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

Juliette Lambert,[1] Cécile Pautas,[2] Christine Terré,[3] Emmanuel Raffoux,[4] Pascal Turlure,[5] Denis Caillot,[6] Ollivier Legrand,[7] Xavier Thomas,[8] Claude Gardin,[9] Karïn Gogat-Marchant,[10] Stephen D. Rubin,[11] Rebecca J. Benner,[12] Pierre Bousset,[13] Claude Preudhomme,[14] Sylvie Chevret,[15] Herve Dombret[16] and Sylvie Castaigne[17]

[1]Service d'Hématologie et Oncologie, Centre Hospitalier de Versailles, Le Chesnay, France; [2]Service d'Hématologie et de Thérapie Cellulaire, Hôpital Henri Mondor, Créteil, France; [3]Laboratoire de Cytogénétique, Centre Hospitalier de Versailles, France; [4]Hôpital Saint-Louis (AP-HP), Université Paris Diderot, France; [5]Service d'Hématologie Clinique et Thérapie Cellulaire, Centre Hospitalier Universitaire, Limoges, France; [6]Hematologie Clinique, Hôpital François Mitterrand, Centre Hospitalier Universitaire, Dijon, France; [7]Hôpital Saint-Antoine (AP-HP), Université Paris Pierre et Marie Curie, France; [8]Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Université Lyon 1, Pierre Benite, France; [9]Hôpital Avicenne (AP-HP), Université Paris 13, Bobigny, France; [10]Global Clinical Development Pfizer Inc., Paris, France; [11]Global Product Development, Pfizer Inc., Collegeville, PA, USA; [12]Global Product Development, Pfizer Inc., Groton, CT, USA; [13]Pfizer Oncology, Pfizer Inc., Paris, France; [14]Université Lille, INSERM, Centre Hospitalier Universitaire Lille, UMR-S 1172 - Jean-Pierre Aubert Center - Centre de Recherche, Lille, France; [15]Departement de Biostatistique, Hôpital Saint-Louis (AP-HP), Universite Paris Diderot, INSERM S 717, France; [16]Hopital Saint-Louis (AP-HP), Universite Paris Diderot, France and [17]Service d'Hématologie et Oncologie, Centre Hospitalier de Versailles, Université de Versailles Saint Quentin, Le Chesnay, France

 doi:10.3324/haematol.2018.188888

Received: January 17, 2018.

Accepted: July 25, 2018.

Pre-published: August 3, 2018.

Correspondence: scastaigne@ch-versailles.fr

Supplemental Materials

Gemtuzumab ozogamicin for de novo acute myeloid leukemia: final efficacy and safety updates from the open-label, phase 3 ALFA-0701 trial

Juliette Lambert,[1] Cécile Pautas,[2] Christine Terré,[3] Emmanuel Raffoux,[4] Pascal Turlure,[5] Denis Caillot,[6] Ollivier Legrand,[7] Xavier Thomas,[8] Claude Gardin,[9] Karïn Gogat-Marchant,[10] Stephen D. Rubin,[11] Rebecca J. Benner,[12] Pierre Bousset,[13] Claude Preudhomme,[14] Sylvie Chevret,[15] Herve Dombret,[16] and Sylvie Castaigne[17]

[1]Service d'Hématologie et Oncologie, Centre Hospitalier de Versailles, Le Chesnay, France
[2]Service d' Hématologie et de thérapie cellulaire, Hôpital Henri Mondor, Créteil, France
[3]Laboratoire de Cytogénétique, Centre Hospitalier de Versailles, Le Chesnay, France
[4]Hôpital Saint-Louis (AP-HP), Université Paris Diderot, Paris, France
[5]Service d'hématologie clinique et thérapie cellulaire, Centre Hospitalier Universitaire, Limoges, France
[6]Hematologie Clinique, Hôpital François Mitterrand, Centre Hospitalier Universitaire, Dijon, France
[7]Hôpital Saint-Antoine (AP-HP), Université Paris Pierre et Marie Curie, Paris, France
[8]Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Université Lyon 1, Pierre Benite, France
[9]Hôpital Avicenne (AP-HP), Université Paris 13, Bobigny, France
[10]Global Clinical Development Pfizer Inc, Paris, France
[11]Global Product Development, Pfizer Inc, Collegeville, PA, USA
[12]Global Product Development, Pfizer Inc, Groton, CT, USA
[13]Pfizer Oncology, Pfizer Inc, Paris, France
[14]Université Lille, INSERM, Centre Hospitalier Universitaire Lille, UMR-S 1172 - Jean-Pierre Aubert Center - Centre de Recherche, Lille, France
[15]Departement de Biostatistique, Hôpital Saint-Louis (AP-HP), Universite Paris Diderot, INSERM S 717, Paris, France
[16]Hopital Saint-Louis (AP-HP), Universite Paris Diderot, Paris, France
[17]Service d'Hématologie et Oncologie, Centre Hospitalier de Versailles, Université de Versailles Saint Quentin, Le Chesnay, France

