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ORIGINAL REPORT

Gemtuzumab Ozogamicin in Children and Adolescents With De Novo Acute Myeloid Leukemia Improves Event-Free Survival by Reducing Relapse Risk: Results From the Randomized Phase III Children's Oncology Group Trial AAML0531

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ABSTRACT

Purpose
To improve survival rates in children with acute myeloid leukemia (AML), we evaluated gemtuzumab-ozogamicin (GO), a humanized immunoconjugate targeted against CD33, as an alternative to further chemotherapy dose escalation. Our primary objective was to determine whether adding GO to standard chemotherapy improved event-free survival (EFS) and overall survival (OS) in children with newly diagnosed AML. Our secondary objectives examined outcomes by risk group and method of intensification.

Patients and Methods
Children, adolescents, and young adults ages 0 to 29 years with newly diagnosed AML were enrolled onto Children's Oncology Group trial AAML0531 and then were randomly assigned to either standard five-course chemotherapy alone or to the same chemotherapy with two doses of GO (3 mg/m^2/dose) administered once in induction course 1 and once in intensification course 2 (two of three).

Results
There were 1,022 evaluable patients enrolled. GO significantly improved EFS (3 years: 53.1% *v* 46.9%; hazard ratio [HzR], 0.83; 95% CI, 0.70 to 0.99; $P = .04$) but not OS (3 years: 69.4% *v* 65.4%; HzR, 0.91; 95% CI, 0.74 to 1.13; $P = .39$). Although remission was not improved (88% *v* 85%; $P = .15$), posthoc analyses found relapse risk (RR) was significantly reduced among GO recipients overall (3 years: 32.8% *v* 41.3%; HzR, 0.73; 95% CI, 0.58 to 0.91; $P = .006$). Despite an increased postremission toxic mortality (3 years: 6.6% *v* 4.1%; HzR, 1.69; 95% CI, 0.93 to 3.08; $P = .09$), disease-free survival was better among GO recipients (3 years: 60.6% *v* 54.7%; HzR, 0.82; 95% CI, 0.67 to 1.02; $P = .07$).

Conclusion
GO added to chemotherapy improved EFS through a reduction in RR for children and adolescents with AML.

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INTRODUCTION

Acute myeloid leukemia (AML) is among the most difficult to treat of the childhood cancers because of its disease heterogeneity, high relapse, and toxic mortality.[1,2] Therapeutic advances have included chemotherapy intensification and adding allogeneic stem-cell transplantation (SCT). Children's Oncology Group (COG) legacy AML trials evaluated time-intensive induction and observed improvement in event-free survival rates (EFS) from 27% to 42%.[3,4] Matched family-donor (MFD) transplantation improved disease-free survival rates (DFS) by between 8% and 10% and postremission overall survival (OS) by between 5% and 13% in two previous phase III trials.[4,5] However, treatment-related mortality (TRM) increased substantially with therapy intensification. Supportive care improvements reduced TRM (from 19% to 12%).[4] However, it is increasingly evident that the limits of treatment intensification have been reached,[4,6,7] necessitating alternative approaches.

The cell-surface antigen, CD33, is present in more than 80% of patients with AML but is absent from pluripotent hematopoietic stem cells and is a well established immunoconjugate target.[8,9] Early studies with gemtuzumab-ozogamicin (GO), a humanized anti-CD33 antibody linked to the DNA-binding cytotoxin calicheamicin, showed single-agent activity in refractory pediatric and adult patients with AML (28% to 30% overall response).[10-13] Phase II regimens demonstrated safety and efficacy in combination with chemotherapy.[14-17] Single-agent efficacy resulted in GO's accelerated approval in 2000 by the US Food and Drug Administration[14,18] which mandated a subsequent randomized controlled trial. This trial was the Southwest Oncology Group's trial (SWOG) S0106, and its primary end points of remission induction and safety failed to improve with GO,[19] and in 2010 GO was voluntarily withdrawn. Based on study design and control group outcomes, these results have been controversial,[20] particularly with concurrent adult randomized controlled trials showing reduced relapse with GO in low-risk (LR) and intermediate-risk (IR) subsets of AML patients.[21,22]

Concurrently performed, our trial's primary objective was to determine whether GO added to standard chemotherapy improved EFS and OS in children with newly diagnosed AML. Our secondary objectives examined outcomes by risk group and method of intensification.

PATIENTS AND METHODS

Between August 2006 and June 2010, COG trial AAML0531 enrolled 1,070 patients, ages 1 month to 29.99 years, who had previously untreated primary AML.[23] Data were entered through the COG Web portal by each enrolling institution, and were frozen March 31, 2013, with a median follow-up period of 4.1 years (range, 0 to 7.1 years) for patients alive at last contact. After six patients with Down syndrome 42 patients who failed to meet eligibility criteria were excluded, 1,022 patients were eligible for analysis (Fig 1). No minimal performance status was required. Exclusion criteria included prior chemotherapy (except intrathecal cytarabine), acute promyelocytic leukemia [t(15;17)], juvenile myelomonocytic leukemia, bone marrow failure syndromes, or secondary AML. Pathologic (84%) and cytogenetic findings (96%) were centrally reviewed. The National Cancer Institute's central institutional review board and institutional review boards at each enrolling center (n = 181) approved the study; patients and their families provided informed consent or assent as appropriate. The trial was conducted in accordance with the Declaration of Helsinki. The trial was registered at www.clinicaltrials.gov as NCT00372593.

Patients were randomly assigned once at enrollment. They were assigned to one of two study arms (511 patients in each arm): standard therapy alone (No-GO) or with GO (each dose 3 mg/m^2) administered once on day 6 of induction course 1 (IND1) and once on day 7 of intensification course 2 (INT2; Table 1). Chemotherapy cytoreduction preceded GO administration to maximize CD33 target saturation,[24,25] rather than administering higher GO doses. Concurrent anthracycline administration was avoided to minimize additive hepatotoxicity risk. Risk stratification of both arms determined allocation to SCT based on diagnostic molecular/cytogenetic risk criteria and disease response after IND1 as follows.

LR was defined by the presence of t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22). LR patients were not allocated to SCT. High risk (HR) was defined by presence of monosomy 7, monosomy 5/5q deletion, or persistent disease (PD) at the end of IND1 (bone marrow blasts > 15% by morphology). After 374 eligible patients were enrolled onto the study, *FLT-3* internal tandem duplication high allelic ratio (> 0.4; FLT3-ITD HAR) was added to the HR group assignment.[26] Cytogenetics outweighed response in risk classification, whereas *FLT3*-ITD HAR outweighed favorable cytogenetics.[27,28] All HR patients received best allogeneic SCT (nonsyngeneic MFD or unrelated) after INT1 (delays in donor availability resulted in SCT given after INT2 [n = 6] or INT3 [n = 1]). Choice of alternative donors were at the transplantation center's discretion and included matched or 1-antigen mismatched unrelated donors, 4-to-6 antigen matched cord blood, or mismatched family donor with at least one haplotype match or 5-of-6 antigen phenotypic match. HR patients without donors continued with assigned chemotherapy. IR was defined by the absence of low- or high-risk factors, and they only received an MFD SCT if available. Patients allocated to SCT underwent this after INT1. Consequently, those patients randomly assigned to GO only received one dose during IND1 (n = 157).

Response classification was based on morphologic examination of bone marrow blasts: complete remission (CR) had fewer than 5%, partial remission 5% to 15%, and PD more than 15%. Patients with refractory disease (RD) were removed from protocol therapy. Refractory disease was defined as the presence of CNS disease after IND1, or bone marrow blasts ≥ 5%, or any extramedullary disease at the end of IND2.

Blocked randomization with blocks of size 4 that were concealed from enrolling centers was used for treatment arm assignment. The COG Data and Statistical Center assigned patients to the treatment arms, after they were enrolled by the patient's institution through an automated Web portal. The study had a goal to enroll 1,000 eligible patients who did not have Down syndrome and was designed to have 80% power with one-sided 2.5% type I error to detect a 9% improvement in long-term EFS (54% *v* 45%) and long-term OS (59% *v* 50%) between the two study arms. The study was monitored by a data safety monitoring committee. The alpha-spending function αt^2 (truncated at three standard deviations) and 2.5% type I error was used to monitor OS and EFS while futility monitoring was performed by testing the alternative hypothesis at the .005 level.

The primary end points were OS and EFS from study entry. OS was defined as time from study entry, and from end of IND2 for patients in CR, until death. EFS was defined as the time from study entry until death, induction failure, or relapse of any type. The secondary end points were remission rates, relapse risk (RR), postinduction DFS, EFS and OS censoring SCT patients, TRM, and OS and EFS by risk group. RR was defined as the time from the end of IND2 for patients in CR to relapse, where deaths without a relapse were considered competing events. DFS was defined as the time from end of IND2 for patients in CR until relapse or death. TRM was defined as the time from either study entry, or from end of IND2 for patients in CR, to deaths without a relapse with relapses considered as competing events. Patients lost to follow-up were censored at their date of last known contact.

