) results of the secondary end point relapse-free survival for patients experiencing a response; and 4) hematologic response by investigator assessment. The independent review committee analysis was based on the retrospective collection of all data used for efficacy measurements, including reports of BMA, complete blood count, extramedullary disease, or molecular or cytogenetic relapse available at the site from screening until death, or up to 28 days after either induction failure or relapse as determined by the investigator (whichever happened first).

Safety analyses

Safety data presented in this report were collected retrospectively and consist of events of special interest considered the most important for understanding the safety profile of GO and serious AEs (SAEs). This includes all grades of hemorrhage, all grades of veno-occlusive disease (VOD), severe (grade ≥3) infections, any adverse event (AE) that led to early permanent discontinuation of either GO or chemotherapy, and laboratory data. Serious AE reporting contains all SAEs reported to the Pfizer safety database throughout the study and was not restricted to causality or predefined categories.

Statistical analyses

Sample size calculations have been reported previously.[6] The modified intent-to-treat (mITT) population was the primary population for evaluating efficacy end points and included all patients who were randomized, unless consent was withdrawn before treatment initiation. Analyses were made according to the initial randomization arm, regardless of whether patients received the study drug to which they were randomized.

Results

Patients

Of the 280 patients randomized in this study, data from 9 patients were excluded from the analyses because no signed copy of the informed consent was available in the

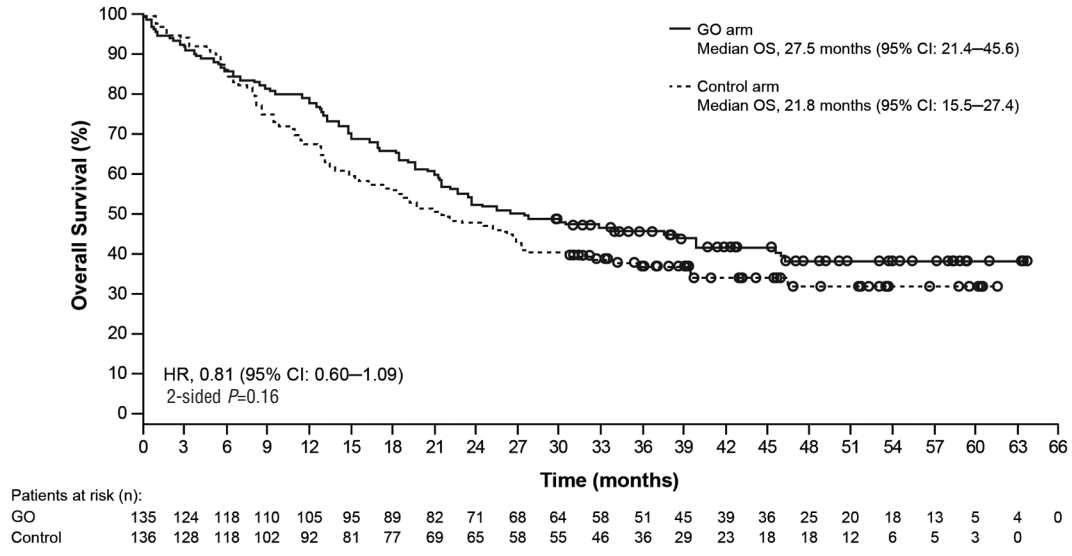

Figure 1. Overall survival. Control: daunorubicin + cytarabine (D+A); GO: gemtuzumab ozogamicin plus D+A; OS: overall survival; HR: hazard ratio; CI: Confidence Interval; n: number.

site file. Thus, the mITT population comprised 271 patients (GO arm, n=135; control arm, n=136). Characteristics of the patients in the mITT population were evenly balanced between treatment arms and were as expected in this AML population (*Online Supplementary Table S1*). Overall, 268 (98.9%) patients (GO arm, n=134; control arm, n=134) received study treatment; however, 3 patients randomized to the GO arm did not receive GO (*Online Supplementary Figure S1*). Of the 131 patients who received GO, 123 (93.9%) received all 3 fractionated GO doses during induction, and 91 (69.5%) and 64 (48.9%) patients received GO during consolidation 1 and 2, respectively. Exposure to DNR and AraC was similar between treatment arms over all study phases, with 62.6% and 65.0% of patients in the GO and control arms, respectively, completing study treatment.