METHODS

This randomized, open-label, multicenter, phase 3 ALFA-0701 study was conducted in 26 hematology centers in France (ClinicalTrials.gov, NCT00927498). The study design and selection criteria have been previously described in detail.[1] Briefly, eligible patients were aged 50 to 70 years with previously untreated de novo acute myeloid leukemia (AML), Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 3, and cardiac function within normal limits.

Following publication of study results based on the cutoff date of August 1, 2011, the Centre Hospitalier de Versailles (CHV), in collaboration with Pfizer, performed a retrospective collection of additional data to provide a more complete assessment of the safety profile of gemtuzumab ozogamicin (GO) and to conduct a retrospective, independent, blinded review of the primary efficacy endpoint.

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 35 mg/m^2/d on days 1 and 2 and AraC 1 g/m^2/12 hours on days 1 to 3, was given if leukemic blasts persisted at the day 15 bone marrow aspirate (BMA). Alternatively, salvage therapy with idarubicin 12 mg/m^2 on days 1 and 2 and AraC 1 g/m^2 twice daily on days 1 to 4 could be administered to patients who did not achieve a complete remission (CR) after induction. Patients with a CR or CR after induction treatment with incomplete platelet recovery after induction treatment received 2 courses of consolidation, including DNR 60 mg/m^2 first on day 1 (and on day 2 during the second consolidation course)and AraC 1 g/m^2/12 hours on days 1 to 4 with or without GO 3 mg/m^2/d infusion over 2 hours on day 1 according to their randomization, provided the platelet count was $\geq$50,000/mm^3 on the planned day 1 of the first or second consolidation course.

Patients who experienced CR could be considered for allogeneic transplant according to ECOG PS, age, existence or not of a donor, and cytogenetic and molecular risk categories. An interval of 2 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 Number: 2007-002933-36).

Efficacy Analyses

This report presents (1) final results of the secondary endpoint of overall survival, defined as the time from date of randomization to date of death from any cause at the cutoff date of April 30, 2013, (2) results of a blinded and independent review of the event-free survival endpoint by hematology experts, performed to study the reproducibility of this clinically important endpoint in AML trials, (3) results of the secondary endpoint relapse-free survival for patients experiencing a response, and (4) hematologic response by investigator assessment. The event-free survival endpoint was defined as the time from randomization to relapse, death from any cause, or failure to achieve CR or CR with incomplete platelet recovery. 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 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.

All AEs were collected from screening up to 28 days after the last dose of study drug in each treatment arm, except for VOD events, which were collected until the patient's death or the retrospective data collection cutoff on November 1, 2013 (whichever occurred first) in order to identify any late study drug toxicity associated with VOD. Hematologic laboratory results were collected from screening until death or 28 days after either induction failure or relapse (whichever came first); all available biochemistry and coagulation results were collected and included from screening until up to 28 days after the last dose of study drug. Infections refer to infections and