The significance of observed difference in proportions was tested using the χ^2 test and Fisher's exact test when data were sparse. The Kruskal-Wallis test was used to determine the significance between differences in medians of groups. The life-table estimates of OS, EFS, and DFS were calculated using the Kaplan-Meier procedure along with corresponding Greenwood SEs.[29]

The significance of predictor variables was tested with the log-rank statistic for OS, EFS, DFS and with Gray's statistic for RR and TRM.[30] Cox proportional hazards models were used to estimate hazard ratios (HzR) for univariable and multivariable analyses of OS, EFS, and DFS.[31] Competing risk regression models were used to estimate the subgroup HzR for univariable and multivariable analyses of RR and TRM.[32] All *P* values are two-sided.

RESULTS

Demographic Characteristics

Random assignment resulted in balanced study arms, except *FLT3*-ITD HAR was more prevalent ($P = .09$) and HR cytogenetics was less prevalent ($P = .03$) in GO recipients (Table 2). Risk-group assignment was similar between arms. Overall, 65% of patients completed all courses of therapy (Fig 1), with no significant difference between arms (Appendix Table A2 [online-only]). The trial remained open until accrual goals were met.

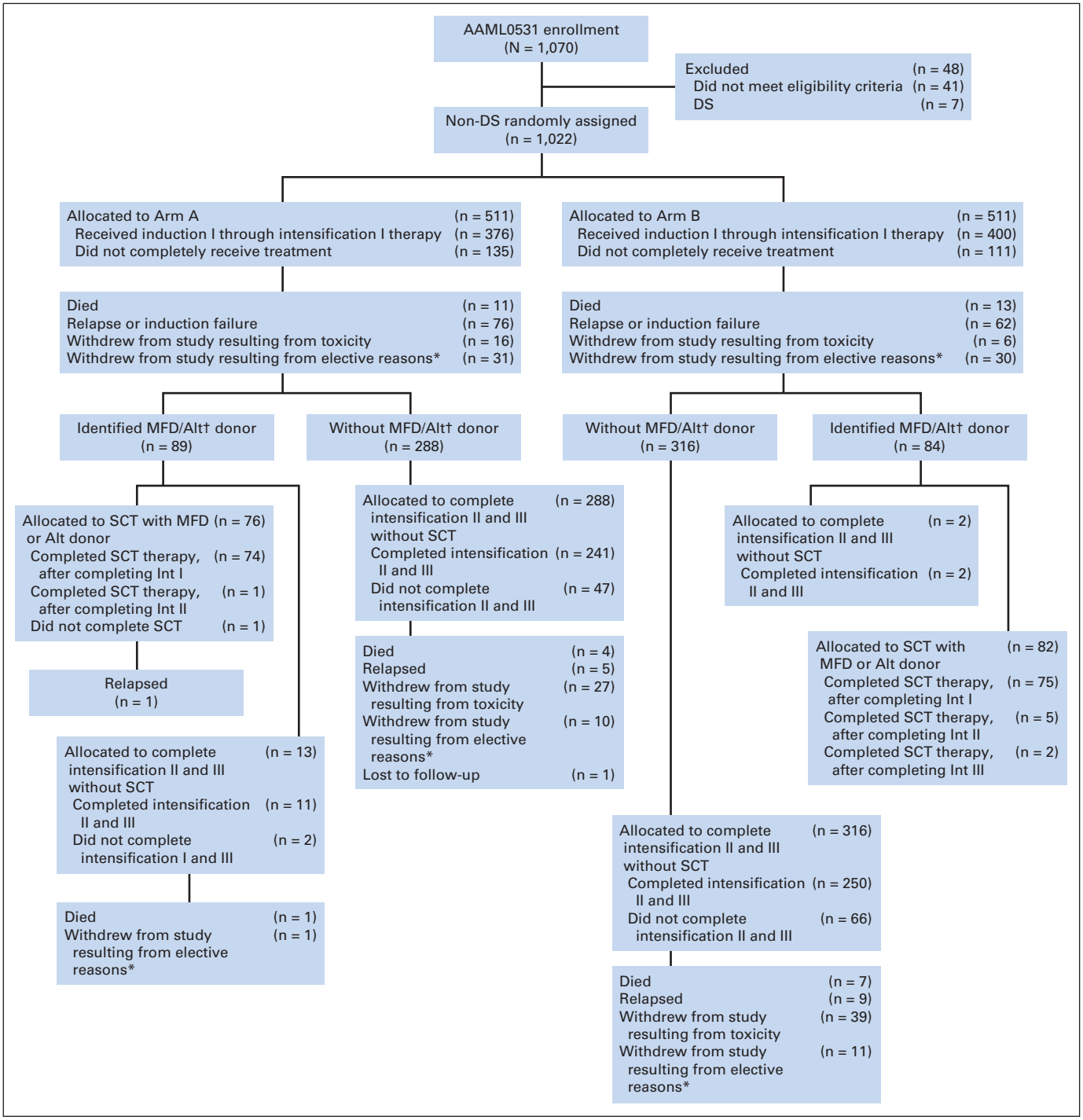

Fig 1. CONSORT diagram. (*) Elective reasons included terminating therapy because of physician's choice or patient's refusal of further protocol therapy. (†) Donor availability defined for intermediate- and high-risk patients only. Alt, alternative donor; DS, Down syndrome; Int, intensification course; MFD, matched family donor; SCT, stem-cell transplantation.

Induction

Remission was assessed after each induction course (Tables 2, 3, and Appendix Table A1) and was compared between GO and No-GO arms. At the end of IND1, early death, refractory CNS disease, and prevalence of PD were similar (Table 2). At the end of IND2 (Table 3), neither CR ($P = .15$) nor RD ($P = .12$) were significantly different between arms. RD was significantly reduced only among LR and IR GO recipients; no LR GO recipient experienced RD. Overall, induction mortality was similar between the arms.

Outcome From Study Entry

Among all patients (Table 3; Fig 2A), from study entry EFS was significantly improved among GO recipients (HzR, 0.83; 95% CI, 0.70 to 0.99; $P = .04$; 3-year EFS: 53.1% ± 4.4% *v* 46.9% ± 4.4%) though

Table 1. COG AAML0531 Therapeutic Regimen

Course and Agent	Dose	Days
IND1		
Cytarabine	100 mg/m^2/dose twice per day IV	1 to 10
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1 to 5
Gemtuzumab, arm B only	3 mg/m^2/dose IV over 2 hours	6
IND2		
Cytarabine	100 mg/m^2/dose twice per day IV	1 to 8
Daunomycin	50 mg/m^2/dose IV	1, 3, 5
Etoposide	100 mg/m^2/dose IV	1 to 5
INT1		
Cytarabine	1,000 mg/m^2/dose twice per day IV	1 to 5
Etoposide	150 mg/m^2/dose IV	1 to 5
For patients not undergoing stem-cell transplantation		
INT2		
Mitoxantrone	12 mg/m^2/dose IV	3 to 6
Cytarabine	1,000 mg/m^2/dose twice per day IV	1 to 4
Gemtuzumab, arm B only	3 mg/m^2/dose IV over 2 hours	7
INT3		
Cytarabine	3,000 mg/m^2/dose twice per day IV	1, 2, 8, 9
Escherichia coli L-asparaginase	6,000 mg/m^2/dose IM	2, 9
For patients receiving matched family-donor stem-cell transplantation		
Busulfan, 16 total doses	Age and weight based	−9
< 10 kg or > 4 years old	0.8 mg/kg/dose once every 6 hours IV	
> 10 kg and < 4 years old	1 mg/kg/dose every 6 hours IV	
All patients	Adjusted AUC based on first dose	−8 to −6
Cyclophosphamide	50 mg/kg/dose IV once per day	−5 to −2

Abbreviations: AUC, area under the concentration-time curve; COG, Children's Oncology Group; IM, intramuscular; IND1, induction course; INT, intensification course; IV, intravenous.

OS was not improved (HzR, 0.91; 95% CI, 0.74 to 1.13; $P = .39$; 3-year OS: 69.4% ± 4.2% *v* 65.4% ± 4.4%). By risk group (Figs 2B to 2D), only EFS in the LR and IR groups suggested improvement with GO. No difference in EFS or OS was detected in the HR patients when analyzed from study entry.

Postremission Outcomes

Postremission analyses suggested consistent differences by arm (Table 3; Figs 3A to 3D). DFS among all GO recipients suggested improvement overall and by risk group ($P = .07$). Exploratory analyses demonstrated a significant decrease in RR overall (HzR, 0.73; 95% CI, 0.58 to 0.91; $P = .006$; 3-year RR: 32.8% ± 4.6% *v* 41.3% ± 4.9%), with qualitatively similar improvements within each risk group. In HR patients, the *FLT3*-ITD HAR cohort was the only one to benefit from GO (Appendix Figs A1B to A1C). However, OS after induction in the entire cohort and in each risk group was not improved. This was partially because of a higher postinduction TRM for GO recipients, particularly for LR patients.