Efficacy

Response rate

Overall, the rate of CR with or without CRp was similar to the results initially published.[6] There was no significant difference in the rate of CR or CRp in the GO arm compared with the control arm (*Online Supplementary Table S2*). A CR was achieved in 95 patients (70.4%) in the GO arm and 95 patients (69.9%) in the control arm; CRp was achieved in 15 patients (11.1%) in the GO arm and 5 patients (3.7%) in the control arm.

Overall survival

At the time of the primary study analysis performed at the data cut-off date of August 1, 2011, the overall median follow up was 14.8 months; 20.0 months in alive patients. At the time of the final OS analysis performed at the data cut off of April 30, 2013, the median follow up was 47.6 months in the GO arm and 41.0 months in the control arm. The final OS analysis shows a numerically longer OS in the GO arm; however, this difference did not reach statistical significance. Median OS was 27.5 months [95% Confidence Interval (CI): 21.4-45.6] in the GO arm and 21.8 months (95%CI: 15.5-27.4) in the control arm [Hazard Ratio (HR), 0.81; 95%CI: 0.60-1.09; 2-sided *P*=0.16). A total of 80 (59.3%) patients in the GO arm and 88 (64.7%) in the control arm died before April 30, 2013 (Figure 1).

Event-free survival

The primary end point of EFS derived from investigator assessment was significantly longer for patients in the GO arm [median 17.3 months (95%CI: 13.4-30.0)] than in the control arm [median 9.5 months (8.1-12.0); HR: 0.56; 95%CI: 0.42-0.76; 2-sided *P*=0.0002 by log-rank test], corresponding to a 44% reduction in the risk of an event for patients in the GO arm compared with those in the control arm (Figure 2). At year 1, the number needed to treat (NNT) with GO to prevent an event was 6; NNT at year 3 was 4. Multiple EFS sensitivity analyses demonstrate the robustness of the primary EFS results (*Online Supplementary Table S3*). Of note, subgroup analyses showed that patients with favorable or intermediate cytogenetic risk (classified according to the International System for Human Cytogenetic Nomenclature criteria[7]) at baseline had significantly longer EFS in the GO arm than in the control arm (HR: 0.46; 95%CI: 0.31-0.68; *P*<0.0001). This advantage in EFS with GO was not apparent for patients with poor cytogenetic risk (HR: 1.11; 95%CI: 0.63-1.95; *P*=0.72). Similarly, activity was more apparent with GO for patients in favorable/intermediate risk groups compared with poor risk group by National Comprehensive Cancer Network or European LeukemiaNet (ELN) risk classifications. Results of all the other subgroup analyses were consistent with the effect of GO on primary EFS (*Online Supplementary Figure S2*). In addition, the results of the blinded independent review support the primary EFS by investigator assessment, with a median EFS of 13.6 months (95%CI: 9.0-19.2) in the GO arm and 8.5 months (95%CI: 7.5-12.0) in the control arm (HR: 0.66; 95%CI: 0.49-0.89; *P*=0.006) (Table 1).

Table 1. Event-free survival (EFS) results (mITT population) by the investigator-assessed and blinded independent review methods.

	Investigator assessed		Blinded independent review	
	GO n=135	Control n=136	GO n=135	Control n=136
EFS				
Events, n (%)	73 (54.1)	102 (75.0)	78 (57.8)	100 (73.5)
Induction failure	17 (12.6)	29 (21.3)	25 (18.5)	34 (25.0)
Relapse	44 (32.6)	58 (42.6)	43 (31.9)	50 (36.8)
Death	12 (8.9)	15 (11.0)	10 (7.4)	16 (11.8)
Censored patients	62 (45.9)	34 (25.0)	57 (42.2)	36 (26.5)
Median time to event, months [95% CI]*	17.3 [13.4–30.0]	9.5 [8.1–12.0]	13.6 [9.0–19.2]	8.5 [7.5–12.0]
HR† [95% CI]	0.56 [0.42–0.76]		0.66 [0.49–0.89]	
P-value‡	0.0002		0.006	
Probability of being event-free [95% CI]§				
At 2 years	42.1 [32.9–51.0]	18.2 [11.1–26.7]	38.5 [29.6–47.3]	18.1 [11.1–26.5]
At 3 years	39.8 [30.2–49.3]	13.6 [5.8–24.8]	36.5 [27.3–45.7]	13.6 [5.8–24.7]

Control: 3+7 daunorubicin + cytarabine (DA); GO: gemtuzumab ozogamicin + 3+7 DA; HR: hazard ratio; mITT: modified intent to treat; n: number. *Median estimated by Kaplan-Meier method; Confidence Interval (CI) based on the Brookmeyer-Crowley method with log-log transformation. †Based on the Cox proportional hazards model. ‡Two-sided *P*-value from the log-rank test. §Estimated from Kaplan-Meier curve. Probability (%) calculated by the product-limit method; CI calculated from the log-log transformation of survival probability using a normal approximation and back transformation, and two-sided CIs for the estimates were computed using the Greenwood formula.