infestations as defined for system organ class. Coded Medical Dictionary for Regulatory Activities (MedDRA v18.0) preferred terms were used for AEs and serious AEs (SAEs) indicating hemorrhage (standardized MedDRA queries for hemorrhage [excluding laboratory results] [narrow]) and VOD (includes the preferred term of veno-occlusive liver disease and veno-occlusive disease) were clustered. SAE 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 were reported previously.[6] The modified intent-to-treat (mITT) population was the primary population for evaluating efficacy endpoints. The mITT population included all patients who were randomized, unless consent was withdrawn before the start of treatment. Analyses were according to the initial randomization arm, regardless of whether patients received the study drug to which they were randomized. Time-to-event endpoints were summarized using the Kaplan-Meier method. Two-sided 95% CIs for median time to event were estimated using the Brookmeyer-Crowley method with log-log transformation. The log-rank test was used for the primary analysis. Hazard ratios (HRs) and the associated 2-sided 95% CIs were estimated using the Cox proportional hazards model. Subgroup efficacy analyses were conducted for the following covariates: age, ECOG PS, National Comprehensive Cancer Network and European LeukemiaNet risk classification, cytogenetics and genotype as classified by CHV, nucleophosmin-1 gene, internal tandem duplication of the FMS-like tyrosine kinase 3 gene, Wilms' tumor suppressor gene status, and percentage of leukemic blasts that were CD33-positive (using 30% and 70% cutoffs). The HRs, 95% CIs from the unstratified Cox model, and *p* values from the log-rank test are provided.

Safety analyses were based on the as-treated population, defined as all patients who received at least 1 dose of study medication. In the case of treatment misallocations, patients in the as-treated population were reported according to whether they received GO or not.

REFERENCE

1. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012;379(9825):1508-1516.

SUPPLEMENTAL TABLES

Table S1. Baseline Patient Characteristics (mITT Population)

	GO (n=135)	Control (n=136)	Total (N=271)
Age, y			
Median (range)	62 (50–70)	61 (50-70)	62 (50–70)
≥60, n (%)	97 (71.9)	84 (61.8)	181 (66.8)
Men, n (%)	74 (54.8)	60 (44.1)	134 (49.4)
ECOG performance status, n (%)			
0–1	121 (89.6)	117 (86.0)	238 (87.8)
≥2	14 (10.4)	18 (13.2)	32 (11.8)
Not available	0	1 (0.7)	1 (0.4)
White blood cell count ($x10^9$/L) categories, n (%)			
<30	108 (80.0)	114 (83.8)	222 (81.9)
≥30	26 (19.3)	21 (15.4)	47 (17.3)
CD33 expression (positivity)			
N	100	94	194
<30%, n (%)	17 (12.6)	20 (14.7)	37 (13.7)
≥30%, n (%)	83 (61.5)	74 (54.4)	157 (57.9)
<70%, n (%)	37 (27.4)	31 (22.8)	68 (25.1)
≥70%, n (%)	63 (46.7)	63 (46.3)	126 (46.5)
Cytogenetics, n (%)*			
Favorable	3 (2.2)	6 (4.4)	9 (3.3)
Intermediate	91 (67.4)	89 (65.4)	180 (66.4)
Unfavorable	27 (20.0)	30 (22.1)	57 (21.0)
Not available	14 (10.4)	11 (8.1)	25 (9.2)
Genotype*			
Favorable risk	27 (20.0)	24 (17.6)	51 (18.8)
Unfavorable risk	44 (32.6)	40 (29.4)	84 (31.0)
Not available	64 (47.4)	72 (52.9)	136 (50.2)

Control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; ECOG, Eastern Cooperative Oncology Group; mITT, modified intent to treat; GO, gemtuzumab ozogamicin plus D+A.

*As classified by Centre Hospitalier de Versailles.

Table S2. Response Rate by Investigator Assessment (mITT Population)

	GO (n=135)	Control (n=136)	*P* Value*
Overall response, n (%)	110 (81.5)	100 (73.5)	
95% CI	73.9–87.6	65.3–80.7	0.15
CR, n (%)	95 (70.4)	95 (69.9)	
CRp, n (%)	15 (11.1)	5 (3.7)	

Control, daunorubicin + cytarabine; CR, complete remission; CRp, complete remission with incomplete platelet recovery; D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A; mITT, modified intent to treat.

*Fisher's exact test.