Stem-Cell Transplantation

SCT was recommended for all patients with HR AML and for patients with IR AML if a MFD was available. Thus, the ability to directly analyze the affect of SCT is restricted to IR AML. Fewer No-GO patients (45of 62 patients) received SCT as assigned than did GO recipeients (48 of 53 patients; $P = .015$), primarily because of donor availability. Intent-to-treat analysis (Appendix Table A3; Appendix Fig A1A) showed significantly improved DFS ($P = .02$) and OS ($P = .02$) with SCT. This benefit was limited to GO recipients and, conversely, GO only benefited those patients who received SCT.

Univariable and Multivariable Analyses

Risk factors found to be significant in univariable analysis (Appendix Tables A4 and A5) were included in multivariable models to better define the impact of GO (Table 4). In multivariable analyses adjusted for age, diagnostic WBC, race, and risk group, GO was independently associated with better EFS (HzR, 0.80; 95% CI, 0.67 to 0.96; $P = .02$), DFS (HzR, 0.80; 95% CI, 0.64 to 0.99; $P = .04$), and RR (HzR, 0.72; 95% CI, 0.57 to 0.91; $P = .006$), as well as higher TRM (HzR, 1.84; 95% CI, 0.97 to 3.47; $P = .06$).

Toxicity

Common Terminology Criteria for Adverse Events v4 grade 3 to 5 toxicities were similar between study arms (Appendix Table A6). Life-threatening sinusoidal obstruction syndrome (SOS) was similar with one event in the No-GO arm during IND1, during SCT (No-GO *v* GO: two of 76 patients *v* three of 82 patients; P = not significant [NS]), as was SOS of any degree (14 of 511 patients *v* 18 of 511 patients; P = NS). Acute left-ventricular systolic dysfunction was equivalent in both arms (4.9% ± 1.9% *v* 4.0% ± 1.8%; P = NS). Hematologic toxicity was similar between study arms, including median time to neutrophil recovery, which was more than 500/uL. However, posthoc analysis to examine causes for TRM differences found a higher proportion of GO patients during INT2 with prolonged (> 59 days) neutrophil recovery times (12.0% *v* 6.3%; $P = .01$).

Though therapy reductions occurred in similar proportions between arms (Appendix Table A6), death in remission was qualitatively higher among GO recipients (4.2% *v* 2.6%; $P = .21$). Cumulative TRM from enrollment through last follow-up without relapse or induction failure was higher in GO recipients (5-year TRM: GO, 8.6% ± 2.5% *v* No-GO, 5.9% ± 2.1%; $P = .09$). This difference was primarily limited to the LR patients (two *v* eight patients; $P = .02$) during INT2 and INT 3 (Appendix Table A6), among those patients 11 years old or older (eight of 10 patients). All but one non-SCT TRM event during intensification occurred before neutrophil recovery and primarily late in the course (mean, 56 days; range, 17 to 93 days) and was infection-related. Day-100 TRM rates for MFD and alternative-donor SCT patients were 1.8% (n = 2) and 10.9% (n = 5), respectively, and were similar between arms. TRM beyond day 100 was equivalent.

DISCUSSION

Using the largest randomized pediatric de novo AML trial to date and the only pediatric randomized controlled trial that added GO to induction and intensification, we have shown that EFS is significantly improved by a significant reduction in relapse. These findings are consistent with recent randomized controlled trials in adults[21,22,33] and together strongly supports the need to pursue therapeutic options using anti-CD33 antibody-drug conjugates added to traditional chemotherapy and allogeneic SCT.

Table 2. Demographic Characteristics and Risk Classification

Characteristic	All Patients		No-GO Arm		GO Arm	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Total enrolled	1,070		538		532	
Ineligible, non-DS	41		20		21	
Ineligible, DS	1		1		0	
Eligible, DS	6		6		0	
Eligible, non-DS	1,022		511		511	
Patient characteristics						
Sex						
Male	508	49.7	264	51.7	244	47.7
Female	514	50.3	247	48.3	267	52.3
Age at diagnosis, years						
Median	9.7		9.5		9.9	
Range	0.003-29.8		0.003-29.8		0.02-29.4	
0-1 [0-730 days old]	207	20.3	114	22.3	93	18.2
2-10	354	34.6	167	32.7	187	36.6
11-15	298	29.2	157	30.7	141	27.6
16-20	150	14.7	69	13.5	81	15.9
$\geq$ 21	13	1.3	4	0.8	9	1.8
Race						
American Indian or Alaska Native	4	0.4	3	0.7	1	0.2
Asian	50	5.4	27	5.9	23	5.0
Native Hawaiian or other Pacific Islander	2	0.2	1	0.2	1	0.2
Black or African American	116	12.6	61	13.3	55	12.0
White	748	81.3	368	80.0	380	82.6
Unknown	102		51		51	
Ethnicity						
Hispanic or Latino	189	19.2	97	19.8	92	18.7
Not Hispanic or Latino	794	80.8	394	80.2	400	81.3
Unknown	39		20		19	
WHO classification						
AML WHO disease classification						
AML with t(8;21)(q22;q22), AML1/ETO	131	12.8	65	12.7	66	12.9
AML with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(p13;q22), CBF/MYH11	100	9.8	47	9.2	53	10.4
AML with 11q23 (MLL) abnormalities	183	17.9	93	18.2	90	17.6
AML with multilineage dysplasia	61	6.0	35	6.9	23	5.1
AML with multilineage dysplasia: following MDS or MDS/MPD	1	0.1	0	0	1	0.2
AML with multilineage dysplasia: without antecedent MDS or MDS/MPD	3	0.3	2	0.4	1	0.2
AML, not otherwise categorized	19	1.9	10	2.0	9	1.8
AML, minimally differentiated	32	3.1	13	2.5	19	3.7
AML without maturation	107	10.5	56	11.0	51	10.0
AML with maturation	104	10.2	50	9.8	54	10.6
Acute myelomonocytic leukemia	111	10.9	55	10.8	56	11.0
Acute monoblastic/acute monocytic leukemia	97	9.5	45	8.8	52	10.2
Acute erythroid leukemia	15	1.5	6	1.2	9	1.8
Acute megakaryoblastic leukemia	49	4.8	31	6.1	18	3.5
Acute panmyelosis with myelofibrosis	1	0.1	0	0	1	0.2
Myeloid sarcoma	8	0.8	3	0.6	5	1.0
Leukemic burden						
WBC, $\times 10^3/\mu$L						
Median	24		24.3		23.6	
Range	0.2-827.2		0.2-526		0.4-827.2	
No. of patients with $> 100 \times 10^3/\mu$L	198	19.4	95	18.6	103	20.2
CNS disease classification at study entry						
CNS1	712	70.8	360	71.3	352	70.3
CNS2	197	19.6	99	19.6	98	19.6
CNS3	97	9.6	46	9.1	51	10.2
Unknown	16		6		10	
Extramedullary disease	140	13.7	74	14.5	66	12.9

(continued on following page)

Table 2. Demographic Characteristics and Risk Classification (continued)

Characteristic	All Patients		No-GO Arm		GO Arm	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Risk factors and classification						
Cytogenetics, affecting risk classification						
t(8;21)*	137	13.4	69	13.5	68	13.3
Inv16, t(16;16)*	109	10.7	52	10.2	57	11.2
−7†	25	2.5	16	3.1	9	1.8
−5/5q-†	14	1.4	10	2.0	4	0.8
Institution FLT3 results‡						
High FLT3-ITD allelic ratio (> 0.4)†	63	9.7	25	7.7	38	11.7
End of IND1 response, BM aspirate						
Complete remission	727	72.4	350	69.6	377	75.6§
Partial remission, 5%–15% blasts	122	12.2	71	14.1	51	10.2
Persistent disease, > 15% blasts by morphology†	114	11.4	61	12.1	53	10.6
No IND1 marrow evaluation¶						
Died before end of IND1¶	18	1.8	9	1.8	9	1.8
Refractory CNS disease¶	23	2.3	14	2.8	9	1.8
Not evaluable	18	2.9	6	1.2	12	2.3
Risk-group assignment‖						
Low	246	24.1	121	23.7	125	24.5
Intermediate	607	59.4	302	59.1	305	59.7
High	169	16.5	88	17.2	81	15.9

Abbreviations: AML, acute myeloid leukemia; BM, bone marrow; DS, Down syndrome; GO, gemtuzumab-ozogamicin; IND, induction course; MDS, myelodysplastic syndrome; MDS/MPD, myelodysplastic/myeloproliferative neoplasms; MLL, mixed-lineage leukemia; No-Go, did not receive gemtuzumab-ozogamicin (control arm).