Table 2. Post-study treatment (mITT population).

	GO n=135	Control n=136
Patients with ≥1 follow-up therapy, n (%)	96 (71.1)	109 (80.1)
Patients receiving GO as a component of follow-up therapy, n (%)	2 (1.5)	30 (22.1)
Patients with HSCT, n (%)	32 (23.7)	53 (39.0)
Timing of HSCT, n (%)		
In first remission for responder patients	17 (12.6)	22 (16.2)
After induction failure	2 (1.5)	9 (6.6)
After relapse	13 (9.6)	22 (16.2)

Data are number (n) (%) unless otherwise indicated. Control: 3+7 daunorubicin + cytarabine (DA); GO: gemtuzumab ozogamicin + 3+7 DA; HSCT: hematopoietic stem cell transplant; mITT: modified intent to treat.

Of interest, it did not appear that low CD33 expression (<30% of blasts positive) had an influence on the EFS benefit with GO; however, few enrolled patients (13.7%) had low CD33 expression. Similarly, analysis using a Cox proportional hazards model incuding treatment and CD33 expression as a continuous variable did not show any effect of CD33 expression on EFS.

Relapse-free survival

Relapse-free survival (RFS) was significantly longer for patients in the GO arm compared with control (*Online Supplementary Figure S3*). Median RFS was 28.0 months (95%CI: 16.3-not estimable) in the GO arm and 11.4 months (95%CI: 10.0-14.4) in the control arm, corresponding to a 47% reduction in the risk of an event for patients in the GO arm compared with those in the control arm.

Post-study treatment

The majority of patients [96 (71.1%) in the GO arm and 109 (80.1%) in the control arm] (Table 2) received at least 1 subsequent therapy for AML following study treatment. Overall, 32 patients (23.7%) in the GO arm and 53 (39.0%) in the control arm received a hematopoietic stem cell transplant (HSCT) either in first remission or after induction failure or relapse. All transplants were allogeneic, except one autologous transplant in the control arm. This included 17 patients (12.6%) in the GO arm and 22 (16.2%) in the control arm who received HSCT in first remission. Additional analysis of OS censoring the patients at the time of transplant showed no impact on the OS results (P=0.240). The other patients received rescue therapy after either induction failure or relapse, including 30 patients (22.1%) in the chemotherapy arm who subsequently received GO as rescue therapy as part of a compassionate use program.

Safety

A summary of treatment-emergent AEs of special interest is shown in Table 3. Overall, 208 (77.6%) patients experienced a severe (grade ≥3) infection; the incidence was similar between arms [GO arm, 102 (77.9%); control arm, 106 (77.4%)]. Hemorrhage of any grade occurred in the majority of patients in both treatment arms [225 (84.0%)]; the rate was significantly higher (P=0.008) among patients in the GO arm [118 (90.1%)] than the control arm [107 (78.1%)]. Grade ≥3 hemorrhages were reported in 30 (22.9%) patients in the GO arm and 13 (9.5%) patients in the control arm. Six (4.6%) patients in the GO arm and 2 (1.5%) patients in the control arm experienced veno-occlusive disease (VOD; P=0.165) (Table 3

Table 3. Summary of all-causality adverse events of special interest by maximum CTCAE grade (as-treated population*).

Retrospective data, n (%)	GO (n=131)	Control (n=137)	Total (n=268)
Infections: severe (grade ≥3)	102 (77.9)	106 (77.4)	208 (77.6)
Hemorrhage: all grades (grade ≥1), total†	118 (90.1)	107 (78.1)	225 (84.0)
Grade 3	23 (17.6)	12 (8.8)	35 (13.1)
Grade 4	4 (3.1)	0	4 (1.5)
Grade 5	3 (2.3)	1 (0.7)	4 (1.5)
VOD: all grades (grade ≥1), total†	6 (4.6)	2 (1.5)	8 (3.0)
Grade 3	2 (1.5)	1 (0.7)	3 (1.1)
Grade 4	1 (0.8)	1 (0.7)	2 (0.7)
Grade 5	2 (1.5)	0	2 (0.7)

Control: 3+7 daunorubicin + cytarabine (D+A); CTCAE: Common Terminology Criteria for Adverse Events; GO: gemtuzumab ozogamicin plus D+A; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; VOD: veno-occlusive disease; n: number. *Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received. †Adverse events were graded in accordance with the NCI CTCAE v.3.0 and coded by MedDRA v.18.0.