Table S3. EFS Sensitivity Analyses (mITT Population)

Endpoint by Method Cutoff Date, Censoring	GO vs Control		
	Hazard Ratio*	**95% CI**	***P* Value**[†]
EFS by investigator assessment			
August 1, 2011	0.56	[0.42–0.76]	0.0002
April 30, 2013	0.64	[0.48–0.84]	0.001
August 1, 2011, SCT censored	0.59	[0.43–0.81]	0.001
EFS by blinded independent review			
August 1, 2011	0.66	[0.49–0.89]	0.006
April 30, 2013	0.71	[0.54–0.93]	0.012
August 1, 2011, SCT censored	0.71	[0.52–0.96]	0.026

Control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; EFS, event-free survival; mITT, modified intent to treat; GO, gemtuzumab ozogamicin plus D+A; SCT, stem cell transplant.

*Based on the Cox proportional hazards model.

[†]2-sided *p* value from the log-rank test.

Table S4. Summary of VOD Events in Patients (As-Treated Population*)

Grade	Treatment Phase (Time After Last GO Dose)	Rechallenge	Prior HSCT	Outcome
GO Patients				
Grade 5	Induction (7 days)	No	No	Fatal
Grade 5	Consolidation (1 day)	No	No	Fatal
Grade 4	Follow-up (301 days)	No	Yes[†]	Not recovered
Grade 3	Induction (10 days)	No	No	Recovered
Grade 3[‡]	Induction (10 days)	No	No	Recovered
Grade 3[‡]	Follow-up (9 months)	No	Yes	Recovered
Grade 2	Induction (4 weeks)	Yes	No	Recovered
Control Patients[§]				
Grade 4	Follow-up (49 days)	No	No	Recovered
Grade 3	Follow-up (75 days)	No	Yes	Recovered

Control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A; HSCT, hematopoietic stem cell transplant; VOD, veno-occlusive disease.

*Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received.

[†]VOD developed while the patient was on the conditioning regimen for HSCT (ie, before the HSCT was completed).

[‡]This patient had 2 events of VOD.

[§]These patients received GO as salvage therapy as part of the compassionate use program.

Table S5. Summary of Treatment-Emergent SAEs Occurring in ≥2% of Patients (As-Treated Population*)

Preferred Term,† n (%)	GO n=131	Control n=137
Any SAE	88 (67.2)	76 (55.5)
Thrombocytopenia	34 (26.0)	6(4.4)
Bronchopulmonary aspergillosis	14 (10.7)	10 (7.3)
Septic shock	12 (9.2)	9 (6.6)
Febrile bone marrow aplasia	12 (9.2)	8 (5.8)
Bacterial sepsis	7 (5.3)	0
Acute kidney injury	6 (4.6)	4 (2.9)
Pneumonia	5 (3.8)	6 (4.4)
Sepsis	5 (3.8)	4 (2.9)
Acute respiratory distress syndrome	5 (3.8)	3 (2.2)
Escherichia sepsis	5 (3.8)	1 (0.7)
Veno-occlusive liver disease	5 (3.8)	0
Acute myeloid leukemia	5 (3.8)	0
Hepatocellular injury	4 (3.1)	2 (1.5)
Cholestatic liver injury	3 (2.3)	2 (1.5)
Febrile neutropenia	3 (2.3)	1 (0.7)
Mucosal inflammation	3 (2.3)	1 (0.7)
Disease progression	3 (2.3)	0
Enterococcal sepsis	3 (2.3)	0
Staphylococcal sepsis	2 (1.5)	5 (3.6)
Toxic skin eruption	1 (0.8)	3 (2.2)

Control, daunorubicin + cytarabine (D+A); GO, gemtuzumab ozogamicin plus D+A; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event.

*Defined as all patients who received at least 1 dose of study medication reported according to whether or not GO was received.

†MedDRA v18.0 applied.