*Low-risk factors (override response at end of IND1; high FLT3-ITD ratio overrides low-risk factors).

†High-risk factors.

‡FLT3 totals and percentages derived from after study point when this was added to risk classification (n = 324 in each arm).

§$P < .05$.

¶These patients were not completely defined for risk classification owing to early death, removal because of refractory CNS disease, or failure to have an end of induction marrow.

‖Risk group assignments are based upon the presence of various factors, and some patients may have had more than one (eg, persistent disease and − 7); numbers in rows are the total for each factor and therefore their total may exceed the No. in the risk group assignment.

In 2010, GO was withdrawn when the SWOG trial S0106 found GO use failed to improve CR (as a primary end point) and had higher induction mortality.[19] This trial was criticized for daunomycin reduction in the GO arm (45 mg/m^2/dose *v* 60 mg/m^2/dose),[20] considering later evidence that anthracycline dosing significantly affects OS.[34,35] Our trial and earlier COG efforts show that intensifying induction, targeted or nontargeted, subsequently reduces RR without improving CR.[3] Similarly, other trials in adult patients have since reported that GO improves survival rates in the LR and IR subtypes of AML without improving CR and without high mortality.[19,21,22,33] A recent meta-analysis of randomized controlled trials of GO in adults further strengthened this association of reduced relapse when adding GO.[36]

AML is a heterogeneous disease caused by a variety of molecular mutations conferring varied prognoses.[9] This led to our a priori secondary objectives to examine how GO might affect AML risk groups' survival rates differently and, by our selective incorporation of SCT (based on benefit in prior COG trials[5]), onto a backbone of intensive induction and high-dose intensification chemotherapy (modified from the Medical Research Council AML12 trial[37]). Adapting the MRC's risk classification,[27] AAML0531 varied from prior COG trials by subdividing patients for selective use of SCT during intensification, permitting further analysis of this and GO's impact on DFS.

Analyzed from study entry by risk group, patients with LR AML at 3 years (Table 3) exhibited a 7% improvement in EFS, primarily from a 10% reduction in relapse consistent with trials of adult patients.[19,21,22] Despite this benefit in first remission, OS was not significantly improved. This is not unusual for LR patients who have high salvage rates after relapse.[38,39] Within the IR-patient group, GO did improve CR rates ($P = .03$) and, with a reduced RR ($P = .13$), saw EFS ($P = .09$) and OS ($P = .19$) improve as well. However, as intensification therapy varied based on availability of MFD SCT, we prospectively evaluated GO's impact without SCT. We found no reduction in RR, DFS, or OS in those patients not receiving SCT. However, in IR SCT patients, despite the small numbers, we saw qualitative improvement in RR ($P = .15$) without a difference in TRM, resulting in similar degrees of DFS ($P = .14$) and OS ($P = .17$) rate improvements with GO (Appendix Table A3; Appendix Fig A1A).

Within the HR cohort, there was no benefit with GO when measured from study entry. However, in our exploratory analyses for this risk group in which all received SCT, RR was nonsignificantly ($P = .08$) reduced and, as TRM was similar between arms, improvement in DFS ($P = .16$) and OS ($P = .13$) was suggested, though they did not achieve statistical significance. Additional inquiry suggests this was limited to patients with *FLT3*-ITD HAR, a mutation associated with high CD33 expression.[40] These positive interactions with SCT are the likely reason we saw benefit in HR patients alone. If validated in future trials, this is particularly important for this cohort of patients which rarely can receive salvage treatment after relapse.[38,39,41]

TRM was increased when GO was added, despite a lack of difference in overall toxicity incidence between arms. However, increased TRM was limited to the LR cohort and occurred in individuals with a markedly delayed recovery of neutrophils in the last two (of five)

Table 3. AAML0531 Outcomes From Study Entry

Patient Group From Study Entry	No. of Patients	CR* (%)	P†	RD* (%)	P†	EM* (%)	P†	3-Year EFS ± 2SE (%)	EFS HR	95% CI	P†	3-Year OS ± 2SE (%)	OS HR	95% CI	P†
All patients															
No-GO	511	85.1	.15	12.6	.12	2.2	.98	46.9 ± 4.4	1			65.4 ± 4.4	1		
GO	511	88.3		9.5		2.3		53.1 ± 4.4	0.83	0.70 to 0.99	.04	69.4 ± 4.2	0.91	0.74 to 1.13	.39
Low risk															
No-GO	121	95	.33	4.2	.03	0.8	.62	64.0 ± 8.8	1			84.6 ± 6.6	1		
GO	125	97.6		0		2.4		71.4 ± 8.2	0.74	0.48 to 1.15	.18	85.4 ± 6.4	1.11	0.60 to 2.06	.74
Intermediate risk															
No-GO	302	87.4	.03	9.2	.04	3.4	.48	45.8 ± 5.8	1			62.6 ± 5.6	1		
GO	305	92.7		4.8		2.4		51.4 ± 5.8	0.82	0.66 to 1.03	.09	68.7 ± 5.4	0.83	0.64 to 1.09	.19
High risk															
No-GO	88	61	.48	39	.59	0	.49	27.2 ± 9.6	1			48.0 ± 11.0	1		
GO	81	55.4		43.2		1.4		31.2 ± 10.4	1.0111	0.70 to 1.45	.96	47.7 ± 11.6	1.06	0.70 to 1.62	.78

From End of IND2

Patient Group From End of IND2	No. of Patients	3-Year TRM ± 2SE (%)	TRM HR	95% CI	P†	3-Year RR ± 2SE (%)	RR HR	95% CI	P†	3-Year DFS ± 2SE (%)	DFS HR	95% CI	P†	3-Year OS ± 2SE (%)	OS HR	95% CI	P†
All patients																	
No-GO	418	4.1 ± 1.9	1			41.3 ± 4.9	1			54.7 ± 5.0	1			70.1 ± 4.6	1		
GO	429	6.6 ± 2.4	1.69	0.93 to 3.08	.08	32.8 ± 4.6	0.73	0.58 to 0.91	.006	60.6 ± 4.8	0.82	0.67 to 1.02	.07	74.0 ± 4.4	0.88	0.68 to 1.13	.32
Low risk																	
No-GO	114	1.8 ± 2.5	1			30.3 ± 8.8	1			67.9 ± 8.8	1			86.4 ± 6.6	1		
GO	120	7.5 ± 4.9	4.39	0.95 to 20.4	.04	19.7 ± 7.4	0.58	0.34 to 0.97	.04	72.8 ± 8.2	0.81	0.51 to 1.30	.38	84.7 ± 7.0	1.11	0.56 to 2.17	.77
Intermediate risk																	
No-GO	257	3.1 ± 2.2	1			45.5 ± 6.3	1			51.4 ± 6.4	1			66.9 ± 6.0	1		
GO	268	4.6 ± 2.6	1.45	0.60 to 3.57	.41	39.6 ± 6.1	0.81	0.63 to 1.06	.13	55.9 ± 6.2	0.86	0.67 to 1.11	.24	70.2 ± 5.8	0.90	0.67 to 1.22	.49
High risk																	
No-GO	47	14.9 ± 10.5	1			44.8 ± 14.8	1			40.3 ± 14.4	1			48.5 ± 14.6	1		
GO	41	17.1 ± 11.9	1.27	0.46 to 3.48	.65	27.0 ± 14.2	0.53	0.25 to 1.09	.08	55.9 ± 15.6	0.66	0.37 to 1.18	.16	67.5 ± 14.8	0.61	0.32 to 1.16	.13

Abbreviations: CR, complete remission; DFS, disease-free survival; EFS, event-free survival; EM, early mortality; GO, received gemtuzumab-ozogamicin; HR, hazard ratio; IND, induction course; No-GO, did not receive gemtuzumab-ozogamicin (control arm); OS, overall survival; RD, refractory disease; RR, relapse rate; TRM, treatment-related mortality from end of induction.

*CR, RD, and EM are cumulative incidences from study entry to end of IND2.

†*P* values are either Gray's *P* value for TRM, RR analyses, or log-rank *P* values for DFS or OS analyses.