Table 4. Summary of deaths (as-treated population*).

Deaths, n (%)	GO (n=131)	Control (n=137)
Deaths within 30 days of initiating study treatment	5 (3.8)	3 (2.2)
Deaths during safety reporting period†	6 (4.6)	5 (3.6)
Mechanism(s) of death‡		
Disease progression or relapse	2 (1.5)	2 (1.5)
Septic shock	2 (1.5)	2 (1.5)
Infection	0	1 (0.7)
Liver toxicity	1 (0.8)	0
Hemorrhage	3 (2.3)	1 (0.7)
Other	2 (1.5)	3 (2.2)

Control: daunorubicin + cytarabine (D+A); GO: gemtuzumab ozogamicin plus D+A; n: number. *Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received. †≤28 days after last dose of any study drug treatment. [GO: daunorubicin, cytarabine and idarubicin (a component of salvage therapy.)] ‡More than 1 mechanism of death could be selected.

and *Online Supplementary Table S4*); the 2 patients in the control arm received GO during the follow-up phase of the study, as part of the compassionate use program after having relapsed before developing VOD.

All-causality SAEs were reported for 164 (61.2%) patients, including 88 (67.2%) in the GO arm and 76 (55.5%) in the control arm (*Online Supplementary Table S5*). Among the most commonly reported SAEs were those related to infection: 54 (41.2%) patients in the GO arm and 52 (38.0%) in the control arm (*data not shown*).

The median number of intensive care unit hospitalizations was similar between the GO and control arms, affecting 25 patients in each arm; median time spent in the intensive care unit was 0.70 (range, 0.3-6.0) weeks and 0.60 (range, 0.1-7.6) weeks, respectively.

A total of 11 (4.1%) patients died during the period in which safety was reported; this included the time from the first dose to 28 days after the last dose of study treatment. The number of patient deaths was similar between treatment arms [GO arm, 6 (4.6%); control arm, 5 (3.6%)] (Table 4). The mechanisms of death were mostly similar between the 2 treatment arms, with the largest difference noted for patients for whom the mechanism of death involved hemorrhage [GO arm, 3 (2.3%); control arm, 1 (0.7%)].

Permanent discontinuation of GO and/or chemotherapy due to treatment-emergent AEs occurred in 41 (31.3%) patients in the GO arm and 10 (7.3%) in the control arm (*Online Supplementary Table S6*). The most common reasons for study drug discontinuation among the 131 patients in the GO arm were thrombocytopenia in 20 (15.3%) patients and hepatobiliary disorders in 8 (6.1%) patients; among the 137 patients in the control arm, no (0%) and 1 (0.7%) patient, respectively, discontinued for the same reasons. Of note, the protocol was amended to withhold GO to patients during consolidation for persisting thrombocytopenia below $100x10^9$/L not recovered ≥14 days after the scheduled date of consolidation therapy. Further investigations of the 20 patients in the GO arm who discontinued study drug because of persistent thrombocytopenia showed that no patients had SAE of hemorrhage reported.

While the majority of patients experienced severe myelosuppression, with similar rates in both treatment arms (*Online Supplementary Table S7*), the median time to recovery of platelets was longer for patients in the GO arm than in the control arm for each treatment course (Table 5). Additional analyses conducted to identify severe (grade 3 and 4) persistent thrombocytopenia (i.e. platelet count $<50x10^9$/L at 45 days after day 1 of the previous treatment phase in which a patient experienced CRp) showed that more patients had severe persistent thrombocytopenia in the GO arm (20.4%) than in the control arm (2.0%).