Table S6. TEAEs Leading to Permanent Discontinuation of Study Drug* (As-Treated Population†)

Preferred Term,‡ n (%)	GO (n=131)	Control (n=137)
Permanent drug discontinuation in patients with AEs	41 (31.3)	10 (7.3)
Thrombocytopenia	20 (15.3)	0
Veno-occlusive liver disease	4 (3.1)	0
Septic shock	3 (2.3)	2 (1.5)
Hepatocellular injury	1 (0.8)	1 (0.7)
Acute coronary syndrome	1 (0.8)	0
Acute kidney injury	1 (0.8)	0
Cerebral hematoma	1 (0.8)	0
Death	1 (0.8)	0
Ejection fraction	1 (0.8)	0
Hepatic cirrhosis	1 (0.8)	0
Hepatitis cholestatic	1 (0.8)	0
Hepatotoxicity	1 (0.8)	0
Intracranial hematoma	1 (0.8)	0
Liver function test abnormal	1 (0.8)	0
Neuropathy peripheral	1 (0.8)	0
Subdural hematoma	1 (0.8)	0
Ventricular hypokinesia	1 (0.8)	0
Acute respiratory distress syndrome	0	1 (0.7)
Cerebral hemorrhage	0	1 (0.7)
Cerebrovascular accident	0	1 (0.7)
Ejection fraction decreased	0	1 (0.7)
Gastrointestinal hemorrhage	0	1 (0.7)
Left ventricular failure	0	1 (0.7)
Oxygen saturation decreased	0	1 (0.7)

AE, adverse event; control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.

*Permanent discontinuation of GO and/or chemotherapy.

†Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received.

‡MedDRA v18.0 applied.

Table S7. Clinically Relevant Laboratory Abnormalities (As-Treated Population*)

Laboratory Abnormality	GO			Control		
	n	All Grades, %	Grade 3/4, %	n	All Grades, %	Grade 3/4, %
Hematologic						
Hemoglobin decreased	130	100	86.2	136	100	89.7
Lymphocytes (absolute) decreased	129	98.5	90.7	135	97.8	89.6
Neutrophils decreased	129	97.7	96.1	135	98.5	97.0
Platelets decreased	131	100	100	136	100	100
WBC count decreased	131	100	100	136	99.3	99.3
Nonhematologic						
ALT increased	129	78.3	10.9	134	81.3	15.7
ALP increased	128	79.7	13.3	132	68.9	5.3
AST increased	129	89.2	14.0	134	73.9	9.0
Blood bilirubin increased	126	51.6	7.1	132	50.8	3.8
Hyperglycemia	125	92.0	19.2	135	91.1	17.8
Hyperuricemia	117	32.5	2.6	123	28.5	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; control, daunorubicin + cytarabine; D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A; WBC, white blood cell.

*Defined as all patients who received at least 1 dose of study medication and reported according to whether or not GO was received.

SUPPLEMENTAL FIGURES

Figure S1. CONSORT diagram

Patients in the control arm were administered standard 3+7 D+A induction chemotherapy. In the GO arm, patients were administered GO via a 3 × 3 mg/m^2 (not exceeding one 5-mg vial per dose) fractionated dosing regimen plus standard D+A chemotherapy. Patients randomized to the GO arm received 1 additional dose of GO 3 mg/m² in each of 2 consolidation courses of D+A.

D+A, daunorubicin + cytarabine; GO, gemtuzumab ozogamicin plus D+A.

*Noted at the time of data transfer (April 30, 2013).
†3 patients not treated (GO arm, n=1; control arm, n=2); reasons were death or eligibility violation because of esophageal cancer or hepatitis B.
‡Reasons for not receiving GO during induction were either abnormal liver function, eligibility criteria not met, or death.