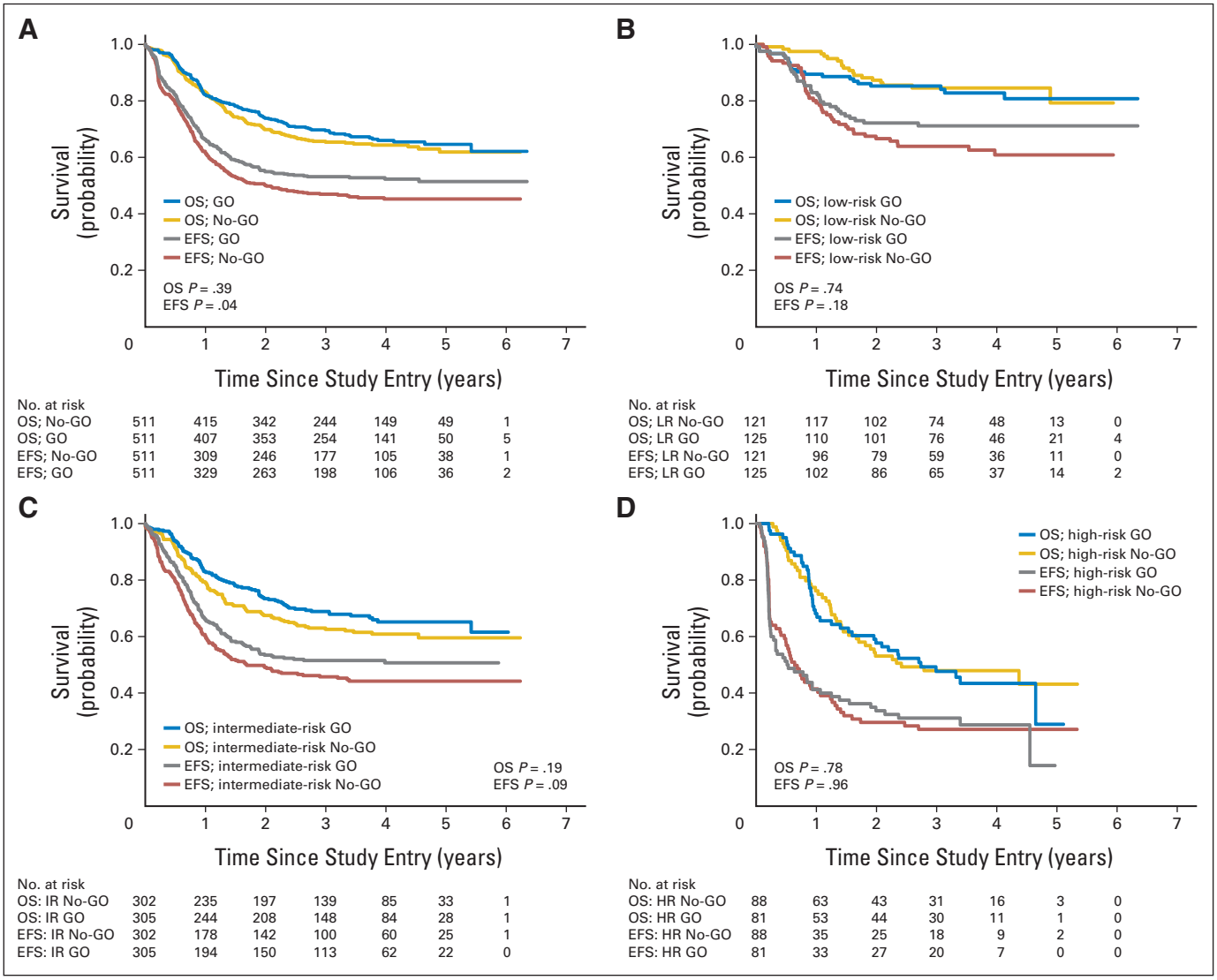

Fig 2. Overall survival (OS) and event-free (EFS) survival rates from study entry by study arm. (A) All patients; (B) low-risk (LR) patients; (C) intermediate-risk (IR) patients; (D) high-risk (HR) patients. GO, gemtuzumab-ozogamicin arm; No-GO, did not receive gemtuzumab-ozogamicin (control arm). Median survival rates for each group is listed in Appendix Table A7, where applicable.

courses of therapy. These last two courses were associated with the most prolonged median times to neutrophil recovery and adding GO seems to have worsened this in a subset of patients. Recent MRC reports showed no benefit with a fifth course of therapy.[7,42] COG no longer includes the final course of chemotherapy, which may lessen this risk in future GO trials. Also, the use of GO after remission may not be beneficial as seen in the NOPHO (Nordic Society of Pediatric Hematology and Oncology) trial.[43]

Although early GO studies saw increased SOS,[44] we did not experience this. This is likely a result of our 3 mg/m^2 GO dose selection and timing, as GO doses of $\geq$ 6 mg/m^2 or SCT received within 120 days of GO administration primarily increased this risk.[44] Overall, toxicity during SCT was not significantly greater in the GO arm. Acute cardiotoxicity, a concern that affected SWOG's choice of anthracycline dosing, was not increased in our trial (although long-term observation is ongoing). Despite a higher infection-related TRM that attenuated GO's affect on DFS and OS in our study, TRM observed in this trial compares favorably with recent COG trials (Appendix Fig A2).[3-5,16]

Limitations of this trial include its ability to show a statistically significant improvement by AML risk group. This is, and will increasingly be, a challenge and a result of expanding heterogeneity of AML with ever smaller cohorts of relevant biologic factors. Even in adults in whom AML is much more prevalent, a five-trial meta-analysis was needed for adequate statistical power to determine GO's impact on outcome.[36] Nevertheless, this is the largest pediatric AML trial reported and likely represents the strongest evidence possible in a pediatric randomized clinical trial.

Our exploratory analyses determining reasons for a postinduction improvement in DFS are admittedly posthoc. However, rather than a broad net of possible factors, this posthoc analysis focused on those associations that have repeatedly been found in recent trials of adult patients. Our findings are consistent with other GO trials and further strengthen the accumulated literature. A new finding from our exploratory analyses was that the benefit of GO was limited to IR patients receiving SCT. This association was further consistent with our finding that HR

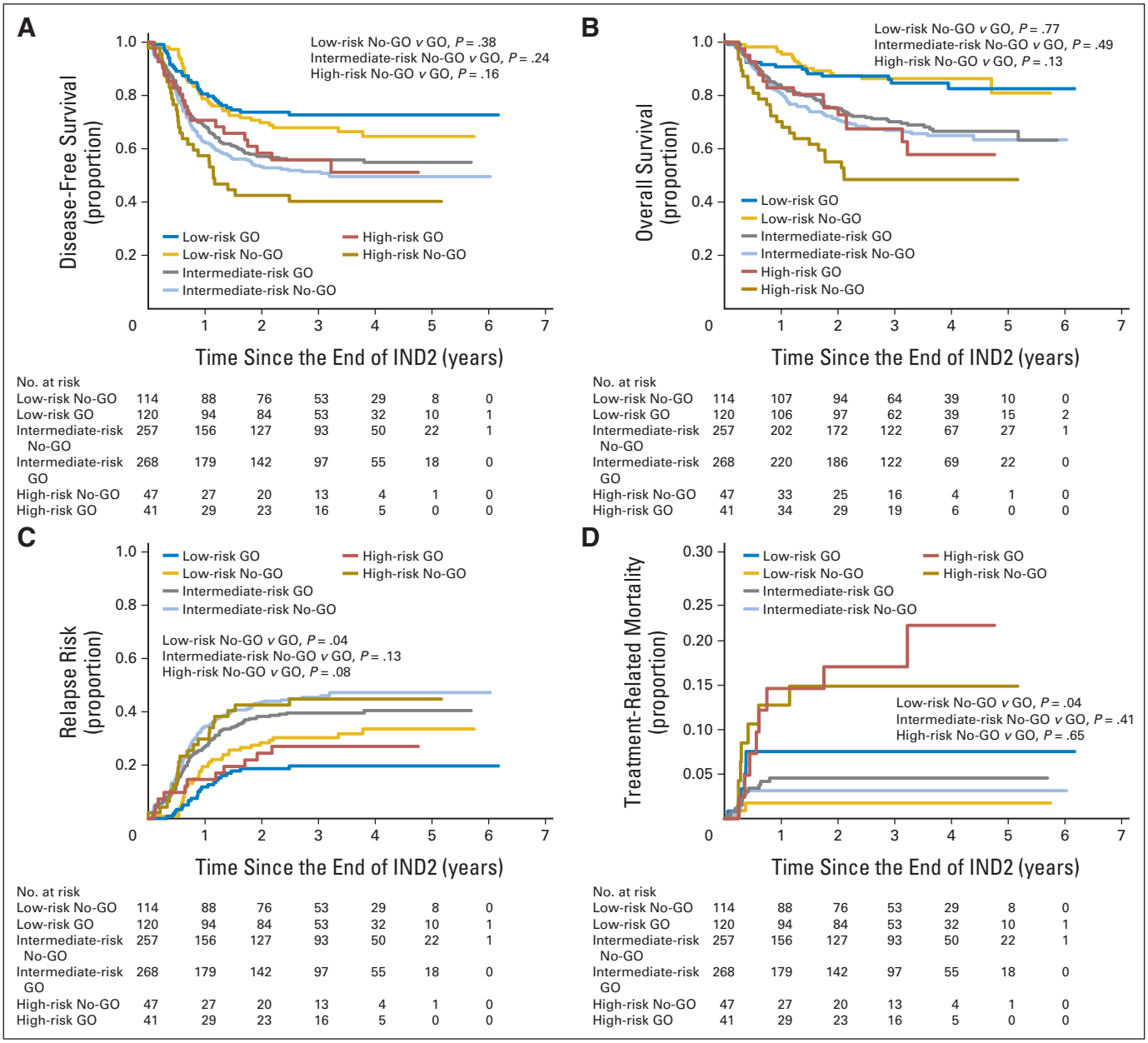

Fig 3. Outcomes among patients from end of induction 2 (IND2) by risk group and study arm among patients in remission after the end of IND2. (A) Disease-free survival from end of IND2. (B) Overall survival from end of IND2. (C) Relapse risk from end of IND2. (D) Treatment-related mortality from end of IND2. GO, gemtuzumab-ozogamicin arm; No-GO, did not receive gemtuzumab-ozogamicin (control arm).