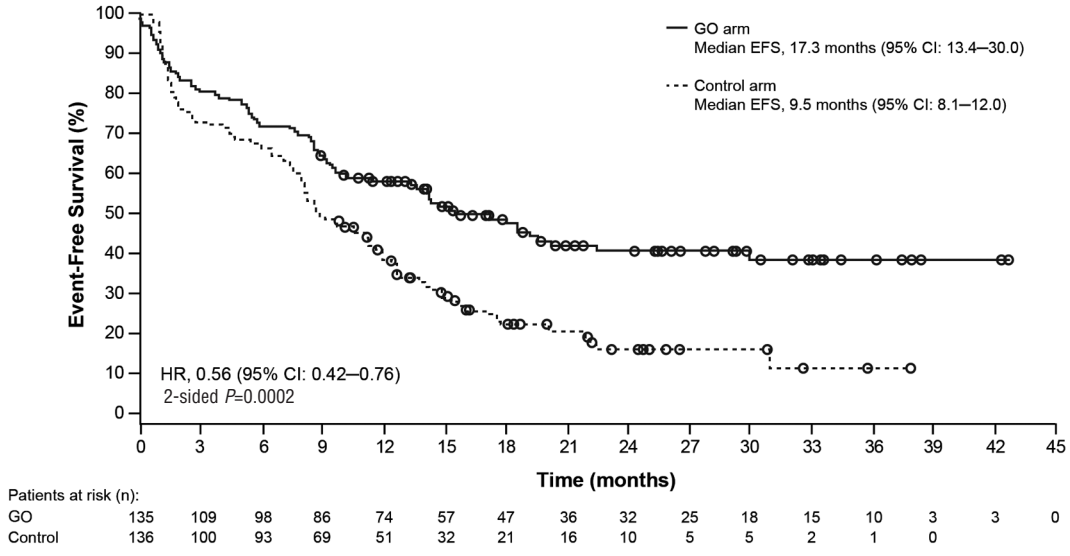

Figure 2. Event-free survival (EFS) (investigator-assessed). Control: daunorubicin + cytarabine (D+A); GO: gemtuzumab ozogamicin plus D+A; EFS: event-free survival; HR: hazard ratio; CI: Confidence Interval; n: number.

Non-hematologic laboratory test results revealed that liver chemistry abnormalities were generally similar between treatment arms, except that GO treatment was associated with more frequent elevations of aspartate aminotransferase than the control treatment (all grades: 89.2% and 73.9%; grade 3 / 4 : 14% and 9.0%, respectively) and more frequent elevations of alkaline phosphatase (all grades: 79.7% and 68.9%; grades 3 / 4: 13.3% and 5.3%, respectively) (*Online Supplementary Table S7*).

Discussion

A previously published analysis of the ALFA-0701 study was based on a cut-off date of August 1, 2011.[6] In this report, we present the final analysis of OS based on a cut-off date of April 30, 2013, and the results of a blinded, independent analysis of the primary end point, EFS.

The final results demonstrate a trend toward longer OS for patients in the GO arm than in the control arm, although this difference did not reach statistical significance. Nevertheless, the longer OS trend in the GO arm observed in ALFA-0701 is consistent with a significant improvement in OS demonstrated in an individual patient data meta-analysis (IPD-MA).[8] This IPD-MA consisted of 5 randomized studies comprising more than 3300 patients and included the ALFA-0701 study, in which GO was used in intensive induction chemotherapy in adult patients with newly diagnosed AML. In this IPD-MA, the primary end point of OS showed a significant improvement at five years for patients who received GO [Odds Ratio (OR): 0.90; 95%CI: 0.82-0.98; log-rank 2-sided *P*=0.01], corresponding to a 10% reduction in risk of death in the GO arm.[8] The OS benefit was the most apparent in patients with favorable (OR: 0.47; 95%CI: 0.31-0.73) and intermediate (OR: 0.84; 95%CI: 0.75-0.95) cytogenetic risk disease.[8] However, as mentioned in the most recent version of the ELN guidelines,[2] OS may not be the best indicator of the efficacy of a new drug because of confounding effects of allogeneic transplant or rescue therapies given after relapse or failure to reach CR. However, EFS, which includes failure to reach CR, relapse, or death due to any cause, including drug toxicity, may better reflect the efficacy of a single treatment. In the ALFA-0701 study, we reported that the majority of patients did receive post-study treatment, including allogeneic transplant and rescue therapy after induction failure or relapse. Of note, this includes 30 patients from the control arm who finally received GO as rescue therapy. Furthermore, in the ALFA-0701 study, the sample size was calculated to show a difference in EFS; thus, the relatively low number of patients in the study was probably not appropriate to show an OS benefit.