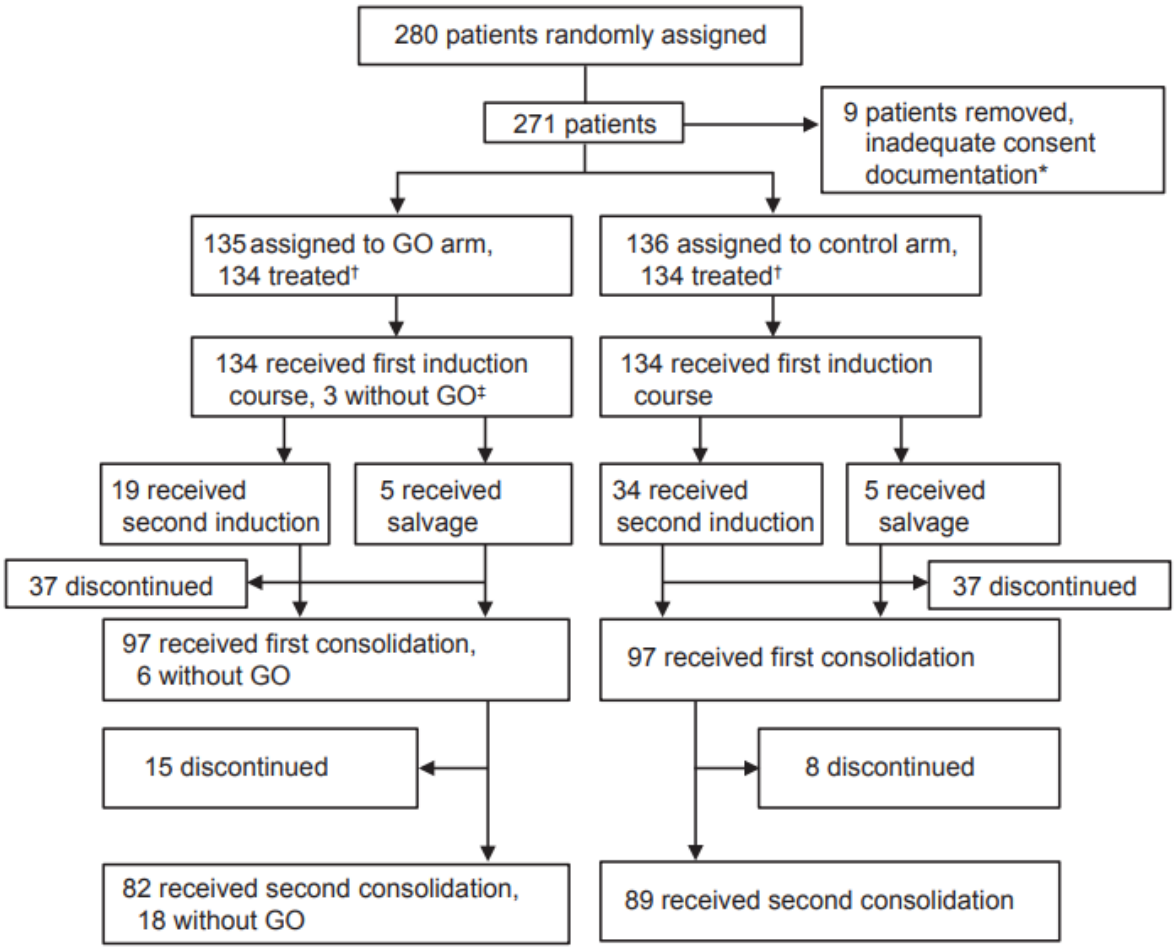
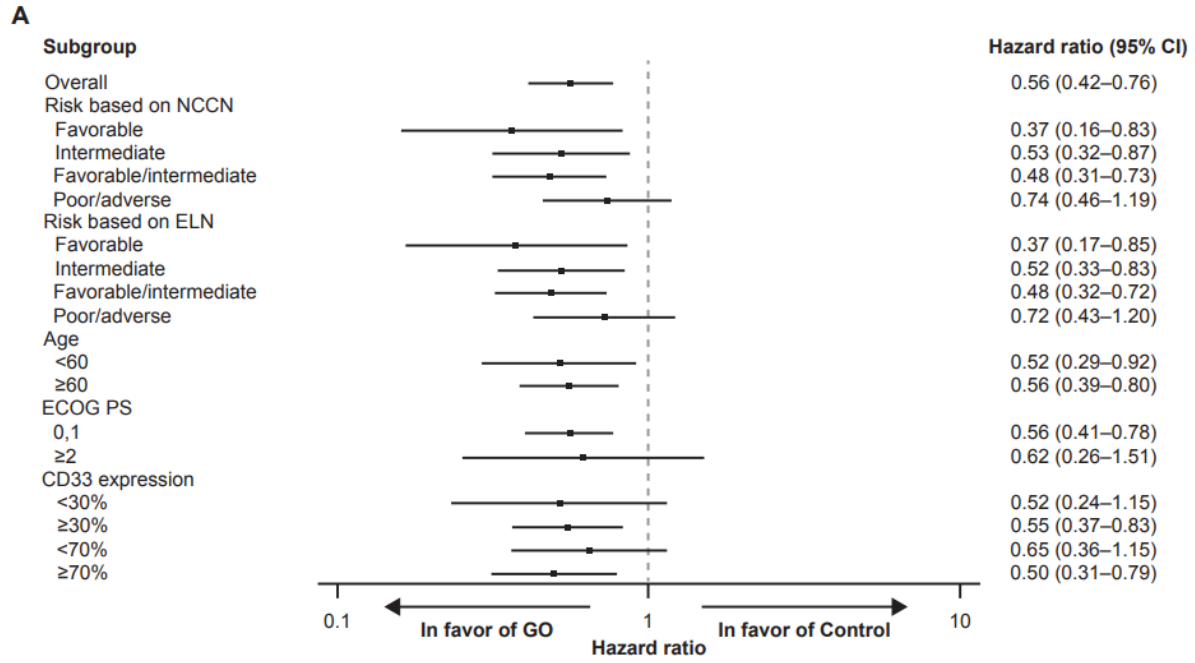