patients, all of whom received best available donor SCT, specifically those who had FLT3-ITD HAR, also benefited from GO. This will require validation in future trials, though is consistent with recent evidence that GO reduces minimal residual disease and that reduced or absent minimal residual disease pre-SCT is associated with improved post-SCT DFS.[45-47]

Finally, our findings confirm CD33-targeted therapy added to intensive chemotherapy improves EFS in de novo AML owing to a reduced relapse risk. As doses and schedules have varied among the reported randomized trials,[19,21,22] further investigation into optimal methods of GO administration and other CD33-targeted agents in development should be pursued in future trials.[10,48]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Table 4. Multivariable Analyses for Outcomes From Study Entry and From End of IND2

	From Study Entry							From End of IND2											
		EFS			OS				DFS			OS			RR			TRM		
Modeled Risk Factors*	No. of Patients	HR	95% CI	*P*	HR	95% CI	*P*	No. of Patients	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Treatment arm																				
No-GO	465	1			1			381	1			1			1			1		
GO	466	0.80	0.67 to 0.96	.02	0.89	0.71 to 1.12	.33	398	0.80	0.64 to 0.99	.04	0.84	0.65 to 1.10	.20	0.72	0.57 to 0.91	.006	1.84	0.97 to 3.47	.06
Age at diagnosis, years																				
2-10	328	1			1			281	1			1			1			1		
0-1	182	1.12	0.86 to 1.45	.40	1.18	0.86 to 1.63	.31	144	1.07	0.78 to 1.47	.67	1.10	0.75 to 1.64	.60	1.04	0.74 to 1.47	.82	1.57	0.36 to 6.74	.55
≥ 11	421	1.15	0.93 to 1.41	.20	1.40	1.08 to 1.81	.01	354	1.25	0.98 to 1.60	.07	1.5	1.11 to 2.04	.009	0.95	0.73 to 1.23	.69	7.32	2.52 to 21.2	< .001
WBC at diagnosis, μL																				
≤ 100,000	757	1			1			648	1			1			1			1		
> 100,000	174	1.41	1.14 to 1.76	.002	1.18	0.89 to 1.55	.25	131	1.28	0.98 to 1.68	.07	1.13	0.81 to 1.59	.48	1.47	1.09 to 1.98	.01	0.38	0.12 to 1.20	.10
Race																				
Not black	818	1			1			687	1			1			1			1		
Black	113	1.37	1.06 to 1.78	.02	2.01	1.51 to 2.68	< .001	92	1.49	1.09 to 2.02	.01	1.99	1.42 to 2.79	< .001	1.29	0.91 to 1.83	.16	1.82	0.84 to 3.97	.13
Cytogenetic risk group																				
Intermediate	666	1			1			536	1			1			1			1		
Low [t(8;21) or inv(16)]	231	0.48	0.37 to 0.61	< .001	0.37	0.26 to 0.52	< .001	220	0.54	0.41 to 0.71	< .001	0.37	0.25 to 0.54	< .001	0.52	0.39 to 0.70	< .001	0.87	0.41 to 1.85	.72
High (−5/del5q or −7)	34	1.32	0.86 to 2.01	.20	1.98	1.27 to 3.07	.002	23	1.28	0.73 to 2.24	.39	2.00	1.13 to 3.54	.02	0.57	0.27 to 1.22	.15	7.86	2.93 to 21.1	< .001

NOTE. Analyses only include patients for whom risk factor data were available.

Abbreviations: DFS, disease-free survival; EFS, event-free survival; GO, gemtuzumab ozogamicin; HR, hazard ratio; IND, induction course; No-GO, did not receive gemtuzumab-ozogamicin (control arm); OS, overall survival; RR, relapse risk; TRM, treatment-related mortality.

*Modeled risk factors were found on univariable analysis to have significant impact on outcomes.

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Appendix

Table A1. Remission Induction by Risk Factor: Percent of Patients Achieving Remission

	End of IND1 (CR/PR %; cyto- or molecular risk factors only)*						End of IND2 (CR only; %)					
	No. of Patients†		% of Patients				No. of Patients‡		% of Patients			
Risk Group*	No-GO	GO	No-GO	GO	Total	*P*§	No-GO	GO	No-GO	GO	Total	*P*§
Low risk	121	125	NA	NA	NA	NA	120	123	95.0	97.6	96.3	.33
t(8;21)	69	68	92.8	86.8	89.8	.25	69	68	92.8	98.5	95.6	.21
inv(16)/t(16;16)	52	57	98.1	94.6	96.3	.62	51	55	98.0	96.4	97.2	1.00
Intermediate risk	302	305	NA	NA	NA	NA	294	289	87.4	92.7	90.1	.03
High risk	88	81	NA	NA	NA	NA	77	74	61.0	55.4	58.3	.48
−7	16	9	75.0	66.7	72.0	.67	13	8	69.2	75.0	71.4	1.00
−5/5q-	10	4	90.0	33.3	76.9	.11	10	3	90.0	100	92.3	1.00
Course 1 > 15% blasts	44	36	NA	NA	NA	NA	36	32	41.7	25.0	33.8	.15
FLT3-ITD: high allelic ratio	25	38	65.2	78.4	73.3	.26	25	37	68.0	73.0	71.0	.67
Total eligible patients¶	511	511	83.4	85.8	84.6	.29	491	486	85.1	88.3	86.7	.15

NOTE. Twenty No-GO patients and 25 GO patients were not evaluable (withdrawal or failure to obtain bone marrow examination) by the end of IND2 and are not included in the remission percentage calculations.

Abbreviations: CR, complete remission; GO, gemtuzumab-ozogamicin arm; IND, induction course; NA, not applicable because risk classification group assignment is defined partially by response at end of IND1; No-GO, did not receive gemtuzumab-ozogamicin (control arm); PR, partial remission (5-15% blasts; only used at end of IND1).

*End of IND1 response rates refer only to the specific, nonresponse-based risk factors.

†No. of patients at start of IND1 for diagnostic risk factors.

‡No. of patients at start of IND2, excluding patients who electively withdrew at IND1 or were not evaluable for response at IND2.

§*P* values compare the complete remission percentages between the No-GO and GO arms of therapy.

¶Overall CR/PR rate regardless of risk group.

Table A2. Treatment Completion Comparisons Between Study Arms

Cumulative Reasons for Not Completing All Therapy	Control Arm (No. of Patients)	GO Arm (No. of Patients)	*P*
Total enrolled	511	511	
Total completing all therapy	327	334	.65
Total of those not completing all therapy	184	177	
Reasons for not completing all therapy			
Elective withdrawal	42	41	.94
Withdrawal because of toxicity	43	45	.65
Toxic mortality	16	20	.41
Refractory disease/relapsed before therapy completion	82	71	.39
Lost to follow-up	1	0	1.00

Abbreviation: GO, gemtuzumab-ozogamicin arm.

Table A3. Impact of GO With Bone Marrow Transplantation Outcomes for Intermediate-Risk Patients As Treated: From End of INT1 Stratified by Treatment Received (matched family-donor bone marrow transplantation or chemotherapy)