At the time of the final EFS analysis of ALFA-0701, the addition of GO to D+A approximately doubled the median EFS compared with chemotherapy alone, with a median EFS of 17.3 months for patients randomized to the GO arm and 9.5 months for patients in the chemotherapy-alone arm. Multiple sensitivity analyses demonstrated the robustness of the EFS results, and in this report, we established the reproducibility of the EFS end point in this trial *via* a blinded, independent review. A significant prolongation of EFS is considered by hematologists to contribute to the clinical benefit received by patients, as this translates into a durable first remission, increasing the probability of a patient being cured. The subgroup analyses of the effect of GO on EFS in ALFA-0701 generally supports the potential benefit with GO for patients with AML independently of the degree of CD33 positivity, although few enrolled patients (13.7%) had low CD33 expression (<30% of blasts positive). The effect of GO on EFS in ALFA-0701 is consistent with the positive effect of GO on RFS, as well as with the previously reported significant effect of GO on minimal residual disease assessed by NPM1 status.[9] This enhancement of the quality of the response and the prolongation of the response are the 2 factors that sustained the prolongation of EFS with GO.

In ALFA-0701, there was no difference in early mortal-

Table 5. Time to recovery of platelets and persistent thrombocytopenia (as-treated population*).

	GO			Control		
Patient with persistent thrombocytopenia†						
Overall, n‡/N (%)§‖	22/108 (20.4)			2/101 (2.0)		
By treatment phase	Induction	Consolidation		Induction	Consolidation	
	Course	Course 1	Course 2	Course	Course 1	Course 2
	8/108 (7.4)	8/94 (8.5)	10/76 (13.2)	1/101 (1.0)	0/94 (0)	2/85 (2.4)
Time to platelet recovery to 50x10⁹/L						
Patients recovered n‡/N (%)¶	109/131 (83.2)	92/97 (94.8)	80/82 (97.6)	118/137 (86.1)	86/97 (88.7)	85/89 (95.5)
Median recovery time,#[d]	34.0	32.0	36.5	29.0	27.0	30.0
Time to platelet recovery to 100x10⁹/L						
Patients recovered, n‡/N (%)¶	99/131 (75.6)	71/97 (73.2)	70/82 (85.4)	111/137 (81.0)	80/97 (82.5)	82/89 (92.1)
Median recovery time,#[d]	35.0	35.0	43.0	30.0	28.0	32.0

Control: daunorubicin + cytarabine (D+A); CRp: complete remission with incomplete platelet recovery; GO: gemtuzumab ozogamicin plus D+A. *Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received. †Persistent thrombocytopenia was defined as platelet count not recovered to 50x10⁹/L at 45 days after day 1 of the respective treatment phase in patients experiencing CRp. ‡n: number of patients with events. §Overall number of patients with persistent thrombocytopenia after any phase. ‖N: number of patients evaluable for thrombocytopenia was used as the denominator for calculating the percentage of patients with persistent thrombocytopenia. Patients evaluable for thrombocytopenia were those who received each of the courses and had platelet laboratory results collected during the retrospective data collection. N: number of patients who received each of the courses of treatment. #Based on Kaplan-Meier estimate.

ity rate between the 2 arms. The rationale for fractionated GO dosed at 3 mg/m² on days 1, 4, and 7, as used in ALFA-0701, is further supported by results of the IPD-MA, which showed less early mortality with the 3 mg/m² dose compared to 6 mg/m².[8] Furthermore, study NCRI AML17, in which a single dose of 6 mg/m² of GO was used in combination with induction chemotherapy, provided no advantage in response, disease-free survival, or OS compared with a 3-mg/m² dose; however, in this study, the 30- and 60-day mortality was significantly higher in the patients receiving 6 mg/m².[8,10]

Regarding AEs of special interest for GO, in the GO arm, there was no increase in either the incidence of severe infection or the percentage of patients who died of infection. Hemorrhage, VOD, and the number of patients who discontinued the study drug(s) because of AEs were increased with GO. The most frequent AE that led to permanent discontinuation of study drug in the GO arm (in 20 patients) was persistent thrombocytopenia, influenced in part by a protocol amendment recommending discontinuation of GO in case of persistent thrombocytopenia. Thus, physicians should be aware of thrombocytopenia associated with GO and provide supportive care as required. Similarly, physicians must be aware of the risk of VOD with GO, particularly the increased risk of VOD, either preceding or following HSCT, and closely monitor for clinical signs such as hepatomegaly, rapid weight gain, and ascites, elevations in alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase.

In conclusion, the final results of this study indicate that GO added to standard chemotherapy significantly prolongs EFS in patients with newly diagnosed *de novo* AML and has an acceptable safety profile. This combination may expand front-line treatment options for this difficult-to-treat patient population.

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