Figure S2. EFS subgroup analyses (A) and (B) – by investigator assessment at August 1, 2011, cutoff (mITT population)

The analyses are based on the Cox proportional hazards model. An HR <1 favors the GO arm (receiving GO plus D+A), whereas an HR >1 favors the control arm (receiving D+A alone).

D+A, daunorubicin + cytarabine; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ELN, European LeukemiaNet; *FLT3*-ITD, internal tandem duplication of the FMS-like tyrosine kinase 3 gene; GO, gemtuzumab ozogamicin plus D+A; HR, hazard ratio; mITT, modified intent to treat; NCCN, National Comprehensive Cancer Network; *NPM1,* nucleophosmin-1 gene; *WT1*, Wilms' tumor suppressor gene.



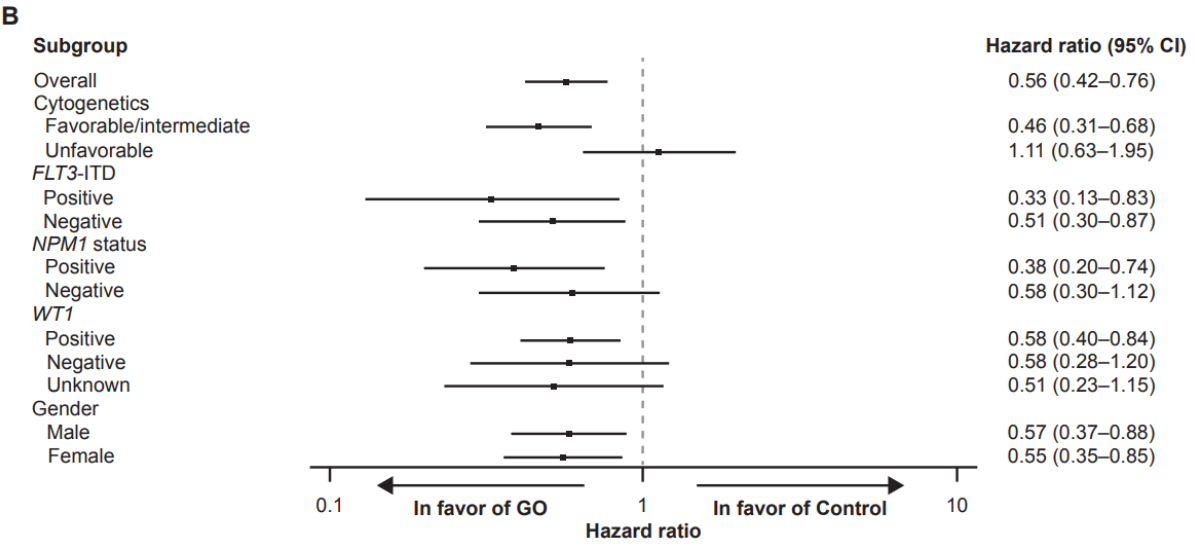


Figure S3. Relapse-free survival

Control, daunorubicin + cytarabine (D+A); GO, gemtuzumab ozogamicin plus D+A; NE, not estimable; RFS, relapse-free survival.