Patient Group	No. of Patients	3-Year TRM ± 2SE (%)	TRM HR	95% CI	*P*	3-Year RR ± 2SE (%)	RR HR	95% CI	*P*	3-Year DFS ± 2SE (%)	DFS HR	95% CI	*P*	3-Year OS ± 2SE (%)	OS HR	95% CI	*P*
All IR patients																	
No-GO	230	3.5 ± 2.4	1			42.6 ± 6.7	1			53.9 ± 6.7	1			69.2 ± 6.3	1		
GO	245	4.5 ± 2.7	1.28	0.51 to 3.18	.60	37.2 ± 6.3	0.83	0.62 to 1.10	.19	58.3 ± 6.4	0.86	0.66 to 1.13	.28	72.8 ± 5.9	0.87	0.63 to 1.21	.41
Chemotherapy only, IR patients																	
No-GO	185	3.8 ± 2.8	1			43.9 ± 7.6	1			52.3 ± 7.6	1			68.5 ± 7.0	1		
GO	197	5.1 ± 3.1	1.33	0.51 to 3.50	.56	40.1 ± 7.1	0.88	0.65 to 1.21	.44	54.8 ± 7.2	0.93	0.69 to 1.25	.62	70.1 ± 6.8	0.95	0.66 to 1.36	.77
BMT recipients only, IR patients																	
No-GO	45	2.2 ± 4.4	1			37.8 ± 14.7	1			60.0 ± 14.6	1			72.6 ± 13.6	1		
GO	48	2.1 ± 4.2	0.93	0.06 to 14.6	.96	25.2 ± 12.8	0.59	0.29 to 1.20	.15	72.7 ± 12.9	0.60	0.30 to 1.19	.14	83.2 ± 10.9	0.55	0.23 to 1.32	.17
IR-No-GO arm patients, chemotherapy *v* BMT recipients																	
HR, CTx *v* BMT*	230		0.58	0.07 to 4.71	.61		0.93	0.55 to 1.58	.80		0.89	0.54 to 1.46	.64		0.84	0.46 to 1.53	.57
IR-GO arm patients, chemotherapy *v* BMT recipients																	
HR, CTx *v* BMT*	245		0.40	0.05 to 3.09	.38		0.63	0.35 to 1.13	.12		0.58	0.33 to 1.02	.06		0.48	0.23 to 1.00	.05

Abbreviations: BMT, as-treated intermediate-risk patients who received matched family-donor transplantations; CTx, chemotherapy; DFS, disease-free survival; GO, received gemtuzumab-ozogamicin; HR, hazard ratio; INT, intensification course; IR, all intermediate-risk patients at end of INT1 who proceeded to next phase; No-GO, did not receive gemtuzumab-ozogamicin (control arm); OS, overall survival; RR, relapse rate; TRM, treatment-related mortality.

*HR (CTx *v* BMT). These HRs used the CTx patient outcomes as the reference group that have a HR = 1.

Table A4. Univariable Risk Factor Analyses From Study Entry

Characteristic	EFS From Study Entry				OS From Study Entry		
	No. of Patients	HR	95% CI	*P*	HR	95% CI	*P*
Treatment Arm							
No-GO	511	1			1		
GO	511	0.83	0.70 to 0.99	**.04**	0.91	0.74 to 1.13	.39
Age, years							
2-10	354	1			1		
0-1	207	1.41	1.11 to 1.79	**.005**	1.38	1.03 to 1.86	**.03**
≥ 11	461	1.13	0.92 to 1.38	.24	1.32	1.03 to 1.69	**.03**
WBC							
≤ 100,000	824	1			1		
100,000	198	1.58	1.29 to 1.94	**< .001**	1.36	1.06 to 1.75	**.02**
Weight group, ≥ 1 year old							
Middleweight	660	1			1		
Underweight	69	0.8	0.54 to 1.18	.25	0.59	0.35 to 1.02	.06
Overweight	167	1.01	0.79 to 1.28	.96	1.16	0.87 to 1.54	.32
Race							
Not black	855	1			1		
black	116	1.4	1.09 to 1.81	**.010**	1.98	1.50 to 2.62	**< .001**
Cytogenetic risk group							
Intermediate	702	1			1		
Low, t(8;21) or inv(16)	244	0.46	0.36 to 0.59	**< .001**	0.38	0.27 to 0.53	**< .001**
High, mono5/del5q or mono7	35	1.32	0.88 to 2.00	.19	1.88	1.22 to 2.91	**.004**
Institutional risk group							
Intermediate	607	1			1		
Low	246	0.53	0.42 to 0.68	**< .001**	0.40	0.29 to 0.56	**< .001**
High	169	1.95	1.58 to 2.41	**< .001**	1.67	1.30 to 2.15	**< .001**

NOTE. Boldfaced *P* values represent statistically significant differences.
Abbreviations: EFS, event-free survival; GO, received gemtuzumab-ozogamicin; HR, hazard ratio; No-GO, did not receive gemtuzumab-ozogamicin (control arm); OS, overall survival.

Table A5. Univariable Risk Factor Analyses From End of IND2

Characteristic	No. of Patients	DFS From End of IND2			OS From End of IND2			RR From End of IND2			TRM From End of IND2		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Treatment arm													
No-GO	418	1			1			1			1		
GO	429	0.82	0.67 to 1.02	.07	0.88	0.68 to 1.13	.32	0.73	0.58 to 0.91	**.006**	1.69	0.93 to 3.08	.09
Age, years													
2-10	302	1			1			1			1		
0-1	159	1.27	0.94 to 1.71	.12	1.26	0.87 to 1.82	.22	1.31	0.95 to 1.80	.10	0.82	0.21 to 3.15	.77
≥ 11	386	1.19	0.94 to 1.51	.14	1.35	1.01 to 1.80	**.04**	0.94	0.73 to 1.20	.62	4.15	1.85 to 9.33	**.001**
WBC													
≤ 100,000	704	1			1			1			1		
100,000	143	1.35	1.04 to 1.75	**.02**	1.19	0.87 to 1.65	.28	1.51	1.15 to 1.98	**.003**	0.59	0.23 to 1.51	.27
Weight group, ≥ 1 year old													
Middleweight	556	1			1			1			1		
Underweight	61	0.86	0.55 to 1.33	.49	0.63	0.34 to 1.16	.14	0.91	0.57 to 1.44	.67	0.63	0.15 to 2.66	.53
Overweight	143	1.10	0.83 to 1.46	.50	1.33	0.97 to 1.83	.08	1.03	0.75 to 1.40	.87	1.36	0.66 to 2.79	0.41
Race													
Not black	715	1			1			1			1		
Black	93	1.48	1.09 to 2.00	**.01**	1.93	1.38 to 2.70	**< .001**	1.29	0.92 to 1.81	.15	1.97	0.95 to 4.11	.07
Cytogenetic risk group													
Intermediate	562	1			1			1			1		
Low, t(8;21) or inv(16)	232	0.54	0.41 to 0.70	**< .001**	0.40	0.28 to 0.57	**< .001**	0.49	0.37 to 0.65	**< .001**	1.11	0.54 to 2.26	.78
High, mono5/del5q or mono7	24	1.28	0.75 to 2.19	.37	1.86	1.06 to 3.27	**.03**	0.67	0.34 to 1.33	.25	6.33	2.64 to 15.2	**< .001**
Institutional risk group													
Intermediate	525	1			1			1			1		
Low	234	0.56	0.43 to 0.72	**< .001**	0.41	0.28 to 0.59	**< .001**	0.51	0.38 to 0.67	**< .001**	1.23	0.59 to 2.56	.59
High	88	1.20	0.88 to 1.64	.25	1.5	1.06 to 2.13	**.02**	0.80	0.55 to 1.16	.25	4.61	2.38 to 8.95	**< .001**

NOTE. Boldfaced *P* values represent statistically significant differences.

Abbreviations: DFS, disease-free survival; HR, hazard ratio; GO, received gemtuzumab-ozogamicin; IND, induction course; No-GO, did not receive gemtuzumab-ozogamicin (control arm); OS, overall survival; RR, relapse rate; TRM, treatment-related mortality.

Table A6. Toxicities by Course and by Arm

Arm	IND1		IND2		INT1		INT2		INT3		SCT	
	No-GO (n = 511)	GO (n = 511)	No-GO (n = 474)	GO (n = 477)	No-GO (n = 417)	GO (n = 434)	No-GO (n = 302)	GO (n = 324)	No-GO (n = 259)	GO (n = 255)	No-GO (n = 75)	GO (n = 82)
Overall nonhematologic toxicity												
Any grade ≥ 3 toxicity												
No. of patients	389	388	305	311	312	317	261	284	216	217	61	71
%	76	76	64	65	75	73	86	88	83	85	81	87
Hematologic recovery*												
Median time to plts > 50,000, days	26	28	24	25	25	26	38	41	42	44	40	45
No. of patients with plts never > 50,000	103	104	75	79	73	62	98	115	78	67	13	14
Median time to ANC > 500, days	30	30	28	28	27	28	37	38	40	39	30	31
No. of patients who needed > 59 days for ANC recovery	1	0	1	0	0	0	19†	39†	9	11	3	1
No. of patients whose ANC was never > 500‡	125	121	78	70	62	49	42	53	47	44	6	6
Infection incidence, No. of patients												
Documented infection	178	182	175	169	206	209	209	224	173	173	41	46
Neutropenic fever	158	163	103	117	97	93	68	77	47	62	14	15
Therapy dose reduced, No. of patients	6	11	10	6	4	6	8	15	10	4	5	5
Toxic mortality during therapy												
Nonleukemic death, No. of patients	9	9	2	2	0	2	5	7	3	7	3	2
Course day of death												
Median	8	10	13, 25	12, 24	—	16, 21	53	59	18	30	50	53, 124
Range	1-56	0-28					14-93	9-88	15-19	17-41	49-60	
LR nonleukemic death, No. of patients	0	3	1	0	0	1	2	4	0	4	NA	NA
LR course day of death												
Median	—	19	13	—	—	21	63, 93	70	—	33	—	—
Range		0-20						59-88		17-42		

Abbreviations: ANC, absolute neutrophil count; GO, received gemtuzumab-ozogamicin; IND, induction course; INT, intensification course; LR, low risk; NA, not applicable; No-GO, did not receive gemtuzumab-ozogamicin (control arm); plts, platelets; SCT, stem-cell transplantation (matched-family and alternative donor).

*Hematologic recovery values do not include those patients who died during their respective courses.

†$P = .01$.

‡If ANC was never > 500, patient proceeded to next course before ANC recovery.

Table A7. Median Survival Rates for Outcomes

	All Patients				Low Risk				Intermediate Risk				High Risk			
	No-GO Arm		GO Arm		No-GO Arm		GO Arm		No-GO Arm		GO Arm		No-GO Arm		GO Arm	
Outcome	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Overall survival	NR		NR		NR		NR		NR		NR		29.0	18.5 to ∞	32.9	4.9 to ∞
Event-free survival	24.2	16.6 to 47.7	NR		NR		NR		20.3	14.1 to 40.7	NR		7.7	4.9 to 12.8	6.3	2.9 to 15.0

NOTE. All values expressed as months. Associated actuarial survival curves are illustrated in Figure 2.
Abbreviations: GO, received gemtuzumab-ozogamicin; No-GO, did not receive gemtuzumab-ozogamicin (control arm); NR, survival exceeds 50%, so median survival was not reached.

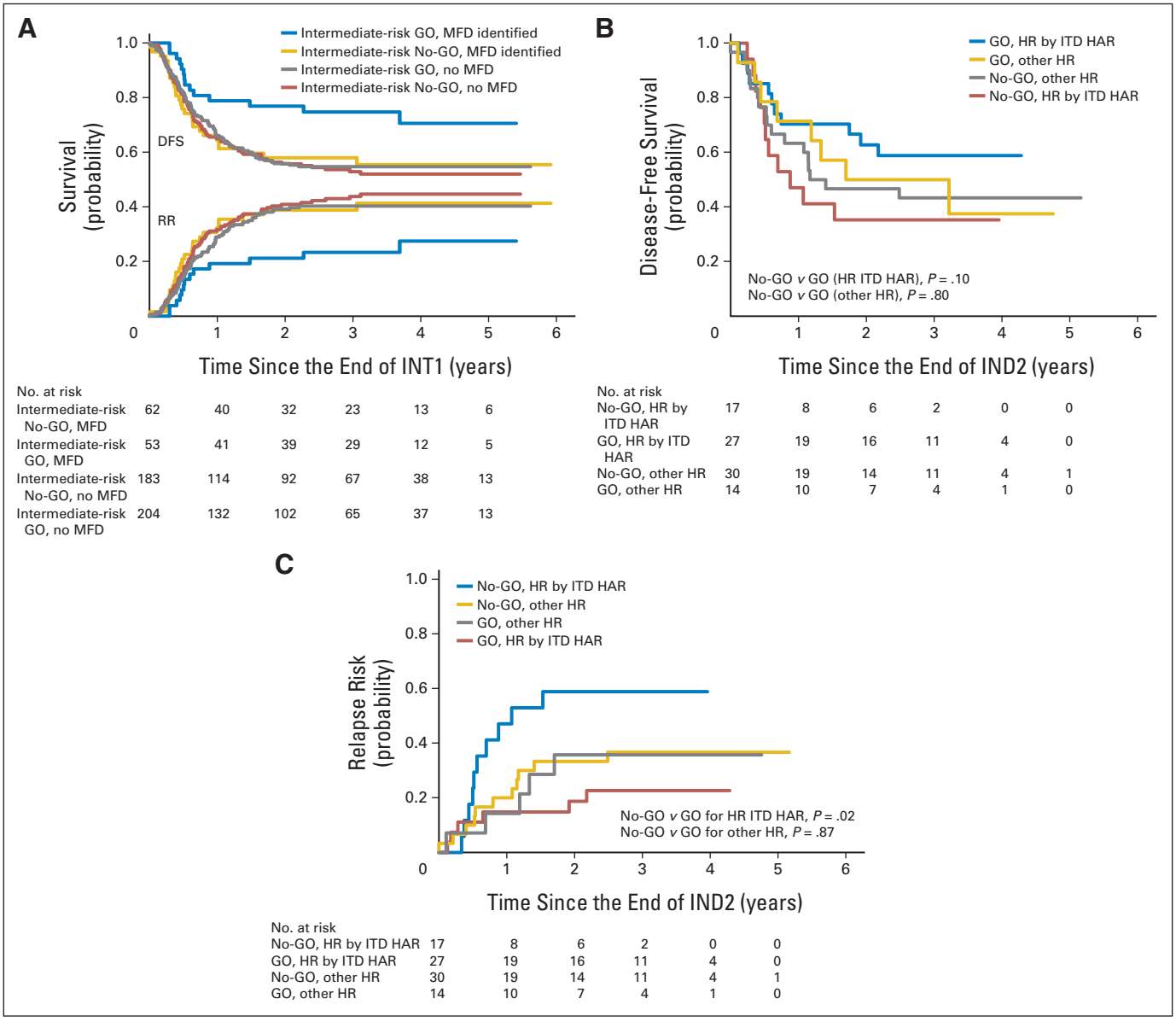

Fig A1. Outcome by study arm in patients who underwent stem-cell transplantation (SCT). (A) Disease-free survival (DFS) and relapse risk (RR) from end of intensification (INT) 1 in intermediate-risk patients by intent-to-treat with matched family donor (MFD) SCT versus chemotherapy and by study arm. (B) DFS from end of induction (IND) 2 by high-risk (HR) factor (*FLT-3* internal tandem duplication high allelic ratio [ITD HAR] or other, such as poor-risk cytogenetics or persistent disease at end of IND1) by study arm. (C) RR from end of IND2 by HR factor (ITD HAR or other, such as poor-risk cytogenetics or persistent disease at end of IND1) by study arm. GO, gemtuzumab-ozogamicin arm; No-GO, did not receive gemtuzumab-ozogamicin (control arm).

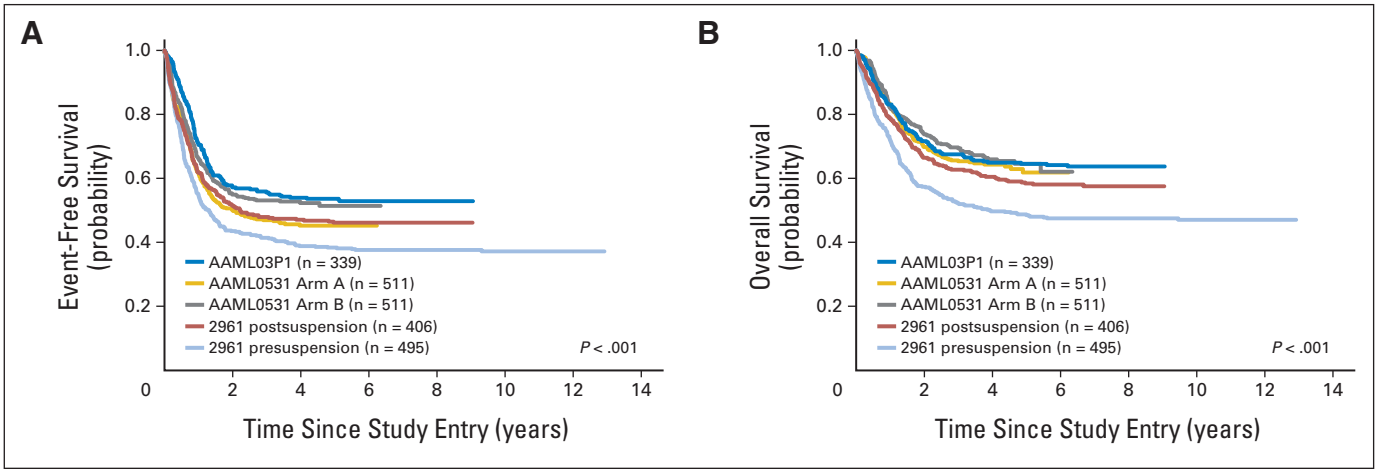

Fig A2. Comparison of Children's Oncology Group Acute Myeloid Lymphoma trials. (A) Event-free and (B) overall survival by AAML0531 treatment arm compared with AAML03P1 (gemtuzumab pilot similar to the gemtuzumab-ozogamicin arm [GO] arm, ie, arm B of AAML0531) and CCG-2961 (used Ida-DCTER [idarubicin, decadron, cytarabine, thioguanine, etoposide, daunorubicin] intensive timing chemotherapy) pre- and postsuspension to add supportive care measures that included mandatory hospitalization until count recovery, avoidance of corticosteroids, prophylactic fluconazole, and intravenous immunoglobulin.